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Systematic Reviews and Meta-analysis

Introduction to Clinical Research:
A Two-week Intensive Course
July 17, 2013

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Key messages

- Systematic reviews (SR) summarize existing evidence for a specific research question.
- SR are important to identify research gaps and limitations of previous studies, to justify new research and to inform decision makers.
- Meta-analyses provide summary estimates from different studies and are based on effect and variance estimates.

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Definition of a systematic review

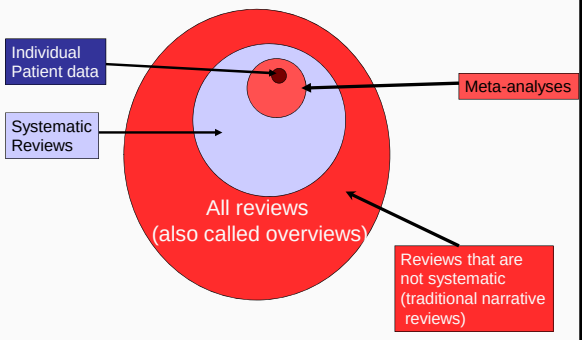
A review of existing evidence that uses a explicit and scientific methods

Contains a clear description of:

- Research question preferably using PICOTS
- Inclusion/exclusion criteria for studies
- Process used to identify studies
- Methods used to assess quality
- Methods use to abstract and summarize data

May or may not combine data quantitatively (meta-analysis)

Types of Reviews



Types of questions addressed by systematic reviews

Research questions	**Type of studies included**
Etiology (some exposure disease association)	Cohort or case-control studies
Diagnostic tests	Test accuracy studies, (RCTs)
Therapy	RCTs, observational studies
Prognosis (some predictor outcome association)	Cohort studies
Outcome measurement	Measurement studies
…	…

Roles of systematic reviews II

- Justification of new research, scientifically and ethically
- Learn about challenges of previous studies → avoid problems
- Inform decision makers
- Become an expert in topic
- Have another publication

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The steps of a systematic reviews

Ingredients of a systematic review

Well-formulated question

↓

Literature search

↓

Selection of studies

↓

Assessment of methodological quality

↓

Data extraction

↓

Synthesis of the data (meta-analysis)

↓

Conclusions

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Well-formulated question

Example

Population	Tobacco users
Intervention	Varenicline
Comparator	Placebo or active control (Nicotine replacement therapy or bupropion
Outcome	Serious adverse cardiovascular events

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Outcomes

Primary Outcome : Any serious ischemic or arrhythmic cardiovascular event reported during the double blind period of the trial [composite]

Secondary outcome : All cause mortality

July 18, 2013

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Identification of Articles

- Work with a librarian!
- Search in multiple databases, at least Medline and EMBASE
- Many studies not in English (>> than for RCTs)
- Hand-searching when time and resources available

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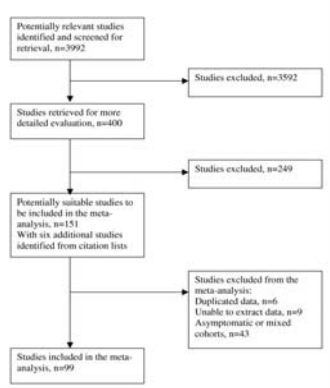
Example for study flow



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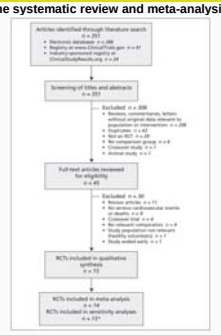
Selection of double-blind placebo-controlled randomized controlled trials (RCTs) for inclusion in the systematic review and meta-analysis



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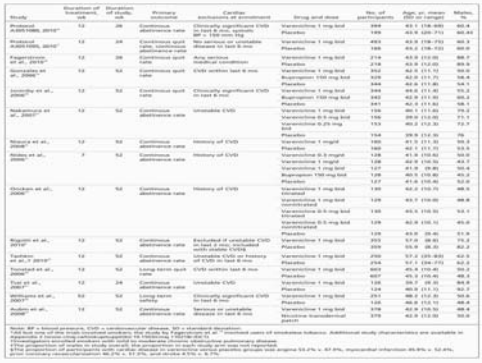
RCTs of Varenicline vs Comparators



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- 14 double-blind placebo-controlled trials-13 trials enrolled smokers; one trial enrolled smokeless tobacco users.
- 13 trials excluded patients with a history of cardiovascular disease; one trial included participants with stable cardiovascular disease but excluded those with unstable cardiovascular disease.
- Sample sizes from 250 to 1210.
- The primary outcome was the continuous abstinence rate in 12 trials the long-term quit rate in 1 trial and long-term safety in 1 trial.
- Duration of treatment ranged from 7 weeks to 52 weeks, and the total duration of study, including treatment and follow-up, ranged from 24 to 52 weeks.

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Risk of Bias

Study	Adequate sequence generation	Adequate allocation concealment	Adequate blinding of personnel and participants	Adequate reporting of withdrawals and loss to follow-up	Adequate reporting of serious adverse events
Double-blind RCTs					
Protocol A3051080[14]	Unclear	Unclear	Yes	Yes	Yes
Protocol A3051095[15]	Unclear	Unclear	Yes	Yes	Yes
Fagerstrom et al.[16]	Yes	Yes	Yes	Yes	Yes
Gonzales et al.[17]	Yes	Yes	Yes	Yes	Yes
Jorenby et al.[18]	Yes	Yes	Yes	Yes	Yes
Nakamura et al.[19]	Yes	Yes	Yes	Yes	Yes
Niaura et al.[20]	Yes	Yes	Yes	Yes	Yes
Nides et al.[21]	Yes	Yes	Yes	Yes	Yes
Oncken et al.[22]	Unclear	Unclear	Yes	Yes	Yes
Rigotti et al.[7]	Yes	Yes	Yes	Yes	Yes
Tashkin et al.[23]	Unclear	Unclear	Yes	Yes	Yes
Torstad et al.[24]	Yes	Yes	Yes	Yes	Yes
Tsai et al.[25]	Yes	Yes	Yes	Yes	Yes
Williams et al.[26]	Unclear	Unclear	Yes	Yes	Yes
Open-label RCT					
Aubin et al.[27]	Yes	Unclear	Yes	Yes	Yes

*Details of the methodology of the studies are available in Appendix 3 (www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.110218/-/DC1).

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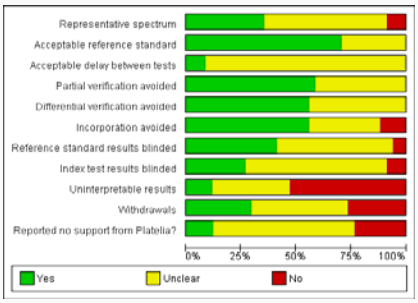
Methodological Quality Graph

QUADAS tool
(**Qu**ality **A**ssessment of **D**iagnostic **A**ccuracy **S**tudies)



Whiting et al. BMC Medical Research Methodology 2003, 3:25

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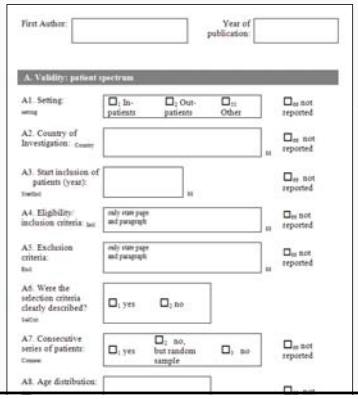
Data extraction – Independently by two reviewers



Challenges because of poor reporting

- Population → purpose of test?
- Index test and reference standard → eligibility? reproducibility?
- Only test accuracy reported without precision or 2x2 table

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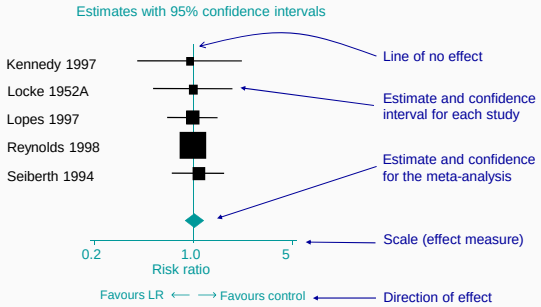
Meta-analysis

What is a Meta-analysis?

- An ***optional*** component of a systematic review
- Definition:
  "the statistical analysis of a large collection of analysis results from individual studies for the purpose of integrating the findings." (Glass 1976)

Presentation: the Forest Plot



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Inverse-variance Weighted Average

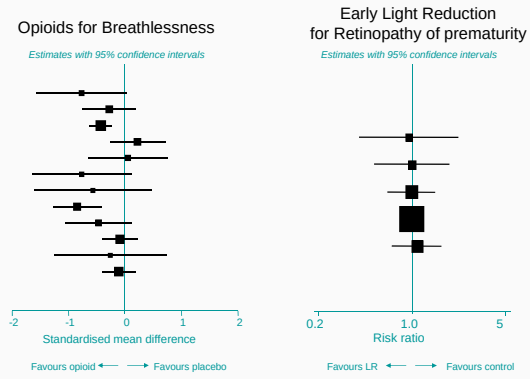
- Require from each study
  - estimate of treatment effect; and
  - standard error (or variance) of estimate
- Combine these using a weighted average:

$$weighted\ average = \frac{sum\ of\ (estimate \times wiehgt)}{sum\ of\ weights} = \frac{\sum Y_i W_i}{\sum W_i}$$

$$Variance\ (weighted\ average) = \frac{1}{sum\ of\ weights} = \frac{1}{\sum W_i}$$

Y_i - intervention effect estimated in the *i* th study
W_i - weight given to the *i* th study, and is usually chosen to be the inverse of the variance of the effect estimate

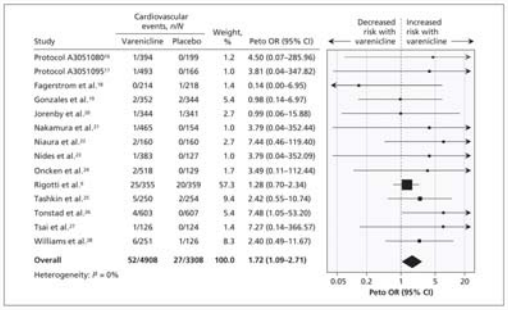
Why Do a Meta-analysis (cont'd)?



Why Do a Meta-analysis (cont'd)?

- **To increase power and precision**
  - detect effect as statistically significant; narrower CIs
- **To quantify effect sizes and their uncertainty**
  - reduce problems of interpretation due to sampling variation
- **To assess homogeneity/heterogeneity of results**
  - quantify between-study variation
- **To answer questions not posed by the individual studies**
  - factors that differ across studies
- **To settle controversies arising from conflicting studies**
  - generate new hypotheses

Meta-analysis of double-blind placebo-controlled randomized trials of the risk of serious adverse cardiovascular events associated with the use of varenicline.



Study	Cardiovascular events, *n/N* Varenicline	Placebo	Weight, %	Peto OR (95% CI)
Protocol A3051080[16]	1/394	0/199	1.2	4.50 (0.07–285.96)
Protocol A3051095[17]	1/493	0/166	1.0	3.81 (0.04–347.82)
Fagerstrom et al.[18]	0/214	1/218	1.4	0.14 (0.00–6.95)
Gonzales et al.[19]	2/352	2/344	5.4	0.98 (0.14–6.97)
Jorenby et al.[20]	1/344	1/341	2.7	0.99 (0.06–15.88)
Nakamura et al.[21]	1/465	0/154	1.0	3.79 (0.04–352.44)
Niaura et al.[22]	2/160	0/160	2.7	7.44 (0.46–119.40)
Nides et al.[23]	1/383	0/127	1.0	3.79 (0.04–352.09)
Oncken et al.[24]	2/518	0/129	1.7	3.49 (0.11–112.44)
Rigotti et al.[5]	25/355	20/359	57.3	1.28 (0.70–2.34)
Tashkin et al.[25]	5/250	2/254	9.4	2.42 (0.55–10.74)
Tonstad et al.[26]	4/603	0/607	5.4	7.48 (1.05–53.20)
Tsai et al.[27]	1/126	0/124	1.4	7.27 (0.14–366.57)
Williams et al.[28]	6/251	1/126	8.3	2.40 (0.49–11.67)
Overall	**52/4908**	**27/3308**	**100.0**	**1.72 (1.09–2.71)**
Heterogeneity: $I^2 = 0\%$				

Singh S et al. CMAJ 2011;183:1359-1366

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Sensitivity Analyses

Sensitivity analysis	Statistical model	No. of RCTs	Group; no. of events, *n/N* Varenicline	Control	OR (95% CI)
Placebo comparator					
Reciprocal of the treatment arm size					
Continuity correction	Fixed (MH)	14[5,16–28]	52/4908	27/3308	1.67 (1.06–2.64)
No continuity correction	Fixed (MH)	14[5,16–28]	52/4908	27/3308	1.77 (1.09–2.88)
Use of unadjudicated cardiovascular event data from one trial	Peto OR	14[5,16–28]	61/4908	29/3308	1.91 (1.25–2.94)
Exclusion of most influential study	Peto OR	13[16–28]	27/4553	7/2949	2.54 (1.26–5.12)
Placebo or active† comparator	Peto OR	15[5,16–29]	52/5286	30/4486	1.67 (1.07–2.62)

Note: CI = confidence interval, OR = odds ratio, MH = Mantel–Haenszel test, RCT = randomized controlled trial.
*Statistical heterogeneity was $I^2 = 0\%$ for all sensitivity analyses.
†Bupropion or nicotine replacement therapy.

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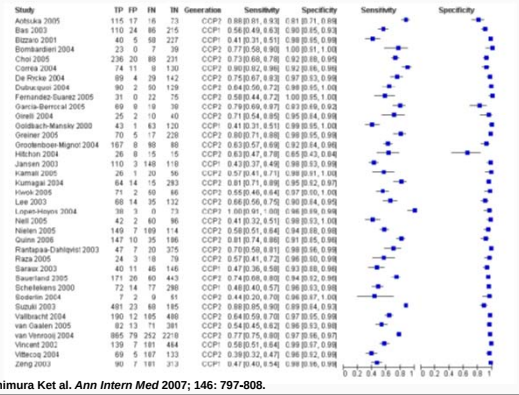
Forest plots: Example for diagnostic studies



Nishimura Ket al. *Ann Intern Med* 2007; 146: 797-808.

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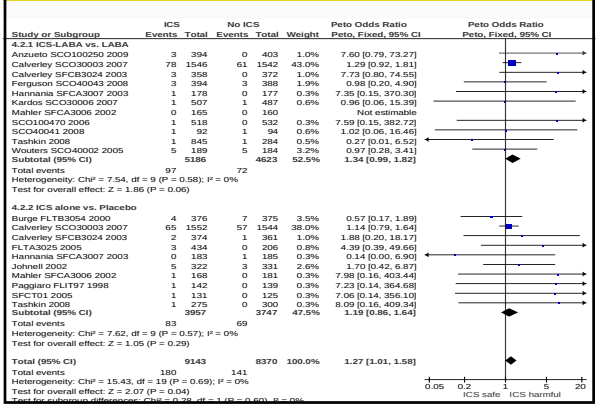
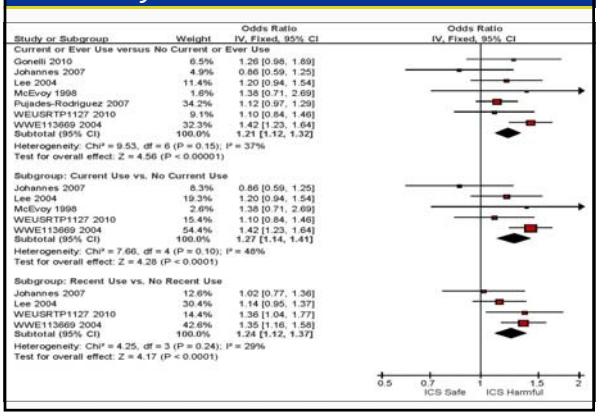
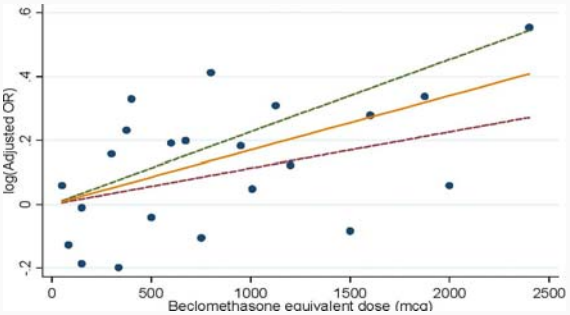
Meta-analysis of RCTs of ICS & Fractures



Meta-analysis of Observational Studies of



Dose Response Meta-Regression of ICS and Fractures in Observational Studies



Each 500 mcg increase in beclometasone dose equivalents was associated with a 9 % increase in the risk f fractures OR: 1.09 (95% CI 1.06 to 1.12; p<0.001).

When Not to Do a Meta-analysis

- **"Garbage in - garbage out"**
  - a meta-analysis is only as good as the studies in it
  - narrower confidence interval around combination of biased studies worse than the biased studies on their own
  - beware of reporting biases (e.g. publication bias)
- **"Mixing apples with oranges"**
  - not useful for learning about apples, although useful for learning about fruit!
  - studies must address the same question
    - though the question can, *and usually must,* be broader

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Number Needed to Harm for Cardiovascular Events based on Meta-analysis

Population	Source of baseline risk	Baseline Risk	Annualized Number Needed to Harm
Smokers without CVD	Control event rate of Meta-analysis	0.82%	167
Smokers with stable CVD	Control event rate of trial among smokers with CVD	5.8%	28

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Limitations

- Trials did not use adjudicated CV definitions
- Could not conduct time to event analysis due to individual patient data

Conclusions

- Among smokers exposure to varenicline is associated with a statistically significant increased risk of CV events

Key messages

- Systematic reviews (SR) summarize existing evidence for a specific research question.
- SR are important to identify research gaps and limitations of previous studies, to justify new research and to inform decision makers.
- Meta-analyses provide summary estimates from different studies and are based on effect and variance estimates.

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