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

# Abstract

Epidemiological 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 measures 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 efficiency from the Attention Network Test (ANT), and tested for possible effect modification by sex. We observed a positive MC for exposure increases from the 10th to the 90th percentile for methyl-paraben (marginal contrast (MC) and confidence interval (CI): 0.042 (0.013, 0.071)), and the phthalate metabolites oxo-MiNP (MC and CI: 0.023 (0.003, 0.044)), oh-MiNP (MC and CI: 0.039 (0.001, 0.076)), and MEHP (MC and CI: 0.036 (0.008, 0.063)), on HRT-SE. 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 inattentiveness outcomes in children and with the homeostasis of the HPA axis.

The prevalence of several neurodevelopmental disorders has increased in the pediatric population ([1](#ref-GrandjeanLandrigan:2014)), and multiple environmental pollutants may play a role in the increased rates of these disorders ([2](#Xd81cf38a3b251ec377f8aa13b097ea9d0c190e3)). 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](#ref-BouchardBellingerWright:2010)–[17](#ref-VilmandBeckBilenberg:2023)). 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)).

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 and few organophosphate pesticide (OP pesticide) metabolites measured ([2](#Xd81cf38a3b251ec377f8aa13b097ea9d0c190e3)). Exposure to phthalates and their metabolites during childhood and early adolescence has been associated to several adverse neurodevelopmental outcomes, but these studies were limited to few phthalate metabolites and small study populations ([2](#Xd81cf38a3b251ec377f8aa13b097ea9d0c190e3)). The effects of exposure to bisphenol A (BPA) during childhood on cognitive functions are still unclear ([2](#Xd81cf38a3b251ec377f8aa13b097ea9d0c190e3)).

Moreover, little is known about the biological mechanisms of action ([2](#Xd81cf38a3b251ec377f8aa13b097ea9d0c190e3)). 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](#ref-KimLeeMoon:2018)–[20](#ref-SearsLiuLanphear:2023)). 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](#ref-SunLiJin:2018),[21](#ref-LupienMcEwenGunnar:2009)). 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](#ref-SearsLiuLanphear:2023),[21](#ref-LupienMcEwenGunnar:2009)).

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 associations between 1) non-persistent EDCs and attention, 2) non-persistent EDCs and glucocorticosteroids, and 3) glucocorticosteroids and attention, using the parametric g-formula and marginal contrasts (MCs), in children of a large cohort in Europe.

# Methods

## 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](#ref-VrijheidSlamaRobinson:2014)). It consists of six existing population-based birth cohort studies across Europe: BiB (Born in Bradford, UK) ([23](#ref-WrightSmallRaynor:2013)), EDEN (Study of determinants of pre- and postnatal developmental, France) ([24](#ref-HeudeForhanSlama:2016)), INMA (Environment and Childhood, Spain) ([25](#ref-GuxensBallesterEspada:2012)), KANC (Kaunas Cohort, Lithuania) ([26](#Xd30c40380c9e99bac70b7fa3b0ada5ae8dec3e4)), MoBa (The Norwegian Mother and Child Cohort Study, Norway) ([27](#ref-MagnusIrgensHaug:2006)), and Rhea (Mother–Child Cohort in Crete, Greece) ([28](#ref-ChatziPlanaDaraki:2009)). 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](#ref-MaitreBontCasas:2018)). 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.

## Variables

### 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](#supptbl-info-chems). 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](#ref-HaugSakhiCequier:2018)).

### 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](#supptbl-info-mets).

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](#ref-MarcosRenauCasals:2014),[32](#ref-Gomez-GomezPozo:2020)).

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 (20α-dihydrocortisol (20aDHF), 20β-dihydrocortisol (20bDHF), 5α,20α-cortol (5a20acortol), 5α,20β-cortol (5a20bcortol), 5α-tetrahydrocortisol (5aTHF), 5β,20α-cortol (5b20acortol), 5β,20β-cortol (5b20bcortol), 5β-dihydrocortisol (5bDHF), 5β-tetrahydrocortisol (5bTHF), 6β-hydroxycortisol (6OHF)), cortisone production as the sum of cortisone and its metabolites (20α-dihydrocortisone (20aDHE), 20β-dihydrocortisone (20bDHE), 5α-tetrahydrocortisone (5aTHE), 5β,20α-cortolone (5b20acortolone), 5β,20β-cortolone (5b20bcortolone), 5β-tetrahydrocortisone (5bTHE), 6β-hydroxycortisone (6OHE)), and corticosterone production as the sum of 11-dehydrocorticosterone (A), 17-deoxycortolone (17-DO-cortolone), 5α-tetrahydrocorticosterone (5aTHB), 5β-tetrahydrocorticosterone (5bTHB).

### Neurodevelopment

Neurodevelopmental outcomes were assessed with standardized, non-linguistic, and culturally blind computer tests, including the Attention Network Test (ANT) ([33](#ref-RuedaFanMcCandliss:2004)), which provides a measure of efficiency in three different functions of attention: alerting, orienting, and executive attention. The tests were administered in a standardized way, and with minimal interference from the field workers. Further information can be found in ([29](#ref-MaitreBontCasas:2018)). The outcome of interest for the present study is the hit reaction time standard error (HRT-SE) ([34](#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.

### 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](#ref-TextorvanderZanderGilthorpe:2016)) and ggdag ([36](#ref-Barrett:2023)). 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. 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 [3](#supptbl-codebook-1), [4](#supptbl-codebook-2), [5](#supptbl-codebook-3).

## Statistical methods

### 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 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 glucocorticosteroids is provided in [Table S6](#supptbl-lloq-mets). The remaining missing values were imputed using kNN from the VIM R package ([37](#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 ([38](#ref-LudeckeBen-ShacharPatil:2021)). 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](#ref-lazar2015imputelcmd)). Information about the lower limits of detection can be found in ([30](#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 (g/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).

### 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](#ref-Greifer:2023)). This methods estimates weights by minimizing an energy statistic related to covariate balance ([41](#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 ([42](#ref-Greifer:2023a)). Specifically, we used *Love* plots to visualize covariate balance before and after adjusting.

### 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 . 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](#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 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](#ref-Zeileis:2004),[45](#ref-ZeileisKollGraham:2020)). 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).

### 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 MCs were aggregated separately for each level of sex. We further tested for significance of the difference between the MCs of females and males.

# Results

[Table 1](#tbl-pop-desc) and [Table S7](#supptbl-pop-desc) 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](#suppfig-flow-pop). 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 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](#tbl-edc-desc), [Table 3](#tbl-met-new-desc), and [Table S8](#supptbl-met-desc). Supplementary Figures [2](#suppfig-desc-chems) and [3](#suppfig-desc-mets) 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 [9](#supptbl-balance-1), [10](#supptbl-balance-2), [11](#supptbl-balance-3), while basic summary statistics of the estimated balancing weights are presented in Supplementary Tables [12](#supptbl-weights-1), [13](#supptbl-weights-2), [14](#supptbl-weights-3). As expected, the median value of the weights for each exposure was close to .

[Figure 1](#fig-marginal-1) presents the forest plot for the MCs of the non-persistent EDCs on HRT-SE. For most EDCs, a cohort-specific decrease in the levels of the exposures from the 90th to the 10th percentiles was associated with a positive MC, indicating an increase in the values of HRT-SE. Most of the confidence interval (CIs) included the null effect, though. Statistically significant effects were observed for the phenol MEPA (MC and CI: 0.042 (0.013, 0.071)), and the phthalate metabolites oxo-MiNP (MC and CI: 0.023 (0.003, 0.044)), oh-MiNP (MC and CI: 0.039 (0.001, 0.076)), and MEHP (MC and CI: 0.036 (0.008, 0.063)). The OP pesticide DETP was negatively associated with HRT-SE (MC and CI: -0.026 (-0.054, 0.001)).

[Figure 2](#fig-marginal-2) presents the forest plot for the MCs of the non-persistent EDCs on total cortisone, cortisol, and corticosterone production. For most EDCs, a cohort-specific decrease in the levels of the exposures from the 90th to the 10th 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 and CI: 0.264 (0.131, 0.397); cortisol production, MC and CI: 0.275 (0.105, 0.444); corticosterone production, MC and CI: 0.285 (0.105, 0.466)).

[Figure 3](#fig-marginal-3) presents the forest plot for the MCs of the glucocorticosteroids on HRT-SE. All MCs included the null, with no clear indication of directionality of the effect.

## Effect modification by sex

Basic summary statistics of the estimated balancing weights for effect modification are presented in Supplementary Tables [15](#supptbl-weights-1sa), [16](#supptbl-weights-2sa), [17](#supptbl-weights-3sa). As expected, the median value of the weights for each exposure was close to .

[Table 4](#tbl-hypothesis-1and2) presents the results of a hypothesis test for the difference between estimates of the MCs 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 and CI: -0.032 (-0.059, -0.004)) and the phthalate metabolites MEP (MC and CI: 0.092 (0.017, 0.167)) and MbZP (MC and CI: 0.063 (0.002, 0.124)). 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 and CI: 0.211 (0.088, 0.333)) and DETP (corticosterone production, (MC and CI: 0.233 (0.033, 0.433)); cortisone production, (MC and CI: 0.214 (0.048, 0.381))). The forest plots of the individual MCs are presented in Supplementary Figures [4](#suppfig-marginal-1sa) and [5](#suppfig-marginal-2sa).

[Table 5](#tbl-hypothesis-3) presents the results of a hypothesis test for the difference between estimates of the MCs for females and males, for the glucocorticosteroids on HRT-SE. Significant differences were present for cortisone production (MC and CI: -0.135 (-0.241, -0.028)) and corticosterone production (MC and CI: -0.13 (-0.253, -0.006)). 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](#suppfig-marginal-3sa).

# 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](#Xd81cf38a3b251ec377f8aa13b097ea9d0c190e3)), 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 non-persistent EDCs had negative effects on HRT-SE and total production of cortisol, cortisone, and corticosterone, although the majority of the CIs included the null effect. Increased production of these glucocorticosteroids did not seem to affect HRT-SE. 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.

We are not aware of prior studies specifically investigating the effects of exposure to EDCs in relation to HRT-SE. The literature on EDCs and neurodevelopment in children has mostly focused on OP pesticides ([3](#ref-BouchardBellingerWright:2010),[4](#X2a5c5c17453fffe785b7f0bcffd564283892c6c),[6](#Xa0cc0fdd8206e54b0a9b4bdcd9d2102efd24cb7),[8](#ref-YuDuChiou:2016)), phthalate metabolites ([5](#ref-HuangChenSu:2015),[9](#ref-HuangTsaiChen:2017),[10](#ref-KimHongShin:2017),[17](#ref-VilmandBeckBilenberg:2023)), and BPA ([7](#ref-TewarAuingerBraun:2016),[13](#ref-LiZhangKuang:2018),[14](#X71fca68020aad3c79232160399444b9923ab76e)), in relation to Attention-Deficit / Hyperactivity Disorder (ADHD) ([3](#ref-BouchardBellingerWright:2010),[7](#ref-TewarAuingerBraun:2016),[8](#ref-YuDuChiou:2016),[13](#ref-LiZhangKuang:2018)), and intelligence scales ([4](#X2a5c5c17453fffe785b7f0bcffd564283892c6c)–[6](#Xa0cc0fdd8206e54b0a9b4bdcd9d2102efd24cb7),[9](#ref-HuangTsaiChen:2017),[10](#ref-KimHongShin:2017),[17](#ref-VilmandBeckBilenberg:2023)). Few studies have looked into different classes of EDCs ([15](#ref-ShoaffCoullWeuve:2020) in relation with the Conners Attention Deficit Scale and the Behavior Assessment System for Children,[16](#ref-OhKimKannan:2023) in relation with ADHD symptoms). Overall, and consistent with our results, these studies seem to provide further evidence of the adverse effects of several EDCs on neurodevelopment in children. While not all these studies have investigated effect modification by sex, it seems that these adverse effects are stronger in males. A major limitation of these studies is the reliance on spot urine samples, that might not be representative of long-term exposures.

Our results are consistent with prior epidemiological research that associated exposure to certain EDCs with higher levels of cortisol ([18](#ref-KimLeeMoon:2018)–[20](#ref-SearsLiuLanphear:2023)). There are some differences, though. First, these studies only focus on phthalates, either as individual metabolites or as mixture. Second, exposure assessment in ([19](#ref-SunLiJin:2018)) and ([18](#ref-KimLeeMoon:2018)) was performed during gestation or the first 15 months of life, respectively. Finally, the glucocorticosteroids were measured in cord blood ([19](#ref-SunLiJin:2018)) and hair ([20](#ref-SearsLiuLanphear:2023)). Contrary to these studies, we did find effect modification by sex. We are not aware of other epidemiological studies investigating phthalates metabolites, phenols, and OP pesticides, in relation to urinary glucocorticosteroids in childhood. Nonetheless, previous toxicological studies provide evidence for the inhibition by phthalates of human 11-hydroxysteroid dehydrogenase 2 (11-HSD2) activity, responsible for the conversion of active cortisol into inactive cortisone ([46](#ref-ZhaoChuHuang:2010),[47](#ref-MaLianDong:2011)). There is also *in silico* evidence suggesting that BPA, a phenol, and Triazophos (TAP), a organophosphorus insecticide, can bind to the human glucocorticoid receptor ([48](#ref-PrasanthDivyaSadasivan:2010),[49](#ref-YangLiRen:2019)).

We are also not aware of prior epidemiological studies specifically investigating the effects of elevated levels of glucocorticosteroids in relation to HRT-SE, although there is evidence that under- or over-production of glucocorticosteroids interfere with the normal development of the brain ([21](#ref-LupienMcEwenGunnar:2009)). 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 remove 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, since it is known that these specific EDCs have very short half-lives ([50](#ref-CasasBasaganaSakhi:2018)). 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 the 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 EDCs on childhood neurodevelopment in larger populations.

# References

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# Tables for descriptive data

## Study populations

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| Table 1: **Participant characteristics (HELIX subcohort; 2013-2016).**   | **Characteristic** | **N = 1,297***a* | | --- | --- | | 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 neuropsychological diagnosis | 95.0 (7.3%) | | 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 (hours) | 3.3 (2.8, 4.0) | | Financial situation |  | | 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 | | Head circumference (cm) | 51.8 (50.6, 52.9) | | Unknown | 3 | | Height (m) | 1.3 (1.2, 1.4) | | Hit reaction time standard error (ms) | 299.6 (231.3, 368.2) | | Unknown | 18 | | Marital status |  | | Living alone | 1,212.0 (94.5%) | | Living with the father | 39.0 (3.0%) | | Other situation | 31.0 (2.4%) | | Unknown | 15 | | Mood before assessment |  | | Usual | 1,232.0 (95.1%) | | Not usual | 64.0 (4.9%) | | Unknown | 1 | | 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 | | Rest before assessment |  | | Yes | 1,209.0 (93.3%) | | Not as well as usual | 87.0 (6.7%) | | Unknown | 1 | | Sex |  | | Female | 710.0 (54.7%) | | Male | 587.0 (45.3%) | | 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 | | Vegetables (times/week) | 6.5 (4.0, 10.0) | | Unknown | 6 | | Weight (kg) | 26.9 (22.9, 32.6) | | *a*n (%); Median (IQR) | | |

## Endocrine disruptors

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
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| Table 2: **Participants endocrine disruptors concentrations expressed in grams/L (HELIX subcohort; 2013-2016).**   | **Characteristic** | **N = 1,297***a* | | --- | --- | | **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); N missing (% missing) | | |

## Glucocorticosteroids

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| 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. | | | |

# Tables for other analyses

## Marginal hypotheses for effect modification

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| Table 4: **Pairwise differences between sex-specific marginal contrasts for the effect of a decrease from the 90th to the 10th percentile of EDCs on HRT-SE, expressed in ms, and the glucocorticosteroids, expressed in ng/ml (HELIX subcohort; 2013-2016).**   |  | HRT-SE*a* | corticosterone production*a* | cortisol production*a* | cortisone production*a* | | --- | --- | --- | --- | --- | | **OP pesticide metabolites** | | | | | | DEP | -0.006 (-0.033, 0.021) | 0.009 (-0.179, 0.198) | 0.102 (-0.123, 0.327) | 0.046 (-0.162, 0.254) | | DETP | -0.024 (-0.12, 0.072) | 0.233 (0.033, 0.433) | 0.178 (-0.024, 0.379) | 0.214 (0.048, 0.381) | | DMP | 0.027 (-0.031, 0.085) | -0.002 (-0.187, 0.184) | 0.033 (-0.063, 0.13) | 0.065 (-0.1, 0.23) | | DMTP | -0.002 (-0.1, 0.097) | 0.045 (-0.092, 0.182) | 0.211 (0.088, 0.333) | 0.15 (-0.038, 0.338) | | **Phenols** | | | | | | BPA | -0.038 (-0.095, 0.019) | 0.142 (0.027, 0.257) | 0.111 (-0.023, 0.245) | 0.073 (-0.059, 0.205) | | BUPA | 0.022 (-0.024, 0.067) | 0.111 (-0.019, 0.241) | 0.126 (0.041, 0.211) | 0.007 (-0.095, 0.109) | | ETPA | -0.015 (-0.056, 0.026) | 0.133 (-0.011, 0.277) | 0.089 (-0.108, 0.287) | 0.119 (-0.101, 0.339) | | MEPA | -0.032 (-0.095, 0.031) | 0.106 (0.002, 0.211) | 0.142 (0.012, 0.272) | 0.103 (0.016, 0.191) | | OXBE | -0.032 (-0.059, -0.004) | 0.213 (-0.058, 0.484) | 0.078 (-0.149, 0.306) | 0.067 (-0.133, 0.267) | | PRPA | -0.021 (-0.081, 0.04) | 0.108 (-0.018, 0.233) | 0.086 (-0.103, 0.274) | 0.109 (-0.008, 0.227) | | TRCS | -0.001 (-0.035, 0.033) | 0.041 (-0.113, 0.195) | 0.049 (-0.091, 0.19) | 0.092 (0.039, 0.144) | | **Phthalate metabolites** | | | | | | MBzP | 0.063 (0.002, 0.124) | 0.01 (-0.053, 0.073) | 0.003 (-0.115, 0.12) | 0.07 (-0.041, 0.181) | | MECPP | -0.005 (-0.087, 0.077) | 0.06 (-0.12, 0.24) | 0.072 (0.005, 0.139) | 0.017 (-0.078, 0.112) | | MEHHP | -0.017 (-0.113, 0.079) | 0.079 (-0.125, 0.282) | 0.105 (-0.008, 0.218) | 0.022 (-0.056, 0.101) | | MEHP | -0.009 (-0.105, 0.086) | 0.144 (0.045, 0.244) | 0.178 (0.084, 0.272) | 0.144 (0.032, 0.255) | | MEOHP | -0.005 (-0.086, 0.076) | 0.1 (-0.086, 0.286) | 0.1 (0.01, 0.191) | 0.014 (-0.066, 0.093) | | MEP | 0.092 (0.017, 0.167) | -0.124 (-0.289, 0.041) | -0.118 (-0.201, -0.035) | -0.029 (-0.185, 0.127) | | MiBP | 0.025 (-0.089, 0.14) | -0.027 (-0.247, 0.193) | 0.047 (-0.189, 0.284) | 0.022 (-0.126, 0.169) | | MnBP | 0.026 (-0.09, 0.143) | 0.092 (-0.188, 0.372) | 0.053 (-0.189, 0.295) | 0.11 (-0.054, 0.273) | | oh-MiNP | -0.053 (-0.112, 0.007) | 0.098 (-0.07, 0.267) | 0.146 (0.004, 0.288) | 0.137 (-0.001, 0.274) | | oxo-MiNP | 0.02 (-0.016, 0.055) | 0.066 (-0.1, 0.232) | 0.107 (-0.069, 0.283) | 0.091 (-0.019, 0.201) | | *a*Estimate and 95% CI. | | | | | |

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| Table 5: **Pairwise differences between sex-specific marginal contrasts for the effect of a decrease from the 90th to the 10th percentile of the glucocorticosteroids on HRT-SE expressed in ms (HELIX subcohort; 2013-2016).**   |  | HRT-SE*a* | | --- | --- | | **Glucocorticosteroids** | | | corticosterone pruduction | -0.13 (-0.253, -0.006) | | cortisol production | -0.1 (-0.238, 0.039) | | cortisone production | -0.135 (-0.241, -0.028) | | *a*Estimate and 95% CI. | | |

# Figures for main results

## Marginal contrasts

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| Figure 1: **Marginal contrasts for the effect of a decrease from the 90th to the 10th percentile of the EDCs on HRT-SE expressed in ms (HELIX subcohort; 2013-2016).** Circles indicate effect estimates. Solid lines indicate the CI. |

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| Figure 2: **Marginal contrasts for the effect of a decrease from the 90th to the 10th percentile of the EDCs on the glucocorticosteroids expressed in ng/ml (HELIX subcohort; 2013-2016).** Circles, triangles, and squares indicate effect estimates. Solid lines indicate the CI. |

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| Figure 3: **Marginal contrasts for the effect of a decrease from the 90th to the 10th percentile of the glucocorticosteroids on HRT-SE expressed in ms (HELIX subcohort; 2013-2016).** Circles indicate effect estimates. Solid lines indicate the CI. Abbreviations: cortisone production (cortisone prod.); cortisol production (cortisol prod.); corticost. prod. (corticosterone production). |

# 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  
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characteristics\_child -> chemical  
characteristics\_child -> creatinine  
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cohort -> characteristics\_child  
cohort -> chemical  
cohort -> child\_diet  
cohort -> creatinine  
cohort -> outcome  
creatinine -> biomarker  
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ethnicity\_child -> creatinine  
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ethnicity\_child -> outcome  
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neuropsychologicalDiagnosis\_child -> outcome  
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paternalSEP\_preg -> bw  
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sex\_child -> child\_smoking  
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time\_lastMeal -> chemical  
type\_sample -> chemical  
type\_sample -> creatinine  
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characteristics\_child  
chemical [exposure]  
child\_diet  
child\_smoking  
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paternalSEP\_preg -> maternalDiet\_preg  
paternalSEP\_preg -> maternalSmoking\_preg  
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paternalSEP\_preg -> outcome  
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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

## Tables for descriptive data

### Information about the endocrine disruptors

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
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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 |  | | 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 EDCs, including the full compound name, the standard symbol, the used variable name, the identifier from PubChem, and the parental compound.** |

### Information about the glucocorticosteroids

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| | 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** | | | | | 11β-hydroxyandrosterone | 11OHAndros | HMDB0002984 | 57-61-4 | | 17-deoxycortolone | 17-DO-cortolone | NA | NA | | 20α-dihydrocortisol | 20aDHF | NA | NA | | 20α-dihydrocortisone | 20aDHE | NA | NA | | 20β-dihydrocortisol | 20bDHF | NA | NA | | 20β-dihydrocortisone | 20bDHE | NA | NA | | 5α,20α-cortol | 5a20acortol | HMDB0003180 | 516-38-1 | | 5α,20β-cortol | 5a20bcortol | HMDB0005821 | 667-65-2 | | 5α-tetrahydrocorticosterone | 5aTHB | HMDB0000449 | 600-63-5 | | 5α-tetrahydrocortisol | 5aTHF | HMDB0000526 | 302-91-0 | | 5α-tetrahydrocortisone | 5aTHE | NA | NA | | 5β,20α-cortol | 5b20acortol | HMDB0003180 | 516-38-1 | | 5β,20α-cortolone | 5b20acortolone | HMDB0003128 | 516-42-7 | | 5β,20β-cortol | 5b20bcortol | HMDB0005821 | 667-65-2 | | 5β,20β-cortolone | 5b20bcortolone | NA | NA | | 5β-dihydrocortisol | 5bDHF | HMDB0003259 | 1482-50-4 | | 5β-tetrahydrocorticosterone | 5bTHB | HMDB0000268 | 68-42-8 | | 5β-tetrahydrocortisol | 5bTHF | HMDB0000949 | 1953-02-01 | | 5β-tetrahydrocortisone | 5bTHE | NA | NA | | 6β-hydroxycortisol | 6OHF | HMDB0247074 |  | | 6β-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 | | 5β-dihydrocortexolone | 5bDHS | NA | NA | | 5β-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.** |

### Codebooks

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| |  | type | description | coding | labels | remarks | comments | included*a* | | --- | --- | --- | --- | --- | --- | --- | --- | | **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 | | *a*Percentage of confounders included in the models: 65.79%. | | | | | | | |   Table S3: **Codebook for the covariates used in the estimation of the marginal comparisons of EDCs on HRT-SE.** |

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| |  | type | description | coding | labels | remarks | comments | included*a* | | --- | --- | --- | --- | --- | --- | --- | --- | | **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 | | *a*Percentage of confounders included in the models: 95%. | | | | | | | |   Table S4: **Codebook for the covariates used in the estimation of the marginal comparisons of EDCs on the glucocorticosteroids.** |

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
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| |  | type | description | coding | labels | remarks | comments | included*a* | | --- | --- | --- | --- | --- | --- | --- | --- | | **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 | | *a*Percentage of confounders included in the models: 74.58%. | | | | | | | |   Table S5: **Codebook for the covariates used in the estimation of the marginal comparisons of the glucocorticosteroids on HRT-SE.** |

### Lower limits of quantification of the glucocorticosteroids

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | 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).** |

### Study populations

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | **Characteristic** | **Overall**, N = 1,297*a* | **BIB**, N = 204*a* | **EDEN**, N = 198*a* | **INMA**, N = 221*a* | **KANC**, N = 203*a* | **MOBA**, N = 272*a* | **RHEA**, N = 199*a* | | --- | --- | --- | --- | --- | --- | --- | --- | | Age (years) | 8.1 (6.5, 8.9) | 6.6 (6.5, 6.8) | 10.9 (10.4, 11.2) | 8.8 (8.4, 9.3) | 6.4 (6.1, 6.9) | 8.5 (8.2, 8.8) | 6.5 (6.4, 6.6) | | Child breastfeeding | 1,093.0 (84.7%) | 147.0 (72.4%) | 128.0 (65.0%) | 195.0 (88.6%) | 187.0 (92.6%) | 260.0 (96.3%) | 176.0 (88.4%) | | Unknown | 6 | 1 | 1 | 1 | 1 | 2 | 0 | | Child ethnicity |  |  |  |  |  |  |  | | Caucasian | 1,157.0 (90.0%) | 87.0 (42.6%) | 196.0 (99.5%) | 221.0 (100.0%) | 200.0 (100.0%) | 254.0 (95.8%) | 199.0 (100.0%) | | Pakistani | 80.0 (6.2%) | 80.0 (39.2%) | 0.0 (0.0%) | 0.0 (0.0%) | 0.0 (0.0%) | 0.0 (0.0%) | 0.0 (0.0%) | | Asian | 21.0 (1.6%) | 13.0 (6.4%) | 1.0 (0.5%) | 0.0 (0.0%) | 0.0 (0.0%) | 7.0 (2.6%) | 0.0 (0.0%) | | Other | 19.0 (1.5%) | 17.0 (8.3%) | 0.0 (0.0%) | 0.0 (0.0%) | 0.0 (0.0%) | 2.0 (0.8%) | 0.0 (0.0%) | | African | 7.0 (0.5%) | 7.0 (3.4%) | 0.0 (0.0%) | 0.0 (0.0%) | 0.0 (0.0%) | 0.0 (0.0%) | 0.0 (0.0%) | | Native American | 2.0 (0.2%) | 0.0 (0.0%) | 0.0 (0.0%) | 0.0 (0.0%) | 0.0 (0.0%) | 2.0 (0.8%) | 0.0 (0.0%) | | White non European | 0.0 (0.0%) | 0.0 (0.0%) | 0.0 (0.0%) | 0.0 (0.0%) | 0.0 (0.0%) | 0.0 (0.0%) | 0.0 (0.0%) | | Unknown | 11 | 0 | 1 | 0 | 3 | 7 | 0 | | Child neuropsychological diagnosis | 95.0 (7.3%) | 3.0 (1.5%) | 58.0 (29.3%) | 24.0 (10.9%) | 1.0 (0.5%) | 1.0 (0.4%) | 8.0 (4.0%) | | Creatinine night sample (g/l) | 1.7 (0.9, 3.0) | 0.8 (0.6, 1.1) | 3.3 (2.0, 4.3) | 2.5 (1.5, 3.8) | 1.7 (0.9, 2.7) | 2.0 (1.2, 3.0) | 0.8 (0.4, 1.3) | | Unknown | 321 | 72 | 64 | 19 | 23 | 72 | 71 | | Creatinine pooled sample (g/l) | 1.0 (0.8, 1.2) | 1.0 (0.8, 1.2) | 1.2 (1.0, 1.5) | 1.0 (0.8, 1.3) | 0.9 (0.7, 1.1) | 0.9 (0.7, 1.1) | 0.9 (0.7, 1.1) | | Date of test (season) |  |  |  |  |  |  |  | | Spring | 358.0 (27.7%) | 48.0 (23.5%) | 64.0 (32.3%) | 71.0 (32.4%) | 61.0 (30.0%) | 37.0 (13.6%) | 77.0 (38.9%) | | Winter | 339.0 (26.2%) | 40.0 (19.6%) | 61.0 (30.8%) | 97.0 (44.3%) | 38.0 (18.7%) | 73.0 (26.8%) | 30.0 (15.2%) | | Autumn | 300.0 (23.2%) | 49.0 (24.0%) | 1.0 (0.5%) | 30.0 (13.7%) | 77.0 (37.9%) | 105.0 (38.6%) | 38.0 (19.2%) | | Summer | 297.0 (23.0%) | 67.0 (32.8%) | 72.0 (36.4%) | 21.0 (9.6%) | 27.0 (13.3%) | 57.0 (21.0%) | 53.0 (26.8%) | | Unknown | 3 | 0 | 0 | 2 | 0 | 0 | 1 | | Family affluence scale |  |  |  |  |  |  |  | | 6 | 410.0 (31.7%) | 34.0 (16.7%) | 64.0 (32.3%) | 75.0 (34.1%) | 50.0 (24.8%) | 142.0 (52.2%) | 45.0 (22.6%) | | 5 | 325.0 (25.1%) | 48.0 (23.5%) | 29.0 (14.6%) | 65.0 (29.5%) | 69.0 (34.2%) | 57.0 (21.0%) | 57.0 (28.6%) | | 7 | 248.0 (19.2%) | 26.0 (12.7%) | 90.0 (45.5%) | 43.0 (19.5%) | 14.0 (6.9%) | 53.0 (19.5%) | 22.0 (11.1%) | | 4 | 174.0 (13.4%) | 40.0 (19.6%) | 13.0 (6.6%) | 22.0 (10.0%) | 38.0 (18.8%) | 16.0 (5.9%) | 45.0 (22.6%) | | 3 | 92.0 (7.1%) | 34.0 (16.7%) | 2.0 (1.0%) | 11.0 (5.0%) | 22.0 (10.9%) | 3.0 (1.1%) | 20.0 (10.1%) | | 2 | 28.0 (2.2%) | 16.0 (7.8%) | 0.0 (0.0%) | 1.0 (0.5%) | 4.0 (2.0%) | 0.0 (0.0%) | 7.0 (3.5%) | | 1 | 12.0 (0.9%) | 4.0 (2.0%) | 0.0 (0.0%) | 2.0 (0.9%) | 4.0 (2.0%) | 1.0 (0.4%) | 1.0 (0.5%) | | 0 | 6.0 (0.5%) | 2.0 (1.0%) | 0.0 (0.0%) | 1.0 (0.5%) | 1.0 (0.5%) | 0.0 (0.0%) | 2.0 (1.0%) | | Unknown | 2 | 0 | 0 | 1 | 1 | 0 | 0 | | Fast food/take away (times/week) | 0.1 (0.1, 0.5) | 0.5 (0.1, 1.0) | 0.1 (0.1, 0.5) | 0.1 (0.1, 0.5) | 0.1 (0.0, 0.1) | 0.1 (0.1, 0.5) | 0.5 (0.1, 0.5) | | Unknown | 7 | 0 | 0 | 5 | 2 | 0 | 0 | | Fasting time (hours) | 3.3 (2.8, 4.0) | 3.3 (2.8, 4.1) | 3.2 (2.8, 3.7) | 3.0 (2.6, 3.8) | 3.3 (2.8, 3.8) | 3.4 (2.8, 3.8) | 4.0 (3.3, 4.8) | | Financial situation |  |  |  |  |  |  |  | | Doing alright | 414.0 (32.1%) | 73.0 (35.8%) | 94.0 (47.5%) | 64.0 (29.2%) | 61.0 (30.5%) | 64.0 (23.5%) | 58.0 (29.3%) | | Living comfortably | 412.0 (31.9%) | 59.0 (28.9%) | 49.0 (24.7%) | 29.0 (13.2%) | 48.0 (24.0%) | 202.0 (74.3%) | 25.0 (12.6%) | | Getting by | 331.0 (25.6%) | 59.0 (28.9%) | 36.0 (18.2%) | 82.0 (37.4%) | 70.0 (35.0%) | 4.0 (1.5%) | 80.0 (40.4%) | | Finding it quite difficult | 86.0 (6.7%) | 8.0 (3.9%) | 9.0 (4.5%) | 29.0 (13.2%) | 12.0 (6.0%) | 1.0 (0.4%) | 27.0 (13.6%) | | Finding it very difficult | 40.0 (3.1%) | 5.0 (2.5%) | 10.0 (5.1%) | 15.0 (6.8%) | 2.0 (1.0%) | 0.0 (0.0%) | 8.0 (4.0%) | | Does not wish to answer | 8.0 (0.6%) | 0.0 (0.0%) | 0.0 (0.0%) | 0.0 (0.0%) | 7.0 (3.5%) | 1.0 (0.4%) | 0.0 (0.0%) | | Unknown | 6 | 0 | 0 | 2 | 3 | 0 | 1 | | Fish and seafood (times/week) | 2.0 (1.1, 3.5) | 2.0 (1.0, 3.1) | 2.1 (1.4, 3.0) | 3.5 (2.1, 5.0) | 1.0 (0.4, 1.6) | 2.6 (1.6, 5.0) | 1.5 (1.0, 2.0) | | Unknown | 5 | 1 | 0 | 2 | 2 | 0 | 0 | | Fruits (times/week) | 9.0 (5.9, 18.0) | 15.5 (10.0, 21.0) | 6.6 (3.3, 13.5) | 7.5 (3.6, 12.6) | 7.3 (3.8, 9.6) | 14.1 (8.6, 21.0) | 8.5 (6.2, 13.5) | | Unknown | 7 | 2 | 0 | 2 | 2 | 1 | 0 | | Head circumference (cm) | 51.8 (50.6, 52.9) | 51.4 (50.3, 52.3) | 50.5 (49.5, 52.0) | 52.3 (51.3, 53.3) | 52.0 (51.0, 53.0) | 52.5 (51.5, 53.6) | 51.2 (50.2, 52.0) | | Unknown | 3 | 0 | 0 | 0 | 0 | 0 | 3 | | Height (m) | 1.3 (1.2, 1.4) | 1.2 (1.2, 1.2) | 1.4 (1.4, 1.5) | 1.3 (1.3, 1.4) | 1.2 (1.2, 1.3) | 1.3 (1.3, 1.4) | 1.2 (1.2, 1.2) | | Hit reaction time standard error (ms) | 299.6 (231.3, 368.2) | 355.1 (292.1, 397.5) | 237.7 (184.7, 307.0) | 256.0 (197.4, 313.8) | 368.4 (324.2, 406.6) | 248.7 (193.0, 300.9) | 340.9 (281.1, 399.2) | | Unknown | 18 | 3 | 11 | 3 | 0 | 0 | 1 | | Marital status |  |  |  |  |  |  |  | | Living alone | 1,212.0 (94.5%) | 178.0 (87.3%) | 193.0 (98.0%) | 219.0 (99.1%) | 168.0 (84.4%) | 260.0 (98.5%) | 194.0 (98.5%) | | Living with the father | 39.0 (3.0%) | 0.0 (0.0%) | 2.0 (1.0%) | 0.0 (0.0%) | 31.0 (15.6%) | 3.0 (1.1%) | 3.0 (1.5%) | | Other situation | 31.0 (2.4%) | 26.0 (12.7%) | 2.0 (1.0%) | 2.0 (0.9%) | 0.0 (0.0%) | 1.0 (0.4%) | 0.0 (0.0%) | | Unknown | 15 | 0 | 1 | 0 | 4 | 8 | 2 | | Mood before assessment |  |  |  |  |  |  |  | | Usual | 1,232.0 (95.1%) | 198.0 (97.1%) | 176.0 (89.3%) | 214.0 (96.8%) | 187.0 (92.1%) | 262.0 (96.3%) | 195.0 (98.0%) | | Not usual | 64.0 (4.9%) | 6.0 (2.9%) | 21.0 (10.7%) | 7.0 (3.2%) | 16.0 (7.9%) | 10.0 (3.7%) | 4.0 (2.0%) | | Unknown | 1 | 0 | 1 | 0 | 0 | 0 | 0 | | Organic food (times/week) | 0.5 (0.0, 3.0) | 0.0 (0.0, 0.5) | 0.5 (0.1, 3.0) | 0.0 (0.0, 0.5) | 1.0 (0.1, 3.0) | 1.0 (0.5, 3.0) | 0.0 (0.0, 1.0) | | Unknown | 7 | 0 | 0 | 5 | 2 | 0 | 0 | | Pregnancy maternal active smoking | 190.0 (15.1%) | 25.0 (13.7%) | 47.0 (23.7%) | 55.0 (25.1%) | 12.0 (6.0%) | 9.0 (3.4%) | 42.0 (21.2%) | | Unknown | 40 | 22 | 0 | 2 | 4 | 11 | 1 | | Pregnancy maternal passive smoking | 514.0 (40.3%) | 55.0 (27.5%) | 43.0 (21.8%) | 126.0 (57.8%) | 97.0 (48.7%) | 14.0 (5.3%) | 179.0 (90.4%) | | Unknown | 21 | 4 | 1 | 3 | 4 | 8 | 1 | | Rest before assessment |  |  |  |  |  |  |  | | Yes | 1,209.0 (93.3%) | 192.0 (94.1%) | 170.0 (86.3%) | 206.0 (93.2%) | 200.0 (98.5%) | 259.0 (95.2%) | 182.0 (91.5%) | | Not as well as usual | 87.0 (6.7%) | 12.0 (5.9%) | 27.0 (13.7%) | 15.0 (6.8%) | 3.0 (1.5%) | 13.0 (4.8%) | 17.0 (8.5%) | | Unknown | 1 | 0 | 1 | 0 | 0 | 0 | 0 | | Sex |  |  |  |  |  |  |  | | Female | 710.0 (54.7%) | 112.0 (54.9%) | 113.0 (57.1%) | 120.0 (54.3%) | 111.0 (54.7%) | 143.0 (52.6%) | 111.0 (55.8%) | | Male | 587.0 (45.3%) | 92.0 (45.1%) | 85.0 (42.9%) | 101.0 (45.7%) | 92.0 (45.3%) | 129.0 (47.4%) | 88.0 (44.2%) | | Tobacco consumption |  |  |  |  |  |  |  | | Non-smoker and has never smoked | 681.0 (52.6%) | 148.0 (72.5%) | 87.0 (43.9%) | 103.0 (46.8%) | 104.0 (51.7%) | 138.0 (50.7%) | 101.0 (50.8%) | | Daily smoker | 200.0 (15.5%) | 27.0 (13.2%) | 45.0 (22.7%) | 45.0 (20.5%) | 24.0 (11.9%) | 6.0 (2.2%) | 53.0 (26.6%) | | Non-smoker but previously smoked daily | 186.0 (14.4%) | 11.0 (5.4%) | 37.0 (18.7%) | 42.0 (19.1%) | 21.0 (10.4%) | 53.0 (19.5%) | 22.0 (11.1%) | | Non-smoker but previously smoked although not daily | 163.0 (12.6%) | 12.0 (5.9%) | 19.0 (9.6%) | 23.0 (10.5%) | 32.0 (15.9%) | 63.0 (23.2%) | 14.0 (7.0%) | | Smoker but not daily | 64.0 (4.9%) | 6.0 (2.9%) | 10.0 (5.1%) | 7.0 (3.2%) | 20.0 (10.0%) | 12.0 (4.4%) | 9.0 (4.5%) | | Unknown | 3 | 0 | 0 | 1 | 2 | 0 | 0 | | Vegetables (times/week) | 6.5 (4.0, 10.0) | 6.0 (4.0, 10.0) | 8.3 (4.4, 11.0) | 6.0 (3.0, 8.5) | 6.0 (3.5, 8.5) | 8.5 (6.0, 14.0) | 6.5 (4.0, 10.0) | | Unknown | 6 | 1 | 0 | 2 | 2 | 1 | 0 | | Weight (kg) | 26.9 (22.9, 32.6) | 22.3 (20.3, 25.0) | 35.7 (32.4, 41.2) | 30.7 (26.8, 36.5) | 23.6 (21.4, 27.1) | 28.5 (25.7, 31.6) | 23.3 (21.2, 27.2) | | *a*Median (IQR); n (%) | | | | | | | |   Table S7: **Participant characteristics, by cohort and overall (HELIX subcohort; 2013-2016).** |

### Concentrations of the glucocorticosteroids

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | **Characteristic** | **Overall**, N = 1,004*a* | **BIB**, N = 154*a* | **EDEN**, N = 137*a* | **INMA**, N = 205*a* | **KANC**, N = 180*a* | **MOBA**, N = 200*a* | **RHEA**, N = 128*a* | | --- | --- | --- | --- | --- | --- | --- | --- | | **Glucocorticosteroid** | | | | | | | | | A | 4.3 (2.4, 8.2) | 4.8 (2.8, 9.0) | 5.1 (2.6, 9.1) | 3.0 (1.6, 5.6) | 3.8 (2.0, 7.3) | 4.3 (2.7, 8.4) | 5.9 (3.5, 14.9) | | Unknown | 1 | 0 | 0 | 1 | 0 | 0 | 0 | | E | 22.9 (13.1, 38.5) | 25.7 (14.5, 41.4) | 28.6 (14.1, 42.0) | 17.1 (10.3, 27.4) | 21.4 (12.0, 33.7) | 23.3 (14.1, 38.1) | 28.9 (19.3, 59.4) | | F | 5.5 (3.2, 9.5) | 6.3 (4.2, 10.4) | 7.8 (4.2, 11.4) | 4.6 (2.9, 7.1) | 4.9 (2.7, 8.2) | 5.2 (3.0, 9.1) | 6.2 (3.4, 13.1) | | Unknown | 2 | 0 | 0 | 0 | 1 | 1 | 0 | | **Glucocorticosteroid metabolite** | | | | | | | | | 11OHAndros | 234.2 (130.3, 390.5) | 259.7 (151.9, 375.0) | 413.0 (221.7, 617.0) | 256.7 (142.9, 365.1) | 163.3 (80.7, 298.5) | 254.4 (151.5, 408.4) | 165.4 (95.9, 304.2) | | Unknown | 3 | 0 | 0 | 0 | 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 (32.5, 102.1) | 43.7 (15.1, 93.4) | 56.4 (26.4, 92.0) | 51.2 (28.5, 94.3) | | Unknown | 2 | 0 | 0 | 0 | 1 | 0 | 1 | | 20aDHE | 16.6 (9.7, 27.5) | 14.2 (7.0, 25.8) | 25.8 (15.1, 37.8) | 15.6 (10.2, 23.0) | 14.8 (7.7, 25.6) | 17.5 (11.7, 26.1) | 14.8 (8.7, 27.6) | | Unknown | 11 | 7 | 0 | 0 | 4 | 0 | 0 | | 20aDHF | 6.6 (3.3, 13.3) | 7.2 (3.8, 14.0) | 10.0 (5.7, 19.5) | 5.5 (3.0, 9.4) | 4.8 (2.2, 11.4) | 7.4 (4.2, 14.0) | 6.5 (2.9, 13.8) | | Unknown | 7 | 4 | 0 | 0 | 3 | 0 | 0 | | 20bDHE | 9.5 (6.2, 14.3) | 8.7 (4.8, 14.8) | 13.2 (9.7, 17.3) | 9.0 (6.6, 11.7) | 8.9 (5.1, 13.7) | 9.0 (5.9, 14.3) | 8.7 (5.3, 15.2) | | Unknown | 17 | 14 | 0 | 0 | 3 | 0 | 0 | | 20bDHF | 15.2 (9.1, 24.8) | 16.5 (10.8, 26.5) | 19.9 (12.0, 32.0) | 13.0 (8.0, 18.1) | 14.0 (8.5, 24.5) | 14.2 (8.4, 23.5) | 14.3 (7.9, 27.5) | | 5a20acortol | 88.9 (52.1, 141.6) | 109.8 (61.7, 177.3) | 103.0 (58.0, 153.8) | 83.0 (45.9, 118.7) | 84.7 (46.9, 145.9) | 88.6 (53.7, 138.2) | 72.4 (47.2, 130.2) | | Unknown | 9 | 9 | 0 | 0 | 0 | 0 | 0 | | 5a20bcortol | 122.4 (70.4, 185.0) | 131.0 (66.3, 182.3) | 148.8 (108.8, 226.1) | 124.3 (68.9, 178.8) | 115.2 (62.9, 189.2) | 114.7 (67.8, 172.7) | 105.3 (72.6, 175.0) | | Unknown | 5 | 5 | 0 | 0 | 0 | 0 | 0 | | 5aTHB | 133.1 (76.1, 222.4) | 159.8 (101.7, 241.3) | 144.2 (87.9, 255.3) | 115.7 (73.3, 171.7) | 148.0 (82.6, 245.6) | 106.1 (61.1, 184.9) | 139.9 (74.6, 260.5) | | 5aTHE | 73.9 (39.7, 124.0) | 82.0 (52.1, 145.7) | 83.9 (41.5, 132.7) | 62.2 (32.3, 97.3) | 71.3 (40.3, 121.7) | 64.5 (36.4, 103.9) | 107.9 (51.2, 183.2) | | Unknown | 1 | 0 | 0 | 0 | 0 | 0 | 1 | | 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 (1,565.6, 3,758.3) | 2,907.3 (1,656.1, 4,621.2) | 2,283.3 (1,259.8, 3,454.6) | 3,001.9 (1,652.3, 4,613.6) | | 5b20acortol | 147.7 (83.5, 225.8) | 177.4 (98.9, 302.3) | 169.7 (91.1, 252.9) | 141.9 (76.6, 187.6) | 143.0 (80.2, 229.8) | 143.7 (86.6, 204.2) | 137.7 (79.6, 220.5) | | Unknown | 11 | 11 | 0 | 0 | 0 | 0 | 0 | | 5b20acortolone | 641.9 (366.0, 983.1) | 638.3 (385.0, 1,028.2) | 903.7 (574.5, 1,296.1) | 654.6 (398.7, 890.7) | 518.0 (261.2, 870.2) | 580.6 (318.0, 901.5) | 629.3 (400.9, 962.4) | | 5b20bcortol | 195.7 (120.1, 302.4) | 242.7 (152.0, 356.8) | 225.2 (142.1, 371.5) | 199.9 (130.5, 289.3) | 155.8 (88.0, 270.4) | 186.3 (115.5, 269.4) | 177.5 (113.7, 301.7) | | Unknown | 3 | 3 | 0 | 0 | 0 | 0 | 0 | | 5b20bcortolone | 546.9 (336.3, 837.1) | 561.3 (331.3, 889.9) | 682.3 (452.0, 1,031.1) | 534.1 (372.6, 792.7) | 505.0 (272.3, 769.3) | 496.1 (289.2, 761.3) | 563.5 (328.4, 881.5) | | 5bDHF | 1.4 (0.9, 2.0) | 1.4 (0.9, 2.2) | 1.8 (1.3, 2.6) | 1.1 (0.6, 1.8) | 1.5 (1.1, 1.9) | 1.1 (0.6, 1.7) | 1.5 (1.0, 2.1) | | Unknown | 2 | 0 | 0 | 1 | 0 | 1 | 0 | | 5bTHB | 49.3 (28.0, 82.7) | 53.3 (27.5, 98.3) | 60.9 (34.9, 94.5) | 50.0 (29.7, 73.1) | 43.8 (27.5, 89.7) | 40.0 (24.7, 65.7) | 53.5 (28.4, 76.7) | | Unknown | 1 | 0 | 0 | 0 | 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 (1,615.2, 4,050.7) | 2,754.6 (1,448.0, 3,989.3) | 3,070.1 (1,785.5, 4,637.7) | 3,541.6 (2,010.1, 5,901.3) | | 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 (542.6, 1,199.8) | 753.9 (389.4, 1,258.7) | 859.7 (492.9, 1,261.3) | 881.5 (565.0, 1,441.1) | | Unknown | 2 | 2 | 0 | 0 | 0 | 0 | 0 | | 6OHE | 11.9 (6.5, 18.4) | 13.2 (7.6, 20.6) | 12.2 (6.1, 17.4) | 9.2 (5.3, 14.1) | 13.1 (7.1, 19.6) | 11.2 (6.4, 18.1) | 14.3 (8.7, 24.3) | | 6OHF | 42.8 (22.5, 76.7) | 51.9 (29.8, 93.9) | 55.8 (29.8, 82.3) | 32.3 (18.5, 53.3) | 36.6 (19.7, 68.7) | 46.0 (27.9, 82.9) | 42.0 (21.1, 93.2) | | **Glucocorticosteroid precursor** | | | | | | | | | S | 0.4 (0.3, 0.8) | 0.5 (0.3, 0.9) | 0.4 (0.3, 0.7) | 0.6 (0.4, 0.9) | 0.3 (0.2, 0.5) | 0.4 (0.3, 0.7) | 0.4 (0.2, 0.8) | | Unknown | 94 | 6 | 5 | 12 | 9 | 51 | 11 | | **Glucocorticosteroid precursor metabolite** | | | | | | | | | 17HP | 22.3 (15.1, 33.5) | 17.0 (11.1, 27.6) | 33.2 (23.5, 44.0) | 20.3 (13.2, 32.2) | 20.3 (10.8, 33.1) | 23.0 (17.5, 31.2) | 21.8 (15.7, 32.2) | | Unknown | 1 | 0 | 0 | 0 | 0 | 0 | 1 | | 5bDHS | 0.3 (0.2, 0.4) | 0.3 (0.2, 0.4) | 0.3 (0.2, 0.5) | 0.3 (0.2, 0.3) | 0.2 (0.2, 0.3) | 0.3 (0.2, 0.4) | 0.3 (0.2, 0.5) | | Unknown | 132 | 5 | 20 | 43 | 0 | 57 | 7 | | 5bTHS | 30.7 (18.5, 50.5) | 35.7 (20.7, 59.2) | 34.5 (19.8, 52.1) | 27.7 (17.6, 43.0) | 31.3 (18.6, 55.1) | 26.2 (14.2, 40.8) | 33.7 (20.0, 58.2) | | Unknown | 2 | 0 | 0 | 1 | 0 | 1 | 0 | | PT | 200.6 (112.8, 342.0) | 149.1 (87.6, 246.3) | 378.8 (230.8, 542.8) | 253.4 (150.0, 404.4) | 142.2 (82.4, 273.7) | 176.4 (112.9, 283.3) | 189.4 (104.9, 306.3) | | **Androgen** | | | | | | | | | AED | 0.2 (0.2, 0.3) | 0.2 (0.2, 0.3) | 0.3 (0.2, 0.5) | 0.2 (0.1, 0.4) | 0.2 (0.1, 0.3) | 0.2 (0.1, 0.3) | 0.2 (0.1, 1.1) | | Unknown | 407 | 0 | 34 | 73 | 117 | 106 | 77 | | T | 0.5 (0.3, 1.0) | 0.7 (0.5, 1.0) | 1.0 (0.5, 1.9) | 0.6 (0.3, 1.0) | 0.3 (0.2, 0.6) | 0.4 (0.3, 0.7) | 0.4 (0.3, 0.7) | | Unknown | 75 | 0 | 5 | 3 | 29 | 24 | 14 | | **Androgen metabolite** | | | | | | | | | Andros | 186.0 (78.1, 394.0) | 148.4 (72.0, 267.9) | 552.2 (308.7, 980.2) | 295.4 (129.1, 513.8) | 98.4 (39.6, 227.5) | 134.7 (63.4, 293.1) | 110.0 (61.6, 226.5) | | Unknown | 1 | 0 | 0 | 0 | 1 | 0 | 0 | | Etio | 110.9 (50.7, 237.8) | 75.1 (32.6, 151.0) | 369.7 (231.8, 561.0) | 169.7 (84.0, 306.1) | 74.8 (37.6, 122.6) | 91.4 (45.8, 184.0) | 76.2 (41.2, 147.0) | | Unknown | 1 | 0 | 0 | 0 | 1 | 0 | 0 | | *a*Median (IQR) | | | | | | | |   Table S8: **Participants glucocorticosteroids concentrations, by cohort and overall (HELIX subcohort; 2013-2016).** |

## Tables for main results

### Balancing weights: sample sizes

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | Exposure | Unadjusted | Adjusted*a* | | --- | --- | --- | | **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** | | | | oxo-MiNP | 1,297 | 1,199 | | oh-MiNP | 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 | 980.0 | | MiBP | 1,297 | 927.1 | | *a*Truncated weights. | | |   Table S9: **Effective sample size before and after balancing weights estimation (exposures: EDCs; outcome: HRT-SE) (HELIX subcohort; 2013-2016).** |

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | Exposure | Unadjusted | Adjusted*a* | | --- | --- | --- | | **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** | | | | oh-MiNP | 976.0 | 878.3 | | oxo-MiNP | 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 | | *a*Truncated weights. | | |   Table S10: **Effective sample size before and after balancing weights estimation (exposures: EDCs; outcomes: glucocorticosteroids) (HELIX subcohort; 2013-2016).** |

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | Exposure | Unadjusted | Adjusted*a* | | --- | --- | --- | | cortisone production | 976.0 | 777.2 | | corticosterone production | 976.0 | 758.1 | | cortisol production | 976.0 | 751.6 | | *a*Truncated weights. | | |   Table S11: **Effective sample size before and after balancing weights estimation (exposures: glucocorticosteroids; outcome: HRT-SE) (HELIX subcohort; 2013-2016).** |

### Balancing weights: summary statistics

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| |  | Median (IQR) | Range | | --- | --- | --- | | **Characteristic***a* | **N = 1,297***a* | **N = 1,297***a* | | **OP pesticide metabolites** | | | | 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 | | **Phenols** | | | | 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 | | **Phthalate metabolites** | | | | 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 | | oh-MiNP | 1.01 (0.74, 1.24) | 0.47, 1.50 | | 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: EDCs; outcome: HRT-SE) (HELIX subcohort; 2013-2016).** |

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| |  | Median (IQR) | Range | | --- | --- | --- | | **Characteristic***a* | **N = 976***a* | **N = 976***a* | | **OP pesticide metabolites** | | | | 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 | | **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) | 0.77, 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 | | **Phthalate metabolites** | | | | 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 | | oh-MiNP | 1.00 (0.73, 1.25) | 0.46, 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: EDCs; outcomes: glucocorticosteroids) (HELIX subcohort; 2013-2016).** |

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| |  | Median (IQR) | Range | | --- | --- | --- | | **Characteristic***a* | **N = 976***a* | **N = 976***a* | | cortisol production | 1.00 (0.54, 1.40) | 0.14, 1.80 | | cortisone production | 1.01 (0.58, 1.39) | 0.19, 1.73 | | corticosterone production | 0.98 (0.56, 1.39) | 0.16, 1.78 | | *a*Truncated weights. | | |   Table S14: **Summary statistics of the estimated balancing weights (exposures: glucocorticosteroids; outcome: HRT-SE) (HELIX subcohort; 2013-2016).** |

## Tables for other results

### Balancing weights for effect modification: summary statistics

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| |  | 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, 1.19) | 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 | | **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) | 0.41, 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 | | **Phthalate metabolites** | | | | | | 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 | | 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 (0.77, 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: EDCs; outcome: 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 (0.76, 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 | | **Phenols** | | | | | | 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 | | **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, 1.38) | 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 | | oh-MiNP | 1.00 (0.73, 1.26) | 1.00 (0.77, 1.24) | 0.49, 1.45 | 0.49, 1.45 | | oxo-MiNP | 1.03 (0.73, 1.27) | 1.02 (0.77, 1.23) | 0.48, 1.45 | 0.48, 1.45 | | *a*Truncated weights. | | | | |   Table S16: **Summary statistics of the estimated balancing weights for effect modification (exposures: EDCs; outcomes: glucocorticosteroids; 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* | | cortisol production | 0.98 (0.57, 1.40) | 1.02 (0.59, 1.34) | 0.23, 1.71 | 0.23, 1.71 | | cortisone production | 1.00 (0.60, 1.40) | 1.00 (0.60, 1.38) | 0.27, 1.69 | 0.27, 1.69 | | corticosterone production | 1.01 (0.61, 1.39) | 1.03 (0.56, 1.37) | 0.22, 1.70 | 0.22, 1.70 | | *a*Truncated weights. | | | | |   Table S17: **Summary statistics of the estimated balancing weights for effect modification (exposures: glucocorticosteroids; outcome: HRT-SE; modifier: sex) (HELIX subcohort; 2013-2016).** |

# Supplementary figures

## Figures for descriptive data

### Study populations

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

### Description of endocrine disruptors

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

### Description of glucocorticosteroids

|  |
| --- |
| 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. |

## Figures for other results

### Marginal contrasts for effect modification

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| --- |
| Figure S4: **Marginal contrasts for effect modification by sex of a decrease from the 90th to the 10th percentile of the EDCs on HRT-SE expressed in ms (HELIX subcohort; 2013-2016).** Circles and triangles indicate effect estimates. Solid lines indicate the CI. |

|  |
| --- |
| Figure S5: **Marginal contrasts for effect modification by sex of a decrease from the 90th to the 10th percentile of the EDCs on the glucocorticosteroids expressed in ng/ml (HELIX subcohort; 2013-2016).** Circles and triangles indicate effect estimates. Solid lines indicate the CI. |

|  |
| --- |
| Figure S6: **Marginal contrasts for effect modification by sex of a decrease from the 90th to the 10th percentile of the glucocorticosteroids on HRT-SE expressed in ms (HELIX subcohort; 2013-2016).** Circles and triangles indicate effect estimates. Solid lines indicate the CI. Abbreviations: cortisone production (cortisone prod.); cortisol production (cortisol prod.); corticost. prod. (corticosterone production). |