# Handling heterogeneity in Cochrane reviews

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**Methods Support Unit**

Trusted evidence.
Informed decisions.
Better health.

# Structure of session

1. Introduction-Definition of heterogeneity
2. Identifying statistical heterogeneity
3. Dealing with heterogeneity
4. Common misconceptions
5. Discussion and questions

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# Introduction

- Meta-analysis is the statistical combination of results from two or more separate studies
- It is a two-stage process
  - First stage: from each study obtain the effect size estimate (e.g. RR, OR, MD) and its standard error
  - Second stage: synthesize effect sizes from the included studies
- Studies brought together in a systematic review will differ
  - differ clinically (PICO) and methodologically
  - unlikely to have the same effect across all studies
- **Heterogeneity**

# Poll: What is heterogeneity?

1. Something to be afraid of
2. Any difference between studies included in a systematic review
3. A quantity that can be measured using statistic measures
4. A criterion for choosing between fixed- and random-effects model

# Definition of heterogeneity

Any kind of variability among studies included in a systematic review

- Clinical: variability in participants, interventions, outcomes
- Methodological: variability in study design, outcome measurement tools, risk of bias
- **Statistical**: variability in intervention effects of the different studies
  - Variation in the true effects underlying the studies
  - Homogeneity does not hold

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# Fixed- & random-effects models

- Fixed-effects (FE) model: ignores heterogeneity
  - the observed differences among study results are solely due to chance
- Random-effects (RE) model: incorporates heterogeneity among studies
  - the observed differences among study results are due to a combination of chance and variation in the intervention effects
- Identical results when there is no heterogeneity among the studies
- In presence of heterogeneity, the confidence interval (CI) around the random-effects summary estimate is wider than a CI around a fixed-effect summary estimate.
- **How will we know if there is statistical heterogeneity?**

# Identifying statistical heterogeneity

- Visual inspection of forest plots
- Using a chi-squared test
- Using $I^2$ index

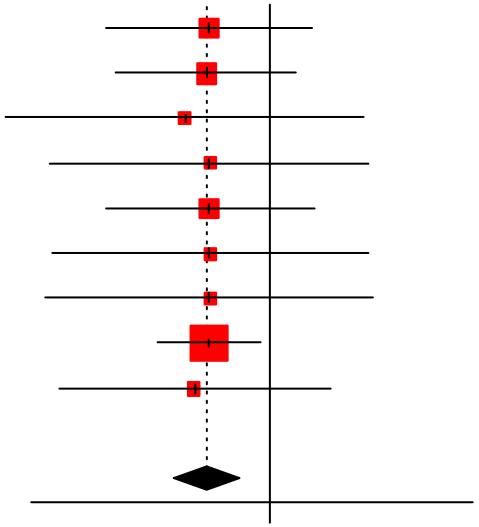
# Identifying statistical heterogeneity

## Visual inspection of forest plots

Check the direction of effects and for any overlap on CIs

What do you think about (c) ?

**a.**



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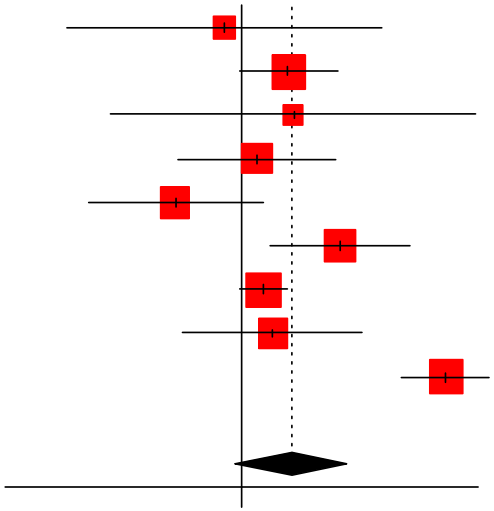

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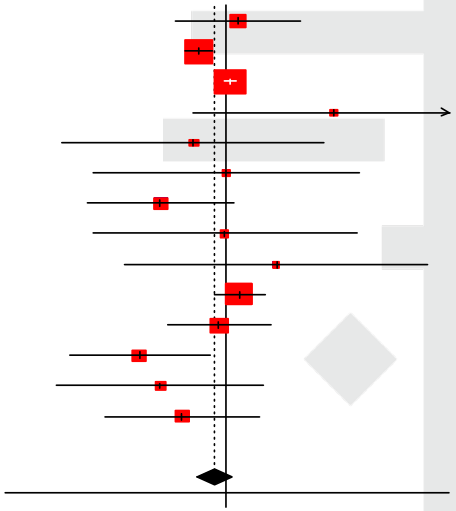


# Identifying statistical heterogeneity

## Using a chi-squared test

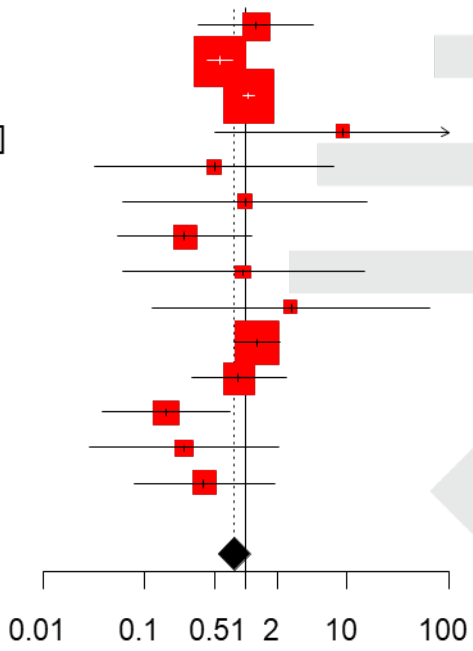
- **Q statistic**
  - $Q = \sum_{i=1}^{k} (y_i - \Theta)^2$
  - Assesses whether observed differences in results are compatible with chance alone
  - Null hypothesis: No between-studies heterogeneity (Homogeneity)
  - Statistically significant when p-value<0.10
- **Attention required!**
  - Low power, when studies have small sample size or are few in number
  - High power to detect small amount of heterogeneity in presence of many studies.

# Identifying statistical heterogeneity

## Using a chi-squared test

| Study | Experimental Events | Experimental Total | Control Events | Control Total | Weight | Risk Ratio MH, Random, 95% CI |
|---|---|---|---|---|---|---|
| Study 1 | 5 | 150 | 4 | 152 | 6.2% | 1.27 [0.35; 4.63] |
| Study 2 | 65 | 2004 | 117 | 2008 | 20.8% | 0.56 [0.41; 0.75] |
| Study 3 | 424 | 2172 | 405 | 2201 | 23.4% | 1.06 [0.94; 1.20] |
| Study 4 | 4 | 74 | 0 | 74 | 1.6% | 9.00 [0.49; 164.23] |
| Study 5 | 1 | 40 | 1 | 20 | 1.8% | 0.50 [0.03; 7.59] |
| Study 6 | 1 | 165 | 1 | 162 | 1.7% | 0.98 [0.06; 15.56] |
| Study 7 | 2 | 70 | 8 | 70 | 4.9% | 0.25 [0.06; 1.14] |
| Study 8 | 1 | 43 | 1 | 41 | 1.7% | 0.95 [0.06; 14.75] |
| Study 9 | 1 | 26 | 0 | 24 | 1.3% | 2.77 [0.12; 64.93] |
| Study 10 | 31 | 2076 | 24 | 2086 | 16.2% | 1.30 [0.76; 2.20] |
| Study 11 | 7 | 68 | 5 | 41 | 8.0% | 0.84 [0.29; 2.49] |
| Study 12 | 2 | 102 | 12 | 100 | 5.1% | 0.16 [0.04; 0.71] |
| Study 13 | 1 | 55 | 4 | 55 | 2.7% | 0.25 [0.03; 2.17] |
| Study 14 | 2 | 57 | 5 | 56 | 4.5% | 0.39 [0.08; 1.94] |
| **Total (95% CI)** | **7102** | | **7090** | | **100.0%** | **0.76 [0.52; 1.11]** |

Heterogeneity: $Tau^2 = 0.1531$; $Chi^2 = 31.40$, df = 13 ($P < 0.01$); $I^2 = 59\%$




*Sethi NJ, Safi S, Korang SK, Hróbjartsson A, Skoog M, Gluud C, Jakobsen JC. Antibiotics for secondary prevention of coronary heart disease. Cochrane Database of Systematic Reviews 2021, Issue 2. Art. No.: CD003610. DOI: 10.1002/14651858.CD003610.pub4.*

# Identifying statistical heterogeneity

## Using $I^2$ index

- $I^2 = \frac{Q-k+1}{Q} \cdot 100\%$
  - Describes the percentage of the variability in effect estimates that is due to heterogeneity rather than chance
  - Rough guide:
    - 0%-40%: might not important
    - 30%-60%: moderate heterogeneity
    - 50%-90%: substantial heterogeneity
    - 75%-100%: considerable heterogeneity
  - Interpretation and importance depend on
    1. magnitude and direction of effects,
    2. strength of evidence for heterogeneity
       (e.g., p-value from the Chi² test, or a confidence interval for I²: uncertainty in the value of I² is substantial when the number of studies is small)

# Identifying statistical heterogeneity

## Using $I^2$ index

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|---|---|---|---|---|---|---|
| Study 1 | 5 | 150 | 4 | 152 | 6.2% | 1.27 [0.35; 4.63] |
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| Study 5 | 1 | 40 | 1 | 20 | 1.8% | 0.50 [0.03; 7.59] |
| Study 6 | 1 | 165 | 1 | 162 | 1.7% | 0.98 [0.06; 15.56] |
| Study 7 | 2 | 70 | 8 | 70 | 4.9% | 0.25 [0.06; 1.14] |
| Study 8 | 1 | 43 | 1 | 41 | 1.7% | 0.95 [0.06; 14.75] |
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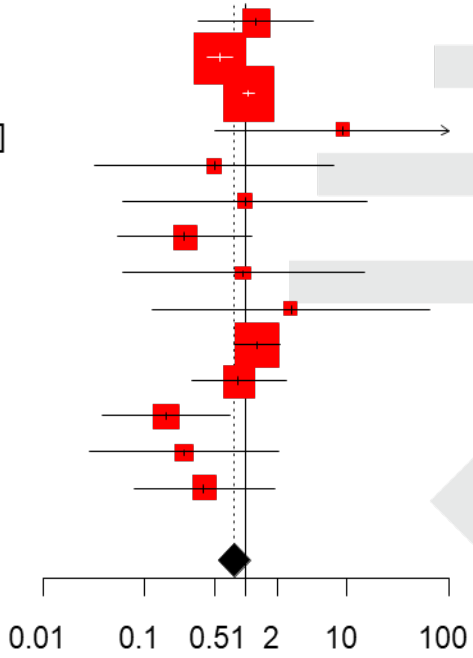
| Study 11 | 7 | 68 | 5 | 41 | 8.0% | 0.84 [0.29; 2.49] |
| Study 12 | 2 | 102 | 12 | 100 | 5.1% | 0.16 [0.04; 0.71] |
| Study 13 | 1 | 55 | 4 | 55 | 2.7% | 0.25 [0.03; 2.17] |
| Study 14 | 2 | 57 | 5 | 56 | 4.5% | 0.39 [0.08; 1.94] |
| **Total (95% CI)** | | **7102** | | **7090** | **100.0%** | **0.76 [0.52; 1.11]** |

Heterogeneity: $Tau^2 = 0.1531$; $Chi^2 = 31.40$, df = 13 ($P < 0.01$); $I^2 = 59\%$

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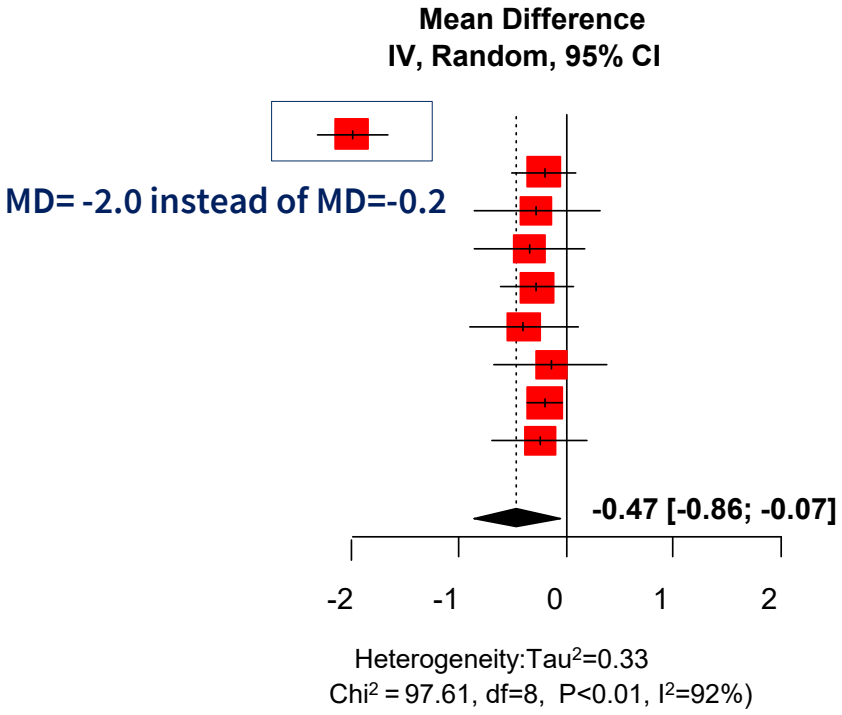
# Dealing with heterogeneity

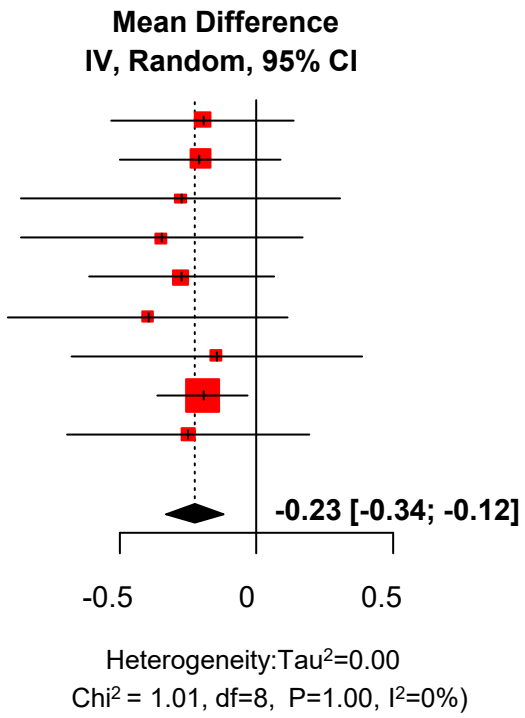
- Heterogeneity is always expected in a systematic review!
- When heterogeneity is located:
  - Check for data entry errors
  - explore heterogeneity with pre-defined subgroup and meta-regression analyses or sensitivity analyses
  - reconsider the effect measure
  - do not synthesize results

# Dealing with heterogeneity

## Check for data entry errors

### Theoretical Example



# Dealing with heterogeneity

- Heterogeneity is always expected in a systematic review!
- When heterogeneity is high,
  - check for data entry errors
  - explore heterogeneity with pre-defined subgroup, meta-regression or sensitivity analyses.
  - reconsider the effect measure
  - do not synthesize results

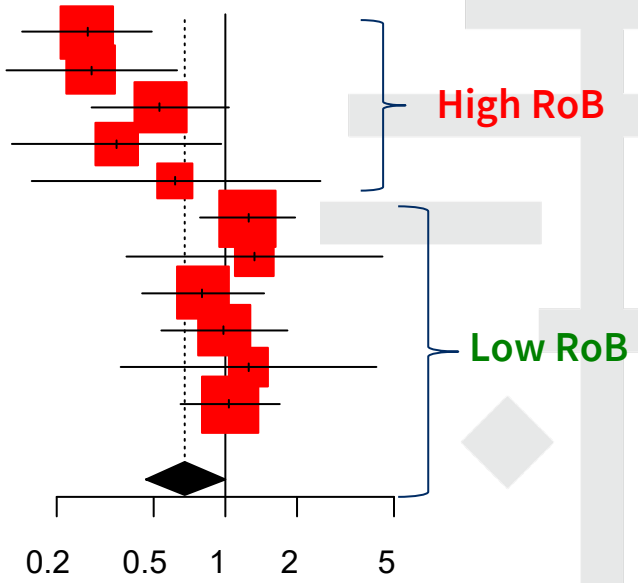
# Dealing with heterogeneity

## Subgroup analysis

### Theoretical Example

| Study | Experimental Events | Experimental Total | Control Events | Control Total | Weight | Risk Ratio MH, Random, 95% CI |
|---|---|---|---|---|---|---|
| Study 1 | 12 | 350 | 45 | 349 | 10.7% | 0.27 [0.14; 0.49] |
| Study 2 | 7 | 289 | 26 | 296 | 8.8% | 0.28 [0.12; 0.63] |
| Study 3 | 12 | 118 | 22 | 116 | 10.3% | 0.54 [0.28; 1.03] |
| Study 4 | 5 | 199 | 14 | 198 | 7.3% | 0.36 [0.13; 0.97] |
| Study 5 | 3 | 59 | 5 | 61 | 5.0% | 0.62 [0.16; 2.48] |
| Study 6 | 24 | 56 | 22 | 64 | 12.3% | 1.25 [0.79; 1.96] |
| Study 7 | 5 | 33 | 4 | 35 | 5.9% | 1.33 [0.39; 4.52] |
| Study 8 | 15 | 65 | 20 | 70 | 11.1% | 0.81 [0.45; 1.44] |
| Study 9 | 11 | 25 | 12 | 27 | 10.8% | 0.99 [0.54; 1.82] |
| Study 10 | 5 | 35 | 4 | 35 | 5.8% | 1.25 [0.37; 4.27] |
| Study 11 | 22 | 60 | 21 | 60 | 12.0% | 1.05 [0.65; 1.69] |
| **Total (95% CI)** | **1289** | | **1311** | | **100.0%** | **0.68 [0.47; 1.00]** |

Heterogeneity: $Tau^2 = 0.2556$; $Chi^2 = 30.66$, df = 10 ($P < 0.01$); $I^2 = 67\%$

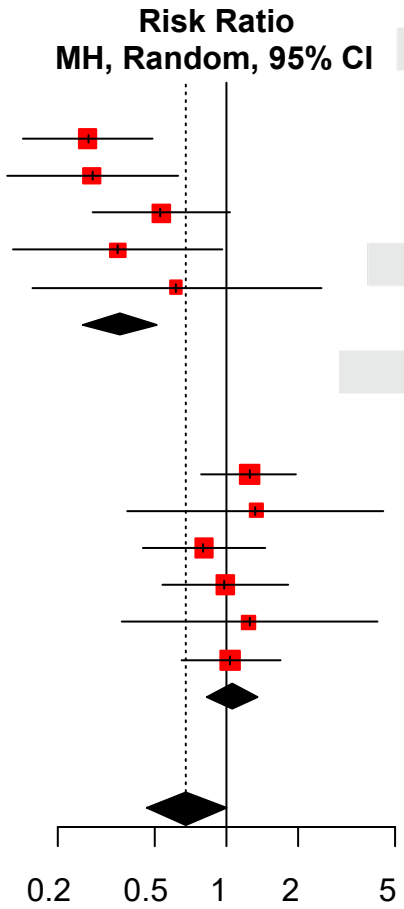


# Dealing with heterogeneity

## Subgroup analysis

### Theoretical Example

| Study or Subgroup | Experimental Events | Experimental Total | Control Events | Control Total | Weight | Risk Ratio MH, Random, 95% CI |
|---|---|---|---|---|---|---|
| **Group = High RoB** | | | | | | |
| Study 1 | 12 | 350 | 45 | 349 | 10.7% | 0.27 [0.14; 0.49] |
| Study 2 | 7 | 289 | 26 | 296 | 8.8% | 0.28 [0.12; 0.63] |
| Study 3 | 12 | 118 | 22 | 116 | 10.3% | 0.54 [0.28; 1.03] |
| Study 4 | 5 | 199 | 14 | 198 | 7.3% | 0.36 [0.13; 0.97] |
| Study 5 | 3 | 59 | 5 | 61 | 5.0% | 0.62 [0.16; 2.48] |
| **Total (95% CI)** | | **1015** | | **1020** | **42.2%** | **0.36 [0.25; 0.51]** |
| Heterogeneity: $Tau^2 = 0$; $Chi^2 = 3.38$, df = 4 (P = 0.50); $I^2 = 0\%$ | | | | | | |
| **Group = Low RoB** | | | | | | |
| Study 6 | 24 | 56 | 22 | 64 | 12.3% | 1.25 [0.79; 1.96] |
| Study 7 | 5 | 33 | 4 | 35 | 5.9% | 1.33 [0.39; 4.52] |
| Study 8 | 15 | 65 | 20 | 70 | 11.1% | 0.81 [0.45; 1.44] |
| Study 9 | 11 | 25 | 12 | 27 | 10.8% | 0.99 [0.54; 1.82] |
| Study 10 | 5 | 35 | 4 | 35 | 5.8% | 1.25 [0.37; 4.27] |
| Study 11 | 22 | 60 | 21 | 60 | 12.0% | 1.05 [0.65; 1.69] |
| **Total (95% CI)** | | **274** | | **291** | **57.8%** | **1.06 [0.83; 1.36]** |
| Heterogeneity: $Tau^2 = 0$; $Chi^2 = 1.59$, df = 5 (P = 0.90); $I^2 = 0\%$ | | | | | | |
| **Total (95% CI)** | | **1289** | | **1311** | **100.0%** | **0.68 [0.47; 1.00]** |
| Heterogeneity: $Tau^2 = 0.2556$; $Chi^2 = 30.66$, df = 10 (P < 0.01); $I^2 = 67\%$ | | | | | | |
| Test for subgroup differences: $Chi^2 = 23.82$, df = 1 (P < 0.01) | | | | | | |



# Dealing with heterogeneity

- Heterogeneity is always expected in a systematic review!
- When heterogeneity is high,
  - check for data entry errors
  - explore heterogeneity with pre-defined subgroup and meta-regression analyses or sensitivity analyses
  - Reconsider the effect measure
  - do not synthesize results

# Dealing with heterogeneity

## Reconsider the effect measure

- **Continuous data**
  - Different scales used to measure the outcome
  - MD may lead to (high) heterogeneity
  - Change to SMD

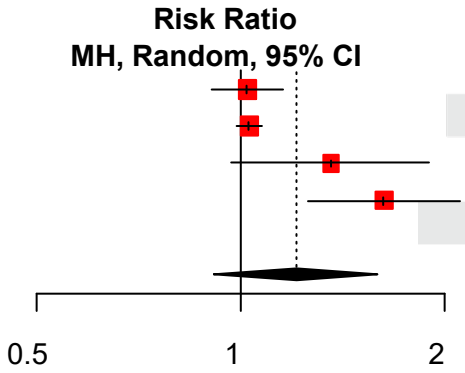
# Dealing with heterogeneity

## Reconsider the effect measure

- **Dichotomous data**
  - Choice of effect measure may affect heterogeneity

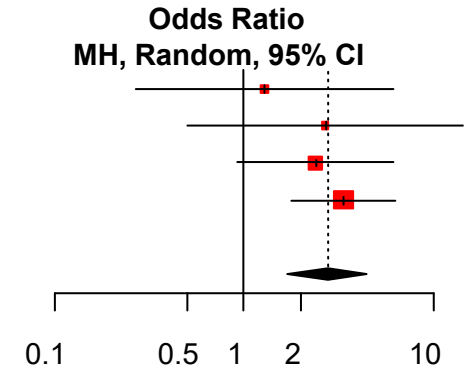
| Study | Experimental Events | Experimental Total | Control Events | Control Total | Weight | Risk Ratio MH, Random, 95% CI |
|---|---|---|---|---|---|---|
| Study A | 40 | 43 | 42 | 46 | 27.5% | 1.02 [0.90; 1.15] |
| Study B | 128 | 130 | 120 | 125 | 28.9% | 1.03 [0.98; 1.07] |
| Study C | 29 | 39 | 22 | 40 | 20.4% | 1.35 [0.97; 1.89] |
| Study D | 63 | 86 | 42 | 93 | 23.2% | 1.62 [1.25; 2.10] |
| **Total (95% CI)** | | **298** | | **304** | **100.0%** | **1.20 [0.91; 1.59]** |

Heterogeneity: $Tau^2 = 0.07$ ; $Chi^2 = 46.54$, df = 3 ($P < 0.01$); $I^2 = 94\%$




| Study | Experimental Events | Experimental Total | Control Events | Control Total | Weight | Odds Ratio MH, Random, 95% CI |
|---|---|---|---|---|---|---|
| Study A | 40 | 43 | 42 | 46 | 9.3% | 1.27 [0.27; 6.03] |
| Study B | 128 | 130 | 120 | 125 | 8.2% | 2.67 [0.51; 14.01] |
| Study C | 29 | 39 | 22 | 40 | 25.0% | 2.37 [0.92; 6.14] |
| Study D | 63 | 86 | 42 | 93 | 57.4% | 3.33 [1.77; 6.23] |
| **Total (95% CI)** | | **298** | | **304** | **100.0%** | **2.74 [1.70; 4.42]** |

Heterogeneity: $Tau^2 = 0$; $Chi^2 = 1.39$, df = 3 ($P = 0.71$); $I^2 = 0\%$



# Dealing with heterogeneity

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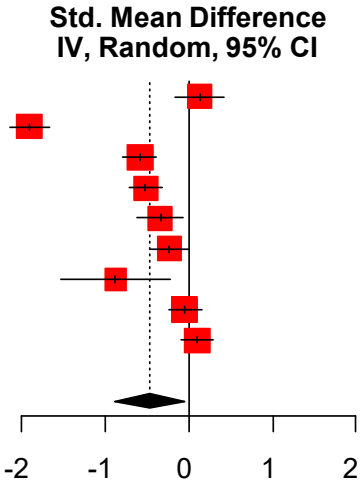
  - explore heterogeneity with pre-defined subgroup and meta-regression analyses or sensitivity analyses
  - reconsider the effect measure
  - do not synthesize results

# Dealing with heterogeneity

## Do not synthesize results!

| Study | TE | SE | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|
| Study 1 | 0.13 | 0.1509 | 11.1% | 0.13 [-0.17; 0.42] |
| Study 2 | -1.91 | 0.1216 | 11.3% | -1.91 [-2.15; -1.67] |
| Study 3 | -0.59 | 0.1017 | 11.5% | -0.59 [-0.79; -0.39] |
| Study 4 | -0.52 | 0.1015 | 11.5% | -0.52 [-0.72; -0.33] |
| Study 5 | -0.34 | 0.1408 | 11.2% | -0.34 [-0.62; -0.07] |
| Study 6 | -0.24 | 0.1222 | 11.3% | -0.24 [-0.48; 0.00] |
| Study 7 | -0.88 | 0.3372 | 9.0% | -0.88 [-1.54; -0.22] |
| Study 8 | -0.05 | 0.1004 | 11.5% | -0.05 [-0.25; 0.14] |
| Study 9 | 0.10 | 0.0933 | 11.5% | 0.10 [-0.09; 0.28] |
| **Total (95% CI)** | | | **100.0%** | **-0.47 [-0.88; -0.06]** |

Heterogeneity:
$Tau^2$= 0.3711; $Chi^2$ = 215.76, df = 8 P(< 0.01); $I^2$=96%



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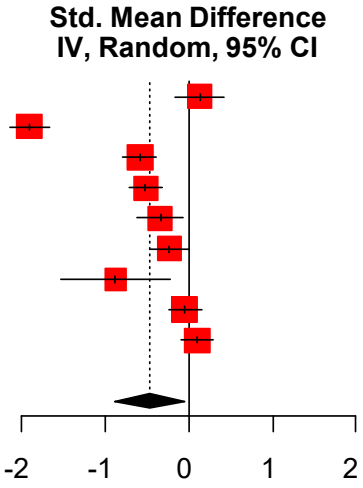


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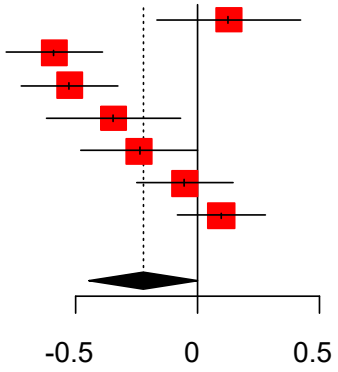
Heterogeneity:
$Tau^2$= 0.0763; $Chi^2$ = 42.62, df = 6 P(< 0.01); $I^2$=86%



# Common misconceptions

- Do not ignore heterogeneity, but assess it properly!
- $I^2$=0% does not mean heterogeneity is not there!
  - In a MA of very large studies or many studies, the sampling error tends to zero, and $I^2$ tends to 100% simply because the single studies have greater sample sizes.
- Do not choose between fixed- and random-effects model based on the Q-statistic or $I^2$ value
  - Fixed-effect or random-effects meta-analysis should be specified a priori and not on the basis of a heterogeneity test
  - Chapter 10, Cochrane Handbook

    *"Some argue that, since clinical and methodological diversity always occur in a meta-analysis, statistical heterogeneity is inevitable (Higgins et al 2003).*
    *Thus, the test for heterogeneity is irrelevant to the choice of analysis; heterogeneity will always exist whether or not we happen to be able to detect it using a statistical test."*

Cochrane

# Common misconceptions

**Richard Riley ($R^2$)** @Richard_D_Riley · Jun 16, 2022

Regular reminder for meta-analysis folk:

I-squared estimates between-study heterogeneity ❌

I-squared is a test for between-study heterogeneity ❌

I-squared > 50% means large heterogeneity ❌

I-squared measures proportion of total variability due to between-study heterogeneity ✅

# Prediction interval

- The interval within which the effect size of a new study would fall if this study was selected at random from the same population of the studies already included in the meta-analysis
- $M \pm t_{k-2} \cdot \sqrt{tau^2 + se(M)^2}$
- Requires a reasonable number of studies and not significant funnel plot asymmetry

*Ades, A. E., Lu, G., & Higgins, J. P. T. (2005). The Interpretation of Random-Effects Meta-Analysis in Decision Models. Medical Decision Making, 25(6), 646–654. doi:10.1177/0272989x05282643*

# Prediction interval

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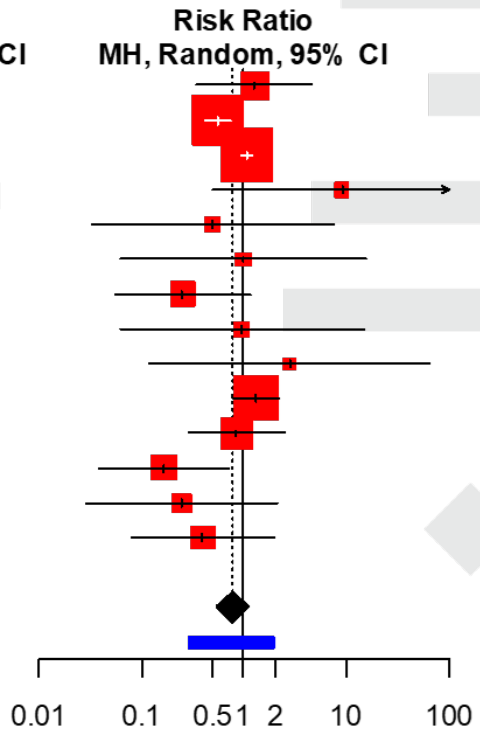
| Study 3 | 424 | 2172 | 405 | 2201 | 23.4% | 1.06 [0.94; 1.20] |
| Study 4 | 4 | 74 | 0 | 74 | 1.6% | 9.00 [0.49; 164.23] |
| Study 5 | 1 | 40 | 1 | 20 | 1.8% | 0.50 [0.03; 7.59] |
| Study 6 | 1 | 165 | 1 | 162 | 1.7% | 0.98 [0.06; 15.56] |
| Study 7 | 2 | 70 | 8 | 70 | 4.9% | 0.25 [0.06; 1.14] |
| Study 8 | 1 | 43 | 1 | 41 | 1.7% | 0.95 [0.06; 14.75] |
| Study 9 | 1 | 26 | 0 | 24 | 1.3% | 2.77 [0.12; 64.93] |
| Study 10 | 31 | 2076 | 24 | 2086 | 16.2% | 1.30 [0.76; 2.20] |
| Study 11 | 7 | 68 | 5 | 41 | 8.0% | 0.84 [0.29; 2.49] |
| Study 12 | 2 | 102 | 12 | 100 | 5.1% | 0.16 [0.04; 0.71] |
| Study 13 | 1 | 55 | 4 | 55 | 2.7% | 0.25 [0.03; 2.17] |
| Study 14 | 2 | 57 | 5 | 56 | 4.5% | 0.39 [0.08; 1.94] |
| **Total (95% CI)** | | **7102** | | **7090** | **100.0%** | **0.76 [0.52; 1.11]** |
| **Prediction interval** | | | | | | **[0.30; 1.97]** |

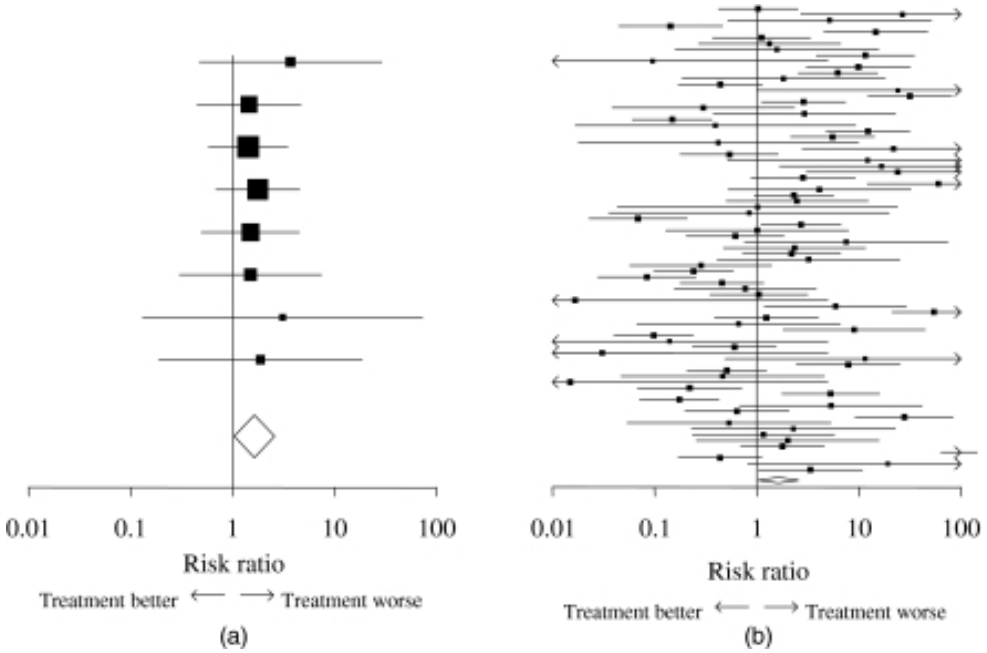
Heterogeneity: $Tau^2 = 0.1531$; $Chi^2 = 31.40$, df = 13 ($P < 0.01$); $I^2 = 59\%$




*Sethi NJ, Safi S, Korang SK, Hróbjartsson A, Skoog M, Gluud C, Jakobsen JC. Antibiotics for secondary prevention of coronary heart disease. Cochrane Database of Systematic Reviews 2021, Issue 2. Art. No.: CD003610. DOI: 10.1002/14651858.CD003610.pub4.*

# Overall…

- Heterogeneity is a common issue in meta-analysis
- Important to be careful when dealing with it to ensure that the derived results are valid and reliable




- **Identical pooled effect estimates**
- **Large heterogeneity challenges**

*Higgins, JPT., Thompson, SG,Spiegelhalter, DJ (2009). A re-evaluation of random effect meta-analysis. JRSC series A 2009; 172(1),137-159.*

# Overall…

- Interpretation of $I^2$ should always be considered in the context of other factors
  - the number and size of the included studies
  - the nature of the research question
  - the quality of the evidence.
- $I^2$ and statistical tests to detect heterogeneity should not be the basis for choosing between FE and RE models
- RE gives more conservative effects
  - When FE and RE give similar result, prefer RE.
  - When FE and RE differ, small-study effects may be present.
    - ! Think about the confidence we place on smaller trials.

# References


- Deeks JJ, Higgins JPT, Altman DG (editors).
  Chapter 10: Analysing data and undertaking meta-analyses. In:
  Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.3
  (updated February 2022). Cochrane, 2022.
  Available from www.training.cochrane.org/handbook.