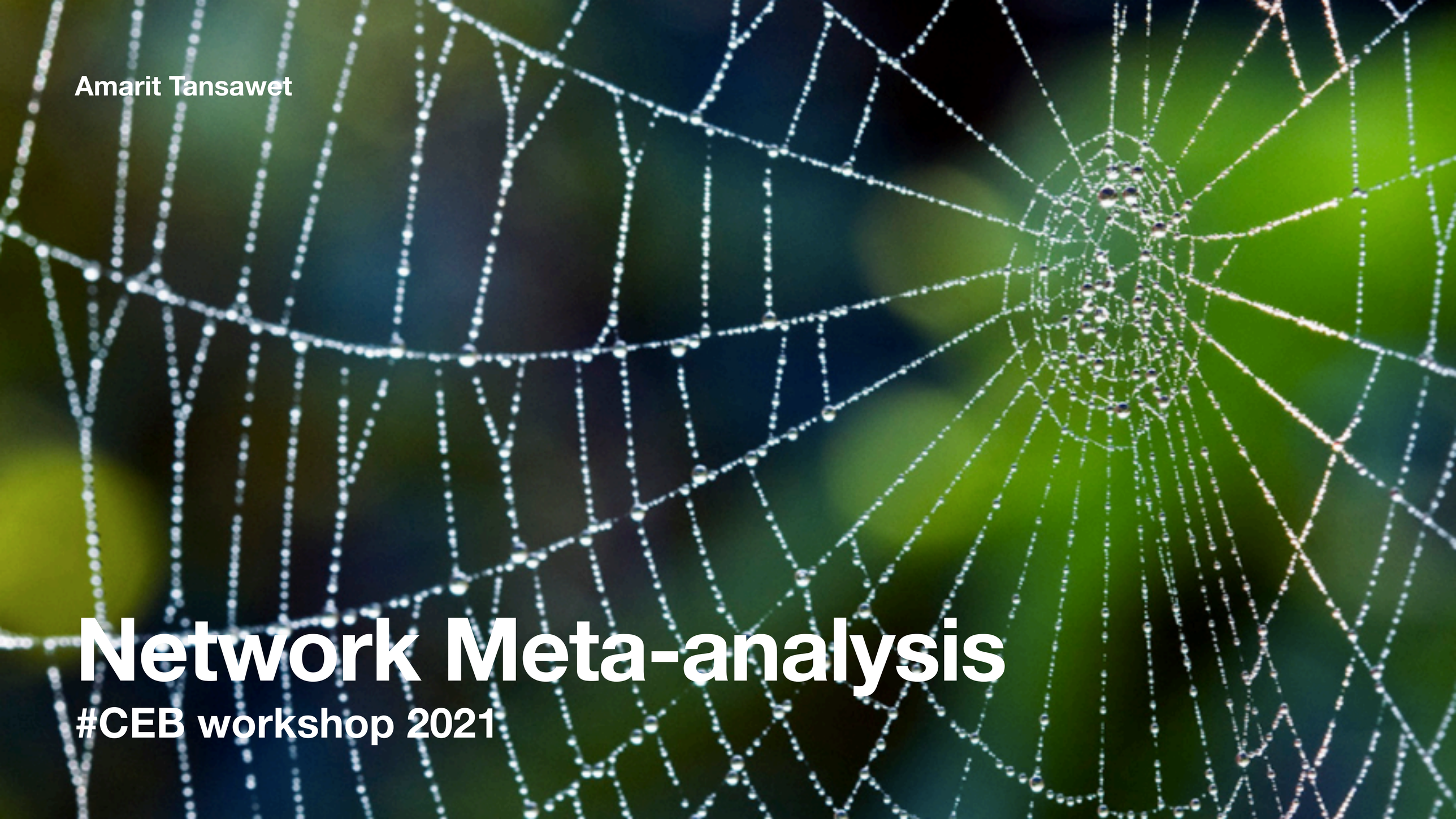
Amarit Tansawet

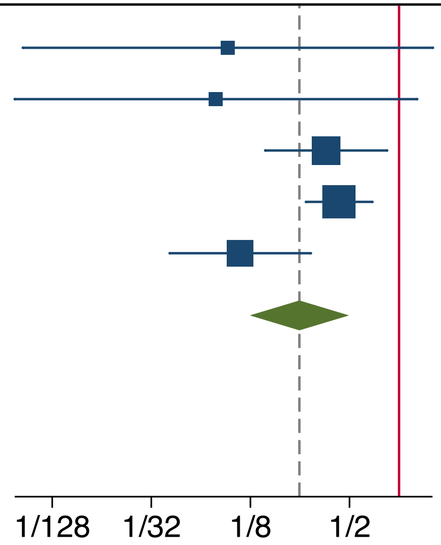


# Network Meta-analysis

## #CEB workshop 2021

# Pairwise Meta-analysis

| Study | OM Yes | OM No | PSC Yes | PSC No | Risk ratio with 95% CI | Weight (%) |
|---|---|---|---|---|---|---|
| Peña, 2003 | 0 | 44 | 5 | 39 | 0.09 [ 0.01, 1.60] | 5.16 |
| Bali, 2015 | 0 | 20 | 6 | 14 | 0.08 [ 0.00, 1.28] | 5.34 |
| García-ureña, 2015 | 6 | 47 | 17 | 37 | 0.36 [ 0.15, 0.84] | 27.23 |
| Jairam, 2017 | 25 | 163 | 33 | 74 | 0.43 [ 0.27, 0.68] | 38.39 |
| Caro-tarrago, 2019 | 4 | 76 | 37 | 43 | 0.11 [ 0.04, 0.29] | 23.88 |
| **Overall** | | | | | 0.25 [ 0.12, 0.50] | |

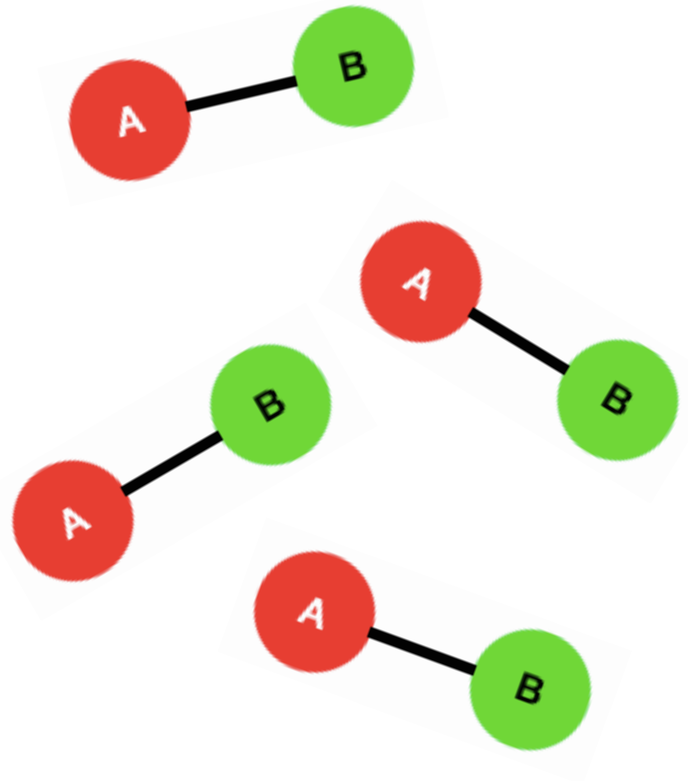



Heterogeneity: $\tau^2 = 0.27$, $I^2 = 50.41\%$, $H^2 = 2.02$

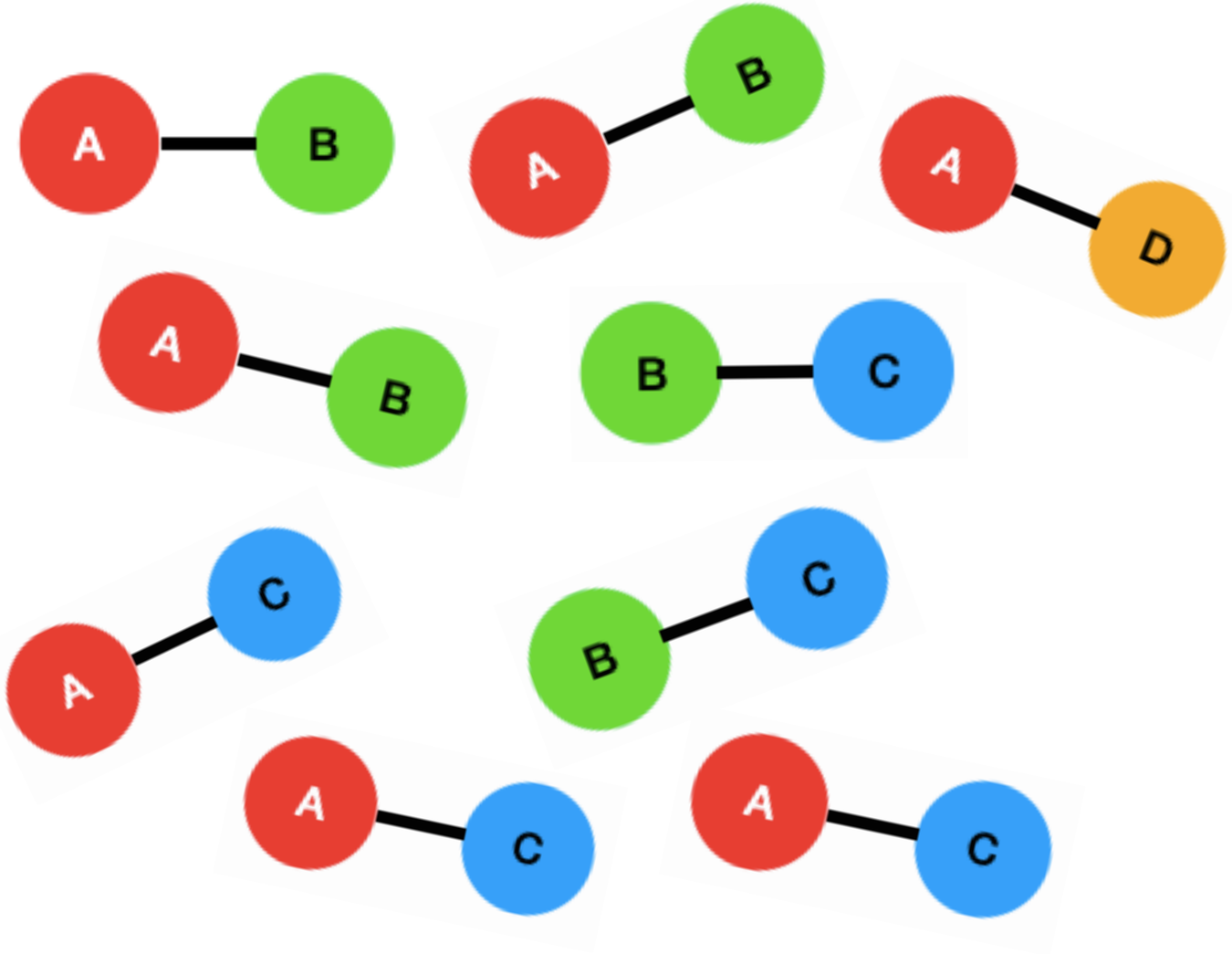
Test of $\theta_i = \theta_j$: $Q(4) = 8.07$, $p = 0.09$

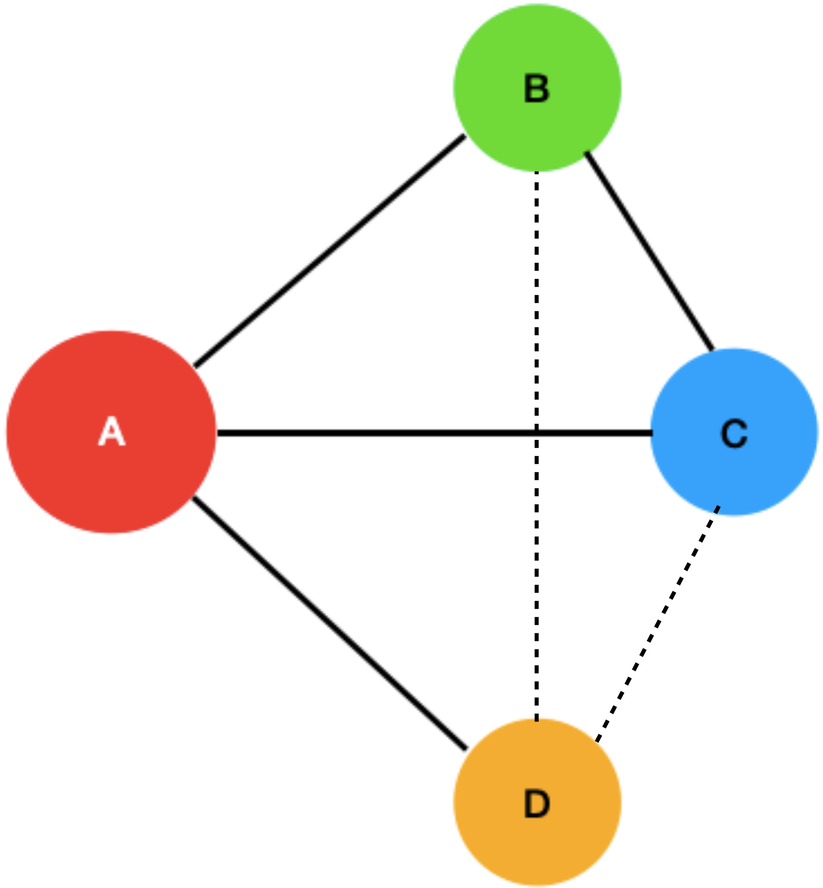
Test of $\theta = 0$: $z = -3.95$, $p = 0.00$

Random-effects DerSimonian–Laird model



# Network Meta-analysis



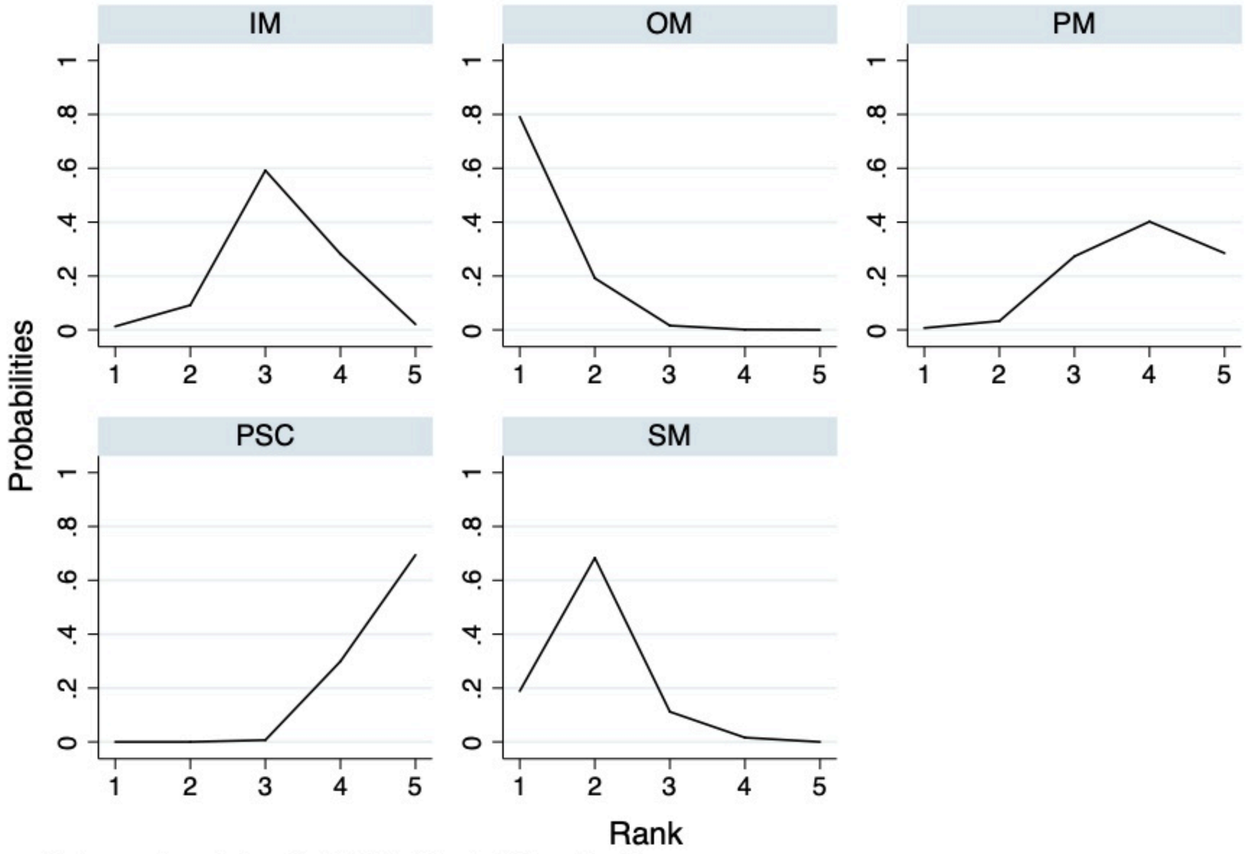

multiple treatment comparison

# Why Network Meta-analysis?

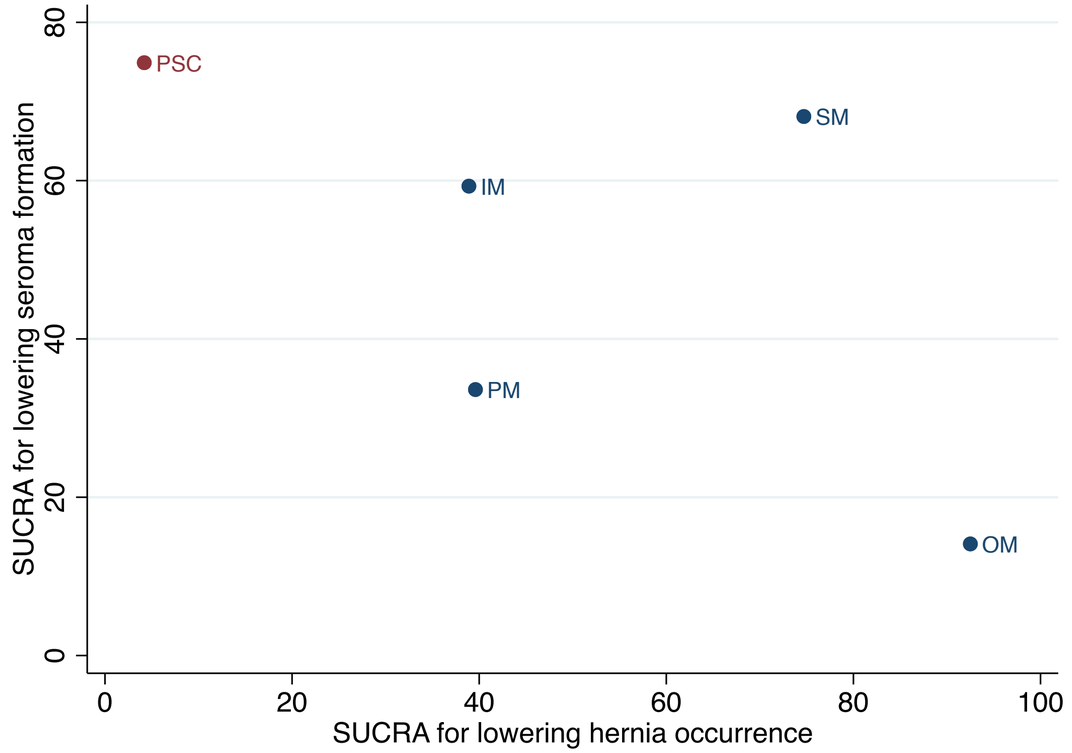
- No direct comparison
- multiple comparison leads to type I error inflation

- Benefit of NMA
  - compare all treatments at the same time
  - treatments can be ranked

| | | | | |
|---|---|---|---|---|
| PSC | 0.24 (0.12,0.46) | 0.32 (0.16,0.66) | 0.58 (0.23,1.47) | 0.58 (0.32,1.06) |
| 4.24 (2.19,8.21) | OM | 1.37 (0.64,2.96) | 2.47 (0.87,7.01) | 2.47 (1.03,5.93) |
| 3.08 (1.52,6.23) | 0.73 (0.34,1.57) | SM | 1.79 (0.63,5.09) | 1.79 (0.73,4.43) |
| 1.72 (0.68,4.33) | 0.41 (0.14,1.15) | 0.56 (0.20,1.58) | PM | 1.00 (0.34,2.95) |
| 1.72 (0.94,3.14) | 0.41 (0.17,0.98) | 0.56 (0.23,1.38) | 1.00 (0.34,2.95) | IM |




Rankogram after exclusion of the high risk of bias study (all mesh type)



# NMA could be

For

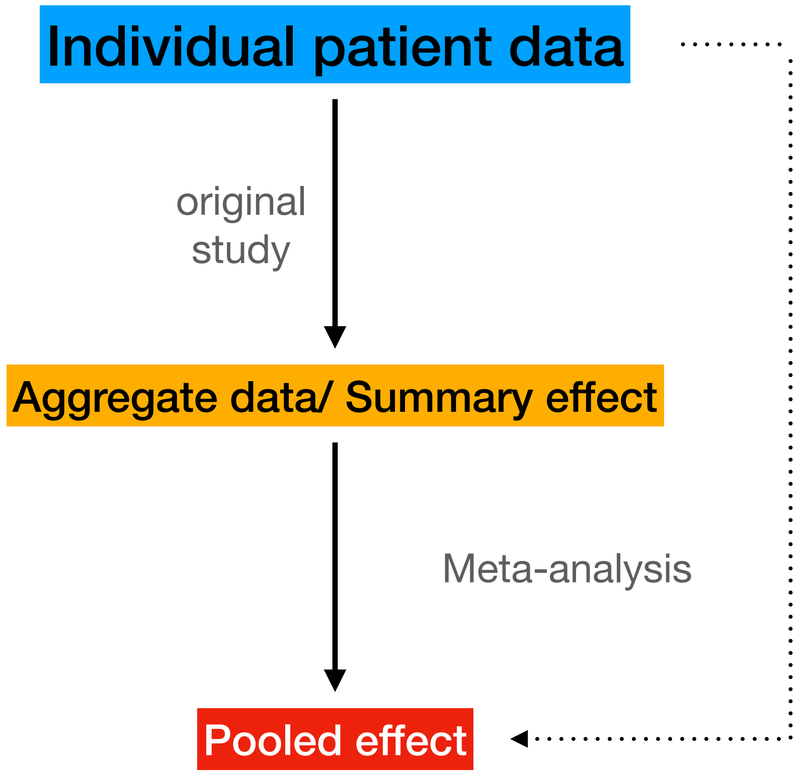
- Therapeutic
  - Binary outcome
  - Continuous outcome
  - Time-to-event outcome
- Economic
- Diagnostic

- One-stage
  - mixed-effect (multilevel) regression: “study” as a random intercept
- Two-stage: first, estimate effect size (ES) for each study
  - multivariate meta-regression

*… Let’s begin with Therapeutic NMA*

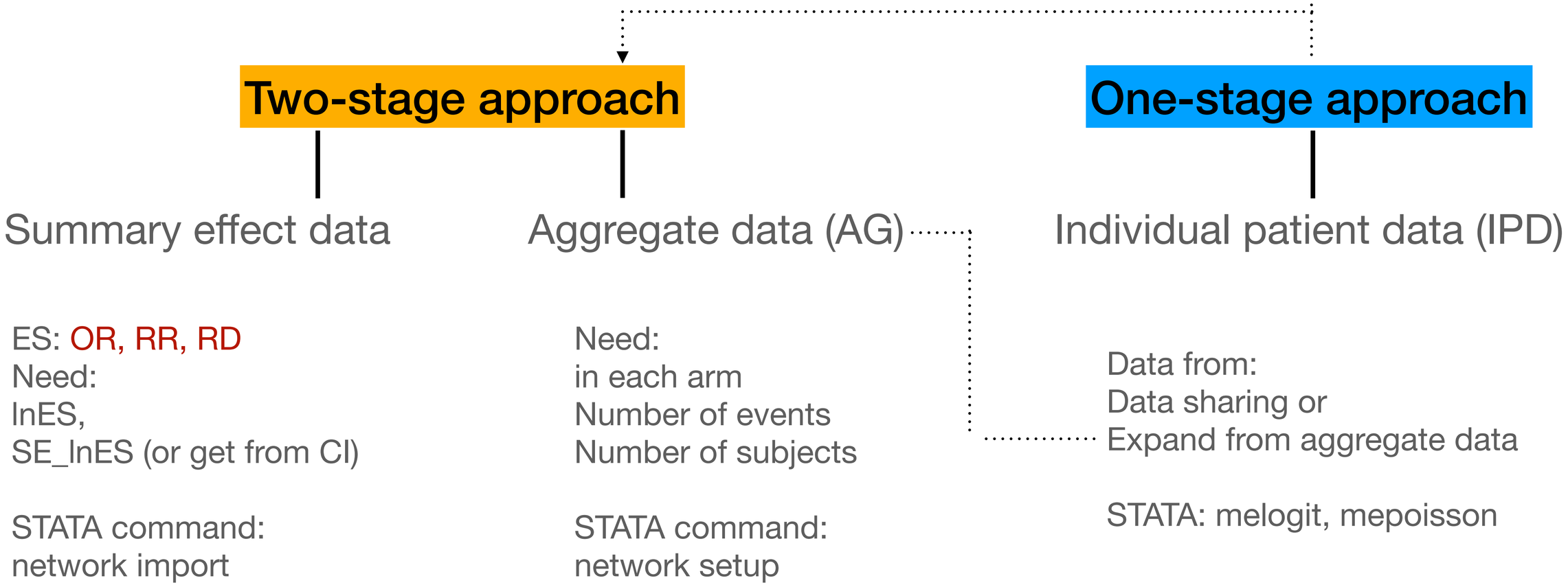
# What kind of data do you have?

- Summary effect
- Aggregate data (AG)
- Individual patient data (IPD)



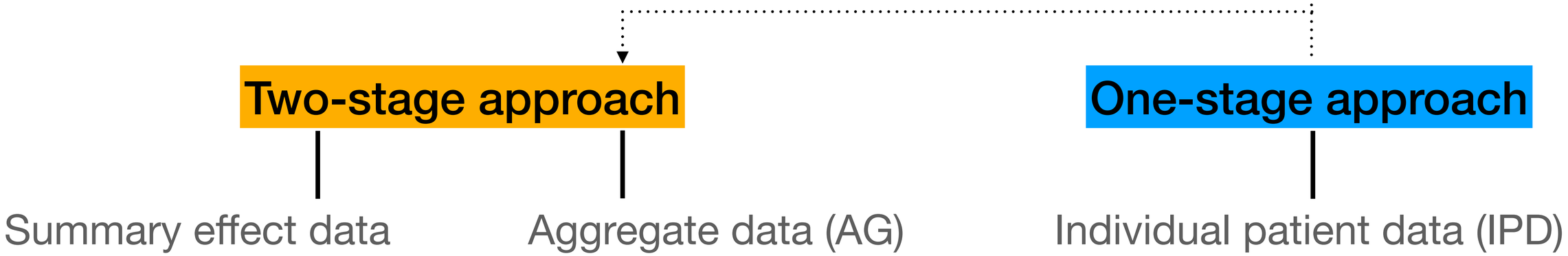
# Therapeutic NMA

## Binary outcome



# Therapeutic NMA

## Time-to-event outcome




ES: HR
Need:
lnES,
SE_lnES (or get from CI)

STATA command:
network import

Need:
in each arm
Number of events
Person-time

STATA command:
network setup

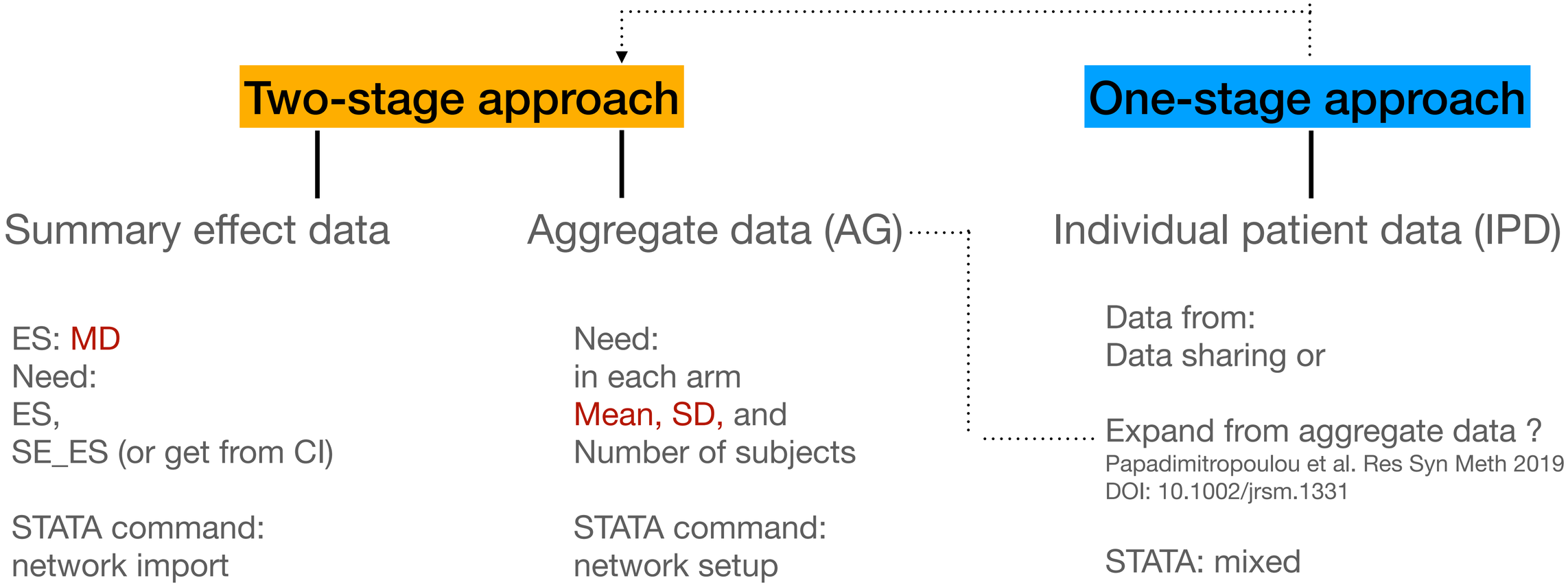
Data from:
Data sharing or

Extract from KM curve
(digitizer + “ipdfc” command)

STATA: mestreg

# Therapeutic NMA

## Continuous outcome



network setup eventvar nvar [if] [in], studyvar(varname) [or|rr|rd|hr zeroadd(#) common_options]

network setup meanvar sdvar nvar [if] [in], studyvar(varname) [md|smd sdpool(on|off) common_options]

| *common_options* | Description |
|---|---|
| **trtvar(***varname***)** | treatment identifier (implies data in long format) |
| **armvars(drop\|keep[(***varlist***)])** | how to handle arm-level variables (only when the data are in long format) |
| **trtlist(***string***)** | list of treatment names to use; default is to use all treatments found in alphabetical order |
| **alpha** | force treatments to be coded in alphabetical order; default except with data in long format when **trtvar()** is numeric with value labels |
| **numcodes** | code treatments as numbers 1, 2, 3, ... or 01, 02, 03, ...; default is to code treatments as letters A, B, C, ... |
| **nocodes** | use current treatment names as treatment codes |
| **format(augmented\|standard\|pairs)** | specify format required |
| **genprefix(***string***)** | prefix to use before default variable names; default is **genprefix(_)** |
| **gensuffix(***string***)** | suffix to use after default variable names; default is no suffix |
| **ref(***trtname***)** | name of reference treatment |
| **augment(#)** | number of individuals to use to augment missing reference treatment arms; default is **augment(0.001)** |
| **augmean(#)** | mean outcome to use to augment missing reference treatment arms |
| **augsd(#)** | standard deviation to use to augment missing reference treatment arms (only for quantitative data) |
| **augoverall** | change default behavior for **augmean()** and **augsd()** to use the overall mean and standard deviation across all studies |

wide format

| A | B | C | D | E | F | G | H | I | J | K | L | M |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ID | author | year | compare | total1 | perstime1 | event1 | total2 | perstime2 | event2 | total3 | perstime3 | event3 |
| 1 | aaa | 2015 | 12 | xx | xx | xx | xx | xx | xx | | | |
| 2 | bbb | 2016 | 12 | xx | | xx | xx | | xx | | | |
| 3 | ccc | 2016 | 12 | xx | | xx | xx | | xx | | | |
| 4 | ddd | 2017 | 12 | xx | | xx | xx | | xx | | | |
| 5 | eee | 2016 | 13 | xx | xx | xx | | | | xx | xx | xx |
| 6 | fff | 2017 | 13 | xx | xx | xx | | | | xx | xx | xx |
| 7 | ggg | 2020 | 13 | xx | | xx | | | | xx | | xx |
| 8 | hhh | 2019 | 23 | | | | xx | xx | xx | xx | xx | xx |
| 9 | iii | 2020 | 23 | | | | xx | | xx | xx | | xx |
| 10 | jjj | 2020 | 23 | | | | xx | | xx | xx | | xx |

long format

| ID | author | year | med | total | perstime | event |
|---|---|---|---|---|---|---|
| 1 | aaa | 2015 | 1 | xx | xx | xx |
| 1 | aaa | 2015 | 2 | xx | xx | xx |
| 2 | bbb | 2016 | 1 | xx | | xx |
| 2 | bbb | 2016 | 2 | xx | | xx |
| 3 | ccc | 2016 | 1 | xx | | xx |
| 3 | ccc | 2016 | 2 | xx | | xx |
| 4 | ddd | 2017 | 1 | xx | | xx |
| 4 | ddd | 2017 | 2 | xx | | xx |
| 5 | eee | 2016 | 1 | xx | xx | xx |
| 5 | eee | 2016 | 3 | xx | xx | xx |
| 6 | fff | 2017 | 1 | xx | xx | xx |
| 6 | fff | 2017 | 3 | xx | xx | xx |
| 7 | ggg | 2020 | 1 | xx | | xx |
| 7 | ggg | 2020 | 3 | xx | | xx |
| 8 | hhh | 2019 | 2 | xx | xx | xx |
| 8 | hhh | 2019 | 3 | xx | xx | xx |
| 9 | iii | 2020 | 2 | xx | | xx |
| 9 | iii | 2020 | 3 | xx | | xx |
| 10 | jjj | 2020 | 2 | xx | | xx |
| 10 | jjj | 2020 | 3 | xx | | xx |

| A | B | C | D | E | F | G | H | I | J |
|---|---|---|---|---|---|---|---|---|---|
| ID | author | year | compare | treat1 | treat2 | hr | se_hr | rr | se_rr |
| 1 | aaa | 2015 | 12 | 1 | 2 | xx | xx | xx | xx |
| 2 | bbb | 2016 | 12 | 1 | 2 | xx | xx | xx | xx |
| 3 | ccc | 2016 | 12 | 1 | 2 | xx | xx | xx | xx |
| 4 | ddd | 2017 | 12 | 1 | 2 | xx | xx | xx | xx |
| 5 | eee | 2016 | 13 | 1 | 3 | xx | xx | xx | xx |
| 6 | fff | 2017 | 13 | 1 | 3 | xx | xx | xx | xx |
| 7 | ggg | 2020 | 13 | 1 | 3 | xx | xx | | |
| 8 | hhh | 2019 | 23 | 2 | 3 | xx | xx | xx | xx |
| 9 | iii | 2020 | 23 | 2 | 3 | xx | xx | | |
| 10 | jjj | 2020 | 23 | 2 | 3 | xx | xx | | |

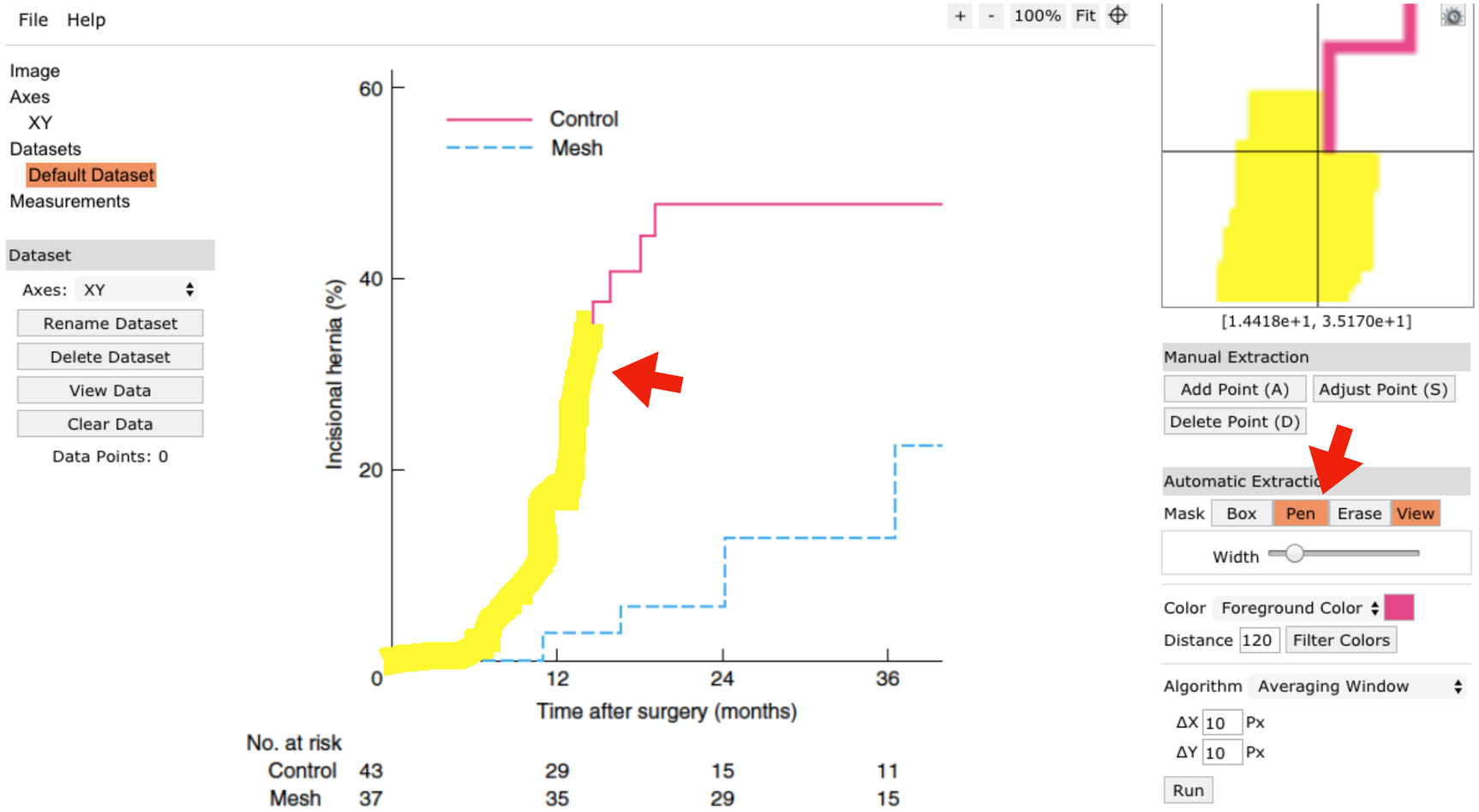
network import [if] [in] , studyvar(varname) treat(trtvar1 trtvar2) effect(effectstub) stderr(varname) [options]

# Benefits of One-stage approach

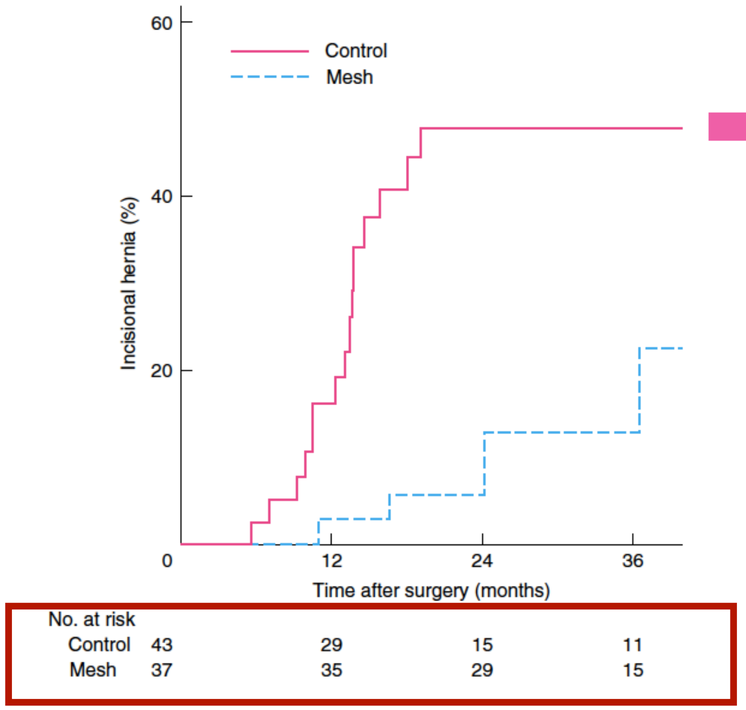
(Real IPD)

- increase precision of estimated treatment effect
- improve network consistency
- could adjust for participant-level effect modifier
- could adopt more advanced model for dealing with missing data

# Extract data from KM curve



# Extract data from KM curve



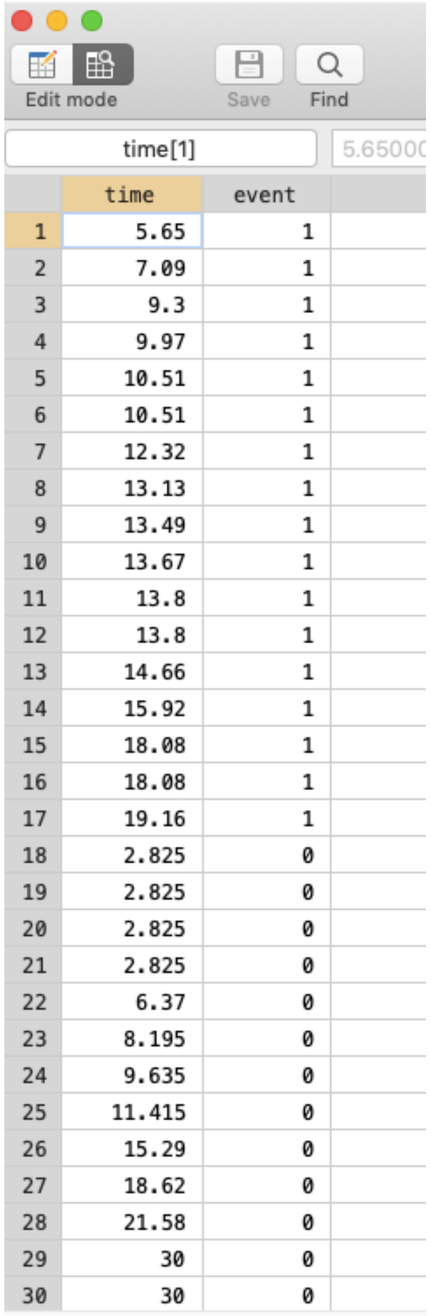

**Risk table**

**CURVE** **RISK TABLE**

| | A | B | C | D |
|---|---|---|---|---|
| 1 | ts0 | f0 | trisk0 | nrisk0 |
| 2 | 0 | 0 | 0 | 43 |
| 3 | 5.65 | 2.53 | 12 | 29 |
| 4 | 7.09 | 5.13 | 24 | 15 |
| 5 | 9.3 | 7.73 | 36 | 11 |
| 6 | 9.97 | 10.71 | | |
| 7 | 10.51 | 16.17 | | |
| 8 | 12.32 | 19.16 | | |
| 9 | 13.13 | 22.14 | | |
| 10 | 13.49 | 26.17 | | |
| 11 | 13.67 | 29.16 | | |
| 12 | 13.8 | 34.09 | | |
| 13 | 14.66 | 37.6 | | |
| 14 | 15.92 | 40.71 | | |
| 15 | 18.08 | 44.48 | | |
| 16 | 19.16 | 47.73 | | |
| 17 | 24 | 47.73 | | |
| 18 | 36 | 47.73 | | |

**<< may have to fill manually**

fill until 36 like trisk




| | time | event |
|---|---|---|
| 1 | 5.65 | 1 |
| 2 | 7.09 | 1 |
| 3 | 9.3 | 1 |
| 4 | 9.97 | 1 |
| 5 | 10.51 | 1 |
| 6 | 10.51 | 1 |
| 7 | 12.32 | 1 |
| 8 | 13.13 | 1 |
| 9 | 13.49 | 1 |
| 10 | 13.67 | 1 |
| 11 | 13.8 | 1 |
| 12 | 13.8 | 1 |
| 13 | 14.66 | 1 |
| 14 | 15.92 | 1 |
| 15 | 18.08 | 1 |
| 16 | 18.08 | 1 |
| 17 | 19.16 | 1 |
| 18 | 2.825 | 0 |
| 19 | 2.825 | 0 |
| 20 | 2.825 | 0 |
| 21 | 2.825 | 0 |
| 22 | 6.37 | 0 |
| 23 | 8.195 | 0 |
| 24 | 9.635 | 0 |
| 25 | 11.415 | 0 |
| 26 | 15.29 | 0 |
| 27 | 18.62 | 0 |
| 28 | 21.58 | 0 |
| 29 | 30 | 0 |
| 30 | 30 | 0 |

**failure curve**
**(default = survival curve)**

**prob**
**if y axis = probability**
**(default = percentage)**

- ipdfc, surv(f0) failure tstart(ts0) trisk(trisk0) nrisk(nrisk0) tot(#event)

  isotonic gen(time event) saving(filename, replace)

**New var**

**New file**

**f0, ts0 from digitizer**
**trisk0, nrisk0 from risk table under KM**

# Zero event

- Single-arm zero-event
  - Peto or Mantel-Haenszel method are recommended
- Double-arm zero-event
  - usually excluded in many software
  - excluding studies with no events in both arms can result in about 10% of the meta- analyses change the statistical significance

# Zero event

**Type 1. MA-SZ**
Zero-events only occur in single arm and no double-arm-zero-events studies exist; the total event count in each arm is non-zero

**Type 2. MA-MZ**
Both single-arm-zero-events studies and double-arm-zero-events studies were included; the total event count in each arm is non-zero

**Type 3. MA-DZ**
Only double-arm-zero-events studies were included, without single-arm-zero studies; the total event count in each arm is non-zero


**Type 4. MA-CSZ**
Zero-events only occur in a single arm and no double-arm-zero-events studies exist, but the total event count in one arm is zero

**Type 5. MA-CMZ**
Both single-arm-zero-events studies and double-arm-zero-events studies were included, but the total event count one arm is zero

**Type 6. MA-CDZ**
All included studies were double-arm-zero-events studies and the total event counts in both arms are zero

1

**Single-arm-zero–events (MA-SZ)**

| *Study* | *r1* | *n1* | *r2* | *n2* |
|---|---|---|---|---|
| 1 | 1 | 50 | 0 | 50 |
| 2 | 0 | 50 | 1 | 50 |
| ⋮ | ⋮ | ⋮ | ⋮ | ⋮ |
| *k* | 1 | 50 | 0 | 50 |

2

**Mixed zero-events (MA-MZ)**

| *Study* | *r1* | *n1* | *r2* | *n2* |
|---|---|---|---|---|
| 1 | 1 | 50 | 0 | 50 |
| 2 | 0 | 50 | 0 | 50 |
| ⋮ | ⋮ | ⋮ | ⋮ | ⋮ |
| *k* | 1 | 50 | 1 | 50 |

3

**Double-arm-zero–events (MA-DZ)**

| *Study* | *r1* | *n1* | *r2* | *n2* |
|---|---|---|---|---|
| 1 | 0 | 50 | 0 | 50 |
| 2 | 1 | 50 | 1 | 50 |
| ⋮ | ⋮ | ⋮ | ⋮ | ⋮ |
| *k* | 1 | 50 | 1 | 50 |

4

**Completely single-arm-zero–events (MA-CSZ)**

| *Study* | *r1* | *n1* | *r2* | *n2* |
|---|---|---|---|---|
| 1 | 1 | 50 | 0 | 50 |
| 2 | 1 | 50 | 0 | 50 |
| ⋮ | ⋮ | ⋮ | ⋮ | ⋮ |
| *k* | 1 | 50 | 0 | 50 |

5

**Completely mixed zero-events (MA-CMZ)**

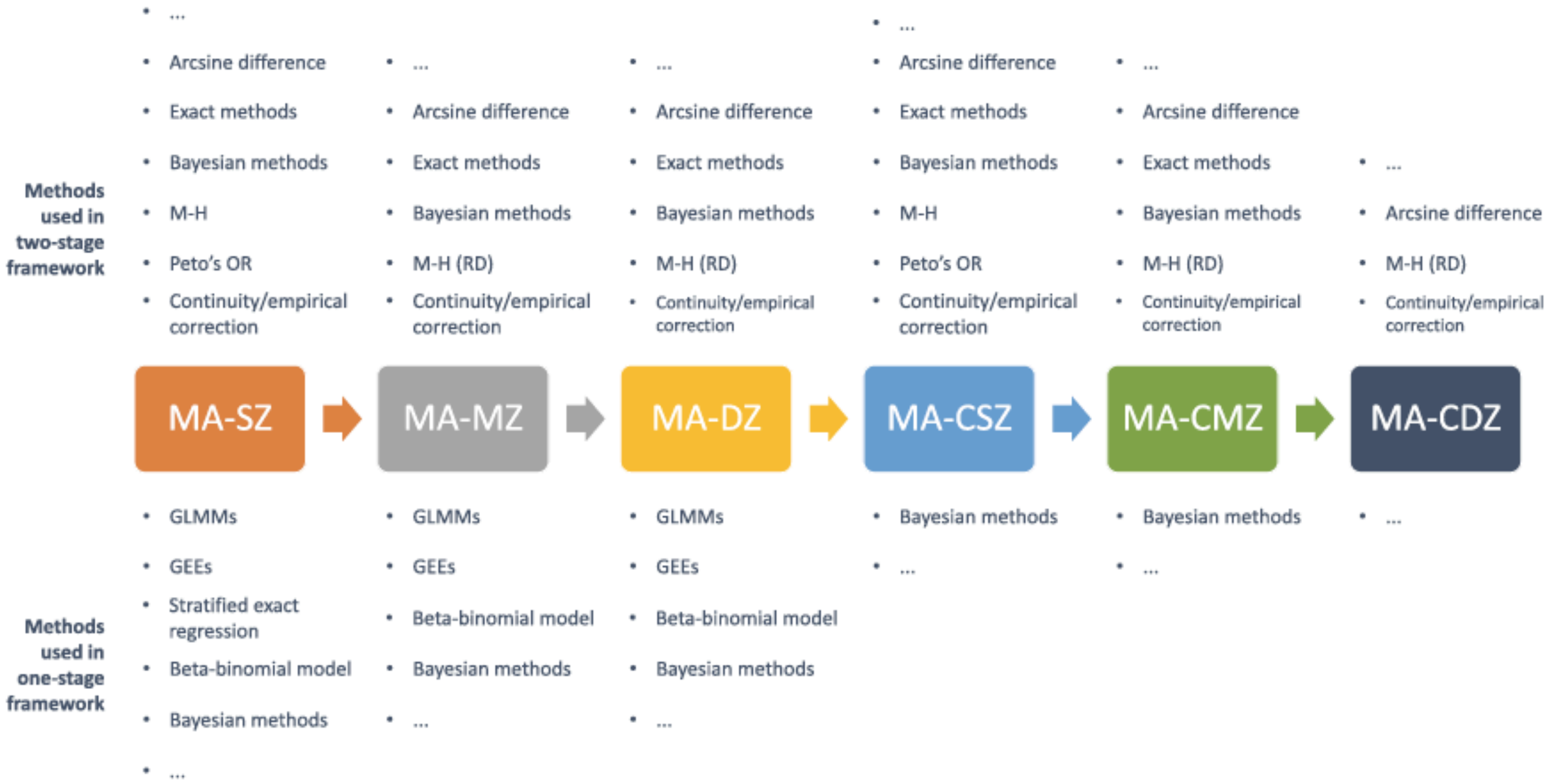
| *Study* | *r1* | *n1* | *r2* | *n2* |
|---|---|---|---|---|
| 1 | 1 | 50 | 0 | 50 |
| 2 | 0 | 50 | 0 | 50 |
| ⋮ | ⋮ | ⋮ | ⋮ | ⋮ |
| *k* | 1 | 50 | 0 | 50 |

6

**Completely double-arm-zero-events (MA-CDZ)**

| *Study* | *r1* | *n1* | *r2* | *n2* |
|---|---|---|---|---|
| 1 | 0 | 50 | 0 | 50 |
| 2 | 0 | 50 | 0 | 50 |
| ⋮ | ⋮ | ⋮ | ⋮ | ⋮ |
| *k* | 0 | 50 | 0 | 50 |

# Zero event


Methods used in two-stage framework
...
Arcsine difference
Exact methods
Bayesian methods
M-H
Peto's OR
Continuity/empirical correction
...
Arcsine difference
Exact methods
Bayesian methods
M-H (RD)
Continuity/empirical correction
...
Arcsine difference
Exact methods
Bayesian methods
M-H (RD)
Continuity/empirical correction
...
Arcsine difference
Exact methods
Bayesian methods
M-H
Peto's OR
Continuity/empirical correction
...
Arcsine difference
Exact methods
Bayesian methods
M-H (RD)
Continuity/empirical correction
...
Arcsine difference
M-H (RD)
Continuity/empirical correction
MA-SZ
MA-MZ
MA-DZ
MA-CSZ
MA-CMZ
MA-CDZ
Methods used in one-stage framework
GLMMs
GEEs
Stratified exact regression
Beta-binomial model
Bayesian methods
...
GLMMs
GEEs
Beta-binomial model
Bayesian methods
...
GLMMs
GEEs
Beta-binomial model
Bayesian methods
...
Bayesian methods
...
Bayesian methods
...
...

# Zero event

**Box 1.** Five steps for meta-analysis with zero-events studies.

| | |
|---|---|
| 1. | Check for zero-events studies; |
| 2. | Check the framework of the classification to identify the meta-analysis belongs to which of MA-SZ, MA-MZ, MA-DZ, MA-CSZ, MA-CMZ, and MA-CDZ; |
| 3. | Check all available methods that could be used under the classification in the flow diagram; |
| 4. | Conduct the meta-analysis by using one or more appropriate methods; |
| 5. | Conduct sensitivity analysis using other available methods to test whether the results are robust. |

# Combining of RCTs and Observational studies

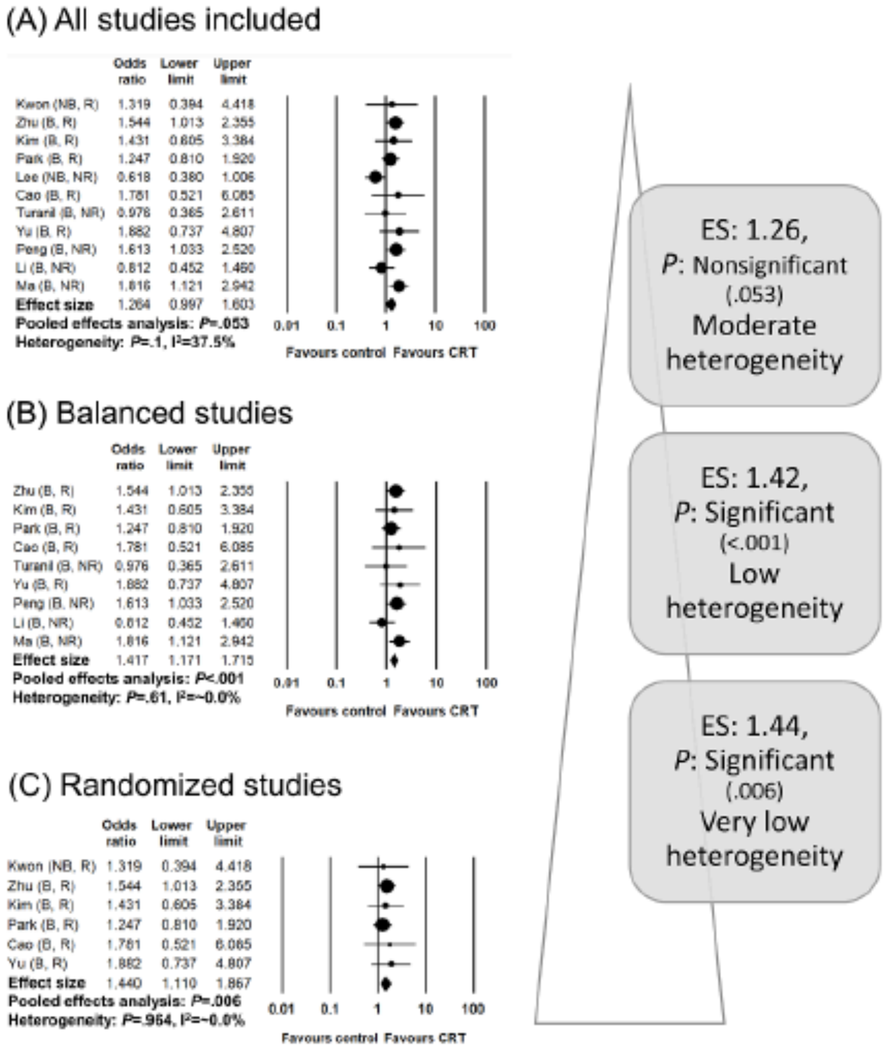
## Why?

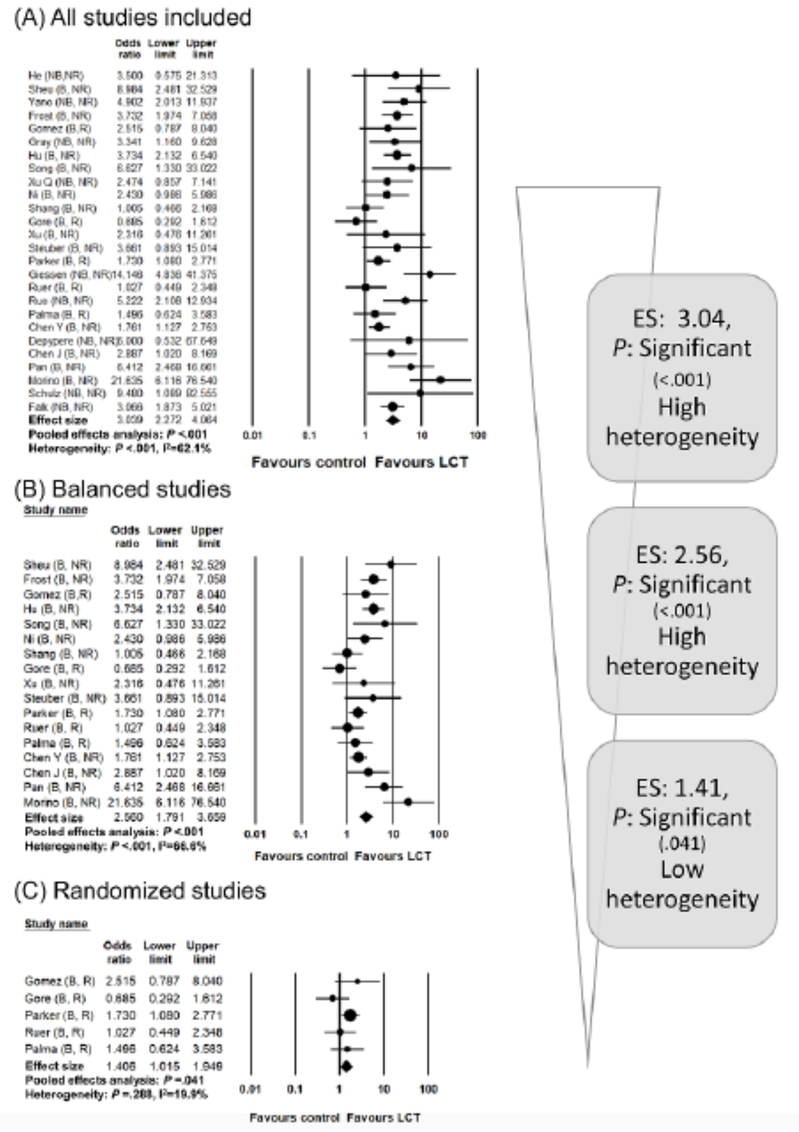
- small number of RCTs
- small number of participants in RCTs

- Naïve pooling
- Sensitivity analysis

# Combining of RCTs and Observational studies

## Stepwise-Hierarchical Pooled Analysis



# Combining of RCTs and Observational studies

## Stepwise-Hierarchical Pooled Analysis

| Pattern type | Results | All studies included | [a]Balanced studies | [b]Randomized studies | Hypothesis | Confounder in OBS | Effect size of OBS | Further interpretation |
|---|---|---|---|---|---|---|---|---|
| Ascending patterns | Effect size |  | | | Strongly true | Possibly | May be smaller than the true effect | OBS may be affected by confounders negative to the hypothesis. |
| | Significance | Non-significant | | Significant | | | | |
| | Effect size |  | | | Strongly true | Less likely | | |
| | Significance | Significant | | Significant | | | | |
| Descending patterns | Effect size |  | | | Not true | Very likely | Less reliable | OBS may be affected by researchers' bias, or confounders positive to hypothesis. |
| | Significance | Significant | | Non-significant | | | | |
| | Effect size |  | | | True | Possibly | May be larger than the true effect | |
| | Significance | Significant | | Significant | | | | |

[a]Designed to reasonably control for possible confounders, including randomized studies.

[b]Studies with a flawed design or too few subjects might be downgraded.

# Combining of RCTs and Observational studies

## in NMA

- design-adjusted synthesis
- using non-randomized evidence as prior information
- three-level hierarchical model

Efthimiou et al. 2017 DOI: 10.1002/sim.7223

# Health Economic study

## Data that can be pooled

- NMB (or INB)

$$\mathrm{ICER} < K$$

$$\frac{(\hat{\mu}_{C1} - \hat{\mu}_{C2})}{(\hat{\mu}_{E1} - \hat{\mu}_{E2})} < K$$

$$K(\hat{\mu}_{E1} - \hat{\mu}_{E2}) - (\hat{\mu}_{C1} - \hat{\mu}_{C2}) > 0$$

$$\mathrm{INB} = K(\hat{\mu}_{E1} - \hat{\mu}_{E2}) - (\hat{\mu}_{C1} - \hat{\mu}_{C2}) > 0$$

$$\begin{aligned}\mathrm{Var}(\mathrm{INB}) &= \mathrm{Var}\left[K(\hat{\mu}_{E1} - \hat{\mu}_{E2}) - (\hat{\mu}_{C1} - \hat{\mu}_{C2})\right] \\ &= K^2\mathrm{Var}((\hat{\mu}_{E1} - \hat{\mu}_{E2}) + \mathrm{Var}(\hat{\mu}_{C1} - \hat{\mu}_{C2}) - 2K\mathrm{Cov}\left[(\hat{\mu}_{E1} - \hat{\mu}_{E2})(\hat{\mu}_{C1} - \hat{\mu}_{C2})\right] \\ &= K^2\sigma^2_{\Delta E} + \sigma^2_{\Delta C} - 2K\rho_{CE}\sigma_{\Delta C}\sigma_{\Delta E}\end{aligned}$$

- Don’t use ICER

  e.g. ICER = -4000 may come from

  △cost = 40,000 & △QALY = -10 or △cost = -40,000 & △QALY = 10

# Health Economic study

## Scenario

*Scenario 1:* Studies that reported means along with the variance of all parameters; C and E for each treatment, ΔC, ΔE, ICER and also K. The INB and its variance were estimated by the following equation:

$$\text{INB} = \Delta E\ (\text{K} - \text{ICER})$$

$$\text{Var (INB)} \cong \text{K}^2\sigma^2_{\Delta E} + \sigma^2_{ICER}$$

Where $\sigma^2_{\Delta E}$ is the variance of $\Delta E$ and $\sigma^2_{ICER}$ is the variance of ICER.

*Scenario 2:* Studies that reported only 95%CI of C or ΔC, E or ΔE, and ICER. The SE of ICER was estimated by following formula:

$$UL = \mu + 1.96\ SE$$

$$SE = \frac{UL - \mu}{1.96}$$

The INB and its variance were estimated as following equation.

$$\text{INB} = \Delta E\ (\text{K} - \text{ICER})$$

$$\text{Var (INB)} \cong \text{K}^2\sigma^2_{\Delta E} + \sigma^2_{ICER}$$

Chaiyakittisopon et al. DOI: 10.1007/s10198-021-01275-3 (appendix)

# Health Economic study

## Scenario

*Scenario 3:* Studies that reported mean and 95% CI for C or ΔC, E or ΔE, but did not report the ICER and its variance. The data of ΔC and ΔE were simulated by a Monte Carlo- simulation with 1000 simulations using gamma distribution for ΔC and normal distribution for ΔE. The ICER and covariance between ΔC and ΔE ($\rho_{CE}\sigma_{\Delta C}\sigma_{\Delta E}$) was estimated. As a result, the INB and its variance were estimated by the following equations.

$$\mathrm{INB} = \mathrm{K}(\Delta E) - \Delta C$$

$$\mathrm{Var}\,(\mathrm{INB}) = \mathrm{K}^2\sigma_{\Delta E}^2 + \sigma_{\Delta C}^2 - 2\mathrm{K}(\rho_{CE}\sigma_{\Delta C}\sigma_{\Delta E})$$

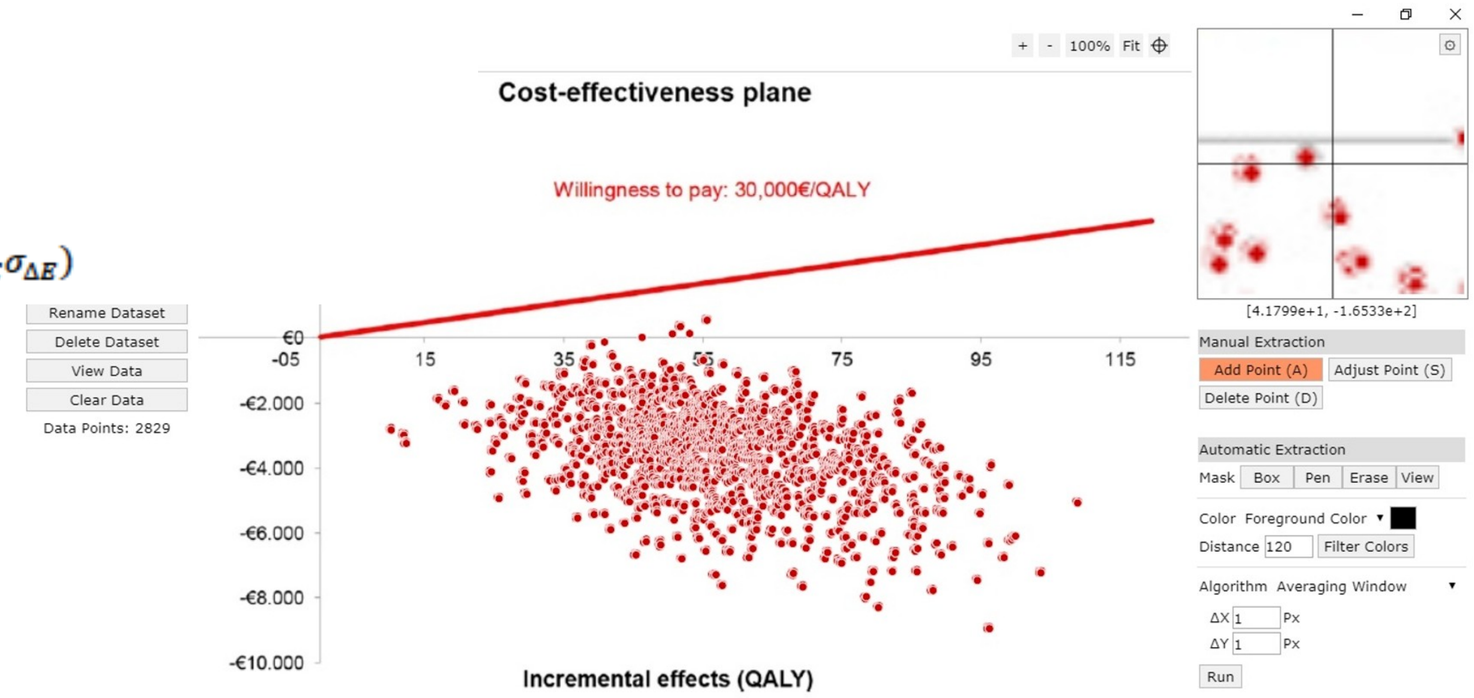
# Health Economic study

## Scenario

*Scenario 4:* Studies that reported only the mean outcome without its dispersion, but provided a cost-effective plane graph for ΔC and ΔE. Data of ΔC and ΔE were extracted from the graph using Web-Plot Digitizer software version 4.2. Subsequently, means and SE of ΔC and ΔE as well as the covariance of ΔC and ΔE, were estimated. As a result, the INB and its variance were estimated by the following equations.

$$\mathrm{INB} = \mathrm{K}(\Delta E) - \Delta C$$

$$\mathrm{Var}\,(\mathrm{INB}) = \mathrm{K}^2\sigma_{\Delta E}^2 + \sigma_{\Delta C}^2 - 2\mathrm{K}(\rho_{CE}\sigma_{\Delta C}\sigma_{\Delta E})$$




Cr. Kamolpat

# Health Economic study

## Scenario

*Scenario 5:* Studies that reported only the mean outcome without its dispersion and also the cost-effective plane. Data for pooling were used from other similar studies; in terms of participant, intervention, comparator, level of income country, country or gross domestic product (GDP) per capita, model inputs (e.g., type of cost/effectiveness, type of model, discount rate, time horizon, etc.).

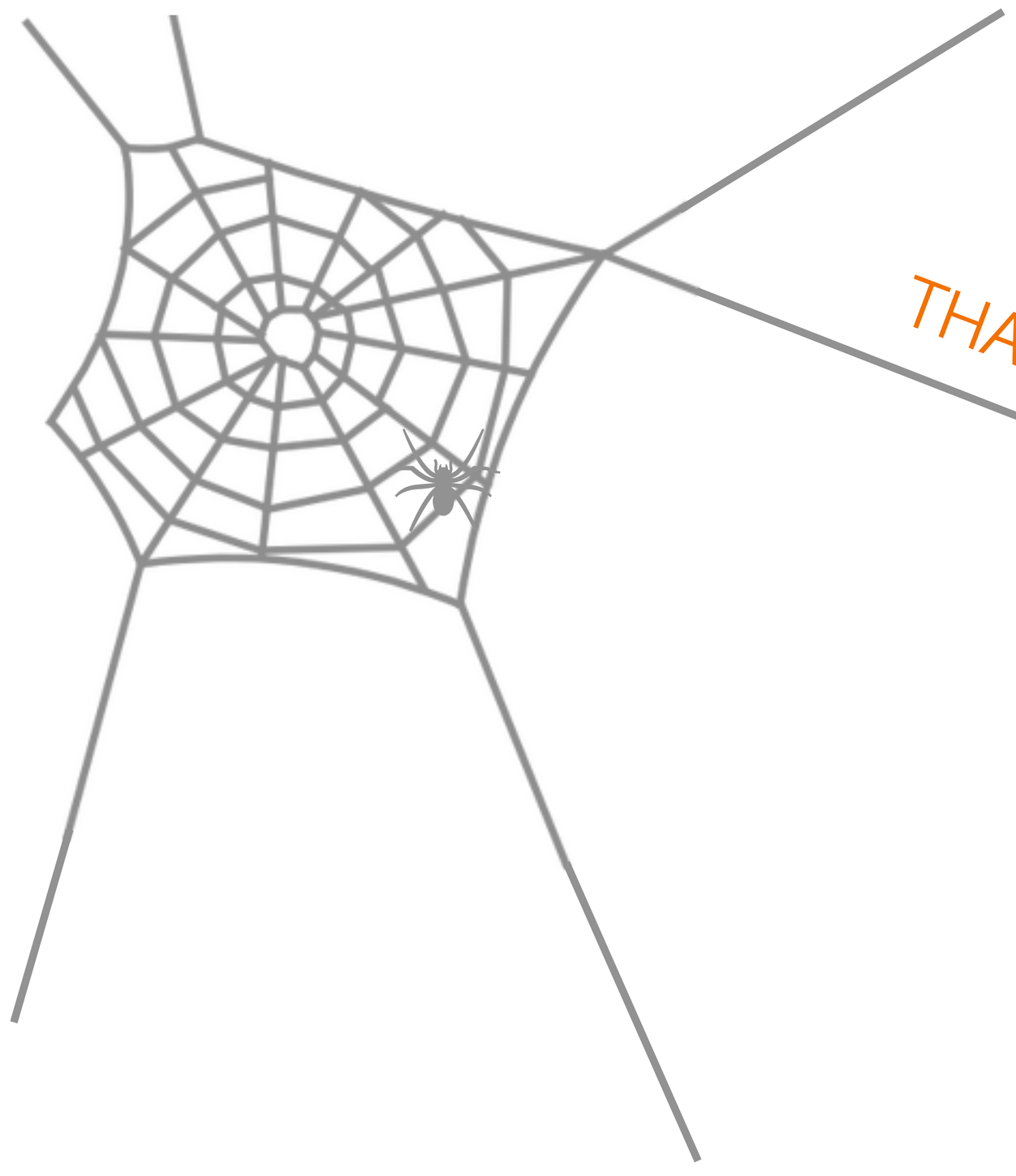
# Diagnostic test accuracy NMA

## Challenge

- most studies are single-test study (against reference standard – to verify outcome of the index test)
- In multiple-test studies, tests are performed
  - in the same individuals = within-participant comparison
    - unlikely to report the correlation
  - random participants to different tests = between-participant comparison
- Threshold difference
- Correlation of sensitivity & specificity (bivariate character)

# Diagnostic test accuracy NMA

- Trikalinos et al. 2014: Bayesian framework, Joint meta-analysis (DOI: 10.1002/jrsm.1115)
- Menten & Lesaffre 2015: Bayesian framework (DOI: 10.1186/s12874-015-0061-7)
- Dimou et al. 2016: Bivariate random-effect meta-analysis using log-transformed sensitivity & specificity (DOI: 10.1002/sim.6919)
- Hoyer & Kuss 2016: Quadrivariate generalized linear mixed model (DOI: 10.1177/0962280216661587)
- Nyaga et al. 2016:
  - ANOVA arm-based hierarchical model, 2-stage (DOI: 10.1177/0962280216669182)
  - Beta-binomial arm-based, 1-stage based on copula model (DOI: 10.1177/0962280216682532)
- Owen et al. 2018: Bayasian beta-binomial arm-based (DOI: 10.1016/j.jclinepi.2018.03.005)



THANK YOU

FOR YOUR ATTENTION