Bias adjustment methods for meta-analyses of published observational studies

Simon Thompson, Adrian Mander, Rebecca Turner
MRC Biostatistics Unit, Cambridge, UK

Ulf Ekelund, Stephen Sharp
MRC Epidemiology Unit, Cambridge, UK

Susan Jebb, Anna Karin Lindroos, Désirée Wilks
MRC Human Nutrition Research, Cambridge, UK

ISCB, August 2009
Meta-analysis of published observational studies

PROBLEMS

• Varying quality
• Poor reporting / different presentations
• Different measures / outcomes
• Many sources of bias

Can we combine apparently ‘incompatible’ studies: meta-analysis rather than systematic review?

Example: Six longitudinal observational studies of objectively measured physical activity and subsequent change in obesity in children
Outline of approach

1. List sources of bias in each study
2. Transform results from each study onto a common scale
3. Elicit opinions about the size of each bias in each study, and their uncertainty
4. Adjust results in each study for the biases
5. Combine bias-adjusted results across studies in conventional meta-analysis
**Target setting**

1. **Population:** UK children aged 4-11 years
2. **Exposure:** Objectively measured physical activity energy expenditure
3. **Outcome:** Subsequent change in % body fat
4. **Timescale:** 2-year period
**Internal biases**  
(rigour / quality)  
Sample selection  
Adjustment for confounders  
Measurement of exposure  
Attrition  
Measurement of outcome  
Other bias suspected

**External biases**  
(relevance)  
Population  
Exposure measure  
Outcome measure  
Timescale

Categories of bias are considered independent
Choice of common scale for results

Relationship between baseline physical activity and change in obesity presented as:

(Adjusted) regression coefficient
(Adjusted) correlation coefficient

Often no SE or CI
Sample size (n) and P-value available

Calculations done on Fisher-transformed correlation scale (z):

\[ z = \frac{1}{2} \ln \left( \frac{1+r}{1-r} \right) \]

\[ \text{SE}(z) = \frac{1}{\sqrt{n-3}} \]

Correlation scale \((r)\) used for bias elicitations and presentation

Note: \(z\) is close to \(r\) in range \(-0.3\) to \(+0.3\)
Examples of bias checklist items

Attrition bias (internal)
• Are the results unlikely to be affected by losses to follow-up?
• Are the results unlikely to be affected by exclusions from analysis (e.g. because of extreme values or missing values of confounders)?

Timescale bias (external)
• Is follow-up time in idealised study identical to target follow-up time?
Elicitation scales for biases

For each potential bias, assessor marks a 67% interval on the following scales (i.e. believes there is a two-thirds chance that the bias lies in this interval)

Scale for additive biases

- Bias favouring a negative relationship between variables
- Bias favouring a positive relationship between variables

Scale for proportional biases

- Bias reduces magnitude of the relationship
- Bias increases magnitude of the relationship
Example of internal bias assessments

Made independently by 6 quantitatively trained assessors

Attrition bias in Figueroa-Colon et al, 2000:
• 39 out of 47 children had follow-up measurements
• Characteristics of exclusions not mentioned

Considered an additive bias
Example of external bias assessments

Made independently by 5 subject matter specialists

Timescale bias in Figueroa-Colon et al, 2000:
• Mean follow-up time: 1.6 (SD 0.4) years
• Target follow-up time: 2 years

Considered a proportional bias
Combining additive biases for each study

67% interval for bias ≡ mean ± 1 SD

Combining across biases for each assessor:
Total bias = sum of each mean bias
Variance (total bias) = sum of variances of each bias

Pooling across assessors:
Median total bias
Median variance (total bias) “typical assessor”

Application to study results:
Adjusted estimate = study estimate − total bias
Variance (adjusted estimate) =
Variance (study estimate) + Variance (total bias)

Proportional biases can also be handled
## Unadjusted and bias-adjusted results for Figueroa-Colon et al, 2000

Correlation of baseline physical activity energy expenditure and change in % body fat

<table>
<thead>
<tr>
<th></th>
<th>Correlation (95% CI)</th>
<th>Corresponds to:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>-0.34 (-0.67 to -0.01)</td>
<td>Published study</td>
</tr>
<tr>
<td>Adjusted for internal biases</td>
<td>-0.27 (-0.73 to +0.19)</td>
<td>Idealised version of study</td>
</tr>
<tr>
<td>Adjusted for internal and external biases</td>
<td>-0.28 (-0.82 to +0.27)</td>
<td>Target setting</td>
</tr>
</tbody>
</table>
Random-effects meta-analysis of 6 studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Unadjusted</th>
<th>Adjusted for internal biases</th>
<th>Adjusted for internal and external biases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% Weight</td>
<td>% Weight</td>
<td>% Weight</td>
</tr>
<tr>
<td>DeLany</td>
<td>17.96</td>
<td>27.95</td>
<td>36.24</td>
</tr>
<tr>
<td>Fig-Colon</td>
<td>12.36</td>
<td>14.21</td>
<td>9.49</td>
</tr>
<tr>
<td>Johnson</td>
<td>17.96</td>
<td>6.39</td>
<td>6.13</td>
</tr>
<tr>
<td>Moore</td>
<td>17.24</td>
<td>8.23</td>
<td>2.22</td>
</tr>
<tr>
<td>Salbe</td>
<td>17.96</td>
<td>23.05</td>
<td>12.39</td>
</tr>
<tr>
<td>Treuth</td>
<td>16.52</td>
<td>20.17</td>
<td>33.52</td>
</tr>
<tr>
<td>Overall</td>
<td>100.00</td>
<td>100.00</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Results presented using Fisher transformed correlation scale
Unadjusted and bias-adjusted meta-analysis

Correlation of baseline physical activity energy expenditure and change in % body fat

<table>
<thead>
<tr>
<th></th>
<th>Correlation (95% CI)</th>
<th>Heterogeneity ($I^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>-0.04 (-0.22 to +0.14)</td>
<td>78%</td>
</tr>
<tr>
<td>Adjusted for</td>
<td>0.00 (-0.18 to +0.19)</td>
<td>15%</td>
</tr>
<tr>
<td>internal biases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted for</td>
<td>-0.01 (-0.18 to +0.16)</td>
<td>0%</td>
</tr>
<tr>
<td>internal and</td>
<td></td>
<td></td>
</tr>
<tr>
<td>external biases</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Comments

Adaptation of Turner *et al*, JRSS(A) 2009 to the context of observational studies

Assumptions:
- Bias categories are independent
- Biases considered additive or proportional
- Assessors are informed and sensible

Sensitivity analysis: e.g. results for each assessor

Publication bias is not addressed
Conclusions

Process has become possible by breaking down task into small components (each source of bias in each study discussed and assessed)

Results from apparently incompatible observational studies have been combined to address a specific policy question

In our example, inconsistency between studies was reduced to zero after adjusting for biases

The system for bias assessment and adjustment can be applied by others, and adapted to different contexts

Approach for handling biases

Study result

Adjusted for:

Known bias

‘Unbiased bias’

Uncertain bias