Dissemination of results in Systematic reviews

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Key Characteristics of Systematic Reviews

- Clearly stated title and objectives
- Comprehensive strategy to search for relevant studies (unpublished and published)
- Explicit and justified criteria for the inclusion or exclusion of any study
- Clear presentation of characteristics of each study included and an analysis of methodological quality
- Comprehensive list of all studies excluded and justification for exclusion

Linda N. Meurer, MD, MPH Department of Family and Community Medicine. "Systematic Synthesis of the Literature: Introduction to Meta-analysis". Power Point Presentation.

Characteristics of Systematic Reviews (cont.)

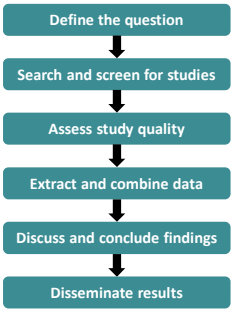
- Clear analysis of the results of the eligible studies
  - statistical synthesis of data (meta-analysis) if appropriate and possible;
  - or qualitative synthesis
- Structured report of the review clearly stating the aims, describing the methods and materials and reporting the results

Linda N. Meurer, MD, MPH Department of Family and Community Medicine. "Systematic Synthesis of the Literature: Introduction to Meta-analysis". Power Point Presentation.

An author of a good Systematic Review…

- Formulates a Question
- Conducts a Literature Search
- Refines the search by applying predetermined inclusion and exclusion criteria
- Extracts the appropriate data and assess their quality and validity
- Synthesizes, interprets, and reports data

Cochrane graphic illustration of the systematic review process



When can data in a systematic review be synthesized numerically?

- When data are NOT too sparse, of too low quality or too heterogeneous
  - For example: the patients, interventions and outcomes in each of the included studies are sufficiently similar

Meta-Analysis

- "Meta-analysis is a statistical technique for combining the results of independent, but similar, studies to obtain an overall estimate of treatment effect."

Margaliot, Zvi, Kevin C. Chung. "Systematic Reviews: A Primer for Plastic Surgery Research." PRS Journal. 120/7 (2007) p.1840

Meta-Analysis (cont.)

- "While all meta-analyses are based on systematic review of literature, not all systematic reviews necessarily include meta-analysis."

Margaliot, Zvi, Kevin C. Chung. "Systematic Reviews: A Primer for Plastic Surgery Research." PRS Journal. 120/7 (2007) p.1840

SR & Meta-analysis: Reporting the Results

- A SR & meta-analysis should include:
  - A title, abstract, an introduction
  - Methods, results, and discussion sections

The Introduction

- "The introduction should indicate the clinical question of interest, the hypothesis being tested, the types of treatment or exposure being studied, the study designs to be included, and a description of the study population."

Kevin C. Chung, MD, Patricia B. Burns, MPH, H. Myra Kim, ScD. "Clinical Perspective: A Practical Guide to Meta-Analysis." The Journal of Hand Surgery. Vol.31A No.10 December 2006. p. 1675

The Methods Section

- "The methods section should
  - describe the literature search, specifically the databases used, and if the search was restricted in any way.
  - The selection process for articles, quality assessment, methods of data abstraction, and synthesis."

Kevin C. Chung, MD, Patricia B. Burns, MPH, H. Myra Kim, ScD. "Clinical Perspective: A Practical Guide to Meta-Analysis." The Journal of Hand Surgery. Vol.31A No.10 December 2006. p. 1675

The Results Section

- The results section should
  - Include a flow chart of studies included
  - A figure displaying the results from each individual study (forest plot), results of heterogeneity testing, overall summary statistic, and results of a sensitivity analysis and meta-regression, if performed.
  - Funnel plots, trim & fill analysis

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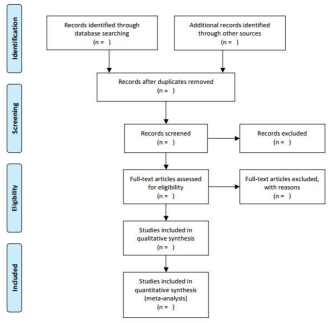
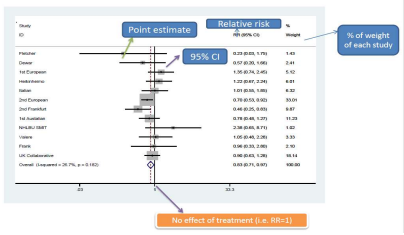
Interpretation of results

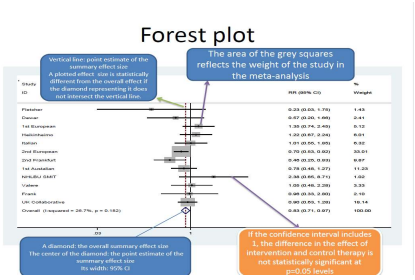
1. Quality of available evidence (number of studies in the review, risk of bias)
2. Precision of study-level effects
3. Homogeneity of effects across studies
4. Pooled effects
   a. magnitude and direction of point estimate
   b. precision (confidence intervals)
   c. statistical and clinical significance
   d. potential sources of bias
5. Moderator analysis



Forest plot



Forest plot



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)

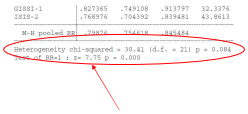
H_a: Effect estimate in each study is not the same (or heterogeneous)

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

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

To Test Homogeneity

- Compare Q to the (1 – α) critical value of the chi-square distribution with k-1 degrees of freedom
- Significant Q = heterogeneity
- Non-significant Q = homogeneity



X^2 (21)= 30.41, p=0.084, S

The I^2 statistic

- *What proportion of the observed variance reflects real differences in effect size?*

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%,$$

that is, the ratio of true heterogeneity to total variance across the observed effect estimates. The scale of I^2 has a range of 0–100%.

- Importantly, I^2 is not directly affected by the number of studies in the analysis.

The I^2 statistic

- I^2= 0% indicates that the variability of the study results is entirely due to random fluctuations. At a value of 100%, the variability would be explained solely by differences between the studies.

I^2 = 0%	no heterogeneity
I^2 = 25%	low heterogeneity
I^2 = 50%	moderate heterogeneity
I^2 = 75%	high heterogeneity

L'Abb´e plot in meta-analysis of RCTs

- The L'Abb´e plot provides an alternative way of displaying the data which allows inspection of the variability in treatment and control group event risks (rates).
- L' Abbé plots can be used for studies with Yes/No results, called dichotomous endpoints.

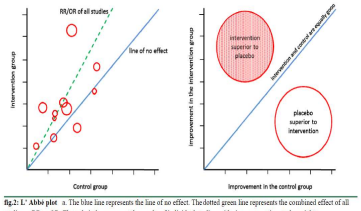
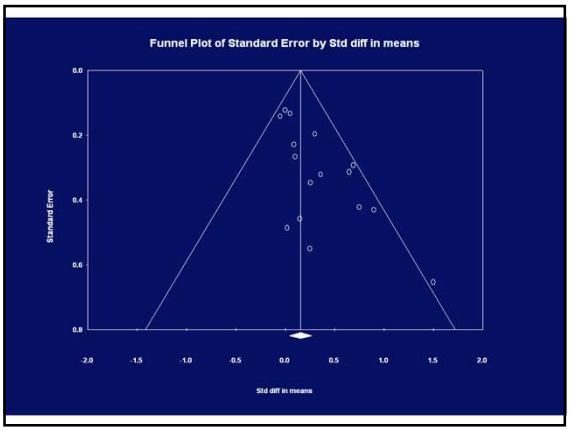


fig.2: L' Abbé plot a. The blue line represents the line of no effect. The dotted green line represents the combined effect of all studies as RR or OR. The red circles represent the results of individual studies, with size representing study weight. b. Schematic representation of a L' Abbé plot [11, 12]

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)



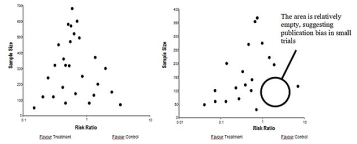
Funnel Plot

- Precision in the estimation of the true treatment effect increases as the sample size increases.
- Small studies scatter more widely at the bottom of the graph.
- In the absence of bias the plot should resemble a symmetrical inverted funnel.

A Funnel Plot

- "A funnel plot is used as a way to assess publication bias in meta-analysis."

Kevin C. Chung, MD, Patricia B. Burns, MPH, H. Myra Kim, ScD. "Clinical Perspective: A Practical Guide to Meta-Analysis." The Journal of Hand Surgery. Vol.31A No.10 December 2006. p. 1676



Publication bias caveat

- Funnel plot asymmetry does not always indicate bias
  - It is possible that smaller studies enrolled higher risk patients, for example, and therefore found a greater effect.
  - Small studies are often conducted before larger studies.

Statistical methods to assess publication bias

- Examine associations between study size and treatment effect.
  - Sensitivity is poor when < 20 studies
- Begg's test: an adjusted rank correlation
- Egger's test: a weighted regression of effect size vs. standard error.
  - Basically asks if the regression line has a non-zero slope
  - More sensitive than Begg's test, but more false positives, especially when 1) large treatment effects, 2) few events per trial, 3) all trials of similar size. (In these cases, one may decide *a priori* to use Begg's test).

Meta-Regression

- Subgroup analyses
- Identification of important covariates
- Control for baseline differences
- Control for quality score or sponsorship
- Caveat: Need sufficient studies to use this

Meta-Regression

- Meta-regression constitutes an effort to explain statistical heterogeneity in terms of study-level variables, thus summarizing the information not as a single value but as function.
- Since fixed effects models assume zero heterogeneity, it seems generally inappropriate to use a fixed effects meta-regression model.

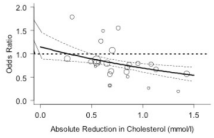
```
. metareg logor cholreduc, wsse(selogor)

Meta-regression                                 Number of obs =     28
REML estimate of between-study variance         tau2          =  .0097
% residual variation attributable to heterogeneity  I-squared_res =  31.34%
Proportion of between-study variance explained  Adj R-squared =  69.02%
With Knapp-Hartung modification
```

logor	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
cholreduc	-.5056849	.1834858	-2.76	0.011	-.8828453	-.1285244
_cons	.1467225	.1374629	1.07	0.296	-.1358367	.4292816

Example of a bubble plot with linear predictions

- When a single continuous covariate is fit, one common way to present the fitted model, sometimes referred to as a "bubble plot", is to graph the fitted regression line together with circles representing the estimates from each study, sized according to the precision of each estimate



Subgroup & Sensitivity Analysis

- Subgroup Analysis – MA of a subgroup of eligible studies
  - age
  - ethnicity
  - risk factors
  - treatment
- Sensitivity Analysis – add or delete questionable studies
  - eligibility
  - treatment

Subgroup Analysis

		OR	95% CI	N
Ever user Of estrogen:	All eligible studies	2.3*	2.1 - 2.5	29
	Cohort studies	1.7*	1.3 - 2.1	4
	Case-Control studies	2.4*	2.2 - 2.6	25
Dose of estrogen:	0.3 mg	3.9	1.6 - 9.5	3
	0.625 mg	3.4	2.0 - 5.6	4
	≥1.25 mg	5.8	4.5 - 7.5	9
Duration of use:	< 1 year	1.4	1.0 - 1.8	9
	1-5 years	2.8	2.3 - 3.5	12
	5-10 years	5.9	4.7 - 7.5	10
	≥10 years	9.5*	7.4 - 12.3	10
Regimen:	Cyclic	3.0*	2.4 - 3.8	8
	Daily	2.9*	2.2 - 3.8	8

Guidelines & Standards

1. Conduct of systematic reviews
- Cochrane Handbook(s) for systematic reviews of
  - Intervention effects (Higgins & Green, 2008)
  - Diagnostic test accuracy

2. Reporting
- PRISMA (Moher et al., 2009) - preferred reporting items for systematic reviews and meta-analysis

3. Assessing methodological quality of SRs

AMSTAR (Shea et al., 2007)

Meta-analysis (cont.)

- "Protocols for the reporting of meta-analysis results were developed for RCTs (Quality of Reports of Meta-analysis [QUOROM] and Observational Studies in Epidemiology [MOOSE]."

Kevin C. Chung, MD, Patricia B. Burns, MPH, H. Myra Kim, ScD. "Clinical Perspective: A Practical Guide to Meta-Analysis." The Journal of Hand Surgery. Vol.31A No.10 December 2006. p. 1672

Protocols

- The purpose of QUOROM and MOOSE guidelines is to provide proper procedures for conducting a meta-analysis and to standardize the methods of reporting a meta-analysis.

Kevin C. Chung, MD, Patricia B. Burns, MPH, H. Myra Kim, ScD. "Clinical Perspective: A Practical Guide to Meta-Analysis." The Journal of Hand Surgery. Vol.31A No.10 December 2006. p. 1672

Recommended Resources:

- "Reading Medical Articles," in Statistics in Medicine. Robert H. Riffenburgh. 2nd edition. Boston: Academic Press, 2006.
- Meta-analysis: New Developments and Applications in Medical and Social Sciences. Ralph Schulze, Heinz Holling, Dankmar Bohning (eds.) Toronto: Hogrefe & Huber Publishers, 2003.
- "Finding and Using Health Statistics" - an online course offered by the National Library of Medicine
- Margaliot, Zvi, Kevin C. Chung. Systematic Reviews: A Primer for Plastic Surgery Research. PRS Journal. 120/7 2007 .
- Kevin C. Chung, MD, Patricia B. Burns, MPH, H. Myra Kim, ScD. "Clinical Perspective: A Practical Guide to Meta-Analysis." The Journal of Hand Surgery. vol. 31A no.10 December 2006.

Thank you

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