Estimation of Indirect and mixed Treatment Effect

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Acknowledgments for sharing a couple of slides: Jo McKenzie and Anna Chaimani

Medical decision making

Clinicians, policy makers and consumers of health care services

Blocked ears, earwax removal techniques:

- **Cerumol, Sodium bicarbonate, Olive oil, Dry and wet irrigation,TP, Self irrigation, Irrigation by nurse, Endoscopic and microscoping de-waxin**
- *Is any of the interventions effective?*
- *How much more effective they are compared to no intervention?*
- *Are some interventions more effective than other?*

Health Technology Assessment 2010; Vol. 14: No. 28

The safety and effectiveness of different methods of earwax removal: a systematic review and economic evaluation

AJ Clegg, E Loveman, E Gospodarevskaya,
P Harris, A Bird, J Bryant, DA Scott,
P Davidson, P Little and R Coppin

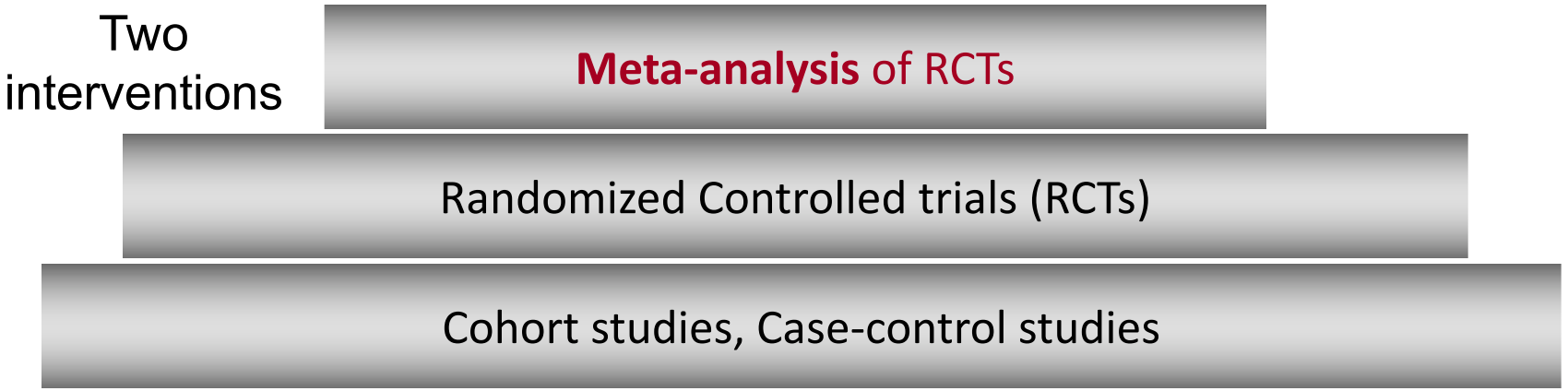
- Cerumol
- Sodium bicarbonate
- Olive oil
- Dry and wet irrigation
- TP
- Self irrigation
- Irrigation by nurse
- Endoscopic and microscoping de-waxing

ials conducted in
ndary care (8 studies)
s), met the inclusion
Ts and 4 CCTs. The
l 16 different softeners,
in various different
comes, timing of
thodological quality
easures of wax clearance
olive oil and water are
all more effective than no treatment; triethanolamine polypeptide (TP) is better than olive oil; wet irrigation is better than dry irrigation; sodium bicarbonate drops followed by irrigation by nurse is more effective than
is better than microscopic de-waxing. AEs appeared to be minor and of limited extent. Resuts of the

The results from many pairwise meta-analyses are not useful when you want to compare many treatments!

Evidence Based Medicine

- Backbone: **meta-analysis**
- Rigorous statistical models
- Clinical practice guidelines
  - NICE, WHO, The Cochrane Collaboration, HuGENet

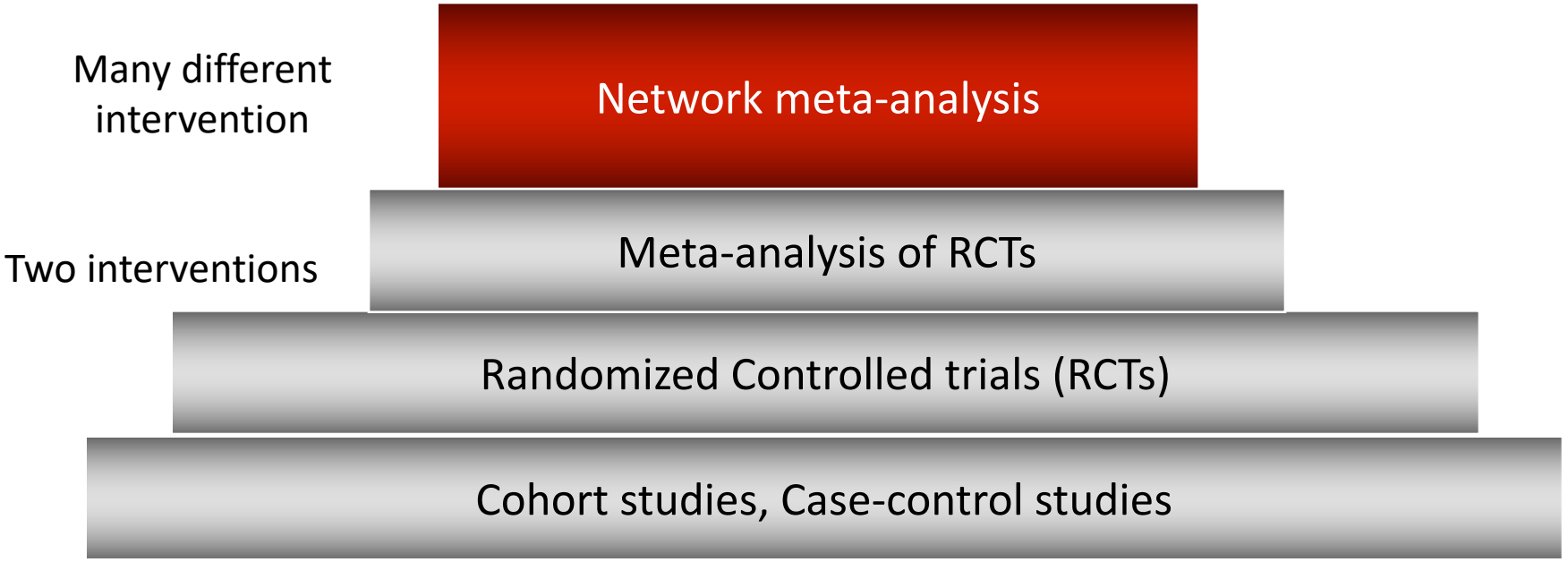


Levels of evidence For Therapy, Prevention, Aetiology and Harm

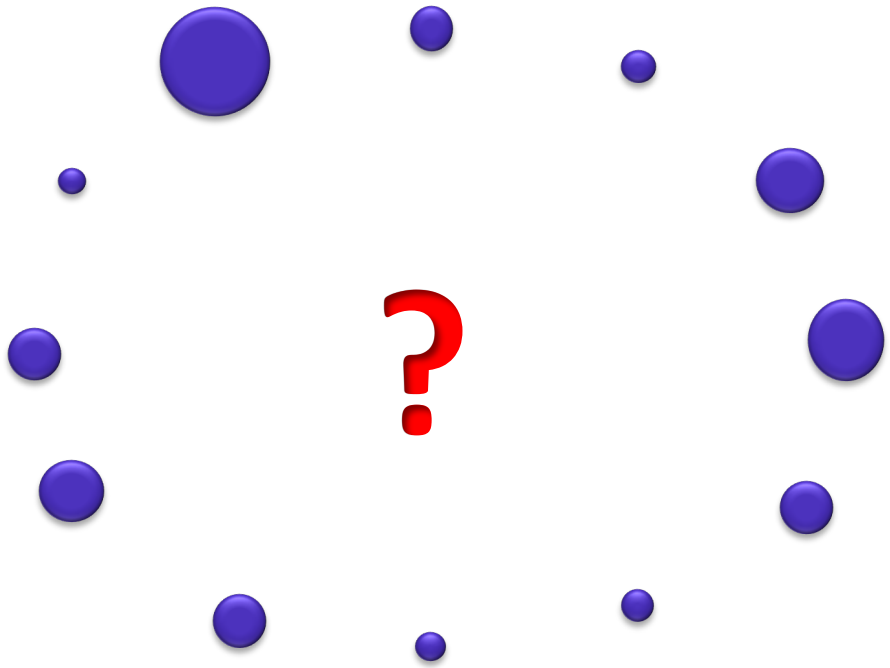
Centre for Evidence Based Medicine, University of Oxford

A new methodological framework

Other names: Multiple-treatments meta-analysis, Mixed-treatment comparison



Many treatments



Network meta-analysis:

"which are the most appropriate treatments to recommend, for which population and under which setting"

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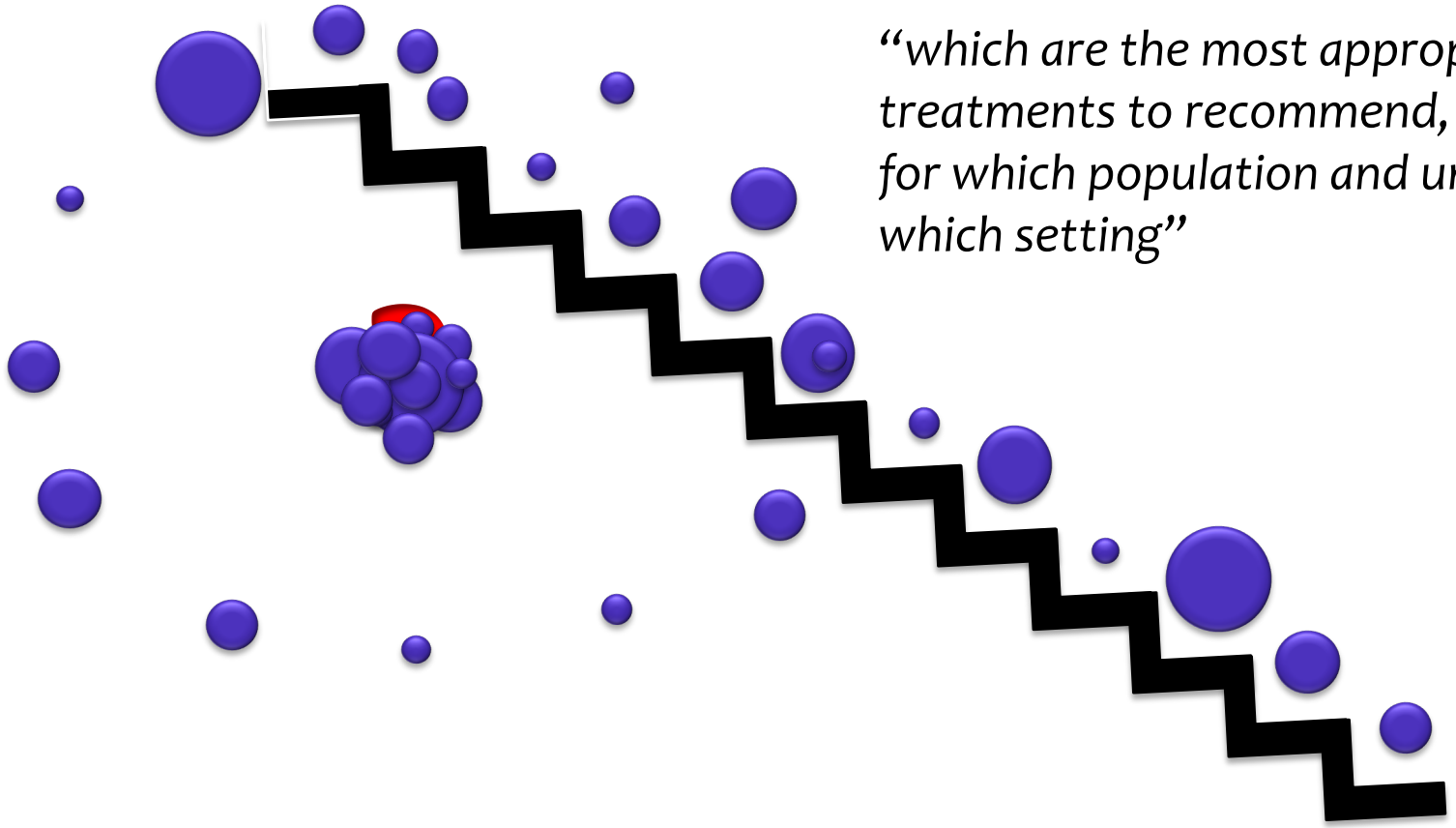

Many treatments

Network meta-analysis:

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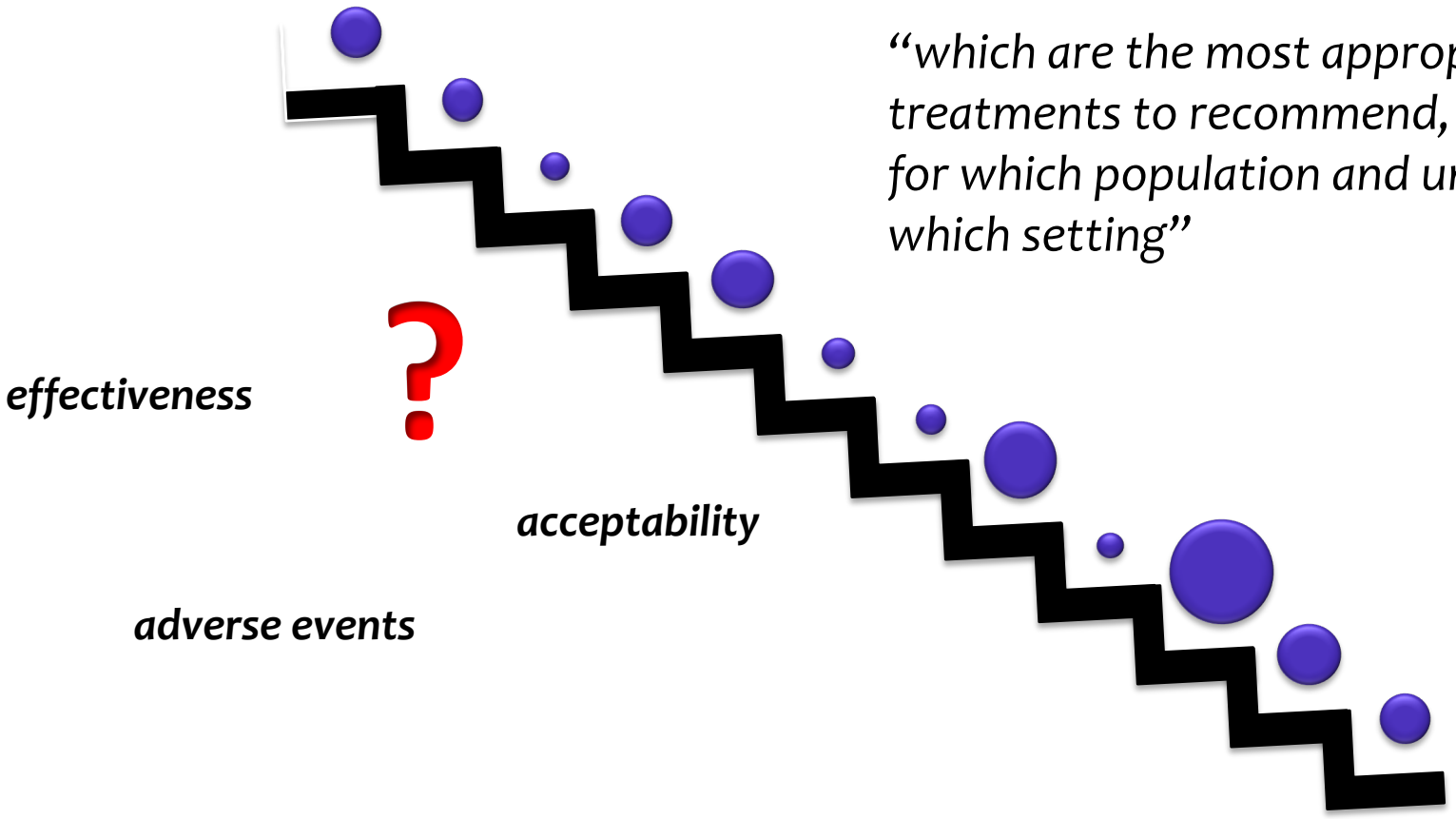

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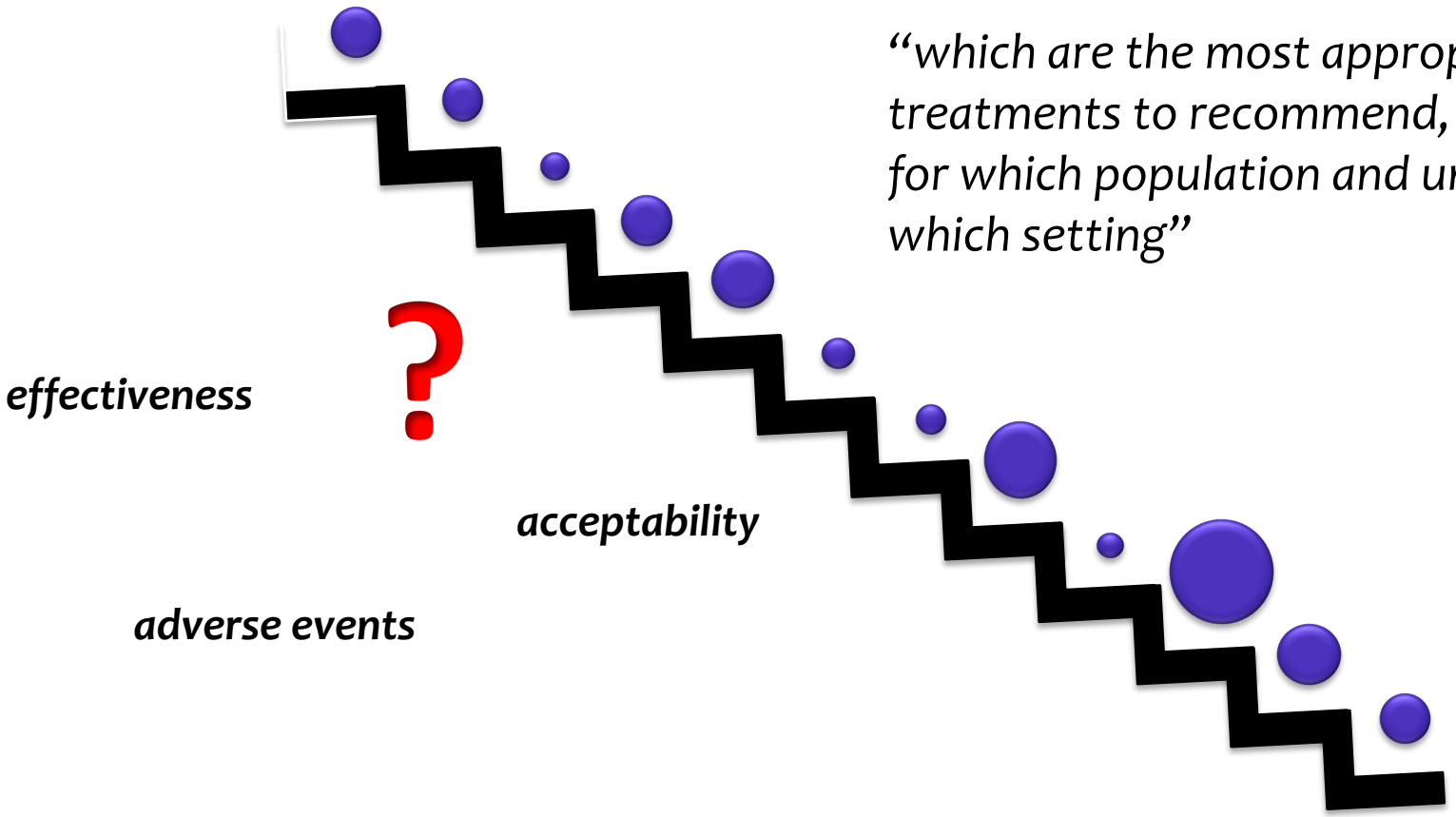
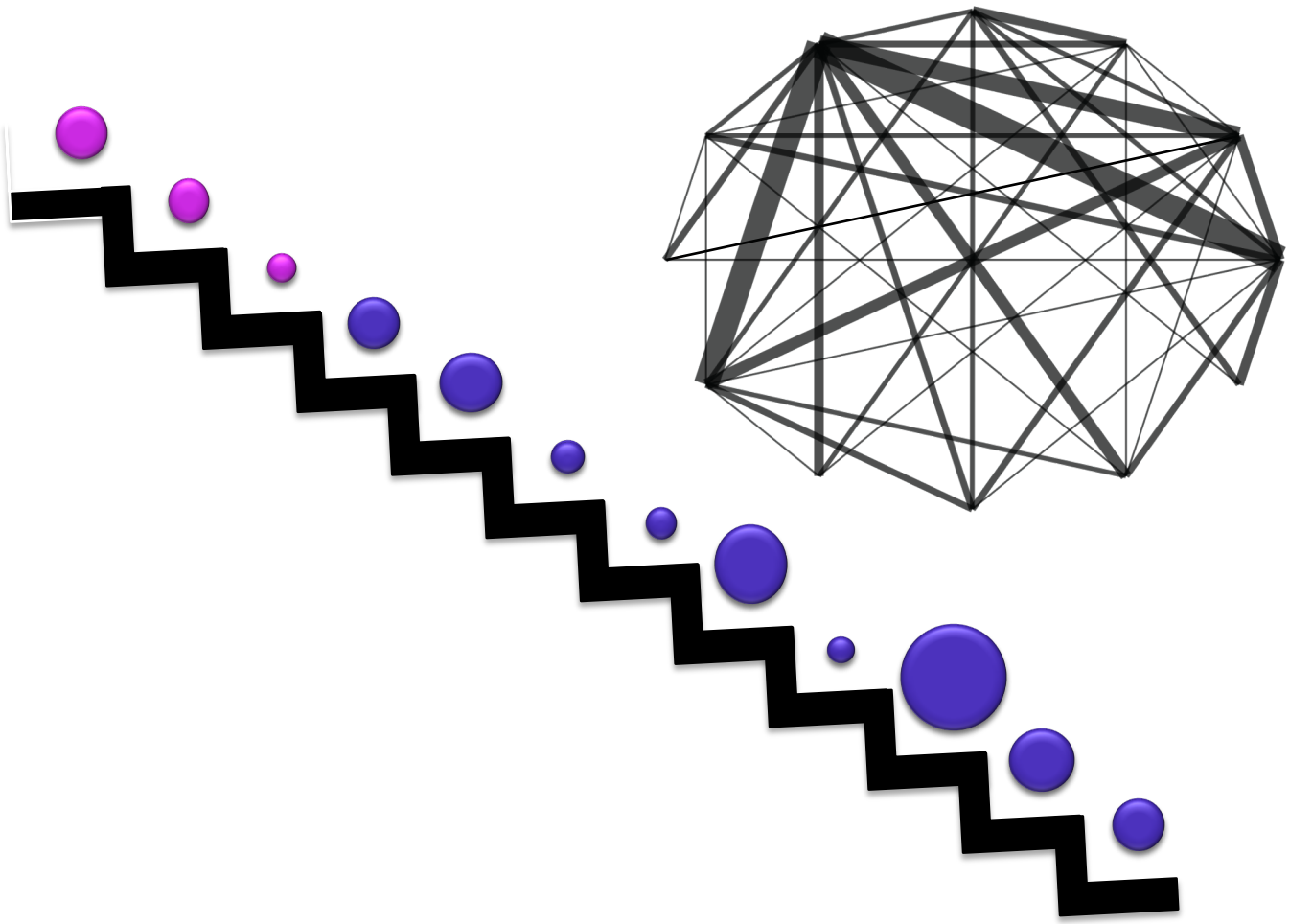


Many treatments



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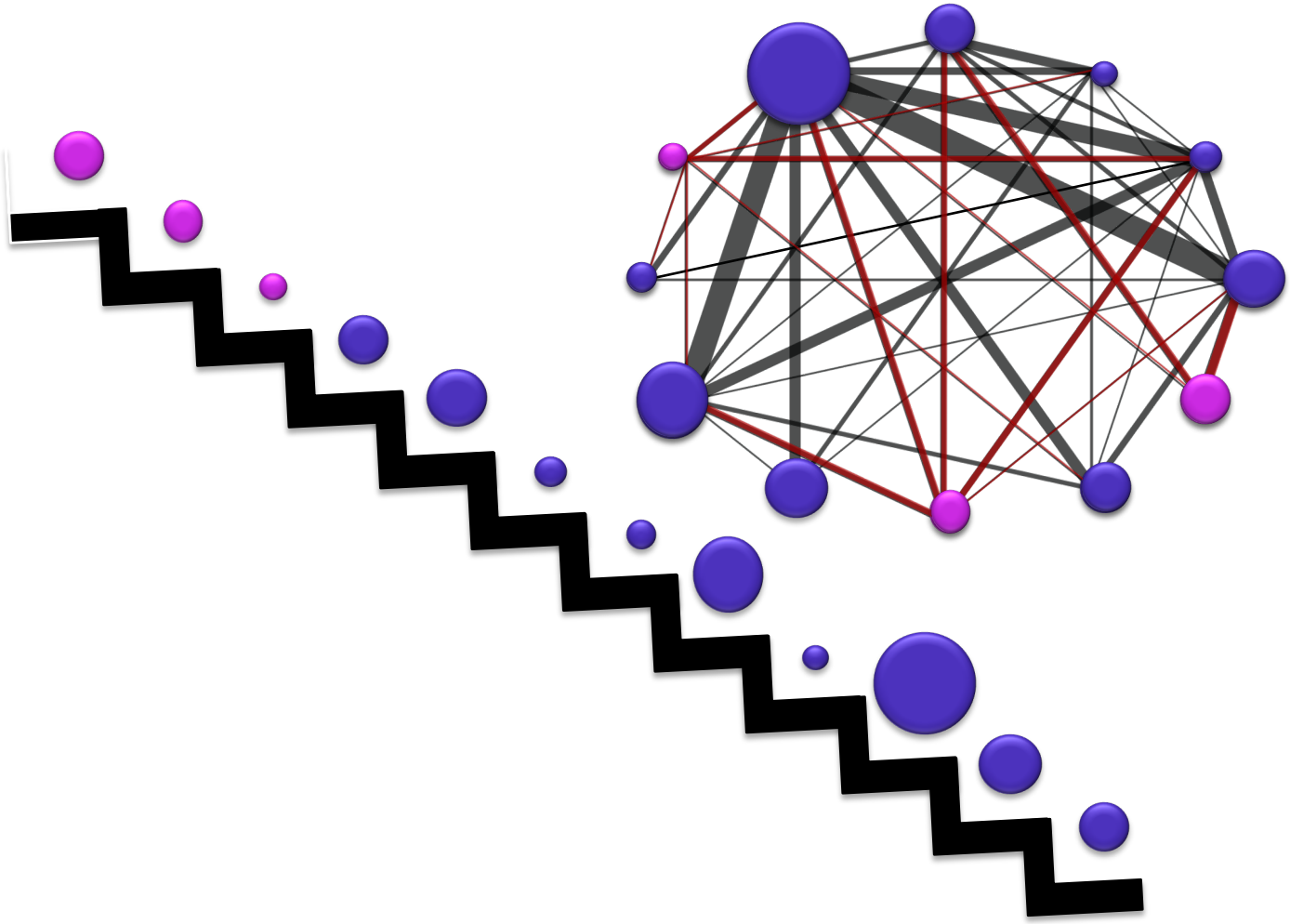
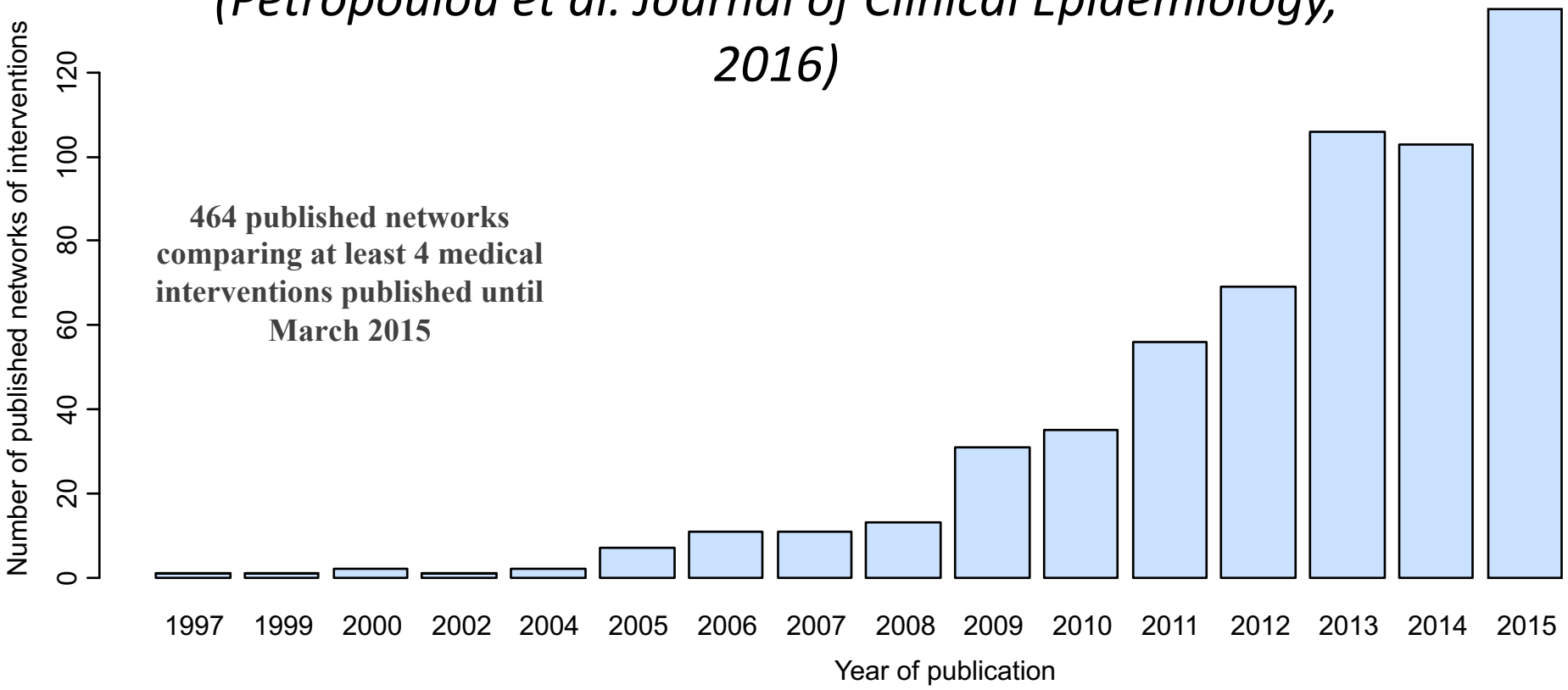


Network meta-analysis is…

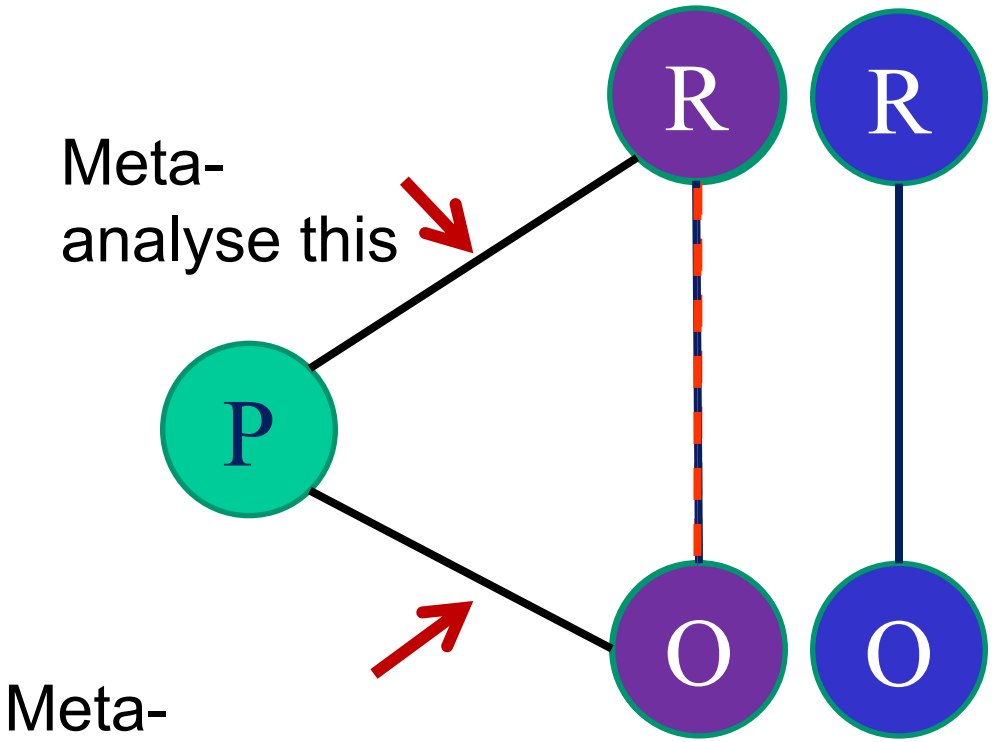
A statistical technique that synthesizes evidence about the relative efficacy or safety of many competing interventions and ranks the treatments according to their outcomes

Number of published systematic reviews that use network meta-analysis or indirect comparisons to synthesize the data

(Petropoulou et al. Journal of Clinical Epidemiology, 2016)



Indirect and mixed treatment effects



Meta-analyse this

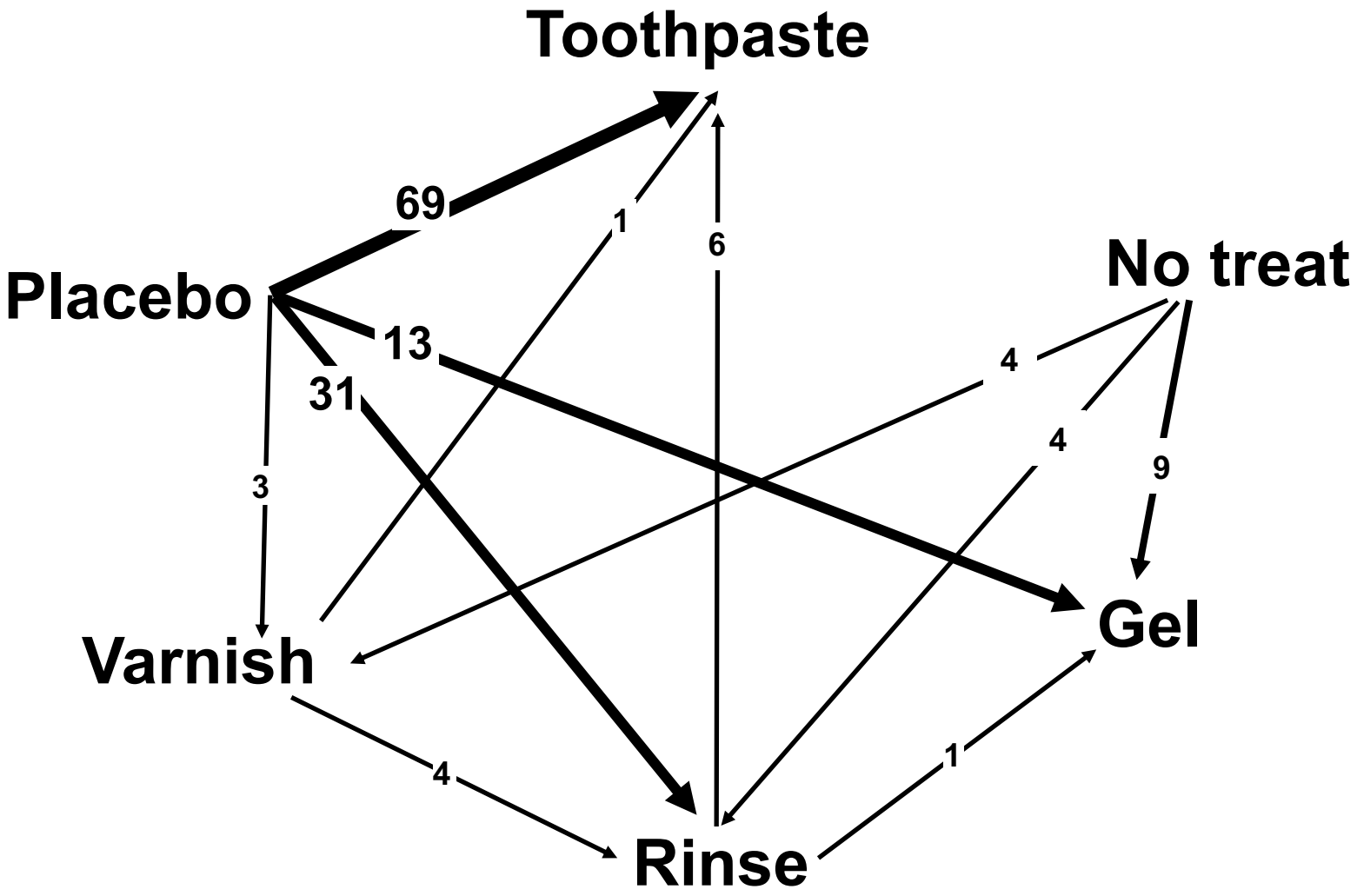
Meta-analyse this

Indirect treatment effect

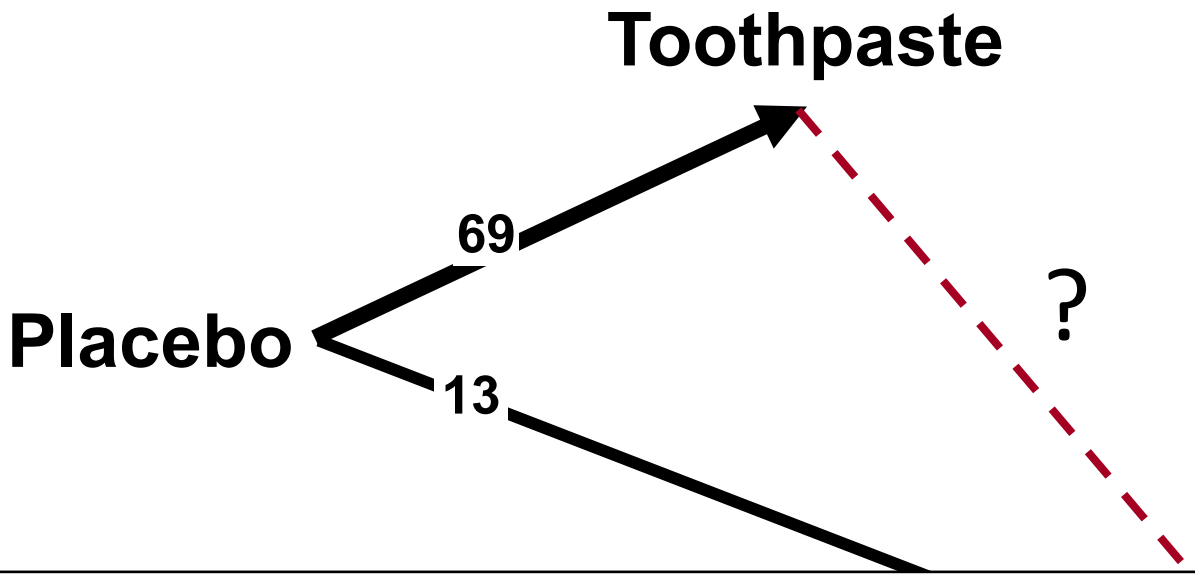
Direct treatment effect

Mixed treatment effect

Example: Treatments for the prevention of dental caries



Example: Toothpaste versus Gel



Variance $SMD_{PvsT} = ((high\ CI - low\ CI)/3.92)^2$

Variance $SMD_{PvsT} = ((-0.28 - (-0.41))/3.92)^2 = 0.0011$

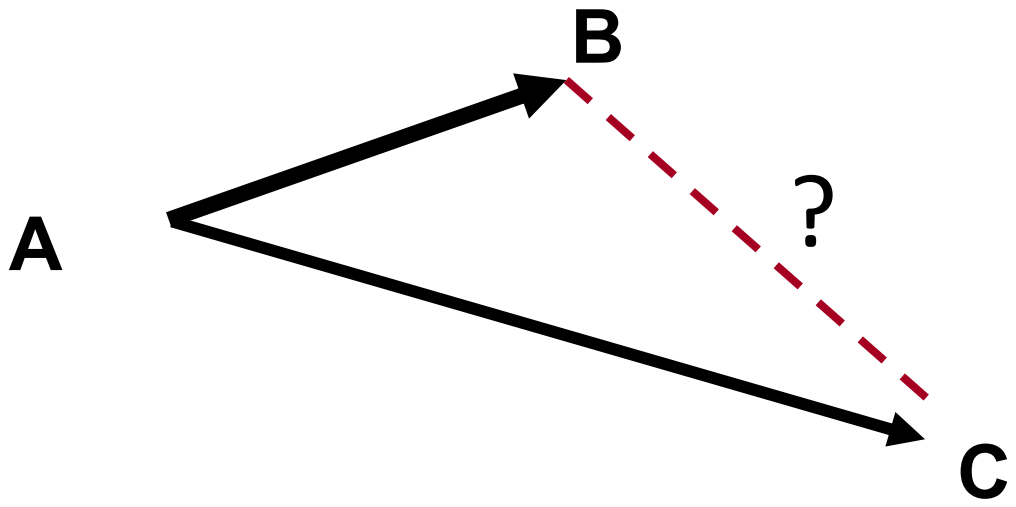
Comparison	SMD	95% CIs	Variance
Placebo vs Toothpaste	-0.34	(-0.41, -0.28)	0.0011
Placebo vs Gel	-0.19	(-0.30, -0.10)	0.0026

How to compare Gel to Toothpaste?

✓ Estimate indirect SMD and a 95% CI

Indirect comparison (Bucher method)

- We can obtain an indirect estimate for the relative treatment effects **B vs. C** from RCTs comparing **A vs. B** and **A vs. C**:



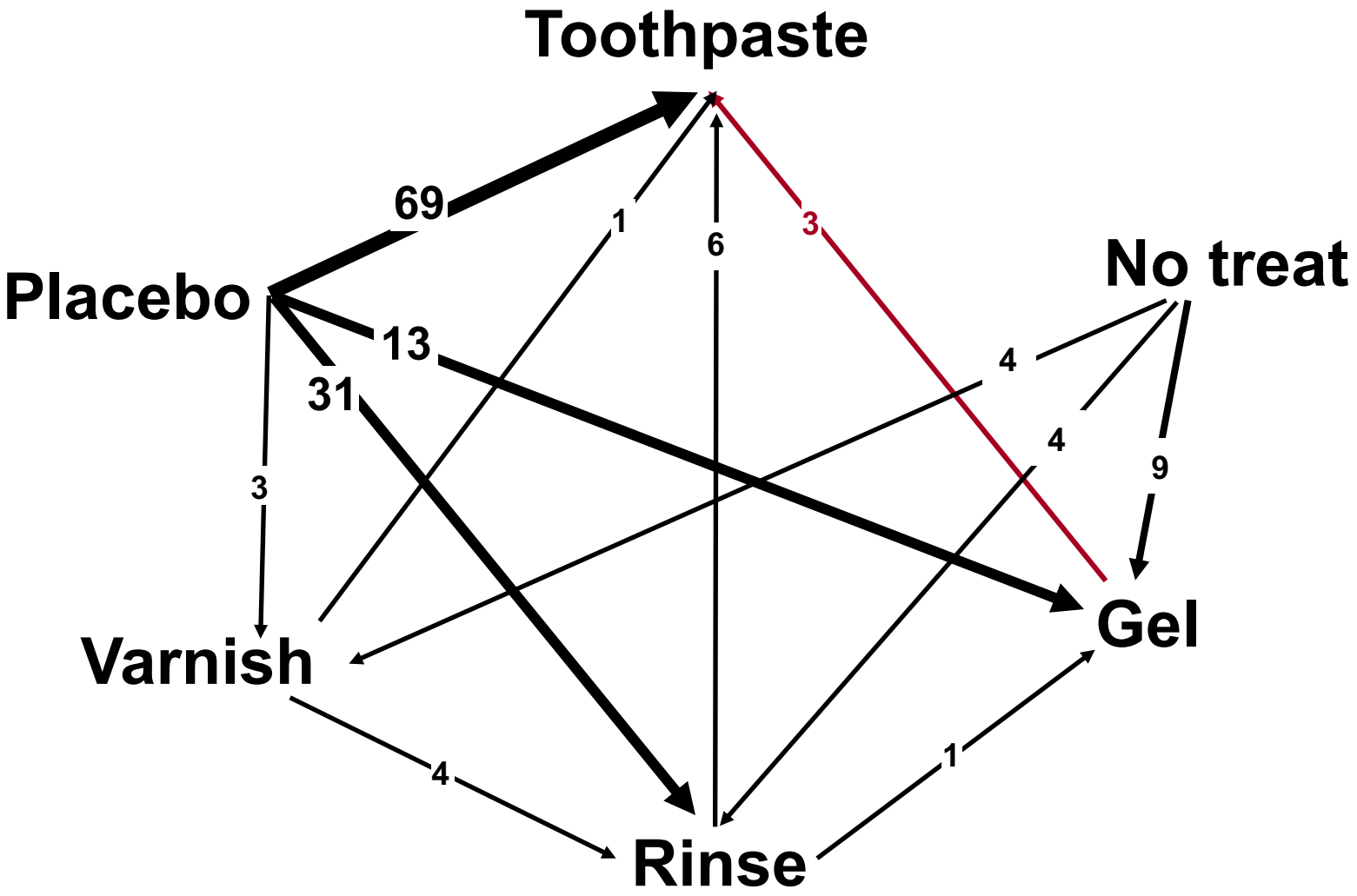
$$\mu_{\mathrm{BC}} = \mu_{\mathrm{AC}} - \mu_{\mathrm{AB}}$$

$$Var(\mu_{BC}) = Var(\mu_{AC}) + Var(\mu_{AB})$$

Example: Toothpaste versus Gel

- Indirect $SMD_{GvsT} = SMD_{PvsT} - SMD_{PvsG}$
- Indirect $SMD_{GvsT} = -0.34 - (-0.19) = \mathbf{-0.15}$
- Variance Indirect $SMD_{GvsT} = Var(SMD_{PvsT}) + Var(SMD_{PvsG})$
- Variance $SMD_{PvsT} = ((high\ CI - low\ CI)/3.92)^2$
- Variance $SMD_{PvsT} = ((-0.28 - (-0.41))/3.92)^2 = 0.0011$
- Variance $SMD_{PvsG} = ((-0.10 - (-0.30))/3.92)^2 = 0.0026$
- Variance Indirect $SMD_{GvsT} = 0.0011 + 0.0026 = \mathbf{0.0037}$
- SE Indirect $SMD_{GvsT} = sqrt(0.0037) = \mathbf{0.061}$
- 95% CI for Indirect $SMD_{GvsT} = (-0.15 - 1.96\times0.061, -0.15 + 1.96\times0.061)$
- 95% CI for Indirect $SMD_{GvsT} = \mathbf{(-0.27, -0.03)}$

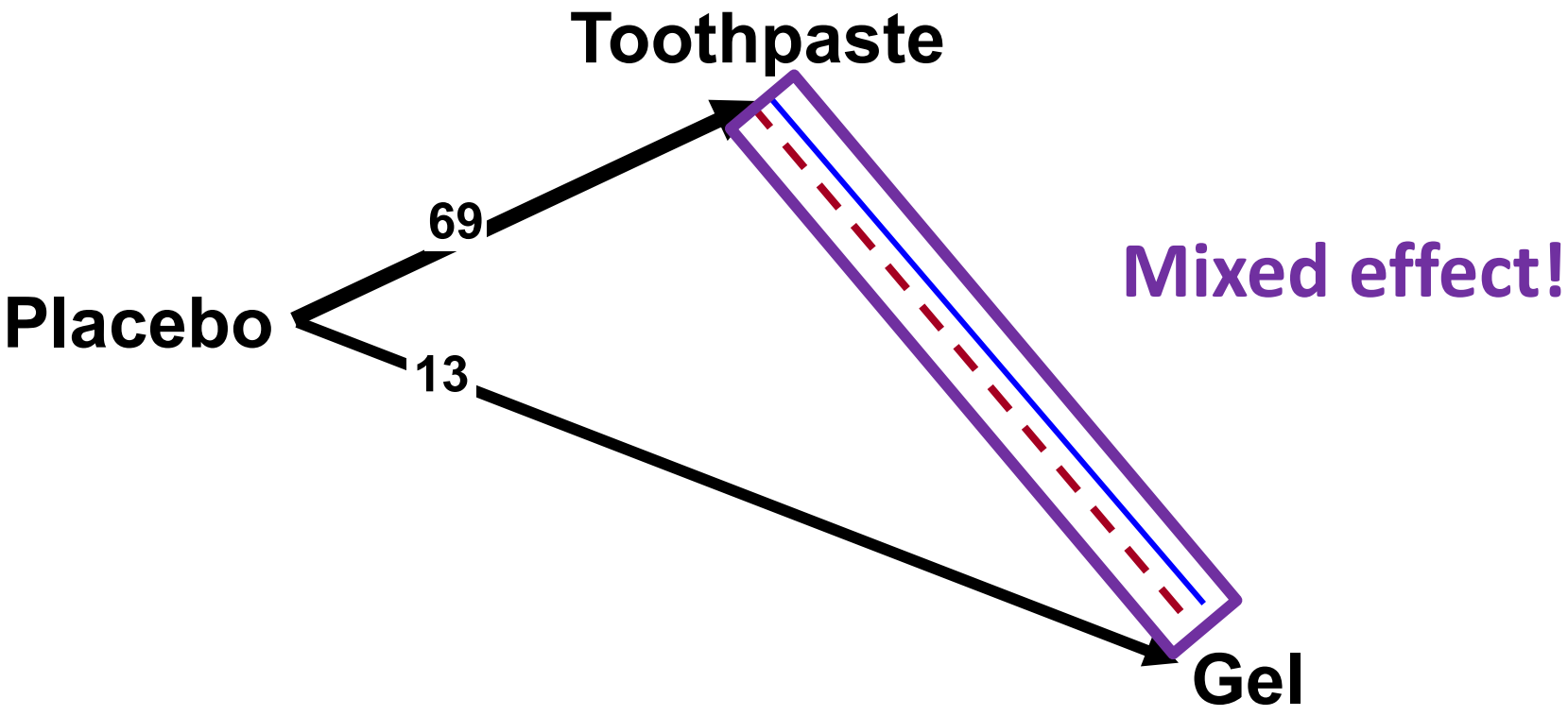
Example: Toothpaste versus Gel



3 additional studies that directly compare toothpaste to gel

- Can we include all available information the analysis?

Example: Toothpaste versus Gel



Direct + Indirect → Mixed

Mixed comparator: combining direct and indirect comparison

- Use the Inverse Variance method
- Each estimate is 'weighted' by the inverse of the variance
- A '**mixed**' result is obtained

$$\mu^{Mixed} = \frac{\frac{1}{var(\mu^{Direct})}\mu^{Direct} + \frac{1}{var(\mu^{Indirect})}\mu^{Indirect}}{\frac{1}{var(\mu^{Direct})} + \frac{1}{var(\mu^{Indirect})}}$$

$$var(\mu^{Mixed}) = \frac{1}{\frac{1}{var(\mu^{Direct})} + \frac{1}{var(\mu^{Indirect})}}$$

Example: Toothpaste versus Gel

Indirect $SMD_{GvsT} = -0.15$

Variance Indirect $SMD_{GvsT} = 0.0037$

Direct $SMD_{GvsT} = 0.04$

Variance Direct $SMD_{GvsT} = 0.011$

- Mixed SMD^{M}_{GvsT} ?
- Variance of Mixed SMD^{M}_{GvsT}?
- 95% CI ?

Example: Toothpaste versus Gel

Indirect $SMD_{GvsT} = -0.15$

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- Mixed SMD^{M}_{GvsT} ?
- Variance of Mixed SMD^{M}_{GvsT}?
- 95% CI ?

$$SMD^{M}_{GvsT} = \frac{\frac{1}{0.011}0.04 - \frac{1}{0.0037}0.15}{\frac{1}{0.011} + \frac{1}{0.0037}} \qquad var(SMD^{M}_{GvsT}) = \frac{1}{\frac{1}{0.011} + \frac{1}{0.0037}}$$

- Mixed $SMD^{M}_{GvsT} = -0.102$
- Variance Mixed $SMD^{M}_{GvsT} = 0.0028$
- 95%CI: (-0.205, 0.001)

Mixed estimate: more precise!

Indirect $SMD_{GvsT} = -0.15$

Variance Indirect $SMD_{GvsT} = 0.0037$

Direct $SMD_{GvsT} = 0.04$

Variance Direct $SMD_{GvsT} = 0.011$

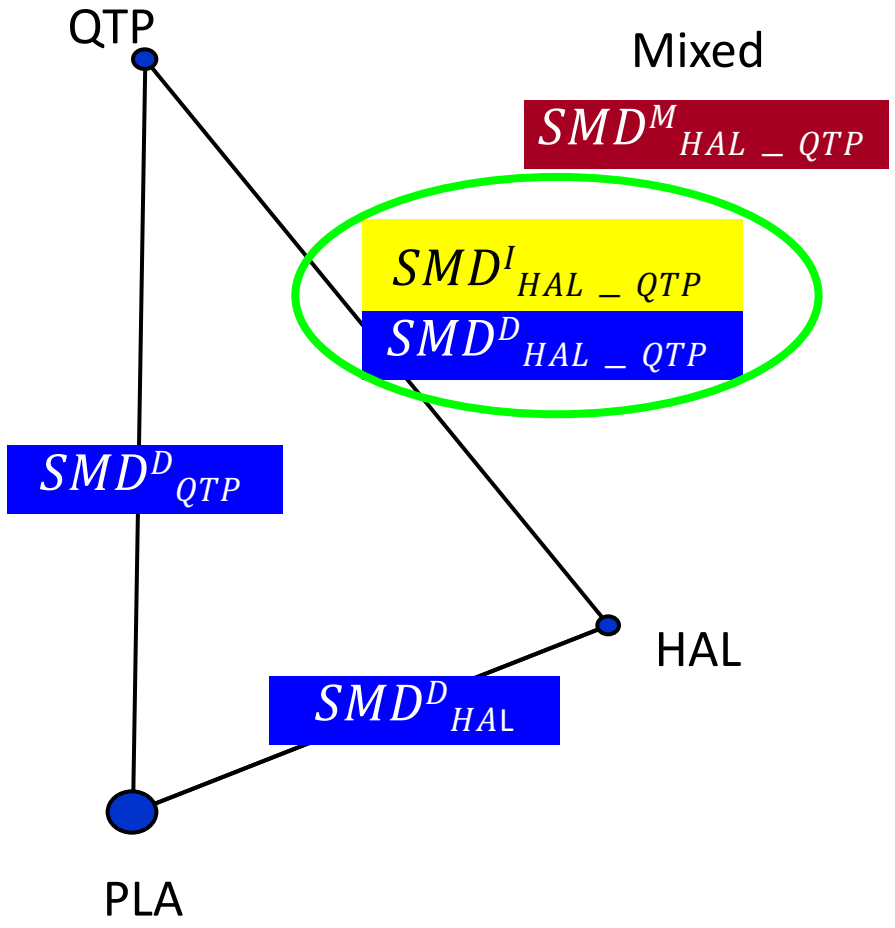
- Mixed $SMD^{M}_{GvsT} = -0.102$
- Variance$(SMD^{M}_{GvsT}) = 0.0028$
- 95%CI: (-0.205, 0.001)

- Mixed estimates are **more precise** than the direct or the indirect estimate as they use both sources of information

- This might not be the case in the full NMA models when:
  - ✖ Direct and indirect estimates **disagree**
  - ✖ There is larger **heterogeneity** in the indirect rather in the direct evidence (for random effects NMA)

Summary of the two steps approach to estimate mixed effects

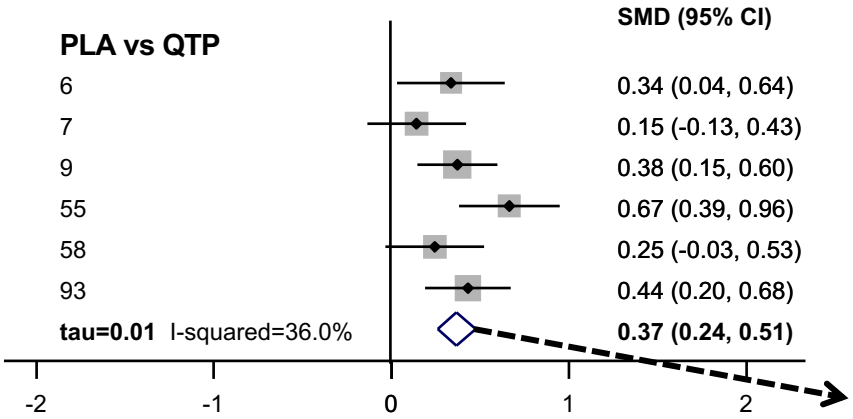
Response to treatment with antimanic drugs

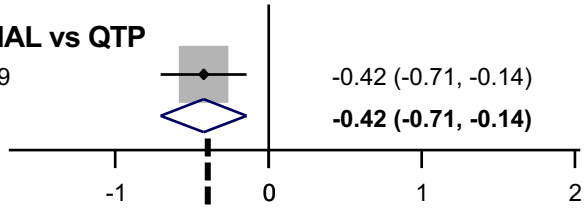


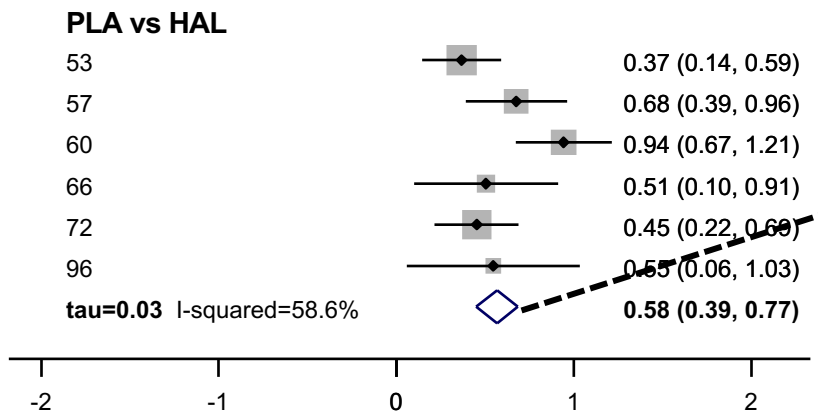
Summary of the two steps approach to estimate mixed effects

Response to treatment with antimanic drugs

Do three separate meta-analyses



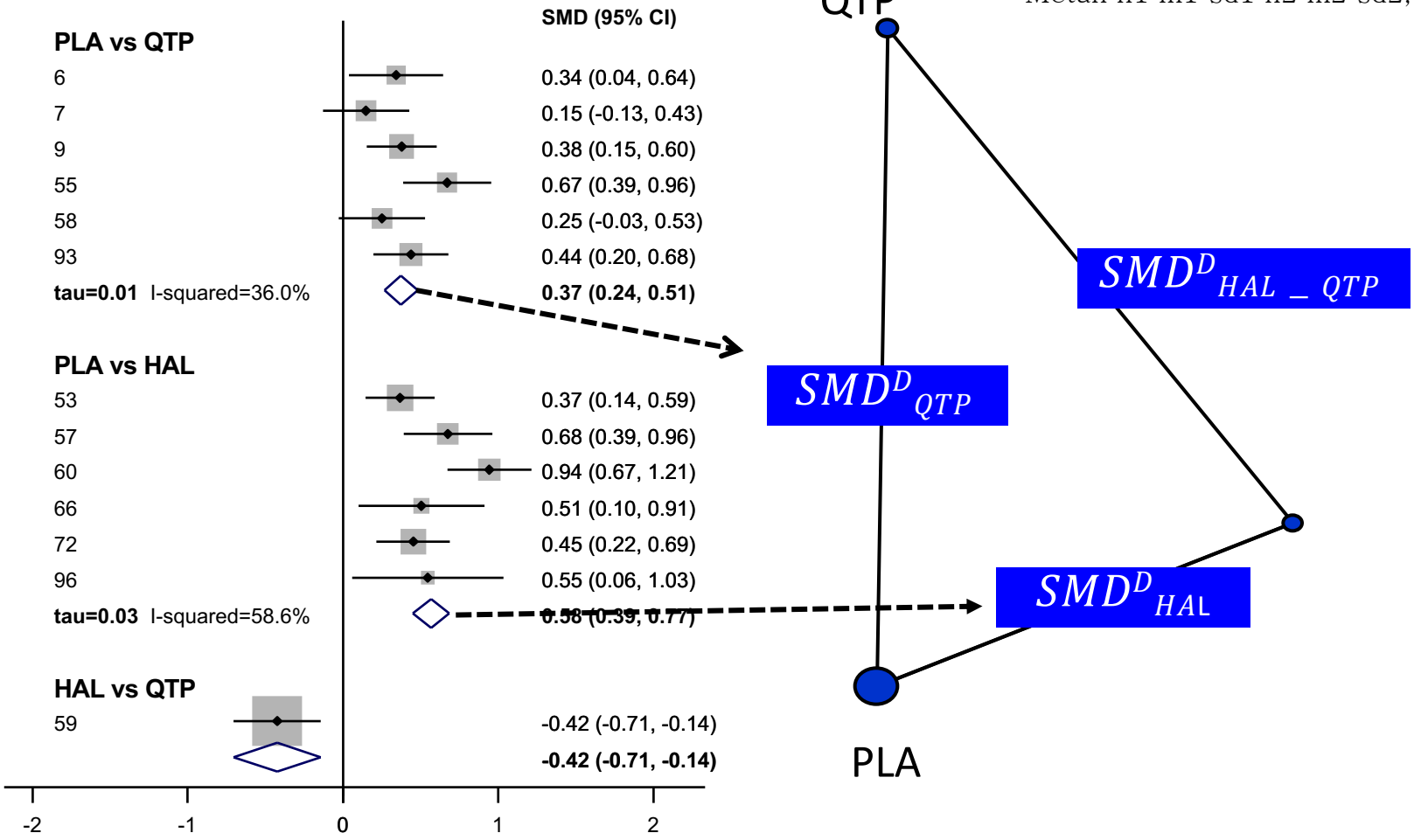




Summary of the two steps approach to estimate mixed effects

Response to treatment with antimanic drugs

Do a meta-analysis in three subgroups



Metan n1 m1 sd1 n2 m2 sd2, by(comp)