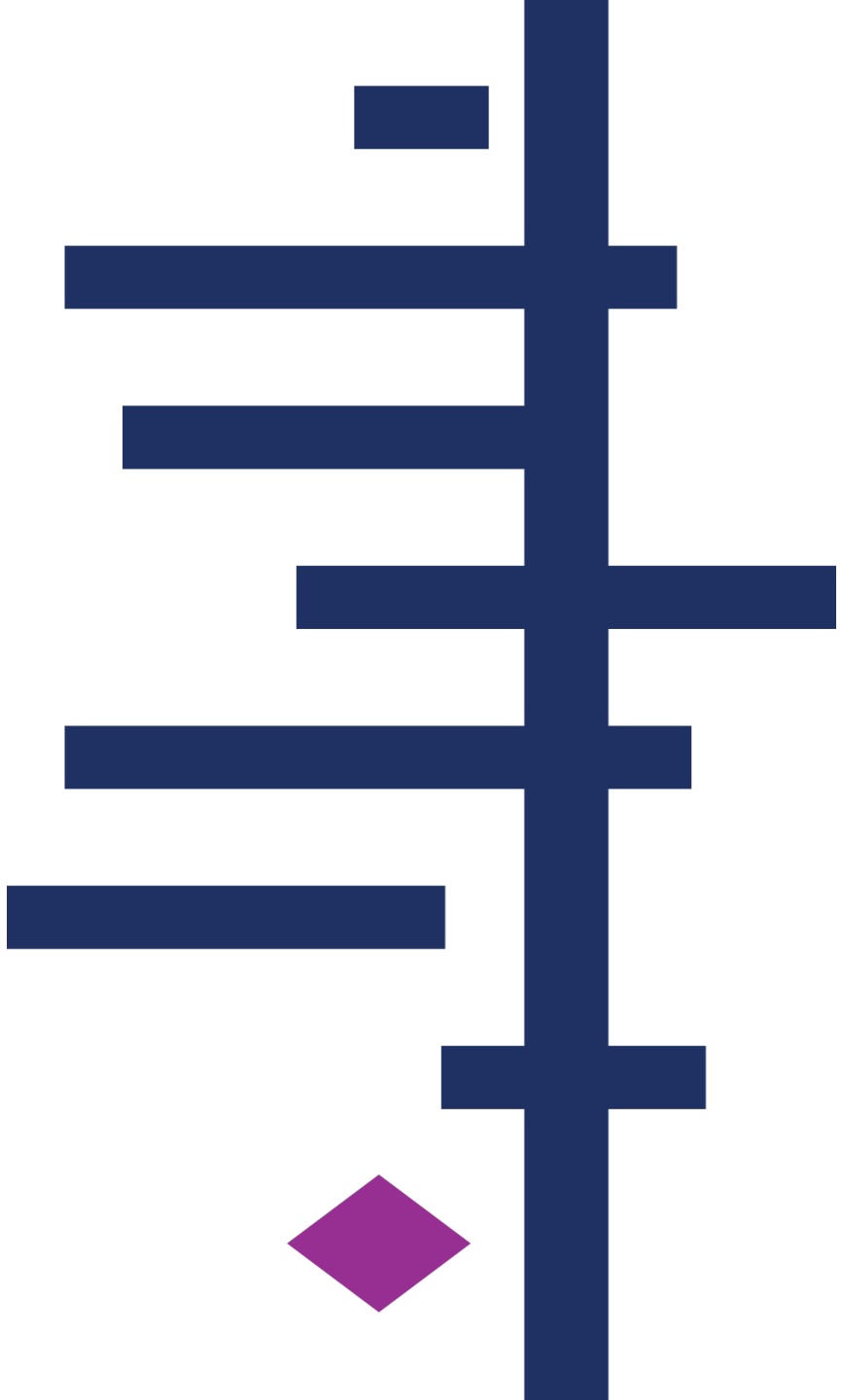
Cochrane

Component network meta-analysis: concepts and insights

Sofia Tsokani

Methods Support Unit

Trusted evidence.
Informed decisions.
Better health.



Structure of session

1. Moving from pairwise to network meta-analysis
2. Complex interventions
3. Component network meta-analysis

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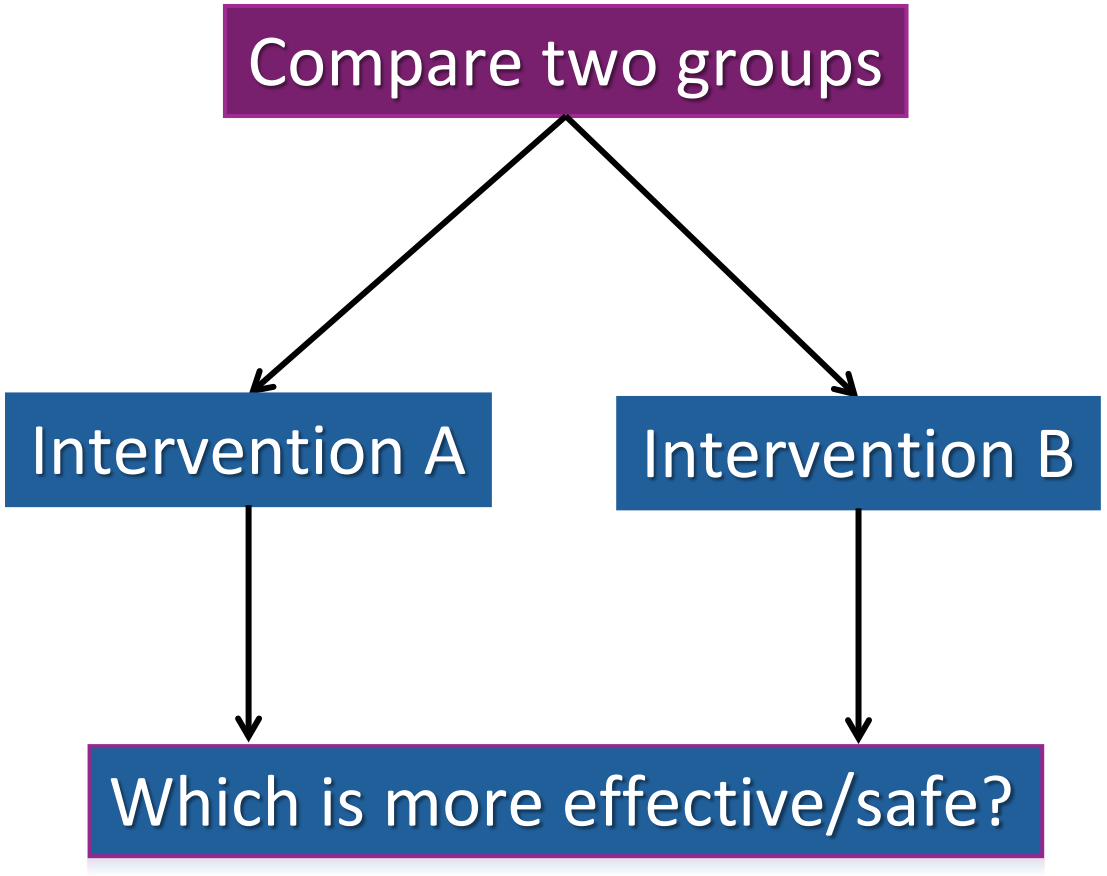
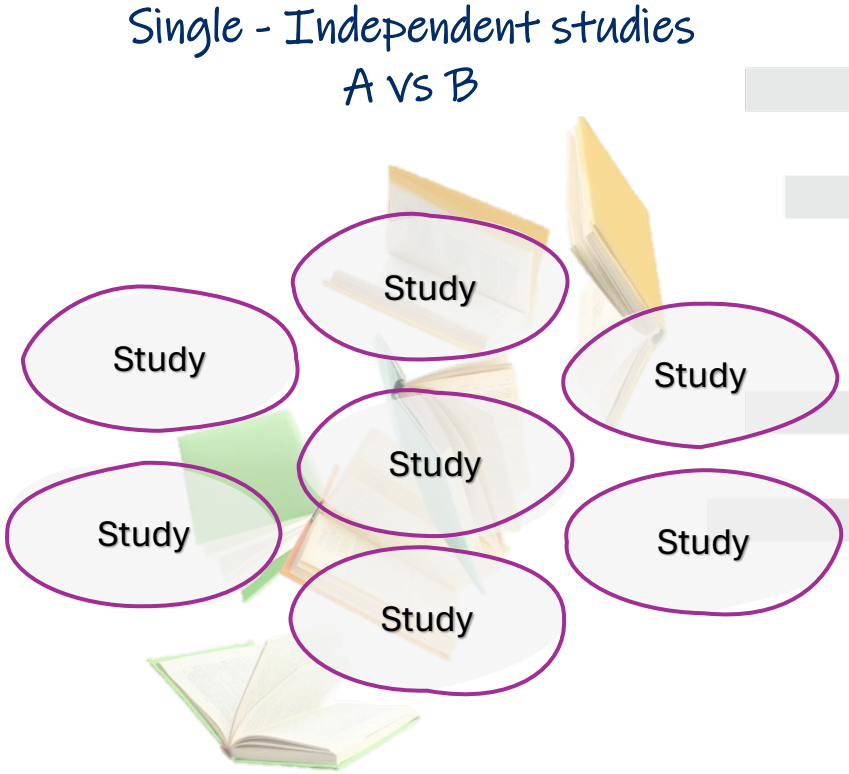
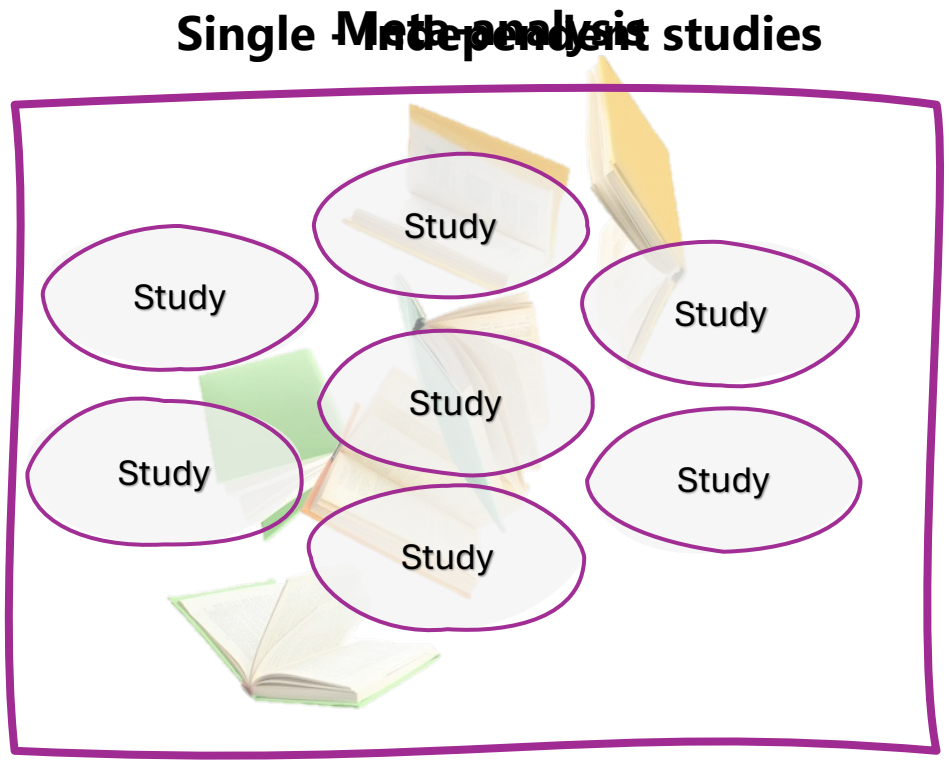

Compare two groups
Intervention A
Intervention B
Which is more effective/safe?


Single - Independent studies
A Vs B
Study
Study
Study
Study
Study
Study
Study

Plethora of clinical trials – possibly contradictory results

How to quantify all this information?

Meta-analysis

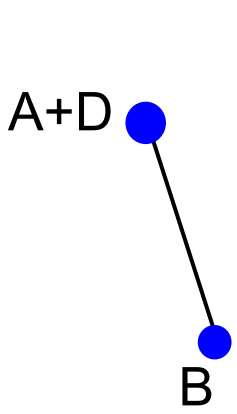


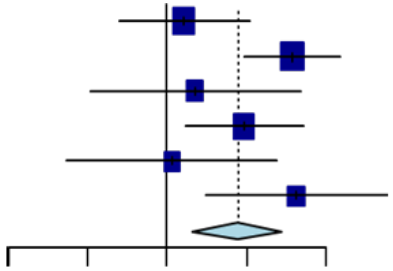
Statistical method for contrasting and combining results from different studies.

Benefits

- Combine multiple sources of evidence
- Increased precision
- Resolve uncertainty when studies disagree

Meta-analysis

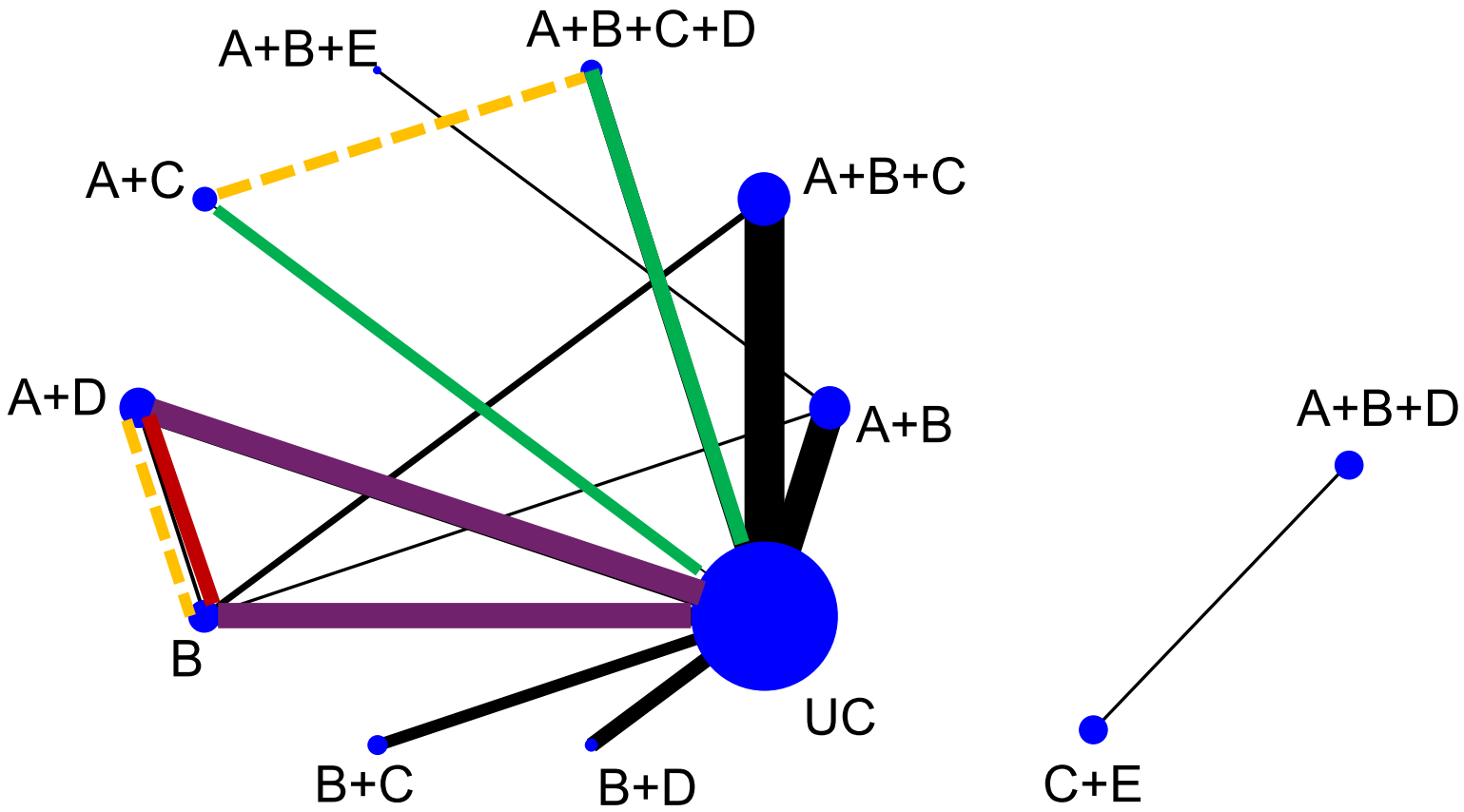




e.g., weight loss

Network Meta-analysis

- Extension of meta-analysis
- Compare multiple interventions

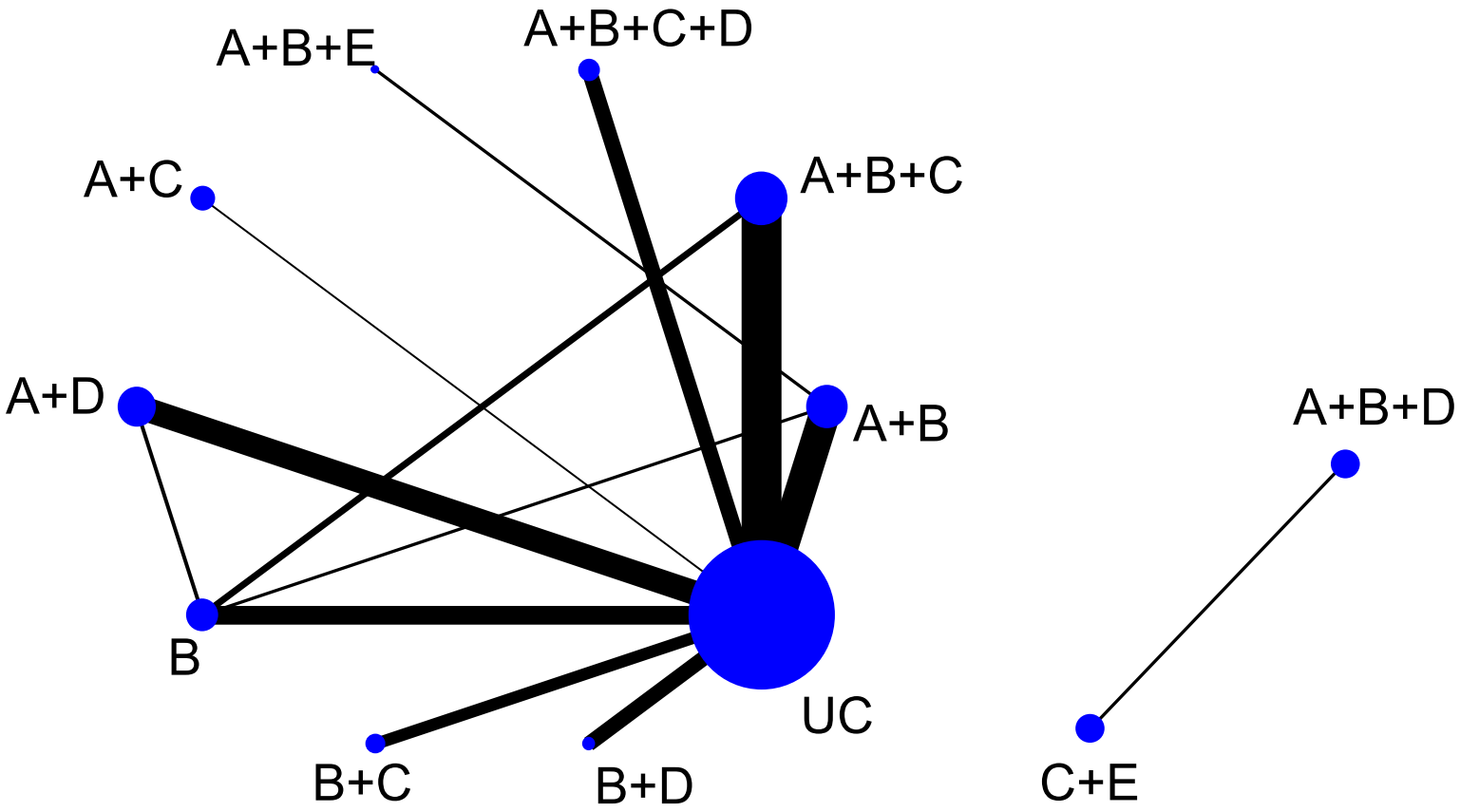


Benefits

- Increase precision: two sources of evidence (direct and indirect)
- Compare interventions that have never been compared before
- Rank interventions based on efficacy/safety

Network Meta-analysis

- ‘Complex’ or ‘Multicomponent ’ interventions
- Certain components (A–E)



Complex/Multicomponent interventions

An intervention may consist of several (possibly interacting) components

What are these components?

- Integral parts of the intervention
- Any intervention characteristics may impact on the intervention's effect.
  - *What* is the intervention (properties the intervention)
  - *How* is it provided (mode of delivery: e.g., face-to-face, remotely, individually, or intensity)
  - *Who* provides the intervention (e.g., doctor, nurse, nutritionist)
  - *Where* is the intervention provided (e.g., hospital, home, other setting)

Examples

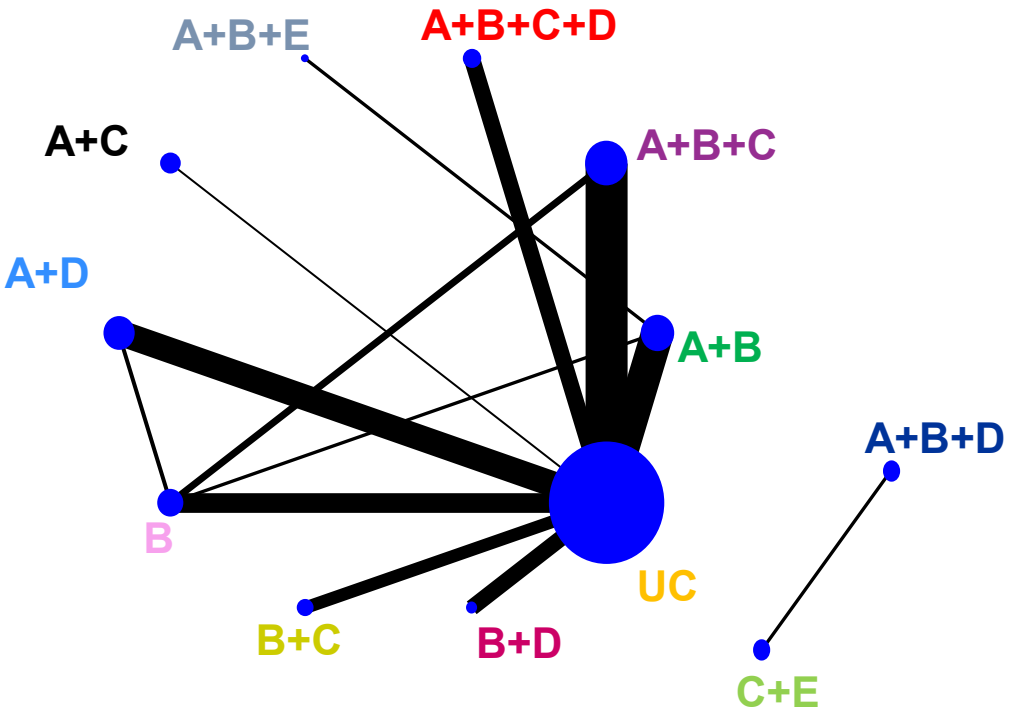
- Psychological, behavioral and self-management interventions (SMIs)
  Educating patients about the disease and focuses on changing behavioral patterns
- Falls and Fractures
  Exercise + Medication + Environmental assessment and modifications

Seitidis G. et al. Graphical tools for visualizing the results of network meta-analysis of multicomponent interventions. Res Syn Meth. 2023; 14(3): 382-395. doi:10.1002/jrsm.1617

Standard NMA vs Component NMA

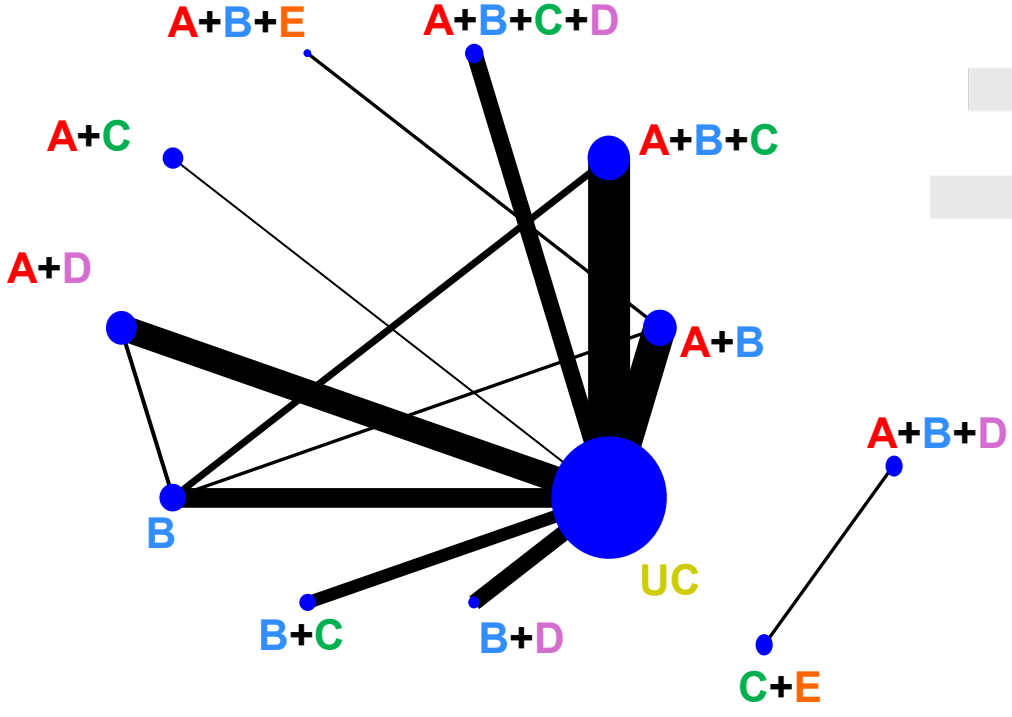
Standard NMA

'which interventions work?'



Component NMA

'which components work?'



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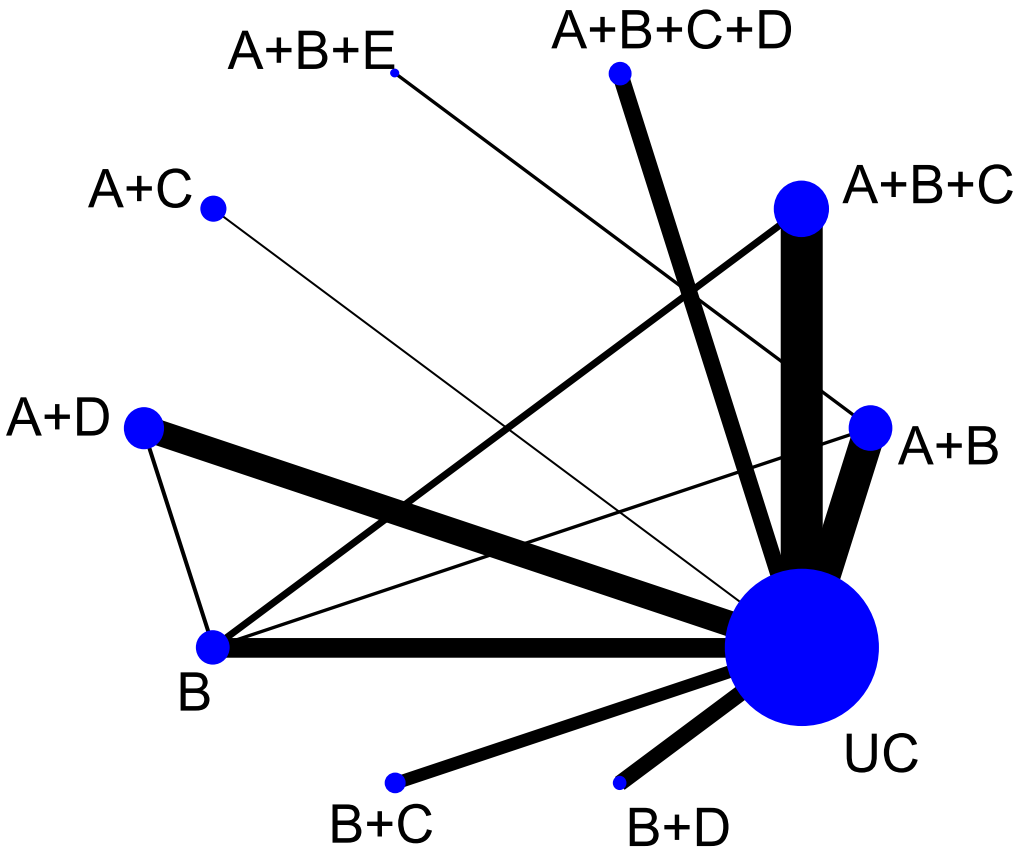
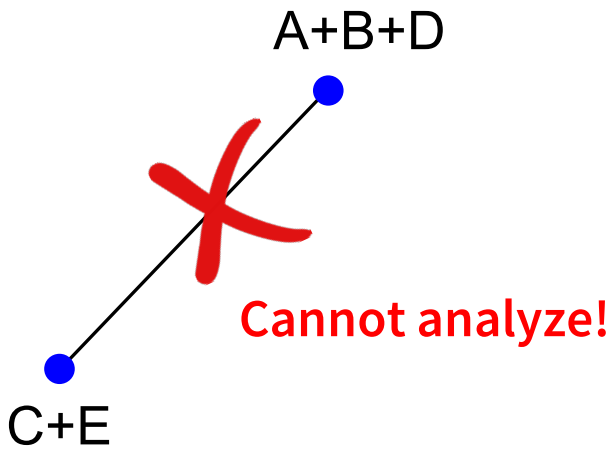
Network meta-analysis

'Which interventions work?'





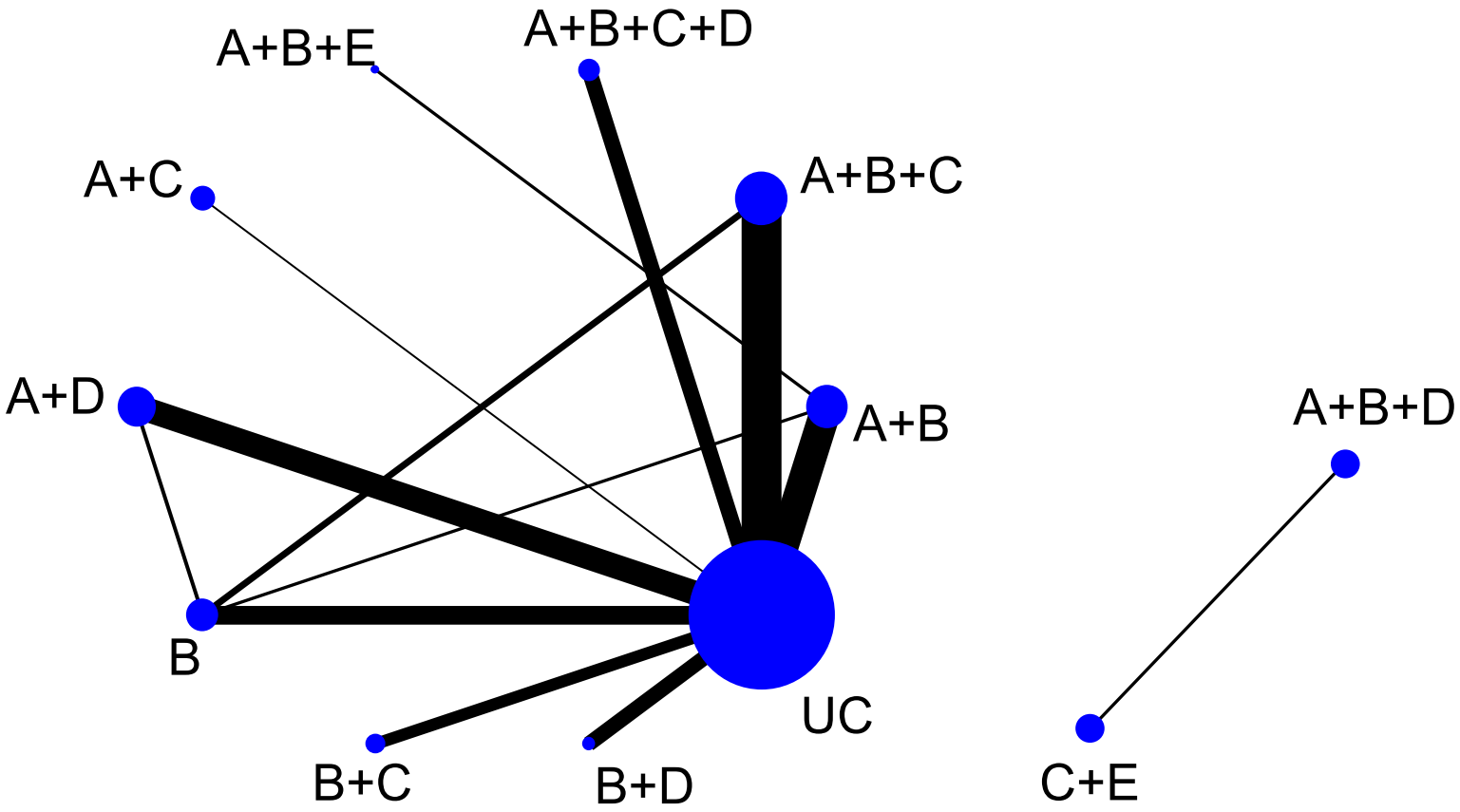
Cannot analyze!

Intervention	Effect
A+B+E	d1
A+B+C+D	d2
A+B+C	d3
A+B	d4
B+D	d5
A+C	d6
A+D	*d7*
B	*d8*
B+C	*d9*
UC	*reference*

Component Network meta-analysis

Decomposition of multicomponent interventions

'Which components work?'



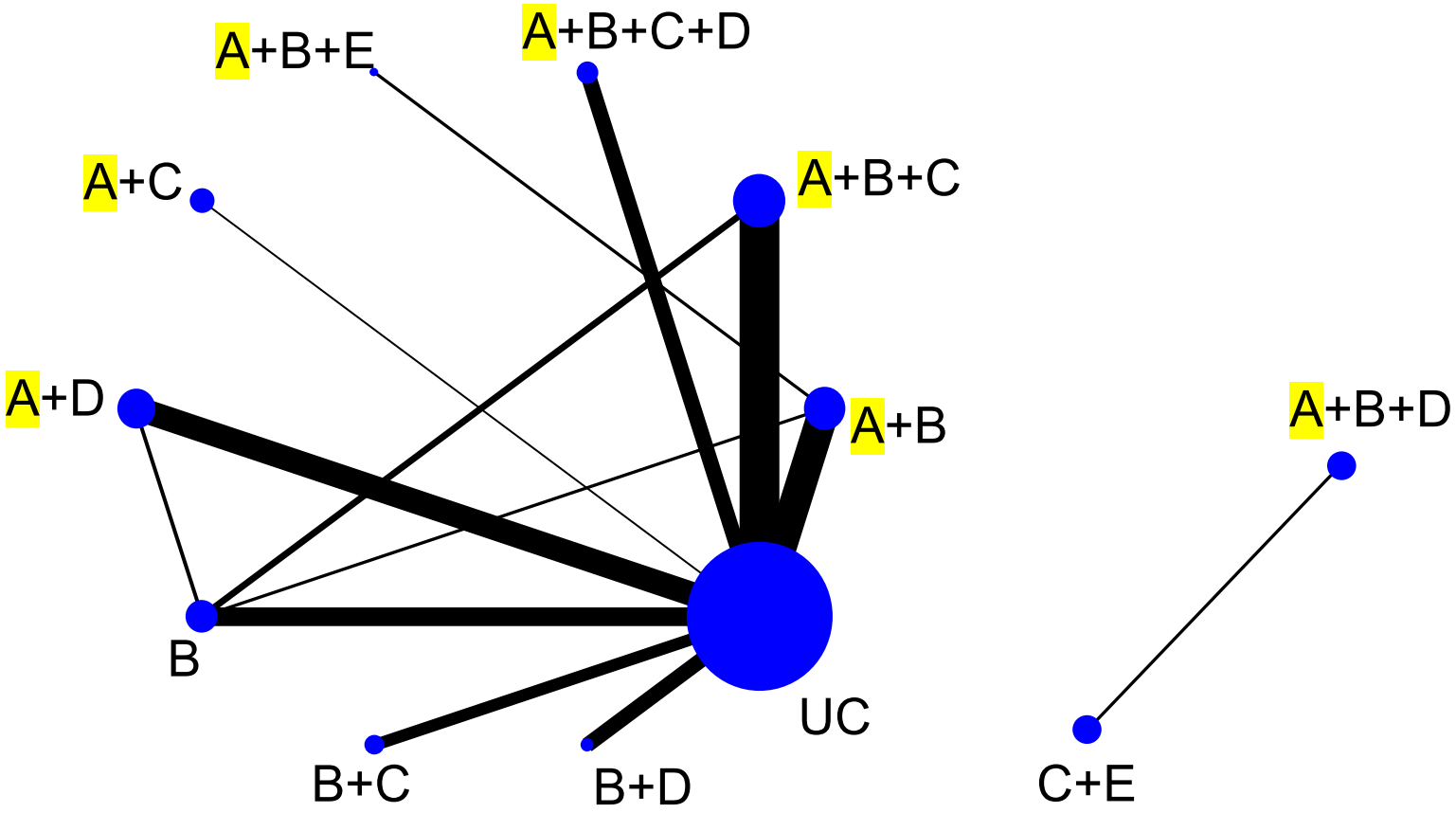
Component	Effect
A	d_A
B	d_B
C	d_C
D	d_D
E	d_E
UC	*reference*

Intervention	Effect
A+B+E	$d_A+d_B+d_E$
A+B+C+D	$d_A+d_B+d_C+d_D$
A+B+C	$d_A+d_B+d_C$
A+B	d_A+d_B
B+D	d_C+d_D
A+C	d_A+d_C
A+D	d_A+d_D
B	d_B
B+C	d_B+d_C
UC	*reference*

Component Network meta-analysis

Decomposition of multicomponent interventions

'Which components work?'



Component	Effect
A	d_A
B	d_B
C	d_C
D	d_D
E	d_E
UC	*reference*

Intervention	Effect
A+B+E	$d_A+d_B+d_E$
A+B+C+D	$d_A+d_B+d_C+d_D$
A+B+C	$d_A+d_B+d_C$
A+B	d_A+d_B
B+D	d_C+d_D
A+C	d_A+d_C
A+D	d_A+d_D
B	d_B
B+C	d_B+d_C
UC	*reference*

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Standard NMA vs Component NMA

Standard NMA

'Which interventions work?'

- Connected networks
- Compare any pair of interventions
- Two sources of evidence
  - Direct
  - Indirect
- Increase precision
- Ranking options

Component NMA

'Which components work?'

- (Dis)connected networks
- Compare any pair of interventions
- Two sources of evidence
  - Direct
  - Indirect
- More evidence
  - More precise intervention effects
  - More moderate effects
- Effect of all combinations of components
- Intervention estimates are based on the components estimates

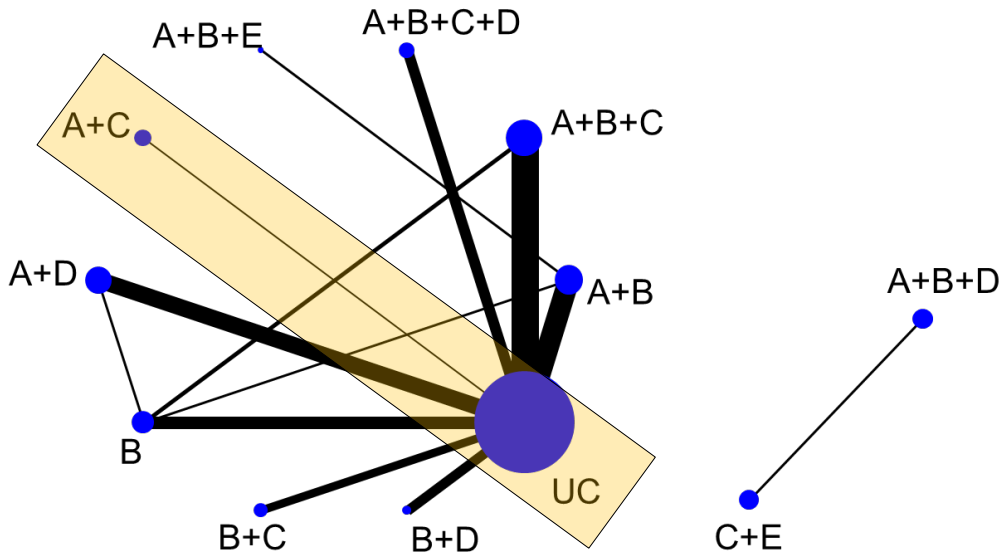
Component Network meta-analysis

Additive and interaction models

- Additive model:
  - **effect(A+C)=effect(A)+effect(C)** or $\mathbf{d_{A+C}=d_A+d_C}$ (additivity assumption)
  - no interaction between components
- Interaction model:
  - Components may interact with each other
  - **effect(A+C)=effect(A)+effect(C)+interaction(A, C)** or $\mathbf{d_{A+C}=d_A+d_C+d_{A+C}}$
    - antagonistically $d_{A+C} < 0$
    - synergistically $d_{A+C} > 0$

Sparse networks

- Sparse network of multicomponent interventions
  - efficacy of interventions may be confounded with study characteristics



- 1 study-large effect
- Unclear if the efficacy is observed is due to study characteristics or intervention

Real data example

DOI: 10.1111/jgs.17375

Journal of the American Geriatrics Society

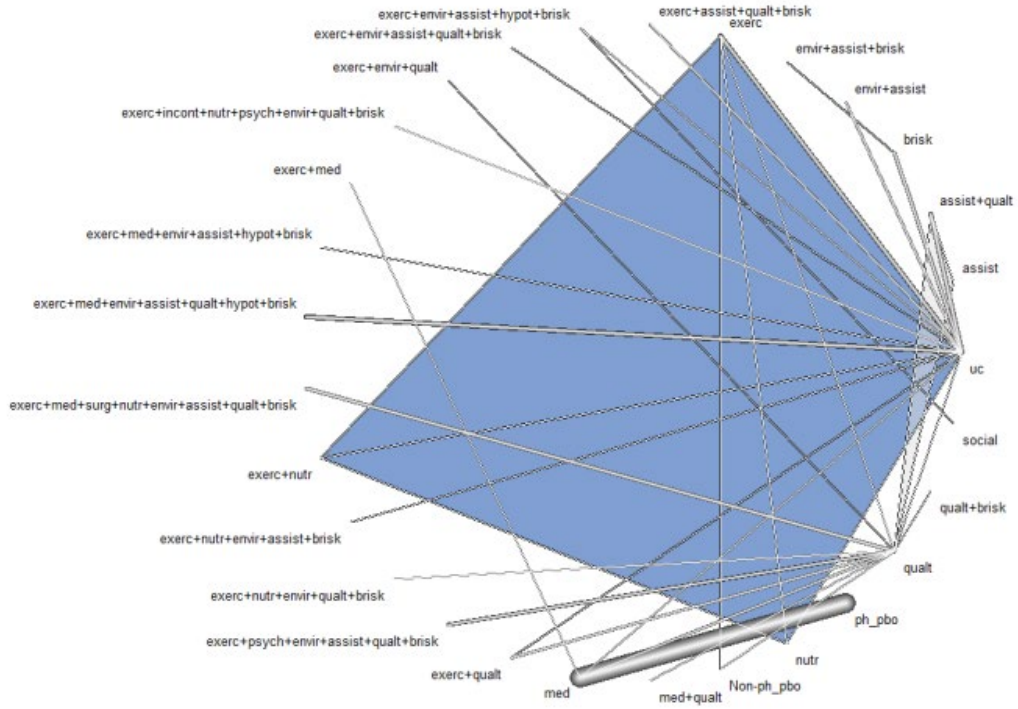
Interventions for preventing falls and fall-related fractures in community-dwelling older adults: A systematic review and network meta-analysis

- Explored single, multiple and multifactorial interventions and their individual components
- Outcome: preventing fall-related fractures in community-dwelling persons, aged ≥65 years
- NMA and additive CNMA model

Network details:

- 46 studies (43,811 participants)
- 27 interventions
- 14 components+ Usual care (UC)

Component	Abbreviation
assist	Assistive technology
brisk	Basic falls risk assessment
envir	Environmental assessment and modifications
exerc	Exercise
nutr	Fluid or nutrition therapy
med	Medication
hypot	Management of orthostatic hypotension
incont	Management of urinary incontinence
non_ph_pbo	Non-pharmacological placebo
ph_pbo	Pharmacological placebo
psych	Psychological interventions
qualt	Quality improvement strategies
social	Social engagement
surg	Surgery



Dautzenberg L et al. Interventions for preventing falls and fall-related fractures in community-dwelling older adults: A systematic review and network meta-analysis. J Am Geriatr Soc. 2021;69(10):2973-2984.
Tsokani S, Seitidis G, Mavridis D. Component network meta-analysis in a nutshell. BMJ Evidence-Based Medicine 2023;28:183–186.

Real data example

Component effects

Table 2 Additive CNMA results (components of interventions preventing fall-related fractures)

Component	Abbreviation	logRR (95% CI)	RR (95% CI)
assist	Assistive technology	0.51 (0.06 to 0.95)	1.66 (1.07 to 2.59)
brisk	Basic falls risk assessment	−0.13 (−0.49 to 0.23)	0.88 (0.61 to 1.26)
envir	Environmental assessment and modifications	0.17 (−0.38 to 0.73)	1.19 (0.68 to 2.07)
exerc	Exercise	−0.19 (−0.44 to 0.07)	0.83 (0.64 to 1.07)
nutr	Fluid or nutrition therapy	0.07 (−0.51 to 0.64)	1.07 (0.60 to 1.90)
med	Medication	−0.17 (−0.57 to 0.24)	0.85 (0.56 to 1.27)
hypot	Management of orthostatic hypotension	0.01 (−0.73 to 0.74)	1.01 (0.48 to 2.10)
incont	Management of urinary incontinence	0.79 (−0.45 to 2.02)	2.20 (0.64 to 7.57)
non_ph_pbo	Non-pharmacological placebo	0.00 (−0.83 to 0.83)	1.00 (0.44 to 2.30)
ph_pbo	Pharmacological placebo	−0.26 (−0.68 to 0.16)	0.77 (0.51 to 1.17)
psych	Psychological interventions	−0.31 (−1.03 to 0.41)	0.73 (0.36 to 1.50)
qualt	Quality improvement strategies	−0.31 (−0.69 to 0.07)	0.73 (0.50 to 1.07)
social	Social engagement	1.09 (−0.24 to 2.43)	2.98 (0.79 to 11.31)
surg	Surgery	−0.52 (−1.33 to 0.29)	0.60 (0.26 to 1.34)

CNMA, component network meta-analysis; logRR, log (risk ratio); RR, risk ratio.

Real data example

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CNMA, component network meta-analysis; logRR, log (risk ratio); RR, risk ratio.

Component effects can be used to calculate the effect of any combination

- assist+envir+qualt+psych=0.51+0.17-0.31-0.31=0.06

Real data example

Component effects

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CNMA, component network meta-analysis; logRR, log (risk ratio); RR, risk ratio.

Effect (assist + brisk) =?

a. 0.51
b. -0.13
c. 0.64
d. 0.38

Real data example

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CNMA, component network meta-analysis; logRR, log (risk ratio); RR, risk ratio.

Effect (assist + brisk) =?

a. 0.51
b. -0.13
c. 0.64
d. 0.38

Real data example

Interventions effects

Table 3 NMA and additive CNMA results for interventions preventing fall-related fractures

Intervention (#studies*)	Model			
	NMA		Additive CNMA	
	logRR (95% CI)	RR (95% CI)	logRR (95% CI)	RR (95% CI)
qualt+brisk (1)	−1.97 (−4.61 to 1.11)	0.14 (0.01 to 3.02)	−0.44 (−0.92 to 0.04)	0.64 (0.40 to 1.04)
exerc+med (1)	−0.89 (−2.04 to 0.25)	0.41 (0.13 to 1.28)	−0.35 (−0.83 to 0.13)	0.70 (0.43 to 1.13)
exerc+nutr (1)	−0.73 (−1.71 to 0.25)	0.48 (0.18 to 1.28)	−0.12 (−0.74 to 0.50)	0.89 (0.48 to 1.64)
exerc+med+surg+nutr+envir+assist+qualt+brisk (1)	−0.65 (−1.43 to 0.11)	0.52 (0.24 to 1.12)	−0.56 (−1.14 to 0.02)	0.57 (0.32 to 1.02)
brisk (2)	−0.51 (−0.94 to to 0.06)	0.60 (0.39 to 0.94)	−0.13 (−0.49 to 0.23)	0.88 (0.61 to 1.26)
exerc (10)	−0.48 (−0.87 to to 0.11)	0.62 (0.42 to 0.90)	−0.19 (−0.44 to 0.07)	0.83 (0.64 to 1.07)
med+qualt (1)	−0.46 (−1.51 to 0.61)	0.63 (0.22 to 1.84)	−0.48 (−1.09 to 0.14)	0.62 (0.34 to 1.15)

*Studies including the intervention as combination.

CNMA, component network meta-analysis; logRR, log (risk ratio); NMA, network meta-analysis; RR, risk ratio.

- CNMA more precise and moderate effect estimates
- qualt+brisk: compared in one study (114 participants)
- Component ‘social’
- Additivity assumption holds

Overall…

With CNMA…

- more precise intervention effects
  - Use evidence from all studies that share the same components.
- more moderate effects
  - Not driven mainly by individual studies
- estimation of the effect of all combinations of component
  - Even if not observed in included studies
- may reduce confounding in sparse networks
  - Transitivity assumption may be threatened

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Overall…

However…

- Additivity assumption is strong!
  - Biased estimates, if it doesn't hold
  - Statistical test, only for connected networks
- Interaction model relaxes the additivity assumption
  - Challenging to define interaction terms
- Consistency cannot be assessed in CNMA
- Cannot test for small study effects using
  - Do it using the classical methods employed in NMA

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Presenting results

Cochrane Library

Cochrane Database of Systematic Reviews

Pharmacological and electronic cigarette interventions for smoking cessation in adults: component network meta-analyses (Review)

Lindson N, Theodoulou A, Ordóñez-Mena JM, Fanshawe TR, Sutton AJ, Livingstone-Banks J, Hajizadeh A, Zhu S, Aveyard P, Freeman SC, Agrawal S, Hartmann-Boyce J

Summary of findings 1. Summary of findings table: components of pharmacological and e-cigarette interventions for smoking cessation: smoking cessation at 6+ months

Components of pharmacological and e-cigarette interventions for smoking cessation: smoking cessation at 6 + months

Population: adults (aged ≥ 18 years) who smoked cigarettes

Components: components of pharmacological and e-cigarette (EC) interventions for smoking cessation

Comparator: no pharmacological or e-cigarette intervention (64 RCTs of 15,793 participants had data on this component)

Outcome: smoking cessation at 6 months to 5 years (although predominantly 6 months to 12 months)

Setting: predominantly USA and Europe

Component	Number of participants (studies) with data on component	Relative effect* (95% CrI)	Anticipated absolute effect**			Certainty of the evidence	Notes
			Without intervention	With intervention	Difference		
Varenicline	16,430 (67 RCTs)	**OR 2.33** (2.02 to 2.68)	6 per 100	14 per 100 (12 to 16)	8 per 100 (6 to 10)	**High**[a]	Prediction interval: 1.31 to 4.11
Cytisine	3848 (7 RCTs)	**OR 2.21** (1.66 to 2.97)	6 per 100	13 per 100 (10 to 18)	7 per 100 (4 to 12)	**High**	Prediction interval: 1.19 to 4.22
Nicotine patch	37,319 (105 RCTs)	**OR 1.37** (1.20 to 1.56)	6 per 100	8 per 100 (7 to 9)	2 per 100 (1 to 3)	**High**[b]	Prediction interval: 0.77 to 2.41
Fast-acting NRT (nicotine other)	31,756 (120 RCTs)	**OR 1.41** (1.29 to 1.55)	6 per 100	9 per 100 (8 to 9)	3 per 100 (2 to 3)	**High**[b]	Prediction interval: 0.81 to 2.49
Nicotine EC	3828 (16 RCTs)	**OR 2.37** (1.73 to 3.24)	6 per 100	14 per 100 (10 to 19)	8 per 100 (4 to 13)	**High**	Prediction interval: 1.26 to 4.48
Non-nicotine/placebo EC	1094 (8 RCTs)	**OR 1.16** (0.74 to 1.80)	6 per 100	7 per 100 (4 to 11)	1 per 100 (−2 to 5)	**Low**[c]	Prediction interval: 0.57 to 2.36
Bupropion	14,759 (71 RCTs)	**OR 1.43** (1.26 to 1.62)	6 per 100	9 per 100 (8 to 10)	3 per 100 (2 to 4)	**High**[a,b]	Prediction interval: 0.81 to 2.52
Nortriptyline	1290 (10 RCTs)	**OR 1.35** (1.02 to 1.81)	6 per 100	8 per 100 (6 to 11)	2 per 100 (0 to 5)	**Moderate**[b,d]	Prediction interval: 0.72 to 2.55
Nicotine tapering	33,156 (111 RCTs)	**OR 1.14** (1.00 to 1.29)	6 per 100	7 per 100 (6 to 8)	1 per 100 (0 to 2)	**Low**[d,e]	Prediction interval: 0.64 to 2.00

How and when to apply?

- Multicomponent interventions
- Both Bayesian and frequentist framework
- NMA and CNMA are complimentary models
  - Summary NMA effects
  - Explore which components are observed in the most efficacious interventions

  - Visualization tools-viscomp package
    - Ways of visualizing NMA results consisting of interventions with multiple components
    - E.g., Insights on how components are combined

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  - Ways of visualizing NMA results consisting of interventions with multiple components
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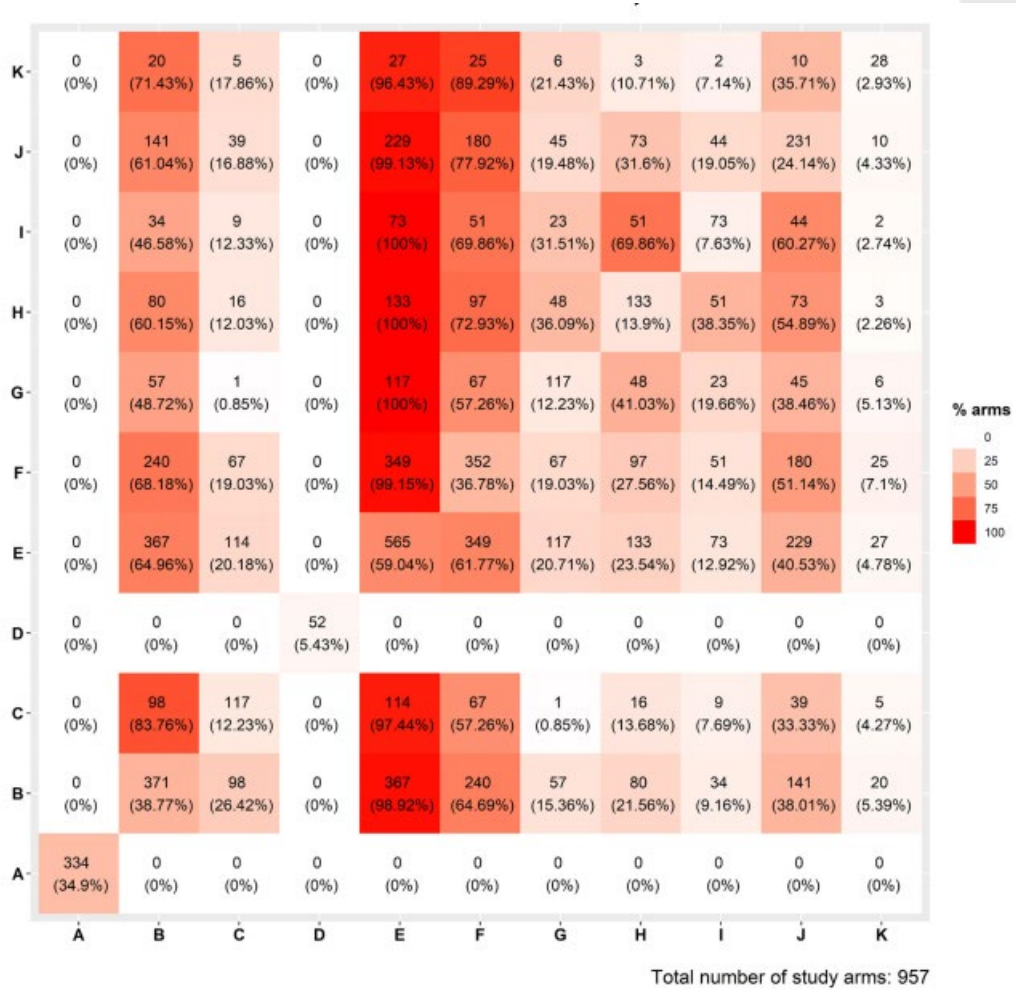
- Components cross-table: Explore number of arms that include a component or any pair of components
  - Diagonal elements refer to components
  - off-diagonal elements to components combinations.



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Thank you!

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Data extraction for components

- Extract data as in standard NMA
  - If available in the software used for analysis, employ a common separator for all combined treatments within the network. (e.g., in netmeta R-package, the default is the plus sign "+"; however, any other symbol can be used. In this way component matrix is automatically calculated).
  - Create component matrix, using dummy variables for components. See fictional example below for multicomponent interventions using 3 different components A,B,C.

				Treatment 1 components			Treatment 2 components			Treatment 3 components		
Study	**treat1**	**treat2**	**treat3**	**Tr1_A**	**Tr1_B**	**Tr1_C**	**Tr2_A**	**Tr2_B**	**Tr2_C**	**Tr3_A**	**Tr3_B**	**Tr3_C**
1	A+B+C	C		1	1	1	0	0	1			
2	B	A+B+C	B+C	0	1	0	1	1	1	0	1	1