An alternative approach to outliers in meta-analysis

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Outline

- Motivating examples
- Related work
- Random effect variance shift outlier model (RVSOM) in meta-analysis
- Variance parameter estimation and inference under the RVSOM
- Illustration of RVSOM
- Conclusions and remarks
The CDP-choline data
Intravenous magnesium in acute myocardial infarction data
Fluoride toothpaste for preventing dental caries data
Related work

The CDP-choline data
Intravenous magnesium in acute myocardial infarction data
Fluoride toothpaste for preventing dental caries

Study number

Fixed effect estimate

Rothamsted Research
A random effect variance shift outlier model

- Random effects model for meta-analytic data is

\[ y = \mu 1_n + u + e , \]
\[ \sim N (\mu 1_n, \sigma^2 I_n + R) , \]  

where \( R = \text{diag}(\sigma^2_1, \sigma^2_2, \ldots, \sigma^2_n) \).

- A RVSOM for the \( i \)th observation in the random effects model for meta-analytic data takes the form

\[ y = \mu 1_n + \delta_i d_i + u + e \]
\[ \sim N (\mu 1_n, \omega_i^2 d_i d_i' + \sigma^2_s I_n + R) , \]

where: \( d_i \) is a unit vector of length

\[ \delta_i \sim N (0, \omega_i^2) . \]
Variance parameter estimation and hypothesis testing in a *RVSOM*

- Set of parameters to be estimated: $\mu, \omega_i^2, \sigma_s^2$.

  $\Rightarrow$ Variance parameters $\omega_i^2, \sigma_s^2$ are estimated iteratively using REML.

- Likelihood ratio test statistic (LRT):

  $$LRT_i = \begin{cases} 
  -2 \{ RL(\hat{\sigma}_s^2; y) - RL_i(\hat{\omega}_i^2, \hat{\sigma}_s^2; y) \} & \hat{\omega}_i^2 > 0 \\
  0 & \text{otherwise.} 
  \end{cases}$$

- Sampling distribution of LRT via parametric bootstrap

  $\Rightarrow$ parametric bootstrap also deals with problem of multiple testing.
The CDP-choline data
## The CDP-choline data

<table>
<thead>
<tr>
<th>Para.</th>
<th>Est.</th>
<th>95% CI</th>
<th>Est.</th>
<th>95% CI</th>
<th>Est.</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\mu$</td>
<td>0.401</td>
<td>(0.08;0.72)</td>
<td>0.191</td>
<td>(0.058;0.324)</td>
<td>0.189</td>
<td>(0.056;0.32)</td>
</tr>
<tr>
<td>$\sigma_s^2$</td>
<td>0.192</td>
<td>-</td>
<td>6.4 × 10^{-8}</td>
<td>-</td>
<td>6.4 × 10^{-8}</td>
<td>-</td>
</tr>
<tr>
<td>$\omega_8^2$</td>
<td>-</td>
<td>-</td>
<td>3.951</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Intravenous magnesium in acute myocardial infarction data
# Intravenous magnesium in acute myocardial infarction data

<table>
<thead>
<tr>
<th>Para.</th>
<th>$M_0$ Est.</th>
<th>95% CI</th>
<th>$M_1$ Est.</th>
<th>95% CI</th>
<th>$M_4^+$ Est.</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\mu$</td>
<td>-0.766</td>
<td>(-1.18; -0.35)</td>
<td>-0.820</td>
<td>(-1.21; -0.43)</td>
<td>-0.875</td>
<td>(-1.28; -0.47)</td>
</tr>
<tr>
<td>$\sigma^2_s$</td>
<td>0.293</td>
<td>-</td>
<td>0.172</td>
<td>-</td>
<td>0.191</td>
<td>-</td>
</tr>
<tr>
<td>$\omega^2_{16}$</td>
<td>-</td>
<td>-</td>
<td>0.695</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Fluoride toothpaste for preventing dental caries data
**Fluoride toothpaste for preventing dental caries data**

<table>
<thead>
<tr>
<th>Para.</th>
<th>$M_0$ 95% CI</th>
<th>$M_1$ 95% CI</th>
<th>$M_4^*$ 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\mu$</td>
<td>-0.3008 (-0.33;-0.27)</td>
<td>-0.284 (-0.32;-0.25)</td>
<td>-0.283 (-0.31;-0.25)</td>
</tr>
<tr>
<td>$\sigma^2_s$</td>
<td>0.015</td>
<td>-</td>
<td>0.009</td>
</tr>
<tr>
<td>$\omega^2_{38}$</td>
<td>-</td>
<td>-</td>
<td>0.897</td>
</tr>
<tr>
<td>$\omega^2_{50}$</td>
<td>-</td>
<td>-</td>
<td>2.082</td>
</tr>
<tr>
<td>$\omega^2_{63}$</td>
<td>-</td>
<td>-</td>
<td>5.879</td>
</tr>
</tbody>
</table>
Conclusion and remarks

- A RVSOM downweights outliers but does not eliminate them from the analysis.

- The LRT gives an objective measure for detecting outliers in meta-analytic data.

- Variance shift outlier model (VSOM) under fixed effects model in meta-analysis.

- RVSOM may not be appropriate when there are many outliers are detected.
  - Use heavy-tailed distributions for the random effect (Baker and Jackson, 2008).

- Computation of thresholds for LRTs.