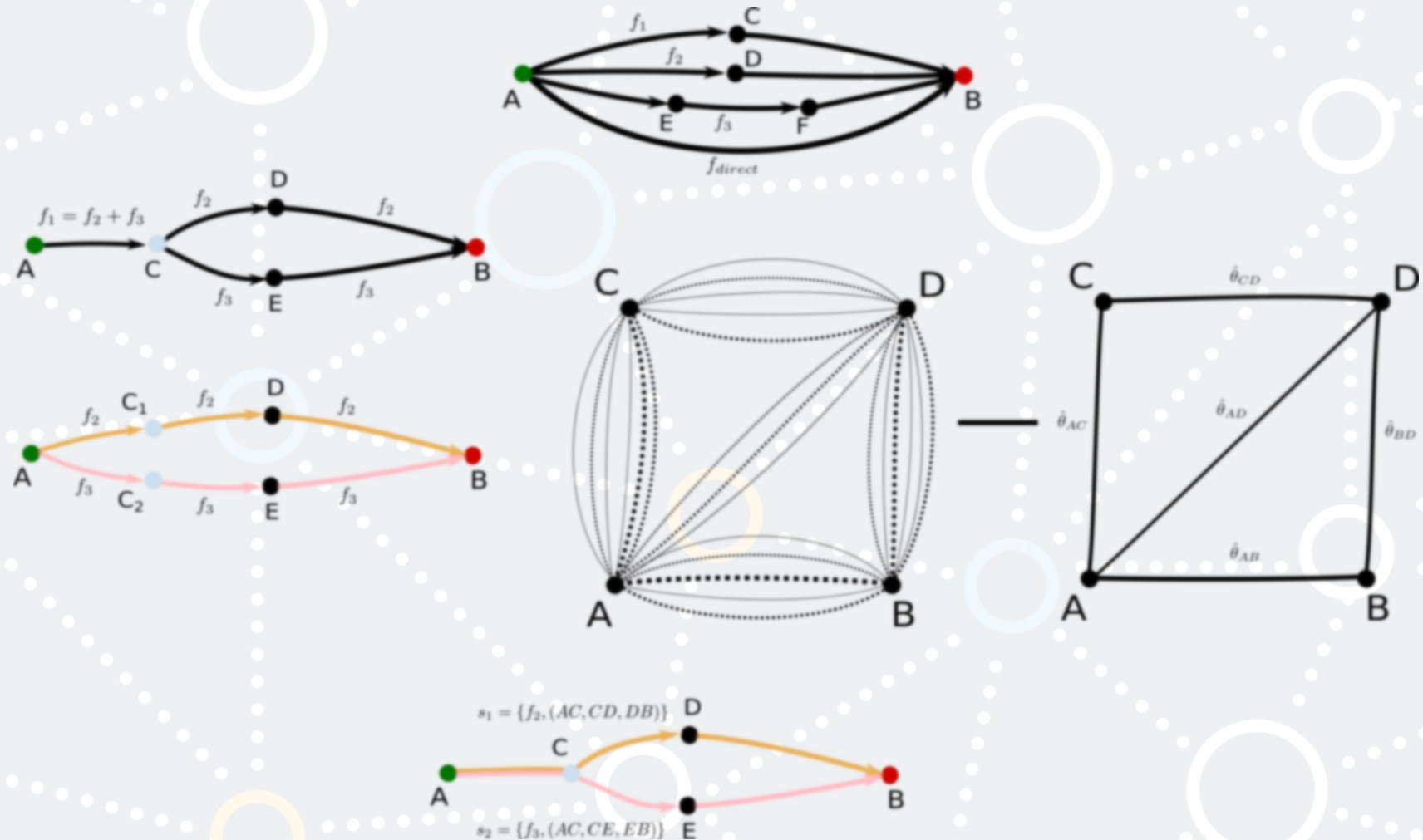


USING FLOW TO ESTIMATE THE PERCENTAGE CONTRIBUTION OF STUDIES IN NETWORK META-ANALYSIS

Theodore Papakonstantinou

Institute of Social and Preventive Medicine, University of Bern Switzerland

ISCB Melbourne 2018



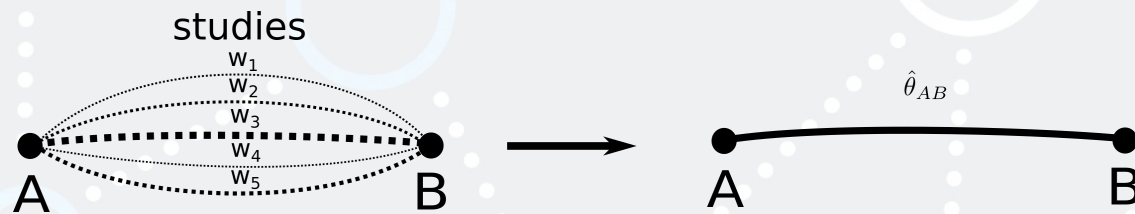
CONTRIBUTION OF STUDIES IN PAIRWISE META-ANALYSIS

Pairwise meta-analysis

- Multiple studies
- Single comparison A:B

c_i : contribution of study i :

- $c_i = \frac{w_i}{\sum_{i=1}^n w_i}, w_i = \frac{1}{v_i}$
- $\hat{\theta}_{AB} = \sum_{i=1}^n c_i y_i$

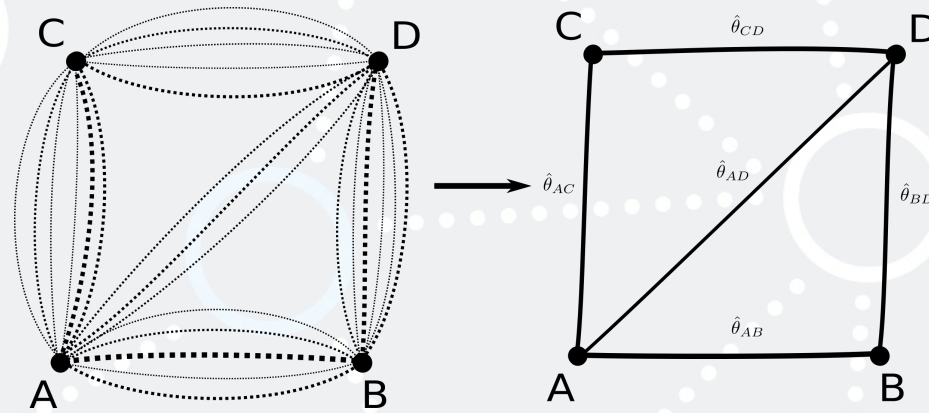


Contribution depends on the **variance** of studies **not** the effect size

- $\sum_{i=1}^n c_i = 1$

FROM PAIRWISE TO NETWORK META-ANALYSIS

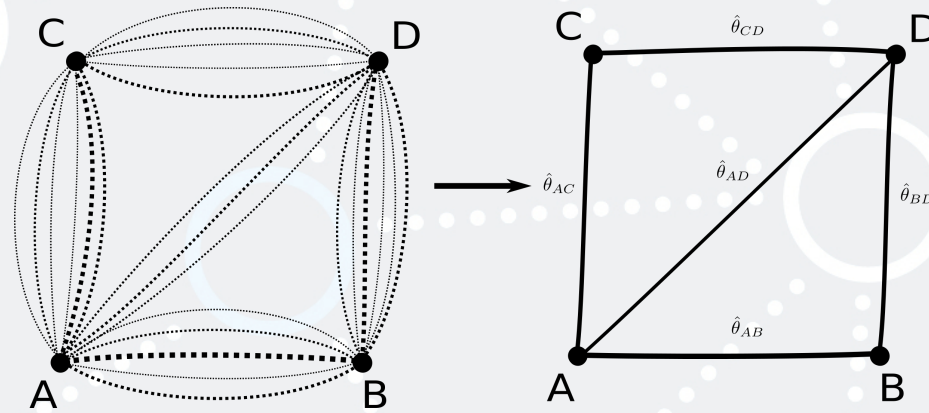
- Multiple studies
- Multiple comparisons:
 - Direct: A:B, A:C, C:D, B:D
 - Indirect: B:C



Two-Stage network meta-analysis

FROM PAIRWISE TO NETWORK META-ANALYSIS

- Multiple studies
- Multiple comparisons:
 - Direct: A:B, A:C, C:D, B:D
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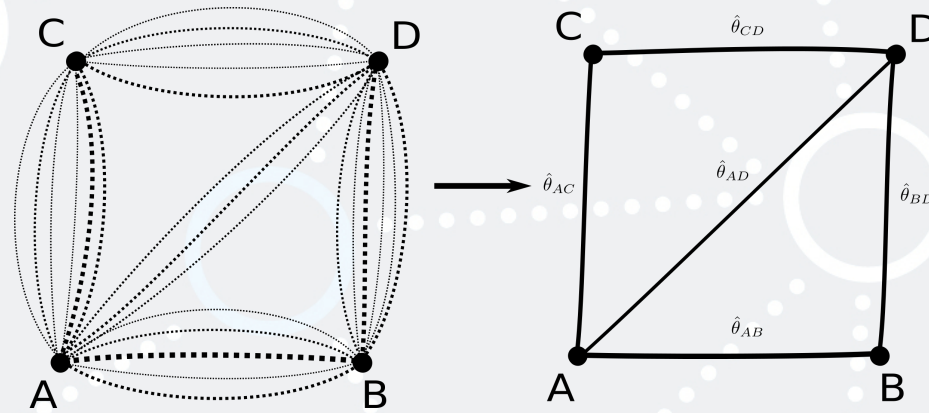


Two-Stage network meta-analysis

- Estimate pairwise summary effects: $\hat{\theta}^D = \{\hat{\theta}_{AB}, \hat{\theta}_{AC}, \hat{\theta}_{AD}, \hat{\theta}_{BD}, \hat{\theta}_{CD}\}$

FROM PAIRWISE TO NETWORK META-ANALYSIS

- Multiple studies
- Multiple comparisons:
 - Direct: A:B, A:C, C:D, B:D
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Two-Stage network meta-analysis

- Estimate pairwise summary effects: $\hat{\theta}^D = \{\hat{\theta}_{AB}, \hat{\theta}_{AC}, \hat{\theta}_{AD}, \hat{\theta}_{BD}, \hat{\theta}_{CD}\}$
- Calculate relative network effect sizes: $\hat{\theta}^N = \mathbf{H}\hat{\theta}^D = \{\hat{\theta}_{AB}^N, \hat{\theta}_{AC}^N, \hat{\theta}_{AD}^N, \hat{\theta}_{BC}^N, \hat{\theta}_{BD}^N, \hat{\theta}_{CD}^N\}$

PROJECTION **H** MATRIX

- Resembles the **hat matrix** in a linear regression model
- Each row h_{AB} refers to a single comparison

$$\hat{\theta}^N = \mathbf{H} \hat{\theta}^D$$

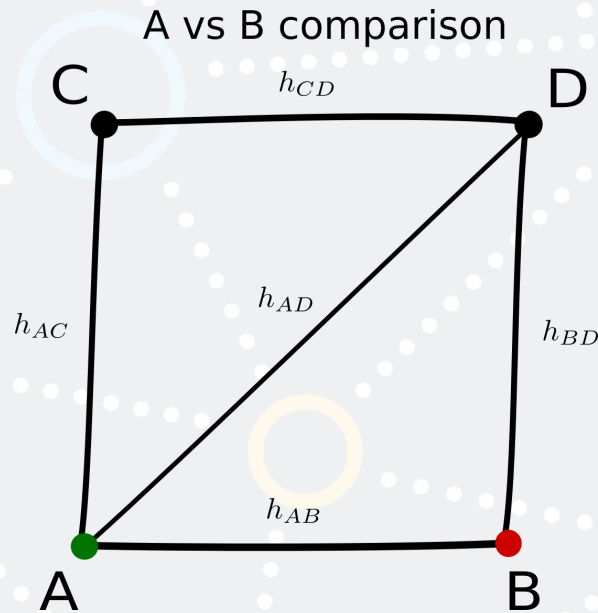
$$\begin{pmatrix} \hat{\theta}_{AB}^N \\ \hat{\theta}_{AC}^N \\ \hat{\theta}_{AD}^N \\ \hat{\theta}_{BC}^N \\ \hat{\theta}_{BD}^N \\ \hat{\theta}_{CD}^N \end{pmatrix} = \begin{pmatrix} h_{AB}^{AB} & h_{AC}^{AB} & h_{AD}^{AB} & h_{BD}^{AB} & h_{CD}^{AB} \\ h_{AB}^{AC} & h_{AC}^{AC} & h_{AD}^{AC} & h_{BD}^{AC} & h_{CD}^{AC} \\ h_{AB}^{AD} & h_{AC}^{AD} & h_{AD}^{AD} & h_{BD}^{AD} & h_{CD}^{AD} \\ h_{AB}^{BC} & h_{AC}^{BC} & h_{AD}^{BC} & h_{BD}^{BC} & h_{CD}^{BC} \\ h_{AB}^{BD} & h_{AC}^{BD} & h_{AD}^{BD} & h_{BD}^{BD} & h_{CD}^{BD} \\ h_{AB}^{CD} & h_{AC}^{CD} & h_{AD}^{CD} & h_{BD}^{CD} & h_{CD}^{CD} \end{pmatrix} \times \begin{pmatrix} \hat{\theta}_{AB}^D \\ \hat{\theta}_{AC}^D \\ \hat{\theta}_{AD}^D \\ \hat{\theta}_{BD}^D \\ \hat{\theta}_{CD}^D \end{pmatrix}$$

PROJECTION **H** MATRIX

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$$\hat{\theta}_{AB}^N = h_{AB}^{AB} \hat{\theta}_{AB} + h_{AC}^{AB} \hat{\theta}_{AC} + h_{AD}^{AB} \hat{\theta}_{AD} + h_{BD}^{AB} \hat{\theta}_{BD} + h_{CD}^{AB} \hat{\theta}_{CD}$$

The elements of hatmatrix can be seen as generalization of weights in pairwise meta-analysis **but** they do not add up to 1 $\sum h_{XY}^{AB} \neq 1$ and are not strictly positive since $h_{XY}^{AB} = -h_{YX}^{AB}$.



superscript AB denoting the comparison is omitted

NO EASY FIX

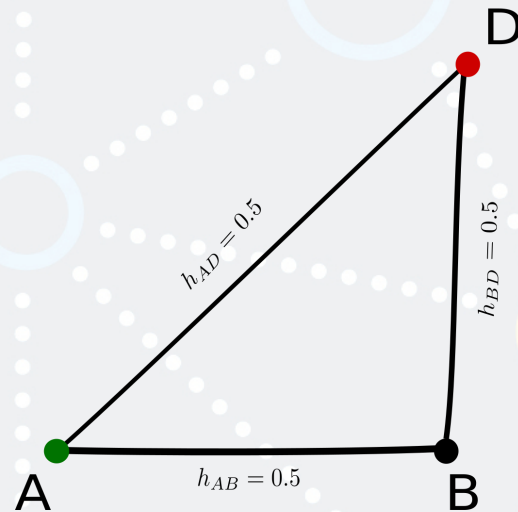
Naive normalization: $c_{XY} = \frac{|h_{XY}|}{\sum_i |h_i|}$

Contribution should be **independent** for parallel comparisons.

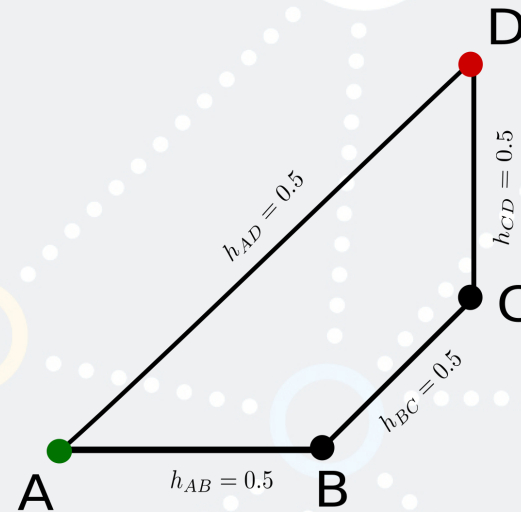
In both networks I and II contribution should be equal but normalisation in network I gives:

$$c_{AD} = \frac{1}{3} \text{ and in network II gives: } c_{AD} = \frac{1}{4}$$

A vs D network I



A vs D network II



contribution of direct should be: $c_{direct} = h_{direct} = 1 - h_{indirect}$

h^{AB} ROW AS A **COMPARISON GRAPH** G_{AB}

- Each h matrix row can be transformed into a directed graph $G_{AB} = (V, E, F)$
 - V : Set of interventions
 - E : Comparisons with direct evidence (studies)
 - F : Flow, property of edges, equals the elements of h row.

Köning J. Krahn U. Binder H. Statistics in Medicine 2013

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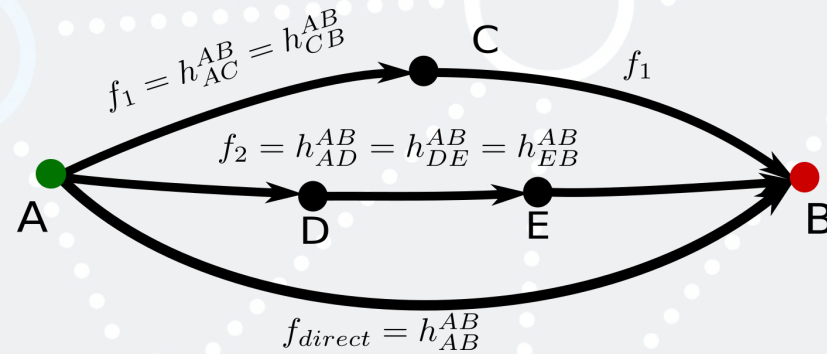
Assumptions for contribution in a contribution graph

Contribution of *parallel* paths (sequence of edges-comparisons) is **equal to the their flow**.

$$c_{ACB} = c_{AC} + c_{CB} = f_1$$

$$c_{ADEB} = c_{AD} + c_{DE} + c_{EB} = f_2$$

$$c_{AB} = f_{direct}$$



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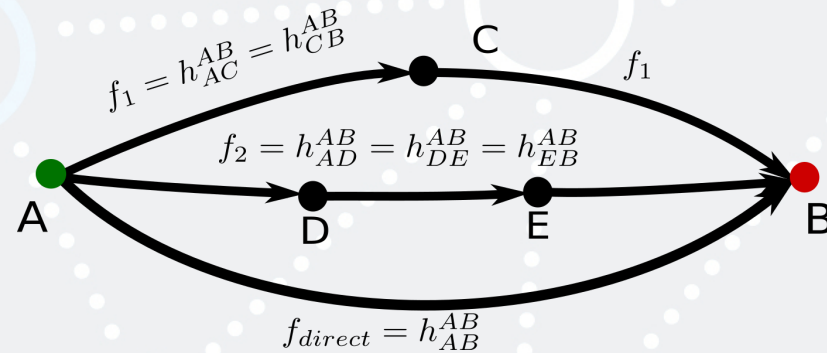
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$$c_{AB} = f_{direct}$$



Contribution of individual edge inside a path

Each comparison **contributes equally** in a path so the contribution of each comparison is its **flow** divided by its **length**:

$$c_{AC} = c_{CD} = c_{DB} = \frac{f_{ACDB}}{3}$$

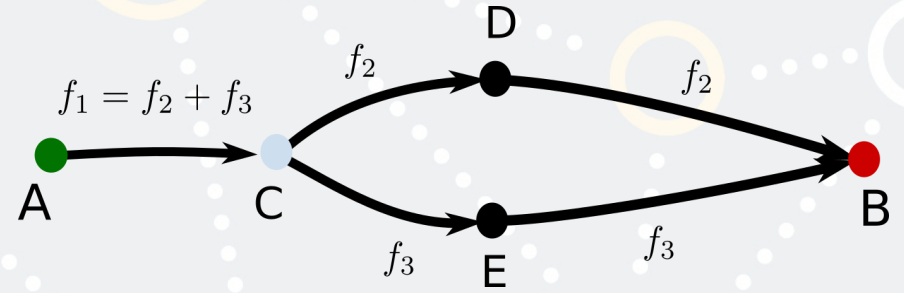
$$c_{comparison} = \frac{f_{path}}{\text{length of path}}$$



STREAMS

Mixed paths

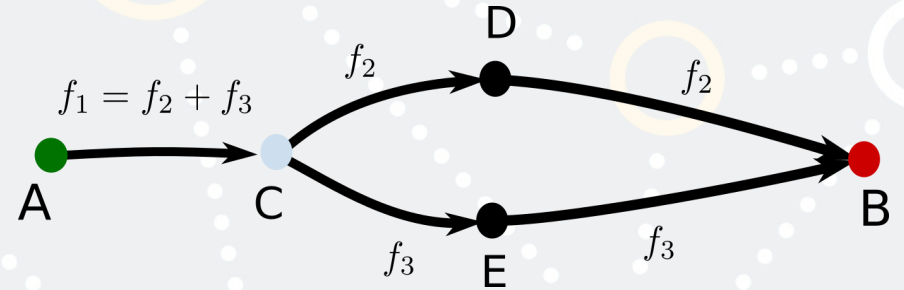
A comparison (edge) is shared between two parallel paths.



STREAMS

Mixed paths

A comparison (edge) is shared between two parallel paths.



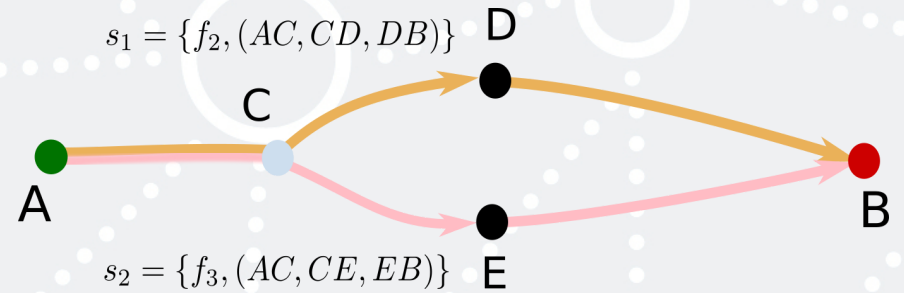
Decompose flow into **streams**

A stream is defined by its flow ϕ and the path π

$$s_i = \{\phi_i, \pi_i\}$$

Total contribution of a comparison is the sum over the streams that contain

$$c_{AC} = \frac{f_2}{3} + \frac{f_3}{3}$$



ALGORITHM FROM FLOW TO STREAMS TO CONTRIBUTION

Comparison $A : B$ The first step is to locate all streams by decomposing flow

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Repeat until all flow is depleted and all streams are found: $S = \{s_1, s_2, \dots, s_k\}$

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Calculate contribution of comparison X vs Y to the network estimate of A vs B : $c_{XY}^{AB} = \sum_i^k \frac{\phi_i}{|\pi_i|}, (XY) \in \pi_i$
where $|\pi_i|$ is the length of path i of stream s_i and k the number of streams.

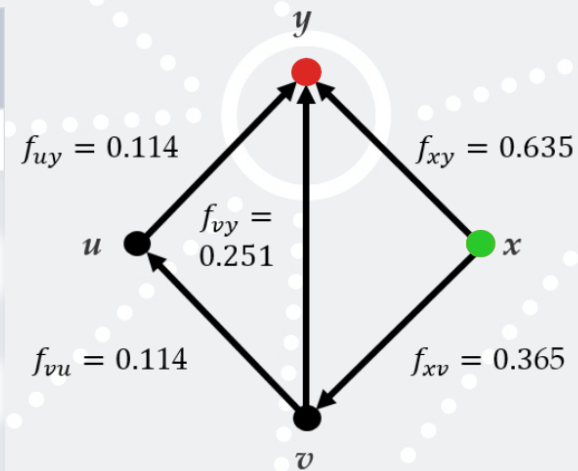
EXAMPLE: TOPICAL ANTIBIOTICS WITHOUT STEROIDS FOR CHRONICALLY DISCHARGING EARS WITH UNDERLYING EARDRUM PERFORATIONS.

Macfadyen CA, Acuin JM, Gamble C: Cochrane Database Syst Rev. 2005; (4): CD004618.

x: no treatment, **y**: quinolone antibiotic, **u**: non-quinolone antibiotic, **v**: antiseptic

h matrix

	<i>xy</i>	<i>xv</i>	<i>yu</i>	<i>yv</i>	<i>uv</i>
<i>xy</i>	0.635	0.365	−0.114	−0.251	−0.114
<i>xu</i>	0.603	0.397	0.632	−0.029	−0.368
<i>xv</i>	0.545	0.455	0.170	0.375	0.170
<i>yu</i>	−0.032	0.032	0.745	0.223	−0.255
<i>yv</i>	−0.090	0.090	0.284	0.627	0.284
<i>uv</i>	−0.058	0.058	−0.462	0.404	0.538

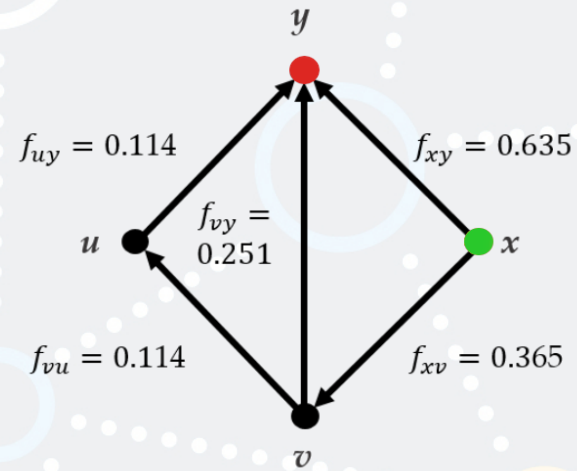


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comparison $x : y$

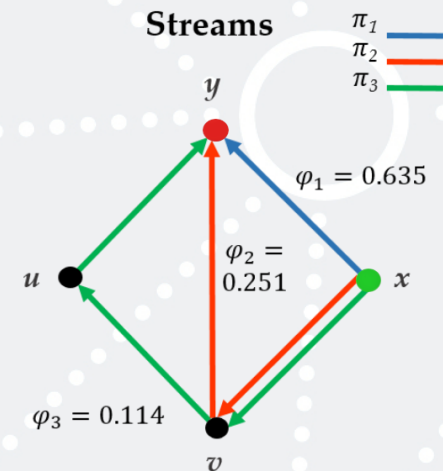
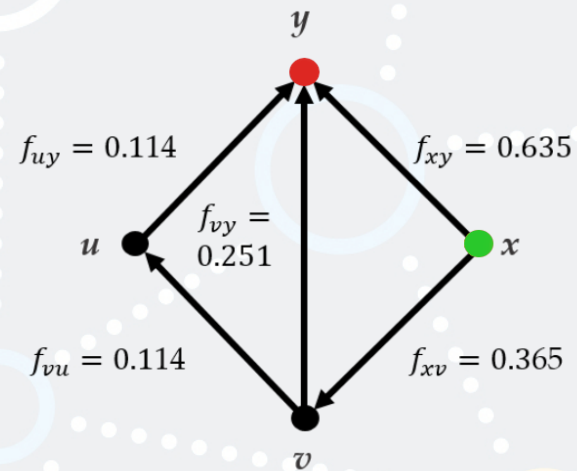


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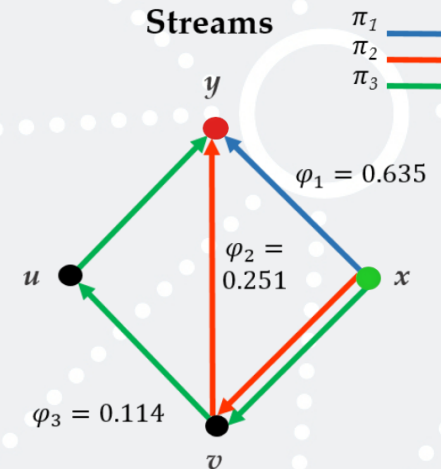
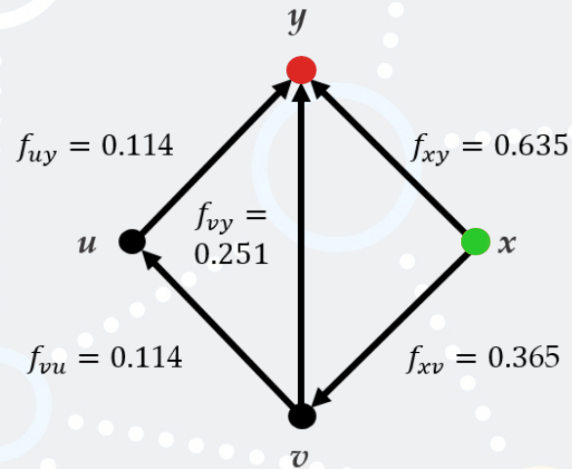


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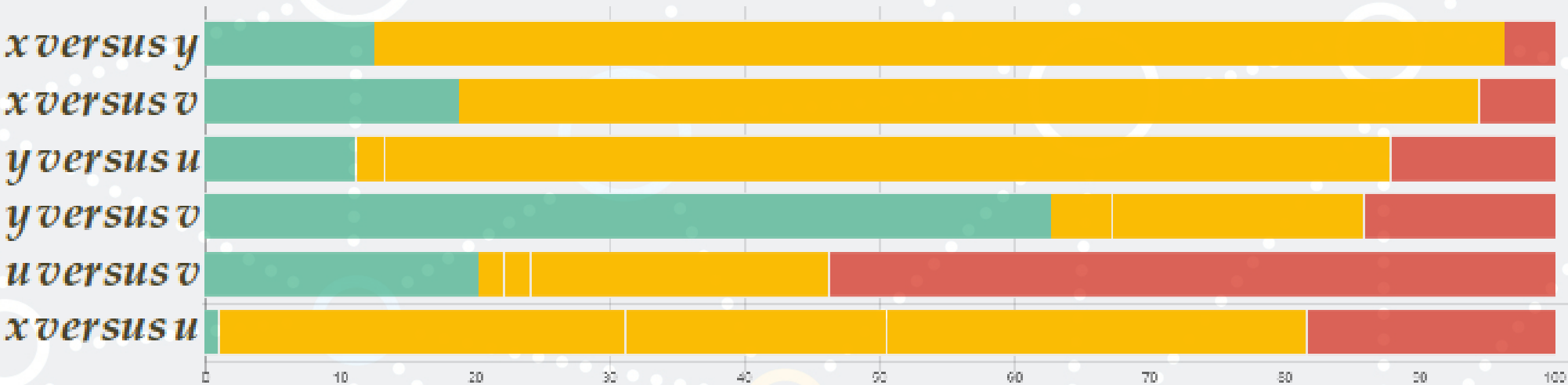
- $c_{xy} = \phi_1 = 0.635$
- $c_{vy} = \frac{\phi_2}{2} = \frac{0.251}{2} = 0.126$
- $c_{xv} = \frac{\phi_2}{2} + \frac{\phi_3}{3} = \frac{0.251}{2} + \frac{0.114}{3} = 0.164$
- $c_{vu} = c_{uy} = \frac{\phi_3}{3} = \frac{0.114}{3} = 0.038$

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Bar chart for Risk of Bias for all comparisons



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CINeMA (Confidence in Network Meta-Analysis) is a web application that simplifies the evaluation of confidence in the findings from network meta-analysis.

It is based on a framework described in [1] which considers the five GRADE domains: **study limitations, indirectness, inconsistency, imprecision and publication bias.** The framework combines judgments about direct evidence with their statistical contribution to network meta-analysis results, enabling evaluation of the credibility of NMA treatment effects.


[1. Salanti G, Del Giovane C, Chaimani A, Caldwell DM, Higgins JPT. Evaluating the quality of evidence from a network meta-analysis. *PLoS One*. 2014;9(7):e99682.]

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CINeMA: *Confidence in Network Meta-Analysis* [Software]. Institute of Social and Preventive Medicine, University of Bern, 2017. Available from cinema.ispm.ch


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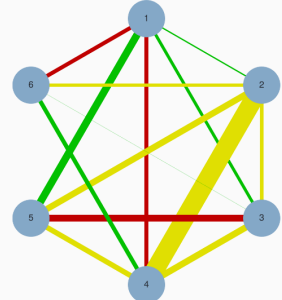
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Network Plot

Node size by: Equal sizeNode color by: No colorEdge width by: Sample SizeEdge color by: Majority Indirectness

RedrawSave Plot



	id	t1	t2	r1	r2	n1	n2	rob	indirectness
1	1	2	5	70	45	405	410	1	2
2	1	2	4	70	32	405	202	1	2
3	1	4	5	32	45	202	410	1	2
4	2	3	4	302	154	6766	3954	1	2
5	2	3	5	302	119	6766	4096	1	2
6	2	4	5	154	119	3954	4096	1	2
7	3	3	6	8	1	196	196	1	1
8	4	3	5	200	138	2826	2800	1	3
9	5	2	4	799	567	7040	7072	1	2
10	6	2	5	380	337	5230	5183	2	2
11	7	1	6	202	163	2721	2715	1	1
12	8	1	5	489	449	2646	2623	1	3
13	9	1	3	20	29	424	416	2	2
14	10	1	4	154	177	4870	4841	1	3
15	11	2	3	86	75	3297	3272	3	2
16	12	1	5	155	102	2883	2837	1	1
17	13	3	4	176	136	2511	2508	1	1
18	14	2	4	665	569	8078	8098	1	2
19	15	2	6	320	242	3979	4020	1	2
20	16	2	4	251	216	5059	5095	1	1
21	17	1	5	399	335	3472	3432	1	1
22	18	1	6	115	93	2175	2167	1	3
23	19	1	3	110	140	1870	1871	1	1

Define your analysis

Analysis model: Fixed effect Random effects

Effect measure: Odds Ratio

Select intervention comparisons for evaluation

Interventions: ☒ 1 ☒ 2 ☒ 3 ☒ 4 ☒ 5 ☒ 6

Select comparisons:

☐ Containing any of the above interventions

☐ Between the above interventions

You have selected the following 15 comparisons. Confidence in the results will be graded for:

1x02

1x03

1x04

1x05

1x06

2x03

2x04

2x05

2x06

3x04

3x05


3x06

4x05

4x06


5x06

Analysis is performed including all studies




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
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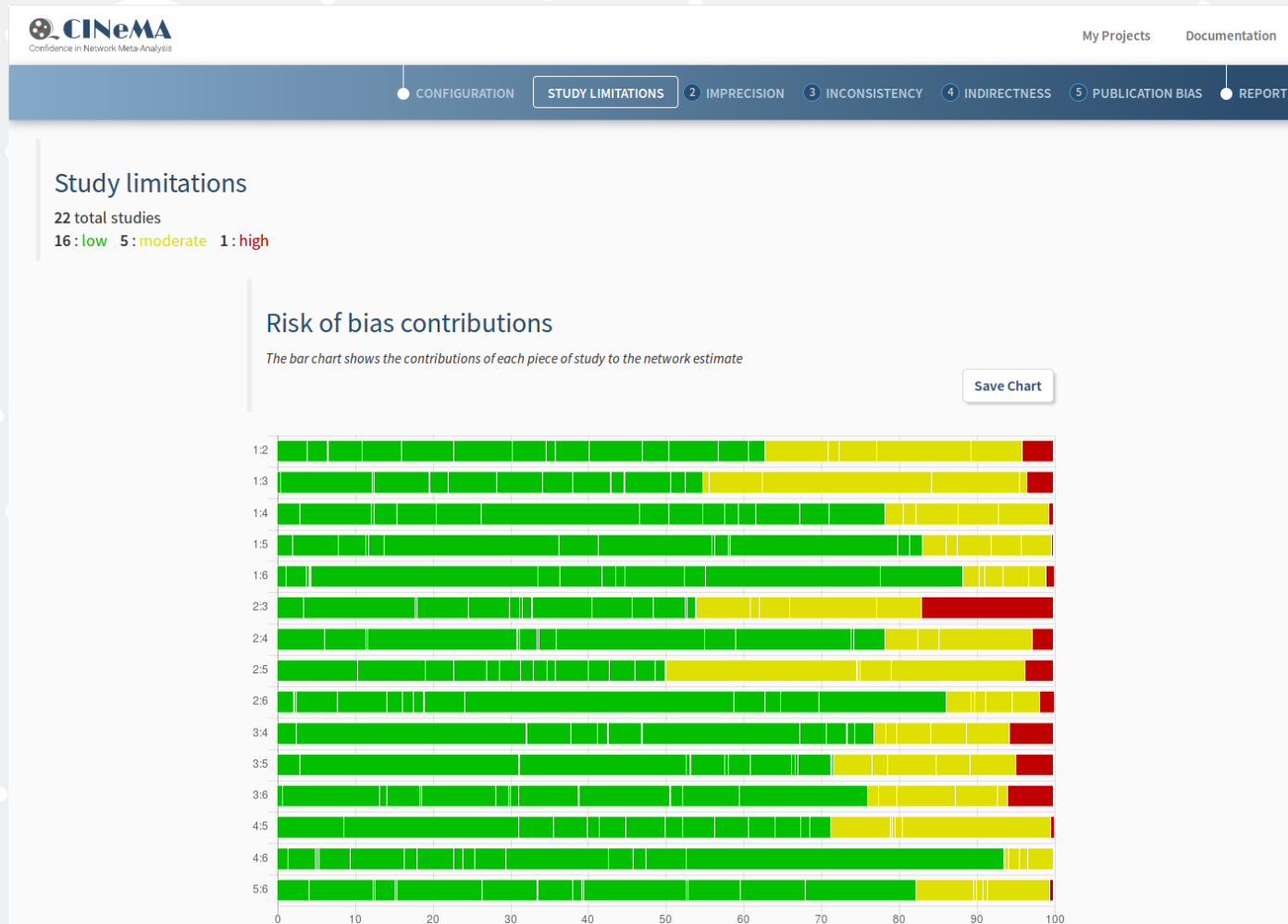
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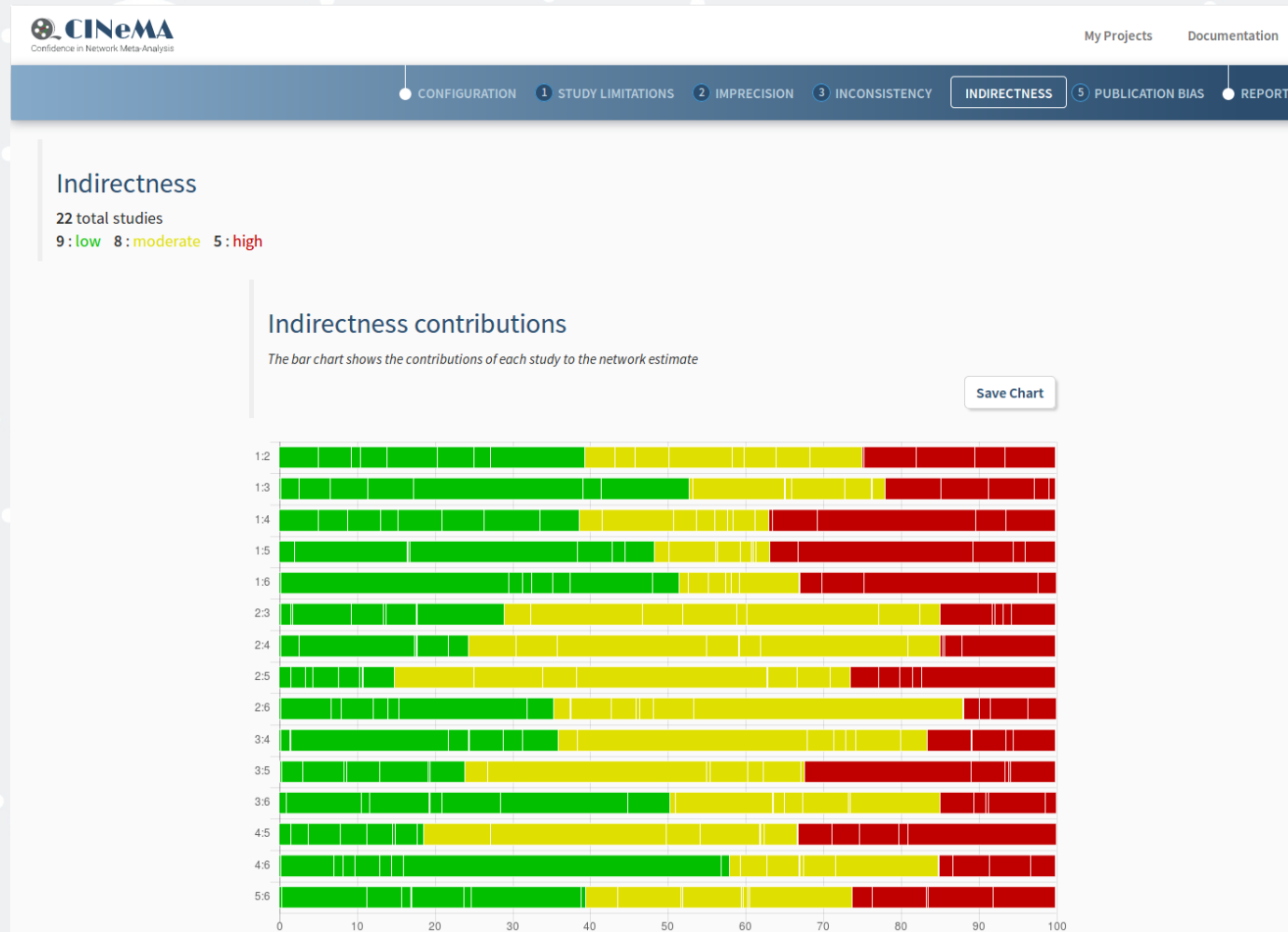
contributions for assessing **Risk of Bias**



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contributions for assessing Indirectness



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final report



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Comparison	Number of Studies	Study Limitations	Imprecision	Inconsistency		Indirectness	Publication bias	Confidence rating
				Heterogeneity	Incoherence			
Mixed evidence								
1 vs 2	1	No concerns	No concerns	Major concerns	Major concerns	No concerns	Suspected	High
1 vs 3	3	No concerns	No concerns	Major concerns	Major concerns	No concerns	Suspected	High
1 vs 4	1	No concerns	Major concerns	No concerns	No concerns	No concerns	Suspected	High
1 vs 5	3	No concerns	Major concerns	No concerns	Major concerns	No concerns	Suspected	High
1 vs 6	2	No concerns	No concerns	Major concerns	No concerns	No concerns	Suspected	High
2 vs 3	2	No concerns	Major concerns	No concerns	No concerns	Some concerns	Suspected	High
2 vs 4	5	No concerns	No concerns	Major concerns	Major concerns	Some concerns	Suspected	High
2 vs 5	3	No concerns	No concerns	No concerns	Major concerns	Some concerns	Suspected	High
2 vs 6	1	No concerns	No concerns	No concerns	No concerns	Some concerns	Suspected	High
3 vs 4	2	No concerns	No concerns	Major concerns	Major concerns	Some concerns	Suspected	High
3 vs 5	2	No concerns	No concerns	No concerns	No concerns	Some concerns	Suspected	High
3 vs 6	1	No concerns	No concerns	No concerns	No concerns	No concerns	Suspected	High
4 vs 5	3	No concerns	No concerns	Major concerns	No concerns	Some concerns	Suspected	High
4 vs 6	1	No concerns	No concerns	Major concerns	Major concerns	No concerns	Suspected	High
Indirect evidence								
5 vs 6	--	No concerns	Major concerns	No concerns	No concerns	No concerns	Suspected	High



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Thank you

paper: <https://f1000research.com/articles/7-610/v1>

Estimating the contribution of studies in network meta-analysis: paths, flows and streams

R package: https://github.com/esm-ispm-unibe-ch/flow_contribution



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