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Sensitivity of treatment decisions to bias adjustment in network meta-analysis

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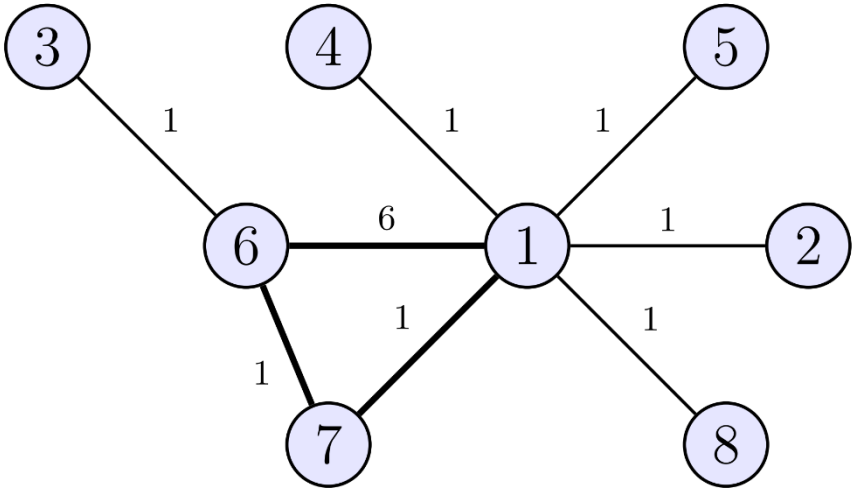
Overview

- Background and motivation
  - Network Meta-Analysis (NMA)
  - Quality vs. influence
- Threshold method
- Examples

Background – Network Meta-Analysis

- Combines evidence on multiple treatments from several studies
- Arranges treatments on a network structure joined by study evidence
- Provides consistent estimates of treatment effects
- Routinely used to inform clinical guideline recommendations, technology appraisals

Motivation – Headaches Example



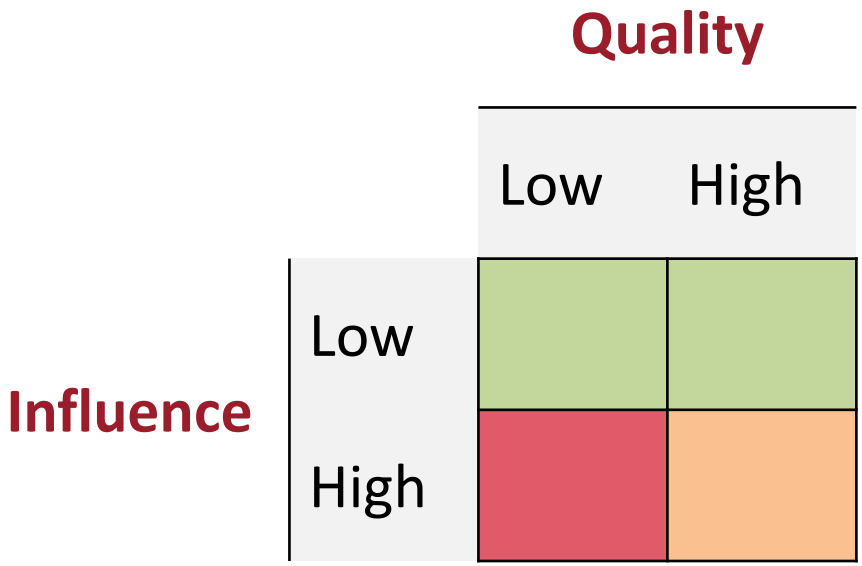
	Treatment	Mean change in headache days per month (95% CrI)
1	Placebo	0
2	Telmisartan	-0.51 (-2.32, 1.27)
3	Amitriptyline	-1.14 (-2.45, 0.16)
4	Divalproex Sodium	0.13 (-0.99, 1.23)
5	Gabapentin	0.00 (-1.60, 1.58)
6	Topiramate	-1.04 (-1.52, -0.58)
7	Propranolol	-1.19 (-2.20, -0.20)
8	Propranolol/Nadolol	-0.60 (-1.65, 0.45)

(NICE, 2015)

Motivation

How robust are the results to bias?

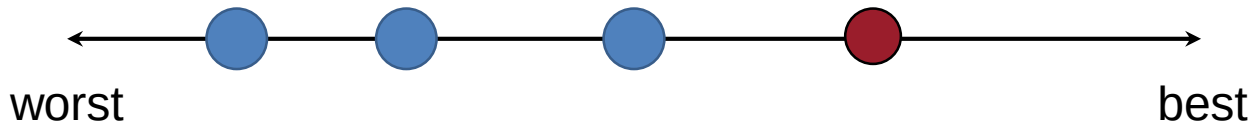
- Evidence quality is only half the story



The Threshold Method

Derive *bias adjustment thresholds*:

How much can we change a data point before the treatment recommendation changes?



The Threshold Method

Derive *bias adjustment thresholds*:

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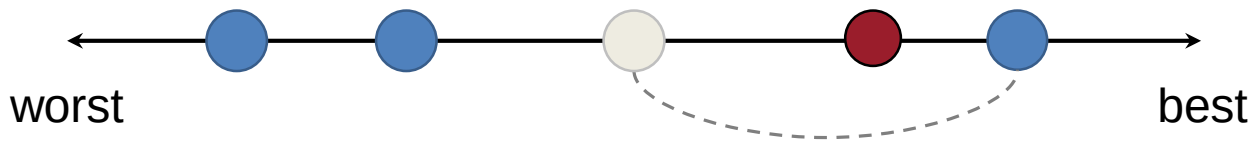
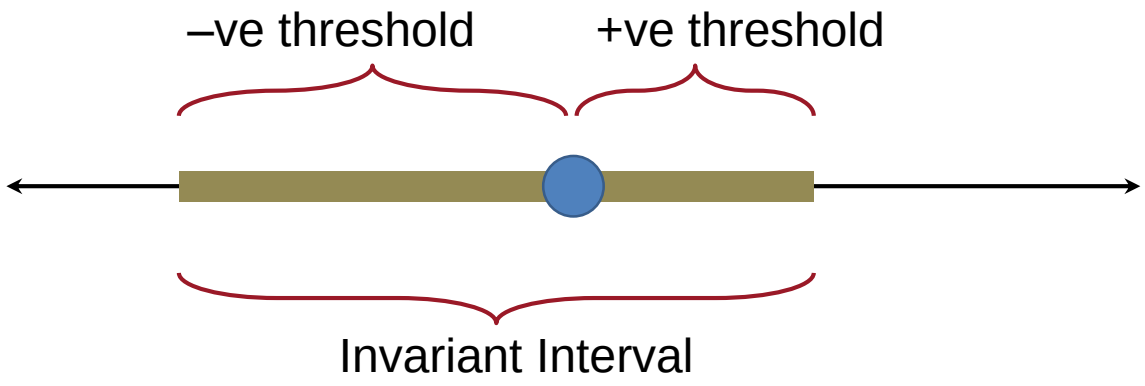


The Threshold Method

Once we have thresholds we can create a *decision invariant bias adjustment interval* for a data point

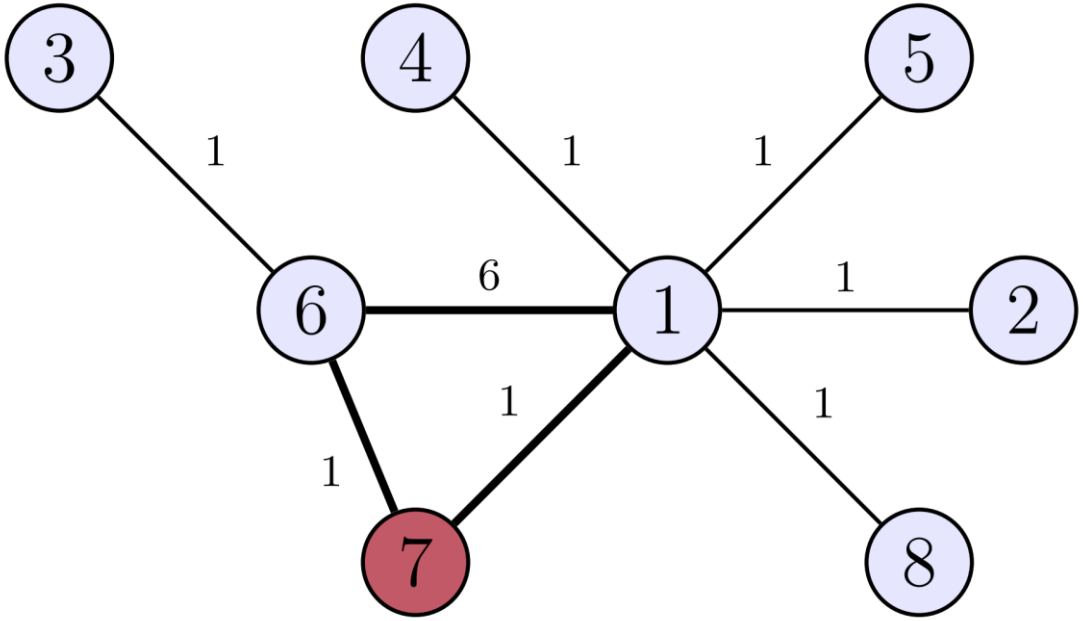


The Threshold Method

- Study level
  - Thresholds for each individual study estimate

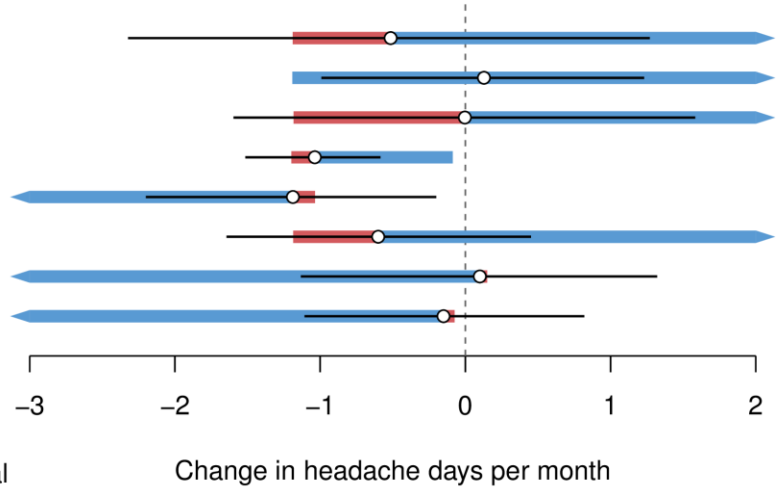
- Contrast level
  - Thresholds for combined body of evidence on a contrast
  - Highly flexible due to an approximation step

Example: Headaches



Example: Headaches – contrast level

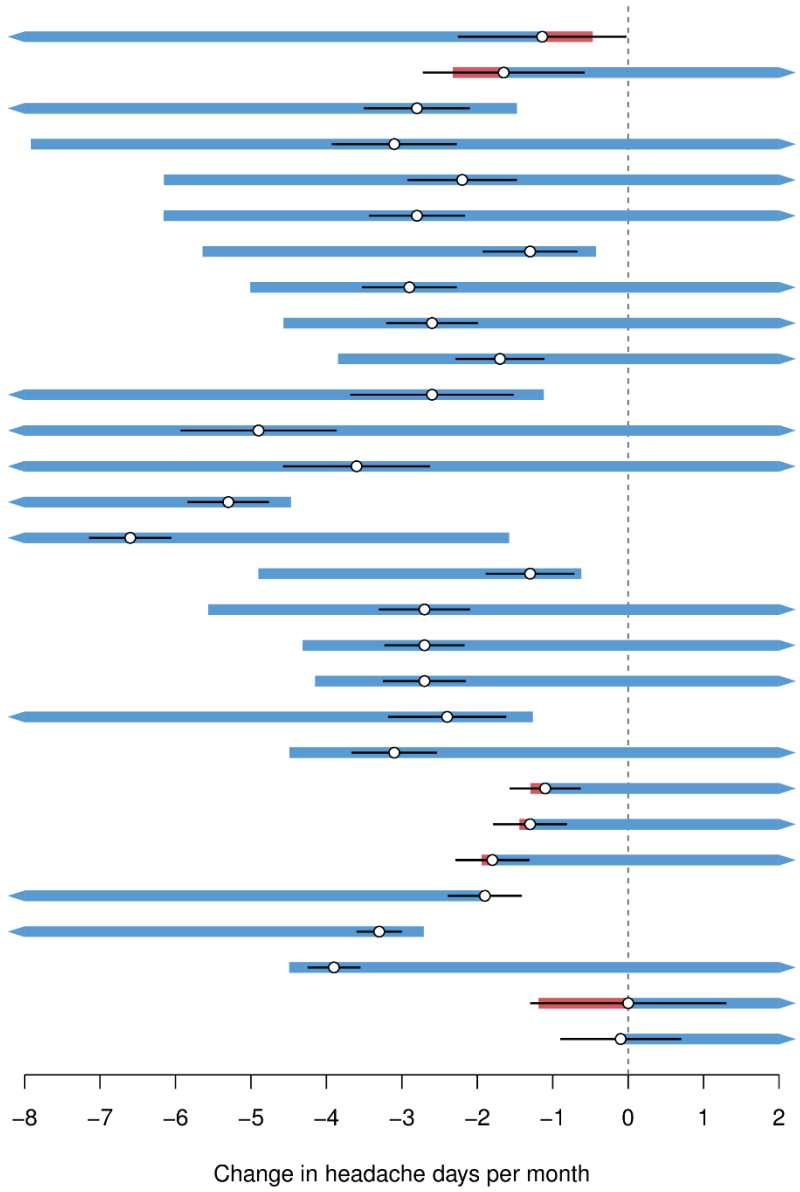
Contrast	Posterior Mean	95% Credible Interval	Invariant Interval with $\tilde{k}^*$		
2 vs. 1	–0.51	(–2.32, 1.27)	2	(–1.19, NT)	–
4 vs. 1	0.13	(–0.99, 1.23)	4	(–1.19, NT)	–
5 vs. 1	–0.00	(–1.60, 1.58)	5	(–1.18, NT)	–
†**6 vs. 1**	–1.04	(–1.51, –0.58)	3	(–1.20, –0.09)	8
†**7 vs. 1**	–1.19	(–2.20, –0.20)	–	(NT, –1.04)	3
8 vs. 1	–0.60	(–1.64, 0.45)	8	(–1.19, NT)	–
†**6 vs. 3**	0.10	(–1.13, 1.32)	–	(NT, 0.15)	3
†**7 vs. 6**	–0.15	(–1.11, 0.82)	–	(NT, –0.07)	3



Shows thresholds for changes to a body of evidence between two treatments

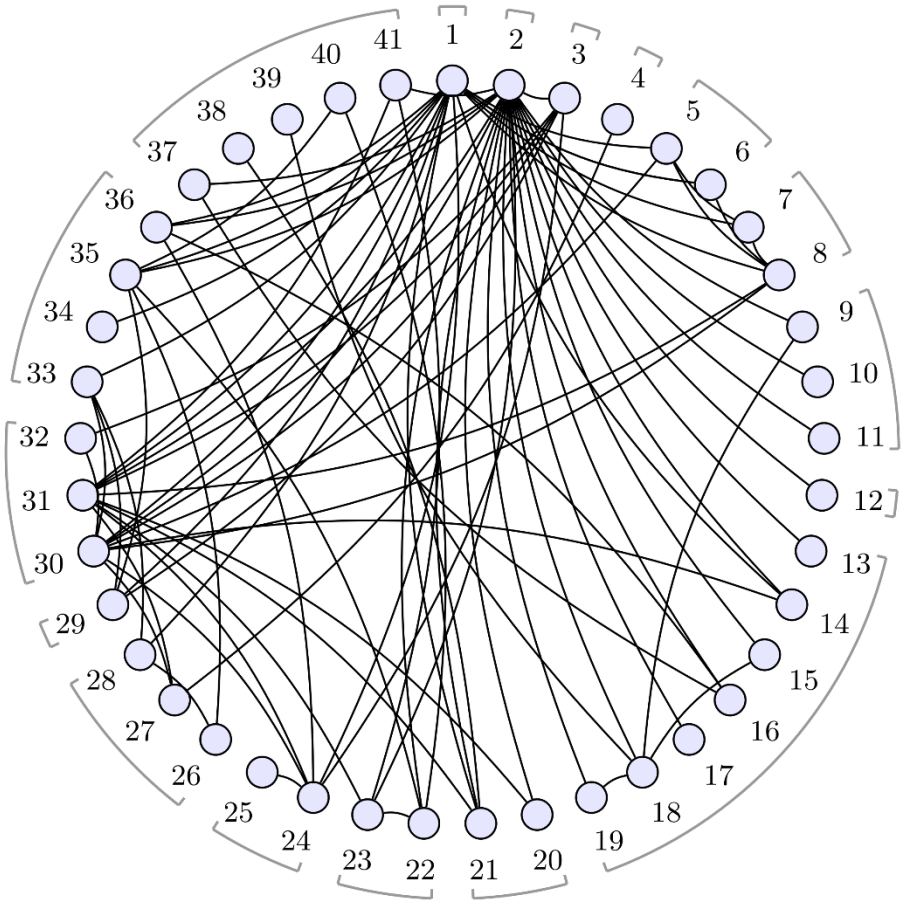
Example: Headaches – study level

Study (Trt.)	Posterior Mean	95% Confidence Interval		Invariant Interval with $\tilde{k}^*$	
Dien09 (1)	–1.14	(–2.26, –0.02)	–	(NT, –0.47)	2
Dien09 (2)	–1.65	(–2.72, –0.58)	2	(–2.32, NT)	–
Apos08 (1)	–2.80	(–3.50, –2.10)	–	(NT, –1.48)	4
Apos08 (4)	–3.10	(–3.93, –2.27)	4	(–7.92, 6.08)	3
Apos08 (4)	–2.20	(–2.93, –1.47)	4	(–6.15, 3.50)	3
Apos08 (4)	–2.80	(–3.43, –2.17)	4	(–6.16, 16.23)	3
Bran04 (1)	–1.30	(–1.93, –0.67)	8	(–5.64, –0.43)	3
Bran04 (6)	–2.90	(–3.53, –2.27)	3	(–5.01, 6.96)	8
Bran04 (6)	–2.60	(–3.21, –1.99)	3	(–4.57, 9.43)	8
Bran04 (6)	–1.70	(–2.29, –1.11)	3	(–3.85, NT)	–
Lewi09 (1)	–2.60	(–3.68, –1.52)	8	(–12.65, –1.12)	3
Lewi09 (6)	–4.90	(–5.93, –3.87)	3	(–8.24, 10.40)	8
Lewi09 (6)	–3.60	(–4.57, –2.63)	3	(–8.22, 19.98)	8
Lipt11 (1)	–5.30	(–5.84, –4.76)	8	(–11.50, –4.47)	3
Lipt11 (6)	–6.60	(–7.14, –6.06)	3	(–8.38, –1.58)	8
Silb04 (1)	–1.30	(–1.89, –0.71)	8	(–4.90, –0.62)	3
Silb04 (6)	–2.70	(–3.30, –2.10)	3	(–5.56, 9.63)	8
Silb04 (6)	–2.70	(–3.23, –2.17)	3	(–4.31, 9.00)	8
Silb04 (6)	–2.70	(–3.25, –2.15)	3	(–4.15, 8.36)	8
Winn05 (1)	–2.40	(–3.18, –1.62)	2	(–12.07, –1.26)	3
Winn05 (6)	–3.10	(–3.67, –2.53)	3	(–4.49, 5.40)	8
†**Dien04 (1)**	–1.10	(–1.57, –0.63)	3	(–1.29, NT)	–
†**Dien04 (6)**	–1.30	(–1.79, –0.81)	3	(–1.44, NT)	–
†**Dien04 (6)**	–1.80	(–2.29, –1.31)	3	(–1.94, NT)	–
†**Dien04 (7)**	–1.90	(–2.39, –1.41)	–	(NT, –1.85)	3
Holr10 (1)	–3.30	(–3.60, –3.00)	–	(NT, –2.71)	8
Holr10 (8)	–3.90	(–4.25, –3.55)	8	(–4.49, NT)	–
Silb13 (5 vs. 1)	0.00	(–1.30, 1.30)	5	(–1.19, NT)	–
†**Dodi09 (3 vs. 6)**	–0.10	(–0.90, 0.70)	3	(–0.15, NT)	–



○ Posterior Mean — 95% Confidence Interval ▬ Invariant Interval

Example: Social Anxiety

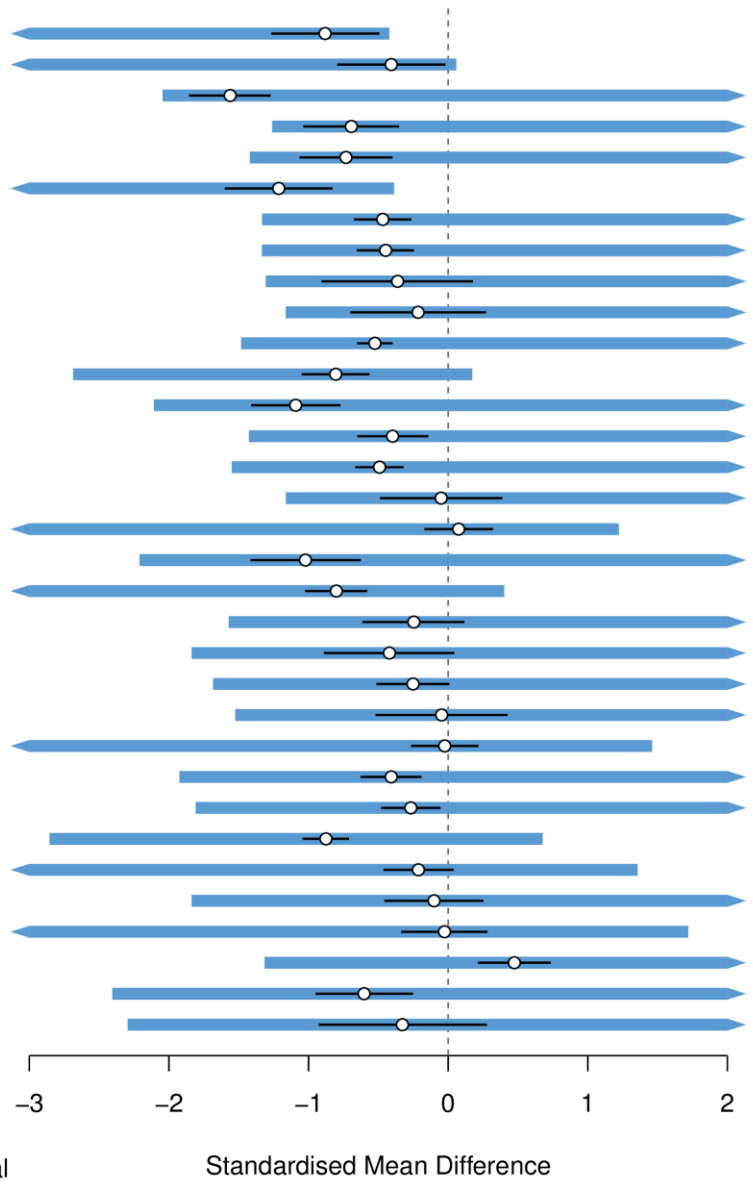


- 41 treatments, 100 studies
- Class effect model with 17 classes
- NMA fed into CEA to give decision on net benefit scale

(NCC-MH, 2013)

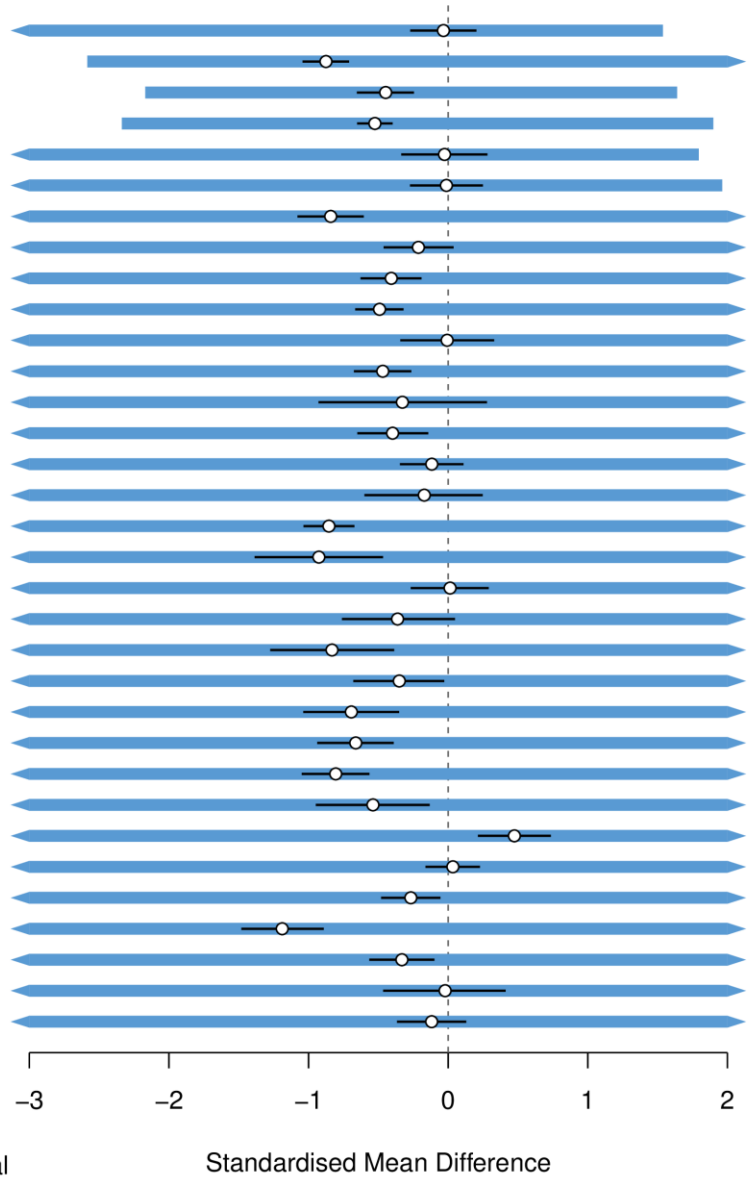
Example: Social Anxiety – contrast level (efficacy)

Contrast	Posterior Mean	95% Credible Interval	Invariant Interval with $\tilde{k}^*$		
41 vs. 31	−0.88	(−1.27, −0.49)	–	(NT, −0.42)	36
41 vs. 23	−0.41	(−0.80, −0.02)	–	(NT, 0.06)	36
36 vs. 1	−1.56	(−1.86, −1.27)	36	(−2.05, 13.61)	7
36 vs. 16	−0.69	(−1.04, −0.35)	36	(−1.26, 4.91)	16
36 vs. 24	−0.73	(−1.06, −0.40)	36	(−1.42, 5.61)	25
41 vs. 2	−1.21	(−1.60, −0.83)	–	(NT, −0.39)	36
17 vs. 2	−0.47	(−0.68, −0.26)	17	(−1.33, 50.71)	12
13 vs. 2	−0.45	(−0.65, −0.25)	13	(−1.33, 139.66)	4
39 vs. 18	−0.36	(−0.91, 0.18)	39	(−1.31, 3.60)	36
38 vs. 21	−0.22	(−0.70, 0.27)	38	(−1.16, 3.71)	36
18 vs. 2	−0.53	(−0.65, −0.40)	39	(−1.48, 8.79)	36
23 vs. 2	−0.81	(−1.05, −0.56)	23	(−2.69, 0.17)	36
36 vs. 2	−1.09	(−1.41, −0.77)	36	(−2.11, 34.05)	18
16 vs. 2	−0.40	(−0.65, −0.14)	36	(−1.43, 17.40)	12
19 vs. 2	−0.49	(−0.67, −0.32)	19	(−1.55, 29.73)	23
25 vs. 24	−0.05	(−0.49, 0.39)	25	(−1.16, 554.74)	39
31 vs. 8	0.07	(−0.17, 0.32)	31	(−13.67, 1.22)	36
34 vs. 1	−1.02	(−1.42, −0.63)	34	(−2.21, 101.29)	5
31 vs. 1	−0.80	(−1.02, −0.58)	31	(−16.38, 0.40)	36
32 vs. 30	−0.25	(−0.61, 0.12)	32	(−1.57, 5.66)	36
11 vs. 2	−0.42	(−0.89, 0.04)	11	(−1.84, 856.05)	34
9 vs. 2	−0.25	(−0.51, 0.01)	9	(−1.68, 46.63)	36
40 vs. 35	−0.05	(−0.52, 0.43)	40	(−1.53, 3.12)	36
30 vs. 24	−0.02	(−0.27, 0.22)	30	(−8.80, 1.46)	36
15 vs. 2	−0.41	(−0.63, −0.19)	15	(−1.92, 49.40)	23
22 vs. 2	−0.27	(−0.48, −0.06)	22	(−1.81, 5.92)	18
8 vs. 1	−0.88	(−1.04, −0.71)	8	(−2.86, 0.68)	36
8 vs. 6	−0.21	(−0.46, 0.04)	8	(−13.40, 1.36)	6
37 vs. 30	−0.10	(−0.46, 0.25)	37	(−1.84, 7.10)	36
8 vs. 7	−0.03	(−0.34, 0.28)	8	(−17.13, 1.72)	7
31 vs. 23	0.47	(0.21, 0.74)	36	(−1.32, 2.58)	23
21 vs. 2	−0.60	(−0.95, −0.25)	21	(−2.41, 10.57)	36
12 vs. 2	−0.33	(−0.93, 0.28)	12	(−2.30, 59.55)	36



Example: Social Anxiety – contrast level (net benefit)

Contrast	Posterior Mean	95% Credible Interval	Invariant Interval with $\tilde{k}^*$		
8 vs. 5	−0.03	(−0.27, 0.20)	5	(−6.05, 1.54)	5
8 vs. 1	−0.88	(−1.04, −0.71)	5	(−2.58, 5.66)	5
13 vs. 2	−0.45	(−0.65, −0.25)	13	(−2.17, 1.64)	13
18 vs. 2	−0.53	(−0.65, −0.40)	18	(−2.34, 1.90)	18
8 vs. 7	−0.03	(−0.34, 0.28)	–	(NT, 1.80)	7
30 vs. 5	−0.01	(−0.27, 0.25)	5	(−7.57, 1.96)	5
5 vs. 1	−0.84	(−1.08, −0.60)	5	(−3.15, 7.99)	5
8 vs. 6	−0.21	(−0.46, 0.04)	8	(−18.57, 2.19)	6
15 vs. 2	−0.41	(−0.63, −0.19)	15	(−3.31, 2.99)	15
19 vs. 2	−0.49	(−0.67, −0.32)	19	(−3.42, 2.86)	19
7 vs. 5	−0.01	(−0.34, 0.33)	7	(−3.44, 4.55)	5
17 vs. 2	−0.47	(−0.68, −0.26)	17	(−4.06, 3.34)	17
12 vs. 2	−0.33	(−0.93, 0.28)	12	(−4.27, 3.63)	12
16 vs. 2	−0.40	(−0.65, −0.14)	16	(−5.18, 5.19)	16
18 vs. 15	−0.12	(−0.35, 0.11)	15	(−5.74, 4.67)	15
28 vs. 26	−0.17	(−0.60, 0.25)	–	(NT, 4.72)	27
30 vs. 1	−0.85	(−1.04, −0.67)	5	(−6.42, 9.85)	16
35 vs. 26	−0.93	(−1.39, −0.47)	–	(NT, 4.70)	27
30 vs. 16	0.01	(−0.27, 0.29)	16	(−6.60, 5.67)	16
14 vs. 2	−0.36	(−0.76, 0.05)	14	(−7.20, 7.15)	14
14 vs. 1	−0.83	(−1.27, −0.39)	14	(−8.51, 7.60)	14
33 vs. 29	−0.35	(−0.68, −0.03)	–	(NT, 7.90)	30
36 vs. 16	−0.69	(−1.04, −0.35)	16	(−10.61, 7.78)	16
6 vs. 1	−0.66	(−0.94, −0.39)	6	(−9.17, NT)	–
23 vs. 2	−0.81	(−1.05, −0.56)	24	(−9.38, 11.46)	18
33 vs. 28	−0.54	(−0.95, −0.13)	–	(NT, 8.79)	27
31 vs. 23	0.47	(0.21, 0.74)	12	(−18.59, 9.80)	24
19 vs. 18	0.03	(−0.16, 0.23)	19	(−9.48, 10.94)	19
22 vs. 2	−0.27	(−0.48, −0.06)	12	(−13.06, 9.81)	18
35 vs. 1	−1.19	(−1.48, −0.89)	27	(−11.79, 17.33)	18
31 vs. 2	−0.33	(−0.57, −0.10)	18	(−14.95, 10.60)	18
30 vs. 14	−0.02	(−0.47, 0.41)	14	(−12.55, 11.38)	14
33 vs. 30	−0.12	(−0.37, 0.13)	–	(NT, 11.47)	5



Conclusions

- Provides insight into the effects of bias adjustment on treatment decisions
- Application to combined data on contrasts is highly flexible
- More confidence in recommendations where thresholds are large
- Focusses attention on the quality of decision-sensitive trials and contrasts

Acknowledgements

NICE
National Institute for Health and Care Excellence

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MRC Medical Research Council

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Phillippo D M, Welton N J, Dias S, Didelez V, Ades A E. *Bias-Adjustment Thresholds for Bayesian Network Meta-Analysis*. Submitted.

Additional slides

The Threshold Method

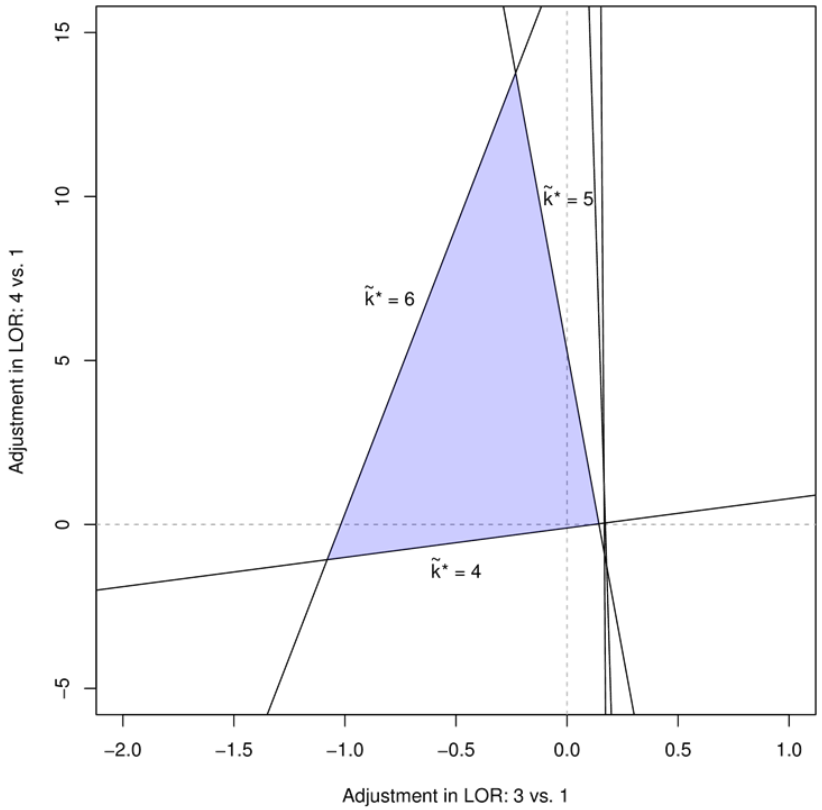
Thresholds are derived for a data point by:

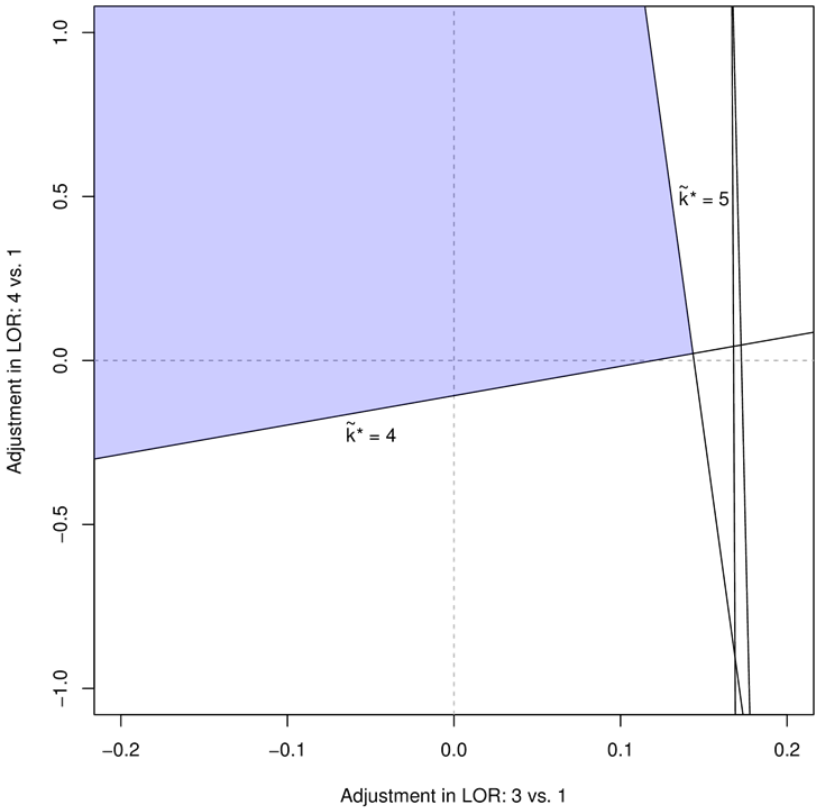
1. Asking for each non-optimal treatment how much adjustment would make that treatment optimal

$$\frac{\text{Difference to overturn}}{\text{Influence of data point}}$$

2. Taking the smallest positive and negative adjustments as the positive and negative thresholds

Extensions: Multiple simultaneous adjustments





Extensions: Psychological treatment bias