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

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# List of Acronyms

ADHD

Attention-Deficit / Hyperactivity Disorder

ANT

Attention Network Test

BPA

Bisphenol A

CI

Confidence interval

DAG

Directed acyclic graph

DAP

Dialkylphosphate

EDC

Endocrine disrupting chemical

HELIX

Human Early-Life Exposome

HPA

Hypothalamic-pituitary-adrenocortical

HRT-SE

Hit reaction time standard error

IQ

Intelligence quotient

IQR

Interquartile range

**LC**

Liquid chromatography

LLOQ

Lower limit of quantification

LOD

Limit of detection

LOQ

Limit of quantification

MC

Marginal contrast

**MS**

Mass spectrometry

NPSEM

Non-parametric structural equation model

OP pesticide

Organophosphate pesticide

**TOFMS**

Time-of-flight mass spectrometry

**UHPLC**

Ultra-high performance liquid chromatography

# Abstract

**Background**

Evidence suggests that endocrine disrupting chemicals (EDCs) may perturb the hypothalamic-pituitary-adrenocortical (HPA) axis, which has a major role in brain development. We aimed to evaluate the effects of childhood exposure to organophosphate pesticides, phenols, and phthalate metabolites, on urinary glucocorticosteroids and inattention in childhood.

**Methods**

We used data from the Human Early-Life Exposome (HELIX) cohort (2013-2016) and the parametric g-formula to estimate associations between EDCs, glucocorticosteroids, and hit reaction time standard error (HRT-SE), a measure of inattention, and tested for possible effect modification by sex.

**Results**

We observed a positive marginal contrast (MC) for exposure increases from the 10th to the 90th percentile for methyl-paraben (MC: 0.042 and confidence interval (CI): (0.013, 0.071)), and the phthalate metabolites oxo-MiNP (MC: 0.023 and CI: (0.003, 0.044)), oh-MiNP (MC: 0.039 and CI: (0.001, 0.076)), and MEHP (MC: 0.036 and CI: (0.008, 0.063)), on HRT-SE, indicating lower attention. Several EDCs were also associated with a positive MC for cortisone, cortisol, and corticosterone production. Increased levels of the glucocorticosteroids were not associated with HRT-SE, although we found a possible effect modification by sex.

**Conclusions**

Our results suggest that multiple EDCs might interfere with inattention and with the homeostasis of the HPA axis.

**Keywords:** Endocrine Disruptors, Cortisone, Hydrocortisone, Neuropsychological Tests, Causality.

# 1. Introduction

The prevalence of several neurodevelopmental disorders has increased in the pediatric population ([Grandjean and Landrigan, 2014](#ref-GrandjeanLandrigan:2014)), and multiple environmental pollutants may play a role in the increased rates of these disorders ([Ramírez et al., 2022](#Xd81cf38a3b251ec377f8aa13b097ea9d0c190e3)). 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 ([Bouchard et al., 2010](#ref-BouchardBellingerWright:2010); [Braun, 2017](#ref-Braun:2017); [Cartier et al., 2016](#Xa0cc0fdd8206e54b0a9b4bdcd9d2102efd24cb7); [Furlong et al., 2017](#ref-FurlongHerringBuckley:2017); [González-Alzaga et al., 2015](#X2a5c5c17453fffe785b7f0bcffd564283892c6c); [Huang et al., 2015](#ref-HuangChenSu:2015); [Huang et al., 2017](#ref-HuangTsaiChen:2017); [Kim et al., 2017](#ref-KimHongShin:2017); [Li et al., 2018](#ref-LiZhangKuang:2018); [Oh et al., 2023](#ref-OhKimKannan:2023); [Rodríguez-Carrillo et al., 2019](#X71fca68020aad3c79232160399444b9923ab76e); [Shoaff et al., 2020](#ref-ShoaffCoullWeuve:2020); [Tewar et al., 2016](#ref-TewarAuingerBraun:2016); [Vilmand et al., 2023](#ref-VilmandBeckBilenberg:2023); [Yu et al., 2016](#ref-YuDuChiou:2016)). Among the EDCs that have raised such concerns are non-persistent EDCs, including phthalates, phenols (including bisphenol A, parabens, triclosan, oxybenzone) and organophosphate pesticides (OP pesticides) (Braun, 2017). While most of the available literature focuses on the effects of prenatal exposure to EDCs on child neurodevelopment (Ramírez et al., 2022), mid-childhood is also a crucial stage of (neuro)development (Mah and Ford-Jones, 2012), but there are few studies focusing on whether exposure to EDCs during this time period may be harmful to the developing brain.

Exposure to phthalates and their metabolites during childhood and early adolescence has been associated with several adverse neurodevelopmental outcomes, but these studies were limited to few phthalate metabolites and small study populations ([Ramírez et al., 2022](#Xd81cf38a3b251ec377f8aa13b097ea9d0c190e3)). The effects of exposure to bisphenol A (BPA) during childhood on cognitive functions are still unclear ([Ramírez et al., 2022](#Xd81cf38a3b251ec377f8aa13b097ea9d0c190e3)). Similarly, the few studies assessing exposure to OP pesticides during childhood through the use of biomarkers suffered from a series of limitations, including a small sample size ([Ramírez et al., 2022](#Xd81cf38a3b251ec377f8aa13b097ea9d0c190e3)). Given the scarcity of studies on the neurodevelopmental effects of exposure to non-persistent EDCs during childhood, further studies are needed to understand the impact of exposure in this life stage.

Moreover, little is known about the biological mechanisms of action that may underlie the effects of these chemicals on neurodevelopment ([Ramírez et al., 2022](#Xd81cf38a3b251ec377f8aa13b097ea9d0c190e3)). There is some toxicological evidence, however, that exposure to certain EDCs, specifically phthalates, might interfere with the hypothalamic-pituitary-adrenocortical (HPA) axis, which is responsible for the production of glucocorticosteroids, and might interact with the glucocorticoid receptor ([Kim et al., 2018](#ref-KimLeeMoon:2018); [Sears et al., 2023](#ref-SearsLiuLanphear:2023); [Sun et al., 2018](#ref-SunLiJin:2018)). This potential mechanism is corroborated by the presence of receptors for these hormones in the brain ([Lupien et al., 2009](#ref-LupienMcEwenGunnar:2009); [Sun et al., 2018](#ref-SunLiJin:2018)). While glucocorticosteroids are necessary for brain maturation, their under- or over-production might interfere with its normal development and ultimately lead to long-term impaired functioning ([Lupien et al., 2009](#ref-LupienMcEwenGunnar:2009); [Sears et al., 2023](#ref-SearsLiuLanphear:2023)). Taken together, these results suggest that disruption of the HPA axis’ homeostasis may be one biological mechanism by which EDCs may affect neurodevelopment.

The aim of this study was twofold. First, we examined the impact of childhood exposure to OP pesticides, phenols, and phthalate metabolites on glucocorticosteroids and attentional function in children of a multi-country cohort in Europe. Second, we examined the impact of changes in glucocorticosteroid levels on attentional function. To do so, we used the parametric g-formula, a causal inference technique, and marginal contrasts (MCs).

# 2. Material and methods

## 2.1 Study population and design

The Human Early-Life Exposome (HELIX) project aims to characterize early-life exposures and their potential association with endogenous biomarkers and health outcomes ([Vrijheid et al., 2014](#ref-VrijheidSlamaRobinson:2014)). It consists of six existing population-based birth cohort studies across Europe: BiB (Born in Bradford, UK) ([Wright et al., 2013](#ref-WrightSmallRaynor:2013)), EDEN (Study of determinants of pre- and postnatal developmental, France) ([Heude et al., 2016](#ref-HeudeForhanSlama:2016)), INMA (Environment and Childhood, Spain) ([Guxens et al., 2012](#ref-GuxensBallesterEspada:2012)), KANC (Kaunas Cohort, Lithuania) ([Grazuleviciene et al., 2009](#Xd30c40380c9e99bac70b7fa3b0ada5ae8dec3e4)), MoBa (The Norwegian Mother and Child Cohort Study, Norway) ([Magnus et al., 2006](#ref-MagnusIrgensHaug:2006)), and Rhea (Mother–Child Cohort in Crete, Greece) ([Chatzi et al., 2009](#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 ([Maitre et al., 2018](#ref-MaitreBontCasas:2018)). Eligibility criteria for inclusion in the HELIX subcohort included: a) age 6-11 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 or the volunteer’s safety (e.g., acute respiratory infection). The HELIX subcohort protocols and characteristics are fully described elsewhere (Maitre et al., 2018). Ethical permission was obtained from the relevant authorities in the corresponding country for each cohort.

## 2.2 Variables

### 2.2.1 Endocrine disrupting chemicals

Children were assessed between December 2013 and February 2016, and assessments included neurological testing and urine collection. Briefly, two spot urine samples were collected, one sample before bedtime on the night before the visit, and one first morning void on the day of the visit. Samples were collected in high-quality polypropylene tubes and the aliquots were stored at -80°C. The two urine samples were combined and analysed as a pool to provide a more reliable exposure assessment. Concentrations of the phthalate metabolites, phenols, and OP pesticide metabolites were determined in the urine samples using online column-switching LC-MS/MS, online column-switching UHPLC-MS/MS, and UHPLC-TOFMS, respectively. Procedure blanks and internal quality control samples were analyzed along with each batch of samples. Laboratory protocols for the analysis are described in (Haug et al., [2018](#ref-HaugSakhiCequier:2018)), while quality control and interlaboratory comparison are described in (Maitre et al., [2018](#ref-MaitreBontCasas:2018)). 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 (Supplementary [Table 1](#supptbl-info-chems)).

### 2.2.2 Glucocorticosteroids

Urine samples of the night before the day of the visit were used to measure levels of the glucocorticosteroids. These included glucocorticosteroids, glucocorticosteroid metabolites, glucocorticosteroid precursors, glucocorticosteroid precursor metabolites, androgens, and androgen metabolites. A list of the glucocorticosteroids determined in urine samples and used for the present study is given in Supplementary [Table 2](#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 ([Gomez-Gomez and Pozo, 2020](#ref-Gomez-GomezPozo:2020); [Marcos et al., 2014](#ref-MarcosRenauCasals:2014)).

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).

### 2.2.3 Attentional function

Cognitive and motor function outcomes were assessed during the visit with standardized, non-linguistic, and culturally blind computer tests, including the Attention Network Test (ANT) ([Rueda et al., 2004](#ref-RuedaFanMcCandliss:2004)), which provides a measure of efficiency of attentional function. The tests were administered in a standardized way, and with minimal interference from the field workers. Further information can be found elsewhere ([Forns et al., 2014](#ref-FornsEsnaolaLopez-Vicente:2014); [Maitre et al., 2018](#ref-MaitreBontCasas:2018); [Rueda et al., 2004](#ref-RuedaFanMcCandliss:2004)). The outcome of interest for the present study is the hit reaction time standard error (HRT-SE) ([Sunyer et al., 2015](#ref-SunyerEsnaolaAlvarez-Pedrerol:2015)), a measure of response speed consistency throughout the test. A high HRT-SE indicates highly variable reaction times and is considered a measure of inattentiveness.

### 2.2.4 Confounders

For each research question, defined by a specific type of exposure and outcome, the minimal set of covariates for inclusion in the analyses was selected on the basis of a directed acyclic graph (DAG) (Greenland et al., 1999) built with DAGitty ([Textor et al., 2016](#ref-TextorvanderZanderGilthorpe:2016)) and ggdag ([Barrett, 2023](#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 included in the models to adjust for possible dilution effects. Further, each minimal adjustment set was *augmented* with precision covariates, defined as the set of parent variables of the outcome that are not parents of the exposure. Common confounders were cohort, ethnicity, sex, age, height, weight, and head circumference of the child, urine creatinine, consumption of fish, fruit, vegetables, organic food, and fast food with a food frequency questionnaire, maternal tobacco consumption, family financial situation and affluence scale (FAS). Models for estimating the effects of EDCs on HRT-SE were further adjusted for child breastfeeding, prenatal maternal active and passive smoking, child mood and rest before assessment, child neuropsychological diagnosis, maternal marital status, season, and fasting time before assessment. Models for estimating the effects of EDCs on glucocorticosteroids were further adjusted for season, and fasting time before assessment. Models for estimating the effects of glucocorticosteroids on HRT-SE were further adjusted for child breastfeeding, prenatal maternal active and passive smoking, marital status, EDCs, child mood and rest before assessment, and child neuropsychological diagnosis. The adjustment sets are provided in the Supplementary Material as text files compatible with DAGitty. A simplified DAG is provided in [Figure 1](#fig-dag). Codebooks for the used covariates are provided in Supplementary [Table 3](#supptbl-codebooks).

## 2.3 Statistical methods

### 2.3.1 Data pre-processing

Concentrations of the glucocorticosteroids, expressed in nanograms per millilitre (ng/ml), were classified as quantifiable, below the limit of quantification (LOQ), possible interference or out of range, and not detected. For each glucocorticosteroid, we computed the fraction of values below the LOQ and not detected, both within each cohort and overall. We proceeded to impute these values using half the value of the corresponding LOQ, for those glucocorticosteroids that had less than 30% of non-detected within each cohort and 20% of non-detected overall. Information about the lower limit of quantification (LLOQ) for the glucocorticosteroids is provided in Supplementary [Table 4](#supptbl-lloq-mets). Values classified as possible interference or out of range were imputed using kNN from the VIM R package ([Kowarik and Templ, 2016](#ref-KowarikTempl:2016)) for those glucocorticosteroids that had less than 40% of missings within each cohort and 30% of missings overall. For each glucocorticosteroid, imputation was based on the median of the 5 nearest glucocorticosteroids, and the Gower distance was computed based on non-missing glucocorticosteroids after standardization by the interquartile range (IQR). 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 ([Lüdecke et al., 2021](#ref-LudeckeBen-ShacharPatil:2021)).

Concentrations of the non-persistent EDCs, expressed in grams per litre (g/L), were classified as quantifiable, below the limit of detection (LOD), possible interference or out of range, and not analysed. Concentrations of each chemical 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 ([Lazar, 2015](#ref-lazar2015imputelcmd)). Information about the lower limits of detection can be found in (Haug et al., [2018](#ref-HaugSakhiCequier:2018)). Chemicals with more than 70% of observations below the LOD were excluded from the present study. Values classified as possible interference or out of range were also imputed using the aforementioned kNN procedure based on non-missing data from the remaining EDCs.

Missing values in the clinical outcome, expressed in milliseconds (ms), and the covariates were similarly imputed using the aforementioned kNN procedure based on non-missing data from the clinical outcome and the remaining covariates, respectively. Values of the clinical outcome were natural log-transformed to improve model fit, assessed with posterior predictive checks. 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).

### 2.3.2 Estimation of balancing weights

To reduce the effect of measured confounders on the exposure-outcome association, stabilized balancing weights were estimated using the energy method available in the WeightIt R package ([Greifer, 2023a](#ref-Greifer:2023)). This method estimates weights by minimizing an energy statistic related to covariate balance ([Huling et al., 2023](#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 ([Greifer, 2023b](#ref-Greifer:2023a)). Specifically, we used *Love* plots to visualize covariate balance before and after weighting (available in Supplementary Material – Love plots).

### 2.3.3 G-computation

We estimated MCs with the parametric g-formula, a method of standardization. The parametric g-formula has some advantages over traditional regression approaches, even in the point-exposure scenario. First, assuming that the identifiability conditions hold, it allows to estimate causal effects in complex scenarios, including dynamic treatment regimes and non-linear relationships (Robins et al., 2004). Second, it allows to flexibly simulate counterfactual scenarios under different exposure regimes. Lastly, by directly computing expected outcomes under specific interventions, it provides estimates that are easier to interpret.

The parametric g-formula involves the following steps: 1) fit a weighted outcome model including both exposure and covariates, with balancing weights estimated from the nuisance exposure models (Smith et al., 2022); 2) create two counterfactual datasets identical to the original one but with the exposures shifted according to a user-specified dynamic 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 between the expected value of the outcomes in the counterfactual datasets under the shifted exposure levels and specified below: . 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 ([Arel-Bundock, 2023](#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 to account for cross-cohort differences in the levels of the exposures. 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 ([Zeileis et al., 2020](#ref-ZeileisKollGraham:2020); [Zeileis, 2004](#ref-Zeileis:2004)). For each outcome, we report the results as differences between MCs with 95% confidence intervals (CIs).

### 2.3.4 Effect-modification analysis

We further estimated separate MCs for possible effect-modification by sex. To do so, balancing weights were estimated separately for each level of the sex variable, and an interaction term between the exposure and sex was included in the outcome model. Similarly, the MCs were estimated with the avg\_comparisons function. For each outcome, we report the results as pairwise differences between female MCs and male MCs, with 95% confidence intervals (CIs).

# 3. Results

A total of 1,297 children of the HELIX subcohort had measurements of the non-persistent EDCs. The study population was 55% male, and, at the time of visit, the median age of the children was 8.06 years (Table 1, and Supplementary Table 5 for cohort-specific characteristics). The children were mostly Caucasian (90%), and the largest minority were of Pakistani origin (6.2%). Measurements of both non-persistent EDCs and glucocorticosteroids were available for 976 children of the subcohort, as shown in Supplementary Figure 1. The median HRT-SE was 300 ms (IQR, 231-368), with lower median values for EDEN, MOBA, and INMA, corresponding to the cohorts with older children. Concentrations of unprocessed non-persistent EDCs, after imputation of values below the LOD, and glucocorticosteroids, are presented in [Table 2](#tbl-edc-desc) and [Table 3](#tbl-met-new-desc), respectively (Supplementary [Table 6](#supptbl-chems-desc) and Supplementary [Table 7](#supptbl-met-desc) for results by cohort). Generally, the EDCs showed high levels of detection, with the exception of some of the OP pesticide metabolites (e.g., DEDTH and DMDTP) and shown in Supplementary Figure 2. Similarly, the glucocorticosteroids showed high levels of detection (Supplementary Figure 3).

Associations between exposure to EDCs and HRT-SE are shown in [Figure 2](#fig-marginal-1) (with effective sample sizes before and after balancing weights estimation, and summary statistics of the estimated balancing weights shown in Supplementary Table 8 and Supplementary Table 9, respectively). For most EDCs, a cohort-specific increase in the levels of the exposures from the 10th to the 90th percentiles was associated with a positive MC, indicating an increase in the values of HRT-SE and thus lower attention. Most of the CIs included the null effect, though. Noteworthy associations were observed for the paraben MEPA (MC: 0.042 and CI: (0.013, 0.071)), and the phthalate metabolites oxo-MiNP (MC: 0.023 and CI: (0.003, 0.044)), oh-MiNP (MC: 0.039 and CI: (0.001, 0.076)), and MEHP (MC: 0.036 and CI: (0.008, 0.063)). The organophosphate pesticide (OP pesticide) DETP was associated with lower HRT-SE (MC: -0.026 and CI: (-0.054, 0.001)). There was little evidence for effect modification by sex, with significant differences between males and females present only for the phenol OXBE (MC: 0.032 and CI: (0.004, 0.061)) and the phthalate metabolite MbZP (MC: -0.066 and CI: (-0.126, -0.007)) (Supplementary Table 10 for the marginal differences on the logarithmic scale between females and males; Supplementary Table 11 for summary statistics of the estimated balancing weights; Supplementary Table 12 and Supplementary Figure 4 for the individual MCs).

Associations between exposure to EDCs and total cortisone, cortisol, and corticosterone production are shown in [Figure 3](#fig-marginal-2) (with effective sample sizes before and after balancing weights estimation, and summary statistics of the estimated balancing weights shown in Supplementary Table 13 and Supplementary Table 14, respectively). For most EDCs, a cohort-specific increase in the levels of the exposures from the 10th to the 90th percentiles was associated with a positive MC, indicating an increase in the total production of these metabolites. Exceptions were BUPA, which was associated with negative MCs for all three outcomes, and MiBP, which was associated with a negative MC for total cortisone production only. Most of the effects for the phenols and phthalate metabolites included the null. The phenol BPA showed the largest MCs across all three outcomes (cortisone production, MC: 0.263 and CI: (0.131, 0.394); cortisol production, MC: 0.274 and CI: (0.107, 0.441); corticosterone production, MC: 0.285 and CI: (0.106, 0.464)). Regarding effect modification by sex, significant differences between males and females were present across all three classes of EDCs and for all outcomes, generally showing weaker associations in males (Supplementary Table 10 for the marginal differences on the logarithmic scale between females and males; Supplementary Table 15 for summary statistics of the estimated balancing weights; Supplementary Table 16 and Supplementary Figure 5 for the individual MCs). The largest differences were attributable to the phenol ETPA (corticosterone production, MC: -0.254 and CI: (-0.416, -0.092)) and the phthalate metabolite MEHP (cortisol production, (MC: -0.221 and CI: (-0.289, -0.153)); cortisone production, (MC: -0.177 and CI: (-0.299, -0.055))).

Associations between the glucocorticosteroids and HRT-SE are shown in [Figure 4](#fig-marginal-3) (with effective sample sizes before and after balancing weights estimation, and summary statistics of the estimated balancing weights shown in Supplementary Table 17 and Supplementary Table 18, respectively). In the overall study population, all MCs included the null, with no clear indication of directionality of the effect. However, for all exposures, the MCs had opposite signs in males and females (positive for males and negative for females) (Figure 4). Significant differences were present for cortisone production (MC: 0.14 and CI: (0.019, 0.261)) and corticosterone production (MC: 0.126 and CI: (0.009, 0.243)) (Supplementary Table 19 for the marginal differences on the logarithmic scale between females and males; Figure 4 for the individual MCs; Supplementary Table 20 for summary statistics of the estimated balancing weights).

# 4. Discussion

In this study, consisting of 1,297 children from 6 European birth cohorts, we observed that short-term childhood exposure to certain non-persistent EDCs was associated with lower attentional function (MEPA, MEHP, oh-MiNP, and oxo-MiNP), and with an increase in total production of cortisol, cortisone, and corticosterone (DEP, DMP, DMTP, BPA, ETPA, MEPA, MEHP, oh-MiNP, and oxo-MiNP). Some of these associations differed for females and males. Increased production of these glucocorticosteroids was not associated with attentional function in the study population overall, but showed associations with lower attentional function in males and higher attentional function in females.

To the best of our knowledge, no other study has investigated the effects of childhood exposure to multiple classes of non-persistent EDCs in relation to attentional function. More generally, the literature on childhood exposure to non-persistent EDCs and other neurodevelopment outcomes in children has mostly focused on OP pesticides ([Bouchard et al., 2010](#ref-BouchardBellingerWright:2010); [Cartier et al., 2016](#Xa0cc0fdd8206e54b0a9b4bdcd9d2102efd24cb7); [González-Alzaga et al., 2015](#X2a5c5c17453fffe785b7f0bcffd564283892c6c); [Yu et al., 2016](#ref-YuDuChiou:2016)), phthalate metabolites ([Balalian et al., 2019](#ref-BalalianWhyattLiu:2019); [Huang et al., 2015](#ref-HuangChenSu:2015); [Huang et al., 2017](#ref-HuangTsaiChen:2017); [Jankowska et al., 2019](#ref-JankowskaPolanskaHanke:2019); [Kim et al., 2017](#ref-KimHongShin:2017); [Li et al., 2019](#ref-LiPapandonatosCalafat:2019); [Shoaff et al., 2020](#ref-ShoaffCoullWeuve:2020); [Vilmand et al., 2023](#ref-VilmandBeckBilenberg:2023)), and BPA ([Li et al., 2018](#ref-LiZhangKuang:2018); [Rodríguez-Carrillo et al., 2019](#X71fca68020aad3c79232160399444b9923ab76e); [Tewar et al., 2016](#ref-TewarAuingerBraun:2016)).

Regarding OP pesticide exposure in childhood, previous studies reported that higher levels of dialkylphosphate (DAP) metabolites were associated with lower scores of intelligence quotient (IQ) and verbal comprehension in children aged 6 to 11 years, especially in boys ([González-Alzaga et al., 2015](#X2a5c5c17453fffe785b7f0bcffd564283892c6c)), while higher levels of diethylphosphate metabolites were associated with lower working memory scores ([Cartier et al., 2016](#Xa0cc0fdd8206e54b0a9b4bdcd9d2102efd24cb7)). There is also preliminary evidence of a possible association between exposure to certain OP pesticides and Attention-Deficit / Hyperactivity Disorder (ADHD) in children ([Bouchard et al., 2010](#ref-BouchardBellingerWright:2010); [Yu et al., 2016](#ref-YuDuChiou:2016)). In our study we found higher levels of DETP to be associated with better attentional function, with concordant results in the sex-stratified analysis. While we cannot exclude a protective effect of DETP in relation to attentional function, we note that in our study DETP has a higher percentage of missing values compared to the other OP pesticides and that other imputation strategies might lead to different associations.

Previous evidence is also available for exposure to several phthalate metabolites in childhood, in relation to cognitive development in childhood. Higher levels of di(2-ethylhexyl) phthalate metabolites (including MEHP, MEHHP, and MEOHP) were associated with lower intelligence scores in children aged 2 to 12 years ([Huang et al., 2015](#ref-HuangChenSu:2015)), lower scores of IQ and verbal intelligence, more omission errors (a measure of inattention), and higher scores of response time variability (a measure of sustained attention) in 6-year old Korean children ([Kim et al., 2017](#ref-KimHongShin:2017)), poorer fine motor skills in preadolescent boys ([Balalian et al., 2019](#ref-BalalianWhyattLiu:2019)), and lower intelligence scores in 7-year old children ([Vilmand et al., 2023](#ref-VilmandBeckBilenberg:2023)). Further associations were found for higher levels of MEOHP with lower scores of IQ ([Huang et al., 2015](#ref-HuangChenSu:2015)) and verbal intelligence in Taiwanese children aged 6 to 12 years ([Huang et al., 2017](#ref-HuangTsaiChen:2017)), and for higher levels of dibutyl phthalate metabolites (MnBP and MiBP) with impaired verbal intelligence ([Huang et al., 2017](#ref-HuangTsaiChen:2017)). Few studies have investigated different classes of non-persistent EDCs. Shoaff et al. investigated cross-sectional associations between multiple EDCs and ADHD-related behaviors in 15-year old adolescents, finding a higher risk of ADHD-related behavior problems with higher levels of antiandrogenic phthalate metabolites (molar sum of MnBP, MiBP, MBzP, MEHP, MEHHP, MEOHP, MECPP, monocarboxyoctyl phthalate, monohydroxyisobutyl phthalate (MHiBP), monohydroxybutyl phthalate (MHBP), and mono-isononyl phthalate) and the molar sum of di(2-ethylhexyl) phthalate (DEHP) metabolites (MECPP, MEHHP, MEOHP, and MEHP), especially in boys ([Shoaff et al., 2020](#ref-ShoaffCoullWeuve:2020)). Our findings, indicating that short-term childhood exposure to certain phthalate metabolites (MEHP, oh-MiNP, and oxo-MiNP) was associated with attentional function, adds to this growing evidence base suggesting that childhood phthalate exposure may impact child neurodevelopment.

Regarding phenol exposure during childhood, some studies provide preliminary evidence of an association between BPA and ADHD in children aged 8 to 15 years ([Tewar et al., 2016](#ref-TewarAuingerBraun:2016)) and in a case-control study of children aged 6 to 12 years ([Li et al., 2018](#ref-LiZhangKuang:2018)), especially in boys. Except for working memory, there was no evidence of an association between BPA and cognitive abilities in Spanish boys aged 9 to 11 years ([Rodríguez-Carrillo et al., 2019](#X71fca68020aad3c79232160399444b9923ab76e)). We did not observe an association between BPA and attention function in the present study, but this study is the first to suggest that childhood exposure to MEPA may be associated with lower attentional function.

We are not aware of other epidemiological studies investigating childhood exposure to phthalates metabolites, phenols, and OP pesticides in relation to urinary glucocorticosteroid levels in childhood. However, prior epidemiological research provides preliminary evidence for an association between certain non-persistent EDCs measured at other time points with higher levels of glucocorticoids measured in other biological matrices ([Kim et al., 2018](#ref-KimLeeMoon:2018); [Sears et al., 2023](#ref-SearsLiuLanphear:2023); [Sun et al., 2018](#ref-SunLiJin:2018)). Repeated measures up to 15 months of age of the phthalate metabolites MEHHP, MEOHP, MiBP, and MnBP showed positive associations with free urine cortisol in Korean children ([Kim et al., 2018](#ref-KimLeeMoon:2018)). In a cohort of Chinese pregnant women, phthalate metabolites were measured at 14, 24, and 36 weeks of gestation, and the glucocorticoids cortisol and cortisone were measured in cord blood. Third-trimester levels of MEHP were positively associated with cortisol, while MECPP and MEOHP were negatively associated with cortisone ([Sun et al., 2018](#ref-SunLiJin:2018)). Time- and chemical-dependent sex differences were also found: during the third trimester, MEHHP and MEOHP were positively associated with cortisol in females, while negatively associated in males ([Sun et al., 2018](#ref-SunLiJin:2018)). In a longitudinal study, a mixture of several phthalate metabolites, driven by MEP, MiBP, and MBzP, measured in childhood, showed a positive association with hair cortisol measured at 12 years of age ([Sears et al., 2023](#ref-SearsLiuLanphear:2023)). Our findings also indicate associations between certain phthalate metabolites (MEHP, oh-MiNP, and oxo-MiNP) and glucocorticosteroids, but differences in the exposure assessment time points, the biological matrices used for glucocorticosteroids determinations, and the possible effect of parturition on cord concentrations of cortisol ([Tribe et al., 2018](#ref-TribeTaylorKelly:2018)), make a direct comparison difficult. Adding to these epidemiological studies, previous toxicological research 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 ([Ma et al., 2011](#ref-MaLianDong:2011); [Zhao et al., 2010](#ref-ZhaoChuHuang:2010)).

Regarding the association between glucocorticosteroids and attentional function, we are not aware of prior epidemiological studies specifically investigating the effects of elevated levels of glucocorticosteroids in relation to attentional function. However, there is evidence that under- or over-production of glucocorticosteroids interfere with the normal development of the brain, possibly in a sex-specific manner ([Lupien et al., 2009](#ref-LupienMcEwenGunnar:2009)). We did not find an association between glucocorticosteroid levels and attentional function in our overall study population, but our findings of an association with lower attentional function in males and higher attentional function in females support evidence for such sex-specific interference. Further longitudinal follow-up of these associations is needed since the effects of glucocorticosteroids may be long-term (Lupien et al., 2009).

Our findings should be interpreted considering the following strengths and limitations. Strengths include its relatively large sample size and its inclusion of multiple classes of non-persistent EDCs. Further, this study used pooled urine samples for chemical assessment to reduce measurement error, since it is known that these specific EDCs have very short half-lives ([Casas et al., 2018](#ref-CasasBasaganaSakhi:2018); [Perrier et al., 2016](#ref-PerrierGiorgis-AllemandSlama:2016)). We decided to model both the *treatment* mechanisms, for the estimation of balancing weights, and the outcomes, with traditional covariates adjustment, to obtain *doubly robust* effect estimates. Finally, we decided not to interpret our results by focusing on the estimated coefficients of possibly misspecified regression models, but by making use of the g-computation procedure.

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. Cross-sectional designs also have limitations to study the etiologic period of susceptibility of attentional function. Prior studies have investigated associations between short-term effects of air pollution and attentional function, with null results in adolescents but higher response times in adults ([Gignac et al., 2022](#ref-GignacRighiToran:2022), [2021](#ref-GignacBarrera-GomezPersavento:2021)). 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. We decided not to include prenatal levels of the EDCs as confounders due to the *small* correlation between prenatal and childhood levels of these non-persistent chemicals ([Haug et al., 2018](#ref-HaugSakhiCequier:2018)). 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 and doubly robust estimators are consistent if either the outcome model or the exposure model is specified correctly (Naimi et al., 2023). While the parametric g-computation has several benefits over traditional regression approaches, we recognize that other representative values of the dose-response curve might be worth exploring (e.g., comparison of potential outcomes at different percentiles of the exposure). We further acknowledge that the present study does not consider the possible mixture effect of these chemicals. While methods for causal mixture analysis are available ([Keil et al., 2020](#ref-KeilBuckleyO:2020)), we also emphasize that using these tools without thoughtful consideration may lead to misleading results ([Webster and Weisskopf, 2020](#ref-WebsterWeisskopf:2020)). Finally, longitudinal studies are necessary for a formal causal mediation analysis (Fairchild and McDaniel, 2017), which is why we did not attempt such a analysis even for the sex-stratified case, where glucocorticosteroids were associated with HRT-SE.

## 4.1 Conclusion

In conclusion, in a study of 1,297 children from 6 European birth cohorts, we observed that (i) exposure to certain non-persistent EDCs is associated with higher values of HRT-SE and might disrupt the HPA axis, and (ii) certain glucocorticosteroids are associated with HRT-SE in a sex-specific manner.

While several of our results are *statistically significant*, the estimates are generally *small* in magnitude. Nevertheless, two important factors should be considered when discussing the public health significance of these findings. First, while the marginal associations are *small* in magnitude, individual-level effects might still be clinically significant. Second, EDCs are ubiquitous chemicals present in many every-day products and diet. Thus, even *small* marginal associations might be significant at the population level. For non-persistent EDCs, larger studies with repeated measurements of the exposures at several time points are necessary to fully understand their impact on neurodevelopment.

# 5. Data Sharing and Code

Access to HELIX data is based on approval by the HELIX Project Executive Committee and by the individual cohorts. Further details on the content of the data warehouse (data catalog) and procedures for external access are described on the project website (http://www.projecthelix.eu/index.php/es/data-inventory).

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

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

|  |  |
| --- | --- |
| **Characteristic** | **N = 1,297***a* |
| Child age (years) | 8.1 (6.5, 8.9) |
| Child breastfeeding | 1,093.0 (84.7%) |
| Unknown | 6 |
| Child ethnicity |  |
| Caucasian | 1,157.0 (90.0%) |
| Pakistani | 80.0 (6.2%) |
| Asian | 21.0 (1.6%) |
| Other | 19.0 (1.5%) |
| African | 7.0 (0.5%) |
| Native American | 2.0 (0.2%) |
| White non European | 0.0 (0.0%) |
| Unknown | 11 |
| Child head circumference (cm) | 51.8 (50.6, 52.9) |
| Unknown | 3 |
| Child height (m) | 1.3 (1.2, 1.4) |
| Child neuropsychological diagnosis | 95.0 (7.3%) |
| Child rest before assessment |  |
| Yes | 1,209.0 (93.3%) |
| Not as well as usual | 87.0 (6.7%) |
| Unknown | 1 |
| Child sex |  |
| Male | 710.0 (54.7%) |
| Female | 587.0 (45.3%) |
| Child weight (kg) | 26.9 (22.9, 32.6) |
| Chiod mood before assessment |  |
| Usual | 1,232.0 (95.1%) |
| Not usual | 64.0 (4.9%) |
| Unknown | 1 |
| Cohort |  |
| MOBA | 272.0 (21.0%) |
| INMA | 221.0 (17.0%) |
| BIB | 204.0 (15.7%) |
| KANC | 203.0 (15.7%) |
| RHEA | 199.0 (15.3%) |
| EDEN | 198.0 (15.3%) |
| Creatinine night sample (g/l) | 1.7 (0.9, 3.0) |
| Unknown | 321 |
| Creatinine pooled sample (g/l) | 1.0 (0.8, 1.2) |
| Date of test (season) |  |
| Spring | 358.0 (27.7%) |
| Winter | 339.0 (26.2%) |
| Autumn | 300.0 (23.2%) |
| Summer | 297.0 (23.0%) |
| Unknown | 3 |
| Family affluence scale |  |
| 6 | 410.0 (31.7%) |
| 5 | 325.0 (25.1%) |
| 7 | 248.0 (19.2%) |
| 4 | 174.0 (13.4%) |
| 3 | 92.0 (7.1%) |
| 2 | 28.0 (2.2%) |
| 1 | 12.0 (0.9%) |
| 0 | 6.0 (0.5%) |
| Unknown | 2 |
| Fast food/take away (times/week) | 0.1 (0.1, 0.5) |
| Unknown | 7 |
| Fasting time before visit (hours) | 3.3 (2.8, 4.0) |
| Financial situation of the parents |  |
| Doing alright | 414.0 (32.1%) |
| Living comfortably | 412.0 (31.9%) |
| Getting by | 331.0 (25.6%) |
| Finding it quite difficult | 86.0 (6.7%) |
| Finding it very difficult | 40.0 (3.1%) |
| Does not wish to answer | 8.0 (0.6%) |
| Unknown | 6 |
| Fish and seafood (times/week) | 2.0 (1.1, 3.5) |
| Unknown | 5 |
| Fruits (times/week) | 9.0 (5.9, 18.0) |
| Unknown | 7 |
| Hit reaction time standard error (ms) | 299.6 (231.3, 368.2) |
| Unknown | 18 |
| Marital status |  |
| Living with the father | 1,212.0 (94.5%) |
| Living alone | 39.0 (3.0%) |
| Other situation | 31.0 (2.4%) |
| Unknown | 15 |
| Maternal tobacco consumption |  |
| Non-smoker and has never smoked | 681.0 (52.6%) |
| Daily smoker | 200.0 (15.5%) |
| Non-smoker but previously smoked daily | 186.0 (14.4%) |
| Non-smoker but previously smoked although not daily | 163.0 (12.6%) |
| Smoker but not daily | 64.0 (4.9%) |
| Unknown | 3 |
| Organic food (times/week) | 0.5 (0.0, 3.0) |
| Unknown | 7 |
| Pregnancy maternal active smoking | 190.0 (15.1%) |
| Unknown | 40 |
| Pregnancy maternal passive smoking | 514.0 (40.3%) |
| Unknown | 21 |
| Vegetables (times/week) | 6.5 (4.0, 10.0) |
| Unknown | 6 |
| *a*n (%); Median (IQR) | |

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

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

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 (2,859.9, 6,789.5); 18.0 (1.79) | 4,559.5 (2,828.4, 6,750.2); 17.0 (1.74) |
| cortisone production | 4,608.1 (2,920.8, 6,843.9); 19.0 (1.89) | 4,580.7 (2,894.4, 6,802.4); 18.0 (1.84) |
| corticosterone production | 257.8 (157.9, 410.5); 3.0 (0.30) | 256.7 (157.5, 409.7); 3.0 (0.31) |
| *a*Median (Q1, Q3); N Missing (% Missing) | | |
| *b*Measurements available for the HELIX subcohort. | | |