Cochrane Training

Analysing other outcomes and study designs

Trusted evidence.
Informed decisions.
Better health.

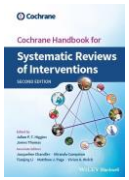
Cochrane Training

Steps of a Cochrane Review

1. define the question
2. plan eligibility criteria
3. plan methods
4. search for studies
5. apply eligibility criteria
6. collect data
7. assess studies for risk of bias
8. **analyse and present results**
9. interpret results and draw conclusions
10. improve and update review

Session outline

- **generic inverse variance meta-analysis**
- other outcome types
- multi-arm studies
- cluster-randomised trials
- cross-over trials
- non-randomised studies



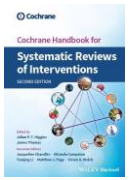
See Chapters 10, 23 & 24 of the Handbook

Analysing effect estimates

- When you have an overall effect estimate, not separate group summaries
  - standard effect estimates (RR, OR, MD)
  - non-randomised studies, cluster or cross-over trials
  - time-to-event (HR), rate data (RR), ordinal data (POR)
  - adjusted data (e.g. from regression analysis)

The generic inverse-variance method

- ‘generic’ = can apply to any summary statistic
- ‘inverse-variance’ = uses the inverse of the variance to weight each study in meta-analysis

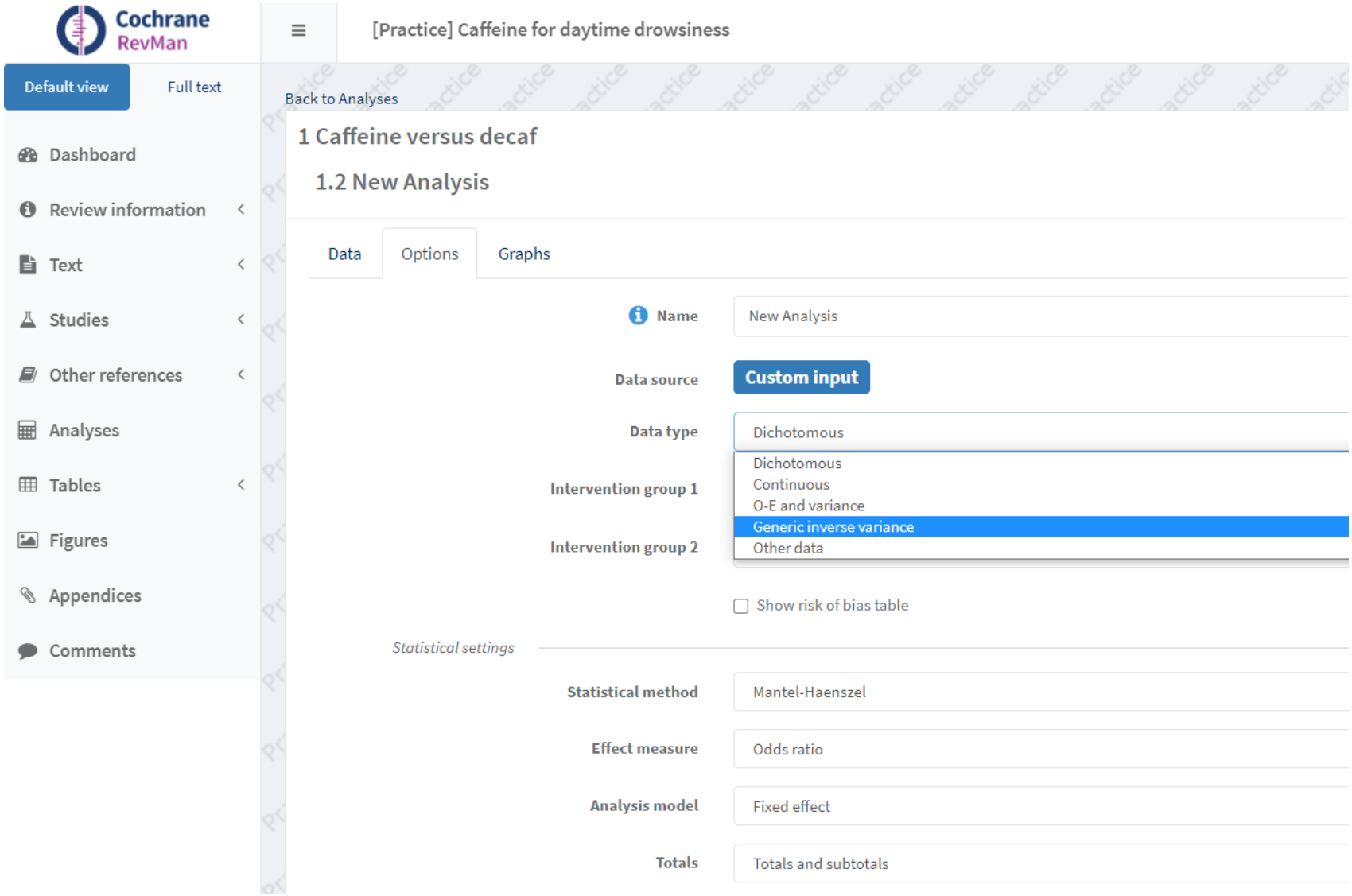


See Section 10.3 of the Handbook

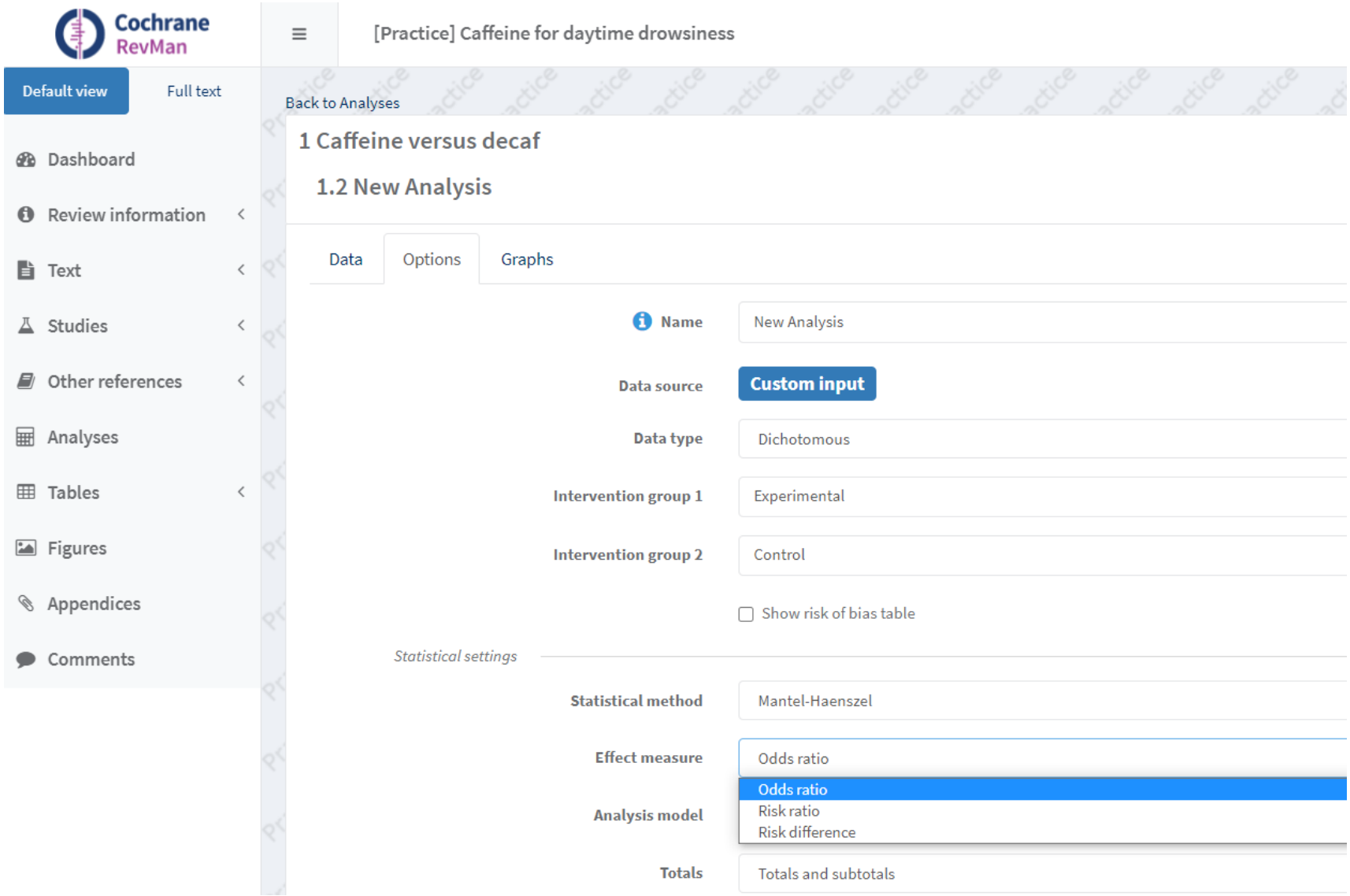
What do I do?

- identify the statistic you wish to use
  - you will need the same statistic for each study
  - if using one of RevMan's standard statistics, use the ordinary method to calculate results for other studies, and combine with your problem study using GIV
- for each study, enter two numbers:
  - the summary statistic
  - the **standard error** of the summary statistic

Generic inverse-variance meta-analysis



Generic inverse-variance outcomes



Generic inverse-variance outcomes

1.2 New Analysis

Data | Options | Graphs

+Add Data row | +Add Subgroup | Add Note

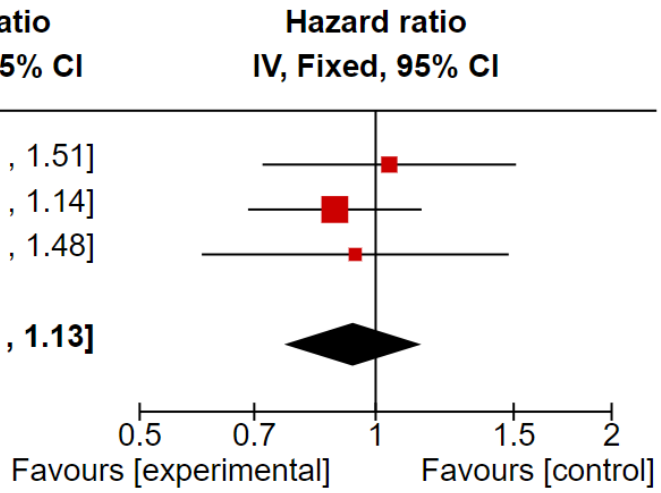
Study	log[Hazard ratio]	SE	Weight	Hazard ratio IV, Fixed, 95% CI	Action
Amore-Coffea 2000	0.04	0.19	26.2%	1.04 [0.72 , 1.51]	Action
Deliciozza 2004	-0.12	0.13	55.9%	0.89 [0.69 , 1.14]	Action
Norscafe 1998	-0.06	0.23	17.9%	0.94 [0.60 , 1.48]	Action
Total (95% CI)			**100.0%**	**0.93 [0.77 , 1.13]**	

Study or Subgroup	log[Hazard ratio]	SE	Weight	Hazard ratio IV, Fixed, 95% CI
Amore-Coffea 2000	0.04	0.19	26.2%	1.04 [0.72 , 1.51]
Deliciozza 2004	-0.12	0.13	55.9%	0.89 [0.69 , 1.14]
Norscafe 1998	-0.06	0.23	17.9%	0.94 [0.60 , 1.48]
Total (95% CI)			**100.0%**	**0.93 [0.77 , 1.13]**

Heterogeneity: Chi² = 0.48, df = 2 (P = 0.78); I² = 0%

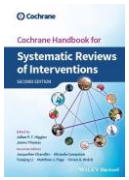
Test for overall effect: Z = 0.69 (P = 0.49)

Test for subgroup differences: Not applicable



Important: if your statistic is a ratio

- ratios are not normally distributed
- must enter natural logarithms into RevMan
  - e.g. log OR and SE of log OR
  - check that the data reported in the study are not already in this form
  - RevMan will automatically convert the results back for display as normal



See Section 10.3.3 of the Handbook and seek statistical advice

Statistical settings

Statistical settings

Statistical method Inverse variance

Effect measure Other | Hazard ratio

Analysis model Fixed effect

Totals Totals and subtotals

☑ Test for subgroup differences

Study confidence interval 95%

Total confidence interval 95%

☑ Entered data are on log scale

☐ Enter number of participants

Calculator

Given

Hazard ratio	1.040811	**Confidence interval**	0.7172	**to** 1.5104
log[Hazard ratio]		**log[Confidence interval]**		**to**
Standard error				
Variance				
z-test				
p-value				

○ 90% ◉ 95% ○ 99%

Calculated

log[Hazard ratio]	0.040000	**Standard error**	0.189997

Update data table Cancel

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- cross-over trials
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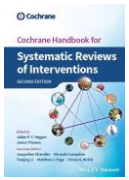

See Chapter 10 of the Handbook

Types of data

- dichotomous
- continuous
- **ordinal**
- **counts and rates**
- **time-to-event**

Ordinal outcomes

- ordered categories implying magnitude
  - short: e.g. pain scores, Likert scales
  - long measurement scales: e.g quality of life, function
- analysing ordinal outcomes
  - dichotomous
    - short scales can be dichotomised
    - e.g. pain vs no pain, mild vs severe pain
  - continuous
    - longer scales – report mean scores
  - proportional odds ratio (POR)
    - analyse using GIV method

Counts and rates

- counts of events that may happen more than once
  - e.g. hospitalisation, no. of decayed teeth
  - rates also consider the length of time in which events occurred
  - beware unit-of-analysis error
- analysing counts and rates
  - dichotomous
    - number of participants with at least one event
  - continuous
    - mean no. of events per person
  - time to first event
  - rate ratio
    - analyse using GIV method

$$\text{rate} = \frac{\text{number of events}}{\text{length of time}}$$

Time-to-event (survival) outcomes

- length of time until an event occurs
  - e.g. time until death, time free of epileptic fits
  - includes ‘censored’ data – people who did not experience the event during the study
- analysing time-to-event data
  - dichotomous
    - data from a specific time point
  - continuous
    - mean days to event – not appropriate for censored data
  - hazard ratios
    - analyse using generic inverse variance method
  - O – E and V

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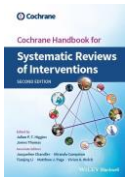
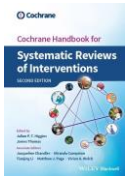


See Chapter 23.3 of the Handbook

Studies with more than two groups

- pair-wise comparisons are required for RevMan
- consider your question of interest
  - ignore any groups not relevant to your question
  - compare arms two at a time in separate comparisons
  - pool two of the arms if appropriate
  - multiple treatments meta-analysis
- be careful not to double-count any group in a meta-analysis
  - unit-of-analysis error



See Chapter 23.3 of the Handbook

Example: antibiotics to inhibit preterm labour

- included a four-arm trial (ORACLE) - largest and best trial in the review
  - erythromycin
  - co-amoxiclav
  - erythromycin + co-amoxiclav
  - neither

- author decided all three antibiotic arms were comparable

Source: Craig Ramsay

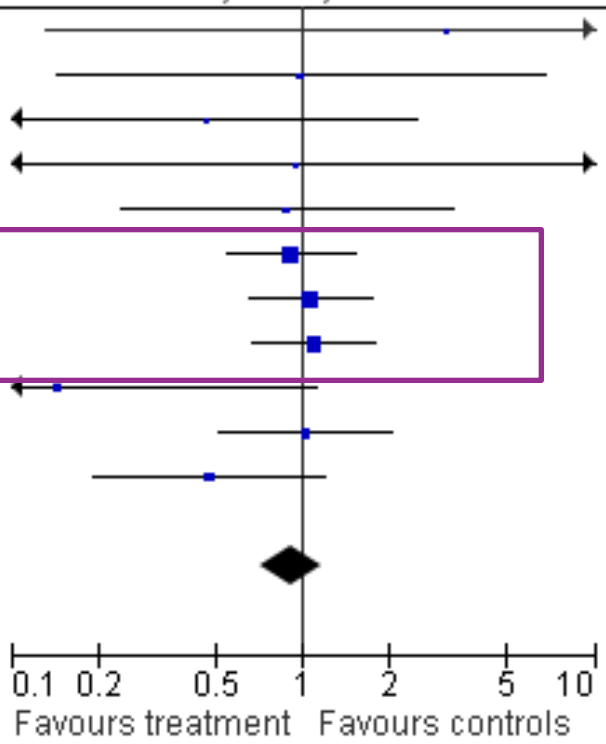
King JF, Flenady V, Murray L. Prophylactic antibiotics for inhibiting preterm labour with intact membranes. *Cochrane Database of Systematic Reviews* 2002, Issue 4. Art. No.: CD000246. DOI: 10.1002/14651858.CD000246.

Example: Is this OK?

Study or Subgroup	Events	Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cox 1996	1	40	0	42	0.4%	3.15 [0.13, 75.05]
Gordon 1995	2	70	2	69	1.5%	0.99 [0.14, 6.80]
McGregor 1991	2	53	4	50	3.0%	0.47 [0.09, 2.46]
Newton 1991	1	47	1	45	0.7%	0.96 [0.06, 14.85]
Norman 1994	4	43	4	38	3.1%	0.88 [0.24, 3.29]
ORACLE II 2001a	28	1534	31	1556	22.2%	0.92 [0.55, 1.52]
ORACLE II 2001b	34	1600	31	1556	22.7%	1.07 [0.66, 1.73]
ORACLE II 2001c	34	1551	31	1556	22.4%	1.10 [0.68, 1.78]
Oyarzun 1998	1	78	8	90	5.4%	0.14 [0.02, 1.13]
Romero 1993	14	131	15	144	10.3%	1.03 [0.52, 2.04]
Svare 1997	6	58	11	51	8.5%	0.48 [0.19, 1.20]
Total (95% CI)		**5205**		**5197**	**100.0%**	**0.92 [0.73, 1.16]**
Total events	127		138			

Heterogeneity: Chi² = 7.24, df = 10 (P = 0.70); I² = 0%

Test for overall effect: Z = 0.70 (P = 0.49)



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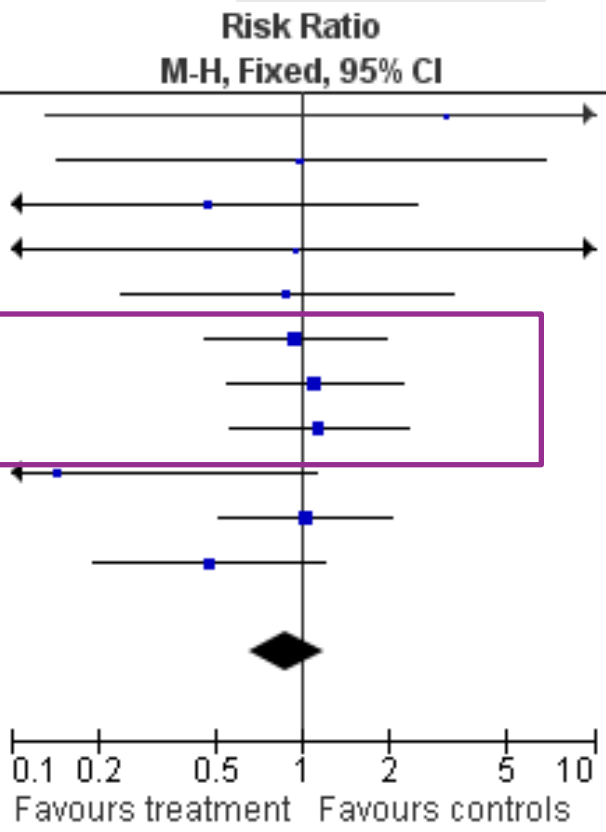
Example: shared control group

Study or Subgroup	Events	Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cox 1996	1	40	0	42	0.5%	3.15 [0.13, 75.05]
Gordon 1995	2	70	2	69	2.2%	0.99 [0.14, 6.80]
McGregor 1991	2	53	4	50	4.6%	0.47 [0.09, 2.46]
Newton 1991	1	47	1	45	1.1%	0.96 [0.06, 14.85]
Norman 1994	4	43	4	38	4.7%	0.88 [0.24, 3.29]
ORACLE II 2001a	28	1534	10	519	16.5%	0.95 [0.46, 1.94]
ORACLE II 2001b	34	1600	10	519	16.7%	1.10 [0.55, 2.22]
ORACLE II 2001c	34	1551	10	519	16.6%	1.14 [0.57, 2.29]
Oyarzun 1998	1	78	8	90	8.2%	0.14 [0.02, 1.13]
Romero 1993	14	131	15	144	15.8%	1.03 [0.52, 2.04]
Svare 1997	6	58	11	51	13.0%	0.48 [0.19, 1.20]
Total (95% CI)		**5205**		**2086**	**100.0%**	**0.88 [0.65, 1.18]**
Total events	127		75			

Heterogeneity: Chi² = 6.98, df = 10 (P = 0.73); I² = 0%

Test for overall effect: Z = 0.86 (P = 0.39)



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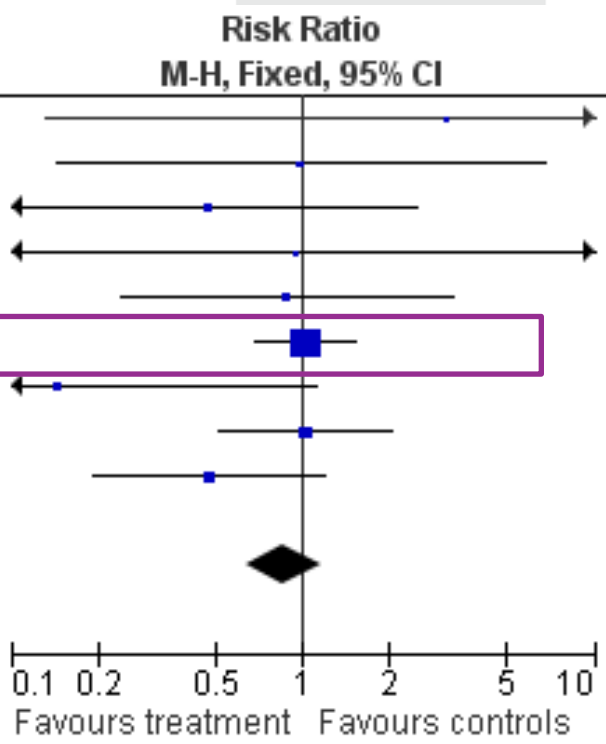
Example: combined arms

Study or Subgroup	Events	Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cox 1996	1	40	0	42	0.5%	3.15 [0.13, 75.05]
Gordon 1995	2	70	2	69	2.2%	0.99 [0.14, 6.80]
McGregor 1991	2	53	4	50	4.5%	0.47 [0.09, 2.46]
Newton 1991	1	47	1	45	1.1%	0.96 [0.06, 14.85]
Norman 1994	4	43	4	38	4.6%	0.88 [0.24, 3.29]
ORACLE II 2001	96	4685	31	1556	50.7%	1.03 [0.69, 1.54]
Oyarzun 1998	1	78	8	90	8.1%	0.14 [0.02, 1.13]
Romero 1993	14	131	15	144	15.6%	1.03 [0.52, 2.04]
Svare 1997	6	58	11	51	12.7%	0.48 [0.19, 1.20]
Total (95% CI)		**5205**		**2085**	**100.0%**	**0.86 [0.64, 1.16]**
Total events	127		76			

Heterogeneity: Chi² = 6.62, df = 8 (P = 0.58); I² = 0%

Test for overall effect: Z = 0.97 (P = 0.33)



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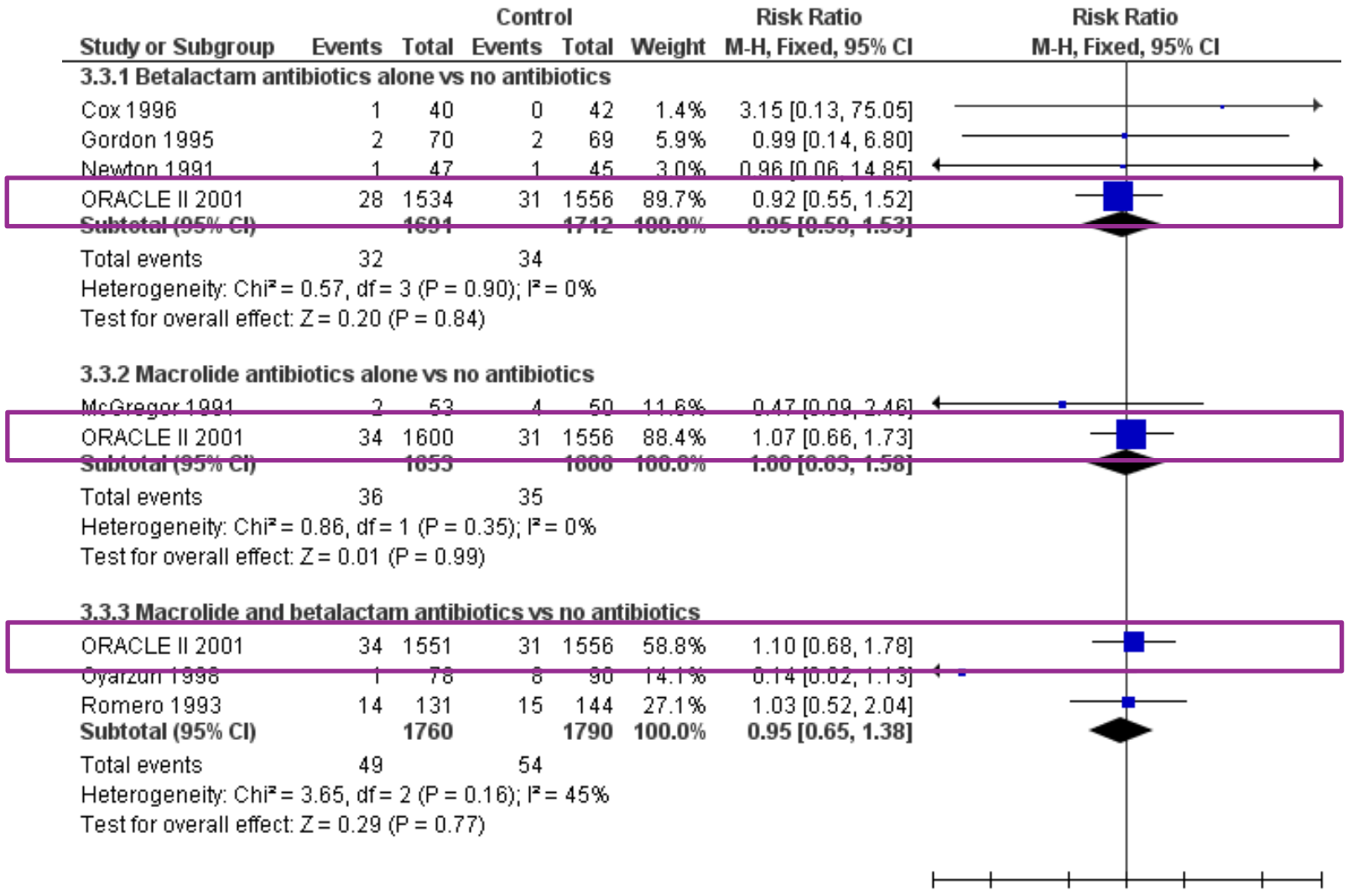
Example: separated arms



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- cross-over trials
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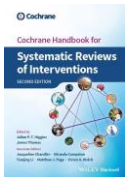


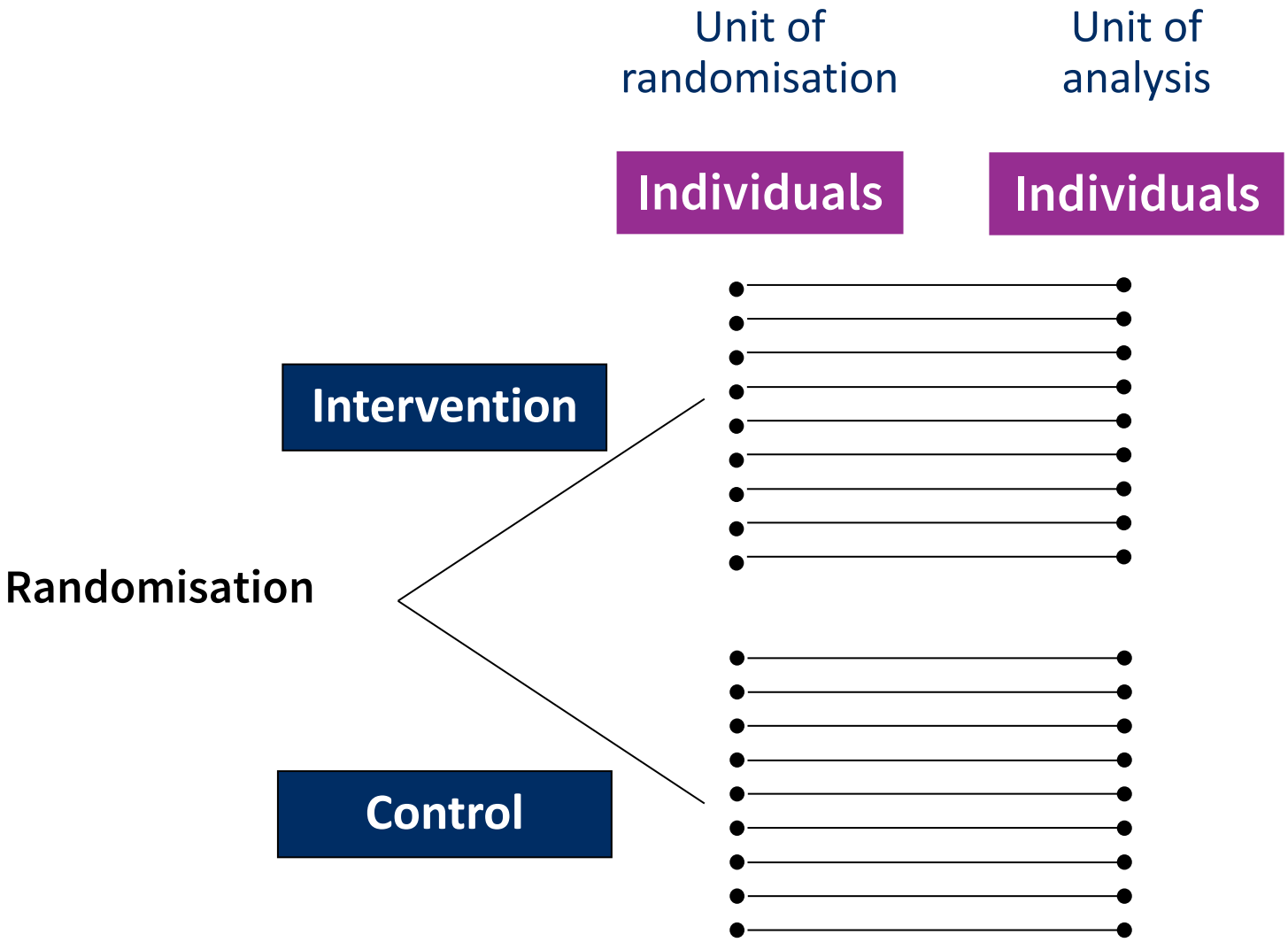
See Chapter 23.1 of the Handbook

Cochrane Training

Cluster-randomised trials

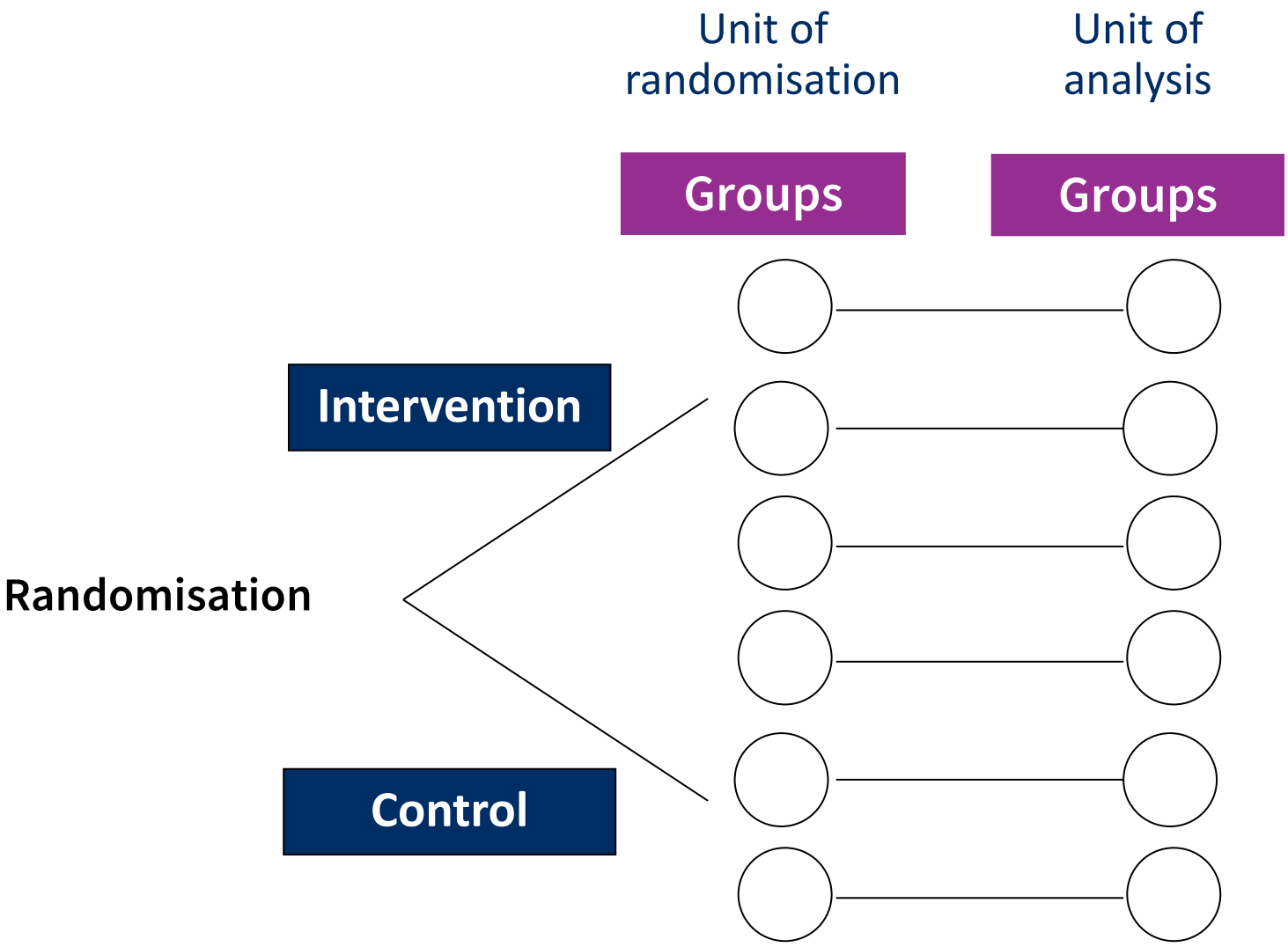
- groups of individuals randomised together
  - e.g. clinics, schools, towns, families
  - may be used to test effects of interventions on groups
  - may be more practical to implement
  - avoids ‘contamination’ of randomised individuals

Simple trial design



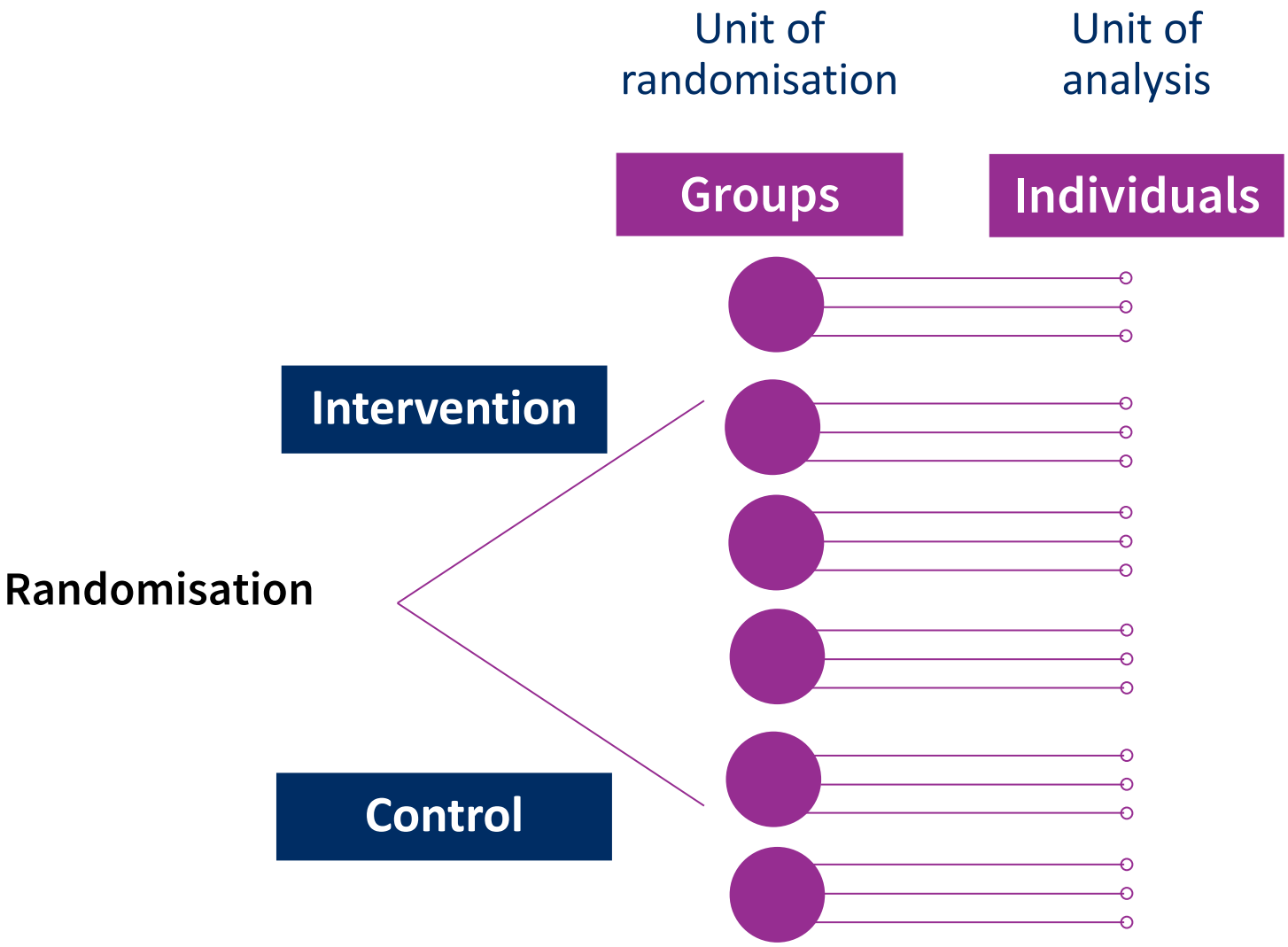
Source: Julian Higgins

Cluster-randomised design



Source: Julian Higgins

Cluster-randomised design



Source: Julian Higgins

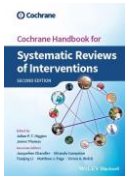
Unit-of-analysis issues

- individuals within a cluster are correlated
- when we are interested in outcomes at the individual level:
  - analysing by individuals gives too much precision
    - false positive conclusions
    - more weight in meta-analysis
  - analysing by clusters gives too little precision
  - correct weight should be somewhere in between
- may also occur in other studies
  - clustered delivery, e.g by practitioner
  - multiple treatments, e.g. cycles, body parts

Source: Julian Higgins

Taking correlation into account

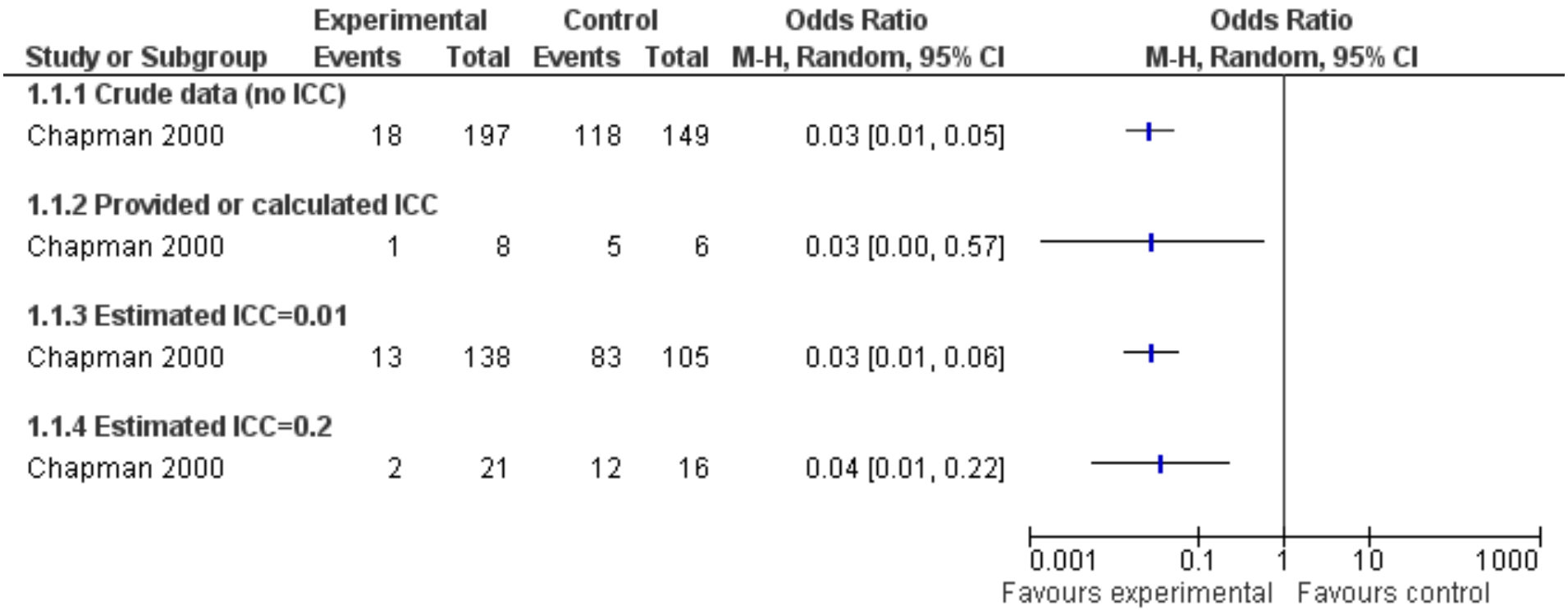
- study may use appropriate analysis method
  - e.g. a mixed (multilevel) model, GEEs
  - meta-analyse using GIV method
- if not, adjust the analysis for correlation
- get statistical advice
- clearly identify cluster-randomised trials and explain how you have dealt with the data



See Chapter 23.1 of the Handbook

Source: Julian Higgins

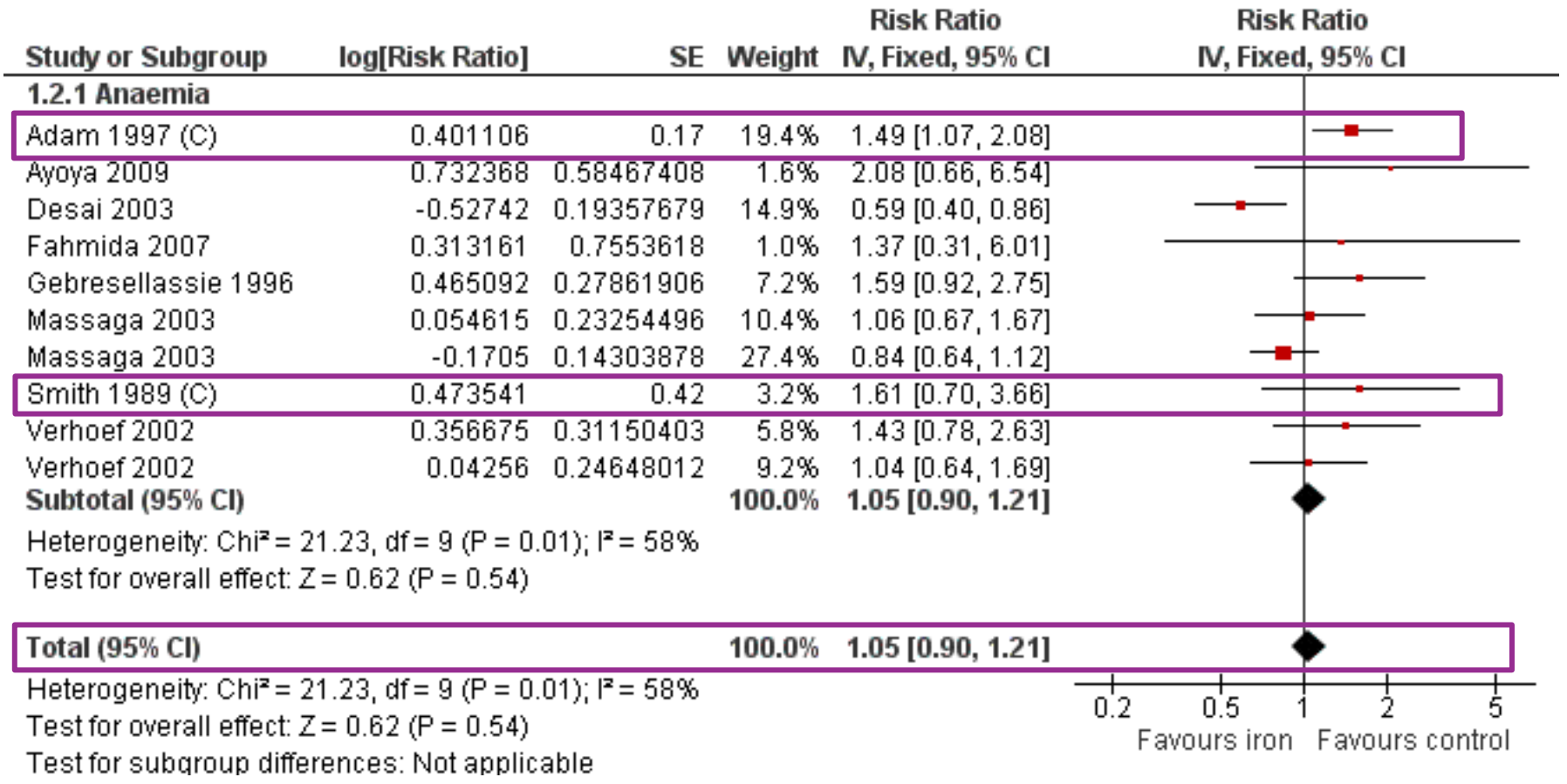
Example: Education to prevent dog bites



Source: Craig Ramsay

Duperrex O, Blackhall K, Burri M, Jeannot E. Education of children and adolescents for the prevention of dog bite injuries. Cochrane Database of Systematic Reviews 2009, Issue 2. Art. No.: CD004726. DOI: 10.1002/14651858.CD004726.pub2.

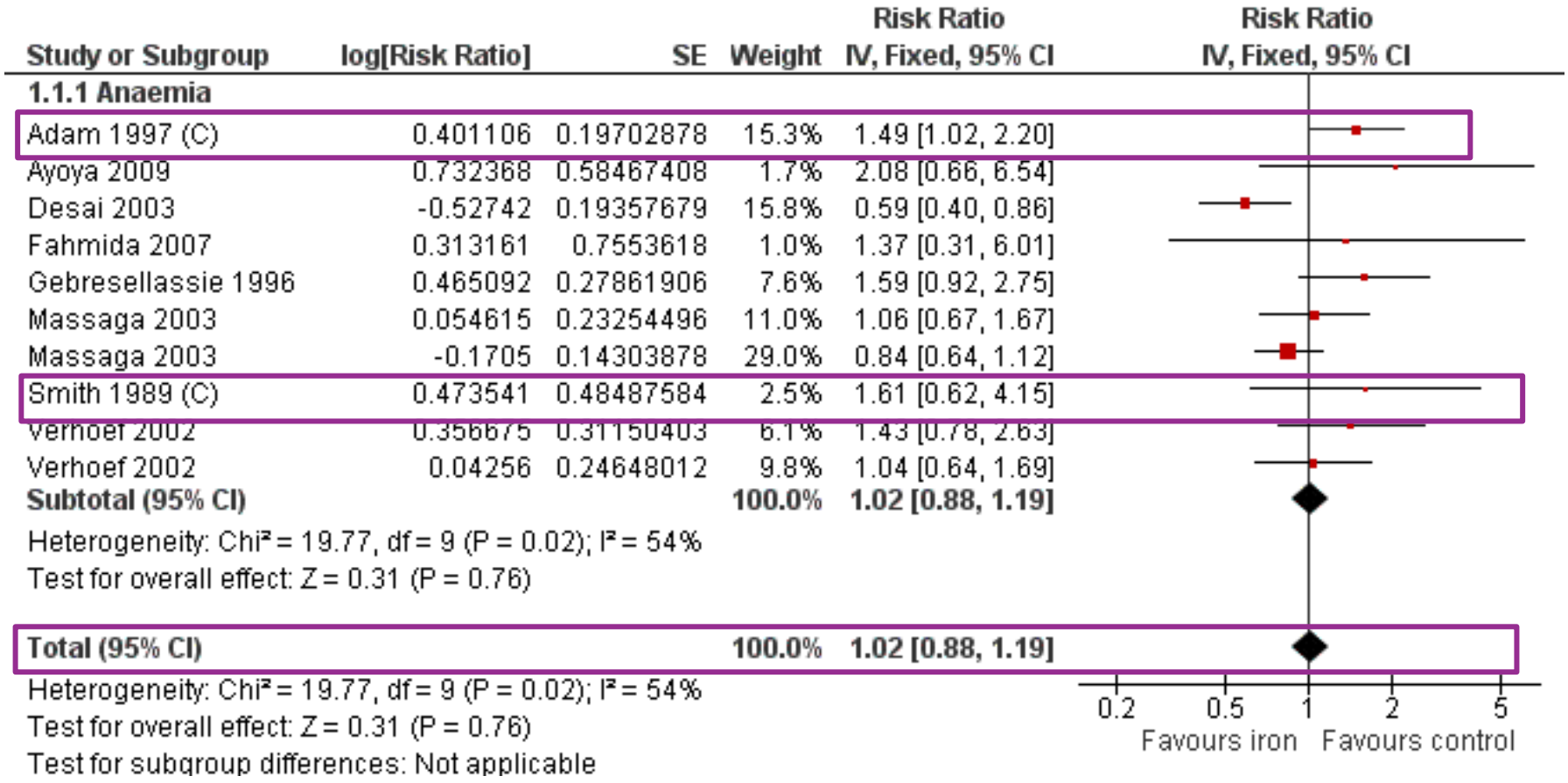
Example: Oral iron supplements to prevent malaria



Source: Matt Page

Adapted from Okebe JU, Yahav D, Shbita R, Paul M. Oral iron supplements for children in malaria-endemic areas. Cochrane Database of Systematic Reviews 2011, Issue 10. Art. No.: CD006589. DOI: 10.1002/14651858.CD006589.pub3.

Example: Oral iron supplements to prevent malaria



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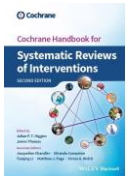
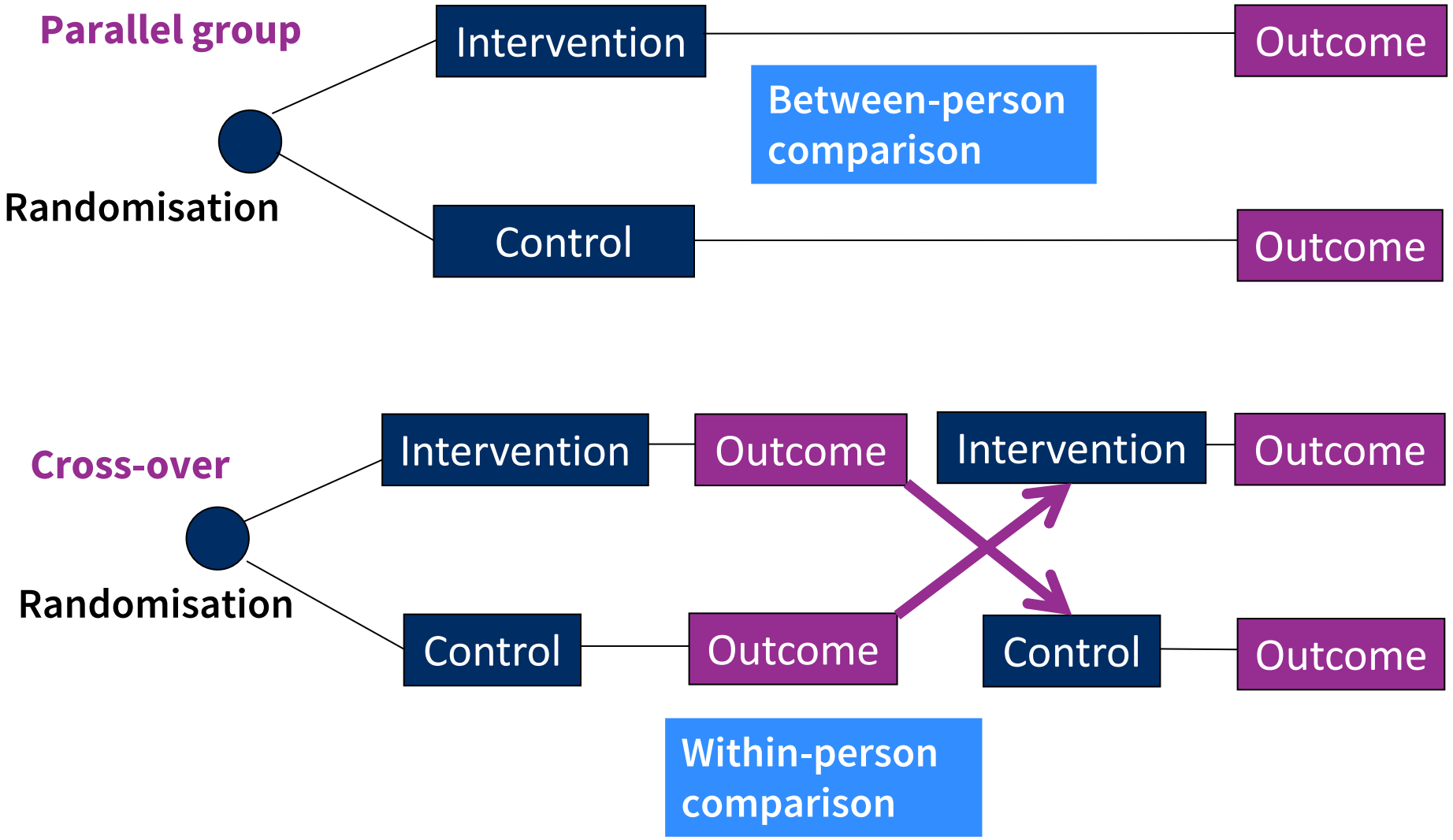


See Chapter 23.2 of the Handbook

Cross-over trials

- all participants receive both intervention and control
  - ideally in random order
- takes advantage of correlation
  - eliminates among-participant variation
  - fewer participants required to achieve desired power

Cross-over trials



Source: Julian Higgins

Suitability of cross-over design

- appropriate for:
  - chronic, stable conditions
  - short-term outcomes (e.g. relief of symptoms)
  - sufficient washout period between treatments
- possible problems affecting the second intervention period
  - irreversible outcomes (e.g. death, cure)
  - period effect (e.g. degenerative conditions)
  - carryover effect (e.g. long-acting intervention)
  - consider using first period only as a parallel group trial
    - this information is rarely and selectively reported

Source: Julian Higgins

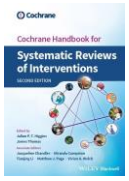
Unit of analysis issues

- measurements within individuals are correlated
- within-person design should be taken into account
  - if not, study will receive too little weight in meta-analysis
- may also occur in studies of multiple body parts

Source: Julian Higgins

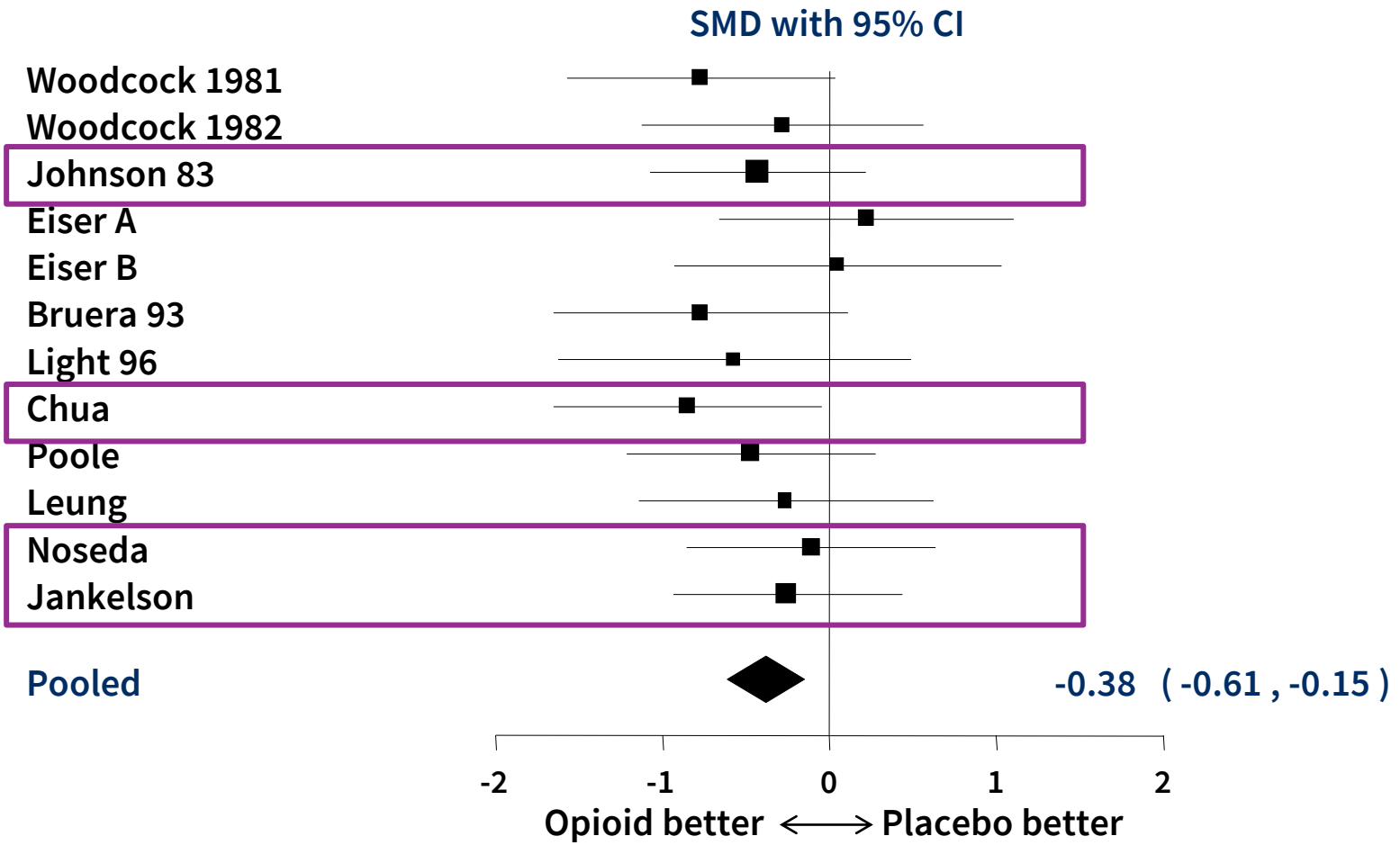
Taking correlation into account

- study may use appropriate paired analysis
  - participant-specific differences between intervention & control
  - meta-analyse using GIV method
- study may use simple comparison between intervention & control
  - if not, adjust the analysis for correlation
- get statistical advice
- clearly identify cross-over studies and explain how you have dealt with the data



See Chapter 23.2 of the Handbook

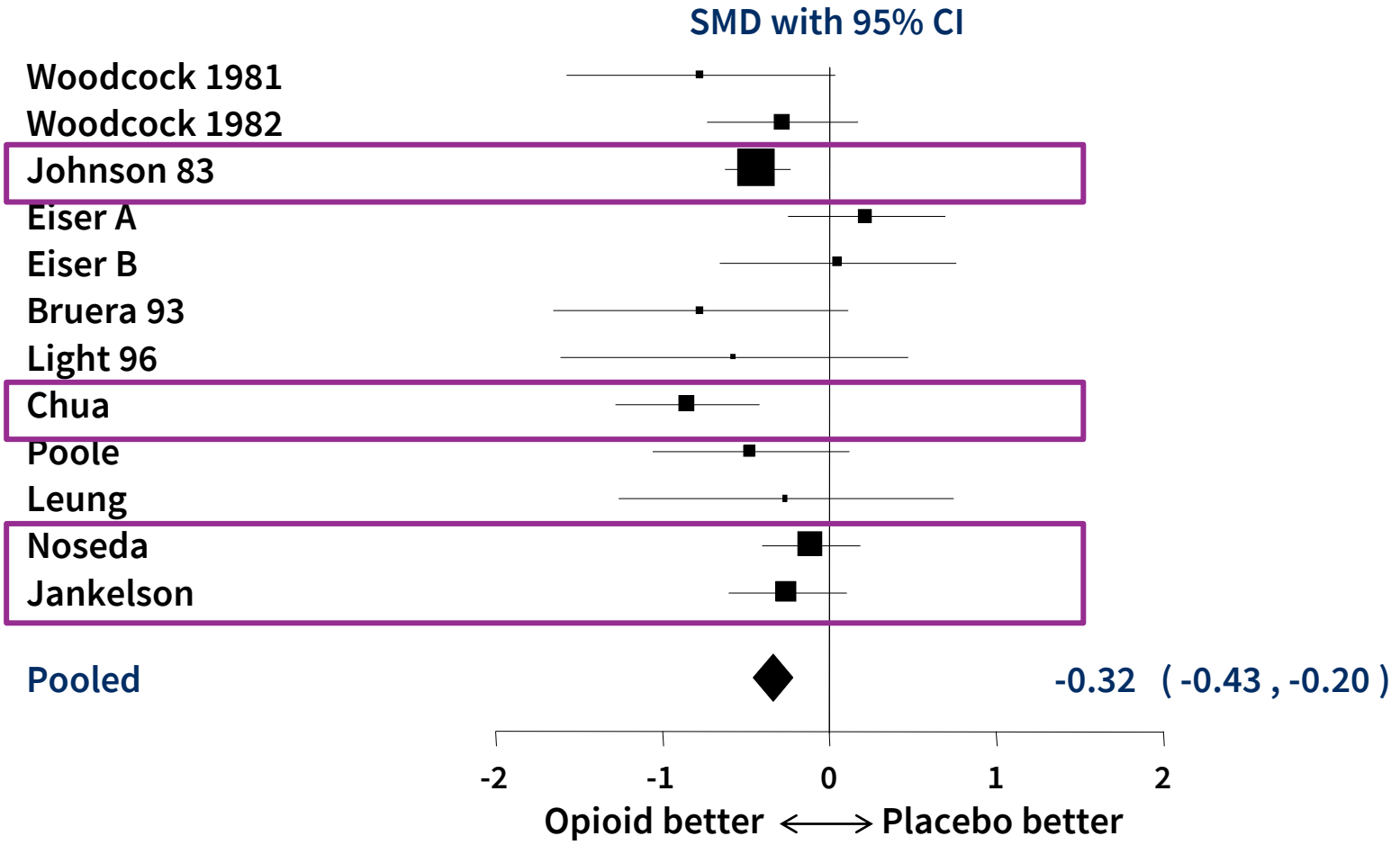
Example: ignoring cross-over design



Source: Julian Higgins.

Adapted from Jennings AL, Davies AN, Higgins JPT, Anzures-Cabrera J, Broadley KE. Opioids for the palliation of breathlessness in terminal illness. Cochrane Database of Systematic Reviews 2001, Issue 3. Art. No.: CD002066. DOI: 10.1002/14651858.CD002066.

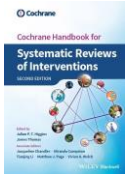
Example: accounting for cross-over design



Source: Julian Higgins.
Adapted from Jennings AL, Davies AN, Higgins JPT, Anzures-Cabrera J, Broadley KE. Opioids for the palliation of breathlessness in terminal illness. Cochrane Database of Systematic Reviews 2001, Issue 3. Art. No.: CD002066. DOI: 10.1002/14651858.CD002066.

Session outline

- generic inverse variance meta-analysis
- other outcome types
- multi-arm studies
- cluster-randomised trials
- cross-over trials
- **non-randomised studies**



See Chapter 24 of the Handbook

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Non-randomised trials

- may sometimes be included in reviews
  - controlled before and after studies
  - interrupted time series
  - for adverse events: other observational designs
  - economics
  - qualitative data
- different methods and conditions apply
- get advice before proceeding

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What to include in your protocol

- no need to predict every possible issue
- describe how to handle any expected:
  - statistical measures
  - outcome types
  - study designs

Take home message

- special methods may be needed to address some outcome types and study designs
- be aware of the issues - read the Handbook carefully and seek statistical advice if these apply to your review
- the generic inverse-variance method can be used to meta-analyse overall summary statistics

References

- Higgins JPT, Li T, Deeks JJ (editors). **Chapter 6: Choosing effect measures and computing estimates of effect**.
- Deeks JJ, Higgins JPT, Altman DG. **Chapter 10: Analysing data and undertaking meta-analyses.**
- Higgins JPT, Eldridge S, Li T. **Chapter 23: Including variants on randomized trials.**
- Reeves BC, Deeks JJ, Higgins JPT, Shea B, Tugwell P, Wells GA. **Chapter 24: Including non-randomized studies on intervention effects**.

All the above in: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.1 (updated September 2020). Cochrane, 2020. Available from www.training.cochrane.org/handbook.

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