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

# Abstract

* Authorship must follow the ICMJE’s criteria. Author names should be listed in ScholarOne and author contributions should be detailed in the cover letter (“Author A…”). Neither names nor contributions should appear in the blinded manuscript. Do not include conflicts of interest.
* 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.
* The length must be <4,000 words, excluding abstract, references, tables, figure captions, acknowledgments, and Supplementary Material.
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In the present study, we estimated associations between 1) non-persistent endocrine disruptors (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.

* Brief review of the literature to summarize current knowledge.
  + Acknowledge inconsistencies.
  + For each study, indicate whether it was observational or experimental, and note key characteristics of study populations or experimental models.
* Explain the scientific background and rationale for the investigation being reported.
  + Identify knowledge gaps addressed by the current study.
* Provide context for the study: include information on exposures and outcomes, and why they are relevant to environmental health.

# 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[1](#ref-VrijheidSlamaRobinson:2014). It consists of six existing population-based birth cohort studies across Europe: BiB (Born in Bradford, UK)[2](#ref-WrightSmallRaynor:2013), EDEN (Study of determinants of pre- and postnatal developmental, France)[3](#ref-HeudeForhanSlama:2016), INMA (Environment and Childhood, Spain)[4](#ref-GuxensBallesterEspada:2012), KANC (Kaunas Cohort, Lithuania)[5](#Xd30c40380c9e99bac70b7fa3b0ada5ae8dec3e4), MoBa (The Norwegian Mother and Child Cohort Study, Norway)[6](#ref-MagnusIrgensHaug:2006), and Rhea (Mother–Child Cohort in Crete, Greece)[7](#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[8](#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[9](#ref-TextorvanderZanderGilthorpe:2016) and ggdag[10](#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**?@tbl-info-chems**. The laboratory protocols for the analysis are described elsewhere[11](#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**?@tbl-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[12](#ref-MarcosRenauCasals:2014),[13](#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)[14](#ref-RuedaFanMcCandliss:2004). Further information can be found in[8](#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)[15](#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 20% of missings within each cohort and 10% of missings overall. Information about the LLOQ for the corticosteroids is provided in**?@tbl-lloq-mets**. The remaining missing values were imputed using kNN from the VIM R package[16](#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[17](#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[18](#ref-lazar2015imputelcmd). Information about the lower limits of detection can be found in[11](#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[19](#ref-Greifer:2023). This methods estimates weights by minimizing an energy statistic related to covariate balance[20](#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[21](#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[22](#ref-BartlettPartnoy:2020).

To estimate the average contrasts, we used the avg\_comparisons function from the marginaleffects R package[23](#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[24](#ref-Zeileis:2004),[25](#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

* Give reasons for non-participation at each stage.

## Descriptive data

## Outcome data

## Main results

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

## Other analyses

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

# Discussion

## Key results

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

### What does the literature say?

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

## Limitations

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

Some limitations:

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

## Interpretation

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

## Generalisability

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

# Funding

# References

1. Vrijheid M, Slama R, Robinson O, et al. The human early-life exposome (HELIX): Project rationale and design. *Environ Health Perspect*. 2014;122(6):535-544. doi:[10.1289/ehp.1307204](https://doi.org/10.1289/ehp.1307204)

2. Wright J, Small N, Raynor P, et al. Cohort Profile: The Born in Bradford multi-ethnic family cohort study. *International Journal of Epidemiology*. 2013;42(4):978-991. doi:[10.1093/ije/dys112](https://doi.org/10.1093/ije/dys112)

3. Heude B, Forhan A, Slama R, et al. Cohort Profile: The EDEN mother-child cohort on the prenatal and early postnatal determinants of child health and development. *International Journal of Epidemiology*. 2016;45(2):353-363. doi:[10.1093/ije/dyv151](https://doi.org/10.1093/ije/dyv151)

4. Guxens M, Ballester F, Espada M, et al. Cohort Profile: The INMA—INfancia y Medio Ambiente—(Environment and Childhood) Project. *International Journal of Epidemiology*. 2012;41(4):930-940. doi:[10.1093/ije/dyr054](https://doi.org/10.1093/ije/dyr054)

5. Grazuleviciene R, Danileviciute A, Nadisauskiene R, Vencloviene J. Maternal Smoking,GSTM1 and GSTT1 Polymorphism and Susceptibility to Adverse Pregnancy Outcomes. *International Journal of Environmental Research and Public Health*. 2009;6(3, 3):1282-1297. doi:[10.3390/ijerph6031282](https://doi.org/10.3390/ijerph6031282)

6. Magnus P, Irgens LM, Haug K, et al. Cohort profile: The Norwegian Mother and Child Cohort Study (MoBa). *International Journal of Epidemiology*. 2006;35(5):1146-1150. doi:[10.1093/ije/dyl170](https://doi.org/10.1093/ije/dyl170)

7. Chatzi L, Plana E, Daraki V, et al. Metabolic Syndrome in Early Pregnancy and Risk of Preterm Birth. *American Journal of Epidemiology*. 2009;170(7):829-836. doi:[10.1093/aje/kwp211](https://doi.org/10.1093/aje/kwp211)

8. Maitre L, Bont J de, Casas M, et al. Human Early Life Exposome (HELIX) study: A European population-based exposome cohort. *BMJ Open*. 2018;8(9):e021311. doi:[10.1136/bmjopen-2017-021311](https://doi.org/10.1136/bmjopen-2017-021311)

9. Textor J, van der Zander B, Gilthorpe MS, Liśkiewicz M, Ellison GT. Robust causal inference using directed acyclic graphs: The R package “dagitty.” *International Journal of Epidemiology*. 2016;45(6):1887-1894. doi:[10.1093/ije/dyw341](https://doi.org/10.1093/ije/dyw341)

10. Barrett M. Ggdag: Analyze and Create Elegant Directed Acyclic Graphs. Published online 2023. <https://github.com/r-causal/ggdag>

11. Haug LS, Sakhi AK, Cequier E, et al. In-utero and childhood chemical exposome in six European mother-child cohorts. *Environment International*. 2018;121:751-763. doi:[10.1016/j.envint.2018.09.056](https://doi.org/10.1016/j.envint.2018.09.056)

12. Marcos J, Renau N, Casals G, Segura J, Ventura R, Pozo OJ. Investigation of endogenous corticosteroids profiles in human urine based on liquid chromatography tandem mass spectrometry. *Analytica Chimica Acta*. 2014;812:92-104. doi:[10.1016/j.aca.2013.12.030](https://doi.org/10.1016/j.aca.2013.12.030)

13. Gomez-Gomez A, Pozo OJ. Determination of steroid profile in hair by liquid chromatography tandem mass spectrometry. *Journal of Chromatography A*. 2020;1624:461179. doi:[10.1016/j.chroma.2020.461179](https://doi.org/10.1016/j.chroma.2020.461179)

14. Rueda MR, Fan J, McCandliss BD, et al. Development of attentional networks in childhood. *Neuropsychologia*. 2004;42(8):1029-1040. doi:[10.1016/j.neuropsychologia.2003.12.012](https://doi.org/10.1016/j.neuropsychologia.2003.12.012)

15. Sunyer J, Esnaola M, Alvarez-Pedrerol M, et al. Association between Traffic-Related Air Pollution in Schools and Cognitive Development in Primary School Children: A Prospective Cohort Study. *PLOS Medicine*. 2015;12(3):e1001792. doi:[10.1371/journal.pmed.1001792](https://doi.org/10.1371/journal.pmed.1001792)

16. Kowarik A, Templ M. Imputation with the R Package VIM. *Journal of Statistical Software*. 2016;74:1-16. doi:[10.18637/jss.v074.i07](https://doi.org/10.18637/jss.v074.i07)

17. Lüdecke D, Ben-Shachar MS, Patil I, Waggoner P, Makowski D. performance: An R package for assessment, comparison and testing of statistical models. *Journal of Open Source Software*. 2021;6(60):3139. doi:[10.21105/joss.03139](https://doi.org/10.21105/joss.03139)

18. Lazar C. imputeLCMD: A collection of methods for left-censored missing data imputation. *R package, version*. 2015;2.

19. Greifer N. *WeightIt: Weighting for Covariate Balance in Observational Studies*.; 2023.

20. Huling JD, Greifer N, Chen G. Independence Weights for Causal Inference with Continuous Treatments. *Journal of the American Statistical Association*. 2023;0(0):1-14. doi:[10.1080/01621459.2023.2213485](https://doi.org/10.1080/01621459.2023.2213485)

21. Greifer N. *Cobalt: Covariate Balance Tables and Plots*.; 2023.

22. Bartlett RP, Partnoy F. The Ratio Problem. *SSRN Journal*. Published online 2020. doi:[10.2139/ssrn.3605606](https://doi.org/10.2139/ssrn.3605606)

23. Arel-Bundock V. *Marginaleffects: Predictions, Comparisons, Slopes, Marginal Means, and Hypothesis Tests*.; 2023. <https://marginaleffects.com/>

24. Zeileis A. Econometric computing with HC and HAC covariance matrix estimators. *Journal of Statistical Software*. 2004;11(10):1-17. doi:[10.18637/jss.v011.i10](https://doi.org/10.18637/jss.v011.i10)

25. Zeileis A, Köll S, Graham N. Various versatile variances: An object-oriented implementation of clustered covariances in R. *Journal of Statistical Software*. 2020;95(1):1-36. doi:[10.18637/jss.v095.i01](https://doi.org/10.18637/jss.v095.i01)

1. Vrijheid M, Slama R, Robinson O, et al. The human early-life exposome (HELIX): Project rationale and design. *Environ Health Perspect*. 2014;122(6):535-544. doi:[10.1289/ehp.1307204](https://doi.org/10.1289/ehp.1307204)

2. Wright J, Small N, Raynor P, et al. Cohort Profile: The Born in Bradford multi-ethnic family cohort study. *International Journal of Epidemiology*. 2013;42(4):978-991. doi:[10.1093/ije/dys112](https://doi.org/10.1093/ije/dys112)

3. Heude B, Forhan A, Slama R, et al. Cohort Profile: The EDEN mother-child cohort on the prenatal and early postnatal determinants of child health and development. *International Journal of Epidemiology*. 2016;45(2):353-363. doi:[10.1093/ije/dyv151](https://doi.org/10.1093/ije/dyv151)

4. Guxens M, Ballester F, Espada M, et al. Cohort Profile: The INMA—INfancia y Medio Ambiente—(Environment and Childhood) Project. *International Journal of Epidemiology*. 2012;41(4):930-940. doi:[10.1093/ije/dyr054](https://doi.org/10.1093/ije/dyr054)

5. Grazuleviciene R, Danileviciute A, Nadisauskiene R, Vencloviene J. Maternal Smoking,GSTM1 and GSTT1 Polymorphism and Susceptibility to Adverse Pregnancy Outcomes. *International Journal of Environmental Research and Public Health*. 2009;6(3, 3):1282-1297. doi:[10.3390/ijerph6031282](https://doi.org/10.3390/ijerph6031282)

6. Magnus P, Irgens LM, Haug K, et al. Cohort profile: The Norwegian Mother and Child Cohort Study (MoBa). *International Journal of Epidemiology*. 2006;35(5):1146-1150. doi:[10.1093/ije/dyl170](https://doi.org/10.1093/ije/dyl170)

7. Chatzi L, Plana E, Daraki V, et al. Metabolic Syndrome in Early Pregnancy and Risk of Preterm Birth. *American Journal of Epidemiology*. 2009;170(7):829-836. doi:[10.1093/aje/kwp211](https://doi.org/10.1093/aje/kwp211)

8. Maitre L, Bont J de, Casas M, et al. Human Early Life Exposome (HELIX) study: A European population-based exposome cohort. *BMJ Open*. 2018;8(9):e021311. doi:[10.1136/bmjopen-2017-021311](https://doi.org/10.1136/bmjopen-2017-021311)

9. Textor J, van der Zander B, Gilthorpe MS, Liśkiewicz M, Ellison GT. Robust causal inference using directed acyclic graphs: The R package “dagitty.” *International Journal of Epidemiology*. 2016;45(6):1887-1894. doi:[10.1093/ije/dyw341](https://doi.org/10.1093/ije/dyw341)

10. Barrett M. Ggdag: Analyze and Create Elegant Directed Acyclic Graphs. Published online 2023. <https://github.com/r-causal/ggdag>

11. Haug LS, Sakhi AK, Cequier E, et al. In-utero and childhood chemical exposome in six European mother-child cohorts. *Environment International*. 2018;121:751-763. doi:[10.1016/j.envint.2018.09.056](https://doi.org/10.1016/j.envint.2018.09.056)

12. Marcos J, Renau N, Casals G, Segura J, Ventura R, Pozo OJ. Investigation of endogenous corticosteroids profiles in human urine based on liquid chromatography tandem mass spectrometry. *Analytica Chimica Acta*. 2014;812:92-104. doi:[10.1016/j.aca.2013.12.030](https://doi.org/10.1016/j.aca.2013.12.030)

13. Gomez-Gomez A, Pozo OJ. Determination of steroid profile in hair by liquid chromatography tandem mass spectrometry. *Journal of Chromatography A*. 2020;1624:461179. doi:[10.1016/j.chroma.2020.461179](https://doi.org/10.1016/j.chroma.2020.461179)

14. Rueda MR, Fan J, McCandliss BD, et al. Development of attentional networks in childhood. *Neuropsychologia*. 2004;42(8):1029-1040. doi:[10.1016/j.neuropsychologia.2003.12.012](https://doi.org/10.1016/j.neuropsychologia.2003.12.012)

15. Sunyer J, Esnaola M, Alvarez-Pedrerol M, et al. Association between Traffic-Related Air Pollution in Schools and Cognitive Development in Primary School Children: A Prospective Cohort Study. *PLOS Medicine*. 2015;12(3):e1001792. doi:[10.1371/journal.pmed.1001792](https://doi.org/10.1371/journal.pmed.1001792)

16. Kowarik A, Templ M. Imputation with the R Package VIM. *Journal of Statistical Software*. 2016;74:1-16. doi:[10.18637/jss.v074.i07](https://doi.org/10.18637/jss.v074.i07)

17. Lüdecke D, Ben-Shachar MS, Patil I, Waggoner P, Makowski D. performance: An R package for assessment, comparison and testing of statistical models. *Journal of Open Source Software*. 2021;6(60):3139. doi:[10.21105/joss.03139](https://doi.org/10.21105/joss.03139)

18. Lazar C. imputeLCMD: A collection of methods for left-censored missing data imputation. *R package, version*. 2015;2.

19. Greifer N. *WeightIt: Weighting for Covariate Balance in Observational Studies*.; 2023.

20. Huling JD, Greifer N, Chen G. Independence Weights for Causal Inference with Continuous Treatments. *Journal of the American Statistical Association*. 2023;0(0):1-14. doi:[10.1080/01621459.2023.2213485](https://doi.org/10.1080/01621459.2023.2213485)

21. Greifer N. *Cobalt: Covariate Balance Tables and Plots*.; 2023.

22. Bartlett RP, Partnoy F. The Ratio Problem. *SSRN Journal*. Published online 2020. doi:[10.2139/ssrn.3605606](https://doi.org/10.2139/ssrn.3605606)

23. Arel-Bundock V. *Marginaleffects: Predictions, Comparisons, Slopes, Marginal Means, and Hypothesis Tests*.; 2023. <https://marginaleffects.com/>

24. Zeileis A. Econometric computing with HC and HAC covariance matrix estimators. *Journal of Statistical Software*. 2004;11(10):1-17. doi:[10.18637/jss.v011.i10](https://doi.org/10.18637/jss.v011.i10)

25. Zeileis A, Köll S, Graham N. Various versatile variances: An object-oriented implementation of clustered covariances in R. *Journal of Statistical Software*. 2020;95(1):1-36. doi:[10.18637/jss.v095.i01](https://doi.org/10.18637/jss.v095.i01)