Meta-analyses: how do they help, and when can they not?

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Systematic Reviews

Aims

- Discuss the scientific requirements for obtaining meaningful results for health benefits of foods or food constituents using meta-analyses
- Consider the advantages and disadvantages of systematic reviews & meta-analyses
What is a systematic review?

A systematic review attempts to collate all empirical evidence that fits pre-specified eligibility criteria in order to answer a specific research question. It uses explicit, systematic methods that are selected with a view to minimizing bias, thus providing more reliable findings from which conclusions can be drawn and decisions made ...

Supplemental Calcium in the Chemoprevention of Colorectal Cancer: A Systematic Review and Meta-Analysis

Christopher Carroll, PhD¹; Katy Cooper, PhD¹; Diana Papaioannou, MSc¹; Daniel Hind, PhD²; Hazel Pilgrim, MSc¹; and Paul Tappenden, MSc¹

¹Health Economics and Decision Science, School of Health and Related Research, University of Sheffield, Sheffield, United Kingdom; and ²Clinical Trials Research Unit, School of Health and Related Research, University of Sheffield, Sheffield, United Kingdom

ABSTRACT

Objective: The aim of the review was to assess the evidence for the effectiveness of calcium in reducing the recurrence of adenomas and the occurrence of colorectal cancer among populations at high, intermediate, and low risk of the disease.

Methods: A systematic review of randomized controlled trials (RCTs) was performed to compare calcium

Results: The original and update searches of electronic databases produced 3835 citations, of which 6 studies (8 papers) met the inclusion criteria. Supplemental calcium had no effect on the number of adenomas in 1 small trial of patients with FAP. Meta-analysis of 3 trials in individuals with a history of adenomas showed a statistically significant reduction in the RR for adenoma recurrence (RR = 0.80 [95% CI, 0.69–0.94], P = 0.006) for those
What is meta-analysis?

- What do you think?
- One definition is:
  - "...the use of statistical methods to summarize the results of independent studies (Glass 1976)."

Meta-analysis: supplemental calcium vs. placebo, outcome adenoma, population those with history of adenoma
What is meta-analysis?

- It is ONLY useful where it is part of a systematic review.
Imagine you are a practicing medical doctor

- You have diagnosed a patient with an illness
- You have recently heard colleagues discussing a new and much better drug treatment for this illness
- How do you decide whether this new treatment is really the best option for the patient?
Hierarchy of evidence
(questions about efficacy of interventions)
What are the requirements for meaningful SR results for health benefits of foods or constituents?

Systematic reviews (with or without meta-analyses) can be useful if:

- They ask a clear and specific question
- They are carried out rigorously - so as to minimise bias and random error
<table>
<thead>
<tr>
<th>A clear and specific question?</th>
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<tbody>
<tr>
<td>1. Does calcium improve the health of adults?</td>
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<td>2. Do micronutrient supplements reduce the risk of cancer?</td>
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<td>3. Does calcium supplementation reduce the risk of adenoma?</td>
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<td>4. Does calcium supplementation reduce the risk of adenoma in those with/without a history of adenoma?</td>
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- Protocol published
- Pre-specified inclusion criteria
- Exhaustive search strategy - so no studies are missed
- Duplicate assessments of inclusion, validity, data extraction
- Validity assessed
- Data pooled and synthesised
- Sources of heterogeneity discussed
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- Protocol published
- Carroll et al did not mention any published protocol
- PROSPERO now allows pre-registration of SR protocols: http://www.crd.york.ac.uk/prospero/
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A clear and specific question leading into inclusion criteria

<table>
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<th>A good question includes (PICOT):</th>
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<td>1.</td>
<td><strong>Participants</strong>: adults with/without adenoma</td>
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<td>2.</td>
<td><strong>Intervention</strong>: calcium supps (alone or with other chemo-preventive agents)</td>
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<tr>
<td>3.</td>
<td><strong>Control</strong>: placebo or other agents</td>
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<tr>
<td>4.</td>
<td><strong>Outcome</strong>: adenoma or bowel cancer</td>
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<tr>
<td>5.</td>
<td><strong>Time</strong>: any duration</td>
</tr>
<tr>
<td>6.</td>
<td><strong>Methodology</strong>: randomised cont. trial</td>
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Exhaustive search strategy – so no studies are missed

Carroll et al:
- thesaurus and free text terms for calcium and adenomas or colorectal CA
- RCT filter used
- 9 databases searched: including Cochrane, MEDLINE, CINAHL, EMBASE, WoS
- No language or date restrictions
- Searched to January 2010
- Reference lists checked
Figure 1. Flow diagram of randomized controlled trials (RCTs) comparing supplemental calcium, with or without other agents, versus placebo for effectiveness in reducing the recurrence of adenomas and the occurrence of colorectal cancer among populations at high, intermediate, and low risk of the disease. FAP = familial adenomatous polyposis.
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- Validity assessed
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Duplicate assessments of inclusion, validity, data extraction

Carroll et al:
- Titles and abstracts assessed by 1 reviewer (10% duplicated)
- Inclusion of full papers by 1 reviewer (where unclear several discussed)
- Data extracted and validity assessed by 1 reviewer, checked by second reviewer
They are carried out rigorously to minimise bias and random error.

- Protocol published
- Clear pre-specified inclusion criteria
- Exhaustive search strategy – so no studies are missed
- Duplicate assessments of inclusion, validity, data extraction
- **Validity assessed**
- Data pooled and synthesised
- Sources of heterogeneity discussed
fied were left in situ, and only new polyps were reported as outcome events at the follow-up colonoscopy.

The Baron et al\textsuperscript{31} and Bonithon-Kopp et al\textsuperscript{32} trials were both judged to be good quality. In both studies, allocation concealment was adequate; a central, computer-generated randomization sequence was used, and methods of blinding were adequate. The Hofstad et al\textsuperscript{34} trial was of lower quality: methods of allocation, randomization, and blinding were all unclear. Event data were also unpublished, but were provided by the author on request. In all 3 studies, between 10\% and 20\% of randomized participants were excluded from the analyses because of death, failure to have a colonoscopy, or loss to follow-up, but intent-to-treat analyses and power calculations were performed by all 3 studies and the required sample size was achieved.

Meta-analysis of all 3 trials (1279 participants in the comparison and a
<table>
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<th>Tools for assessing study validity</th>
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<tr>
<td><strong>Cochrane Handbook</strong> is ideal for assessing validity of RCTs (chapter 8, <a href="http://www.cochrane.org/training/cochrane-handbook">www.cochrane.org/training/cochrane-handbook</a>)</td>
</tr>
<tr>
<td><strong>Tools for other types of study:</strong></td>
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<tr>
<td>- <strong>Newcastle Ottawa Scale</strong> (<a href="http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp">www.ohri.ca/programs/clinical_epidemiology/oxford.asp</a>)</td>
</tr>
<tr>
<td>- <strong>Downs &amp; Black</strong> (<a href="http://jepid.oxfordjournals.org/content/52/5/377.full">J Epid Comm Health 1998;52:377–84</a>)</td>
</tr>
<tr>
<td>- <strong>Summary of tools in Cochrane Handbk, ch 13</strong></td>
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Why is validity so vital?

- Studies are approximating the truth.
- Their methodological flaws limit how closely they mirror the truth.
- If, despite randomisation, ill-er people tend to be found in the intervention group, they will tend to recover to a greater degree.
- This will happen even if the intervention is useless.
Why is validity so vital?

- Methodological rigour in randomisation and allocation concealment are key to how far we trust results of a randomised controlled trial.
- Combining biased studies can produce a consistently biased answer.
- Regulatory agencies will also focus on study validity in making decisions about claims.
They are carried out rigorously—to minimise bias and random error

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- **Data pooled and synthesised**
- Sources of heterogeneity discussed
Meta-analysis: supplemental calcium vs. placebo, outcome adenoma, population those with history of adenoma


- How many studies of what methodology? – 2 RCTs
- How many included participants? – overall almost 1200 people, 350 events
- What is the answer? - RR 0.82 (95% CI 0.69 to 0.98)
- Are different studies consistent? - $I^2$ 0%

Figure 3. Results of meta-analysis comparing supplemental calcium alone versus placebo for effectiveness in reducing the recurrence of any adenoma among populations with a history of adenomas.
They are carried out rigorously - to minimise bias and random error

- Protocol published
- Clear pre-specified inclusion criteria
- Exhaustive search strategy - so no studies are missed
- Duplicate assessments of inclusion, validity, data extraction
- Validity assessed
- Data pooled and synthesised
- Sources of heterogeneity discussed
Where studies are not consistent

e.g. different sorts of studies or statistical heterogeneity

- Explore the (pre-specified) reasons for heterogeneity
  - Dose
  - Duration
  - Level of risk or degree of illness etc
• This analysis is of those at low risk of adenomas
• Both compare calcium and vit D vs. placebo
• 2 studies, but one very small
• 37000 people, over 300 adenomas
• RR 0.62 (95% CI 0.11 to 3.40)
• $I^2$ 58%

Figure 6. Results of meta-analysis comparing supplemental calcium, with or without vitamin D, versus placebo for reducing the incidence of colorectal cancer among populations with no increased baseline risk of colorectal cancer.
Summary: does supplemental calcium reduce future adenoma in those with history of adenoma?

- Yes, significant reduction in new adenomas in those on supplementation compared to those without in those with a history of adenoma (2 high quality, consistent ($I^2$ 0%) studies, RR 0.82 (95% CI 0.69 to 0.98) in 1200 people experiencing 350 new adenomas).
- BUT only 2 trials, would be useful to check generalisability in another population.
- The review is not perfect, but is of reasonable validity in its own methodology.
Summary: does supplemental calcium reduce future adenoma in those with history of adenoma?

- Systematic reviews allow us to understand not just whether an intervention works, but for whom it works better (or which dose works). 
- Carroll suggests that calcium supplementation is protective of adenoma in those who have had adenoma in the past, 
- BUT there is no evidence of this protection in those at low risk (though we need more studies to check this), 
- This allows us to understand how to target the intervention.
So how is this different from a normal (literature) review?

- Literature reviews often only discuss the studies that support the overall opinion of the review - may be biased, or from a partial perspective.
Is this a good systematic review?

- Is there a clearly focussed question?
- How well have they searched for all the studies that might be relevant?
- How well have studies been filtered to select those that meet the review’s criteria?
- Has the quality of studies been assessed?
- How well have the results been synthesised?
- How skilled was the analysis and interpretation?

(the CASP criteria are useful, see www.phru.nhs.uk/Pages/PHD/resources.htm)
In summary:

A systematic review is only useful when it reduces bias by:

- Addressing a specific question (PICOT)
- Pre-publishing a protocol
- Searching carefully to find ALL relevant studies
- Assessing inclusion in duplicate against pre-specified criteria
- Duplicating data extraction
- Assessing study validity carefully & in duplicate

Meta-analysis is only useful when:

- It is part of a systematic review
- It pools similar studies
- It explores any heterogeneity
What are the scientific requirements for obtaining meaningful results for health benefits of foods or food constituents using meta-analyses?

Systematic reviews (with or without meta-analyses) can be useful if:

- They ask a clear and specific question
- They are carried out rigorously - so as to minimise bias and random error
Advantages and disadvantages of systematic review & meta-analysis:

- Systematic reviews take time, money, skill and determination to ensure they are of high quality

- They provide the highest quality (best) current answer to your question
  - Can guide practice by providing a solid answer to the question OR
  - Guide further research to achieve the answer
Meta-analyses: how do they help, and when can they not?
Further reading

