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 \rightarrow \text{Social/mental states} \rightarrow \text{Suicide}
Confounding factors

Coffee consumption

Smoking

Risk of myocardial infarction
The protective effect of beta-carotene

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></td>
</tr>
<tr>
<td>Observational (30–60 mg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomized, controlled (30–60 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</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomized, controlled</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta-blockers vs. control†</td>
<td>Mortality</td>
<td></td>
</tr>
<tr>
<td>Observational</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomized, controlled</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 1. Results of Observational Studies and Randomized Controlled Studies.
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

Relative Risk or Odds Ratio
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>
<tr>
<td>Search Procedure</td>
<td>19 meta-analyses</td>
<td>13 systematic reviews</td>
<td></td>
</tr>
<tr>
<td>-------------------------------------------------------</td>
<td>------------------</td>
<td>-----------------------</td>
<td></td>
</tr>
<tr>
<td>Numerous Databases Searched (versus just MEDLINE)</td>
<td>13 (68%)</td>
<td>6 (46%)</td>
<td></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>
<td></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>
<td></td>
</tr>
<tr>
<td>Contacted Experts to Find Unpublished Data</td>
<td>7 (37%)</td>
<td>2 (15%)</td>
<td></td>
</tr>
<tr>
<td>Cochrane Databases Searched</td>
<td>8 (42%)</td>
<td>4 (31%)</td>
<td></td>
</tr>
<tr>
<td>All Methods Employed</td>
<td>4 (21%)</td>
<td>1 (8%)</td>
<td></td>
</tr>
</tbody>
</table>

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

Electronic search

• Electronic databases (Medline, Embase, Popline, Cinahl, SocioFile, LILACS, CAB, Econlit, Biosis, PAIS)
• WHO on-line regional databases
• Internet searches (Google, web of science…)
Search strategy

Other searches

- Experts active in the field
- WHO regional offices
- Hand searching
- References lists
- Circulating documents
### 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: ________________
   - (2) Non-random sample
     - 4b. Specify the method of sampling: ________________
   - (3) Total population (i.e. census)
   - (4) Unknown

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

<table>
<thead>
<tr>
<th>9. Population studied</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Urban</td>
</tr>
<tr>
<td>(2) Rural</td>
</tr>
<tr>
<td>(3) Mixed</td>
</tr>
<tr>
<td>(4) Unknown</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>10. Description of the characteristics of the population studied (e.g. socio-economic status, ethnic group, age group, etc.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>___________________________________________________________________________________________________________________</td>
</tr>
</tbody>
</table>
### 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>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>26a.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>26a.4)</td>
<td></td>
<td></td>
<td></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>
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</tr>
<tr>
<td>26a.7)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
### 32. Infections

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>32a) Condition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>32b) Does the study include a definition?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>32c) If definition is included, please specify:</td>
<td></td>
<td></td>
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<tr>
<td></td>
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</tr>
<tr>
<td>32d) Does the study explain the method of assessment of the infection?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>32e) If method of assessment is explained, please specify:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Maternal Mortality

25a. Maternal mortality estimates

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>i) Year</td>
<td>From</td>
<td>To</td>
</tr>
<tr>
<td>ii) Age group</td>
<td>From</td>
<td>To</td>
</tr>
<tr>
<td>iii) No. of deaths</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Denominator</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>iv)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>vi) MM Rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>vii) CI (95%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>viii) MM Ratio</th>
<th></th>
<th>ix) CI (95%)</th>
<th></th>
</tr>
</thead>
</table>

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

Excluded 59,960

Full-text evaluation (Articles and reports) 4,626

Reasons for exclusion
• 57% – no relevant data
• 15% – sample size < 200
• 11% – no dates reported
• 17% – other reasons

Excluded 1,988
Included 2,443
In process 195

Data processing complete 2,204
Regional distribution (n=2204)

- Australia/NZ: 32%
- North America: 26%
- South America: 22%
- Central America: 17%
- Caribbean: 3%
- Northern Europe: 32%
- Western Europe: 26%
- Southern Europe: 22%
- Eastern Europe: 17%
- South-central Asia: 3%
- Western Asia: 32%
- Eastern Asia: 26%
- South-eastern Asia: 22%
- Western Africa: 17%
- Eastern Africa: 3%
- Northern Africa: 32%
- Southern Africa: 26%
- 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%)
  - postpartum - 2.7%
  - antepartum / intrapartum - 2.2%
  - placenta praevia - 1.8%
  - abruptio placenta - 2.6%
  - other haemorrhage / unspecified - 1.8%
- Haemorrhage (11.1%)
- 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%)

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