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

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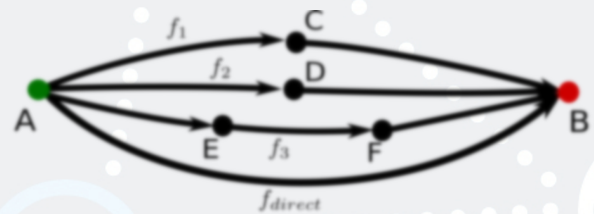
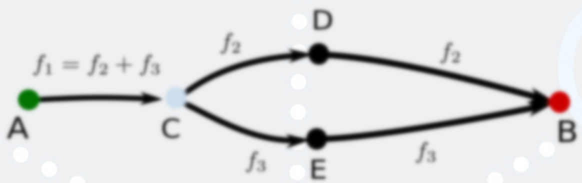
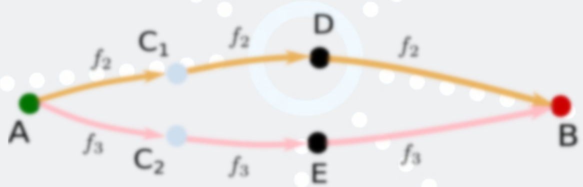
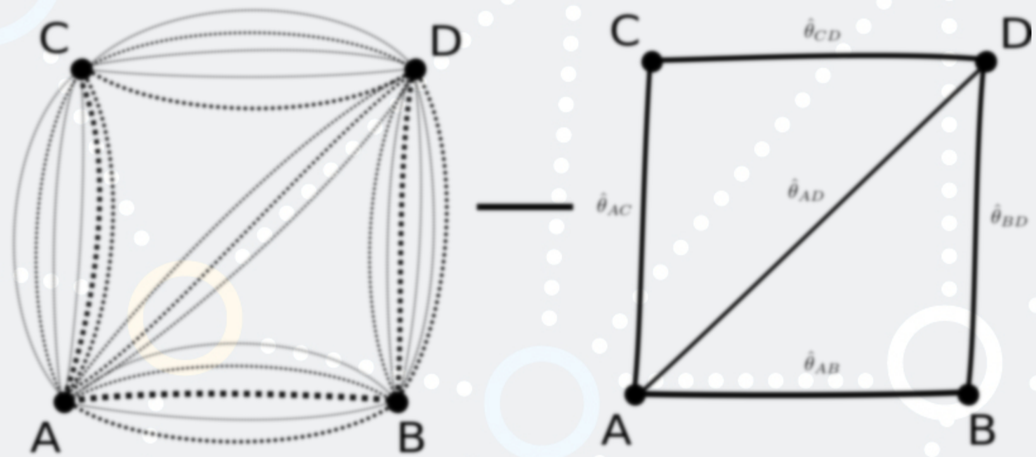
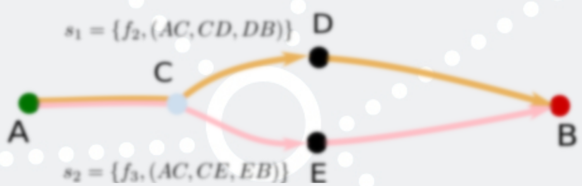
ISCB Melbourne 2018











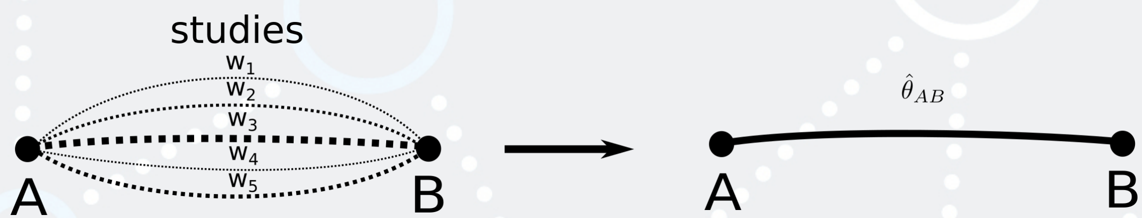
CONTRIBUTION OF STUDIES IN PAIRWISE META-ANALYSIS

Pairwise meta-analysis

- Multiple studies
- Single comparison A:B

c_i : contribution of study i:

- $c_i = \frac{w_i}{\sum_1^n w_i}, w_i = \frac{1}{v_i}$
- $\hat{\theta}_{AB} = \sum_{i=1}^{n} c_i y_i$

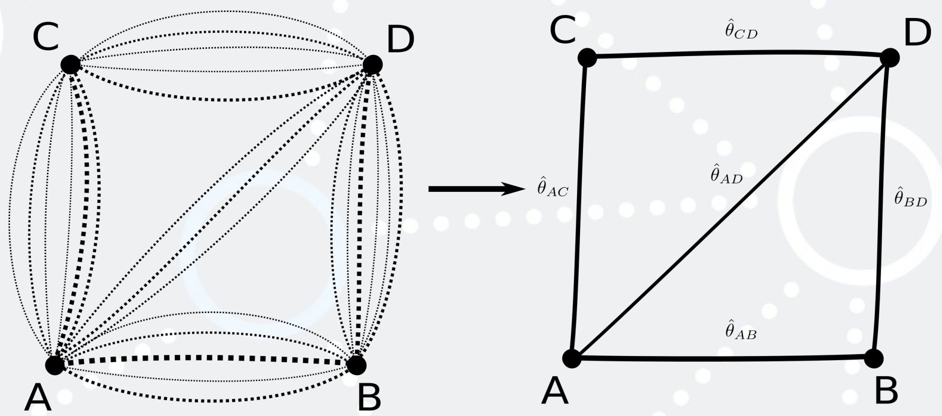


Contribution depends on the **variance** of studies **not** the effect size

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

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

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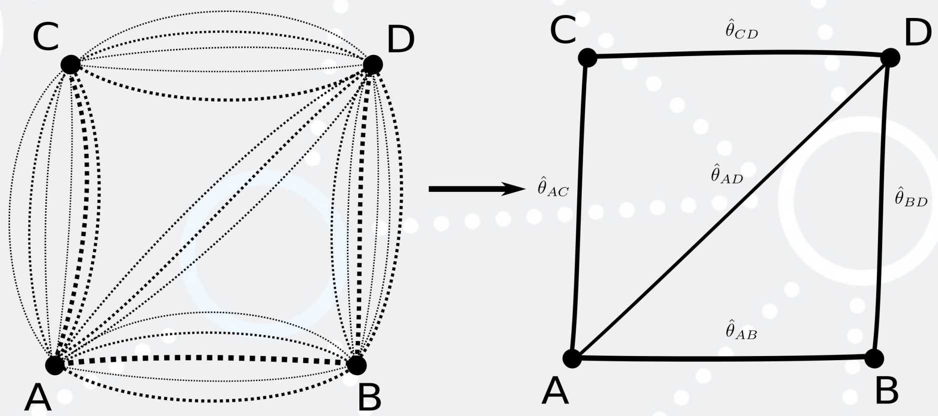

Two-Stage network meta-analysis

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

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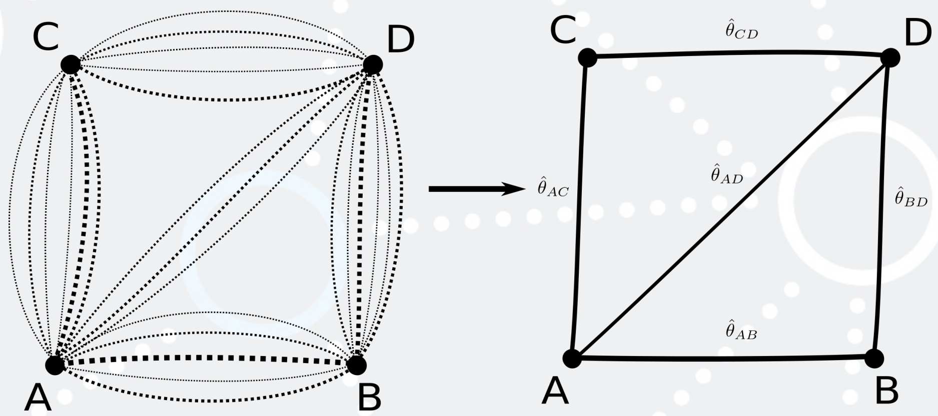

Two-Stage network meta-analysis

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

PROJECTION $\mathbf{H}$ MATRIX

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

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

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

PROJECTION $\mathbf{H}$ MATRIX

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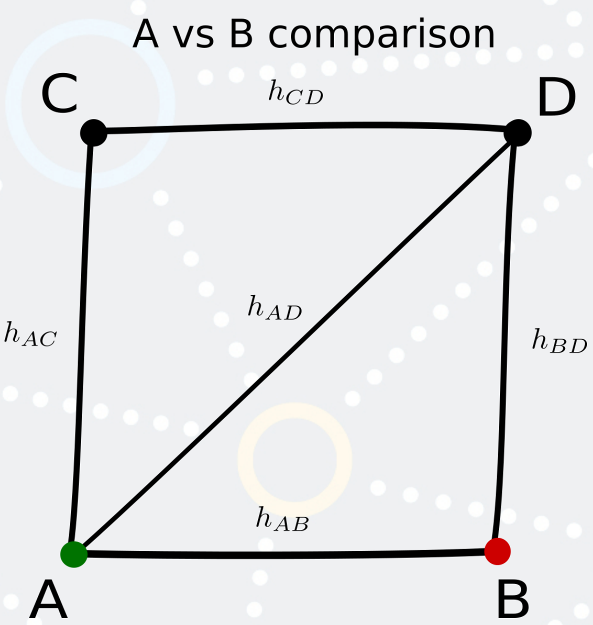
$$\hat{\theta}^N_{AB} = h^{AB}_{AB}\hat{\theta}_{AB} + h^{AB}_{AC}\hat{\theta}_{AC} + h^{AB}_{AD}\hat{\theta}_{AD} + h^{AB}_{BD}\hat{\theta}_{BD} + h^{AB}_{CD}\hat{\theta}_{CD}$$

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



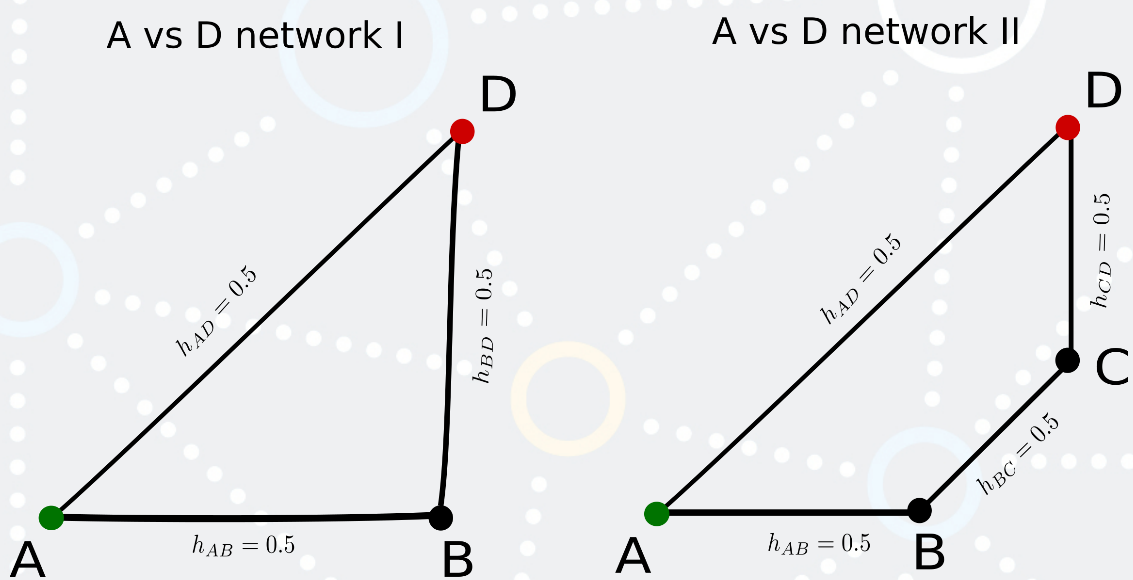
superscript AB denoting the comparison is omitted

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



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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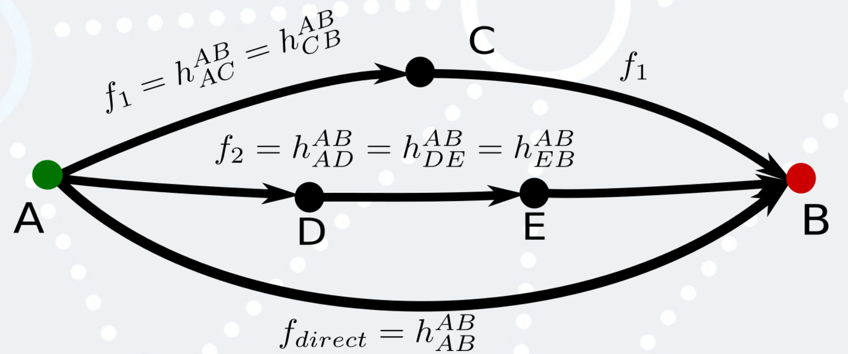
Assumptions for contribution in a contribution graph

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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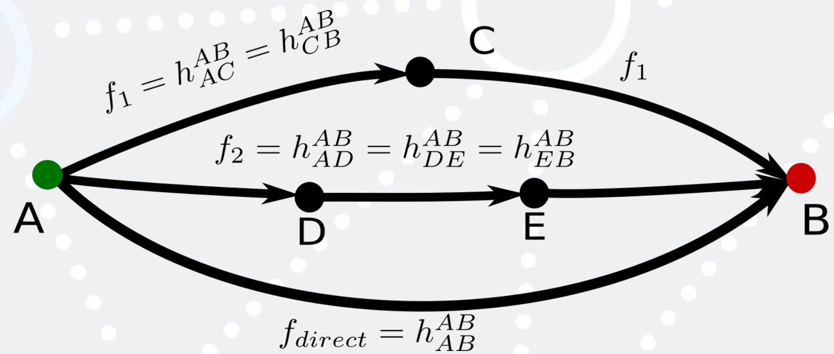


Contribution of individual edge inside a path

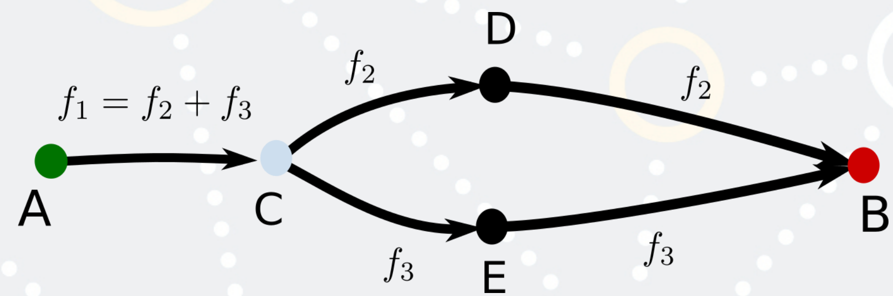
Each comparison **contributes equally** in a path so the contribution of each comparison is its **flow** divided by its **length**:

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

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

STREAMS

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



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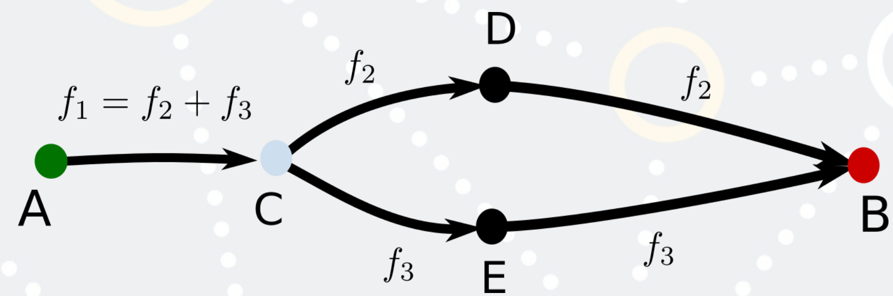
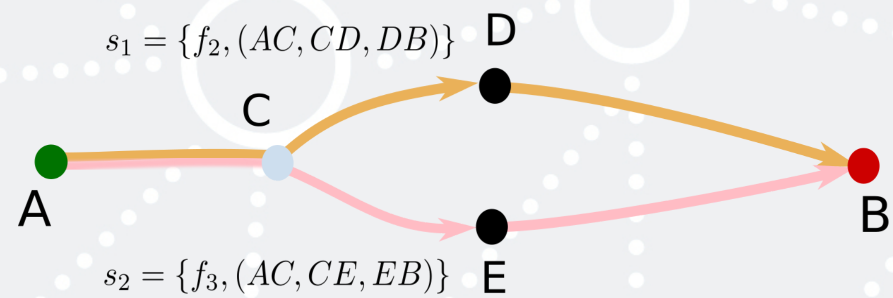


Decompose flow into **streams**
A stream is defined by its flow ϕ and the path π
$\mathbf{s_i} = \{\boldsymbol{\phi_i}, \boldsymbol{\pi_i}\}$
Total contribution of a comparison is the sum over the streams that contain
$c_{AC} = \frac{f_2}{3} + \frac{f_3}{3}$



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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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 lenght 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

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

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comparison $x : y$

	xy	***xv***	***yu***	***yv***	***uv***
xy	0.635	0.365	–0.114	–0.251	–0.114
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
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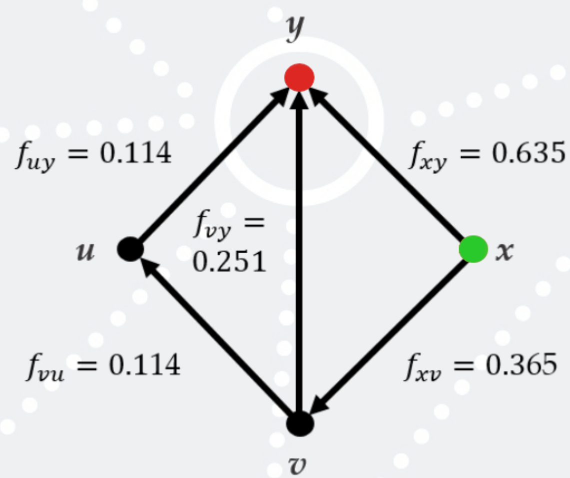

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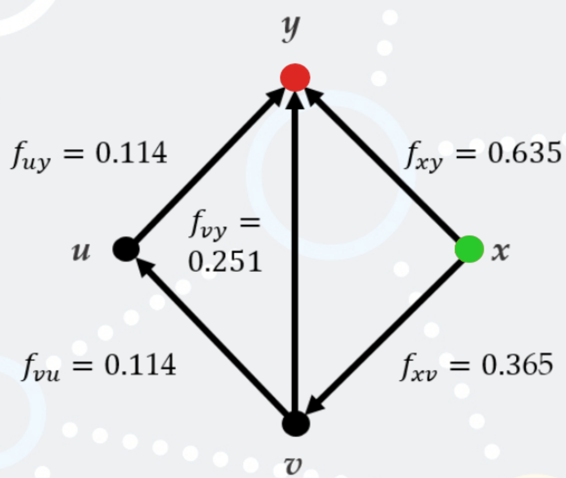

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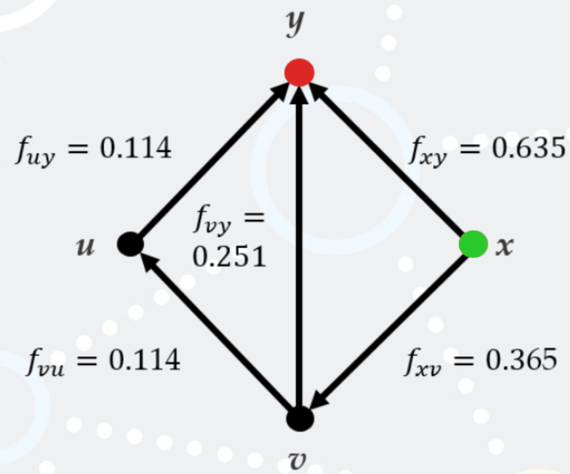

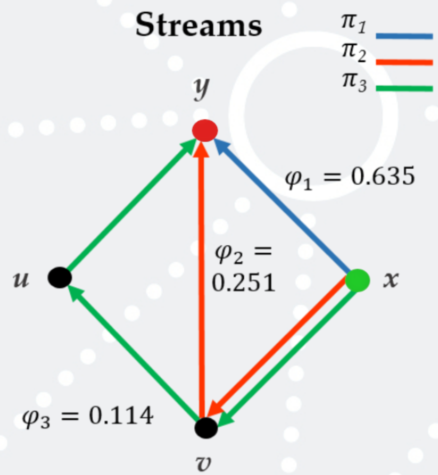

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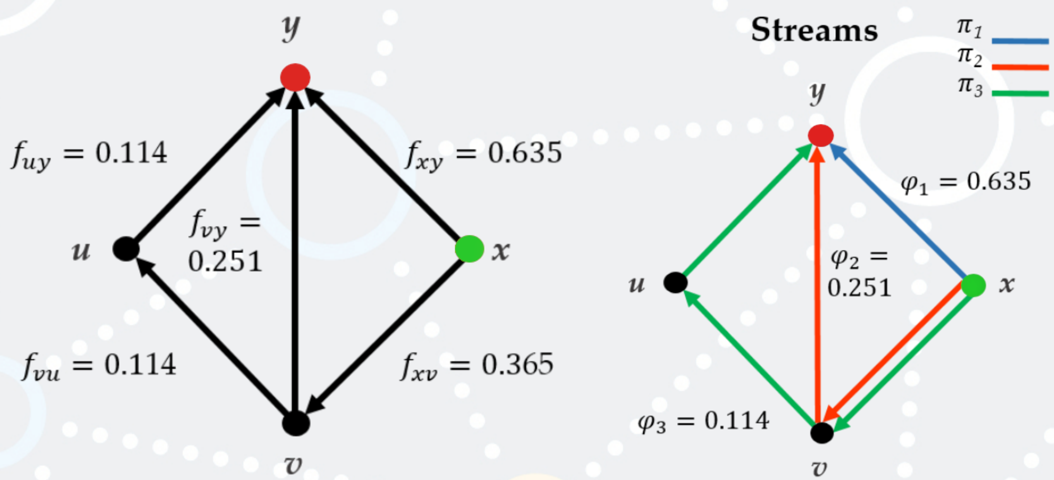

- $c_{xy} = \phi_1 = 0.635$
- $c_{vy} = \frac{\phi_2}{2} = \frac{0.251}{2} = 0.126$
- $c_{xv} = \frac{\phi_2}{2} + \frac{\phi_3}{3} = \frac{0.251}{2} + \frac{0.114}{3} = 0.164$
- $c_{vu} = c_{uy} = \frac{\phi_3}{3} = \frac{0.114}{3} = 0.038$

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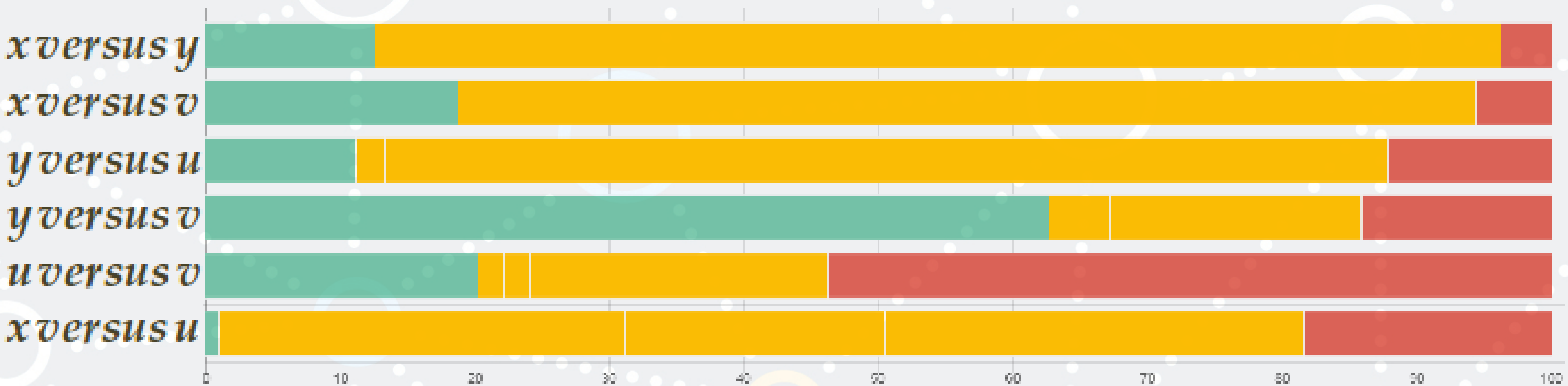
Bar chart for Risk of Bias for all comparisons



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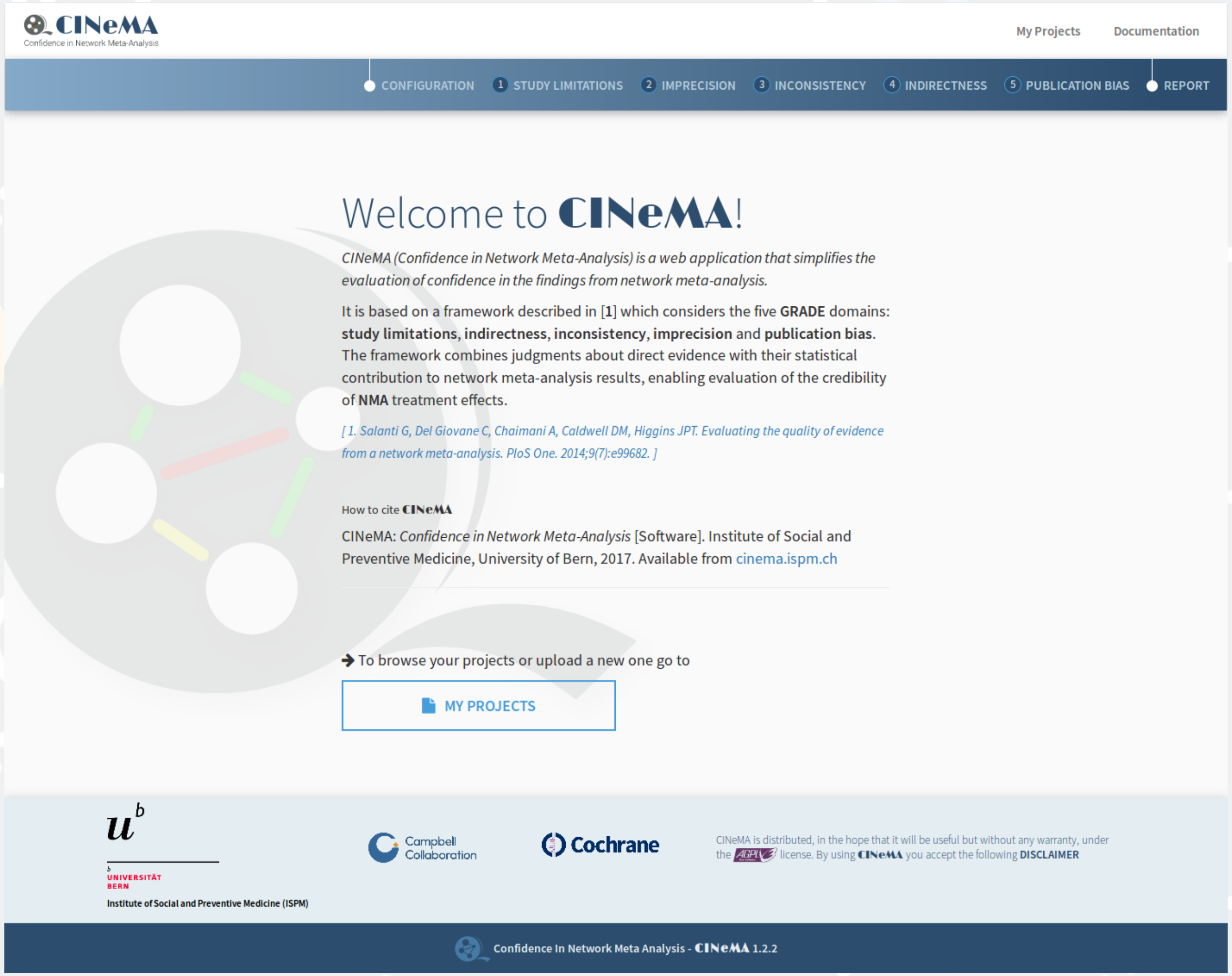

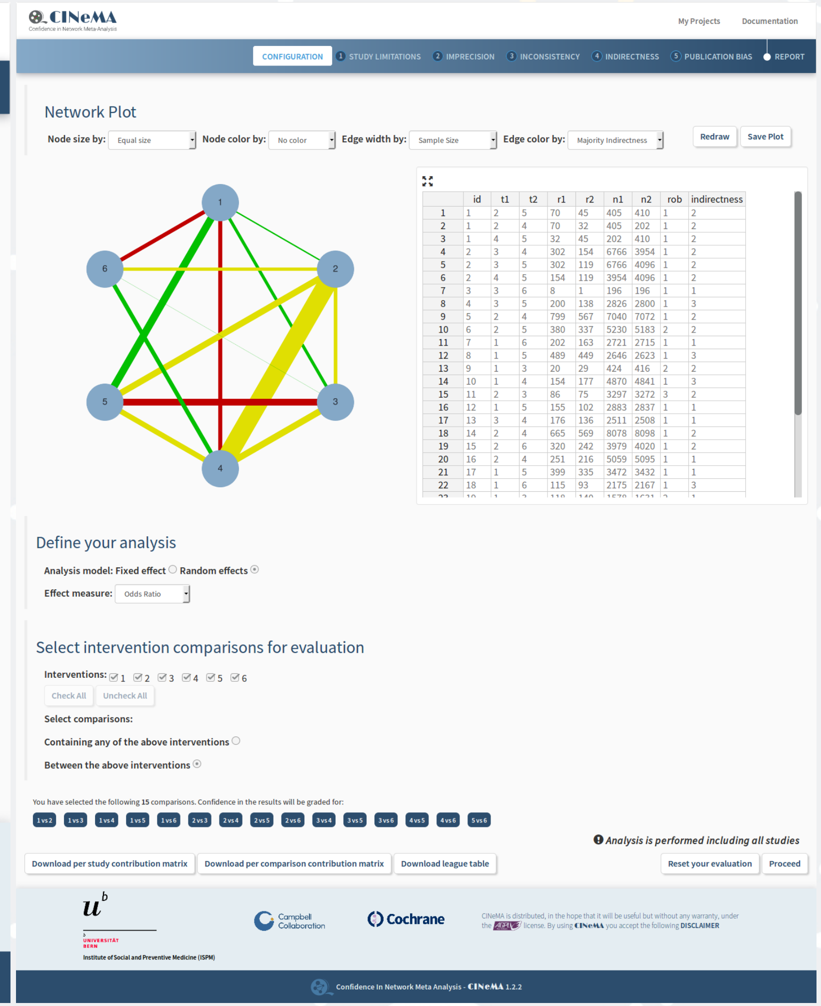

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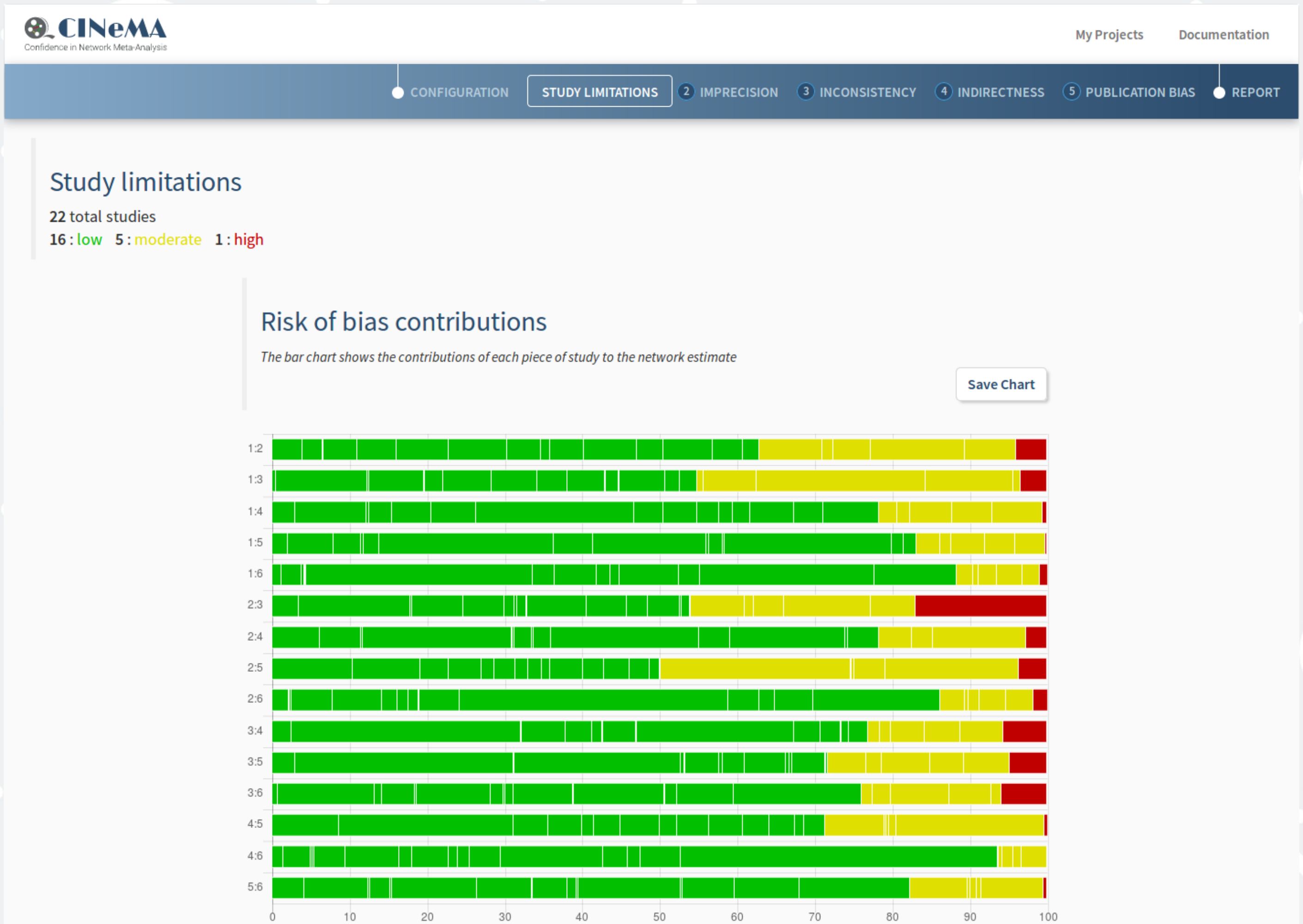
contributions for assessing **Risk of Bias**



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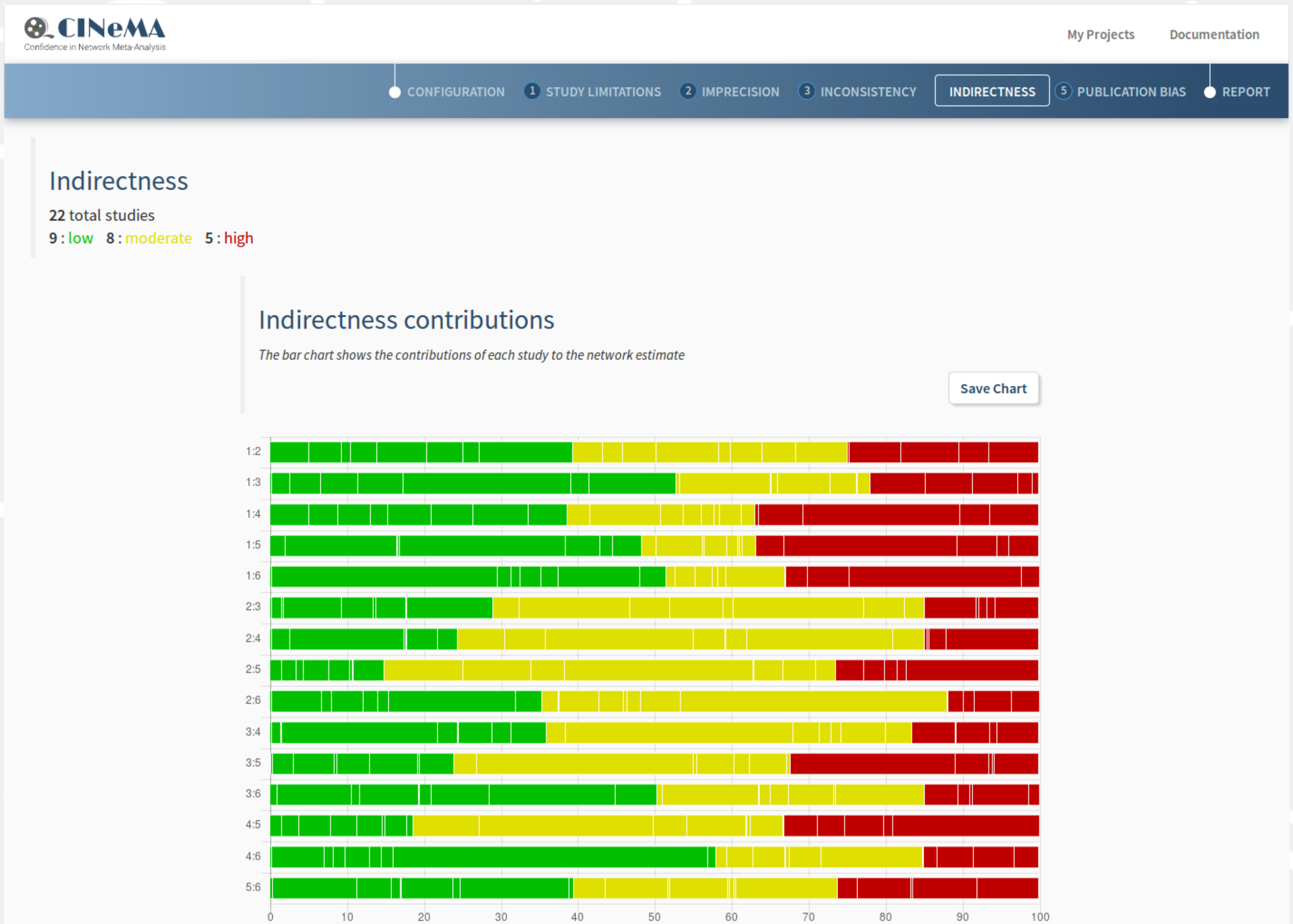
contributions for assessing **Indirectness**



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final report

CINeMA
Confidence in Network Meta-Analysis

My Projects Documentation

CONFIGURATION | 1 STUDY LIMITATIONS | 2 IMPRECISION | 3 INCONSISTENCY | 4 INDIRECTNESS | 5 PUBLICATION BIAS | 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

UNIVERSITÄT BERN
Institute of Social and Preventive Medicine (ISPM)

Campbell Collaboration | Cochrane

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

Adriani Nikolakopoulou
Gerta Rücker
Anna Chaimani
Guido Schwarzer
Matthias Egger
Georgia Salanti