Interpreting Heterogeneity in Meta Analyses of Clinical Trials

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Introduction

- Outline how to investigate heterogeneity
- Give statistical test
- Highlight graphical methods
- Use worked examples throughout

Assessing Statistical Assumptions

Statistical Tests

- The test of homogeneity of the treatment effect across studies is based on the statistic

$$Q = \sum_{i=1}^{k} \left(\hat{\theta}_i - \hat{\theta} \right)^2 w_i$$

The Residuals from a Meta Analysis

- The weighted residuals from fitting a fixed-effects meta-analysis are given by

$$q_i = (\hat{\theta}_i - \hat{\theta})\sqrt{w_i}$$

- Under the standard fixed-effects meta-analysis the standardised weighted residuals are

$$q_i' = \frac{(\hat{\theta}_i - \hat{\theta})\sqrt{w_i}}{\sqrt{1 - w_i \Big/ \sum_{i=1}^{k} w_i}}$$

Assessing the Residuals

- The standardised residuals should follow a standard Normal distribution
- Under the standard random-effects meta-analysis the weighted residuals and standardised weighted residuals would be calculated from same equations by replacing w_i and $\hat{\theta}$ with w_i^* and $\hat{\theta}^*$

Assessing the Residuals

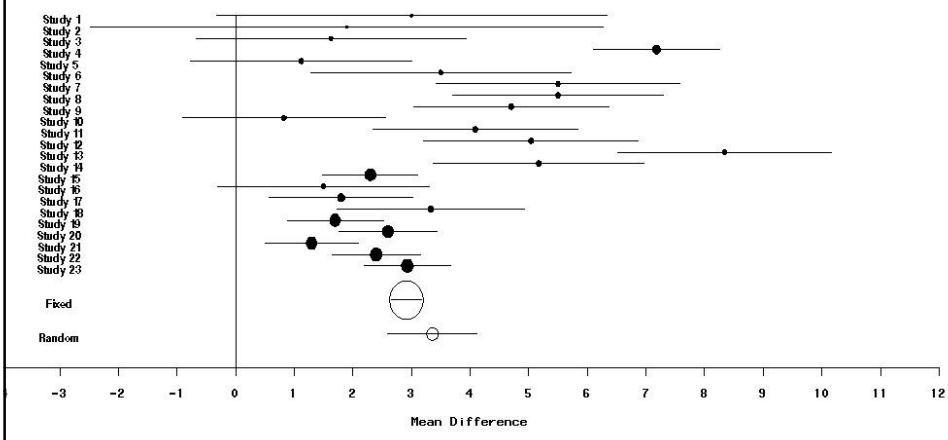
- A Normal probability plot of the q_i or q_i' may be used to check the distributional assumptions of the meta-analysis model

Multi-Centre Trials v Meta Analysis

- A multi-centre trial may be analysed in the same way as a meta-analysis
  - That is by treating centres as studies.
- Multi-centre trials can be analysed using an overall model which includes the terms centre and treatment.
- Homogeneity of treatment effects across centres can be undertaken by fitting a treatment by centre interaction to obtain an estimate of treatment effect with its variance for each centre.
- The standardised residual can be calculated replacing the w's with the inverse of the variance.

Worked Example Paroxetine in Adults

Meta analysis of 23 Paroxetine Trials

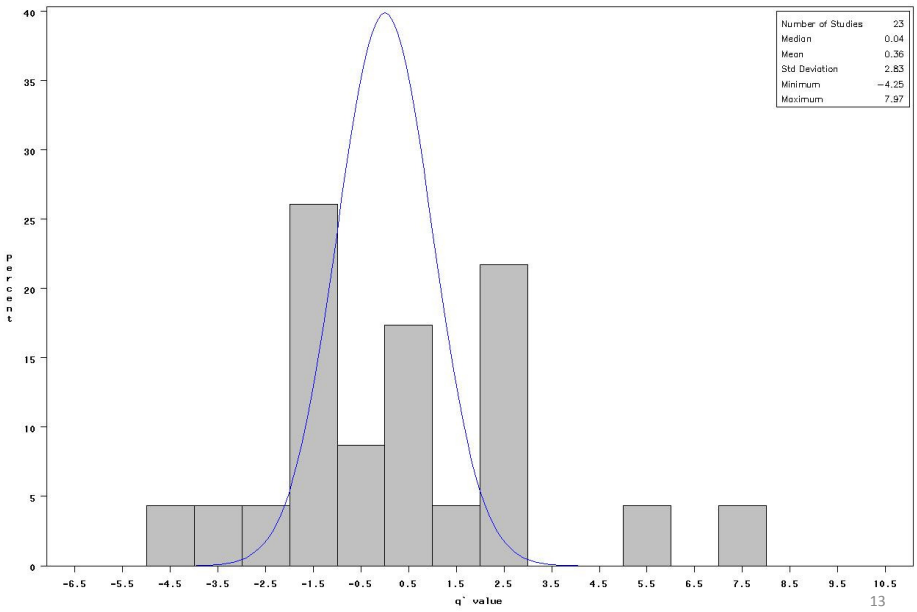


Paroxetine Trials

- The treatment effect is measured by the difference in mean HAMD between Paroxetine and placebo.
- There seems to be some evidence of heterogeneity in treatment effect though most of the heterogeneity seems to be in the smaller trials
- The fixed effect meta-analysis gave an overall mean difference of 2.91 with a 95% confidence interval of (2.66 to 3.17).
  - The test of homogeneity gives a P-value of <0.001 (chi-squared of 170.23 on 22 degrees of freedom).
- The overall mean difference from the random effects meta-analysis is 3.36 with 95% confidence interval of (2.59 to 4.12)

Fixed Effects

Histogram of q_i'



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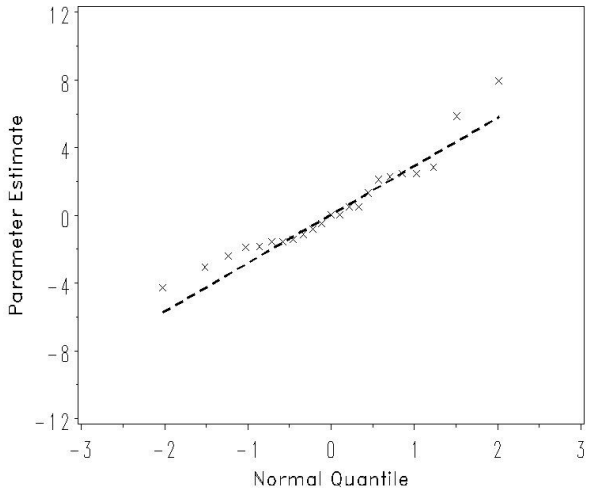
Normality Probability Plot for q_i' Estimating the Mean and Variance from the Data



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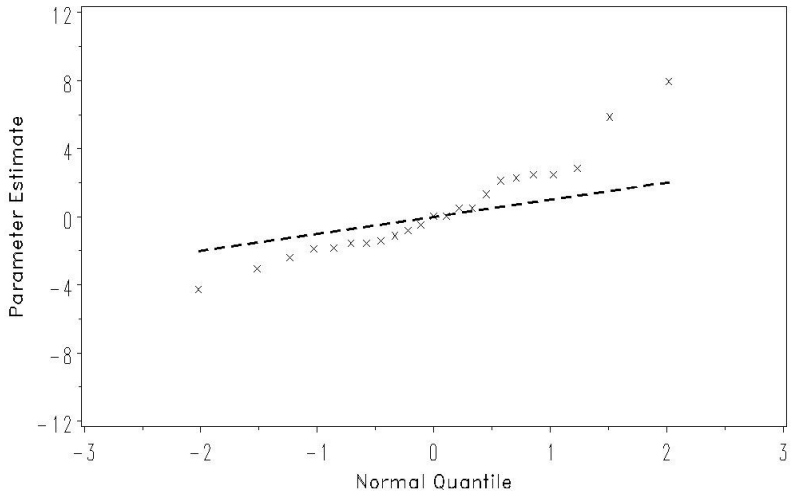
Normal Probability Plot for q_i' Setting the Mean and Variance to be 0 and 1 Respectively



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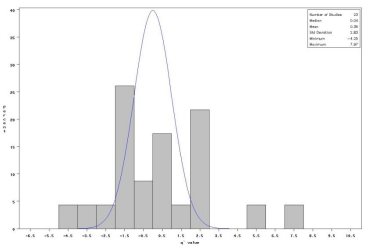
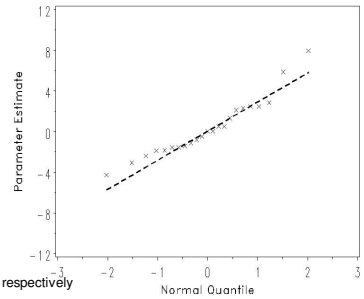
Assessment of Homogeneity of Treatment Effects with Normality Assumption of Fixed Effects Meta-analysis

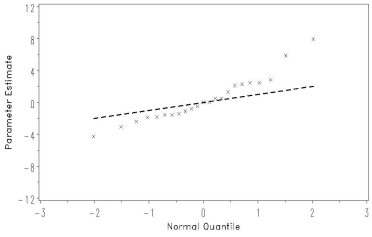
Histogram



Normal probability plot estimating the mean and variance from the data



Normal probability plot setting the mean and variance to be 0 and 1 respectively



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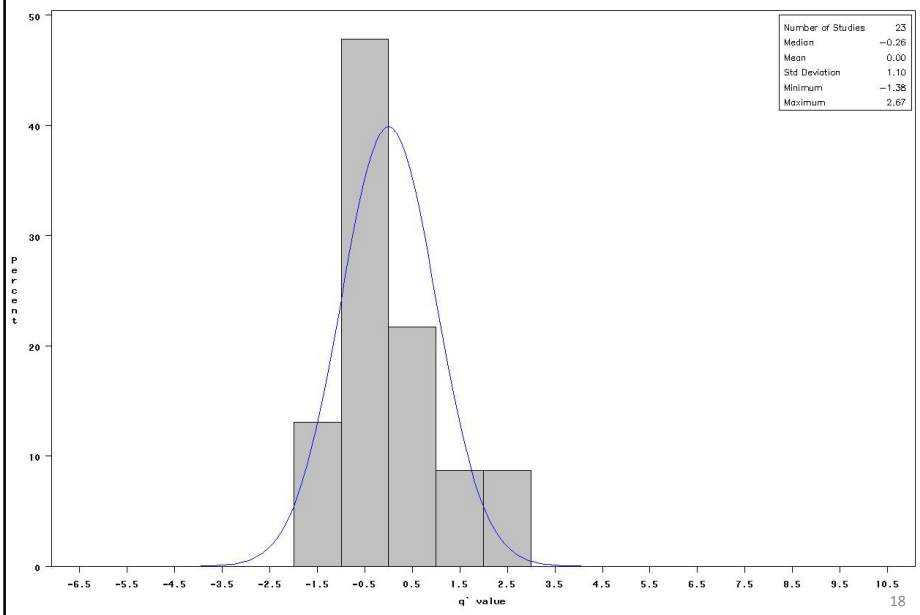
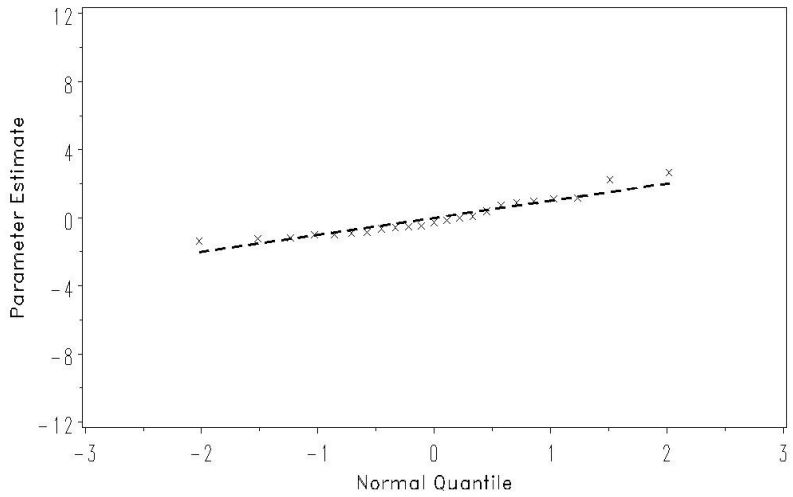
Random Effects

Histogram of q_i'



Normality Probability Plot for q_i' Estimating the Mean and Variance from the Data



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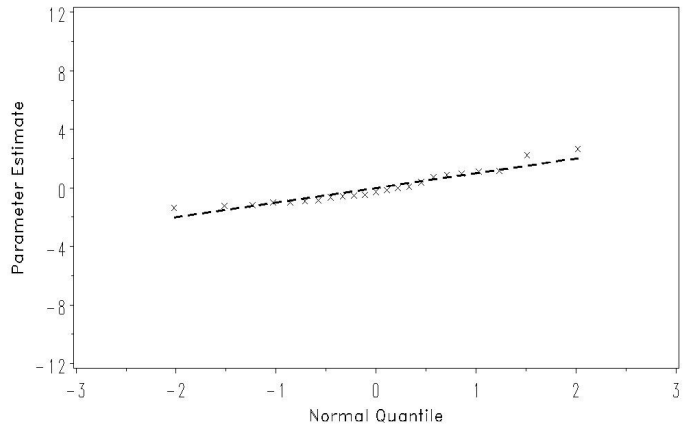
Normal Probability Plot for q_i' setting the Mean and Variance to be 0 and 1 Respectively



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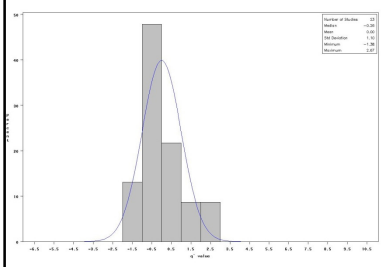
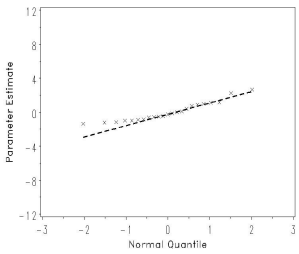
Assessment of Homogeneity of Treatment Rffects with Normality Assumption of Random Effects meta-Analysis

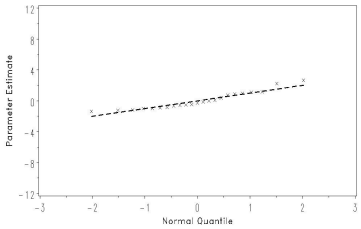
Histogram



Normal probability plot estimating the mean and variance from the data



Normal probability plot setting the mean and variance to be 0 and 1 respectively



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Summary of Results so Far

- There seems to be deviation from the assumptions for a fixed effects meta analysis although the data do seem to take a Normal form
- The assumptions seem to hold better for a random effects meta analysis
- If a fixed effects analysis was the primary analysis then the results would need to be interpreted with care
- The diagnostics so far although easy to produce in most statistics packages but have limitations
- Could an assessment of outliers better be made?

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Confidence Bands for the Normal Probability Plots

- Confidence bands for the Normal probability plots can be constructed to assist in interpretation
- For the Normal probability line confidence bands can be calculate
  - Using Normal approximation (using the Friendly macro)
  - Using simulation
- For the observed data a confidence band can be calculated
  - Using bootstrapping

Simulation Envelopes

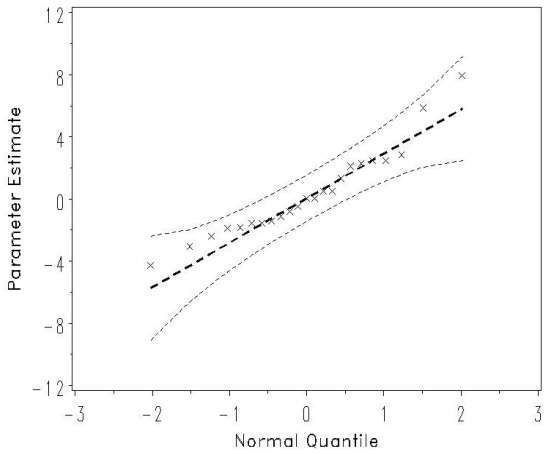
1. Simulate a value for the estimated treatment effect from study i from a $N(0, w_i^{-1})$, for i = 1,…, k .
2. Perform the fixed-effects meta-analysis and calculate the q_i'
3. Order the q_i' from smallest to largest
4. Repeat 1. to 3. a number of times, for example 1,000
5. For each i, calculate the 2.5^{th} and 97.5 percentile of the 1,000 values, to give the 95% lower and upper bounds for all points

Bootstrapping

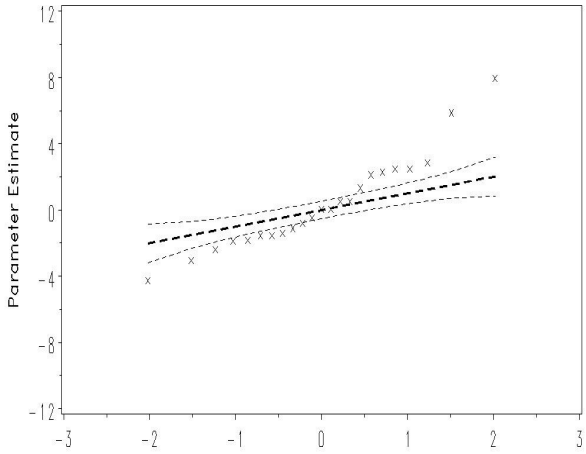
1. From the observed data pairs (θ_i ,w_i^{-1}), i = 1,…,k, take a random sample with replacement of size k
2. Perform the fixed-effects meta-analysis and calculate the $q_i^{'}$
3. Order the $q_i^{'}$ from smallest to largest
4. Repeat 1. to 3. a number of times, for example 1,000.
5. For each i, calculate the 2.5th and 97.5 percentile of the 1,000 values, to give the 95% lower and upper bounds for all points

Fixed Effects

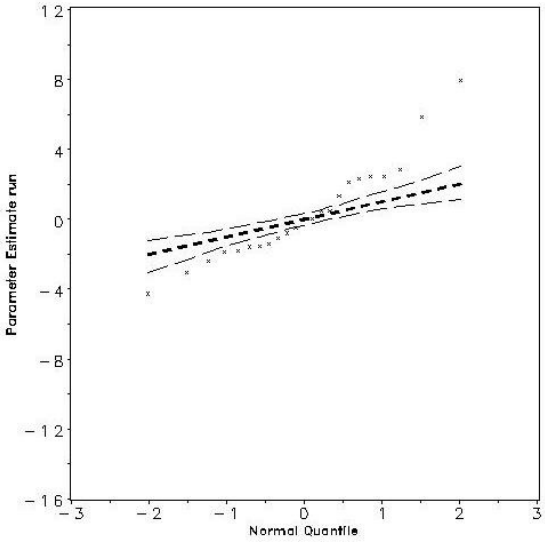
Normal Approximation, Estimating the Expected Values with the Mean and Variance from the Data



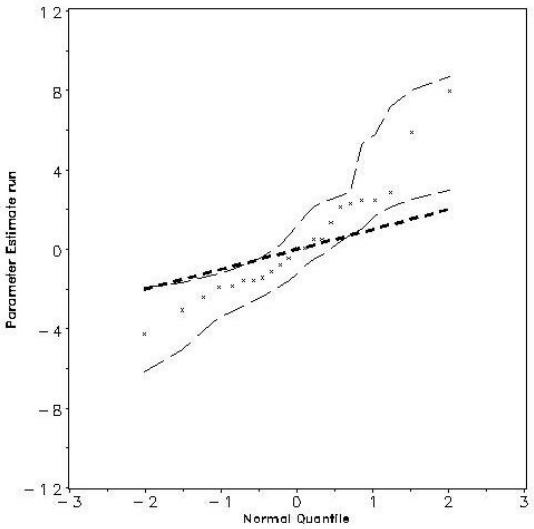
Normal Approximation, Estimating the Expected Values from N(0,1)



Simulated Envelopes

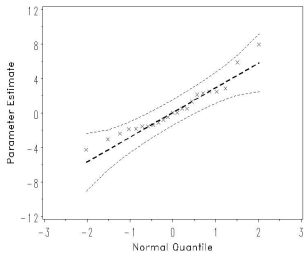


Bootstrap Envelopes

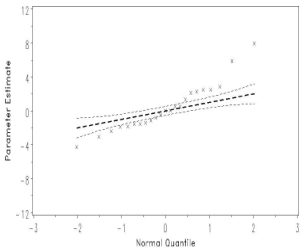


Comparison of Plots

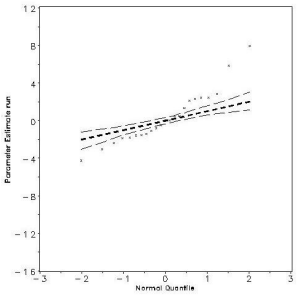
Normal using data



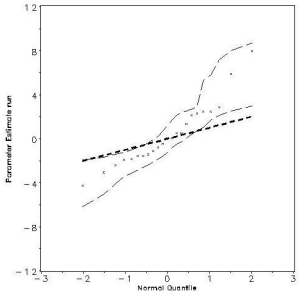
Normal using N(0,1)



Simulation using N(0,1)



Simulation



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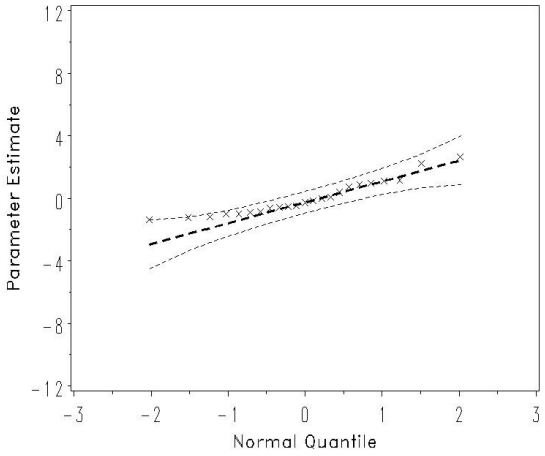
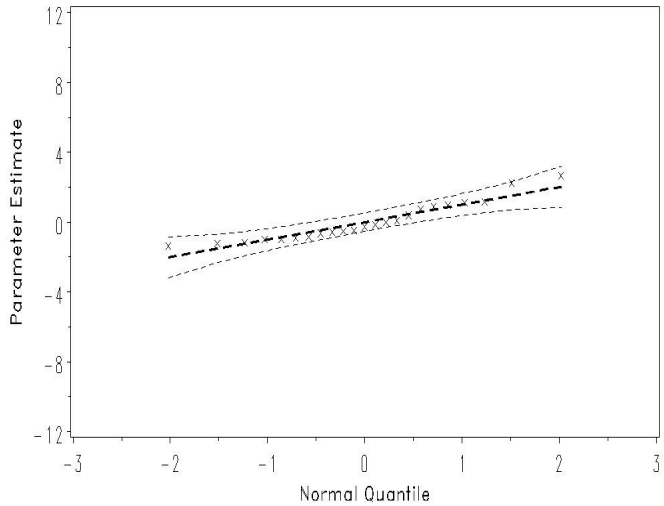
Random Effects

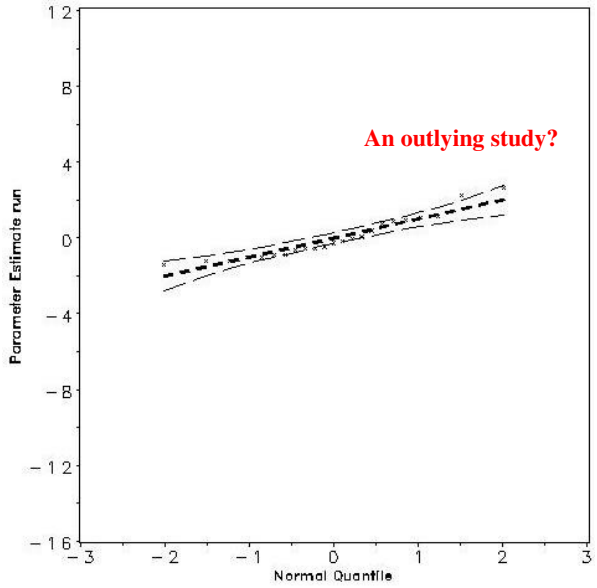
Normal Approximation, Estimating the Expected Values with the Mean and Variance from the Data



Normal Approximation, Estimating the Expected Values from N(0,1)



Simulated Envelopes



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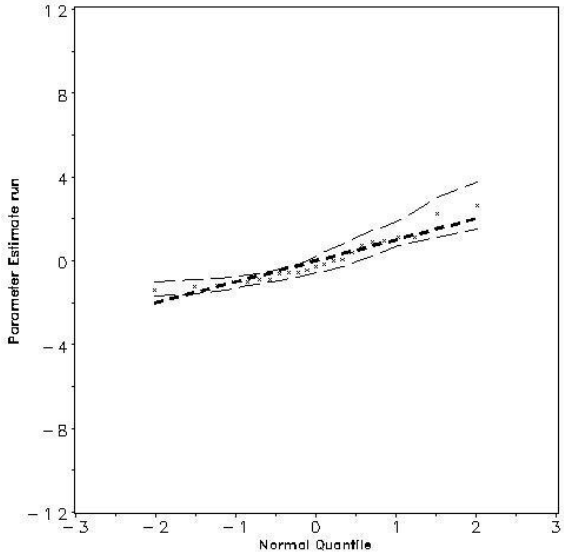
Bootstrap Envelopes



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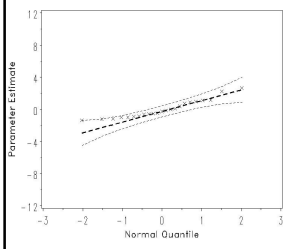
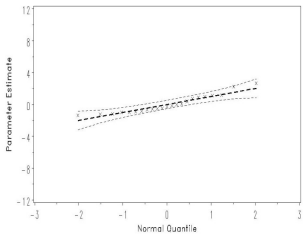
Comparison of Plots

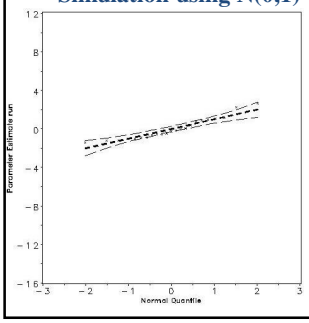
Normal using data



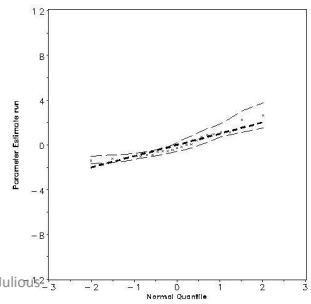
Normal using N(0,1)



Simulation using N(0,1)



Bootstrapping



Summary of Results so Far (Again)

- The additional analyses confirm the original analysis
- The bands are wider at the extremes of the range
- For this example bootstrapping has wide bands at one end
- Allows for an assessment of outliers

What if the Treatment Effects Differ Study to Study?

- Find explanation
  - Investigate baseline imbalances
  - Look at subgroups
- Are there any possible explanations?

Summary of Meta Analysis

- Gave overview of how to investigate heterogeneity in a meta analysis
- Recommended not to rely on statistical tests to assess heterogeneity
- Described graphical approaches to assess heterogeneity


QUESTIONS
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