Publication Bias:

- Is It Also Present In The Secondary Literature?

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AUTHORS

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Publication Bias

- Tendency of investigators, reviewers, and editors to submit or accept manuscripts for publication based on the direction or strength of the study findings.

- In particular, bias associated with the direction of the findings being positive (finding a significant difference between two or more of the groups studied)
Background

- Good evidence of publication bias in the primary literature
- Is there publication bias in translation of evidence from primary to secondary literature?
- We chose to look at RCT`s of therapy
- Primary literature - Medline
- Secondary literature - ACP Journal Club
Methods

- Cross sectional survey of RCT’s of therapy between 1994 and 2002 in English in Medline
- Summaries of therapy trials in ACP Journal Club between same dates
ACP Journal Club

- Search engine was Ovid
- ACP Journal Club Database was searched for term ‘trial’
- All articles with ‘review’ in title were removed
- Limit to therapeutics
- Limit to August 1994 to October 2002
Medline

- Search engine Pubmed
- using Mesh term ‘therapeutics’
- Limits of RCT, human, Medline db,
- Abstract available, English, August 1994 to October 2002
- Random selection of 1000 taken
METHODS

Inclusion criteria:

- Single RCT of Therapy
- Had to report results
- Had to be a direct comparison between treatment and control groups
Data abstracted

- Trial result negative or positive
- Trial trying to find a difference or equivalence
- Sample size
- Blinding
- Multi-centered or not
- “No active treatment control” or not
- Pharmaceutical product or not
- Medical specialty – up to 3 per trial
- If positive, whether it favoured newer treatment
- If journal was on ACPJC selection list
Statistical methods

- p < .05 (2 tailed) considered statistically significant
- Differences in proportions tested for significance by Chi-square
- Continuous variable (sample size) was not normally distributed - tested by Mann-Whitney U
- Chi Square for trend calculated using EpiInfo 6
- All variables significantly associated with selection by ACP journal club entered a multivariate logistic regression to determine if selection for + outcome remained significant when rest were controlled
Results

- Medline search yielded 30,250 abstracts. 1000 were randomly selected, 831 met inclusion criteria, 206 (25%) of which were on list of journals from which ACPJC selects.

- ACPJC yielded 882 abstracts, 823 met inclusion criteria, rest were reviews.
Blinding of trials summarized in ACP Journal Club or catalogued in Medline p<0.01

- ACP Journal Club n=823
- Medline n=831
Health Field of trials summarized in ACP Journal Club or catalogued in Medline

- CVD p<.001
- Allergy p=.13
- Endocrine p=.13
- GI p=.02
- Oncol p<.001
- Renal p<.001
- Pulmonary p=.81
- ID p<.001
- Neuro p=.002
- Ortho p=.15
- Peds p=.34
- Psych p=.27
- Women p<.001

ACP Journal Club n=823
Medline n=831
Characteristics of trials summarized in ACP Journal Club or catalogued in Medline

Multicentred $p < 0.001$
No active Rx control $p < 0.001$
Pharmaceutical product $p = 0.90$
Favours new treatment $p = 0.04$

ACP Journal Club $n = 823$
Medline $n = 831$
Outcome of trials summarized in ACP Journal Club or catalogued in Medline $p<0.001$

ACP Journal Club $n=823$
Medline $n=831$
Multivariate logistic regression analysis of potential determinants of selection of Randomized Controlled Trials by ACP Journal Club n=1654

<table>
<thead>
<tr>
<th>Determinant</th>
<th>Odds Ratio</th>
<th>95% Confidence interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Larger sample size</td>
<td>1.001</td>
<td>1.001-1.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No active treatment control</td>
<td>1.327</td>
<td>1.040-1.692</td>
<td>0.02</td>
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<td>Multi-centered</td>
<td>4.798</td>
<td>3.690-6.237</td>
<td>&lt;.001</td>
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<td>Positive, aim difference compared to negative, aim difference</td>
<td>2.806</td>
<td>2.002-3.933</td>
<td>&lt;.001</td>
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<tr>
<td>Negative, aim equivalence compared to negative, aim difference</td>
<td>2.098</td>
<td>1.242-3.544</td>
<td>0.01</td>
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<td>Endocrinology</td>
<td>0.490</td>
<td>0.316-0.761</td>
<td>0.001</td>
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<tr>
<td>GI tract disease</td>
<td>1.642</td>
<td>1.110-2.431</td>
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<tr>
<td>Hematology/oncology</td>
<td>0.252</td>
<td>0.167-0.380</td>
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<tr>
<td>Renal/Male urogenital disease</td>
<td>0.262</td>
<td>0.139-0.491</td>
<td>&lt;.001</td>
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<tr>
<td>Women’s health</td>
<td>0.380</td>
<td>0.230-0.628</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>
Results

- Distribution of positive and negative trials in journals from which ACPJC selects similar to medline (p=.74) and different from ACPJC (p=.00)
- Over time there was no change in Medline variables but ACPJC gradually increased quality of trials selected
- Drug trials were more likely to be multi-centered, blinded, and larger (P<0.01) but not more likely to be +ve or favour new treatment
Discussion

- Publication bias **DOES** exist in translation of therapeutic evidence from primary to secondary literature (at least for ACPJC).
- Could lead to overestimation of effectiveness of therapeutic interventions.
- Finding is not due to the journals ACPJC selects from but the articles it chooses to select from those journals.
Discussion

- Quality of Medline trials is not improving over time
- Many abstracts in Medline are of poor quality
- Drug trials were of higher quality & did not show higher rate of +ve outcomes or favor new treatment (surprise!)
Limitations

- Only ACPJC was studied
- Only trials published in English were studied—appropriate for ACPJC
- A few trials would appear in both databases
- Some -ve trials are -ve because they lack power. ACPJC is correct to not select these causing bias against negative trials. This is partially controlled in logistic regression by controlling for sample size
Acknowledgements

- I would like to thank my co-authors, who are in the audience today:
  - Dr. Glenn Griffin
  - Dr. Thomas Carter
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