The Science of Research Synthesis: Limiting Bias and Error in Reviews

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The Science of Research Synthesis: Limiting Bias and Error in Reviews

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Society for Social Work and Research
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Agenda

- Purposes and types of research reviews
- Empirical evidence for review methods
- Evidence- and consensus-based standards for systematic reviews and meta-analysis
- Current sources of information and global partnerships
- Potential uses of research synthesis to inform policy, practice, and research
Purposes of Reviews

- Summarize existing empirical research to:
  - Take stock of the body of research
  - Identify and address knowledge gaps
  - Organize knowledge (master the information tsunami)
  - Provide directions for further research
  - Inform policy and practice

Questions

- What do we know and how do we know it?
- Possible topics include
  - Rates and trends (e.g., incidence/prevalence, differences over time/place/subgroups)
  - Correlates and causes (e.g., risk and protective factors)
  - Prevention and treatment (e.g., outcomes, impacts, cost effectiveness, comparative effectiveness)
  - Diagnosis (e.g., accuracy of various dx categories/tests)
  - Prognosis (e.g., predictively validity of categories/tests)
  - Methods and measures (e.g., reliability, validity)
Questions and Methods

- Different review questions call for
  - Different types of evidence
  - Different synthesis methods

- Evidence hierarchies do not work across questions

Research Synthesis

Combining results of multiple studies
1. Provides more compelling evidence than results of any single study
   - Single studies can have undue influence on practice & policy
   - We don't use single subject (N=1) designs to assess public opinion, shouldn't rely on single studies to answer important questions

2. Provides new opportunities to investigate
   - What works for whom under what conditions
   - Why results may vary across studies
   - Using analyses that capitalize on natural variations across studies
Building Evidence

“Science is suppose to be cumulative, but scientists only rarely accumulate evidence scientifically” (Chalmers, Hedges, & Cooper, 2002, p. 12)

Scientific methods of research synthesis are

- Available
- Rapidly advancing

The Problem: Studies Pile Up

- “What can you build with thousands of bricks?” (Lipsey, 1997)
- Many studies are conducted on the same topic
- Which one(s) do we use? How do we use them?
Types of Research Synthesis

- Reviews vary in amount of planning, transparency, and rigor
- Different approaches to research synthesis:
  - Traditional, narrative reviews (may include “vote counting”)
  - Systematic reviews (aim to minimize bias)
    - Some “systematic reviews” aren’t
  - Meta-analysis (quantitative synthesis)
  - Rapid evidence assessment (AKA rapid reviews) - hybrids

Traditional Narrative Reviews

- Convenience samples of published studies
- Narrative description of studies
- Cognitive algebra or “vote counting” to synthesize results
  - How many studies had positive, null, negative, or mixed results
  - Relies on statistical significance in primary studies
    - Counting the wrong thing. Significance depends, in part, on sample size (studies may be too small to detect meaningful effects, large studies can detect differences that are meaningless)
- Decision rules are not transparent
- Vulnerable to many sources of bias and error
Research, Reports, and Reviews: Ideal

Research, Reports, and Reviews: Reality
Empirical Evidence of Bias

- Dissemination of research results is a biased process (Song et al., 2009, 2010)
  - Selective reporting, publication, citation, selection of evidence
  - Confirms favored theories
  - Overestimates benefits and underestimates harms of favored treatments

Outcome Reporting Bias

- Reviews
- Publications
- Research reports
- Studies (all data collected)

Outcome reporting bias

Positive

Negative
Outcome Reporting Bias (ORB)

- Reporting of results is influenced by their direction and/or statistical significance
- “Cherry picking”

Evidence of ORB - 1

- Statistically significant and positive results are more likely to be
  - reported (mentioned at all)
  - fully reported (data provided)

- These reporting biases occur within studies (Chan et al., 2004a, 2004b; Chan & Altman, 2005; Dwan et al., 2008; Hahn et al., 2002; Pigott et al., 2011; Williamson et al., 2006)

- Unrelated to study or outcome “quality” (Chan et al., 2004, 2005; Pigott et al., 2011; Williamson et al., 2006)
Evidence of ORB - 2

Systematic Review of the Empirical Evidence of Study Publication Bias and Outcome Reporting Bias

Kerry Dwan1,*, Douglas G. Altman2, Juan A. Arniaiz3, Jill Bloom3, An-Wen Chan3, Eugenia Cronin4, Evelyne Decullier5, Philippa J. Easterbrook6, Erik Von Elm7,8, Carrol Gamble9, Davina Ghersi10, John P. A. Ioannidis10,11, John Simes11, Paula R. Williamson1

- Statistically significant outcomes are more likely to be reported than nonsignificant outcomes
- Odds rations 2.2 to 4.7 (Dwan et al., 2008)

Evidence of ORB - 3

Frequency and reasons for outcome reporting bias in clinical trials: interviews with trialists

R M D Smyth, research associate,12 J Kirkham, research associate,1 A Jacoby, professor of medical sociology,2 D G Altman, professor of statistics in medicine,1 C Gamble, senior lecturer,1 P R Williamson, professor of medical statistics1

- BMJ (2010)
- “The prevalence of incomplete reporting is high. Trialists seem generally unaware of the implications for the evidence base of not reporting all outcomes...”
The impact of outcome reporting bias in randomised controlled trials on a cohort of systematic reviews

Jamie J Kirkham,1 Kenny M Dwan,1 Douglas G Altman,2 Carrol Gamble,1 Susanna Dodd,1 Rebecca Smyth,3 Paula R Williamson1

- BMJ (2010)
- 19/42 (45%) of meta-analyses had substantial errors due to ORB
  - 8 (19%) became non-significant after adjusting for ORB
  - 11 (26% overestimated treatment effect by 20% or more

Publication Bias
Publication Rates

- 50% of completed studies are published (Dwan et al., 2008; Jones et al., 2013)
- Publication rates may be lower in social sciences, observational studies, and low/middle income countries
- 31% publication rate in psychology

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Total published (percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Galderisi, 1991 (26)</td>
<td>138/265 (52%)</td>
</tr>
<tr>
<td>Dicken, 1992 (27)</td>
<td>265/567 (47%)</td>
</tr>
<tr>
<td>Dickersin, 1993 (3)</td>
<td>584/108 (54%)</td>
</tr>
<tr>
<td>Salt, 1994 (1)</td>
<td>12/40 (30%)</td>
</tr>
<tr>
<td>Garey, 1997 (12)</td>
<td>38/121 (31%)</td>
</tr>
<tr>
<td>Wark, 2000 (4)</td>
<td>200/692 (29%)</td>
</tr>
<tr>
<td>Kristiansen, 1998 (13)</td>
<td>36/24 (5%)</td>
</tr>
<tr>
<td>Per, 2000 (28)</td>
<td>30/123 (24%)</td>
</tr>
<tr>
<td>Creasy, 2004 (15)</td>
<td>28/79 (36%)</td>
</tr>
<tr>
<td>Deculler, 2005 (29)</td>
<td>205/649 (32%)</td>
</tr>
<tr>
<td>Deculler, 2006 (30)</td>
<td>40/55 (73%)</td>
</tr>
<tr>
<td>Hahn, 2002 (10)</td>
<td>18/48 (38%)</td>
</tr>
<tr>
<td>Chen, 2004a (14)</td>
<td>48/185 (26%)</td>
</tr>
<tr>
<td>Chen, 2004b (13)</td>
<td>102/374 (27%)</td>
</tr>
<tr>
<td>Gurev, 2006 (15)</td>
<td>103/220 (47%)</td>
</tr>
<tr>
<td>Von Elm, 2008 (18)</td>
<td>233/431 (54%)</td>
</tr>
</tbody>
</table>

Publication Status

- Publication status is not a proxy for methodological quality (McLeon & Weitz, 2004; Moyer et al., 2010)
- Should never be used as an inclusion criteria in reviews (Chandler et al., 2013; Higgins & Green, 2011; Institute of Medicine, 2011)
Evidence of Publication Bias

- Studies with statistically significant, positive results are 2-3 times more likely to be published than similar studies with null or negative results (Song et al., 2009, 2010)
  - likelihood of publication is related to direction and significance of results—net of influence of other variables
  - (Begg, 1994; Cooper et al., 1997; Coursol & Wagner, 1986; Dickersin, 1987, 2005; Dwan et al., 2008; Easterbrook et al., 1991; Hopewell et al., 2007, 2009; Scherer et al., 2007; Song et al., 2000, 2009, 2010; Torgerson, 2006; Vecchi et al., 2009)

Sources of Publication Bias

- Sources of publication bias are complex
  - Investigators
    - don’t think null/negative results are worthwhile and/or don’t expect these results to be accepted/published
    - are less likely to submit null results for conference presentations (Song et al., 2009) and publication (Dickersin, 2005; Song et al., 2009)
  - Peer reviewers & editors may be less likely to accept/publish null results? (Mahoney, 1977 vs. Song et al., 2009)

- “Publication bias appears to occur early, mainly before the presentation of findings at conferences or submission of manuscripts to journals” (Song et al., 2009).
Evidence of Effects of Publication Bias

- Publication bias appears to inflate overall effect size estimates in some meta-analyses (Lipsey & Wilson, 1993; Sutton et al., 2000)

- A recent example...

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**Efficacy of cognitive–behavioural therapy and other psychological treatments for adult depression: meta-analytic study of publication bias**

Pim Cuijpers, Filip Smits, Ernst Bohlmeijer, Steven D. Hollon and Gerhard Andersson

**Background**
It is not clear whether the effects of cognitive–behavioural therapy and other psychotherapies have been overestimated because of publication bias.

**Aims**
To examine indicators of publication bias in randomised controlled trials of psychotherapy for adult depression.

**Method**
We examined effect sizes of 117 trials with 175 comparisons between psychotherapy and control conditions. As indicators of publication bias we examined funnel plots, calculated adjusted effect sizes after publication had been taken into account using Ornel & Twose’s procedure, and tested the symmetry of the funnel plots using the Egger & MacMundar rank correlation test and Egger’s test.

**Results**
The mean effect size was 0.67, which was reduced after adjustment for publication bias to 0.40 (9 imputed studies). Both Egger & MacMundar’s test and Egger’s test were highly significant (p < 0.05).

**Conclusions**
The effects of psychotherapy for adult depression seem to be overestimated considerably because of publication bias.

**Declaration of Interest**
None.
Dissemination Bias

- Studies with significant results are
  - Published faster (Hopewell et al., 2001)
  - Cited and reprinted more often (Egger & Smith)
- Easier to locate (esp. in English)

Reporting, Publication, Dissemination

Reporting, publication, dissemination biases
- Are ubiquitous
- Are cumulative
- Inflate effect size estimates
- (Altman, 2006; Hopewell et al., 2005, 2007, 2009; Song et al., 2009)
Biases in Haphazard Reviews

Haphazard reviews → Reviews → Publications → Research reports → Studies (all data collected) → Negative → Positive
Bias and Error in the Review Process

- Can occur at several stages, including:
  - Searching for studies
  - Selection of studies
  - Data extraction
  - Data analysis
  - Synthesis of results across studies

- Some examples...

Searching

- Bibliographic databases
  - Largely limited to published studies
  - Search results are likely to be affected by publication bias
Selection Bias

- Trivial properties of studies or reports affect recall and evaluation of information
- Memorable titles (Bushman & Wells, 2001)

Data Extraction

- Extracting data from studies is difficult
- Errors are common (Gøtzsche et al., 2007)
- Initial agreement is low (Tendal et al., 2009)
- Experimental evidence shows that duplicate extraction reduces errors (Buscemi et al., 2006)
Synthesis

- Narrative synthesis is
  - Unduly influenced by trivial properties of studies (Bushman & Wells, 2001)
  - Less accurate than meta-analysis (Bushman & Wells, 2001; Cooper & Rosenthal, 1980; Mann, 1994)
- Vote counting is not a good alternative
  - Does not consider sample size or heterogeneity
  - E.g., 10 studies: 6 positive, 2 null, 2 negative
    - Overall results depend on N and SE
    - Overall effect could be positive, null, or negative

Traditional Reviews and Well-Meaning Experts can be Misleading

- Scholars are human
- Rely on “natural” methods to filter and synthesize data
- The human brain is
  - Good at detecting patterns, maintaining homeostasis, defending territory
  - Bad at complex math, revising beliefs (Runciman, 2007)
- Research synthesis is too complex for informal methods, “cognitive algebra”
- Vulnerable to many sources of bias.
Summary

- Bias and error are common at every stage
  - Reporting
  - Publication
  - Dissemination
  - Reviews

Research, Reports, and Reviews: Reality

- Studies (all data collected)
- Research reports
- Publications
- Reviews

Negative Positive
A concrete example
One study published in 1987
  - How did investigators make use of data?
  - How did reviewers make use of data?
Littell, 2008

Parent Training vs Multisystemic Therapy (Brunk et al., 1987)

- 43 families of abused/neglected children randomly assigned to
- Parent training (PT) groups or Multisystemic Therapy (MST)
- 33 / 43 families completed treatment and provided data on outcomes immediately after treatment
- 30 outcomes (scales and subscales)
Results Obtained (Brunk et al., 1987)

Parent Training vs Multisystemic Therapy

- Data provided on
- All (7) statistically significant results
- 12/22 non-significant results
- Outcome reporting bias
Investigators’ Summary

- Both groups showed decreased psychiatric symptoms, reduced stress, and reduced severity of identified problems.
- MST was more effective than PT at restructuring parent-child relations.
- PT was more effective than MST at reducing identified social problems.

Reviewers’ Summaries

- Analysis of 14 published reviews of Brunk et al. (Littell, 2008)
- Most (12/14) reviewers used a single phrase to characterize results of this study, highlighting advantages of one approach (MST)
- Ignoring valuable information on relative advantages, disadvantages, and equivalent results of different approaches
Methods Matter

- Haphazard reviews may be hazardous to public health and wellbeing
  - Over-estimate positive effects of interventions
  - Under-estimate or ignore potential harmful effects
  - Minimize or ignore viable alternatives
  - Promote ineffective or potentially harmful interventions

Systematic Reviews

- Treat review process as a form of survey research and follows basic steps in research process
  - Research reports, rather than people, are surveyed
  - Each research report is “interviewed” by a coder who codes information and quantitative findings
- Aim to sum up the best available evidence in a way that minimizes errors and biases
- Use explicit, replicable research methods to identify relevant studies and objective techniques to analyze those studies
  - Develop and follow pre-determined plan (protocol)
  - Secondary analysis of existing data
Systematic Reviews (SRs)

Steps to reduce bias and error:
1. Set explicit inclusion/exclusion criteria
2. Develop and document strategies for locating all relevant studies (regardless of publication status)
3. Inter-rater agreement (reliability) on key decisions, data extraction, coding
4. Formal study quality assessment (risk of bias)
5. Meta-analysis (when possible) to synthesize results across studies

1. Explicit Criteria

- Protocol (detailed plans) for reviews made public
  - Check on review bias
- Study inclusion/exclusion criteria
  - PICOS: Populations, Interventions, Comparisons, Outcomes, Study designs
- Search strategy plans are explicit and replicable
- Data extraction forms are public
- Plans for analysis and synthesis are explicit
2. Comprehensive Search

- To reduce publication bias in reviews
- Aim to get all relevant studies, not just published studies
- Broad range of sources in addition to electronic databases
  - Personal contacts, listservs
  - Websites, research registries, research centers, government and professional organizations
  - Conference abstracts
  - Reference lists

3. Reliable Data Extraction and Coding

- Reduce bias and error in data collection and analysis
- Double screening, selection, extraction, and coding
- Inter-rater agreement (disagreements resolved with 3rd person)
- Cohen’s Kappa
- May not be possible to double code everything, identify key item and decisions -- a priori
4. Formal Risk of Bias Assessment

Identify potential sources of bias in studies:

**Selection bias** - Systematic differences between groups at baseline

**Performance bias** - Something other than the intervention affects groups differently

**Attrition bias** - Participant loss affects initial group comparability

**Detection bias** - Method of outcome assessment affects group comparisons

**Reporting bias** - Selective reporting of outcomes

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**Risk of Bias (ROB) Tables and Graphs**

Liu, Jian, & Mao, 2013, Figure 5: (a) ROB table (left): ROB ratings for each included study; (b) ROB graph (above): summary of ROB ratings (percentage of all included studies).
5. Reliable Synthesis

Using appropriate techniques, meta-analysis if possible
- Meta-analysis is possible with 2 or more studies that report quantitative results

- Sensitivity analysis to check on effects of decisions made during the review
  - Especially departures from the protocol
  - Run synthesis under different assumptions

Meta-Analysis (MA)

Set of statistical procedures used to assess
- Averages across studies
- Variations across studies
- Potential sources of variation (moderators)
- Risk of bias (e.g., tests for publication & small sample bias)
- Systematic reviews don’t always include meta-analysis
  - Might include narrative synthesis (or no synthesis)
  - Can include multiple meta-analyses

- Meta-analyses are not always based on systematic reviews
  - Many use convenience sample of published studies
  - Vulnerable to publication and dissemination biases

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Some “Systematic Reviews” Aren’t

- Evidence-based standards for SRs & MA
  - Based on methodological research (Cochrane Library)

- Standards for conduct of SRs
  - Developed by Cochrane and Campbell Collaborations (Higgins & Green, 2011; IOM, 2011; MECIR, 2013)

- Standards for reporting SRs & MA
  - PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses; Moher et al., 2009)

- Standards not followed by US Evidence-based Practice Centers, most peer-reviewed journals, etc.
Minimum Standards Important

- Reviews should take reporting and publication biases into account
  - Include extensive search for grey literature
  - Assess risk of bias (in original studies and in review)
    - Many methods available for assessing potential effects of reporting and publication biases in reviews (Dwan et al., 2010; Rothstein, Sutton, Bornstein, 2005; Moreno et al., 2009)
- Reviews should use adequate synthesis methods
  - Narrative reviews are unreliable
  - Vote counting is inadequate
  - Meta-analysis is the best available method for quantitative data
    - And it’s not hard to do

Evidence-based Standards for Reviews

- Cochrane MECIR standards (Chandler et al., 2013)
  - [http://www.editorial-unit.cochrane.org/mecir](http://www.editorial-unit.cochrane.org/mecir)
- Cochrane Handbook (Higgins & Green, 2011)
  - [http://handbook.cochrane.org/](http://handbook.cochrane.org/)
- Institute of Medicine (IOM, 2011)
- PRISMA (Moher et al., 2009)
Using Evidence in Context

Policy and practice are informed by
- Many types of evidence (qualitative, quantitative, anecdotal) on
- Many topics

Evidence isn’t enough
- Need to consider values, preferences, resources, ethics, legal constraints, etc.

Adapted from: Gibbs (2003), Davies (2004)

Thank You

Questions/Comments?

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  [www.cochranecollaboration.org](http://www.cochranecollaboration.org)
- Campbell Collaboration:  
  [www.campbellcollaboration.org](http://www.campbellcollaboration.org)
- David B. Wilson’s effect size calculator:  
  [http://www.campbellcollaboration.org/resources/effect_size_input.php](http://www.campbellcollaboration.org/resources/effect_size_input.php)

Books

- Borenstein et al. (2009). Introduction to meta-analysis.