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

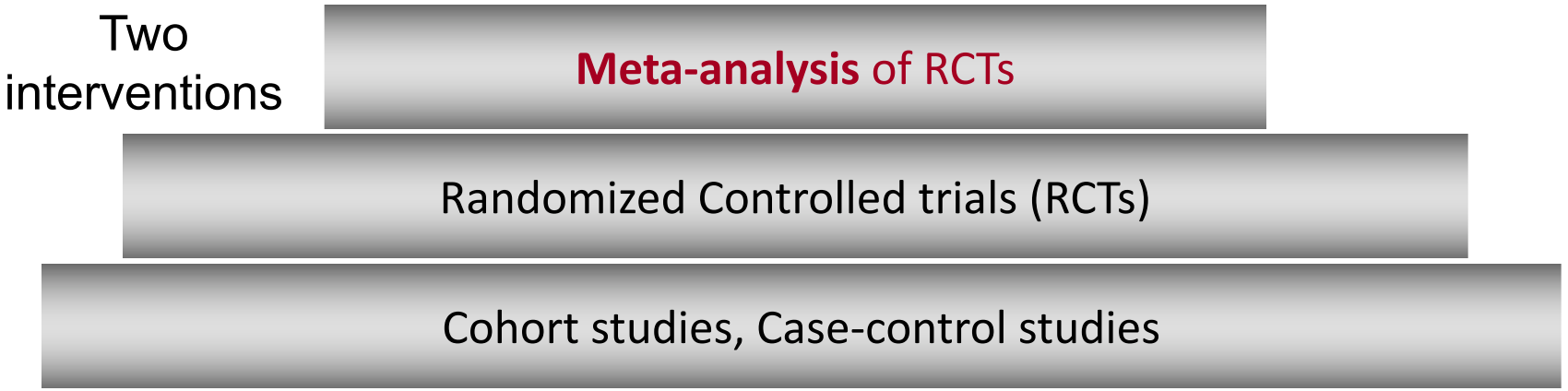
- Cerumol
- Sodium bicarbonate
- Olive oil
- Dry and wet irrigation
- TP
- Self irrigation
- Irrigation by nurse
- Endoscopic and microscoping de-waxing

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

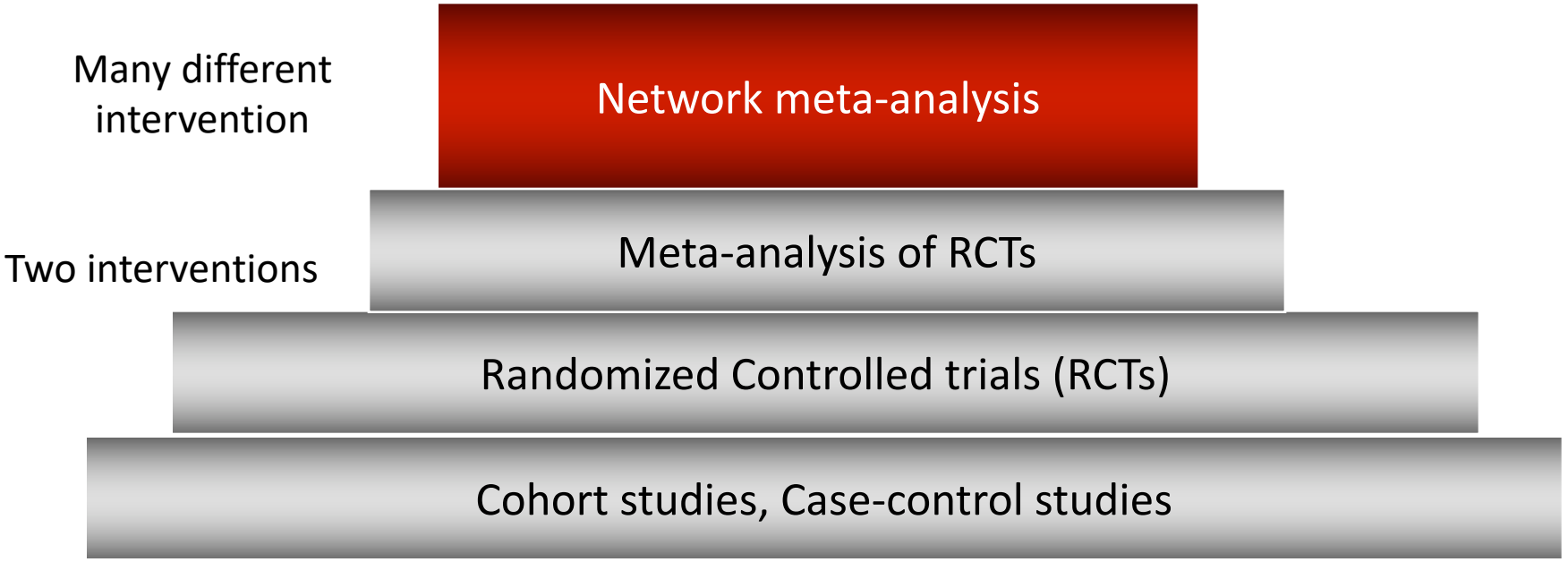


Levels of evidence For Therapy, Prevention, Aetiology and Harm

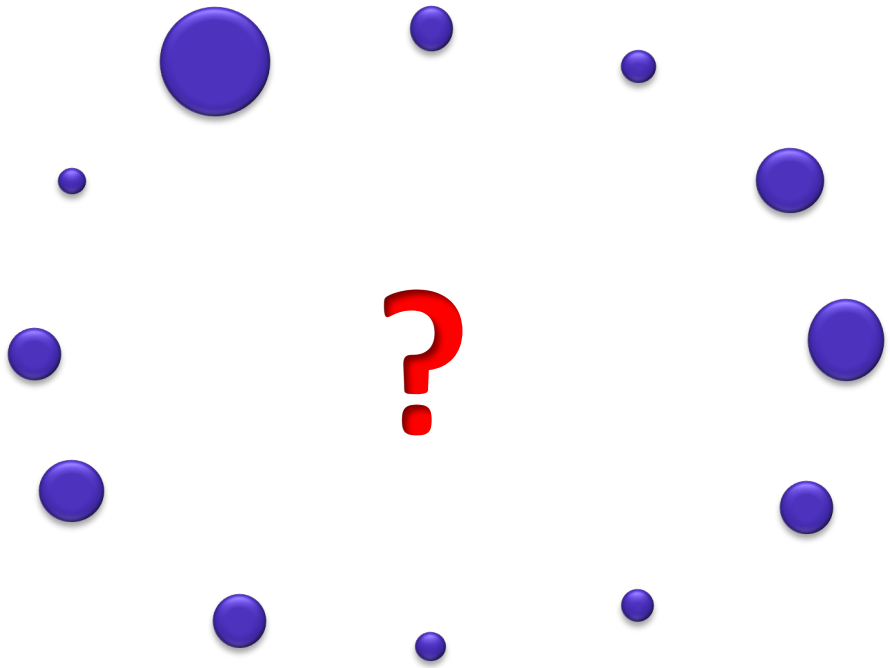
Centre for Evidence Based Medicine, University of Oxford

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"

Many treatments

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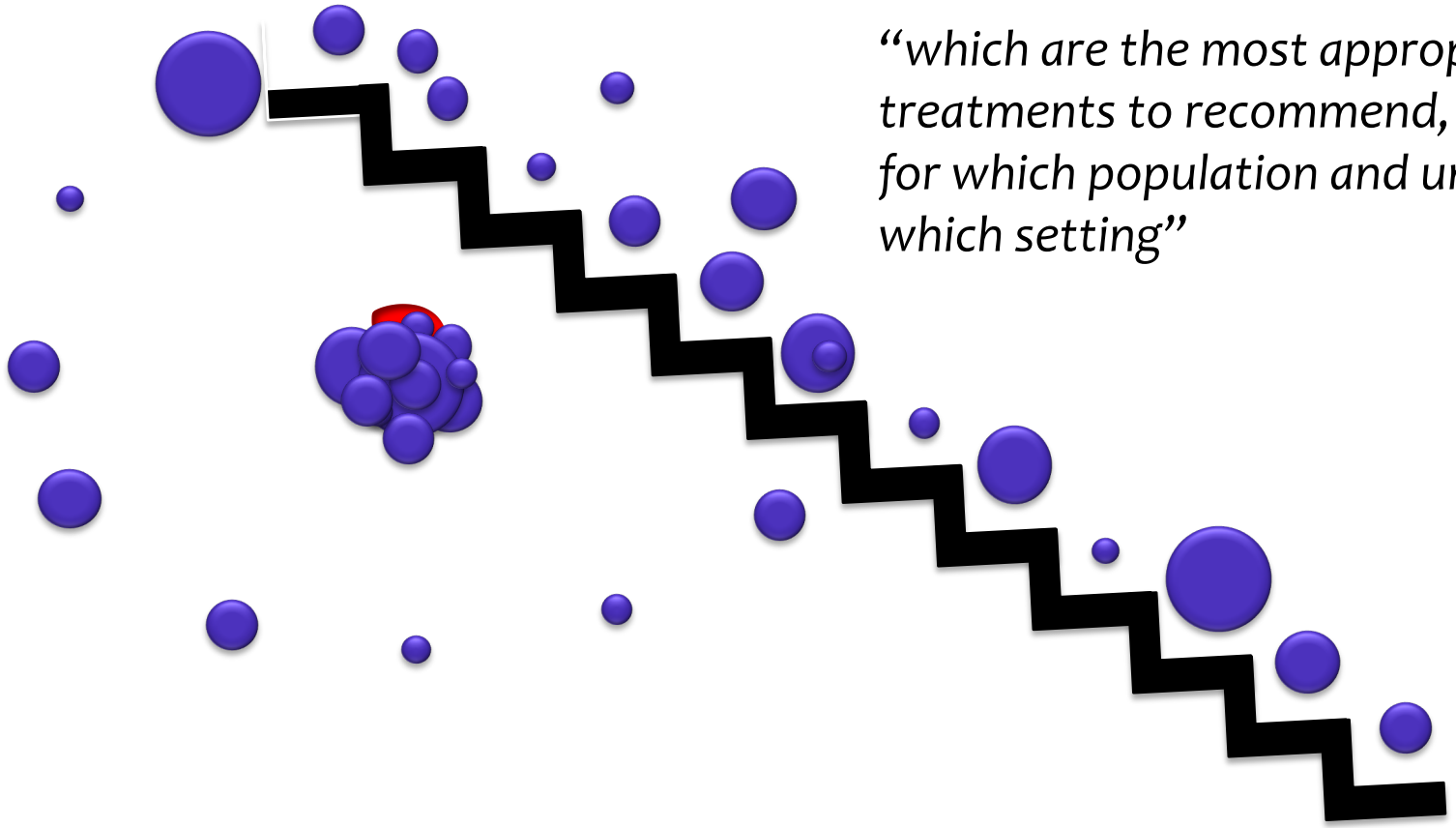
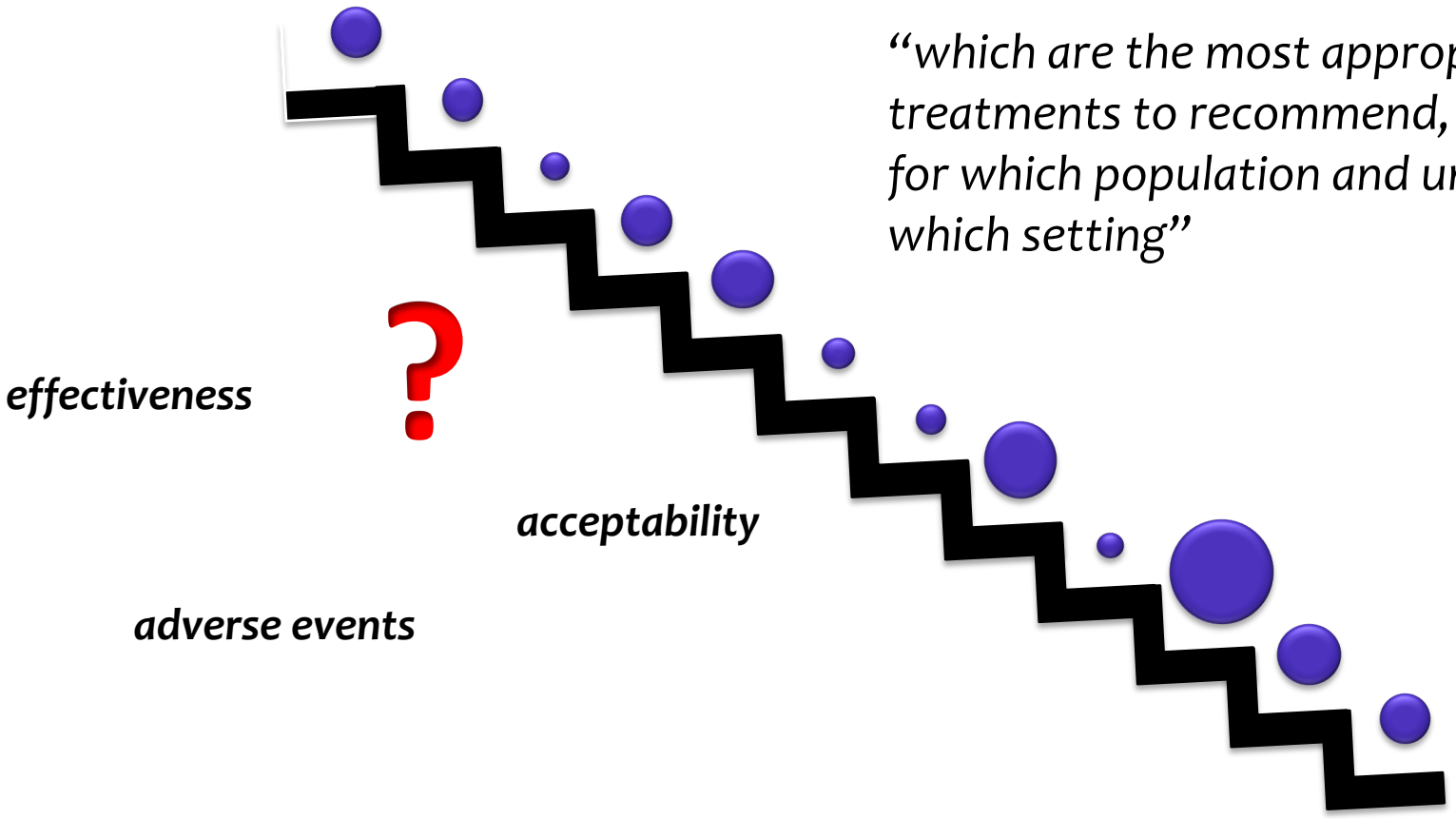
"which are the most appropriate treatments to recommend, for which population and under which setting"



Many treatments

Network meta-analysis:

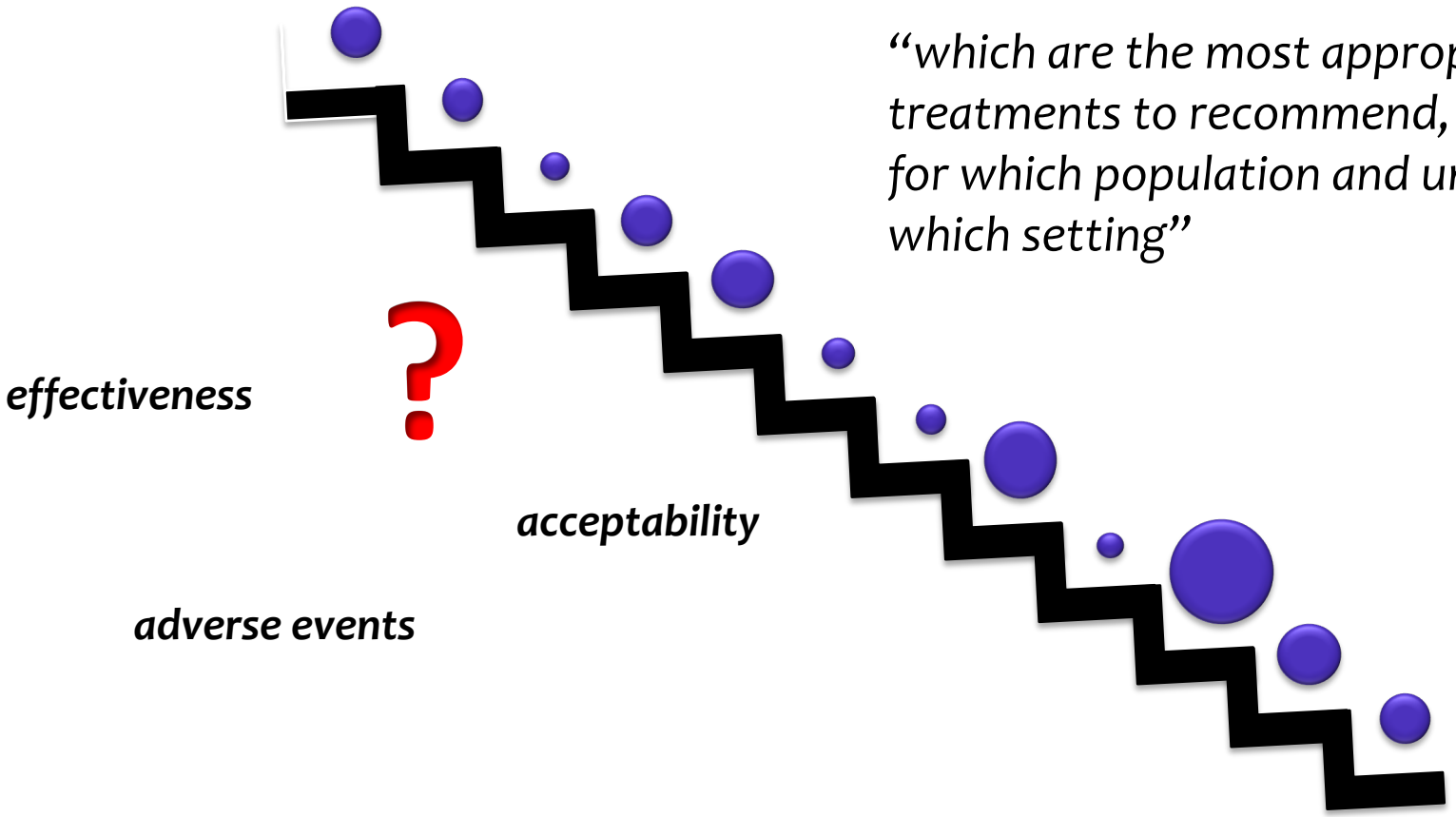
"which are the most appropriate treatments to recommend, for which population and under which setting"



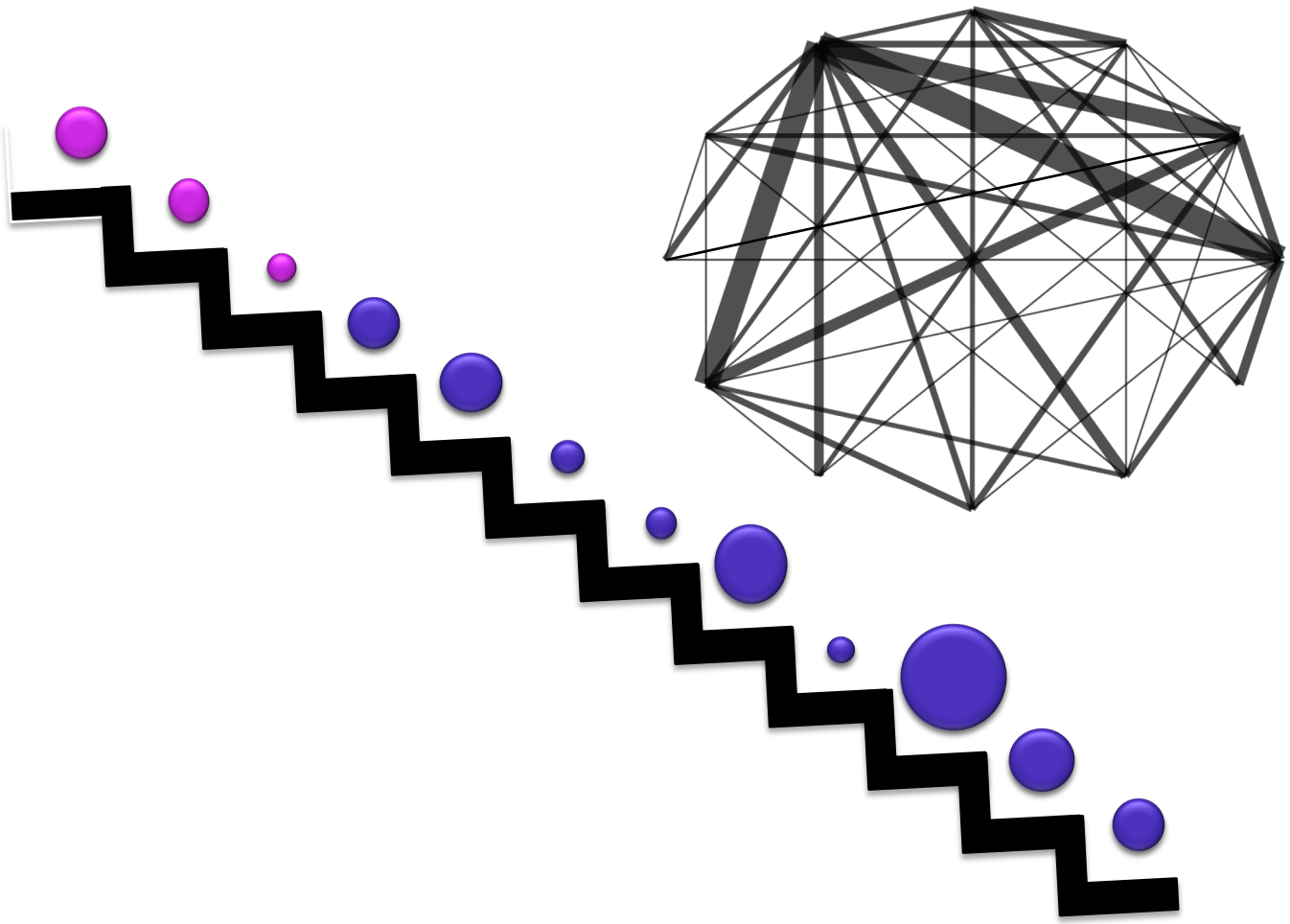
Many treatments

Network meta-analysis:

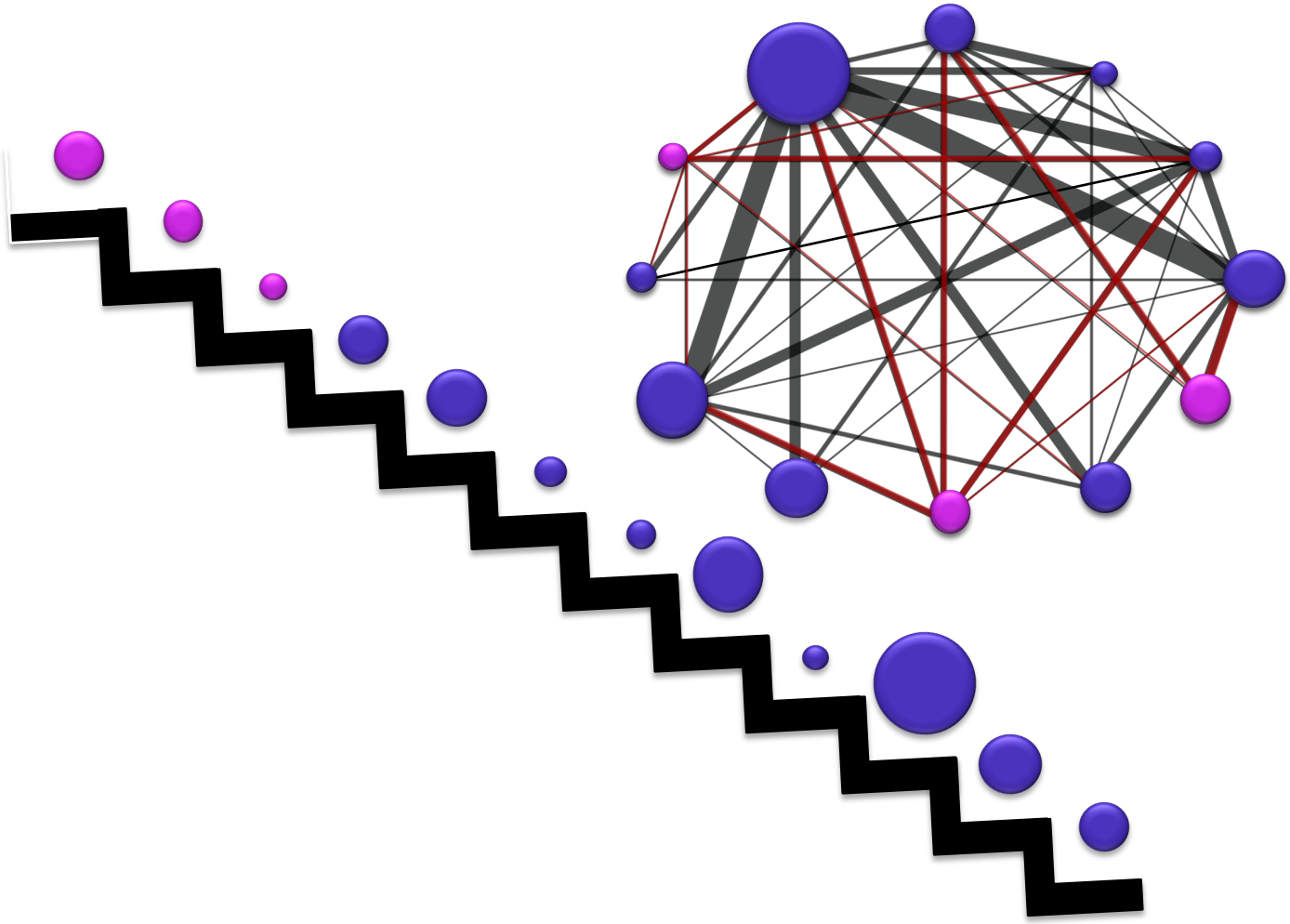
"which are the most appropriate treatments to recommend, for which population and under which setting"



Many treatments

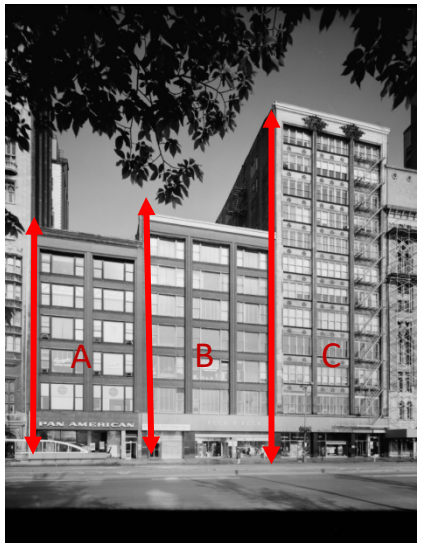


Many treatments



Indirect comparison

- If we know how much taller is **C to A** and how much taller is **B to A,** we know how much taller is **C compared to B**



- For any pair B and C:

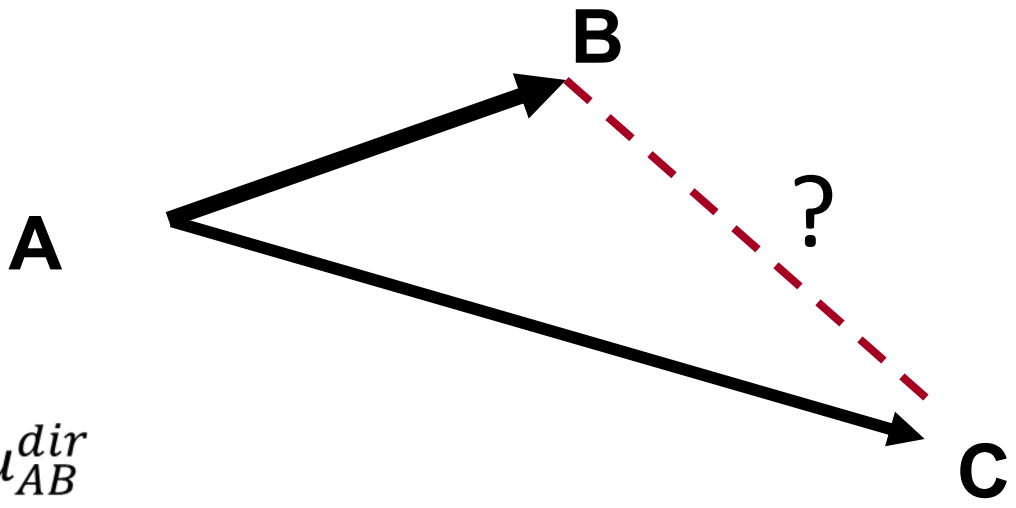
typical (or mean) advantage of **C over B** =

advantage of **C over A –** advantage of **B over A**

➢ *If C is 10 meters higher than A and B is 3 meters higher than A then C is 10-3=7 meters higher than B*

Indirect comparison

We can obtain an *indirect* estimate for B vs C from RCTs comparing A vs B and A vs C:

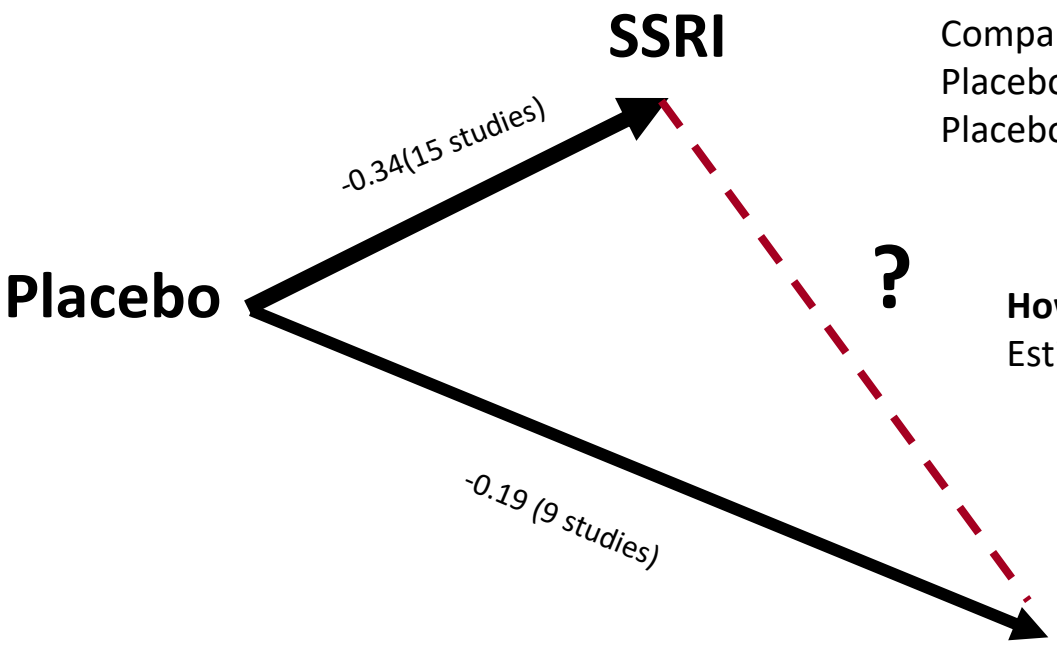


$$\mu_{BC}^{ind} = \mu_{AC}^{dir} - \mu_{AB}^{dir}$$

$$var\left(\mu_{BC}^{ind}\right) = var\left(\mu_{AC}^{dir}\right) + var\left(\mu_{AB}^{dir}\right)$$

95% C.I. $\mu_{BC}^{ind} \pm 1.96\sqrt{var\left(\mu_{BC}^{ind}\right)}$

Fictional example: CBT vs SSRI for depression



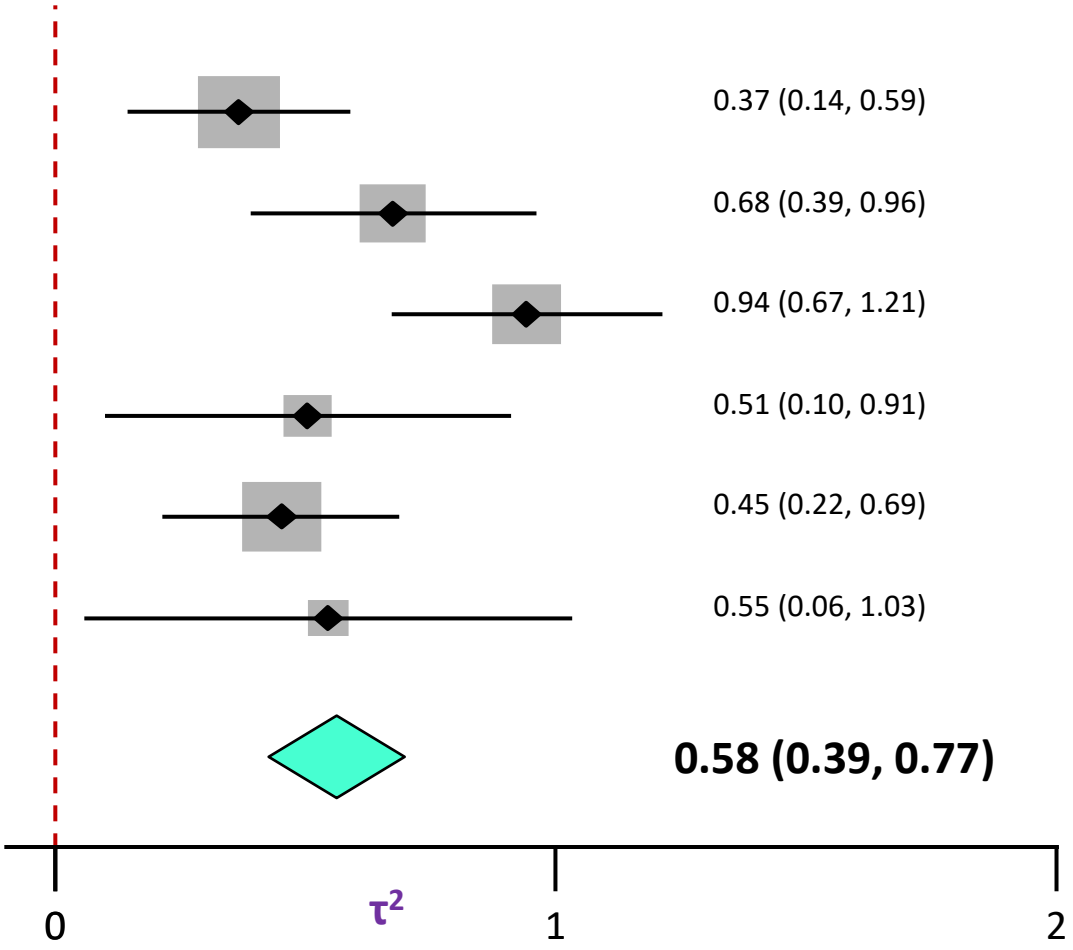
Comparison	SMD	CI	S.E.
Placebo vs SSRI	-0.34	(-0.41, -0.28)	0.03
Placebo vs CBT	-0.19	(-0.30, -0.10)	0.05

How to compare SSRI to CBT ?
Estimate indirect SMD and a 95% CI

$$SMD^{ind}_{CBTvSSRI} = -0.34 - (-0.19) = -0.15 \qquad var(SMD^{ind}_{CBTvSSRI}) = 0.03^2 + 0.05^2 = 0.0034$$

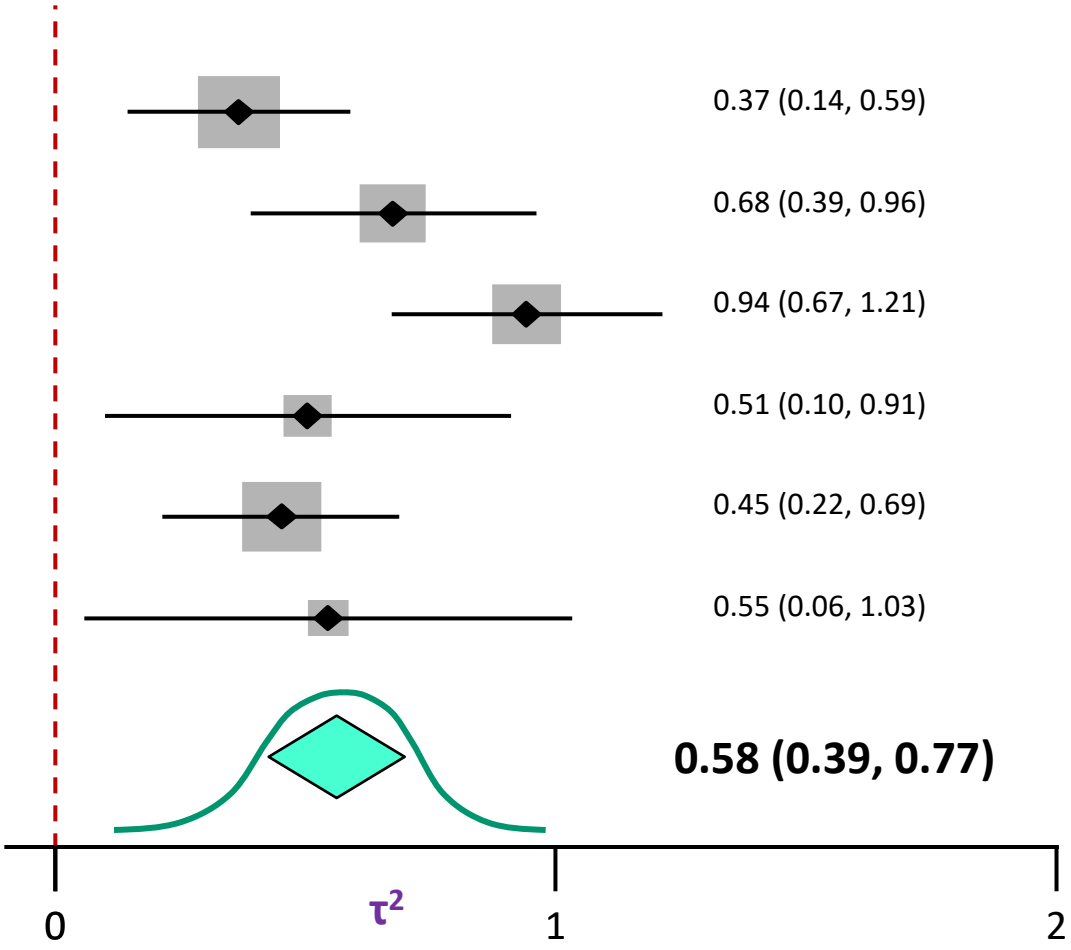
$$SMD^{ind}_{CBTvSSRI} \pm 1.96\sqrt{v^{ind}_{CBTvSSRI}} = -0.15 \pm 1.96\sqrt{0.0034} = (-0.26, -0.04)$$

HAL vs PLA for reducing manic symptoms



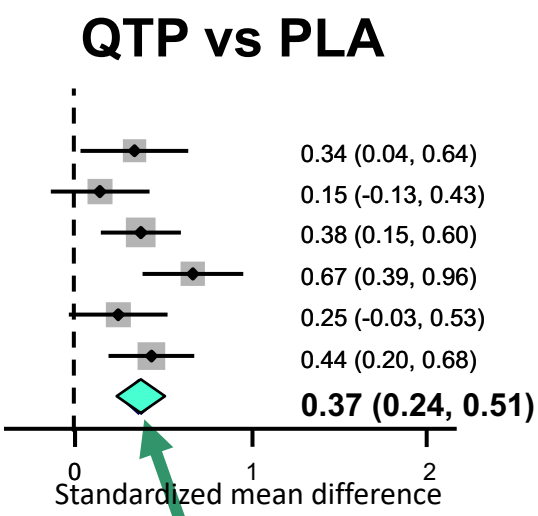
Six eligible studies

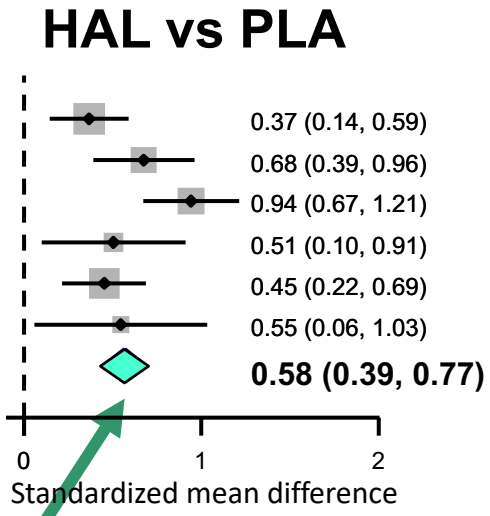
HAL vs PLA for reducing manic symptoms



Six eligible studies

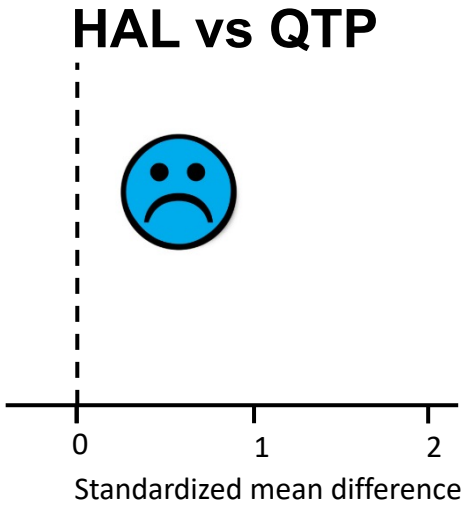
Using the **random effects model:** There is not a single effect of haloperidol, but a whole distribution of effects with mean 0.58 and variance τ^2=0.009





HAL is 0.58 better than P

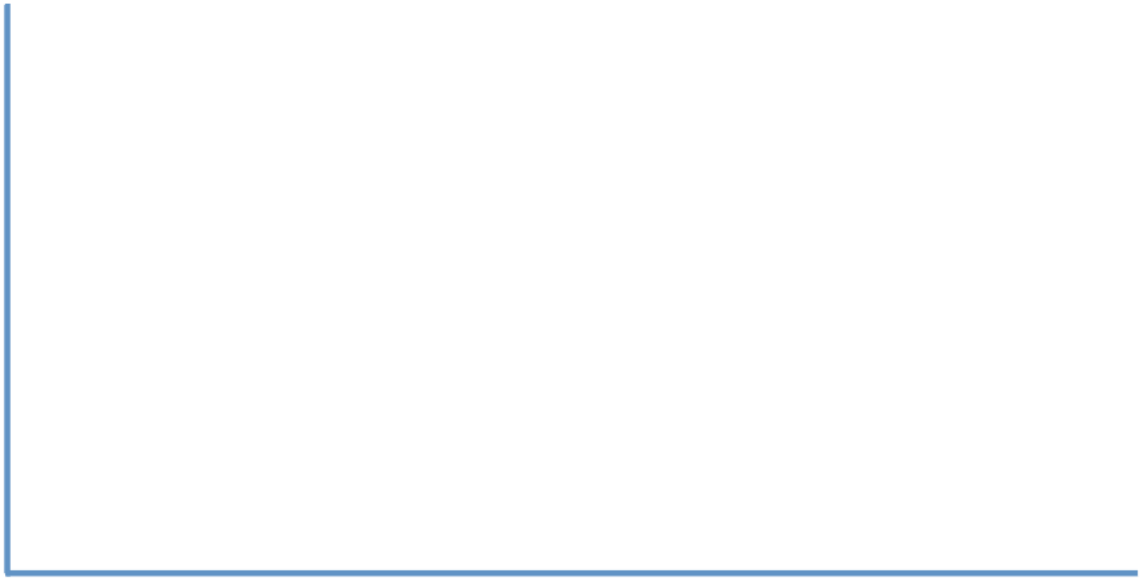
QTP is 0.37 better than P



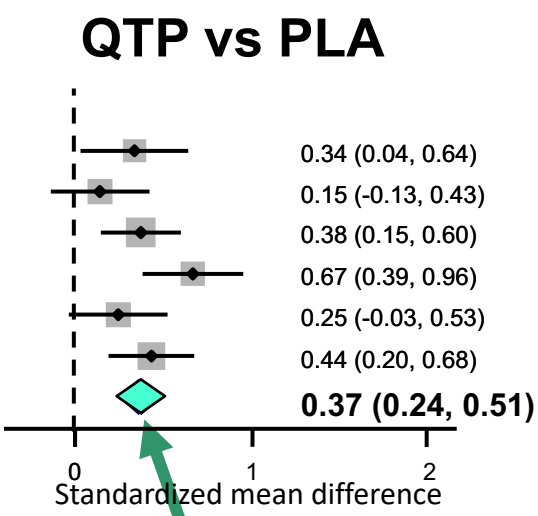
Would you judge that QTP

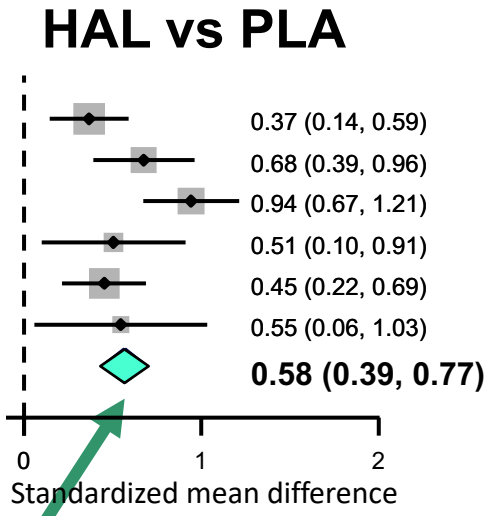
Wenn die Umfrage aktiv ist, antworten unter **PollEv.com/gmhbe**.

GMHBE an **079 807 15 49** simsen, um teilzunehmen



Help





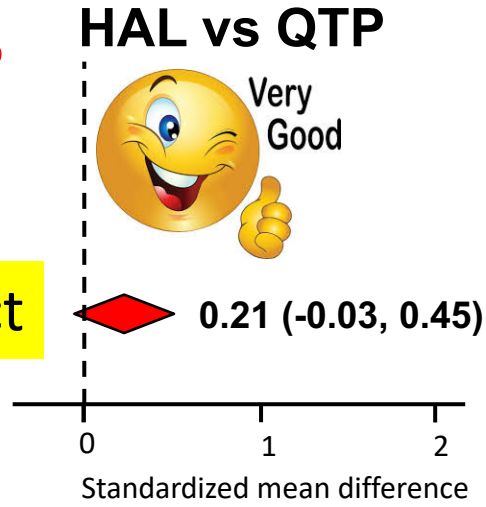
HAL is 0.58 better than P

QTP is 0.37 better than P

...so HAL is 0.21 better than QTP

but we need to combine the uncertainty in both

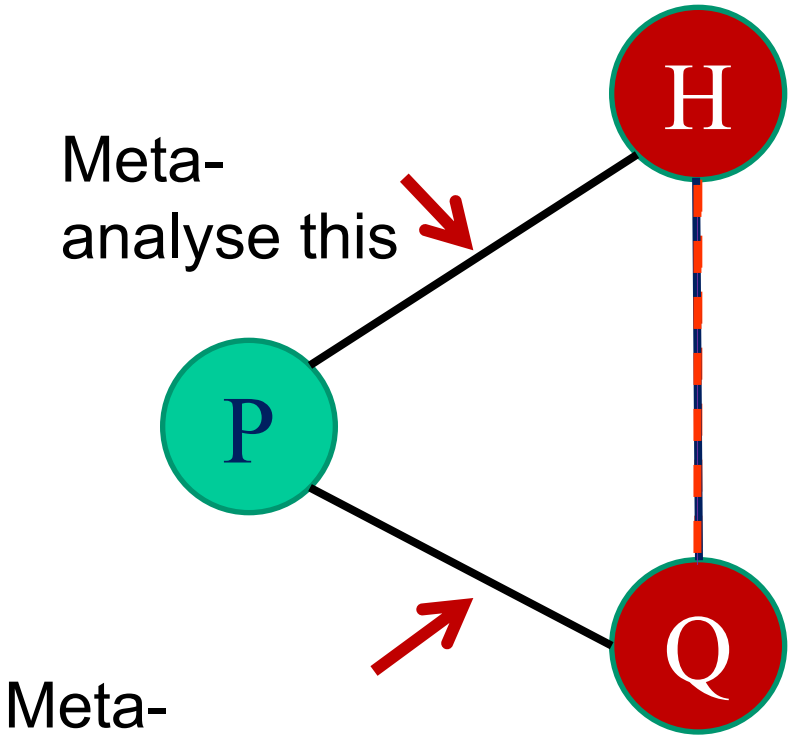
Indirect



Indirect comparison

advantage of HAL over QTP =
advantage of HAL over PLA
–
advantage of QTP over PLA

Indirect and mixed treatment effects



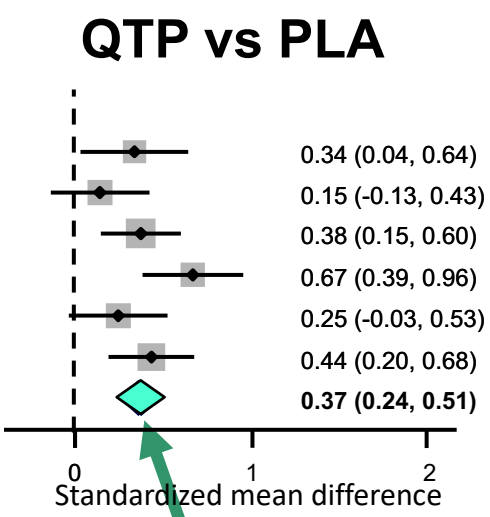
Indirect
treatment
effect

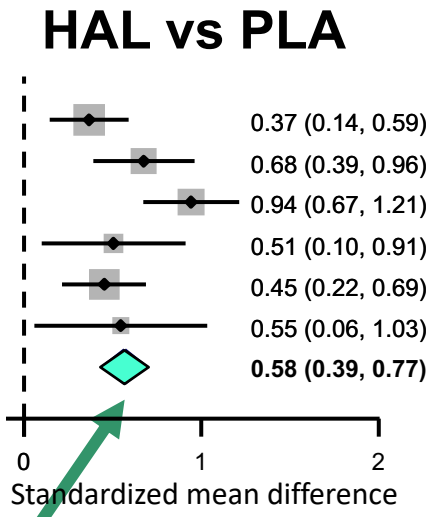
$$SMD_{HQ} = SMD_{HP} - SMD_{QP}$$

$$Var(SMD_{HQ}) = Var(SMD_{HP}) + Var(SMD_{QP})$$

…. in the meanwhile

A new study was published!
It compares HAL and QTP!!!





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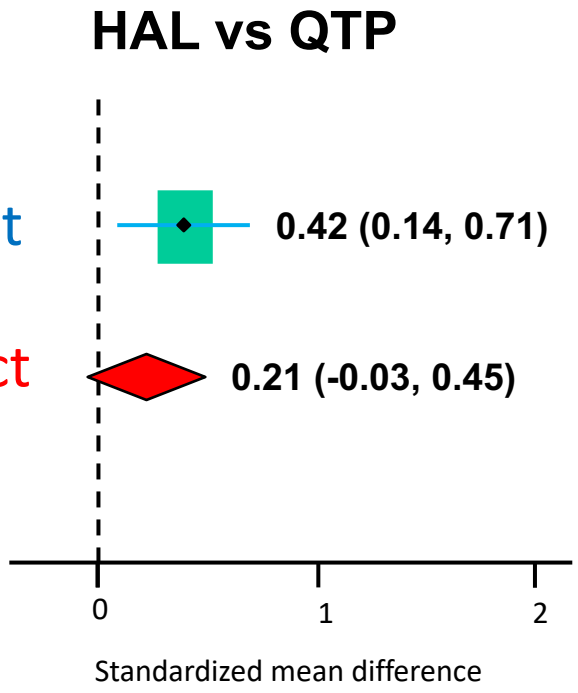
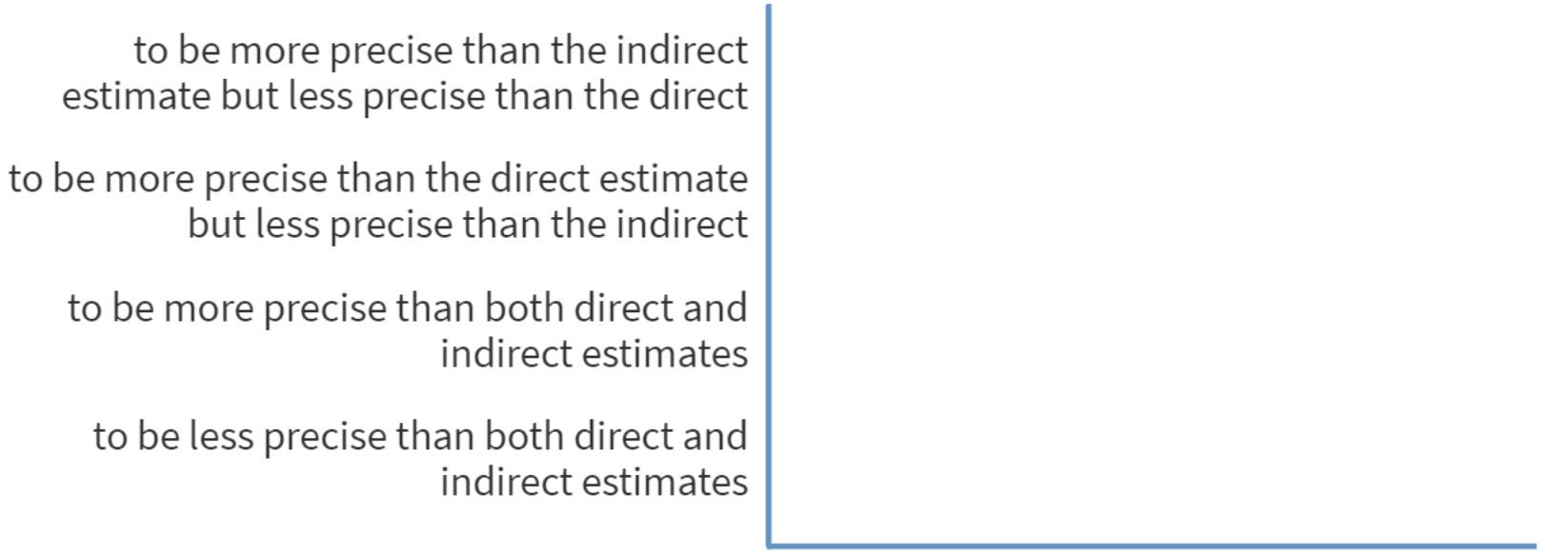
Synthesize direct and indirect



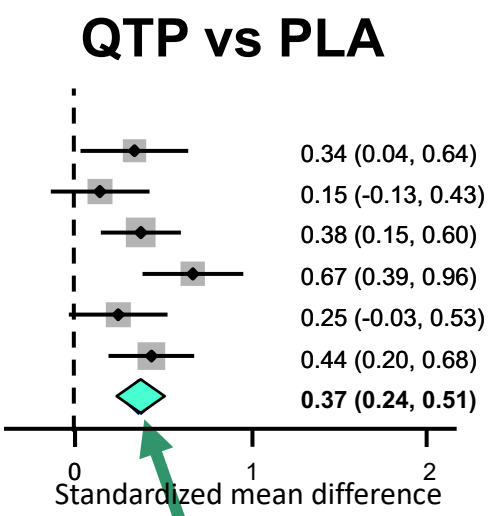
Do you expect the mixed estimate

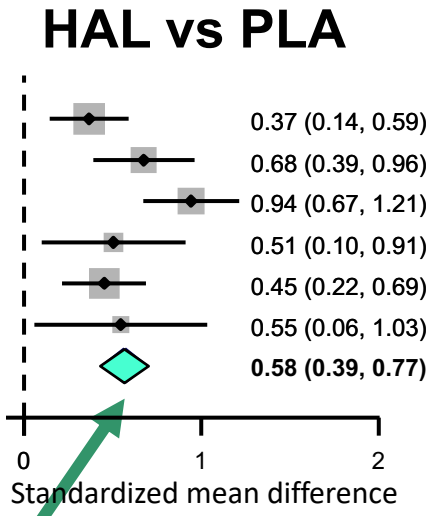
Wenn die Umfrage aktiv ist, antworten unter **PollEv.com/gmhbe**.

GMHBE an **079 807 15 49** simsen, um teilzunehmen



Help





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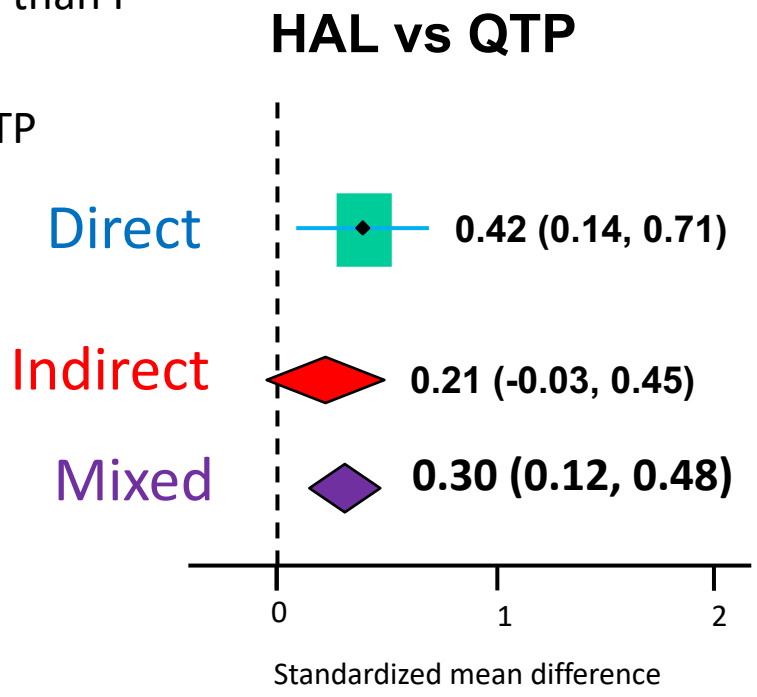


Mixed effect

Summarize direct and indirect effect size into a single mixed effect

$$mixed\ SMD = \frac{\frac{SMD_{direct}}{var(SMD_{direct})} + \frac{SMD_{indirect}}{var(SMD_{indirect})}}{\frac{1}{var(SMD_{direct})} + \frac{1}{var(SMD_{indirect})}}$$

$$var(mixed\ SMD) = \frac{1}{\frac{1}{var(SMD_{direct})} + \frac{1}{var(SMD_{indirect})}}$$

Could a direct estimate be more precise than its mixed estimate counterpart?

Wenn die Umfrage aktiv ist, antworten unter **PollEv.com/gmhbe**.

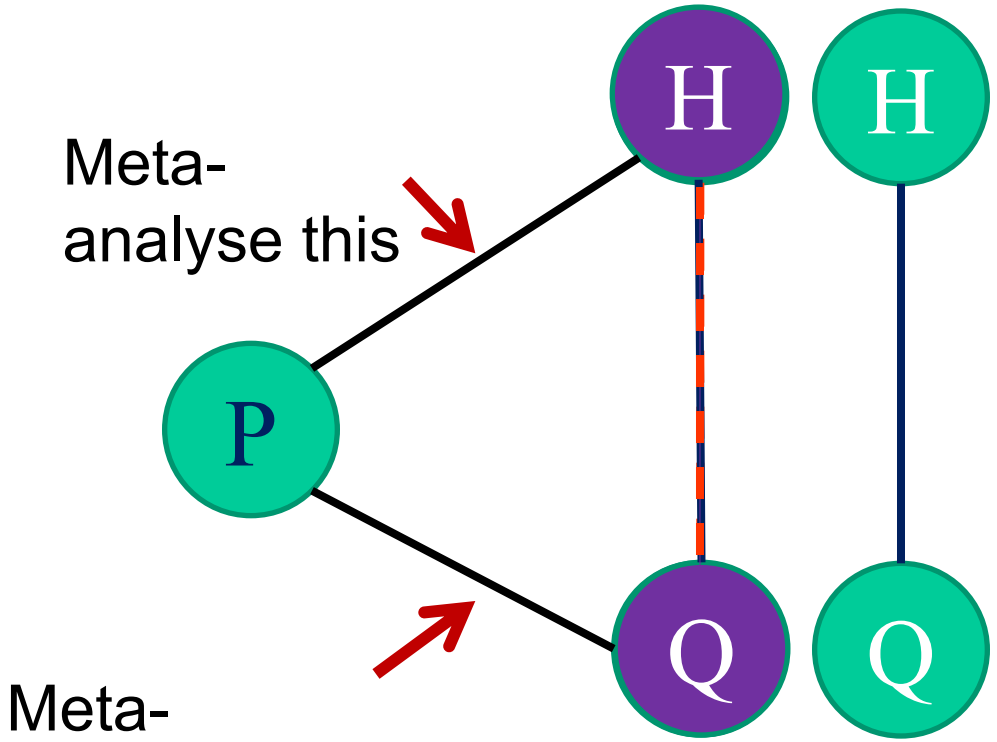
GMHBE an **079 807 15 49** simsen, um teilzunehmen

Help

$$var(SMD_{direct}) = \frac{1}{\frac{1}{var(SMD_{direct})}}$$

$$var(mixed\ SMD) = \frac{1}{\frac{1}{var(SMD_{direct})} + \frac{1}{var(SMD_{indirect})}}$$

Indirect and mixed treatment effects

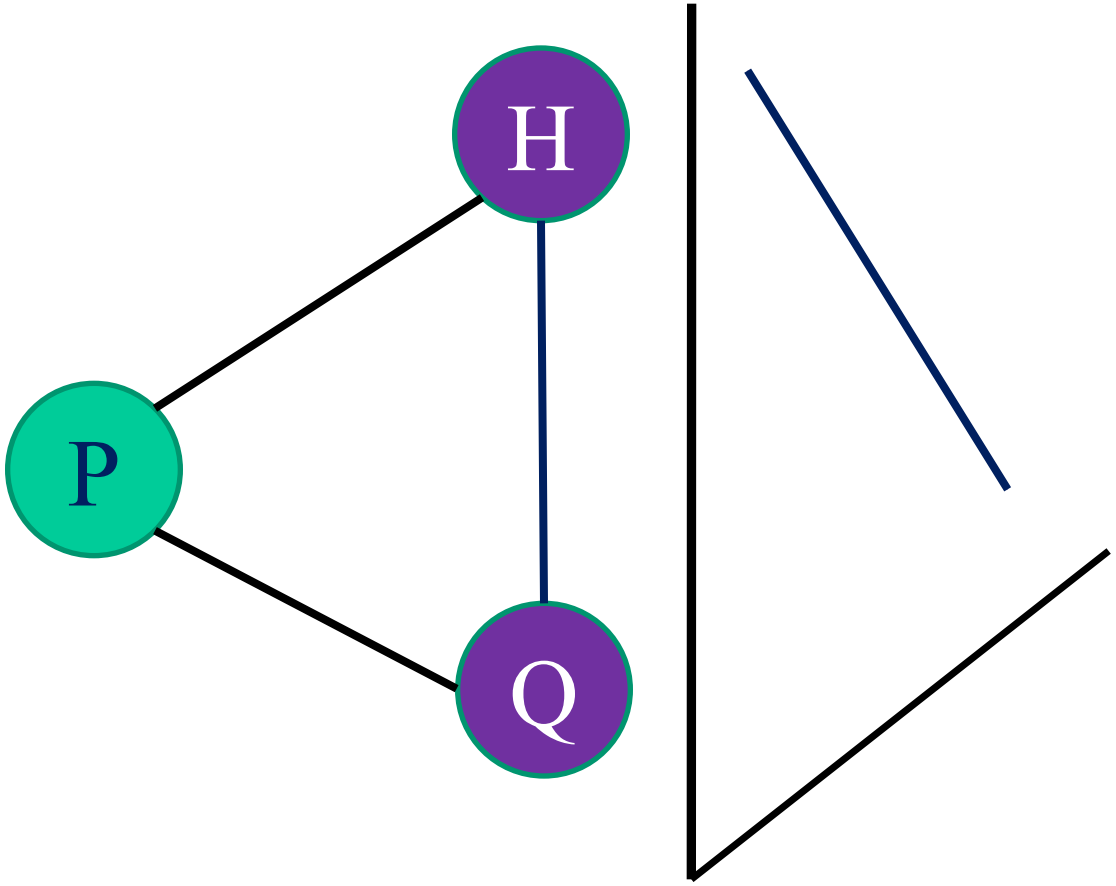


Indirect treatment effect

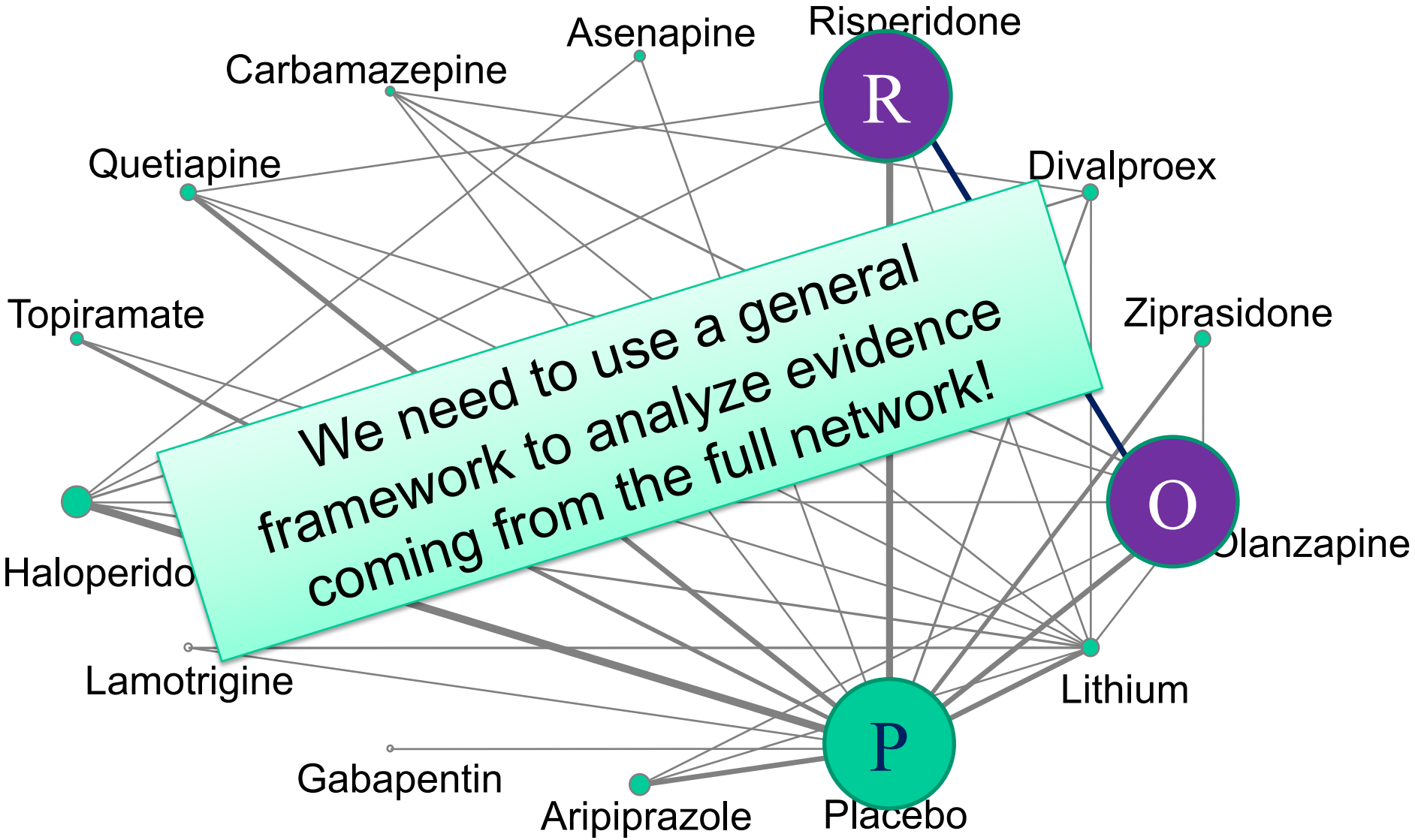
Direct treatment effect

Mixed treatment effect

Indirect and mixed treatment effects

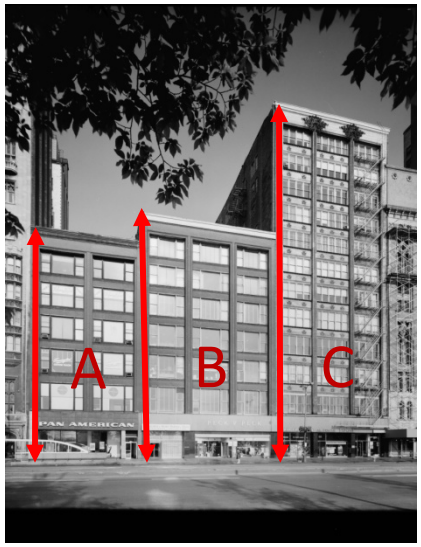


Network of interventions for Acute Mania



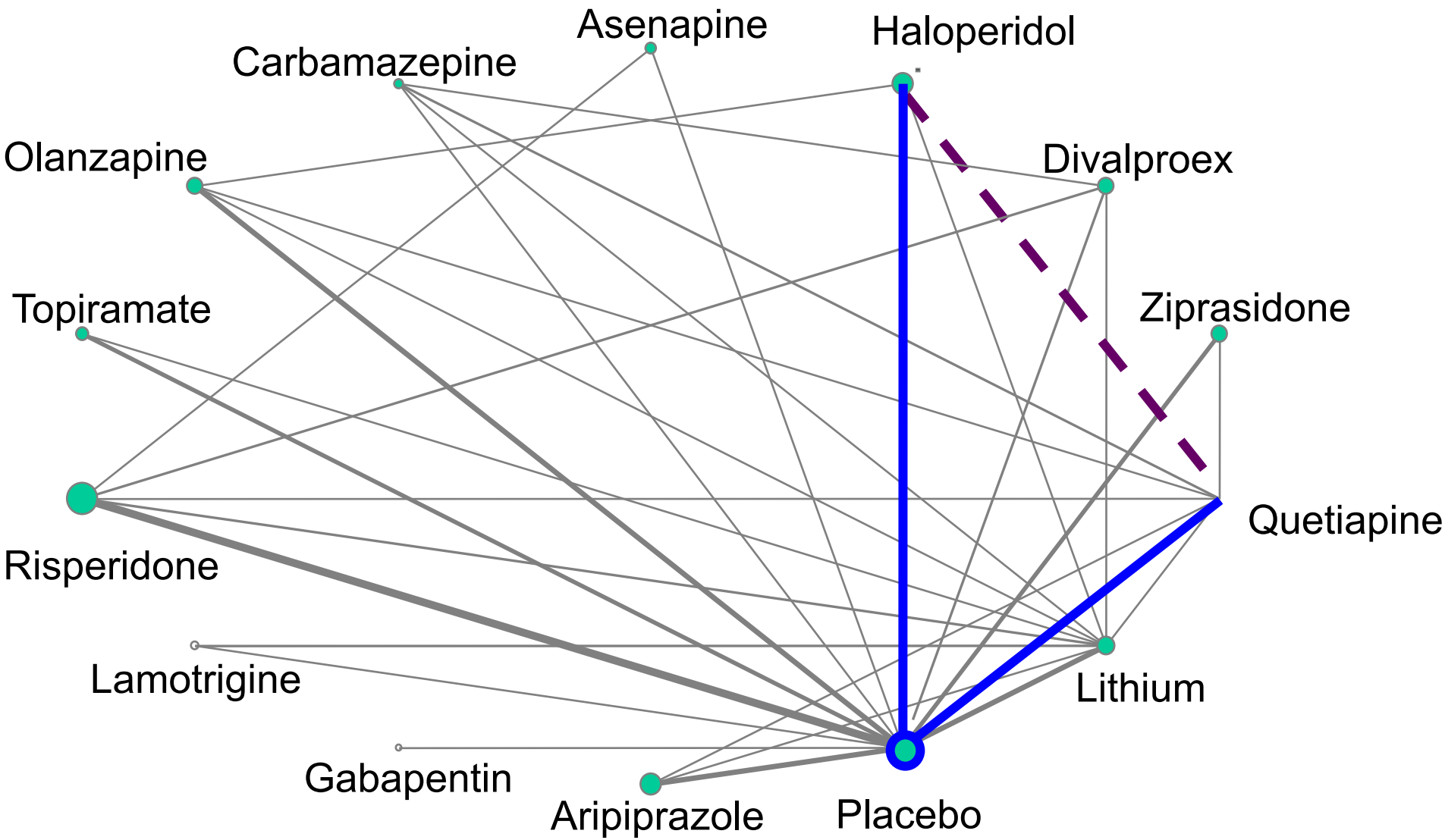
Cipriani A et al Lancet 2011

What if instead of this:



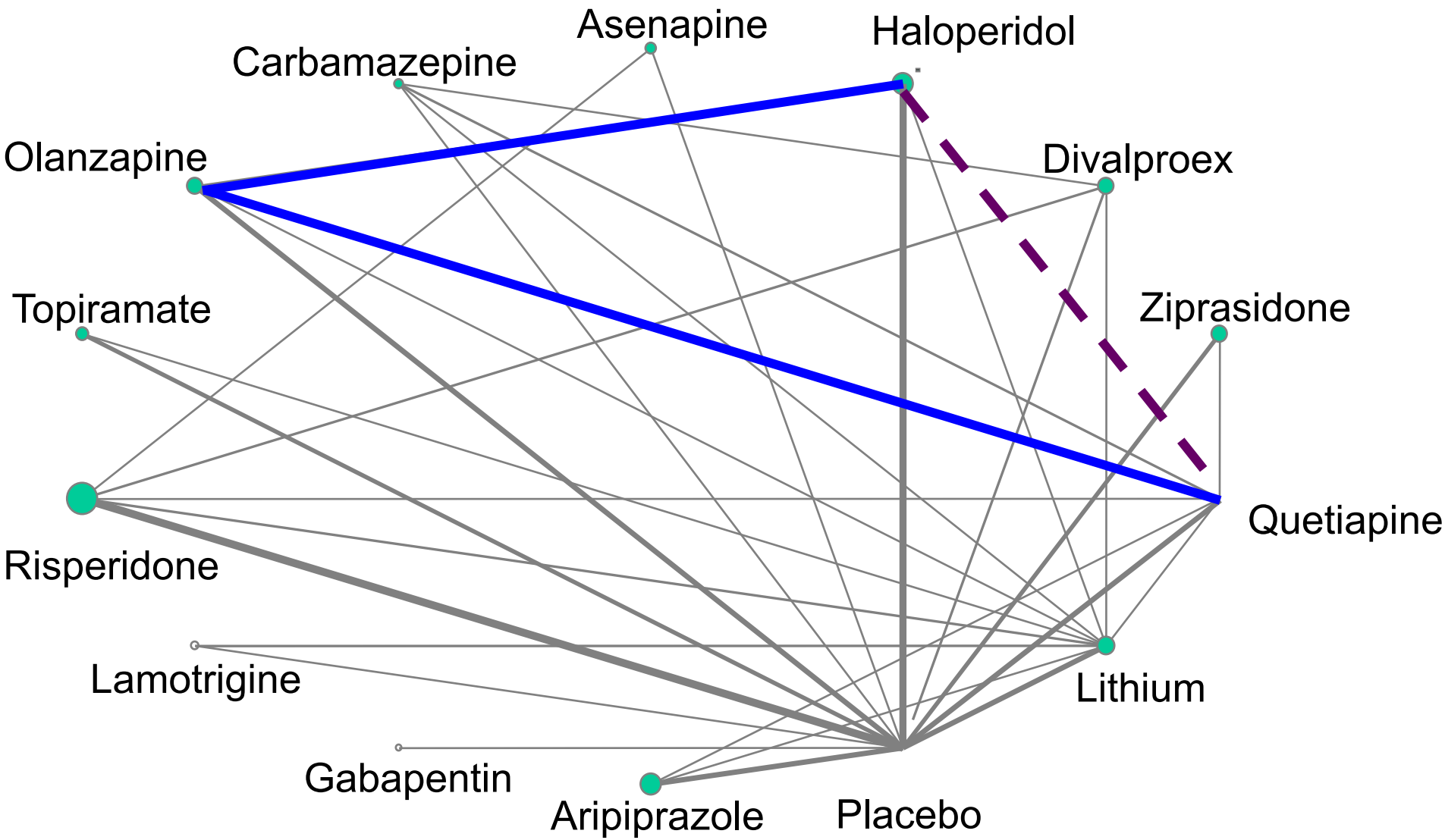
We have this:

Direct and Indirect evidence is synthesized in the entire network



Comparative efficacy and acceptability of antimanic drugs. *Cipriani et al.* **Lancet** 2011

Direct and Indirect evidence is synthesized in the entire network



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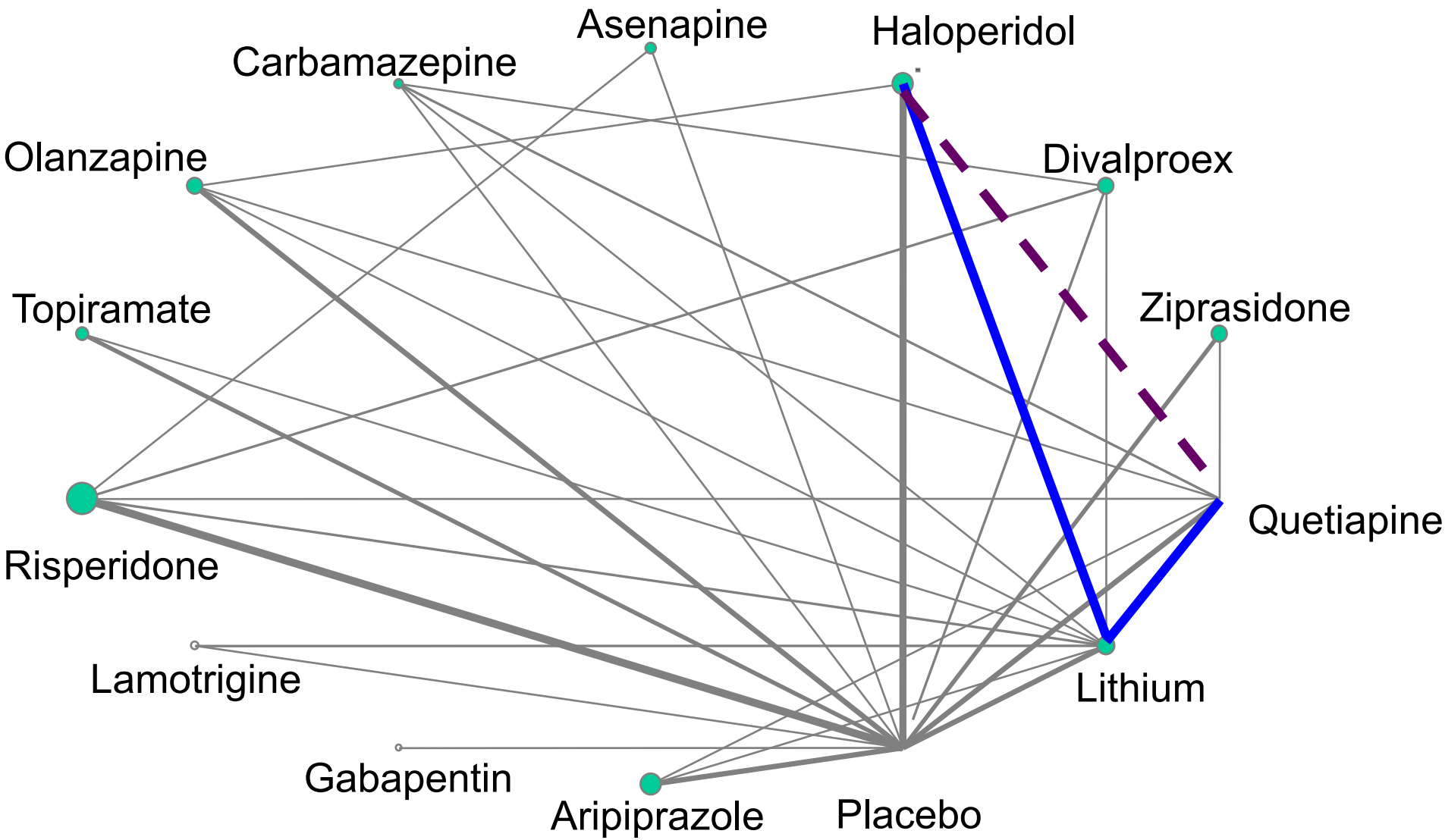

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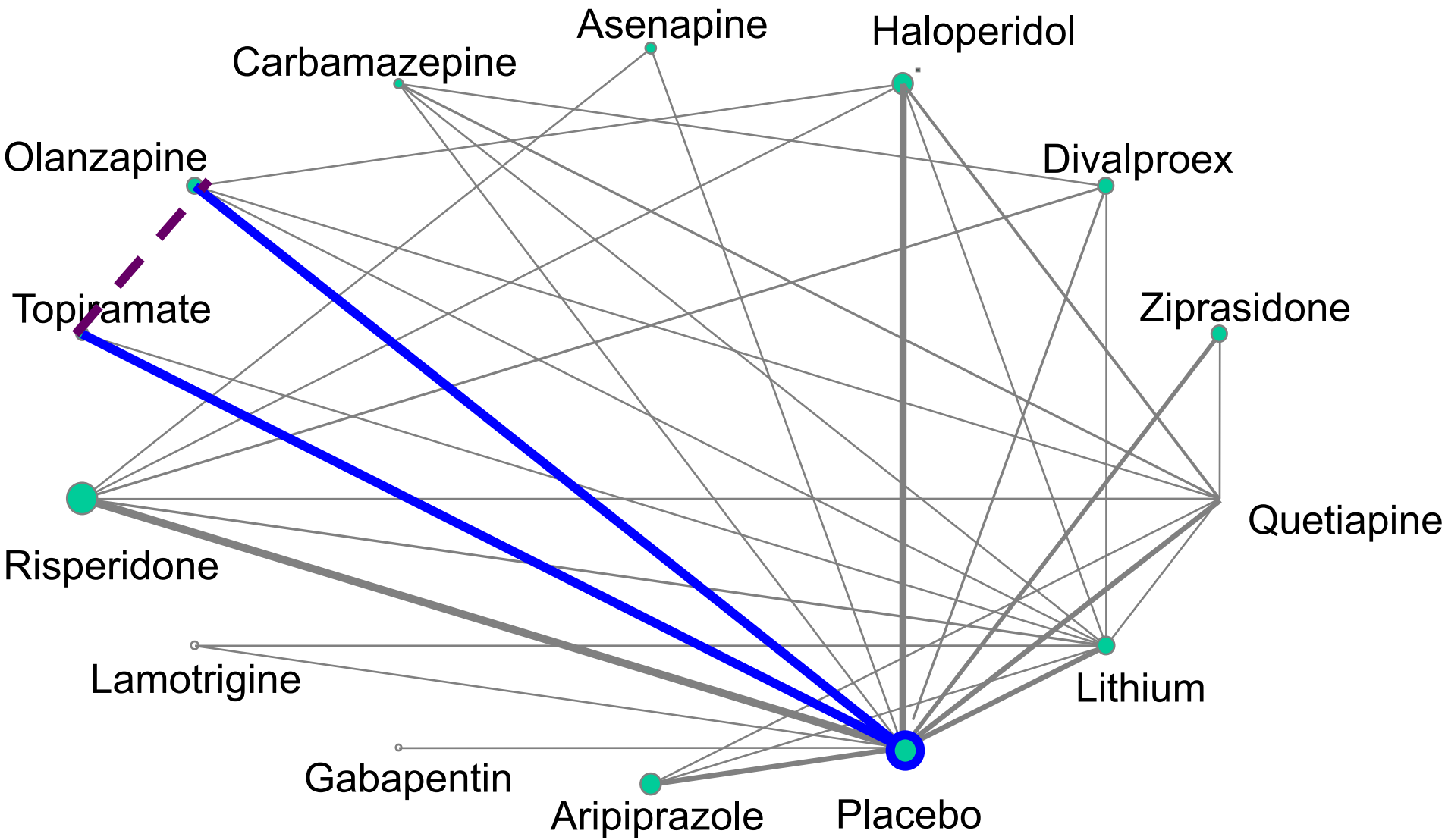

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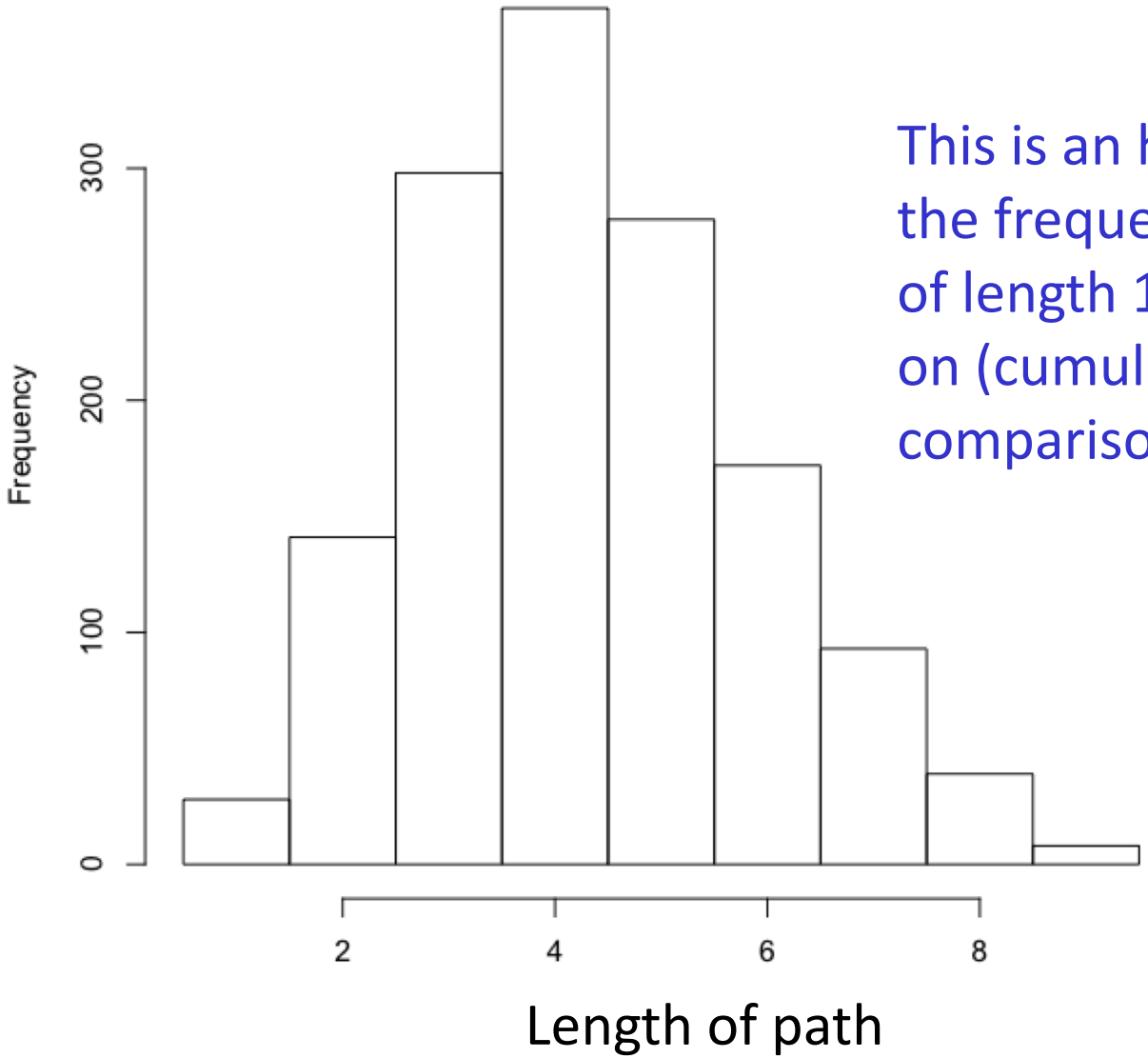
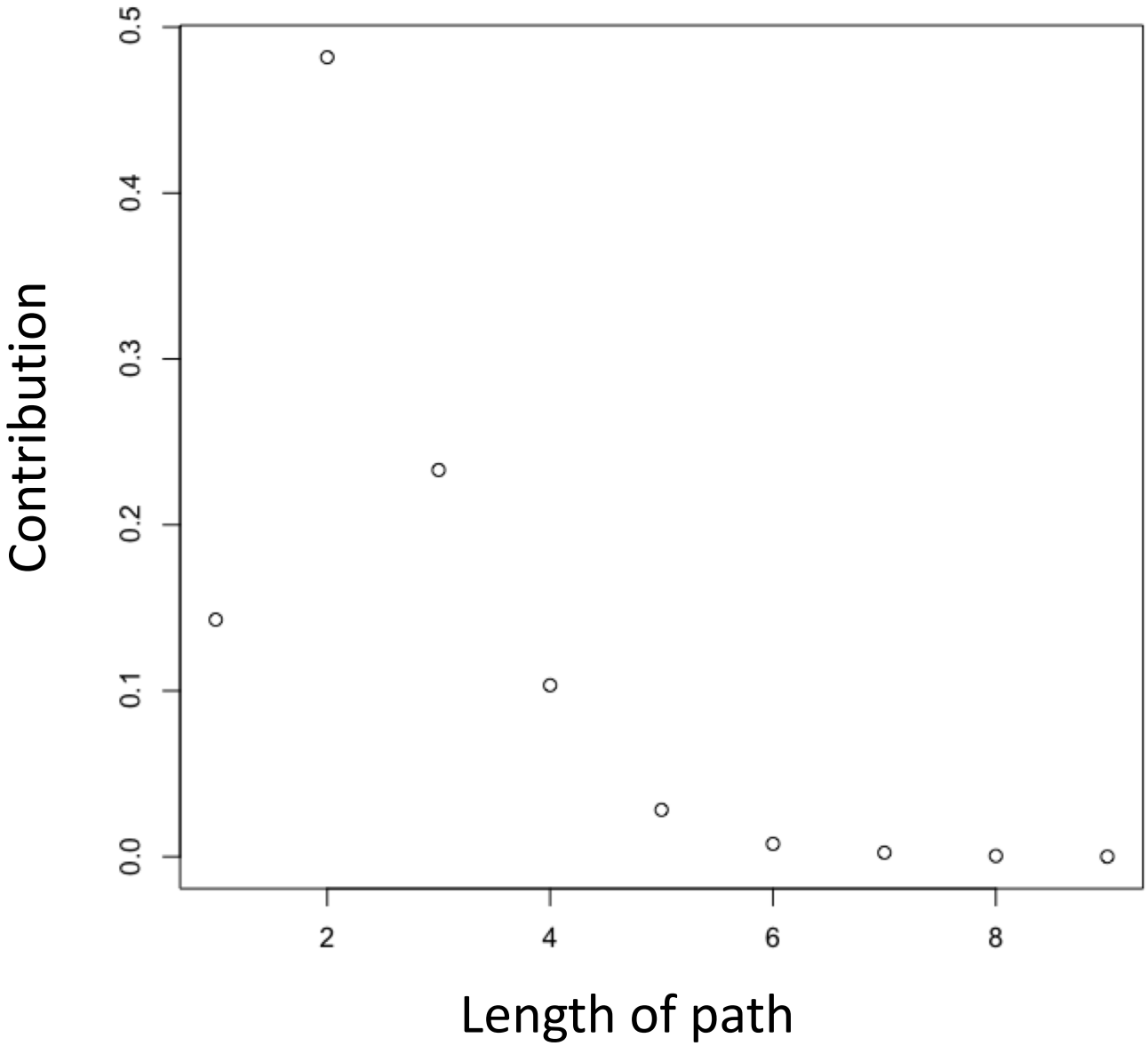
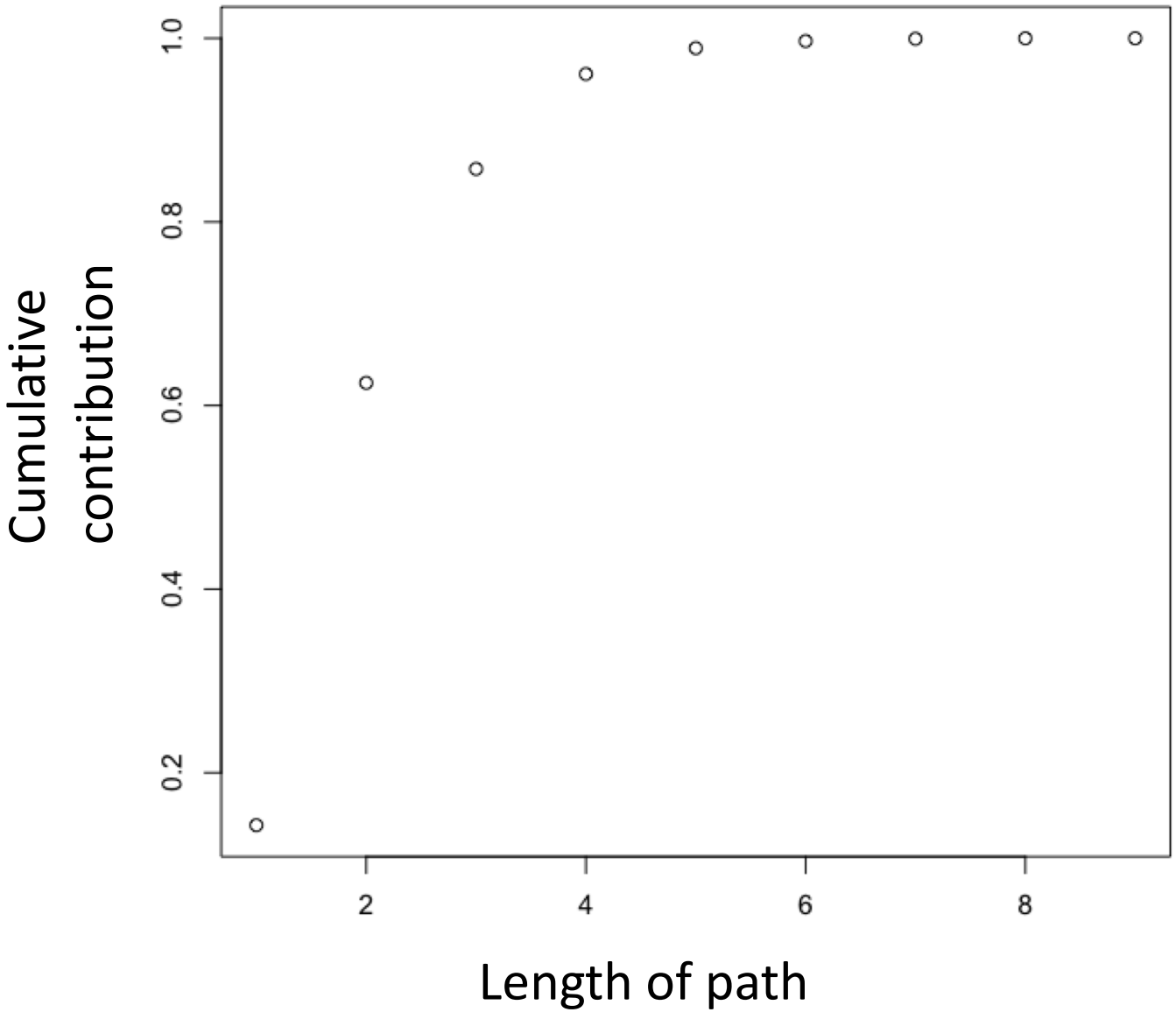
Frequency of length of paths in acute mania dataset



This is an histogram of the frequency of paths of length 1, 2, 3 and so on (cumulatively for all comparisons)



This graph shows the average percentage contribution of all paths of length 1, 2, 3 and so on.



And this is the cumulative version of the previous one. Interestingly, on average 40% contribution comes from paths > 2.

What network meta-analysis can do for you?

- Make the best use of all available evidence
- Avoid selective use of indirect evidence
- We compare interventions which haven’t been directly compared in any experiment

SMD<0 favor the treatment in column

Direct relative treatment effects

HAL							
0.02 (-0.17,0.21)	RIS						
-0.15 (-0.32,0.03)	0.04 (-0.18,0.25)	OLZ					
-1.11 (-1.89,0.33)	-0.67 (-1.40,0.07)		LIT				
-0.42 (-0.71,0.14)	-0.17 (-0.37,0.03)	-0.40 (-0.70, 0.13)	0.11 (-0.20,0.43)	QTP			
-0.05 (-0.20,0.10)			0.06 (-0.16,0.28)		ARI		
0.09 (-0.56,0.38)			-0.23 (-0.76,0.30)			CBZ	
-0.58 (-0.77,-0.39)	**-0.50 (-0.67,-0.33)**		**-0.40 (-0.54,-0.26)**	**-0.37 (-0.51,-0.24)**	**-0.31 (-0.42,-0.20)**	**-0.50 (-0.69,-0.30)**	PBO

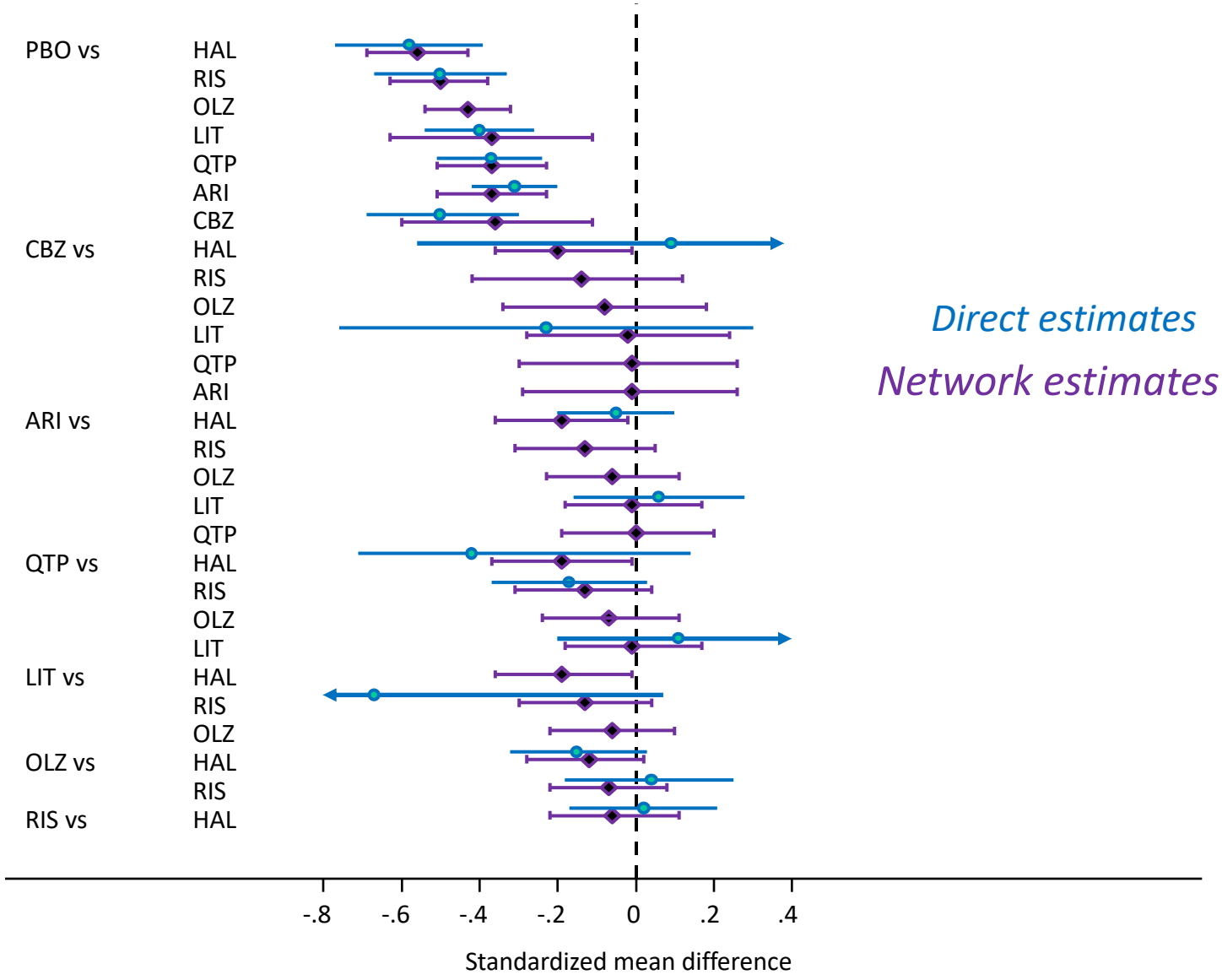
NMA relative treatment effects

HAL							
-0.06 (-0.22,0.11)	RIS						
-0.12 (-0.28,0.02)	-0.07 (-0.22,0.08)	OLZ					
-0.19 (-0.36,-0.01)	-0.13 (-0.30,0.04)	-0.06 (-0.22,0.10)	LIT				
-0.19 (-0.37,-0.01)	-0.13 (-0.31,0.04)	-0.07 (-0.24,0.11)	-0.01 (-0.18,0.17)	QTP			
-0.19 (-0.36,-0.02)	-0.13 (-0.31,0.05)	-0.06 (-0.23,0.11)	-0.01 (-0.18,0.17)	0.00 (-0.19,0.20)	ARI		
-0.20 (-0.36,-0.01)	-0.14 (-0.42,0.12)	-0.08 (-0.34,0.18)	-0.02 (-0.28,0.24)	-0.01 (-0.30,0.26)	-0.01 (-0.29,0.26)	CBZ	
-0.56 (-0.69,-0.43)	**-0.50 (-0.63,-0.38)**	**-0.43 (-0.54,-0.32)**	**-0.37 (-0.63,-0.11)**	**-0.37 (-0.51,-0.23)**	**-0.37 (-0.51,-0.23)**	**-0.36 (-0.60,-0.11)**	PBO

What network meta-analysis can do for you?

- Make the best use of all available evidence
- Avoid selective use of indirect evidence
- We compare interventions which haven't been directly compared in any experiment
- It can increase precision in the estimations

Precision is gained!



What network meta-analysis can do for you?

- Make the best use of all available evidence
- Avoid selective use of indirect evidence
- We compare interventions which haven't been directly compared in any experiment
- It can increase precision in the estimations
- It can rank all competing treatments and hence it can answer policy-relevant questions

Network meta-analysis

key messages

Network meta-analysis is an extension of traditional, pairwise meta-analysis

Network meta-analysis synthesises both **direct and indirect evidence** in a network of trials that contain multiple interventions

Network meta-analysis facilitates “all way” comparisons, and generates relative effect estimates between any two interventions and ranking probabilities for interventions

Network meta-analysis can give valuable insight into the **comparative benefits and harms** of multiple alternative treatment options