A ROBUST TEST FOR MULTIVARIATE PUBLICATION BIAS IN META-ANALYSIS

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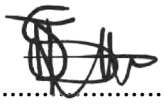
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I Maleshwane Dimpho Tshwang, with student ID 16101174, hereby declare that this thesis has been composed by myself and that it has never been submitted for a degree at this or any other university or institution of higher learning. I confirm that the work contained in this thesis is my own research work under the supervision of Dr N. Ndwapi and Prof A. Abebe. Any work done by others has been acknowledged and referenced accordingly.

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Abstract

A rank regression based procedure for testing for the existence of publication bias in meta-analysis is proposed. The method is designed to possess the robustness of the Begg rank correlation test for publication bias and the efficiency of Egger's regression approach. The procedure uses the Jaeckel rank-regression framework along with a rank prediction protocol for estimating the intercept term of Egger-type regression models for a robust and efficient test of publication bias in univariate meta-analysis. Application on several real-life meta-analyses studies demonstrate the use of the proposed procedure. This approach of using the Jaeckel rank-regression with rank prediction protocol is extended to the nested mixed model framework to develop a robust and efficient test for publication bias in multivariate meta-analyses. Commonly used statistical methods detect publication bias in univariate meta-analysis. This procedure is compared to the only other existing test for publication bias in multivariate meta-analysis, Hong's composite pseudo likelihood test, using simulation experiments. It is shown that the proposed method is better at maintaining the nominal size of the test and more powerful than the existing test especially in meta analyses that contain studies with possibly outlying effect sizes.

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Chapter 1

Introduction

1.1 Background

Meta analysis is a statistical procedure used to integrate results of several studies asking the same (or similar) questions into a single consensus finding (Borenstein et al., 2009). This often requires finding and statistically integrating effect size and associated uncertainty estimates from published literature. Such studies often rely on performing keyword searches of published literature and including studies that conform to previously specified study protocol (eg. PRISMA Protocol, Moher et al., 2009) and eliminating those that do not. While there are biases introduced in the process of screening articles, there is also a source of bias that is outside the control of the meta analyst – publication bias.

Publication bias is a widespread problem that can potentially distort the results of meta-analytical efforts to estimate the overall effect (Thornton and Lee, 2000). Publication bias occurs when the research on a particular topic does not include the whole population of studies that have been performed. If the omission is systemic, then meta-analysis can lead to misleading or wrong conclusions that are not in line with the underlying evidence. For instance, if small effect sizes are not submitted for publication or rejected at review time (file drawer problem) in an area of interest, then the overall effect size found via meta-analysis from published sources is likely to overestimate the true effect size. Thus the validity of meta-analytical studies is then dependent upon our ability to detect and correct publication bias in the studies included in the meta

analysis.

Publication bias should be checked prior to conducting a meta-analysis. Failing to account for publication bias may (Hong, 2016)

1. skew results,
2. provide misleading or inaccurate effect size,
3. make induce the lack of repeatability, and
4. increase the probability of Type I error.

When the meta-analysis deals with multivariate effect sizes (that is more than one outcome variable measured), then detection of publication bias is often complicated. Very little work has been done to deal with multivariate publication bias in which the effects can be correlated. Often standard methods of univariate publication bias detection are applied on each dimension but this ignores the correlation and is inefficient when the correlation is strong (Hong, 2016).

1.2 Purpose

The purpose of this thesis is to propose and investigate the efficiency of a nonparametric test of publication bias. First,the Jaeckel (1972) rank dispersion function is used to construct a test of publication bias in univariate meta-analysis. This test is compared to existing tests of publication bias. This is then extended to the multivariate setting. The proposed test for publication bias in multivariate meta-analysis is based on an extension of Jaeckel's (1972) rank dispersion function in combination the rank prediction protocol for estimating the intercept term in a mixed model. The results are compared to Hong (2016) which used the method of composite pseudo likelihood to test for multivariate publication bias.

1.3 Motivation

The commonly used statistical methods for detecting and correcting publication bias can only deal with univariate meta analyses. These methods are often based on sta-

tistical hypothesis tests of funnel plot asymmetry. The two well known tests for funnel plot asymmetry are Begg's rank correlation test (Begg and Mazumdar, 1994) and Egger's regression test (Egger et al., 1997).

There are three major challenges in testing publication bias in multivariate meta analysis. Hong (2016) observed some challenges in testing publication bias in multivariate meta analysis. The first challenge is to account for the multivariate nature of multivariate meta analysis by including the correlation among the outcomes in the analysis. Univariate tests like Egger's regression or Begg's rank correlation test may be used, but they will likely suffer from lack of power due to their inability to properly account for the correlation among the univariate effects. The second challenge comes from the fact that multivariate publication bias can occur in more than one way in that some studies may be completely unpublished while others may selectively report only some of their effect sizes. The third challenge is that within study correlations which are required by multivariate meta analysis methods are often not reported.

The other challenge of multivariate publication bias detection comes reduced power due to outlying effect sizes as well as effect sizes that deviate significantly from an assumed Gaussian distribution. The effect of outliers is could be quite pronounced if we have a small number of studies in our meta-analysis. The effect of non-Gaussian distribution may be large if the number of subjects per study are small.

Our proposed approach may be considered a hybrid of Egger's regression and Begg's rank score test in the univariate meta-analysis setting. We demonstrate that we can achieve both efficiency and robustness when we have contamination in effect sizes or heavy-tailed effect-size distribution. Egger's test uses more information to characterize each study by using a weighted regression approach. If it is significant then there is publication bias. Begg's test is underpowered especially when the number of studies is small. Hong (2016) has demonstrated through a simulation experiment that her composite pseudo likelihood method for multivariate publication bias detection

1. controls Type I error well than the existing univariate methods, and
2. has better power compared to other univariate methods.

Our motivating reasons for proposing a nonparametric multivariate publication bias detection method are

1. to combine the strengths of robust rank estimation and Egger's regression in a univariate setting

2. to extend this to the multivariate setting for efficient detection of publication bias in multivariate meta-analysis when there are of outlying effect sizes, especially for a small number of studies, and

3. to efficiently detect publication bias in multivariate meta-analysis when the effect sizes are non-Gaussian, especially for a small number of subjects per study.

1.4 Contribution

To our knowledge the only work on multivariate publication bias detection is the Ph.D. dissertation of (Hong 2016) who used a mixed model profile likelihood approach. Her method is susceptible to the influence of outlying effect sizes. Our proposed approach will use rank-based estimation of mixed-models with rank-prediction-protocol (RPP) for robust multivariate publication bias detection. Thus it can be considered a robustification of Hongs profile likelihood approach or an extension to the multivariate setting of Beggs rank correlation approach.

To the best of our knowledge, this will be the second test for detecting publication bias in a multivariate meta-analysis. Our simulation experiments will demonstrate that the proposed methodology will provide higher power of detection of publication bias in a multivariate meta-analysis in studies containing outlying or heavy-tailed effect sizes.

Meta-analyses are widely used in various disciplines including medicine, psychology, pharmacy, ecology, and neuroscience among others. Investigators often eliminate outlying studies from their meta-analysis often following a sensitivity analysis. This often has to be justified and can result in a loss of power. The proposed methodology eliminates the need to discard outlying studies hence addressing the issue of selection bias as well as loss of power. We anticipate the methodology to be used widely in future meta-analyses even in the univariate setting.

Chapter 2

Review of Methods for Detecting Publication bias

2.1 Introduction

In the following sections we will review existing methods for the detection of publication bias in univariate meta-analysis. These methods are all based on measuring the asymmetry in funnel plots; hence, known as funnel plot-based methods. These include Egger's regression and Begg's rank score tests. A funnel plot is a plot of effect size estimates against the inverse of the standard error of the effect size (precision) or in some cases the sample size. Effect size estimates from the most precise studies typically scatter narrowly while those estimated from less precise studies scatter widely. An example of a funnel plot is given in Figure 3.1.

When there is no publication bias, the funnel plot will be symmetric. This symmetry is violated if there is publication bias. For instance, if studies with positive statistically significant results are more likely to be published, then the funnel plot will become asymmetric since the negative and/or non-significant results will be missing.

A straightforward test of funnel plot asymmetry uses the method of simple linear regression. One would first regress the standardized effect size on its precision. A test of funnel plot asymmetry (publication bias) then tests whether the intercept is zero. When there is no publication bias, the intercept of the regression line becomes exactly zero an if there is publication bias the intercept becomes different from zero. In practice, we

declare publication bias if the intercept term is significantly different from zero.

2.2 Univariate Meta-Analysis

As mentioned above, meta-analysis is the process of combining and analyzing results from separate studies. In the following, we will assume that the meta-analysis of interest is evaluating n studies with effect sizes $Y_1, \ldots, Y_n$ and associated standard errors $S_1, \ldots, S_n$.

A normal fixed-effects meta-analysis assumes all the studies have the same theoretical mean effect size, θ. This can be represented as a heteroscedastic regression model as

$$Y_i = \theta + S_i \varepsilon_i \ , \quad \varepsilon_i \sim N(0,1) \ .$$

A maximum likelihood estimator of θ is then

$$\hat{\theta} = \frac{\sum_{i=1}^{n} Y_i / S_i^2}{\sum_{i=1}^{n} 1/S_i^2}$$

which is just the mean of the effect sizes weighted by the square of their precision.

In a random-effects meta-analysis, it is assumed that that $Y_i \ \sim \ N(\theta_i, S_i^2)$. for $i = 1, \ldots, n$, where θ_i represents the effect size of study i (unobserved). We assume that θ_i vary around a global mean θ with variance τ^2

$$\theta_i \ \sim \ N(\theta, \tau^2) \ .$$

The quantity τ^2 is the between study variability. Once again, we can write this as a heteroscedastic regression model

$$Y_i = \theta + \left(\sqrt{\tau^2 + S_i^2} \right) \varepsilon_i \ , \quad \varepsilon_i \sim N(0,1) \ .$$

The maximum likelihood estimator of θ is $\hat{\theta} = \sum_{i=1}^{n} \lambda_i \hat{\theta}_i$, where

$$\lambda_i = \frac{1/(\tau^2 + S_i^2)}{\sum_{i=1}^{n} 1/(\tau^2 + S_i^2)}$$

represent the study contributions. There are several estimators of the between-study

variance τ^2 (Normand, 1999). We will use the REML estimator of τ^2 in this thesis.

2.3 Egger's regression

Egger's regression approach is one of the simplest tests of publication bias in meta-analysis. It uses the linear regression approach described in the introduction of this chapter. We will assume we are in the random effects meta analysis framework and that we have obtained the REML estimator of the between study variance as $\hat{\tau}^2$. For each study, the standard normal deviate (SND)

$$\tilde{Z}_i = \frac{Y_i}{\sqrt{\hat{\tau}^2 + S_i^2}}$$

and the precision

$$\tilde{P}_i = \frac{1}{\sqrt{\hat{\tau}^2 + S_i^2}}$$

are calculated. We then regress standard normal deviates $\tilde{Z}_i$ on the precision $\tilde{P}_i$

$$\tilde{Z}_i = a + b\tilde{P}_i + \varepsilon_i \ .$$

Egger's test for publication bias then tests

$$H_0 : a = 0 \text{ against } H_a : a \neq 0 \ .$$

The intercept should not significantly differ from zero if there is no publication bias.

Egger's regression test in the random effects model requires the estimation of the between study variance τ^2. When the between study variance is close to zero, Egger's regression test can suffer from very low power. Moreover, its dependence on the least squares approach means that the test can be quite sensitive to the existence of a few studies with outlying effect sizes.

2.4 Begg's rank score test

Begg's rank score test is a direct interpretation of the funnel plot. It is based on the Kendall correlation (Tau) between the standardized effect size and the standard errors of the effects. Tau determines if there is significant correlation between the effect estimates and their variances and hence it is interpreted as any other correlation. Tau zero indicates no relationship and hence no publication bias. If large effects are represented by low values, tau will be positive. If large effects are represented by high values then tau will be negative. Either of these would represent publication bias.

Begg's rank score test may be under powered if the number of studies in a meta analysis is small to moderate. On the other hand, since Kendall's Tau is based on rank scores, Begg's test is not affected by outlying effect sizes.

2.5 Bias Correction – Trim-and-Fill

When publication bias is detected, the standard approach is to make a correction using the so-called trim and fill method. This method introduced by Dual and Tweedie (2000) provides an effective correction of meta-analysis parameters when there is publication bias. The methods proceeds by first removing the remote and asymmetric part of funnel after estimating the number of such studies. The remaining studies are used for estimating of the true center of the funnel. Finally, the removed studies are replaced. Moreover, the missing counterpart of the trimmed are included by reflecting the trimmed studies around the center. The completed funnel plot is used for performing meta-analysis.

Chapter 3

Rank-regression for Robust Egger Type Test

3.1 Introduction

Regression is widely used in health research and other related researches to model the relationship between the dependent variable and independent variables of interest. As discussed in the previous chapter, it is used by Egger's test in the detection of publication bias. In particular, consider n studies with reported effect sizes $Y_1, \ldots, Y_n$ and associated standard errors $S_1, \ldots, S_n$, respectively. A funnel plot displays Y_i on the x-axis against their precision $1/S_i$ on the y-axis. An example of a funnel plot is given in Figure 3.1

Since Y_i are heteroscedastic with variances S_i^2, a regression using Y_i as a response needs to be properly standardized. Thus, Egger's test is based on the Galbraith radial plot (Galbraith, 1988) which plots Y_i/S_i versus $1/S_i$ with the constraint that the regression line pass through zero. If there is no publication bias; i.e. if the points on the funnel plot Figure 3.1 are symmetric within the triangle, then a regression of Y_i/S_i on $1/S_i$ will have a Y-intercept of 0. If there is no publication bias, then the Egger's regression plot and Galbraith radial plot will coincide.

We will use the notation $SND = Y/S$ and $P = 1/S$ in the following. Egger's regression is then

$$SND_i = \alpha + \beta P_i + \varepsilon_i \tag{3.1}$$

Figure 3.1: Example of a funnel plot. Data are from de Bruin et al. (2009)

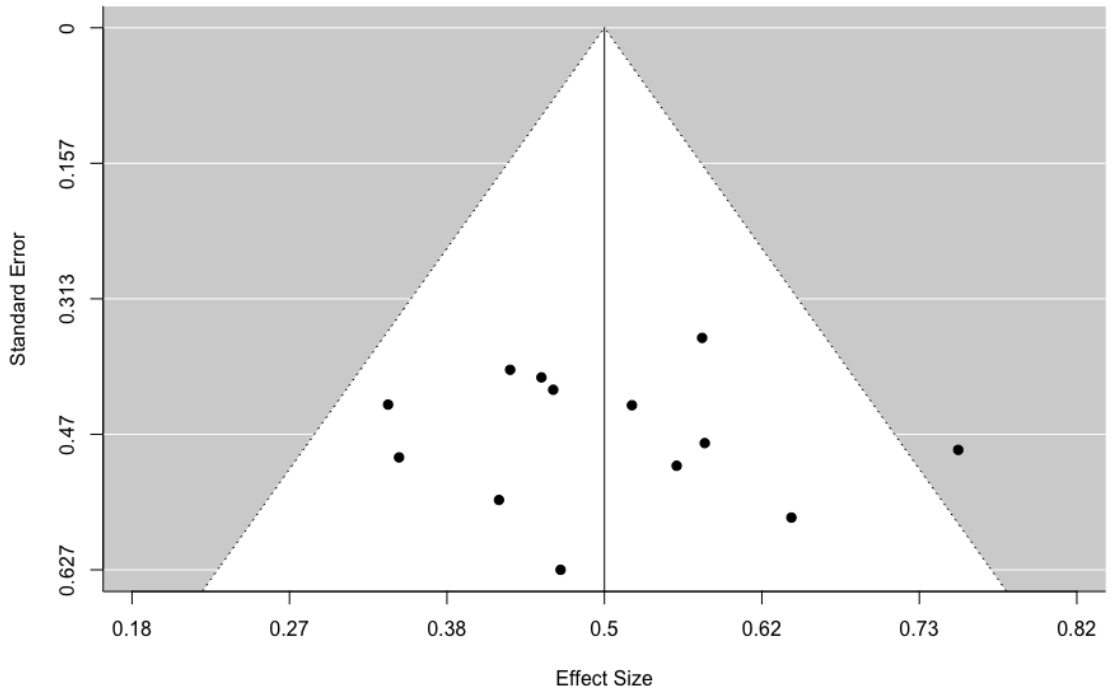
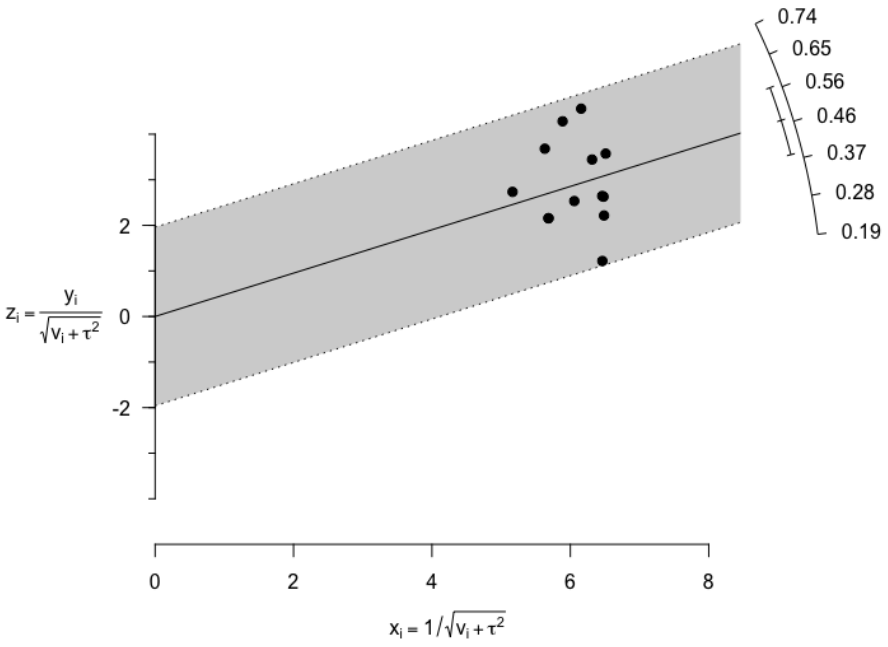


Figure 3.2: Example of a Galbraith radial plot. Data are from de Bruin et al. (2009)



and Egger's test for publication bias is the test of

$$H_0 : \alpha = 0 \qquad \text{versus} \qquad H_1 : \alpha \neq 0 \, .$$

We claim that publication bias has been detected if H_0 is rejected. This simple test for publication bias, however, becomes biased if there are studies with outlying effect sizes. Thus we propose a rank-regression based Egger's test for robust detection of publication bias.

3.2 Egger's Test

We first define the model residuals as $Z_i(\alpha, \beta) = SND_i - \alpha - \beta P_i$. To perform Egger's test, we first minimize the objective function

$$O_n(\alpha, \beta) = \sum_{i=1}^{n} [Z_i(\alpha, \beta)]^2 \, .$$

Noting that $\overline{P} = 1/n \sum_{i=1}^{n} (1/S_i)$ and $\overline{SND} = 1/n \sum_{i=1}^{n} (Y_i/S_i)$, by elementary calculation we can determine the estimators

$$\widehat{\beta} = \frac{\sum (P_i - \overline{P})(SND_i - \overline{SND})}{\sum (P_i - \overline{P})^2}$$

and

$$\widehat{\alpha} = \overline{SND} - \widehat{\beta}\overline{P} \, .$$

Since by standard Central Limit Theorems, $\widehat{\alpha}$ is approximately $N(\alpha, SE(\widehat{\alpha}))$, a Wald-type test of $H_0 : \alpha = 0$ rejects the null if

$$\left| \frac{\widehat{\alpha}}{SE(\widehat{\alpha})} \right| \; > \; z_{\alpha/2} \, .$$

This is the basis of Egger's regression test for publication bias.

3.3 Rank Regression Test

Consider once again the regression model (3.1). Let the ranks of the residuals be $R(Z_i(\alpha, \beta)) = \sum_{j=1}^{n} I\{Z_j(\alpha, \beta) \leq Z_i(\alpha, \beta)\}$. Now consider a nondecreasing function

$\varphi : (0,1) \to \mathbb{R}$ standardized such that $\int_0^1 \varphi(u)du = 0$, $\int_0^1 \varphi^2(u)du = 1$, and is odd about $1/2$; i.e., $\varphi(1-u) = -\varphi(u)$. The rank dispersion function given by Jaeckel (1972) is then

$$D_n(\alpha, \beta) = \sum_{i=1}^{n} \varphi\left(\frac{R(Z_i(\alpha,\beta))}{n+1}\right) Z_i(\alpha,\beta) \tag{3.2}$$

The rank-regression estimator of β is then

$$\widehat{\beta}_R = \text{Argmin}_\beta D_n(\alpha, \beta)\ . \tag{3.3}$$

Since D_n is a pseudo-norm on $\mathbb{R}^n$, it is invariant to α. That is

$$D_n(\alpha, \beta) = D_n(0, \beta)$$

Thus it is not useful for the estimation of α. However, since φ is odd about $1/2$, a consistent estimator of α (Sievers and Abebe, 2004) is

$$\widehat{\alpha}_R = \text{median}_i\{SND_i - \widehat{\beta}_R P_i\}$$

It is shown in Hettmansperger and McKean (2011) that $\widehat{\alpha}_R$ follows an approximate $N(\alpha, SE(\widehat{\alpha}_R))$ distribution. Thus a Wald-type test for $H_0 : \alpha = 0$ rejects the null if

$$\left|\frac{\widehat{\alpha}_R}{SE(\widehat{\alpha}_R)}\right| > z_{\alpha/2}\ .$$

3.4 Computing Rank Regression Estimator

We will provide an iteratively reweighted least squares (IRLS) algorithm for calculating the rank estimator of α. Note once again that D_n is a pseudo-norm; hence, invariant to constant translations. Thus

$$
\begin{aligned}
D_n(\beta) &= \sum_{i=1}^{n} \varphi\left(\frac{R(Z_i(\alpha,\beta))}{n+1}\right) Z_i(\alpha,\beta) \\
&= \sum_{i=1}^{n} \varphi\left(\frac{R(Z_i(\alpha,\beta))}{n+1}\right) (Z_i(\alpha,\beta) - c) \\
&= \sum_{i=1}^{n} \frac{\varphi\left(\frac{R(Z_i(\alpha,\beta))}{n+1}\right)}{Z_i(\alpha,\beta) - c} (Z_i(\alpha,\beta) - c)^2 \\
&= \sum_{i=1}^{n} w_i(\alpha,\beta,c)(Z_i(\alpha,\beta) - c)^2
\end{aligned}
$$

which is a weighted least squares minimization problem if the weights w_i are known. We, however, need all $w_i \geq 0$ to perform a weighted least squares estimation. It is shown in Sievers and Abebe (2004) that the value of c that guarantees $w_i \geq 0$ is $c = \text{median}_i\{Z_i(\alpha,\beta)\}$. This gives rise to the following algorithm:

Step 0: Use Egger's regression to find $\widehat{\beta}$, say, $\widehat{\beta}^{(0)}$.

Step 1: Form $Z_i(0,\widehat{\beta}^{(0)}) = SND_i - \widehat{\beta}^{(0)} P_i$ and calculate $\widehat{\alpha}^{(0)} = \text{median}_i\{Z_i(0,\widehat{\beta}^{(0)})\}$.

Step 2: Form $w_i(0,\widehat{\beta}^{(0)},\widehat{\alpha}^{(0)}) = \dfrac{\varphi\left(\frac{R(Z_i(0,\widehat{\beta}^{(0)}))}{n+1}\right)}{Z_i(0,\widehat{\beta}^{(0)}) - \widehat{\alpha}^{(0)}}$.

Step 3: Let $\widehat{\beta}^{(1)} = \text{Argmin}_\beta \sum_{i=1}^{n} w_i(0,\widehat{\beta}^{(0)},\widehat{\alpha}^{(0)})(Z_i(0,\beta) - \widehat{\alpha}^{(0)})^2$ and $\widehat{\alpha}^{(1)} = \text{median}_i\{Z_i(0,\widehat{\beta}^{(1)})\}$.

Step 4: If $|\widehat{\beta}^{(1)} - \widehat{\beta}^{(0)}| < \text{tol} \times |\widehat{\beta}^{(0)}|$, then take $\widehat{\beta}_R = \widehat{\beta}^{(1)}$ and $\widehat{\alpha}_R = \widehat{\alpha}^{(1)}$ and **STOP**. Else let $\widehat{\beta}^{(0)} \leftarrow \widehat{\beta}^{(1)}$ and $\widehat{\alpha}^{(0)} \leftarrow \widehat{\alpha}^{(1)}$ and return to **Step 1**.

Using fixed-point theory, Sievers and Abebe (2004) have shown that this algorithm converges to the minimizer of D_n. To improve the stability of the algorithm, cases for which $Z_i(0,\widehat{\beta}^{(0)}) - \widehat{\alpha}^{(0)} \approx 0$ are excluded from the data in **Step 2**. Since φ is non-decreasing and odd about $1/2$, $\varphi \approx 0$ whenever $Z_i(0,\widehat{\beta}^{(0)})$ is close to its median $\widehat{\alpha}^{(0)}$. Thus the corresponding summand in D_n in (3.2) is close to zero. Thus these points are low leverage points that contribute minimally to D_n and hence the regression estimator. However, their presence results in weights that are quite large and can destabilize the regression estimator. Thus we set a tolerance for the weights, say, tol_w, and take

$$
w(0,b,a) = \begin{cases} \frac{\varphi\left(\frac{R(Z(0,b))}{n+1}\right)}{Z(0,b)-a} & \text{if } |Z(0,b)-a| \geq \text{tol}_w \\ 0 & \text{otherwise.} \end{cases}
$$

3.5 Examples

In the following we will consider three examples to illustrate the uses of the rank-based Egger's test for publication bias. All examples use publicly available data and could be accessed through the `metafor` package (Viechtbauer, 2010) of the R software (R Core Team, 2018). Egger's test and Begg's rank score test are performed using the `metafor` package. All rank-regression estimators use the linear score function (Wilcoxon) $\varphi(u) = \sqrt{12} \cdot (u - \frac{1}{2})$.

3.5.1 Standard Care Quality and HAART-Adherence

Highly active antiretroviral therapy (HAART) is a combination of antiretroviral drugs that can be effective in suppressing HIV. However, high level of adherence is required to achieve viral suppression. Adherence is often not achieved due to the complicated medication regimen. Several trials have looked at interventions other than standard care with the aim of improving HAART-adherence. However, the quality of standard care shows great variation among these studies. de Bruin et al. (2009) assessed whether the quality of standard care provided was related to the proportion of patients with effective viral suppression.

We performed a random effect meta-analysis. The funnel plot and Galbraith radial plot for this data given in Figures 3.1 and 3.2, respectively, seem to indicate no publication bias. Below are the test results using Egger's test, Begg's rank score test, and our proposed rank regression test.

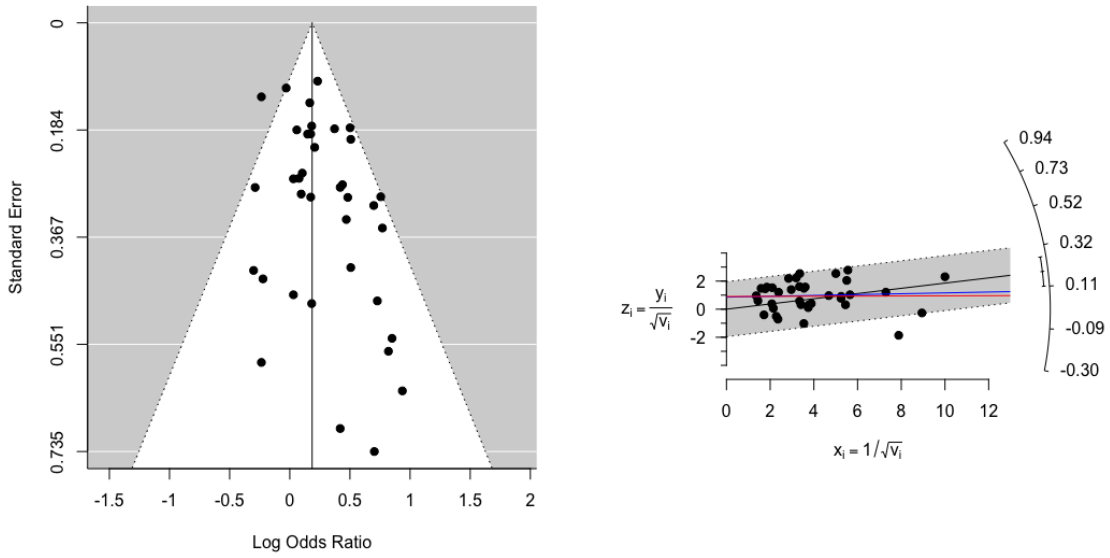
Egger's Test		Begg's Test		Rank Reg Test	
Z	P-value	Tau	P-value	Z	P-value
1.2204	0.2223	0.1948	0.3583	0.6182	0.5491

3.5.2 Lung Cancer and Passive Smoking

The data for this study come from Hackshaw (1998). The dataset includes results from 37 studies on the risk of lung cancer from environmental tobacco smoke exposure from the spouse in women who are lifelong nonsmokers. Values of the log odds ratio greater than 0 indicate an increased risk of cancer in exposed women compared to women not exposed to ETS from their spouse.

We applied a fixed-effects meta analysis of the log-odds of cancer. The funnel plot and Galbraith radial plot for this data are given in Figure 3.3.

Figure 3.3: Funnel and Galbraith radial plots for Hachshaw (1998) data; Red line is Egger's regression and Blue line is rank regression



The plots seem to indicate some publication bias with studies on the bottom left side of the funnel plot missing. This generally says that studies that showed the opposite effect but with high standard error or low number of participants are likely not published. Below are the test results using Egger's test, Begg's rank score test, and our proposed rank regression test.

Egger's Test		Begg's Test		Rank Reg Test	
Z	P-value	Tau	P-value	Z	P-value
2.5759	0.0100	0.1441	0.2157	1.7948	0.0813

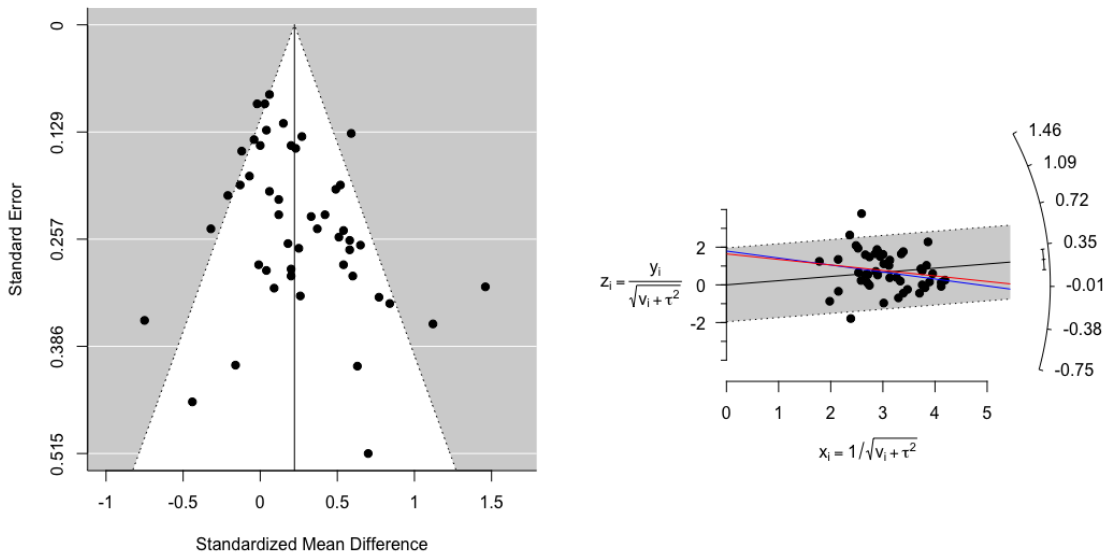
It can be seen that Begg's test fails to indicate publication bias while Egger's test shows significant bias. The proposed rank regression test is suggestive of publication bias. In this case the results disagree and the rank regression approach seems to provide a compromise between the other two approaches.

3.5.3 Effectiveness of Writing-to-Learn Interventions

Bangert-Drowns et al. (2004) performed a meta-analysis of studies that considered a group of students that received instruction with increased emphasis on writing tasks

against a group of students that received conventional instruction. The outcome variable was some content-related measure of academic achievement and the associated effect size measure was the standardized mean difference (positive score = higher mean level of academic achievement in the intervention group). The funnel plot and Galbraith radial plot from a random effect meta-analysis are given in Figure 3.4.

Figure 3.4: Funnel and Galbraith radial plots for Bangert-Drowns et al. (2004) data; Red line is Egger's regression and Blue line is rank regression



The plots seem to indicate the possibility of some publication bias with studies on the bottom left side of the funnel plot missing. This generally says that lower quality studies that showed the opposite effect are likely not published. The lines from Egger's and rank regression seem to differ from the Galbraith line giving evidence of some publication bias. The test results using Egger's test, Begg's rank score test, and our proposed rank regression test are

Egger's Test		Begg's Test		Rank Reg Test	
Z	P-value	Tau	P-value	Z	P-value
2.4904	0.0128	0.2179	0.0294	2.2479	0.0294

All three tests agree in confirming the existence of publication bias.

Chapter 4

Multivariate Publication Bias Tests

We consider a meta-analysis with n studies and a common set of d outcomes of interest for each study. Let Y_{ij} and S_{ij} denote the outcome and standard error of the jth outcome of study i, both assumed to be known, $i = 1, \ldots, n$ and $j = 1, \ldots, d$. Let $\mathbf{Y}_i \in \mathbb{R}^d$ be outcome vector for study i. We assume that $\mathbf{Y}_i$ is an estimate of the true effect size $\boldsymbol{\theta}_i$. In a random effect meta-analysis the true effects can be heterogeneous; that is, $\boldsymbol{\theta}_i$ are independently drawn from distributions with mean $\boldsymbol{\mu}$ and between study variance τ^2. More specifically, using the notation in Hong (2016),

$$E[\boldsymbol{\theta}_i] = \boldsymbol{\mu} \quad \text{and} \quad Var[\boldsymbol{\theta}_i] \equiv \Omega = \begin{pmatrix} \tau_1^2 & \cdots & \tau_1\tau_d\rho_{b(1d)} \\ \vdots & \ddots & \vdots \\ \tau_d\tau_1\rho_{b(1d)} & \cdots & \tau_d^2 \end{pmatrix}$$

where ρ_b is the between-study correlation. This means

$$E[\mathbf{Y}_i] = \boldsymbol{\mu} \quad \text{and} \quad Var[\mathbf{Y}_i] = \Omega + \Delta_i$$

where

$$\Delta_i = \begin{pmatrix} S_{i1}^2 & \cdots & S_{i1}S_{id}\rho_{wi(1d)} \\ \vdots & \ddots & \vdots \\ S_{id}S_{i1}\rho_{wi(1d)} & \cdots & S_{id}^2 \end{pmatrix}, \qquad i = 1, \ldots, n$$

are the within-study covariance matrices and ρ_w is the within-study correlation.

It is under this setting that we develop our rank-based test for multivariate publication bias. Before proceeding with that, we will give a quick review of the only existing test for multivariate publication bias.

4.1 Existing method – A Score Test for Multivariate Meta-Analysis

A test that could be regarded as a multivariate extension of Egger's regression test was first proposed by Hong (2016). To our knowledge this is the only existing test for publication bias under multivariate meta analysis approach. Hong's approach is based on the method of pseudo likelihood using the estimated residuals in the regression model of the univariate Egger's test and then using of the idea of composite likelihood to combine individual pseudo likelihoods.

As in Egger, for the j^{th} outcome of the i^{th} study, define the standardized effect size as $Z_{ij} = Y_{ij}(S_{ij}^2 + \tau_j^2)^{\frac{-1}{2}}$ and the precision as $P_{ij} = (S_{ij}^2 + \tau_j^2)^{\frac{-1}{2}}$. Then individual Egger's regression lines are fit using (4.1)

$$Z_{ij} = a_j + \beta_j P_{ij} + \varepsilon_{ij} \tag{4.1}$$

where ε_{ij} is a standard normal random variable. Let $\widetilde{\tau_j}^2$ denote any consistent estimator of τ_j^2. By substituting $\widetilde{\tau_j^2}$ into the model (4.1), a log pseudo likelihood can be constructed as given in (4.2) below

$$\log L_p^j(a_j, b_j) = \frac{-1}{2}\sum_{i=1}^{n}(\widetilde{Z}_{ij} - a_j - b_j\widetilde{P}_{ij})^2 \tag{4.2}$$

where $\widetilde{Z}_{ij} = Y_{ij}(S_{ij}^2+\widetilde{\tau}_j^2)^{\frac{-1}{2}}$ and $\widetilde{P}_{\text{ij}} = (S_{ij}^2+\widetilde{\tau}_j^2)^{\frac{-1}{2}}$. Interest is in the regression coefficient a_j. These pseudo likelihoods are then combined to find the composite likelihood (4.3)

$$\log L_p(a, b) = \sum_{i=1}^{d} \log L_p^i(a_j, b_j) \tag{4.3}$$

where $\mathbf{a} = (a_1, ..., a_d)^T$ and $\mathbf{b} = (b_1, ..., b_d)^T$. Because each summand in the composite likelihood is a pseudo likelihood, its score function is not an unbiased estimating equation.

Using equation (4.3), a test of publication bias in multivariate meta-analysis tests H_0 : $\mathbf{a} = \mathbf{0}$. To this end, the maximum pseudo likelihood estimator under $a_j = 0$ can be calculated as

$$\tilde{b}_j(0) = \left(\sum_{i=1}^{n} \widetilde{P}_{ij}^2\right)^{-1} \left(\sum_{i=1}^{n} \widetilde{Z}_{ij}\widetilde{P}_{ij}\right)$$

A pseudo-score function under the null can be calculated as $\mathbf{U_a}[\mathbf{0}, \tilde{\mathbf{b}}(\mathbf{0}), \tilde{\tau}^2] = \left(\sum_{i=1}^{n} \widetilde{Z}_{\mathrm{i1}} - R_1, ..., \sum_{i=1}^{n} \widetilde{Z}_{\mathrm{id}} - R_d\right)^T$ where $R_j = \tilde{b}_j(0) \sum_i^m \widetilde{P}_{ij}$.

The negative Hessian of the log pseudo likelihood function evaluated at $(\mathbf{0}, \tilde{\mathbf{b}}(\mathbf{0}))$ is calculated as

$$\mathbf{I_0} = \begin{pmatrix} \mathbf{I_{0aa}} & \mathbf{I_{0ab}} \\ \mathbf{I_{0ab}} & \mathbf{I_{0bb}} \end{pmatrix} \tag{4.4}$$

where $\mathbf{I_{0aa}} = \mathrm{diag}(n, ..., n)$ is a d-dimensional diagonal matrix with n as its diagonal elements, $\mathbf{I_{0ab}} = \mathrm{diag}\left(\sum_{i=1}^{n} P_{i1}, ..., \sum_{i=1}^{n} P_{id}\right)$ is a d-dimensional diagonal matrix with $\sum_{i=1}^{n} P_{ij}$ as its j^{th} element, and $\mathbf{I_{0bb}} = \mathrm{diag}\left(\sum_{i=1}^{n} P_{i1}^2, ..., P_{id}^2\right)$ is d-dimensional diagonal matrix with $\sum_{i=1}^{n} P_{ij}^2$ as its j^{th} element. The $d \times d$ sub matrix of the inverse of $\mathbf{I_0}$ with respect to $\mathbf{a}$, denoted by $\mathbf{I_0^{aa}}$, can be calculated as $\left(\mathbf{I_{0aa}} - \mathbf{I_{0aa}}{\mathbf{I_{0bb}}}^{-1}\mathbf{I_{0ab}}\right)^{-1}$.

Let $\sum_{aa}$ denote the asymptotic variance of $\sqrt{n}(\hat{\mathbf{a}} - \mathbf{a}_0)$. The calculation of $\sum_{aa}$ requires properly accounting for the additional uncertainty in $\tilde{\tau}^2$. Let $\bar{\lambda}$ denote the arithmetic mean of the eigenvalues of $(\mathbf{I_0^{aa}}^{-1} \sum_{aa})$. The proposed multivariate publication bias test (MPBT) is given by (4.5)

$$\mathbf{MPBT} = (n\bar{\lambda})^{-1}\mathbf{U_a}[\mathbf{0}, \tilde{\mathbf{b}}(\mathbf{0}), \tilde{\tau}^{\mathbf{2}}]^T \mathbf{I_0^{aa}} \mathbf{U_a}[\mathbf{0}, \tilde{\mathbf{b}}(\mathbf{0}), \tilde{\tau}^{\mathbf{2}}] \tag{4.5}$$

The p-value of the test is given by $P(X > \mathbf{MPBT})$ for $X \sim \chi_d^2$.

4.2 Proposed Method – Rank Prediction Protocol (RPP) Test for Multivariate Meta-Analysis

Instead of combining individual Egger regression likelihoods using a composite likelihood approach, we adopt a nested mixed model framework in our approach.

4.2.1 A two-level nested model framework

Instead of the independent regression models considered in (4.1), we will set up our model as a two-level nested mixed model to account for within study correlations. This is given as

$$Z_{ij} = a_j + \beta_j P_{ij} + \varepsilon_{j(i)} \,, \quad i = 1, \ldots, n; \; j = 1, \ldots, d \,, \tag{4.6}$$

where $\varepsilon_{j(i)}$ are assumed to be independent of the random effects a_j. After plugging in estimated $\widetilde{\tau}$ for τ, model (4.6) is given in vector notation as

$$\widetilde{\mathbf{Z}}_i = \mathbf{a} + \boldsymbol{\beta}^T \widetilde{\mathbf{P}}_i + \boldsymbol{\varepsilon}_i \,, \quad i = 1, \ldots, n,$$

where as in the previous section

$$Var(\widetilde{\mathbf{Z}}_i) = \widetilde{\Omega} + \widetilde{\Delta}_i \,.$$

Now let $\widetilde{\mathbf{Z}} = (\widetilde{\mathbf{Z}}_1^T, \ldots, \widetilde{\mathbf{Z}}_n^T)^T$, $\widetilde{\mathbf{P}} = (\widetilde{\mathbf{P}}_1^T, \ldots, \widetilde{\mathbf{P}}_n^T)^T$, and $\mathbf{e} = (\boldsymbol{\varepsilon}_1^T, \ldots, \boldsymbol{\varepsilon}_n^T)^T$. Then the model above can be given in a stacked form as

$$\widetilde{\mathbf{Z}} = \mathbf{a} \otimes \mathbf{1}_n + \boldsymbol{\beta}^T \widetilde{\mathbf{P}} + \mathbf{e} \,,$$

where $\mathbf{1}_n$ is an n-vector of ones and $\otimes$ is the Kronecker product. Now

$$Var(\widetilde{\mathbf{Z}}) \equiv \boldsymbol{\Sigma}_{\widetilde{\mathbf{Z}}} = \boldsymbol{\Gamma} + \boldsymbol{\Xi}$$

with $\boldsymbol{\Gamma} = \text{diag}(\widetilde{\Omega}, \ldots, \widetilde{\Omega})$ and $\boldsymbol{\Xi} = \text{diag}(\widetilde{\Delta}_1, \ldots, \widetilde{\Delta}_n)$ being in $\mathbb{R}^{nd \times nd}$. Without loss of generality, we will take $\boldsymbol{\theta}$ to represent the vector of parameters of $\boldsymbol{\Sigma}_{\widetilde{\mathbf{Z}}}$.

The generalized least squares estimator of $\boldsymbol{\beta}$ given in Goldstein (2011) is

$$\hat{\boldsymbol{\beta}} = (\widetilde{\mathbf{P}}^T \boldsymbol{\Sigma}_{\widetilde{\mathbf{Z}}}^{-1} \widetilde{\mathbf{P}})^{-1} \widetilde{\mathbf{P}}^T \boldsymbol{\Sigma}_{\widetilde{\mathbf{Z}}}^{-1} \widetilde{\mathbf{Z}}, \tag{4.7}$$

with $Var(\hat{\boldsymbol{\beta}}) = (\widetilde{\mathbf{P}}^T \boldsymbol{\Sigma}_{\widetilde{\mathbf{Z}}}^{-1} \widetilde{\mathbf{P}})^{-1}$. The estimator of $\boldsymbol{\theta}$ is found as

$$\hat{\boldsymbol{\theta}} = (\mathbf{A}^T M^{-1} \mathbf{A})^{-1} \mathbf{A}^T M^{-1} \boldsymbol{W} \ , \tag{4.8}$$

where $M = \boldsymbol{\Sigma}_{\widetilde{\mathbf{Z}}} \otimes \boldsymbol{\Sigma}_{\widetilde{\mathbf{Z}}}$, $\mathbf{A}$ is the design matrix of the random effects, and $\boldsymbol{W} = \text{vec}\{(\widetilde{\mathbf{Z}} - \widetilde{\mathbf{P}}\hat{\boldsymbol{\beta}})(\widetilde{\mathbf{Z}} - \widetilde{\mathbf{P}}\hat{\boldsymbol{\beta}})^T\}$. Thus the random effect parameters are estimated by regressing $\boldsymbol{W}$ on $\mathbf{A}$. It is easy to see that $E(\boldsymbol{W}) = \mathbf{A}\boldsymbol{\theta}$. Since both $\boldsymbol{\beta}$ and $\boldsymbol{\theta}$ are initially unknown, the process starts by taking an initial estimator of $\boldsymbol{\beta}$ through fitting the regression model

$$\widetilde{\mathbf{Z}} = \boldsymbol{\beta}^T \widetilde{\mathbf{P}} + \mathbf{e} \ .$$

This gives $\hat{\boldsymbol{\beta}}^{(0)} = (\widetilde{\mathbf{P}}^T \widetilde{\mathbf{P}})^{-1} \widetilde{\mathbf{P}}^T \widetilde{\mathbf{Z}}$, which is a consistent estimator of $\boldsymbol{\beta}$. The parameters $\boldsymbol{\theta}$ and $\boldsymbol{\beta}$ are then estimated by iterating between equations (4.7) and (4.8) until convergence.

4.2.2 The Rank prediction protocol (RPP)

In the following we will describe a rank regression version of the iterative generalized LS approach for estimating 2-level nested mixed model parameter estimation.

As described in Chapter 3, rank-based estimation uses the pseudo-norm

$$\|\boldsymbol{w}\|_{\varphi} = \sum_{i}^{n} \varphi\left[R(w_i)/(n+1)\right] w_i, \quad w \in R^n, \tag{4.9}$$

for a non-decreasing square-integrable function $\varphi(u)$ described in Chapter 3 (defined on the interval $(0,1)$, odd about $1/2$, $\int \phi = 0$). The most commonly used score function is the Wilcoxon $\varphi(u) = \sqrt{12} \cdot (u - \frac{1}{2})$;and we will be using this function for the remainder of the thesis.

The rank-based estimate of $\boldsymbol{\beta}$ for the independent error model $\widetilde{\mathbf{Z}} = \boldsymbol{\beta}^T \widetilde{\mathbf{P}} + \mathbf{e}$ is given by

$$\text{Argmin} \left\| \widetilde{\mathbf{Z}} - \boldsymbol{\beta}^T \widetilde{\mathbf{P}} \right\|_{\varphi} . \tag{4.10}$$

This will be used to obtain our initial estimator of $\boldsymbol{\beta}$. Our estimation algorithm is given below:

Step 0: (Initialize) Use (4.10) to obtain an initial estimator $\hat{\boldsymbol{\beta}}^{(0)}$. Use $\hat{\boldsymbol{\beta}}^{(0)}$ in (4.8) to obtain an initial estimate of the vector $\boldsymbol{\theta}$, $\hat{\boldsymbol{\theta}}^{(0)}$. Use this initial estimate to obtain an estimate of $\boldsymbol{\Sigma}_{\widetilde{\mathbf{Z}}}$, $\hat{\boldsymbol{\Sigma}}(\hat{\boldsymbol{\theta}}^{(0)})$. Set $k = 1$.

Step 1: Use (4.10) to obtain $\hat{\boldsymbol{\beta}}^{(k)}$, the rank-based fit of $\widetilde{\mathbf{Z}}^* = \widetilde{\mathbf{P}}^*\boldsymbol{\beta} + \boldsymbol{e}^*$, where $\widetilde{\mathbf{Z}}^* = \hat{\boldsymbol{\Sigma}}_{\widetilde{\mathbf{Z}}}^{-1/2}\widetilde{\mathbf{Z}}$, $\widetilde{\mathbf{P}}^* = \hat{\boldsymbol{\Sigma}}_{\widetilde{\mathbf{Z}}}^{-1/2}\widetilde{\mathbf{P}}$, $\boldsymbol{e}^* = \hat{\boldsymbol{\Sigma}}_{\widetilde{\mathbf{Z}}}^{-1/2}\boldsymbol{e}$, and $\hat{\boldsymbol{\Sigma}}_{\widetilde{\mathbf{Z}}} = \boldsymbol{\Sigma}_{\widetilde{\mathbf{Z}}}(\hat{\boldsymbol{\theta}}^{(l-1)})$.

Step 2: Use the residuals $\hat{\boldsymbol{e}}^{(k)} = \widetilde{\mathbf{Z}} - \widetilde{\mathbf{P}}\hat{\boldsymbol{\beta}}^{(k)} \equiv (\hat{e}_{ij}^{(k)})$ to obtain the Hodges-Lehmann estimator of the random effects as $\hat{a}_j^{(k)} = \text{HL}\{\hat{e}_{1j}^{(k)}, \ldots, \hat{e}_{nj}^{(k)}\}$ for $j = 1, \ldots, d$.

Step 3: Use $\hat{\boldsymbol{\beta}}^{(k)}$ to obtain $\hat{\boldsymbol{\theta}}^{(k)}$ using (4.8).

Step 4: If $\left\|\hat{\boldsymbol{\beta}}^{(k)} - \hat{\boldsymbol{\beta}}^{(k-1)}\right\| < \text{TOL}\left\|\hat{\boldsymbol{\beta}}^{(k-1)}\right\|$ and $\left\|\hat{\boldsymbol{\theta}}^{(k)} - \hat{\boldsymbol{\theta}}^{(k-1)}\right\| < \text{TOL}\left\|\hat{\boldsymbol{\theta}}^{(k-1)}\right\|$, then set $\hat{\boldsymbol{\beta}} = \hat{\boldsymbol{\beta}}^{(k)}, \hat{\boldsymbol{\theta}} = \hat{\boldsymbol{\theta}}^{(k)}$, $\hat{\boldsymbol{b}} = \hat{\boldsymbol{b}}^{(l)}$ and stop. Else goto **Step 5**.

Step 5: Set $k = k + 1$ and return to **Step 1**.

In the algorithm, we used the well known Hodges-Lehmann estimator. Given a sample $\{x_1, \ldots, x_m\}$, this estimator is

$$\text{HL}\{x_1, \ldots, x_m\} = \text{med}_{i \le j}\{(x_i + x_j)/2\},$$

the median of Walsh averages.

The rank-based Egger type regression test of publication bias is based on the estimates $\hat{a}_j$ given in **Step 2**. A discussion of the motivation for **Step 2** is warranted. Note that by (4.6)

$$\hat{e}_{ij}^{(k)} \doteq a_j + \varepsilon_{j(i)}$$

Since studies are considered independent of each other, when j is fixed, this represents a simple location model with independent errors and location a_j. Thus it is natural to use the Hodges-Lehmann estimator since it is the conjugate location estimator of the Wilcoxon score function.

The consistency of the above procedure follows from the work of Groggel (1983) and Groggel et al. (1988). In these papers, the prediction of random effects and the estimation of variance components is based on means or medians and associated scale

estimators. The consistency argument in the Groggel papers remains true for our proposed approach. The asymptotic normality of $\hat{a}_j$ follows from the asymptotic normality of the Hodges-Lehmann estimator (Hettmansperger and McKean, 2011). In particular,

$$\sqrt{n}(\hat{a}_j - a_j) \;\rightarrow\; N(0, \sigma_j^2)$$

where $\sigma_j^2 \;=\; 12\left[\int f_j^2(\varepsilon_j)d\varepsilon_j\right]^2$. A consistent estimator $\hat{\sigma}_j^2$ of this variance can be estimated using the density estimator of Koul et al. (1987) on the basis of $\{\hat{e}_{1j}^{(k)}, \ldots, \hat{e}_{nj}\}$.

Let $\hat{\mathbf{a}} = (\hat{a}_1, \ldots \hat{a}_d)^T$ and $S_{\mathbf{a}} = \text{diag}(\hat{\sigma}_1^2, \ldots, \hat{\sigma}_d^2)$. A test of publication bias tests $H_0 : \mathbf{a} = \mathbf{0}$. Then the RPP rejects the null if

$$n\hat{\mathbf{a}}^T S_{\mathbf{a}}^{-1}\hat{\mathbf{a}} \;>\; \chi_d^2\,.$$

Chapter 5

Monte Carlo Evaluation of RPP

To study the finite sample performance of the proposed estimator, we perform simulation experiments with randomly generated data. In particular, we studied the influence of two phenomena on publication bias. These are contamination and correlation structure.

5.1 Effect of Contamination on Publication Bias Detection

To study the effect of contamination on the Type I error of tests for publication bias, we randomly generated d effect sizes each from n studies as

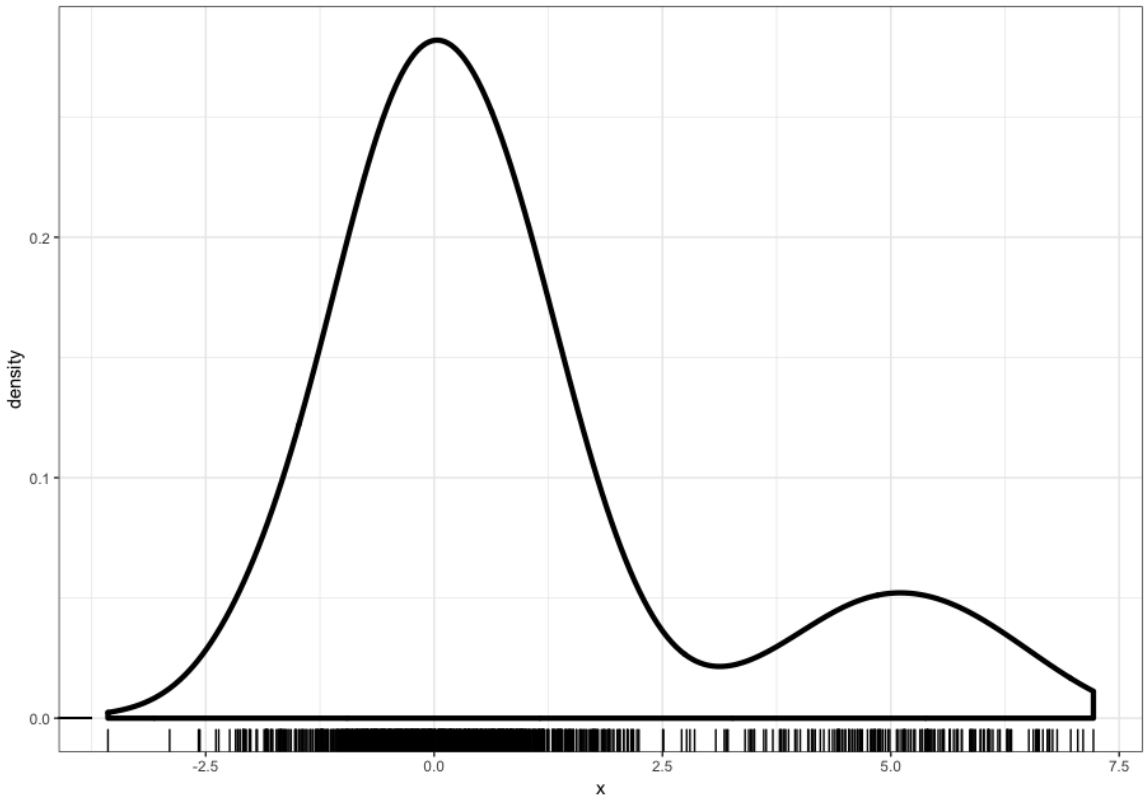
$$\mathbf{Y}_i \ \sim \ CN_d(\boldsymbol{\mu}_{1i}, \boldsymbol{\mu}_{2i}, \Sigma_{1i}, \Sigma_{2i}, \xi)$$

where $\mathbf{Y}_i \in \mathbb{R}^d$, $i = 1, \ldots, n$, and

$$CN_d(\boldsymbol{\mu}_{1i}, \boldsymbol{\mu}_{2i}, \Sigma_{1i}, \Sigma_{2i}, \xi) \equiv (1-\xi)N_d(\boldsymbol{\mu}_{1i}, \Sigma_{1i}) \ + \ \xi N_d(\boldsymbol{\mu}_{2i}, \Sigma_{2i})$$

is a Huber mixture (Huber, 1964) in which $1-\xi$ proportion of the time d effect sizes $\mathbf{Y}_i$ are generated from the d-variate normal distribution with mean $\boldsymbol{\mu}_{1i}$ and covariance matrix Σ_{1i} and ξ proportion of the time effect sizes $\mathbf{Y}$ are sampled from the d-variate normal distribution with mean $\boldsymbol{\mu}_{2i}$ and covariance matrix Σ_{2i}. The first distribution is the main source of effect sizes and the second is referred to as the contaminant distri-

Figure 5.1: A Normal-Normal Huber Mixture Density



bution and will be the source of studies with outlying effect sizes. A schematic of this is given in Figure 5.1.

Using the notation in Hong (2016), in our experiment, we took $\Sigma_{1i} = \Sigma_{2i} = \Sigma_i \equiv \Omega + \Delta_i$, where

$$\Delta_i = \begin{pmatrix} S_{i1}^2 & \cdots & S_{i1}S_{id}\rho_{wi(1d)} \\ \vdots & \ddots & \vdots \\ S_{id}S_{i1}\rho_{wi(1d)} & \cdots & S_{id}^2 \end{pmatrix}, \qquad i = 1, \ldots, n$$

are the within-study covariance matrices and

$$\Omega = \begin{pmatrix} \tau_1^2 & \cdots & \tau_1\tau_d\rho_{b(1d)} \\ \vdots & \ddots & \vdots \\ \tau_d\tau_1\rho_{b(1d)} & \cdots & \tau_d^2 \end{pmatrix}$$

is the between study covariance matrix. In our experiment, we only focused on studies with two end-points ($d = 2$) and generated studies under the following specifications:

- nominal $\alpha = 0.10$,
- the means of the main and contaminant distribution were set as $\boldsymbol{\mu_1} = (0, 0)'$ and

$\boldsymbol{\mu_2} = (\mu_c, \mu_c)'$, where $\mu_c = 0, \ldots, 10$,

- the proportion of contamination was $\xi = 0.2$,
- the within study variances were generated as $S_{ij}^2 \sim (N(0.3, 0.25))^2$, $i = 1, \ldots, n$; $j = 1, 2$,
- between-study standard deviations were $\tau_1^2 = \tau_2^2 = \tau^2$, where $\tau^2 = 0.1, 0.9, 1.9$,
- within and between study correlations were $\rho_b = \rho_w = -0.5$, and
- the number of studies per simulation were $n = 10, 25, 50, 100$.

This was replicated 1000 times and the proportion of times the publication bias tests rejected the null hypothesis of no publication bias in favor of publication bias were recorded. In particular, we compared the multivariate publication bias test of Hong (2016) labeled as *ML* with the methodology proposed in this thesis labeled as *RPP*. The resulting Type I error rates are reported in Table 5.1.

From the results given in Table 5.1, we note the following:

- Both ML and RPP tests tended to be liberal (more rejections than specified in nominal α) for small sample sizes, low to moderate contamination, and moderate to high between-study variance.
- Both ML and RPP tests tended to be conservative (fewer rejections than specified in nominal α) for cases with high contamination and low between-study variance. However, ML remains conservative while RPP approaches the nominal α as n increased.
- For a large number of studies included ($n = 100$) ML became increasingly conservative as the contaminant size increased while RPP maintained the nominal $\alpha = 0.10$ fairly closely.

In summary, both ML and RPP tests tended to be suboptimal when the number of studies included in the meta-analysis was small ($n = 10$) and both performed relatively well under no or small amounts of contamination in reported effect sizes. However, the RPP test gave vastly superior performance for large sample sizes and higher levels of contamination in the reported effect sizes. The criticism that rank-based tests for publication bias (eg. Begg's test) are suboptimal when the number of studies is low remains true for our proposed RPP test.

Table 5.1: Type I error rates of the ML and RPP methods compared under various levels of contamination (μ_c), between-study variability (τ), and sample sizes (n). Contamination rate was 20% and nomial $\alpha = 0.10$.

		ML				RPP			
μ_c	τ^2	$n = 10$	$n = 25$	$n = 50$	$n = 100$	$n = 10$	$n = 25$	$n = 50$	$n = 100$
0	0.1	0.132	0.106	0.110	0.118	0.107	0.098	0.126	0.115
	0.9	0.126	0.132	0.135	0.118	0.127	0.127	0.126	0.108
	1.9	0.125	0.110	0.112	0.103	0.144	0.119	0.105	0.097
1	0.1	0.128	0.088	0.095	0.087	0.091	0.091	0.087	0.084
	0.9	0.134	0.122	0.132	0.104	0.126	0.115	0.120	0.110
	1.9	0.130	0.112	0.110	0.090	0.129	0.113	0.107	0.094
2	0.1	0.111	0.082	0.087	0.073	0.082	0.098	0.104	0.100
	0.9	0.122	0.125	0.109	0.102	0.101	0.110	0.111	0.097
	1.9	0.133	0.113	0.108	0.081	0.140	0.116	0.107	0.086
3	0.1	0.095	0.072	0.065	0.063	0.080	0.091	0.106	0.107
	0.9	0.124	0.125	0.101	0.090	0.099	0.105	0.105	0.093
	1.9	0.143	0.108	0.104	0.079	0.127	0.114	0.102	0.085
4	0.1	0.082	0.065	0.051	0.062	0.070	0.087	0.104	0.111
	0.9	0.122	0.122	0.093	0.085	0.104	0.107	0.109	0.094
	1.9	0.139	0.115	0.096	0.079	0.110	0.112	0.099	0.090
5	0.1	0.069	0.053	0.046	0.063	0.064	0.076	0.096	0.101
	0.9	0.116	0.112	0.095	0.086	0.106	0.106	0.119	0.096
	1.9	0.133	0.120	0.101	0.079	0.113	0.109	0.097	0.092
6	0.1	0.062	0.050	0.045	0.051	0.059	0.065	0.088	0.094
	0.9	0.111	0.105	0.092	0.078	0.107	0.106	0.115	0.098
	1.9	0.128	0.120	0.092	0.079	0.118	0.110	0.096	0.095
7	0.1	0.058	0.045	0.041	0.049	0.054	0.058	0.077	0.092
	0.9	0.105	0.106	0.088	0.079	0.102	0.100	0.115	0.096
	1.9	0.121	0.118	0.098	0.078	0.116	0.109	0.100	0.098
8	0.1	0.057	0.037	0.041	0.045	0.051	0.050	0.072	0.086
	0.9	0.105	0.114	0.089	0.081	0.101	0.097	0.109	0.096
	1.9	0.120	0.114	0.093	0.078	0.114	0.109	0.097	0.099
9	0.1	0.055	0.037	0.042	0.047	0.048	0.043	0.066	0.080
	0.9	0.098	0.110	0.093	0.086	0.097	0.090	0.107	0.097
	1.9	0.115	0.111	0.093	0.078	0.106	0.108	0.096	0.100
10	0.1	0.047	0.041	0.039	0.047	0.048	0.038	0.058	0.075
	0.9	0.098	0.110	0.096	0.085	0.095	0.087	0.104	0.096
	1.9	0.114	0.113	0.092	0.081	0.103	0.100	0.097	0.100

5.2 Effect of Within and Between Study Correlations on Publication Bias Detection

To study the effect of within- and between-study correlations on the Type I error of ML and RPP tests for publication bias, we randomly generated d effect sizes each from n

studies as

$$\mathbf{Y}_i \sim N_d(\boldsymbol{\mu}, \Sigma_i)$$

where $\mathbf{Y}_i \in \mathbb{R}^d$, $i = 1, \ldots, n$, and $\Sigma_i \equiv \Omega + \Delta_i$ with Δ_i and Ω are the within- and between-study covariance matrices as defined above. In particular, Δ_i depends on the within-study correlations ρ_w and study standard errors S_{ij} while Ω depends on the between-study correlations ρ_b and between-study variances τ^2. Once again, we only focused on studies with two end-points ($d = 2$) and generated studies under the following specifications:

- nominal $\alpha = 0.10$,
- the within study variances were generated as $S_{ij}^2 \sim (N(0.3, 0.25))^2$, $i = 1, \ldots, n$; $j = 1, 2$,
- between-study standard deviations were $\tau_1^2 = \tau_2^2 = \tau^2$, where $\tau^2 = 0.1, 0.9, 1.9$,
- within-study correlations ρ_w and between-study correlations ρ_b ranged in $\{-0.9, -0.5, 0.0, 0.5, 0.9\}$, and
- the number of studies per simulation was $n = 10$.

This was replicated 1000 times and the proportion of times the publication bias tests rejected the null hypothesis of no publication bias in favor of publication bias were recorded. Again, we compared the multivariate publication bias test of Hong (2016) labeled as *ML* with the methodology proposed in this thesis labeled as *RPP*. The resulting Type I error rates are reported in Table 5.2.

The results in Table 5.2 indicate the following:

- When the between-study variation was low ($\tau^2 = 0.1$), the RPP test was found to be conservative for strongly negatively correlated effects $\rho_w = -0.9$ but generally maintained the nominal α when reported effects were uncorrelated or positively correlated. ML was very liberal for such cases reaching a rejection rate more that twice α for cases where both between and within-study correlations were strongly positive.
- Both ML and RPP were generally liberal when the between-study variation was moderate ($\tau^2 = 0.9$) or high ($\tau^2 = 1.9$). However, with few exceptions, ML was far more liberal than RPP.

Table 5.2: Type I error rates of the ML and RPP methods compared under various levels of within-study correlations (ρ_w), between-study correlations (ρ_b), and between-study variability (τ). The number of studies was $n = 10$ and nomial $\alpha = 0.10$.

		ML					RPP				
		ρ_w					ρ_w				
τ^2	ρ_b	-0.9	-0.5	0.0	0.5	0.9	-0.9	-0.5	0.0	0.5	0.9
0.1	-0.9	0.097	0.114	0.122	0.134	0.179	0.092	0.105	0.109	0.099	0.120
	-0.5	0.092	0.107	0.125	0.126	0.161	0.080	0.108	0.111	0.099	0.111
	0.0	0.097	0.093	0.143	0.153	0.162	0.087	0.087	0.117	0.098	0.120
	0.5	0.095	0.131	0.149	0.174	0.179	0.072	0.107	0.100	0.113	0.096
	0.9	0.114	0.137	0.144	0.174	0.215	0.088	0.072	0.100	0.097	0.115
0.9	-0.9	0.123	0.140	0.125	0.126	0.140	0.119	0.126	0.125	0.127	0.135
	-0.5	0.116	0.127	0.127	0.126	0.145	0.119	0.129	0.126	0.127	0.149
	0.0	0.145	0.128	0.152	0.152	0.148	0.121	0.119	0.141	0.124	0.131
	0.5	0.136	0.155	0.184	0.155	0.161	0.130	0.123	0.126	0.124	0.127
	0.9	0.174	0.204	0.195	0.211	0.213	0.118	0.136	0.137	0.127	0.128
1.9	-0.9	0.122	0.132	0.120	0.123	0.123	0.135	0.135	0.125	0.141	0.145
	-0.5	0.112	0.120	0.118	0.120	0.133	0.121	0.139	0.129	0.139	0.164
	0.0	0.148	0.124	0.143	0.139	0.140	0.138	0.136	0.149	0.127	0.135
	0.5	0.133	0.149	0.164	0.142	0.158	0.139	0.127	0.130	0.134	0.128
	0.9	0.177	0.193	0.187	0.203	0.194	0.126	0.137	0.145	0.137	0.115

5.3 The Power Publication Bias Tests

To evaluate the power of the ML and the proposed RPP tests for publication bias, we generated sets of studies with publication bias as

$$\mathbf{Y}_i \sim N_d(\boldsymbol{\mu}, \Sigma_i)$$

where $\mathbf{Y}_i \in \mathbb{R}^d$, $i = 1, \ldots, n$, and $\Sigma_i \equiv \Omega + \Delta_i$ with Δ_i and Ω are the within- and between-study covariance matrices as defined above. In particular, Δ_i depends on the within-study correlations ρ_w and study standard errors S_{ij} while Ω depends on the between-study correlations ρ_b and between-study variances τ^2. We looked at studies with two endpoints and considered two scenarios of publication bias:

Scenario 1: The investigators published their results if both endpoints were found to be significant in individual tests at $\alpha = 0.10$.

Scenario 2: The investigators published their results if one or both endpoints were found to be significant in individual tests at $\alpha = 0.10$.

Scenario 1 is an extreme case of publication bias where no non-significant studies are

seen while Scenario 2 gives a less severe case where studies may be published even if all the results are not significant. Naturally, we expect the two scenarios to be similar if the two study endpoints are synchronous (strongly positively correlated).

We generated studies under the following specifications:

- nominal $\alpha = 0.10$,
- the within study variances were generated as $S_{ij}^2 \sim (N(0.3, 0.25))^2$, $i = 1, \ldots, n$; $j = 1, 2$,
- between-study standard deviations were $\tau_1^2 = \tau_2^2 = \tau^2$, where $\tau^2 = 0.1, 0.9, 1.9$,
- within-study correlations ρ_w and between-study correlations ρ_b ranged in $\{-0.9, -0.5, 0.0, 0.5, 0.9\}$, and
- the total number of studies performed per simulation was $n = 10000$.

Of the 10000 studies, those that did not conform to Scenario 1 or Scenario 2 were excluded from publication. This was replicated 1000 times and the proportion of times the publication bias tests rejected the null hypothesis of no publication bias in favor of publication bias were recorded. Again, we compared the multivariate publication bias test of Hong (2016) labeled as *ML* with the methodology proposed in this thesis labeled as *R*. The resulting rejection rates are reported in Table 5.3.

In all the cases evaluated, the power of RPP test was vastly superior to ML in identifying publication bias. The ML test has very low power in detecting publication bias when the endpoints are asynchronous (negative within-study correlations), which is particularly worrisome. This is especially the case when the investigators decide to publish only when both effects are significant.

Table 5.3: The power of the ML and RPP methods compared under various levels of within-study correlations (ρ_w), between-study correlations (ρ_b), and between-study variability (τ^2). The number of studies performed was $n = 10000$ with exclusion from publication as given in Scenarios 1 and 2, and nominal $\alpha = 0.10$.

		ML			RPP		
		τ^2			τ^2		
Scenario	$\rho_w = \rho_s$	0.1	0.9	1.9	0.1	0.9	1.9
1	-0.9	0.069	0.100	0.114	0.529	0.202	0.156
	-0.5	0.091	0.107	0.119	0.901	0.483	0.292
	0.0	0.634	0.240	0.160	1.000	0.943	0.709
	0.5	1.000	1.000	0.993	1.000	1.000	1.000
	0.9	1.000	1.000	1.000	1.000	1.000	1.000
2	-0.9	0.195	0.149	0.145	0.848	0.530	0.396
	-0.5	0.739	0.298	0.191	0.986	0.676	0.417
	0.0	0.985	0.472	0.256	1.000	0.869	0.584
	0.5	0.997	0.655	0.373	1.000	0.978	0.792
	0.9	0.997	0.807	0.591	1.000	1.000	0.983

Chapter 6

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Appendix

6.1 R Code for Studying Contamination Effects

```
library(MASS)
library(rlme)
library(lme4)
library(lmerTest)
library(jrfit)
library(quantreg)



B <- 1000
rb <- -.5
rw <- -.5
b <- c(0,0)

# contaminant effect
bc <- c(0,0)

taus <- c(0.1, 0.9, 1.9)
ns <- c(10, 25, 50, 100)
lmer.table0.0 <- jrfit.table0.0 <- matrix(NA, 3, 4)
set.seed(100)



# Multivariate Miture Normal

mixmvrnorm <- function(p, mu1, sig1, mu2, sig2)
{
group <- rbinom(1, size = 1, prob = p)
z <- if(group == 0) mvrnorm(1, mu1, sig1)else mvrnorm(1, mu2, sig2)
return(z)
```

```
}

for(l in 1:3){
for(m in 1:4){
tau1sq <- tau2sq <- taus[l]
n <- ns[m]
lmer.pval <-jrfit.pval <- rep(NA, B)
Dmat <- matrix(NA, nrow = n, ncol = 4)
Omega <- matrix(c(tau1sq, sqrt(tau1sq*tau2sq)*rb, sqrt(tau1sq*tau2sq)*rb, tau2
for(j in 1:B){
for(i in 1:n){
s1sq <- (rnorm(1, 0.3, 0.5))^2
s2sq <- (rnorm(1, 0.3, 0.5))^2
Delta <- matrix(c(s1sq, sqrt(s1sq*s2sq)*rw, sqrt(s1sq*s2sq)*rw, s2sq), nrow =
Sigma <- Delta + Omega
Y <- mixmvrnorm(.2, b, Sigma, bc, Sigma)
Dmat[i,] <- c(Y[1], sqrt(Sigma[1,1]), Y[2], sqrt(Sigma[2,2]))
}
Dmat <- data.frame(Dmat)
names(Dmat) <- c("y1", "s1", "y2", "s2")
y <- as.vector(rbind(Dmat$y1, Dmat$y2))
x <- as.vector(rbind(Dmat$s1, Dmat$s2))
snd <- y/sqrt((x^2 + tau1sq))
p <- 1/sqrt(x^2 + tau1sq)
grp <- as.vector(rbind(1:n,1:n))
data.r <- data.frame(y = y, x = x, snd = snd, p=p, grp=grp)
names(data.r) <- c("y", "x", "snd", "p" , "grp")
lmer.fit <- lmer(snd ~ 1 + p + (1 | grp), data = data.r)
lmer.pval[j] <- summary(lmer.fit)$coef[1,5]
jrfit.fit <- jrfit(p, snd, grp)
jrfit.pval[j] <- summary(jrfit.fit)$coef[1,4]
}
lmer.table0.0[l, m] <- mean(lmer.pval < .1)
jrfit.table0.0[l, m] <- mean(jrfit.pval < .1)
```

```
}
}

## lmer
colnames(lmer.table0.0) <- ns
row.names(lmer.table0.0) <- taus
lmer.table0.0
write.csv(lmer.table0.0, file = "ls00.csv")

## JRfit
colnames(jrfit.table0.0) <- ns
row.names(jrfit.table0.0) <- taus
jrfit.table0.0
write.csv(jrfit.table0.0, file = "jr00.csv")
```

6.2 R Code for Studying Correlation Effects

```
library(MASS)
library(rlme)
library(lme4)
library(lmerTest)
library(jrfit)
library(quantreg)



B <- 1000

b <- c(0,0)

tau1sq <- tau2sq <- 0.9
n <- 10

rbs <- rws <- c(-.9, -.5, 0, .5, .9)
```

```
lmer.table <- jrfit.table <- matrix(NA, 5, 5)
colnames(lmer.table) <- rws
row.names(lmer.table) <- rbs
colnames(jrfit.table) <- rws
row.names(jrfit.table) <- rbs

set.seed(100)


for(l in 1:5){
for(m in 1:5){
rb <- rbs[l]
rw <- rws[m]
lmer.pval <-jrfit.pval <- rep(NA, B)
Dmat <- matrix(NA, nrow = n, ncol = 4)
Omega <- matrix(c(tau1sq, sqrt(tau1sq*tau2sq)*rb, sqrt(tau1sq*tau2sq)*rb, tau2
for(j in 1:B){
for(i in 1:n){
s1sq <- (rnorm(1, 0.3, 0.5))^2
s2sq <- (rnorm(1, 0.3, 0.5))^2
Delta <- matrix(c(s1sq, sqrt(s1sq*s2sq)*rw, sqrt(s1sq*s2sq)*rw, s2sq), nrow =
Sigma <- Delta + Omega
Y <- mvrnorm(1, b, Sigma)
Dmat[i,] <- c(Y[1], sqrt(Sigma[1,1]), Y[2], sqrt(Sigma[2,2]))
}
Dmat <- data.frame(Dmat)
names(Dmat) <- c("y1", "s1", "y2", "s2")
y <- as.vector(rbind(Dmat$y1, Dmat$y2))
x <- as.vector(rbind(Dmat$s1, Dmat$s2))
snd <- y/sqrt((x^2 + tau1sq))
p <- 1/sqrt(x^2 + tau1sq)
grp <- as.vector(rbind(1:n,1:n))
data.r <- data.frame(y = y, x = x, snd = snd, p=p, grp=grp)
```

```
names(data.r) <- c("y", "x", "snd", "p" , "grp")
lmer.fit <- lmer(snd ~ 1 + p + (1 | grp), data = data.r)
lmer.pval[j] <- summary(lmer.fit)$coef[1,5]
jrfit.fit <- jrfit(p, snd, grp)
jrfit.pval[j] <- summary(jrfit.fit)$coef[1,4]
}
lmer.table[l, m] <- mean(lmer.pval < .1)
jrfit.table[l, m] <- mean(jrfit.pval < .1)
}
}

## lmer
write.csv(lmer.table, file = "ls09.csv")

## JRfit
write.csv(jrfit.table, file = "jr09.csv")
```

6.3 R Code for Power Simulation

```
library(MASS)
library(rlme)
library(lme4)
library(lmerTest)
library(jrfit)
library(quantreg)


B <- 1000

b <- c(0,0)
n <- 10000

rs <- c(-.9,-.5,0,.5,.9)
```

```
taus <- c(0.1,0.9,1.9)

lmer.table1 <- jrfit.table1 <- matrix(NA, 5, 3)
colnames(lmer.table1) <- taus
row.names(lmer.table1) <- rs
colnames(jrfit.table1) <- taus
row.names(jrfit.table1) <- rs
lmer.table2 <- jrfit.table2 <- matrix(NA, 5, 3)
colnames(lmer.table2) <- taus
row.names(lmer.table2) <- rs
colnames(jrfit.table2) <- taus
row.names(jrfit.table2) <- rs

set.seed(1)


for(l in 1:5){
for(m in 1:3){
rb <- rw <- rs[l]
tau1sq <- tau2sq <- taus[m]
lmer.pval1 <-jrfit.pval1 <- lmer.pval2 <- jrfit.pval2 <- rep(NA, B)
Dmat <- matrix(NA, nrow = n, ncol = 4)
Omega <- matrix(c(tau1sq, sqrt(tau1sq*tau2sq)*rb, sqrt(tau1sq*tau2sq)*rb, tau2
for(j in 1:B){
for(i in 1:n){
s1sq <- (rnorm(1, 0.3, 0.5))^2
s2sq <- (rnorm(1, 0.3, 0.5))^2
Delta <- matrix(c(s1sq, sqrt(s1sq*s2sq)*rw, sqrt(s1sq*s2sq)*rw, s2sq), nrow =
Sigma <- Delta + Omega
Y <- mvrnorm(1, b, Sigma)
Dmat[i,] <- c(Y[1], sqrt(Sigma[1,1]), Y[2], sqrt(Sigma[2,2]))
}

Dmat <- data.frame(Dmat)
```

```
names(Dmat) <- c("y1", "s1", "y2", "s2")

## Pub scenarios
# All significant

Dmat1 <- subset(Dmat, (abs(y1/s1) > 1.65 & abs(y2/s2 > 1.65)))
n1 <- dim(Dmat1)[1]
y <- as.vector(rbind(Dmat1$y1, Dmat1$y2))
x <- as.vector(rbind(Dmat1$s1, Dmat1$s2))
snd <- y/sqrt((x^2 + tau1sq))
p <- 1/sqrt(x^2 + tau1sq)
grp <- as.vector(rbind(1:n1,1:n1))
data.r <- data.frame(y = y, x = x, snd = snd, p=p, grp=grp)
names(data.r) <- c("y", "x", "snd", "p" , "grp")
lmer.fit <- lmer(snd ~ 1 + p + (1 | grp), data = data.r)
lmer.pval1[j] <- summary(lmer.fit)$coef[1,5]
jrfit.fit <- jrfit(p, snd, grp)
jrfit.pval1[j] <- summary(jrfit.fit)$coef[1,4]


## Pub scenarios
# One significant

Dmat1 <- subset(Dmat, (abs(y1/s1) > 1.65 | abs(y2/s2 > 1.65)))
n1 <- dim(Dmat1)[1]
y <- as.vector(rbind(Dmat1$y1, Dmat1$y2))
x <- as.vector(rbind(Dmat1$s1, Dmat1$s2))
snd <- y/sqrt((x^2 + tau1sq))
p <- 1/sqrt(x^2 + tau1sq)
grp <- as.vector(rbind(1:n1,1:n1))
data.r <- data.frame(y = y, x = x, snd = snd, p=p, grp=grp)
names(data.r) <- c("y", "x", "snd", "p" , "grp")
lmer.fit <- lmer(snd ~ 1 + p + (1 | grp), data = data.r)
lmer.pval2[j] <- summary(lmer.fit)$coef[1,5]
```

```
jrfit.fit <- jrfit(p, snd, grp)
jrfit.pval2[j] <- summary(jrfit.fit)$coef[1,4]

}
print(l)
lmer.table1[l, m] <- mean(lmer.pval1 < .1)
jrfit.table1[l, m] <- mean(jrfit.pval1 < .1)
lmer.table2[l, m] <- mean(lmer.pval2 < .1)
jrfit.table2[l, m] <- mean(jrfit.pval2 < .1)
}
}

## lmer
write.csv(lmer.table1, file = "ls1.csv")

## JRfit
write.csv(jrfit.table1, file = "jr1.csv")


## lmer
write.csv(lmer.table2, file = "ls2.csv")

## JRfit
write.csv(jrfit.table2, file = "jr2.csv")
```