Systematic reviews of observational data

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“Epidemiologist know a lot about the correct way to conduct a research study but less about how to review and synthesize data from multiple studies and this, I suggest, is a principal source of the public’s confusion when faced with a new result from an epidemiological study”

Bracken MB. IJE 2001:954
What is a systematic review?

A review:

- clearly formulated question
- uses systematic and explicit methods to identify and collect relevant research
- uses systematic and explicit methods to select, critically appraise and analyse relevant research included.
What is a systematic review?

Statistical methods (meta-analysis) may or may not be used to summarise the results of the included studies.
How much work is a systematic review?

~ 1139 hours

~ 30 person-weeks of full-time work

- 588 for protocol, searching and retrieval
- 144 for statistical analysis
- 206 for report writing
- 201 for administration

Source: Allen IE. JAMA, 1999;282:634
What are observational studies?

✓ Data from existing database
✓ Cross-sectional study
✓ Case series
✓ Case-control study
✓ Cohort study
Observational studies
Why do we need systematic reviews of observational studies?

- Test aetiological hypothesis
- Evaluation of interventions designed to prevent rare outcomes
- Evaluation if outcomes of interest are far in the future
- Evaluation of effectiveness in a community
## MAOS are common

<table>
<thead>
<tr>
<th>Type of article</th>
<th>Articles (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meta-analysis of:</td>
<td></td>
</tr>
<tr>
<td>Controlled trials</td>
<td>34</td>
</tr>
<tr>
<td>Observational studies</td>
<td>25</td>
</tr>
<tr>
<td>Methodological article</td>
<td>15</td>
</tr>
<tr>
<td>Tradicional review</td>
<td>15</td>
</tr>
<tr>
<td>Other</td>
<td>11</td>
</tr>
</tbody>
</table>

RCT

(Lack of precision)

Meta-analysis

More reliable estimates
Observational studies
(Confounding, bias)

Meta-analysis

More reliable estimates????
Confounding factors

Smoking → Suicide

Social/mental states
Confounding factors

Coffee consumption → Risk of myocardial infarction

Smoking
Helicobacter pylori

Coronary heart disease

1122 cases

Response rate: 60%

1122 controls

Response rate: 20%

The protective effect of beta-carotene that wasn’t

**Cohorts**
- Male health workers
- Social insurance, men
- Social insurance, women
- Male chemical workers
- Hyperlipidaemic men
- Nursing home residents

**Trials**
- Male smokers
- Skin cancer patients
- (Ex)-smokers, asbestos workers
- Male physicians
There are examples of observational studies producing similar results of those from RCT.

But observational studies will always have to deal with bias and confounding because the intervention was deliberately chosen and not randomly allocated.
<table>
<thead>
<tr>
<th>Treatment Evaluated</th>
<th>Outcome</th>
<th>OR and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nifedipine vs. control in patients with CAD*</td>
<td>Mortality</td>
<td>0.10 First treatment better</td>
</tr>
<tr>
<td>Observational (30–60 mg) Randomized, controlled (30–50 mg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CABG vs. PTCA in diabetic patients*</td>
<td>Mortality</td>
<td></td>
</tr>
<tr>
<td>Observational Randomized, controlled</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CABG vs. PTCA in patients at high risk*</td>
<td>Mortality</td>
<td></td>
</tr>
<tr>
<td>Observational Randomized, controlled</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CABG vs. PTCA in patients at low risk*</td>
<td>Mortality</td>
<td></td>
</tr>
<tr>
<td>Observational Randomized, controlled</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CABG vs. medical treatment in CASS patients</td>
<td>Mortality</td>
<td></td>
</tr>
<tr>
<td>Observational Randomized, controlled</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CABG vs. medical treatment in Duke study patients†</td>
<td>Mortality</td>
<td></td>
</tr>
<tr>
<td>Observational Randomized, controlled</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta-blockers vs. control†</td>
<td>Mortality</td>
<td></td>
</tr>
<tr>
<td>Observational Randomized, controlled</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 1. Results of Observational Studies and Randomized Clinical Trials.
Concato et al.,
NEJM, 2000;342:1887-92

- Bacille Calmette–Guérin vaccine and tuberculosis
- Mammography and mortality from breast cancer
- Cholesterol levels and death due to trauma
- Treatment of hypertension and stroke
- Treatment of hypertension and coronary heart disease
This does not mean to return to narrative reviews
Benefits of MAOS:

- Systematic and explicit rules
- Statistical power
- Insight into variable interaction
- Detection of discrepancies
- Deepness into heterogeneity
- Identification of gaps in knowledge
Reporting of background should include:

1. Problem definition, hypothesis statement
2. Description of study outcome(s)
3. Type of exposure or intervention used
4. Type of study designs used
5. Study population
Reporting of search should include:

6 Qualifications of researchers
7 Search strategy including time period
8 Effort to include all available studies
9 Databases and registries searched
10 Searching software used
11 Use of hand searching
12 List of citations located and those excluded, including justification
13 Methods of addressing articles not published in English
14 Methods of handling abstracts and unpublished studies
15 Descriptions of any contact with authors
Reporting of methods should include:

16. Description of relevance/appropriateness of papers assembled for assessing the hypothesis to be tested

17. Rational for the selection and coding of data

18. Documentation about how data were classified and coded

19. Assessment of confounding

20. Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results

21. Assessment of heterogeneity

22. Description of statistical methods in sufficient detail to be replicated

23. Provision of appropriate tables and graphics
Reporting of results should include:

24 Graphic summarizing individual study estimates and overall estimate

25 Table giving descriptive information for each study included

26 Results of sensitivity testing (e.g. subgroup analysis)

27 Indication of statistical uncertainty of findings
Reporting of discussion should include:

28 Quantitative assessment of bias

29 Justification for exclusion

30 Assessment of quality of included studies
Reporting of conclusions should include:

31 Consideration of alternative explanations for observed results

32 Generalization of the conclusions

33 Guidelines for future research

34 Disclosure of funding source
Quality of reviews in Epidemiology
Breslow R. AJPH, 1998;88:475-7

All 1995 issues of 7 widely read epidemiology journals were searched for reviews

29 reviews were found
### Reviews following quality guidelines

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Yes</th>
<th>Unable to determine</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Search methods stated</td>
<td>6 (21)</td>
<td>1 (3)</td>
<td>22 (76)</td>
</tr>
<tr>
<td>Inclusion criteria reported</td>
<td>5 (17)</td>
<td>4 (14)</td>
<td>20 (69)</td>
</tr>
<tr>
<td>Bias in selecting studies avoided</td>
<td>3 (10)</td>
<td>26 (90)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Criteria for assessing validity reported</td>
<td>2 (7)</td>
<td>15 (52)</td>
<td>12 (41)</td>
</tr>
<tr>
<td>Methods for combining findings reported</td>
<td>10 (34)</td>
<td>6 (21)</td>
<td>13 (45)</td>
</tr>
<tr>
<td>Conclusions supported by data</td>
<td>24 (83)</td>
<td>4 (14)</td>
<td>1 (3)</td>
</tr>
</tbody>
</table>
Search restriction: General medical journal, 2001

<table>
<thead>
<tr>
<th>Search Procedure</th>
<th>19 meta-analyses</th>
<th>13 systematic reviews</th>
</tr>
</thead>
<tbody>
<tr>
<td>Numerous Databases Searched (versus just MEDLINE)</td>
<td>13 (68%)</td>
<td>6 (46%)</td>
</tr>
<tr>
<td>Additional Searches Conducted (e.g., manual search of reference lists or textbooks)</td>
<td>17 (89%)</td>
<td>10 (77%)</td>
</tr>
<tr>
<td>Gray Literature Searched (e.g., manual search of conference or dissertation abstracts)</td>
<td>5 (26%)</td>
<td>4 (31%)</td>
</tr>
<tr>
<td>Contacted Experts to Find Unpublished Data</td>
<td>7 (37%)</td>
<td>2 (15%)</td>
</tr>
<tr>
<td>Cochrane Databases Searched</td>
<td>8 (42%)</td>
<td>4 (31%)</td>
</tr>
<tr>
<td>All Methods Employed</td>
<td>4 (21%)</td>
<td>1 (8%)</td>
</tr>
</tbody>
</table>

Source: Becker B, Morton S (see http://www.msri.org/calendar/talks/TalkInfo/1268/show_talk)
### Search restriction: General medical journal, 2001

<table>
<thead>
<tr>
<th>Language Restriction</th>
<th>19 meta-analyses</th>
<th>13 systematic reviews</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>6 (32%)</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>English plus other lang.</td>
<td>2 (11%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>English only</td>
<td>7 (37%)</td>
<td>7 (54%)</td>
</tr>
<tr>
<td>Unclear</td>
<td>4 (21%)</td>
<td>5 (38%)</td>
</tr>
<tr>
<td>Attempted to include unpublished studies</td>
<td>7 (37%)</td>
<td>5 (38%)</td>
</tr>
</tbody>
</table>

Source: Becker B, Morton S (see http://www.msri.org/calendar/talks/TalkInfo/1268/show_talk)
Other citations:


Summary

- SR and MA of observational studies are as common as reviews of RCT
- Confounding and selection bias often distort the findings
- Danger in producing very precise but spurious results
- More is gained by examining heterogeneity
WHO Systematic review of incidence/prevalence of maternal mortality and morbidity 1997-2002
Objectives

- To provide a comprehensive, standardised and reliable tabulation of available data on maternal morbidity
- To provide up-to-date data for future maternal mortality estimates
- To provide case-fatality rates
### CHARACTERISTICS OF THE STUDY

3. Study design
   - (1) Census
   - (2) Cross-sectional
   - (3) Cohort/longitudinal
   - (4) Controlled trial
   - (5) Incidence/Prevalence survey
   - (6) Unknown
   - (7) Other, specify

4. Sampling
   - (1) Random sample
     - 4a. Specify the method of randomization:
       [WHO CODE]
   - (2) Non-random sample
     - 4b. Specify the method of sampling:
       [WHO CODE]
   - (3) Total population (i.e. census)
   - (4) Unknown

---

### WHO systematic review

5. Data source
   - (1) Vital statistics/census
   - (2) Medical record
   - (3) Special survey/interview
   - (4) Multiple sources
   - (5) Clinical data collected for the study
   - (6) Other, specify

6. Lowest unit of data source
   - (1) Cluster
     - 6a. Number of clusters
   - (2) Individual
   - (3) Other, specify
WHO systematic review

9. Population studied
   (1) Urban
   (2) Rural
   (3) Mixed
   (4) Unknown

10. Description of the characteristics of the population studied (e.g. socio-economic status, ethnic group, age group, etc.)
## WHO systematic review

### MATERNAL MORTALITY (cont.)

26a. Cause distribution of maternal mortality

<table>
<thead>
<tr>
<th>Condition</th>
<th>(i) WHO code</th>
<th>(ii) No. of deaths</th>
<th>(iii) Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>26a.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>26a.2)</td>
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<td></td>
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<td>26a.3)</td>
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<td></td>
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<td>26a.4)</td>
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<tr>
<td>26a.5)</td>
<td></td>
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</tr>
<tr>
<td>26a.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>26a.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
32. **Infections**

32a) Condition

32b) Does the study include a definition?

32c) If definition is included, please specify:

32d) Does the study explain the method of assessment of the infection?

32e) If method of assessment is explained, please specify:
### MATERNAL MORTALITY

**25a. Maternal mortality estimates**

- **i) Year**
  - From: 
  - To: 

- **ii) Age group**
  - From: 
  - To: 

- **iii) No. of deaths**
  - 

<table>
<thead>
<tr>
<th>Denominator</th>
<th>1. Live births</th>
<th>2. Pregnancies</th>
<th>3. Deliveries</th>
</tr>
</thead>
<tbody>
<tr>
<td>iv)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MM Rate</th>
<th>Cl (95%)</th>
<th>Cl (95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>vi)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MM Ratio</th>
<th>Cl (95%)</th>
<th>Cl (95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>viii)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**WHO systematic review**
Citations identified (Titles and/or abstracts) 64 586

Full-text evaluation (Articles and reports) 4626

Excluded 59 960

Reasons for exclusion
• 92% – no relevant data
• 6% – sample size < 200
• 2% – other reasons

Excluded 1988

Included 2443

In process 195

Data processing complete 2204

Reasons for exclusion
• 57% – no relevant data
• 15% – sample size < 200
• 11% – no dates reported
• 17% – other reasons
Regional distribution (n=2204)

- Australia/NZ: 32%
- North America: 32%
- South America: 26%
- Central America: 22%
- Caribbean: 17%
- Northern Europe: 13%
- Western Europe: 10%
- Southern Europe: 9%
- Eastern Europe: 9%
- South-central Asia: 9%
- Western Asia: 8%
- Eastern Asia: 8%
- South-eastern Asia: 5%
- Western Africa: 5%
- Eastern Africa: 5%
- Northern Africa: 3%
- Southern Africa: 3%
- Middle Africa: 3%
Development status (n=2204)

- Industrialised countries: 1085
- Less developed countries: 854
- Least developed countries: 228
- Multicountry: 37
## Results: methodological quality of reported data

<table>
<thead>
<tr>
<th></th>
<th>Morbidity (n = 3215)</th>
<th>Mortality (n = 335)</th>
<th>Total (n = 3550)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>103</td>
<td>8</td>
<td>111</td>
</tr>
<tr>
<td>Medium</td>
<td>1670</td>
<td>250</td>
<td>1920</td>
</tr>
<tr>
<td>Low</td>
<td>1442</td>
<td>77</td>
<td>1519</td>
</tr>
</tbody>
</table>
Reported morbidities (n=3215)

- Hypertensive disorders of pregnancy (16.3%)
- Haemorrhage (11.1%)
  - postpartum - 2.7%
  - antepartum / intrapartum - 2.2%
- Placenta praevia - 1.8%
- Abdominal pregnancy - 2.6%
- Other haemorrhage / unspecified - 1.8%
- Abortion (10.7%)
- Preterm delivery (8.3%)
- Stillbirth (6.3%)
- Diabetes in pregnancy (4.4%)
- Anaemia in pregnancy (4.3%)
- Ectopic pregnancy (3.0%)
- Perineal tears (2.6%)
- PROM (2.6%)
- Uterine rupture (2.1%)
- Postpartum sepsis (1.6%)
- Depression (1.9%)
- Obstructed labour (1.8%)
"And it was so typically brilliant of you to have invited an epidemiologist."

William Hamilton, New Yorker, 2001