

Meta-Analysis

Susan Stewart, Ph.D.

Division of Biostatistics

Department of Public Health Sciences

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Acknowledgements

Jimmy Hwang, Ph.D.
UCSF Biostatistics Core

Topics Covered

- Definitions: systematic review and meta-analysis
- PRISMA checklist: guide to good practice
- Example 1: Recently published meta-analysis
- Example 2: Meta-analysis calculations

Systematic Review

- Attempts to collate all empirical evidence that fits pre-specified eligibility criteria in order to answer a specific research question.
- 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.

Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0. Updated March 2011.

Key Characteristics

- Clearly stated set of objectives with pre-defined eligibility criteria for studies
- Explicit, reproducible methodology
- Systematic search that attempts to identify all studies that would meet the eligibility criteria
- Assessment of the validity of the findings of the included studies
- Systematic presentation and synthesis of the characteristics and findings of the included studies.

What is meta-analysis?

- **Meta-analysis** is the use of statistical methods to summarize the results of independent studies.
 - Many systematic reviews contain meta-analyses, but not all.
 - Can provide more precise estimates than individual studies.
- Purpose: arrive at conclusions about the body of research

The Logic of Meta-Analysis

- Traditional methods of review focus on statistical significance testing
- Meta-analysis changes the focus to the direction and magnitude of the effects across studies

When Can We Do Meta-Analysis?

- Meta-analysis is applicable to collections of research that
 - examine the same constructs and relationships
 - have findings that can be configured in a comparable statistical form (e.g., as effect sizes, correlation coefficients, odds-ratios, etc.)
 - are “comparable” given the question at hand
 - Objective of study (effect or variability)
 - Population of study
 - Type of study (RCT, Case-Control, or Case Report)
 - Patient Characteristics

Research Findings Suitable to Meta-Analysis

- Central Tendency Research: prevalence rates
- Pre-Post Contrasts: growth rates
- Group Contrasts
 - experimentally created groups
 - naturally occurring groups
- Association Between Variables

Effect Size: The Key to Meta-Analysis

- The **effect size** makes meta-analysis possible
 - it standardizes findings across studies such that they can be directly compared
- Any standardized index can be an “effect size” (e.g., standardized mean difference, correlation coefficient, odds-ratio) as long as it :
 - is comparable across studies (generally requires standardization)
 - represents the magnitude and direction of the relationship of interest
 - is independent of sample size

Examples of Different Types of Effect Sizes

- **Standardized Mean Difference**
 - group contrast research
 - treatment groups
 - naturally occurring groups
 - inherently continuous construct
- **Odds Ratio**
 - group contrast research
 - treatment groups
 - naturally occurring groups
 - inherently dichotomous construct
- **Correlation Coefficient**
 - association between variables research

Interpreting Effect Size Results

- “Rules-of-Thumb”:
 - **standardized mean difference effect size**
small = 0.20 medium = 0.50 large = 0.80
 - **correlation coefficient**
small = 0.10 medium = 0.25 large = 0.40
 - **odds-ratio**
small = 1.50 medium = 2.50 large = 4.30
- A small effect may still be meaningful, depending on the context

Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA)

- Developed by 29 review authors, methodologists, clinicians, medical editors, and consumers.
- PRISMA statement with 27 item checklist (2009)
- PRISMA-P for systematic review and meta-analysis protocols (17 items, 2015)

PRISMA 2009 Checklist

- Title
 1. **Title:** Identify the report as a systematic review, meta-analysis, or both.
- Abstract
 2. **Structured summary:** Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.

Example 1: Tai et al., 2015

- Calcium intake and bone mineral density: systematic review and meta-analysis
 - Examined RCTs of dietary sources of calcium or calcium supplements in older adults to determine whether increasing calcium intake has effects on bone mineral density, and whether the effects differ by calcium source (dietary or supplement).

Tai V, Leung W, Grey A, Reid IR, Bolland MJ. BMJ 351:h4183, 2015. doi: 10.1136/bmj.h4183.

Checklist (continued)

- Introduction
 3. **Rationale:** Describe the rationale for the review in the context of what is already known.
 4. **Objectives:** Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).

Tai et al., 2015: Rationale

- Calcium has long been recommended for older adults to prevent and treat osteoporosis.
- Recently concerns have emerged about the risk/benefit ratio of calcium supplements—so dietary calcium has been recommended.
- Most previous studies have shown no association between dietary calcium and risk of fracture, but few of these studies were RCTs.
- Bone mineral density (BMD) is a surrogate endpoint for fracture risk, and can be studied with modest sized RCTs.

Checklist (continued)

- **Methods**

- 5. Protocol and registration:** Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.
- 6. Eligibility criteria:** Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.

Locating Studies: Which Studies to Include?

- Need explicit inclusion and exclusion criteria
- To include or exclude low quality studies?
 - the findings of all studies are potentially in error
 - being too restrictive may limit ability to generalize
 - being too inclusive may weaken the confidence that can be placed in the findings
 - must strike a balance that is appropriate to your research question

Which Studies to Include?

- Want to avoid publication bias
- Try to identify and retrieve all studies that meet the eligibility criteria
- Potential sources
 - computerized bibliographic databases
 - authors working in the research domain
 - conference programs
 - dissertations
 - review articles
 - hand searching relevant journals
 - government reports, bibliographies, clearinghouses

Tai et al. , 2015: Inclusion/Exclusion Criteria

- Participants aged >50 at baseline
- BMD measured by DXA or precursor technology
- Included
 - Studies reporting bone mineral content (BMC)
 - Studies of calcium supplements + other treatment, if other treatment was in both arms
 - Studies of calcium supplements with vitamin D
 - Studies of hydroxyapatite as dietary calcium
- Excluded
 - Studies where most participants had major systemic pathology other than osteoporosis

Checklist (continued)

- **Methods**

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

Tai et al., 2015—beginning of Appendix 1—Search

In July 2013, we searched Ovid Medline and Embase since inception for English language studies of calcium, milk, or dairy intake, or calcium supplements that reported on a broad range of skeletal and non-skeletal endpoints including BMD. The full text of the search was designed with assistance from a professional librarian and is shown below. We also identified 120 systematic reviews or meta-analyses on these topics from the search and hand-searched these articles and any other articles included in our review for other relevant articles. In September 2014, we updated the results with a focused search (no language restrictions) of Pubmed (below) and Embase for studies with fracture or BMD as an endpoint.

Ovid Medline search July 2013

1. Randomized Controlled Trials as Topic/
2. randomized controlled trial.pt. or randomi?ed controlled trial.mp. or Randomized Controlled Trial/
3. controlled clinical trial.pt. or Controlled Clinical Trial/
4. Random Allocation/
5. Double-Blind Method/
6. Single-Blind Method/
7. clinical trial.pt. or exp Clinical Trials/
8. multicenter study.pt. or multicenter study.tw.
9. or/1-8
10. (clinical adj trial\$.tw.
11. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj (mask\$ or blind\$)).tw.
12. placebo\$.tw. or Placebos/ or (control adj (arm or group)).tw.
13. (allocat\$ adj2 random\$).tw.
14. or/10-13
15. 9 or 14
16. case report.tw.
17. letter/
18. historical article/
19. or/16-18
20. 15 not 19

Methods

9. Study selection:

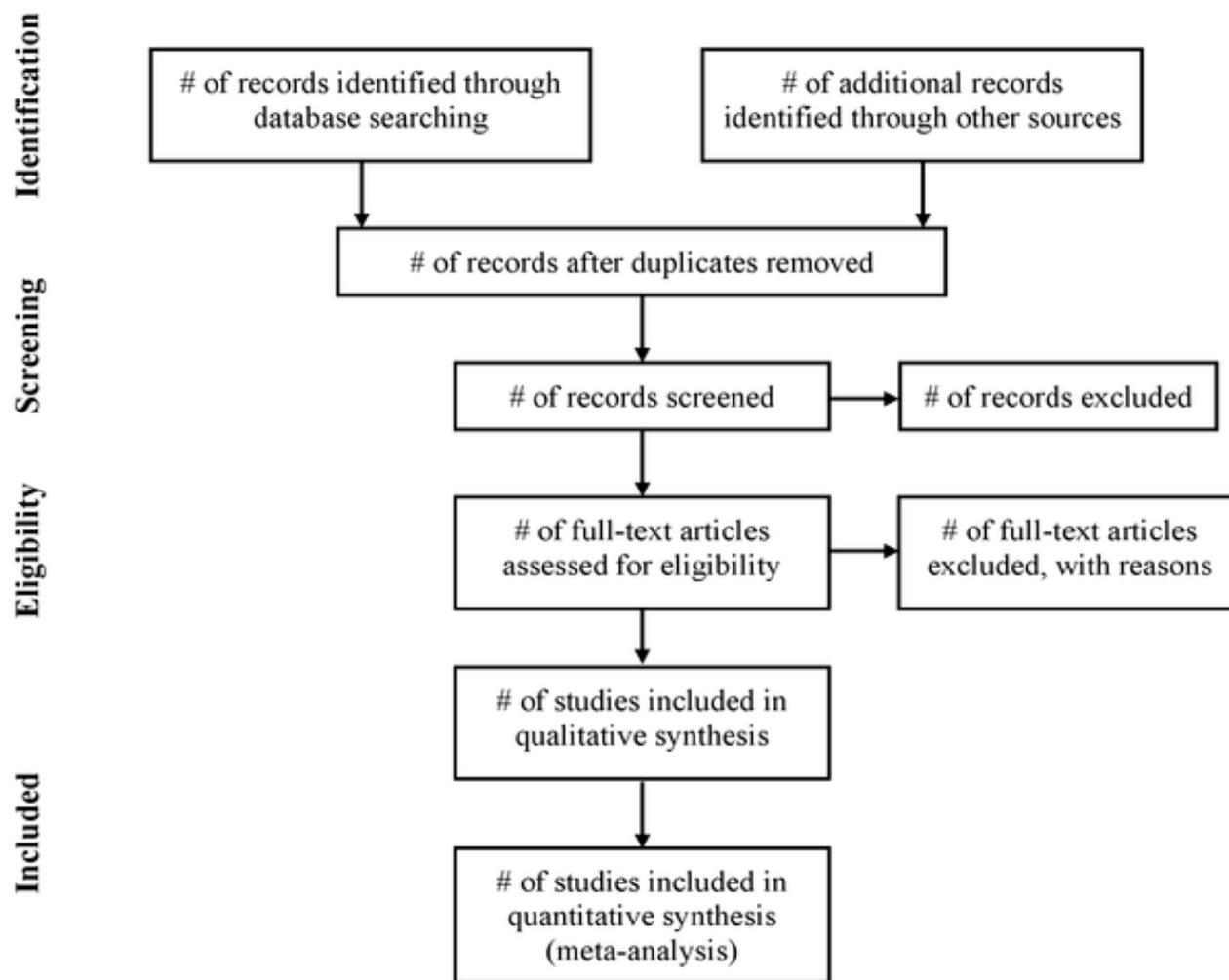
State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).

Results

17. Study selection:

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.

Figure 1. Flow of information through the different phases of a systematic review.

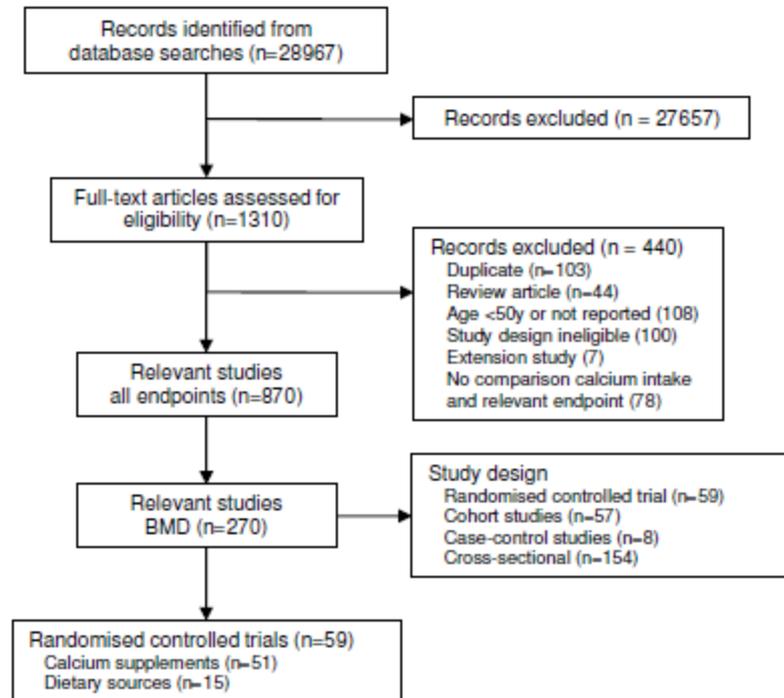


Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, et al. (2009) The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration. *PLoS Med* 6(7): e1000100. doi:10.1371/journal.pmed.1000100

<http://journals.plos.org/plosmedicine/article?id=info:doi/10.1371/journal.pmed.1000100>

Tai et al., 2015—Appendix 2 Flow of Studies

Figure A: flow of studies



Methods

10. Data collection

process: Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.

11. Data items: List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.

Results

18. Study characteristics:

For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.

Tai et al., 2015

Baseline Characteristics of Dietary Calcium Trials

Table 1 | Design of randomised controlled trials and selected baseline characteristics of eligible trials of dietary calcium

Trial	Design	Calcium dose (mg/d)	Vitamin D dose (IU/d)	Duration	Care setting	Total No of participants*	No in Ca/controls group†	% women	Mean age (years)
Recker 1985 ¹⁶	2 arm: milk and control	NS	—	2 y	Community	30	16/14	100	59
Polley 1987 ¹⁷	4 arm: dairy, Ca, dairy/salt restrict, control	≥1250	—	9 mo	Community	269	58/52	100	57
Nelson 1991 ¹⁸	2×2 factorial: ex/milk, ex/control, sed/milk, sed/control	831	—	1 y	Community	41	18/18	100	60
Chevalley 1994 ¹⁹	3 arm: OMC/D, CaD, P/D	800	300 000 IM stat	18 mo	Community	93	31/31	85	72
Prince 1995 ²⁰	4 arm: milk, Ca, Ca/ex, P	1000	—	2 y	Community	168	42/42	100	63
Storm 1998 ²¹	3 arm: milk, Ca, P	NS	—	2 y	Community	40	20/20	100	71
Castelo-Branco 1999 ²²	3 arm: OHC, Ca, control	3320	—	2 y	Community	60	17/16	100	55
Cleghorn 2001 ²³	2 arm: milk, control	700	—	1 y	Community	142	56/59	100	52
Lau 2001 ²⁴	2 arm: milk, control	800	—	24 mo	Community	200	95/90	100	57
Chee 2003 ²⁵	2 arm: milk, control	1200	—	24 mo	Community	200	91/82	100	59
Albertazzi 2004 ²⁶	3 arm: OHC, Ca, P	500	—	6 mo	Community	153	52/50	100	68
Daly 2006 ²⁷	2 arm: milk, control	1000	800	2 y	Community	167	85/82	0	62
Manios 2007 ²⁸	3 arm: dairy, Ca, control	1200	300	12 mo	Community	112	39/36	100	61
Kukuljan 2009 ²⁹	2×2 factorial: milk, milk/ex, ex, control	1000	800	12 mo	Community	180	90/90	0	61
Gui 2012 ³⁰	3 arm: milk, soy milk, control	250	—	18 mo	Community	141	100/41	100	56

Ca=calcium; restrict=restriction; ex=exercise; sed=sedentary; OMC=ossein-mineral complex; D=vitamin D; CaD=co-administered Ca and vitamin D; P=placebo; IM=intramuscular; OHC=ossein-hydroxyapatite complex.

*Total number of randomised participants in all treatment arms.

†Number of participants in relevant arms from trial in whom bone mineral density was reported.

Methods

12. Risk of bias in individual studies:

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.

Results

19. Risk of bias within studies:

Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).

Tai et al., 2015—Appendix 2

Risk of bias—Dietary Calcium Studies

Table C: Risk of bias assessment for eligible trials

Study	Random sequence generation described	Allocation concealment	Blinding of participants/ personnel	Blinding of BMD assessment	Differential loss to follow-up	Selective reporting	BMD as primary endpoint	Overall risk of bias ^a	Funding	Conflicts of interest
Dietary calcium trials										
Recker 1985 ¹⁶	NS	NS	N	N	N	N	Y	High	IF, Ind	NS
Polley 1987 ¹⁷	NS	NS	N	N	Y	N	Y	High	IF, Tab	NS
Nelson 1991 ¹⁸	NS	NS	Y	Y	Y	N	Y	High	IF, Ind	NS
Chevalley 1994 ¹⁹	NS	NS	Y	Y	N	N	Y	Low	IF, Tab	NS
Prince 1995 ²⁰	NS	Y	N	N	NS	N	Y	Moderate	IF, Tab	NS
Storm 1998 ²¹	NS	NS	N	Y	N	N	Y	High	Ind	NS
Castelo-Branco 1999 ²²	Y	NS	N	N	N	N	Y	High	NS	No
Cleghorn 2001 ²³	NS	NS	N	N	N	N	Y	Moderate	Ind, Tab	NS
Lau 2001 ²⁴	NS	NS	N	NS	N	N	Y	Moderate	Ind	NS
Chee 2003 ²⁵	NS	NS	N	N	Y	N	Y	High	Ind	NS
Albertazzi 2004 ²⁶	Y	Y	Y	Y	N	N	Y	Low	Ind, Tab	No
Daly 2006 ²⁷	Y	NS	N	Y	N	N	Y	Moderate	IF, Ind, Tab	No
Manios 2007 ²⁸	NS	NS	N	N	N	N	Y	Moderate	Ind	Yes
Kukuljan 2009 ²⁹	NS	NS	N	NS	N	N	Y	Moderate	IF, Ind, Tab	No
Gui 2012 ³⁰	Y	NS	N	Y	Y	N	Y	High	IF, Tab	No

Risk of bias considerations: lack of blinding, high/differential dropout, small study, non-random selection of participants for BMD measurement.
 IF=independent funders, Ind=industry, Tab=tablets/milk provided by industry

Methods

13. Summary measures:

State the principal summary measures (e.g., risk ratio, difference in means).

Results

20. Results of individual

studies: For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.

Tai et al., 2015—Primary Endpoints

- % changes in BMD from baseline
- 5 BMD sites
 - Lumbar spine
 - Femoral neck
 - Total hip
 - Forearm
 - Total body
- 3 durations
 - 1 year (< 18 months)
 - 2 years (18 months – 2.5 years)
 - > 2.5 years

Methods

14. Synthesis of results:

Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.

Results

21. Synthesis of results:

Present results of each meta-analysis done, including confidence intervals and measures of consistency.

Combining Individual Study Results

- Must be able to calculate a standard error for the effect size (ES)
 - the standard error is needed to calculate the ES weights, called **inverse variance weights**
 - all meta-analytic analyses are weighted

The Inverse Variance Weight

- Studies generally vary in size.
- An ES based on 100 subjects is assumed to be a more “precise” estimate of the population ES than is an ES based on 10 subjects.
- Therefore, larger studies should carry more “weight” in our analyses than smaller studies.
- Simple approach: weight each ES by its sample size.
- Better approach: weight by the inverse variance.

What is the Inverse Variance Weight?

- The standard error (SE) is a direct index of ES precision.
- SE is used to create confidence intervals.
- The smaller the SE, the more precise the ES.
- The optimal weights for meta-analysis are:

$$w = \frac{1}{SE^2}$$

Example 2: Weighted Mean Effect Size

Study	ES	w	w*ES
1	-0.33	11.91	-3.93
2	0.32	28.57	9.14
3	0.39	58.82	22.94
4	0.31	29.41	9.12
5	0.17	13.89	2.36
6	0.64	8.55	5.47
7	-0.33	9.80	-3.24
8	0.15	10.75	1.61
9	-0.02	83.33	-1.67
10	0.00	14.93	0.00
		269.96	41.82

- Start with the effect size (ES) and inverse variance weight (w) for 10 studies.
- Next, multiply w by ES.
- Repeat for all effect sizes.
- Sum the columns, w and ES.
- Divide the sum of (w*ES) by the sum of (w).

$$\overline{ES} = \frac{\sum (w \times ES)}{\sum w} = \frac{41.82}{269.96} = 0.15$$

The Standard Error of the Mean ES

Study	ES	w	w*ES
1	-0.33	11.91	-3.93
2	0.32	28.57	9.14
3	0.39	58.82	22.94
4	0.31	29.41	9.12
5	0.17	13.89	2.36
6	0.64	8.55	5.47
7	-0.33	9.80	-3.24
8	0.15	10.75	1.61
9	-0.02	83.33	-1.67
10	0.00	14.93	0.00
		269.96	41.82

- The standard error of the mean is the square root of (1 divided by the sum of the weights).

$$se_{\overline{ES}} = \sqrt{\frac{1}{\sum w}} = \sqrt{\frac{1}{269.96}} = 0.061$$

Mean, Standard Error, Z-test and Confidence Intervals

Mean ES

$$\overline{ES} = \frac{\sum (w \times ES)}{\sum w} = \frac{41.82}{269.96} = 0.15$$

SE of the Mean ES

$$se_{\overline{ES}} = \sqrt{\frac{1}{\sum w}} = \sqrt{\frac{1}{269.96}} = 0.061$$

Z-test for the Mean ES

$$Z = \frac{\overline{ES}}{se_{\overline{ES}}} = \frac{0.15}{0.061} = 2.46$$

95% Confidence Interval

$$Lower = \overline{ES} - 1.96(se_{\overline{ES}}) = 0.15 - 1.96(.061) = 0.03$$

$$Upper = \overline{ES} + 1.96(se_{\overline{ES}}) = 0.15 + 1.96(.061) = 0.27$$

Homogeneity Analysis

- **Homogeneity analysis** tests whether the assumption that all of the effect sizes are estimating the same population mean is a reasonable assumption.
- If homogeneity is rejected, the distribution of effect sizes is assumed to be heterogeneous.
 - Single mean ES not a good descriptor of the distribution
 - There are real between study differences, that is, different population mean effect sizes.
 - Two options:
 - model between study differences
 - fit a random effects model

Q - The Homogeneity Statistic

Study	ES	w	w*ES	w*ES ²
1	-0.33	11.91	-3.93	1.30
2	0.32	28.57	9.14	2.93
3	0.39	58.82	22.94	8.95
4	0.31	29.41	9.12	2.83
5	0.17	13.89	2.36	0.40
6	0.64	8.55	5.47	3.50
7	-0.33	9.80	-3.24	1.07
8	0.15	10.75	1.61	0.24
9	-0.02	83.33	-1.67	0.03
10	0.00	14.93	0.00	0.00
		269.96	41.82	21.24

- Calculate a new variable that is the ES squared multiplied by the weight.
- Sum new variable.

Calculating Q

There are 3 sums:

$$\sum w = 269.96$$

$$\sum (w \times ES) = 41.82$$

$$\sum (w \times ES^2) = 21.24$$

Q is can be calculated using these 3 sums:

$$Q = \sum (w \times ES^2) - \frac{[\sum (w \times ES)]^2}{\sum w} = 21.24 - \frac{41.82^2}{269.96} = 21.24 - 6.48 = 14.76$$

Interpreting Q

- Q is distributed as a Chi-Square
- $df = \text{number of ES's} - 1$
- Running example has 10 ES's, therefore, $df = 9$
- Critical Value for a Chi-Square with $df = 9$ and $p = .05$ is: 16.92
- Since the calculated Q (14.76) is less than 16.92, we **fail to reject** the null hypothesis of homogeneity.
- Thus, the variability across effect sizes does not exceed what would be expected based on sampling error.

Another Statistic for Assessing Heterogeneity: I^2

- $I^2 = (Q - df) / Q * 100$, if $Q > df$
- $I^2 = 0$, if $Q < df$
- Quantifies the amount of variation across studies beyond that expected by chance
- In the previous example,
$$I^2 = (14.76 - 9) / 14.76 = 39\%.$$

Interpretation of I^2

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity*;
- 50% to 90%: may represent substantial heterogeneity*;
- 75% to 100%: considerable heterogeneity*.

*The importance of the observed value of I^2 depends on (i) magnitude and direction of effects and (ii) strength of evidence for heterogeneity

Heterogeneous Distributions

- Analyze excess between-study (ES) variability
 - categorical variables with the analog to the one-way ANOVA
 - continuous variables and/or multiple variables with weighted multiple regression
- Assume variability is random and fit a random effects model.

The Logic of a Random Effects Model

- Fixed effects model assumes that all of the variability between effect sizes is due to sampling error.
- Random effects model assumes that the variability between effect sizes is due to sampling error **plus** variability in the population of effects (unique differences in the set of true population effect sizes).

The Basic Procedure of a Random Effects Model

- Fixed effects model weights each study by the inverse of the sampling variance.
- Random effects model weights each study by the inverse of the sampling variance **plus** a constant that represents the variability across the main effects.

$$w_i = \frac{1}{se_i^2}$$

$$w_i = \frac{1}{se_i^2 + \hat{v}_\theta}$$

This is the random effects variance component.

How To Estimate the Random Effects Variance Component

- The random effects variance component is based on Q .
- The formula is:

$$\hat{v}_\theta = \frac{Q - (k - 1)}{\sum w - \left(\frac{\sum w^2}{\sum w} \right)}$$

Calculation of the Random Effects Variance Component

Study	ES	w	w*ES	w*ES ²	w ²
1	-0.33	11.91	-3.93	1.30	141.73
2	0.32	28.57	9.14	2.93	816.30
3	0.39	58.82	22.94	8.95	3460.26
4	0.31	29.41	9.12	2.83	865.07
5	0.17	13.89	2.36	0.40	192.90
6	0.64	8.55	5.47	3.50	73.05
7	-0.33	9.80	-3.24	1.07	96.12
8	0.15	10.75	1.61	0.24	115.63
9	-0.02	83.33	-1.67	0.03	6944.39
10	0.00	14.93	0.00	0.00	222.76
		269.96	41.82	21.24	12928.21

- Calculate a new variable that is the w squared.
- Sum new variable.

Calculation of the Random Effects Variance Component

- The total Q for this data was 14.76
- k is the number of effect sizes (10)
- The sum of w = 269.96
- The sum of $w^2 = 12,928.21$

$$\hat{v}_\theta = \frac{Q - (k - 1)}{\sum w - \left(\frac{\sum w^2}{\sum w} \right)} = \frac{14.76 - (10 - 1)}{269.96 - \frac{12,928.21}{269.96}} = \frac{5.76}{269.96 - 47.89} = 0.026$$

Rerun Analysis with New Inverse Variance Weight

- Add the random effects variance component to the variance associated with each ES.
- Calculate a new weight.
- Rerun analysis.

$$w_i = \frac{1}{se_i^2 + \hat{v}_\theta}$$

Comparison of Random Effect with Fixed Effect Results

- The biggest difference is in the significance levels and confidence intervals.
 - Confidence intervals will get bigger.
 - Effects that were significant under a fixed effect model may no longer be significant.
- Random effects models are more conservative.

Tai et al., 2015—Table 1: Lumbar Spine

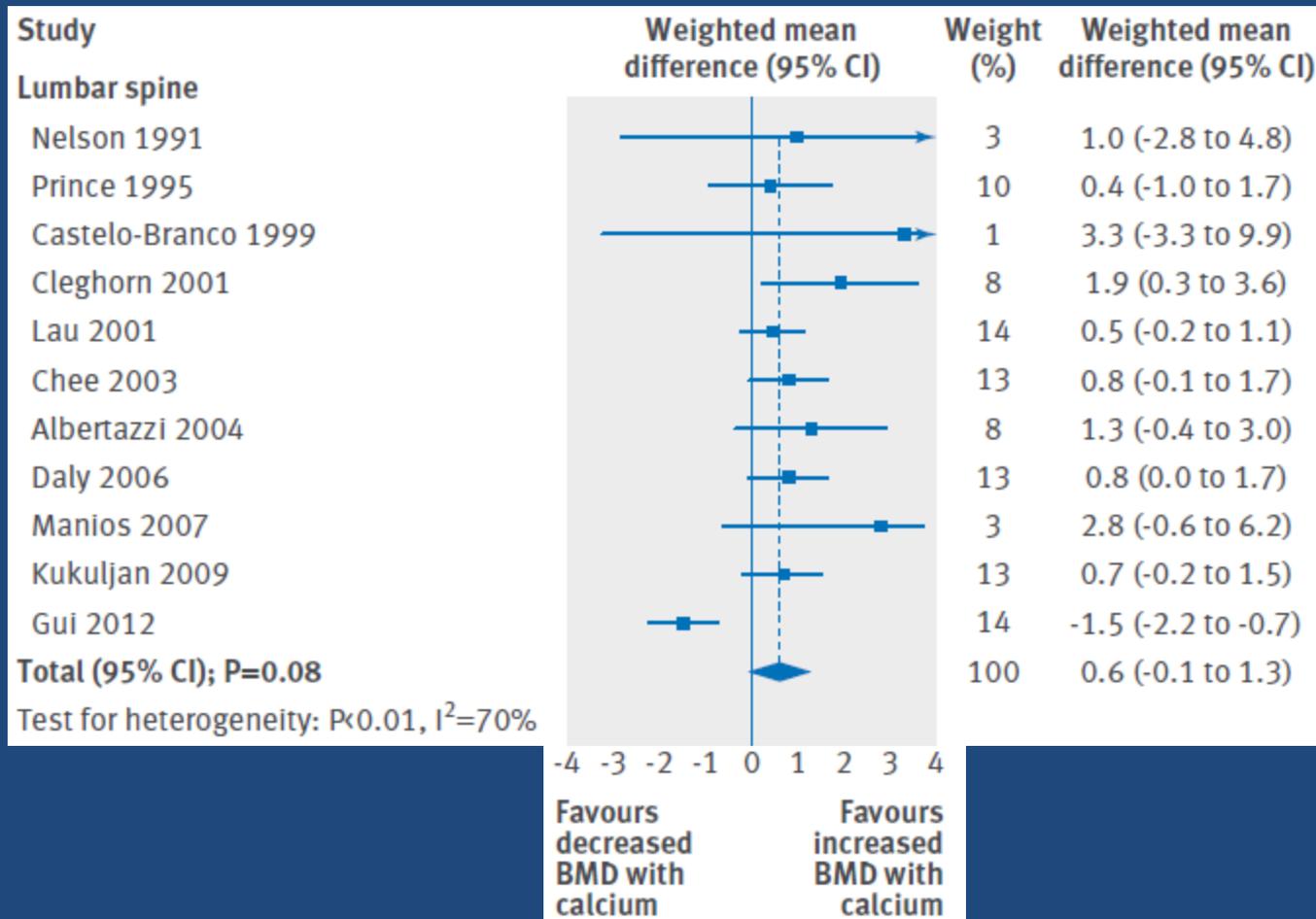


Fig 1 | Random effects meta-analysis of effect of dietary sources of calcium on percentage change in bone mineral density (BMD) from baseline at one year

Methods

15. Risk of bias across studies: Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).

Results

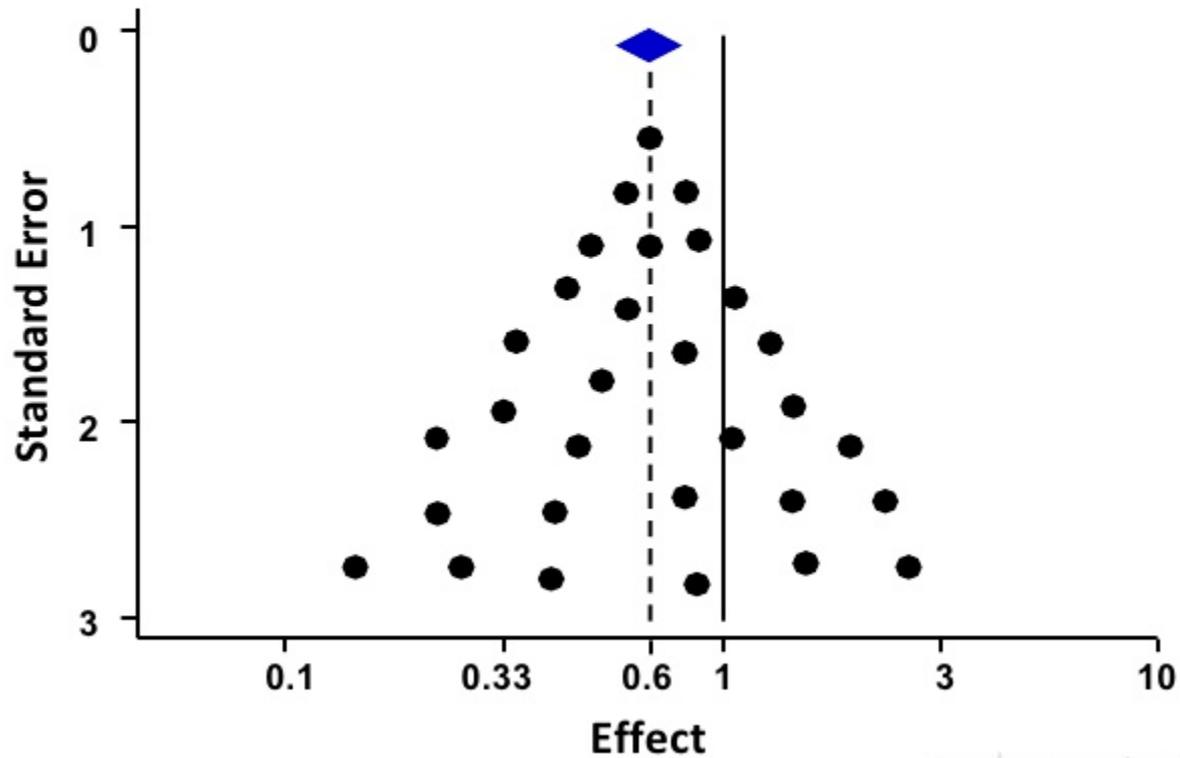
22. Risk of bias across studies: Present results of any assessment of risk of bias across studies (see Item 15).

Funnel Plots—a Tool for Detecting Bias

- Scatter plots of precision (e.g., $1/SE$) or sample size vs. effect size.
- If no bias
 - Small studies should have a wide range of effect sizes
 - Large studies should have a narrow range of effect sizes



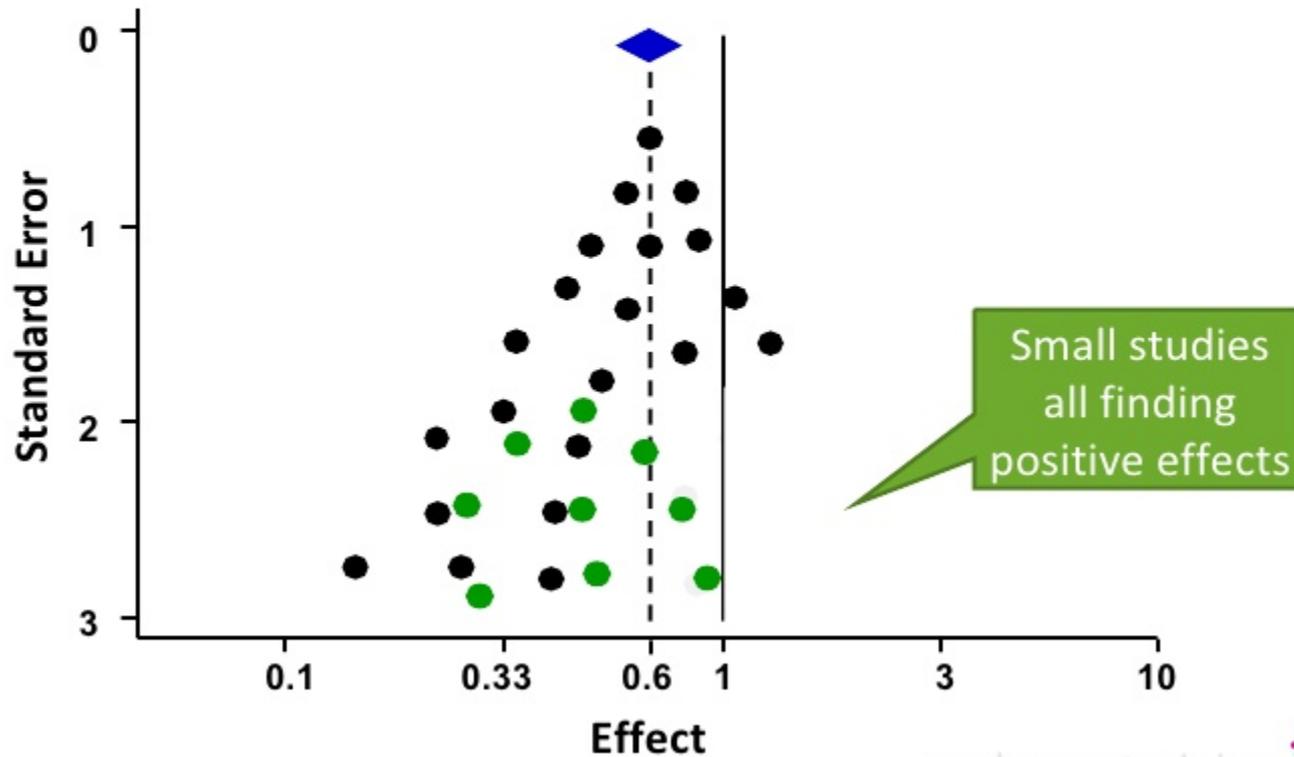
Symmetrical funnel plot



Source: Matthias Egger & Jonathan Sterne



Asymmetrical funnel plot



Source: Matthias Egger & Jonathan Sterne

Methods

16. Additional analyses:

Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.

Results

23. Additional analyses :

Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).

Tai et al., 2015- 2 Subgroup Analyses

Table E: Subgroup analyses

Site/ Time-point/ Intervention	Subgroup	Studies (N)	BMD difference ^a (95% CI)	P ^b	Site/ Time-point/ Intervention	Subgroup	Studies (N)	BMD difference ^a (95% CI)	P ^b
Calcium monotherapy vs Co-administered CaD					Age (y)				
LS/1/diet	Ca mono	8	0.5 (-0.4 to 1.5)	0.62	LS/1/supp	50-65	15	1.2 (0.7 to 1.7)	0.97
	CaD	3	0.8 (0.2 to 1.4)			65+	12	1.2 (0.5 to 2.0)	
LS/1/supp	Ca mono	21	1.3 (0.8 to 1.7)	0.81	LS/2/supp	50-65	12	0.8 (0.3 to 1.3)	0.08
	CaD	7	1.1 (0.2 to 2.1)			65+	9	1.5 (0.9 to 2.2)	
LS/2/supp	Ca mono	18	1.3 (0.8 to 1.8)	0.007	FN/1/supp	50-65	10	1.1 (0.4 to 1.7)	0.36
	CaD	3	0.4 (0.1 to 0.8)			65+	8	1.6 (0.6 to 2.7)	
FN/1/supp	Ca mono	13	1.3 (0.5 to 2.0)	0.86	FN/2/supp	50-65	7	0.8 (0.3 to 1.4)	0.58
	CaD	7	1.2 (0.4 to 1.9)			65+	7	1.1 (0.3 to 2.0)	
FN/2/supp	Ca mono	9	1.2 (0.6 to 1.7)	0.16	TB/1/supp	50-65	7	0.9 (0.3 to 1.5)	0.24
	CaD	5	0.5 (-0.1 to 1.2)			65+	3	0.5 (0.2 to 0.8)	
TB/1/supp	Ca mono	7	0.6 (0.2 to 1.0)	0.21	F/2/supp	50-65	7	1.1 (0.3 to 1.8)	0.23
	CaD	3	1.1 (0.5 to 1.7)			65+	3	5.6 (-1.7 to 13.0)	

^a Weighted mean difference in percentage change in bone mineral density (BMD) from baseline.

^b Test for interaction between subgroups

Abbreviation: CI- confidence interval; Ca mono- calcium monotherapy, CaD- calcium and vitamin D; LS- lumbar spine; FN- femoral neck; TB- total body; F- forearm; supp- calcium supplement trials; diet- dietary calcium intake trials.

Checklist (continued)

- Discussion

24. Summary of evidence: Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).

25. Limitations: Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).

26. Conclusions: Provide a general interpretation of the results in the context of other evidence, and implications for future research.

- Funding

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

Tai et al., 2015

Findings, Limitations, Conclusions , Funding

- Findings: Increasing calcium intake slightly increased BMD over 1-2 years.
 - Dietary calcium: 0.6-1.8%
 - Calcium supplements: 0.7-1.8%
- Limitations
 - BMD is only a surrogate for fracture
 - High heterogeneity between studies
- Conclusions
 - Small effects on BMD are unlikely to produce clinically important reductions in fracture risk (5-10%).
 - Increasing calcium intake is unlikely to be beneficial for persons concerned about their bone density.
- Funding: Health Research Council of New Zealand

Strengths of Meta-Analysis

- Imposes a discipline on the process of summing up research findings
- Capable of finding relationships across studies that are obscured in other approaches
- Protects against over-interpreting differences across studies
- Can handle a large numbers of studies

Weaknesses of Meta-Analysis

- Requires a good deal of effort
- “Apples and oranges”; comparability of studies is often in the “eye of the beholder”
- Most meta-analyses include “blemished” studies
- Selection bias poses continual threat
 - negative and null finding studies that you were unable to find
 - outcomes for which there were negative or null findings that were not reported

In conclusion, meta-analysis:

- Is a replicable and defensible method of synthesizing findings across studies
- Often points out gaps in the research literature, providing a solid foundation for the next generation of research on that topic
- Illustrates the importance of replication
- Facilitates generalization of the knowledge gained through individual evaluations