On some aspects of robust HC-type covariance estimators for meta analyses

Markus Pauly
joint work with **Thilo Welz** (Daichii) and many other great colleagues (see below)

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Why to use HC-type estimators in meta-analysis?

- They have a long tradition in heteroscedastic settings, particularly for linear models (White, 1980[1], MacKinnon & White, 1985).

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- However, you don't meet them very often in biostatistics

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What we did

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- the classical random-effect meta-analysis setting (Welz, 2018, Pauly & Welz, 2018)
- 'truncated versions' of it to deal with Pearson correlations (Welz, Doebler, Pauly, 2022)
- univariate mixed-effects meta regressions without and with interaction (Welz & Pauly, 2020, Welz et al., 2022, Knop et al., 2023)
- bivariate mixed-effects meta regression (Welz et al., 2023)

How do these HC-estimators look like?

Consider a univariate mixed-effects meta-regression model:

$$y_i = \beta_0 + \beta_1 x_{i1} + \ldots + \beta_m x_{im} + u_i + \varepsilon_i, \; i = 1, \ldots, K$$

where $u_i \sim N(0, \tau^2)$, $\varepsilon_i \sim N(0, \sigma_i^2)$ are independent, $K > m$.
Matrix notation:

$$\mathbf{y} = \boldsymbol{X}\boldsymbol{\beta} + \mathbf{u} + \boldsymbol{\varepsilon}$$

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Weighted least squares estimator:

$$\hat{\boldsymbol{\beta}} = (\mathbf{X}'\hat{\mathbf{W}}\mathbf{X})^{-1}\mathbf{X}'\hat{\mathbf{W}}\mathbf{y},$$

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To construct confidence regions or tests for $\boldsymbol{\beta}$, e.g.

$$H_0 : \{\beta_j = 0\} \text{ vs. } H_1 : \{\beta_j \neq 0\}$$

we need 'good' covariance estimators $\hat{\boldsymbol{\Sigma}} = \widehat{cov}(\hat{\boldsymbol{\beta}})$

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For fixed-effects regressions $\mathbf{y} = \boldsymbol{X}\beta + \varepsilon$, White (1980) suggested the HC_0-type estimator

$$\hat{\mathbf{\Sigma}}_{HC_0} = (\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}'\hat{\mathbf{\Omega}}_0\mathbf{X}(\mathbf{X}'\mathbf{X})^{-1},$$

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As HC_0 often leads to liberal results, there exist refinements $HC_1 - HC_5$ for the fixed effects model (MacKinnon & White, 1985, Long & Ervin, 2000, Cribari-Neto, 2004, Cribari-Neto et al., 2007), where $\hat{\boldsymbol{\Omega}}_0$ is replaced by

$$\hat{\boldsymbol{\Omega}}_i = diag((1 - x_{jj})^{-\lambda_i})_{j=1}^K \cdot \mathrm{diag}(\hat{\varepsilon}_j^2)_{j=1}^K,$$

where $x_{jj} = j$-th diagonal element of $\mathbf{X}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}'$ and which differ in the exponents λ_i, e.g. $\lambda_2 = 1/2$ or $\lambda_3 = 1$.

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Motivation behind: Adjust for observations with large variances. x_{jj} stems from $Var(\hat{\varepsilon}_j) = \sigma^2(1 - x_{jj})$ in the homoscedastic case.

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Properties: Asymptotically consistent. HC_2 is even unbiased in the homoscedastic case. Often HC_3 or HC_4 recommended for small samples

How do these HC-estimators look like?

Previous definitions for fixed-effects model $\mathbf{y} = \boldsymbol{X}\beta + \varepsilon$.

Adjustments for mixed-effects model:

- $\hat{\mathbf{W}} = \text{diag}(\sigma_i^2 + \hat{\tau}^2)^{-1}$ appears in weighted LSE
- $\hat{\boldsymbol{\beta}} = (\mathbf{X}'\hat{\mathbf{W}}\mathbf{X})^{-1}\mathbf{X}'\hat{\mathbf{W}}\mathbf{y}$
- New hat matrix: $\mathbf{X}(\mathbf{X}'\hat{\mathbf{W}}\mathbf{X})^{-1}\mathbf{X}'\hat{\mathbf{W}}$
- Gives new 'bread' in sandwich estimators for meta regression:

$$\hat{\boldsymbol{\Sigma}}_{HC_i} = (\mathbf{X}'\hat{\mathbf{W}}\mathbf{X})^{-1}\mathbf{X}'\hat{\mathbf{W}}\hat{\boldsymbol{\Omega}}_i\hat{\mathbf{W}}\mathbf{X}(\mathbf{X}'\hat{\mathbf{W}}\mathbf{X})^{-1}$$

What we studied and found out – univariate meta regression

- HC_0 and HC_1 are known in MA and were, e.g. studied in Viechtbauer et al. (2015) for meta regression with rather poor small K results.
- We introduced the $HC_2 - HC_5$ versions and analyzed inference procedures based upon and
- compared its behaviour with the gold-standard (untruncated) Knapp-Hartung approach

What we studied and found out – univariate meta regression

- In particular, for testing $H_0 : \{\beta_j = 0\}$ vs. $H_1 : \{\beta_j \neq 0\}$ we (a) proved the asymptotic validity of t-type tests

$$\mathbf{1}\left(\hat{\beta}_j / \hat{\boldsymbol{\Sigma}}_{jj}^{1/2} > t_{K-m-1,1-\frac{\alpha}{2}}\right)$$

for all choices of HC-estimators

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  - Exception: Binary moderators ($K \leq 10$)

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  - Details for all 30k configurations can be found in Welz & Pauly (2020)

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- First findings for model $y_i = \beta_0 + \beta_1 x_{i1} + \beta_2 x_{i2} + \beta_{12} x_{i1} x_{i2} + u_i + \varepsilon_i$:
  - HC_0 and HC_1 too liberal
  - HC_2 too liberal wrt coverage for β_1, accurate for β_{12}
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  - Example plot (similar behaviour for $HC_2 - HC_5$):

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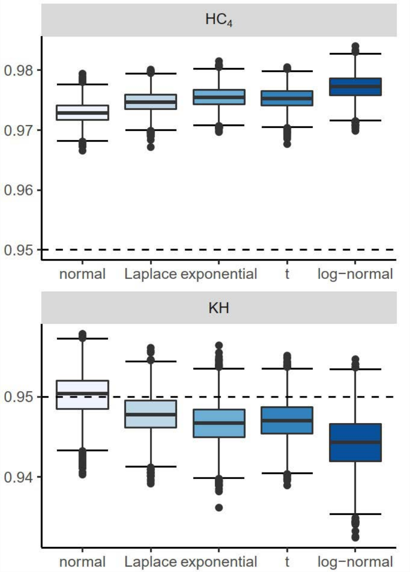

Figure 1: Coverage for β_{12} wrt different random effects distributions, $K = 10$

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  - Details for all $\approx 80k$ simulatoin settings in Welz, Knop, Friede & Pauly (2022, under major revision)
    (Need to run more simulations, e.g. investigate distribution of ε_i etc.)

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What we also studied and found out in bivariate meta analyses

- We also proposed new HC-type estimators for d-dimensional multivariate meta regression

$$\boldsymbol{Y}_i = \boldsymbol{X}_i \boldsymbol{\beta} + \boldsymbol{u}_i + \boldsymbol{\varepsilon}_i, \; i = 1, \ldots, K$$

- Form is similar to above

$$\widehat{\boldsymbol{\Sigma}}_{CR} = (\boldsymbol{X}'\widehat{\boldsymbol{W}}\boldsymbol{X})^{-1} \left(\sum_{i=1}^{K} \mathbf{X}_i' \widehat{\mathbf{W}}_i \widehat{\boldsymbol{\Omega}}_i \widehat{\mathbf{W}}_i \mathbf{X}_i \right) (\boldsymbol{X}'\widehat{\boldsymbol{W}}\boldsymbol{X})^{-1}$$

  while the choices of $\widehat{\boldsymbol{\Omega}}_i$ are a bit more complex and include so-called adjustment matrices. Here, they are often called CR-(cluster robust) estimators (e.g., Tipton & Pustejovsky 2015).
- Findings from Welz, Viechtbauer, Pauly (2023):
  - Refinements CR_3^* and CR_4^* (extensions of HC_3 and HC_4) most tempting for inference about $\boldsymbol{\beta}$ in the bivariate case
  - Considerable improvements wrt to the bias reduced linearization approach CR_2 considered in Tipton & Pustejovsky (2015) or Pustejovsky & Tipton (2018)

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- Need to study in more detail robustness wrt distributions
- Want fo find better solutions for constrained estimators such as Pearson correlation (one idea: refined or adaptive transformations) and non-metric outcome/moderators
- I apologize for omitting all practical motivations, the performed real data analyses and the concrete simulation settings and resulting graphics and tables – looking forward to discuss this with you during the coffee breaks :-)

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Our own MA References with robust covariance estimators

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