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

RCT

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

Type of article	Articles (n)
Meta-analysis of:	
Controlled trials	34
Observational studies	25
Methodological article	15
Tradicional review	15
Other	11

Source: Egger M. Systematic reviews in Health Care. Meta-analysis in context. BMJ Books. 2001

RCT

(Lack of precision)

Meta-analysis

More reliable estimates

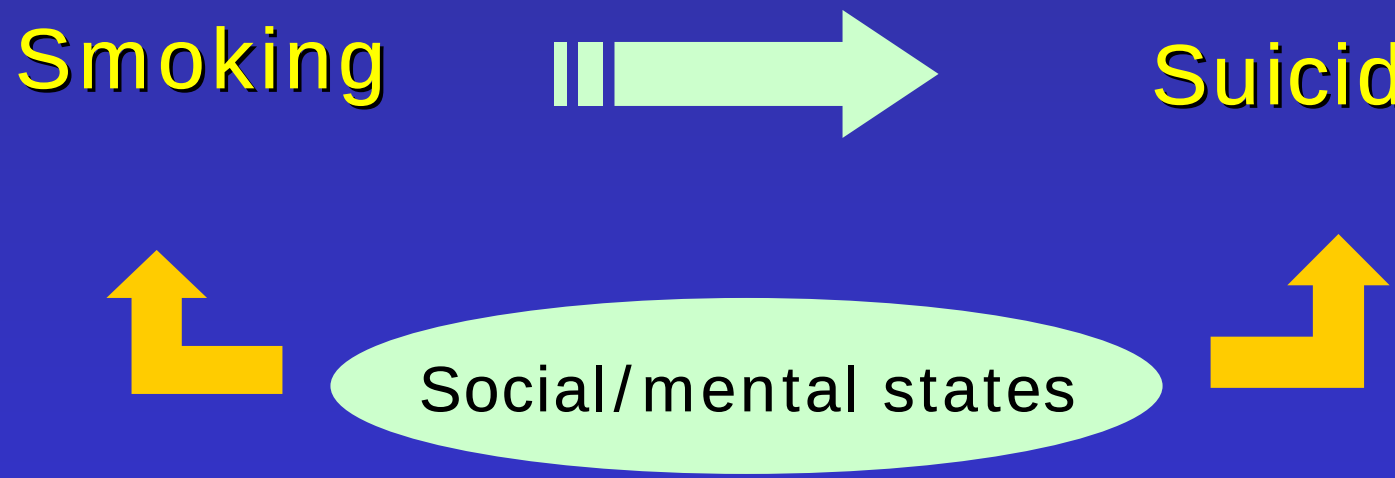
Observational studies

(Confounding, bias)

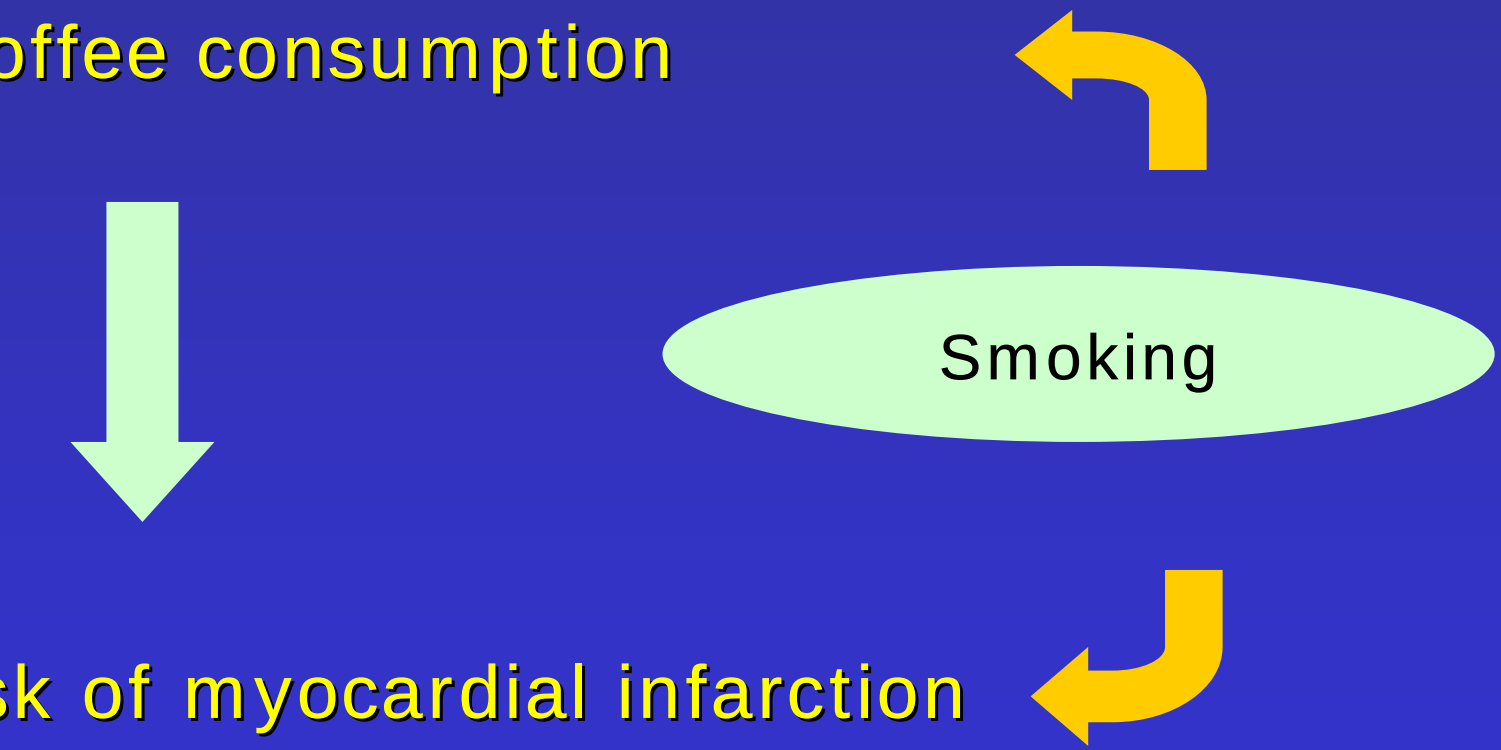
Meta-analysis

More reliable estimates????

Confounding factors



Confounding factors



Helicobacter pylori

↕

Coronary heart disease

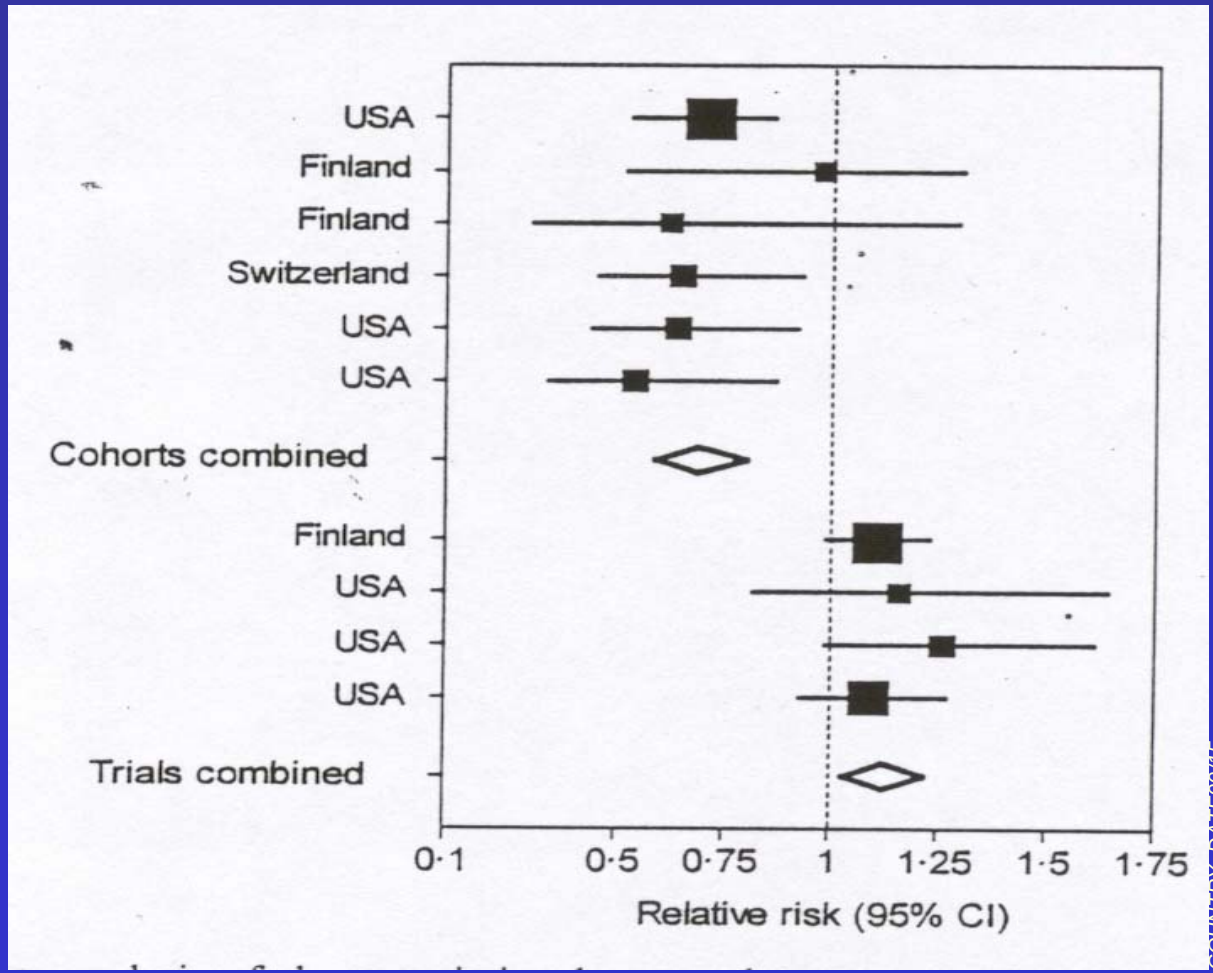
1122 cases	1122 controls
↓	↓
Response rate: **60%**	Response rate: **20%**

Source: Danesh J. Helicobacter pylori infection and early onset myocardial infarction: case control and sibling pair study. BMJ 1999;319;1157.

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

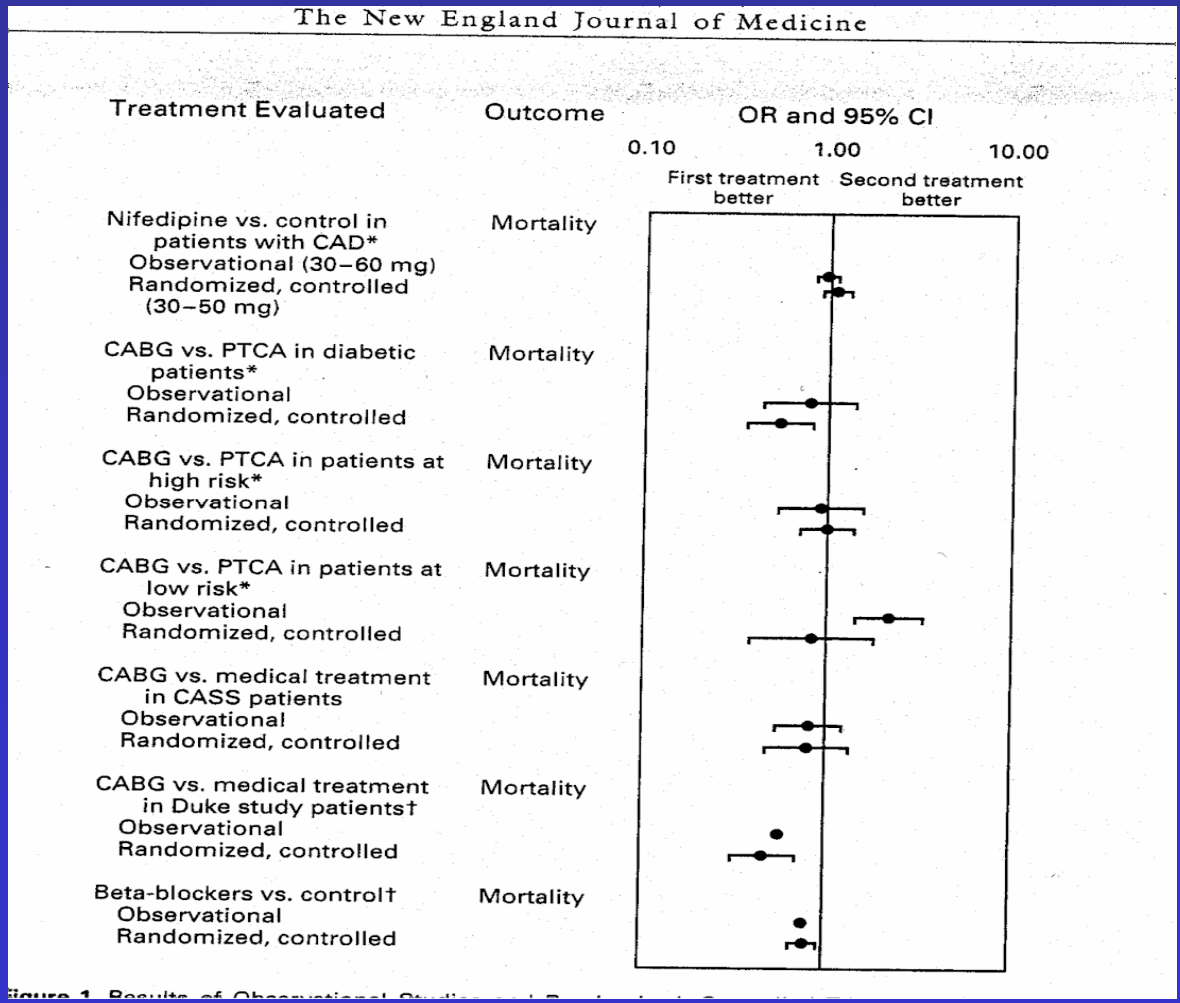
Trials
Male smokers
Skin cancer patients
(Ex)-smokers, asbestos workers
Male physicians



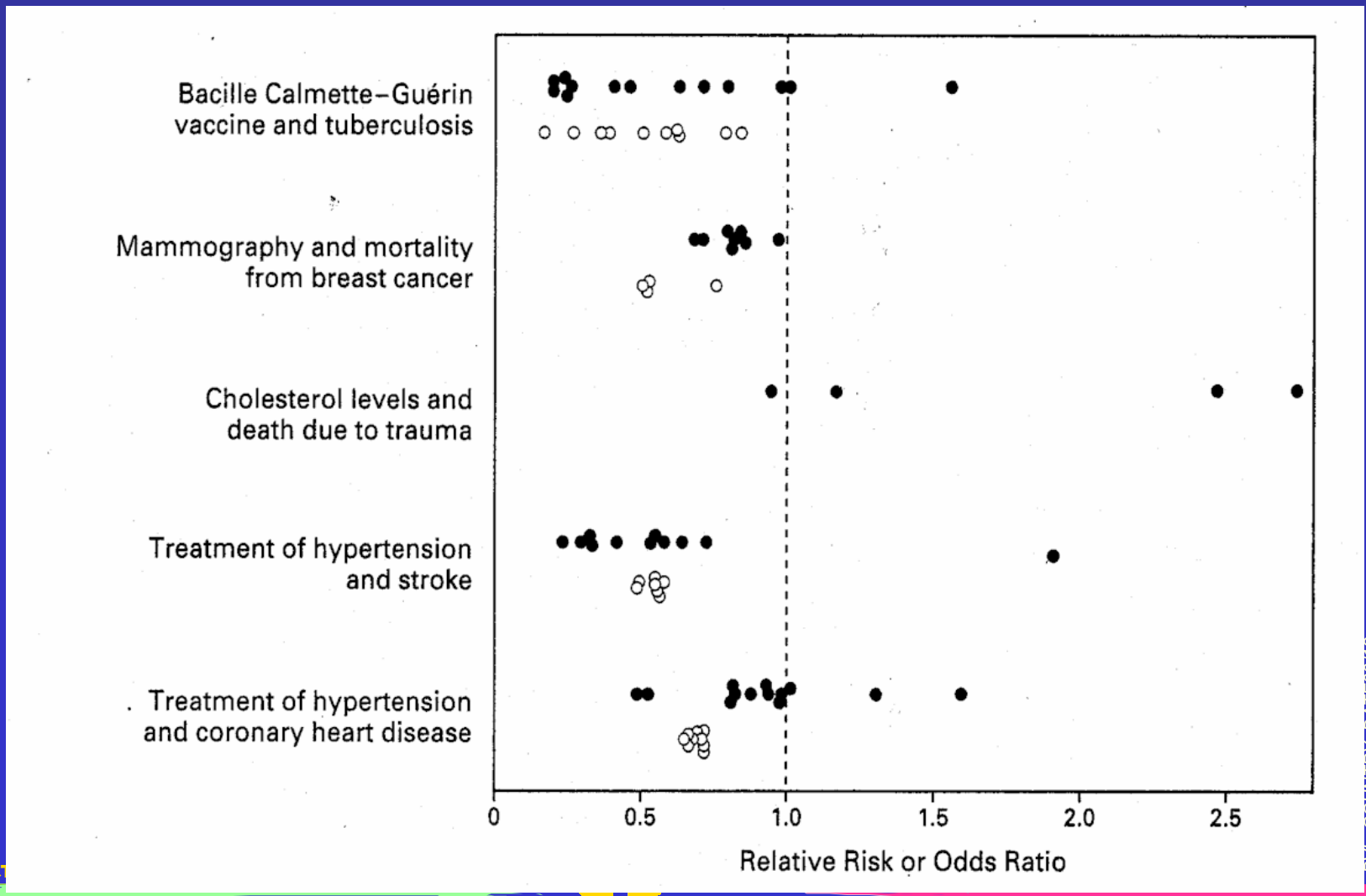
There are examples of observational studies producing similar results of those from RCT

But observational studies will always have to deal with **bias** and **confounding** because the intervention was deliberately chosen and not randomly allocated

Benson and Hartz, NEJM, 2000;342:1878-86



Concato et al., NEJM, 2000;342:1887-92



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

Guideline	Yes	Unable to determine	No
Search methods stated	6 (21)	1(3)	22(76)
Inclusion criteria reported	5(17)	4(14)	20(69)
Bias in selecting studies avoided	3(10)	26(90)	0(0)
Criteria for assessing validity reported	2(7)	15(52)	12(41)
Methods for combining findings reported	10(34)	6(21)	13(45)
Conclusions supported by data	24(83)	4(14)	1(3)

Search restriction: General medical journal, 2001

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

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

Search restriction: General medical journal, 2001

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

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

Other citations:

- Mulrow CD. The medical review article: state of the science. *Ann Intern Med* 1987, 6:233-240.
- McAlister FA, Clark HD, van Walraven C et al. The medical review article revisited: has the science improved? *Ann Intern Med* 1999, 131:947-951
- Bracken MB. Commentary: towards systematic reviews in epidemiology. *IJE* 2001, 30:954-957.

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

WHO systematic review

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 _____ WHO CODE

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

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 _____ WHO CODE

6. Lowest unit of data source

(1) Cluster

6a. Number of clusters

(2) Individual

(3) Other, specify _____ WHO CODE

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 CODE

WHO systematic review

MATERNAL MORTALITY (cont.)

26a. Cause distribution of maternal mortality

Condition	(i) WHO code	(ii) No. of deaths	(iii) Percentage
26a.1) _____			.
26a.2) _____			.
26a.3) _____			.
26a.4) _____			.
26a.5) _____			.
26a.6) _____			.
26a.7) _____			.

WHO systematic review

32. **Infections**

32a) Condition _____ WHO code ☐☐☐

32b) Does the study include a definition? Yes ☐ No ☐

32c) If definition is included, please specify: ☐☐☐ WHO code

_____

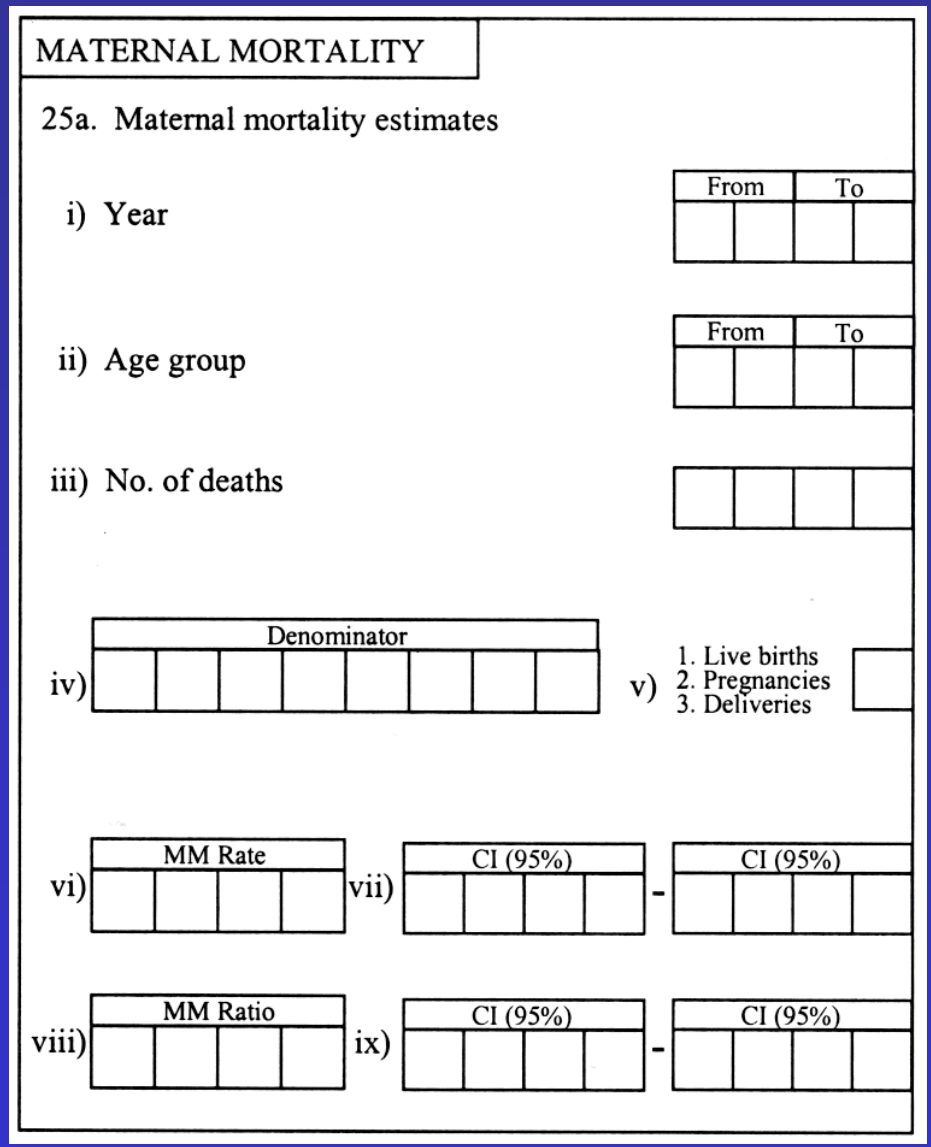
_____

32d) Does the study explain the method of assessment of the infection? Yes ☐ No ☐

32e) If method of assessment is explained, please specify: ☐☐☐ WHO code

_____

_____



MATERNAL MORTALITY

25a. Maternal mortality estimates

i) Year — From | To

ii) Age group — From | To

iii) No. of deaths

iv) Denominator

v) 1. Live births 2. Pregnancies 3. Deliveries

vi) MM Rate

vii) CI (95%) - CI (95%)

viii) MM Ratio

ix) CI (95%) - CI (95%)

WHO systematic review

Citations identified
(Titles and/or abstracts)
64 586

Excluded
59 960

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

Full-text evaluation
(Articles and reports)
4626

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

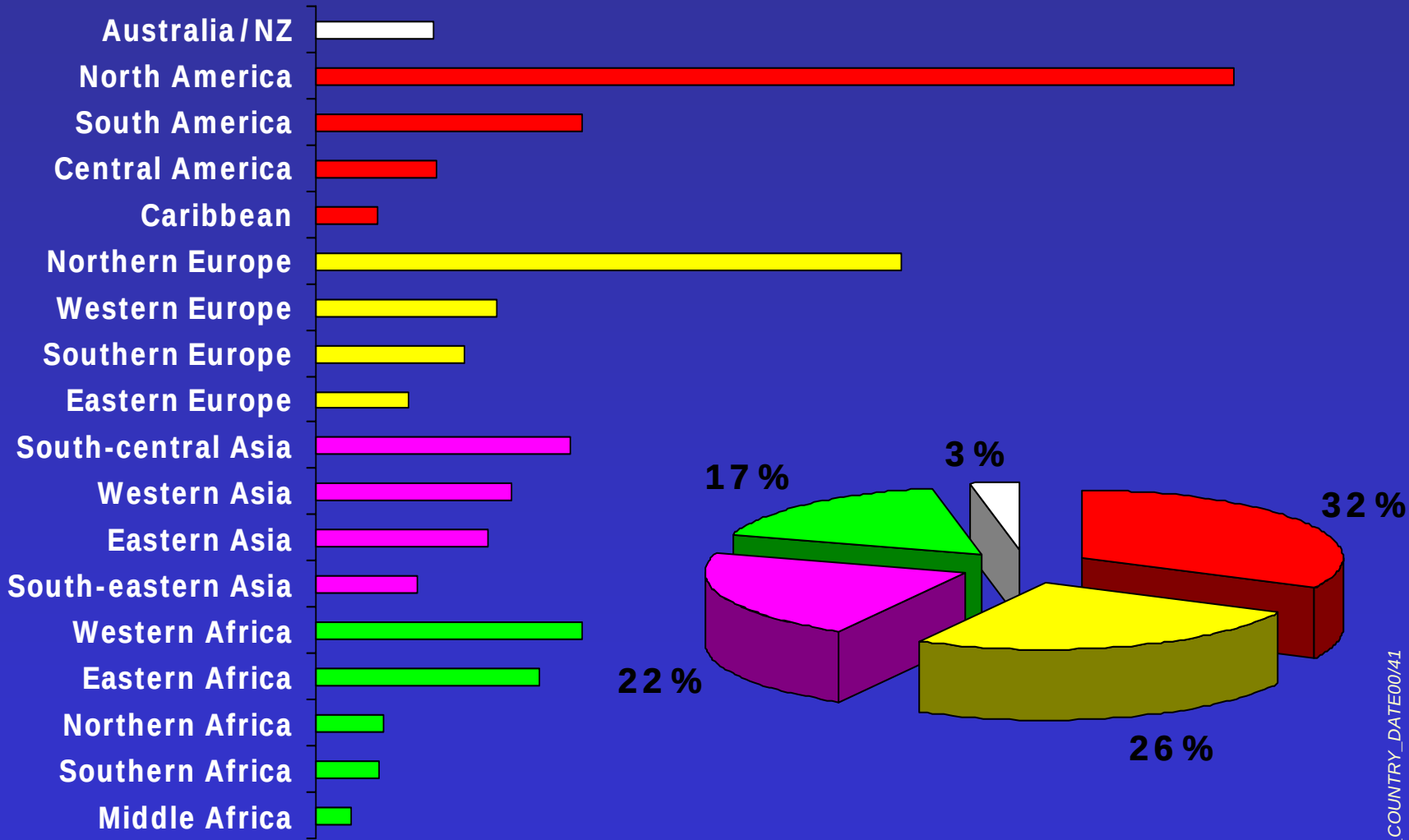
Excluded
1988

Included
2443

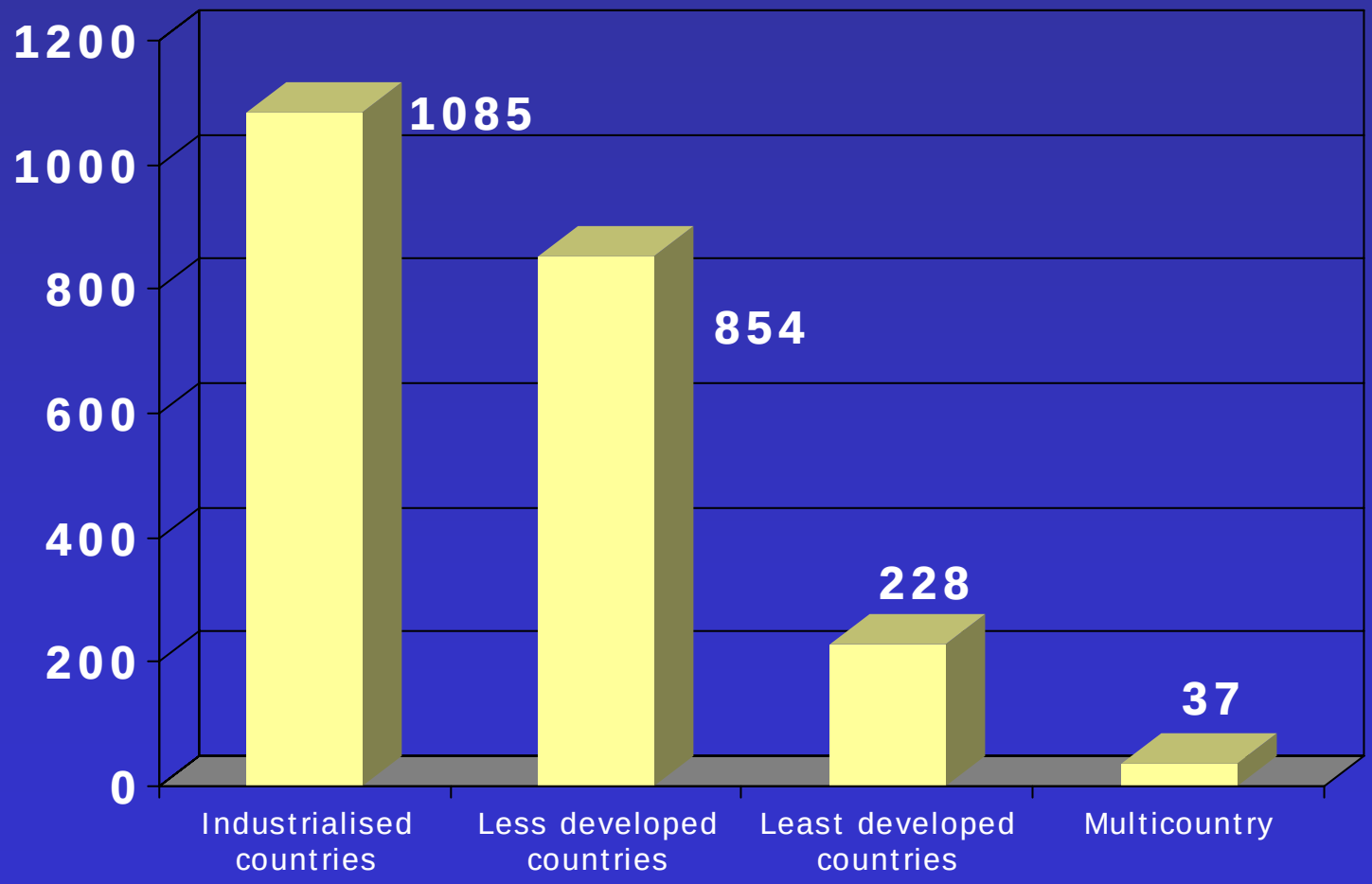
In process
195

Data processing complete
2204

Regional distribution (n=2204)



Development status (n=2204)



Results: methodological quality of reported data

	Morbidity (n = 3215)	Mortality (n = 335)	Total (n = 3550)
High	103	8	111
Medium	1670	250	1920
Low	1442	77	1519

Reported morbidities (n=3215)

- Hypertensive disorders of pregnancy (16.3%)
- Haemorrhage (11.1%)
  - postpartum - 2.7%
  - antepartum / intrapartum - 2.2%
  - placenta praevia - 1.8%
  - abruptio placenta - 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