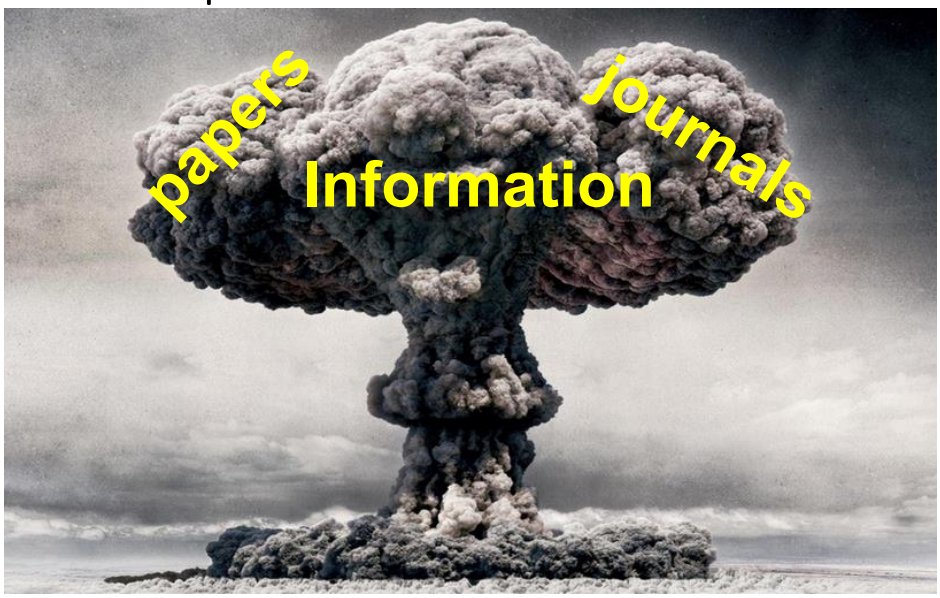
Introduction to Systematic review

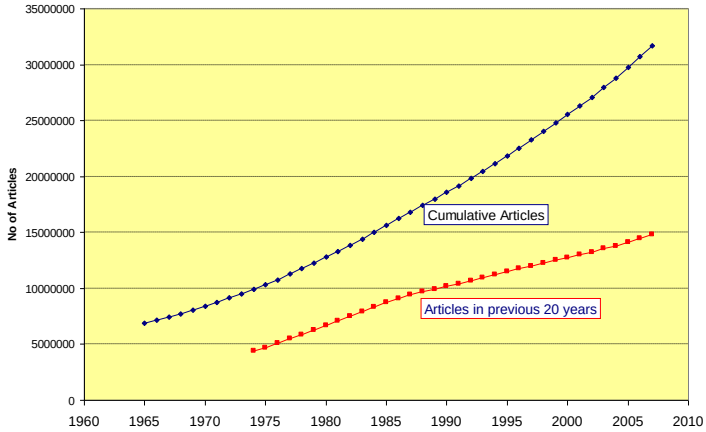
Yahya Salimi
PhD in Epidemiology
Department of Epidemiology
Kermanshah University of Medical Sciences

A Information explosion...



More being published

- In 2007 a researcher was faced with 15 million articles published in the past 20 years compared to a researcher in 1977 who saw 5 million articles published in the previous 20 years



Most research published in medical journals is

too poorly done

or

insufficiently relevant

to be clinically useful

Too much information, too little time

- There is simply too much information around for people to keep up to date.
- On top of this, high quality information is often not easy to find.

Review articles

- A '**review'** is the generic term for any attempt to synthesis the results and conclusions of two or more publications on a given topic.

Some reviews are usually based on narrative or commentary and are produced by a

'content expert'

What's the problem with
"**Expert Opinion**"?

The use of unsystematic approaches to collecting and summarizing the evidence.

Table 1 Main review types characterized by methods used

		Methods used (SALSA)			
Label	Description	Search	Appraisal	Synthesis	Analysis
Critical review	Aims to demonstrate writer has extensively researched literature and critically evaluated its quality. Goes beyond mere description to include degree of analysis and conceptual innovation. Typically results in hypothesis or model	Seeks to identify most significant items in the field	No formal quality assessment. Attempts to evaluate according to contribution	Typically narrative, perhaps conceptual or chronological	Significant component: seeks to identify conceptual contribution to embody existing or derive new theory
Literature review	Generic term: published materials that provide examination of recent or current literature. Can cover wide range of subjects at various levels of completeness and comprehensiveness. May include research findings	May or may not include comprehensive searching	May or may not include quality assessment	Typically narrative	Analysis may be chronological, conceptual, thematic, etc.
Mapping review/ systematic map	Map out and categorize existing literature from which to commission further reviews and/or primary research by identifying gaps in research literature	Completeness of searching determined by time/scope constraints	No formal quality assessment	May be graphical and tabular	Characterizes quantity and quality of literature, perhaps by study design and other key features. May identify need for primary or secondary research
Meta-analysis	Technique that statistically combines the results of quantitative studies to provide a more precise effect of the results	Aims for exhaustive, comprehensive searching. May use funnel plot to assess completeness	Quality assessment may determine inclusion/ exclusion and/or sensitivity analyses	Graphical and tabular with narrative commentary	Numerical analysis of measures of effect assuming absence of heterogeneity
Mixed studies review/mixed methods review	Refers to any combination of methods where one significant component is a literature review (usually systematic). Within a review context it refers to a combination of review approaches for example combining quantitative with qualitative research or outcome with process studies	Requires either very sensitive search to retrieve all studies or separately conceived quantitative and qualitative strategies	Requires either a generic appraisal instrument or separate appraisal processes with corresponding checklists	Typically both components will be presented as narrative and in tables. May also employ graphical means of integrating quantitative and qualitative studies	Analysis may characterise both literatures and look for correlations between characteristics or use gap analysis to identify aspects absent in one literature but missing in the other
Overview	Generic term: summary of the [medical] literature that attempts to survey the literature and describe its characteristics	May or may not include comprehensive searching (depends whether systematic overview or not)	May or may not include quality assessment (depends whether systematic overview or not)	Synthesis depends on whether systematic or not. Typically narrative but may include tabular features	Analysis may be chronological, conceptual, thematic, etc.
Qualitative systematic review/qualitative evidence synthesis	Method for integrating or comparing the findings from qualitative studies. It looks for 'themes' or 'constructs' that lie in or across individual qualitative studies	May employ selective or purposive sampling	Quality assessment typically used to mediate messages not for inclusion/exclusion	Qualitative, narrative synthesis	Thematic analysis, may include conceptual models

Table 1 *Continued*

		Methods used (SALSA)			
Label	Description	Search	Appraisal	Synthesis	Analysis
Rapid review	Assessment of what is already known about a policy or practice issue, by using systematic review methods to search and critically appraise existing research	Completeness of searching determined by time constraints	Time-limited formal quality assessment	Typically narrative and tabular	Quantities of literature and overall quality/direction of effect of literature
Scoping review	Preliminary assessment of potential size and scope of available research literature. Aims to identify nature and extent of research evidence (usually including ongoing research)	Completeness of searching determined by time/scope constraints. May include research in progress	No formal quality assessment	Typically tabular with some narrative commentary	Characterizes quantity and quality of literature, perhaps by study design and other key features. Attempts to specify a viable review
State-of-the-art review	Tend to address more current matters in contrast to other combined retrospective and current approaches. May offer new perspectives on issue or point out area for further research	Aims for comprehensive searching of current literature	No formal quality assessment	Typically narrative, may have tabular accompaniment	Current state of knowledge and priorities for future investigation and research
Systematic review	Seeks to systematically search for, appraise and synthesis research evidence, often adhering to guidelines on the conduct of a review	Aims for exhaustive, comprehensive searching	Quality assessment may determine inclusion/exclusion	Typically narrative with tabular accompaniment	What is known; recommendations for practice. What remains unknown; uncertainty around findings, recommendations for future research
Systematic search and review	Combines strengths of critical review with a comprehensive search process. Typically addresses broad questions to produce 'best evidence synthesis'	Aims for exhaustive, comprehensive searching	May or may not include quality assessment	Minimal narrative, tabular summary of studies	What is known; recommendations for practice. Limitations
Systematized review	Attempt to include elements of systematic review process while stopping short of systematic review. Typically conducted as postgraduate student assignment	May or may not include comprehensive searching	May or may not include quality assessment	Typically narrative with tabular accompaniment	What is known; uncertainty around findings; limitations of methodology
Umbrella review	Specifically refers to review compiling evidence from multiple reviews into one accessible and usable document. Focuses on broad condition or problem for which there are competing interventions and highlights reviews that address these interventions and their results	Identification of component reviews, but no search for primary studies	Quality assessment of studies within component reviews and/or of reviews themselves	Graphical and tabular with narrative commentary	What is known; recommendations for practice. What remains unknown; recommendations for future research

What is a Systematic Review?

Systematic review

Comprehensively

- **locates**
- **evaluates**
- **synthesizes**

all the available literature on a given topic

using a strict scientific design which must itself be reported in the review

A 'systematic review', therefore, aims to be:

- Systematic (e.g. in its identification of literature)
- Explicit (e.g. in its statement of objectives, materials and methods)
- Reproducible (e.g. in its methodology and conclusions)

The 'systematic' part of systematic reviews is all about

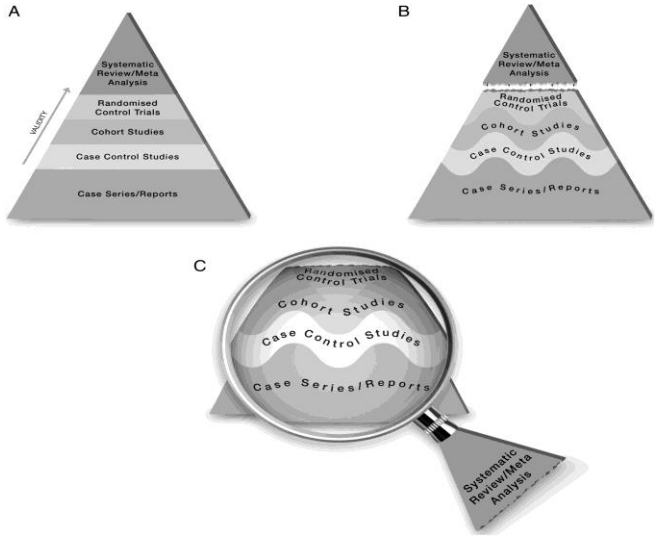
minimizing bias in the way the review is carried out

Systematic reviews are the same as ordinary reviews, only bigger!

- Not simply "comprehensive" but to answer a specific question
- To reduce bias in the selection and inclusion of studies (language, database, publication, reporting, citation, multiple publication)
- To appraise the quality of the included studies
  - *Internal validity: minimised* systematic error (bias)
  - *External validity:* generalisability of findings
- To summarise them objectively

They are different!!

The proposed new evidence-based medicine pyramid.



M Hassan Murad et al. Evid Based Med 2016;21:125-127

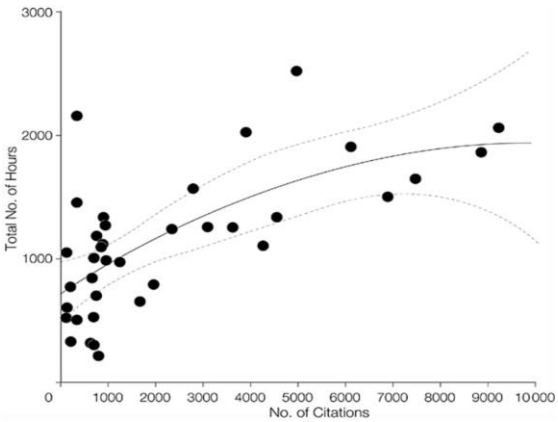
Can Systematic reviews be used in study designs that are not clinical trials?

- Observational studies
- Studies evaluating diagnostic tests
- "IPD" = individual patient data studies
- Qualitative studies (meta-ethnography)

What kind of resources are required for systematic reviewing?

- Can be time consuming
- Team science (to reduce bias)
- Bibliographic software (e.g. Endnote)
- Statistical software (if appropriate)

Citations Retrieved for a Meta-analysis and Total Hours Required to Complete the Meta-analysis*



Total time=721 + 0.243x − 0.0000123x^2, where x is the number of citations before exclusion criteria are applied.

The mean total number of hours was 1139 (median, 1110), with a wide range from 216 to 2518 hours.

(1) Pre-analysis search, retrieval, and database development: 588 (337) hours;
(2) statistical analysis & validation: 144 (106) hours;
(3) report and manuscript writing: 206 (125) hours;
(4) other (administrative): 201 (193) hours.

*IE Allen & I Olkin: JAMA. 1999;282(7):634-635. doi:10-1001/pubs.JAMA-ISSN-0098-7484-282-7-jbk0818

8 Steps of Systematic Review

- 1. Research Question
- 2. Protocol
- 3. Search
- 4. Study selection (inclusion/exclusion)
- 5. Quality assessment
- 6. Data abstraction
- 7. Analysis
  - A) Create summary measure
  - B) Assess for heterogeneity
  - C) Assess for publication bias
  - D) Conduct sensitivity/subgroup analyses
  - E) Advanced issues/techniques
- 8. Interpretation

Advantages of Met-analysis

- Results can be generalized to a larger population
- The precision of estimates can be improved as more data is used. This, in turn, may increase the statistical power to detect an effect.
- Inconsistency of results across studies can be quantified and analyzed. For instance, does inconsistency arise from sampling error, or are study results (partially) influenced by between-study heterogeneity.
- Hypothesis testing can be applied on summary estimates,
- Moderators can be included to explain variation between studies,
- The presence of publication bias can be investigated

Framing the Question (PICO/PECO/ PIRT)

➢A clearly defined, focused review begins with a well framed question.

Well-formulated questions determine:

- Criteria used to select studies
- Development of the search strategy
- Data to be abstracted
- The Question Informs the Process

Components of Well-Constructed and "Answerable" Clinical Questions

- **Patient:**
  - Disease or condition
  - Demographic characteristics
- **Intervention (or "Exposure"):**
  - Type of intervention
  - Dose, duration, timing, etc.
- **Comparison:**
  - Absence of risk or treatment
  - Placebo or alternative therapy
- **Outcome:**
  - Risk or protective
  - Dichotomous or continuous
  - Type: mortality, quality of life, etc.
- **Type of Study:**
  - RCTs
  - Cohort
  - Case-control
  - Cross-sectional
  - All

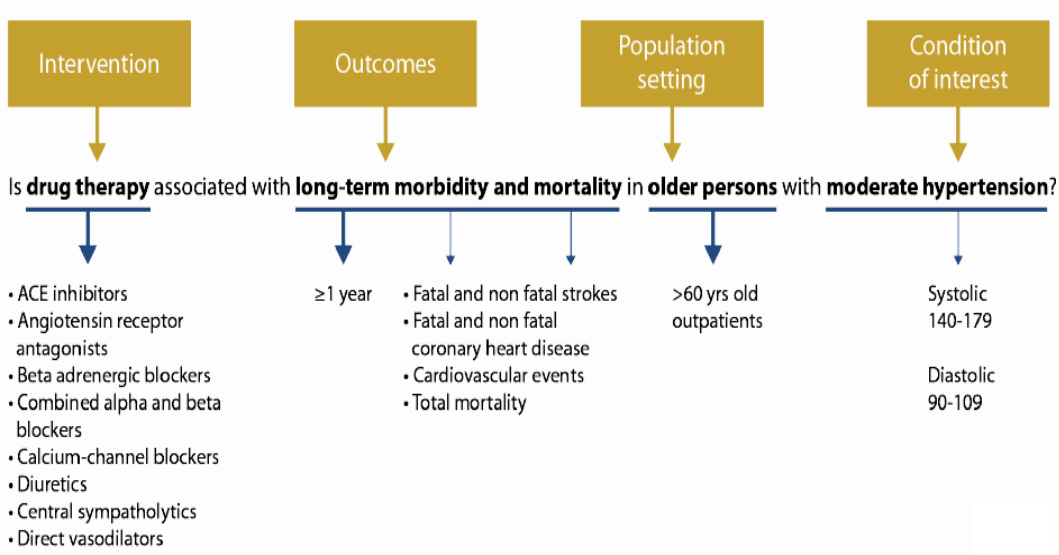
Examples of Types of Questions

Type question	Example
Incidence, prevalence	What is the incidence of low birth weight in minority populations compared to the white population?
Therapy	Is exercise effective in improving quality of life in persons with COPD?
Screening	Is PSA to detect prostate cancer effective in reducing mortality?
Diagnostic accuracy	How effective is an MRI at detecting new breast cancers in follow-up of women with breast cancer having lumpectomy?
Prognosis	What is the effect of pregnancy on exacerbating the symptoms of MS
Harm	What proportion of postmenopausal women receiving Ca++/vita D can expect to have kidney stones?
Etiology	Is coffee consumption causally associated with developing pancreatic cancer?

Research question 1

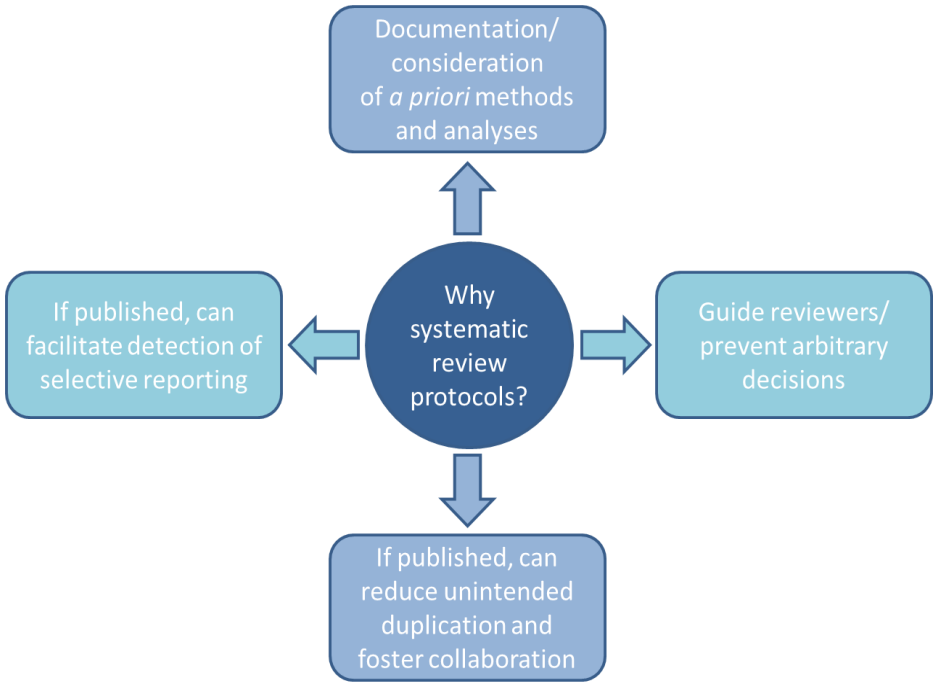
- Is drug therapy associated with long-term morbidity and mortality in older persons with moderate hypertension?

- **P** = Older persons with moderate hypertension
- **I** = Drug therapy
- **C** = Not stated (presumably any intervention other than the named drug therapy)
- **O** = Long-term morbidity and mortality



Why worry about protocols?

- Progress
- Validity



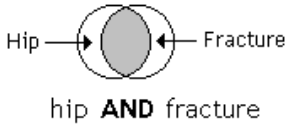
Search strategy

- Search #1: Population **OR** synonyms
- Search #2: Determinant **OR** synonyms
- Search #3: Outcome **OR** synonyms

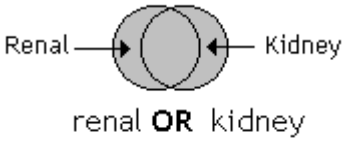
- Search #4: Combine #1, #2 and #3
  - Population (#1) **AND** Determinant (#2) **AND** Outcome (#3)

Boolean operators

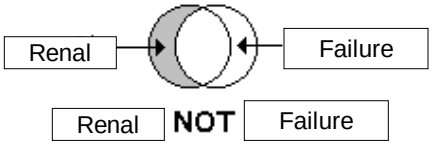
- AND



- OR



- NOT



8 Steps of Systematic Review

- 1. Research Question
- 2. Protocol
- 3. Search
- 4. Study selection (inclusion/exclusion)
- 5. Quality assessment
- 6. Data Extraction
- 7. Analysis
  - A) Create summary measure
  - B) Assess for heterogeneity
  - C) Assess for publication bias
  - D) Conduct sensitivity/subgroup analyses
  - E) Advanced issues/techniques
- 8. Interpretation

Why Quality assessment

- Because of the critical role of systematic reviews in decision making (including clinical interventions and resource allocation), policymakers need valid evidence.
- One of the distinguishing points of systematic review studies with narrative review is quality assessment.
- The main purpose of quality assessment is not to exclude poor quality primary studies.

How to measure the quality of studies

- In order to achieve the objective of quality assessment, the method of assessment must be quantitative (not qualitative).
  - **We can use :**
  - **Critical Appraisal Tools (CAT)**
  - **Reporting Standards/Guidelines (RG)**

The choice

- Reporting guidelines have greater diversity (more adaptability to a variety of study designs) and more attention to detail.

- Reporting guidelines that can be use in different systematic review:

- **Systematic review on prevalent studies (cross- sectional study):STROBE**
- **Systematic review on observational studies (cohort/ case-control): STROBE**
- **Systematic review on RCTs: CONSORT**
- **Systematic review on diagnostic studies: QUADAS**

Where we can find the tools?

http://www.equator-network.org/

Example for observational studies

Table S3e. Newcastle-Ottawa Scale Quality Assessment Results, Individual Cohort Studies

		Domain and Topic									
		Selection				Comparability		Outcome			
Author	Year	Representativeness of the Exposed Cohort	Selection of the Non-Exposed Cohort	Ascertainment of Exposure	Outcome Was Not Present at Study Start	Comparability: Age and Sex	Comparability: Additional Factors	Assessment of Outcome	Was Follow-Up Long Enough for Outcomes to Occur?	Adequacy of Follow-up of Cohorts	Total
Chou[a]	2011		★	★	★	★	★	★	★	★	8
Delea	2003	★		★	★	★	★	★	★		7
Graham[a]	2010	★	★	★	★	★	★	★		★	8
Habib	2009	★	★	★		★	★	★	★	★	8
Horsdal[a]	2008	★	★	★	★	★	★	★	★	★	9
Horsdal	2009	★	★	★	★	★	★	★	★	★	9
Hsiao[a]	2009	★	★	★		★	★	★	★		7
Hsiao	2010	★	★	★		★	★	★	★		7
Juurlink[a]	2009	★	★	★		★	★	★		★	7
Karter[a]	2005	★	★	★	★	★	★	★		★	8
Loebstein[a]	2011	★	★	★		★	★	★	★	★	8
McAlister[a]	2008		★	★	★	★	★	★	★		7
Rajagopalan	2004	★	★	★	★	★	★	★	★		8
Toprani	2011		★	★	★	★	★		★		6
Tzoulaki[a]	2009	★	★	★		★	★	★	★	★	8
Wertz[a]	2010	★	★	★		★	★	★	★	★	8
Winkelmayer[a]	2008	★	★	★	★	★	★	★	★	★	9

Example for RCTs

J Clin Epidemiol Vol. 51, No. 12, pp. 1235–1241, 1998

0895-4356/98/$–see front matter
PII S0895-4356(98)00131-0

The Delphi List: A Criteria List for Quality Assessment of Randomized Clinical Trials for Conducting Systematic Reviews Developed by Delphi Consensus

Arianne P. Verhagen,[1,4,] Henrica C. W. de Vet,[1,4] Robert A. de Bie,[1,4] Alphons G. H. Kessels,[1,4] Maarten Boers,[2,4] Lex M. Bouter,[3,4] and Paul G. Knipschild[1,4]*

TABLE 3. Final Delphi List after three Delphi rounds

1. Treatment allocation	
a) Was a method of randomization performed?	Yes/No/Don't know
b) Was the treatment allocation concealed?	Yes/No/Don't know
2. Were the groups similar at baseline regarding the most important prognostic indicators?	Yes/No/Don't know
3. Were the eligibility criteria specified?	Yes/No/Don't know
4. Was the outcome assessor blinded?	Yes/No/Don't know
5. Was the care providor blinded?	Yes/No/Don't know
6. Was the patient blinded?	Yes/No/Don't know
7. Were point estimates and measures of variability presented for the primary outcome measures?	Yes/No/Don't know
8. Did the analysis include an intention-to-treat analysis?	Yes/No/Don't know

STROBE

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up

QUADAS

Table 2: The QUADAS tool

Item		Yes	No	Unclear
1.	Was the spectrum of patients representative of the patients who will receive the test in practice?	( )	( )	( )
2.	Were selection criteria clearly described?	( )	( )	( )
3.	Is the reference standard likely to correctly classify the target condition?	( )	( )	( )
4.	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	( )	( )	( )
5.	Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis?	( )	( )	( )
6.	Did patients receive the same reference standard regardless of the index test result?	( )	( )	( )
7.	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	( )	( )	( )
8.	Was the execution of the index test described in sufficient detail to permit replication of the test?	( )	( )	( )
9.	Was the execution of the reference standard described in sufficient detail to permit its replication?	( )	( )	( )
10.	Were the index test results interpreted without knowledge of the results of the reference standard?	( )	( )	( )
11.	Were the reference standard results interpreted without knowledge of the results of the index test?	( )	( )	( )
12.	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	( )	( )	( )
13.	Were uninterpretable/ intermediate test results reported?	( )	( )	( )
14.	Were withdrawals from the study explained?	( )	( )	( )

8 Steps of Systematic Review

- 1. Research Question
- 2. Protocol
- 3. Search
- 4. Study selection (inclusion/exclusion)
- 5. Quality assessment
- 6. Data Extraction
- 7. Analysis
  - A) Create summary measure
  - B) Assess for heterogeneity
  - C) Assess for publication bias
  - D) Conduct sensitivity/subgroup analyses
  - E) Advanced issues/techniques
- 8. Interpretation

The Purpose of Data Extraction

1. To describe the study in general,
2. To extract the findings from each study in a consistent manner to enable later synthesis, and
3. To extract information to enable quality appraisal so that the findings can be interpreted
   - ❖Ideally this should be undertaken in such a way as to require minimal reference to the original papers at data synthesis stage." (Social Care Institute for Excellence, 2006)

Data Extraction Form Types

Paper Advantages

- convenience or preference;
- can be undertaken anywhere;
- easier to create and implement (no need for computer programming or specialist software);
- provides a permanent record of all manipulations and modifications; and
- simple comparison of forms completed by different review authors

Electronic Advantages

- convenience or preference;
- combines data extraction and data entry;
- forms may be programmed with bridges/levels;
- accommodates large numbers of studies—more easily stored, sorted and retrieved;
- rapid comparison of forms completed by different review authors; and
- environmental considerations

Bias and heterogeneity

Type of error in research

- **Chance (random error)**
  - statistics are used to reduce it by appropriate design of the study
  - statistics are used to estimate the probability that the observed results are due to chance
- **Bias (Systematic error)**
  - must be considered in the design of the study

YS

Bias

- An error in the conception and design of a study—or in the collection, analysis, interpretation, reporting, publication, or review of data—leading to results or conclusions that are systematically (as opposed to randomly) different from truth.

- (Porta, M. S., Greenland, S., Hernán, M., dos Santos Silva, I., & Last, J. M. (2014). *A dictionary of epidemiology*. Oxford University Press).

YS

There are three possible sources of bias in reviews

- bias arising from the studies included in the review
- bias arising from the studies not included in the review
- Bias arising from the way the review is done.

YS

Validity of the main finding

- Are the searches adequate?
- Is there a risk of publication and related biases?
- Is the quality of the included studies high enough?

YS

Type of reporting bias

- Publication bias
- The publication or non-publication of research findings, depending on the nature and direction of the results

YS

Publication bias

- 1-Arising from the researchers deciding whether or not to submit result
- 2- Arising from the tendency of journals to reject negative studies
- 3-Sponsorship
- ….

YS

Methods of preventing publication bias

- 1-Registeries
- 2-Editorial policy

YS

Analytical Methods: Summary Points

Summary Points

- Always start the meta-analysis with a "visual meta-analysis" (i.e., a great table 1).
  - A clinician should be able to interpret the results
- Step 1: Calculate a summary measure = "weighted mean effect estimate"
  - You can combine anything, but use judgment
- Step 2: Assess for heterogeneity
  - Heterogeneity is not always a problem
- Step 3: Assess for publication bias
  - Both visual and statistical methods
- Step 4: Perform subgroup/sensitivity analyses
  - Ideally specify these a priori

How do you create a summary measure?

- Clinical example: Children with ear pain and an acute otitis media.
- Should they get antibiotics?

Research Questions:

1. In children with OM, are antibiotics effective for pain relief?
2. In children with OM, do antibiotics reduce the rate of complications (mastoiditis, hearing problems)?

3 studies are identified (examining effect of Abx on Pain)

- Study 1: N = 100 RR=1.41
- Study 2: N=200 RR=0.98
- Study 3: N=300 RR=1.01

- You could take the average effect: (1.41 + 0.98 + 1.01) / 3 = 1.13

- Is this a good summary measure?

Summary measure weighted by sample size

- Provide "weight" for studies based on their sample size

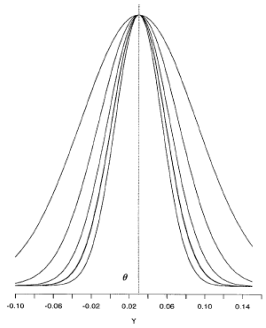
Study	N	RR
1	100	1.41
2	200	0.98
3	300	1.01
Total	600	

summary effect estimate= $\frac{\Sigma (N_i \times \text{effect estimate}_i)}{\Sigma(N_i)} = \frac{640}{600} = 1.07$

More refined: Provide "weight" by using inverse of variance

Study	N	RR	Var RR	Weight
1	100	1.41	3.0	0.33
2	200	0.98	0.1	10
3	300	1.01	0.05	20
Total	700			

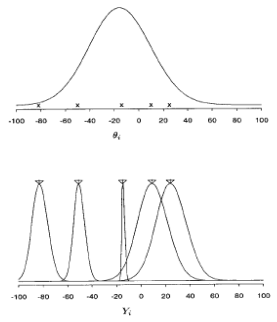
Fixed-effects model



Fixed-effects meta-analysis assumes that the intervention has a single true effect.

$$\frac{\sum_{i=1}^{k} W_i Y_i}{\sum_{i=1}^{k} W_i} \qquad W_i = \frac{1}{s_i^2}$$

Random-effects model



Random-effects meta-analysis assumes that the effect of the intervention varies across studies.

$$W_i(\tau) = \frac{1}{s_i^2 + \hat{\tau}^2} \qquad \frac{\sum_{i=1}^{k} W_i(\tau) Y_i}{\sum_{i=1}^{k} W_i(\tau)}$$

YS

Analytical Methods: Summary Points

- Always start the meta-analysis with a "visual meta-analysis" (i.e., a great table 1).
  - A clinician should be able to interpret the results
- Step 1: Calculate a summary measure = "weighted mean effect estimate"
  - You can combine anything, but use judgment
- Step 2: Assess for heterogeneity
  - Heterogeneity is not always a problem
- Step 3: Assess for publication bias
  - Both visual and statistical methods
- Step 4: Perform subgroup/sensitivity analyses
  - Ideally specify these a priori

Heterogeneity

- It is common for researchers who perform a meta-analysis to ask whether or not the effects are 'heterogeneous'.

- Formal evaluation of heterogeneity, should clarify whether and to what extent random variability is responsible for the differences

Heterogeneity is your friend!

- Clinical diversity
- Methodological diversity
- Statistical heterogeneity
  - I^2 Statistics or Cochran's Q
  - Bias testing or adjustment
  - Funnel plots
  - Subgroup analyses
  - Meta-regression

YS

Sources of Heterogeneity

- Differences in design (patient selection or treatment schedule)
- Heterogeneity at study level (patient mix or quality of the trial)
- Heterogeneity at the patient level (prognostic factors)
- Heterogeneity of outcomes (chance results)
- …it is common in meta-analysis, get used to it.

YS

Do you want Apples & Oranges or Fruit Salad?

OR

YS

Statistical tests of Heterogeneity

- Is the variation in the individual study findings likely due to chance?

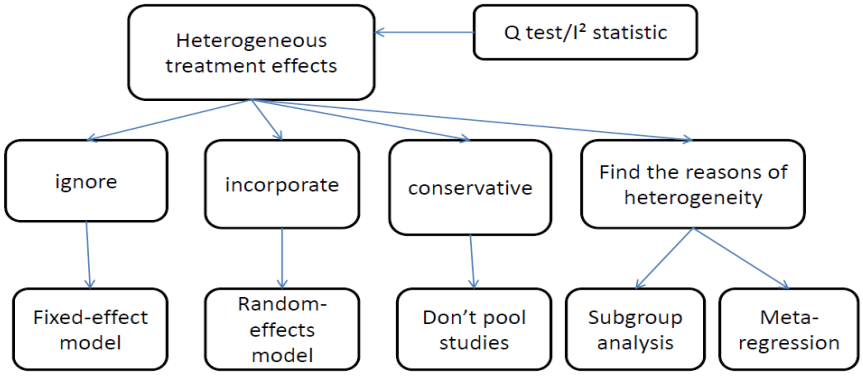
H_o: Effect estimate in each study is the same (or homogeneous)

H_a: Effect estimate in each study is not the same (or heterogeneous)

$Q = \Sigma(w_i \times (\ln OR_{mh} - \ln OR_i)^2)$ df = (N studies -1)

$p < 0.05$ or 0.10 = reject null, i.e., studies are heterogeneous

How to deal with heterogeneity



YS

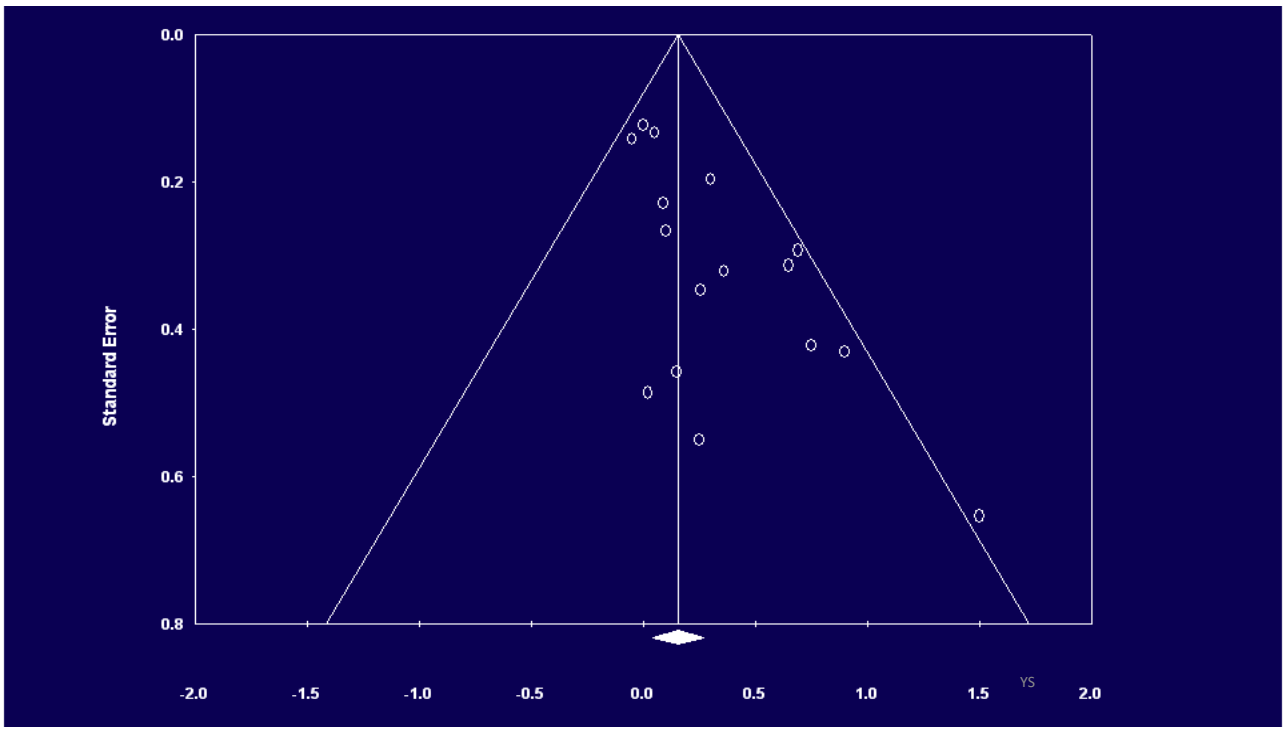
Analytical Methods: Summary Points

- Always start the meta-analysis with a "visual meta-analysis" (i.e., a great table 1).
  - A clinician should be able to interpret the results
- Step 1: Calculate a summary measure = "weighted mean effect estimate"
  - You can combine anything, but use judgment
- Step 2: Assess for heterogeneity
  - Heterogeneity is not always a problem
- Step 3: Assess for publication bias
  - Both visual and statistical methods
- Step 4: Perform subgroup/sensitivity analyses
  - Ideally specify these a priori

Assessing risk of publication bias

1. Funnel plots – plot study effect sizes by their standard errors
   - "interoccular analysis" of funnel plots is unreliable
2. Statistical tests (Egger's test and others)
3. Trim and fill analysis (need ~ 10+ studies)

YS



Test for bias: Begg's or Egger's tests

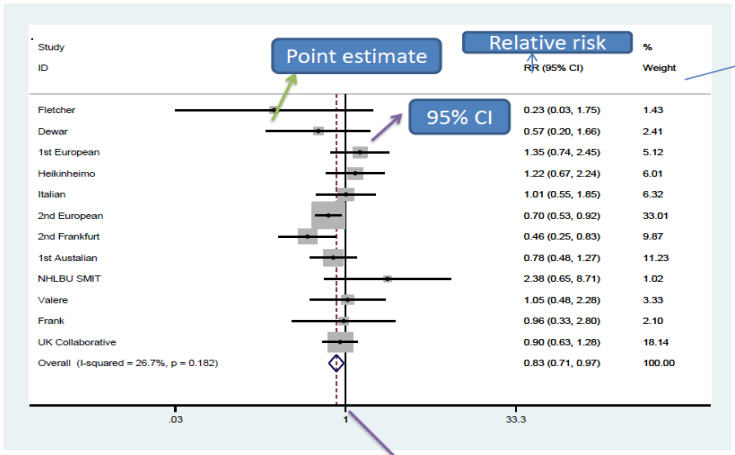
```
. metabias logrr _selogES, begg

Note: data input format theta se_theta assumed.

Begg's test for small-study effects:
Rank correlation between standardized intervention effect and its standard error

  adj. Kendall's Score (P-Q) =      18
         Std. Dev. of Score =    8.08
          Number of Studies =       8
                          z  =    2.23
                    Pr > |z| =   0.026
                          z  =    2.10 (continuity corrected)
                    Pr > |z| =   0.035 (continuity corrected)

. metabias logrr _selogES, egger

Note: data input format theta se_theta assumed.

Egger's test for small-study effects:
Regress standard normal deviate of intervention
effect estimate against its standard error

Number of studies =  8                                  Root MSE      =   1.213
------------------------------------------------------------------------------
     Std_Eff |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       slope |   -.083044   .0578502    -1.44   0.201    -.2245982    .0585102
        bias |   2.822296   .7860244     3.59   0.011     .8989634    4.745628
------------------------------------------------------------------------------

Test of H0: no small-study effects          P = 0.011

. metafunnel logrr _selogES, xtitle(Log Relative Risk) ytitle(Standard error of Log Relative Risk) xlab
> .01 0.1 1) xscale(log)
```

YS

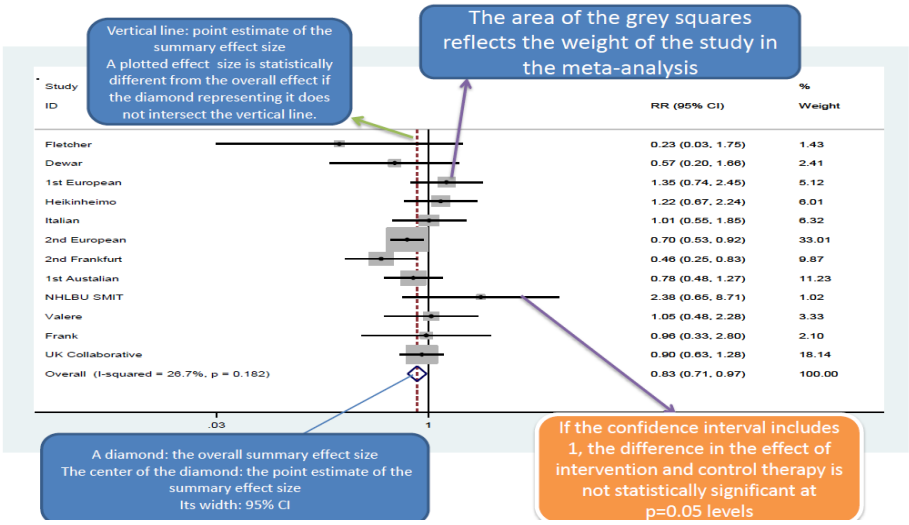
Analytical Methods: Summary Points

- Always start the meta-analysis with a "visual meta-analysis" (i.e., a great table 1).
  - A clinician should be able to interpret the results
- Step 1: Calculate a summary measure = "weighted mean effect estimate"
  - You can combine anything, but use judgment
- Step 2: Assess for heterogeneity
  - Heterogeneity is not always a problem
- Step 3: Assess for publication bias
  - Both visual and statistical methods
- Step 4: Perform subgroup/sensitivity analyses
  - Ideally specify these a priori

Forest plot



Forest plot



YS

Guidelines for Reporting Meta-Analyses and Critiquing Studies for Inclusion in your Analyses

http://www.consort-statement.org/ - reporting guidelines for reporting RCT's

http://www.prisma-statement.org/ - reporting guidelines for meta-analyses

http://www.emgo.nl/kc/analysis/statement/quorum%20review%20lancet%201991.pdf – reporting guidelines for meta-analyses of RCT's

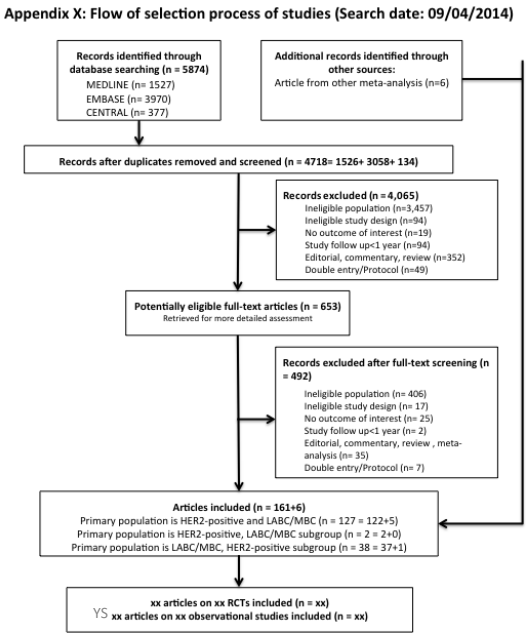
http://www.stard-statement.org/ - reporting guidelines for diagnostic studies

http://www.emgo.nl/kc/analysis/statements/MOOSE.pdf - reporting guidelines for meta-analyses of observation studies in Epidemiology

YS

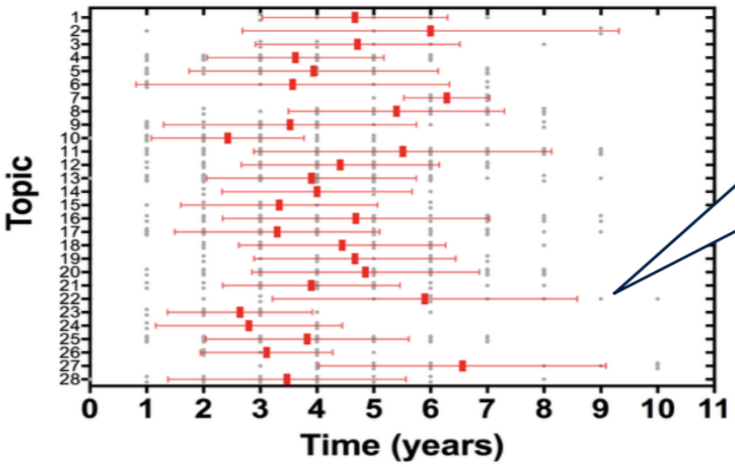
PRISMA flowchart for the Herceptin Project*

*Systematic evaluation of trends in survival among patients with HER2-positive advanced breast cancer



Update a systematic review

Time from study to systematic review



Elliott 2014 PLoS Med 11(2

Living systematic review

- Living systematic review (LSR) is an emerging approach to the updating of systematic reviews in which the review is updated frequently, typically at least each month, and usually published as online-only systematic reviews.

YS

Jump In and Do One!

Thank you
Yahya.salimi@kums.ac.ir