Systematic Reviews and Meta-Analysis

Ilir Agalliu MD, ScD
Associate Professor
Dept. of Epidemiology and Population Health

Dec 13th, 2023

Objectives

01

Understand the purpose of systematic reviews

02

Understand the advantages of adding a meta-analysis to a systematic review

- What do we gain?

03

Interpret the results of a meta-analysis and assess heterogeneity of various studies

04

Identify the limitations of a systematic review and meta-analysis

Systematic Reviews

A narrative review of different study results

More of a qualitative approach

Identify and critique relevant research studies

Common research question

Discuss factors that may explain heterogeneity

Synthesize the knowledge based on each individual study without trying to do any quantitative approach

Systematic Review Process

1. Formulate a clear research question and eligibility criteria for studies
2. Prepare a protocol
3. Search for potentially relevant studies
4. Select eligible studies into the systematic review
5. Collection of data / Extract relevant info
6. Assessment of methodological quality of included studies
7. Synthesis of findings (possibly using meta-analysis)
8. Presentation of data and results
9. Interpretation and drawing conclusions

The PRISMA 2020 statement: an updated guideline for reporting systematic reviews

Matthew J Page,[1] Joanne E McKenzie,[1] Patrick M Bossuyt,[2] Isabelle Boutron,[3] Tammy C Hoffmann,[4] Cynthia D Mulrow,[5] Larissa Shamseer,[6] Jennifer M Tetzlaff,[7] Elie A Akl,[8] Sue E Brennan,[1] Roger Chou,[9] Julie Glanville,[10] Jeremy M Grimshaw,[11] Asbjørn Hróbjartsson,[12] Manoj M Lalu,[13] Tianjing Li,[14] Elizabeth W Loder,[15] Evan Mayo-Wilson,[16] Steve McDonald,[1] Luke A McGuinness,[17] Lesley A Stewart,[18] James Thomas,[19] Andrea C Tricco,[20] Vivian A Welch,[21] Penny Whiting,[17] David Moher[22]

SUMMARY POINTS

- To ensure a systematic review is valuable to users, authors should prepare a transparent, complete, and accurate account of why the review was done, what they did, and what they found
- The PRISMA 2020 statement provides updated reporting guidance for systematic reviews that reflects advances in methods to identify, select, appraise, and synthesize studies
- The PRISMA 2020 statement consists of a 27-item checklist, an expanded checklist that details reporting recommendations for each item, the PRISMA 2020 abstract checklist, and revised flow diagrams for original and updated reviews
- We anticipate that the PRISMA 2020 statement will benefit authors, editors, and peer reviewers of systematic reviews, and different users of reviews, including guideline developers, policy makers, healthcare providers, patients, and other stakeholders

Recommended Items for Systematic Reviews: PRISMA 2020

Table 1 | PRISMA 2020 item checklist

Section and topic	Item #	Checklist item	Loc ite
Title			
Title	1	Identify the report as a systematic review.	
Abstract			
Abstract	2	See the PRISMA 2020 for Abstracts checklist (table 2).	
Introduction			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	
Methods			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	
	13d	Describe any methods used to synthesise results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesised results.	
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	

Recommended Items for Systematic Reviews

Results		
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram (see fig 1).
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.
Study characteristics	17	Cite each included study and present its characteristics.
Risk of bias in studies	18	Present assessments of risk of bias for each included study.
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.
	20c	Present results of all investigations of possible causes of heterogeneity among study results.
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesised results.
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.
Discussion		
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.
	23b	Discuss any limitations of the evidence included in the review.
	23c	Discuss any limitations of the review processes used.
	23d	Discuss implications of the results for practice, policy, and future research.
Other information		
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.
	24c	Describe and explain any amendments to information provided at registration or in the protocol.
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.
Competing interests	26	Declare any competing interests of review authors.
Availability of data, code, and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.

Meta-Analysis

Quantitative approach to systematically combine results of previous research studies considered to be "combinable" to arrive at conclusions about the evidence of research (treatment or exposure effect on a particular outcome)

Quantitative: numbers, statistical methods, results

Systematic: methodologically sound approach

Previous research: what's already done

Conclusions: New knowledge

Goals of Meta-Analysis

To test whether the studies' results are homogeneous

To obtain a global index about the magnitude of the relationship / treatment effect

- Also a confidence interval and associated statistical significance

If there is heterogeneity among studies, to identify possible sources of variation

Why is Meta-Analysis Warranted?

- One study cannot provide a definitive answer
- Existing studies have reported different results or there is inconsistent evidence
- Summarize the results of ‘good’ existing studies to obtain a magnitude of an effect with adequate precision
  - RCT are considered the gold standard

- Meta-analysis combines the effects from all studies to give an overall mean/average effect and other important information regarding heterogeneity (or not) of studies

Parental Smoking Cessation to Protect Young Children: A Systematic Review and Meta-analysis

Laura J. Rosen, Michal Ben Noach, Jonathan P. Winickoff and Mel F. Hovell
Pediatrics 2012;129;141; originally published online December 26, 2011;
DOI: 10.1542/peds.2010-3209

BACKGROUND: Young children can be protected from much of the harm from tobacco smoke exposure if their parents quit smoking. Some researchers encourage parents to quit for their children's benefit, but the evidence for effectiveness of such approaches is mixed.

OBJECTIVE: To perform a systematic review and meta-analysis to quantify the effects of interventions that encourage parental cessation.

Principles of a Meta-Analysis

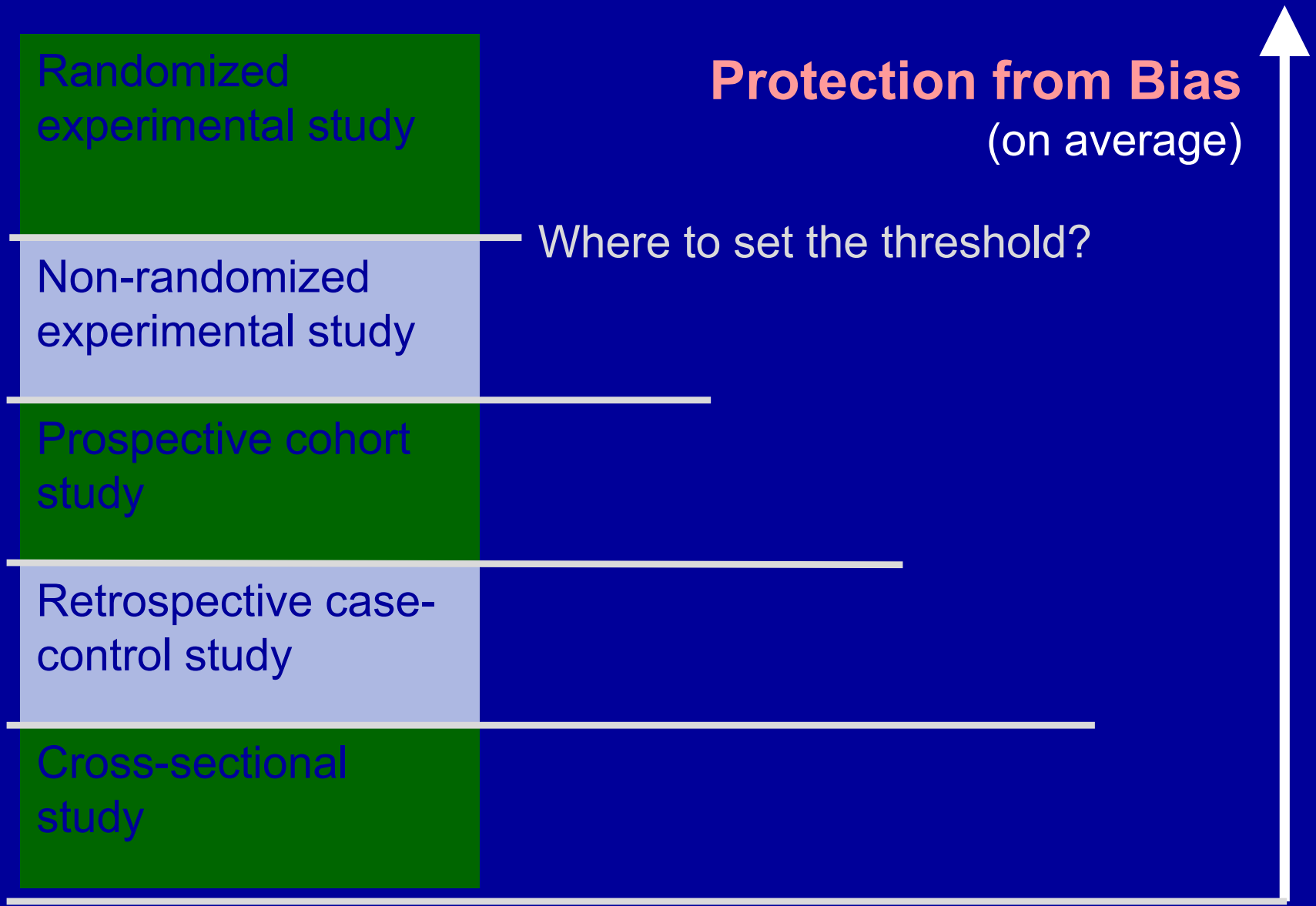
- Formulate the Research Question to be Addressed
- Define search criteria for the studies you want to include in your meta-analysis
  - What kind of Studies (RCT, Observational)
  - Period of study publication
  - Outcome you are interested in (continuous; discrete)

METHODS: We searched PubMed, the Cochrane Library, Web of Science, and PsycINFO. Controlled trials published before April 2011 that targeted smoking parents of infants or young children, encouraged parents to quit smoking for their children's benefit, and measured parental quit rates were included. Study quality was assessed. Relative risks and risk differences were calculated by using the DerSimonian and Laird random-effects model.

Studies to be included in Meta-Analysis

- Thorough literature review of existing studies on a particular topic
- Ideally '<u>homogenously</u>' designed studies
  - RCT
  - Observational (cohort or case-control; however, need to keep in mind design issues)
- Individual results need to be expressed in a standardized format to allow for comparison between studies
  - Continuous (mean difference between 2 groups can be used)
  - Categorical (diseased vs. non-diseased or dead vs. alive) preference would be to collect OR or RR
    - Keep in mind that for rare diseases OR approximates RR

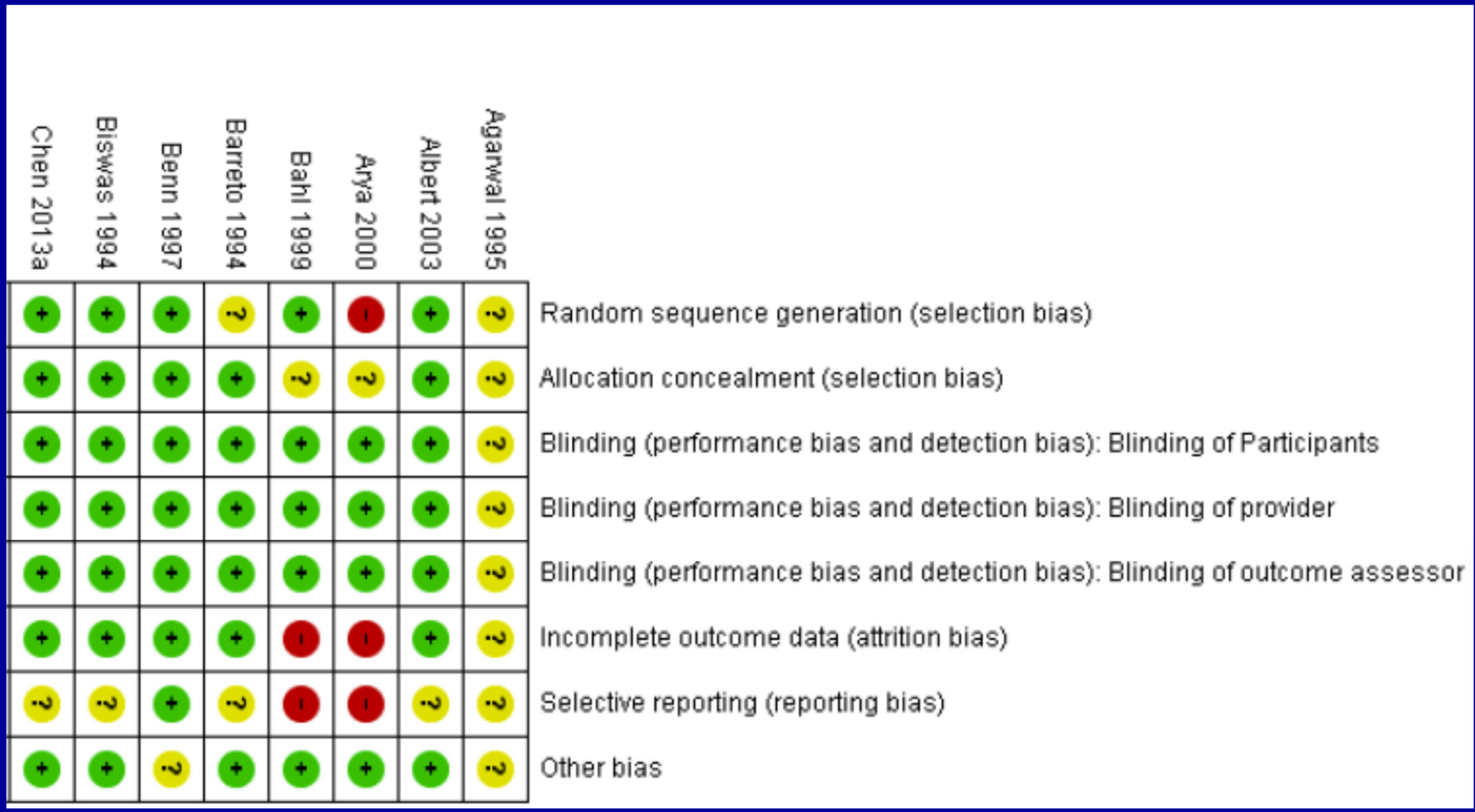
Choosing study designs for questions about interventions and exposures



Issues with quality of studies in a Meta-Analysis

- You may also score the quality of a study (covariate)
  - Study Design: RCT, Observational (Cohort vs. Case-Control approach)
  - Quality of Data Collected
    - Exposure or Treatment effect
    - Outcome (confirmed or self-reported; etc)
  - Sample size of the study (this is currently used as default for weighting the evidence)
  - Research funded by impartial agency or by industry?
  - Study performed by experienced researchers?
  - Published in a peer-reviewed journal?

Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Parental Smoking Cessation to Protect Young Children: A Systematic Review and Meta-analysis

Laura J. Rosen, Michal Ben Noach, Jonathan P. Winickoff and Mel F. Hovell
Pediatrics 2012;129;141; originally published online December 26, 2011;
DOI: 10.1542/peds.2010-3209

Methodological Quality

The following parameters describing methodologic quality were assessed: study design (randomized controlled trial [RCT] using a cluster randomization scheme, RCT, quasi-RCT, controlled trial [CT]), randomization concealment (yes, no, or not reported), blinding of observers (yes, no, or not reported), biochemical validation of quit rates (yes, no), follow-up (percentage of follow-up at last time point measured), fidelity to treatment (percentage of participants receiving full intervention).

Study outcome: Quit rates of parents, mothers, or fathers must have been monitored.

Study Eligibility

To be included, the studies had to meet the following criteria:

Study design: RCT using a cluster or individual-level randomization scheme, quasi-randomized RCT, CT.

Participants: Parents (mother, father or both parents) of children between the ages of 0 and 6 years in one of the following cohorts: well (including children visiting well-child clinics and population cohorts), asthmatic children, or children visiting hospitals or pediatric clinics. Trials that included children older than 6 years were acceptable only if children 6 years old or less were eligible for inclusion.

Types of interventions: Unrestricted.

Program providers: Unrestricted.

Study objectives: Primary goal must have been either reduction or cessation of parental smoking to benefit children, or child tobacco smoke exposure reduction.

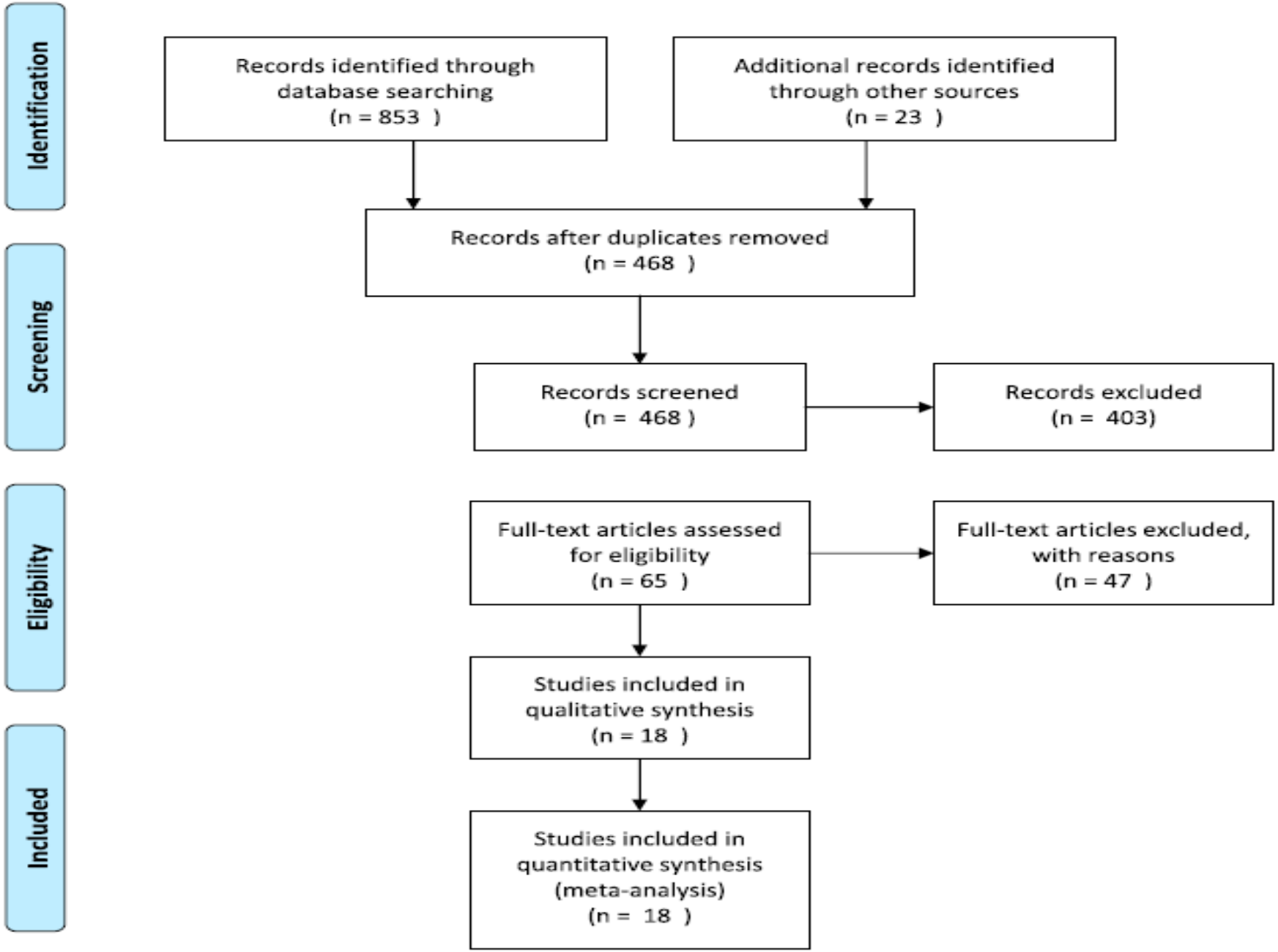


FIGURE 1
Flowchart for identification of studies.

Principles of a Meta-Analysis

Data need to be extracted from each study

Calculate the overall effect by combining the data

The main outcome is the overall magnitude of the treatment effect or measure of association

Summary estimate (OR, RR) is a weighted average giving more weights to studies with more precise estimates (i.e. larger sample size)

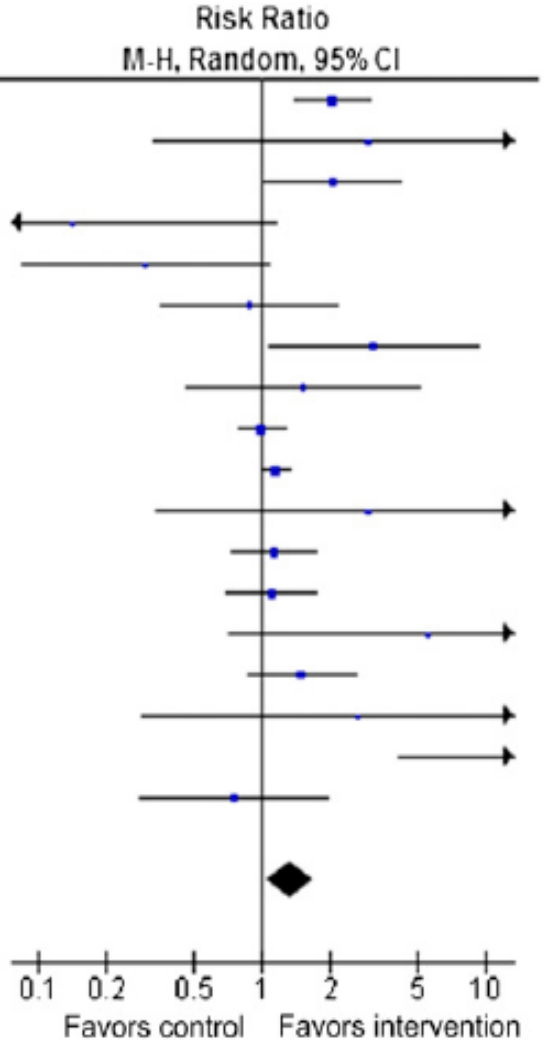
- Fixed effects: assumes that studies are equal and variability is due to random variation
- Random effect assumes a different underlying effect for each study (takes into consideration additional sources of variation)

Meta-Analysis of Effects of Intervention on Parental Smoking Cessation

Study or Subgroup	Intervention Events	Intervention Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Abdullah et al 2005[18]	68	444	34	459	10.9%	2.07 [1.40, 3.06]
Chan et al 2005[19]	3	40	1	40	1.1%	3.00 [0.33, 27.63]
Curry et al 2003[20]	22	156	10	147	6.6%	2.07 [1.02, 4.23]
EriKsen et al 1996[21]	1	221	7	222	1.3%	0.14 [0.02, 1.16]
Greenberg et al 1994[22]	3	329	10	330	2.9%	0.30 [0.08, 1.08]
Hovell et al 2002[23]	8	97	9	96	4.9%	0.88 [0.35, 2.18]
Hovell et al 2009[24]	13	76	4	74	3.9%	3.16 [1.08, 9.26]
Hughes et al 1991[25]	6	47	4	48	3.3%	1.53 [0.46, 5.08]
Kallio et al 2006[26]	101	505	108	537	13.1%	0.99 [0.78, 1.27]
Krieger et al 2005[27]	92	110	75	104	14.2%	1.16 [1.00, 1.34]
Ralston and Roohi et al 2008[28]	3	21	1	21	1.2%	3.00 [0.34, 26.56]
Severson et al 1997[29]	47	862	31	644	10.1%	1.13 [0.73, 1.76]
Vineis et al 1993[30]	30	247	36	328	9.9%	1.11 [0.70, 1.75]
Wahlgren et al 1997[31]	6	28	1	26	1.3%	5.57 [0.72, 43.22]
Wilson et al 2010[32]	27	169	18	170	8.4%	1.51 [0.86, 2.63]
Woodward et al 1987[13]	3	50	1	45	1.1%	2.70 [0.29, 25.04]
Yilmaz et al 2006[33]	27	111	1	121	1.4%	29.43 [4.07, 213.01]
Zakarian et al 2004[34]	6	60	9	68	4.5%	0.76 [0.29, 2.00]
Total (95% CI)		3573		3480	100.0%	1.34 [1.05, 1.71]
Total events	466		360			

Heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 42.27$, $df = 17$ ($P = 0.0006$); $I^2 = 60\%$

Test for overall effect: $Z = 2.32$ ($P = 0.02$)



Fixed vs. Random Effects Model

- Fixed effect does NOT take into account variability between studies
- Random effects generally yield larger variances and CI
  - It incorporates variances between studies: σ_B^2
- If heterogeneity between studies is large, σ_B^2 will dominate the weights and all studies will be weighted more equally
- Model weight for large studies less in random vs fixed effects model

Heterogeneity of Studies

- Variability due to sampling error (within-study variability)
- Variability due to different studies' populations, design quality and treatment effect (between study variability)

- In random-effect meta-analysis, one assumes there are real differences between all studies in the magnitude of the effect
- Assessing heterogeneity between studies
  - Q test only informs about the presence vs. absence of heterogeneity
  - I^2 statistic quantifies the percent of variation due to real differences among studies

Potential Sources of Between Study Heterogeneity

- Differences in Study Designs
- Study quality
- Potential biases in ascertainment of study population / eligibility criteria
- Differences in incidence rates among unexposed (in different cohort studies)
- Different lengths of follow-up
- Different distributions of confounders and effect modifiers
- Different statistical methods / adjustment models used

Meta-Analyses: Sensitivity Analyses

- Exclude studies with heterogeneous results
- Conduct separate analyses based on
  - Study design
    - Cohort, Case-Control, RCT
  - Geographic location
  - Time period
  - Study Quality: e.g. Poor, Moderate, Good
  - Other characteristic (e.g. age, race/ethnicity, etc.) if data are available

Sensitivity Analysis

- Assumptions of statistical model
  - Fixed vs. random effects
- Methodological quality
  - Good vs. doubtful
- Study size
  - Small vs. large trials
- Other covariates
  - Age, follow-up or length of observation, blindness of reviewers…etc
- Publication Bias
  - Positive studies are more likely to be published and in better impact journals

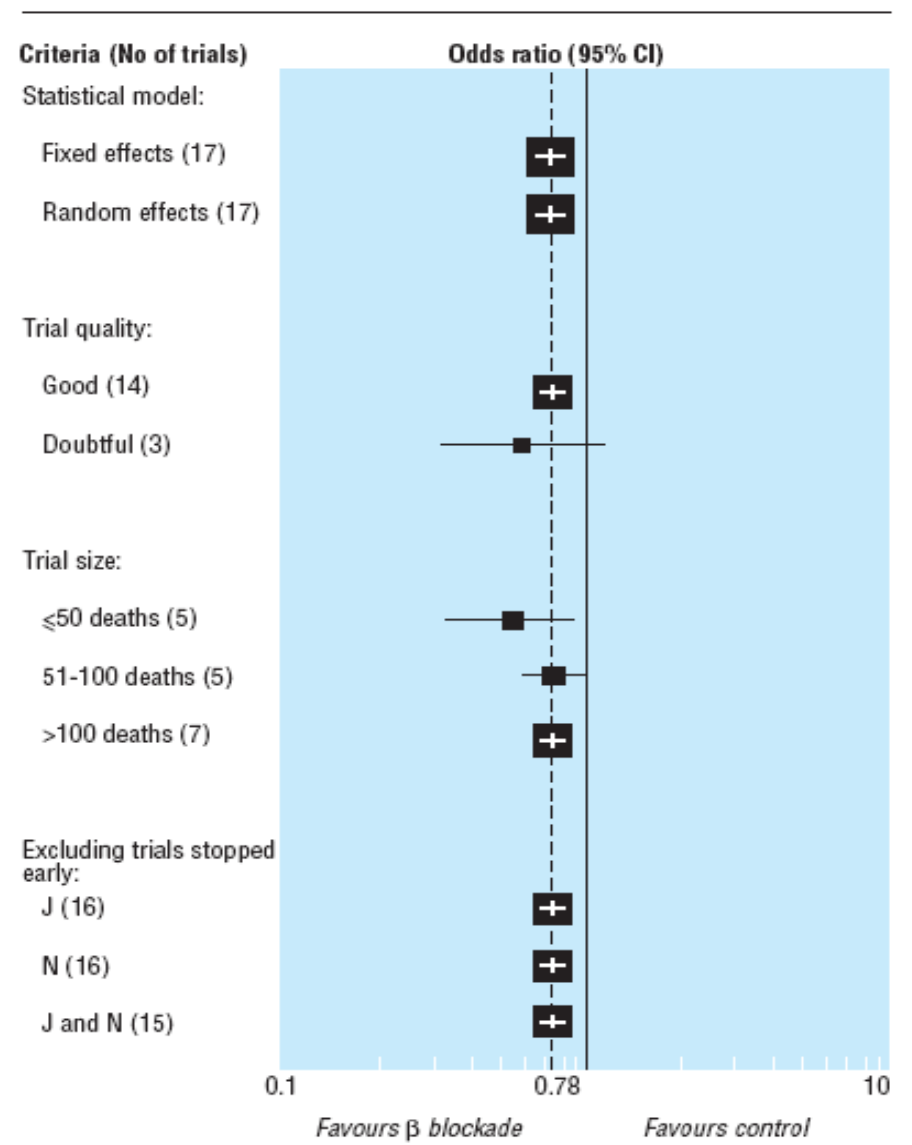


Fig 2 Sensitivity analysis of meta-analysis of β blockers in secondary prevention after myocardial infarction (see text for explanation)

Examples of Subgroup Analyses

TABLE 4 Effects of Intervention Programs on Parental Quit Rate Stratified According to Child-Related, Intervention-Related, and Design-Related Subgroup

Analysis	RR (CI)	*P**	No. of Studies	No. of Participants
Age				
Infants (0-1 y)	0.99 (0.6, 1.63)	.98	7	3556
Preschool (2-4 y)	1.14 (0.48, 2.68)	.77	4	1060
Children (4-17 y)	1.57 (1.14, 2.16)	.006*	11	3497
Child cohort				
Well	1.26 (0.83, 1.92)	.29	710	5733
Asthmatic	1.20 (1.00, 1.44)	.05	5	895
Hospital/clinic visit	2.21 (1.16, 4.23)	.02	3	425
Setting				
Well-baby clinic	1.46 (0.92, 2.33)	.11	5	4258
Hospital	1.28 (0.86, 1.90)	.22	5	1818
Pediatric clinic	1.30 (0.23, 7.40)	.77	3	800
Family home	1.16 (0.83, 1.63)	.39	7	1778
Study design				
RCT	1.40 (1.01, 1.92)	.04	14	4782
Quasi-RCT	1.74 (0.61, 5.00)	.3	2	190
CT	1.11 (0.70, 1.75)	.66	1	575
Cluster RCT	1.13 (0.73, 1.76)	.58	1	1506

Assessing Publication Bias: Funnel Plots

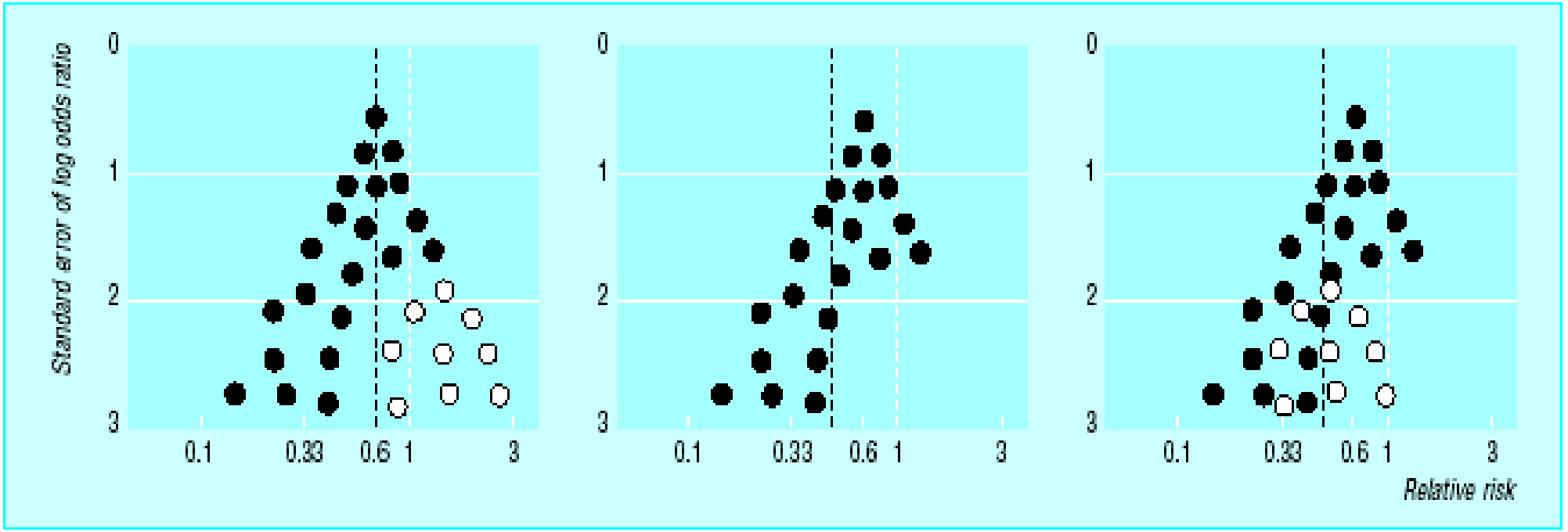


Fig 1 Hypothetical funnel plots: left, symmetrical plot in absence of bias (open circles are smaller studies showing no beneficial effects); centre, asymmetrical plot in presence of publication bias (smaller studies showing no beneficial effects are missing); right, asymmetrical plot in presence of bias due to low methodological quality of smaller studies (open circles are small studies of inadequate quality whose results are biased towards larger effects). Solid line is pooled odds ratio and dotted line is null effect (1). Pooled odds ratios exaggerate treatment effects in presence of bias

Sterne 2001

Situations Where Publication Bias Can Occur?

- Project dropped when preliminary analyses suggest results are negative
- Authors do not submit negative study
- Results reported in small, non-indexed journal
- Editor rejects manuscript
- Reviewers reject manuscript (several times)
- Author does not resubmit rejected manuscript
- Journal delays publication of negative study
- Results not reported by news, policy makers, or narrative reviews

Assessing Publication Bias

Parental Smoking Cessation to Protect Young Children: A Systematic Review and Meta-analysis

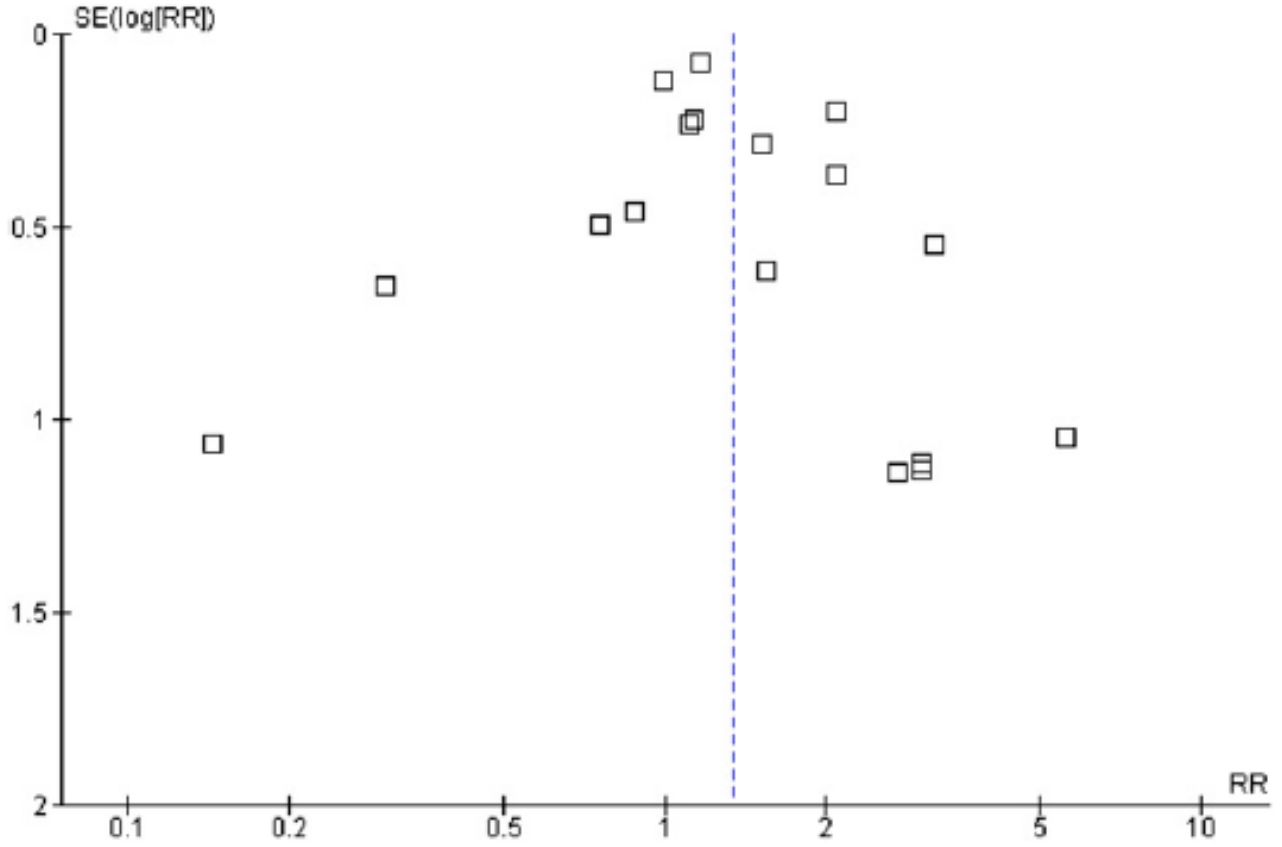


FIGURE 3
Plot to assess presence of publication bias.

Limitations of Meta-Analysis

- If conducted poorly are very misleading
  - Carefully consider methodological aspects of each study
  - Study population
  - Treatment (dose, duration) / Exposure assessment
  - Outcome (confirmed medical tests, self-reported)
  - Observational studies: need to consider that each study has controlled for different confounders and might have issues with bias
- Focus on average effect and assessment of differences between studies
  - Need to know which subject characteristics (e.g. age, gender, genotype) might predict individual responses
- Publication bias