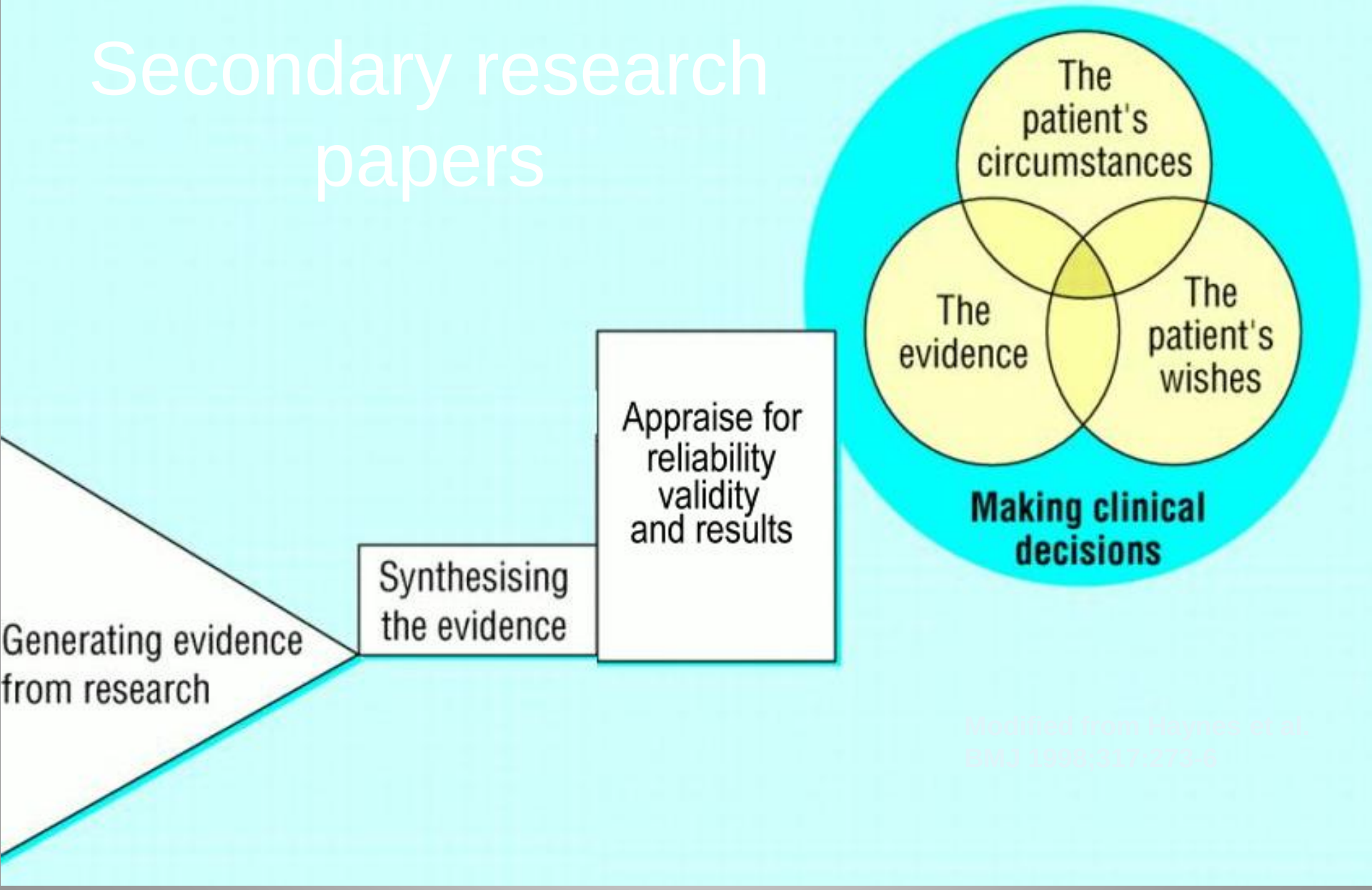
Reviews – March 7, DEN1014 Clinical Epidemiology

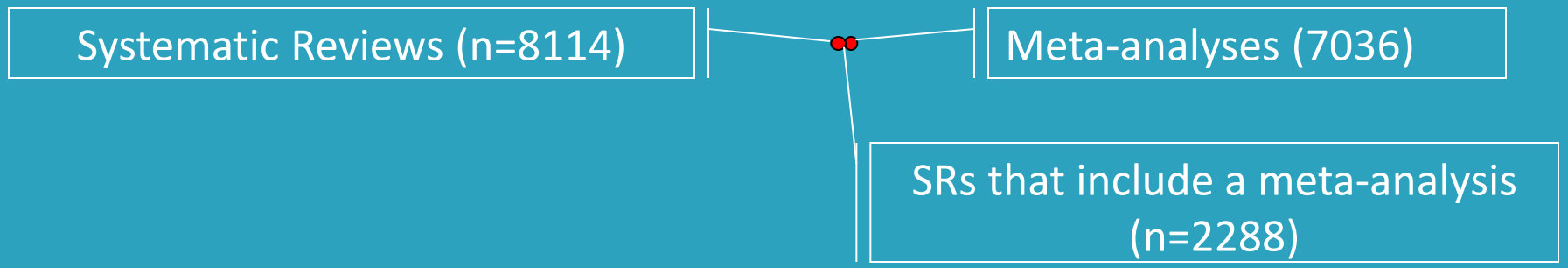
Secondary research papers



Modified from Haynes et al. BMJ 1996;312:273-6

Medline

Reviews (n=1 307 569)



What can SRs show us?

Example: How effective is Guided Tissue Regeneration (GTR) for patients with localized bone loss?

JOURNAL OF Periodontology

March 1998 (Volume 69, No. 3

Treatment of Intrabony Defects by Different Surgical Procedures. A Literature Review

Lars Laurell, Jan Gottlow, Michael Zybutz, and Rutger Persson

This article reviews studies presented during the last 20 years on the surgical treatment of intrabony defects. Treatments include open flap debridement alone (OFD); OFD plus demineralized freeze-dried bone allograft (DFDBA), freeze-dried bone allografts (FDBA), or autogenous bone; and guided tissue regeneration (GTR). The review includes only studies that presented baseline and final data on probing depths, intrabony defect depths as measured during surgery, clinical attachment level (CAL) gain, and/or bone fill. Some reports were case studies and some controlled studies comparing different treatments. In order to assess what can be accomplished in terms of pocket reduction, clinical attachment level gain, and bone fill with the various treatment modalities, data from studies of each treatment category were pooled for meta-analysis in which the data from and power of each study were weighted according to the number of defects treated. In addition, where there were data for each individual defect treated, these were used for simple regression analysis evaluating the influence of intrabony defect depth on treatment outcome in terms of CAL gain and bone fill. This was done in an effort to assess some predictability of the outcome of the various treatments. OFD alone resulted in limited pocket reduction, CAL gain averaged 1.5 mm and bone fill 1.1 mm. Bone fill, but not CAL gain, correlated significantly to the depth of the defect ($R = 0.3$; $P < 0.001$), but the regression coefficient was only 0.25. OFD plus bone graft resulted in limited pocket reduction. CAL gain and bone fill averaged 2.1 mm. Bone fill showed a somewhat stronger correlation to defect depth than following OFD alone ($R = 0.43$; $P < 0.001$) with a regression coefficient of 0.37. GTR resulted in significant pocket reduction, CAL gain of 4.2 mm and bone fill averaging 3.2 mm. CAL gain and bone fill correlated significantly ($P < 0.001$) to defect depth ($R = 0.52$ and 0.53 respectively) with the largest regression coefficients (0.54 and 0.58 respectively) among the three treatment modalities. By comparing outcomes following the various treatments it became obvious that to benefit from GTR procedures, the intrabony defect has to be at least 4 mm deep. *J Periodontol 1998;69:303-313.*

Key Words: Bone and bones; bone regeneration; guided tissue regeneration; surgical flaps; periodontal diseases/therapy; periodontal diseases/surgery.

1.5 mm *vz* 4.2 mm = 2.7 mm diff.

Cortellini P, Tonetti M. Focus on intrabony defects: guided tissue regeneration. Periodontology 2000 2000;22:104-132.

Table 2. Controlled clinical trials comparing guided tissue regeneration procedure with access flap procedures

Authors	Type of membrane	*n* (guided tissue regeneration)	Guided tissue regeneration probing attachment gain±SD (mm)	*n* (flap)	Flap probing attachment gain±SD (mm)
Chung et al. (18)	Collagen	10	0.6±0.6	10	−0.7±0.9
Quteish & Dolby (75)	Collagen	26	3.0±1.5	26	1.8±0.9
Proestakis et al. (74)	Expanded polytetrafluoroethylene	9	1.2±2.0	9	0.6±1.0
Al-Arrayed et al. (1)	Collagen	14	3.9	14	2.7
Mattson et al. (59)	Collagen	9	2.4±2.1	9	0.4±2.1
Cortellini et al. (27)*	Expanded polytetrafluoroethylene	15	4.1±1.9	15	2.5±0.8
Cortellini et al. (27)	Titanium-reinforced expanded polytetrafluoroethylene	15	5.3±2.2	–	–
Cortellini et al. (33)*	Expanded polytetrafluoroethylene	12	5.2±1.4	12	2.3±0.8
Cortellini et al. (33)	Polymer	12	4.6±1.2	–	–
Kim (53)	Expanded polytetrafluoroethylene	19	4.0±2.1	18	2.0±1.7
Kilic (52)	Expanded polytetrafluoroethylene	10	3.7±2.0	10	2.1±2.0
Tonetti (84)	Polymer	69	3.6±1.6	67	2.2±1.5
Cortellini (19)	Polymer	23	3.0±1.7	23	1.6±1.8
Weighted mean		243	**3.4±1.8**	213	**1.8±1.4**

* Three-arm studies. Comparisons were made among two different barrier membranes and access flap.

1.8 mm *vz* 3.4 mm = 1.6 mm diff.

GUIDED TISSUE REGENERATION FOR PERIODONTAL INFRA-BONY DEFECTS

Needleman IG, Giedrys-Leeper E, Tucker RJ, Worthington HV

Date of most recent update: 6 August 2001
Date of most recent substantive update: 20 May 1999

treatment arms)).

For attachment level change, the weighted mean difference between GTR alone and open flap debridement was 1.11 mm
= 9), p<0.001) and for GTR+bone substitutes was 1.25 mm (95% CI: 0.89 to 1.61, chi-square for heterogeneity 0.01 (

ABSTRACT

Background
Conventional treatment of destructive periodontal (gum) disease arrests the disease but does not regain the bone support or connective tissue lost in the disease process. Guided tissue regeneration (GTR) is a surgical procedure that aims to regenerate the periodontal tissues when the disease is advanced and could overcome some of the limitations of conventional therapy.

Objectives
To assess the efficacy of GTR in the treatment of periodontal infra-bony defects measured against the current standard of surgical periodontal treatment, open flap debridement.

Search Strategy
We conducted an electronic search of the Cochrane Oral Health Group specialised trials register and MEDLINE up to October 2000. Hand searching included Journal of Periodontology, Journal of Clinical Periodontology, Journal of Periodontal Research and bibliographies of all relevant papers and review articles up to October 2000. In addition, we contacted experts/groups/companies involved in surgical research to find other trials or unpublished material or to clarify ambiguous or missing data and posted requests for data on two periodontal electronic discussion groups.

Selection Criteria
Randomised, controlled trials of at least 12 months duration comparing guided tissue regeneration (with or without graft materials) with open flap debridement for the treatment of periodontal infra-bony defects. Furcation involvements and studies specifically treating early onset diseases were excluded.

Data collection and analysis
Screening of possible studies was conducted independently by two reviewers (RT & IN) and data abstraction by three reviewers (RT, IN & EGL). The methodological quality of studies was assessed in duplicate (RT & IN) using both individual components and a quality scale (Jadad 1998) and agreement determined by Kappa scores. Methodological quality was used in sensitivity analyses to test the robustness of the conclusions. The Cochrane Oral Health Group statistical guidelines were followed (HW) and the results expressed as weighted mean differences (WMD and 95% CI) for continuous outcomes and relative risk (RR and 95% CI) for dichotomous outcomes calculated using random effects models where significant heterogeneity was detected (P < 0.1). The final analysis was conducted using STATA 6 in order to combine both parallel group studies and intra-individual (split-mouth) studies. The primary outcome measure was gain in clinical attachment. Any heterogeneity was investigated.

Main Results
We initially included 21 trial reports. Twelve were subsequently excluded. Of these, seven presented six-months data only, four were not fully randomised controlled trials, one used a non-comparable radiographic technique. Eleven studies were finally included in the review, ten testing GTR alone and two testing GTR+bone substitutes (one study had both test treatment arms).

For attachment level change, the weighted mean difference between GTR alone and open flap debridement was 1.11 mm (95% CI: 0.63 to 1.59), chi-square for heterogeneity 31.4 (df = 9), p<0.001) and for GTR+bone substitutes was 1.25 mm (95% CI: 0.89 to 1.61, chi-square for heterogeneity 0.01 (df = 1), p=0.91). GTR showed a significant benefit when comparing the numbers of sites failing to gain 2 mm attachment, with relative risk 0.58 (95% CI: 0.38, 0.88, chi-square for heterogeneity 5.72 (df = 2), p=0.13). The number needed to treat (NNT) for GTR to achieve one extra site gaining 2 mm or more attachment over open flap debridement was 8 (95% CI: 4, 33), based on an incidence of 32% of sites in the control group failing to gain 2 mm or more of attachment. For baseline incidences in the range of the control groups of 10% and 55% the NNTs are 24 and 3.

GTR attachment gain compared to open flap debridement

Laurell et al. *J Periodontol* 1998: 2.7 mm

- Uncontrolled and unblinded studies

Cortellini et al. *Periodontology 2000* 2000: 1.6 mm

- Unclear selection criteria for studies
- Inclusion of studies of short duration

Needleman et al. *Cochrane Review* 2001: 1.1 mm

- Randomised, controlled trials
- Trials only comparing GTR vs flap debridrement
- Trials > 12 months
- Furcation involvements excluded

SRs can show:

- The selection of studies to include in reviews will reflect conclusions
- The study methodology aspects will reflect conclusions
- Need to focus on studies with good methodological designs

Systematric reviews are not necessarily true or of relevance.

But,

they should be repeatable

Advantages of Systematic Reviews

- Reduce quantity of data
- Plan research, purchasing and guidelines
- Make efficient use of existing data
- Ensure generalisability
- Check consistency
- Explain inconsistency
- Quantify with meta-analysis
- Improve precision
- Reduce bias

Systematic Reviews & Meta-analyses – in sum:

SHIT IN

SHIT OUT

Dangers of systematic reviews and meta-analysis

- Publication bias
  - Unpublished data
  - Covert duplicate publications
  - Limitation to positive findings
- Language bias
- Funding bias
- Study quality bias
- Retrieval bias – they remain “observational studies”

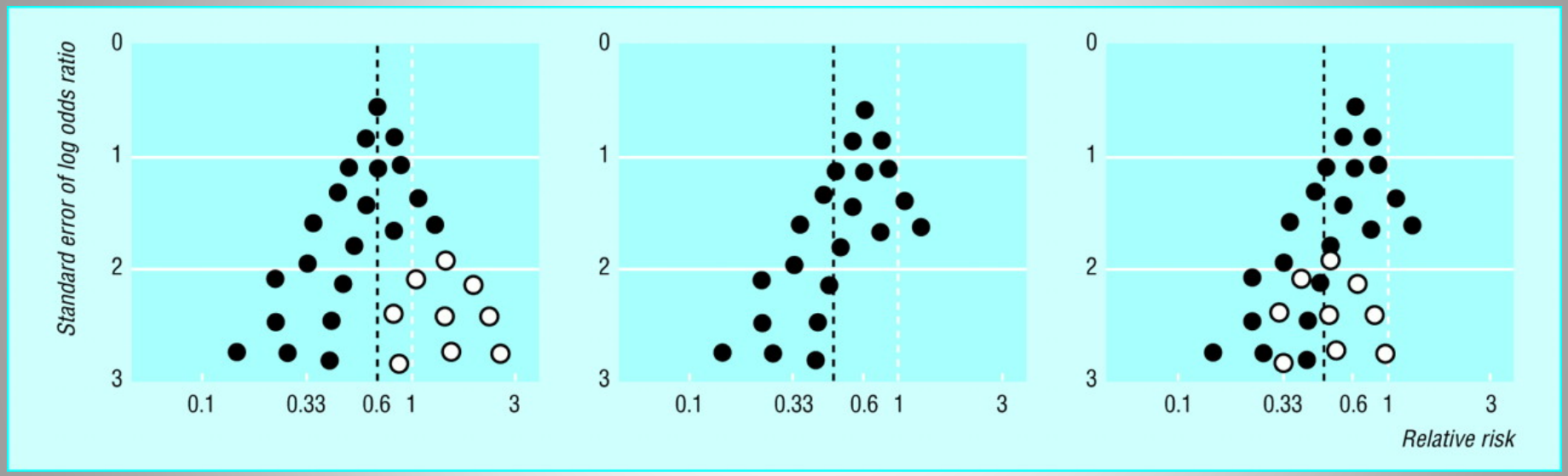
Why does study bias matter?

When bias leads to incorrect conclusions about the safety and efficacy of elements of clinical care, it raises not only scientific, but also ethical concerns.

Publication Bias

A tendency among investigators, peer reviewers and journal editors to allow the direction and statistical significance of research findings to influence decisions regarding submission and acceptance for publication.

Study Bias



Favours treatment	Favours control

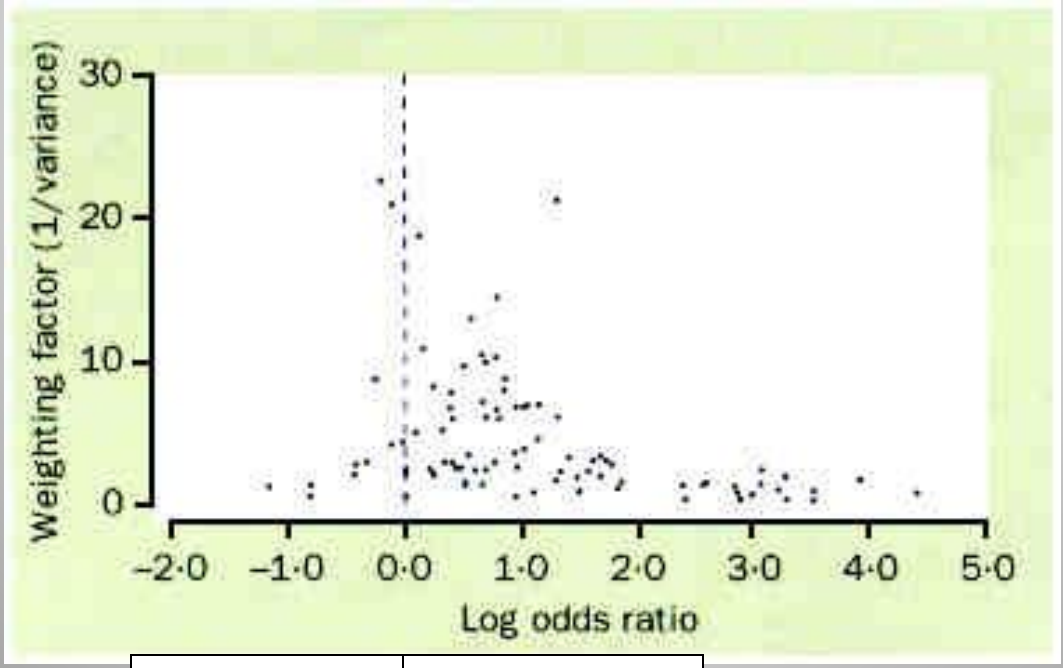
No bias

Publication Bias

Bias due to poor methodology

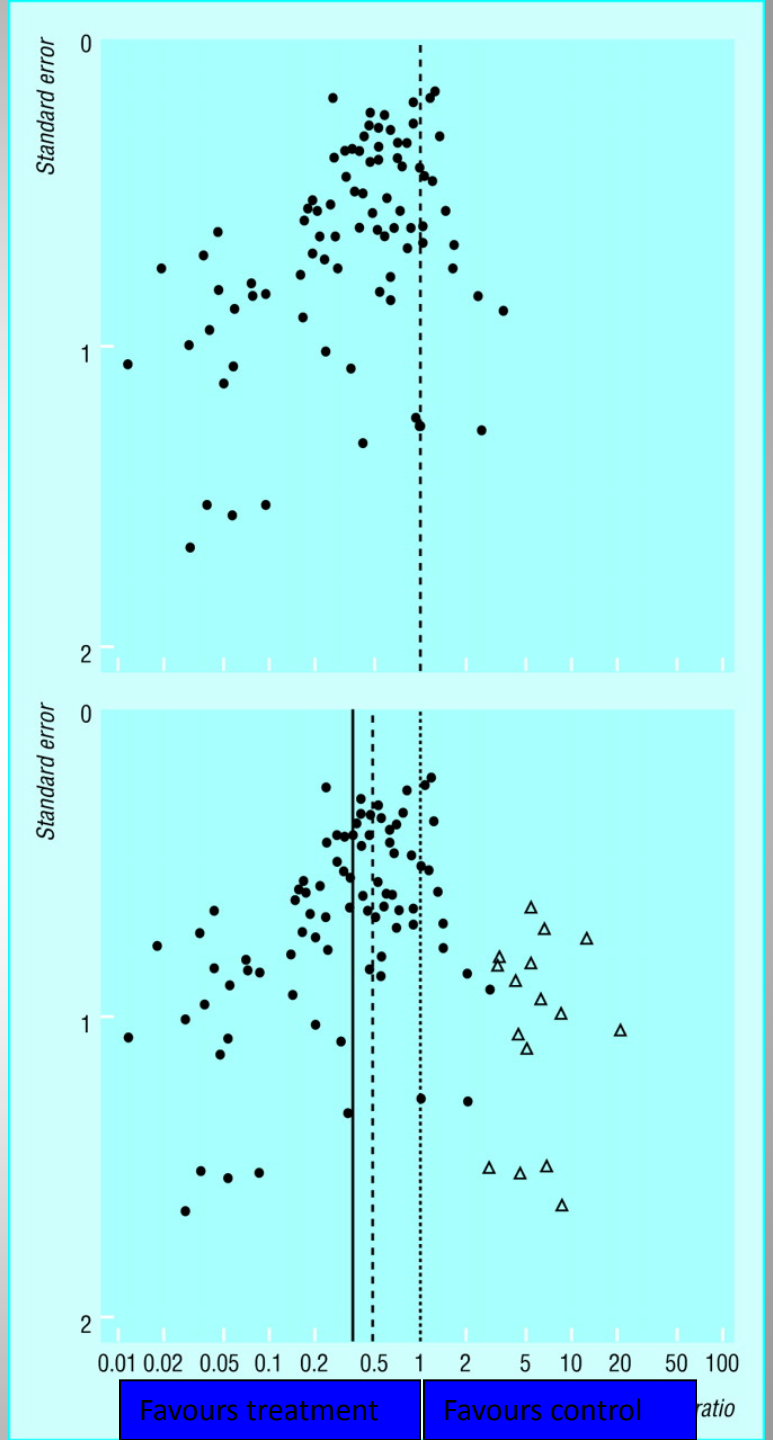
Publication Bias

- Positive findings are published - regardless of size
- Negative findings less often published - especially if study is small



Checking for Publication Bias

Effects on meta-analytic averages

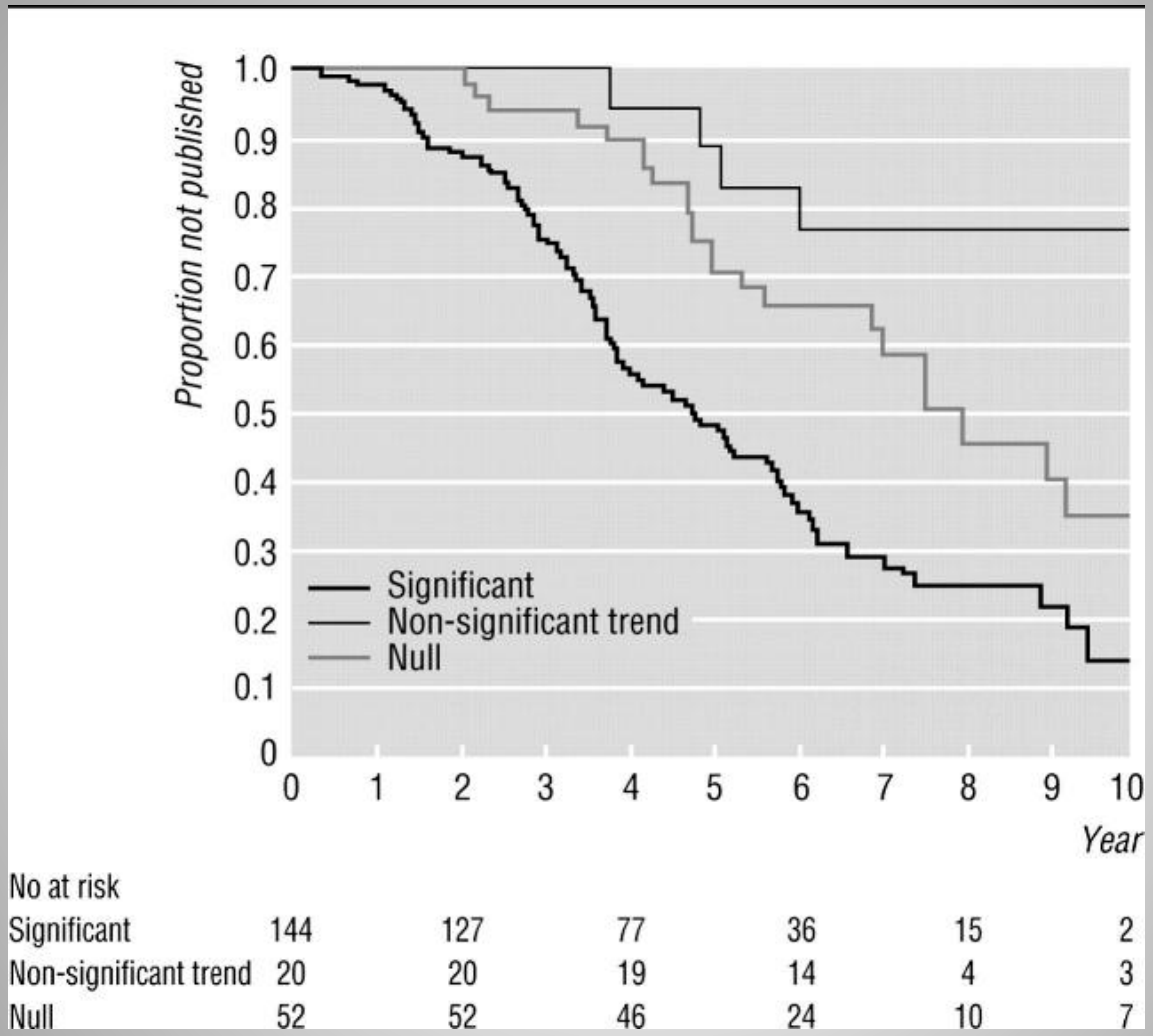


Linde et al. Homeopathic studies. Lancet 1997.

Reasons for Not Publishing

Reasons	%
Manuscript in the system" or published elsewhere	19
Non-significant results	15
Publication not aim of study	13
Incomplete analysis	11
Rejected manuscript	9
Too busy	9
Unimportant results	6
Funding source has the data	5

Dickersin & Meinert (1990)



Stern JM, Simes RJ. Publication bias: evidence of delayed publication in a cohort study of clinical research projects. BMJ 1997; 315

Funding Bias

Article Conclusion	No. (%) of Reviews: Tobacco-Affiliated Authors (n = 31)	No. (%) of Reviews: Non–Tobacco-Affiliated Authors (n = 75)
Passive smoking harmful	2 (6)	65 (87)
Passive smoking not harmful	29 (94)	10 (13)
Significance	$\chi^2_1 = 60.69$; $P<.001$	

Barnes & Bero. Why review articles on health effects of passive smoking reach different conclusions. JAMA 1998.

Cho & Bero. The Quality of Drug Studies Published in Symposium Proceedings . Ann Int Med, 1996.

Outcome of Study	Studies Supported by a Drug Company (n = 40)	Studies Not Supported by a Drug Company (n = 112)
	n(%)	
Favorable	39 (98)	89 (79)
Not favorable	1 (2)	23 (21)

* The proportion of studies with favorable outcomes was significantly higher for studies supported by a drug company than for studies without drug company support ($P < 0.01$).

Retrieval Bias - What causes it?

- Selective reading
  - –trials showing statistically significant differences more likely to be read in journals
- Selective indexing
- Selective citation
  - –reports showing positive features of a drug or therapy are more likely to be cited than those casting doubt on its value or safety