Choice of priors in rare events meta-analysis

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Outline:

• The problem
  • Rare events meta-analysis
  • Possible solutions

• Bayesian approach
  • Choice of priors
    • Fixed effect Meta-analysis
    • Random effects Meta-analysis

• Simulation scenarios
• Example of Rosiglitazone
Meta-analysis

- Meta-analysis (MA) combines statistical information across related studies
- MA has been widely utilized to combine data from clinical studies in order to summarize treatment efficacy
- Has also been used to assess drug safety. However, because adverse events are typically rare, standard methods may not work well in this setting.
The Problem

- Meta-analysis (MA) on adverse events often include randomized controlled trials (RCTs) in which *zero events* have been observed in one or both arms.
- In MA of rare events RCTs, where computation may involve zero cells, effect measures, like odds ratio (OR) or relative risk (RR), are difficult to calculate.
- When the events are rare, but not all zeros, the variance estimates for these methods are not robust which may lead to unreliable statistical inferences.
Example: Risoglitazone

• Rosiglitazone was used to treat patients with Type II diabetes mellitus

• RCTs of Rosiglitazone were designed to study cardiovascular morbidity and mortality

• For myocardial infarction (MI) out of 48 trials
  • 28 trials had zero in one arm
  • 8 trials with zero in both arms
Part of Rosiglitazone trials used in (Lane, 2013)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Rosiglitazone</th>
<th>Comparator</th>
<th>Duration (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>MI</td>
<td>N</td>
</tr>
<tr>
<td>011</td>
<td>357</td>
<td>2</td>
<td>176</td>
</tr>
<tr>
<td>020</td>
<td>391</td>
<td>2</td>
<td>207</td>
</tr>
<tr>
<td>024</td>
<td>774</td>
<td>1</td>
<td>185</td>
</tr>
<tr>
<td>093</td>
<td>213</td>
<td>0</td>
<td>109</td>
</tr>
<tr>
<td>094</td>
<td>232</td>
<td>1</td>
<td>116</td>
</tr>
<tr>
<td>684</td>
<td>43</td>
<td>0</td>
<td>47</td>
</tr>
<tr>
<td>143</td>
<td>121</td>
<td>1</td>
<td>124</td>
</tr>
<tr>
<td>211</td>
<td>110</td>
<td>5</td>
<td>114</td>
</tr>
<tr>
<td>284</td>
<td>382</td>
<td>1</td>
<td>384</td>
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<tr>
<td>008</td>
<td>284</td>
<td>1</td>
<td>135</td>
</tr>
<tr>
<td>264</td>
<td>294</td>
<td>0</td>
<td>302</td>
</tr>
<tr>
<td>185</td>
<td>563</td>
<td>2</td>
<td>142</td>
</tr>
<tr>
<td>334</td>
<td>278</td>
<td>2</td>
<td>279</td>
</tr>
<tr>
<td>347</td>
<td>418</td>
<td>2</td>
<td>212</td>
</tr>
<tr>
<td>015</td>
<td>395</td>
<td>2</td>
<td>198</td>
</tr>
<tr>
<td>079</td>
<td>203</td>
<td>1</td>
<td>106</td>
</tr>
<tr>
<td>080</td>
<td>104</td>
<td>1</td>
<td>99</td>
</tr>
<tr>
<td>082</td>
<td>212</td>
<td>2</td>
<td>107</td>
</tr>
<tr>
<td>085</td>
<td>138</td>
<td>3</td>
<td>139</td>
</tr>
<tr>
<td>095</td>
<td>196</td>
<td>0</td>
<td>96</td>
</tr>
<tr>
<td>097</td>
<td>122</td>
<td>0</td>
<td>120</td>
</tr>
</tbody>
</table>
Possible approaches

• Excluding trials with zero events in both arms
  • Which makes it more likely that the magnitude of the pooled treatment effect will be inflated

• Using a continuity correction
  • Allows the log-odds ratio or log-risk ratio to be estimated even when zero events are observed
  • The standard value of continuity correction is \( k = 0.5 \)
    • Possible biases, specially in trials not having 1:1 randomization
Other approaches

- Various statistical methods were proposed for using information from trials with no events
  - (Cai et al., 2010) proposed a method using Poisson regression modeling that uses the idea of **conjugacy** in the same way as **beta-binomial** model
  - (Kuss, 2015) used beta-binomial regression methods to make inference about OR, RR and risk difference (RD)
  - (Böhning et al., 2015) proposed a Poisson model for random effects (REs)

Another approach to MA of rare events is to use **fully probabilistic (Bayesian)** methods
Bayesian approach

• $Y \rightarrow \text{observed data}$

• $\theta \rightarrow \text{unknown parameter(s)}$

• Prior $\rightarrow p(\theta)$

• Likelihood $\rightarrow p(Y|\theta)$

• Posterior $\rightarrow p(\theta|Y)$

$\text{Posterior} \propto \text{Prior} \times \text{Likelihood}$

$p(\theta|Y) \propto p(\theta) \times p(Y|\theta)$
Formulation for Bayesian methods

• Our outcome of interest is binary, so for each study $i$ control group $c$ and treatment group $t$
  
  • $x_{ic} \sim Binomial(p_{ic}, n_{ic})$
  
  • $x_{it} \sim Binomial(p_{it}, n_{it})$ where $i = 1, 2, \ldots, n$

• Odds ratio (OR) is our target effect measure

  • $OR_i = \left( \frac{p_{it}}{1-p_{it}} / \frac{p_{ic}}{1-p_{ic}} \right)$
• For FE MA, Assuming a common OR across studies in a Bayesian framework
  
  \[
  \logit(p_{it}) = \log(\text{OR}) + \logit(p_{ic})
  \]
  
  Where \(\logit(p_{it}) = \log\left(\frac{p_{it}}{1-p_{it}}\right)\)

• For REs MA
  
  \[
  \log(\text{OR}_i) \sim normal(\log(\text{OR}), \tau)
  \]
  
  • \(\tau\) is statistical heterogeneity

Prior distribution for

\[
\log(\text{OR}) \sim \text{Normal}(0, 10)
\]
Prior distributions

• In an MA context, prior distributions could include expert beliefs of health professionals
• Priors can be derived from information from studies not explicitly included in the MA
• Necessity to explore sensitivity to choice of prior distributions
  • Risk in control group ($p_{ic}$)
  • heterogeneity ($\tau$), in case of REs MA
For **FE** models we used several sets of priors on risk of control group \( p_{ic} \)

### Table I. List of prior distributions for \( p_{ic} \)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Prior distribution</th>
</tr>
</thead>
</table>
| a. \( p_{ic} \) | \( beta(1, 1) \)  
                           \( beta(0.5, 0.5) \) |
| a. \( \text{logit}(p_{ic}) \) | \( \text{unif}(-10, 10) \)  
                               \( \text{normal}(0, 10) \)  
                               \( \text{normal}(0, 100) \) |
| a. \( \text{logit}(p_{ic})* \) | \( \text{normal}(\mu, \sigma) \) \text{ where}  
                               \( \mu \text{ is bounded away from zero } (0.0025, 0.048) \)  
                               \( \mu \sim \text{unif}(-6, -3) \)  
                               \( \sigma \sim \text{unif}(0, 1) \) |

* hierarchical structure on \( \text{logit}(p_{ic}), i = 1, 2, ..., n \)
Figure I. Histograms of different priors for $\text{logit}(p_{ic})$
• In **REs** models

• For **τ**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Prior distribution</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>τ</td>
<td>( \exp(2) )</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>( \text{unif}(0, 2) )</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>half-normal</td>
<td>0.5</td>
</tr>
</tbody>
</table>

**Table II.** List of prior distributions for \( \tau \)

• For \( p_{ic} \)

  • \( \logit(p_{ic}) \sim \text{Normal}(0, 10) \)
  • \( \logit(p_{ic}) \sim \text{Normal}(0, 100) \)
  • \( \logit(p_{ic}) \sim \text{Hierarchical} \)
### Table III. Parameter values used in the simulation of MA data sets

#### FE scenarios

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>log(OR)</td>
<td>0 or 0.69</td>
</tr>
<tr>
<td>Number of patients in treatment group (n&lt;sub&gt;it&lt;/sub&gt;)</td>
<td>[20, 60]</td>
</tr>
<tr>
<td>Risk of control group (p&lt;sub&gt;ic&lt;/sub&gt;)</td>
<td>[0.001, 0.04]</td>
</tr>
<tr>
<td>Number of trials in each MA</td>
<td>10, 20 or 50</td>
</tr>
</tbody>
</table>

#### RE scenarios

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>log(OR&lt;sub&gt;i&lt;/sub&gt;)*</td>
<td></td>
</tr>
<tr>
<td>log(OR)</td>
<td>0 or 0.69</td>
</tr>
<tr>
<td>Random effects standard deviation (τ)</td>
<td>0.2 or 0.5</td>
</tr>
<tr>
<td>Number of patients in treatment group (n&lt;sub&gt;it&lt;/sub&gt;)</td>
<td>[10, 60]</td>
</tr>
<tr>
<td>Risk of control group (p&lt;sub&gt;ic&lt;/sub&gt;)</td>
<td>[0.001, 0.035]</td>
</tr>
<tr>
<td>Number of trials in each MA</td>
<td>20 or 50</td>
</tr>
</tbody>
</table>

#### Both FE & REs scenarios

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ratio of group sizes**</td>
<td>1:1, 1:2 or 1:4</td>
</tr>
<tr>
<td>Number of simulated MA data sets</td>
<td>1000</td>
</tr>
</tbody>
</table>

* follows a normal distribution with specified characteristics

** We assigned treatment vs. control group for the ratio of group sizes
Simulation steps

**R:**
- Data simulation (144)
- Linking R to JAGS
- Collect JAGS result
  - MeanlogOR(s)
  - 95% credible interval(s)

**JAGS:**
- MCMC
  - Number of Markov chains = 4
  - Number of iterations = 15000
  - Length of burn in = 5000

We used result of JAGS to calculate
- 95% coverage probability
- bias = True log(OR) – median log(OR)
Results of FE Bayesian methods
Figure II. Results for FE Bayesian methods -- DL = FALSE

For log(OR) = 0 : A. Ratio 1:1

For log(OR) = 0.69 : A. Ratio 1:1
Results of REs
Bayesian methods
Figure III. Results for REs methods for log(OR) = 0 with different SDs -- DL=FALSE
Figure IV. Results for REs methods for log(OR) = 0.69 with different SDs -- DL=FALSE
Summary of the results I

• When we used different prior distributions for meta-analytical approaches, we found that our Bayesian methods returned similar interval statements for log(OR), and matched the MH calculation method

• For FE

  • The conjugate Beta distributions calculation method did not provide good coverage or a precise mean estimate

  • Weakly informative and hierarchical priors provided coverage similar to the MH without CCs
Summary of the results II

• For REs
  
  • In summary, results showed that uniform is a poor choice to account for $\tau$ in REs MA due to high bias from true log(OR) and low 95% coverage [results not shown today]

  • For $\tau$, halfnormal and exp(2) with mean 0.5 performed very similar in all aspects

For both FE & REs Bayesian methods in different scenarios, results were almost identical when studies with no events were included or excluded.
Figure V. Forest plot of an MA of Rosiglitazone for MI

<table>
<thead>
<tr>
<th>Bayesian methods</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FE--normal(0,10)</td>
<td>1.366 (1.00, 1.90)</td>
</tr>
<tr>
<td>FE--normal(0,100)</td>
<td>1.430 (1.04, 1.99)</td>
</tr>
<tr>
<td>FE--hierarchical</td>
<td>1.326 (0.97, 1.81)</td>
</tr>
<tr>
<td>RES--normal(0,10)</td>
<td>1.368 (0.92, 2.04)</td>
</tr>
<tr>
<td>RES--normal(0,100)</td>
<td>1.449 (1.00, 2.26)</td>
</tr>
<tr>
<td>RES--hierarchical</td>
<td>1.302 (0.93, 1.83)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Frequentist methods</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mantel-Haenszel</td>
<td>1.428 (1.03, 1.98)</td>
</tr>
<tr>
<td>Peto</td>
<td>1.429 (1.03, 1.98)</td>
</tr>
<tr>
<td>LR by Lane</td>
<td>1.430 (1.03, 1.98)</td>
</tr>
<tr>
<td>REs model by Shuster</td>
<td>1.510 (0.98, 2.48)</td>
</tr>
</tbody>
</table>
Conclusion

• Our results demonstrate that calculations of coverage are very sensitive to the specification of the prior for $p_{ic}$ and for $\tau$

• In MA of rare events, the performance of the Bayesian CIs and log(OR) were not affected by excluding studies with no events in both arms

• In MA of rare events, one might be really careful interpreting the result since the results are highly method dependent
Thank you
References: