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

# Abstract

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* The use of the word “effect(s)” as a proxy for “association(s)” is discouraged.
* The length of the abstract must be less or equal than 200 words, and should be unstructured, stating the research questions, the methods used, and the results and conclusions of the research.
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The prevalence of several neurodevelopmental disorders has increased in the pediatric population[1](#ref-GrandjeanLandrigan:2014), and multiple environmental pollutants play a role in the increased rates of these disorders[2](#Xd81cf38a3b251ec377f8aa13b097ea9d0c190e3). endocrine disruptors (EDCs), chemicals that are capable of interfering with the endocrine system, have been shown to have a role in childhood neurodevelopment[3](#ref-Braun:2017). Although both pregnancy and early childhood are crucial stages of (neuro)development, most of the available literature is focused on the effects of prenatal exposure to EDCs on child neurodevelopment[2](#Xd81cf38a3b251ec377f8aa13b097ea9d0c190e3). Moreover, little is known about the biological mechanisms of action[2](#Xd81cf38a3b251ec377f8aa13b097ea9d0c190e3).

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

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

Something about corticosteroids…

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

# Methods

## Study population and design

The Human Early-Life Exposome (HELIX) is an ongoing project which aims to characterize early-life exposures and their potential association with endogenous biomarkers and health outcomes[4](#ref-VrijheidSlamaRobinson:2014). It consists of six existing population-based birth cohort studies across Europe: BiB (Born in Bradford, UK)[5](#ref-WrightSmallRaynor:2013), EDEN (Study of determinants of pre- and postnatal developmental, France)[6](#ref-HeudeForhanSlama:2016), INMA (Environment and Childhood, Spain)[7](#ref-GuxensBallesterEspada:2012), KANC (Kaunas Cohort, Lithuania)[8](#Xd30c40380c9e99bac70b7fa3b0ada5ae8dec3e4), MoBa (The Norwegian Mother and Child Cohort Study, Norway)[9](#ref-MagnusIrgensHaug:2006), and Rhea (Mother–Child Cohort in Crete, Greece)[10](#ref-ChatziPlanaDaraki:2009), for a total of 32,000 mother-child pairs. A HELIX subcohort of 1,200 mother-child pairs was fully characterized for the external and internal exposome, including exposure and omics biomarkers during childhood. Eligibility criteria for inclusion in the HELIX subcohort included: a) age 6-11 years, with a preference for 7-9 years; b) availability of sufficient stored pregnancy blood and urine samples; c) availability of complete address history from first to last follow-up; d) no serious health problems, which might affect the results of the clinical testing. Further information can be found in[11](#ref-MaitreBontCasas:2018).

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

## Variables

### Confounders

For each research question, defined by a specific type of exposure and outcome, the minimal set of covariates for inclusion in the analyses was selected on the basis of a directed acyclic graph (DAG) built with DAGitty[12](#ref-TextorvanderZanderGilthorpe:2016) and ggdag[13](#ref-Barrett:2023). The sets of covariates were selected to estimate the total effect of the exposure on the outcome. Further, each minimal adjustment set was *augmented* with precision covariates, defined as the set of parents variable of the outcome that are not parents of the exposure. The adjustment sets are provided in the Supplementary Material as text files compatible with DAGitty.

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

### Endocrine disrupting chemicals

Children were assessed between December 2013 and February 2016, and included neurological testing and urine collection. Urine samples of the night before and the first morning void on the day of the visit were combined to provide a more reliable exposure assessment. Non-persistent EDCs assessed in urine samples from children included phthalate metabolites, phenols, and organophosphate (OP) pesticide metabolites. A list of the environmental chemicals determined in urine samples and used for the present study is given in **?@supptbl-info-chems**. Briefly, we analyzed a total of 7 phenols, 4 non-specific organophosphate pesticide metabolites, and 10 phthalate metabolites originating from 6 distinct phthalate parent compounds. The laboratory protocols for the analysis are described elsewhere[14](#ref-HaugSakhiCequier:2018).

### Corticosteroids

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

To assess the levels of corticosteroids and their metabolites, LC-MS/MS analysis was applied at the Applied Metabolomics Research Group, IMIM (Hospital del Mar Medical Research Institute). The laboratory protocols for the analysis are described elsewhere[15](#ref-MarcosRenauCasals:2014),[16](#ref-Gomez-GomezPozo:2020). Of the 1,004 urine samples, 980 children were matched to the HELIX subcohort.

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

### Neurodevelopment

Neurodevelopmental outcomes were assessed with standardized, non-linguistic, and culturally blind computer tests, including the Attention Network Test (ANT)[17](#ref-RuedaFanMcCandliss:2004). Further information can be found in[11](#ref-MaitreBontCasas:2018). Briefly, it is a computerized test that provides a measure of efficiency in three different functions of attention: alerting, orienting, and executive attention. The outcome of interest for the present study is the hit reaction time standard error (HRT-SE)[18](#ref-SunyerEsnaolaAlvarez-Pedrerol:2015), a measure of response speed consistency throughout the test. A high HRT-SE indicates highly variable reactions, and is considered a measure of inattentiveness.

## Statistical methods

### Data pre-processing

Concentrations of the corticosteroids were classified as quantifiable, below the limit of quantification (LOQ), possible interference or out of range, and not detected. For each metabolite, we computed the fraction of values below the LOQ and not detected, both within each cohort and overall. We proceeded to impute these values using half the value of the corresponding lower limit of quantification (LLOQ), for those metabolites that had less than 30% of missings within each cohort and 20% of missings overall. Information about the LLOQ for the corticosteroids is provided in **?@supptbl-lloq-mets**. The remaining missing values were imputed using kNN from the VIM R package[19](#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[20](#ref-LudeckeBen-ShacharPatil:2021). Values of cortisol production and cortisone production were expressed in nanograms per millilitre, whereas values of cortisol metabolism and 11bHSD activity were unitless.

Concentrations of the non-persistent EDCs were classified as quantifiable, below the limit of detection (LOD), possible interference or out of range, and not analysed. Concentrations below the LOD were singly imputed using a quantile regression approach for the imputation of left-censored missing data, as implemented in the impute.QRILC function from the imputeLCMD R package[21](#ref-lazar2015imputelcmd). Information about the lower limits of detection can be found in[14](#ref-HaugSakhiCequier:2018). Chemicals with more than 70% of observations below the LOD were not considered in the present study. Remaining missing values were imputed similarly using kNN. Values of the chemicals were expressed in grams per litre.

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

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

### Estimation of balancing weights

Stabilized balancing weights were estimated using the energy method available in the WeightIt R package[22](#ref-Greifer:2023). This methods estimates weights by minimizing an energy statistic related to covariate balance[23](#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[24](#ref-Greifer:2023a). Specifically, we used *Love* plots to visualize covariate balance before and after adjusting.

### G-computation

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

We fit the outcome model using the glm function and a Gaussian family with identity link from base R. The exposure variable was modeled using natural cubic splines with 3 degrees of freedom, to more flexibly capture the average dose-response function (ADRF). When the outcome was a ratio, as was the case for cortisol metabolism and 11bHSD activity, we included the logarithm of its denominator, cortisol and cortisol production, respectively, as a control variable[25](#ref-BartlettPartnoy:2020).

To estimate the average contrasts, we used the avg\_comparisons function from the marginaleffects R package[26](#ref-Arel-Bundock:2023). The two counterfactual datasets were obtained by setting the exposures levels to 90th percentile () and the 10th percentile (), for each cohort separately. The average contrasts were computed using the estimated balancing weights above. Robust standard errors were computed with the sandwich R package, using cohort as variable indicating clustering of observations[27](#ref-Zeileis:2004),[28](#ref-ZeileisKollGraham:2020). For each outcome, we report the results as differences between average contrasts.

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

### Effect-modification analysis

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

# Results

## Participants

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

## Descriptive data

Levels of unprocessed non-persistent EDCs and corticosteroids, by cohort and overall, are presented in **?@tbl-edc-desc** and **?@tbl-met-desc**, respectively.

## Main results

The effective sample sizes before and after balancing weights estimation are presented in Tables **?@supptbl-balance-1?@supptbl-balance-2?@supptbl-balance-3**, while basic summary statistics of the estimated balancing weights are presented in Tables **?@supptbl-weights-1?@supptbl-weights-2?@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 marginal effects of the non-persistent EDCs on HRT-SE. Overall, a cohort-specific increase in the levels of the exposures from the 10th to the 90th percentiles was associated with a positive marginal contrast, indicating an increase in the values of HRT-SE. Most of the ci included the null effect, though. Statistically significant associations were observed for the phenol MEPA (mc = , ci: ), and the phthalate metabolites oxo-MiNP (mc = , ci: ), oh-MiNP (mc = , ci: ), and MEHP (mc = , ci: ). The OP pesticide DETP was strongly negatively associated with HRT-SE (mc = , ci: ).

Figures **?@fig-marginal-2-cortisolprod?@fig-marginal-2-cortisoneprod?@fig-marginal-2-corticosteroneprod?@fig-marginal-2-11b** present the forest plots for the marginal effects of the non-persistent EDCs on cortisol production, cortisone production, corticosterone production, and 11bHSD activity, respectively.

[Figure 3](#fig-marginal-3) presents the forest plot for the marginal effects of the corticosteroids on HRT-SE.

Results are presented as effect estimate of the marginal contrast and the ci.

suppfig-adrfs-rq…

## Other analyses

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

# Discussion

## Key results

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

## Limitations

These 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, whereas the corticosteroids were measured in the night urine sample only. 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[29](#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 average comparisons.

## Interpretation

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

In conclusion, in a study of…

# Funding

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

# Figures for main results

## Marginal comparisons

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| Figure 1: Marginal comparison results for |

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| Figure 2: Marginal comparison results for |

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| Figure 3: Marginal comparison results for |