Robust Confidence Intervals for Meta-Regression with Correlated Moderators

Eric S. Knop[1], Markus Pauly[1], Tim Friede[23] and Thilo Welz[1]

January 17, 2022

Abstract Mixed-effects meta-regression models provide a powerful tool for evidence synthesis. In fact, modelling the study effect in terms of random effects and moderators not only allows to examine the impact of the moderators, but often leads to more accurate estimates of the involved parameters. Nevertheless, due to the often small number of studies on a specific research topic, interactions are often neglected in meta-regression. This was also the case in a recent meta-analysis in acute heart failure where a significant decline in death rate over calendar time was reported. However, we believe that an important interaction has been neglected. We therefore reanalyzed the data with a meta-regression model, including an interaction term of the median recruitment year and the average age of the patients. The model with interaction suggests different conclusions.

This led to the new research questions (i) how moderator interactions influence inference in mixed-effects meta-regression models and (ii) whether some inference methods are more reliable than others. Focusing on confidence intervals for main and interaction parameters, we address these questions in an extensive simulation study. We thereby investigate coverage and length of seven different confidence intervals under varying conditions. We conclude with some practical recommendations.

Keywords: Confidence Intervals; Heart failure; Meta-Analysis; Random effects; Robust covariance estimation

---

[1]Department of Statistics, TU Dortmund University
[2]Department of Medical Statistics, University of Göttingen
[3]DZHK (German Center for Cardiovascular Research), partner site Göttingen

1 Introduction

The aim of a meta-analysis is to synthesize the results of multiple studies regarding the same research question. A meta-regression combines the advantages of a linear regression model and a meta-analysis. On the one hand information from different studies is taken into account. On the other hand one is able to test not only for an overall effect, which is the case for most meta analyses, but also on effects of relevant study characteristics. The characteristics are used as covariates and often called moderators. In contrast to a usual regression model, the mixed-effects model assumes that the estimated treatment effect is influenced by two different types of uncertainty: First, the estimated effect of a single study is assumed to be different from the studies' true effect by a random error. Second, the analyzed studies are assumed to have different true effects caused by differences between the studies, the so called between-study heterogeneity. Therefore, the treatment effects of the studies differ from the treatment effect for the entire population. It is important to account for this additional variation when confidence intervals of moderators are calculated (Raudenbush, 2009).

A simulation study by Viechtbauer et al. (2015) showed that the choice of heterogeneity estimator had a neglectable impact on performed test results. However, Viechtbauer et al. (2015) also showed that when heterogeneity is present, the choice of estimator for the covariance of the vector of model coefficients has a large impact on test results. More specifically, in a model with only one moderator large differences in Type 1 error rates and the power of *t*-type tests were determined. Amongst others, tests based on a heteroscedasticity consistent (**HC**) estimate of the covariance matrix introduced by White (1980) and a modified covariance matrix estimate (**KH**) introduced by Knapp and Hartung (2003) (and also Sidik and Jonkman (2002)) were considered. The **HC** estimate is an established approach in econometrics. Because of its structure, it is also known as sandwich estimator and is used for robust inference. The **KH** estimate is common in biomedical meta-analyses. In Viechtbauer et al.'s (2015) simulation study, tests based on the **HC** estimator turned out to be too lib-

eral. In contrast, the test based on the **KH** estimate performed the best among all considered tests. Since their results are limited to special settings, Viechtbauer et al. (2015) suggested additional future simulation studies that consider, e.g., non-normal random effects, multiple covariates with multicollinearity and coverage probability of coefficients' confidence intervals. Welz and Pauly (2020) extended their research by comparing tests on the significance of the moderator based on six different versions of White's covariance matrix estimator and the Knapp-Hartung covariance matrix estimator for several random effect distributions. The six heteroscedasticity consistent covariance estimators are known as $\mathbf{HC}_0, ..., \mathbf{HC}_5$. In a simulation study they also found the **KH** based tests to perform the best compared to the **HC** estimators. Amongst the **HC** estimators the $\mathbf{HC}_3 - \mathbf{HC}_5$ based tests controlled the nominal significance level well and had power close to the **KH** based tests for larger number of studies. The distribution of the random effect turned out to have almost no effect on the results (Welz & Pauly, 2020).

In a recent meta-analysis, including meta-regression analyses, Kimmoun et al. (2021) analyzed mortality and readmission to hospital after acute heath failure. They found a statistically significant decline of death rates over calendar time. However, the median year of recruitment is correlated with the average age of the patients. This suggests that the observed trend might be explained by a neglected interaction of those variables.

Motivated by this meta-analysis, the current paper extends the research of Welz and Pauly (2020) in two directions. Firstly, confidence intervals are considered instead of hypothesis tests. Secondly, two moderators and their interaction term are modelled. Modelling interactions is required in situations where not only the influence of a moderator itself is of interest but its influence in the presence of other factors. Interactions are also helpful to assess the circumstances under which the influences of certain moderators on the estimated effect size are stronger or weaker (Aiken et al., 1991). Although modelling interaction terms is useful in providing additional insights, they are often neglected in meta-regression. However, neglecting existing interactions may dramatically alter conclusions drawn from quantitative research

synthesis. Beyond simulations, this will be exemplified by a detailed re-analysis of the Kimmoun et al. (2021) study.

The methodological aim of this work is to determine the performance of confidence intervals based on the seven covariance estimators $\mathbf{HC_0} - \mathbf{HC_5}$ and $\mathbf{KH}$ in extensive simulations. On the one hand, it is investigated whether the confidence intervals of a single moderator's coefficient perform different in presence of an interaction. On the other hand, confidence intervals for the interaction coefficient itself are considered. For this more complex models it is of interest whether the estimators have the same properties as in the univariate model. The focus was additionally set on situations where the $\mathbf{KH}$ estimator does not perform the best among the considered estimators.

The work is structured as follows. In Section 2 the motivating example, a cardiological study by Kimmoun et al. (2021) regarding acute heart failure, is introduced and re-analyzed. It is explained why it can be essential to consider models with more than one moderator and interaction. The statistical methods used in the example and for the simulation study are presented in Section 3. These include the mixed-effects meta-regression model in general, seven covariance estimators, estimators for model parameters, estimators for the mean difference and confidence intervals. The set-up of the simulation study is explained in Section 4 and the obtained results are presented and discussed in Section 5. In Section 6 conclusions from the analysis are drawn and an outlook on further research is given.

2 Motivating Example

Acute heart failure (AHF) is defined as a rapid onset of signs and symptoms of heart failure. It is a potentially life-threatening disease, which often requires hospitalization and medical treatment. However, there are no well-known therapies that substantially increase the chance of long-term survival. Admissions because of AHF often result in readmission to hospital or death of the patient (Kurmani & Squire, 2017).

For this reason readmission and death frequencies after discharge are frequently used outcome measures in clinical trials on AHF (Ponikowski et al., 2020).

To assess whether the treatment of AHF improved over the last decades, Kimmoun et al. (2021) analyzed 285 studies (243 surveys and 42 clinical trials) using meta-analyses. In the following we briefly summarize the information provided by the studies with focus on the variables that are important for our purpose. For more information on the data we refer to Kimmoun et al. (2021); the authors made their dataset publicly available.

The studies were published between 1998 and 2017 and carried out all over the world, but mostly in North America (134), Europe (123) and Asia (54). Outcome measures were 30-day and 1-year readmission and death rates. Furthermore, study characteristics like the year of recruitment, the number of patients for the follow-up and the average age of the patients were reported. Other variables provided information about the medication and medical history of the patients.

A major finding of the analysis of Kimmoun et al. (2021) was a significant decline in the 30-day and 1-year mortality over calendar time. The decline is shown in the left panel of Figure 1 (adopted from Figures 2B & 1A in Kimmoun et al., 2021). A meta-regression with the respective one-year death rate as outcome variable and the year of recruitment as the only explanatory variable was conducted. The one-year odds ratio (OR) amounts to 0.86 (95%-CI: $(0.77 - 0.96)$). However, significant correlations of study characteristics like the average age with the recruitment year were observed as well. In the right plot of Figure 1 it is shown that the average age of the participants decreased by 1.56 every ten years. Therefore, it is of interest how the effect of the recruitment year changes in a model where the mean age and their interaction are included as well.

For the purpose of illustration, we considered a mixed-effects meta-regression model, where we use centered explanatory variables to reduce the impact of multicollinearity. In the model the (logit transformed) one-year mortality is regressed on the average

age, the year of recruitment and their interaction. While the mean age has a significant effect on the one-year death rate (OR: 1.39, 95%-CI: (1.24, 1.57)) the year of recruitment turned out to be not significant (OR: 0.93, 95%-CI: (0.83, 1.05)) in this bivariate meta-regression model with interaction. The predicted effect of each explanatory variable at median level of the respective other variable is shown in Figure 2. The interaction term is significant at level 0.05 as well (OR: 0.84, 95%-CI: (0.71, 0.99)). Hence, fitting a mixed-effects meta-regression model with interaction reveals that the apparent time trend is captured by the changes in age over calendar time. This can already be seen in the left panel of Figure 2 and is contrary to the conclusion drawn by Kimmoun et al. (2021). Their observed time trend seems to stem from the neglected correlation between the average age and the recruitment year, which was not considered in their simpler meta-regression model with one moderator only.

To illustrate how strongly the neglection of an interaction term impacts the model we
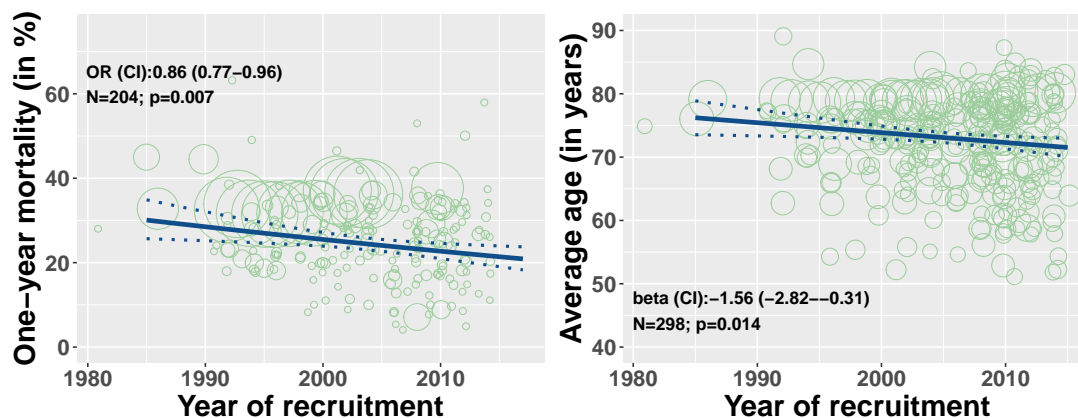
Figure 1: Two models from the analysis by Kimmoun et al. (2021): Meta-regression model of year of recruitment on the one-year mortality (left) and weighted linear model of the year of recruitment on the mean age with the logarithmized study size as weights (right). Point sizes are proportional to the respective study sizes. Straight lines are the models' prediction, dotted lines the corresponding 95% CI.

conducted a mimicking simulation study. To this end, we assumed that the estimated parameters in the model with interaction are the true parameters. Based on these estimates we generated 10,000 models and fitted them by (i) a model with two moderators and their interaction, (ii) a model with no interaction and (iii) a model with only one moderator. For all models we calculated 95% confidence intervals of the estimated moderators based on the estimators HC_0-HC_5 and KH. The full results are shown in Section A of the Supplement and can be summarized as follows:

In the model with only one moderator the intercept is covered by approximately 94% of all intervals (depending on the estimator), whereas the coefficient of the moderator is covered only in $75-77\%$ of all cases. For the model with two moderators the coverage of the moderators is between 91% and 95%. In the model with interaction all coefficients were covered in $93-96\%$ of all cases. Here it is noticeable that only the intervals based on HC_4 and HC_5 have a coverage above the nominal significance level of 95% for all coefficients.
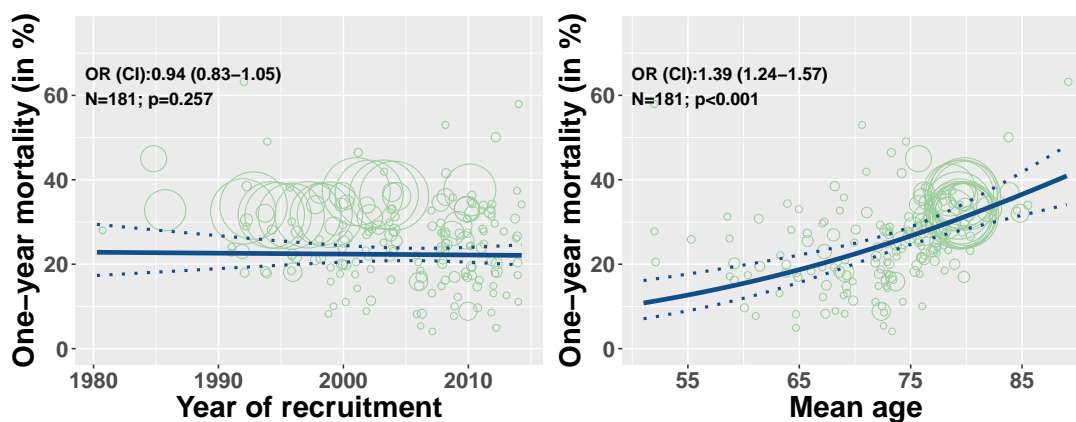
Figure 2: Trends of year of recruitment (left) and mean age (right) on the one-year mortality in a mixed-effects meta-regression model with these two moderators and their interaction. Point sizes are proportional to the respective study sizes. Straight lines are the models' prediction at the median level of the respective other explanatory variable, dotted lines the corresponding 95% CI.

Concluding, one of the main findings from Kimmoun et al. (2021), drawn from a univariate meta-regression model, is in doubt when a model with two moderators and their interaction term is considered. Hence, this example shows that for some data it is essential to consider more complex models in meta-regression. Moreover, the simulation of the example indicates that for a meta-regression model with inter-action the estimators HC_4 or HC_5 might be preferable compared to KH. Therefore, the simulation study by Welz and Pauly (2020) is extended to a model with two moderators and interaction in the sequel.

3 Statistical Methods

In this section the statistical methods used for the analysis of the study and the simulation study are explained. Vectors and matrices are denoted by bold letters to distinguish them from scalars.

3.1 The Mixed-Effects Meta-Regression Model

The study characteristics, which are used as covariates in the meta-regression model are called moderators. The moderators are denoted with $\boldsymbol{x}_j = (x_{j1}, ..., x_{jk})^\top$, where k is the number of studies and $j \in \{0, 1, .., m\}$, with m as the number of moderators (Huizenga et al., 2011). Functions of other moderators such as interactions of the form $x_{3i} = x_{1i}x_{2i}$ could be moderators themselves. The true effect of a single study $i \in \{1, ..., k\}$ is denoted with θ_i and modelled by

$$\theta_i = x_{0i}\beta_0 + x_{1i}\beta_1 + ... + x_{mi}\beta_m + u_i. \tag{1}$$

Usually $x_{0i} = 1$ for all $i = 1, ..., k$, so the model features an intercept β_0. The parameters $\beta_1, ..., \beta_m$ are the regression coefficients of the associated moderators with $m < k$. The deviation of the ith studies true effect θ_i and its linear predictor is

modelled by the random effect u_i. These are usually assumed to be i.i.d. normal with mean 0 and variance τ^2, $u_i \stackrel{iid}{\sim} \mathcal{N}(0, \tau^2)$. The estimated effect y_i of the true effect θ_i depends on the true effect as follows:

$$y_i = \theta_i + \epsilon_i, \quad \epsilon_i \sim \mathcal{N}(0, \sigma_i^2). \tag{2}$$

The error made within study i while estimating the true effect θ_i is denoted with ϵ_i. The variance σ_i^2 of ϵ_i is assumed to be known, although usually estimated from the data. Moreover, the ϵ_i's and u_i's are assumed to be mutually independent. Substituting (1) in (2) we receive the full mixed-effects meta-regression model

$$y_i = \boldsymbol{x}_i^\top \boldsymbol{\beta} + u_i + \epsilon_i = x_{0i}\beta_0 + x_{1i}\beta_1 + ... + x_{mi}\beta_m + u_i + \epsilon_i, \tag{3}$$

with $\boldsymbol{x}_i \in \mathbb{R}^{m+1}$ the vector of moderators in study i, $\boldsymbol{\beta} \in \mathbb{R}^{m+1}$ the corresponding vector of regression parameters and $u_i + \epsilon_i \sim \mathcal{N}(0, \tau^2 + \sigma_i^2)$ (Raudenbush, 2009). Since u_i and ϵ_i are the only random components on the right hand side of (3), the y_i are also normally distributed with $y_i \sim \mathcal{N}(\boldsymbol{x}_i^\top \boldsymbol{\beta}, \tau^2 + \sigma_i^2)$ (Hartung et al., 2008). In matrix notation the Model (3) can be rewritten as

$$\boldsymbol{y} = \boldsymbol{X}\boldsymbol{\beta} + \boldsymbol{u} + \boldsymbol{\epsilon}, \tag{4}$$

where

$$\boldsymbol{y} = \begin{pmatrix} y_1 \\ \vdots \\ y_k \end{pmatrix} \in \mathbb{R}^k, \boldsymbol{X} = \begin{pmatrix} x_{10} & \cdots & x_{1m} \\ \vdots & & \vdots \\ x_{k0} & \cdots & x_{km} \end{pmatrix} \in \mathbb{R}^{k\times(m+1)}, \boldsymbol{u} = \begin{pmatrix} u_1 \\ \vdots \\ u_k \end{pmatrix} \in \mathbb{R}^k \text{ and } \boldsymbol{\epsilon} = \begin{pmatrix} \epsilon_1 \\ \cdots \\ \epsilon_k \end{pmatrix} \in \mathbb{R}^k.$$

The rank $rk(\cdot)$ of the matrix $\boldsymbol{X}$ is assumed to be equal to $(m+1)$ and due to independence the covariance matrix $\boldsymbol{V}$ of $\boldsymbol{y}$ is given by $\boldsymbol{V} = \text{diag}(\tau^2 + \sigma_1^2, ..., \tau^2 + \sigma_k^2)$ (Huizenga et al., 2011).

3.2 Weighted-Least-Squares Estimator and Confidence Intervals

An estimator for the covariance matrix of $\boldsymbol{y}$ is given by $\hat{\boldsymbol{V}} = \mathrm{diag}(\hat{\tau}^2 + \sigma_1^2, ..., \hat{\tau}^2 + \sigma_k^2)$ where $\hat{\tau}^2$ is an approximately unbiased and consistent estimator of τ^2. In the simulation study we focus on continuous outcomes and therefore use the restricted maximum likelihood (REML) estimator (Fahrmeir et al., 2013, pp. 373-374) to estimate τ^2, since it has been recommended as a good choice in continuous settings (Veroniki et al., 2016).

According to Berkey et al. (1995), using $\widehat{\boldsymbol{W}} = \hat{\boldsymbol{V}}^{-1}$ as a weight matrix the weighted-least-squares estimator $\hat{\boldsymbol{\beta}}$ of $\boldsymbol{\beta}$ is given as

$$\hat{\boldsymbol{\beta}} = (\boldsymbol{X}^\top \widehat{\boldsymbol{W}} \boldsymbol{X})^{-1} \boldsymbol{X}^\top \widehat{\boldsymbol{W}} \boldsymbol{y}. \tag{5}$$

With a consistent estimator $\hat{\boldsymbol{\Sigma}} \in \mathbb{R}^{(m+1)\times(m+1)}$ for the covariance matrix of $\hat{\boldsymbol{\beta}}$, an approximate (1-α) confidence interval for a parameter β_j, $j \in \{0, 1, ..., m\}$, is given by

$$\left[\hat{\beta}_j \mp t_{(k-m-1),(1-\frac{\alpha}{2})} \sqrt{\hat{\boldsymbol{\Sigma}}_{jj}} \right], \tag{6}$$

where $t_{(k-m-1),(1-\frac{\alpha}{2})}$ is the $(1 - \frac{\alpha}{2})$ quantile of the t-distribution with $(k - m - 1)$ degrees of freedom and $\hat{\boldsymbol{\Sigma}}_{jj}$ the $(j + 1)th$ diagonal element of $\hat{\boldsymbol{\Sigma}}$ (Sterchi & Wolf, 2017).

3.3 Estimators for the Covariance of $\hat{\boldsymbol{\beta}}$

There are several ways to estimate the covariance of $\hat{\boldsymbol{\beta}}$ in (5)-(6). Here we focus on six heteroscedasticity consistent (**HC**) estimators denoted by $\mathbf{HC}_0$, $\mathbf{HC}_1$, ..., $\mathbf{HC}_5$ and the Knapp-Hartung (**KH**) estimator (Knapp & Hartung, 2003), which performed well in a meta-analytic context in previous research (Viechtbauer et al., 2015; Welz, 2018; Welz and Pauly, 2020; Welz et al., 2021). In the following section we introduce

$\mathbf{HC}_0$, $\mathbf{HC}_1$, $\mathbf{HC}_2$ according to MacKinnon and White (1985), $\mathbf{HC}_3$, $\mathbf{HC}_4$ according to Cribari-Neto (2004) and $\mathbf{HC}_5$ according to Cribari-Neto et al. (2007) if not stated otherwise.

The $\mathbf{HC}$ estimators are all based on $\mathbf{HC}_0$ which was originally introduced by White (1980) for an ordinary least squares (OLS) estimator. For the meta-regression model in (4) and the estimator $\hat{\boldsymbol{\beta}}$ given in Equation (5) the estimator $\mathbf{HC}_0$ can be written as

$$\mathbf{HC}_0 = (\boldsymbol{X}^\top \widehat{\boldsymbol{W}} \boldsymbol{X})^{-1} \boldsymbol{X}^\top \widehat{\boldsymbol{W}} \boldsymbol{E} \boldsymbol{D}_0 \boldsymbol{D}_0^\top \boldsymbol{E}^\top \widehat{\boldsymbol{W}} \boldsymbol{X} (\boldsymbol{X}^\top \widehat{\boldsymbol{W}} \boldsymbol{X})^{-1}, \tag{7}$$

where $\boldsymbol{D}_0 = \boldsymbol{I}_k$ and $\boldsymbol{E} = \operatorname{diag}(\boldsymbol{y} - \boldsymbol{X}\hat{\boldsymbol{\beta}})$ is a matrix containing the residuals $\hat{e}_i = y_i - \boldsymbol{x}_i \hat{\boldsymbol{\beta}}$ on its diagonal (Welz & Pauly, 2020).

How the formula for $\mathbf{HC}_0$ in (7) can be derived from the representation in MacKinnon and White (1985) is shown in Section B of the Supplement. The formulas for $\mathbf{HC}_1 - \mathbf{HC}_5$ can be derived analogously. Because the usual residuals tend to be too small, $\mathbf{HC}_0$ tends to underestimate the variance of the components of $\hat{\boldsymbol{\beta}}$. A simple adjustment of this estimator is given by $\mathbf{HC}_1 = k(k - m - 1)^{-1}\mathbf{HC}_0$, which takes the models' degrees of freedom $(k - m - 1)$ into account.

Another approach to fix this problem of $\mathbf{HC}_0$ is to modify the residuals themselves. One possible modification is to take the leverage scores h_{ii} into account. The h_{ii} denotes the ith diagonal element of the hat matrix $\boldsymbol{H} = \boldsymbol{X}(\boldsymbol{X}^\top \widehat{\boldsymbol{W}} \boldsymbol{X})^{-1}\boldsymbol{X}^\top \widehat{\boldsymbol{W}}$. By using $\tilde{e}_i = \hat{e}_i/\sqrt{1 - h_{ii}}$ instead of $\hat{e}_i$ there is more weight on residuals with higher leverage scores. A representation of $\mathbf{HC}_2$ is given by Equation (7) using $\boldsymbol{D}_2 = \operatorname{diag}((1 - h_{ii})^{-\frac{1}{2}})$ instead of $\boldsymbol{D}_0$. Under homoscedasticity of the ϵ_i the estimator $\mathbf{HC}_2$ is unbiased.

An estimator of similar form is $\mathbf{HC}_3$. It can be written by using $\boldsymbol{D}_3 = \operatorname{diag}((1 - h_{ii})^{-1})$ in place of $\boldsymbol{D}_0$ in Equation (7). The estimator $\mathbf{HC}_3$ introduced here is a close approximation of Efrons' jackknife estimator (Efron, 1982). A property of this estimator is that it takes the leverage scores stronger into account than $\mathbf{HC}_2$.

The following estimator, $\mathbf{HC}_4$, also differs from the former estimator in the way that it incorporates the leverage scores. The idea is to weight the residuals stronger, when the leverage score h_{ii} of a residual is relatively high compared to the average leverage score $\bar{h} = k^{-1} \sum_{i=1}^{k} h_{ii}$. This is done by using some δ_i as exponent for $(1 - h_{ii})$, where $\delta_i = \min\left\{4, h_{ii}/\bar{h}\right\}$. In this way the exponent $h_{ii}/\bar{h}$ is truncated at $\delta_i = 4$. The resulting estimator $\mathbf{HC}_4$ is given by Equation (7) with $\boldsymbol{D}_4 = \operatorname{diag}((1 - h_{ii})^{-\delta_i/2})$instead of $\boldsymbol{D}_0$, see Zimmermann et al. (2020) for a similar choice.

Finally, $\mathbf{HC}_5$ is defined similar to $\mathbf{HC}_4$ but uses exponents $\alpha_i = \min\left\{h_{ii}/\bar{h}, \max\left\{4, \eta \cdot h_{max}/\bar{h}\right\}\right\}$ instead of δ_i. Here, $h_{max} = \max\{h_{11}, ..., h_{kk}\}$ and $\eta \in (0, 1)$ is a predefined constant used as a tuning parameter. The simulation study of Cribari-Neto et al. (2007) suggests $\eta = 0.7$ as a reliable choice for finite samples. Notably α_i is only different from δ_i when $(\eta \cdot h_{max})/\bar{h} > 4$. In this situation α_i is not truncated at $\alpha_i = 4$ but at $\alpha_i = (\eta \cdot h_{max})/\bar{h}$. A representation of $\mathbf{HC}_5$ is given by Equation (7) plugging in $\boldsymbol{D}_5 = \operatorname{diag}((1 - h_{ii})^{-\alpha_i/2})$ for $\boldsymbol{D}_0$.

The Knapp-Hartung estimator for the mixed-effects meta-regression model was originally introduced by Knapp and Hartung (2003). It can be derived as follows. Let $\boldsymbol{P} = \boldsymbol{I} - \boldsymbol{X}(\boldsymbol{X}^\top \widehat{\boldsymbol{W}} \boldsymbol{X})^{-1} \boldsymbol{X}^\top \widehat{\boldsymbol{W}}$ and $s^2 = (k - m - 1)^{-1}(\boldsymbol{y}^\top \boldsymbol{P}^\top \widehat{\boldsymbol{W}} \boldsymbol{P} \boldsymbol{y}) = (k - m - 1)^{-1}(\boldsymbol{y}^\top \widehat{\boldsymbol{W}} \boldsymbol{P} \boldsymbol{y})$. Then the Knapp-Hartung estimator for $\operatorname{Cov}(\hat{\boldsymbol{\beta}})$ is given as

$$\mathbf{KH} = s^2 (\boldsymbol{X}^\top \widehat{\boldsymbol{W}} \boldsymbol{X})^{-1}.$$

3.4 Estimators for Standardized Mean Difference and its Variance

The standardized mean difference (SMD) is a frequently reported effect size measure in trials with metric outcome (Gan et al., 2004; Orci et al., 2016). Therefore, it is also commonly used as the dependent variable in a meta-regression model. In many applications, θ_i in Equation (1) is considered as the true SMD between the means of an experimental group and a control group in the ith study. An approximately

unbiased estimator y_i for θ_i can be derived from a modification of Hedges' g. It is introduced in the following part according to Hedges (1981).

To define g let $\bar{X}_i^E$ and $\bar{X}_i^C$ be the sample means of the experimental and control group in the ith study, S_i^E and S_i^C the corresponding standard deviations as well as n_i^E and n_i^C the corresponding group sizes. Given these quantities, Hedges' g for the ith study is defined as

$$g_i = \frac{\bar{X}_i^E - \bar{X}_i^C}{S_i}, \quad \text{where} \quad S_i^2 = \frac{(n_i^E - 1)(S_i^E)^2 + (n_i^C - 1)(S_i^C)^2}{n_i^E + n_i^C - 2}$$

denotes the pooled sample variance. Finally, the estimator for θ_i is given by

$$y_i = \left(1 - \frac{3}{4(n_i^E + n_i^C) - 9}\right) g_i. \tag{8}$$

Following Hedges and Olkin (1985, p. 86), the sampling variance of y_i can be approximated by

$$v_i = \frac{1}{n_i^E} + \frac{1}{n_i^C} + \frac{y_i^2}{2(n_i^E + n_i^C)}. \tag{9}$$

4 Simulation Set-Up

The setup of the simulation is based on previous research by Welz and Pauly (2020). While Welz and Pauly (2020) analyzed a mixed-effects meta-regression model with only one moderator, in this paper a model with two moderators and their interaction as given in (3) is considered for several adjustments. The dependent variable y_i is assumed to be the estimated standardized mean difference between an experimental and a control group in the ith study, $i = 1, ..., k$. All other simulation parameters are selected as follows:

Number of studies. k is chosen from $k \in \{6, 10, 20, 50\}$. Compared to Welz and Pauly (2020) we start with $k = 6$ instead of five studies as test runs with $k = 5$ often resulted in a rank-deficient matrix $\boldsymbol{X}$.

Sample Sizes. Within the studies we choose a balanced group design with $n_i^E = n_i^C =: n_i$ for the ith study. The study sizes themselves are unbalanced. For each $k \in \{6, 10, 20, 50\}$ three different vectors of group sizes are considered. In the situation $k = 6$ the first five studies contain the group sizes according to the following three vectors as used in Welz and Pauly's (2020) simulation: $\boldsymbol{n}_{15} = (6, 8, 9, 10, 42)^\top, \boldsymbol{n}_{25} = (16, 18, 19, 20, 52)^\top$ or $\boldsymbol{n}_{50} = (41, 43, 44, 45, 77)^\top$. The size of the 6th study is set to the mean $\bar{n}$ of the corresponding vector, i.e. either 15, 25 or 50. For $k \in \{10, 20, 50\}$ the above vectors $\boldsymbol{n}_{15}, \boldsymbol{n}_{25}$ and $\boldsymbol{n}_{50}$ are repeated $k/5$ times and the resulting vector is used as the vector of study sizes.

Meta-Regression Models. The y_i are assumed to be influenced by two moderators and their interaction. The interaction is modelled as $x_{i12} := x_{i1} \cdot x_{i2}$. Thus, the model in Equation (3) is given as

$$y_i = \beta_1 x_{i1} + \beta_2 x_{i2} + \beta_{12} x_{i12} + u_i + \epsilon_i.$$

Possible adjustments for β_1, β_2 and β_{12} are 0, 0.2 and 0.5. Additionally, the situation $\beta_{12} = -0.5$ is considered in order to check whether the estimates differ for a negative coefficient. The ϵ_i´s are assumed to follow a $\mathcal{N}(0, \sigma_i^2)$ distribution.

Distributions for the Moderators. The moderators x_{i1} and x_{i2} are sampled from a joint normal distribution

$$\begin{pmatrix} x_{i1} \\ x_{i2} \end{pmatrix} \sim \mathcal{N}\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} 1 & \rho \\ \rho & 1 \end{pmatrix} \right),$$

where ρ is the correlation between x_{i1} and x_{i2}. Examined adjustments are the situations of no correlation $\rho = 0$, small correlation $\rho = 0.2$, large correlation $\rho = 0.5$ and large negative correlation $\rho = -0.5$ (Cohen, 1988).

Distributions for the Random Effects. Contributing to the discussion *"When should meta-analysis avoid making hidden normality assumptions?"* (Jackson and White, 2018; Pauly and Welz, 2018; Röver and Friede, 2018) we consider different

distributions for the u_i's: The random effects are chosen as $u_i = \sqrt{\tau^2}q_i$, where $\tau^2 \in \{0.1, ..., 0.9\}$ and the q_i's are independently sampled from either a standard normal- or a standardized exponential-, Laplace-, log-normal- or t_3-distribution. Here t_3 denotes the t distribution with three degrees of freedom. In detail, the standard normally distributed q_i's are sampled from $\mathcal{N}(0, 1)$. If q_i is drawn from a standardized exponential distribution, then $q_i := a_i - 1$ were $a_i \sim Exp(1)$. The q_i's following a standardized Laplace distribution, are generated via $q_i = (a_i - b_i)/\sqrt{2}$ where $a_i, b_i \sim Exp(1)$ are sampled independently. For the q_i's following a standardized log-normal distribution, q_i is set to

$$q_i = \frac{\exp(z_i) - \exp(1/2)}{\sqrt{\exp(1)(\exp(1) - 1)}}$$

with $z_i \sim \mathcal{N}(0, 1)$. Finally, q_i's following a standardized t_3 distribution, are set $q_i = t_i/\sqrt{3}$ with $t_i \sim t_3$. The standardization of the q_i's ensures that the corresponding u_i's all have expectation $\mathrm{E}(u_i) = 0$ and variance $\mathrm{Var}(u_i) = \tau^2$. Note, that if u_i is not normally distributed, the y_i are not normally distributed and the quantile $t_{(k-m-1),(1-\frac{\alpha}{2})}$ used in (6) is not correct either. Nevertheless, results by Kontopantelis and Reeves (2012) suggest that the distribution of the study effect has almost no impact on the resulting confidence intervals. Therefore, the quantile of the t-distribution is used for this simulation as well.

Effect Size Generation. Using one of those random effects, the true effect of the ith study θ_i is calculated by using Equation (1). The estimated effect y_i is generated according to the modified Hedges estimator (8), where g_i is calculated according to

$$g_i = \frac{\phi_i}{\sqrt{X_i/(2n_i - 2)}},$$

$\phi_i \sim \mathcal{N}(\theta_i, 2/n_i)$ and $X_i \sim \chi^2_{(2n_i-2)}$ are sampled. The sampling variance σ_i^2 of the y_i is estimated by applying Equation (9).

Combinations and Iterations. In total, there are $77\,760 = 3(\bar{n}) \times 4(k) \times 9(\tau^2) \times 3(\beta_1) \times 3(\beta_2) \times 4(\beta_{12}) \times 5(u_i) \times 4(\rho)$ different combinations of flexible parameters. For every combination of parameters the model is generated $N = 10\,000$ times.

With this choice of N the Monte-Carlo error of the empirical coverage probability is approximately 0.22% (Morris et al., 2019). For each model the estimators $\mathbf{HC}_0 - \mathbf{HC}_5$ and $\mathbf{KH}$ are calculated, where $\hat{\tau}^2$ is estimated using the REML estimator with a maximum of 5 000 iterations and a default step length of 0.5. Based on each estimator a 95% confidence interval is estimated for the coefficient β_1 of a single moderator and for the coefficient β_{12} of the interaction term. Since $\boldsymbol{x}_1$ and $\boldsymbol{x}_2$ have the same distribution, intervals for β_2 are not considered. The proportion of estimated confidence intervals that cover the true coefficient is used as an estimate of the coverage probability of the interval. As an estimate of the interval length, the average length of the estimated intervals is calculated.

5 Simulation Results

In confidence interval estimation two properties are relevant. First, it is of major importance that the actual coverage of the interval is at least equal to the nominal confidence level $(1 - \alpha)$. Second, we want to determine the interval, where the true parameter is included in with probability $(1 - \alpha) \cdot 100\%$, as precisely as possible. Therefore, the coverage and lengths of the simulated intervals for β_1 and β_{12} are compared in respect of the covariance estimators they are based on. Due to the high number of parameter adjustments not every adjustment is considered separately. Hence, the coverage and interval lengths of different settings are summarized by boxplots. That is, e.g., the boxplots in Section 5.1 based upon the results for every adjustment of $\beta_1, \beta_2, \beta_{12}, \rho, \tau^2$, u_i and $\bar{n}$ and thus consider the overall performance of the estimators. The aim of this section is to figure out, whether one estimator has a better overall performance compared to all other estimators. It is also of interest, whether there are any estimators that are outperformed by at least one other estimator in each situation. Because the intervals for β_1 and β_{12} performed similarly for the most estimators and parameter adjustments, only the results for the confidence intervals of β_1 are shown in detail. The differences to the intervals for β_{12}

are highlighted in Section 5.1, the full results for the intervals for β_{12} are shown in Section C the Supplement.

Since the number of studies k strongly affects the coverage and interval lengths (Section 5.2), the results are compared separately for each k. How the adjustments of other simulation parameters affect the coverage and interval length is discussed in Section 5.2. There it is of interest, whether the performance of a certain estimator differs from its overall performance for a special adjustment. For example, it is analyzed whether there is an estimator whose intervals have the best performance but only for large correlations. For ease of presentation "confidence interval" is abbreviated with CI in this section. The CIs based on $\mathbf{HC_0}$ are abbreviated with $\mathbf{HC_0}$-CI, the CIs based on other estimators in an analogous manner.

The analysis is conducted with the software `R` (R Core Team, 2020). For the boxplots also the packages `ggplot2` (Wickham, 2016), `reshape2` (Wickham, 2007), `grid` (R Core Team, 2020) and `gridExtra` (Auguie, 2017) are used. The code is provided as supplementary material.

5.1 Overall Performance of the Estimators

Confidence intervals for $\boldsymbol{\beta_1}$ – Coverage Probability. In Figure 3 the coverage of the CIs for β_1 are summarized using boxplots. Each plot reflects the results for a certain number of studies $k \in \{6, 10, 20, 50\}$. The individual boxplots contain the coverage of all intervals based on the respective estimator and k.

The coverage of the $\mathbf{HC_0}$-CIs ranges from 0.7708 to 0.8078 for $k = 6$. Although the coverage is growing in the number of studies k, the coverages of $\mathbf{HC_0}$-CIs are below the nominal confidence level $(1 - \alpha) = 0.95$ in every setting. For $k = 50$ the coverage ranges from 0.8932 to 0.9474. The $\mathbf{HC_1}$-CIs have higher median coverages than the $\mathbf{HC_0}$-CIs for all k. But only for 1.76% of the adjustments with $k = 50$ the coverage is above the nominal confidence level. Similarly, $\mathbf{HC_2}$-CIs have a higher median coverage than $\mathbf{HC_1}$-CIs. Nevertheless, the coverage is below the nominal

confidence level $(1 - \alpha) = 0.95$ for all adjustments with $k \in \{6, 10\}$ and in 94.68% of the adjustments with $k \in \{20, 50\}$. Thus, $\mathbf{HC_0} - \mathbf{HC_2}$ seem to be inappropriate choices of estimators regarding their CI coverage.
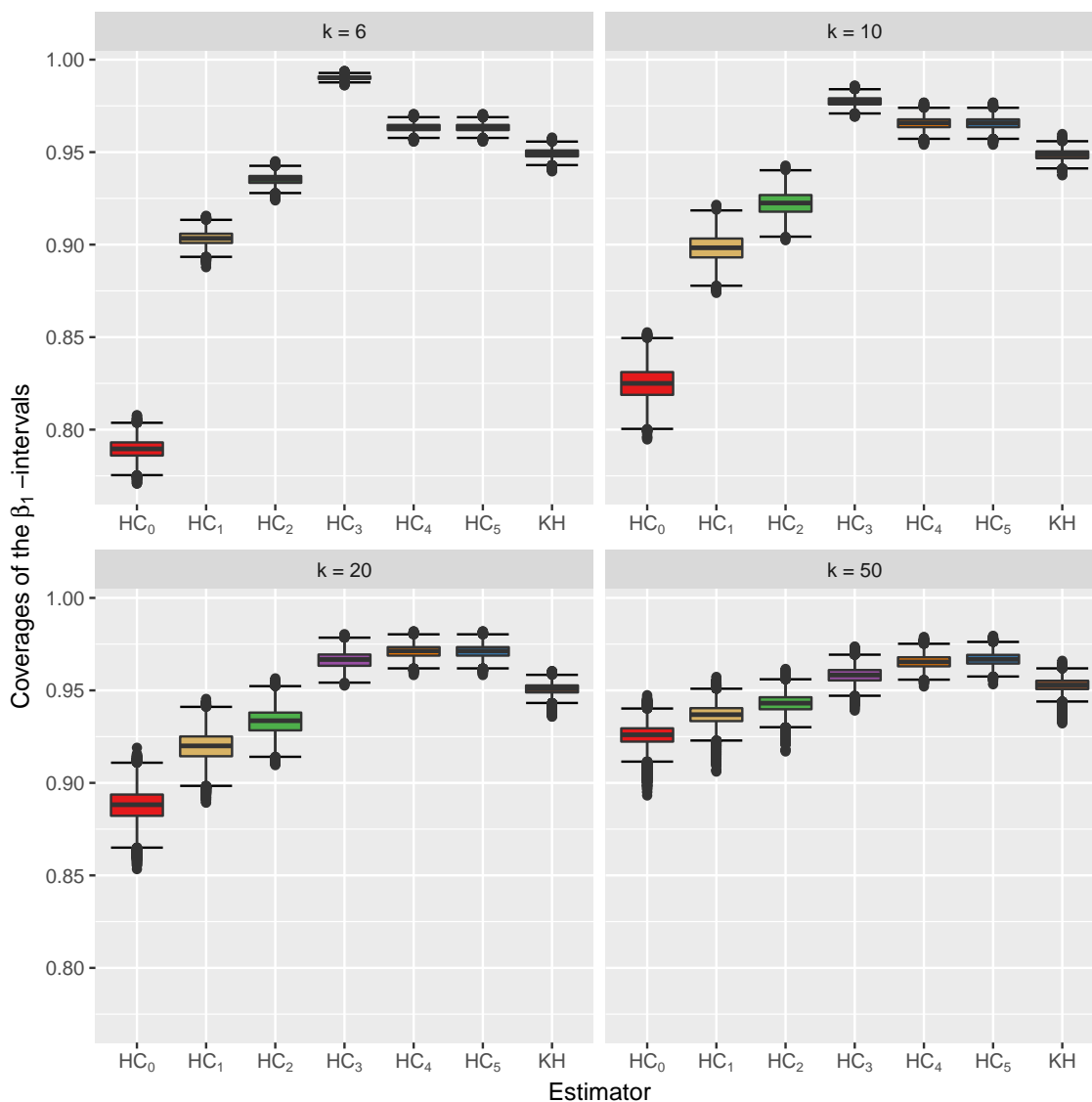
Figure 3: Coverage probabilities of the confidence intervals for the regression parameter β_1 based on the estimators $\mathbf{HC_0} - \mathbf{HC_5}$ and $\mathbf{KH}$ for different numbers of studies k.

$\mathbf{HC}_3 - \mathbf{HC}_5$ based CIs have a higher median coverage than 0.95 for all number of studies k. For $k = 6$ the $\mathbf{HC}_3$-CIs are the most conservative with coverages ranging from 0.9861 to 0.9939. However, the coverage of the $\mathbf{HC}_3$-CI is decreasing in k. Until $k = 20$ the coverage is above the nominal level for every setting but for $k = 50$ the coverage ranges from 0.9391 to 0.9737. But only in 0.06% of the settings the coverages are below the nominal confidence level. Thus, the coverage of the $\mathbf{HC}_3$-CI for β_1 is quite accurate.

The coverages of the $\mathbf{HC}_4$-CIs and $\mathbf{HC}_5$-CIs range from 0.9521 and 0.9533 to 0.9819 and 0.9819, respectively and differ only slightly in respect of the number of studies. Thereby, the $\mathbf{HC}_4$-CIs and $\mathbf{HC}_5$-CIs are the only ones, whose coverages are above the nominal confidence level $(1 - \alpha) = 0.95$ for every adjustment. Thus, regarding coverage these estimators are suitable choices for all number of studies k.

Among all estimators $\mathbf{KH}$-CIs show the closest coverages compared to the nominal confidence level 0.95. The coverage tends to be slightly higher for larger number of studies k. For $k = 6$ the actual coverage of the $\mathbf{KH}$-CI is below the nominal confidence level in 60% of the adjustments. In contrast, for $k = 50$ the coverage is below 0.95 for 18.55% of the settings. However, only in 0.03% of all settings the coverage of the $\mathbf{KH}$-CI is below 0.94. Although the $\mathbf{KH}$-CIs have slightly smaller coverages than the $\mathbf{HC}_3 - \mathbf{HC}_5$-CIs, their coverage is still acceptable for every adjustment.

Confidence intervals for $\boldsymbol{\beta_1}$ – Length. Boxplots of the corresponding interval lengths are shown in Figure 4. Note, that for $k = 6$ the lengths of the $\mathbf{HC}_3$-CIs have some extreme outliers with values up to 312.07, such as the lengths of the $\mathbf{HC}_5$-CIs for $k = 50$ with values up to 48.38. For a better visualization of the other results, outliers are not drawn in Figure 4. The full results are shown in part D of the Supplement. Moreover, the outliers are considered in Section 5.2 in more detail.

The interval lengths of all estimators are monotonically decreasing in the number of studies k. Lengths of the $\mathbf{KH}$-CIs range from 2.66 to 9.62 for $k = 6$ and from 0.21 to 0.73 for $k = 50$. Thereby, they are much shorter compared to the $\mathbf{HC}_4$- and $\mathbf{HC}_5$-CIs for all considered number of studies k. Except for $k = 50$, where the lengths of the

$\mathbf{HC_5}$-CIs tend to be longer, the lengths of the $\mathbf{HC_4}$- and $\mathbf{HC_5}$-CIs behave almost identically. For $k = 6$ the median length of the $\mathbf{KH}$-CIs is equal to 6.20, whereas it is equal to 9.34 for the $\mathbf{HC_4}$- and $\mathbf{HC_5}$-CIs. In the situation of $k = 50$ the median
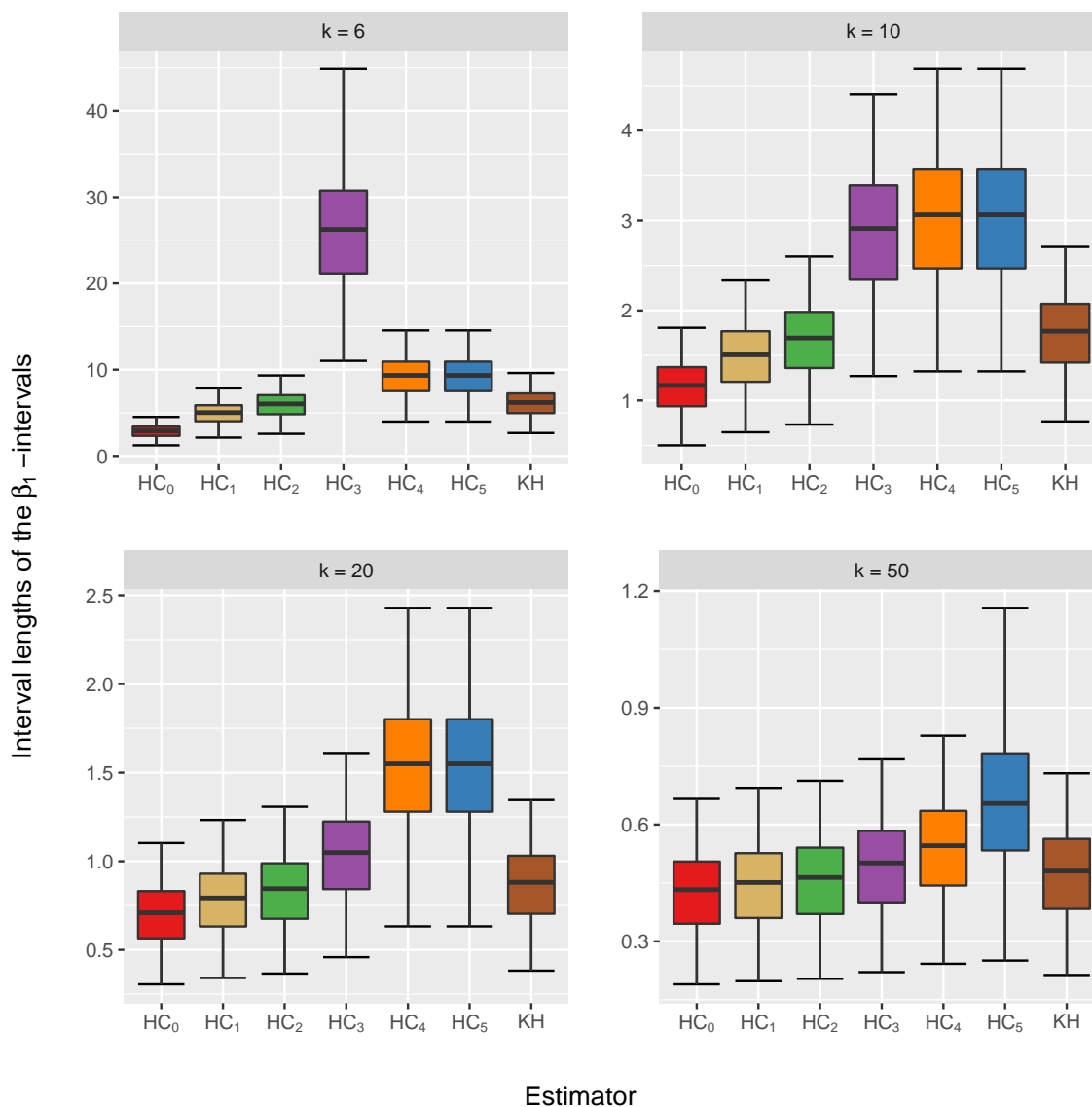
Figure 4: Lengths of the confidence intervals for the regression parameter β_1 based on the estimators $\mathbf{HC_0 - HC_5}$ and $\mathbf{KH}$ for different numbers of studies k without outliers.

interval length of **KH**-CIs is 0.48, which is smaller than the HC_4-CIs with 0.55 and the HC_5-CIs with 0.65.

Lengths of the HC_3-CIs are highly inflated for $k = 6$. The lower quartile is equal to 21.17 and the upper quartile's value is 30.76. For $k = 6$ the HC_4- and HC_5-CIs are shorter in the median than the HC_3-CIs, for the other values of k they are larger. With a value of 0.50 the median interval length of the HC_3-CIs is almost as short as the **KH**-CIs.

So in comparison of all estimators whose intervals have a suitable coverage, the **KH**-CIs are the shortest and therefore preferable. Since their CIs are much shorter for $k = 6$, HC_4 and HC_5 have the second best performance for small k. If the number of studies is equal to 10 or larger, HC_3 is preferable compared to all other **HC** estimators. Due to the higher lengths of the HC_5-CIs for $k = 50$ compared to the HC_4-CIs, HC_4 should be preferred over HC_5 for $k > 20$.

The $HC_0 - HC_2$ based CIs tend to be shorter than the **KH**-CIs for all k, whereas the HC_0-CIs have shorter median lengths than the HC_1-CIs, which again are shorter in the median than the HC_2-CIs. Nonetheless, due to their poor coverage they should not be used when calculating intervals of single parameters.

Performance of the intervals for β_{12} Compared to the intervals for β_1 the intervals for β_{12} tend to be longer for most estimators and adjustments of k. Exceptions are the lengths of the HC_0, HC_1, HC_3 and **KH** based CIs for $k = 50$. For the HC_0- and HC_1-CIs this means, that they perform worse for intervals for β_{12} compared to intervals for β_1, since also their coverages were lower for β_{12}. For the estimators $HC_2 - HC_5$ it is arguable whether they perform worse for interaction coefficients, since the coverage is improved. However, the relatively big difference in the interval lengths of the $HC_3 - HC_5$-CIs compared to the small gain of coverage indicates a worse performance compared to the intervals for β_1. When comparing CIs for β_1 to CIs for β_{12}, the coverage of the HC_2-CIs increased from below the nominal confidence level to above in every situation. Therefore, the HC_2-CIs perform better for interaction coefficients than for single coefficients, although their lengths are longer.

The **KH**-CIs perform worse for β_{12} than for β_1, since the share of coverages below 0.95 is higher for the intervals for β_{12} and the intervals are longer.

Summary of the overall performance Overall the results are similar to the model with one covariate (Welz & Pauly, 2020). Among all considered estimators the **KH** estimator is the most appropriate for a model with an interaction term since it performed the best for the coefficient of the single moderator and the interaction term. Though its coverage is improvable in some situations. Focusing only on the **HC** estimators, **HC**$_3$ is the best choice of estimator when the number of studies is not too small ($k \geq 10$). Otherwise **HC**$_4$ or **HC**$_5$ are preferable. For a larger number of studies **HC**$_4$ is a better choice compared to **HC**$_5$, due to the outliers that occur for the **HC**$_5$-CIs. **HC**$_2$ indeed performs as good as **HC**$_4$ for the interaction coefficient, but in practice it is unlikely that only an interaction but not the single moderators are of interest. Therefore, **HC**$_2$ is not recommendable for a model with interaction. **HC**$_0$ and **HC**$_1$ are not recommendable as well, since their performance is bad for both coefficients intervals.

5.2 Effects of Parameter Adjustments

This section will summarize how the coverages and interval lengths are affected by the adjustments of the flexible parameters. Since both coefficients are effected similar by most parameters they are considered together. We highlight the most important results and refer to the Supplement E for complete results.

Adjustments of the number of studies k Considered numbers of studies are 6, 10, 20 and 50. The lengths of both coefficients intervals are monotonically decreasing in the number of studies k. This is comprehensible since the $t_{(k-p-1),(1-\alpha)}$-quantile in Equation (6) is monotonically decreasing in k. The effect of the number of studies on coverage is not constant and depends on the considered covariance estimator. In general coverage tends towards the nominal level $1 - \alpha$ for increasing k. Therefore, for all estimators a large number of studies is preferable.

Adjustments of study size Small ($\bar{n} = 15$), medium ($\bar{n} = 25$) and large ($\bar{n} = 50$) group sizes are compared. For most covariance estimators the median coverage is slightly increasing in the study size. The corresponding interval lengths are decreasing as the study sizes increase for all k and estimators. This trend may be caused by the impact of n_i on v_i in Equation (9), which leads to decreasing standard errors in equation (6). Thus, overall larger studies lead to better confidence intervals, since both coverages and interval lengths are improved for larger study sizes.

Adjustments of τ^2 Coverages of both coefficients intervals are increasing slightly in the heterogeneity parameter τ^2 for all estimators and k. For a larger number of studies, the effect is stronger. The increasing coverages in τ^2 show that the model used in the simulation is adequate to model a study effect. On the other hand the interval lengths are increasing in τ^2 strongly. This result is explicable by the direct impact the value of τ^2 has on the variances of the coefficients and thus on the interval bounds.

Adjustments of β_1 Examined adjustments of β_1 are 0, 0.2 and 0.5. The CIs for β_{12} were not affected by these adjustments of β_1, whereas the CIs for β_1 have slightly lower coverage for $k \in \{20, 50\}$ studies and all estimators. Adjustments of β_1 had no influence on the interval lengths of the CIs for β_1 and β_{12}.

Adjustments of β_2 For β_2 the adjustments 0, 0.2 and 0.5 were considered as well. None of the intervals was affected by the adjustment of β_2 regarding the coverage or length. Mentionable is that the extreme interval lengths of the **HC$_3$**-CIs for $k = 6$ only occur for small values of β_2.

Adjustments of β_{12} Besides the adjustments 0, 0.2 and 0.5 for β_{12} the adjustment -0.5 was simulated as well, to check whether it differs from the 0.5 adjustment. This is neither the case for the interval lengths nor for the coverages of the CIs for β_1 and the CIs for β_{12}. However, the **HC$_4$**- and **HC$_5$**-CIs for β_1 have slightly lower coverage for a high absolute value of β_{12}. There were no clear general trends, but it is noticeable that most of the extreme outliers of **HC$_5$**-CIs occur for $\beta_{12} \in \{0, 0.2\}$.

Altogether the true values of the considered parameters do not have a strong impact on the intervals of any estimator. Therefore, there is no coefficient for which an estimator performs better or worse compared to the other estimators than in the overall results.

Adjustments of the correlation ρ Examined adjustments of ρ are 0, 0.2, 0.5 and -0.5. In additional simulations we also considered $\rho = 0.9$. The findings did not alter the results. For details see Section F of the supplement.

The sign of the correlation affects neither the coverages nor the interval lengths. Intervals for β_1 that are based on $\mathbf{HC}_3 - \mathbf{HC}_5$ tend to have a lower coverage for higher correlations, whereas CIs based on $\mathbf{HC}_0 - \mathbf{HC}_2$ tend to have higher coverages for $|\rho| = 0.5$. For $\mathbf{HC}_2$ and $\mathbf{HC}_3$ the respective effect is only marginal. Large correlations induce longer CIs for β_1 for all number of studies and estimators. There is no consistent impact of the correlation on the CIs for β_{12}. The changes depend on both the estimator and number of studies k. However, these changes are only slight. $\mathbf{HC}_0$, $\mathbf{HC}_1$, $\mathbf{HC}_3$ and $\mathbf{KH}$ based CIs have shorter lengths for larger values of $|\rho|$ and all k. Intervals based on $\mathbf{HC}_2$, $\mathbf{HC}_4$ and $\mathbf{HC}_5$ have marginally decreasing lengths in $|\rho|$ for $k = 6$, slightly increasing lengths for $k \in \{10, 20\}$ and again marginally decreasing lengths for $k = 50$. It is also interesting to note, that most of the extreme outliers of $\mathbf{HC}_5$ occur for high correlations.

Adjustments of the random effect distribution Simulated random effect distributions are the standard normal distribution and standardized Laplace-, exponential, t_3- and log-normal-distributions. In comparison with the other simulated distributions, the coverages of CIs for β_1 based on $\mathbf{HC}_0 - \mathbf{HC}_5$ are on average the lowest with normal distributed u_i and highest with log-normal distributed random effects. The coverages do not differ much in respect of the other random effect. The $\mathbf{KH}$-CIs for $k \in \{6, 10\}$ have the highest coverage with normal distributed random effects and the lowest with log-normal random effects. Especially for $k = 10$ the coverages of the $\mathbf{KH}$-CIs with non-normal random effects tend to be lower. In 73.71% of the adjustments with non-normal random effects the coverages of the $\mathbf{KH}$-CIs are below

0.95. For $k = 20$ the **KH**-CIs show no observable differences between the random effect distributions, whereas for $k = 50$ the order of the median coverages is the same as for the other estimators.

The coverage of the $\mathbf{HC_0} - \mathbf{HC_5}$ CIs for β_{12} are affected similarly by the random effect distribution for $k \in \{10, 20, 50\}$. For $k \in \{6, 10, 20\}$ the coverage of the **KH**-CIs for β_{12} are below 0.95 in most of the adjustments with non-normal random effects. Thus, in this situation the coverages of the **KH**-CIs for β_{12} are even less adequate than for the intervals for β_1. If $k = 50$, the **KH**-CIs are not affected by the random effects distribution.

The median lengths of both coefficients CIs depends on the underlying distribution can can be ordered in the following way for all k and estimators: normal > Laplace > exponential > t_3 > log-normal. Thus, for $\mathbf{HC_0} - \mathbf{HC_5}$ the confidence intervals have better properties, when the random effect distribution is different from a normal distribution. Therefore, the quantile used as critical value is suitable, even if the distribution of the u_i is not normal. In contrast, the **KH**-CIs depend more on the normality assumption for smaller numbers of studies ($k \in \{6, 10, 20\}$), especially for $k = 10$. Due to the high share of coverage of the **KH**-CIs below the nominal confidence level, for non-normal and particularly log-normal random effects it is arguable whether **KH** is the best estimator in this situation. If a precise control of the nominal confidence level is required $\mathbf{HC_3}$ (for $k \in 10, 20$) or $\mathbf{HC_4}/\mathbf{HC_5}$ (for $k = 6$) may be preferable. For $k = 50$ the performance of the **KH**-CIs is still the best for all distributions of u_i.

In sum, the estimators are affected by most parameter adjustments in the same way or a similar manner. Only the number of studies k shows a strong varying effect on the coverage of some estimators. Besides the number of studies, the group size and the heterogeneity parameter τ^2 have impact on the interval lengths. However, the trend is the same for all estimators and reducible to the direct impact of these parameters on components of the confidence interval in equation (6). The results of the different random effect distributions indicate that the **HC** estimators are more

robust against deviations from the normal distribution. For small numbers of studies it is questionable whether the coverage of the **KH**-CIs for non-normal random effects are still adequate. In this situation $\mathbf{HC_3 - HC_5}$ might be more suitable compared to **KH**. Otherwise, there is no situation where any estimator performs superior compared to its overall performance.

Additional Simulations In additional simulations we analyzed the effect of omitted and redundant interactions. The results were the same as for usual omitted or redundant regressors: Omitted interactions caused lower coverages of the intervals, especially of β_0-CIs, whereas redundant interactions did not result in lower coverages but higher interval lengths. For details see Section F of the Supplement.

6 Discussion

The objective of this work was the comparison of confidence intervals for a mixed-effects meta-regression model with two moderators and an interaction term. The confidence intervals were based on one of the six different heteroscedasticity consistent covariance estimators $\mathbf{HC_0}, ..., \mathbf{HC_5}$ or the Knapp-Hartung covariance estimator **KH**. In a simulation study the confidence intervals based on these estimators were compared regarding their coverage and lengths for numerous combinations of simulation parameters. The simulation settings varied in the number of studies, the study sizes, a heterogeneity parameter, the coefficients of the moderators, the correlation between the covariates and the distribution of the random effect. A total of 77 760 combinations was simulated 10 000 times, respectively.

The coverage of the confidence intervals based on $\mathbf{HC_0}$ and $\mathbf{HC_1}$ turned out to be below the nominal confidence level $(1 - \alpha) = 0.95$ for almost every setting and are therefore not adequate. Although the coverage of the confidence intervals based on $\mathbf{HC_2}$ ($\mathbf{HC_2}$-CIs) for β_{12} were suitable, $\mathbf{HC_2}$ is not recommended due to the low coverage of the intervals for β_1. The CIs based on the estimators $\mathbf{HC_3 - HC_5}$ and **KH** showed suitable coverage for both parameters. Concerning the interval lengths

the **KH**-CIs performed the best for all settings among all estimators with adequate coverage. For a small number of studies ($k = 6$) the lengths of the **HC**$_3$-CIs were highly inflated. Therefore, in this situation the **HC**$_4$ and **HC**$_5$ should be preferred over **HC**$_3$. For larger numbers of studies ($k \geq 10$) the lengths of the **HC**$_3$-CIs are shorter compared to the **HC**$_4$ and **HC**$_5$ intervals. Thus, for $k \geq 10$ **HC**$_3$-CIs are preferable compared to **HC**$_4$- and **HC**$_5$-CIs.

The results for single parameter adjustments differ only slightly from the overall results. The interval lengths were shown to be increasing in the amount of heterogeneity τ^2, whereas they were decreasing in the number of studies k and the mean study sizes $\bar{n}$ for all estimators. Coverages were mostly decreasing in $\bar{n}$ and τ^2. The confidence intervals were only slightly affected by the values of the true coefficients. Only high values of β_1 and strong interactions ($|\beta_{12}| = 0.5$) reduced the coverage of some intervals. For all different estimators the CIs for β_1 had coverage closer to the nominal confidence level for higher correlations ρ but their lengths were increasing in ρ. Concerning coverage and lengths of the CIs for β_{12} no such trend was observable. Surprisingly, all estimators but **KH** performed better for non-normal distributed random effects regarding their coverage and lengths. For small numbers of studies $k \in \{6, 10\}$ the coverage of the **KH**-CIs tend to be below the nominal confidence level $(1 - \alpha) = 0.95$. In these situations the coverage of the **KH**-CIs are still close to 0.95, but if an exact control of the significance level is required **HC**$_3$ is more suitable.

Altogether, for the most parts the results of this work are in accordance with the results of Welz and Pauly (2020). The superior performance of the **KH** estimator and the behavior of the **HC** estimators observed in the model with one moderator also holds for most situations when studying the model with two covariates and an interaction. However, some aspects of this work indicate that **KH** may not be the best estimator for more complex models or more extreme parameter adjustments. In fact, the **KH**-estimator performed worse compared to the model with one covariate in the work of Welz and Pauly (2020). In their simulation study the Type 1 random error of the **KH** based tests was below the nominal significance level $\alpha = 0.05$ in more than 50% of the adjustments for all k. In this work situations were observed where

the coverage of the **KH**-CIs was below the nominal confidence level $(1 - \alpha) = 0.95$ in almost 80% of the adjustments. This may be due to its worse performance for non-normal distributed random effects compared to the other estimators, which was observed especially for small numbers of studies. Additionally, the coverage of all estimators were lower for high values of β_1. Furthermore, the coverage of the **KH**-CIs for β_{12} tended to be lower.

As the model examined in this work still has a simple structure, in further research it might be of interest to consider the performance of **KH** for more complex models. Interesting settings are interaction terms of higher order, other random effect distributions and more extreme coefficients. Based on this simulation study it seems plausible that the good performance of **KH** might be limited to models of simpler structure. For more complex models coverage of **KH**-CIs may be inadequate and alternative estimators may be required. For such situations $\mathbf{HC_4}$ and $\mathbf{HC_5}$ may be suitable choices of estimators for small and large number of studies, since their CIs controlled the nominal confidence level well in every situation and had shorter interval lengths compared to $\mathbf{HC_3}$-CIs for $k = 6$. For a medium number of studies $\mathbf{HC_3}$ might be the most suitable, since its intervals held the nominal confidence level in every situation with $k \in \{10, 20\}$ and were shorter compares to the $\mathbf{HC_4}$- and $\mathbf{HC_5}$-CIs. In further research it may also be of interest to analyze the situations where highly inflated interval lengths of the $\mathbf{HC_3}$- and $\mathbf{HC_5}$-CIs occurred in detail, because they cannot be explained by the results of this work.

Concluding, meta-regression remains an important field of statistical research. The Knapp-Hartung estimator is generally a good choice, especially for simple models and situations where a normality assumption is appropriate. However, for an exact control $\mathbf{HC_3}, \mathbf{HC_4}$ or $\mathbf{HC_5}$ could be preferable choices, depending on the model assumptions.

Conflict of Interest

The authors have declared no conflict of interest.

References

Aiken, L., West, S., & Reno, R. (1991). *Multiple Regression: Testing and Interpreting Interactions*. SAGE Publications, Newbury Park, CA.

Auguie, B. (2017). *gridExtra: Miscellaneous Functions for "Grid" Graphics* [R package version 2.3]. https://CRAN.R-project.org/package=gridExtra

Berkey, C., Hoaglin, D., Mosteller, F., & Colditz, G. (1995). A random-effects regression model for meta-analysis. *Statistics in Medicine*, *14*, 395–411. https://doi.org/10.1002/sim.4780140406

Cohen, J. (1988). *Statistical Power Analysis for the Behavioral Sciences* (2nd ed.). L. Erlbaum Associates, Hilsdale, NJ.

Cribari-Neto, F. (2004). Asymptotic inference under heteroskedasticity of unknown form. *Computational Statistics & Data Analysis*, *45*(2), 215–233. https://doi.org/10.1016/S0167-9473(02)00366-3

Cribari-Neto, F., Souza, T. C., & Vasconcellos, K. L. P. (2007). Inference under heteroskedasticity and leveraged data. *Communications in Statistics - Theory and Methods*, *36*(10), 1877–1888. https://doi.org/10.1080/03610920601126589

Efron, B. (1982). *The Jackknife, the Bootstrap and Other Resampling Plans*. Society for Industrial and Applied Mathematics, Philadelphia, PA. https://doi.org/10.1137/1.9781611970319

Fahrmeir, L., Kneib, T., Lang, S., & Marx, B. (2013). *Regression: Models, Methods and Applications*. Springer-Verlag, Berlin. https://doi.org/10.1007/978-3-642-34333-9

Gan, W. Q., Man, S. F. P., Senthilselvan, A., & Sin, D. D. (2004). Association between chronic obstructive pulmonary disease and systemic inflammation: A systematic review and a meta-analysis. *Thorax*, *59*(7), 574–580. https://doi.org/10.1136/thx.2003.019588

Hartung, J., Knapp, G., & Sinha, B. (2008). *Statistical Meta-Analysis With Applications*. John Wiley & Sons, Inc., Hoboken, New Jersey. https://doi.org/10.1002/9780470386347

Hedges, L. V. (1981). Distribution theory for glass's estimator of effect size and related estimators. *Journal of Educational Statistics*, *6*(2), 107–128. https://doi.org/10.3102/10769986006002107

Hedges, L. V., & Olkin, I. (1985). *Statistical Methods for Meta-Analysis* (L. V. Hedges & I. Olkin, Eds.). Academic Press, San Diego, CA. https://doi.org/10.1016/B978-0-08-057065-5.50010-5

Huizenga, H. M., Visser, I., & Dolan, C. V. (2011). Testing overall and moderator effects in random effects meta-regression. *British Journal of Mathematical and Statistical Psychology*, *64*(1), 1–19. https://doi.org/10.1348/000711010X522687

Jackson, D., & White, I. R. (2018). When should meta-analysis avoid making hidden normality assumptions? *Biometrical Journal*, *60*(6), 1040–1058. https://doi.org/10.1002/bimj.201800071

Kimmoun, A., Takagi, K., Gall, E., Ishihara, S., Hammoum, P., El Bèze, N., Bourgeois, A., Chassard, G., Pegorer-Sfes, H., Gayat, E., et al. (2021). Temporal trends in mortality and readmission after acute heart failure: A systematic review and meta-regression in the past four decades. *European Journal of Heart Failure*, *23*. https://doi.org/10.1002/ejhf.2103

Knapp, G., & Hartung, J. (2003). Improved tests for a random effects meta-regression with a single covariate. *Statistics in Medicine*, *22*(17), 2693–2710. https://doi.org/10.1002/sim.1482

Kontopantelis, E., & Reeves, D. (2012). Performance of statistical methods for meta-analysis when true study effects are non-normally distributed: A simulation study. *Statistical Methods in Medical Research*, *21*(4), 409–426. https://doi.org/10.1177/0962280210392008

Kurmani, S., & Squire, I. (2017). Acute heart failure: Definition, classification and epidemiology. *Current Heart Failure Reports*, *14*(5), 385–392. https://doi.org/10.1007/s11897-017-0351-y

MacKinnon, J. G., & White, H. (1985). Some heteroskedasticity-consistent covariance matrix estimators with improved finite sample properties. *Journal of*

Econometrics, *29*(3), 305–325. https://doi.org/10.1016/0304-4076(85)90158-7

Morris, T. P., White, I. R., & Crowther, M. J. (2019). Using simulation studies to evaluate statistical methods. *Statistics in Medicine*, *38*(11), 2074–2102. https://doi.org/10.1002/sim.8086

Orci, L. A., Gariani, K., Oldani, G., Delaune, V., Morel, P., & Toso, C. (2016). Exercise-based interventions for nonalcoholic fatty liver disease: A meta-analysis and meta-regression. *Clinical Gastroenterology and Hepatology*, *14*(10), 1398–1411. https://doi.org/10.1016/j.cgh.2016.04.036

Pauly, M., & Welz, T. (2018). Contribution to the discussion of "When should meta-analysis avoid making hidden normality assumptions?" *Biometrical Journal*, *60*(6), 1075–1076. https://doi.org/10.1002/bimj.201800184

Ponikowski, P., Kirwan, B.-A., Anker, S. D., McDonagh, T., Dorobantu, M., Drozdz, J., Fabien, V., Filippatos, G., Göhring, U. M., Keren, A., Khintibidze, I., Kragten, H., Martinez, F. A., Metra, M., Milicic, D., Nicolau, J. C., Ohlsson, M., Parkhomenko, A., Pascual-Figal, D. A., ... Stanislavchuk, M. (2020). Ferric carboxymaltose for iron deficiency at discharge after acute heart failure: A multicentre, double-blind, randomised, controlled trial. *The Lancet*, *396*(10266), 1895–1904. https://doi.org/https://doi.org/10.1016/S0140-6736(20)32339-4

R Core Team. (2020). *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing. Vienna, Austria. https://www.R-project.org/

Raudenbush, S. (2009). Analyzing effect sizes: Random-effects models. In H. Cooper, L. V. Hedges, & J. C. Valentine (Eds.), *The Handbook of Research Synthesis and Meta-Analysis* (pp. 295–315). Russell Sage Foundation, New York, NY.

Röver, C., & Friede, T. (2018). Contribution to the discussion of "When should meta-analysis avoid making hidden normality assumptions?": A bayesian perspective. *arXiv preprint arXiv:1809.06143*.

Sidik, K., & Jonkman, J. N. (2002). A simple confidence interval for meta-analysis. *Statistics in Medicine*, *21*(21), 3153–3159. https://doi.org/10.1002/sim.1262

Sterchi, M., & Wolf, M. (2017). Weighted least squares and adaptive least squares: Further empirical evidence. In V. Kreinovich, S. Sriboonchitta, & V.-N. Huynh (Eds.), *Robustness in Econometrics* (pp. 135–167). Springer International Publishing, Cham, Switzerland. https://doi.org/10.1007/978-3-319-50742-2_9

Veroniki, A. A., Jackson, D., Viechtbauer, W., Bender, R., Bowden, J., Knapp, G., Kuss, O., Higgins, J. P., Langan, D., & Salanti, G. (2016). Methods to estimate the between-study variance and its uncertainty in meta-analysis. *Research Synthesis Methods*, *7*(1), 55–79. https://doi.org/10.1002/jrsm.1164

Viechtbauer, W., López-López, J., Sanchez-Meca, J., & Marín-Martínez, F. (2015). A comparison of procedures to test for moderators in mixed-effects meta-regression models. *Psychological Methods*, *20*. https://doi.org/10.1037/met0000023

Welz, T. (2018). A simulation study of random-effects meta-analysis methods in unbalanced designs. Technical Report. Ulm University.

Welz, T., Doebler, P., & Pauly, M. (2021). Fisher transformation based confidence intervals of correlations in fixed-and random-effects meta-analysis. *British Journal of Mathematical and Statistical Psychology*. https://doi.org/10.1111/bmsp.12242

Welz, T., & Pauly, M. (2020). A simulation study to compare robust tests for linear mixed-effects meta-regression. *Research Synthesis Methods*, *11*(3), 331–342. https://doi.org/10.1002/jrsm.1388

White, H. (1980). A heteroskedasticity-consistent covariance matrix estimator and a direct test for heteroskedasticity. *Econometrica*, *48*(4), 817–838. http://www.jstor.org/stable/1912934

Wickham, H. (2007). Reshaping data with the reshape package. *Journal of Statistical Software*, *21*(12), 1–20. http://www.jstatsoft.org/v21/i12/

Wickham, H. (2016). *ggplot2: Elegant Graphics for Data Analysis*. Springer, New York, NY. https://ggplot2.tidyverse.org

Zimmermann, G., Pauly, M., & Bathke, A. C. (2020). Multivariate analysis of covariance with potentially singular covariance matrices and non-normal responses.

Journal of Multivariate Analysis, *177*, 104594. https://doi.org/10.1016/j.jmva.2020.104594

Supplement to:
Robust Confidence Intervals for Meta-Regression with Correlated Moderators

Eric S. Knop[1], Markus Pauly[1], Tim Friede[23] and Thilo Welz[1]

January 17, 2022

Abstract

This is a supplement to the main paper "Robust Confidence Intervals for Meta-Regression with Correlated Moderators". In Section A of this supplement the coverages and interval lengths of the simulation based on example are given in tables. The representation of $\mathbf{HC}_0$ given in Equation (7) of the main paper is derived in section B. In Section C the full results of the confidence intervals for β_{12} are presented. Versions of Figures 3 & 4 of the main paper where outliers are shown are presented in Section D. In Section E the effects of the parameter adjustments are considered in more detail and corresponding boxplots are shown. Finally, the results of the additional simulations are presented in Section F.

---

[1]Department of Statistics, TU Dortmund University
[2]Department of Medical Statistics, University of Göttingen
[3]DZHK (German Center for Cardiovascular Research), partner site Göttingen

Contents

A Simulation of the example

Table 1: Coverages and interval lengths of a model with two moderators and an interaction term when the model with interaction is the true model.

		HC_0	HC_1	HC_2	HC_3	HC_4	HC_5	KH
β_0	Coverage	0.9468	0.9499	0.9495	0.9513	0.9520	0.9531	0.9498
	Interval length	0.1498	0.1519	0.1515	0.1533	0.1536	0.1544	0.1520
β_1	Coverage	0.9391	0.9424	0.9441	0.9483	0.9509	0.9536	0.9471
	Interval length	0.0221	0.0224	0.0226	0.0231	0.0234	0.0236	0.0227
β_2	Coverage	0.9379	0.9401	0.9442	0.9500	0.9584	0.9634	0.9496
	Interval length	0.0230	0.0233	0.0237	0.0245	0.0256	0.0264	0.0239
β_{12}	Coverage	0.9294	0.9336	0.9390	0.9482	0.9602	0.9647	0.9491
	Interval length	0.0032	0.0032	0.0033	0.0034	0.0037	0.0038	0.0034

Table 2: Coverages and interval lengths of a model with two moderators when the model with interaction is the true model.

		HC_0	HC_1	HC_2	HC_3	HC_4	HC_5	KH
β_0	Coverage	0.9153	0.9185	0.9177	0.9208	0.9197	0.9197	0.9189
	Interval length	0.1481	0.1497	0.1494	0.1507	0.1502	0.1502	0.1498
β_1	Coverage	0.9453	0.9481	0.9486	0.9518	0.9525	0.9525	0.9503
	Interval length	0.0227	0.0229	0.0230	0.0233	0.0234	0.0234	0.0228
β_2	Coverage	0.9160	0.9194	0.9207	0.9253	0.9283	0.9283	0.9155
	Interval length	0.0236	0.0239	0.0240	0.0244	0.0247	0.0247	0.0233

Table 3: Coverages and interval lengths of a model with one moderator when the model with interaction is the true model.

		HC_0	HC_1	HC_2	HC_3	HC_4	HC_5	KH
β_0	Coverage	0.9374	0.9387	0.9384	0.9393	0.9387	0.9387	0.9389
	Interval length	0.1588	0.1601	0.1597	0.1606	0.1600	0.1601	0.1602
β_1	Coverage	0.7527	0.7582	0.7600	0.7678	0.7715	0.7724	0.7522
	Interval length	0.0239	0.0241	0.0241	0.0244	0.0245	0.0246	0.0238

B Derivation of HC_0 for Weighted Least Squares Estimators

For $\mathbf{HC}_0$ the form of the estimator given in Equation (7) in the main paper can be obtained by considering the transformed model

$$\tilde{\boldsymbol{y}} = \tilde{\boldsymbol{X}}\boldsymbol{\beta} + \tilde{\boldsymbol{u}} + \tilde{\boldsymbol{\epsilon}}, \tag{1}$$

where $\tilde{\boldsymbol{y}} = \widehat{\boldsymbol{W}}^{\frac{1}{2}}\boldsymbol{y}, \tilde{\boldsymbol{X}} = \widehat{\boldsymbol{W}}^{\frac{1}{2}}\boldsymbol{X}, \tilde{\boldsymbol{u}} = \widehat{\boldsymbol{W}}^{\frac{1}{2}}\boldsymbol{u}$ and $\tilde{\boldsymbol{\epsilon}} = \widehat{\boldsymbol{W}}^{\frac{1}{2}}\boldsymbol{\epsilon}$. The transformed model satisfies at least asymptotically all assumptions of the classical linear regression model, hence the OLS estimator of the transformed model $\hat{\boldsymbol{\beta}}_{OLS} = (\tilde{\boldsymbol{X}}^\top\tilde{\boldsymbol{X}})^{-1}\tilde{\boldsymbol{X}}^\top\boldsymbol{y}$ is an appropriate estimator for $\boldsymbol{\beta}$. Since the OLS estimator of the transformed model is $\hat{\boldsymbol{\beta}}_{OLS} = \hat{\boldsymbol{\beta}}$ (Hayashi, 2000) one simply has to consider the estimator given in equation (5) of MacKinnon and White (1985) for the transformed model:

$$
\begin{aligned}
\mathbf{HC}_0 &= (\tilde{\boldsymbol{X}}^\top\tilde{\boldsymbol{X}})^{-1}\tilde{\boldsymbol{X}}^\top\tilde{\boldsymbol{\Omega}}\tilde{\boldsymbol{X}}(\tilde{\boldsymbol{X}}^\top\tilde{\boldsymbol{X}})^{-1} \\
&= (\boldsymbol{X}^\top\widehat{\boldsymbol{W}}\boldsymbol{X})^{-1}\boldsymbol{X}^\top\widehat{\boldsymbol{W}}^{\frac{1}{2}}\tilde{\boldsymbol{\Omega}}\widehat{\boldsymbol{W}}^{\frac{1}{2}}\boldsymbol{X}(\boldsymbol{X}^\top\widehat{\boldsymbol{W}}\boldsymbol{X})^{-1} \\
&= (\boldsymbol{X}^\top\widehat{\boldsymbol{W}}\boldsymbol{X})^{-1}\boldsymbol{X}^\top\widehat{\boldsymbol{W}}\boldsymbol{E}\boldsymbol{D}_0\boldsymbol{D}_0^\top\boldsymbol{E}^\top\widehat{\boldsymbol{W}}\boldsymbol{X}(\boldsymbol{X}^\top\widehat{\boldsymbol{W}}\boldsymbol{X})^{-1}
\end{aligned}
$$

as

$$
\begin{aligned}
\tilde{\boldsymbol{\Omega}} &= diag(\tilde{e}_1^{\,2}, ..., \tilde{e}_k^2) \\
&= diag\big(\boldsymbol{D}_0(\tilde{\boldsymbol{y}} - \tilde{\boldsymbol{X}}(\tilde{\boldsymbol{X}}^\top\tilde{\boldsymbol{X}})^{-1}\tilde{\boldsymbol{X}}^\top\tilde{\boldsymbol{y}})\big)diag\big(\boldsymbol{D}_0(\tilde{\boldsymbol{y}} - \tilde{\boldsymbol{X}}(\tilde{\boldsymbol{X}}^\top\tilde{\boldsymbol{X}})^{-1}\tilde{\boldsymbol{X}}^\top\tilde{\boldsymbol{y}})\big)^\top \\
&= diag\big(\boldsymbol{D}_0\widehat{\boldsymbol{W}}^{\frac{1}{2}}(\boldsymbol{y} - \boldsymbol{X}\hat{\boldsymbol{\beta}})\big)diag\big(\boldsymbol{D}_0\widehat{\boldsymbol{W}}^{\frac{1}{2}}(\boldsymbol{y} - \boldsymbol{X}\hat{\boldsymbol{\beta}})\big)^\top \\
&= \boldsymbol{D}_0\widehat{\boldsymbol{W}}^{\frac{1}{2}}\boldsymbol{E}\boldsymbol{E}^\top\widehat{\boldsymbol{W}}^{\frac{1}{2}}\boldsymbol{D}_0 \\
&= \widehat{\boldsymbol{W}}^{\frac{1}{2}}\boldsymbol{D}_0\boldsymbol{E}\boldsymbol{E}^\top\boldsymbol{D}_0^\top\widehat{\boldsymbol{W}}^{\frac{1}{2}} \\
&= \widehat{\boldsymbol{W}}^{\frac{1}{2}}\boldsymbol{E}\boldsymbol{D}_0\boldsymbol{D}_0^\top\boldsymbol{E}^\top\widehat{\boldsymbol{W}}^{\frac{1}{2}}.
\end{aligned}
$$

Note that $\boldsymbol{D}_0, \widehat{\boldsymbol{W}}^{\frac{1}{2}}$ and $\boldsymbol{E}_0$ are interconvertible in the calculation above, given that they are all diagonal matrices.

The form of the other **HC** estimators $\mathbf{HC}_1 - \mathbf{HC}_5$ can be derived by analogous transformations using the suitable residuals and $\boldsymbol{D}_i$, $i = 1, ..., 5$.

C Full results of the intervals for β_{12}

Confidence intervals for $\boldsymbol{\beta_{12}}$ – Coverage Probabilities. Boxplots, which summarize the coverage of the confidence intervals for β_{12} are shown in Figure 1. The biggest difference regarding the coverage of those intervals compared to the intervals for β_1, is that all $\mathbf{HC_2}$-CIs are conservative for β_{12}. Other than for the CIs for β_1, the coverage of the $\mathbf{HC_2}$-CIs for β_{12} are higher than the nominal confidence level for all adjustments. The median coverages of the $\mathbf{HC_2}$-CIs are equal to the median coverages of the $\mathbf{HC_4}$-CIs for all considered number of studies k, which again are equal to the median coverage of the $\mathbf{HC_5}$-CIs for $k \in \{6, 10, 20\}$. For $k = 50$ the median coverage of the $\mathbf{HC_5}$-CIs is slightly higher than the median coverages of the $\mathbf{HC_2}$- and $\mathbf{HC_4}$-CIs.

Except for the $\mathbf{HC_2}$-CIs the coverages of the CIs for β_{12} resemble the ones of the CIs for β_1 in the corresponding situation. $\mathbf{HC_0}$- and $\mathbf{HC_1}$-CIs are liberal, whereas $\mathbf{HC_4}$- and $\mathbf{HC_5}$-CIs are conservative. Again the $\mathbf{HC_3}$-CIs are extremely conservative for $k = 6$ and only slightly conservative for $k = 50$. Also the coverage of the $\mathbf{KH}$-CIs are very close to the nominal confidence level $(1 - \alpha) = 0.95$ for most settings. But there are still some interesting minor differences for the other estimators, which need to be considered in detail.

Median coverage of the coefficient of interest β_{12} differs more from the nominal confidence level compared to the CIs for β_1 for most estimators and number of studies. Exceptions are, besides the $\mathbf{HC_2}$-CIs, the $\mathbf{HC_3}$- and $\mathbf{KH}$-CIs for $k = 50$. This results in even more liberal $\mathbf{HC_0}$- and $\mathbf{HC_1}$-CIs, as well as more conservative $\mathbf{HC_3}$ - $\mathbf{HC_5}$ based CIs for β_{12} compared to the CIs for β_1. For the $\mathbf{KH}$-CIs the boxplots of the CIs for β_{12} are very similar to the CIs for β_1.

However, for the $\mathbf{KH}$-CIs for β_{12} the ratio of coverage below the nominal confidence level is larger compared to the CIs for β_1 for all k. For $k = 10$ in 79.88% of the adjustments β_{12} is included in less than 95% of the intervals. For $k = 50$ the ratio is still 38.45%. Nevertheless, only in 1.12% of all adjustments the coverage is below

0.94.

In conclusion, the performance of the estimators can be assessed similar to the CIs for β_1. The only major exception is the performance of the **HC_2**-CI, which is as
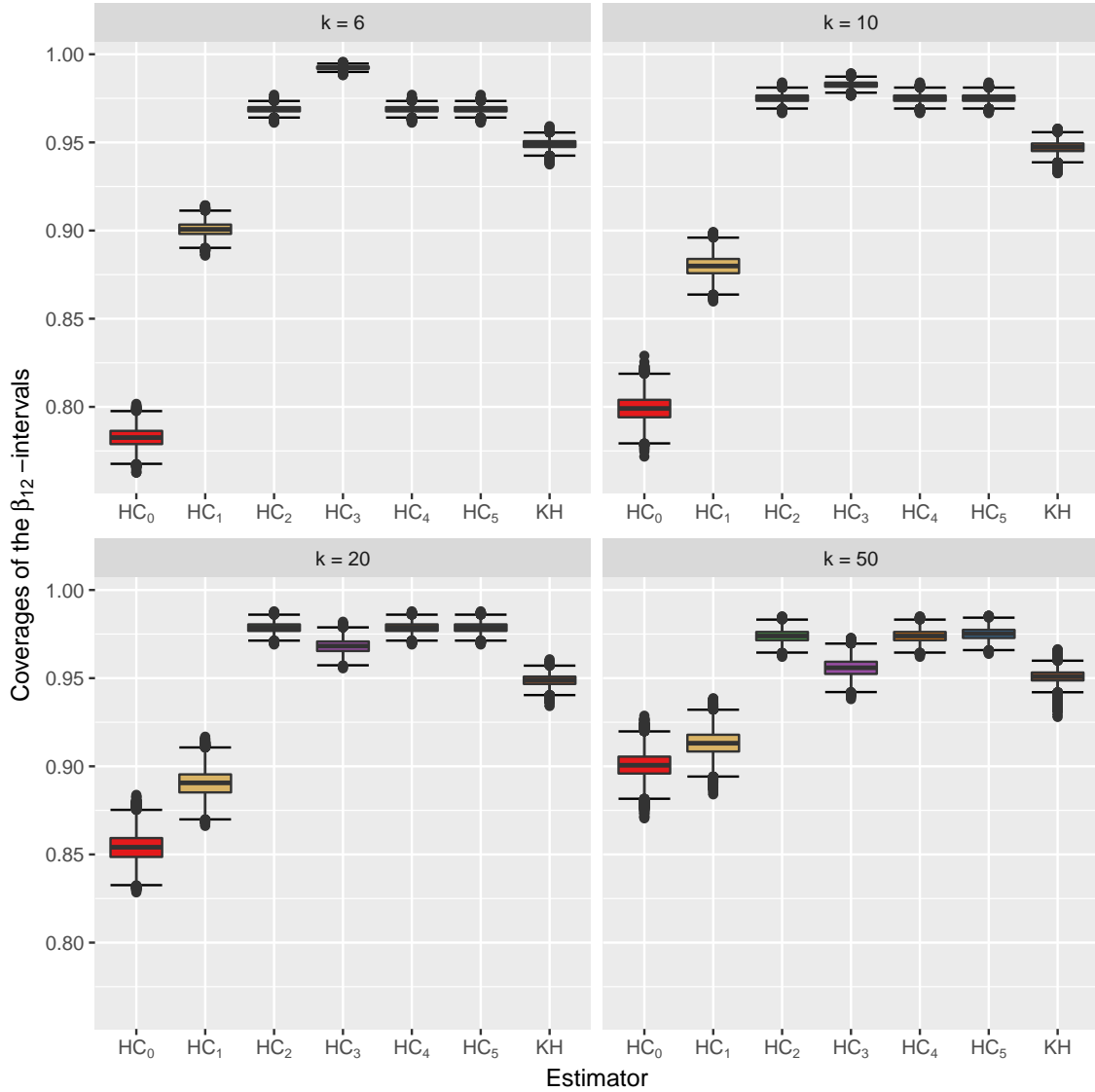
Figure 1: Coverage probabilities of the confidence intervals for β_{12} based on the estimators **$HC_0 - HC_5$** and **KH** for different numbers of studies k.

good as the performance of $\mathbf{HC_4}$-CI. Moreover, the coverage of the $\mathbf{KH}$-CI are still improvable.

Confidence intervals for $\boldsymbol{\beta_{12}}$ – Length. Boxplots containing the interval lengths of the CIs for β_{12} are shown in Figure 2. Regarding the lengths, all intervals except for $\mathbf{HC_2}$-CIs behave similar compared to the CIs for β_1. Again there occurred heavy outliers for the $\mathbf{HC_3}$-CIs with $k = 6$ and the $\mathbf{HC_5}$-CIs with $k = 50$. In this case the $\mathbf{HC_3}$-CIs have a maximum length of 393.1 and the $\mathbf{HC_5}$-CIs of 239.1. For a better visualization in Figure 2 the outliers are not shown. Full results are shown in Section D of this Supplement.

For $k = 6$ the $\mathbf{HC_3}$-CIs are the longest with a median length of 41.30. This is almost triple of the median lengths of the $\mathbf{HC_2}$, $\mathbf{HC_4}$ and $\mathbf{HC_5}$ based CIs, which are 13.81. The shortest median length of the intervals, that have a coverage above 0.95, is portrayed by the $\mathbf{KH}$-CIs with 8.64. $\mathbf{HC_0}$- and $\mathbf{HC_1}$- CIs have a median length of 3.96 and 7.87 respectively for $k = 6$. For all estimators the median interval length is decreasing in the number of studies k. Except for the $\mathbf{HC_3}$-CIs the rank order of the lengths does not change for the different k. The $\mathbf{HC_3}$-CIs are only the longest for $k = 6$. For $k = 50$ their median length is 0.50 and therefore close to the $\mathbf{KH}$-CIs median length of 0.46. This was also the case for the CIs of β_1. Again the $\mathbf{HC_0}$- and $\mathbf{HC_1}$-CIs are the shortest for all numbers of studies k. Regarding the lengths except for $\mathbf{HC_2}$ the same conclusions are drawn as for the intervals for β_1. Of all intervals with adequate coverage, the $\mathbf{KH}$-CIs perform the best. The performance of $\mathbf{HC_2}$ is as good as the performance of $\mathbf{HC_4}$ while estimating intervals for the interaction term.
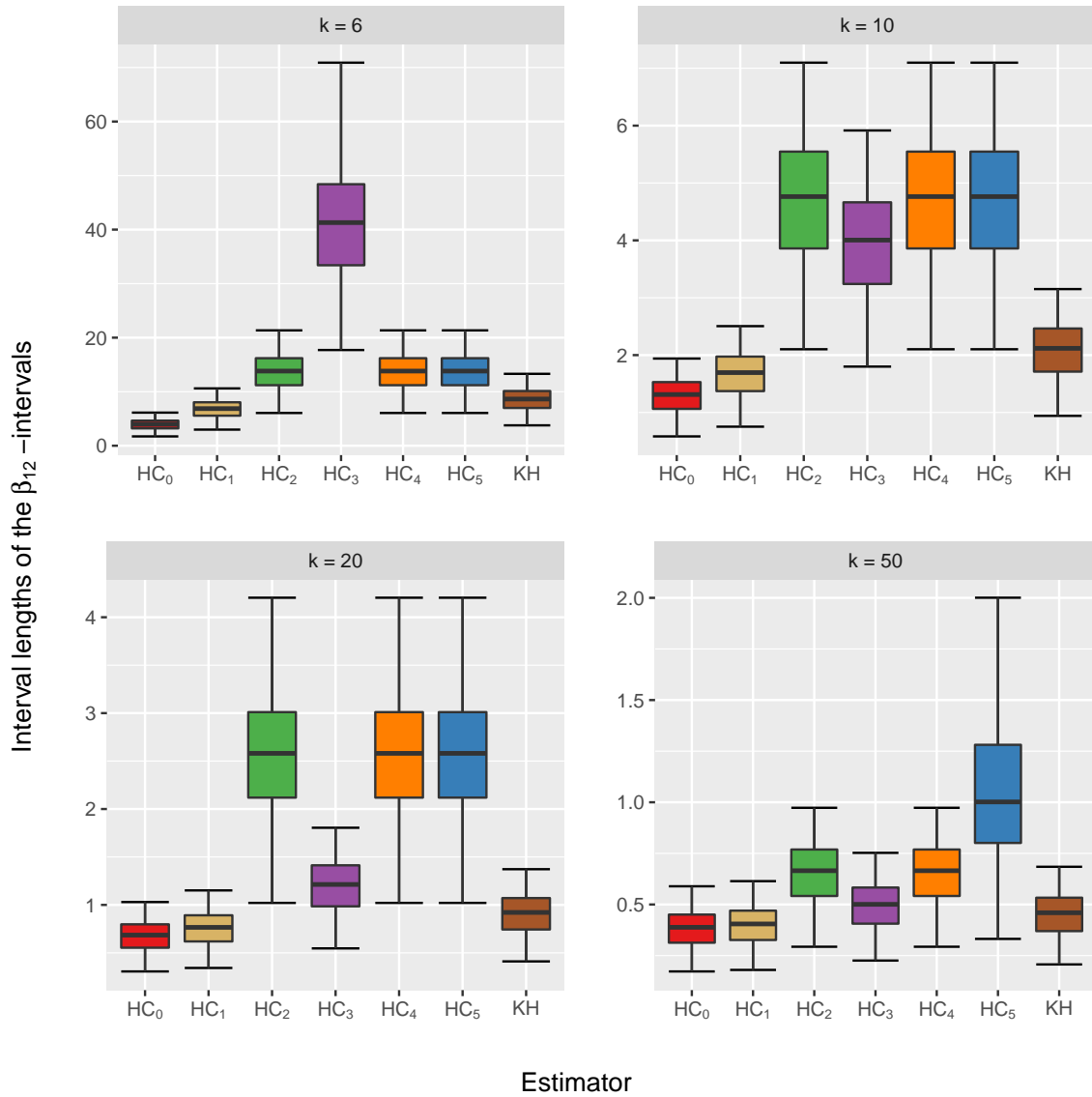
Figure 2: Lengths of the confidence intervals for β_{12} based on the estimators $\mathbf{HC}_0 - \mathbf{HC}_5$ and $\mathbf{KH}$ for different numbers of studies k without outliers.

D Boxplots of Lengths for all Results with Outliers

In Figures 3 and 4 the lengths of all confidence intervals are shown. Due to the large outliers for the $\mathbf{HC}_3$-CIs with $k = 6$ and the $\mathbf{HC}_5$-CIs with $k = 50$ the estimators are not comparable to the others. Therefore in the main paper the lengths are shown without outliers. In Section 5.2 of the main paper and D of this supplement the outliers are considered in more detail.
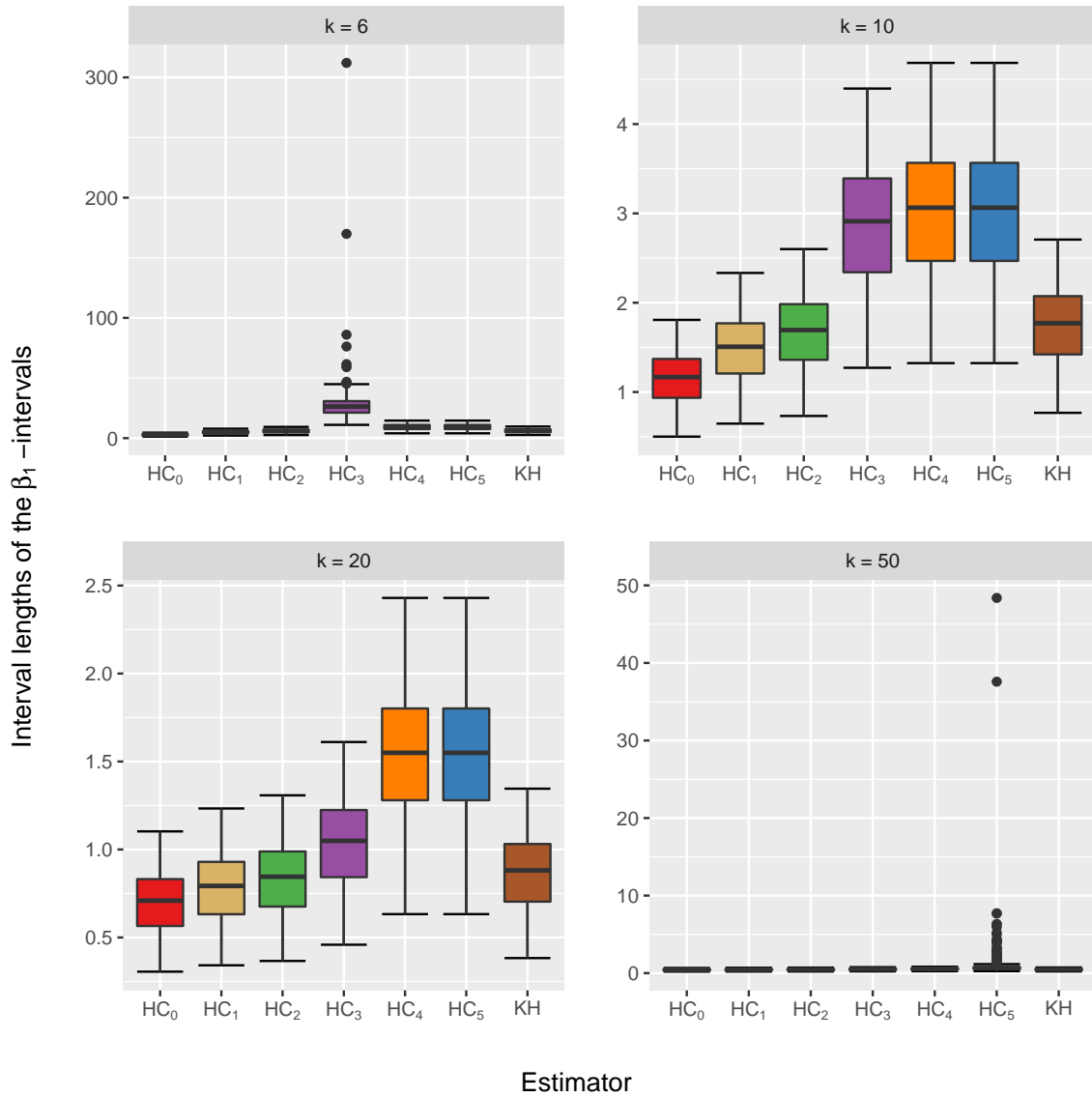
Figure 3: Lengths of the confidence intervals for β_1 based on the estimators $HC_0 - HC_5$ and KH for different numbers of studies k.
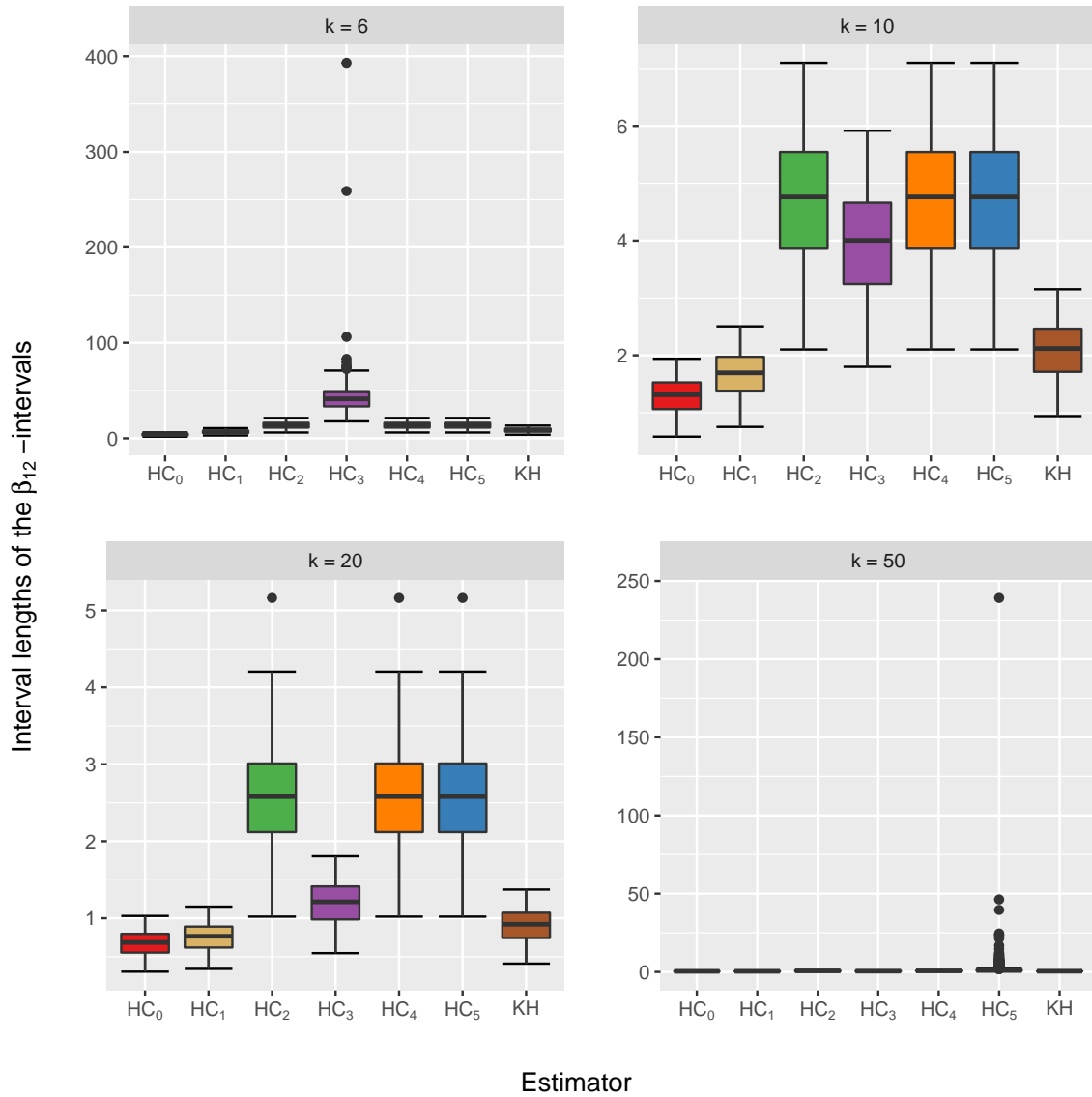
Figure 4: Lengths of the confidence intervals for β_{12} based on the estimators $HC_0 - HC_5$ and KH for different numbers of studies k.

E Boxplots for Separate Parameter Adjustments

This section will focus on how the coverages and interval lengths are affected by the adjustments of the flexible parameters. Since both coefficients are affected similarly by most parameters they are considered together. Situations where the influences differ are emphasized. To assess effects of a flexible parameter each boxplot in Section 5.1 of the main paper is split into parallel boxplots that contain all situations with the considered parameter adjustment. The boxplots of the interval lengths with heavy outliers ($\mathbf{HC}_3$-CIs for $k = 6$ and $\mathbf{HC}_5$-CIs for $k = 50$) are shown twice, once without outliers and once with outliers.

Adjustments of the number of studies k Considered numbers of studies are 6, 10, 20 and 50. The lengths of both coefficients' intervals are monotonically decreasing in the number of studies k (Figures 6 and 8). This is comprehensible since the $t_{(k-p-1),(1-\alpha)}$-quantile in Equation (6) of the main paper is monotonically decreasing in k.

Effects of the number of studies on the coverage depend on the covariance estimator used. The coverages of the $\mathbf{HC}_3$-CIs for β_1 are monotonically decreasing in k, whereas the $\mathbf{HC}_0$-CIs are monotonically increasing in k. Also coverages of the CIs based on $\mathbf{HC}_1$, $\mathbf{HC}_2$ and $\mathbf{KH}$ are increasing in k, but only for $k \geq 10$. For $k = 6$ their coverages are higher than for $k = 10$. Moreover, coverages of $\mathbf{HC}_4$- and $\mathbf{HC}_5$-CIs are increasing in k, but only for $k \leq 20$. For $k = 50$ coverages are lower than for $k = 20$ (Figure 5).

Except for the $\mathbf{HC}_2$-CIs, the effect of the number of studies on the coverage of the CIs for β_{12} is the same. In this situation the $\mathbf{HC}_2$-CIs are affected by k similarly to the $\mathbf{HC}_4$- and $\mathbf{HC}_5$-CIs (Figure 7).

In sum the considered intervals depend highly on the number of studies k. Obviously, for all estimators a large number of studies is preferable.

Adjustments of study size Small ($\bar{n} = 15$), medium ($\bar{n} = 25$) and large ($\bar{n} = 50$) group sizes are compared. For the most numbers of studies k and covariance esti-

mators the median coverage is slightly increasing in the study size (Figures 9-12 and 17-20). For the CIs for β_1 exceptions are the $\mathbf{HC_4}$, $\mathbf{HC_5}$ and $\mathbf{KH}$ based CIs for $k \in \{10, 20\}$ and the $\mathbf{KH}$-CIs for $k = 50$. The coverages of the CIs for β_{12} have no increasing trend for the $\mathbf{KH}$-CIs for all k, nor the coverages of the $\mathbf{HC_0}, \mathbf{HC_1}$ and $\mathbf{HC_3}$ based CIs for $k = 6$ and the $\mathbf{HC_2}$, $\mathbf{HC_4}$ and $\mathbf{HC_5}$ based CIs for $k = 20$.

The corresponding interval lengths are decreasing in the study sizes for all k and estimators (Figures 13-16 and 21-24). This trend may be caused by the impact of n_i on v_i in Equation (9) of the main paper, which leads to decreasing standard errors in equation (6) .

Thus, overall larger studies lead to better confidence intervals, since both coverages and interval lengths are improved for larger study sizes. Among the considered study sizes there is no size where an estimator has a different performance compared to the other estimators.

It is noticeable that the extreme lengths of $\mathbf{HC_3}$-CIs for $k = 6$ appear mostly for small and medium group sizes (Figures 13 and 21).

Adjustments of τ^2 Coverages of both coefficients' intervals are increasing slightly in the heterogeneity parameter τ^2 for all estimators and k (Figures 25-28 and 33-36). The only exception are the $\mathbf{KH}$-CIs for $k \in \{6, 10\}$. For a larger number of studies, the effect is stronger. The increasing coverages in τ^2 show that the model used in the simulation is adequate to model a study effect.

On the other hand the interval lengths are increasing in τ^2 strongly. Intervals for the adjustment $\tau^2 = 0.9$ have more than double median length compared to the intervals with $\tau^2 = 0.1$ (Figures 29-32 and 37-40). This result is explicable by the direct impact the value of τ^2 has on the variances of the coefficients and thus on the interval bounds.

The recommendation for the choice of estimator does not differ from the overall recommendation for any observed τ^2.

Adjustments of β_1 Examined adjustments of β_1 are 0, 0.2 and 0.5. The coverages

12

of CIs for β_{12} are not affected by the adjustment of β_1 (Figures 49-52), whereas the CIs for β_1 have a slightly lower coverage for a number of studies $k \in \{20, 50\}$ and all estimators (Figures 41-44). Neither the interval lengths of the CIs for β_1 nor of the CIs for β_{12} differ regarding the adjustment of β_1 (Figures 45-48 and 53-56).

Adjustments of β_2 For β_2 the adjustments 0, 0.2 and 0.5 were considered as well. None of the intervals were affected by the adjustment of β_2 regarding coverage or length (Figures 57-72). Mentionable is that the extreme interval lengths of the **HC$_3$**-CIs for $k = 6$ only occur for small values of β_2.

Adjustments of β_{12} Besides the adjustments 0, 0.2 and 0.5 for β_{12} the adjustment -0.5 was simulated as well, to check whether it differs from the 0.5 adjustment. This is neither the case for the interval lengths nor for the coverages of the CIs for β_1 and the CIs for β_{12}. However, the **HC$_4$**- and **HC$_5$**-CIs for β_1 have slightly lower coverage for a high absolute value of β_{12}. The effect is increasing in the number of studies k (Figures 73-76). For the CIs for β_{12}, this effect is seen not only for the **HC$_4$**- and **HC$_5$**-CIs but also for the **HC$_2$**- and **HC$_3$**-CIs. Aditionally, for $k = 50$ the effect is observable for **HC$_0$**, **HC$_1$** and **KH** based CIs (Figures 81-84).

The adjustment of β_{12} has a marginal effect on the interval lengths of the CIs for β_1 and β_{12} (Figures 77-80 and 85-88). Only for $k = 20$ the **HC$_4$**- and **HC$_5$**-CIs for β_1 have a slightly shorter length for $\beta_{12} \in \{-0.5, 0.5\}$ than for $\beta_{12} \in \{0, 0.2\}$ (Figure 79). Similarly the CIs for β_{12} based on **HC$_2$**, **HC$_4$** and **HC$_5$** tend to be slightly shorter for higher absolute values of β_{12} and $k = 20$ (Figure 87)

It is also noticeable that most of the extreme outliers of **HC$_5$**-CIs occur for $\beta_{12} \in \{0, 0.2\}$ (Figures 80 and 88).

Altogether the true values of the considered parameters do not have a strong impact on the intervals of any estimator. Therefore, there is no coefficient for which an estimator performs better or worse compared to the other estimators than in the overall results.

Adjustments of the correlation ρ Examined adjustments of ρ are 0, 0.2, 0.5 and -0.5. Intervals for β_1 that are based on $\mathbf{HC}_3 - \mathbf{HC}_5$ tend to have a lower coverages for higher correlations, whereas CIs based on $\mathbf{HC}_0 - \mathbf{HC}_2$ tend to have a higher coverages for $|\rho| = 0.5$. For $\mathbf{HC}_2$ and $\mathbf{HC}_3$ the respective effect is only marginal. The coverages do not differ regarding the sign of the correlation for all estimators (Figures 89-92). Large correlations induce longer CIs for β_1 for all number of studies and estimators (Figures 93-96).

The impact of the correlation on the CIs for β_{12} is a little different. For $k = 6$ the coverages of the $\mathbf{HC}_0$- and $\mathbf{HC}_1$-CIs are higher for larger values of $|\rho|$ (Figure 97). Concerning the other estimators no trend or rather a marginal negative trend in $|\rho|$ for $\mathbf{HC}_2$, $\mathbf{HC}_4$ and $\mathbf{HC}_5$ is observable. The same holds for $k = 10$, but in this situation the trend of $\mathbf{HC}_2$-$\mathbf{HC}_5$ is increasing (Figure 98). When observing $k = 20$ there is no effect of the correlation on any estimators' confidence interval (Figure 99). However, for $k = 50$ the $\mathbf{HC}_0 - \mathbf{HC}_5$ based CIs have a lower coverage for the higher non negative values of ρ. The coverage of the CIs with $\rho = -0.5$ based on $\mathbf{HC}_2 - \mathbf{HC}_5$ is marginally higher than with $\rho = 0.5$. $\mathbf{KH}$-CIs do not differ in their median coverage regarding the positive adjustments of ρ, but the coverage of the CIs with $\rho = -0.5$ is marginally lower (Figure 100).

The sign of ρ does not effect the lengths. $\mathbf{HC}_0$, $\mathbf{HC}_1$, $\mathbf{HC}_3$ and $\mathbf{KH}$ based CIs have shorter lengths for larger values of $|\rho|$ and all k. Intervals based on $\mathbf{HC}_2$, $\mathbf{HC}_4$ and $\mathbf{HC}_5$ have marginally decreasing lengths in $|\rho|$ for $k = 6$, slightly increasing lengths for $k \in \{10, 20\}$ and again marginally decreasing lengths for $k = 50$ (Figures 101-104). It is also interesting to notice, that most of the extreme outliers of $\mathbf{HC}_5$ occur for high correlations (Figures 96 and 104).

Adjustments of the random effect distribution Simulated random effect distributions are the standard normal distribution and standardized Laplace-, exponential-, t_3- and log-normal-distributions. In comparison with the other simulated distributions, the coverages of CIs for β_1 based on $\mathbf{HC}_0 - \mathbf{HC}_5$ are on average the smallest with normal distributed u_i and highest with log-normal distributed random effects.

The coverages do not differ much in respect of the other random effect distributions but in most situations the coverages for Laplace random effects are slightly lower than coverages for exponential random effects, which again are lower than coverages with t_3 random effects. The trend is slightly stronger for a larger number of studies k. The **KH**-CIs for $k \in \{6, 10\}$ have the highest coverage with normal distributed random effects and the lowest with log-normal random effects. Especially for $k = 10$ the coverages of the **KH**-CIs with non-normal distributed random effects tend to be lower. In 73.71% of the adjustments with non-normal distributed random effects the coverages of the **KH**-CIs are below 0.95. Considering only the adjustments with log-normal random effects this holds for 85.16% of the adjustments. Consequently, for non-normal random effects it is questionable whether the coverages of the **KH**-CIs can still be assessed as acceptable.

For $k = 20$ the **KH**-CIs show no observable differences between the random effect distributions, whereas for $k = 50$ the order of the median coverages is the same as for the other estimators (Figures 105-108).

Coverages of the CIs for β_{12} are affected similarly by the random effect distribution for $k \in \{10, 20, 50\}$. In accordance with the CIs for β_1, coverages of the $\mathbf{HC_0} - \mathbf{HC_5}$ based CIs for β_{12} are the lowest with normal distributed u_i and the highest with log-normal u_i. The coverages of the CIs with exponential distributed u_i decrease compared to the other intervals in k. For $k = 10$ they have the second highest median coverage, but for $k = 50$ the second lowest. In the situation of $k = 6$, $\mathbf{HC_2} - \mathbf{HC_5}$ based CIs coverages are not affected by the random effects distribution. The $\mathbf{HC_0}$- and $\mathbf{HC_1}$-CIs have the largest median coverage with normal u_i and the smallest with log-normal. This also holds for **KH**-CIs with $k \in \{6, 10, 20\}$. For $k = 10$ the coverages of the **KH**-CIs for β_{12} are below 0.95 in 88.96% of the adjustments with non-normal random effects and in 96.63% of the adjustments with log-normal random effects. Thus, in these situations the coverages of the **KH**-CIs for β_{12} are even less adequate than for the intervals for β_1. If $k = 50$, the **KH**-CIs are not affected by the random effects' distribution (Figures 113-116).

The median lengths of both coefficients' CIs can be ordered in the following way for all k and estimators: normal > Laplace > exponential > t_3 > log-normal (Figures

15

109-112 and 117-120). Thus, for $\mathbf{HC}_0 - \mathbf{HC}_5$ the confidence intervals have better properties, when the random effect distribution is different from a normal distribution. Therefore the quantile used as critical value is suitable, even if the distribution of the u_i is not normal. In contrast the $\mathbf{KH}$-CIs depend more on the normality assumption for smaller numbers of studies ($k \in \{6, 10\}$), especially for $k = 10$. Due to the high share of coverages of the $\mathbf{KH}$-CIs below the nominal confidence level, for non-normal and particularly log-normal random effects it is arguable whether $\mathbf{KH}$ is the best estimator in this situation. If a precise control of the nominal confidence level is required $\mathbf{HC}_3$ may be preferable, since for $k = 10$ its CIs have higher coverages than 0.95 in every adjustment and are the shorter compared to the $\mathbf{HC}_4$- and $\mathbf{HC}_5$-CIs. For $k \in \{20, 50\}$ the performance of the $\mathbf{KH}$-CIs is still the best for all distributions of u_i.

In summary the estimators are affected by most parameter adjustments in the same way or only slightly different. Only the number of studies k shows a strong varying effect on the coverages of some estimators. Besides the number of studies, the study size and the heterogeneity parameter τ^2 have impact on the interval lengths. However, the trend is the same for all estimators and reducible to the direct impact of these parameters on components of the confidence interval in equation (6) of the main paper. The results of the different random effect distributions indicate that the $\mathbf{HC}$ estimators are more robust against deviations from the normal distribution. For small numbers of studies it is questionable whether the coverages of the $\mathbf{KH}$-CIs for non-normal random effects are still adequate. In this situation $\mathbf{HC}_3 - \mathbf{HC}_5$ might be more suitable compared to $\mathbf{KH}$. In all other simulated adjustments, there is no situation where a certain estimator performs superior compared to its overall performance.
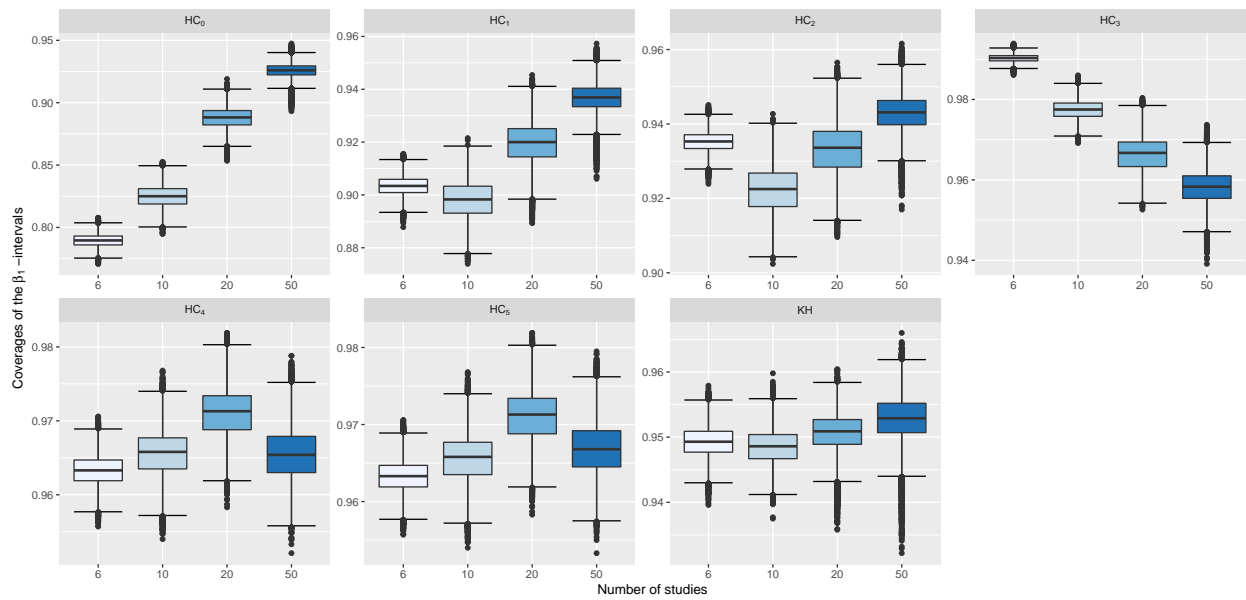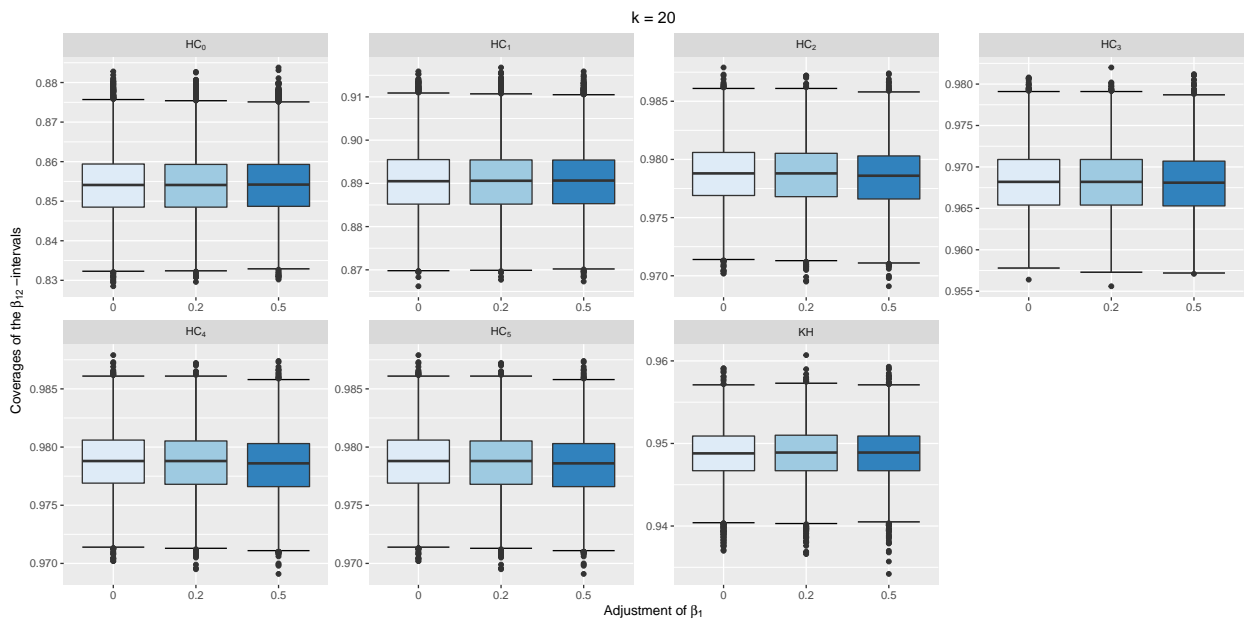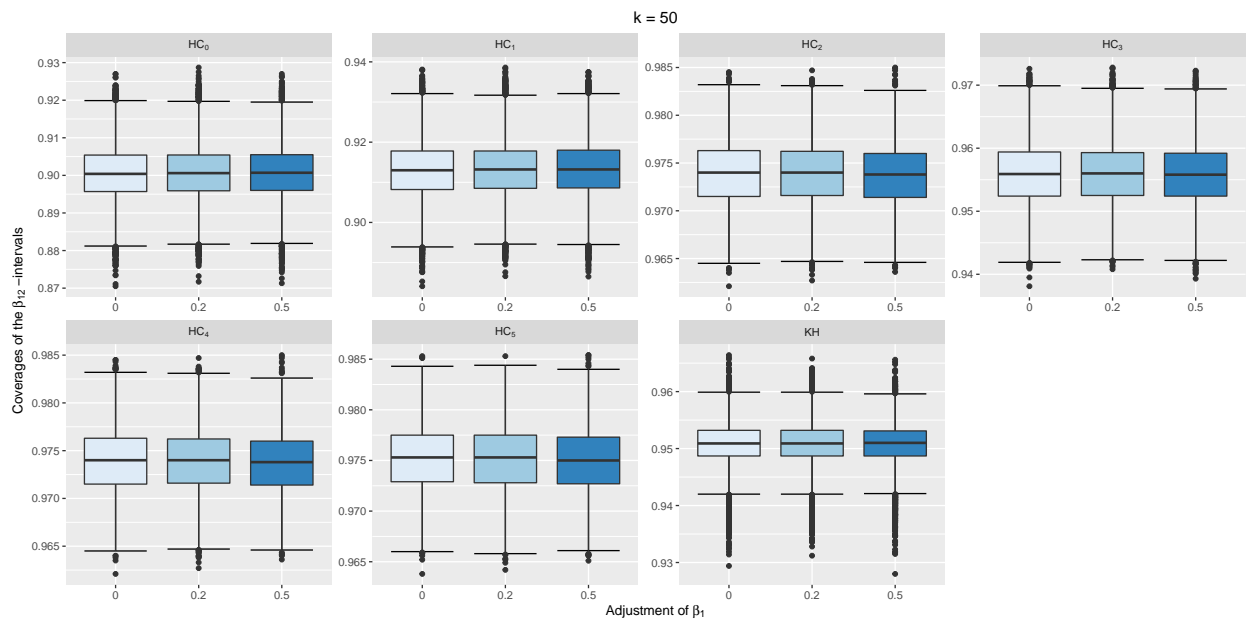
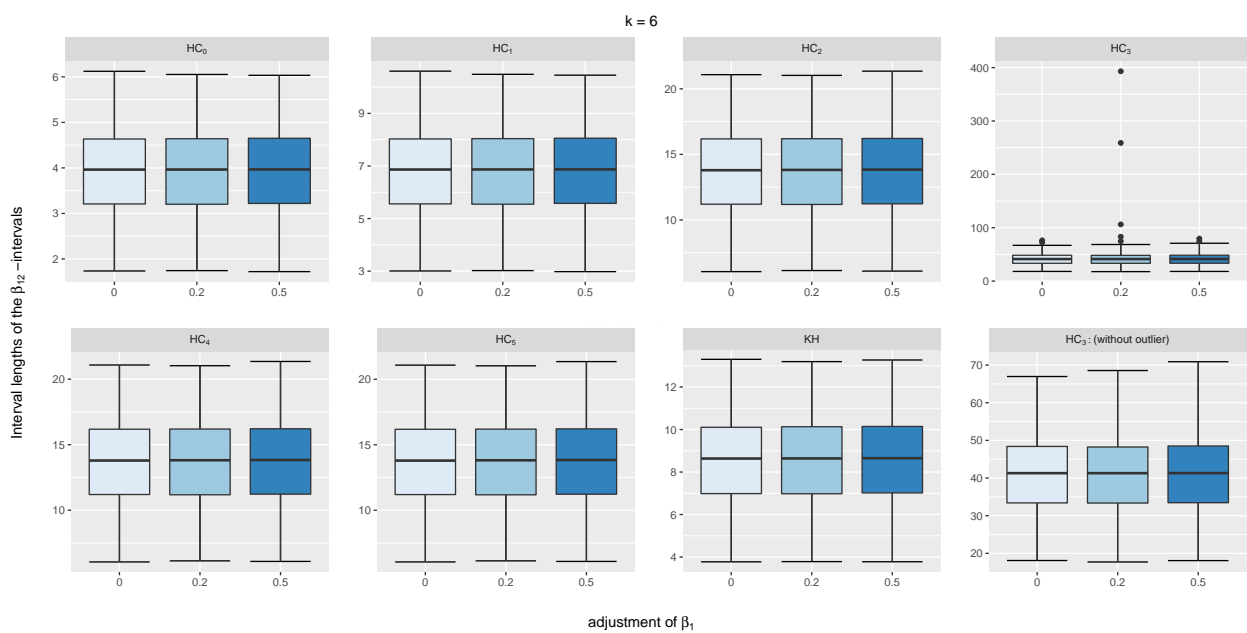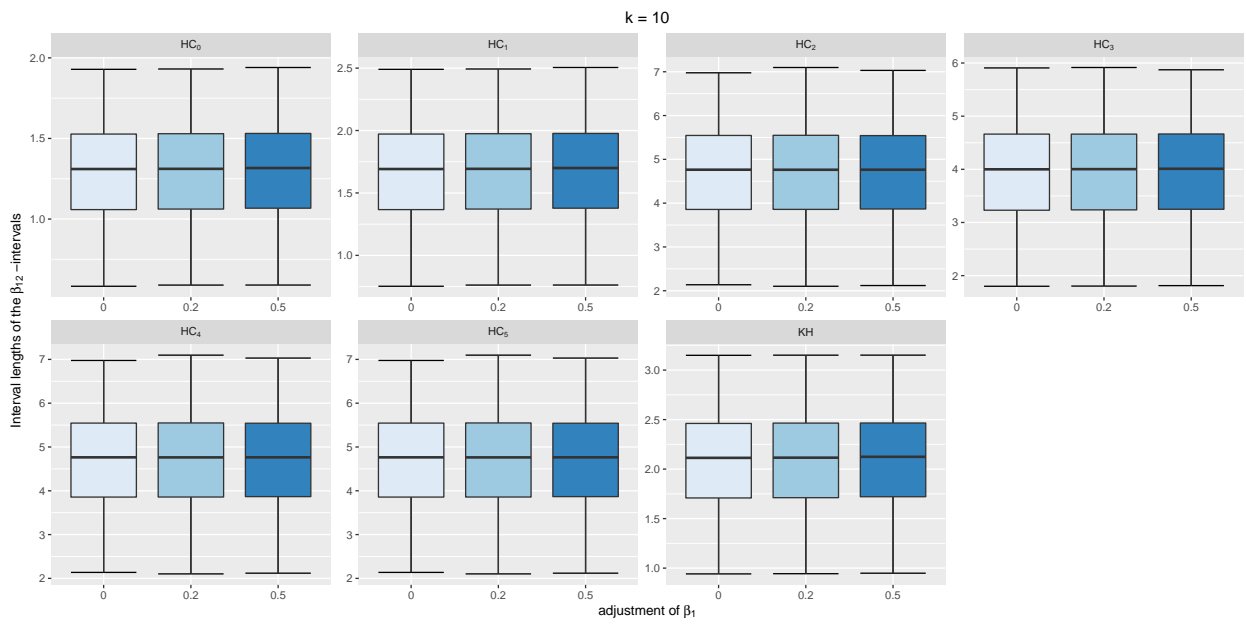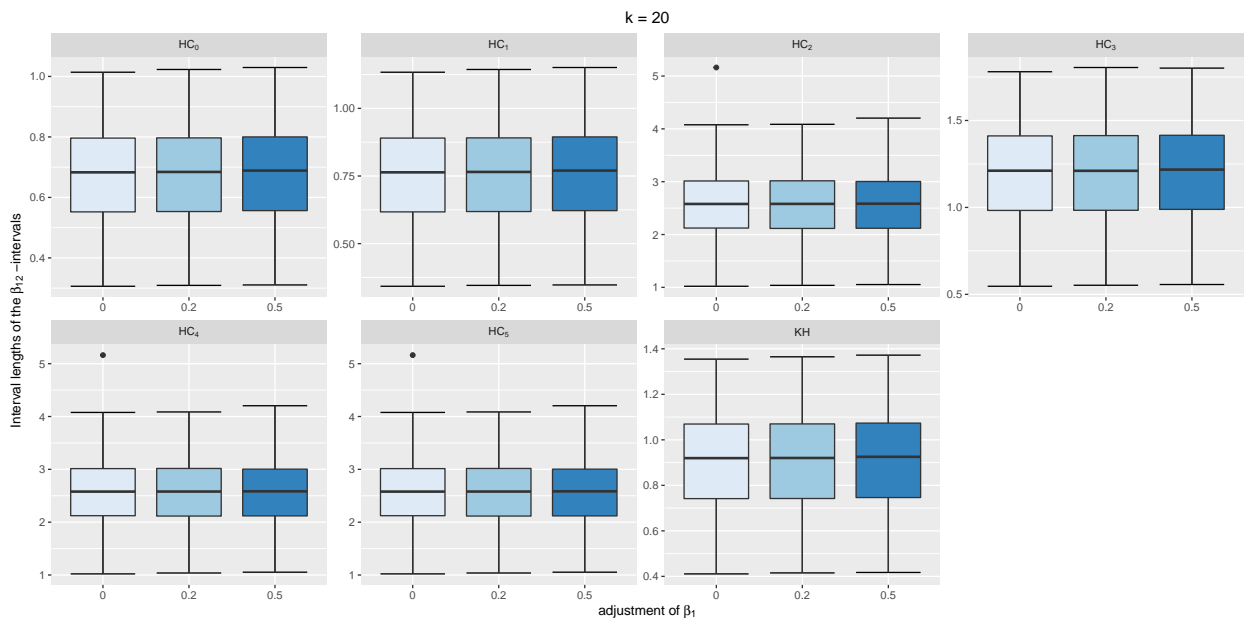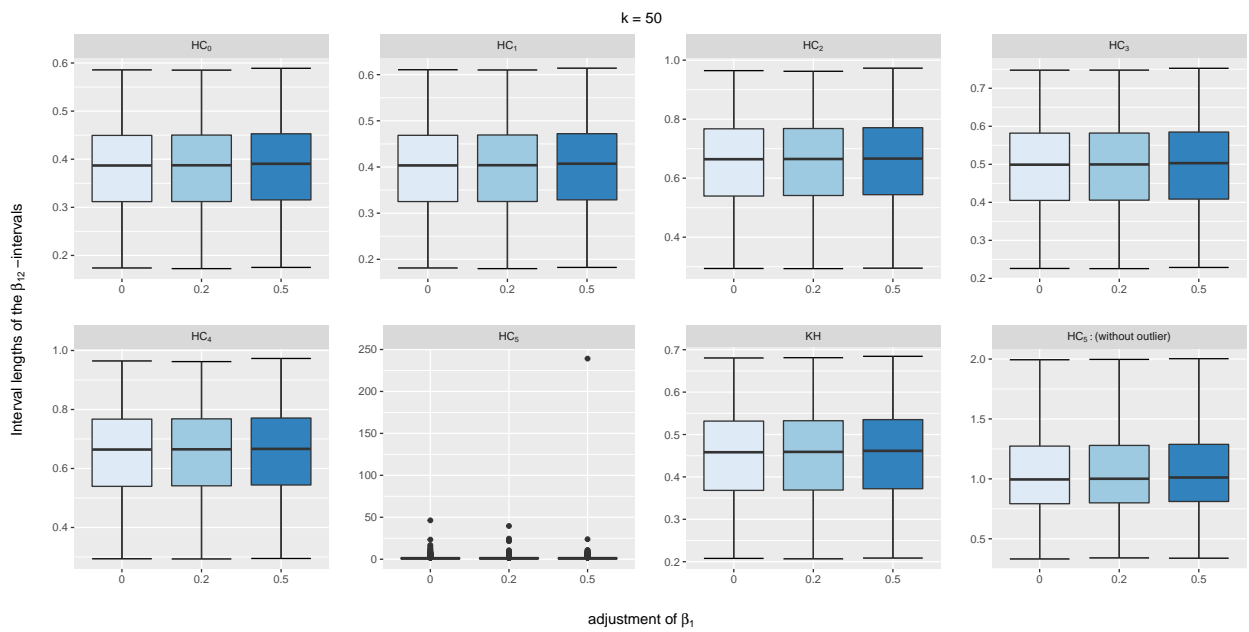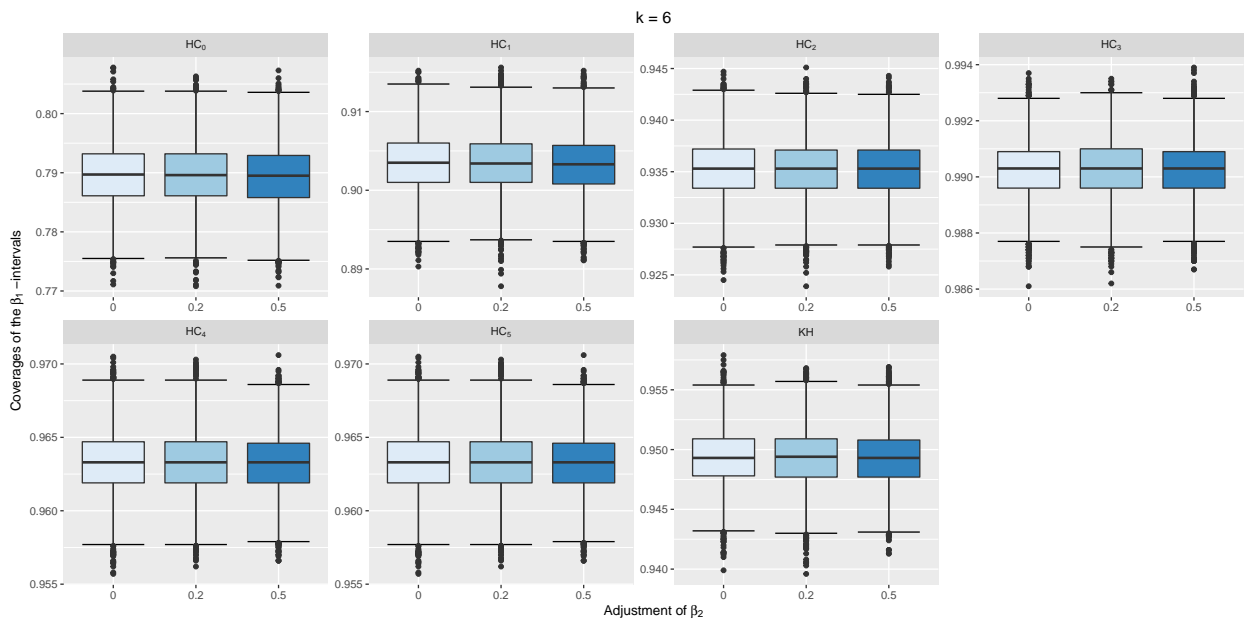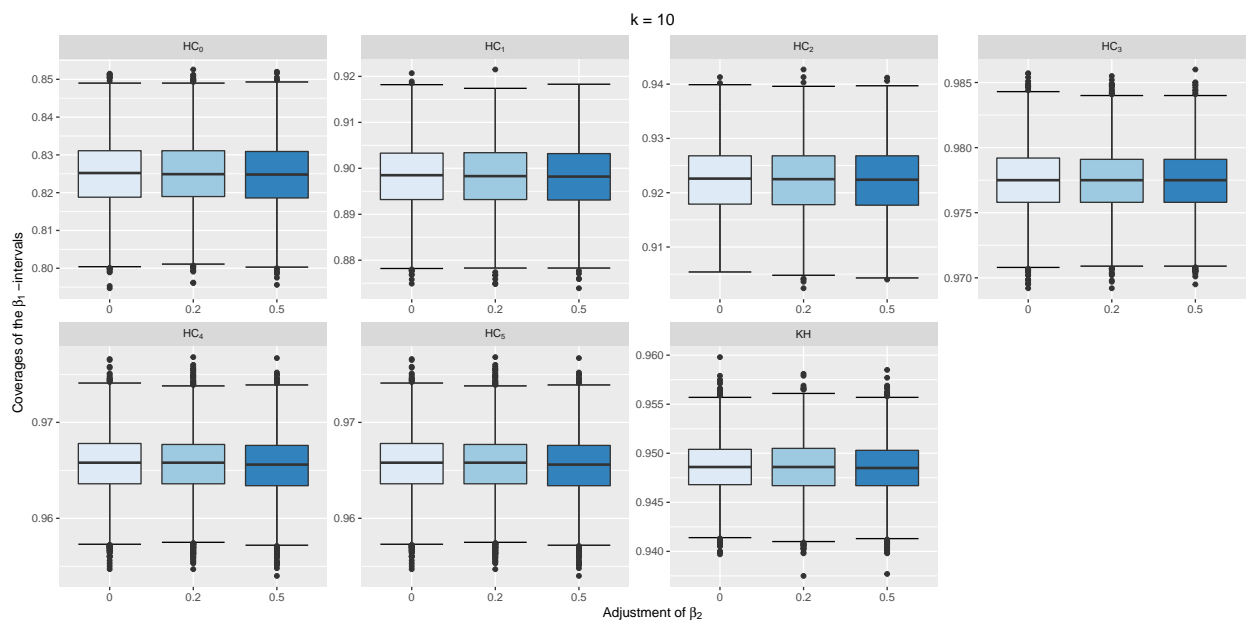Figure 5: Coverages of the β_1-intervals compared regarding the adjustments of k for the estimators $HC_0 - HC_5$ and KH.
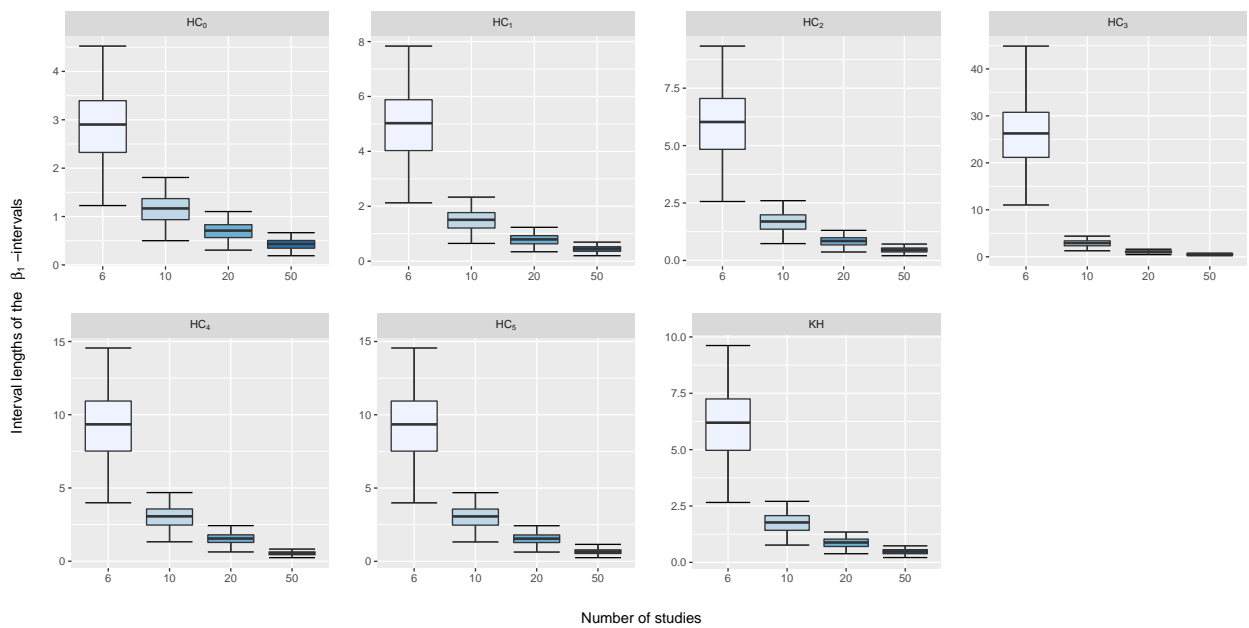
Figure 6: Lengths of the β_1-intervals compared regarding the adjustments of k for the estimators $HC_0 - HC_5$ and KH without outliers.
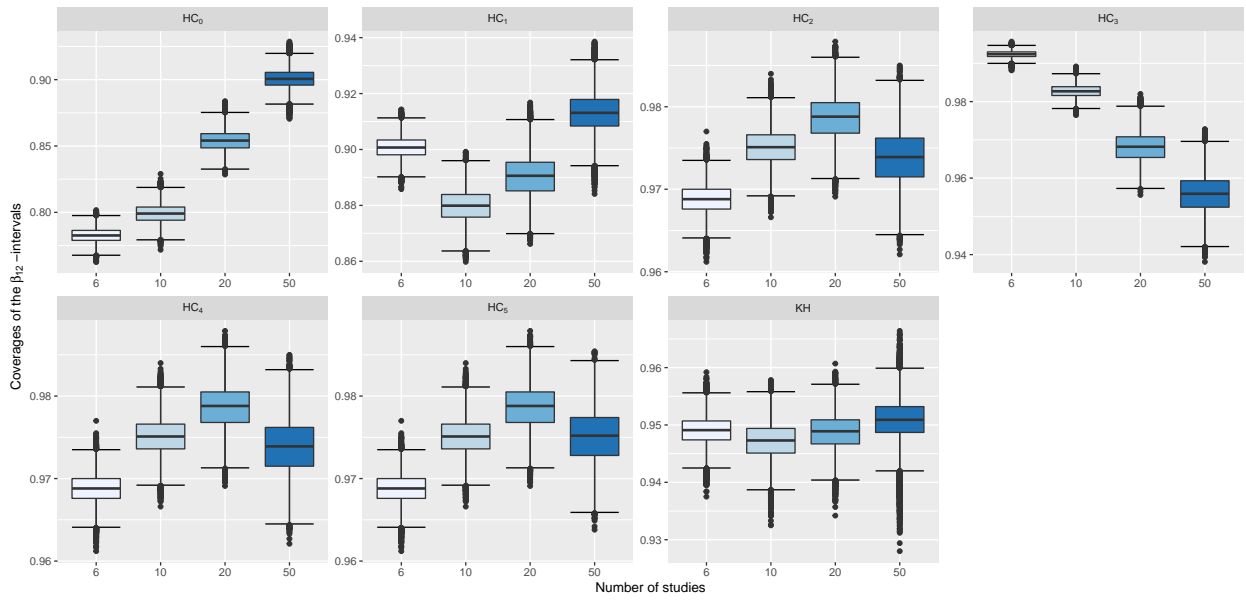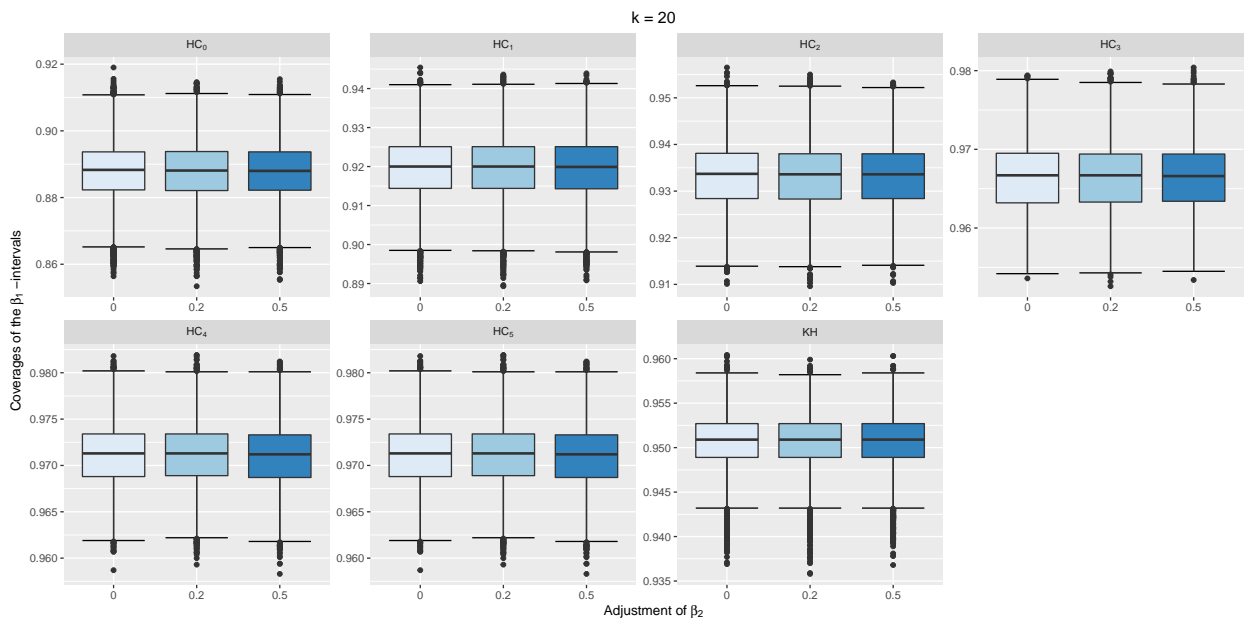
Figure 7: Coverages of the β_{12}-intervals compared regarding the adjustments of k for the estimators $HC_0 - HC_5$ and KH.
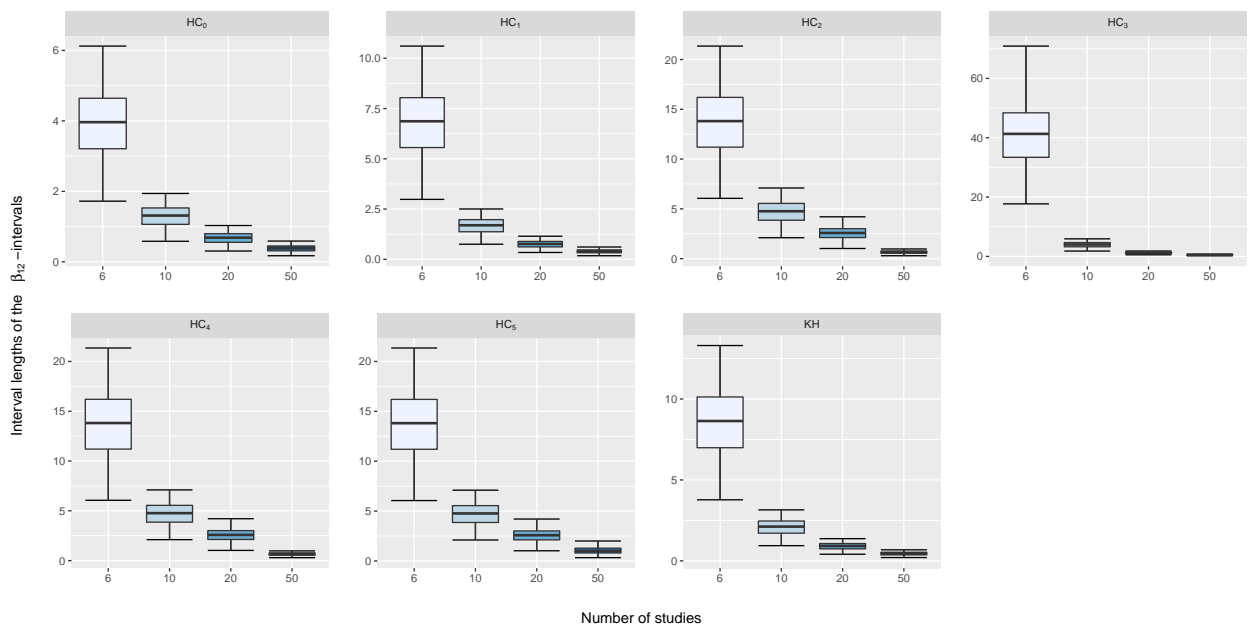
Figure 8: Lengths of the β_{12}-intervals compared regarding the adjustments of k for the estimators $HC_0 - HC_5$ and KH without outliers.
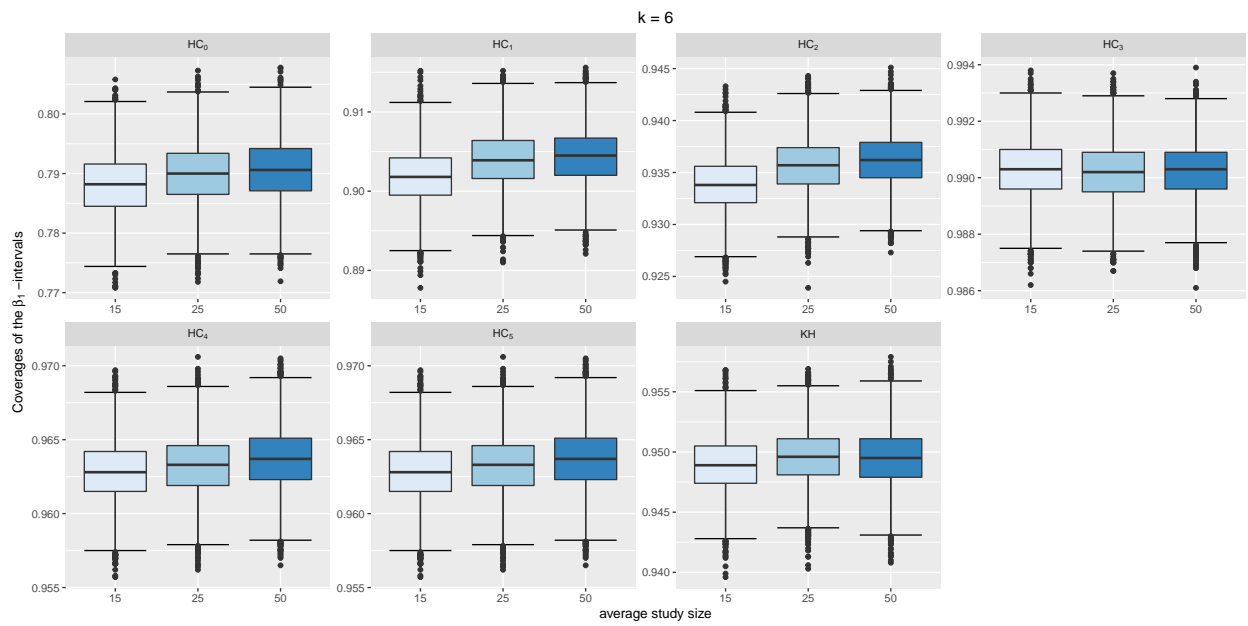
Figure 9: Coverages of the β_1-intervals compared regarding the adjustments of group size (n_i) for the estimators $HC_0 - HC_5$ and KH with $k = 6$.
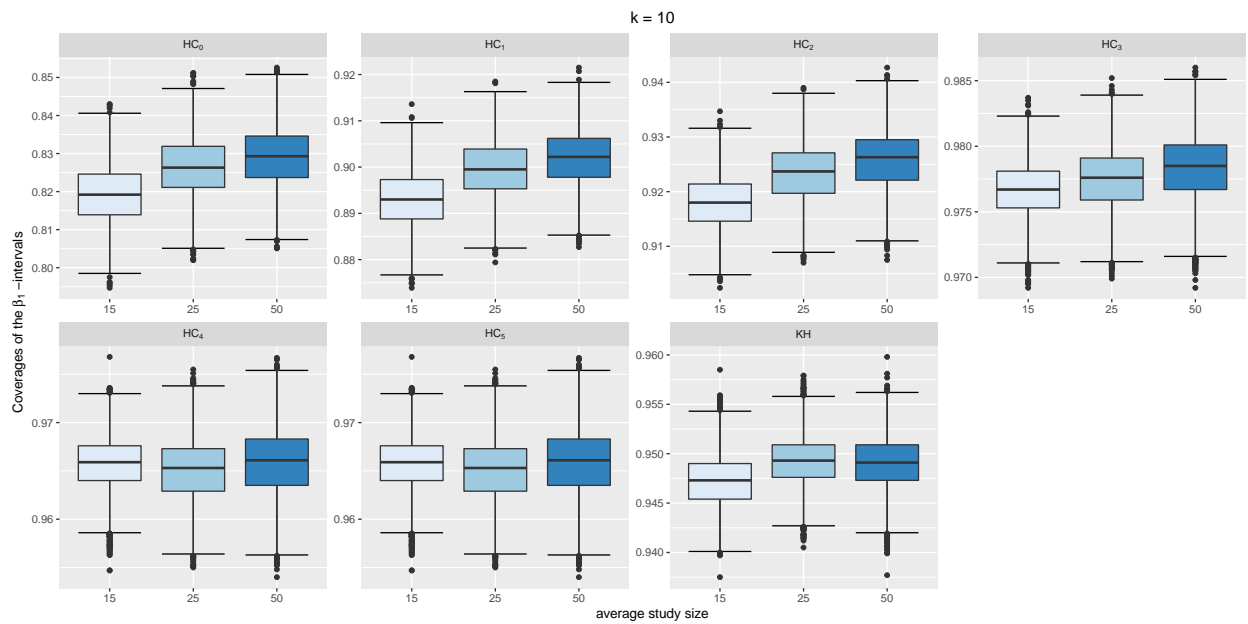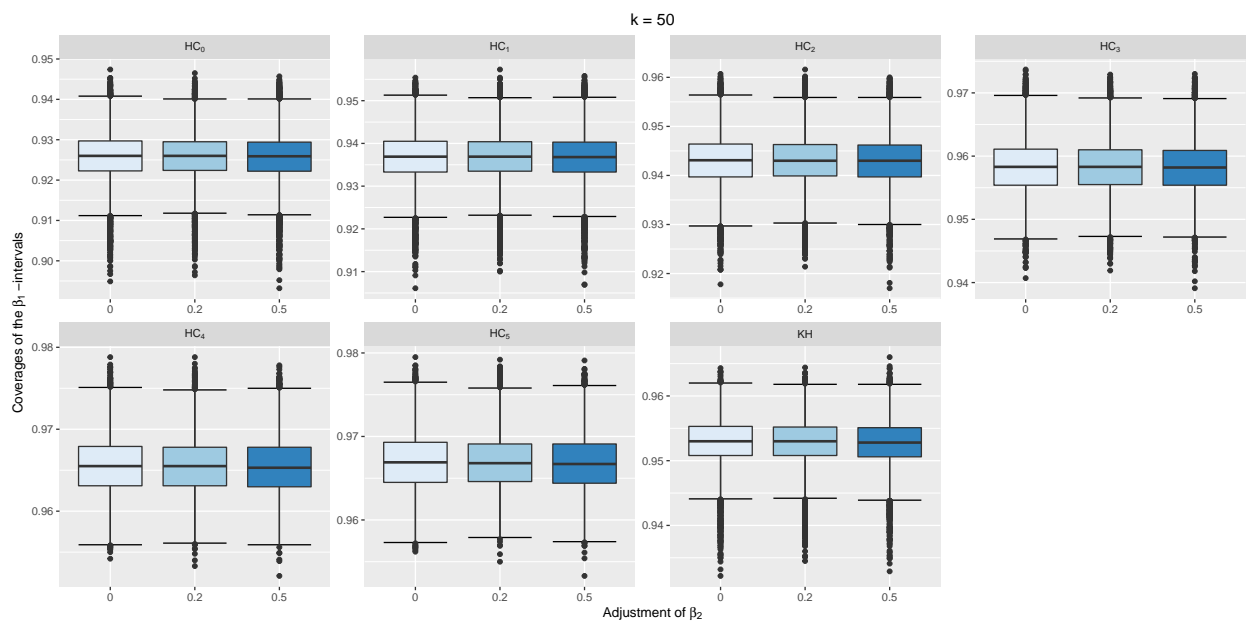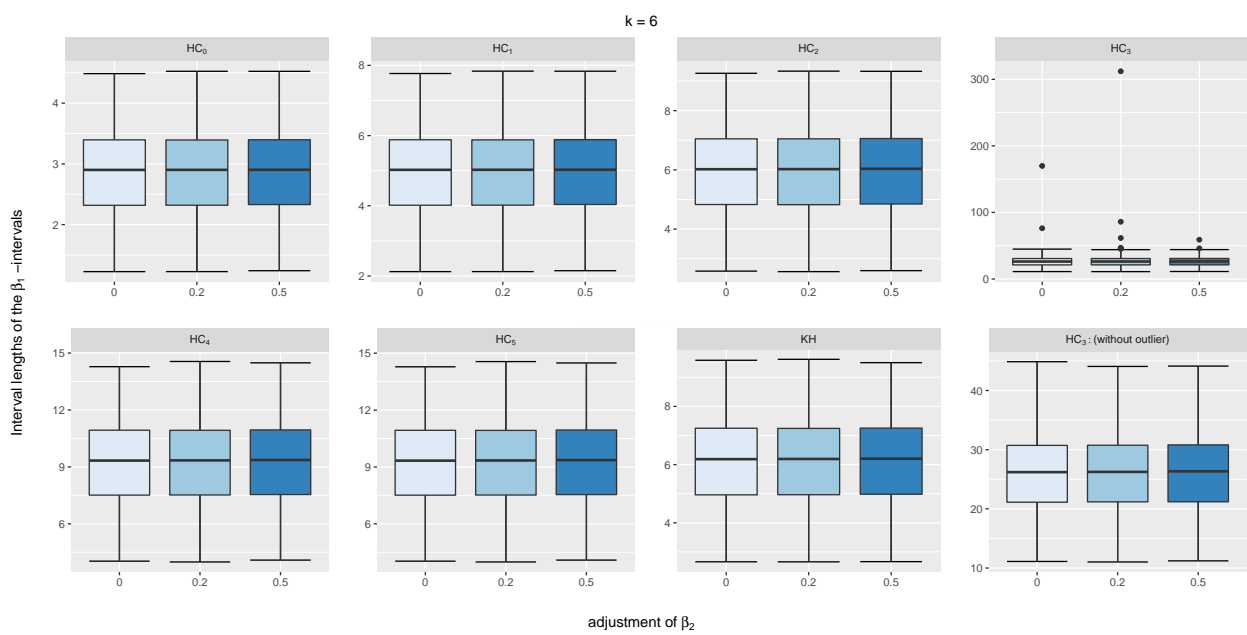
Figure 10: Coverages of the β_1-intervals compared regarding the adjustments of group size (n_i) for the estimators $HC_0 - HC_5$ and KH with $k = 10$.
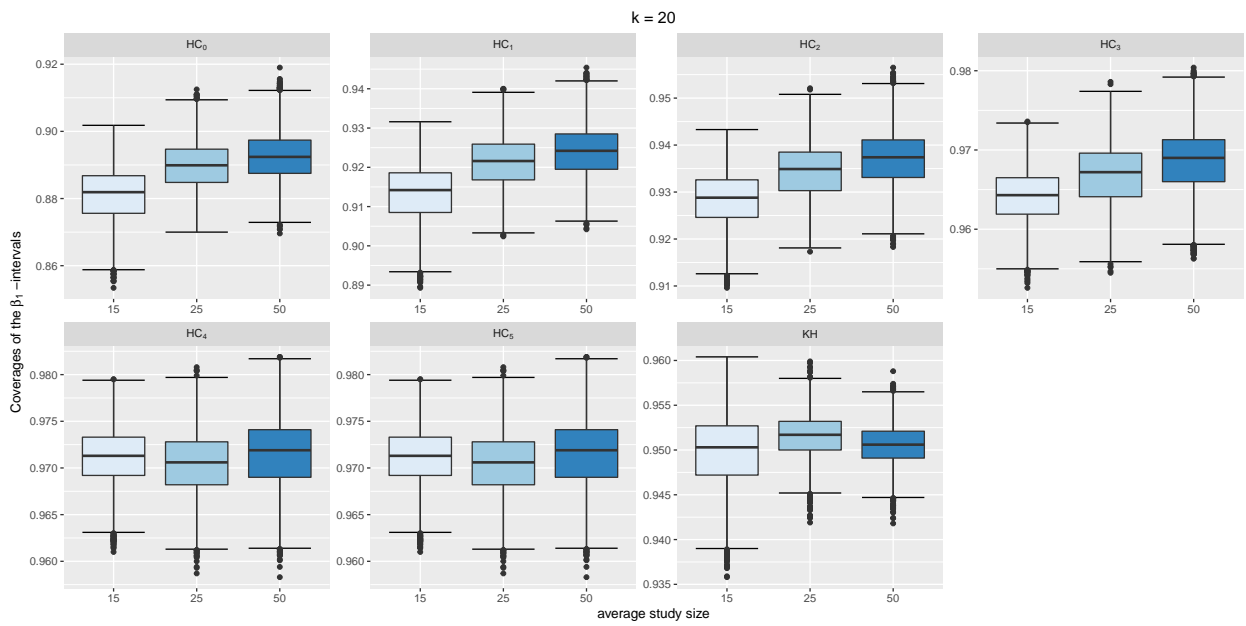
Figure 11: Coverages of the β_1-intervals compared regarding the adjustments of group size (n_i) for the estimators $HC_0 - HC_5$ and KH with $k = 20$.
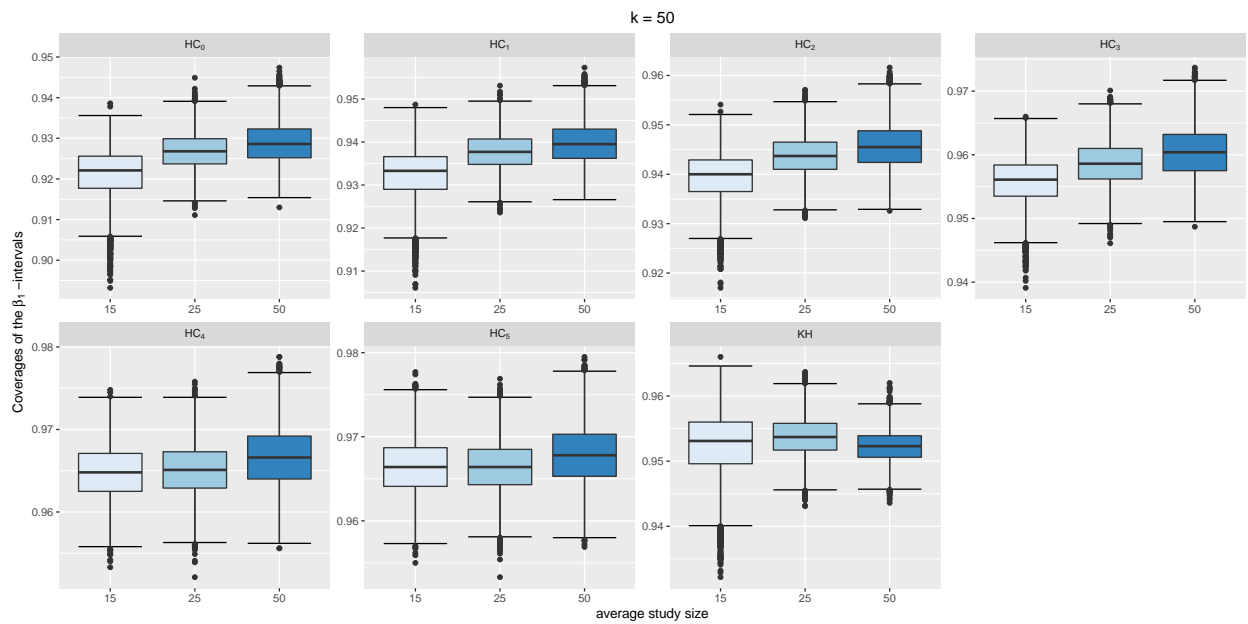
Figure 12: Coverages of the β_1-intervals compared regarding the adjustments of group size (n_i) for the estimators $HC_0 - HC_5$ and KH with $k = 50$.
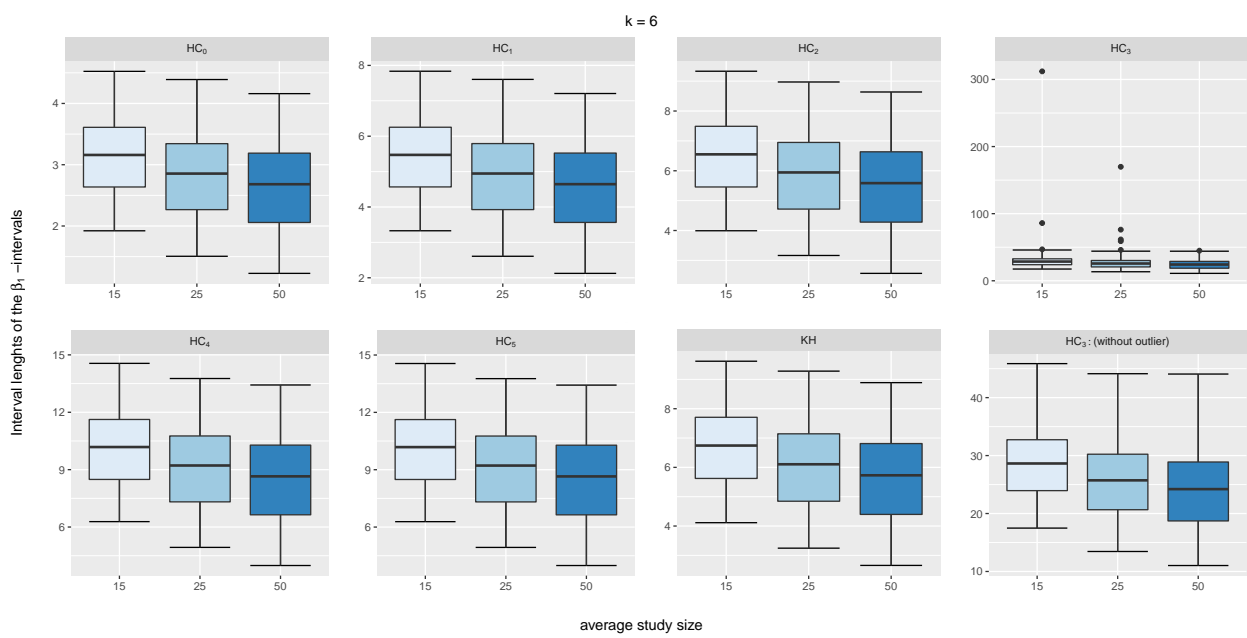
Figure 13: Lengths of the β_1-intervals compared regarding the adjustments of group size (n_i) for the estimators $HC_0 - HC_5$ and KH with $k = 6$.
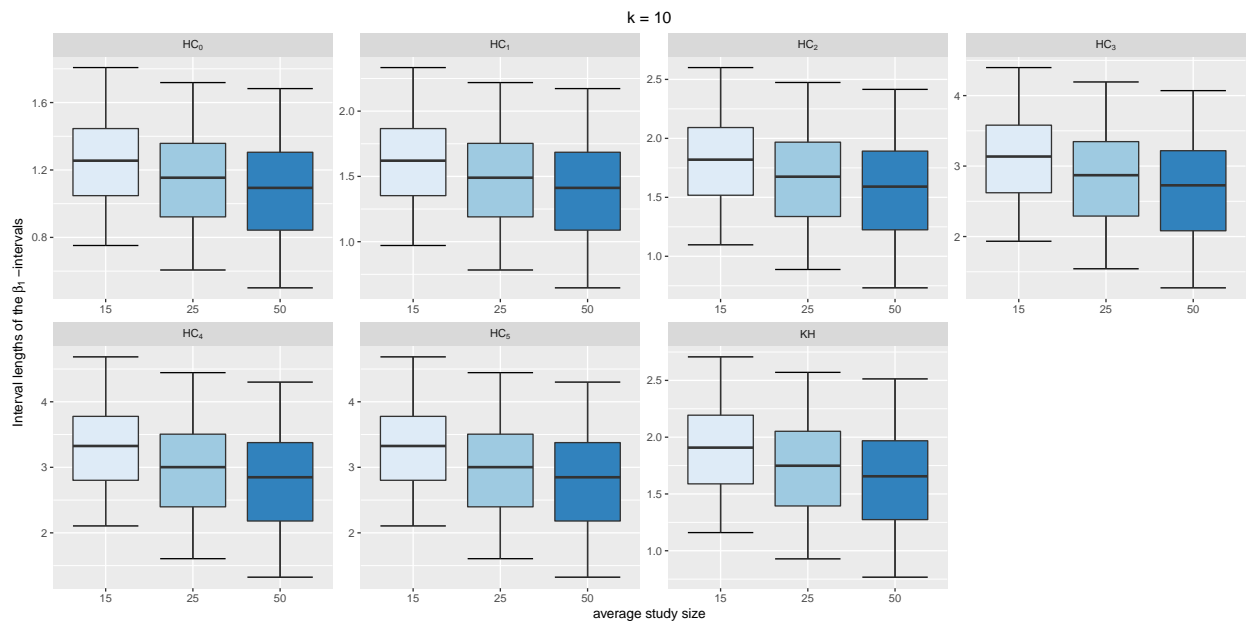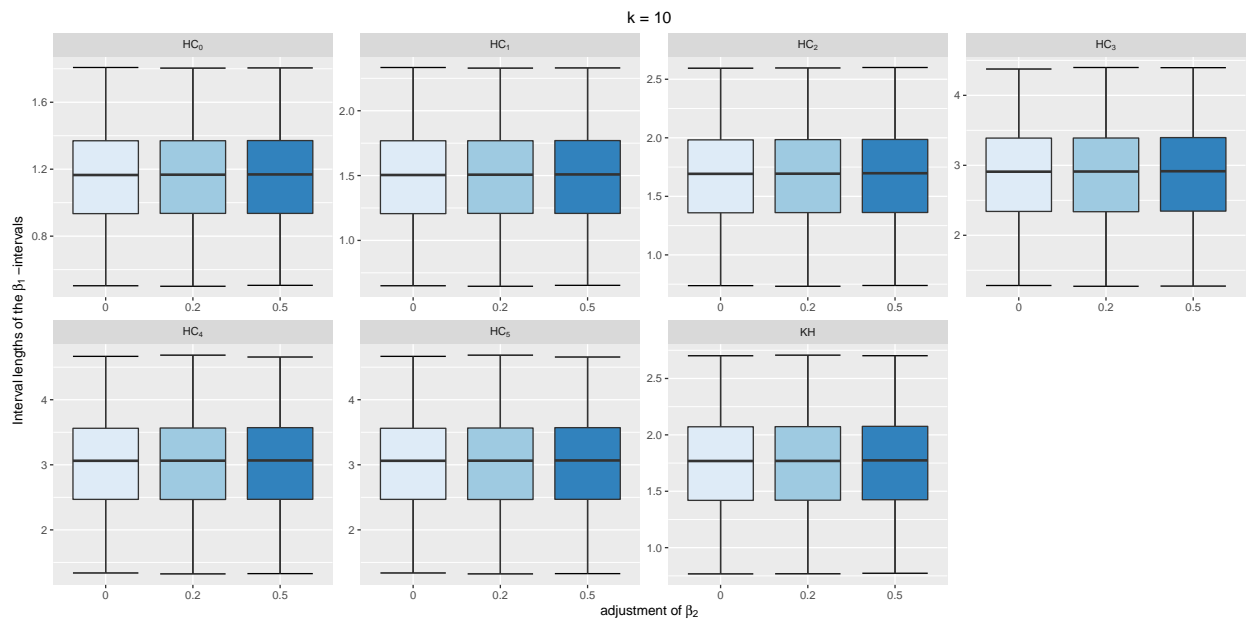
Figure 14: Lengths of the β_1-intervals compared regarding the adjustments of group size (n_i) for the estimators $HC_0 - HC_5$ and KH with $k = 10$.
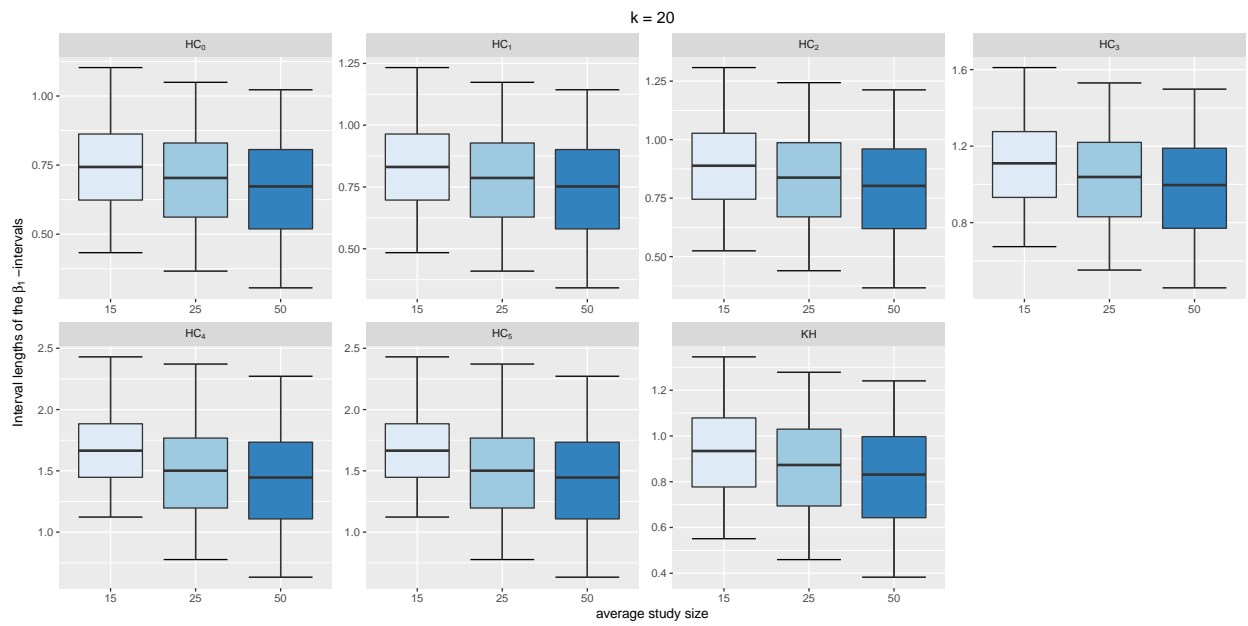
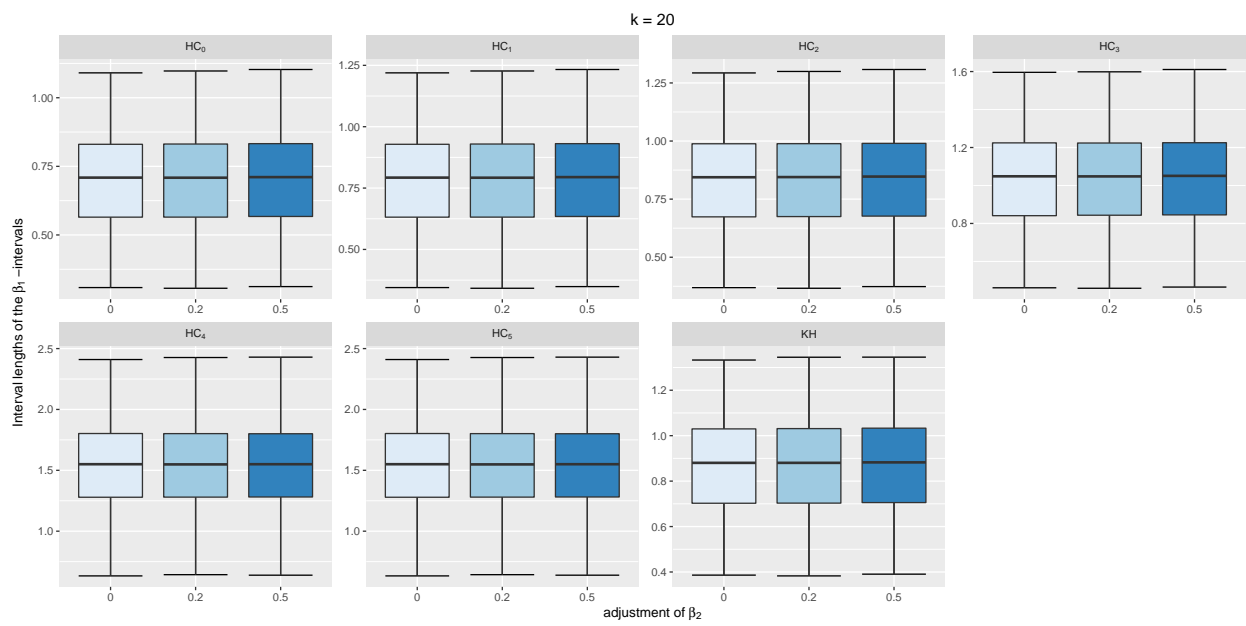Figure 15: Lengths of the β_1-intervals compared regarding the adjustments of group size (n_i) for the estimators $HC_0 - HC_5$ and KH with $k = 20$.
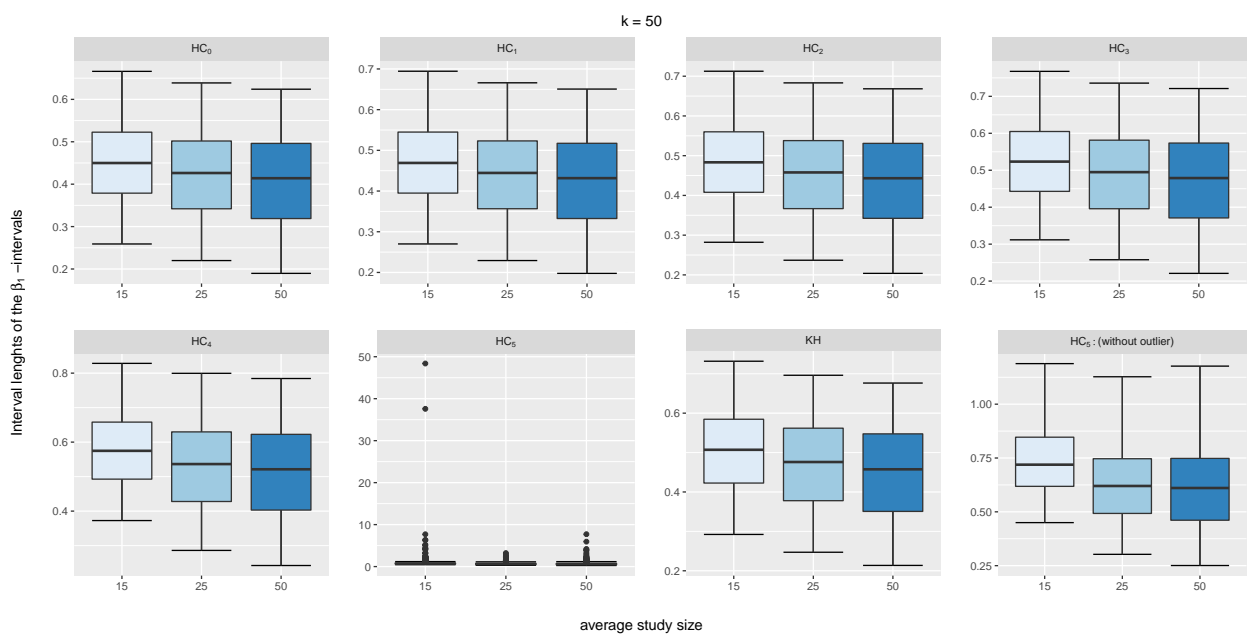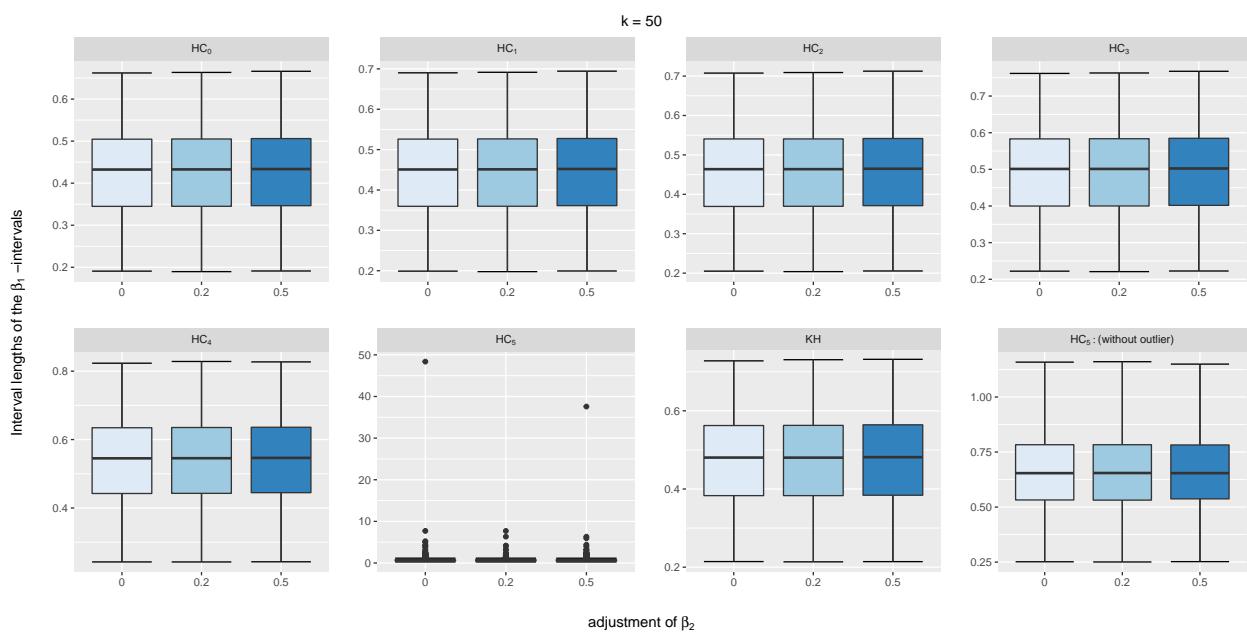
Figure 16: Lengths of the β_1-intervals compared regarding the adjustments of group size (n_i) for the estimators $HC_0 - HC_5$ and KH with $k = 50$.
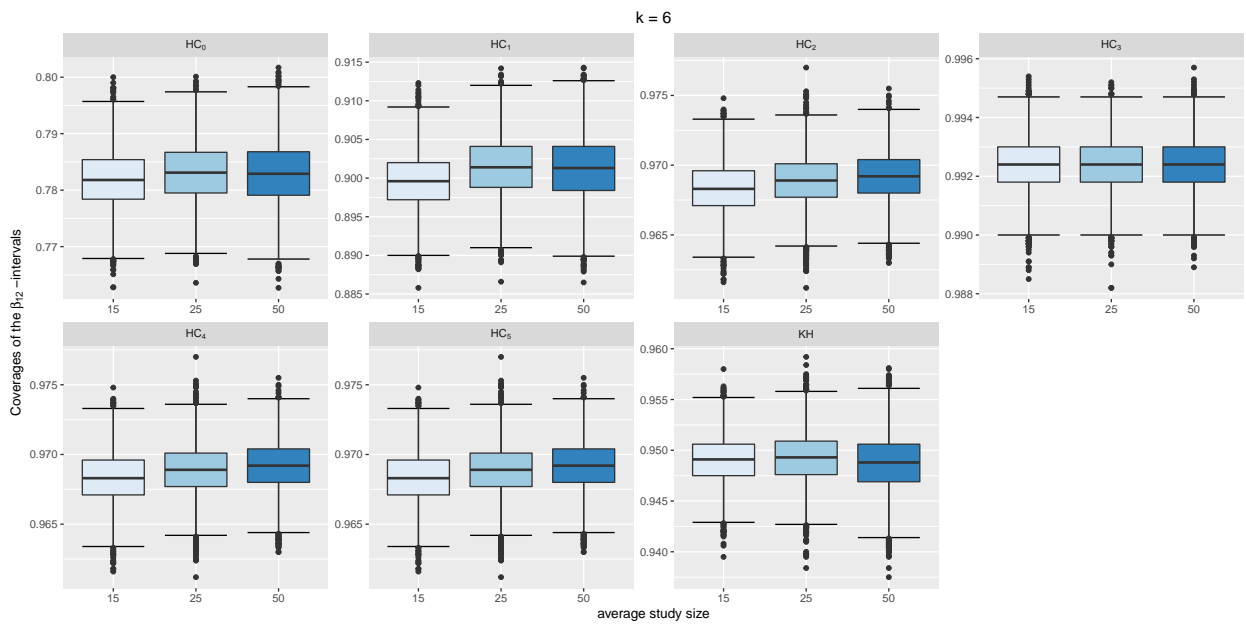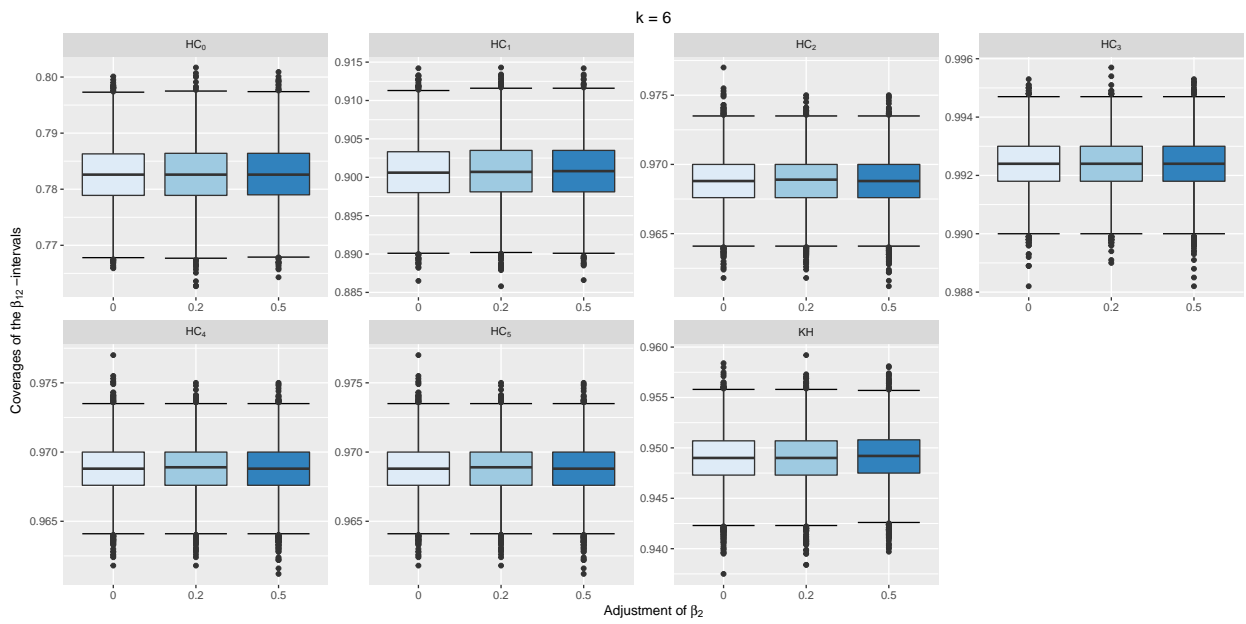
Figure 17: Coverages of the β_{12}-intervals compared regarding the adjustments of group size (n_i) for the estimators $HC_0 - HC_5$ and KH with $k = 6$.
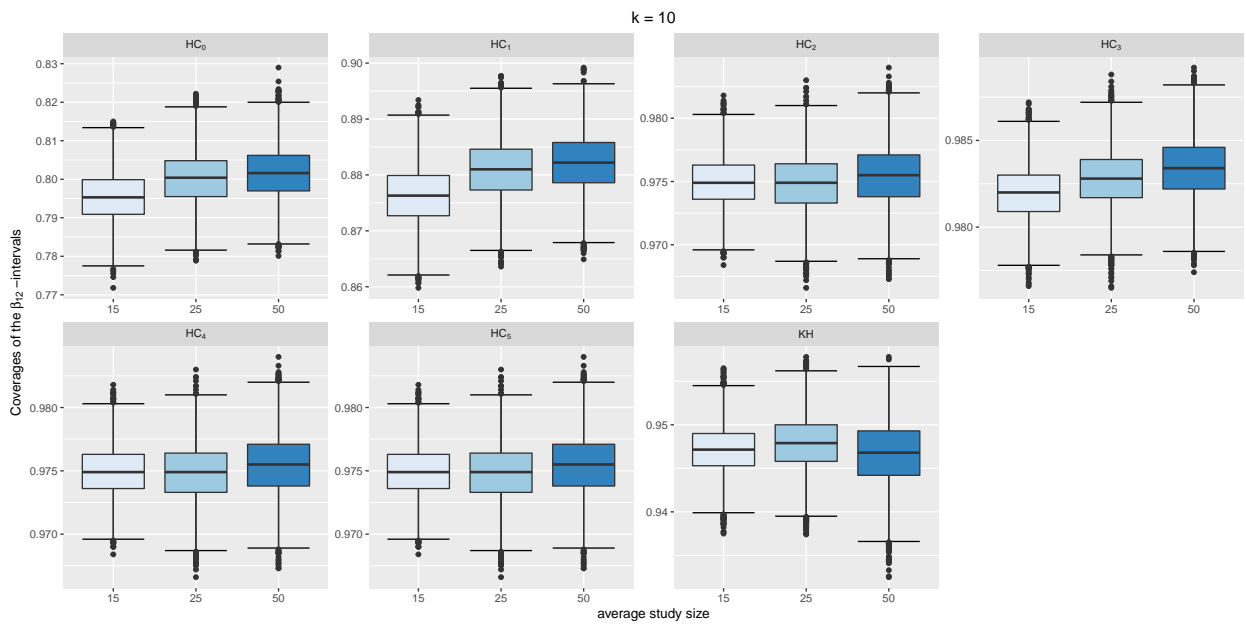
Figure 18: Coverages of the β_{12}-intervals compared regarding the adjustments of group size (n_i) for the estimators $HC_0 - HC_5$ and KH with $k = 10$.
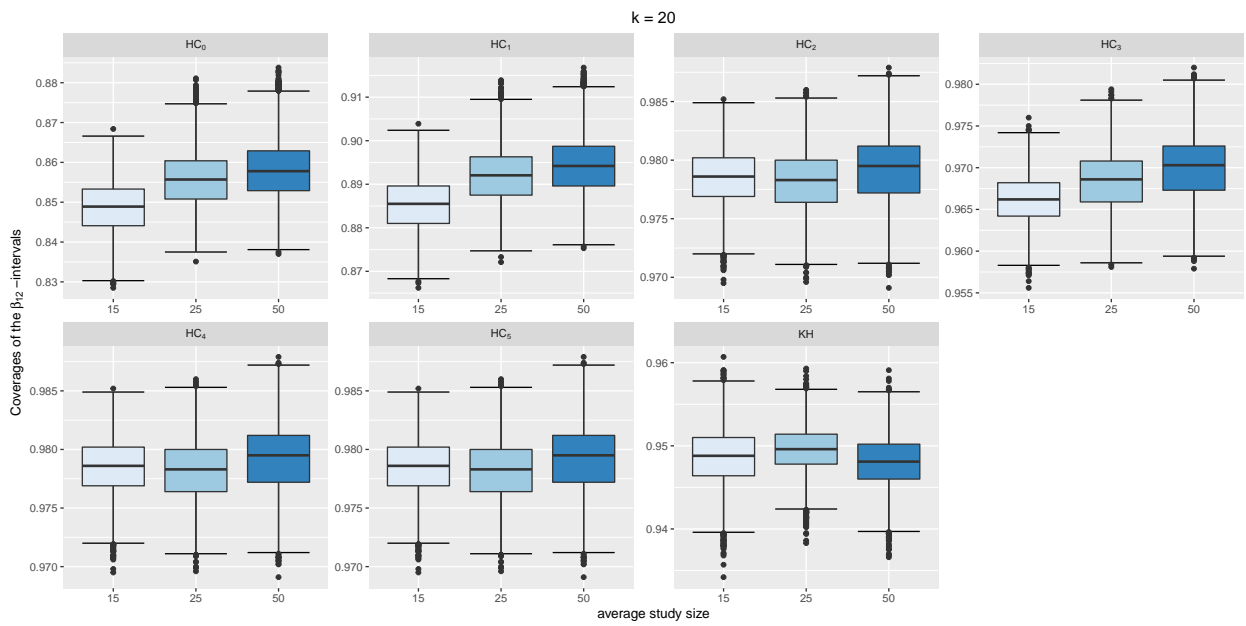
Figure 19: Coverages of the β_{12}-intervals compared regarding the adjustments of group size (n_i) for the estimators $HC_0 - HC_5$ and KH with $k = 20$.
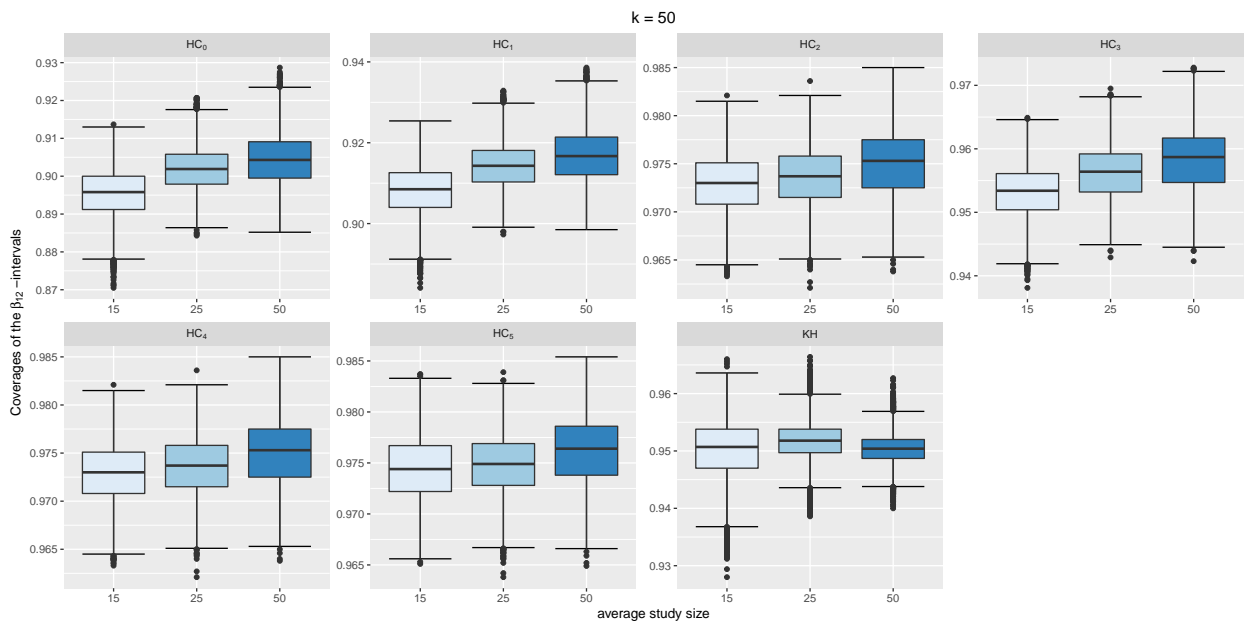
Figure 20: Coverages of the β_{12}-intervals compared regarding the adjustments of group size (n_i) for the estimators $HC_0 - HC_5$ and KH with $k = 50$.
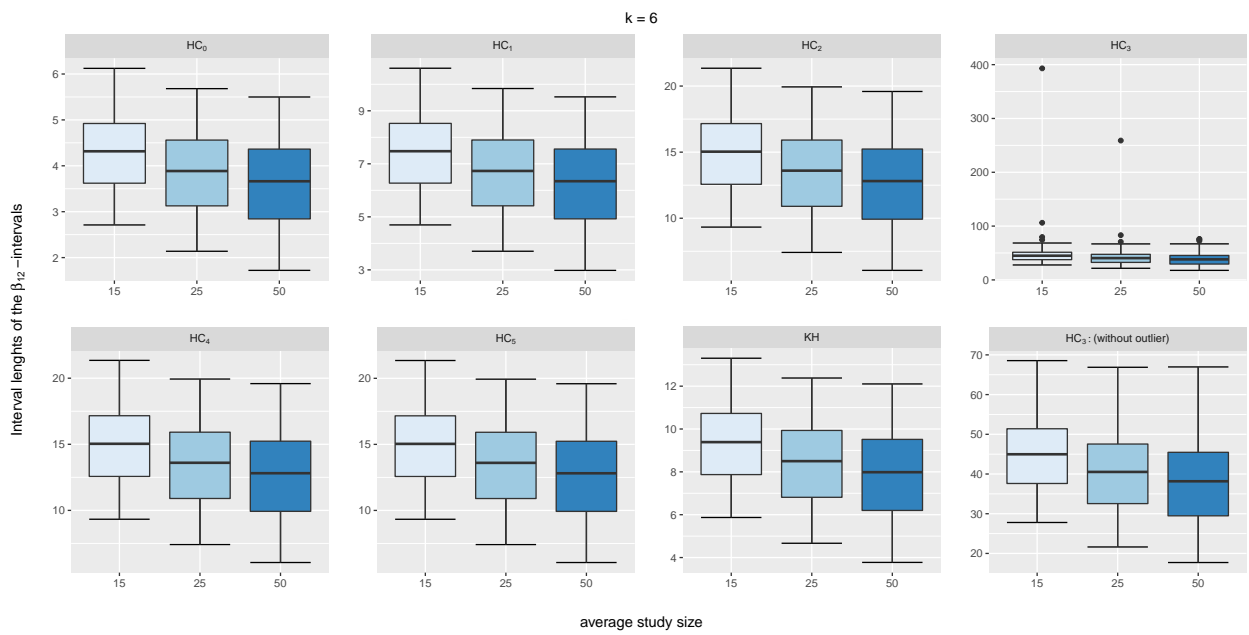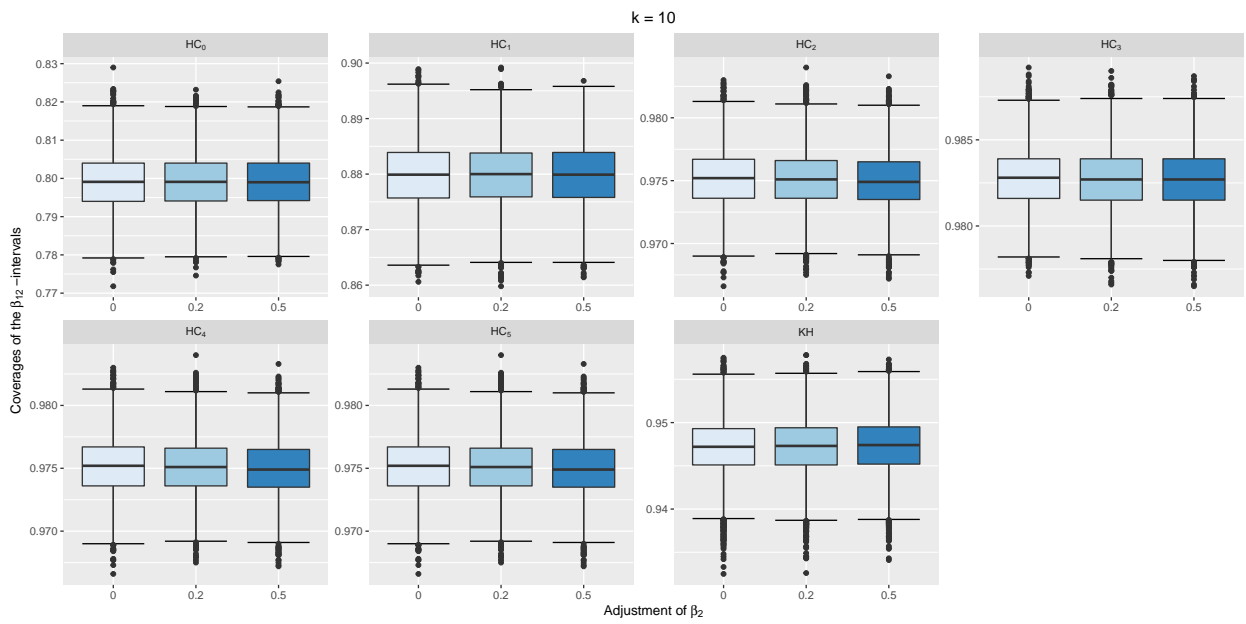
Figure 21: Lengths of the β_{12}-intervals compared regarding the adjustments of group size (n_i) for the estimators $HC_0 - HC_5$ and KH with $k = 6$.
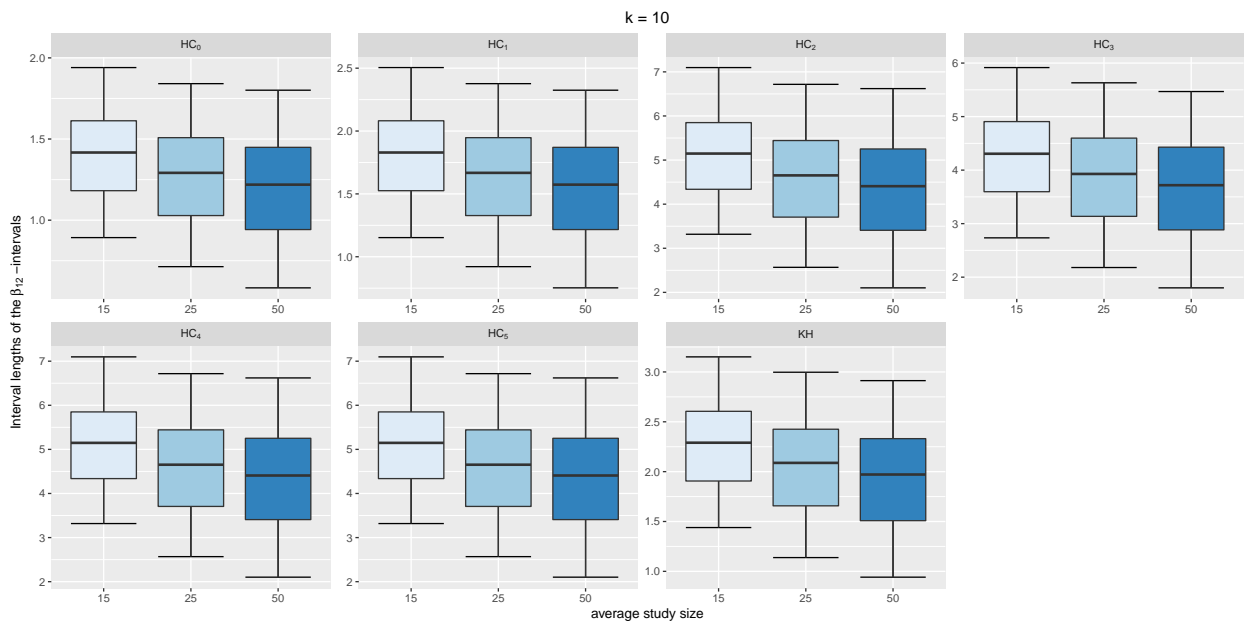
Figure 22: Lengths of the β_{12}-intervals compared regarding the adjustments of group size (n_i) for the estimators $HC_0 - HC_5$ and KH with $k = 10$.
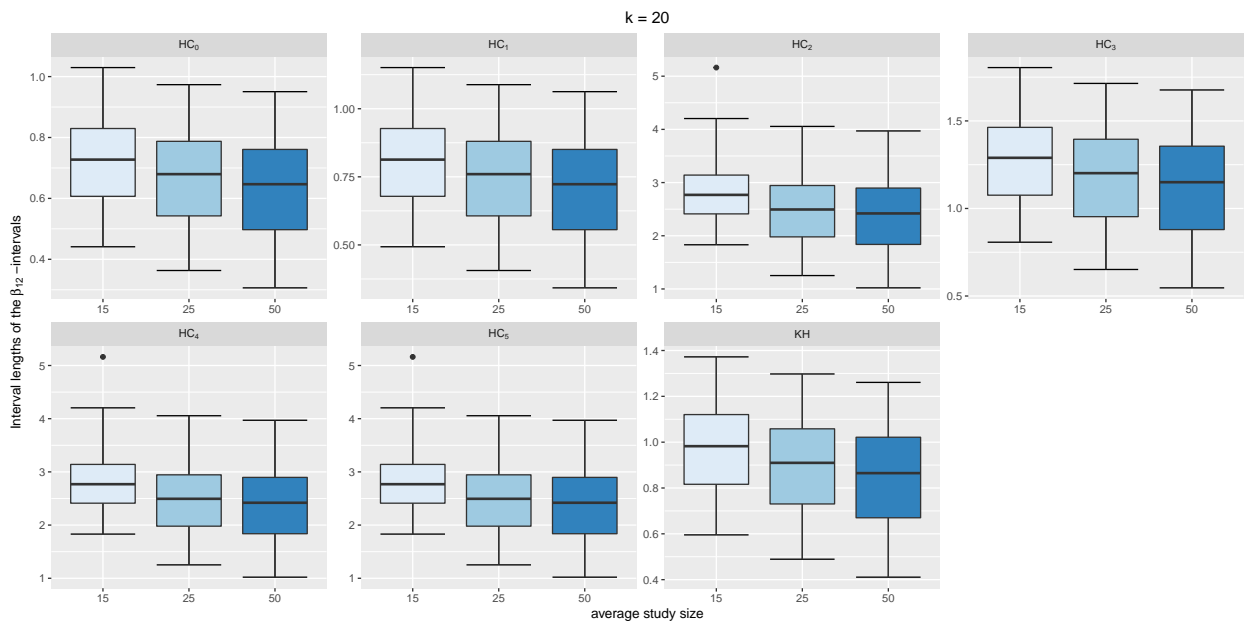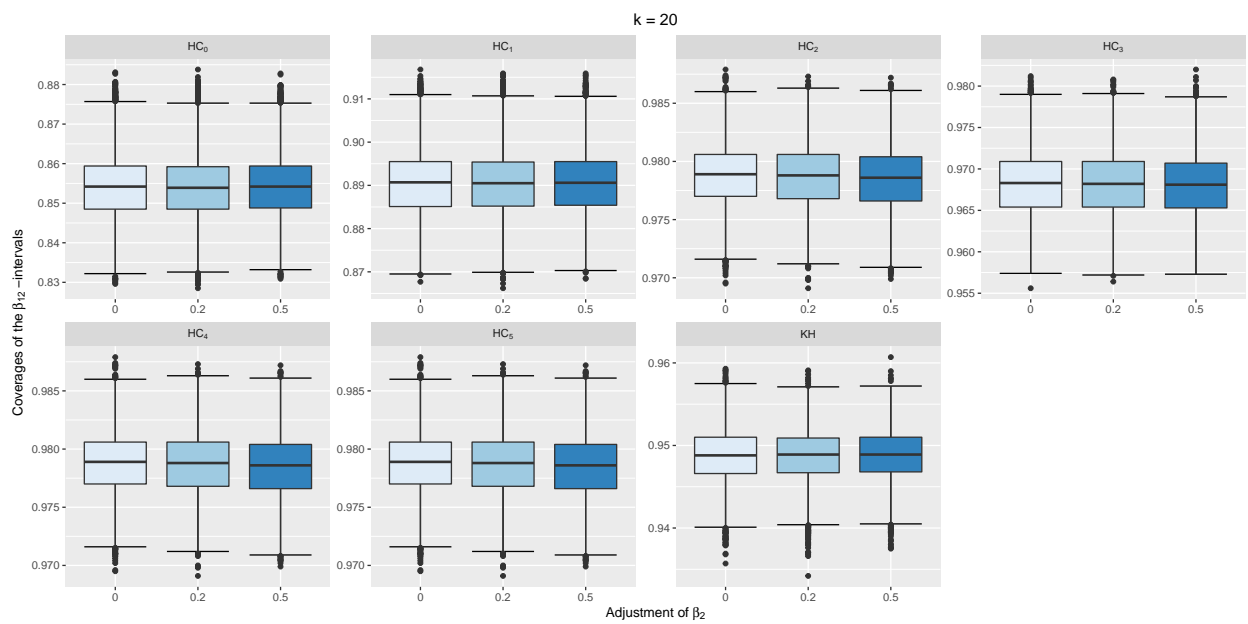
Figure 23: Lengths of the β_{12}-intervals compared regarding the adjustments of group size (n_i) for the estimators $HC_0 - HC_5$ and KH with $k = 20$.
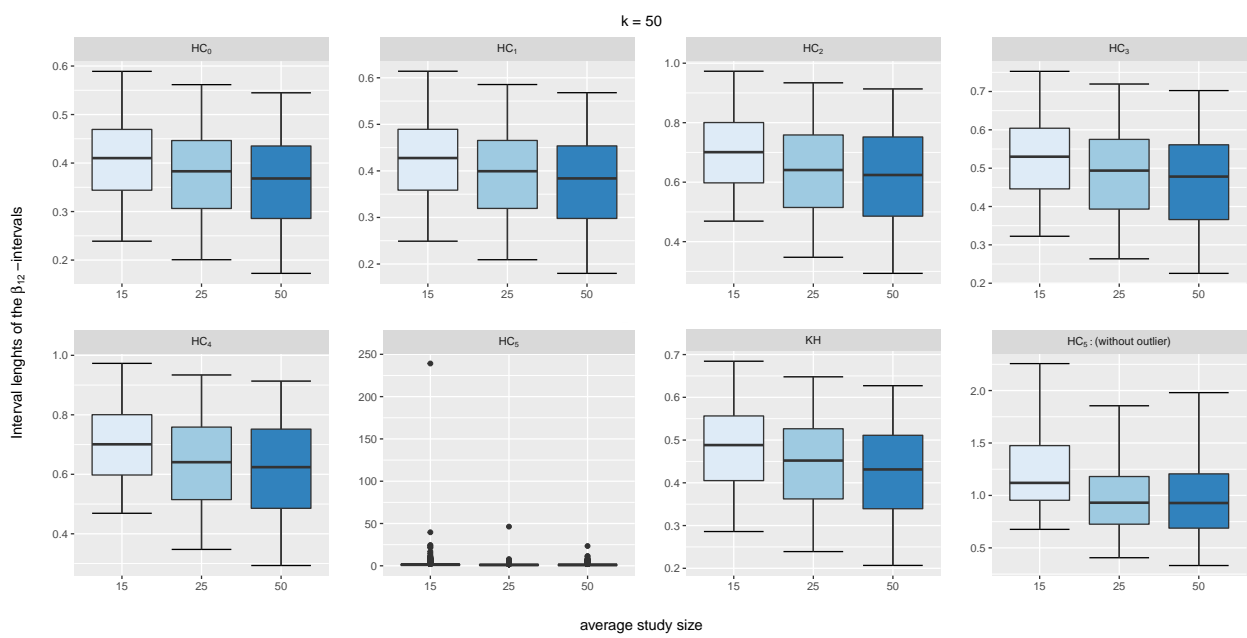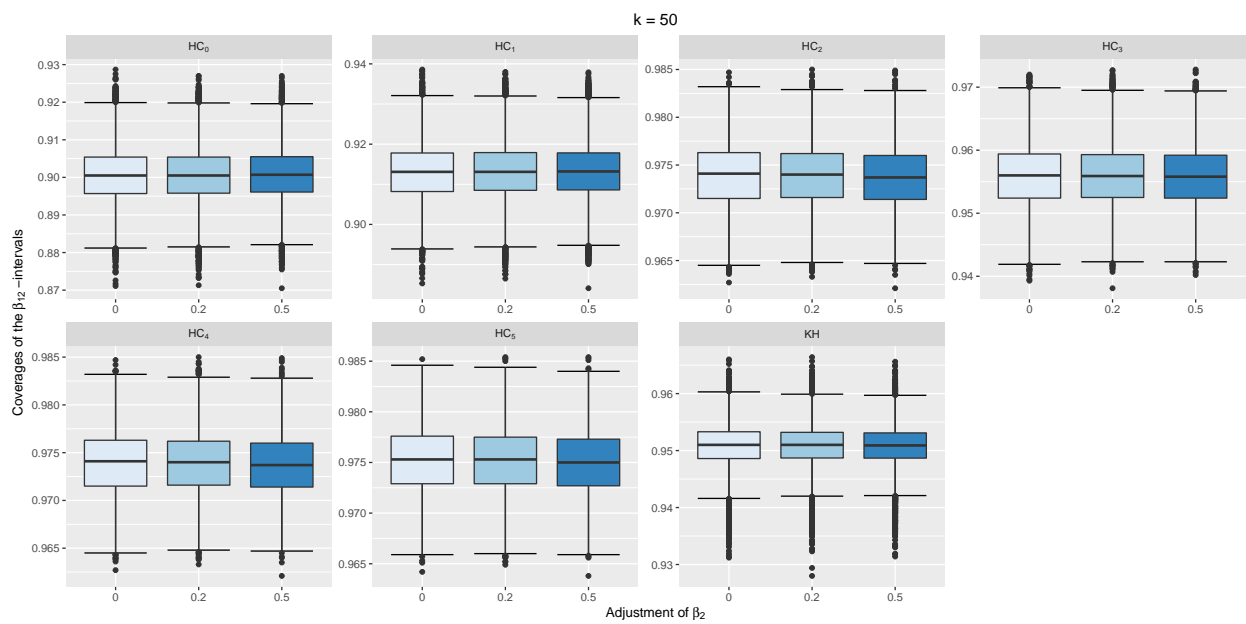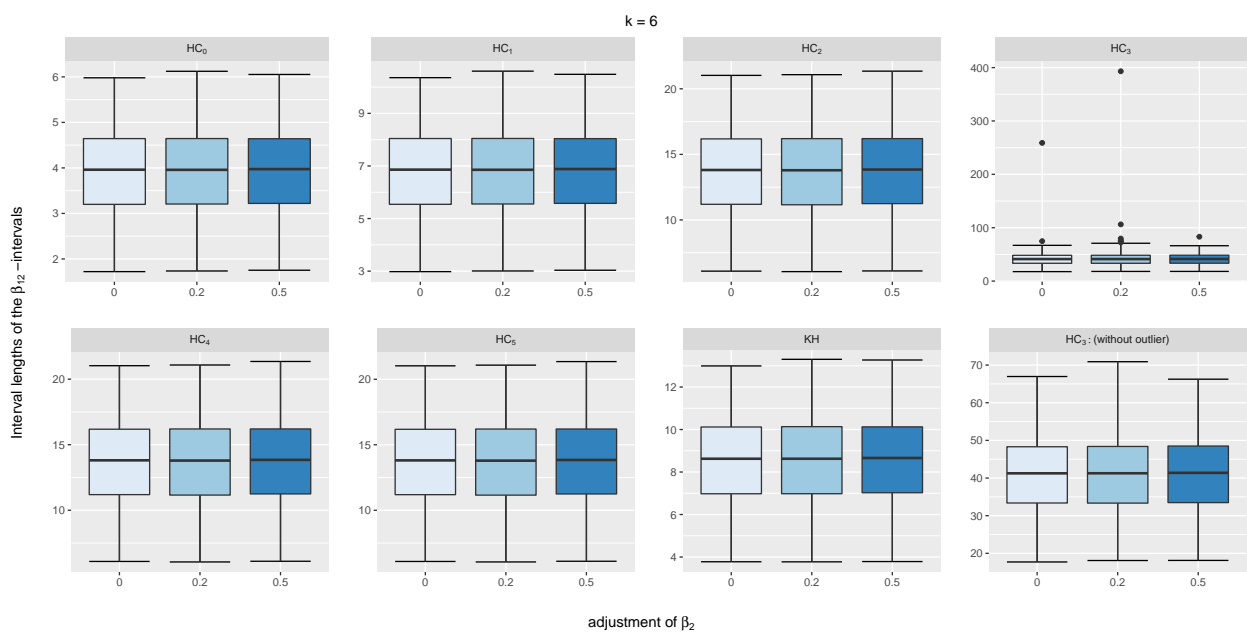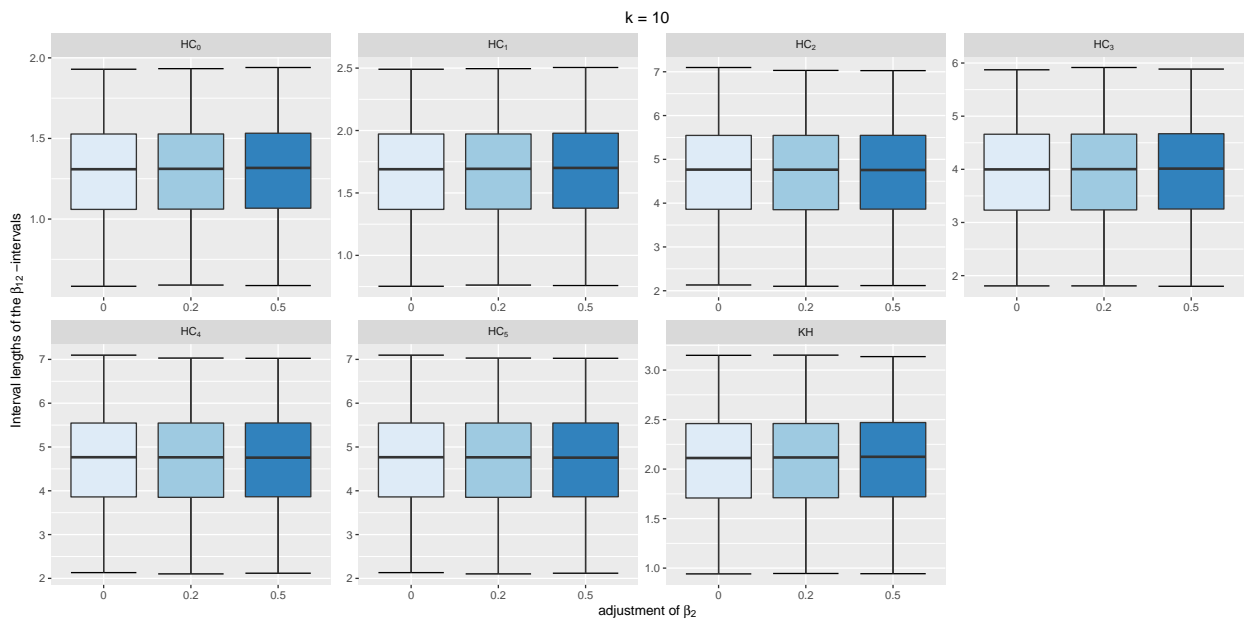
Figure 24: Lengths of the β_{12}-intervals compared regarding the adjustments of group size (n_i) for the estimators $HC_0 - HC_5$ and KH with $k = 50$.
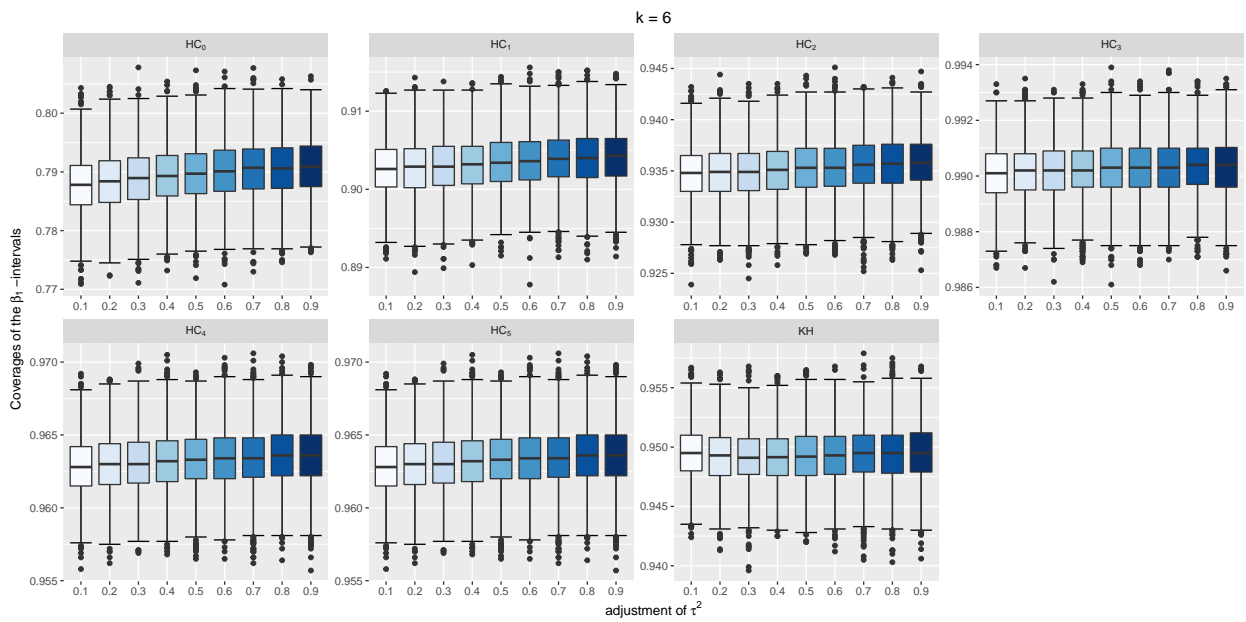
Figure 25: Coverages of the β_1-intervals compared regarding the adjustments of the heterogeneity parameter τ^2 for the estimators $HC_0 - HC_5$ and KH with $k = 6$.
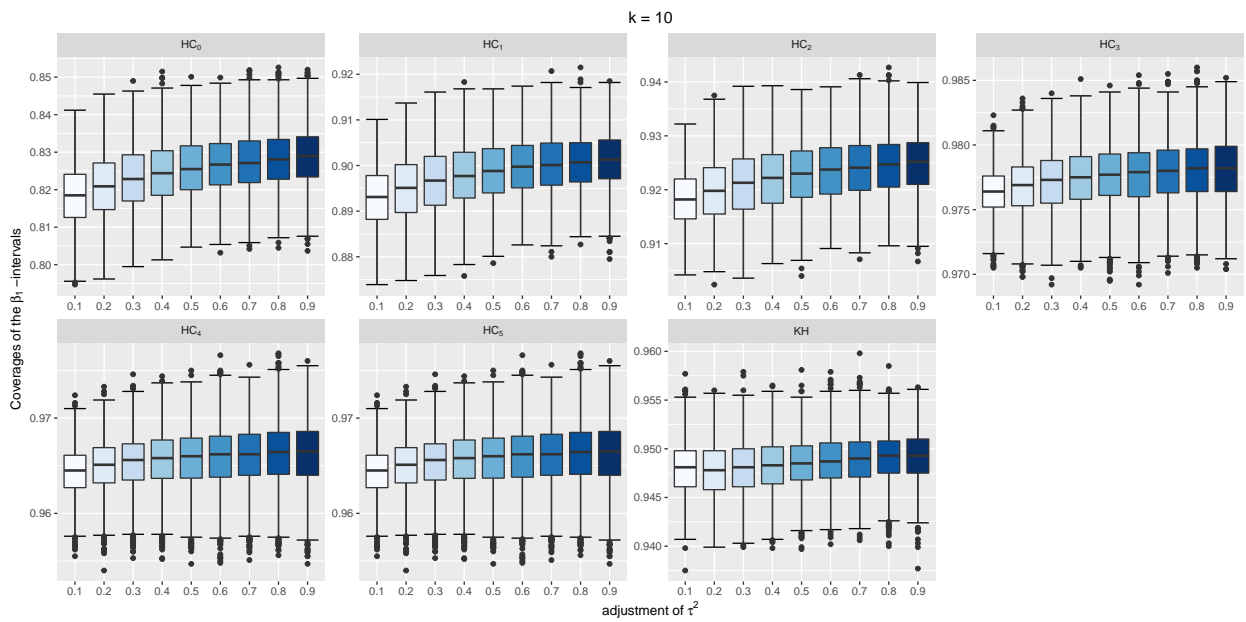
Figure 26: Coverages of the β_1-intervals compared regarding the adjustments of the heterogeneity parameter τ^2 for the estimators $HC_0 - HC_5$ and KH with $k = 10$.
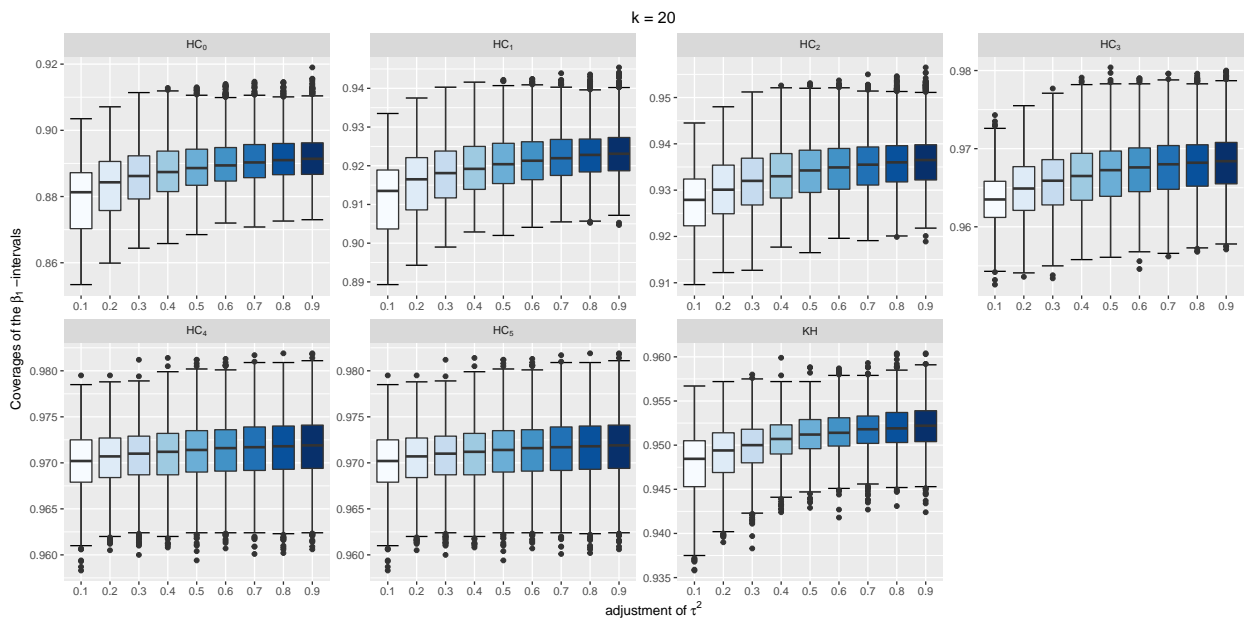
Figure 27: Coverages of the β_1-intervals compared regarding the adjustments of the heterogeneity parameter τ^2 for the estimators $HC_0 - HC_5$ and KH with $k = 20$.
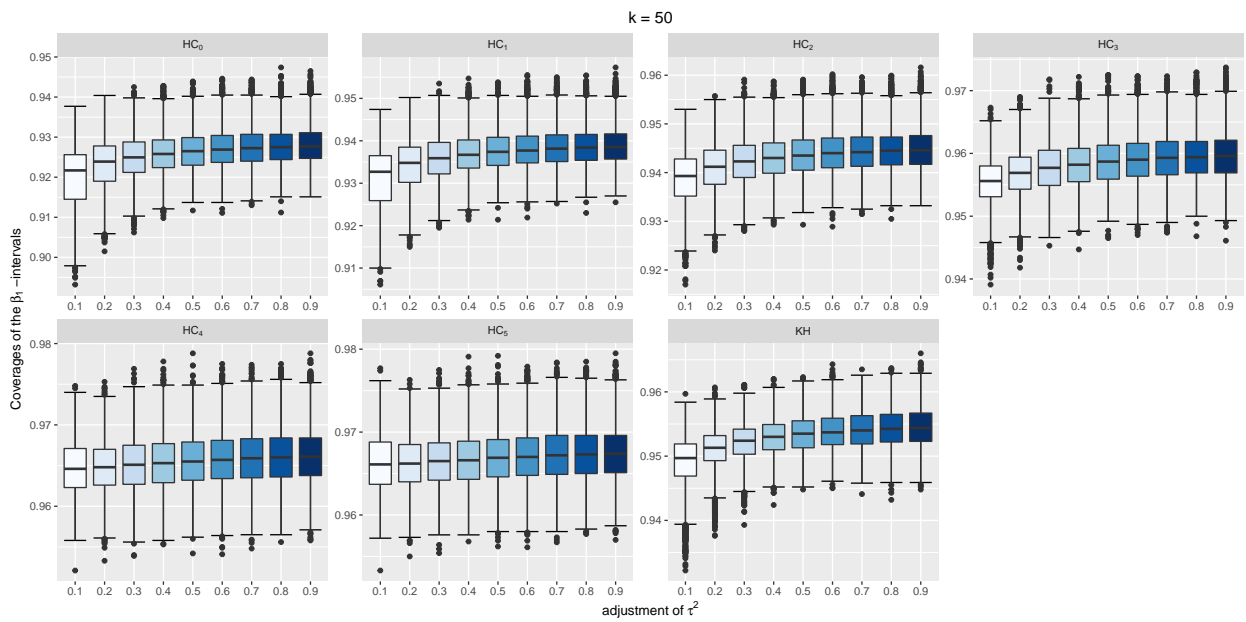
Figure 28: Coverages of the β_1-intervals compared regarding the adjustments of the heterogeneity parameter τ^2 for the estimators $HC_0 - HC_5$ and KH with $k = 50$.
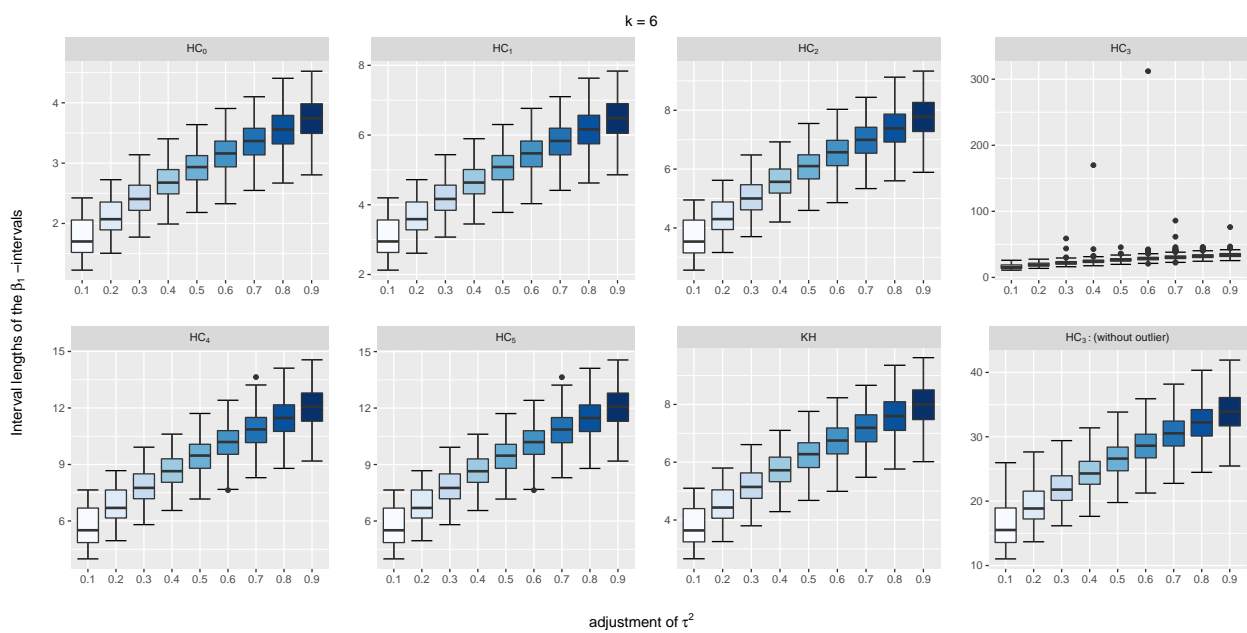
Figure 29: Lengths of the β_1-intervals compared regarding the adjustments of the heterogeneity parameter τ^2 for the estimators $HC_0 - HC_5$ and KH with $k = 6$.
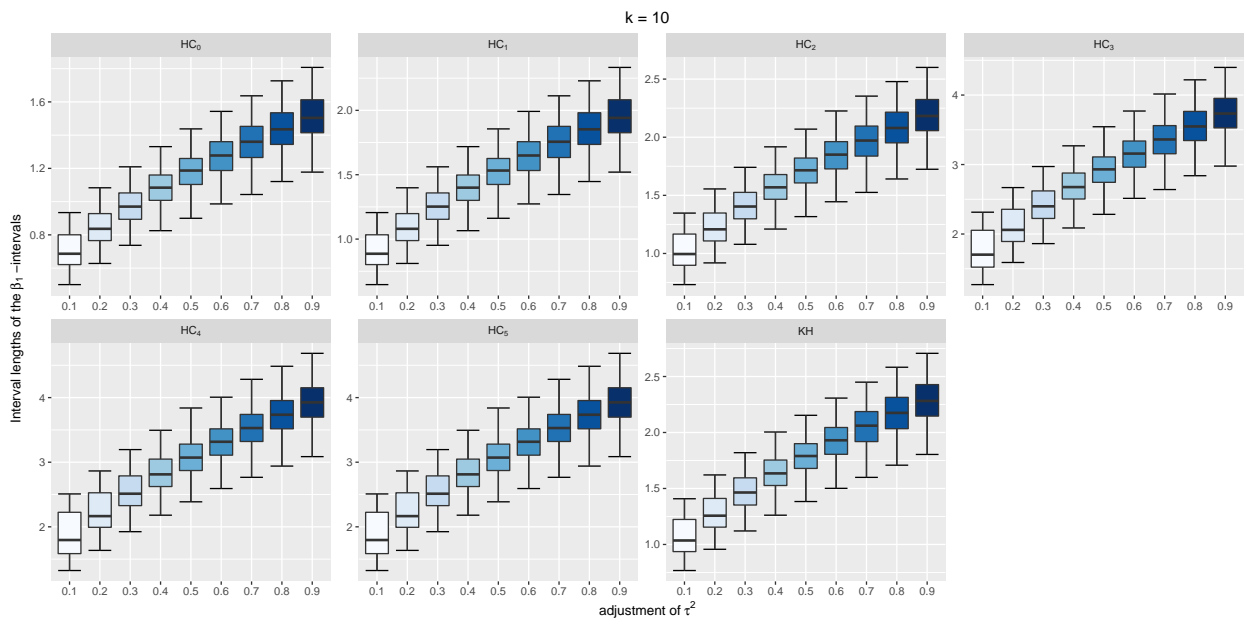
Figure 30: Lengths of the β_1-intervals compared regarding the adjustments of the heterogeneity parameter τ^2 for the estimators $HC_0 - HC_5$ and KH with $k = 10$.
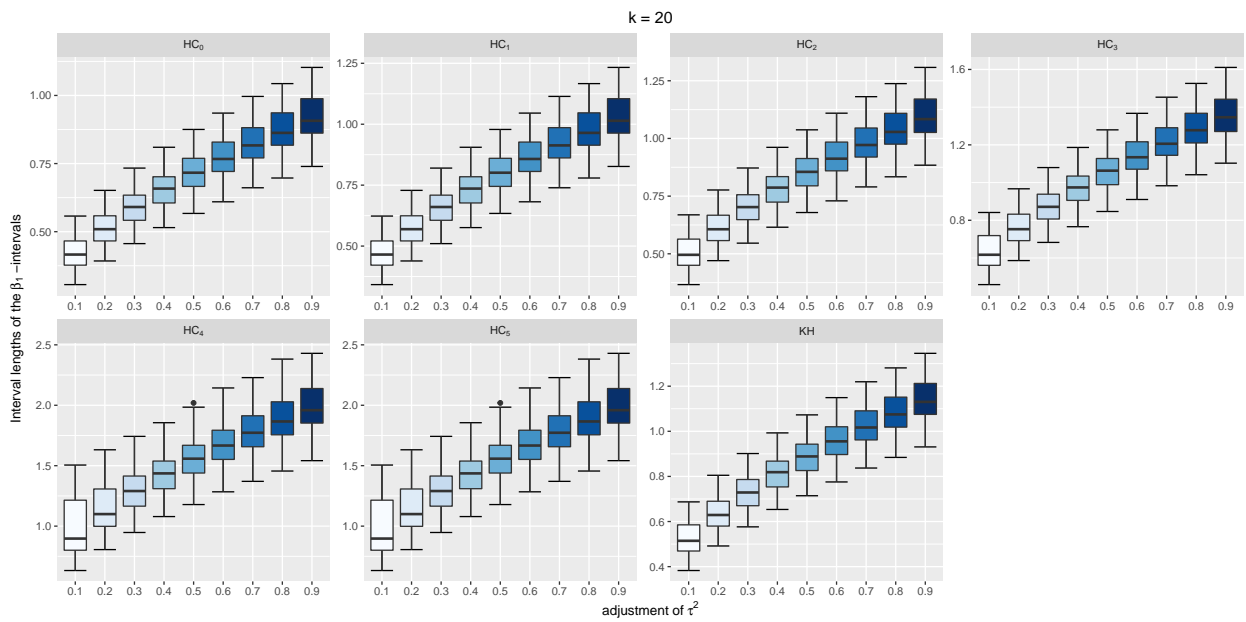
Figure 31: Lengths of the β_1-intervals compared regarding the adjustments of the heterogeneity parameter τ^2 for the estimators $HC_0 - HC_5$ and KH with $k = 20$.
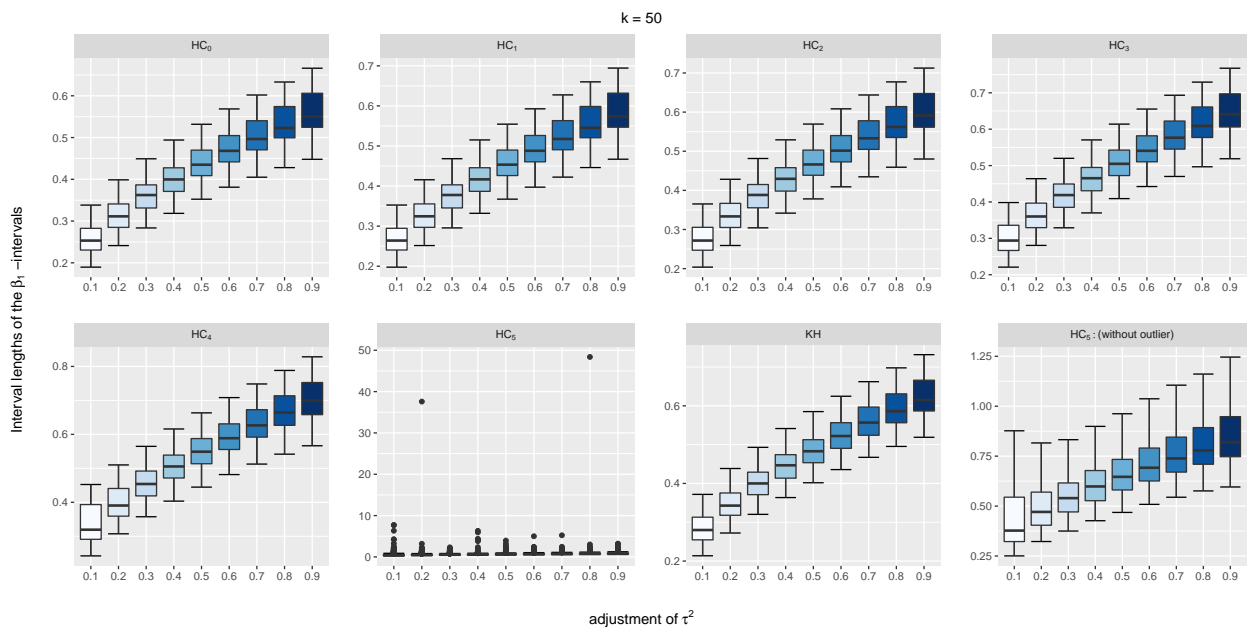
Figure 32: Lengths of the β_1-intervals compared regarding the adjustments of the heterogeneity parameter τ^2 for the estimators $HC_0 - HC_5$ and KH with $k = 50$.
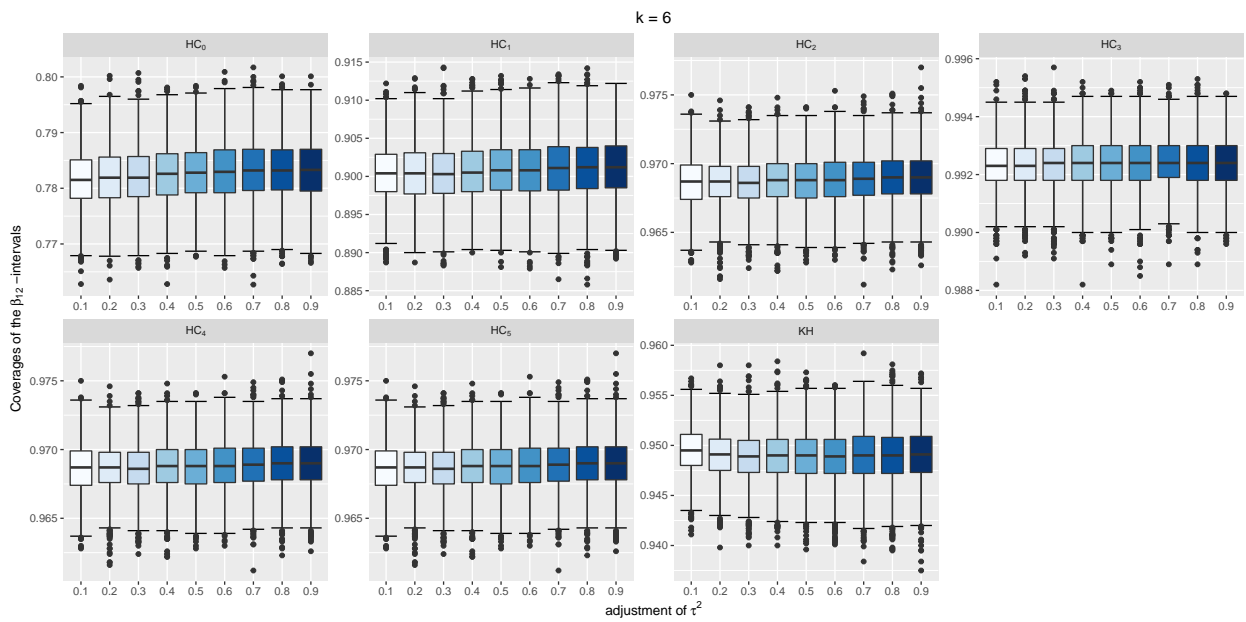
Figure 33: Coverages of the β_{12}-intervals compared regarding the adjustments of the heterogeneity parameter τ^2 for the estimators $HC_0 - HC_5$ and KH with $k = 6$.
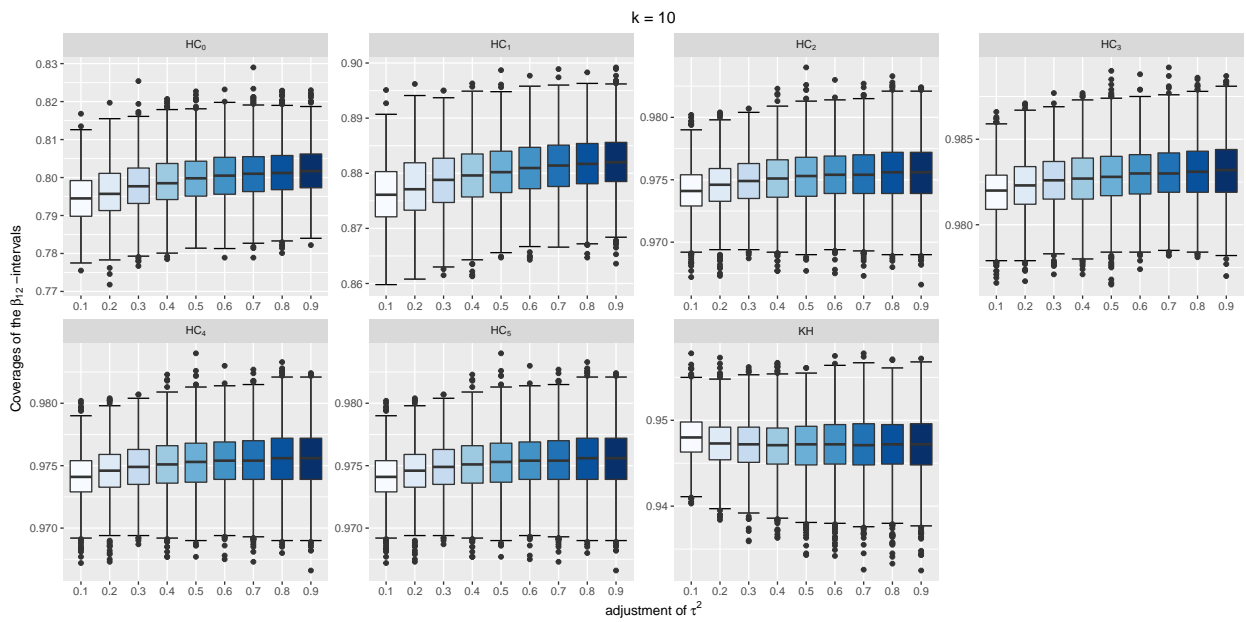
Figure 34: Coverages of the β_{12}-intervals compared regarding the adjustments of the heterogeneity parameter τ^2 for the estimators $HC_0 - HC_5$ and KH with $k = 10$.
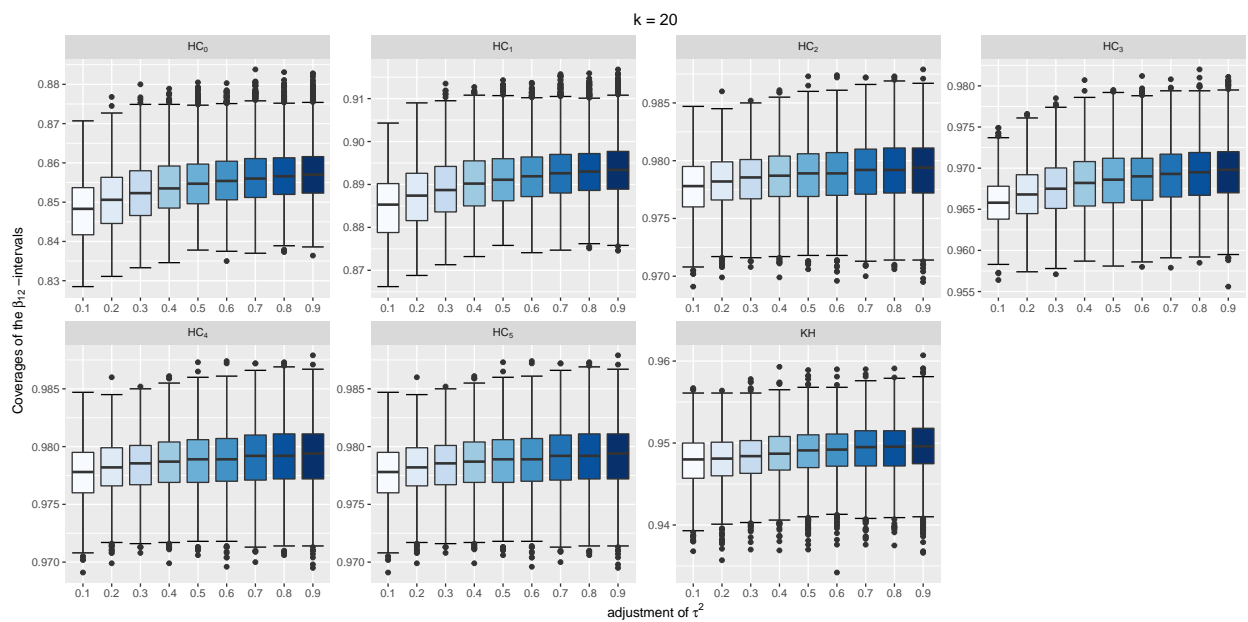
Figure 35: Coverages of the β_{12}-intervals compared regarding the adjustments of the heterogeneity parameter τ^2 for the estimators $HC_0 - HC_5$ and KH with $k = 20$.
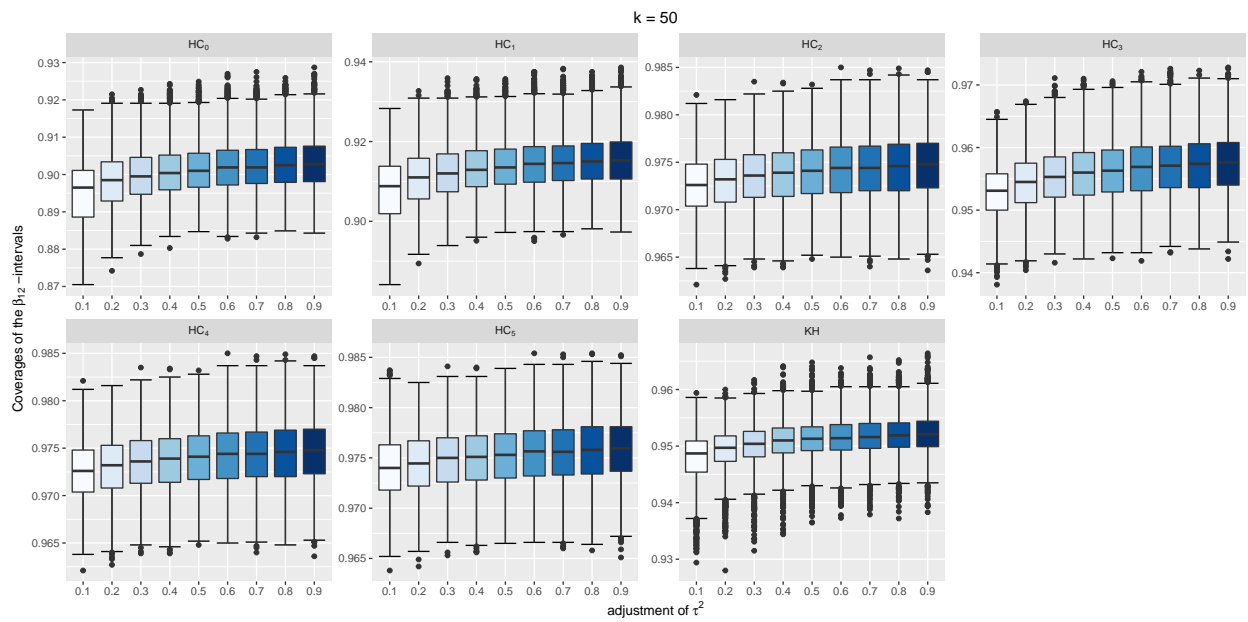
Figure 36: Coverages of the β_{12}-intervals compared regarding the adjustments of the heterogeneity parameter τ^2 for the estimators $HC_0 - HC_5$ and KH with $k = 50$.
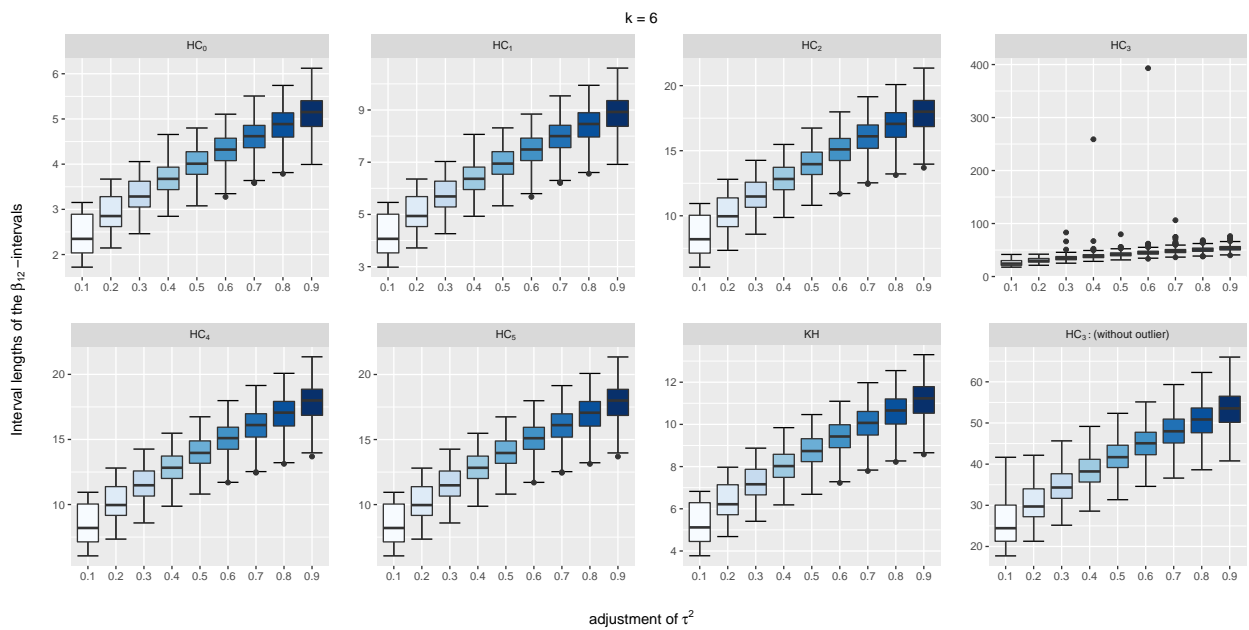
Figure 37: Lengths of the β_{12}-intervals compared regarding the adjustments of the heterogeneity parameter τ^2 for the estimators $HC_0 - HC_5$ and KH with $k = 6$.
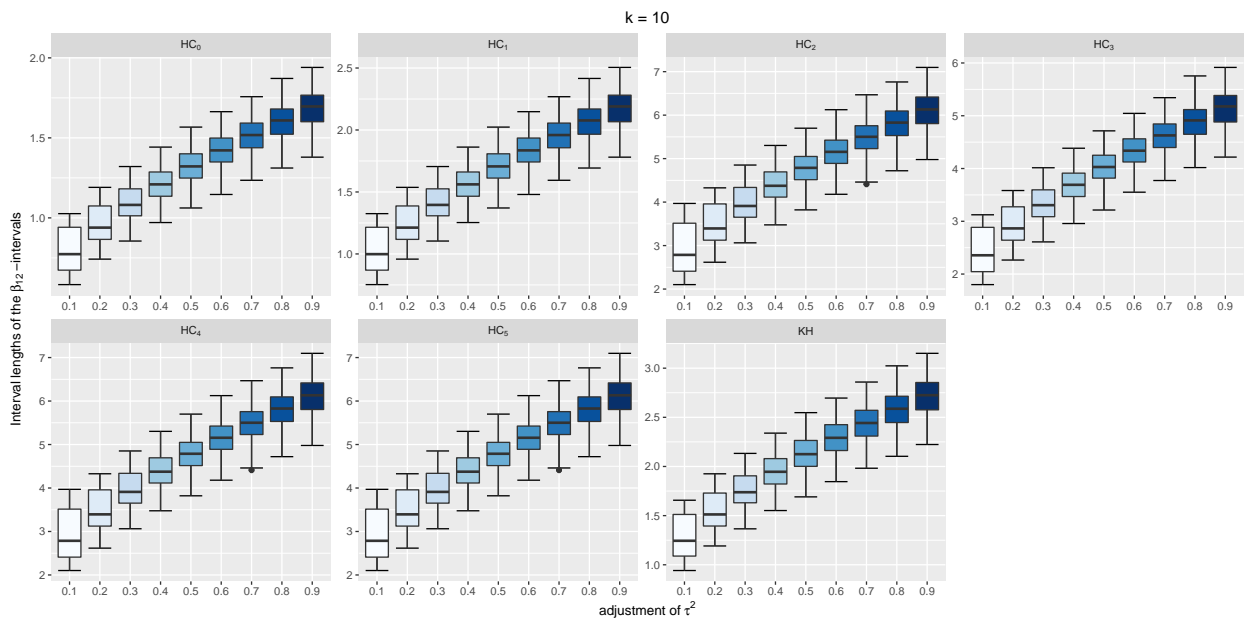
Figure 38: Lengths of the β_{12}-intervals compared regarding the adjustments of the heterogeneity parameter τ^2 for the estimators $HC_0 - HC_5$ and KH with $k = 10$.
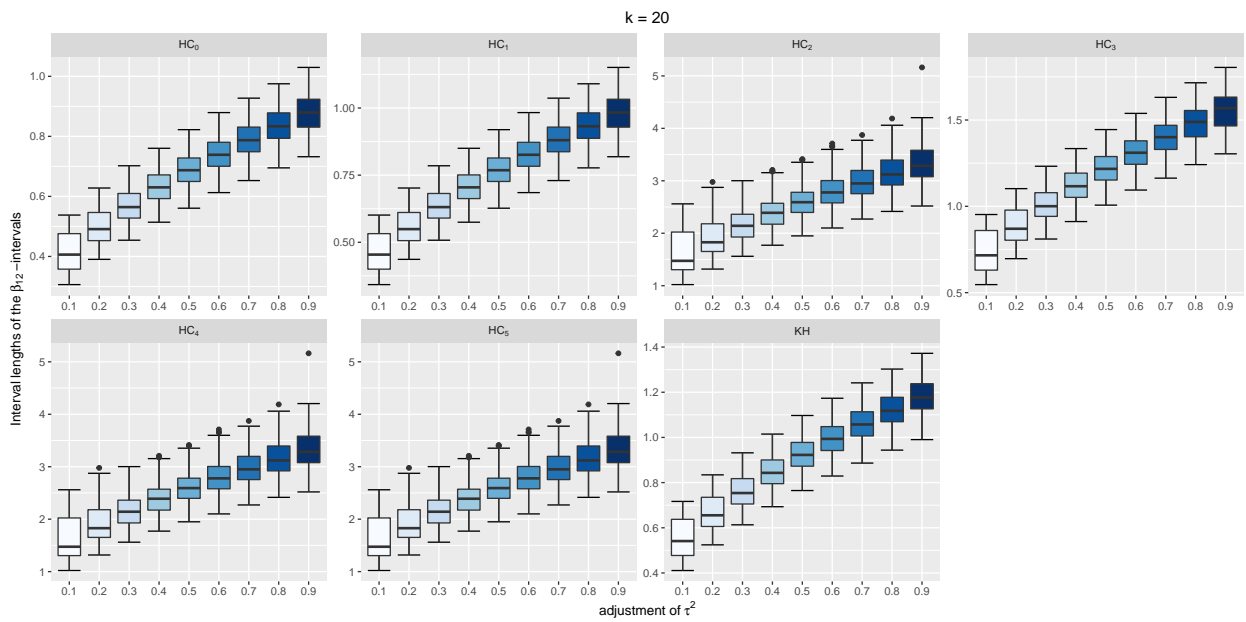
Figure 39: Lengths of the β_{12}-intervals compared regarding the adjustments of the heterogeneity parameter τ^2 for the estimators $HC_0 - HC_5$ and KH with $k = 20$.
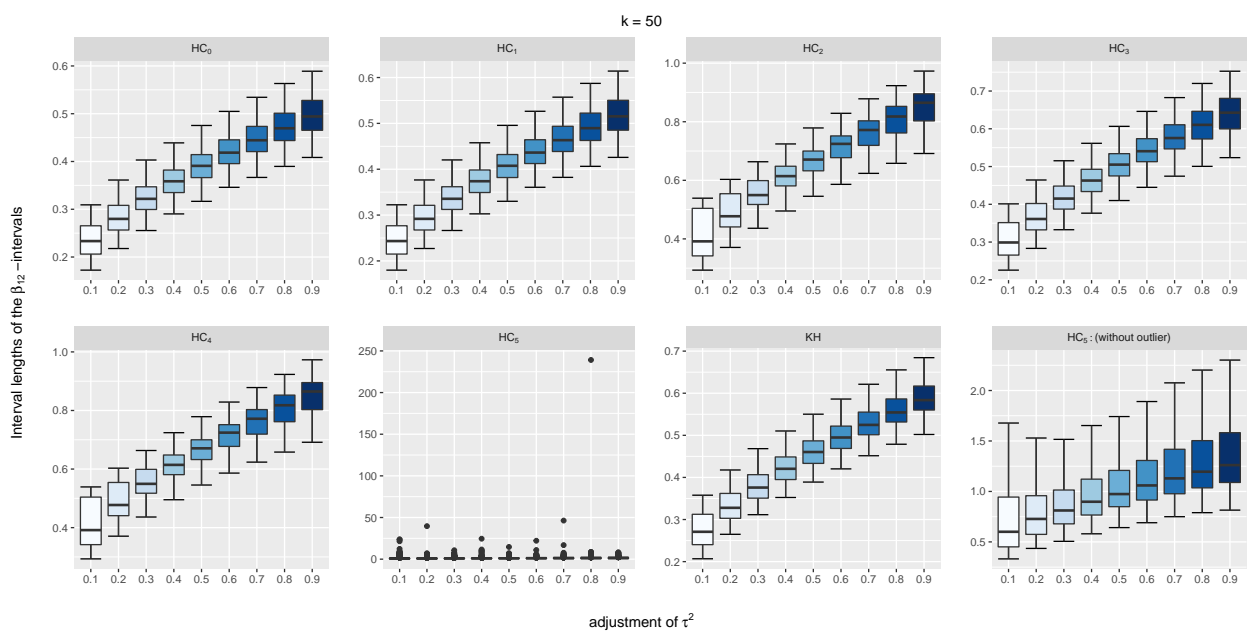
Figure 40: Lengths of the β_{12}-intervals compared regarding the adjustments of the heterogeneity parameter τ^2 for the estimators $HC_0 - HC_5$ and KH with $k = 50$.
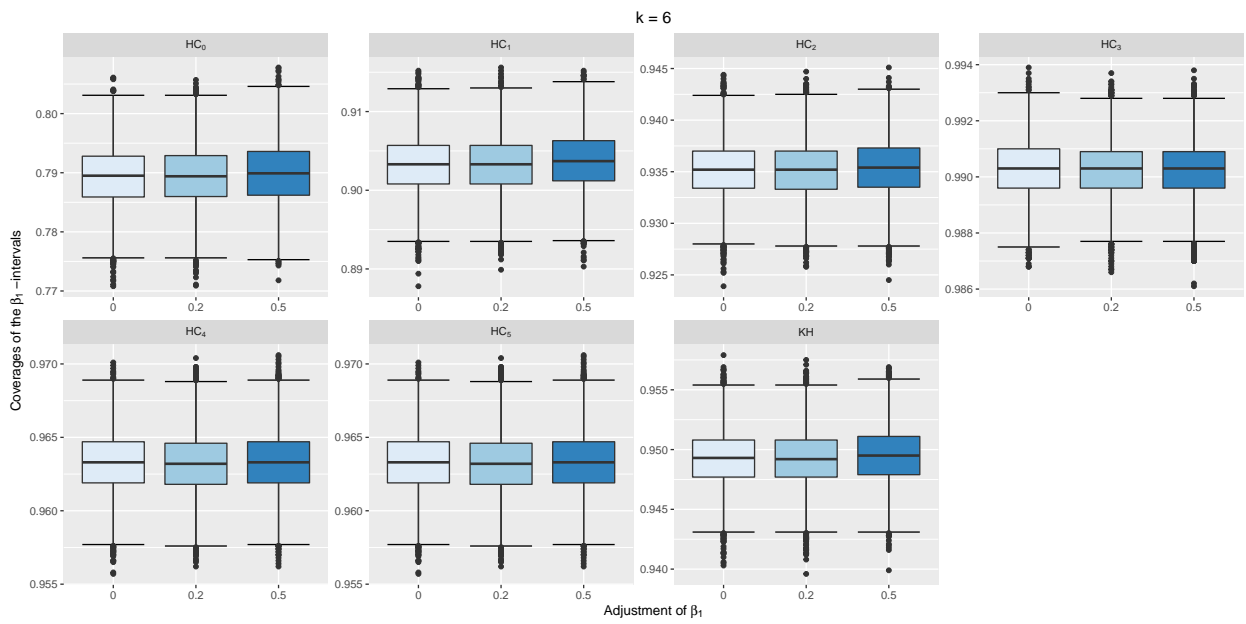
Figure 41: Coverages of the β_1-intervals compared regarding the adjustments of β_1 for the estimators $HC_0 - HC_5$ and KH with $k = 6$.
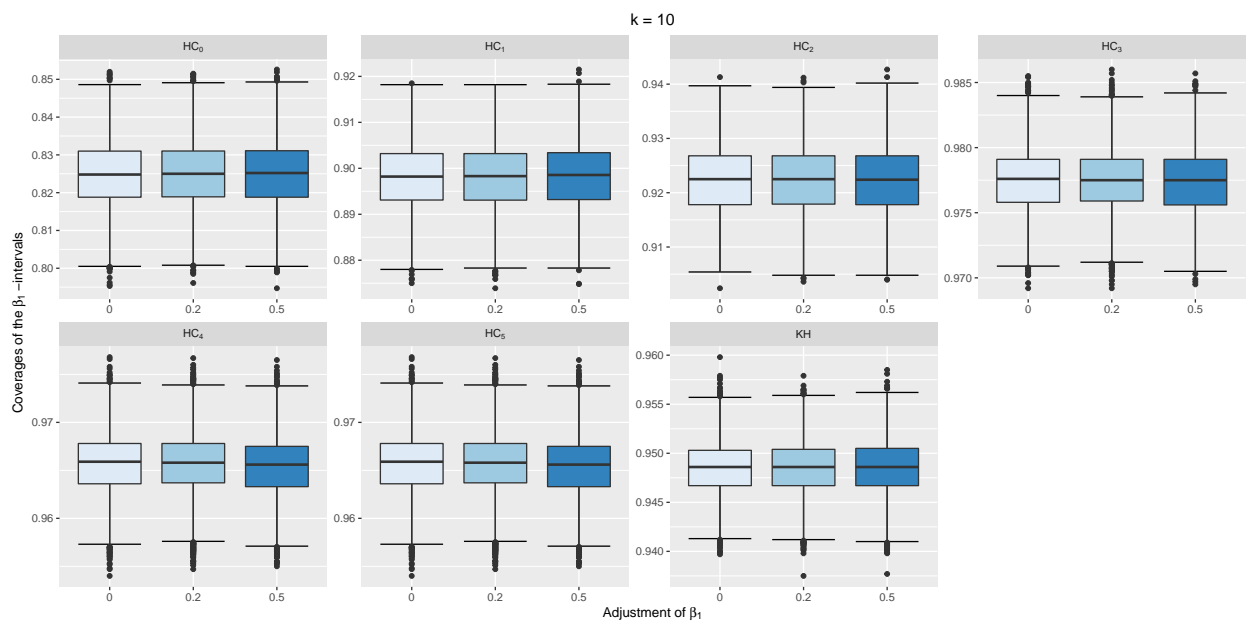
Figure 42: Coverages of the β_1-intervals compared regarding the adjustments of β_1 for the estimators $HC_0 - HC_5$ and KH with $k = 10$.
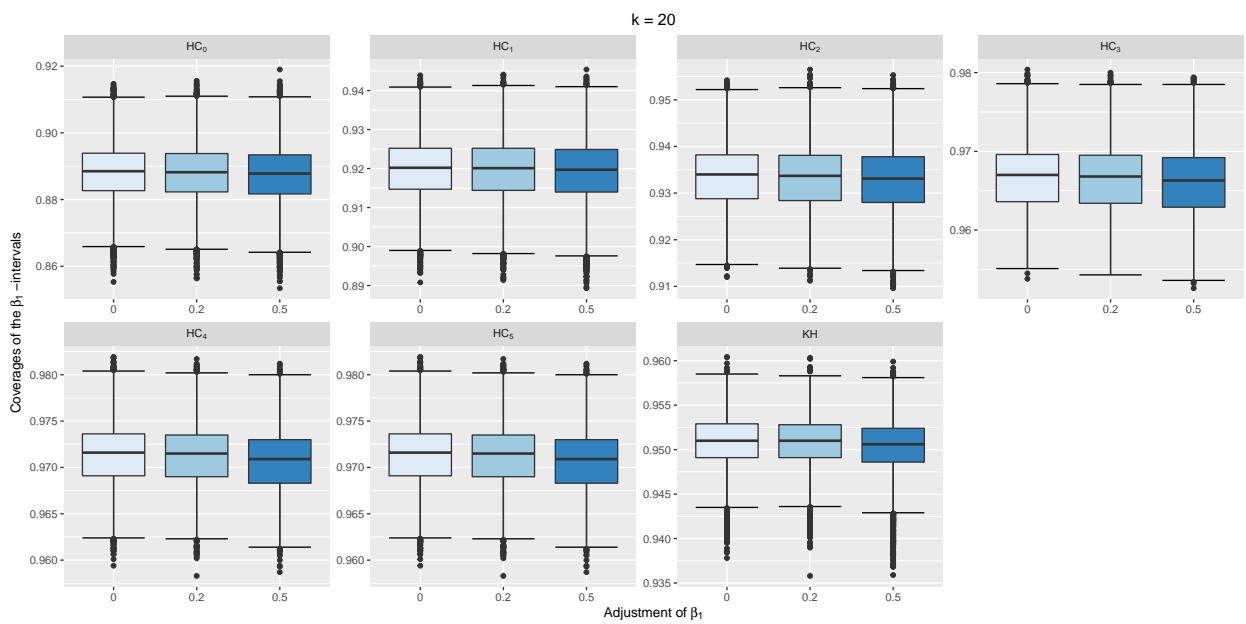
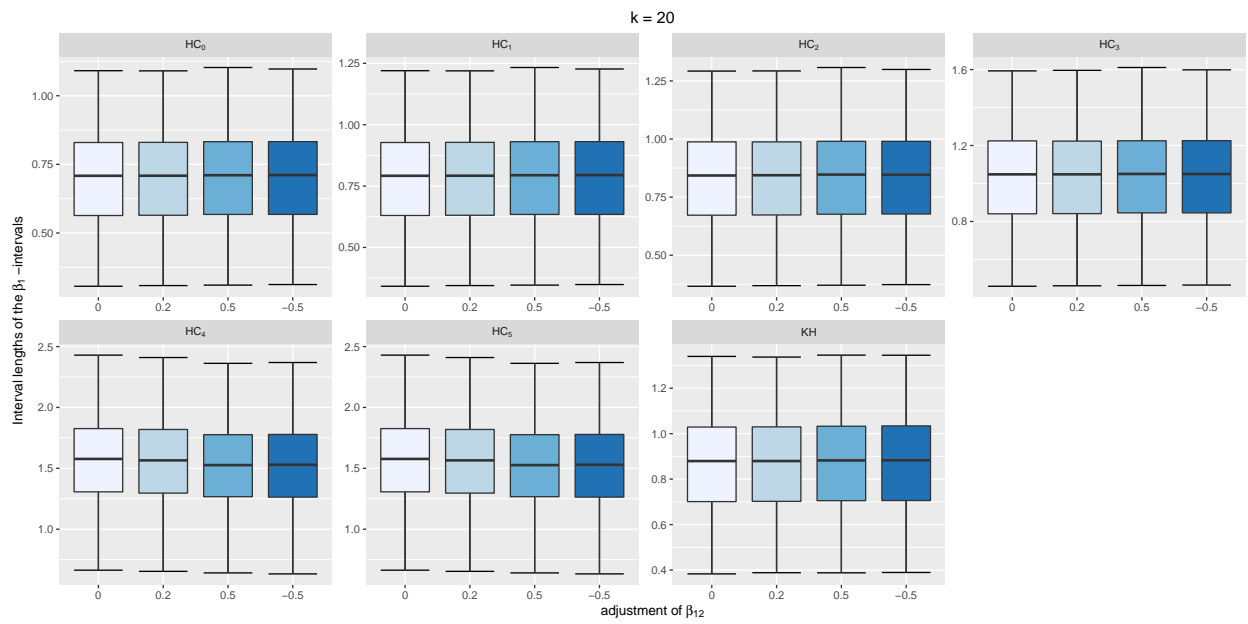Figure 43: Coverages of the β_1-intervals compared regarding the adjustments of β_1 for the estimators $HC_0 - HC_5$ and KH with $k = 20$.
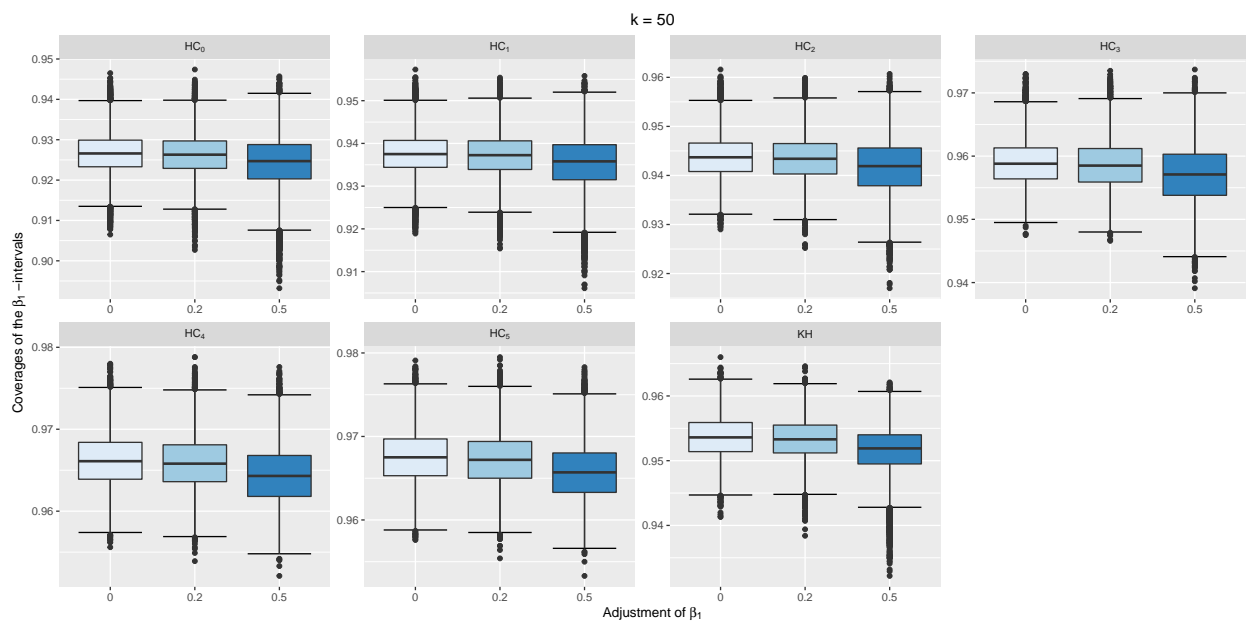
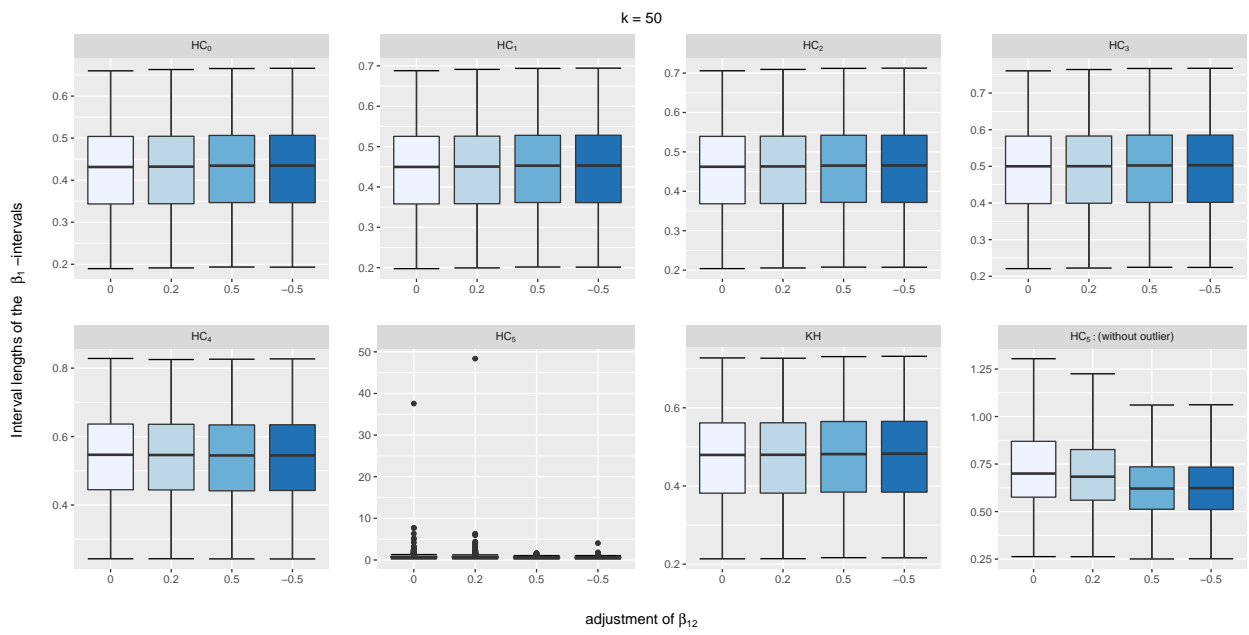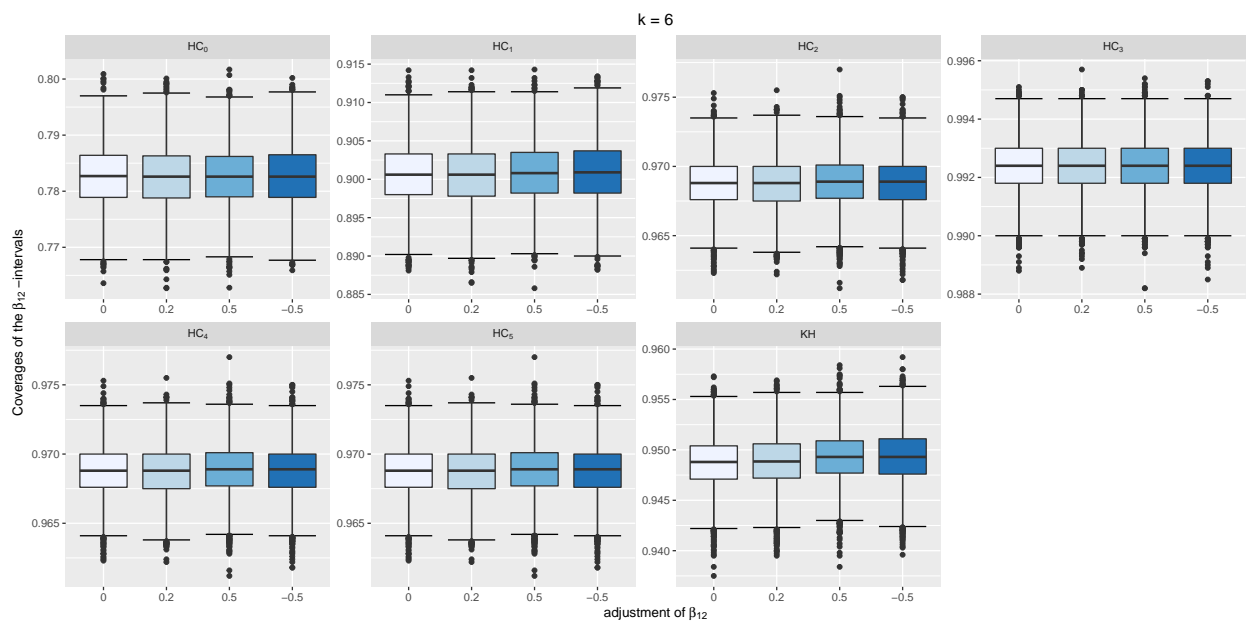Figure 44: Coverages of the β_1-intervals compared regarding the adjustments of β_1 for the estimators $HC_0 - HC_5$ and KH with $k = 50$.
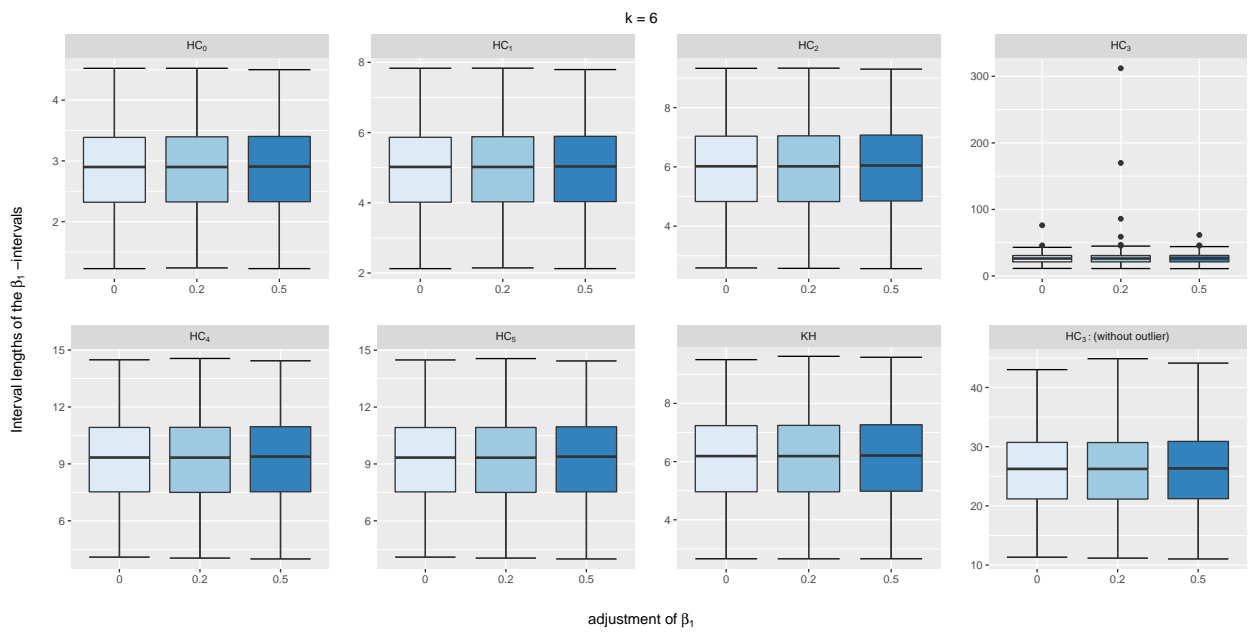
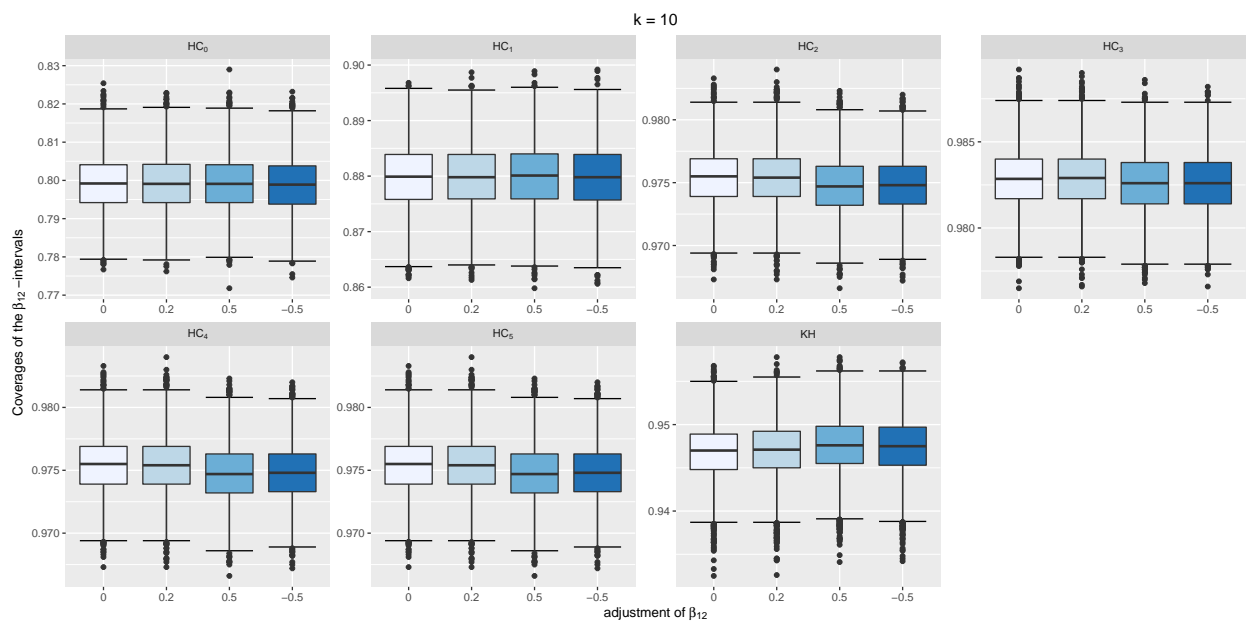Figure 45: Lengths of the β_1-intervals compared regarding the adjustments of β_1 for the estimators $HC_0 - HC_5$ and KH with $k = 6$.
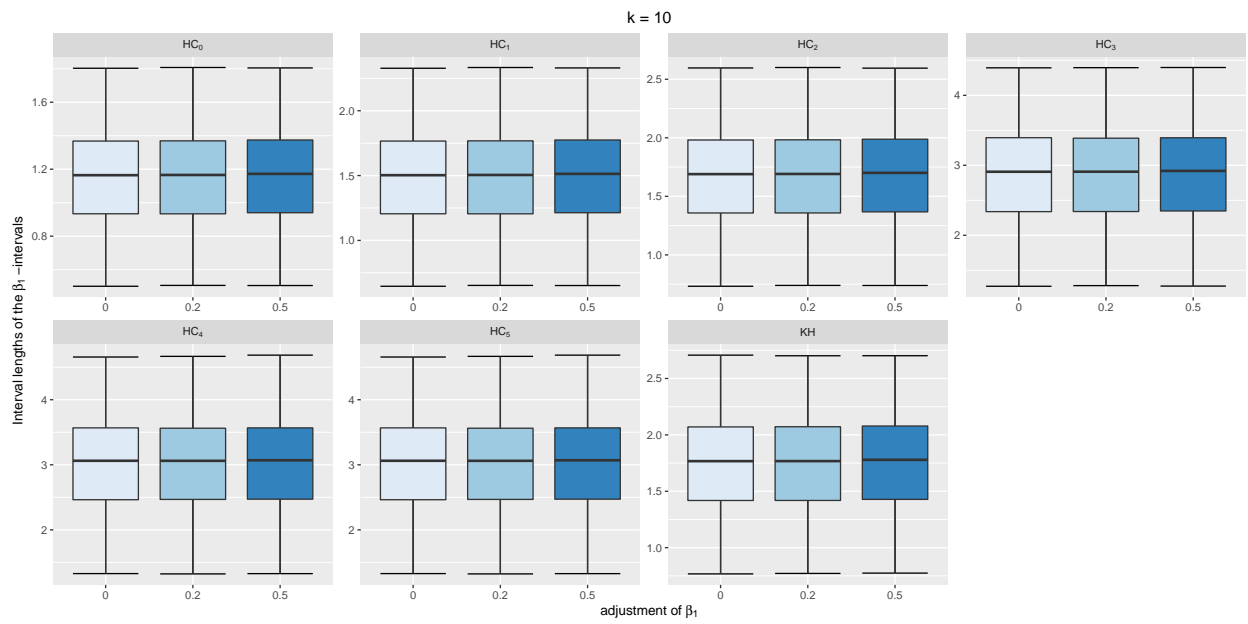
Figure 46: Lengths of the β_1-intervals compared regarding the adjustments of β_1 for the estimators $HC_0 - HC_5$ and KH with $k = 10$.
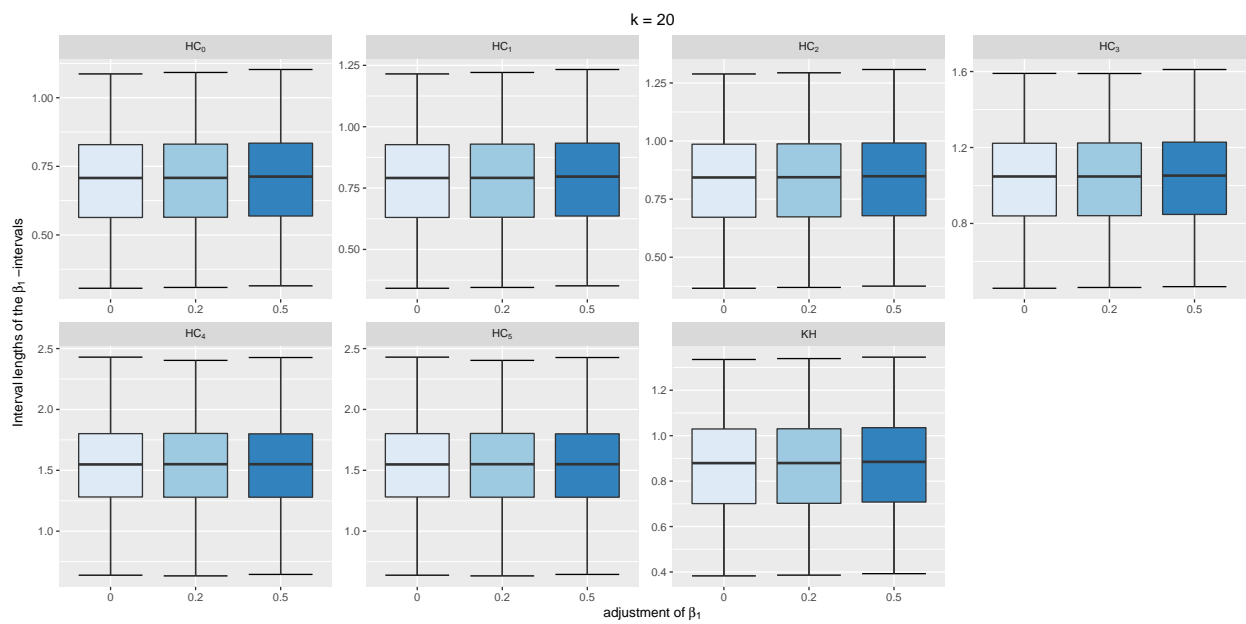
Figure 47: Lengths of the β_1-intervals compared regarding the adjustments of β_1 for the estimators HC_0-HC_5 and KH with $k = 20$.
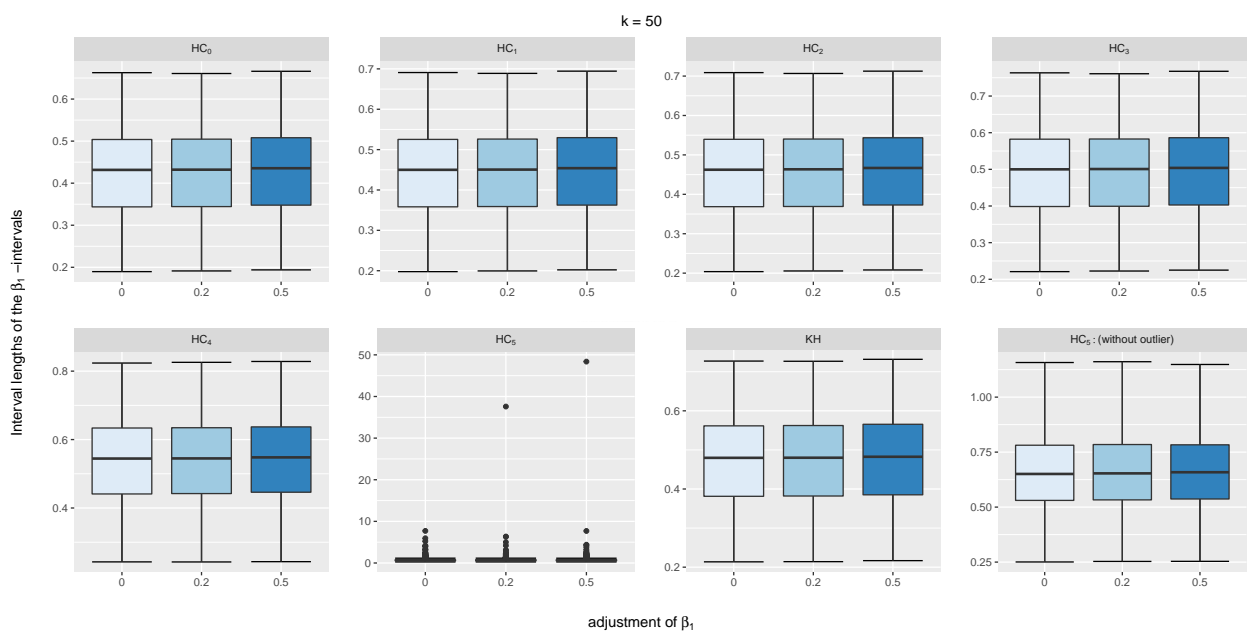
Figure 48: Lengths of the β_1-intervals compared regarding the adjustments of β_1 for the estimators HC_0-HC_5 and KH with $k = 50$.
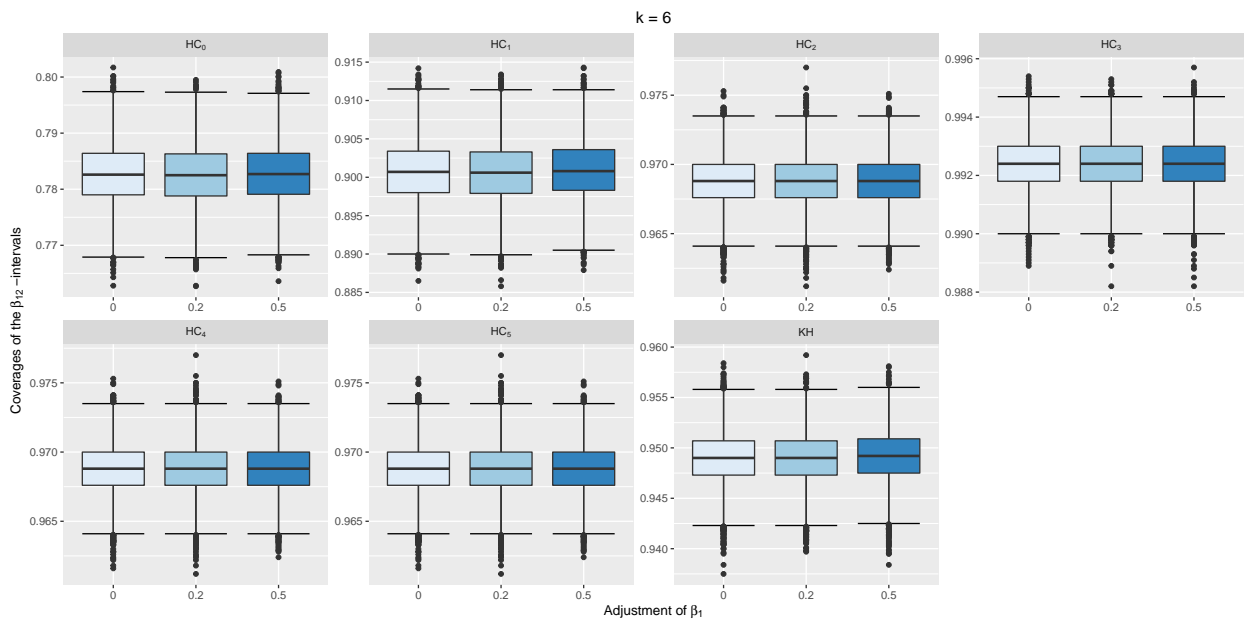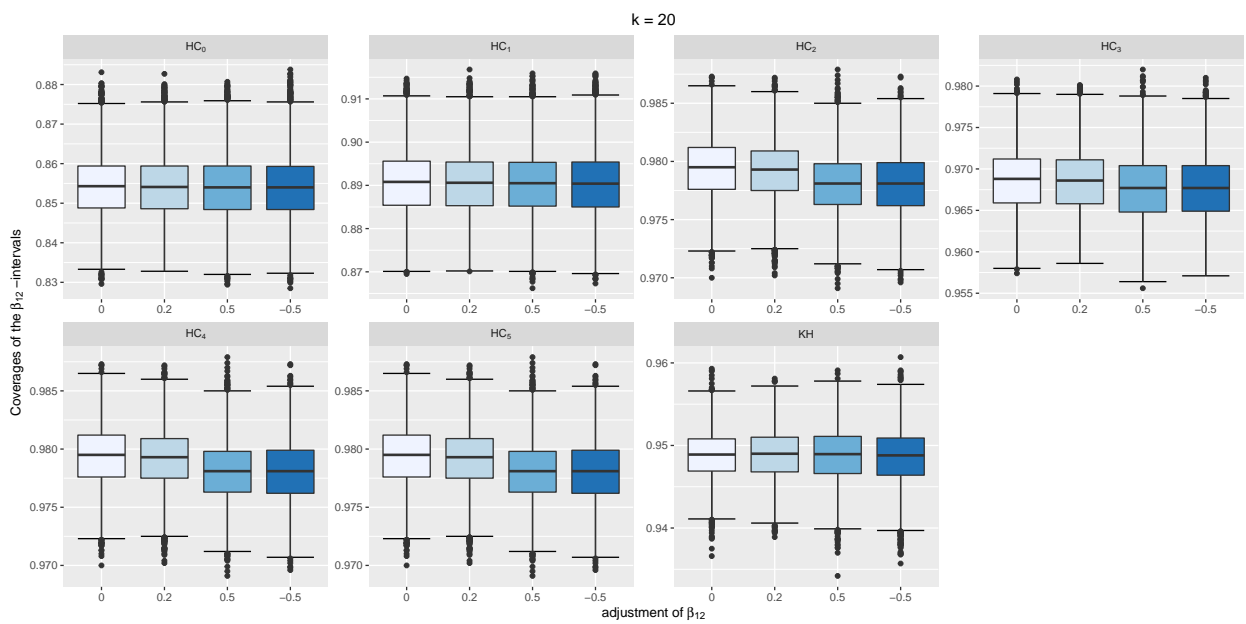
Figure 49: Coverages of the β_{12}-intervals compared regarding the adjustments of β_1 for the estimators $HC_0 - HC_5$ and KH with $k = 6$.
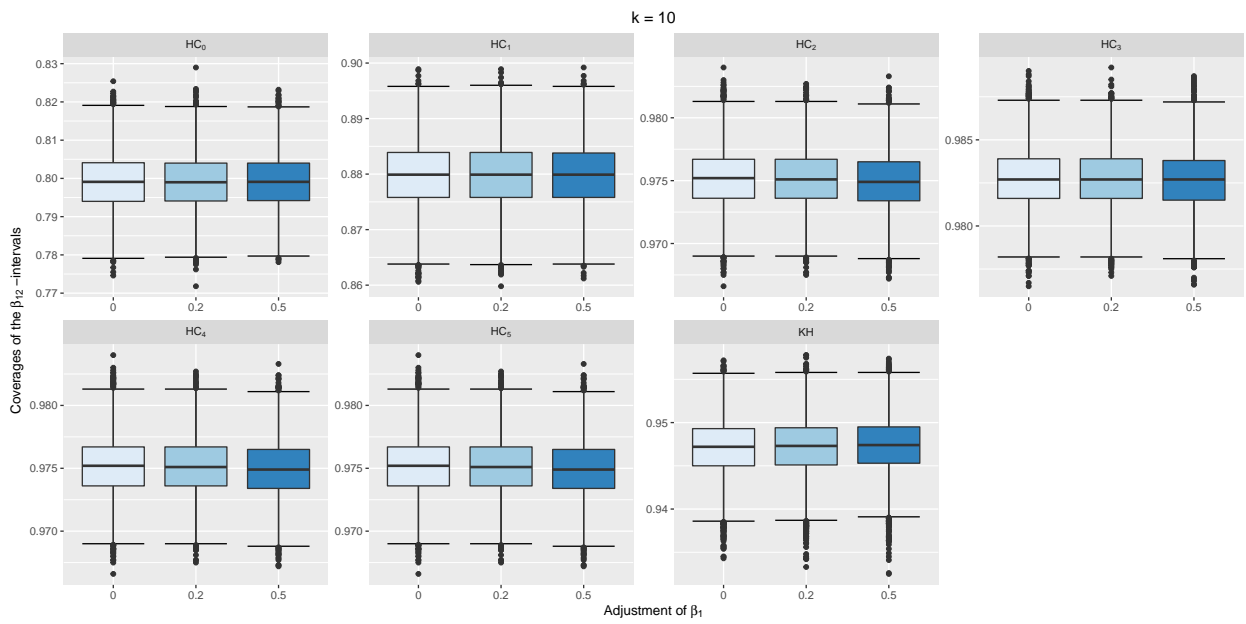
Figure 50: Coverages of the β_{12}-intervals compared regarding the adjustments of β_1 for the estimators $HC_0 - HC_5$ and KH with $k = 10$.

Figure 51: Coverages of the β_{12}-intervals compared regarding the adjustments of β_1 for the estimators $HC_0 - HC_5$ and KH with $k = 20$.
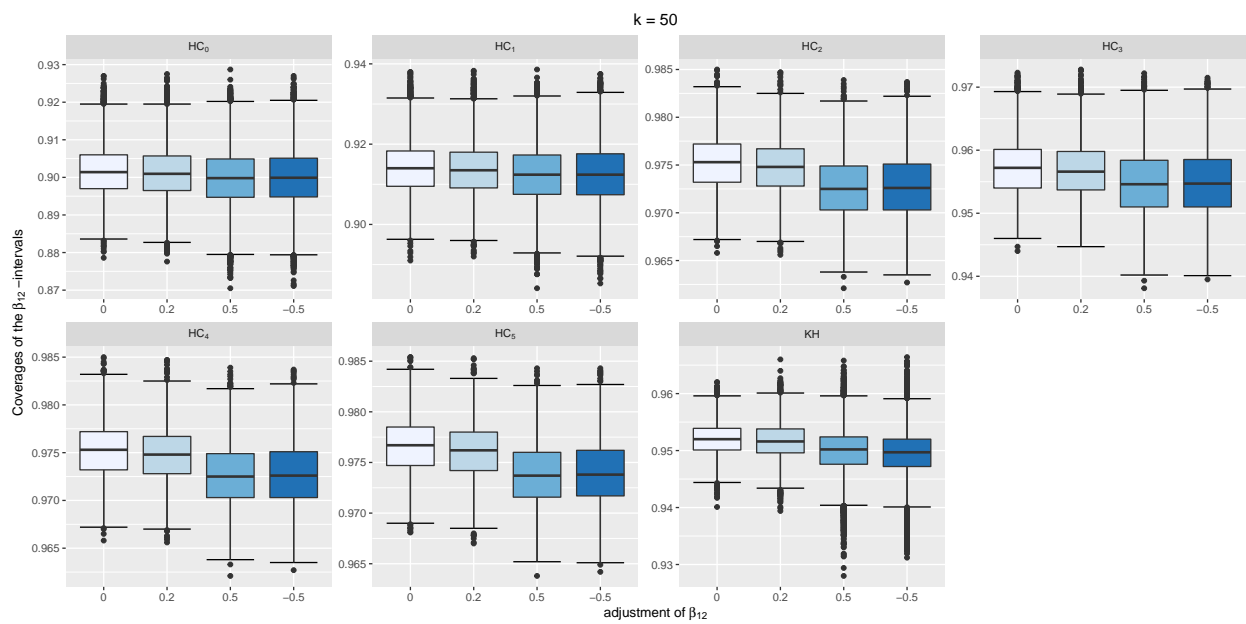
Figure 52: Coverages of the β_{12}-intervals compared regarding the adjustments of β_1 for the estimators $HC_0 - HC_5$ and KH with $k = 50$.
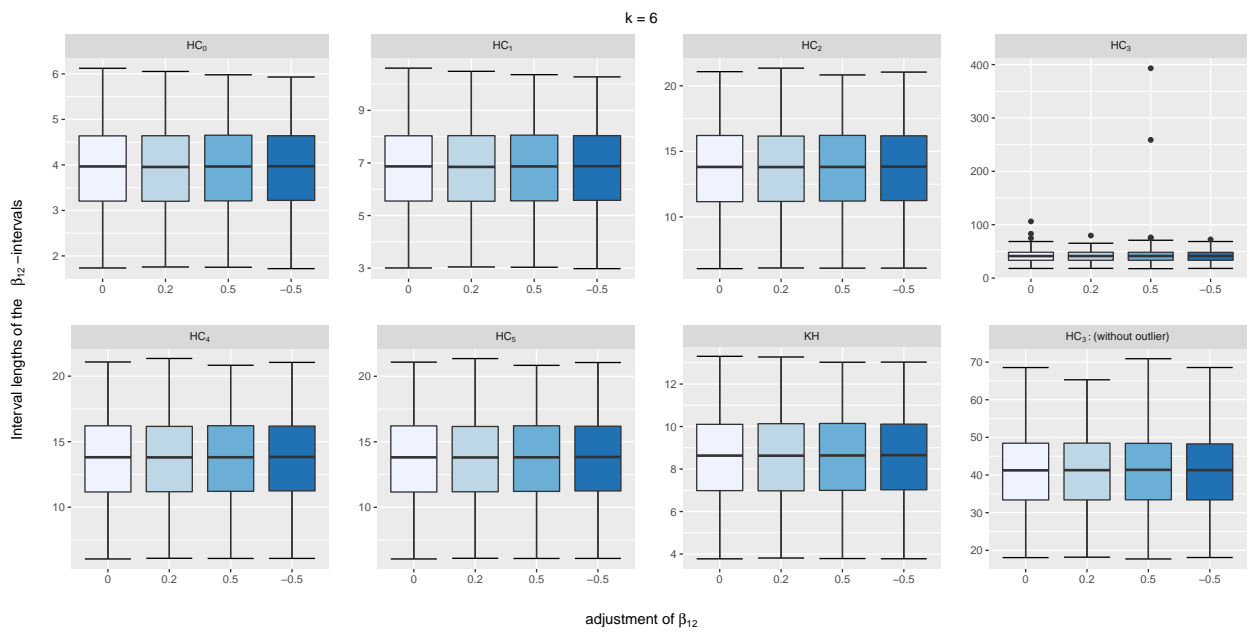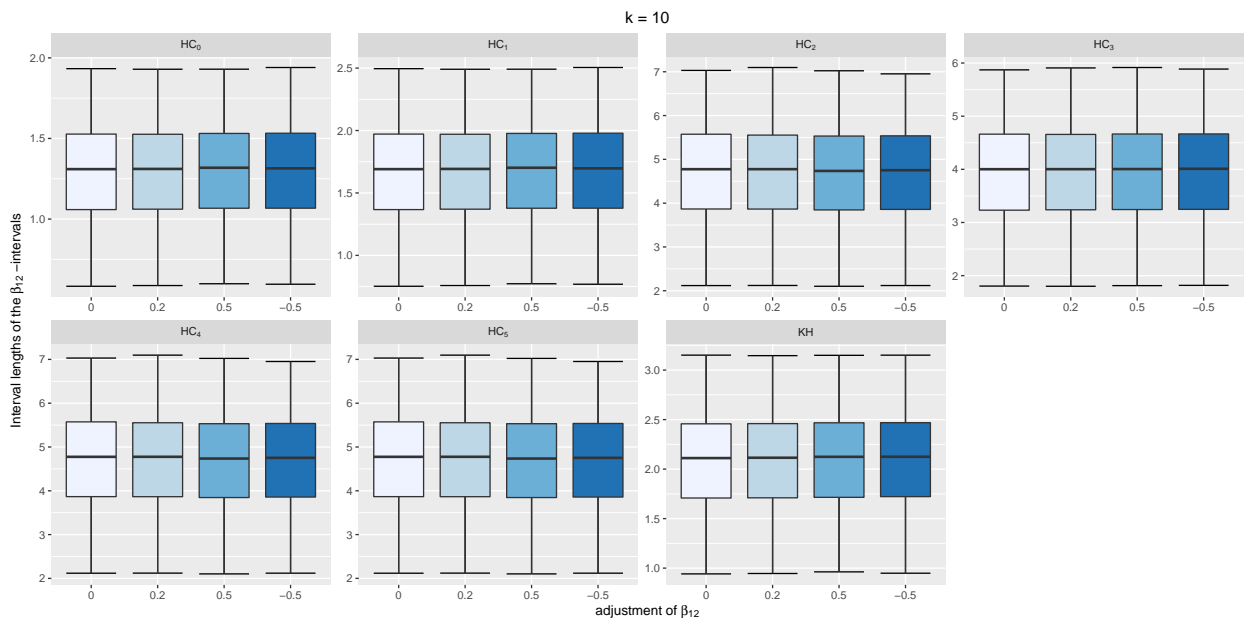
Figure 53: Lengths of the β_{12}-intervals compared regarding the adjustments of β_1 for the estimators $HC_0 - HC_5$ and KH with $k = 6$.

Figure 54: Lengths of the β_{12}-intervals compared regarding the adjustments of β_1 for the estimators $HC_0 - HC_5$ and KH with $k = 10$.
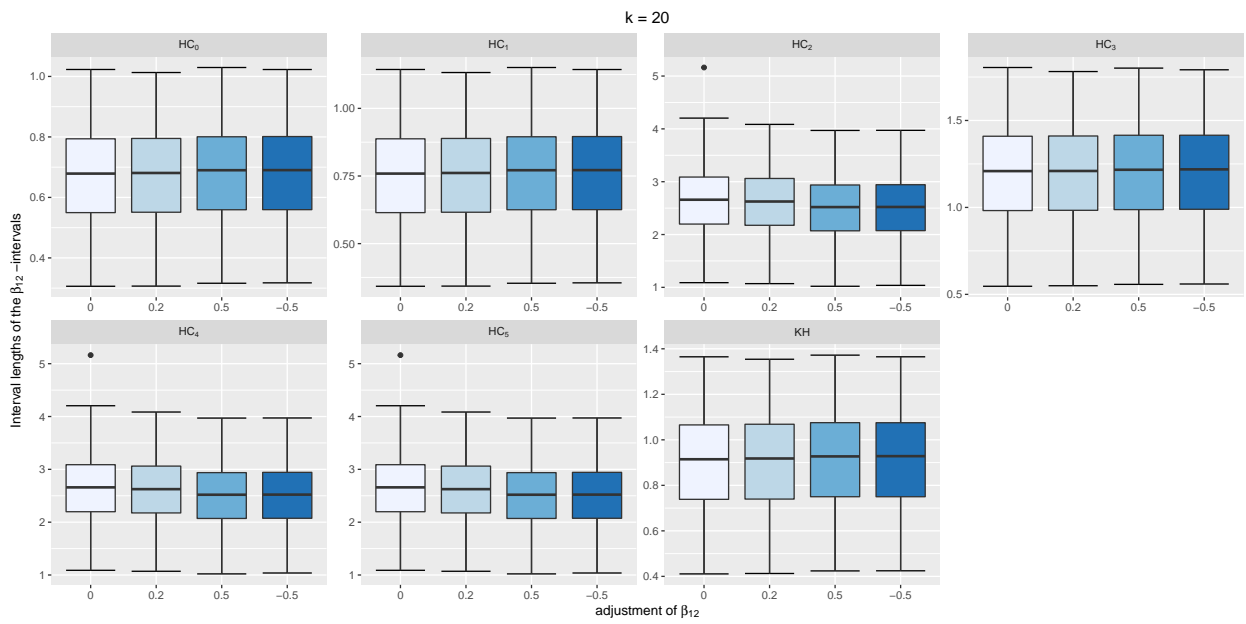
Figure 55: Lengths of the β_{12}-intervals compared regarding the adjustments of β_1 for the estimators $HC_0 - HC_5$ and KH with $k = 20$.

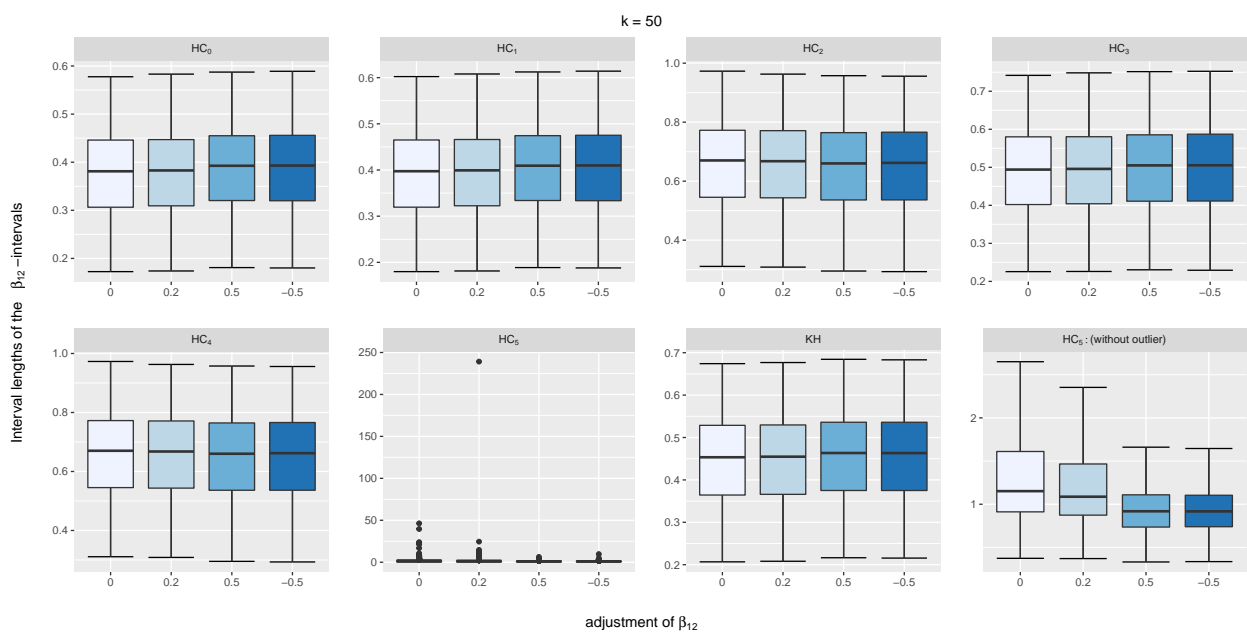Figure 56: Lengths of the β_{12}-intervals compared regarding the adjustments of β_1 for the estimators $HC_0 - HC_5$ and KH with $k = 50$.

Figure 57: Coverages of the β_1-intervals compared regarding the adjustments of β_2 for the estimators $HC_0 - HC_5$ and KH with $k = 6$.

Figure 58: Coverages of the β_1-intervals compared regarding the adjustments of β_2 for the estimators $HC_0 - HC_5$ and KH with $k = 10$.

Figure 59: Coverages of the β_1-intervals compared regarding the adjustments of β_2 for the estimators $HC_0 - HC_5$ and KH with $k = 20$.

Figure 60: Coverages of the β_1-intervals compared regarding the adjustments of β_2 for the estimators $HC_0 - HC_5$ and KH with $k = 50$.

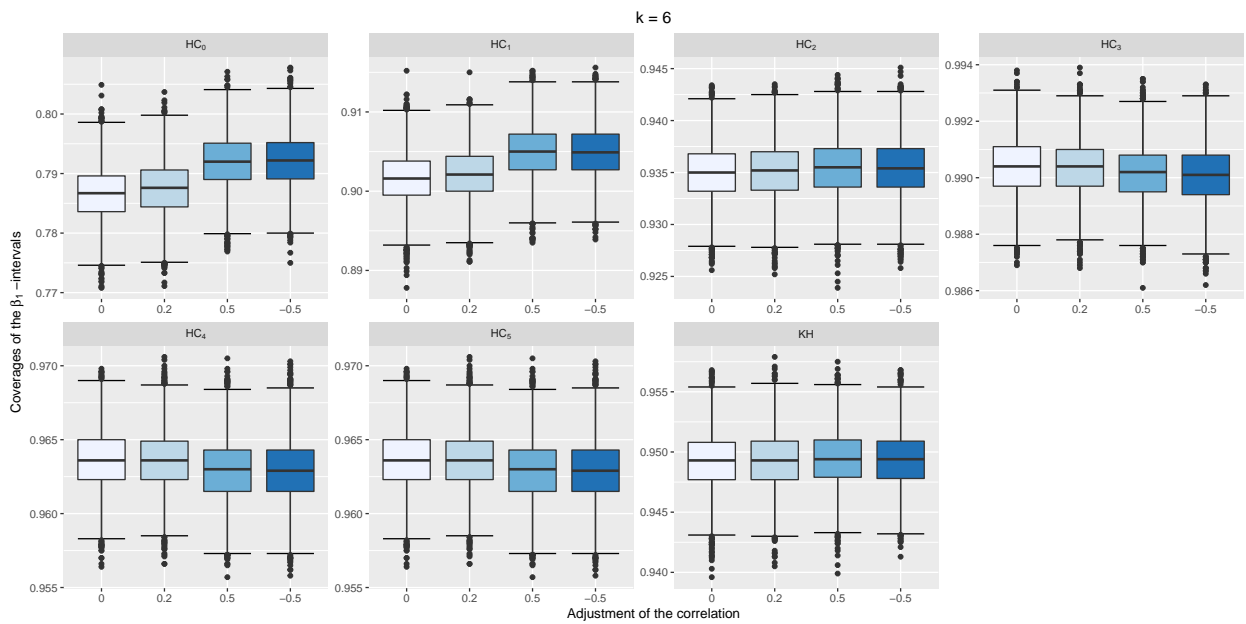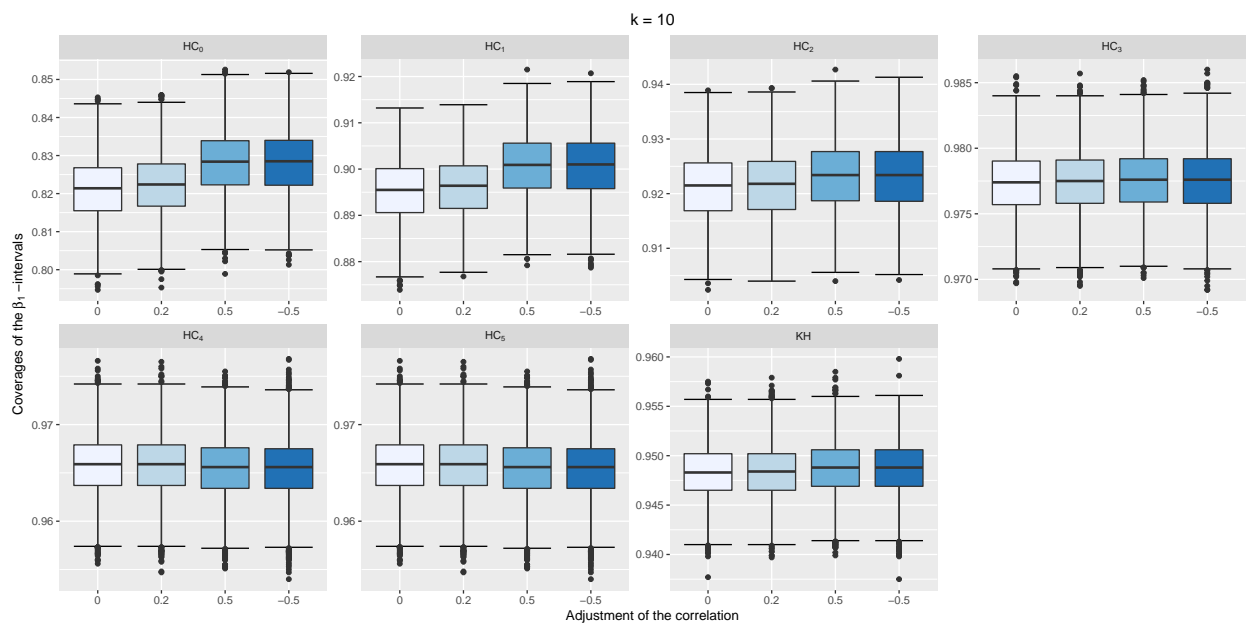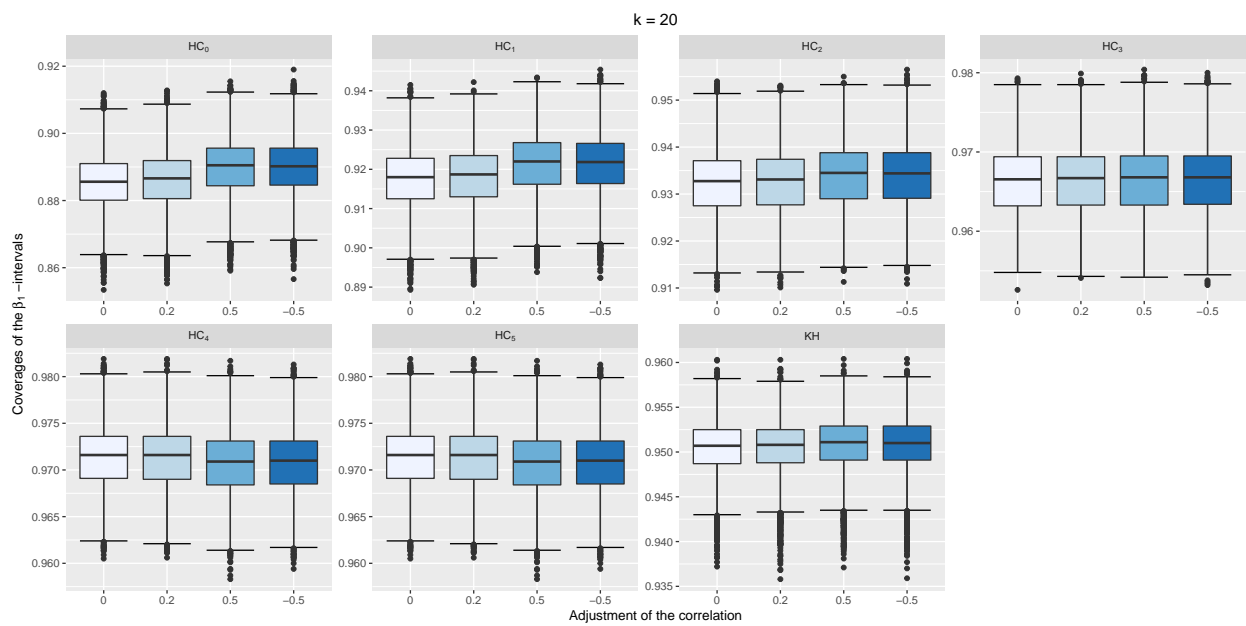Figure 61: Lengths of the β_1-intervals compared regarding the adjustments of β_2 for the estimators $HC_0 - HC_5$ and KH with $k = 6$.

Figure 62: Lengths of the β_1-intervals compared regarding the adjustments of β_2 for the estimators $HC_0 - HC_5$ and KH with $k = 10$.

Figure 63: Lengths of the β_1-intervals compared regarding the adjustments of β_2 for the estimators $HC_0 - HC_5$ and KH with $k = 20$.

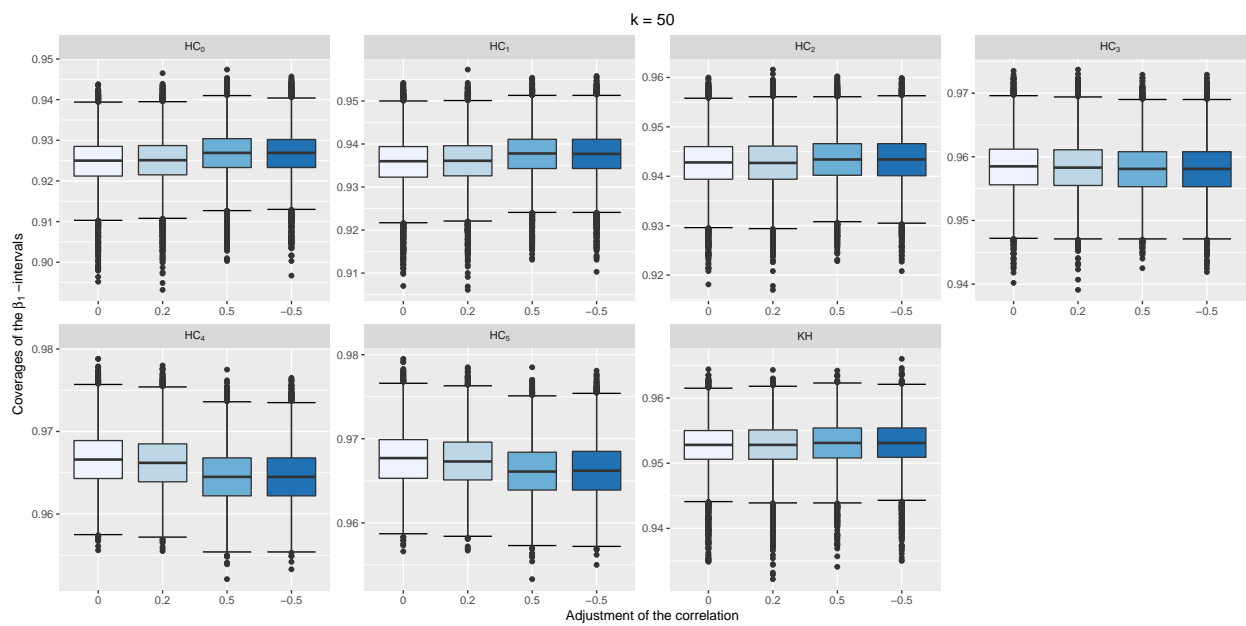Figure 64: Lengths of the β_1-intervals compared regarding the adjustments of β_2 for the estimators $HC_0 - HC_5$ and KH with $k = 50$.

Figure 65: Coverages of the β_{12}-intervals compared regarding the adjustments of β_2 for the estimators $HC_0 - HC_5$ and KH with $k = 6$.

Figure 66: Coverages of the β_{12}-intervals compared regarding the adjustments of β_2 for the estimators $HC_0 - HC_5$ and KH with $k = 10$.

Figure 67: Coverages of the β_{12}-intervals compared regarding the adjustments of β_2 for the estimators $HC_0 - HC_5$ and KH with $k = 20$.
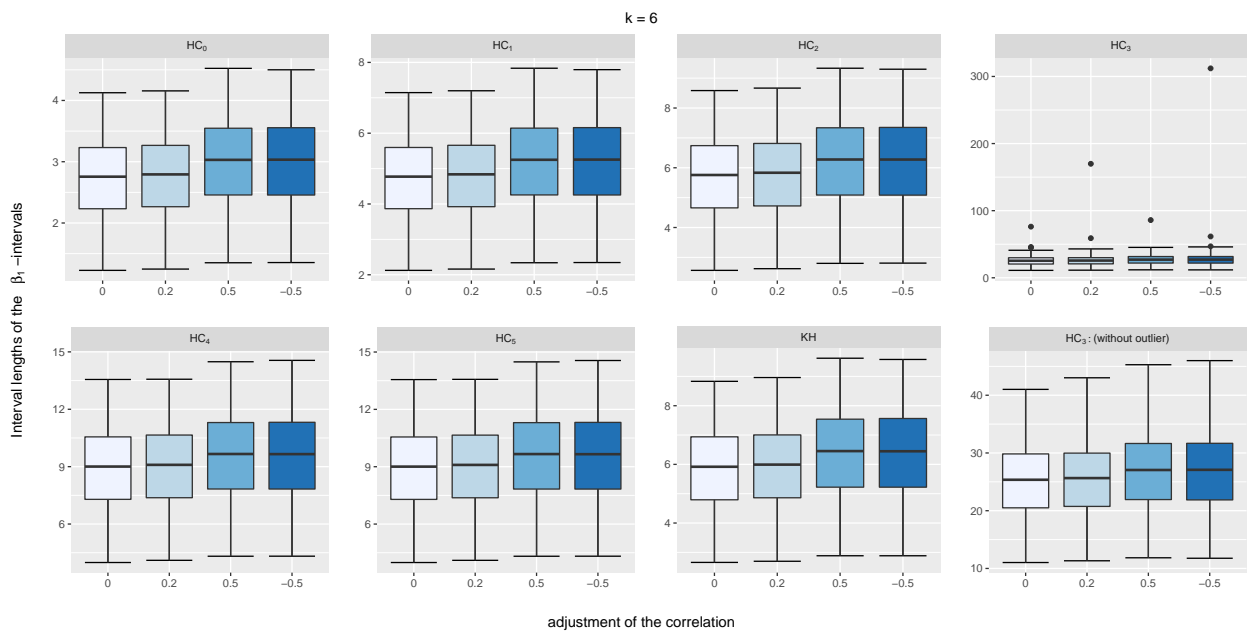
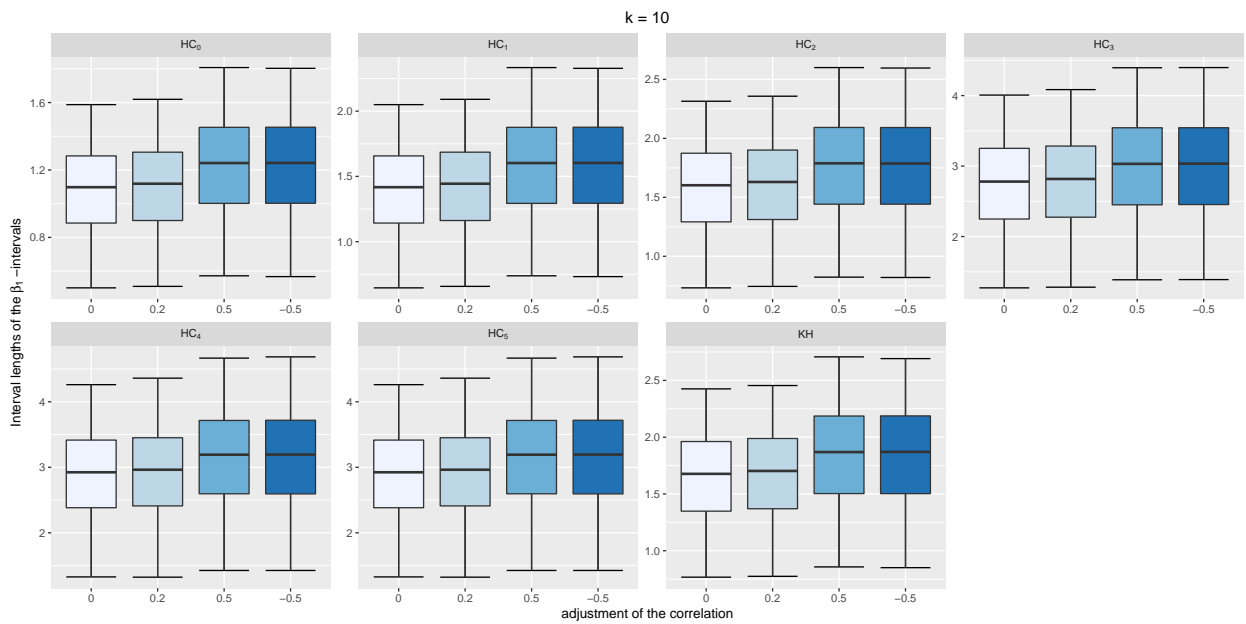Figure 68: Coverages of the β_{12}-intervals compared regarding the adjustments of β_2 for the estimators $HC_0 - HC_5$ and KH with $k = 50$.

Figure 69: Lengths of the β_{12}-intervals compared regarding the adjustments of β_2 for the estimators $HC_0 - HC_5$ and KH with $k = 6$.

Figure 70: Lengths of the β_{12}-intervals compared regarding the adjustments of β_2 for the estimators $HC_0 - HC_5$ and KH with $k = 10$.
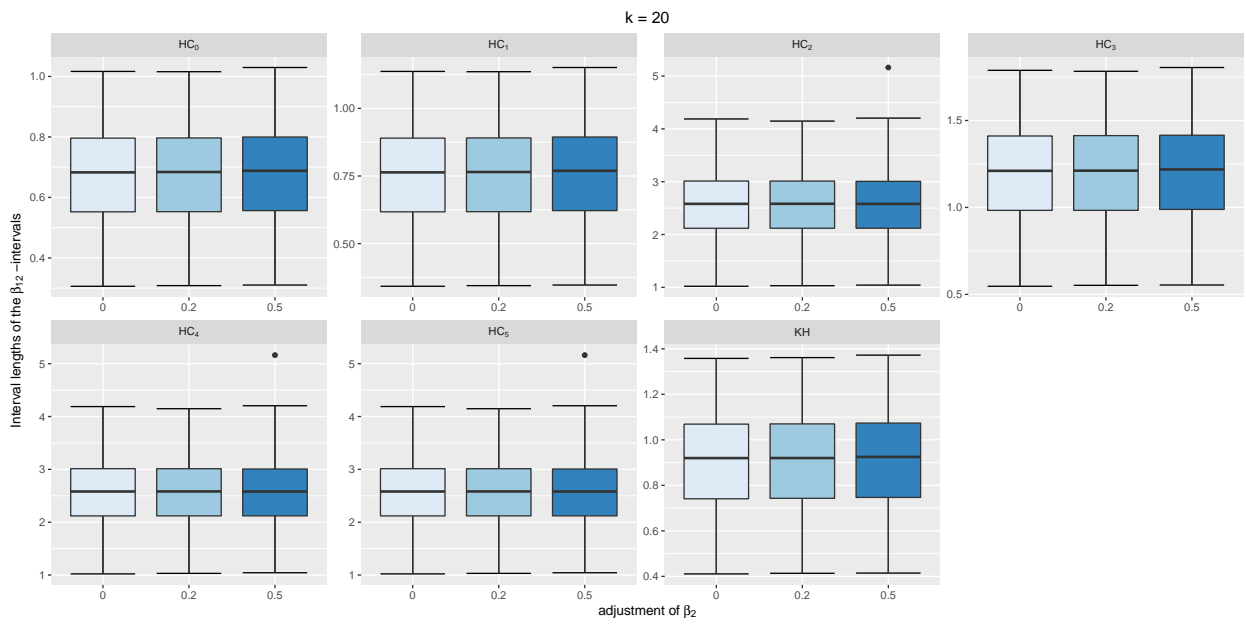
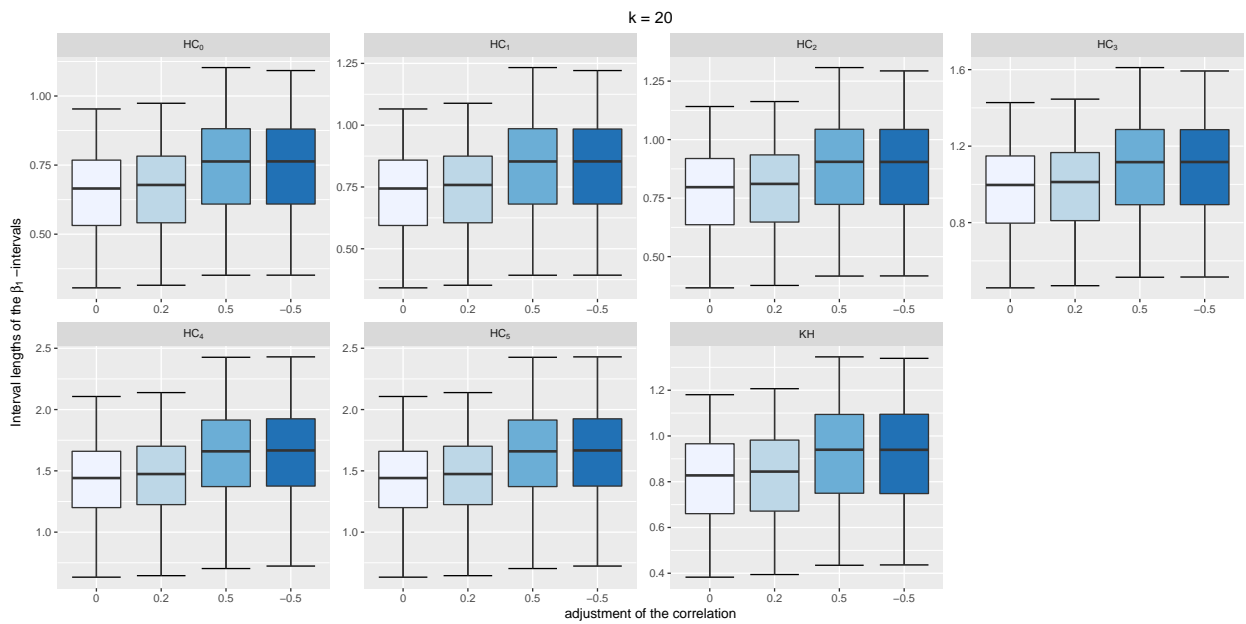Figure 71: Lengths of the β_{12}-intervals compared regarding the adjustments of β_2 for the estimators $HC_0 - HC_5$ and KH with $k = 20$.
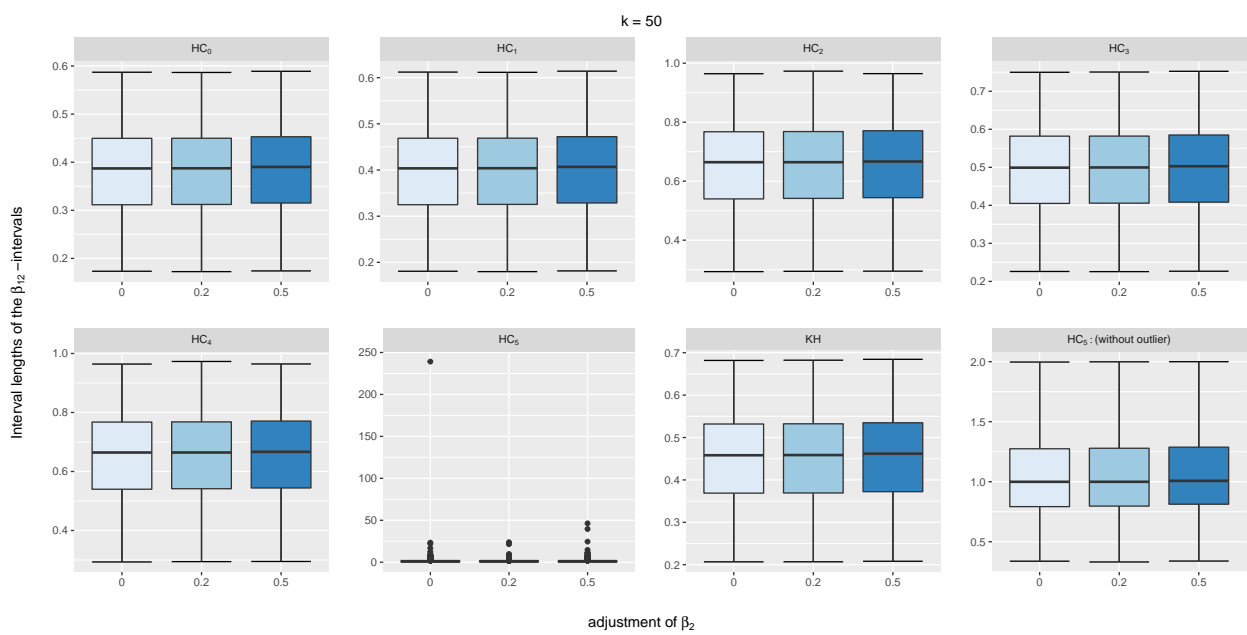
Figure 72: Lengths of the β_{12}-intervals compared regarding the adjustments of β_2 for the estimators $HC_0 - HC_5$ and KH with $k = 50$.
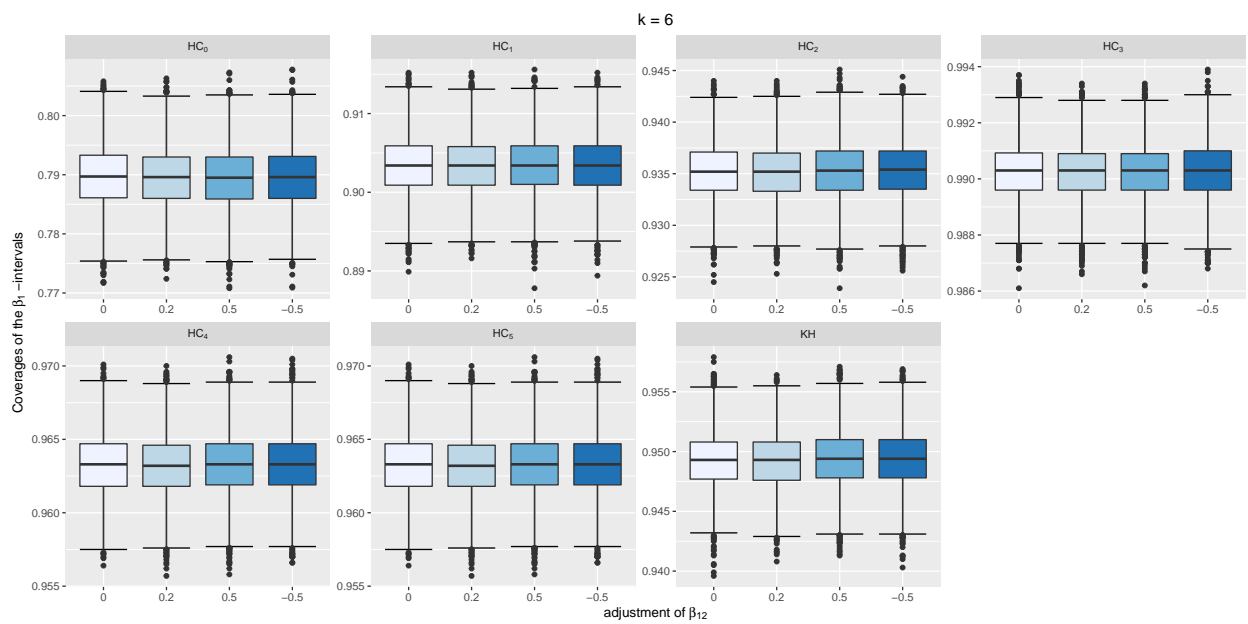
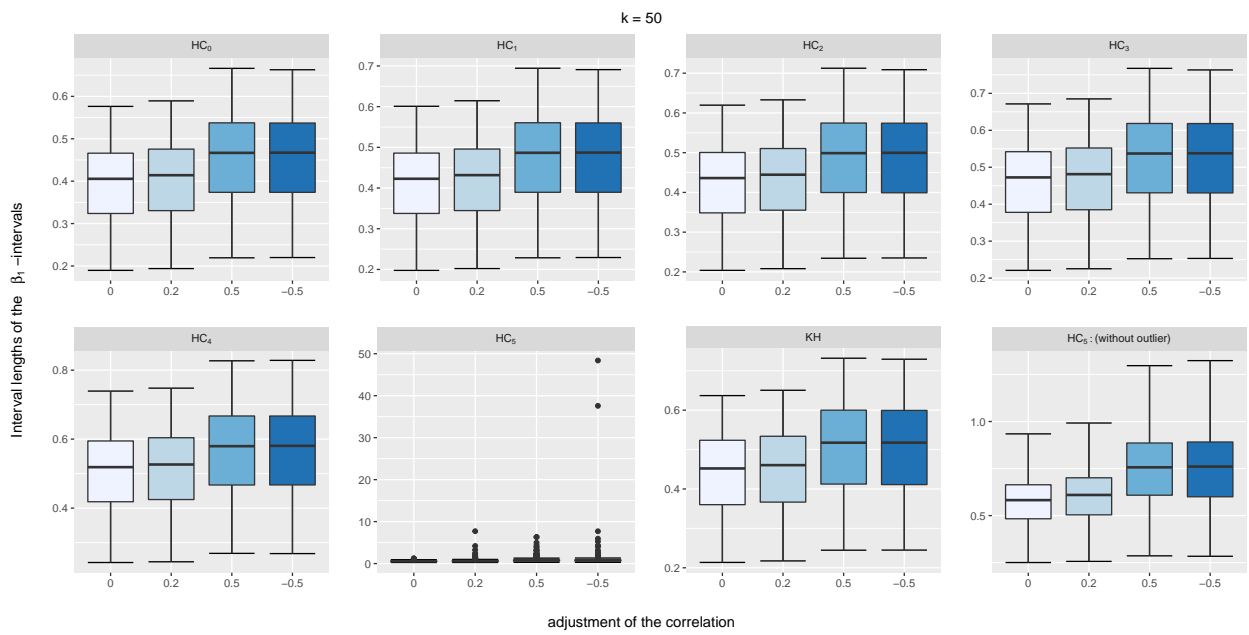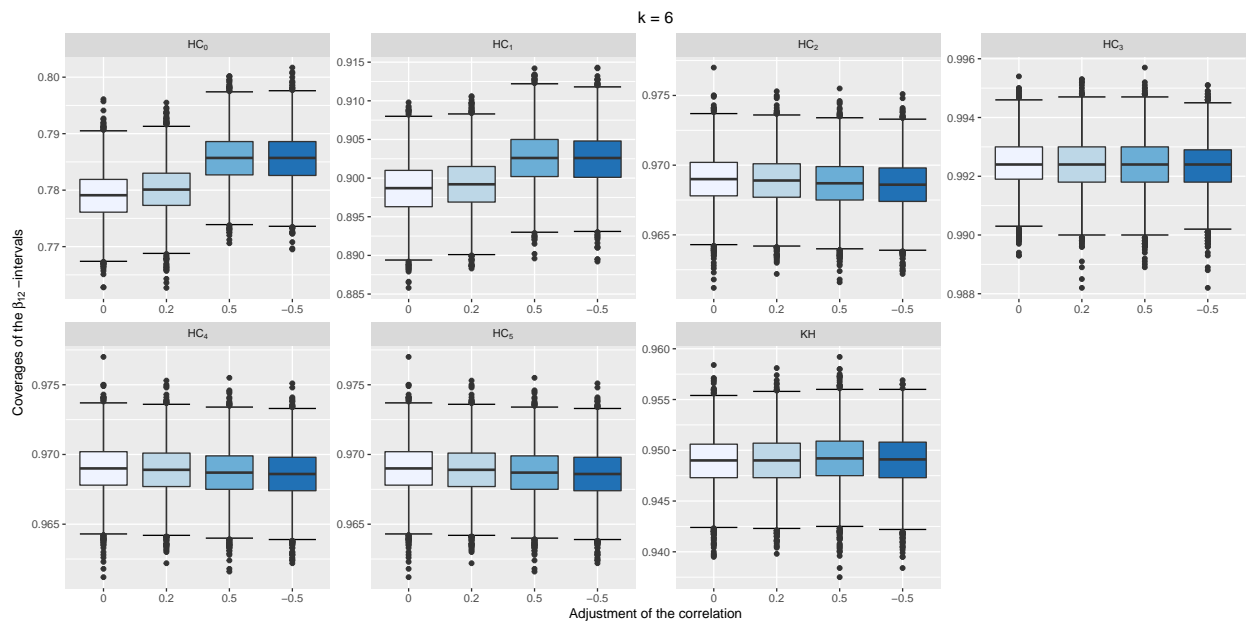Figure 73: Coverages of the β_1-intervals compared regarding the adjustments of β_{12} for the estimators $HC_0 -$ HC_5 and KH with $k = 6$.
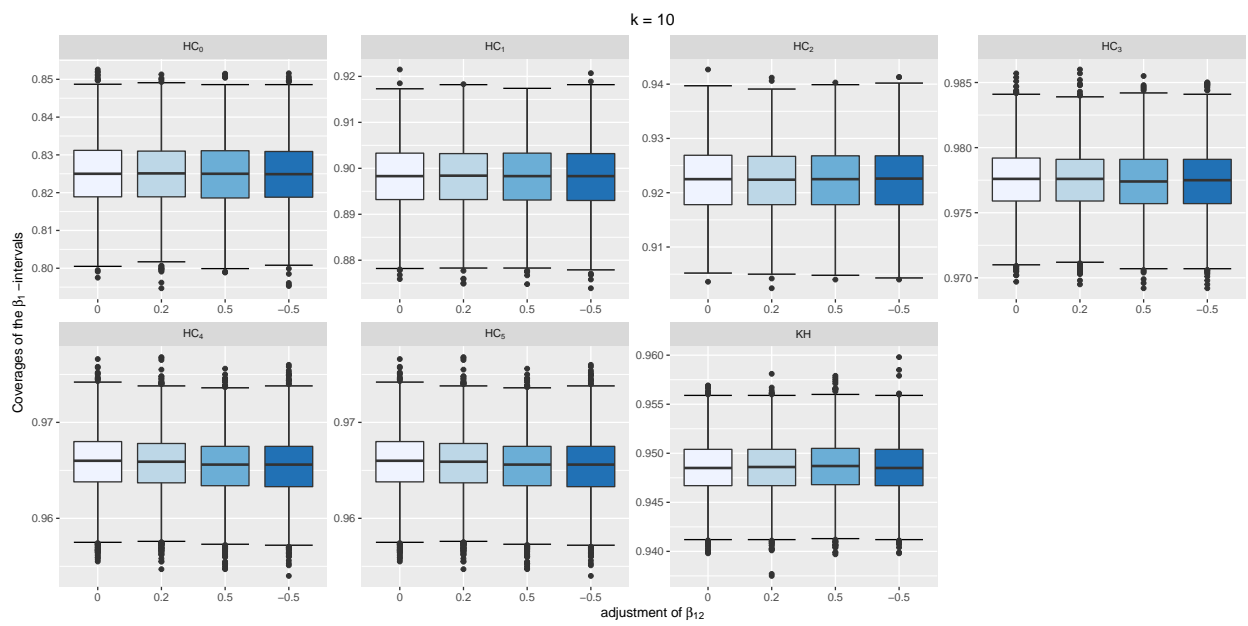
Figure 74: Coverages of the β_1-intervals compared regarding the adjustments of β_{12} for the estimators $HC_0 - HC_5$ and KH with $k = 10$.
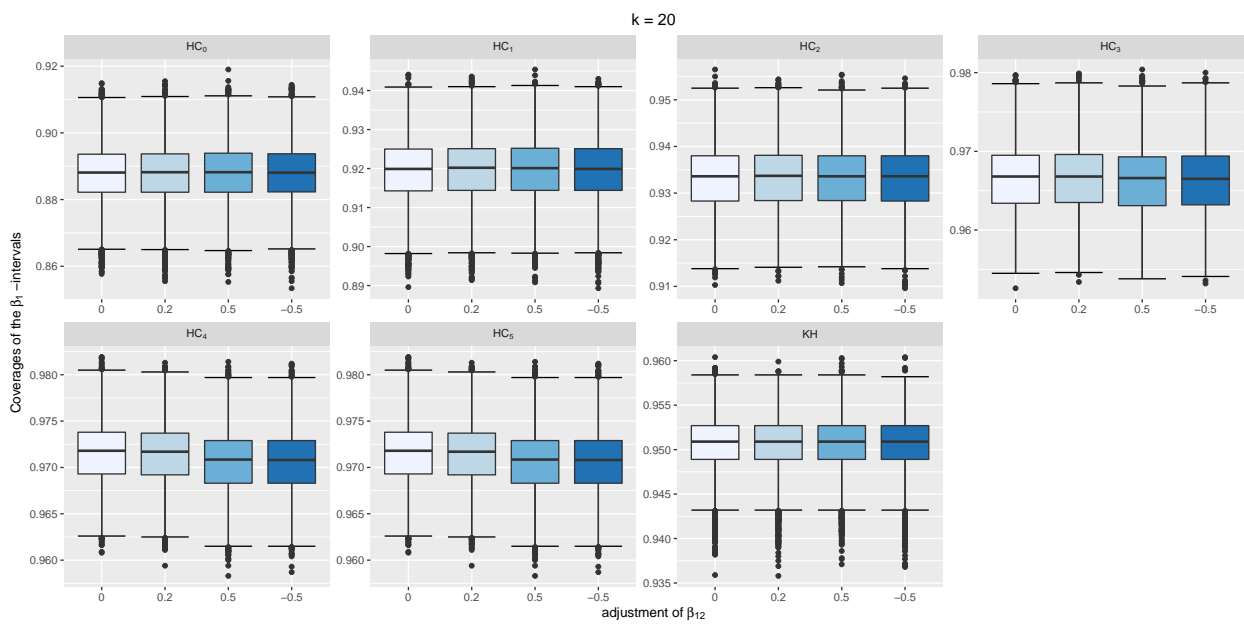
Figure 75: Coverages of the β_1-intervals compared regarding the adjustments of β_{12} for the estimators $HC_0 - HC_5$ and KH with $k = 20$.
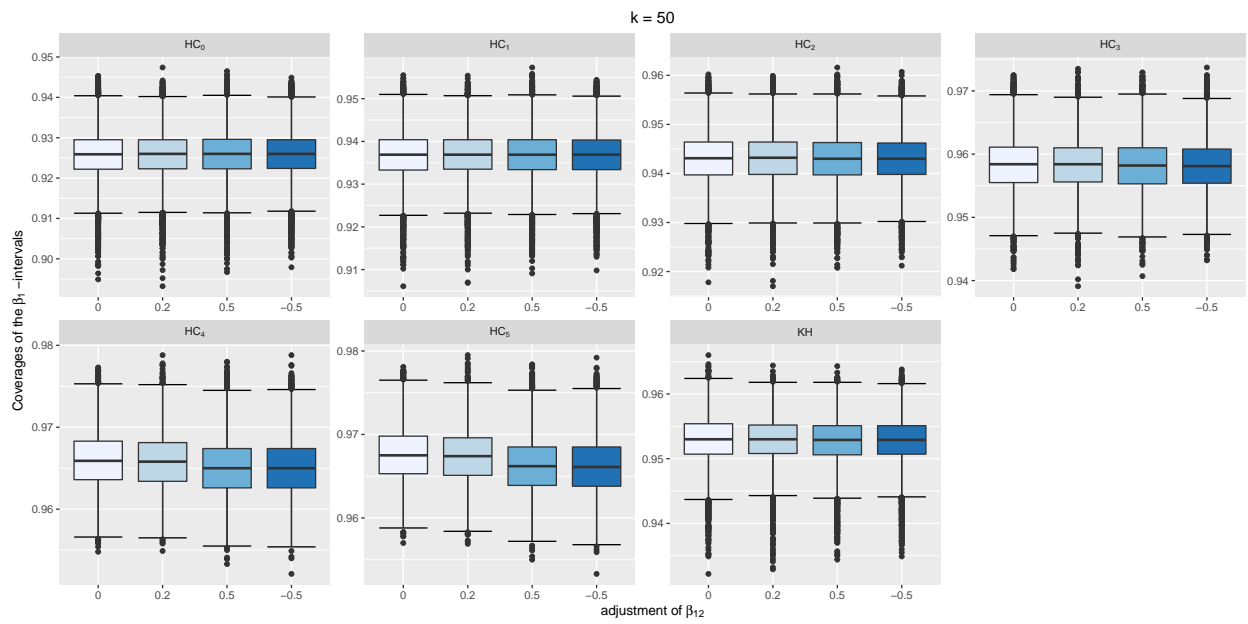
Figure 76: Coverages of the β_1-intervals compared regarding the adjustments of β_{12} for the estimators $HC_0 - HC_5$ and KH with $k = 50$.
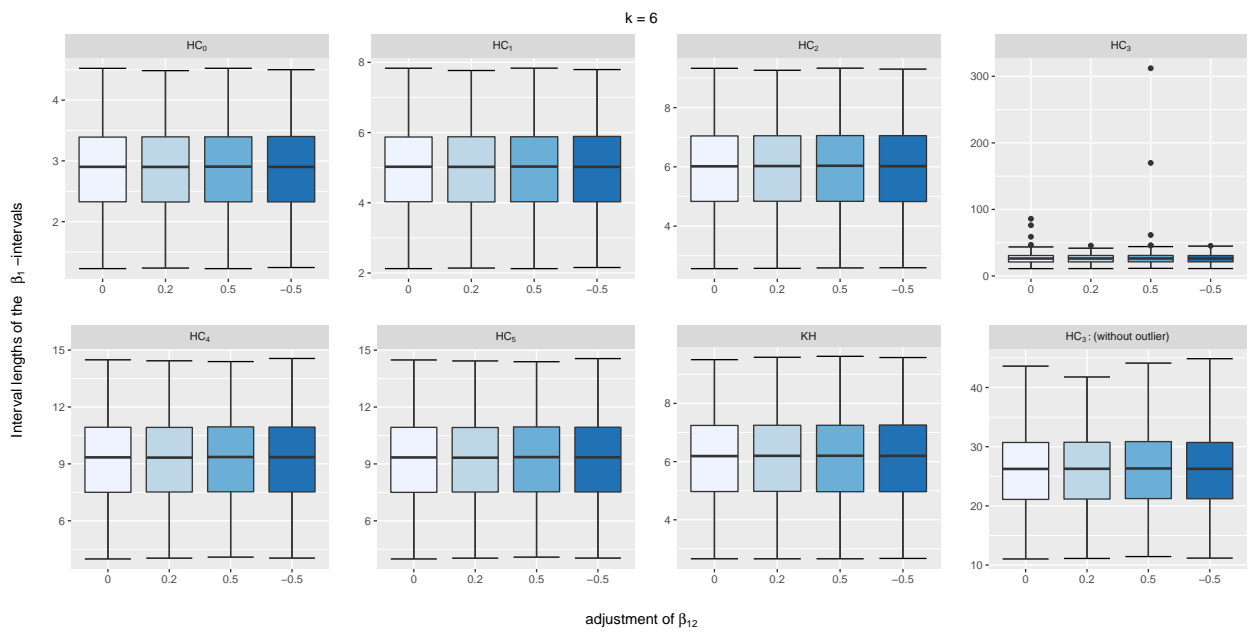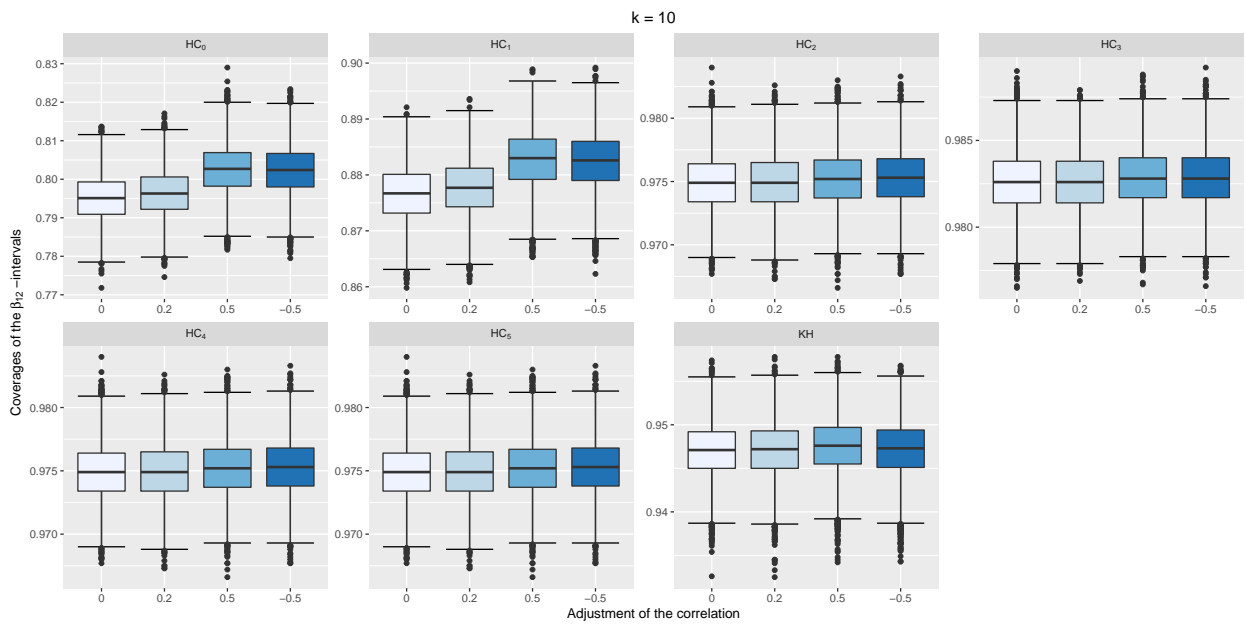
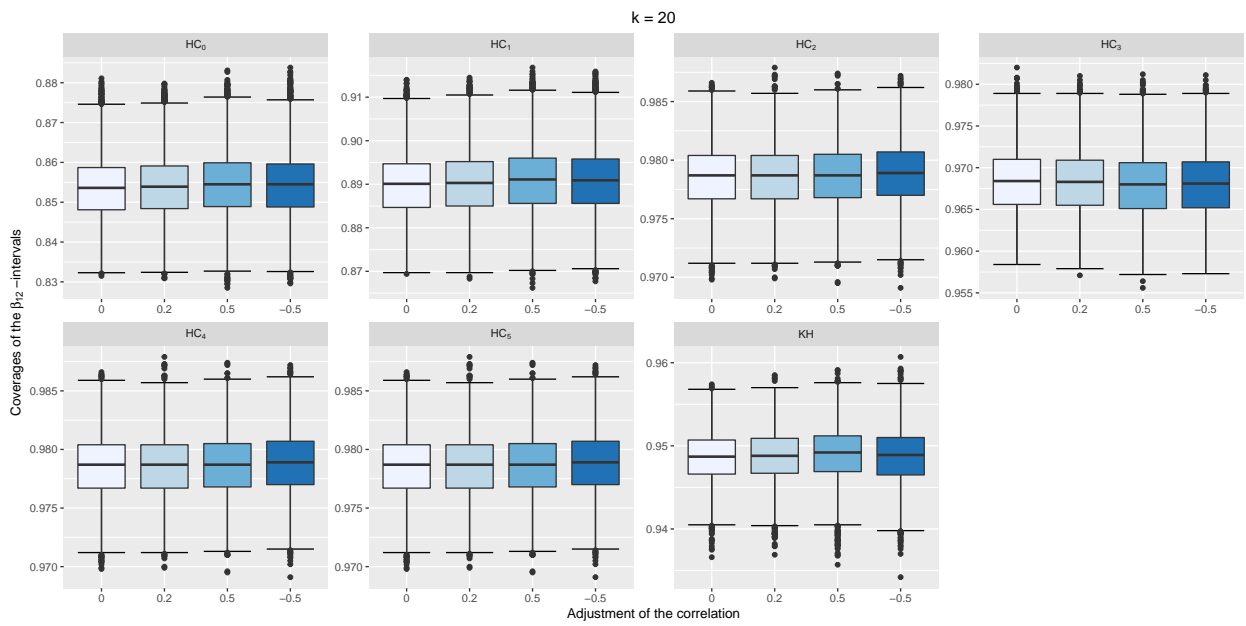Figure 77: Lengths of the β_1-intervals compared regarding the adjustments of β_{12} for the estimators $HC_0 - HC_5$ and KH with $k = 6$.
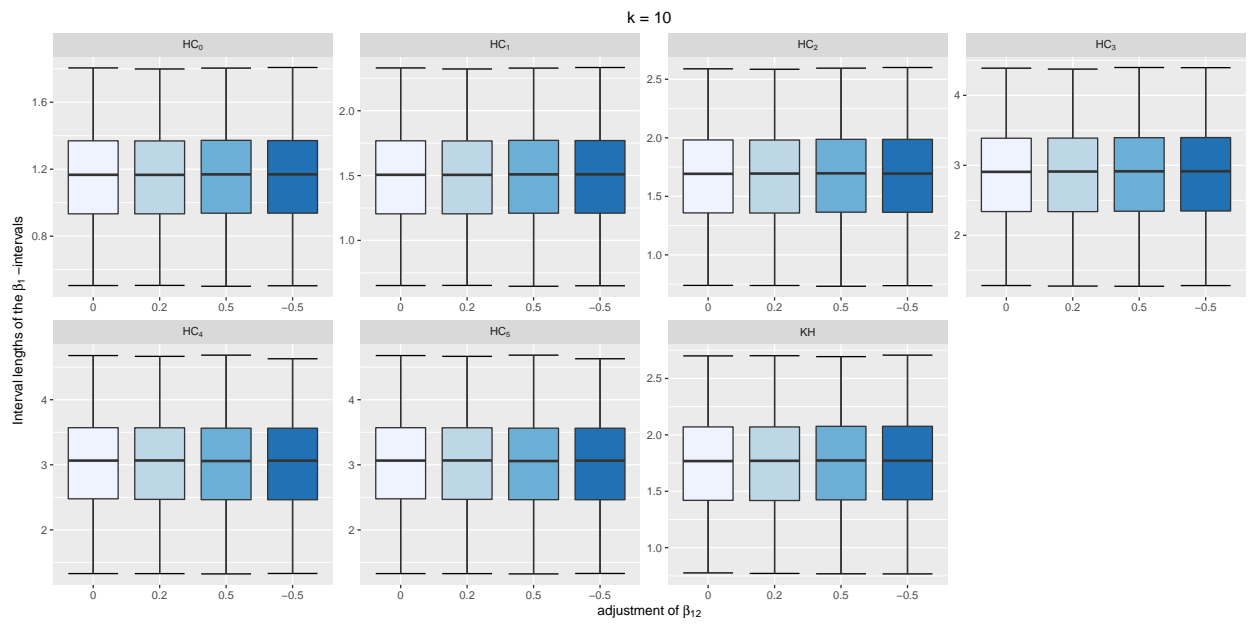
Figure 78: Lengths of the β_1-intervals compared regarding the adjustments of β_{12} for the estimators $HC_0 - HC_5$ and KH with $k = 10$.

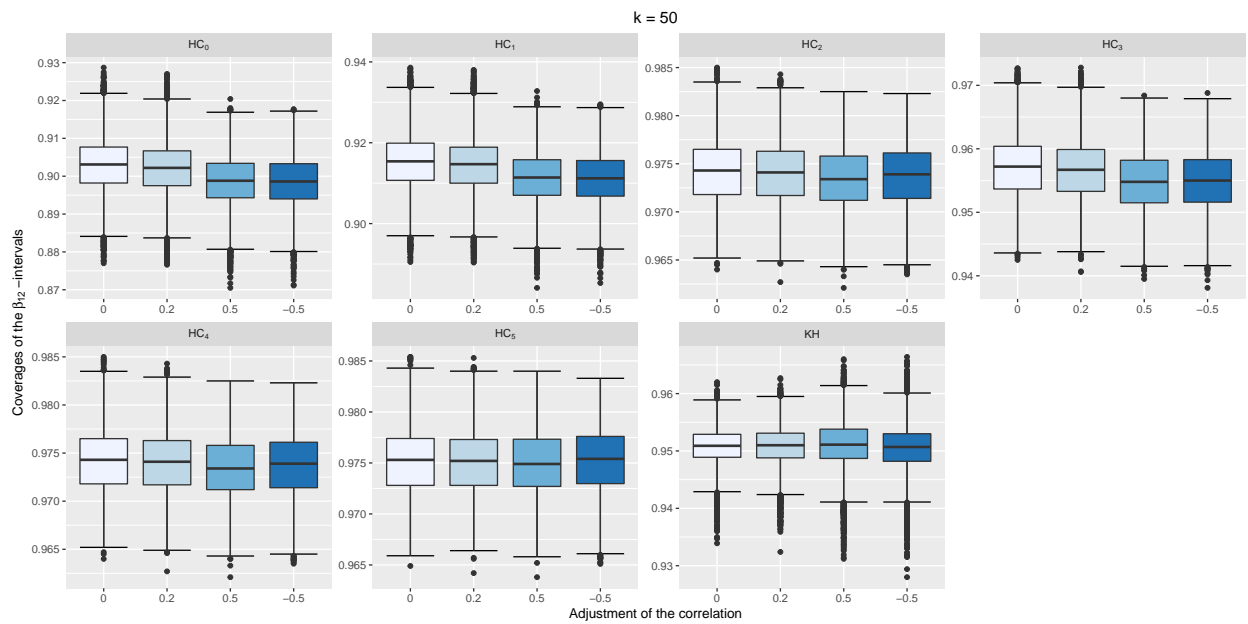Figure 79: Lengths of the β_1-intervals compared regarding the adjustments of β_{12} for the estimators $HC_0 - HC_5$ and KH with $k = 20$.

Figure 80: Lengths of the β_1-intervals compared regarding the adjustments of β_{12} for the estimators $HC_0 - HC_5$ and KH with $k = 50$.

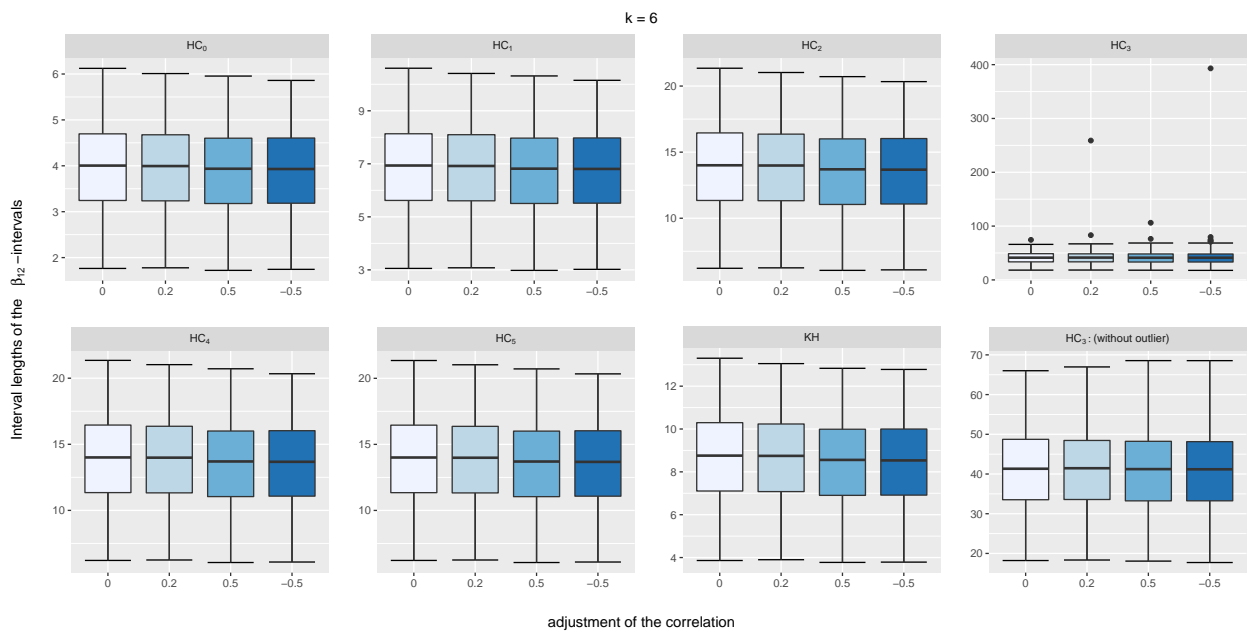Figure 81: Coverages of the β_{12}-intervals compared regarding the adjustments of β_{12} for the estimators $HC_0 - HC_5$ and KH with $k = 6$.

Figure 82: Coverages of the β_{12}-intervals compared regarding the adjustments of β_{12} for the estimators $HC_0 - HC_5$ and KH with $k = 10$.

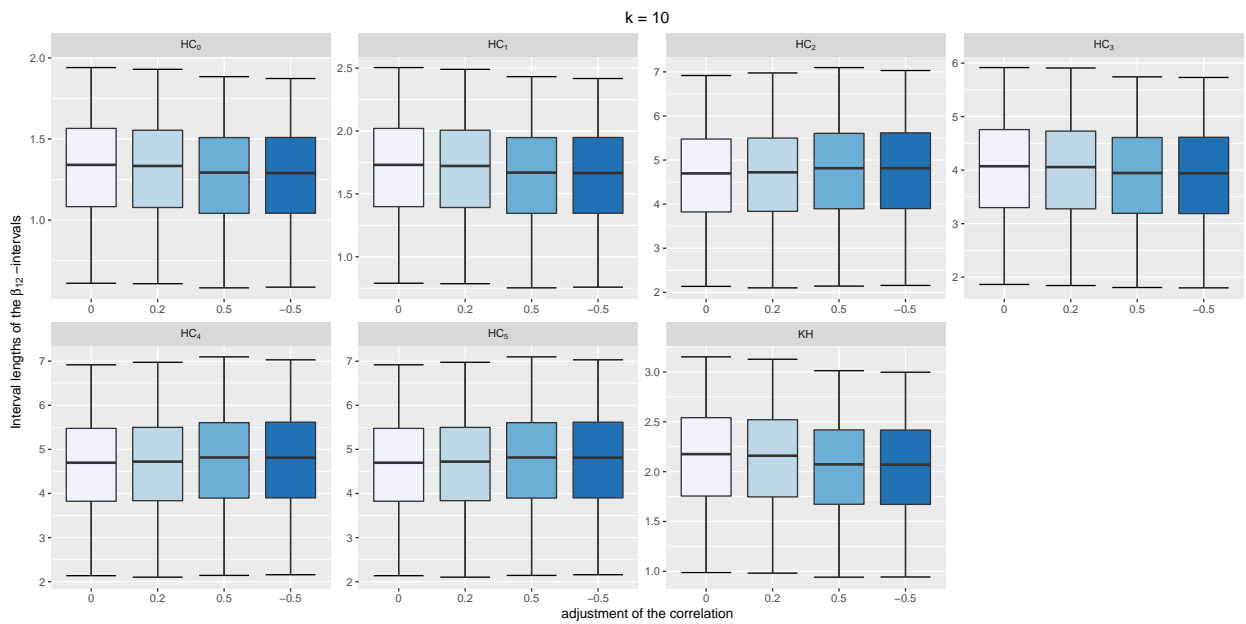Figure 83: Coverages of the β_{12}-intervals compared regarding the adjustments of β_{12} for the estimators HC_0-HC_5 and KH with $k = 20$.

Figure 84: Coverages of the β_{12}-intervals compared regarding the adjustments of β_{12} for the estimators $HC_0 - HC_5$ and KH with $k = 50$.

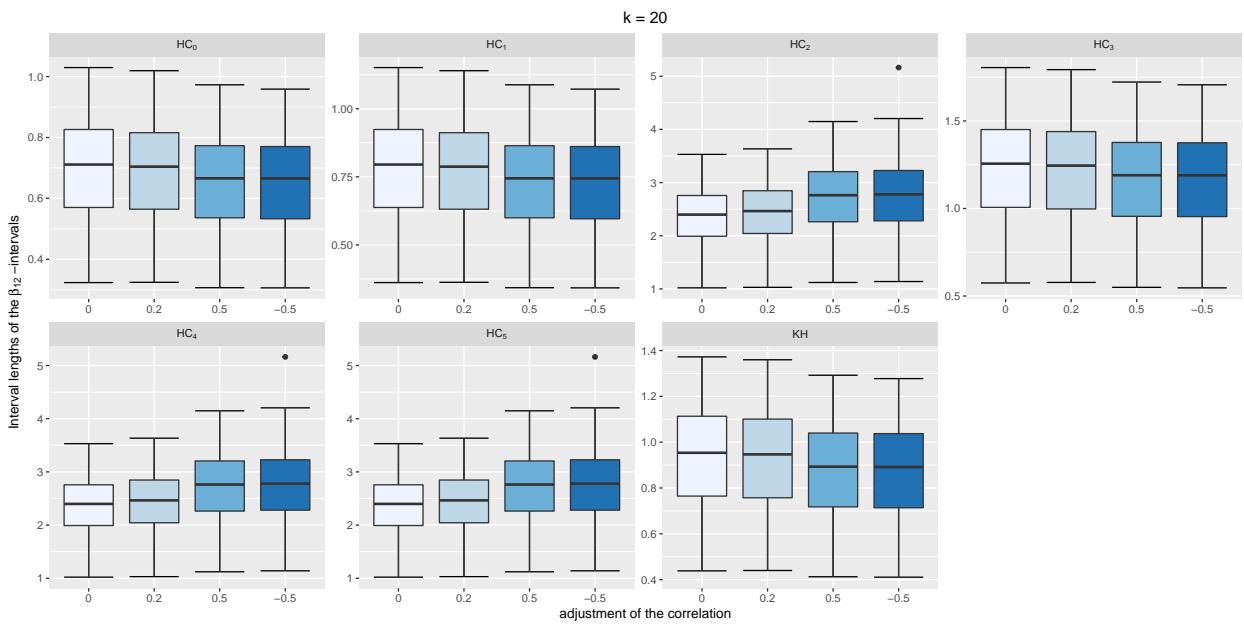Figure 85: Lengths of the β_{12}-intervals compared regarding the adjustments of β_{12} for the estimators $HC_0 - HC_5$ and KH with $k = 6$.

Figure 86: Lengths of the β_{12}-intervals compared regarding the adjustments of β_{12} for the estimators $HC_0 - HC_5$ and KH with $k = 10$.

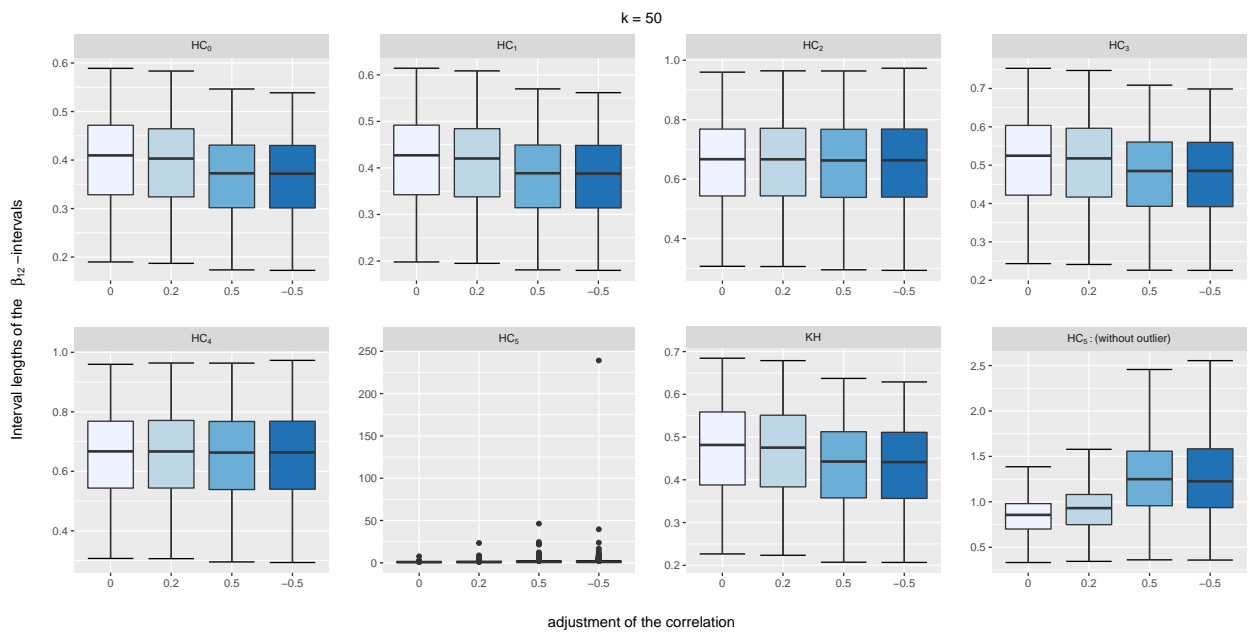Figure 87: Lengths of the β_{12}-intervals compared regarding the adjustments of β_{12} for the estimators $HC_0 - HC_5$ and KH with $k = 20$.

Figure 88: Lengths of the β_{12}-intervals compared regarding the adjustments of β_{12} for the estimators $HC_0 - HC_5$ and KH with $k = 50$.

Figure 89: Coverages of the β_1-intervals compared regarding the adjustments of the correlation ρ for the estimators $HC_0 - HC_5$ and KH with $k = 6$.
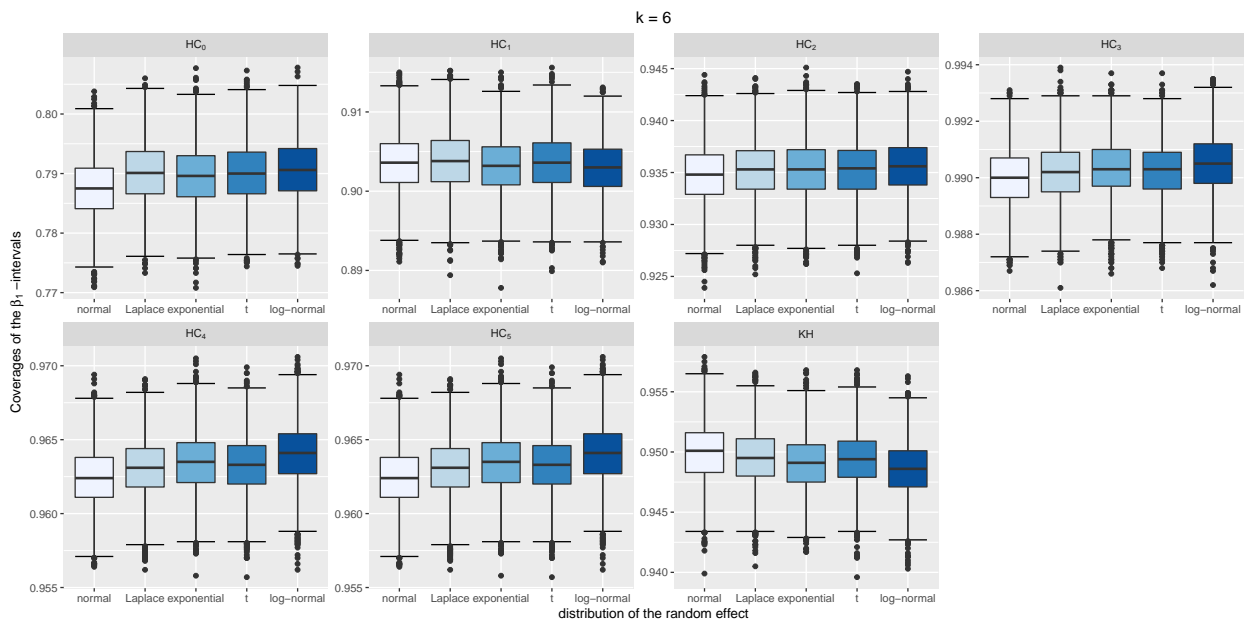
Figure 90: Coverages of the β_1-intervals compared regarding the adjustments of the correlation ρ for the estimators $HC_0 - HC_5$ and KH with $k = 10$.
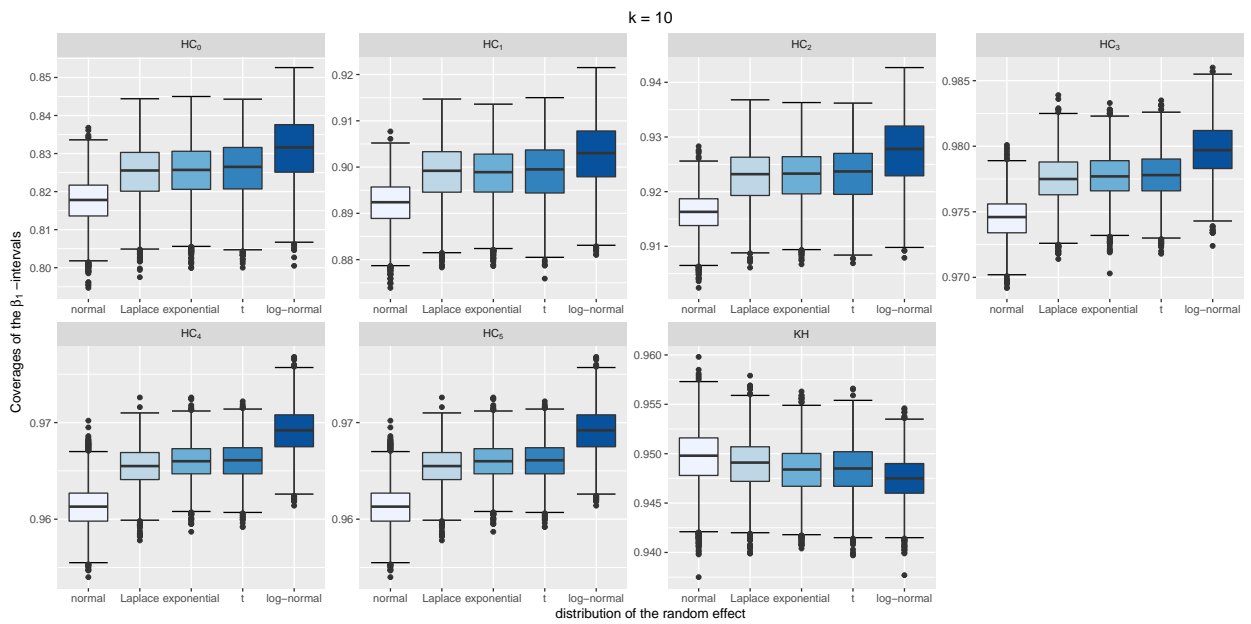
Figure 91: Coverages of the β_1-intervals compared regarding the adjustments of the correlation ρ for the estimators $HC_0 - HC_5$ and KH with $k = 20$.

Figure 92: Coverages of the β_1-intervals compared regarding the adjustments of the correlation ρ for the estimators $HC_0 - HC_5$ and KH with $k = 50$.
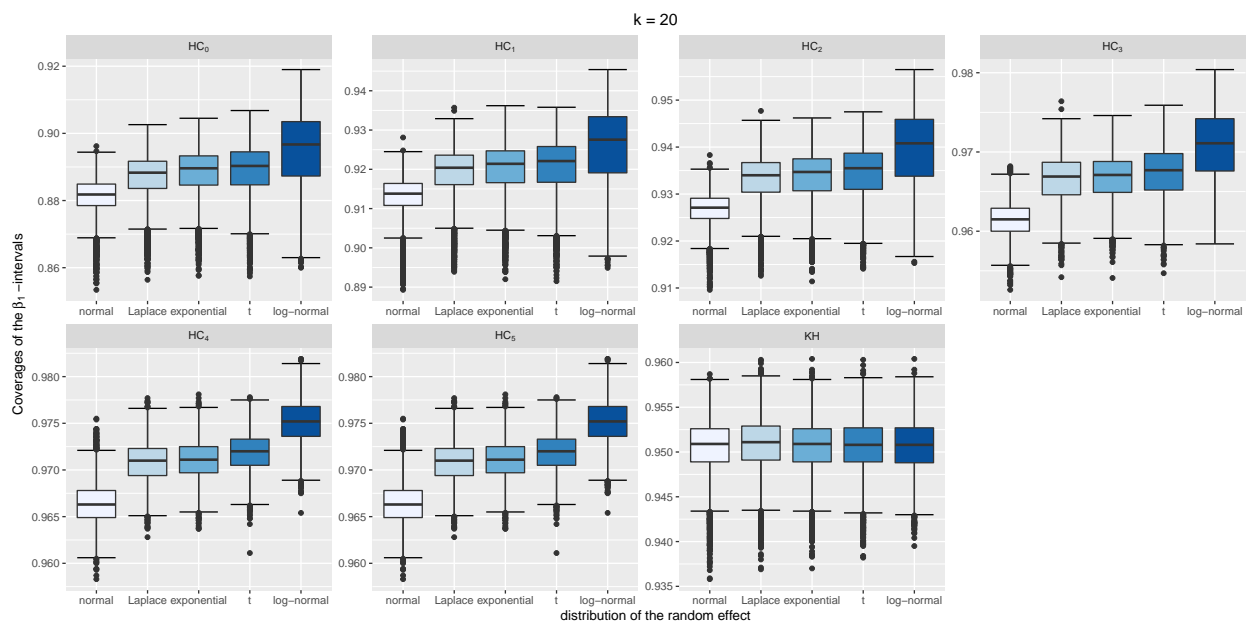
Figure 93: Lengths of the β_1-intervals compared regarding the adjustments of the correlation ρ for the estimators $HC_0 - HC_5$ and KH with $k = 6$.

Figure 94: Lengths of the β_1-intervals compared regarding the adjustments of the correlation ρ for the estimators $HC_0 - HC_5$ and KH with $k = 10$.
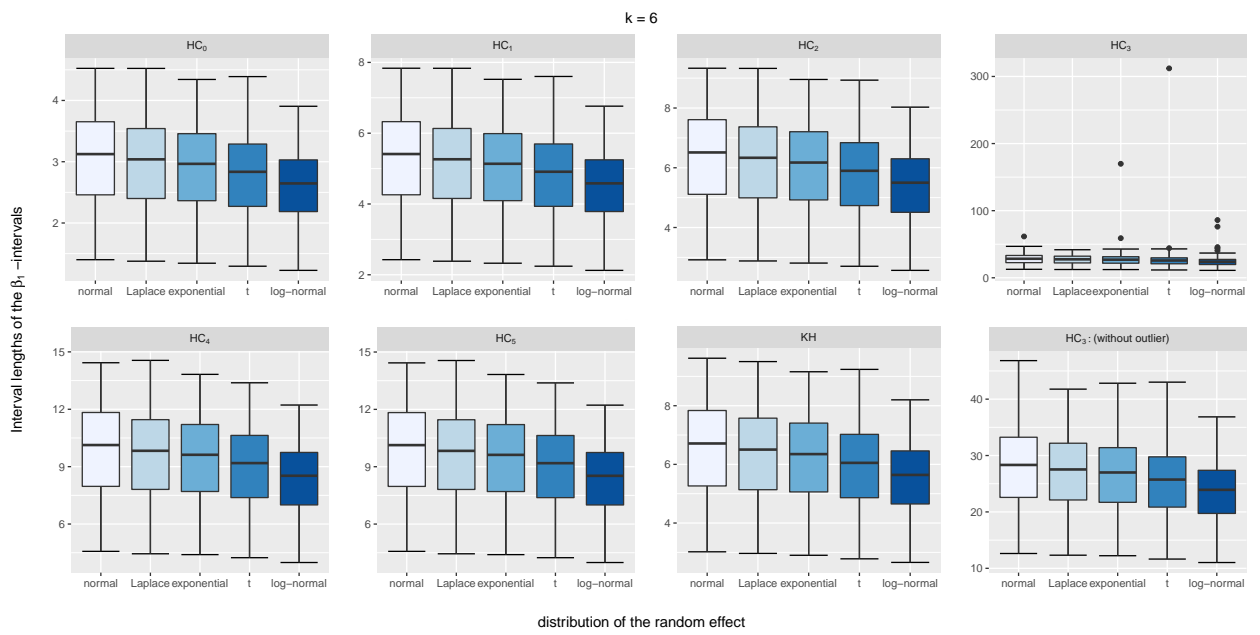
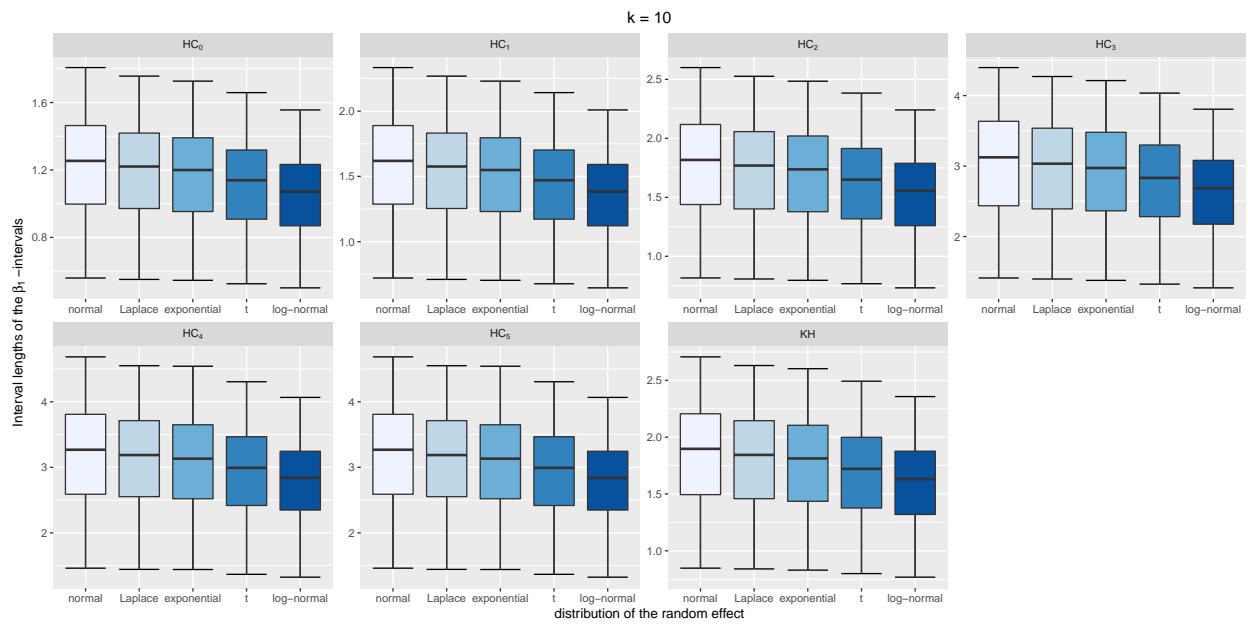Figure 95: Lengths of the β_1-intervals compared regarding the adjustments of the correlation ρ for the estimators $HC_0 - HC_5$ and KH with $k = 20$.

Figure 96: Lengths of the β_1-intervals compared regarding the adjustments of the correlation ρ for the estimators $HC_0 - HC_5$ and KH with $k = 50$.

Figure 97: Coverages of the β_{12}-intervals compared regarding the adjustments of the correlation ρ for the estimators $HC_0 - HC_5$ and KH with $k = 6$.

Figure 98: Coverages of the β_{12}-intervals compared regarding the adjustments of the correlation ρ for the estimators $HC_0 - HC_5$ and KH with $k = 10$.

Figure 99: Coverages of the β_{12}-intervals compared regarding the adjustments of the correlation ρ for the estimators $HC_0 - HC_5$ and KH with $k = 20$.

Figure 100: Coverages of the β_{12}-intervals compared regarding the adjustments of the correlation ρ for the estimators $HC_0 - HC_5$ and KH with $k = 50$.

Figure 101: Lengths of the β_{12}-intervals compared regarding the adjustments of the correlation ρ for the estimators $HC_0 - HC_5$ and KH with $k = 6$.

Figure 102: Lengths of the β_{12}-intervals compared regarding the adjustments of the correlation ρ for the estimators $HC_0 - HC_5$ and KH with $k = 10$.

Figure 103: Lengths of the β_{12}-intervals compared regarding the adjustments of the correlation ρ for the estimators $HC_0 - HC_5$ and KH with $k = 20$.

Figure 104: Lengths of the β_{12}-intervals compared regarding the adjustments of the correlation ρ for the estimators $HC_0 - HC_5$ and KH with $k = 50$.
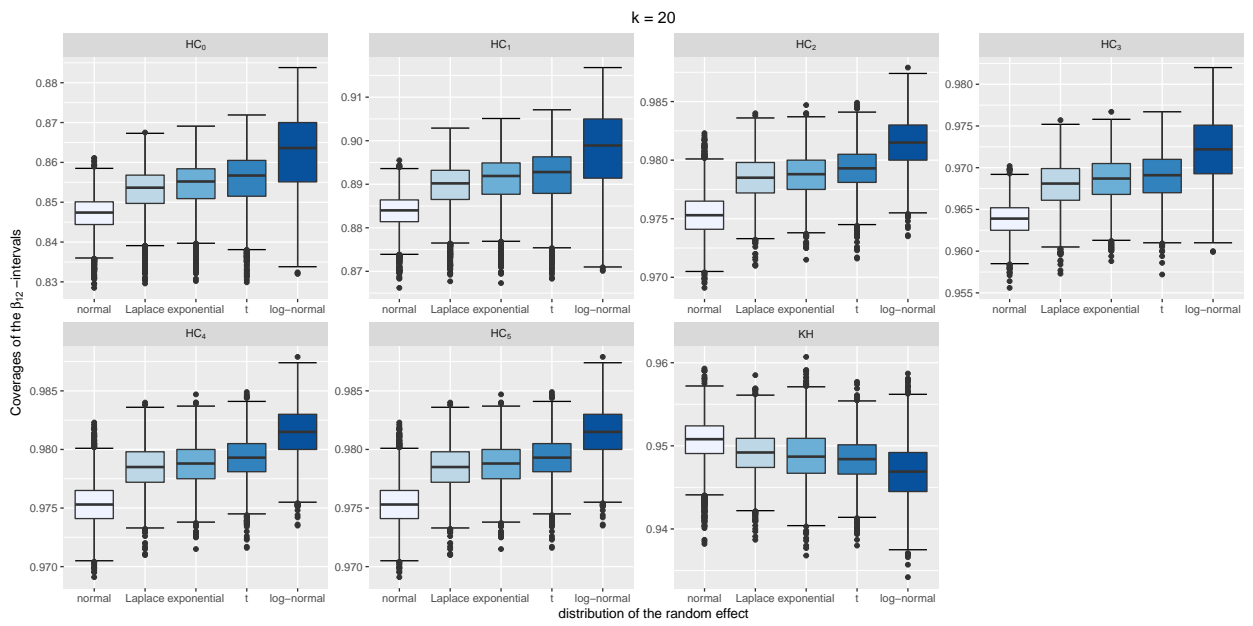
Figure 105: Coverages of the β_1-intervals compared regarding the adjustments of u_i for the estimators $HC_0 - HC_5$ and KH with $k = 6$.
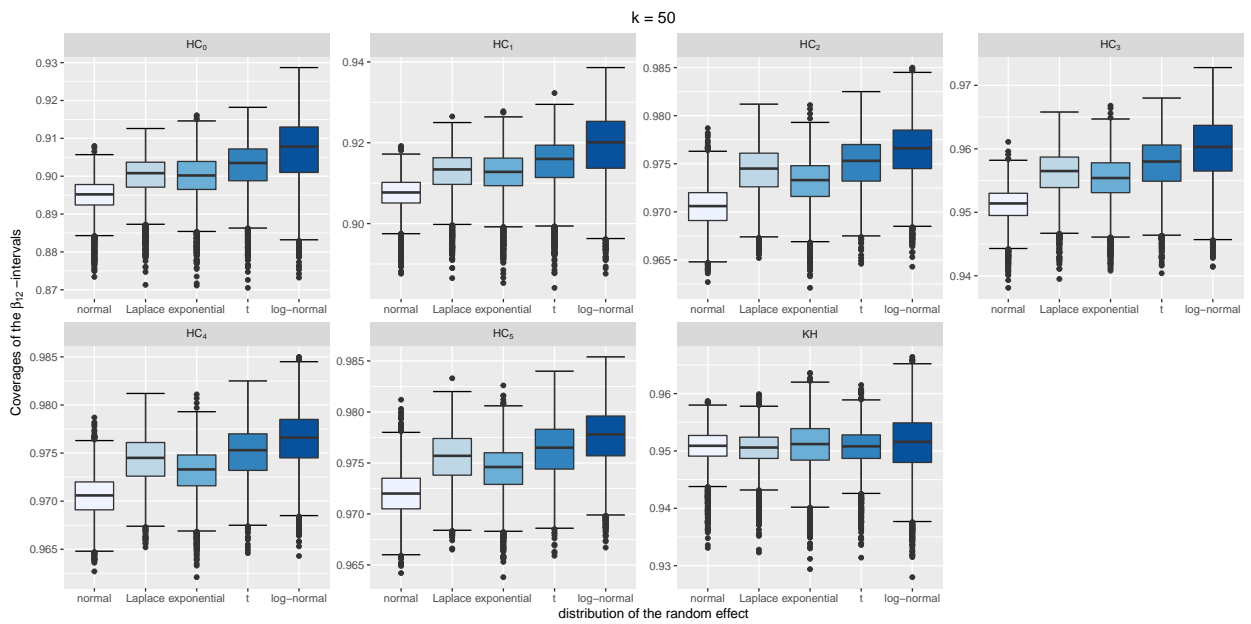
Figure 106: Coverages of the β_1-intervals compared regarding the adjustments of u_i for the estimators $HC_0 - HC_5$ and KH with $k = 10$.

Figure 107: Coverages of the β_1-intervals compared regarding the adjustments of u_i for the estimators $HC_0 - HC_5$ and KH with $k = 20$.
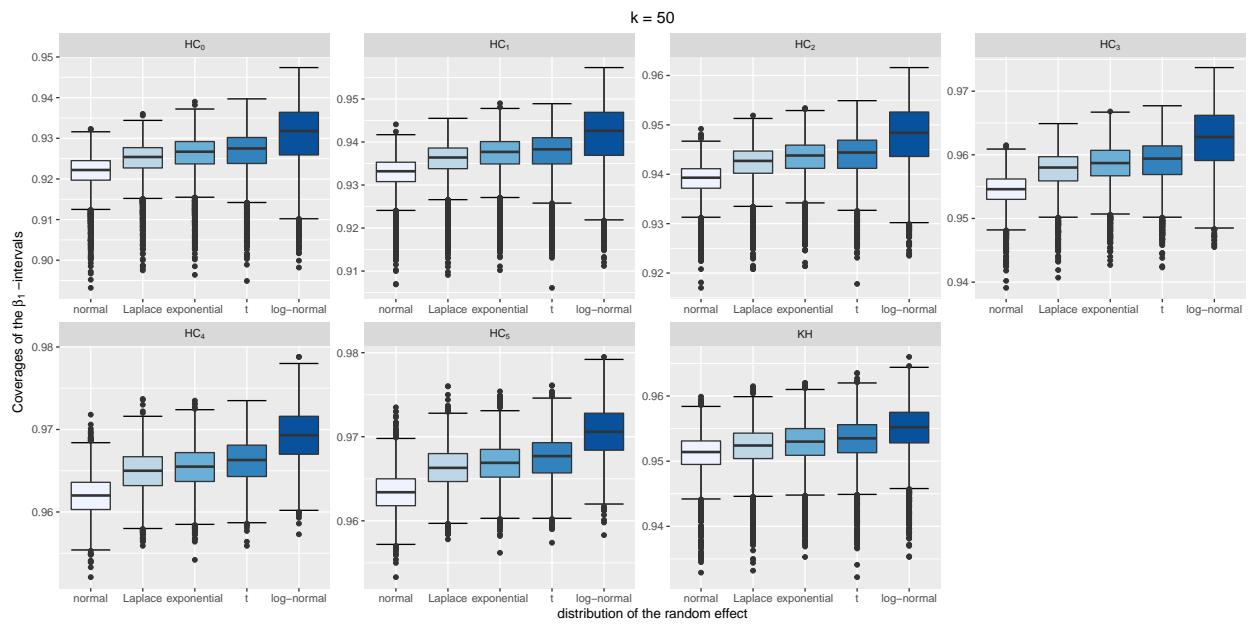
Figure 108: Coverages of the β_1-intervals compared regarding the adjustments of u_i for the estimators $HC_0 - HC_5$ and KH with $k = 50$.
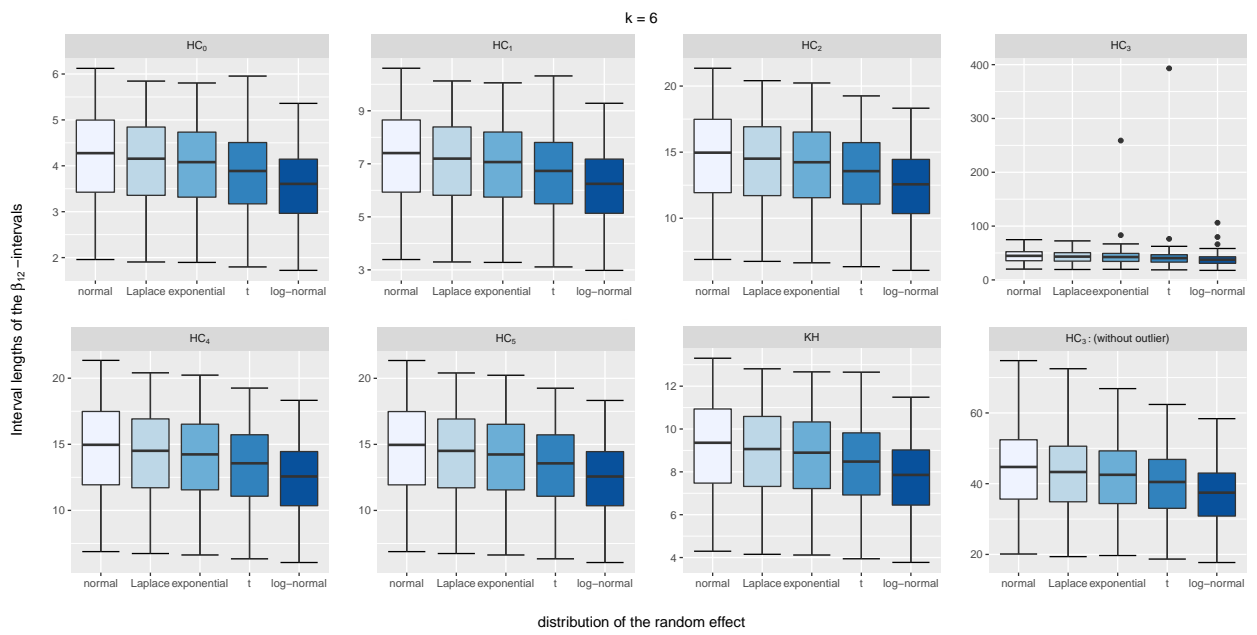
Figure 109: Lengths of the β_1-intervals compared regarding the adjustments of u_i for the estimators $HC_0 - HC_5$ and KH with $k = 6$.
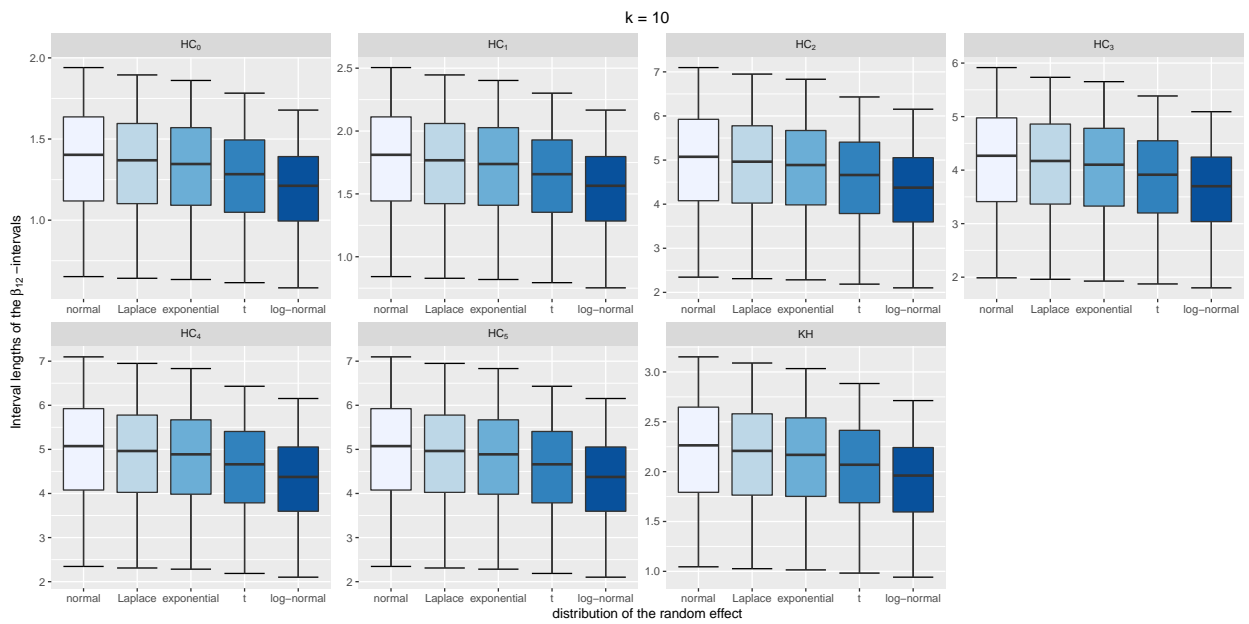
Figure 110: Lengths of the β_1-intervals compared regarding the adjustments of u_i for the estimators $HC_0 - HC_5$ and KH with $k = 10$.
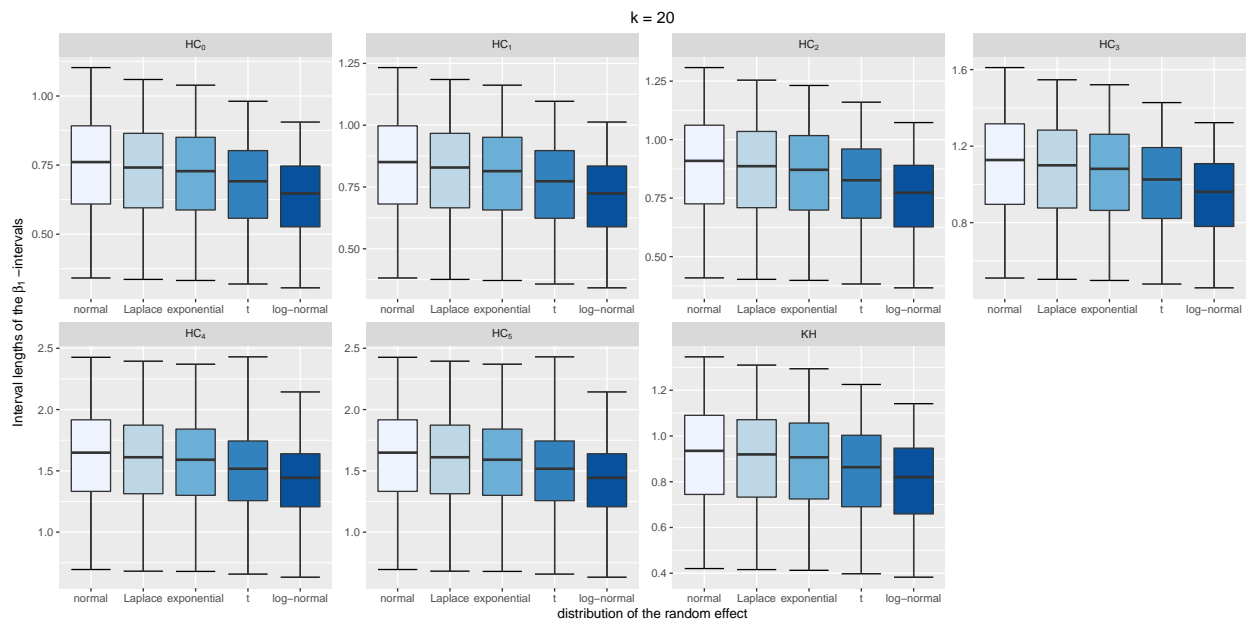
Figure 111: Lengths of the β_1-intervals compared regarding the adjustments of u_i for the estimators $HC_0 - HC_5$ and KH with $k = 20$.
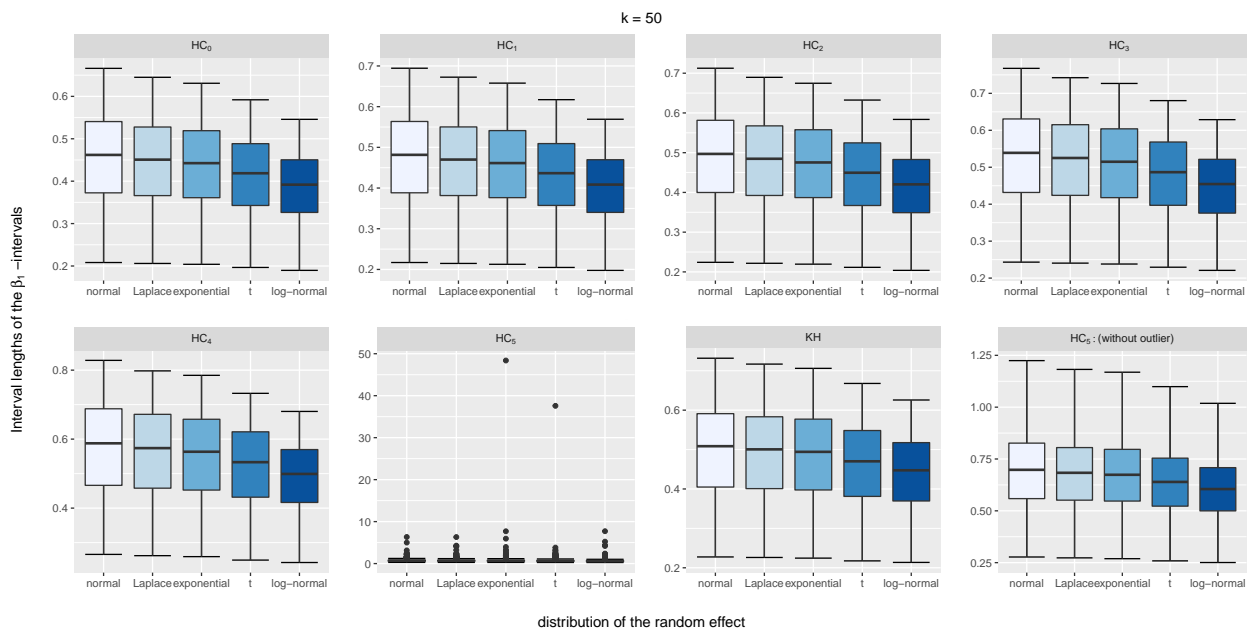
Figure 112: Lengths of the β_1-intervals compared regarding the adjustments of u_i for the estimators $HC_0 - HC_5$ and KH with $k = 50$.
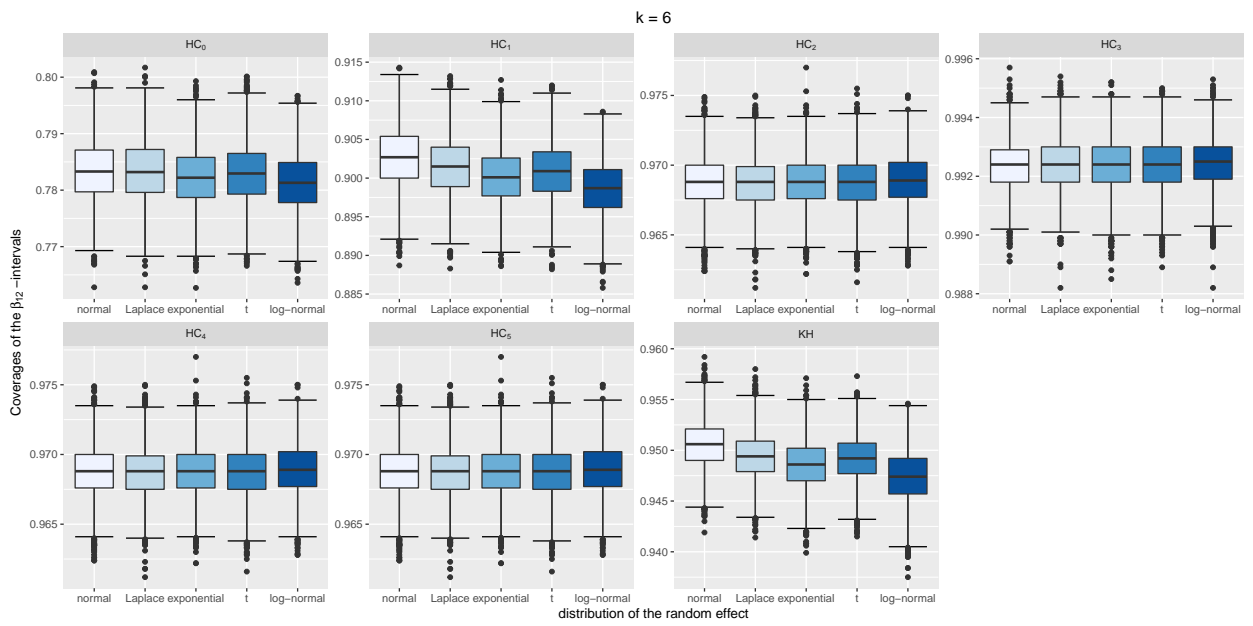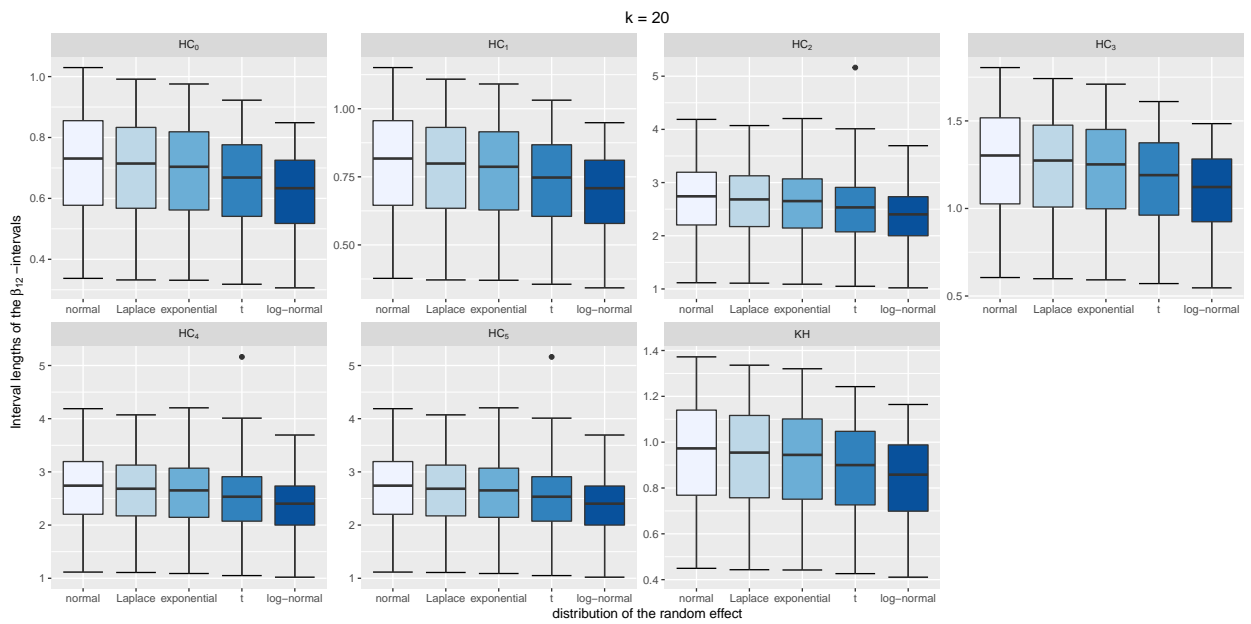
Figure 113: Coverages of the β_{12}-intervals compared regarding the adjustments of u_i for the estimators $HC_0 -$ HC_5 and KH with $k = 6$.
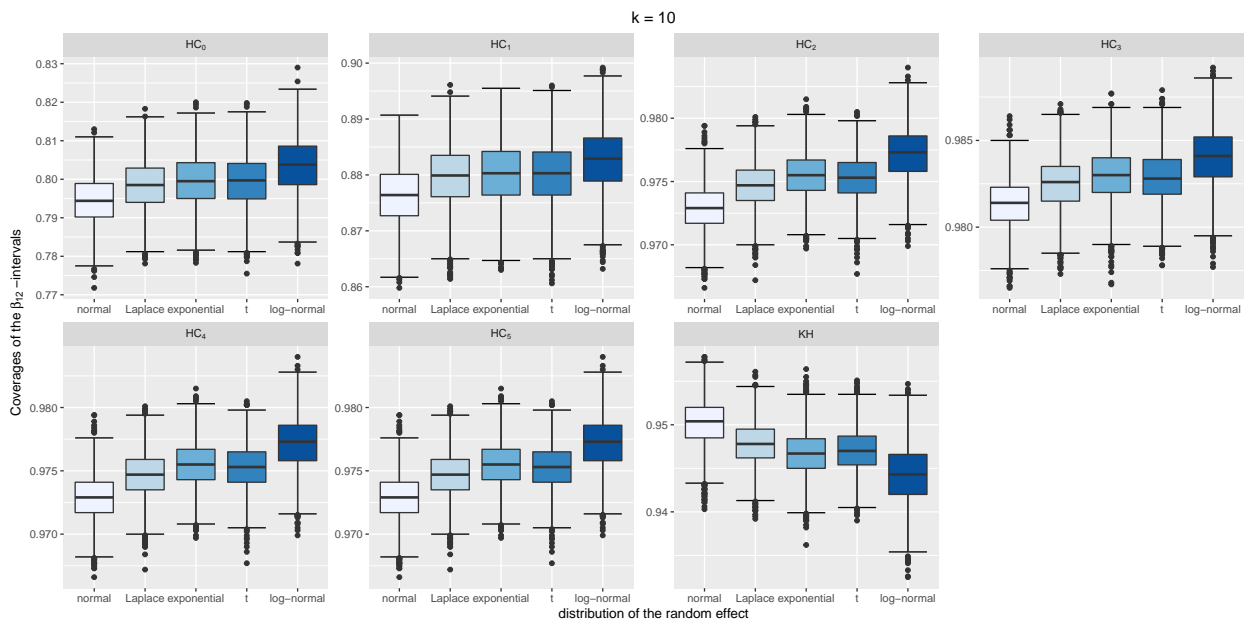
Figure 114: Coverages of the β_{12}-intervals compared regarding the adjustments of u_i for the estimators $HC_0 - HC_5$ and KH with $k = 10$.

Figure 115: Coverages of the β_{12}-intervals compared regarding the adjustments of u_i for the estimators $HC_0 - HC_5$ and KH with $k = 20$.
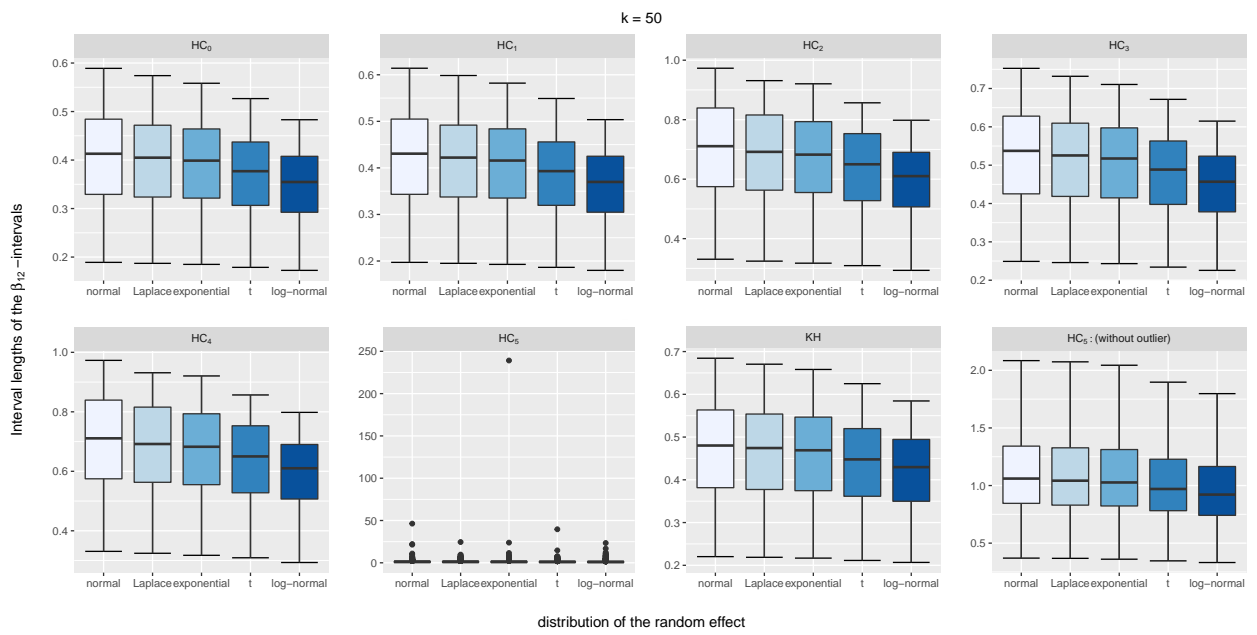
Figure 116: Coverages of the β_{12}-intervals compared regarding the adjustments of u_i for the estimators HC_0- HC_5 and KH with $k=50$.

Figure 117: Lengths of the β_{12}-intervals compared regarding the adjustments of u_i for the estimators $HC_0 - HC_5$ and KH with $k = 6$.

Figure 118: Lengths of the β_{12}-intervals compared regarding the adjustments of u_i for the estimators $HC_0 - HC_5$ and KH with $k = 10$.

Figure 119: Lengths of the β_{12}-intervals compared regarding the adjustments of u_i for the estimators $HC_0 - HC_5$ and KH with $k = 20$.

Figure 120: Lengths of the β_{12}-intervals compared regarding the adjustments of u_i for the estimators $HC_0 - HC_5$ and KH with $k = 50$.

F Additional Simulations

In additional simulations we considered the effects of fitting the wrong model and of very high correlations. The setup of the simulation was the same as in the main simulation, except for the adjustments mentioned below:

To assess the effect of fitting a wrong model, models with only two moderators (short model) and models with two covariates and their interaction (long model) were fitted. The true interaction was simulated as either $\beta_{12} = 0$ or $\beta_{12} = 0.5$. Hence there were two types of a wrong model simulated: (i) when $\beta_{12} = 0$ but the long model was fitted and (ii) when $\beta_{12} = 0.5$ but the short model was fitted. For both the respective right model was simulated as well. In order to analyse the effect of very high correlations, correlations of $\rho = 0$ and $\rho = 0.9$ were simulated.

Since most of the flexible parameters did not alter the results of the main simulation much, the simulation was conducted for less parameter combinations than the main simulation. Like β_{12} also β_1 and β_2 were chosen from $\{0, 0.5\}$. The heterogeneity parameter τ^2 was set to either 0.1, 0.5 or 0.9. Simulated random effects distributions were a normal distribution and the log normal distribution. The vectors of study sizes $\boldsymbol{n}_{15}, \boldsymbol{n}_{25}, \boldsymbol{n}_{50}$ and the number of studies k were chosen like in the main simulation. Every parameter combination was simulated $N = 1,000$ times. Besides the mentioned modifications the simulation was conducted like the main simulation.

To assess the fit of the models, the short and the long model were compared by parallel boxplots of the coverages and interval lengths of β_0 and β_1 for each estimator $\mathbf{HC}_0 - \mathbf{HC}_5$ and $\mathbf{KH}$.

Figure 121 shows the coverages and interval lengths of β_0 when the true model contains no interaction term. For all estimators but $\mathbf{HC}_0$ the coverages of β_0 are slightly higher when an interaction term is fitted. On the other hand the intervals tend to be longer. The same holds for the intervals of β_1 (see Figure 122).

When the true model contains an interaction ($\beta_{12} = 0.5$), the coverage of β_0 tends to be lower if a short model is fitted, compared to the long model. As Figure 123 shows there are many huge outliers towards a coverage of 0. Also the CIs tend to be longer. The coverage of β_1 is higher when the long (correct) model is fitted for all estimators. Again the CIs tend to be longer when the model with interaction is fitted (see Figure 124).

In Figure 125 the coverages of β_0 in the short model are shown for low and high correlations separately. It reveals that the low coverages for β_0 only occur when a large correlation between the moderators is present. To analyse this issue in more detail, this situation is considered again in Figures 126-129 for each number of studies k separately. As Figures 126 and 127 show, the coverages are decreasing in the number of studies. The coverages close to zero occur only for $k = 50$. This is probably caused by the bias in the estimation of β_0 when the moderator β_{12} is omitted. Since the interval lengths are also decreasing in the number of studies (see Figures 128 and 129) the true parameter is covered more often for small k because the estimation is assumed to be uncertain. For large k the estimation is assumed to be more precise and therefore the bias causes a lower coverage.

Finally, the coverages and lengths of β_0 and β_1 in a model with interaction are compared for $\rho = 0$ and $\rho = 0.9$. The coverages of the β_0-CIs and β_1-CIs based on $\mathbf{HC_0 - HC_2}$ tend to be higher for large correlations, whereas for the other estimators they are slightly lower or there is almost no difference. The lengths tend to be higher when large correlations are present for both coefficients. This result is in accordance with the results from the main simulation (see Figures 89-96).

Concluding, fitting a longer model is always related to longer confidence intervals. However, neglecting an interaction may cause a large bias in the estimation and therefore lower coverages, especially when the moderators are correlated. Hence, when in doubt an interaction should always be included in the model. Only when the correct model is fitted do very high correlations have little impact on the performance of the confidence intervals.
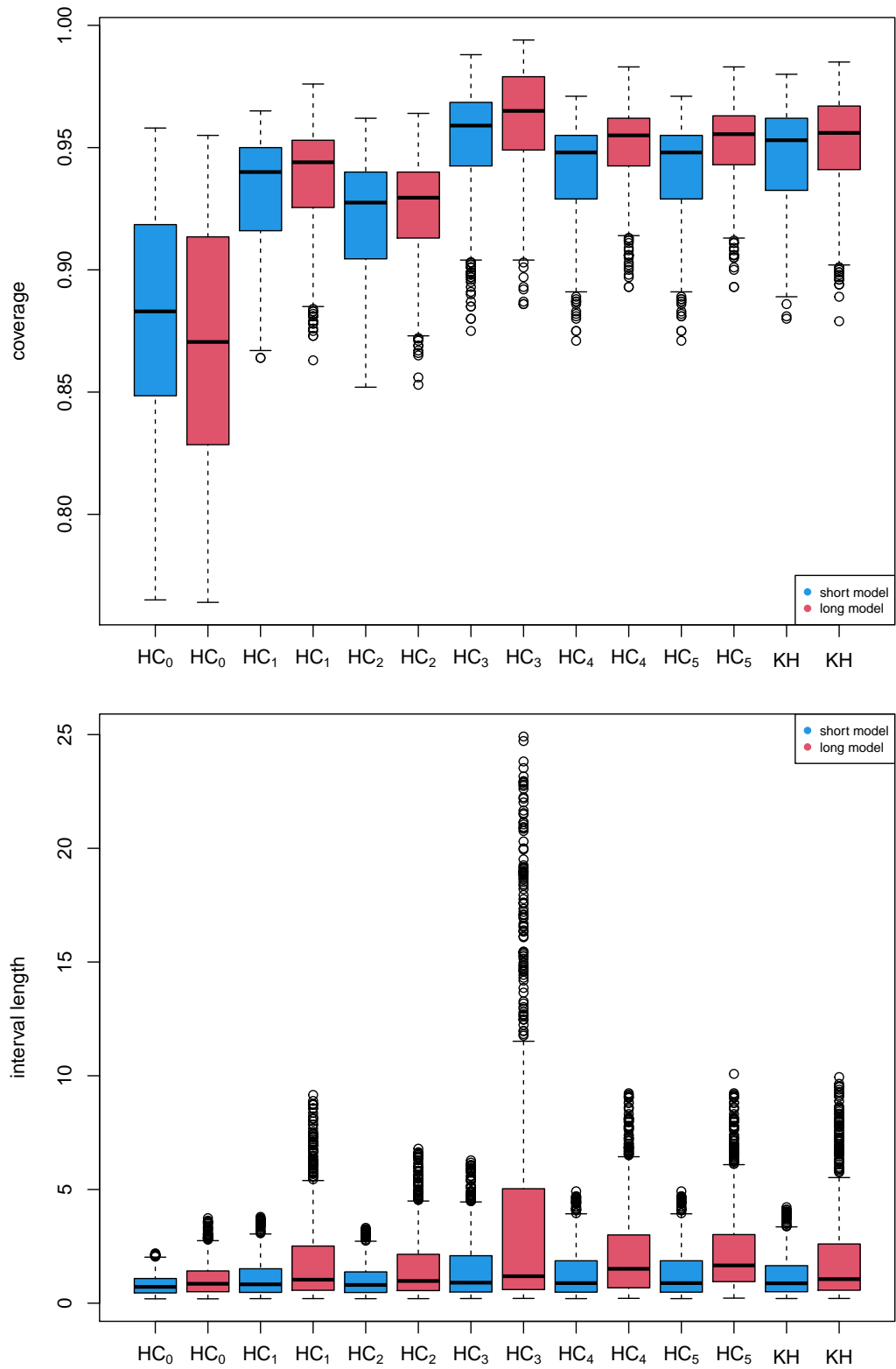
Figure 121: Coverages (upper plot) and interval lengths (lower plot) of β_0 compared for a model without interaction (short) and a model with interaction (long) when $\beta_{12} = 0$.
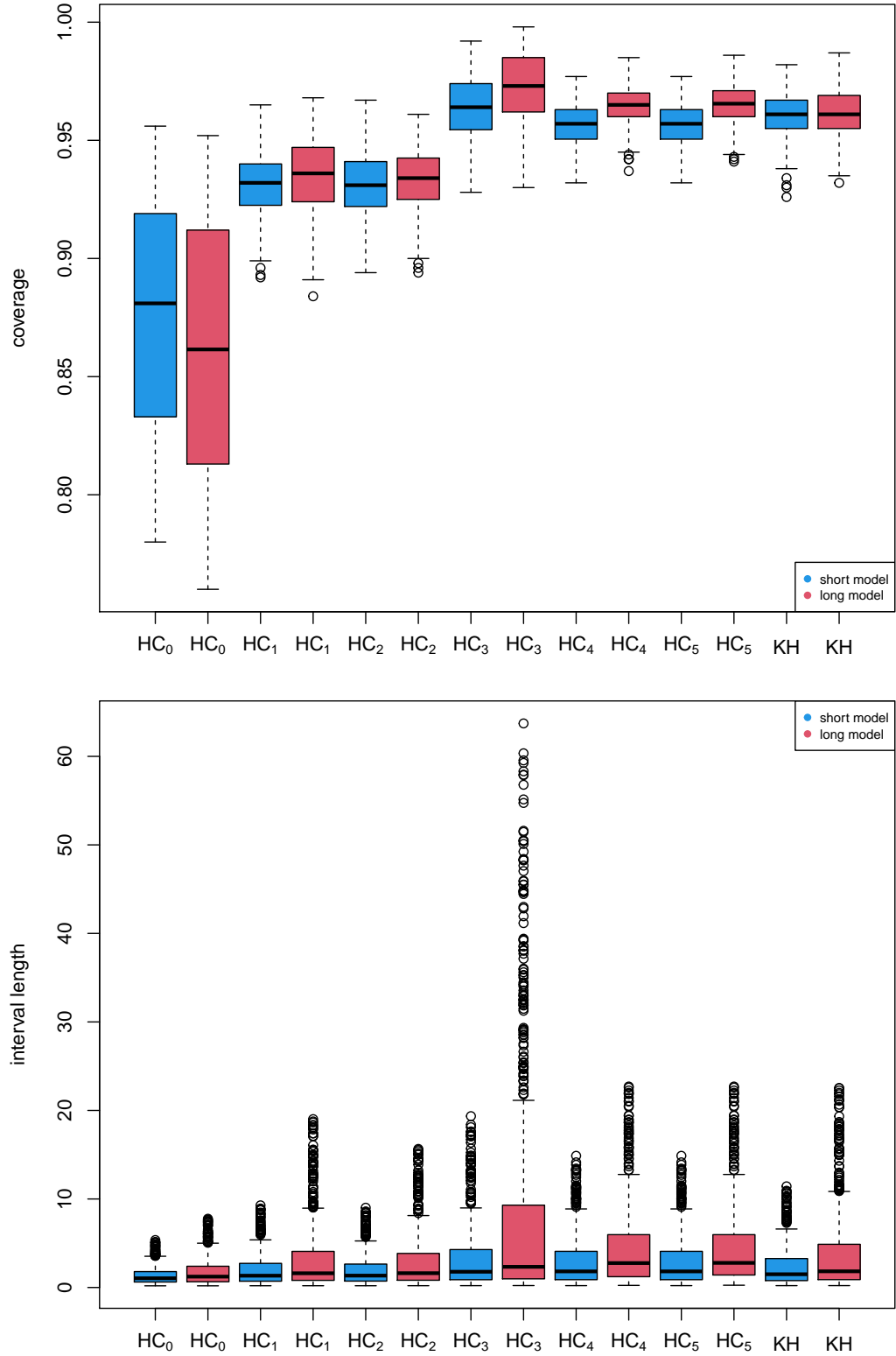
Figure 122: Coverages (upper plot) and interval lengths (lower plot) of β_1 compared for a model without interaction (short) and a model with interaction (long) when $\beta_{12} = 0$.
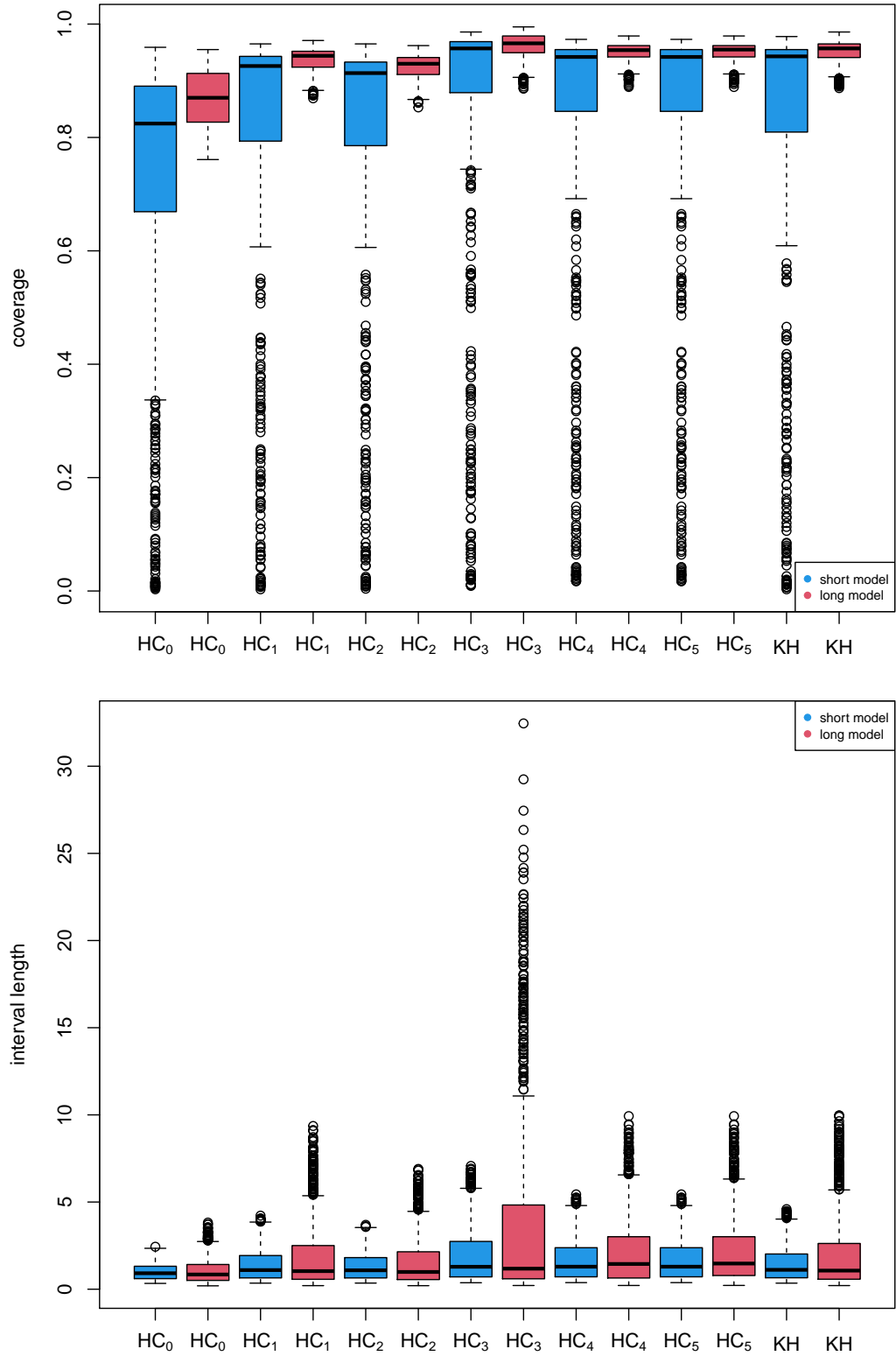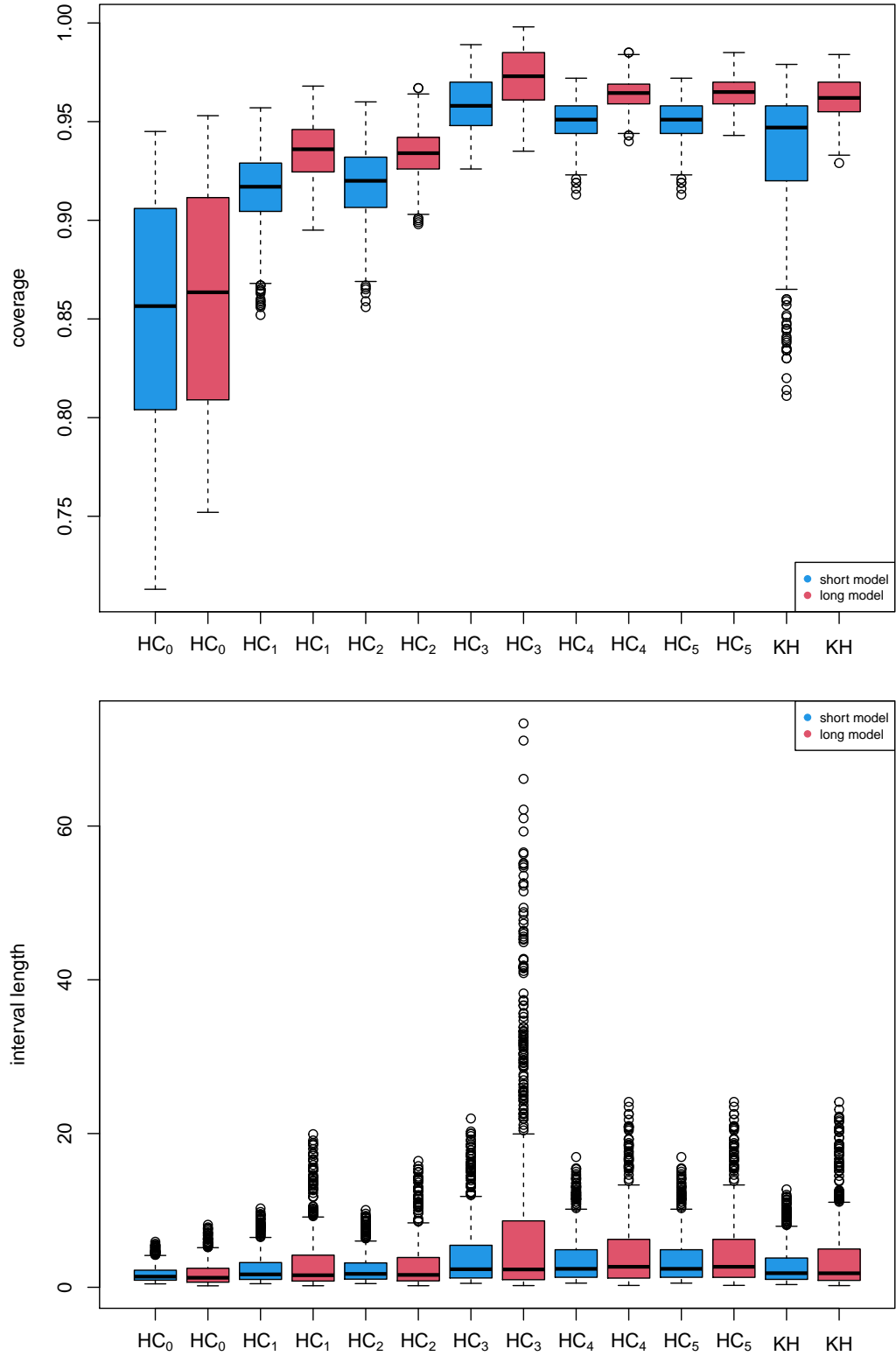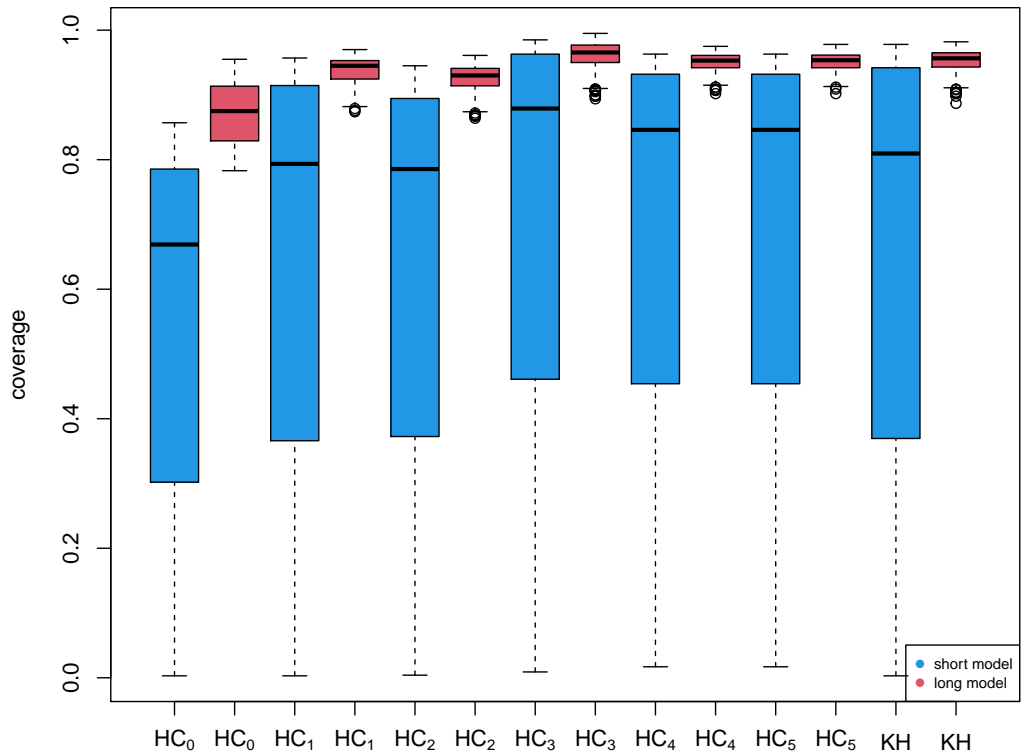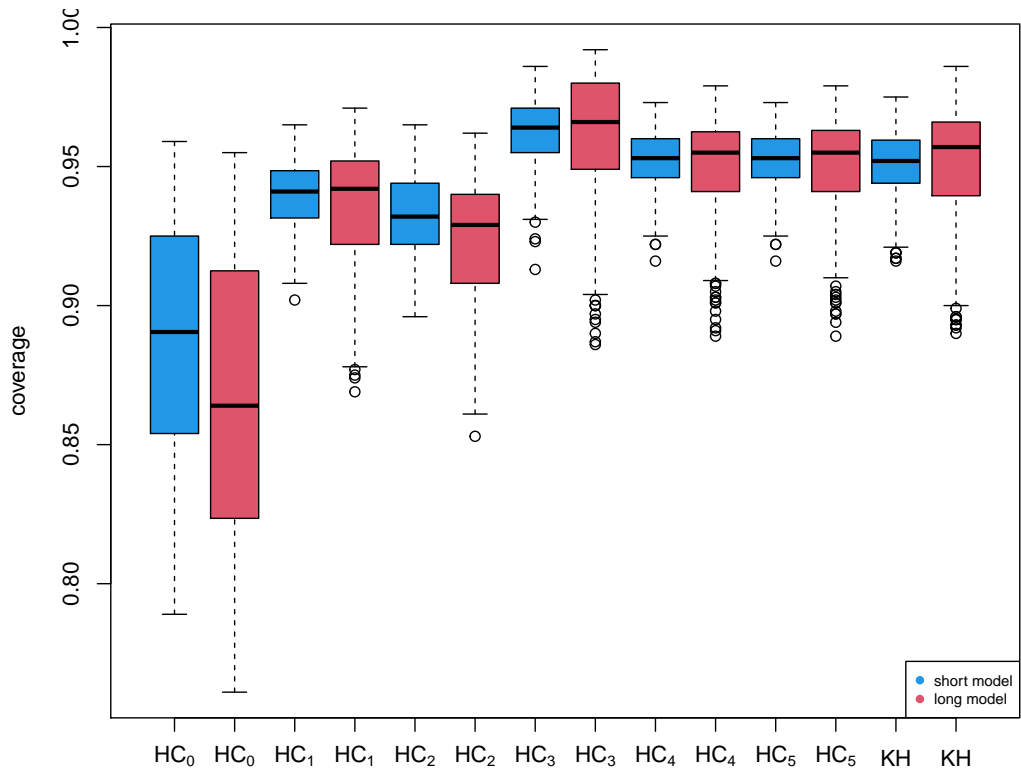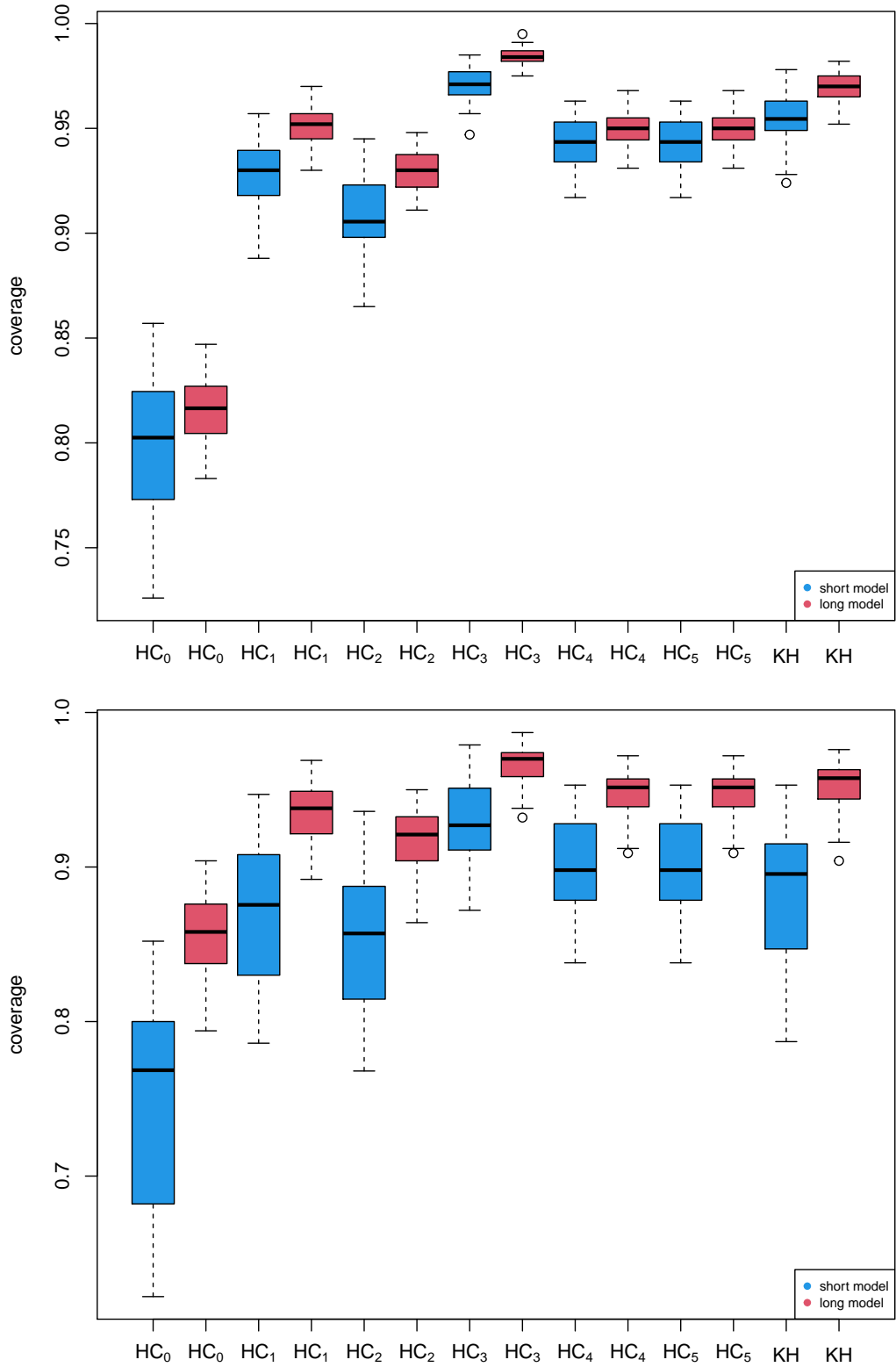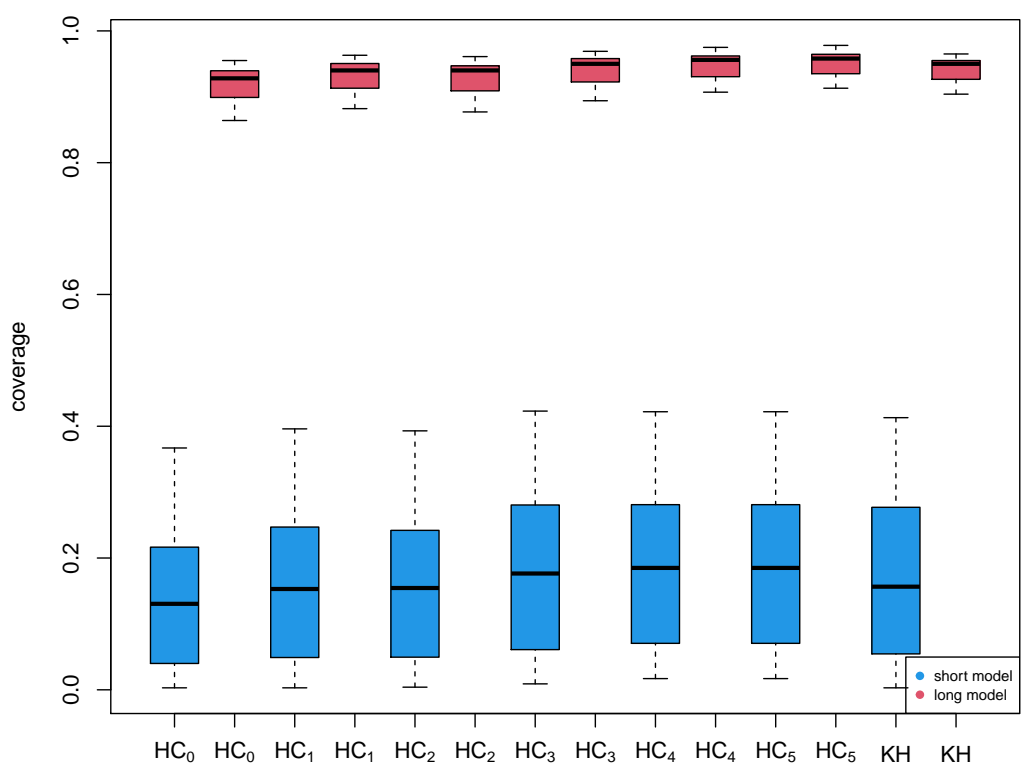
Figure 123: Coverages (upper plot) and interval lengths (lower plot) of β_0 compared for a model without interaction (short) and a model with interaction (long) when $\beta_{12} = 0.5$.

Figure 124: Coverages (upper plot) and interval lengths (lower plot) of β_1 compared for a model without interaction (short) and a model with interaction (long) when $\beta_{12} = 0.5$.
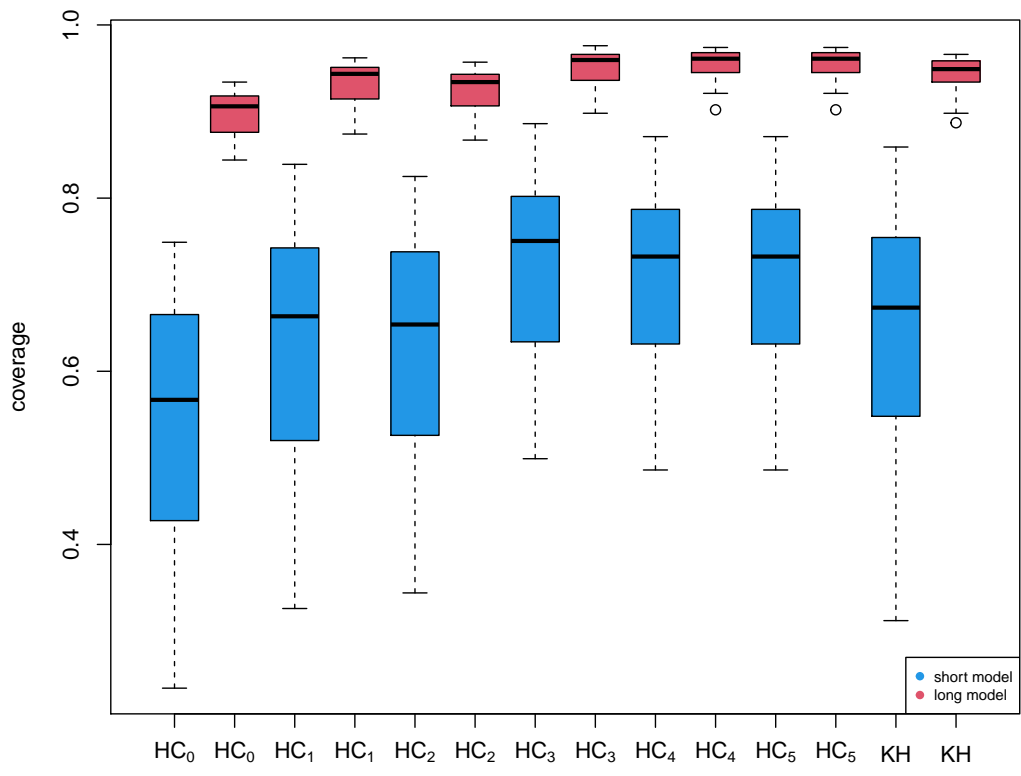
Figure 125: Coverages of β_0 compared for a model without interaction (short) and a model with interaction (long) and correlations of $\rho = 0$ (upper plot) and $\rho = 0.9$ (lower plot) when $\beta_{12} = 0.5$.

Figure 126: Coverages of β_0 compared for a model without interaction (short) and a model with interaction (long) when $\rho = 0.9$, $\beta_{12} = 0.5$ and and the number of studies $k = 6$ (upper plot) or $k = 10$ (lower plot).
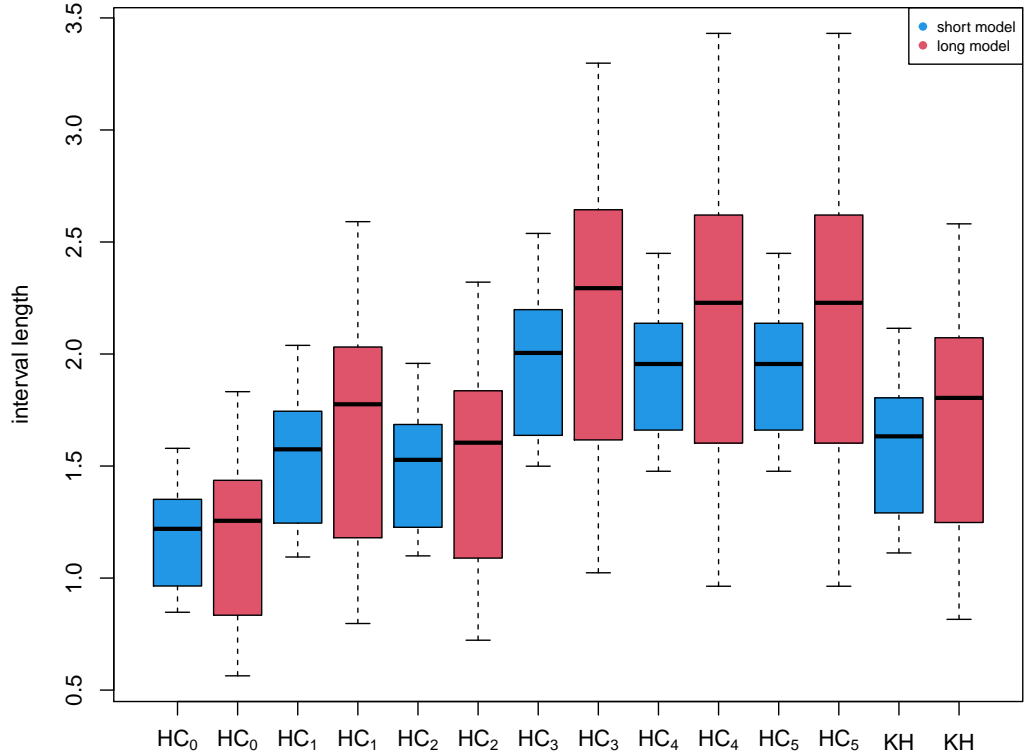
Figure 127: Coverages of β_0 compared for a model without interaction (short) and a model with interaction (long) when $\rho = 0.9$, $\beta_{12} = 0.5$ and and the number of studies $k = 20$ (upper plot) or $k = 50$ (lower plot).
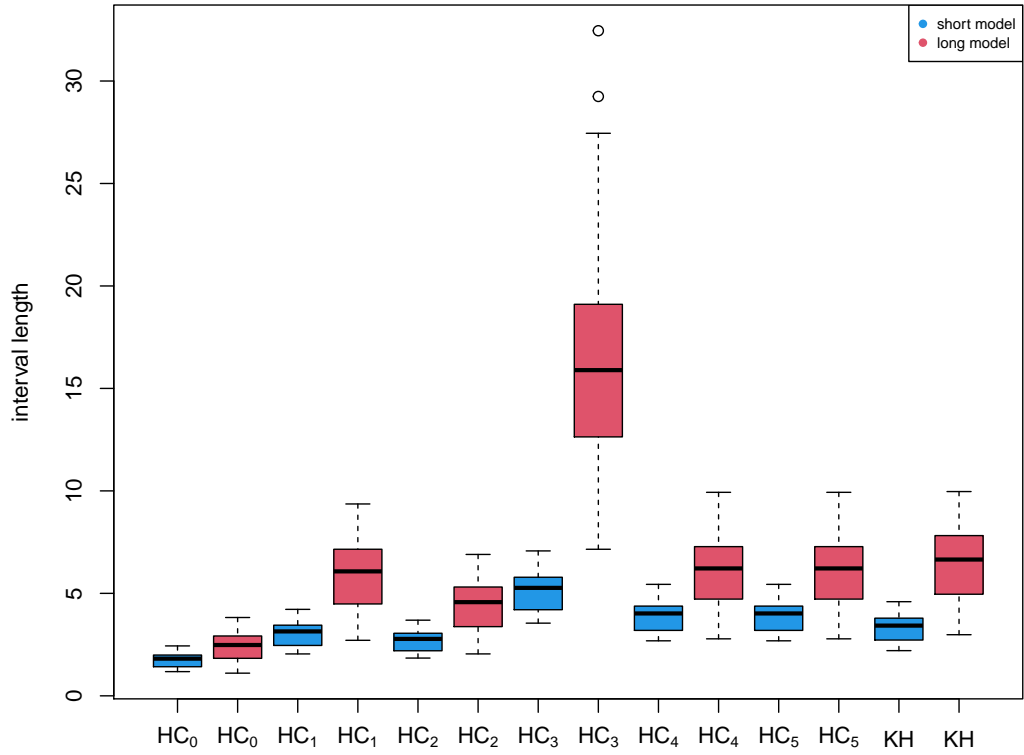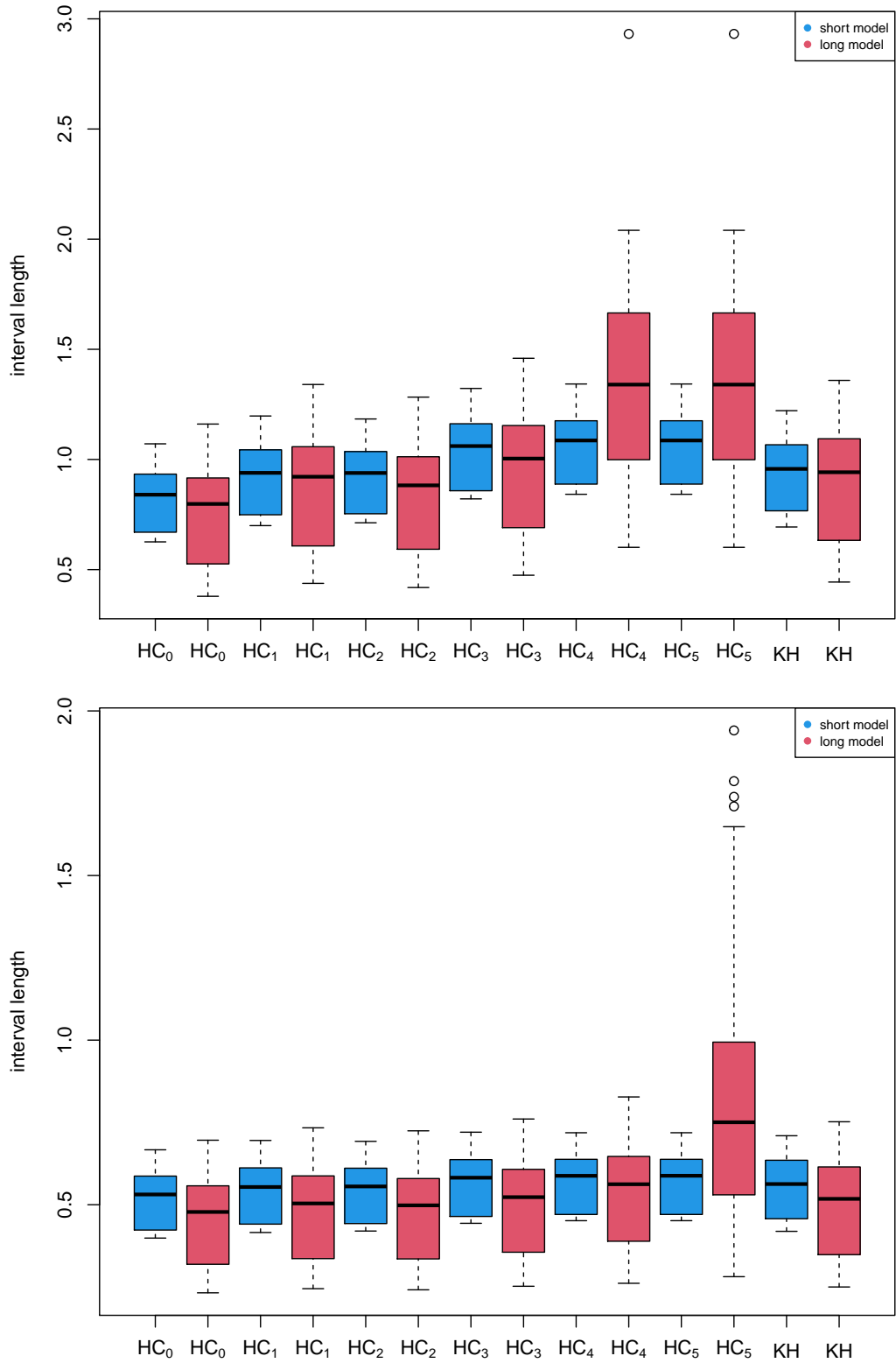
Figure 128: Interval lengths of β_0 compared for a model without interaction (short) and a model with interaction (long) when $\rho = 0.9$, $\beta_{12} = 0.5$ and the number of studies $k = 6$ (upper plot) or $k = 10$ (lower plot).

Figure 129: Interval lengths of β_0 compared for a model without interaction (short) and a model with interaction (long) when $\rho = 0.9$, $\beta_{12} = 0.5$ and the number of studies $k = 20$ (upper plot) or $k = 50$ (lower plot).
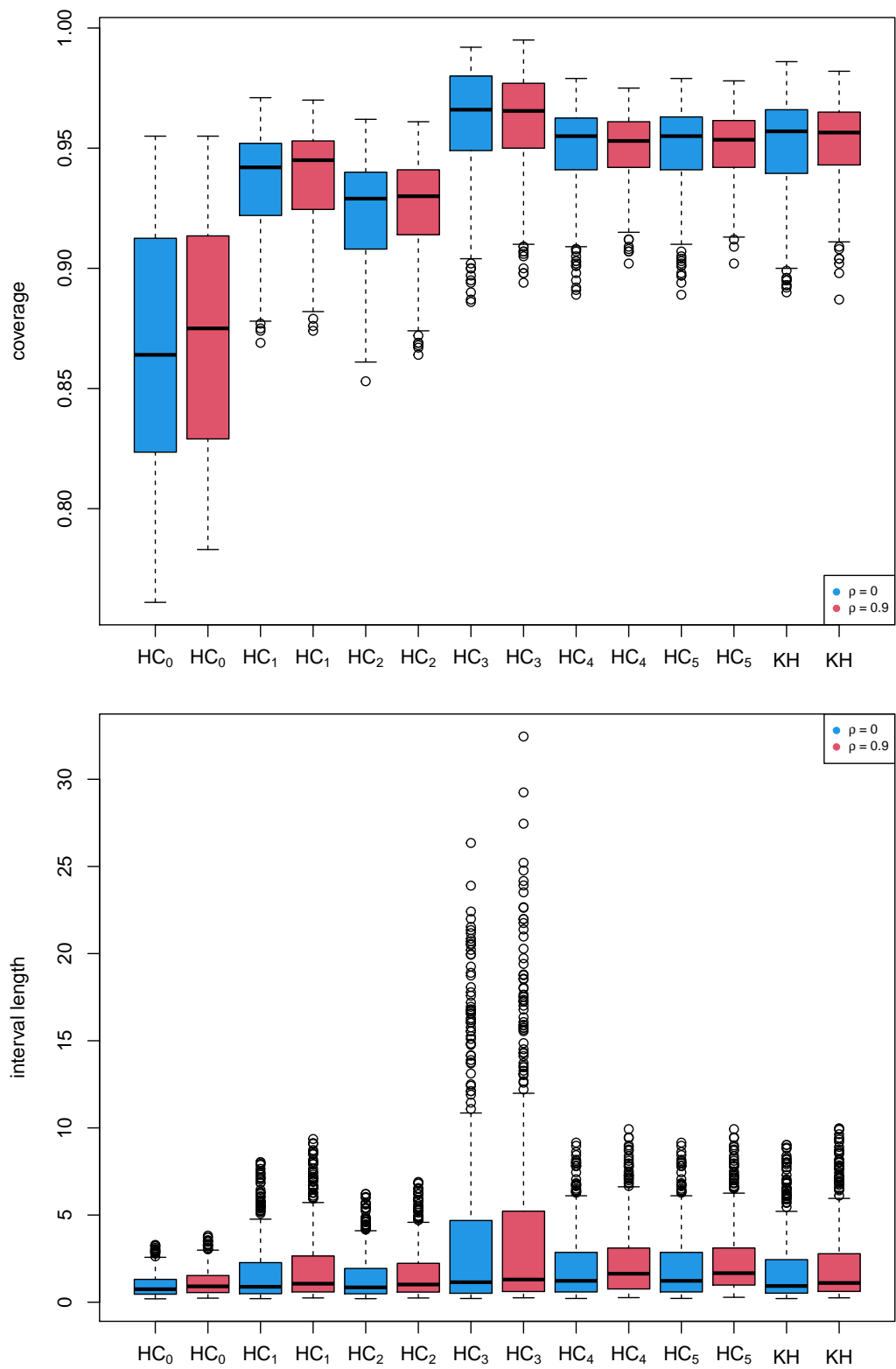
Figure 130: Coverages (upper plot) and interval lengths (lower plot) of β_0 in a model with interaction compared for correlations of $\rho = 0$ and $\rho = 0.9$ when $\beta_{12} = 0.5$.
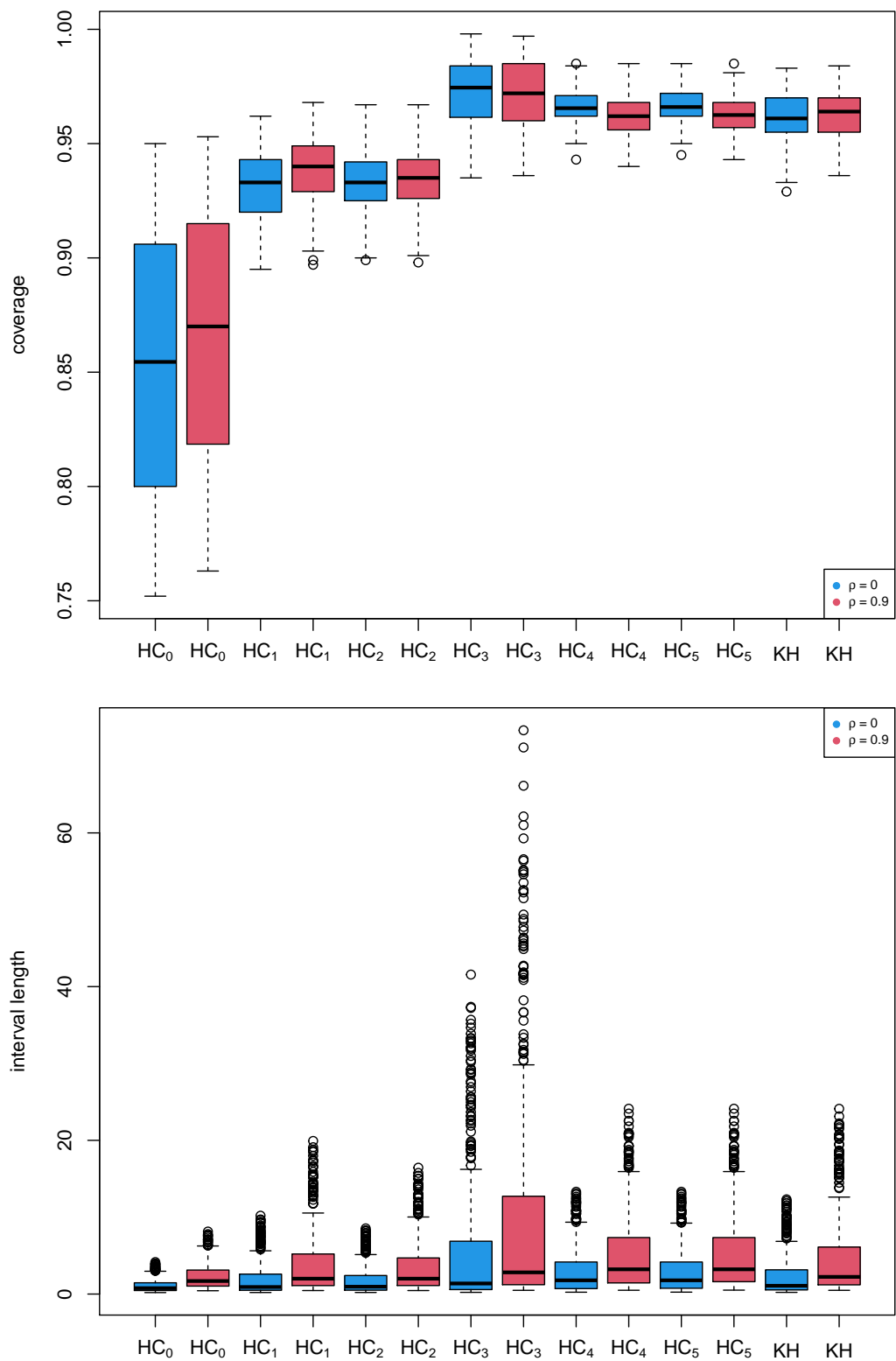
Figure 131: Coverages (upper plot) and interval lengths (lower plot) of β_1 in a model with interaction compared for correlations of $\rho = 0$ and $\rho = 0.9$ when $\beta_{12} = 0.5$.

References

Hayashi, F. (2000). *Econometrics*. Princeton University Press, Princeton, NJ.

MacKinnon, J. G., & White, H. (1985). Some heteroskedasticity-consistent covariance matrix estimators with improved finite sample properties. *Journal of Econometrics*, *29*(3), 305–325. https://doi.org/10.1016/0304-4076(85)90158-7