Systematic reviews and meta-analysis

Hynek Pikhart

Review (narrative review)

- A review is any attempt to synthesize the results and conclusions of two or more publications on a given topic.

Systematic review

- A systematic review is a review that aims comprehensively to identify and synthesize all the literature on a given topic (sometimes called an overview). Each specific study forms a unit of analysis and the same scientific principles and rigour apply as for any study. If a review does not state clearly whether and how all relevant studies were identified and synthesized, it is not a systematic review

- A rigorous, unbiased and systematic summary of available research evidence (usually peer-reviewed) on a certain topic

Meta-analysis

- Meta-analysis is a statistical technique for assembling the results of several studies in a review into a single numerical estimate.

- A systematic review involves
  - a well-formulated question
  - Developing protocol including research question, search and inclusion/exclusion
  - a comprehensive and replicable data search
  - unbiased screening, selection and abstraction
  - critical appraisal of data – analysis of findings and risk of bias
  - valid synthesis of data – interpretation of findings and write up
- A meta-analysis involves systematic analysis of the results, often with the aim to produce a single estimate of an intervention effect.

A meta-analysis can only be done

- when more than one study has estimated an effect
- when there are no differences in the study characteristics that are likely to substantially affect outcome
- when the outcome has been measured in similar ways
- and when the data are available.

Data sources for a systematic review I

- PubMed database

- Web of Science, Google, Google Scholar (books are not in Medline or PubMed but some of them will be in Google Scholar)

- Cochrane library

- Other medical and <u>non-medical</u> databases (PubMed covers medical literature while some literature relevant to social epidemiology will not be covered; other databases are needed, eg. PsychInfo, Social Sciences Citation Index)

# Data sources for a systematic review II

- Foreign language literature
- "Grey literature" (theses, internal reports, non-peer reviewed journals, pharmaceutical industry files)
- References (and references of references, etc) listed in primary sources
- Other unpublished sources known to experts in the field (seek by personal communication)
- Raw data from published trials (seek by personal communication)

Guidance

- Preparation of review and systematic review of literature
- Critical evaluation of papers

PRISMA

TRANSPARENT REPORTING of SYSTEMATIC REVIEWS and META-ANALYSES
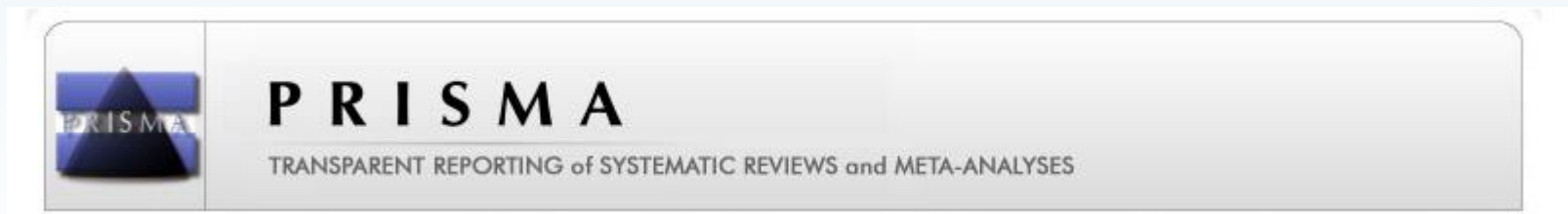
PRISMA stands for Preferred Reporting Items for Systematic Reviews and Meta-Analyses. It is an evidence-based minimum set of items for reporting in systematic reviews and meta-analyses.

Not secure | www.prisma-statement.org

PRISMA
TRANSPARENT REPORTING of SYSTEMATIC REVIEWS and META-ANALYSES
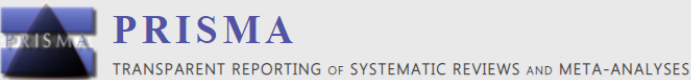
Welcome to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) website!

PRISMA is an evidence-based minimum set of items for reporting in systematic reviews and meta-analyses. PRISMA focuses on the reporting of reviews evaluating randomized trials, but can also be used as a basis for reporting systematic reviews of other types of research, particularly evaluations of interventions.

Who should use PRISMA?

- Authors: PRISMA aims to help authors improve the reporting of systematic reviews and meta-analyses.
- Journal Peer reviewers and editors: PRISMA may also be useful for critical appraisal of published systematic reviews, although it is not a quality assessment instrument to gauge the quality of a systematic review.

News Feed

PRISMA Website re-design

The PRISMA website underwent a much-needed update in October 2015 to update the content of the website. We have updated the look of the site and added the PRISMA extensions, translations, and information about review protocols.

PRISMA Extensions!

Several PRISMA extensions have been published in 2015 so far.
- PRISMA-P for developing review protocols was published in January 2015 in *Systematic Reviews* and the

Key Documents

- PRISMA Checklist
- PRISMA flow diagram
- PRISMA Statement
- PRISMA E&E

PROSPERO
International prospective register of systematic reviews

equator network

Tweets by @PRISMAStatement

PRISMA Statement Retweeted

Dr. Andrea C. Tricco
@ATricco

Dr Matthew Page doing a fantastic job leading us on the PRISMA Statement update in Edinburgh! @mipages

PRISMA 2009 Checklist

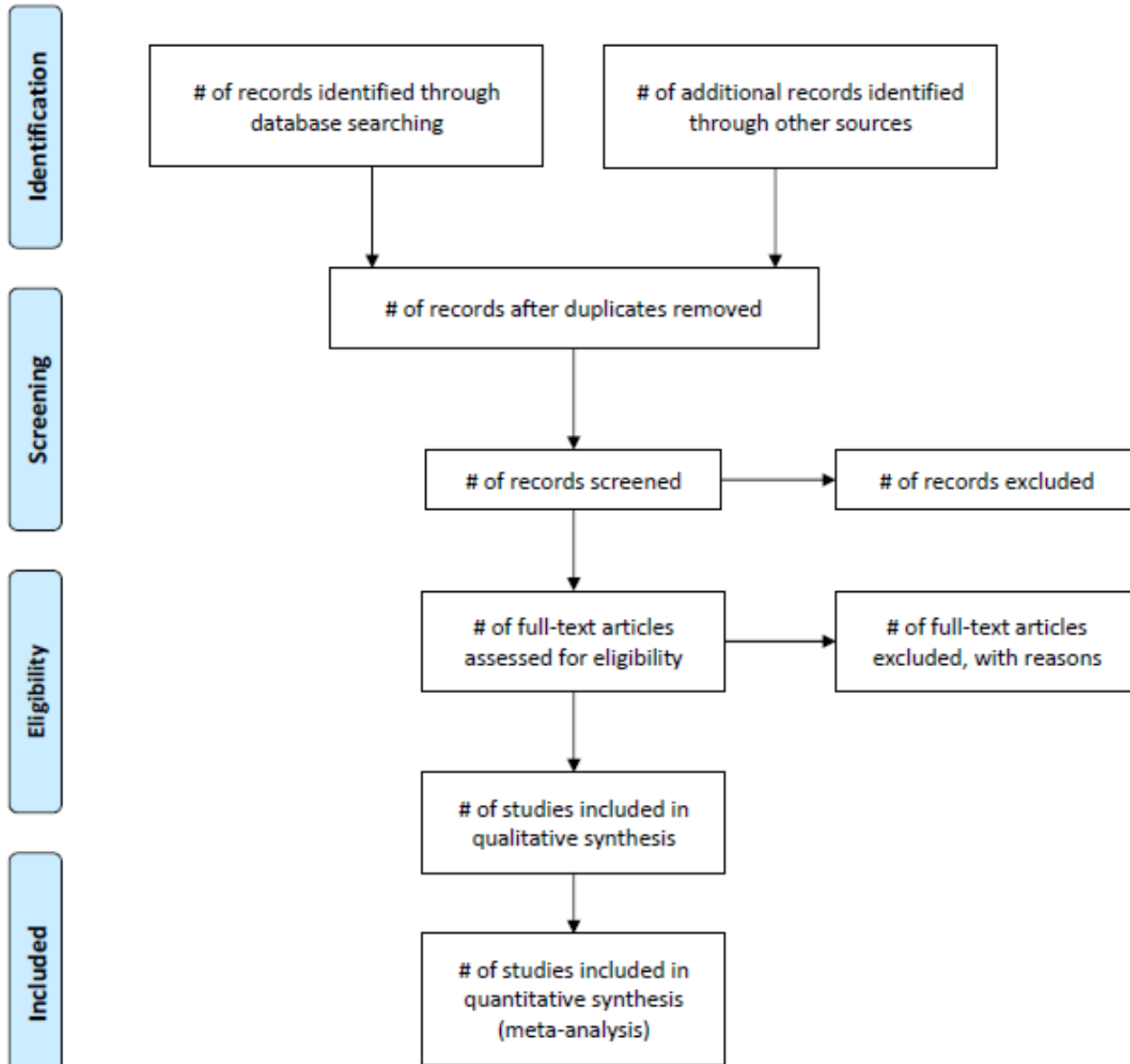| Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	

PRISMA 2009 Checklist

| Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

PRISMA 2009 Flow Diagram

Identification

# of records identified through database searching

# of additional records identified through other sources

Screening

# of records after duplicates removed

# of records screened

# of records excluded

Eligibility

# of full-text articles assessed for eligibility

# of full-text articles excluded, with reasons

# of studies included in qualitative synthesis

Included

# of studies included in quantitative synthesis (meta-analysis)

Meta-analysis

- systematic analysis of the results
- the aim is to produce a single estimate of an intervention effect.
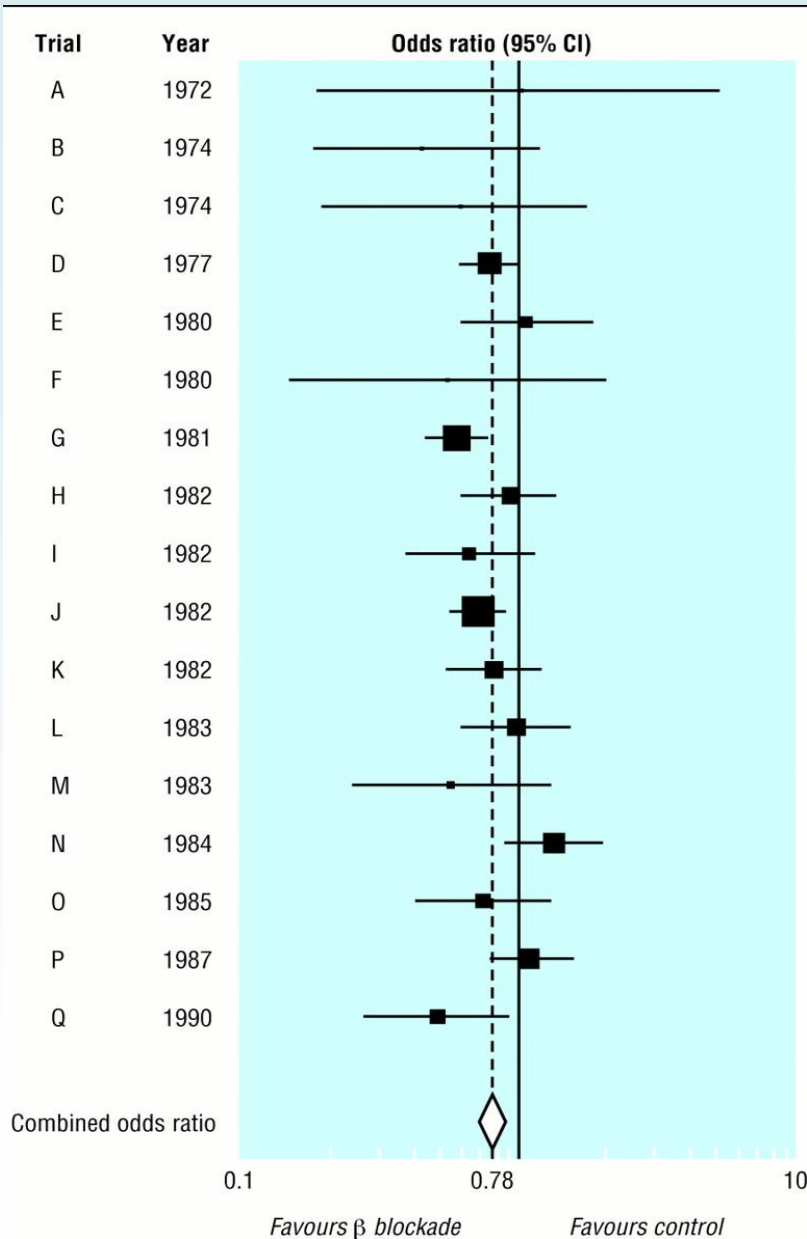
Fig 1 Total mortality from trials of beta blockers in secondary prevention after myocardial infarction. The black square and horizontal line correspond to odds ratio and 95% confidence interval for each trial. The size of the black square reflects the weight of each trial. The diamond represents the combined odds ratio and 95% confidence interval, showing 22% a reduction in the odds of death (references are available from the authors)

Egger, M. et al. BMJ 1997;315:1533-1537

Meta-analysis

- Meta-analysis is a statistical technique for assembling the results of several studies in a review into a single numerical estimate.

- Rationale:
  - Single studies too small to give clear results
  - Single studies not generalizable
  - Increased total size of the combined analysis increases chances of detecting a moderate but clinically and/or epidemiologically important effect

Potential biases in meta-analysis

- Publication bias
- English language bias
- Database bias
- Citation bias
- Multiple publication bias
- Bias in provision of data
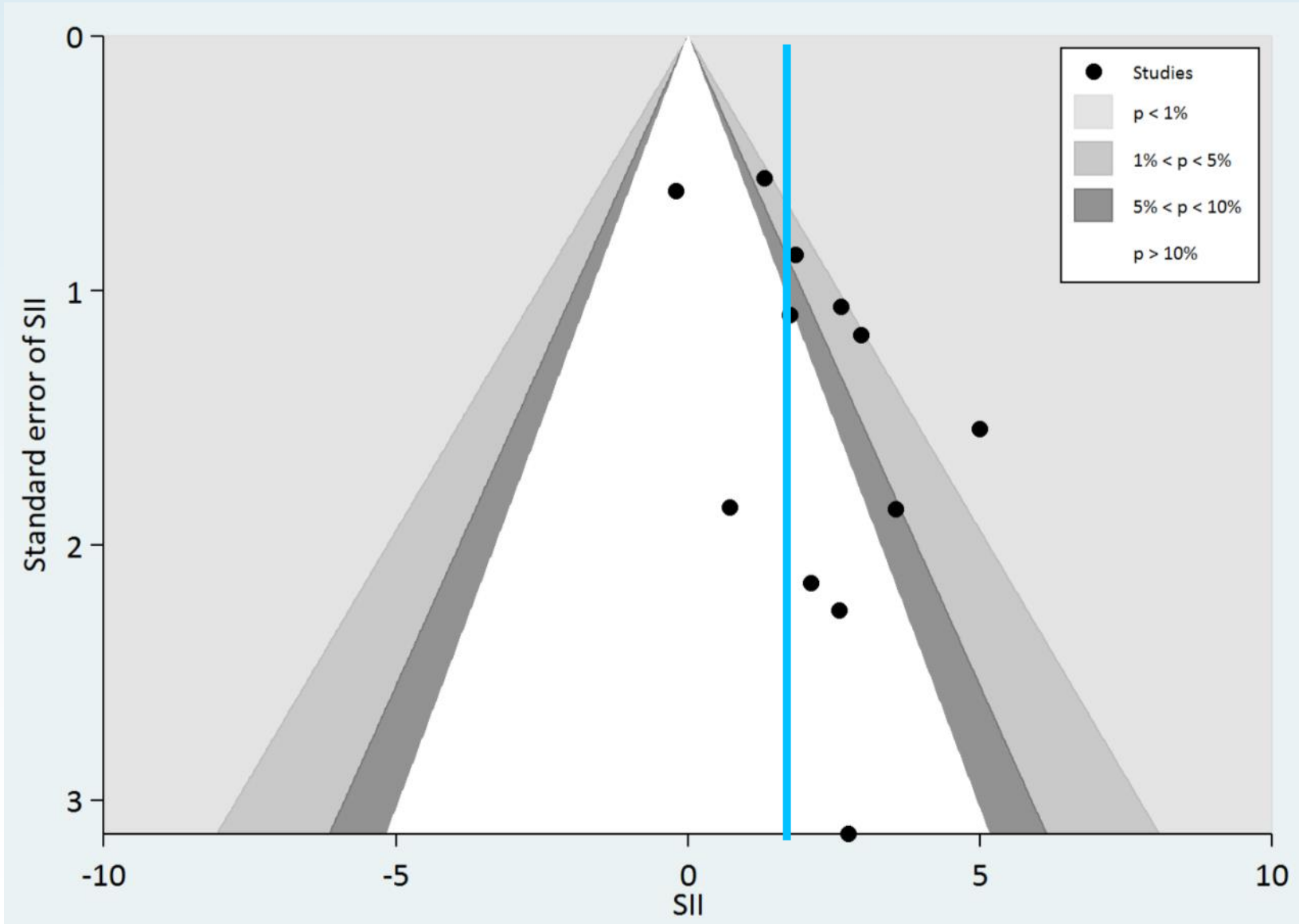- Poor methodological quality of small studies

The Funnel plot

- A screening test for bias

- Plot of the effect estimate against sample size

- If skewed and asymmetric, then bias probably present

- Small negative studies are often missing

Of meta-analyses examined, 38% in medical journals and 19% in Cochrane Library showed evidence of bias (Egger et al BMJ 1997)

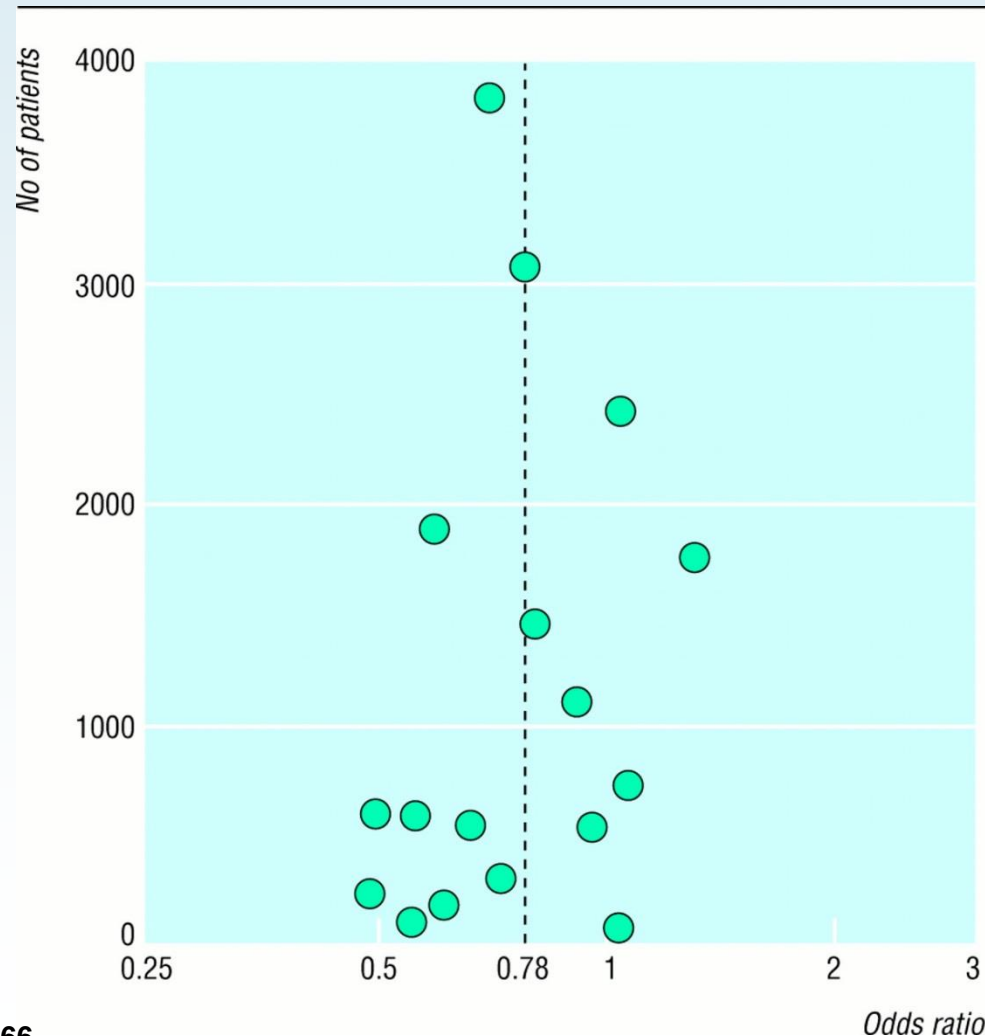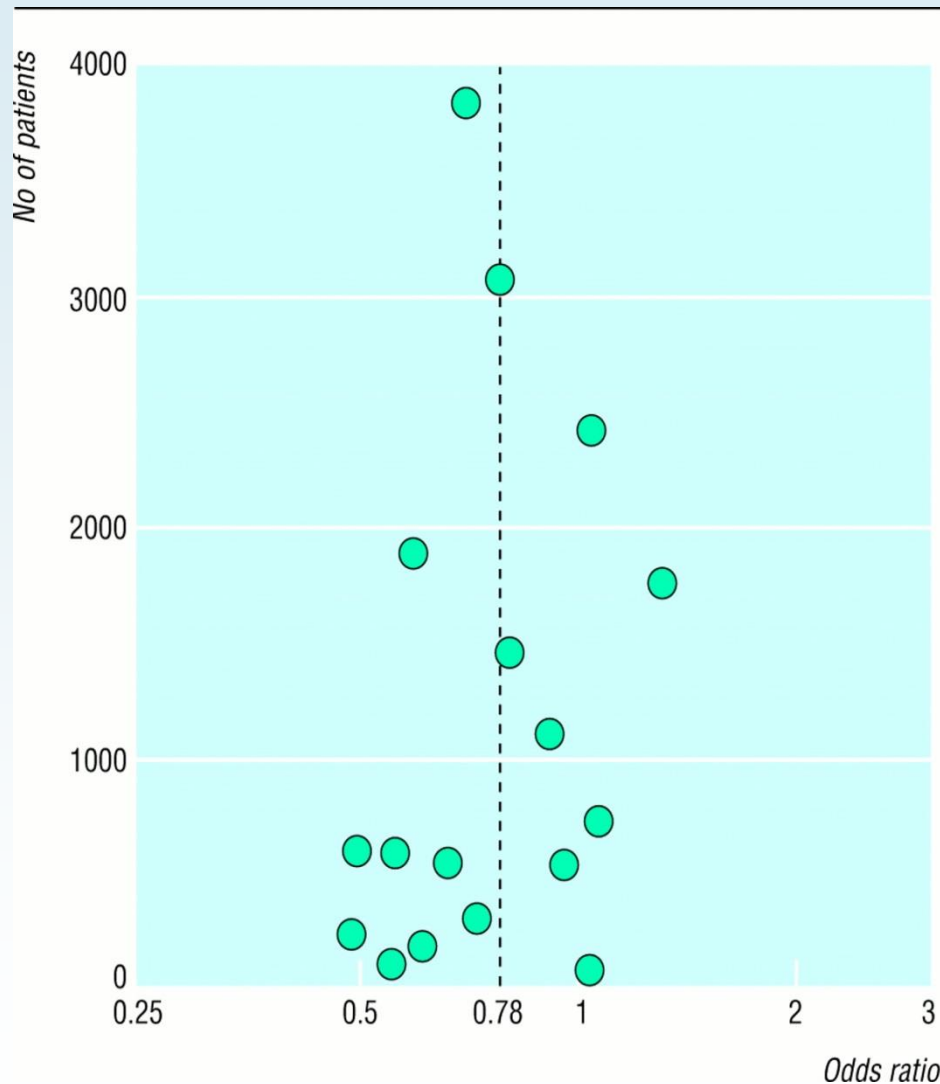# Example of marked publication bias - CRP and prognosis of stable coronary artery disease
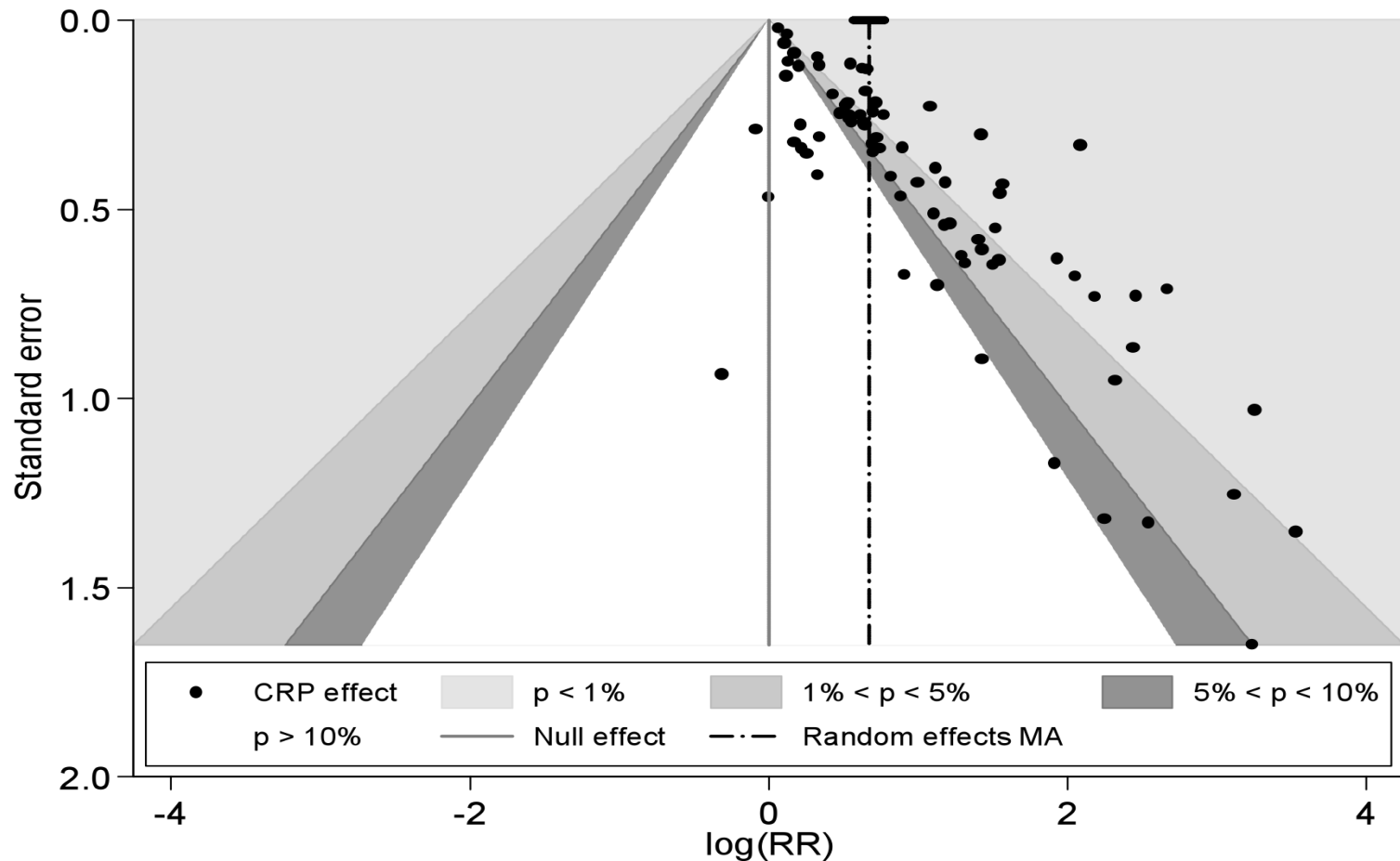
Each dot represents one study, N=83 studies

- Hemingway et al 2010

Funnel plot of mortality results from trials of beta-blockers in secondary prevention after myocardial infarction. The odds ratios are plotted against study sample size

- Visual assessment shows some asymmetry

- It indicates that there was selective non-publication of smaller trials with less sizeable benefit.

- However, in formal statistical analysis the degree of asymmetry is found to be small and non-significant (P>0.1).

- Furthermore, exclusion of the smaller studies had little effect on the overall estimate.

- Bias does not therefore seem to have distorted the findings from this **meta-analysis**.

Egger, M. et al. BMJ 1998;316:61-66

Resources

- Greenhalgh T. Papers that summarise other papers (systematic reviews and meta-analyses). British Medical Journal 1997; 315: 672-675
- Akobeng AK. Understanding systematic reviews and meta-analysis. Arch. Dis. Child., 2005; 90(8): 845 - 848.