Principles and Methodology of Meta-Analysis

PAROS Manuscript-Writing Clinic

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Systematic reviews

- summarize the best available research to to answer a **focused research question**

- Objectives
  - Ascertain need for future study
  - Objective summary of benefit/harms
  - Basis for practice guidelines, risk assessments, health technology assessments and economic evaluations

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What must a SR have?

- clear inclusion/exclusion criteria
- explicit search strategy
- systematic appraisal of the validity of included studies
- systematic coding and analysis
- appropriate synthesis of results
  - A meta-analysis (where possible)

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“Effect size”

- “effect” implies a relationship
  - difference between male and females
  - *treatment effect*, e.g. RR, OR, HR, MD, SMD
  - Correlation
- single group summary
  - mean, risk or rate in a single population,

  e.g. prevalence

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Outcome of a SR

- A description of the **heterogeneity** of effect sizes
  - Consistent effect sizes → summary effect
  - Modest variation → summary effect plus cautious interpretation
  - Substantial variation → focus on dispersion itself
- An estimate of the **summary effect**

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Formulating the question: Descriptive

Population	Intervention /Exposure	Outcome	Search strategy
In hospital ED settings,		how is overcrowding defined?	P and O MEDLINE: (ED OR "emergency department") AND (overcrowding OR crowding) AND definition
In hospital ED settings,	does overcrowding compared with periods of no overcrowding	increase patient mortality or morbidity	P and E MEDLINE:

Coding results systematically

Data abstraction - **identifying pre-specified data elements** from individual studies and **entering the data** into a table or database

1. Characteristics of included studies
2. Validity appraisal
3. Estimates of the effect of interest

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Summarizing characteristics of included studies – Table 1

Study ID	Study Design/ Methods	Population	Intervention/ Exposure	Outcome

Appraising the validity of included studies

- Was target population specified?
- Was sampling method appropriate?
- Were validated instruments used in the assessment of the primary outcome?

  Was a valid and repeatable disease definition given?
- Have reasonable efforts been used to reduce observer bias?
- Was response rate adequate?

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Summarizing results of validity appraisal – Table 2

Item	Authors' Judgement	Support for Judgement
Adequate sample selection	Low/High/Uncertain Risk	Quote : Comment:
Valid and repeatable disease / outcome definition	Low/High/Uncertain Risk	Quote : Comment:
Validated instruments for outcome assessment	Low/High/Uncertain Risk	Quote : Comment:
Blinded outcome assessment (reduction of observer bias)	Low/High/Uncertain Risk	Quote : Comment:
Adequacy of response rate	Low/High/Uncertain Risk	Quote : Comment:
Free of selective reporting	Low/High/Uncertain Risk	Quote : Comment:
Free of other bias	Low/High/Uncertain Risk	Quote : Comment:

Extracting estimates of effect of interest – Table 3

Study	Experimental			Control		
	Mean	SD	n	Mean	SD	N
Carroll 05	94	22	60	92	20	60
Grant 04	98	21	65	92	22	65
Peck 03	98	28	40	88	26	40
Donat 01	94	19	200	82	17	200
Stewart 99	98	21	50	88	22	45
Young 97	96	21	85	92	22	85

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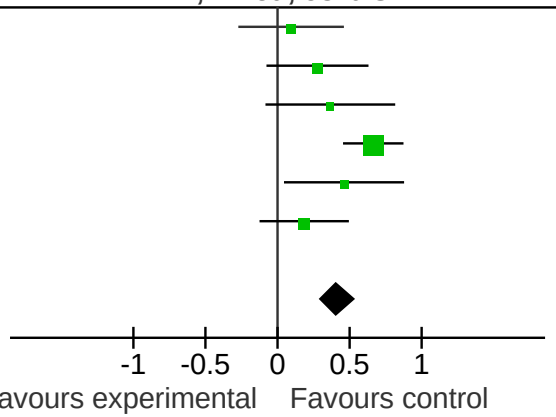
Forest plot

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Carroll 05	94	22	60	92	20	60	12.4%	0.09 [-0.26, 0.45]
Donat 01	98	21	65	92	22	65	13.3%	0.28 [-0.07, 0.62]
Grant 04	98	28	40	88	26	40	8.1%	0.37 [-0.08, 0.81]
Peck 03	94	19	200	82	17	200	39.2%	0.66 [0.46, 0.87]
Stewart 99	98	21	50	88	22	45	9.5%	0.46 [0.05, 0.87]
Young 97	96	21	85	92	22	85	17.5%	0.19 [-0.12, 0.49]
Total (95% CI)			**500**			**495**	**100.0%**	**0.41 [0.29, 0.54]**

Heterogeneity: $Chi^2 = 11.91$, df = 5 (P = 0.04); $I^2 = 58\%$

Test for overall effect: Z = 6.45 (P < 0.00001)



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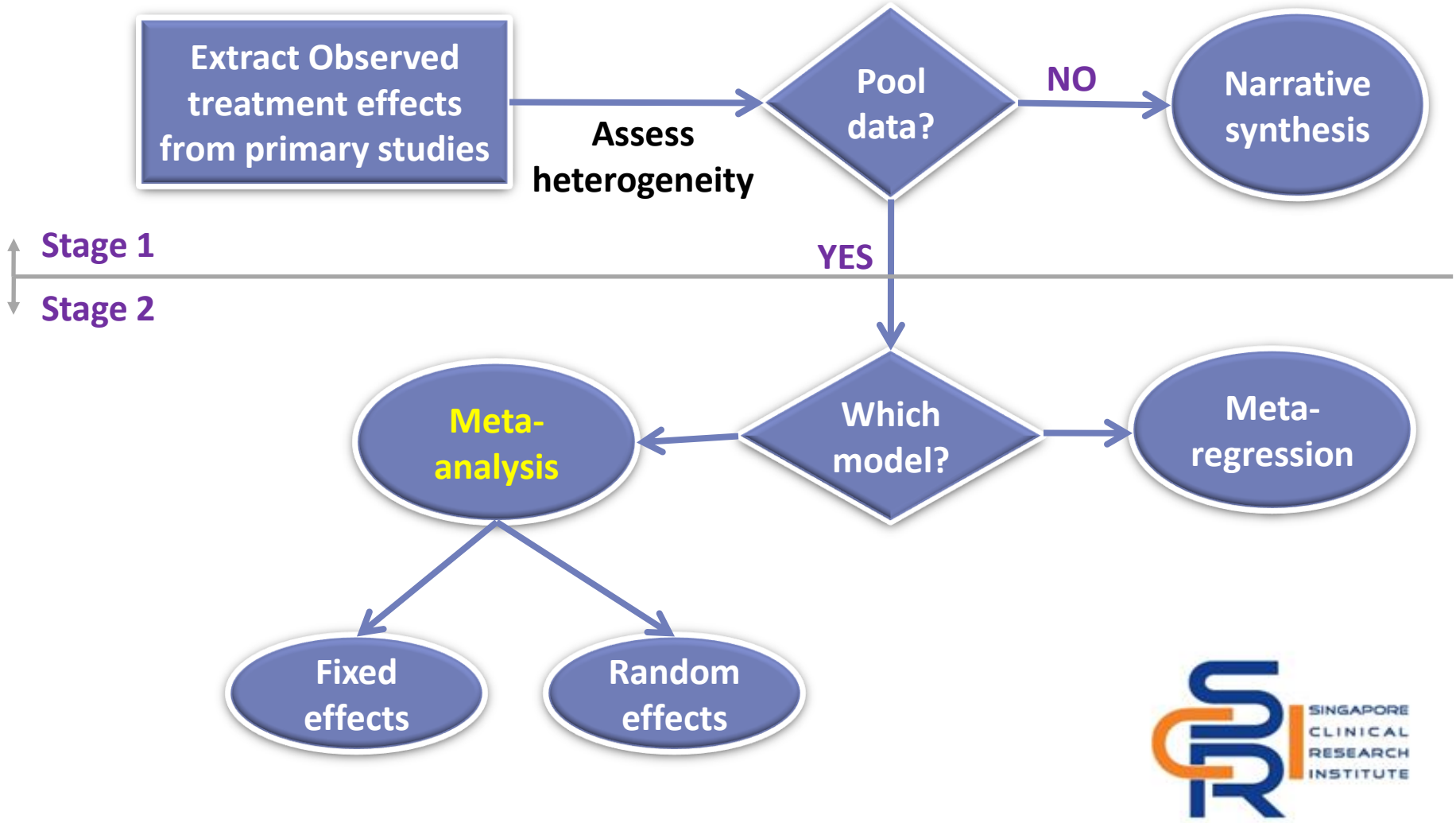
Data synthesis options



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Synthesis via a meta-analysis

- First, from each study extract the estimate of effect of interest and obtain its variance

- Second, compute a weighted mean of these effect estimates

- Third, in weighting studies, assign more weight to the more informative studies (e.g. generic inverse variance method)

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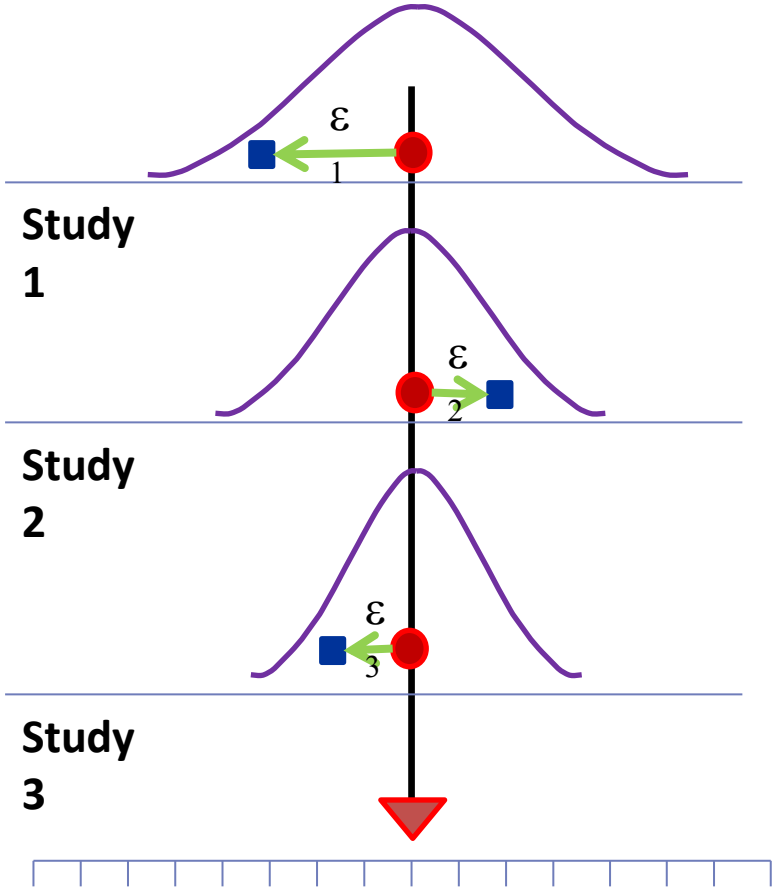
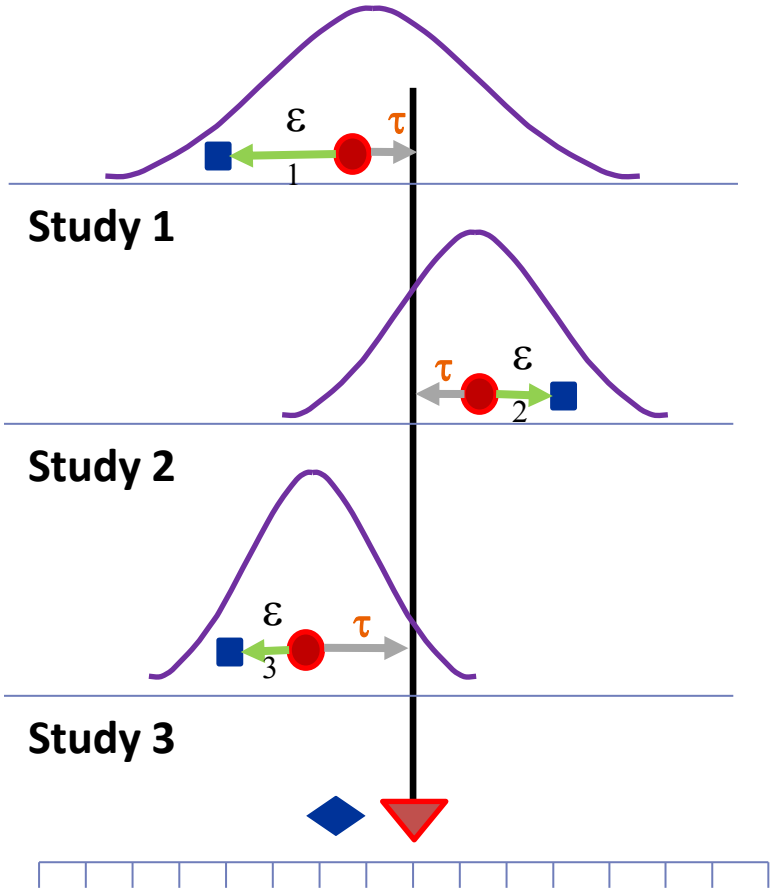
Generic Inverse variance principle

Study	Effect size (Y)	Variance (V)	Weight (W)	W x Y	Relative weight
Carroll 05	0.095	0.033	30.352	2.869	12.43
Grant 04	0.277	0.031	32.568	9.033	13.34
Peck 03	0.367	0.050	20.048	7.349	8.21
Donat 01	0.664	0.011	95.111	63.149	38.95
Stewart 99	0.462	0.043	23.439	10.824	9.60
Young 97	0.185	0.023	42.698	7.906	17.48
Sum			244.215	101.171	100.00
Pooled effect: 101.171 / 244.215 = 0.414					
Variance of pooled effect: 1/244.215 = 0.004					

Fixed Effect versus Random Effects





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Heterogeneity: Are the results combinable?

- Clinical heterogeneity **(Table 1)**
  - Participants
    - Age, sex, co-morbidities, disease severity, medication status at start, eligibility criteria, geographical variation
  - Interventions and Comparators
    - Dose, duration, type of drug, mode of administration, nature of control (none, placebo, standard care)
  - Outcomes
    - follow-up duration, definition of an event, ways of measuring outcomes

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Heterogeneity: Are the results combinable?

- Methodological heterogeneity (Table 2)
  - Study design
    - Randomized vs. non-randomized, parallel group vs. crossover, individual vs. cluster randomized
  - Conduct
    - Allocation concealment, blind outcome assessment
  - Analysis
    - ITT vs per protocol, unit of analysis, imputation methods for missing data

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Quantifying heterogenetiy

- Is there evidence of heterogeneity?

  Null hypothesis: observed dispersion is compatible with chance

- What proportion of the observed variation is real?

✓ **Q** (Chi-square statistic)

✓ **P-value based on Q**

(Test for heterogeneity)

Threshold: p > 0.10

✓ I^2

Rule of thumb:

25% - mild

50% - modest

75% - substantial

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Dealing with heterogeneity

- Don't pool the results

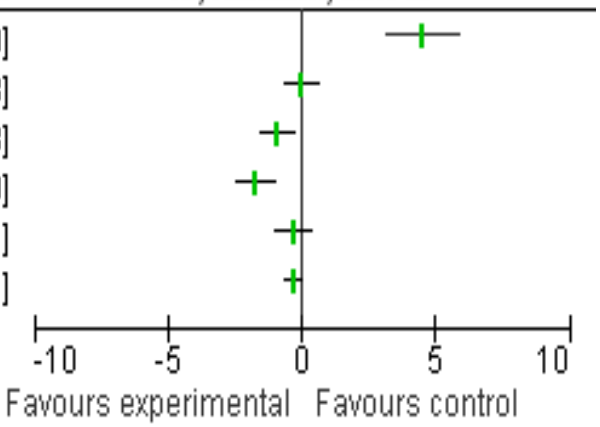
Analysis 1.1. Comparison 1 Exercise versus no intervention - general population, Outcome 1 Anxiety.

Review: Exercise in prevention and treatment of anxiety and depression among children and young people

Comparison: 1 Exercise versus no intervention - general population

Outcome: 1 Anxiety

	Treatment			Control			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI	IV, Random, 95% CI
Smith 1983	35.69	8.06	16	0	7.31	16	4.52 [3.15, 5.89]	
Roth 1987	36.8	8.9	18	37	9.1	18	-0.02 [-0.68, 0.63]	
Jacobs 1984	30.77	7.68	22	38.23	8.47	22	-0.91 [-1.53, -0.28]	
Hilyer 1982	29.17	4.39	23	39.1	6.96	20	-1.70 [-2.41, -0.99]	
Carl 1984	32.12	7.78	15	34.13	4.92	16	-0.30 [-1.01, 0.41]	
Berger 1988	6.49	6.3	66	8.64	7.37	87	-0.31 [-0.63, 0.01]	



Dealing with heterogeneity

- Ignore heterogeneity – apply a fixed effect model

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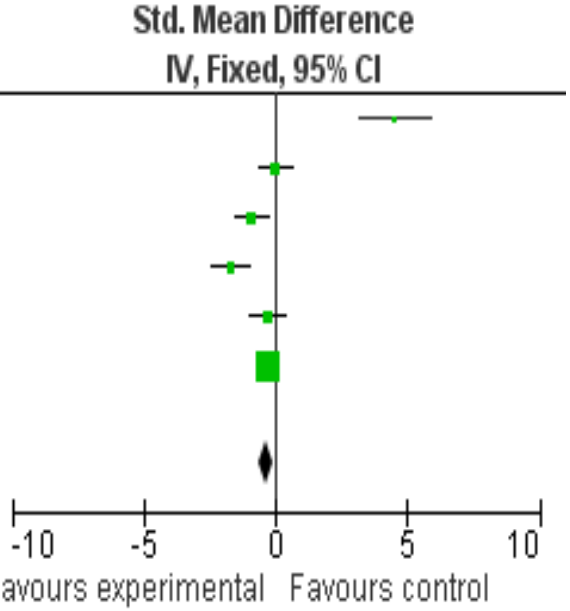
Hilyer 1982	29.17	4.39	23	39.1	6.96	20	10.4%	-1.70 [-2.41, -0.99]
Carl 1984	32.12	7.78	15	34.13	4.92	16	10.4%	-0.30 [-1.01, 0.41]
Berger 1988	6.49	6.3	66	8.64	7.37	87	50.6%	-0.31 [-0.63, 0.01]
Total (95% CI)			**160**			**179**	**100.0%**	**-0.36 [-0.59, -0.14]**

Heterogeneity: Chi² = 66.60, df = 5 (P < 0.00001); I² = 92%

Test for overall effect: Z = 3.12 (P = 0.002)



Dealing with heterogeneity

Explore: Sub-group analysis

- Investigate heterogeneity
- Answer specific questions about patient groups, types of intervention or types of study

– Is the treatment effect different across subgroups?

- Is drug effective for acute and chronic patients?
- Which variant of the intervention is more / most effective?
- Does adequate randomization affect the size of the effect?

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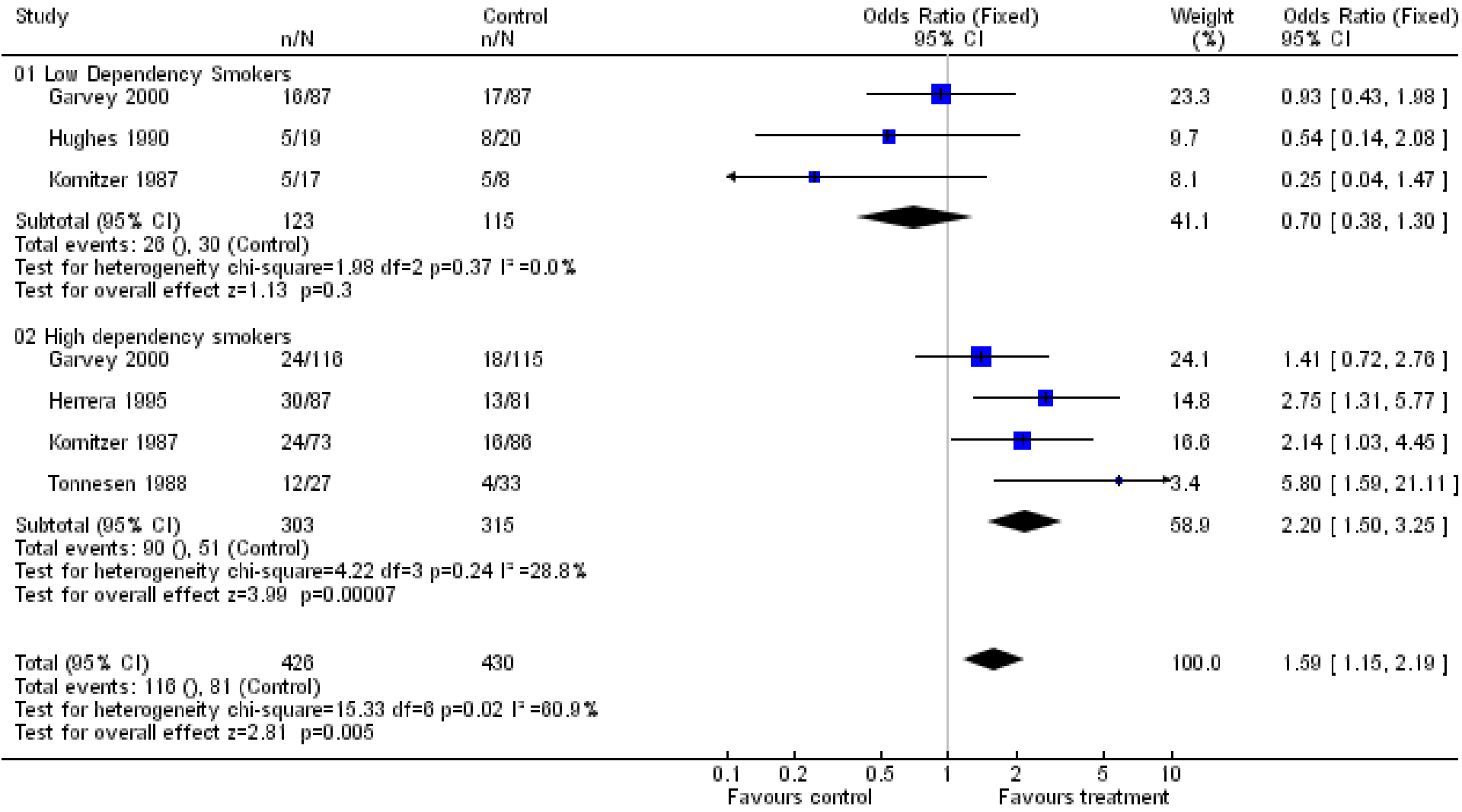
Review: Nicotine replacement therapy for smoking cessation
Comparison: 02 Effect of 4 mg vs 2 mg Nicotine Gum
Outcome: 01 Smoking Cessation



Dealing with heterogeneity

- Apply a random effects model

Analysis 1.1. Comparison 1 Exercise versus no intervention - general population, Outcome 1 Anxiety.

Review: Exercise in prevention and treatment of anxiety and depression among children and young people

Comparison: 1 Exercise versus no intervention - general population

Outcome: 1 Anxiety

Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Smith 1983	35.69	8.06	16	0	7.31	16	13.4%	4.52 [3.15, 5.89]
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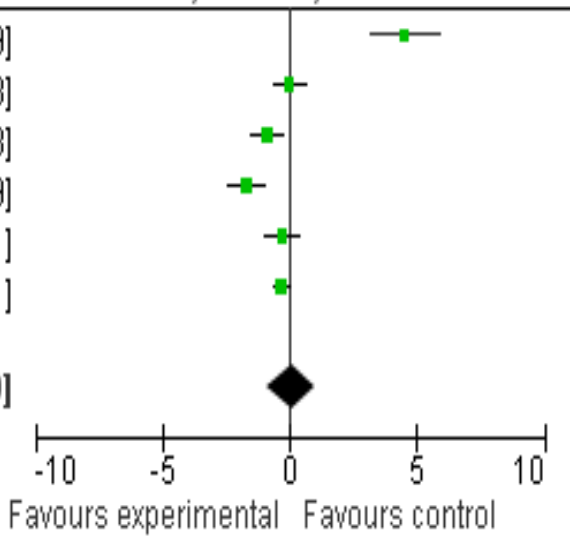
Carl 1984	32.12	7.78	15	34.13	4.92	16	16.9%	-0.30 [-1.01, 0.41]
Berger 1988	6.49	6.3	66	8.64	7.37	87	18.3%	-0.31 [-0.63, 0.01]
Total (95% CI)			**160**			**179**	**100.0%**	**0.05 [-0.89, 0.99]**

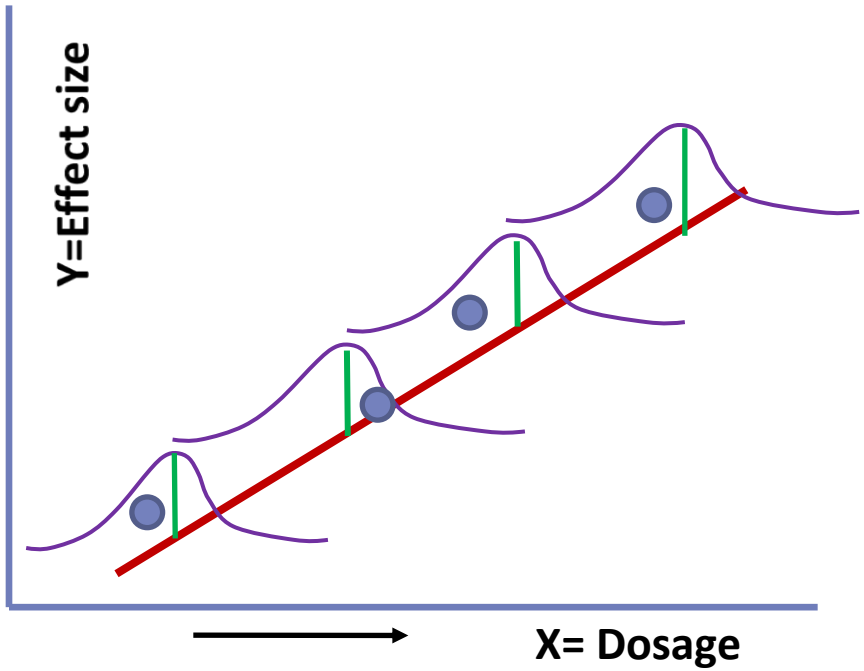
Heterogeneity: $Tau^2 = 1.22$; $Chi^2 = 66.60$, $df = 5$ ($P < 0.00001$); $I^2 = 92\%$

Test for overall effect: $Z = 0.10$ ($P = 0.92$)



Dealing with heterogeneity

- Perform a meta-regression



- **Y** = treatment effect
  - ✓ Log RR, log OR, MD, SMD
- **X** = study level attributes
  - ✓ dosage, length of follow-up
  - ✓ type of comparator
  - ✓ Study design and or quality

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When not to do a meta-analysis

- If studies are clinically diverse /heterogeneous
- If the outcomes are too diverse
  - Requires clinical judgment
- Bias
  - If studies are at high risk of bias, meta-analyses may be seriously misleading
  - If serious publication bias is present and/or serious reporting biases, meta-analyses are likely to produce a wrong summary

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THANK YOU!

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