Improving reporting for systematic reviews & meta-analyses

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Guidance:

Session 7-Improving reporting for systematic reviews and meta-analyses (by Lee Hooper)

Please take the following into consideration:

- **Outline the recommendation of PRISMA (reporting guidelines for systematic reviews of RCTs) and MOOSE (the reporting guidelines for systematic reviews of cohort data)**
  - Emphasis should be given to reporting guidelines for **systematic reviews of RCTs**. Where posssible, it would be helpful to EFSA if you could give examples of **RCTs** in **human nutrition.**
  - The GRADE system should not be covered
- At the end of your presentation, we would appreciate **your view** on:
  - **The extent to which the existing guidelines (**PRISMA, MOOSE) **could apply to or help to improve reporting of systematic reviews & meta-analyses of RCTs for health claim substantiation.**

Aims

- Outline PRISMA & MOOSE recommendations
- Consider why each element is important to consider in guidance
- Discuss the extent to which PRISMA & MOOSE could improve reporting of systematic reviews & meta-analyses of RCTs for health claim substantiation.

Key references

- Moher, Liberati, Tetzlaff, Altman, The PRISMA Group (2009) Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed.1000097
- Liberati, Altman, Tetzlaff et al, (2009) The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration, PLoS Med 6(7): e1000100 doi:10.1371/journal.pmed.1000100
- Stroup, Berlin, Morton et al. (2000) Meta-analysis of Observational Studies in Epidemiology: A Proposal for Reporting *JAMA. 283(15):2008-2012*

Systematic review definition

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

Liberati, Altman et al, PLoS Med 6(7): e1000100

Meta-analysis definition

- "Meta-analysis is the use of statistical techniques to integrate and summarize the results of included studies. Many systematic reviews contain meta-analyses, but not all. By combining information from all relevant studies, meta-analyses can provide more precise estimates of the effects of health care than those derived from the individual studies included within a review."

Liberati, Altman et al, PLoS Med 6(7): e1000100

Carroll et al, Clin Ther. 2010;32:789–803

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

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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 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
- Reported well enough to allow assessment of the level of bias in the underlying evidence & in the review process

A clear and specific question?

INTRODUCTION		
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).

1. Participants – people at high, inter-mediate & low risk of colorectal cancer
2. Intervention – supplemental calcium
3. Comparison – not explicit (lack of supp)
4. Outcome – recurrence of adenoma & occurrence of colorectal cancer
5. Study design – not explicit

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They are carried out rigorously –to minimise bias and random error

- Protocol published
- Pre-specified inclusion criteria
- Exhaustive search strategy – so no studies are missed
- Strong assessments of inclusion, validity, data extraction
- Risk of bias within & between studies
- Data pooled and synthesised, heterogeneity explored

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METHODS		
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (web address), and, if available, provide registration information including registration number.

- 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

Eligibility criteria	6	Specify study characteristics (PICOS, length of follow-up) & report characteristics (years considered, language, publication status) used as criteria for eligibility, giving rationale.

"….RCTs of calcium (with or without other chemo-preventive agents) in adults with FAP, HNPCC, or a history of colorectal adenomas, or with no increased baseline risk of colorectal cancer. Relevant comparators were specified as either placebo or agents other than calcium. Relevant outcomes included the recurrence of adenomas or advanced adenomas, or the occurrence of colorectal cancer."

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Exhaustive search strategy – so no studies are missed

Information sources	7	Describe all info. sources (databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.

- As readers we want to ensure that the reviewers tried hard to find all the relevant included studies

Exhaustive search strategy – so no studies are missed

Carroll et al:

- thesaurus and free text terms for calcium and adenomas or colorectal CA
- Published RCT filter used
- 9 databases searched: including Cochrane, MEDLINE, CINAHL, EMBASE, WoS
- No language or date restrictions
- Searched to January 2010
- Reference lists checked
- **No** full text search strategy provided

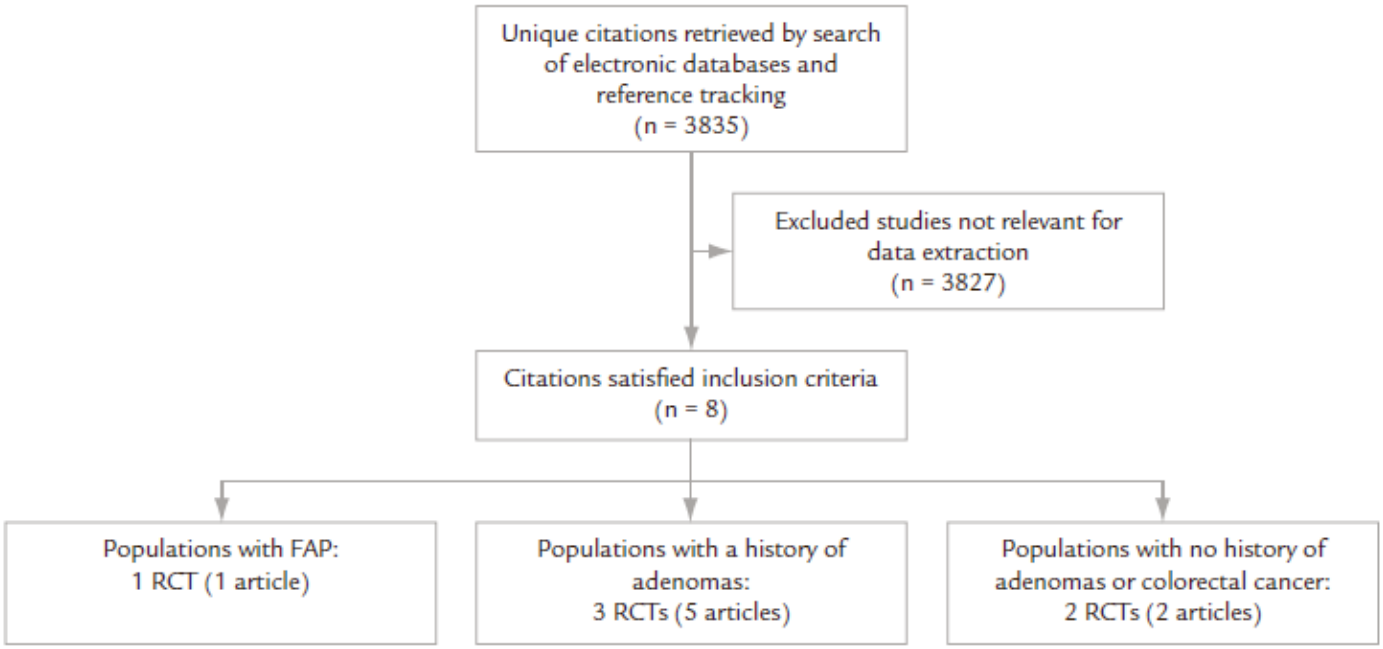

Figure 1. Flow diagram of randomized controlled trials (RCTs) comparing supplemental calcium, with or without other agents, versus placebo for effectiveness in reducing the recurrence of adenomas and the occurrence of colorectal cancer among populations at high, intermediate, and low risk of the disease. FAP = familial adenomatous polyposis.

Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.

tion, and blinding were all unclear. Event data were also

also had an interaction effect with calcium, which could

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Strong assessments of inclusion, validity, data extraction

Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, included in the meta-analysis).
Data collection process	10	Describe method of data extraction from reports (piloted forms, independently, in duplicate) & any processes for obtaining and confirming data from investigators.
Data items	11	List and define all variables for which data were sought (PICOS, funding sources) and any assumptions and simplifications made.

Strong 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 onto form designed for review
- Contact with 1 researcher stated (results)
- No details of what variables extracted

Table I. Characteristics of trials 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.

Study (Year)	Study Design	Population and Age	Intervention	Control	Treatment Duration	Follow-Up Duration
FAP populations						
Thomas et al (1993)[29]	DB, RCT	28 FAP patients with previous colectomy and adenomas, aged 16–65 years (median, 38 years)	Calcium carbonate 1500 mg/d (number of patients not reported)	Placebo (number of patients not reported)	6 Months	6 Months
Populations with an increased risk of colorectal cancer (populations with a history of adenomas)						
Baron et al (1999)[30,31]	DB, RCT	History of adenomas, aged ≤80 years (mean, 61 years)	Calcium 1200 mg/d (n = 464)	Placebo (n = 466)	4 Years	4 Years (from end of year 1 to end of year 4)
Bonithon-Kopp et al (2000)[32]	DB, RCT	History of adenomas, aged 35–75 years eligible (mean, 59 years)	Calcium 2000 mg/d (n = 204)	Placebo (n = 212)	3 Years	3 Years
Hofstad et al	DB,	History of adenomas	Calcium 1600 mg/d + β-carotene	Placebo	3 Years	3 Years

Study charact-eristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.

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Risk of bias within studies assessed

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.

- "…allocation, randomization and blinding, the comparability of the treatment and control groups, and the appropriateness and quality of the analysis performed."
- But exactly how these were assessed and graded was not stated.

Risk of bias within studies assessed

- "the Wactawski-Wende study was found to be of good quality: it used adequate methods of allocation concealment, randomization, and blinding, and excluded <5% of randomized participants. A power calculation was performed, and the required sample size was achieved.
- …Lappe was of lower quality: the generation of the randomization sequence was adequate, but allocation concealment and methods of blinding were unclear; between 5% and 20% of randomized participants were excluded and no power calculation was performed. Intent-to-treat analyses were performed in both studies.

Why is risk of bias 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 risk of bias 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.

Tools for assessing within study bias

- Cochrane Handbook is ideal for assessing validity of RCTs (chapter 8, www.cochrane.org/training/cochrane-handbook)
- Tools for other types of study:
  - Newcastle Ottawa Scale (www.ohri.ca/programs/clinical_epidemiology/oxford.asp)
  - Downs & Black (J Epid Comm Health 1998;52:377–84)
  - Summary of tools in Cochrane Handbk, ch 13

Bias across studies assessed

Risk of bias across studies	22	Present results of any assessment of risk of bias across studies
Additional analysis	23	Give results of additional analyses, if done (sensitivity or subgroup analyses, meta-regression

- Risk of bias across studies not mentioned in the methodology or results
- Results of additional analyses presented but unclear if pre-planned or post-hoc

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Data pooled and synthesised

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).
Synthesis of results	14	Describe methods of handling data and combining results of studies, including measures of consistency (e.g., I^2)
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting).
Additional analyses	16	Describe methods of additional analyses (sensitivity or subgroup analyses, meta-regression), & which were pre-specified.

Data pooled and synthesised

- "…relative risks and risk differences were reported with 95% CIs".
- "random-effects model was used… Statistical heterogeneity described using I^2 statistic. Only randomized participants for whom a valid outcome had been evaluated and reported were included".
- "The different population groups were not pooled in the analyses"
- Publication bias and selective reporting not mentioned, nor additional analyses

Study or Subgroup	Calcium Adenomas	Calcium Total	Placebo Adenomas	Placebo Total	Weight, %	Random Risk Ratio (95% CI)
Baron et al (1999)[30,31]	127	409	159	423	84.8	0.83 (0.68–1.00)
Bonithon-Kopp et al (2000)[32]	28	176	36	178	15.2	0.79 (0.50–1.23)
Total (95% CI)		585		601	100.0	0.82 (0.69–0.98)
Total events	155		195			

Heterogeneity: $\tau^2 = 0.00$, $\chi^2 = 0.04$, $df = 1$ ($P = 0.84$), $I^2 = 0\%$

Test for overall effect: $z = 2.23$ ($P = 0.03$)

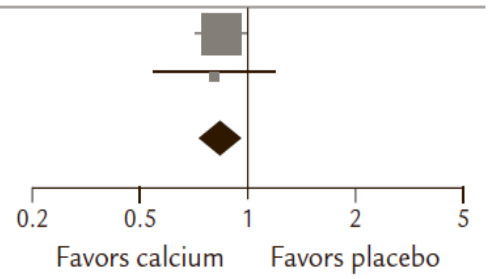

Figure 3. Results of meta-analysis comparing supplemental calcium alone versus placebo for effectiveness in reducing the recurrence of any adenoma among populations with a history of adenomas.

Results of individual studies	20	For all outcomes considered present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.

Carroll et al, Clin Ther. 2010;32:789–803

Meta-analysis: supplemental calcium with or without vitamin D vs. placebo, outcome colorectal cancer, population at normal risk of colorectal cancer

Study or Subgroup	Calcium ± Vitamin D Adenomas	Calcium ± Vitamin D Total	Placebo Adenomas	Placebo Total	Weight, %	Random Risk Ratio (95% CI)
Lappe et al (2007)[35]	1	891	2	288	29.6	0.16 (0.01–1.78)
Wactawski-Wende et al (2006)[36]	168	18,176	154	18,106	70.4	1.09 (0.87–1.35)
Total (95% CI)		19,067		18,394	100.0	0.62 (0.11–3.40)
Total events	169		156			

Heterogeneity: $\tau^2 = 1.06$, $\chi^2 = 2.41$, $df = 1$ ($P = 0.12$), $I^2 = 58\%$
Test for overall effect: $z = 0.55$ ($P = 0.58$)

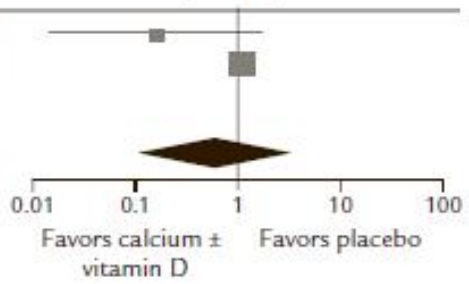

Figure 6. Results of meta-analysis comparing supplemental calcium, with or without vitamin D, versus placebo for reducing the incidence of colorectal cancer among populations with no increased baseline risk of colorectal cancer.

- How many studies of what methodology? – 2 RCTs
- How many included participants? – overall over 37000 people, 325 events
- What is the answer? - RR 0.62 (95% CI 0.11 to 3.40)
- Are different studies consistent? - I^2 58%

Additional reporting guidance

FUNDING		
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.

- "This study was funded, in part, by the UK National Coordinating Centre for Health Technology Assessment. The authors have indicated that they have no conflicts of interest to declare, and that there was no industry support for or involvement in this study.
- The authors wish to thank Bjorn Hofstad for providing unpublished data."

Summary: does supplemental calcium reduce colorectal cancer in the general population?

- No, no significant effect on colorectal cancer of those on supplementation compared to those on placebo in people at low risk (2 studies, 1 high quality & 1 lower, heterogeneous, inconsistent (I^2 58%), RR 0.62 (95% CI 0.11 to 3.40) in 37000 people experiencing 325 new cancers).
- Carroll suggests that calcium supplementation is protective of adenoma in those who have had adenoma in the past
- More cautious about this as it depends on all studies being found and there is an intrinsic bias towards "significant" findings

MOOSE - reporting stds for systematic reviews of observational studies

Reporting standards are very similar, but differ with reference to:

- Assessing confounding
- Validity assessment
- Reasons for exclusion of particular studies requested

Other reporting standards

MECIR: Methodological Expectations of Cochrane Intervention Reviews

- Cochrane has produced both standards of conduct and standards for reporting of Cochrane reviews
- While PRISMA has 27 items in its checklist MECIR reporting standards have 108
- http://www.editorial-unit.cochrane.org/mecir

In summary:

We need to interpret the results (bottom line) of a systematic review in light of:

- Effect size and statistical significance
- The validity of the included studies
- The number of studies and participants
- Any heterogeneity between the studies, and whether this heterogeneity can be explained
- Exploration of the presence of publication bias
- The credibility of the review (finding all the studies, good judgement, not data dredging)
- We can only do this if the process and results of the systematic review are reported in enough detail to allow us to judge appropriately

Discuss the extent to which PRISMA & MOOSE could improve reporting of systematic reviews & meta-analyses of RCTs for health claim substantiation.

- Without this level of detail in reporting of systematic reviews it is not possible to assess how valid the summary answer provided is – so we should not be basing guidance on them
- (and having to report our process may drive higher standards of conduct)

Thank you for your attention!