# Systematic Reviews and Meta-analyses

DEREK SMITH, DDS, PHD

# Types of Reviews

Narrative Reviews- Descriptive overview of a subject. May contain discussions of papers and their results, but the literature review is not necessarily systematic

Systematic Reviews- Comprehensive search strategy is employed with the goal of identifying all relevant studies

Meta-Analyses- A component of a systematic review in which statistical techniques are used to synthesize data from multiple studies into a single quantitative summary

# Process of Systematic Reviews

Formulate a question to be answered in the review

Develop a protocol detailing the entire process for the review

Conduct a literature search

Apply inclusion/exclusion criteria through a series of more comprehensive assessments of the identified articles

Grade individual included articles for bias potential

Perform data abstraction in duplicate for articles meeting the inclusion criteria

Assess overall bias potential in the literature

Synthesize the data and report the analysis in accordance with best reporting practices

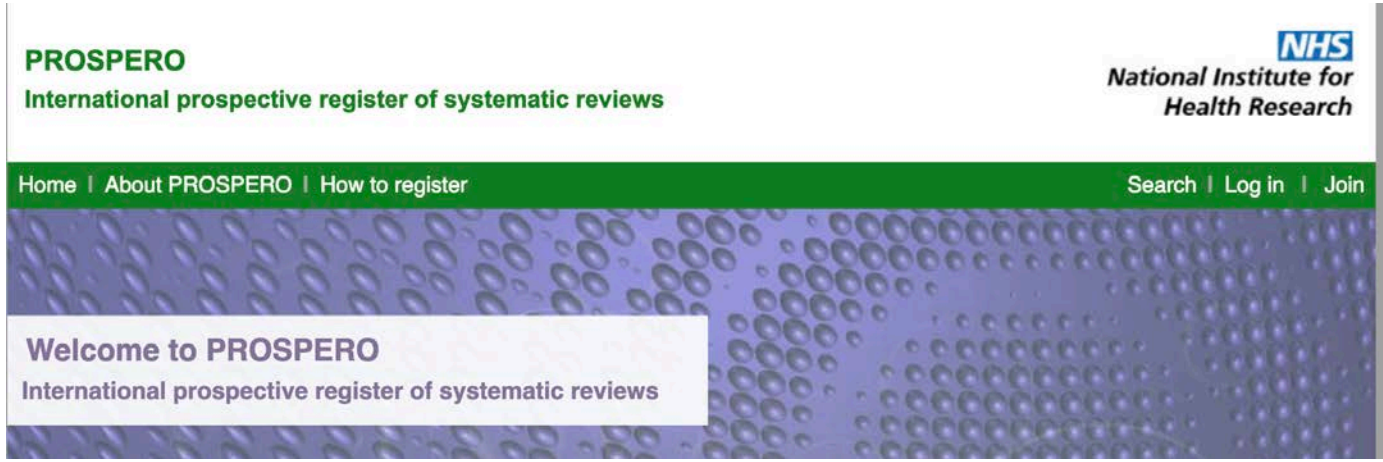
# Registration

One of the PRISMA guidelines for systematic reviews is that they have a predefined, publically available protocol.

Helps reduce bias and keeps the review team on task

**New Change: PROSPERO will only be accepting reviews that have not started abstracting data as of October 1st!**

PROSPERO is an international database of prospectively registered systematic reviews in health and social care... Key features from the review protocol are recorded and maintained as a permanent record. PROSPERO aims to … avoid duplication and reduce opportunity for reporting bias by enabling comparison of the completed review with what was planned in the protocol.



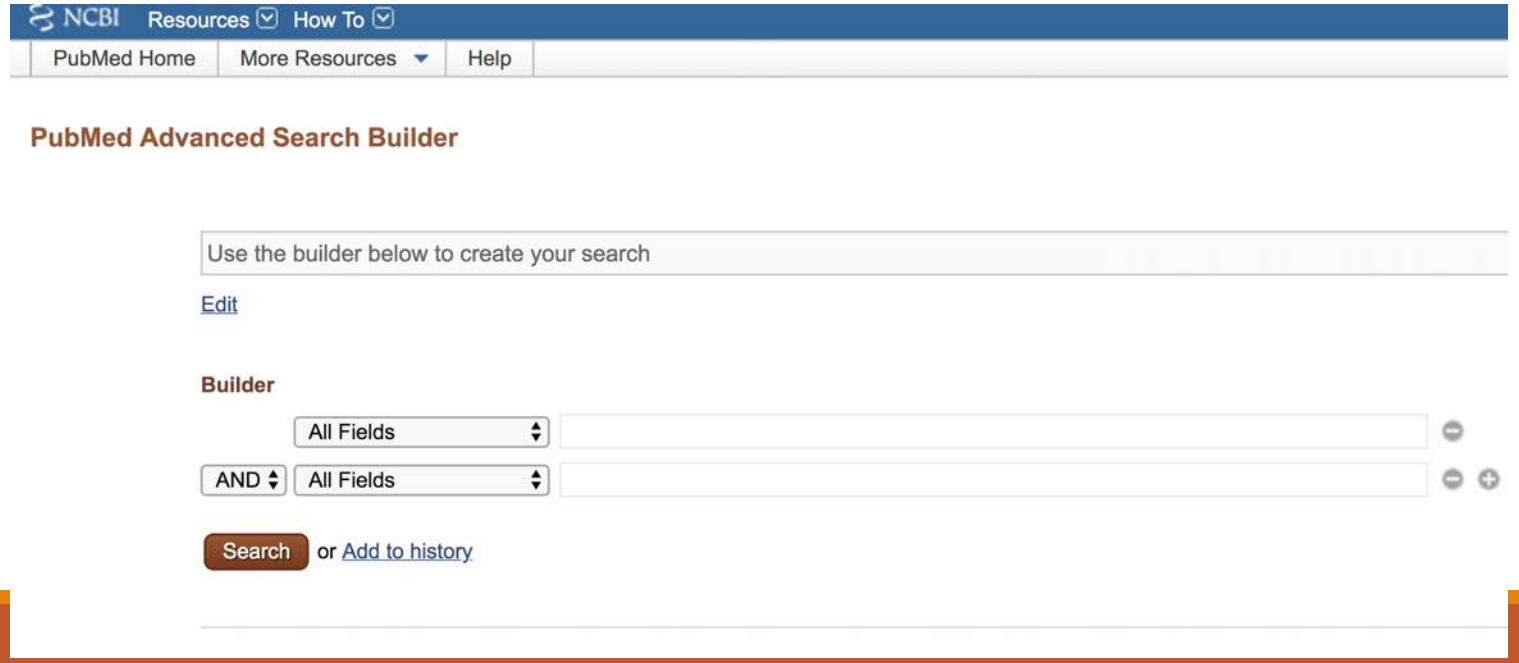
# Systematic Searches

Databases

- Pubmed (and Medline)- Database on medicine compiled by the US National Library of Medicine covering medicine, nursing, pharmacy, dentistry, veterinary, and health care
- Embase- Corporate administered database spanning many biomedical disciplines
- “Grey Literature” – Google Scholar, archivex, dissertations

Search Terms - Keywords

- Type of study
- Topic of research
- Population of interest
- Specific drugs



# Possible problems with a search

Search did not identify all the relevant articles

- Wrong keywords
- Different drug names in different countries

Publication bias

- Positive studies tend to get published more often than negative ones
- Positive significant findings are 27% more likely to be included in meta-analyses of efficacy than other findings.

Selective outcome reporting

Fraud – perioperative beta-blockade and the DECREASE trials

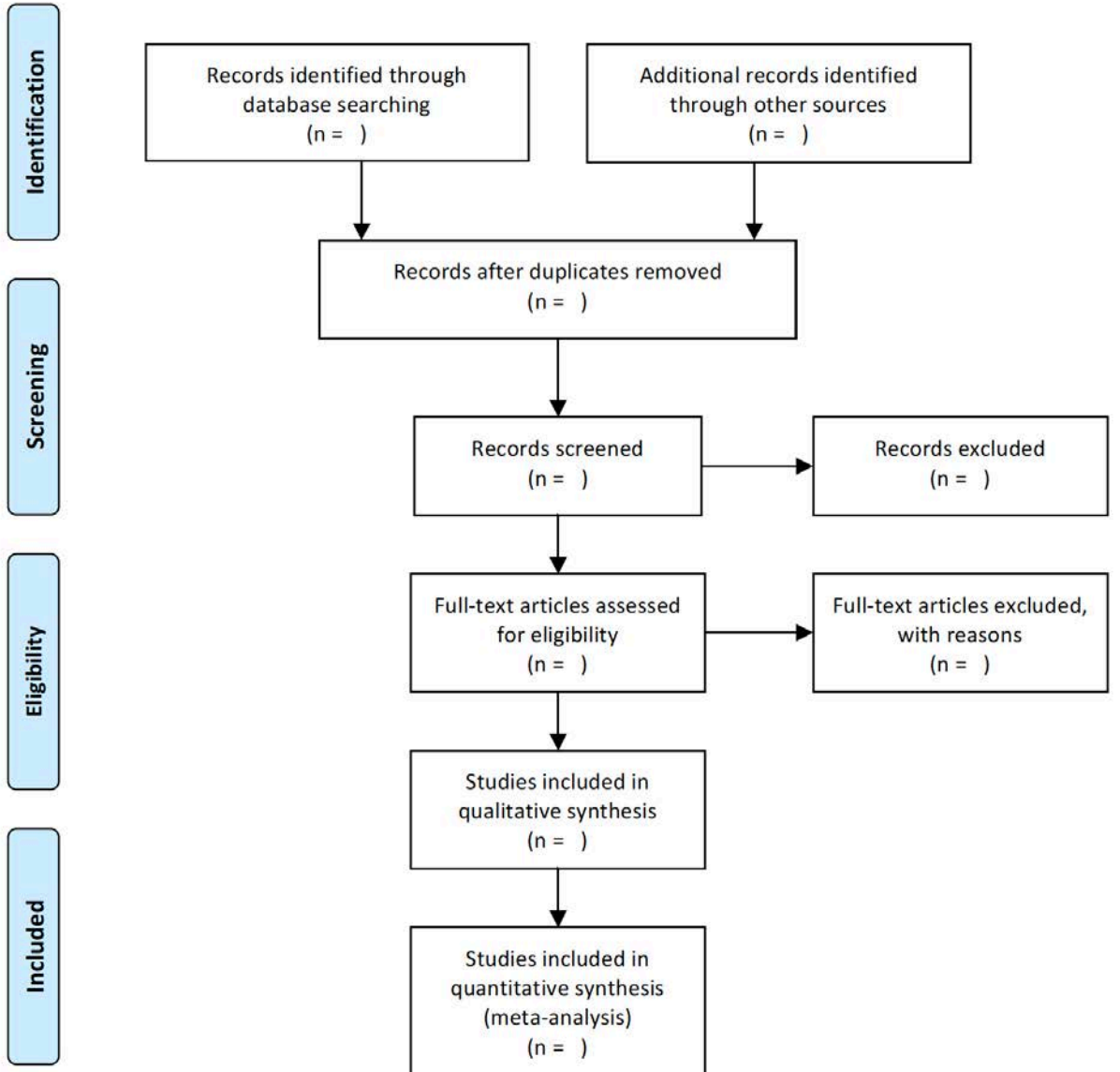
Kicinski, M; Springate, D. A.; Kontopantelis, E (2015). "Publication bias in meta-analyses from the Cochrane Database of Systematic Reviews". *Statistics in Medicine*. **34** (20): 2781–93. doi:10.1002/sim.6525. PMID 25988604.

# Inclusion/Exclusion

Review by title

Review by abstract

Full Review and data abstraction



# Grading Individual Articles

Cochrane Review Criteria

Applicable for RCTs – allocation for example has no role in observational studies

Blinding has a lesser role in observational studies

| Domain | Support for judgement | Review authors' judgement |
|---|---|---|
| *Selection bias.* | | |
| **Random sequence generation.** | Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups. | Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence. |
| **Allocation concealment.** | Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment. | Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment. |
| *Performance bias.* | | |
| **Blinding of participants and personnel** *Assessments should be made for each main outcome (or class of outcomes).* | Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective. | Performance bias due to knowledge of the allocated interventions by participants and personnel during the study. |
| *Detection bias.* | | |
| **Blinding of outcome assessment** *Assessments should be made for each main outcome (or class of outcomes).* | Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective. | Detection bias due to knowledge of the allocated interventions by outcome assessors. |
| *Attrition bias.* | | |
| **Incomplete outcome data** *Assessments should be made for each main outcome (or class of outcomes).* | Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors. | Attrition bias due to amount, nature or handling of incomplete outcome data. |
| *Reporting bias.* | | |
| **Selective reporting.** | State how the possibility of selective outcome reporting was examined by the review authors, and what was found. | Reporting bias due to selective outcome reporting. |
| *Other bias.* | | |
| **Other sources of bias.** | State any important concerns about bias not addressed in the other domains in the tool.<br>If particular questions/entries were pre-specified in the review's protocol, responses should be provided for each question/entry. | Bias due to problems not covered elsewhere in the table. |

Higgins JPT, Green S, Cochrane Collaboration. *Cochrane handbook for systematic reviews of interventions*. Chichester, England ; Hoboken, NJ: Wiley-Blackwell; 2008: xxi, 649 p.

# Grading Individual Articles: Non-Randomized

Robins-I ("Risk Of Bias In Non-randomised Studies - of Interventions")

Addresses issues unique to observational studies such as confounding, selection bias, and selective reporting

This is an example of one of hundreds of tools proposed for this purpose

**Table 1 | Bias domains included in ROBINS-I**

| Domain | Explanation |
|---|---|
| **Pre-intervention** | **Risk of bias assessment is mainly distinct from assessments of randomised trials** |
| Bias due to confounding | Baseline confounding occurs when one or more prognostic variables (factors that predict the outcome of interest) also predicts the intervention received at baseline<br>ROBINS-I can also address time-varying confounding, which occurs when individuals switch between the interventions being compared and when post-baseline prognostic factors affect the intervention received after baseline |
| Bias in selection of participants into the study | When exclusion of some eligible participants, or the initial follow-up time of some participants, or some outcome events is related to both intervention and outcome, there will be an association between interventions and outcome even if the effects of the interventions are identical<br>This form of selection bias is distinct from confounding—A specific example is bias due to the inclusion of prevalent users, rather than new users, of an intervention |
| **At intervention** | **Risk of bias assessment is mainly distinct from assessments of randomised trials** |
| Bias in classification of interventions | Bias introduced by either differential or non-differential misclassification of intervention status<br>Non-differential misclassification is unrelated to the outcome and will usually bias the estimated effect of intervention towards the null<br>Differential misclassification occurs when misclassification of intervention status is related to the outcome or the risk of the outcome, and is likely to lead to bias |
| **Post-intervention** | **Risk of bias assessment has substantial overlap with assessments of randomised trials** |
| Bias due to deviations from intended interventions | Bias that arises when there are systematic differences between experimental intervention and comparator groups in the care provided, which represent a deviation from the intended intervention(s)<br>Assessment of bias in this domain will depend on the type of effect of interest (either the effect of assignment to intervention or the effect of starting and adhering to intervention). |
| Bias due to missing data | Bias that arises when later follow-up is missing for individuals initially included and followed (such as differential loss to follow-up that is affected by prognostic factors); bias due to exclusion of individuals with missing information about intervention status or other variables such as confounders |
| Bias in measurement of outcomes | Bias introduced by either differential or non-differential errors in measurement of outcome data. Such bias can arise when outcome assessors are aware of intervention status, if different methods are used to assess outcomes in different intervention groups, or if measurement errors are related to intervention status or effects |
| Bias in selection of the reported result | Selective reporting of results in a way that depends on the findings and prevents the estimate from being included in a meta-analysis (or other synthesis) |

Sterne JA, et al. *ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions*. BMJ. 2016;355:i4919.

# Visualizing Bias

**Figure 8.6.b: Example of a 'Risk of bias graph' figure**

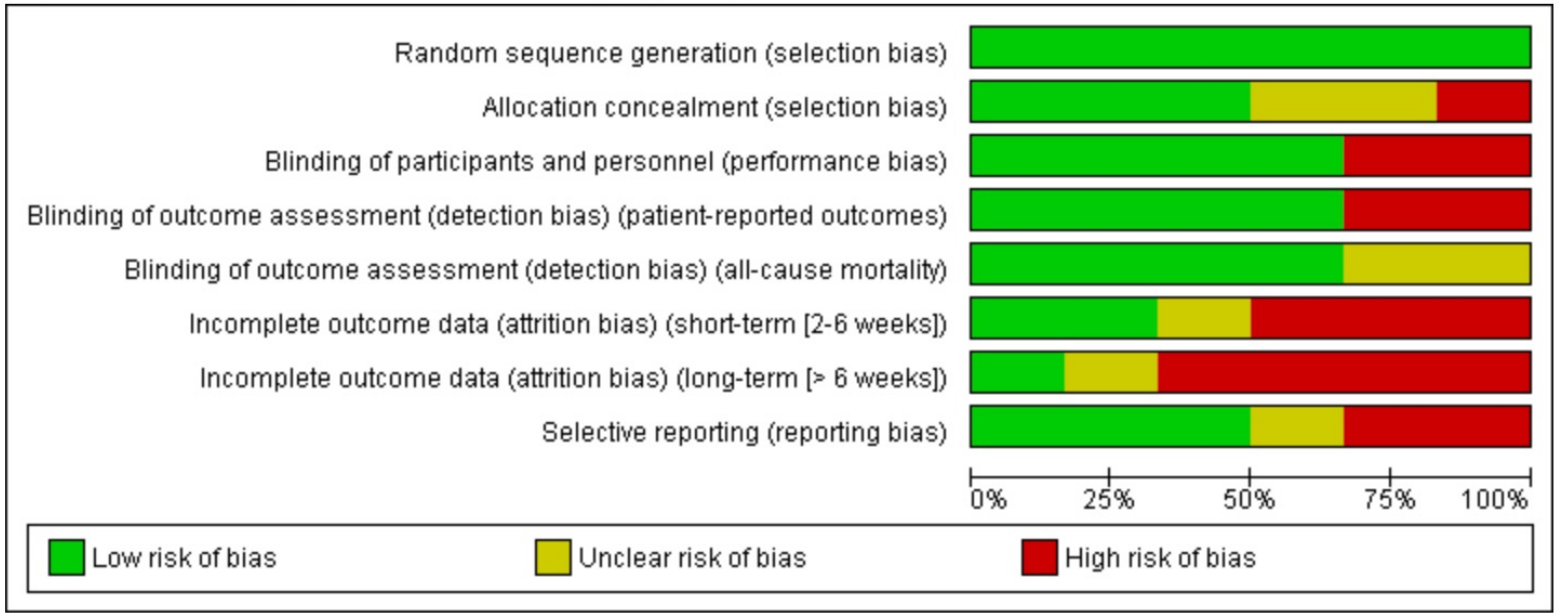
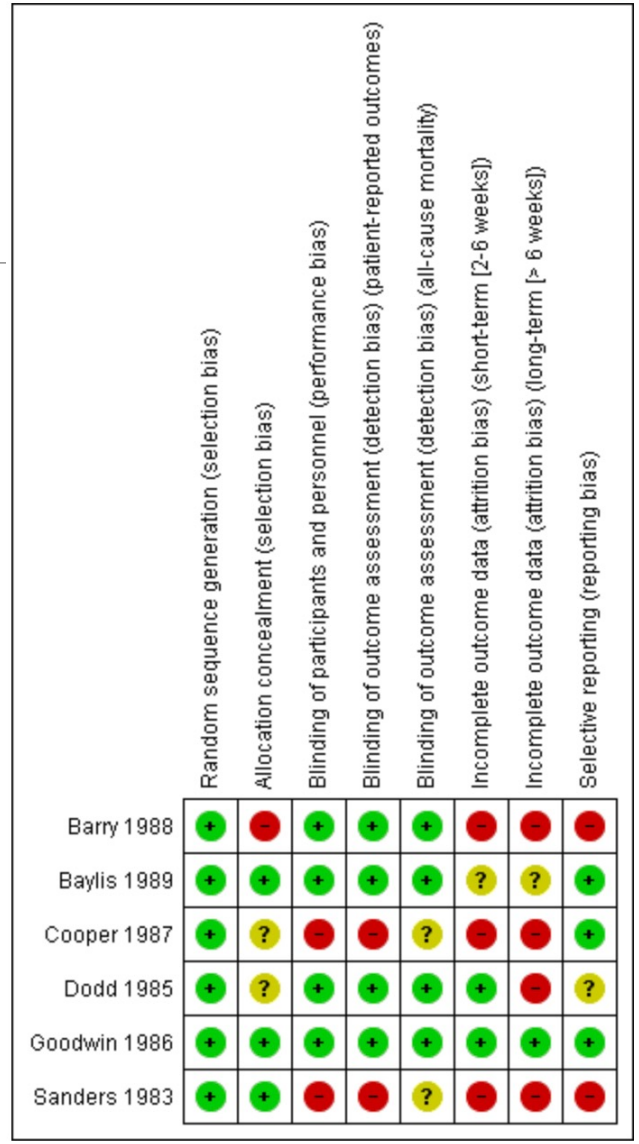



**Figure 8.6.c: Example of a 'Risk of bias summary' figure**

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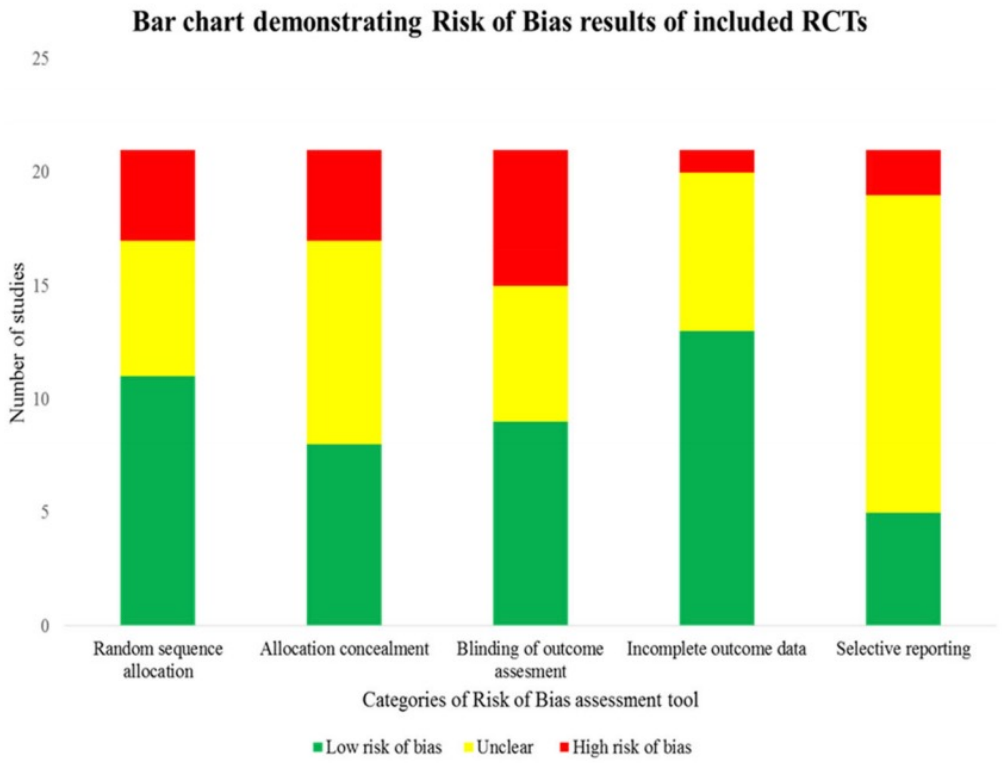
# Grading Example

Supportive Care in Cancer (2018) 26:2503–2509
https://doi.org/10.1007/s00520-018-4216-z

REVIEW ARTICLE

## Systematic review and meta-analysis investigating the efficacy and safety of probiotics in people with cancer

Hadeel Hassan [1,2] · M. Rompola [1,2] · A. W. Glaser [1,2] · S. E. Kinsey [1,2] · R. S. Phillips [1,3]




21 studies of efficacy and 25 of safety

Marked heterogeneity of treatment protocol

Used the Cochrane Review's Bias assessment for RCTs

Found many of the studies to be at significant risk

Author's Conclusion: Insufficient evidence for the efficacy and safety of probiotics, though the data seems to point toward a decrease in diarrhea, septicemia, and central line infection. Caution advised due to heterogeneous studies and **"lack of studies with a clear low risk of bias."**

# Data Abstraction: keys to success

Multiple independent reviews

Consistent entries with error checking (automatically make sure a date field gets a date, a numeric field a number in a given range, etc)

No calculated values- always record the raw data, for example never record a prevalence as 20%, instead record it as 2 cases in a n of 10.

Bias assessment tools

Easy export to analyzable format

Tools: REDCap, Revman

# Data Abstraction

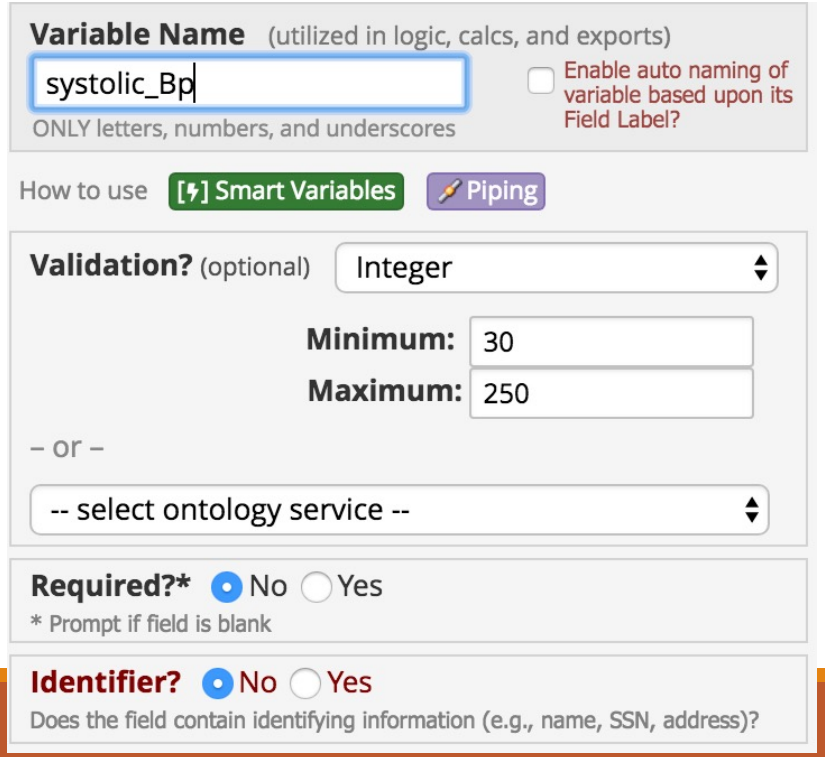
There are a number of modern tools that can enhance the quality of data abstraction:

Duplicate Review – All included studies should be reviewed by not less than two personnel

Data Validation – Modern electronic databases can force reviewers to enter data of a particular format

Data Log- Modern electronic databases keep track of who makes changes to the database and when the change occurred

Archiving – Arrange for your search details, bias assessments, data as abstracted by each reviewer, reproducible analysis scripts, statistical reports, and full text of each article to be stored in case future questions arise

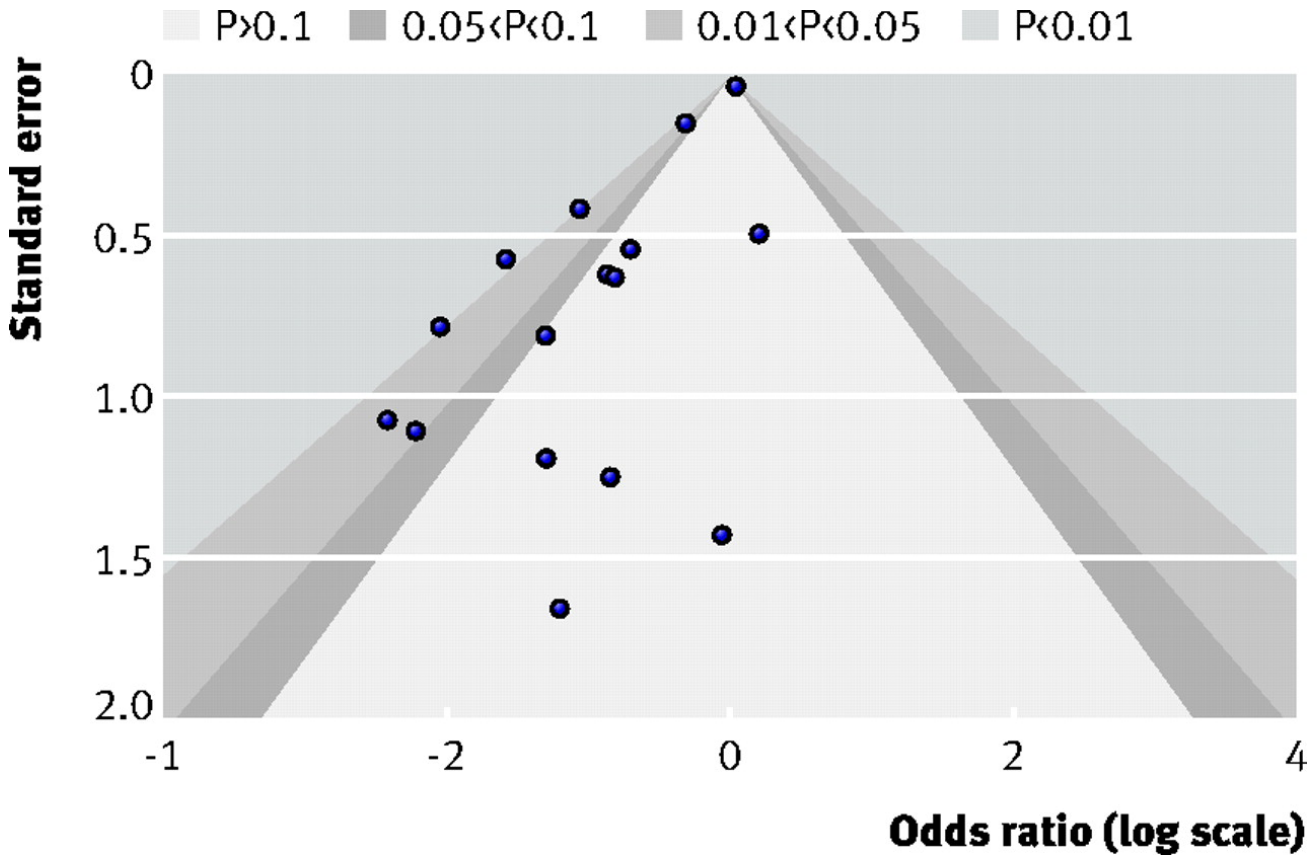


# Assessing Publication Bias

Most precise (largest sample size) studies will be near the average under the presumption of a symmetric distribution of possible outcomes

Less precise studies should be scattered on either side

Asymmetry of smaller studies is evidence of publication bias.



# Publication Bias Example

Support Care Cancer (2016) 24:969–983
DOI 10.1007/s00520-015-2953-9

REVIEW ARTICLE

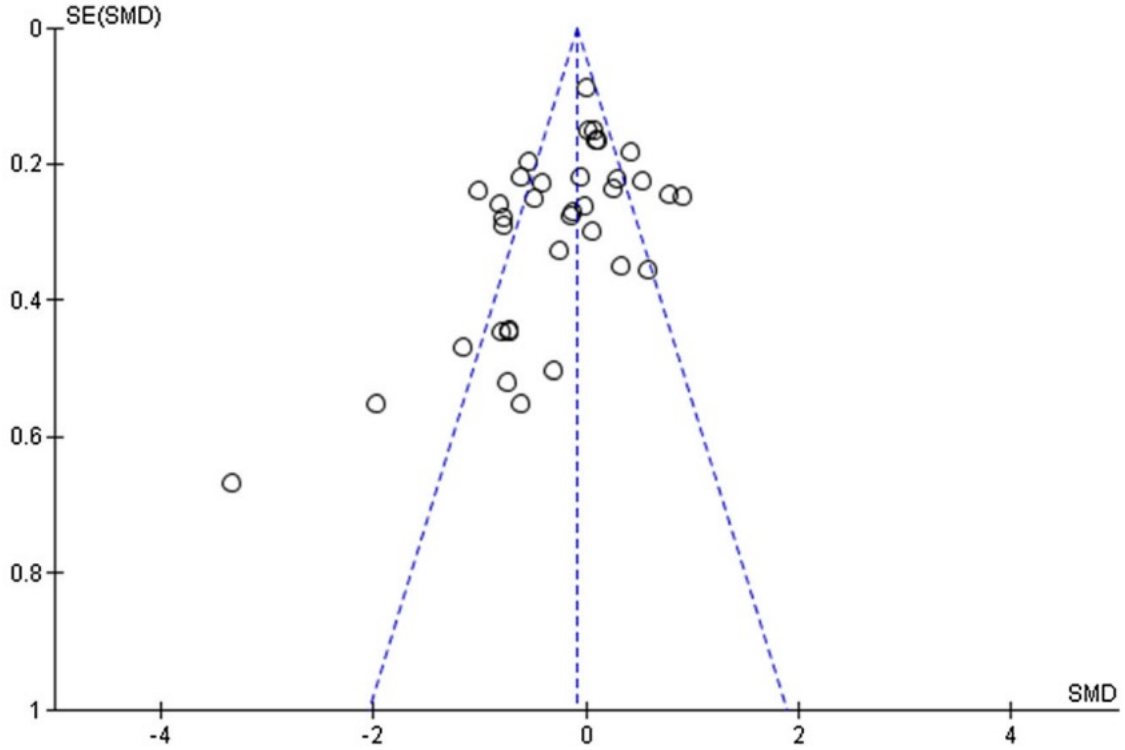
**Effects of aerobic exercise on cancer-related fatigue: a meta-analysis of randomized controlled trials**

Li Tian[1,2] · Hui J. Lu[1] · Lu Lin[3] · Yan Hu[1]

26 studies identified looking at the association between exercise and CRF

Authors identified publication/ small study bias using the funnel plot

Author's Conslusion: "Remains a need for further studies with adequate blinding, larger sample sizes, multicenter design, more rigorous inclusion criteria, and control groups," however the data generally support exercise being associated with a reduction in CRF

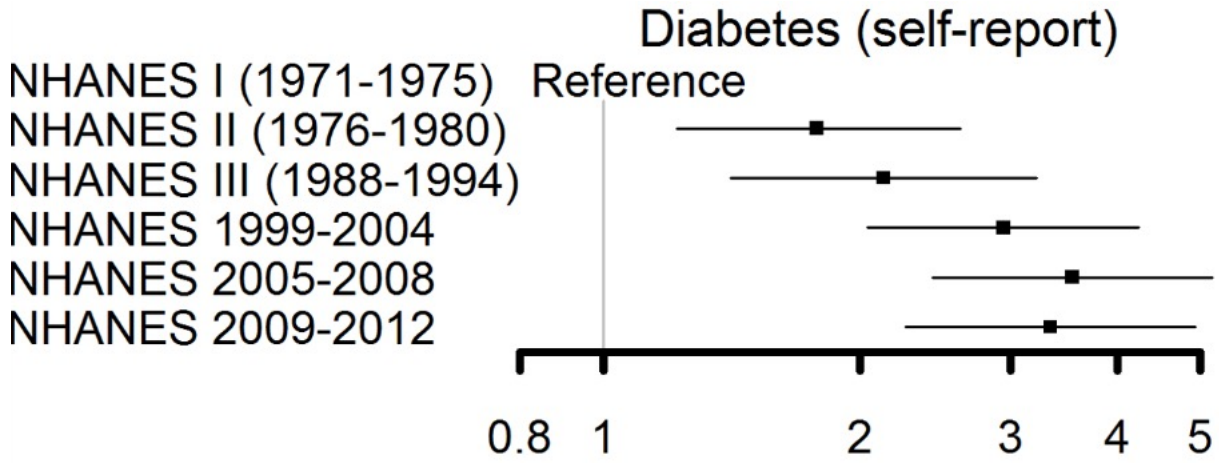


# Temporal Bias

This is an example of a temporal trend in meta-analysis. In this case this is showing a shift in prevalence of diabetes over time.

If we were to see this in a meta-analysis, we would have to consider either:

1. Moving to a meta-regression framework
2. Identifying and accounting for other factors that may have changed over time
3. Excluding all but the most recent studies




Casagrande, SS; et al. Cardiovascular Risk Factors of Adults Age 20-49 Years in the United States, 1971-2012: A Series of Cross-sectional Studies. Plos One. 2016.

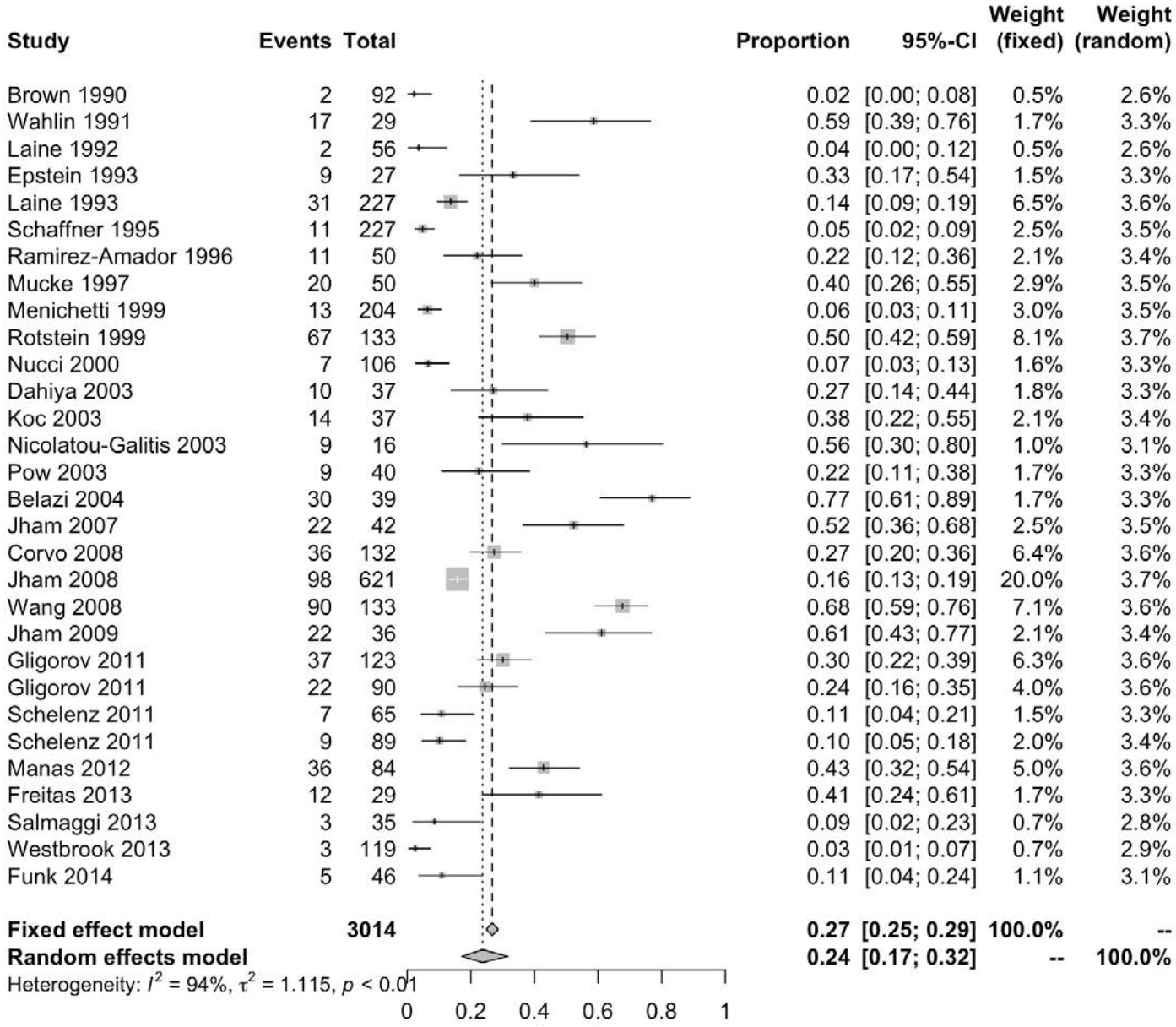
# Representing Results

Each row represents a study and its findings

Results are weighted according to either a fixed or random-effects approach to pooling the result

Pooled estimates appear at the bottom

Measure of heterogeneity included



# Results Example

Research

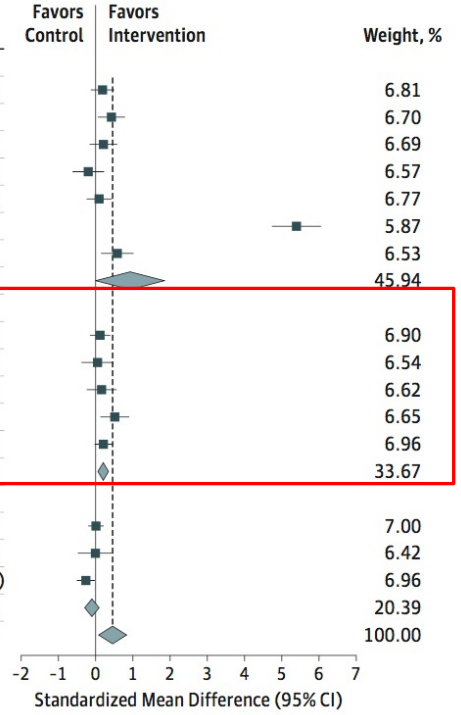
JAMA | Original Investigation

## Association Between Palliative Care and Patient and Caregiver Outcomes
### A Systematic Review and Meta-analysis

Dio Kavalieratos, PhD; Jennifer Corbelli, MD, MS; Di Zhang, BS; J. Nicholas Dionne-Odom, PhD, RN; Natalie C. Ernecoff, MPH; Janel Hanmer, MD, PhD; Zachariah P. Hoydich, BS; Dara Z. Ikejiani; Michele Klein-Fedyshin, MSLS, BSN, RN, BA; Camilla Zimmermann, MD, PhD; Sally C. Morton, PhD; Robert M. Arnold, MD; Lucas Heller, MD; Yael Schenker, MD, MAS

**Figure 2. Random-Effects Meta-analysis of Randomized Clinical Trials on the Association Between Palliative Care and Patient Quality of Life at 1- to 3-Month Follow-up**

| Source | No. of Patients: Intervention | Control | Setting | Instrument | Disease | Standardized Mean Difference (95% CI) | Weight, % |
|---|---|---|---|---|---|---|---|
| **High risk of bias** | | | | | | | |
| Bakitas et al,[20] 2015 | 72 | 83 | Home | FACIT-Pal | Cancer[a] | 0.19 (-0.13 to 0.50) | 6.81 |
| Clark et al,[35] 2013 | 54 | 63 | Ambulatory | FACT-G | Cancer[b] | 0.42 (0.06 to 0.79) | 6.70 |
| Given et al,[54] 2002 | 53 | 59 | Home | SF-36 | Cancer[c] | 0.21 (-0.16 to 0.58) | 6.69 |
| McCorkle et al,[51] 2015 | 36 | 56 | Ambulatory | FACT-G | Cancer[d] | -0.20 (-0.62 to 0.22) | 6.57 |
| Northouse et al,[32] 2005 | 69 | 65 | Ambulatory | SF-36 | Cancer[e] | 0.09 (-0.25 to 0.43) | 6.77 |
| Sidebottom et al,[9] 2015 | 79 | 88 | Hospital | MLHFQ | Heart failure | 5.39 (4.74 to 6.05) | 5.87 |
| Wong et al,[10] 2016 | 43 | 41 | Home | MQOL-HK | Heart failure | 0.58 (0.15 to 1.02) | 6.53 |
| Subtotal ($I^2$ = 97.4%, $P$ = .000) | | | | | | 0.93 (-0.00 to 1.85) | 45.94 |
| **Low risk of bias** | | | | | | | |
| Bakitas et al,[57] 2009 | 108 | 97 | Home | FACIT-Pal | Cancer[f] | 0.12 (-0.16 to 0.39) | 6.90 |
| Higginson et al,[12] 2014 | 42 | 40 | Ambulatory | EQ5D | Mixed[g] | 0.05 (-0.38 to 0.49) | 6.54 |
| Rummans et al,[59] 2006 | 47 | 49 | Ambulatory | Spitzer | Cancer[d] | 0.16 (-0.24 to 0.56) | 6.62 |
| Temel et al,[60] 2010 | 60 | 47 | Ambulatory | FACT-L TOI | Cancer[h] | 0.52 (0.13 to 0.90) | 6.65 |
| Zimmermann et al,[8] 2014 | 140 | 141 | Ambulatory | FACIT-Sp | Cancer[i] | 0.21 (-0.03 to 0.44) | 6.96 |
| Subtotal ($I^2$ = 0.0%, $P$ = .500) | | | | | | 0.20 (0.06 to 0.34) | 33.67 |
| **Unclear risk of bias** | | | | | | | |
| Bekelman et al,[13] 2015 | 172 | 180 | Home | KCCQ | Heart failure | 0.01 (-0.20 to 0.22) | 7.00 |
| Grudzen et al,[11] 2016 | 39 | 30 | Hospital | FACT-G | Cancer[j] | -0.01 (-0.48 to 0.47) | 6.42 |
| Northouse et al,[31] 2013 | 198 | 104 | Ambulatory | FACT-G | Cancer[k] | -0.26 (-0.50 to -0.02) | 6.96 |
| Subtotal ($I^2$ = 33.3%, $P$ = .223) | | | | | | -0.10 (-0.30 to 0.09) | 20.39 |
| Overall ($I^2$ = 94.8%, $P$ < .001) | | | | | | 0.46 (0.08 to 0.83) | 100.00 |




30 Eligible studies

Stratified analysis by risk of bias

Author's Conclusion: "Palliative care was associated with improvements in quality of life and symptom burden but not with improved survival"

Many associations were no longer consistent when analysis was limited to studies with a low risk of bias

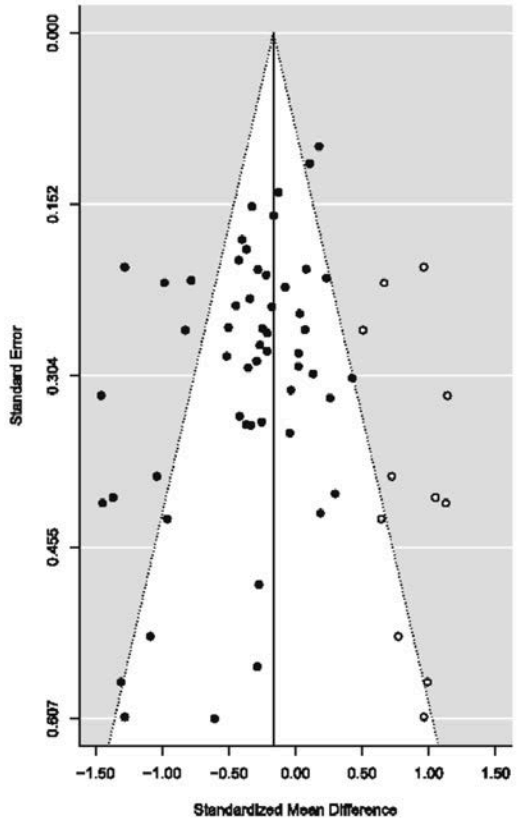
# Heterogeneity

Heterogeneity in a meta-analysis refers to the situation where the included studies are measuring fundamentally different effects

Potential sources include:

- Differences in the treatment protocol
  - Different drug/dose
  - Different timing
- Differences in the target population
  - Genetic
  - Cultural
  - Compliance
- Differences in the healthcare milieu surrounding the intervention

# Diagnosing Heterogeneity




Method 1 – Funnel Plot

Heterogeneity can often be diagnosed graphically when very precise studies show very different effects

Funnel tends to look more cylindrical

Method 2- $I^2$ statistic

- Can think of this as the % of variation between the studies due to heterogeneity as opposed to sampling variation
- Ideally all variation in a study would be sampling variation: $I^2$= 0%
- 0-40%: might not be important
- 30-60%: may represent moderate heterogeneity
- 50-90%: may represent substantial heterogeneity
- 90%+: considerable heterogeneity

Higgins JPT, et al Cochrane Collaboration. *Cochrane handbook for systematic reviews of interventions*. Chichester, England ; Hoboken, NJ: Wiley-Blackwell; 2008: xxi, 649 p.
Mathie RT, et al. Randomised, double-blind, placebo-controlled trials of non-individualised homeopathic treatment: systematic review and meta-analysis. Systematic Reviews 2017. 6:63

# Results Example

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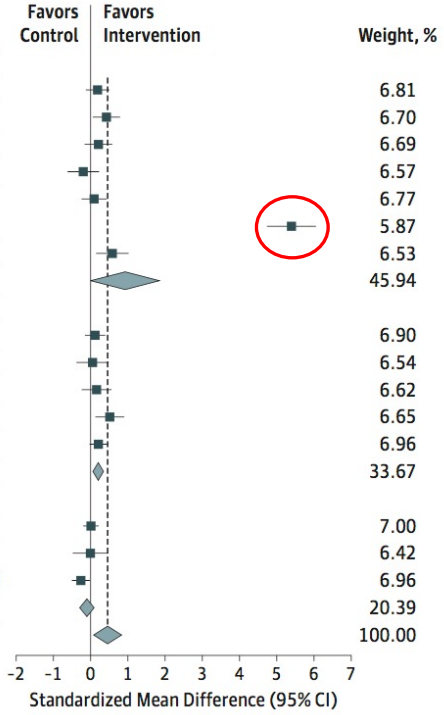


# Dealing With Heterogeneity

Recheck the data

Adjust for differences between approaches using meta-regression

Use a random-effects approach to pooling the results

Try a different effect measure

Exclude studies

Skip the meta-analysis portion: in the face of heterogeneity what does the ‘average’ treatment effect really tell you?

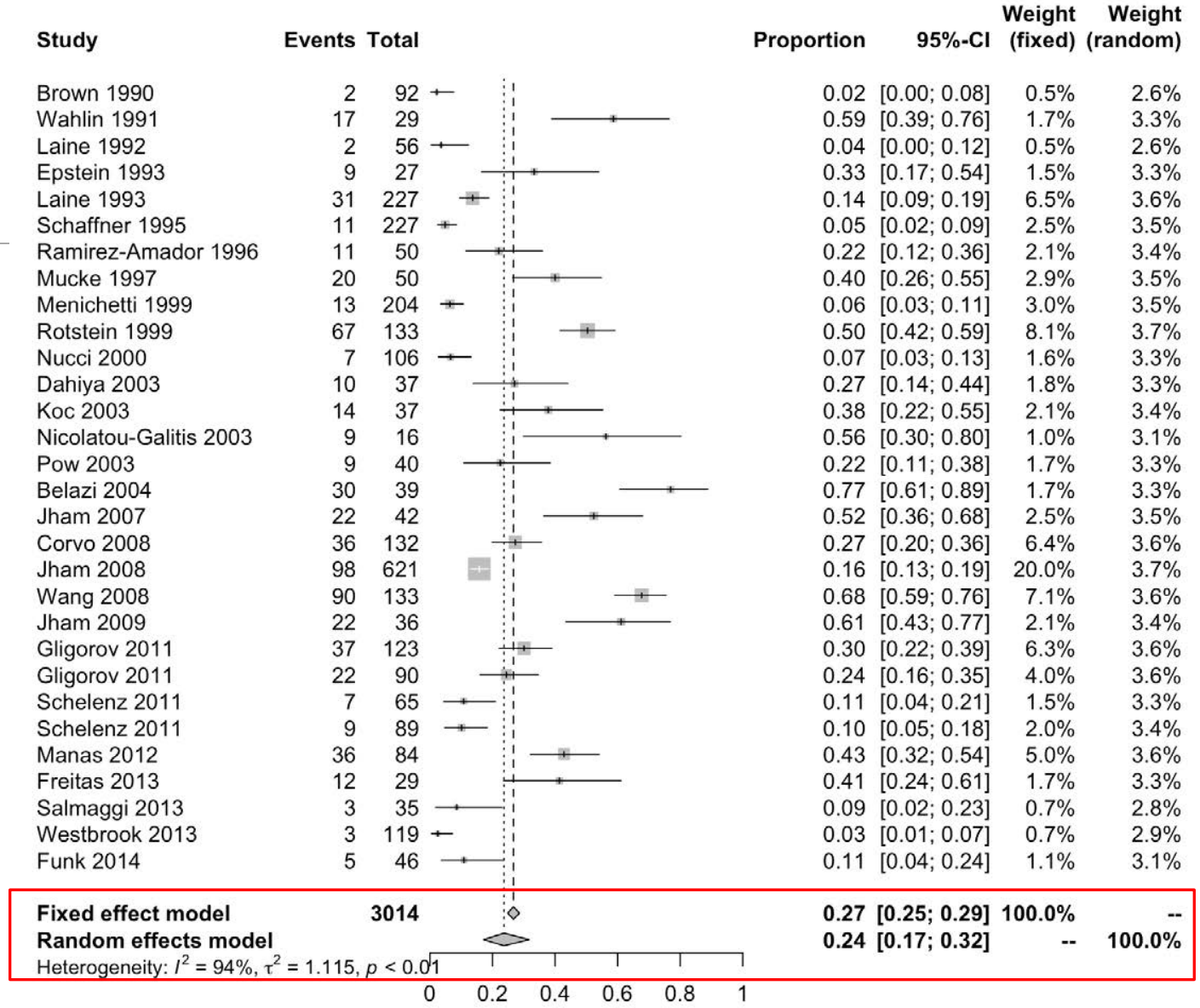
# Random Effects

Meta-analysis estimating the incidence of oral fungal infection in patients undergoing cancer therapy

High heterogeneity: $I^2$=94%

Likely due to a combination of different cancers, different therapies, demographic differences, regional differences, etc.

Note that both the results are presented for both the fixed and random effects models



# Heterogeneity Example

## Cancer Survivors and Unemployment
### A Meta-analysis and Meta-regression

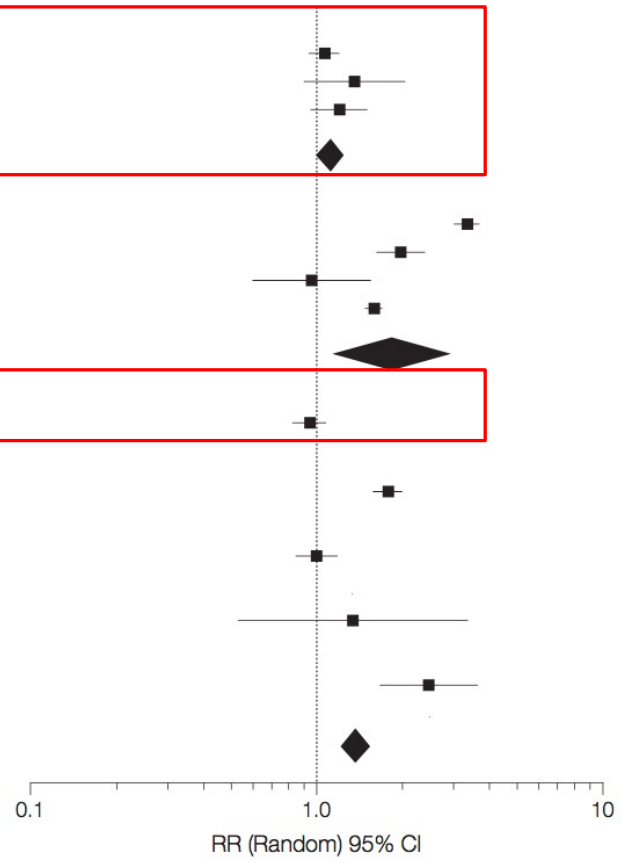
Angela G. E. M. de Boer, PhD
Taina Taskila, PhD
Anneli Ojajärvi, PhD
Frank J. H. van Dijk, PhD, MD
Jos H. A. M. Verbeek, PhD, MD

26 articles identified

Stratified analyses of survivor unemployment by cancer type (excerpt)

Author's Conclusion: "Cancer survivorship is associated with unemployment. "

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Prostate cancer | | | | | | | |
| Taskila-Abrandt et al,[36] 2004 | 168 | 240 | 158 | 240 | 3.54 | | 1.06 (0.94-1.20) |
| Bradley et al,[33] 2005 | 45 | 243 | 35 | 256 | 2.63 | | 1.35 (0.90-2.03) |
| Farley Short et al,[25] 2008 | 62 | 215 | 466 | 1933 | 3.27 | | 1.20 (0.96-1.50) |
| Subtotal | 275 | 698 | 659 | 2429 | 9.44 | 6.0 | 1.11 (1.00-1.25) |
| Mixed cancer diagnoses | | | | | | | |
| Hewitt et al,[1] 2003 | 389 | 2317 | 3874 | 77 489 | 3.59 | | 3.36 (3.05-3.70) |
| Yabroff et al,[38] 2004 | 153 | 897 | 238 | 2746 | 3.38 | | 1.97 (1.63-2.38) |
| Eakin et al,[28] 2006 | 19 | 421 | 122 | 2579 | 2.39 | | 0.95 (0.59-1.53) |
| Sabatino et al,[29] 2006 | 657 | 1710 | 12 178 | 50 023 | 3.63 | | 1.58 (1.48-1.68) |
| Subtotal | 1218 | 5345 | 16 412 | 132 837 | 12.99 | 98.3 | 1.83 (1.13-2.96) |
| Melanoma | | | | | | | |
| Taskila-Abrandt et al,[36] 2004 | 273 | 853 | 290 | 853 | 3.51 | | 0.94 (0.82-1.08) |
| Nervous system cancer | | | | | | | |
| Taskila-Abrandt et al,[36] 2004 | 483 | 878 | 272 | 878 | 3.55 | | 1.78 (1.58-1.99) |
| Thyroid cancer | | | | | | | |
| Taskila-Abrandt et al,[36] 2004 | 189 | 629 | 189 | 629 | 3.43 | | 1.00 (0.84-1.18) |
| Sarcoma | | | | | | | |
| Hoffman et al,[43] 2002 | 8 | 28 | 6 | 28 | 1.21 | | 1.33 (0.53-3.35) |
| Nasopharyngeal cancer | | | | | | | |
| Fang et al,[44] 2002 | 62 | 137 | 26 | 142 | 2.68 | | 2.47 (1.67-3.66) |
| Overall | 6886 | 20 366 | 24 015 | 157 603 | 100.00 | 94.3 | 1.37 (1.21-1.55) |




CI denotes confidence interval; RR, relative risk.

# Heterogeneity Example: Regression

## Cancer Survivors and Unemployment
### A Meta-analysis and Meta-regression

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**Table 4.** Results of Univariate and Multivariate Bayesian Meta-regression Models With Crude and Adjusted Meta-relative Risks for Prognostic Factors

| | | All Studies (n = 36) | | High-Quality Studies[a] | |
|---|---|---|---|---|---|
| Factor | No. of Studies | Crude Meta-RR (95% CrI) Univariate | Adjusted Meta-RR (95% CrI) Multivariate[b] | No. | Adjusted Meta-RR (95% CrI) Multivariate (n = 25)[b] |
| Country | | | | | |
| Europe | 16 | 1 [Reference] | 1 [Reference] | 15 | 1 [Reference] |
| United States | 15 | 1.48 (1.15-1.95) | 1.24 (0.85-1.83) | 7 | 0.98 (0.66-1.56) |
| Other | 5 | 1.47 (1.03-2.12) | 1.16 (0.68-1.96) | 3 | 1.34 (0.85-2.27) |
| Cancer diagnosis | | | | | |
| Testicular | 3 | 1 [Reference] | 1 [Reference] | 3 | 1 [Reference] |
| Breast | 10 | 1.35 (0.76-2.37) | 1.20 (0.65-2.22) | 6 | 1.15 (0.67-1.85) |
| Prostate | 3 | 1.21 (0.62-2.39) | 1.17 (0.55-2.47) | 3 | 1.28 (0.67-2.31) |
| Blood | 7 | 1.42 (0.77-2.64) | 1.38 (0.79-2.50) | 6 | 1.27 (0.74-2.04) |
| Other or mixed | 13 | 1.58 (0.90-2.75) | 1.48 (0.87-2.56) | 7 | 1.35 (0.84-2.09) |
| Patient age | | | | | |
| 18-50 y | 23 | 1 [Reference] | 1 [Reference] | 15 | 1 [Reference] |
| >50 y | 8 | 0.99 (0.70-1.40) | 1.08 (0.70-1.69) | 6 | 1.03 (0.72-1.46) |
| Not reported | 5 | 1.19 (0.81-1.77) | 1.10 (0.70-1.77) | 4 | 1.09 (0.69-1.65) |
| Background unemployment rate | 36 | 0.24 (0.11-0.54) | 0.38 (0.11-1.27) | 25 | 0.63 (0.21-1.99) |

Abbreviations: CrI, credibility interval; RR, relative risk.
[a] High quality denotes 16 points or greater on the MINORS test.
[b] Adjusted for all the other variables in the model.

Performed meta-regression looking for differences in unemployment by survivor age, country, and diagnosis

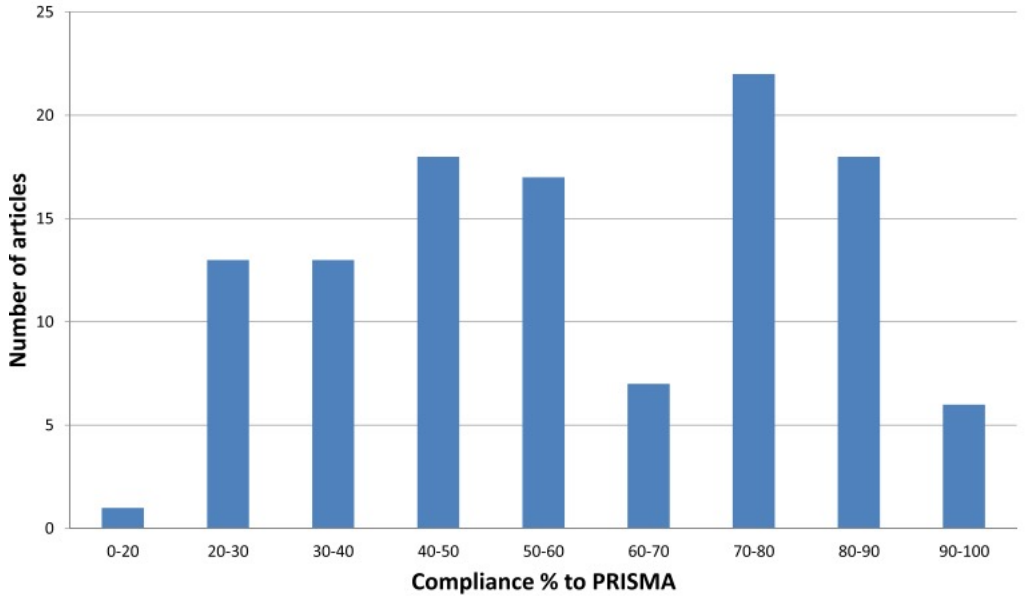
Authors' Conclusions: "For survivors in the United States, the unemployment risk was 1.5 times higher compared with survivors in Europe (meta-RR, 1.48; 95% credibility interval, 1.15-1.95). After adjustment for diagnosis, age, and back- ground unemployment rate, this risk disappeared (meta-RR, 1.24; 95% CI, 0.85-1.83). "

# Reporting Guidelines

Prisma

- Publish a full protocol for each study
- Include the last date included databases were searched
- Give the full electronic search strategy
- Describe how bias is assessed
- Define all items abstracted from papers
- Measures of consistency
- Consider sensitivity analyses
- Give the number screened, excluded, and the reason for any exclusions in a *flow diagram*
- Present the characteristics of each study included in tabular form
- Present the risk of bias for each study
- For each study present the data abstracted in a *forest plot*
- Present the results of each meta-analysis with a confidence interval and a *measure of consistency*
- Discuss limitations at the study outcome and *review level*

# PRISMA in the Literature




RESEARCH ARTICLE Open Access

## Compliance of systematic reviews in ophthalmology with the PRISMA statement

Seon-Young Lee[1*], Harkiran Sagoo[2], Reem Farwana[3], Katharine Whitehurst[4], Alex Fowler[5] and Riaz Agha[6]

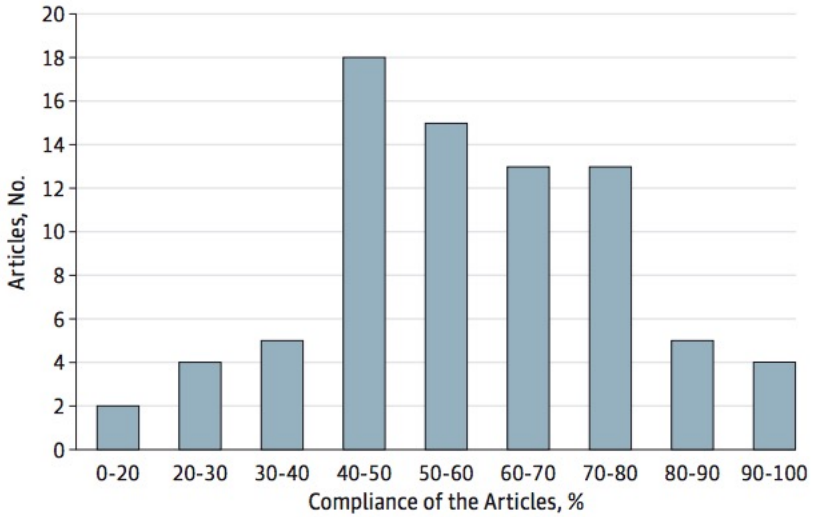
Research

Original Investigation

## Compliance of Systematic Reviews in Plastic Surgery With the PRISMA Statement

Seon-Young Lee, BMedSc; Harkiran Sagoo, BSc(Hons); Katharine Whitehurst, BSc(Hons); Georgina Wellstead, BSc(Hons); Alexander J. Fowler, BSc(Hons), MBBS; Riaz A. Agha, BSc(Hons), MBBS, MSc(Oxf), MRCSEng, FHEA, FRSPH; Dennis Orgill, MD, PhD

**Figure 2. Compliance of 79 Systematic Reviews With the PRISMA Statement**




The number of articles are shown according to the different levels of compliance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.

Lee et al. BMC Medical Research Methodology (2017) 17:178
JAMA Facial Plast Surg. 2016;18(2):101-105. doi:10.1001/jamafacial.2015.1726