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.

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 used to abstract and summarize data
May or may not combine data quantitatively (meta-analysis)
Types of Reviews

- Meta-analyses
- Reviews that are not systematic (traditional narrative reviews)
- All reviews (also called overviews)
- Individual Patient data
- Systematic Reviews

Types of questions addressed by systematic reviews

<table>
<thead>
<tr>
<th>Research questions</th>
<th>Type of studies included</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etiology (some exposure disease association)</td>
<td>Cohort or case-control studies</td>
</tr>
<tr>
<td>Diagnostic tests</td>
<td>Test accuracy studies, (RCTs)</td>
</tr>
<tr>
<td>Therapy</td>
<td>RCTs, observational studies</td>
</tr>
<tr>
<td>Prognosis (some predictor outcome association)</td>
<td>Cohort studies</td>
</tr>
<tr>
<td>Outcome measurement</td>
<td>Measurement studies</td>
</tr>
<tr>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

Roles of systematic reviews II

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

Well-formulated question
Example
- Population: Tobacco users
- Intervention: Varenicline
- Comparator: Placebo or active control (Nicotine replacement therapy or bupropion)
- Outcome: Serious adverse cardiovascular events
Primary Outcome: Any serious ischemic or arrhythmic cardiovascular event reported during the double blind period of the trial [composite]
Secondary outcome: All cause mortality

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

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

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

**RCTs of Varenicline vs Comparators**

- 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.

Singh S et al. CMAJ 2011;183:1359-1366
Features of Clinical Trials: 340.645

Risk of Bias

Methodological Quality Graph

QUADAS tool
(Quality Assessment of Diagnostic Accuracy Studies)

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
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

- Estimates with 95% confidence intervals
- Line of no effect
- Estimate and confidence interval for each study
- Estimate and confidence for the meta-analysis
- Scale (effect measure)
- Direction of effect
- Risk ratio
- Favour LR → Favour control
**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:

\[
\text{weighted average} = \frac{\sum (\text{estimate} \times \text{weight})}{\sum \text{weights}}
\]

\[
\text{Variance (weighted average)} = \frac{1}{\sum \text{weights}} \times \frac{1}{\sum W_i}
\]

- \(Y_i\) - 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

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**Why Do a Meta-analysis (cont’d)?**

**Opioids for Breathlessness**

- Estimates with 95% confidence intervals

**Early Light Reduction for Retinopathy of prematurity**

- Estimates with 95% confidence intervals

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**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.

Sensitivity Analyses

Forest plots: Example for diagnostic studies
Features of Clinical Trials: 340.645

Meta-analysis of RCTs of ICS & Fractures

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>ICS</th>
<th>Meta-ICS</th>
<th>Forest Meta</th>
<th>Peto Odds Ratio</th>
<th>Peto, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anzueto SCO100250 2009</td>
<td>586</td>
<td>606</td>
<td>0.95</td>
<td>0.94</td>
<td>0.82 to 1.08</td>
</tr>
<tr>
<td>Calverley SCO10025 2009</td>
<td>674</td>
<td>606</td>
<td>0.95</td>
<td>0.94</td>
<td>0.82 to 1.08</td>
</tr>
<tr>
<td>Calverley SFCB3024 2003</td>
<td>550</td>
<td>552</td>
<td>0.99</td>
<td>1.00</td>
<td>0.91 to 1.11</td>
</tr>
<tr>
<td>Ferguson SCO40043 2008</td>
<td>178</td>
<td>177</td>
<td>0.99</td>
<td>1.00</td>
<td>0.86 to 1.16</td>
</tr>
<tr>
<td>Hannania SFCA3007 2003</td>
<td>327</td>
<td>327</td>
<td>0.99</td>
<td>1.00</td>
<td>0.86 to 1.16</td>
</tr>
<tr>
<td>Kardos SCO30006 2007</td>
<td>327</td>
<td>327</td>
<td>0.99</td>
<td>1.00</td>
<td>0.86 to 1.16</td>
</tr>
<tr>
<td>Mahler SFCA3006 2002</td>
<td>327</td>
<td>327</td>
<td>0.99</td>
<td>1.00</td>
<td>0.86 to 1.16</td>
</tr>
<tr>
<td>SCO100470 2006</td>
<td>1</td>
<td>1</td>
<td>1.00</td>
<td>1.00</td>
<td>0.60 to 1.65</td>
</tr>
<tr>
<td>SCO40041 2008</td>
<td>1</td>
<td>1</td>
<td>1.00</td>
<td>1.00</td>
<td>0.60 to 1.65</td>
</tr>
<tr>
<td>Tashkin 2008</td>
<td>1</td>
<td>1</td>
<td>1.00</td>
<td>1.00</td>
<td>0.60 to 1.65</td>
</tr>
<tr>
<td>Wouters SCO40002 2005</td>
<td>1</td>
<td>1</td>
<td>1.00</td>
<td>1.00</td>
<td>0.60 to 1.65</td>
</tr>
</tbody>
</table>

Subtotal (95% CI) | Total events | Heterogeneity: Chi² = 7.54, df = 9 (P = 0.58); I² = 0%

Test for overall effect: Z = 1.86 (P = 0.06)

4.2.2 ICS alone vs. Placebo

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>ICS</th>
<th>Meta-ICS</th>
<th>Forest Meta</th>
<th>Peto Odds Ratio</th>
<th>Peto, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burge FLTB3054 2000</td>
<td>128</td>
<td>131</td>
<td>0.99</td>
<td>1.00</td>
<td>0.87 to 1.13</td>
</tr>
<tr>
<td>Calverley SCO30003 2007</td>
<td>128</td>
<td>131</td>
<td>0.99</td>
<td>1.00</td>
<td>0.87 to 1.13</td>
</tr>
<tr>
<td>Calverley SFCB3024 2003</td>
<td>128</td>
<td>131</td>
<td>0.99</td>
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<tr>
<td>FLTA3025 2005</td>
<td>128</td>
<td>131</td>
<td>0.99</td>
<td>1.00</td>
<td>0.87 to 1.13</td>
</tr>
<tr>
<td>Hannania SFCA3007 2003</td>
<td>128</td>
<td>131</td>
<td>0.99</td>
<td>1.00</td>
<td>0.87 to 1.13</td>
</tr>
<tr>
<td>Johnell 2002</td>
<td>128</td>
<td>131</td>
<td>0.99</td>
<td>1.00</td>
<td>0.87 to 1.13</td>
</tr>
<tr>
<td>Mahler SFCA3006 2002</td>
<td>128</td>
<td>131</td>
<td>0.99</td>
<td>1.00</td>
<td>0.87 to 1.13</td>
</tr>
<tr>
<td>Paggiaro FLIT97 1998</td>
<td>128</td>
<td>131</td>
<td>0.99</td>
<td>1.00</td>
<td>0.87 to 1.13</td>
</tr>
<tr>
<td>SFCT01 2005</td>
<td>128</td>
<td>131</td>
<td>0.99</td>
<td>1.00</td>
<td>0.87 to 1.13</td>
</tr>
<tr>
<td>Tashkin 2008</td>
<td>128</td>
<td>131</td>
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<td>1.00</td>
<td>0.87 to 1.13</td>
</tr>
</tbody>
</table>

Subtotal (95% CI) | Total events | Heterogeneity: Chi² = 7.62, df = 9 (P = 0.57); I² = 0%

Test for overall effect: Z = 1.05 (P = 0.29)

Total (95% CI) | Total events | Heterogeneity: Chi² = 15.43, df = 19 (P = 0.69); I² = 0%

Test for overall effect: Z = 2.07 (P = 0.04)

Test for subgroup differences: Chi² = 0.28, df = 1 (P = 0.60), I² = 0%

Meta-analysis of Observational Studies of ICS

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 of 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

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

<table>
<thead>
<tr>
<th>Population</th>
<th>Source of baseline risk</th>
<th>Baseline Risk</th>
<th>Annualized number needed to harm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smokers without CVD</td>
<td>Control event rate of Meta-analysis</td>
<td>0.82%</td>
<td>167</td>
</tr>
<tr>
<td>Smokers with stable CVD</td>
<td>Control event rate of trial among smokers with CVD</td>
<td>5.8%</td>
<td>28</td>
</tr>
</tbody>
</table>

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

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- SR are important to identify research gaps and limitations of previous studies, to justify new research and to inform decision makers.
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