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Confidence in recommendations based on Network Meta-Analysis: threshold analysis as an alternative to GRADE

David M. Phillippo[1], Sofia Dias[1], Nicky J. Welton[1], Deborah M. Caldwell[1], Nichole Taske[2], A. E. Ades[1]

[1]School of Social and Community Medicine, University of Bristol, UK

[2]National Institute for Health and Care Excellence (NICE), London, UK

Background

Network Meta-Analysis (NMA)

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

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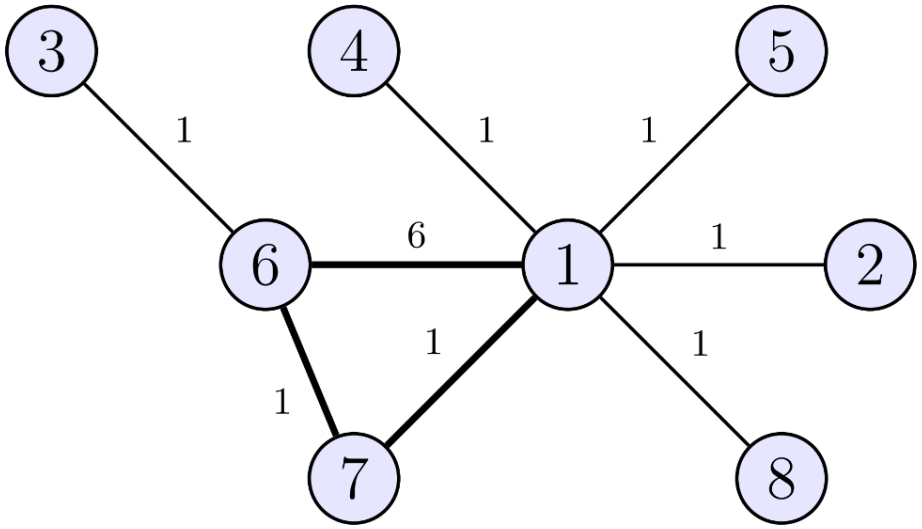
Example: Headaches clinical guideline



Minimal Clinically Important Difference (MCID) = 0.5 days per month

(NICE CG151.1, 2015)

	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)

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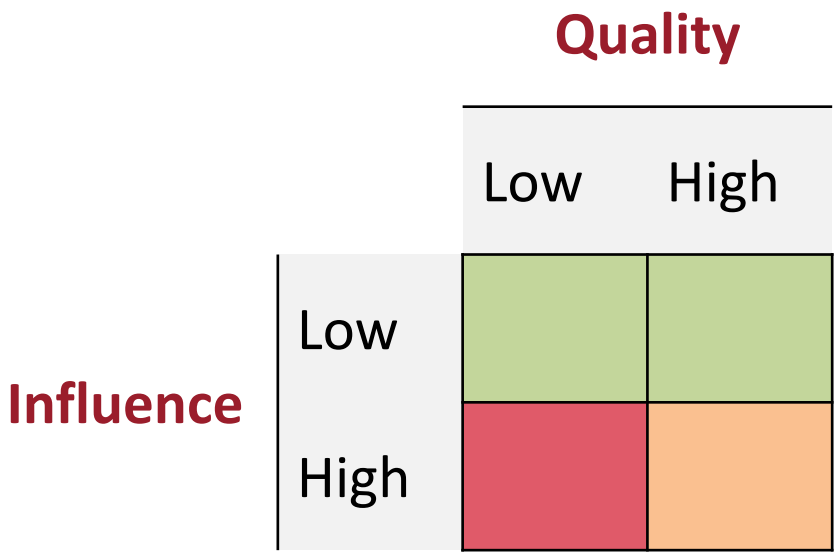
Motivation

How robust are the recommendations based on NMA?

The quality of evidence reflects the extent to which our **confidence in an estimate of the effect** is adequate to **support a particular recommendation**. *(GRADE Handbook, 2013)*



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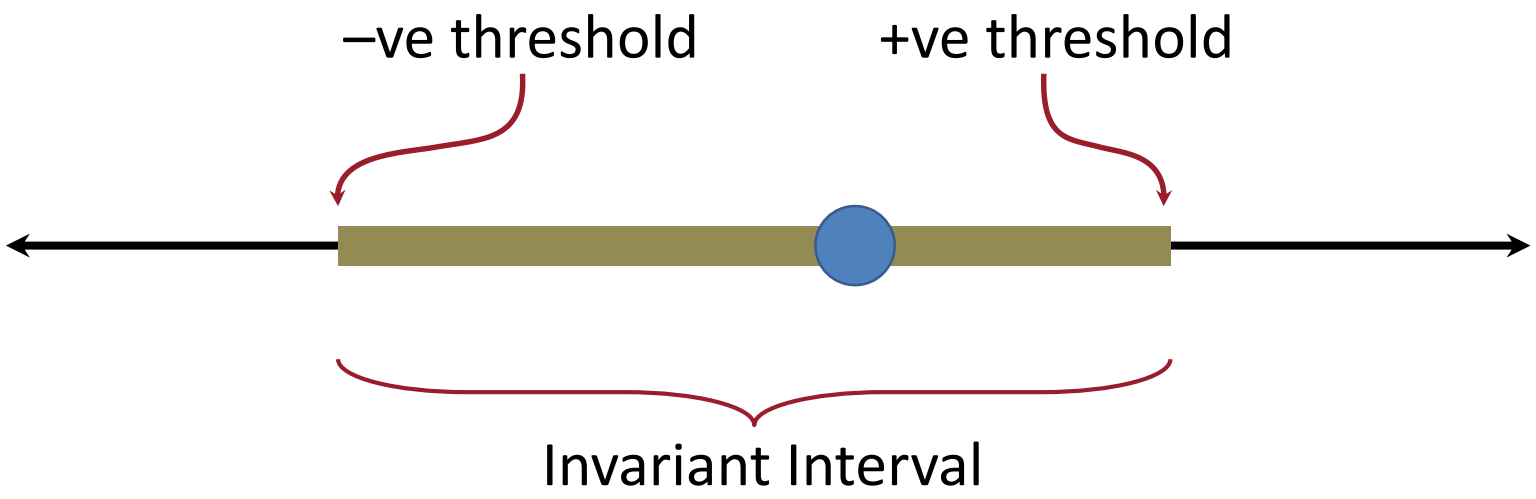
Threshold Analysis

Create an *invariant interval* for a data point:



How much would the evidence have to change before we reach a new recommendation?

Threshold Analysis

We can do this at two “levels”:

- Study level
  - Thresholds for each individual study estimate
- Contrast level
  - Thresholds for combined body of evidence on a contrast
  - Highly flexible due to approximation step

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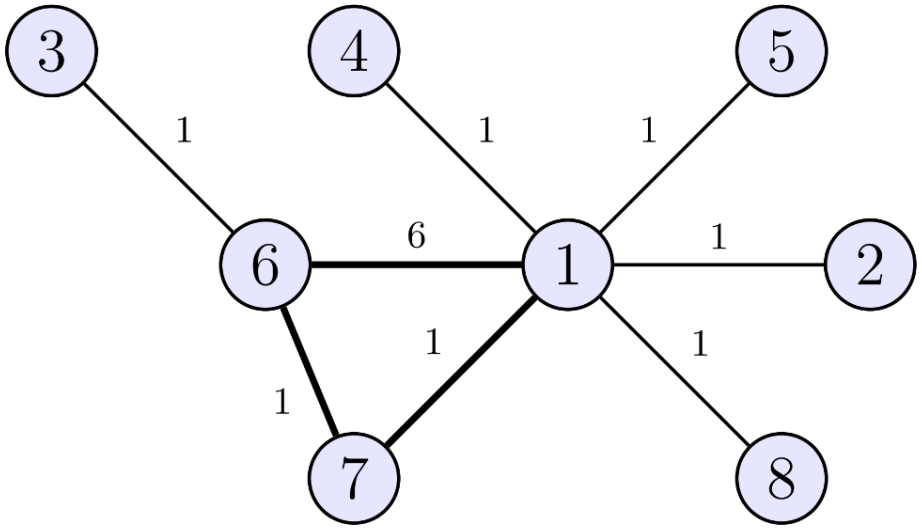
Example: Headaches clinical guideline



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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)

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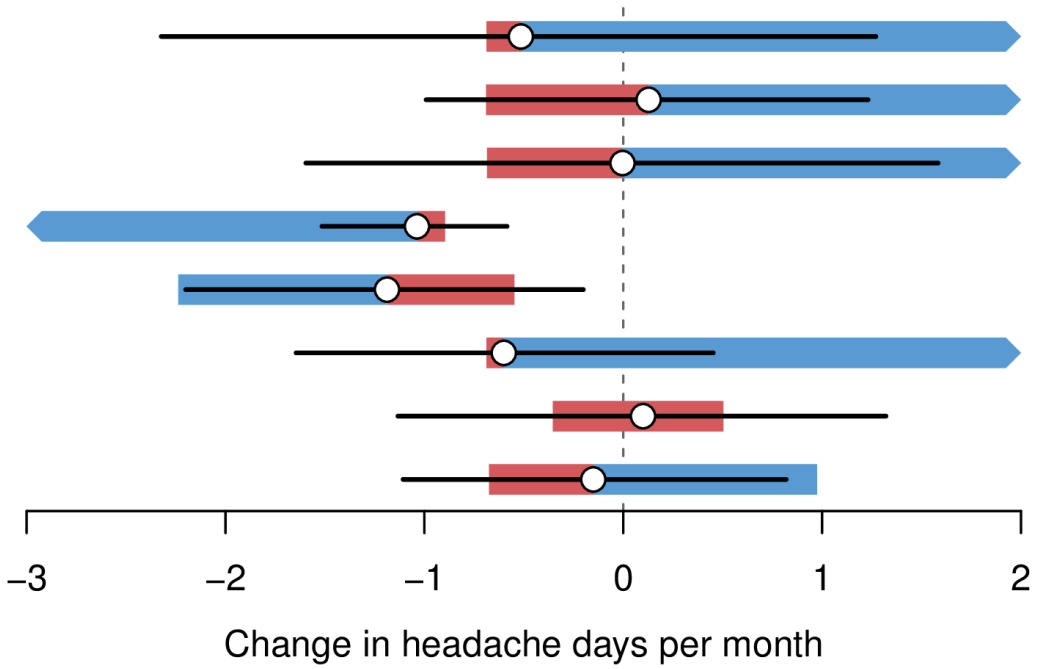
Example: Headaches clinical guideline – contrast level

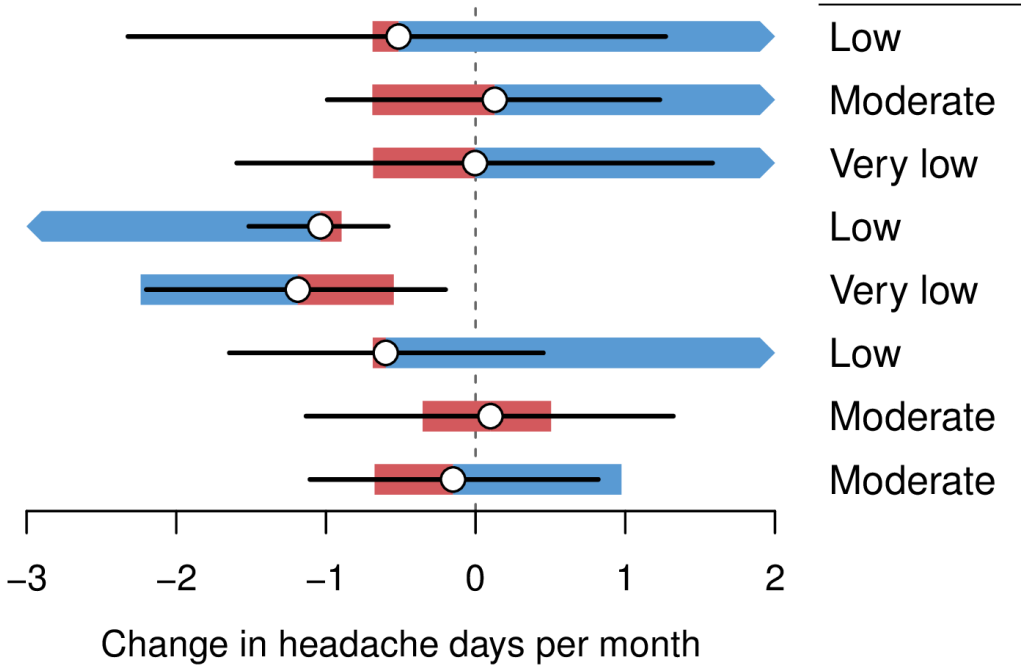
Contrast	Mean	95% CrI	Invariant Interval and $\tilde{k}^*$		
2 vs. 1	–0.51	(–2.32, 1.27)	2, 3, 6, 7	(–0.69, NT)	–
4 vs. 1	0.13	(–0.99, 1.23)	3, 4, 6, 7	(–0.69, 12.02)	3, 6, 7, 8
5 vs. 1	–0.00	(–1.60, 1.58)	3, 5, 6, 7	(–0.69, 24.04)	2, 3, 6, 7
6 vs. 1	–1.04	(–1.51, –0.58)	–	(NT, –0.90)	3, 6, 7, 8
7 vs. 1	–1.19	(–2.20, –0.20)	3, 7	(–2.24, –0.55)	3, 6, 7, 8
8 vs. 1	–0.60	(–1.64, 0.45)	3, 6, 7, 8	(–0.69, NT)	–
6 vs. 3	0.10	(–1.13, 1.32)	6, 7	(–0.35, 0.50)	3, 7
7 vs. 6	–0.15	(–1.11, 0.82)	3, 7	(–0.67, 0.97)	3, 6



Base–case optimal treatment set is 3, 6, 7.

Example: Headaches clinical guideline – contrast level

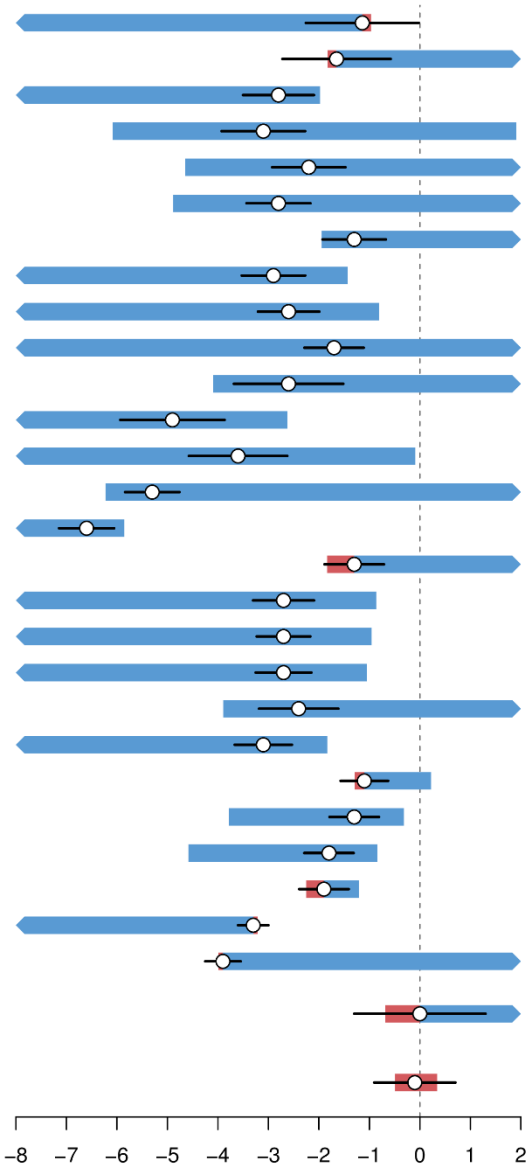
Contrast	Mean	95% CrI	Invariant Interval and $\tilde{k}$*			GRADE
2 vs. 1	–0.51	(–2.32, 1.27)	2, 3, 6, 7	(–0.69, NT)	–	Low
4 vs. 1	0.13	(–0.99, 1.23)	3, 4, 6, 7	(–0.69, 12.02)	3, 6, 7, 8	Moderate
5 vs. 1	–0.00	(–1.60, 1.58)	3, 5, 6, 7	(–0.69, 24.04)	2, 3, 6, 7	Very low
6 vs. 1	–1.04	(–1.51, –0.58)	–	(NT, –0.90)	3, 6, 7, 8	Low
7 vs. 1	–1.19	(–2.20, –0.20)	3, 7	(–2.24, –0.55)	3, 6, 7, 8	Very low
8 vs. 1	–0.60	(–1.64, 0.45)	3, 6, 7, 8	(–0.69, NT)	–	Low
6 vs. 3	0.10	(–1.13, 1.32)	6, 7	(–0.35, 0.50)	3, 7	Moderate
7 vs. 6	–0.15	(–1.11, 0.82)	3, 7	(–0.67, 0.97)	3, 6	Moderate



Base–case optimal treatment set is 3, 6, 7.

Example: Headaches clinical guideline – study level

Study (Trt.)	Mean	95% CI	Invariant Interval and $\tilde{k}^*$		
Diener 2009 (1)	−1.14	(−2.26, −0.02)	–	(NT, −0.97)	2, 3, 6, 7
Diener 2009 (2)	−1.65	(−2.72, −0.58)	2, 3, 6, 7	(−1.82, NT)	–
Apostol 2008 (1)	−2.80	(−3.50, −2.10)	3, 6, 7, 8	(−9.95, −1.98)	3, 4, 6, 7
Apostol 2008 (4)	−3.10	(−3.93, −2.27)	3, 4, 6, 7	(−6.09, 1.91)	3, 6, 7, 8
Apostol 2008 (4)	−2.20	(−2.93, −1.47)	3, 4, 6, 7	(−4.65, NT)	–
Apostol 2008 (4)	−2.80	(−3.43, −2.17)	3, 4, 6, 7	(−4.88, 5.19)	3, 6, 7, 8
Brandes 2004 (1)	−1.30	(−1.93, −0.67)	3, 6, 7, 8	(−1.95, NT)	–
Brandes 2004 (6)	−2.90	(−3.53, −2.27)	–	(NT, −1.43)	3, 6, 7, 8
Brandes 2004 (6)	−2.60	(−3.21, −1.99)	–	(NT, −0.81)	3, 6, 7, 8
Brandes 2004 (6)	−1.70	(−2.29, −1.11)	–	(NT, 15.76)	2, 3, 6, 7
Lewis 2009 (1)	−2.60	(−3.68, −1.52)	3, 6, 7, 8	(−4.10, NT)	–
Lewis 2009 (6)	−4.90	(−5.93, −3.87)	–	(NT, −2.62)	3, 6, 7, 8
Lewis 2009 (6)	−3.60	(−4.57, −2.63)	–	(NT, −0.09)	3, 6, 7, 8
Lipton 2011 (1)	−5.30	(−5.84, −4.76)	3, 6, 7, 8	(−6.22, NT)	–
Lipton 2011 (6)	−6.60	(−7.14, −6.06)	–	(NT, −5.85)	3, 6, 7, 8
Silberstein 2004 (1)	−1.30	(−1.89, −0.71)	3, 6, 7, 8	(−1.84, NT)	–
Silberstein 2004 (6)	−2.70	(−3.30, −2.10)	–	(NT, −0.87)	3, 6, 7, 8
Silberstein 2004 (6)	−2.70	(−3.23, −2.17)	–	(NT, −0.96)	3, 6, 7, 8
Silberstein 2004 (6)	−2.70	(−3.25, −2.15)	–	(NT, −1.05)	3, 6, 7, 8
Winner 2005 (1)	−2.40	(−3.18, −1.62)	3, 6, 7, 8	(−3.89, NT)	–
Winner 2005 (6)	−3.10	(−3.67, −2.53)	–	(NT, −1.83)	3, 6, 7, 8
Diener 2004 (1)	−1.10	(−1.57, −0.63)	3, 6, 7, 8	(−1.29, 0.22)	3, 7
Diener 2004 (6)	−1.30	(−1.79, −0.81)	3, 6	(−3.78, −0.32)	3, 7
Diener 2004 (6)	−1.80	(−2.29, −1.31)	3, 6	(−4.58, −0.85)	3, 7
Diener 2004 (7)	−1.90	(−2.39, −1.41)	3, 7	(−2.25, −1.21)	3, 6
Holroyd 2010 (1)	−3.30	(−3.60, −3.00)	6, 7	(−17.43, −3.21)	3, 6, 7, 8
Holroyd 2010 (8)	−3.90	(−4.25, −3.55)	3, 6, 7, 8	(−3.99, 10.77)	6, 7
Silberstein 2013 (5 vs. 1)	0.00	(−1.30, 1.30)	3, 5, 6, 7	(−0.69, 11.76)	2, 3, 6, 7
Dodick 2009 (3 vs. 6)	−0.10	(−0.90, 0.70)	3, 7	(−0.49, 0.34)	6, 7

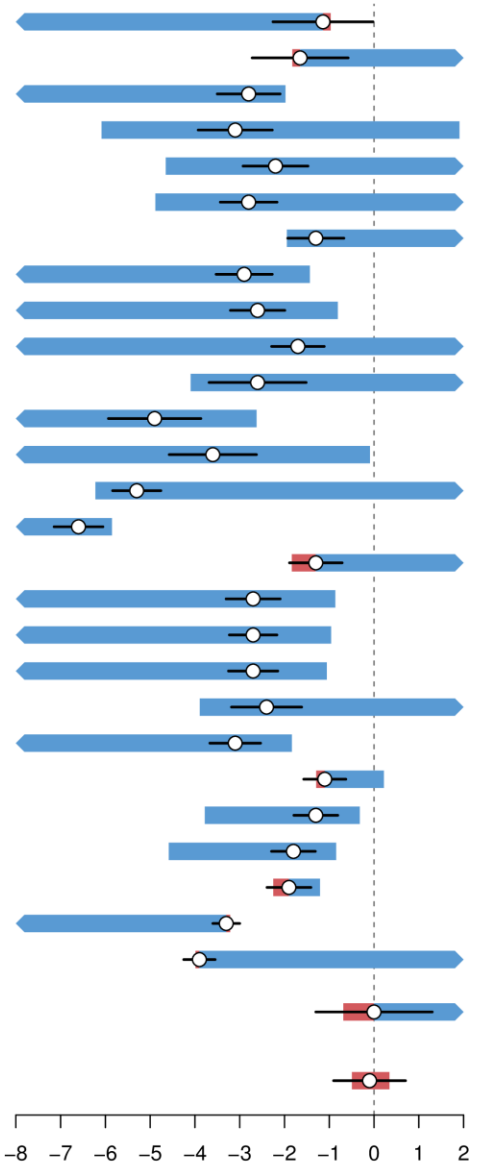


○ Mean — 95% CI ▭ Invariant Interval

Base–case optimal treatment set is 3, 6, 7.

Example: Headaches clinical guideline – study level

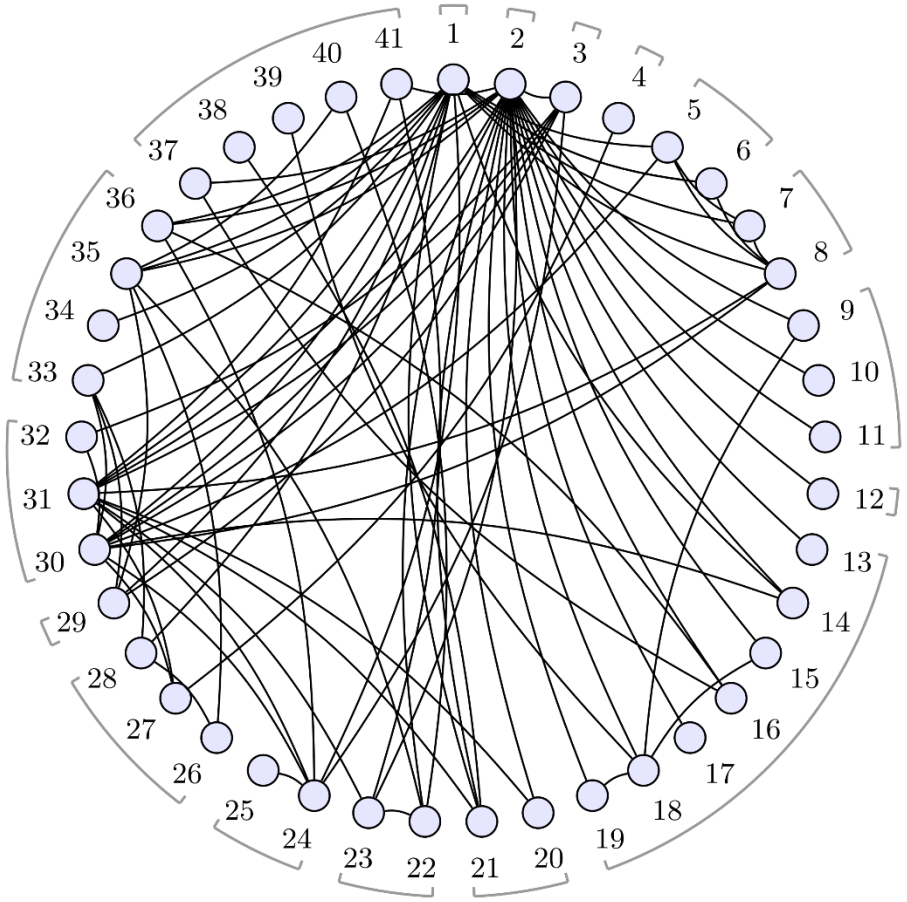
Study (Trt.)	Mean	95% CI	Invariant Interval and $\tilde{k}^*$			Sel	Perf	Det	Att	Rep	Oth
Diener 2009 (1)	−1.14	(−2.26, −0.02)	–	(NT, −0.97)	2, 3, 6, 7	U	L	L	L	U	H
Diener 2009 (2)	−1.65	(−2.72, −0.58)	2, 3, 6, 7	(−1.82, NT)	–						
Apostol 2008 (1)	−2.80	(−3.50, −2.10)	3, 6, 7, 8	(−9.95, −1.98)	3, 4, 6, 7	U	L	L	L	U	L
Apostol 2008 (4)	−3.10	(−3.93, −2.27)	3, 4, 6, 7	(−6.09, 1.91)	3, 6, 7, 8						
Apostol 2008 (4)	−2.20	(−2.93, −1.47)	3, 4, 6, 7	(−4.65, NT)	–						
Apostol 2008 (4)	−2.80	(−3.43, −2.17)	3, 4, 6, 7	(−4.88, 5.19)	3, 6, 7, 8						
Brandes 2004 (1)	−1.30	(−1.93, −0.67)	3, 6, 7, 8	(−1.95, NT)	–	L	L	L	H	U	L
Brandes 2004 (6)	−2.90	(−3.53, −2.27)	–	(NT, −1.43)	3, 6, 7, 8						
Brandes 2004 (6)	−2.60	(−3.21, −1.99)	–	(NT, −0.81)	3, 6, 7, 8						
Brandes 2004 (6)	−1.70	(−2.29, −1.11)	–	(NT, 15.76)	2, 3, 6, 7						
Lewis 2009 (1)	−2.60	(−3.68, −1.52)	3, 6, 7, 8	(−4.10, NT)	–	U	L	L	L	U	L
Lewis 2009 (6)	−4.90	(−5.93, −3.87)	–	(NT, −2.62)	3, 6, 7, 8						
Lewis 2009 (6)	−3.60	(−4.57, −2.63)	–	(NT, −0.09)	3, 6, 7, 8						
Lipton 2011 (1)	−5.30	(−5.84, −4.76)	3, 6, 7, 8	(−6.22, NT)	–	L	L	L	H	U	L
Lipton 2011 (6)	−6.60	(−7.14, −6.06)	–	(NT, −5.85)	3, 6, 7, 8						
Silberstein 2004 (1)	−1.30	(−1.89, −0.71)	3, 6, 7, 8	(−1.84, NT)	–	U	L	L	H	U	L
Silberstein 2004 (6)	−2.70	(−3.30, −2.10)	–	(NT, −0.87)	3, 6, 7, 8						
Silberstein 2004 (6)	−2.70	(−3.23, −2.17)	–	(NT, −0.96)	3, 6, 7, 8						
Silberstein 2004 (6)	−2.70	(−3.25, −2.15)	–	(NT, −1.05)	3, 6, 7, 8						
Winner 2005 (1)	−2.40	(−3.18, −1.62)	3, 6, 7, 8	(−3.89, NT)	–	U	L	L	L	U	L
Winner 2005 (6)	−3.10	(−3.67, −2.53)	–	(NT, −1.83)	3, 6, 7, 8						
Diener 2004 (1)	−1.10	(−1.57, −0.63)	3, 6, 7, 8	(−1.29, 0.22)	3, 7	U	L	L	H	U	U
Diener 2004 (6)	−1.30	(−1.79, −0.81)	3, 6	(−3.78, −0.32)	3, 7						
Diener 2004 (6)	−1.80	(−2.29, −1.31)	3, 6	(−4.58, −0.85)	3, 7						
Diener 2004 (7)	−1.90	(−2.39, −1.41)	3, 7	(−2.25, −1.21)	3, 6						
Holroyd 2010 (1)	−3.30	(−3.60, −3.00)	6, 7	(−17.43, −3.21)	3, 6, 7, 8	L	L	L	L	U	L
Holroyd 2010 (8)	−3.90	(−4.25, −3.55)	3, 6, 7, 8	(−3.99, 10.77)	6, 7						
Silberstein 2013 (5 vs. 1)	0.00	(−1.30, 1.30)	3, 5, 6, 7	(−0.69, 11.76)	2, 3, 6, 7	U	L	L	L	H	L
Dodick 2009 (3 vs. 6)	−0.10	(−0.90, 0.70)	3, 7	(−0.49, 0.34)	6, 7	U	L	L	L	U	L



○ Mean — 95% CI ▬ Invariant Interval

Base−case optimal treatment set is 3, 6, 7.

Example: Social Anxiety



- 41 treatments, 100 studies
- Class effect model with 17 classes
- 84 direct comparisons and many “first order” loops

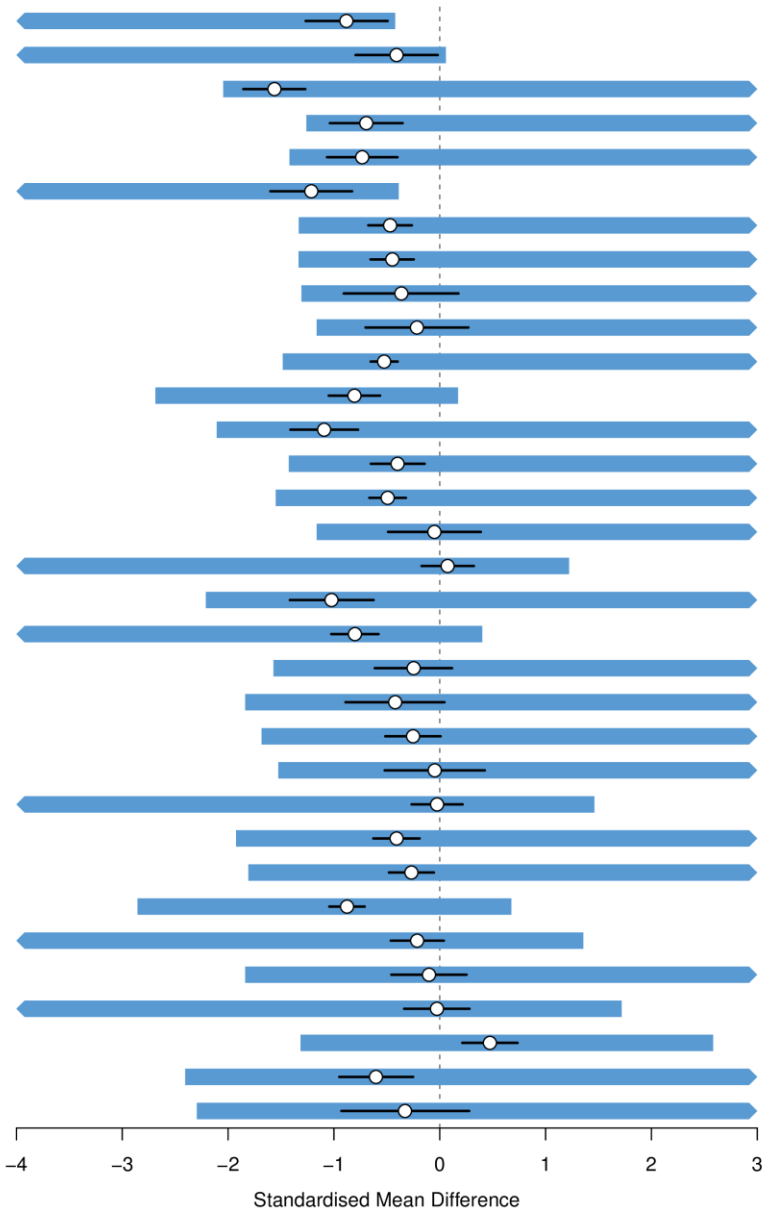
  ⇒ GRADE impractical

Based on efficacy alone recommendation is CBT + Phenelzine (41)

(NCC-MH, 2013)

Example: Social Anxiety – contrast level

Contrast	SMD	95% Credible Interval	Invariant Interval and $\tilde{k}^*$		
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



○ SMD — 95% Credible Interval ■ Invariant Interval

Base−case recommended treatment is 41.

Thresholds smaller than 0.8 SMD

Thresholds larger than 0.8 SMD

Example: Social Anxiety

We can also use threshold analysis to investigate more specific concerns

- E.g. groups of treatments or studies with certain characteristics

Psychological treatment bias – could this affect the recommendation?

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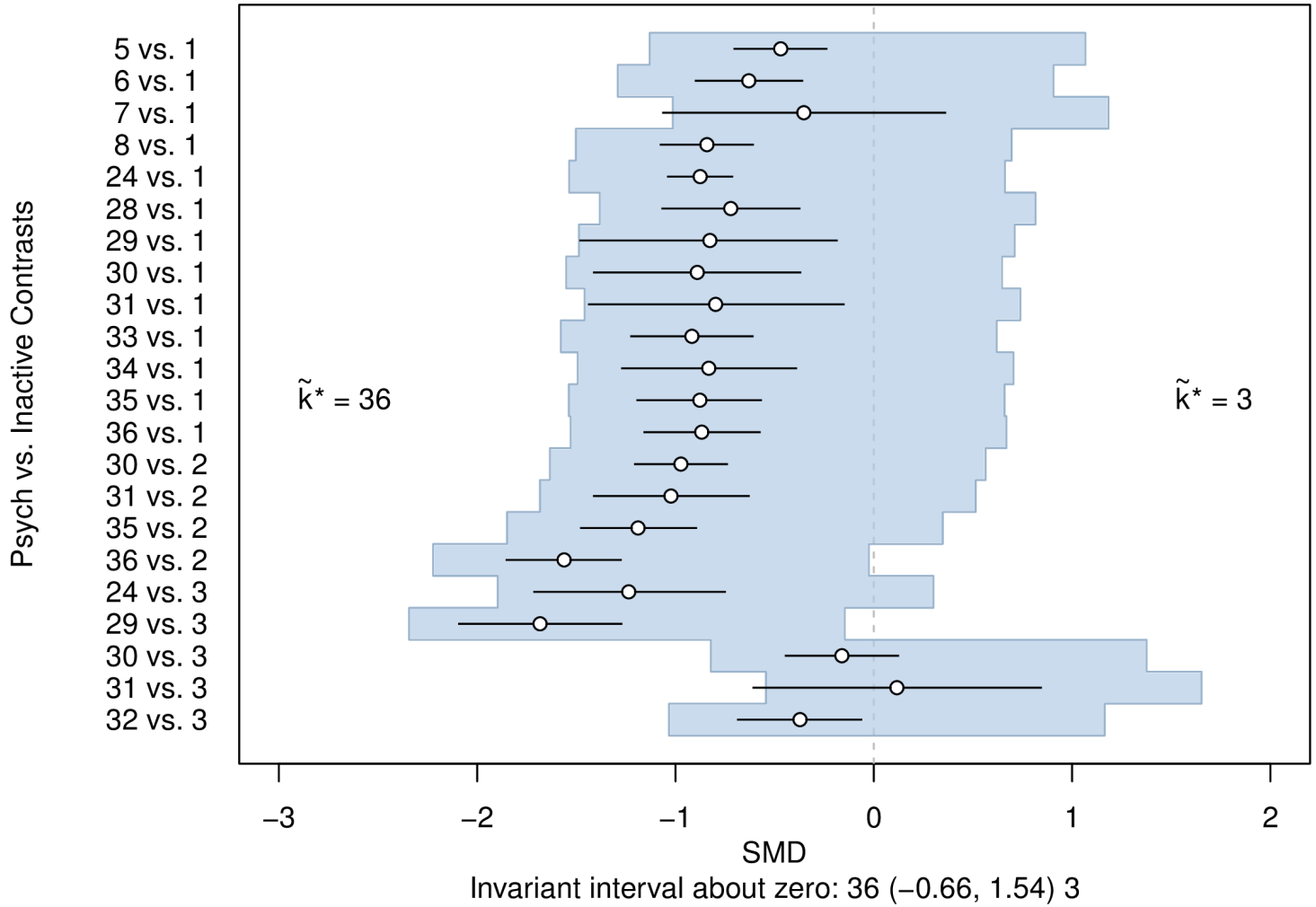
Example: Social Anxiety – psychological treatment bias



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Conclusions

- Evidence quality and risk of bias are not sufficient to assess robustness of decisions
- Threshold analysis provides insight into the effects of changes in the evidence on treatment decisions
  - We can have more confidence in recommendations where thresholds are large
  - We can focus attention on the quality of decision-sensitive trials and contrasts
- More complex analyses can investigate specific concerns in the evidence
- Can be used with a range of decision rules or for decisions based on cost-effectiveness

Phillippo DM, Dias S, Ades AE, Didelez V and Welton NJ (2018). *Sensitivity of treatment recommendations to bias in network meta-analysis*. J. R. Stat. Soc. A, 181: 843-867. doi:10.1111/rssa.12341

R package *nmathresh* package available on CRAN

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Thank You

NICE
National Institute for Health and Care Excellence

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MRC Medical Research Council

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