

Latest GRADE guidance regarding network meta-analysis

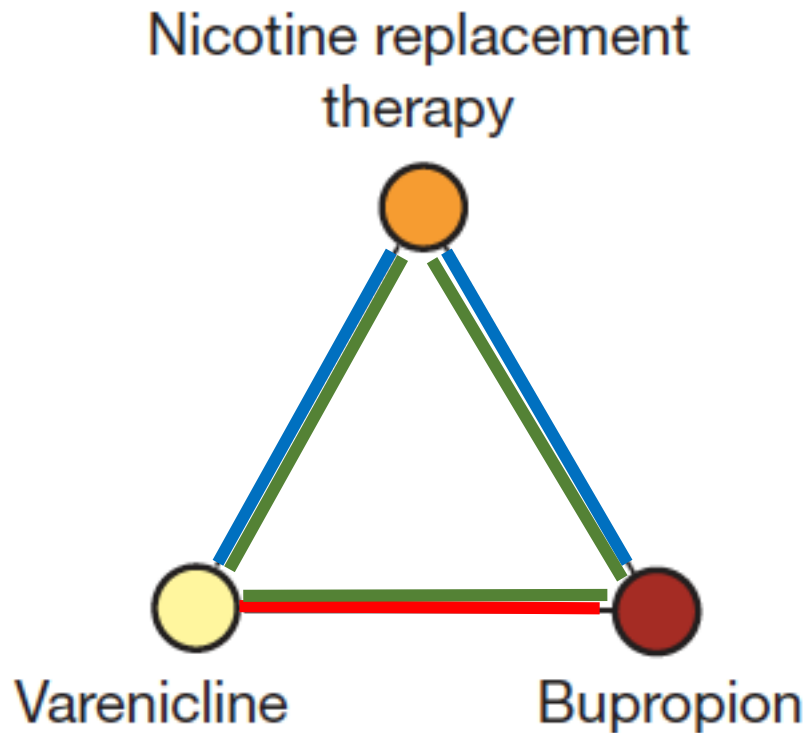
A day with... GRADing methods group: What's new
Romina Brignardello-Petersen

November 19, 2020

Conflicts of interest

- None financial
- Member of GRADE working group and lead of GRADE NMA project group

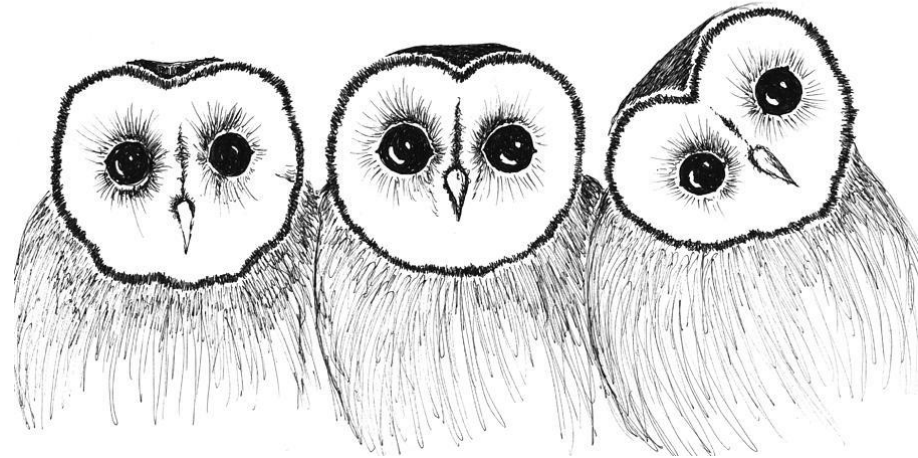
Network meta-analysis



- For the Varenicline- Bupropion comparison:
 - Direct evidence
 - Indirect evidence (via NRT)
 - Network evidence

Outline

1. Available guidance to date
2. To be published, in the works
3. Other work



1. Available guidance to date

GRADE approach to NMA, Advances to the GRADE approach to NMA, Incoherence, Making conclusions



RESEARCH METHODS & REPORTING

A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis

Network meta-analysis (NMA), combining direct and indirect comparisons, is increasingly being used to examine the comparative effectiveness of medical interventions. Minimal guidance exists on how to rate the quality of evidence supporting treatment effect estimates obtained from NMA. We present a four-step approach to rate the quality of evidence in each of the direct, indirect, and NMA estimates based on methods developed by the GRADE working group. Using an example of a published NMA, we show that the quality of evidence supporting NMA estimates varies from high to very low across comparisons, and that quality ratings given to a whole network are uninformative and likely to mislead.

Key messages

- Rating must be done at the pairwise comparison level
 - 3 interventions → 3 comparisons and ratings
 - 6 interventions → 15 comparisons and ratings
- Rating informed by the pieces of evidence that contribute to the network estimate



Advances to the GRADE approach to NMA



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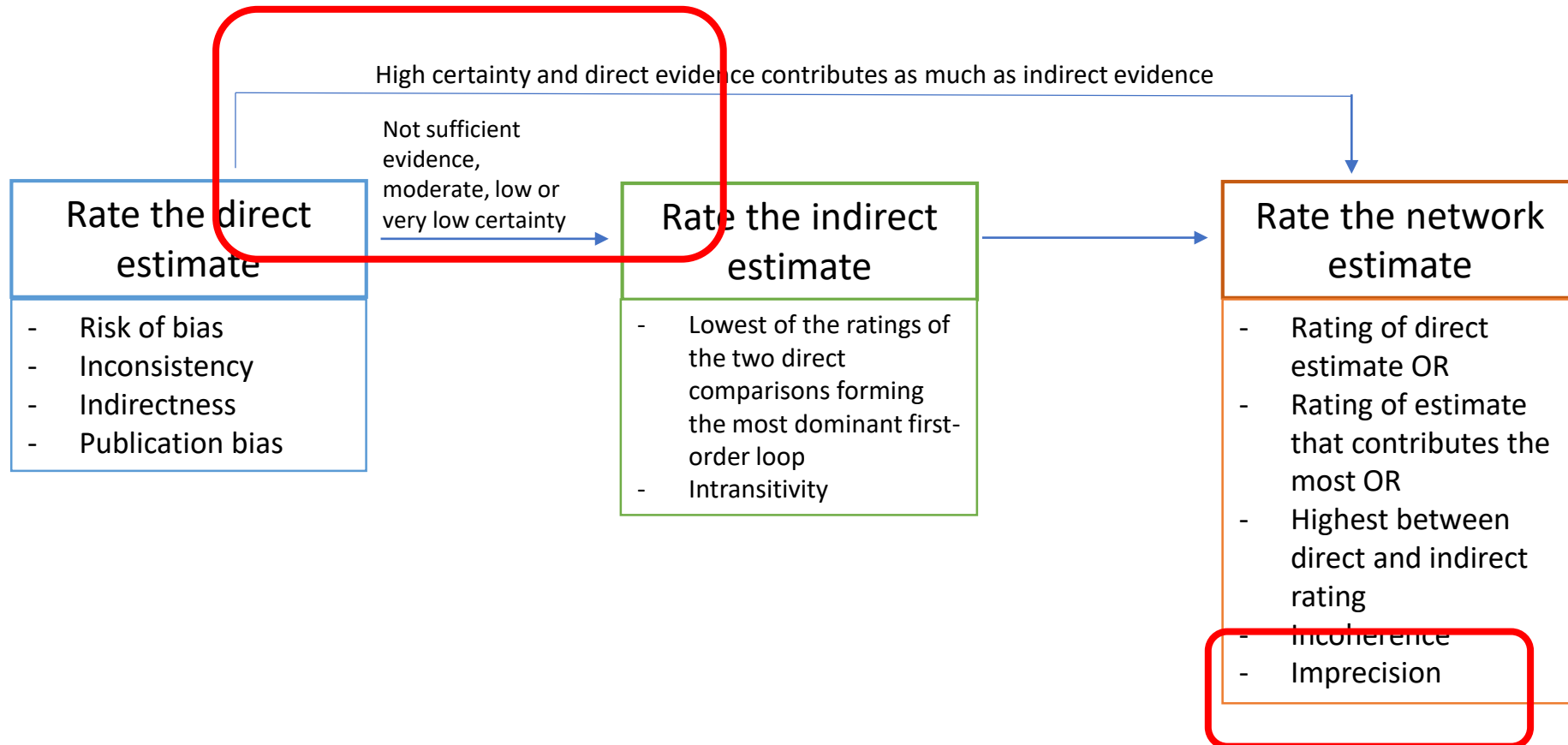
Journal of Clinical Epidemiology 93 (2018) 36–44

**Journal of
Clinical
Epidemiology**

Advances in the GRADE approach to rate the certainty in estimates from a network meta-analysis

Romina Brignardello-Petersen^{a,b}, Ashley Bonner^a, Paul E. Alexander^{a,c}, Reed A. Siemieniuk^{a,d},
Toshi A. Furukawa^{e,f}, Bram Rochweg^{a,g}, Glen S. Hazlewood^{h,i}, Waleed Alhazzani^{a,g},
Reem A. Mustafa^{a,j}, M. Hassan Murad^k, Milo A. Puhan^{l,m}, Holger J. Schünemann^a,
Gordon H. Guyatt^{a,*}, For the GRADE Working Group

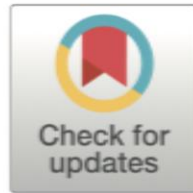
Key messages



Incoherence (agreement between direct and indirect evidence)



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Journal of Clinical Epidemiology 108 (2019) 77–85

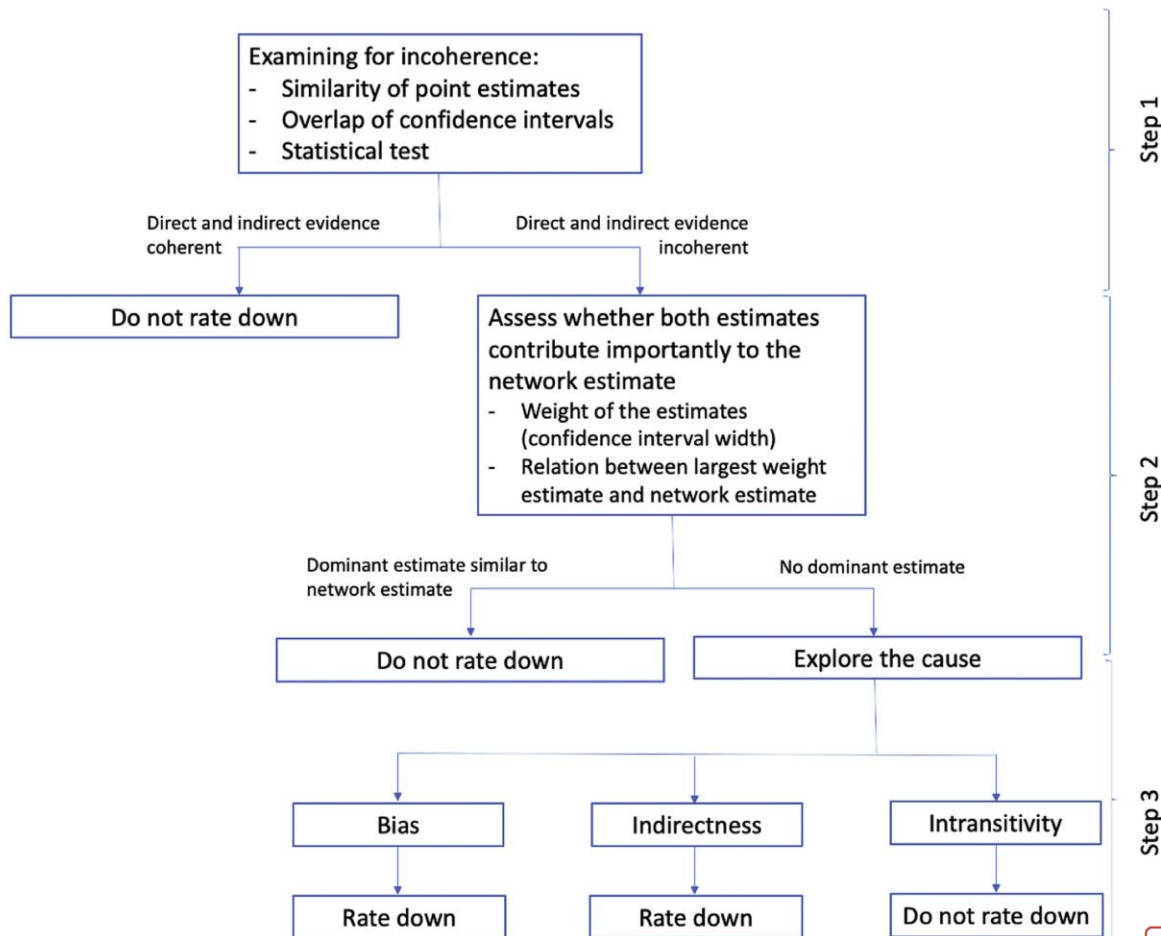
**Journal of
Clinical
Epidemiology**

ORIGINAL ARTICLE

GRADE approach to rate the certainty from a network meta-analysis: addressing incoherence

Romina Brignardello-Petersen^{a,*}, Reem A. Mustafa^{a,b}, Reed A.C. Siemieniuk^a,
M. Hassan Murad^c, Thomas Agoritsas^{a,d}, Ariel Izcovich^e, Holger J. Schünemann^a,
Gordon H. Guyatt^a, for the GRADE Working Group

Key messages



- Not only statistical
- Serious incoherence → makes the network estimate importantly different from the estimate that contributes the most to it

Making conclusions

RESEARCH METHODS AND REPORTING

 Check for updates

GRADE approach to drawing conclusions from a network meta-analysis using a minimally contextualised framework

Romina Brignardello-Petersen,¹ Ivan D Florez,^{1,2} Ariel Izcovich,³ Nancy Santesso,¹ Glen Hazlewood,⁴ Waleed Alhazanni,¹ Juan José Yepes-Nuñez,⁵ George Tomlinson,^{6,7} Holger J Schünemann,¹ Gordon H Guyatt,¹ on behalf of the GRADE working group

Cite this as: *BMJ* 2020;**371**:m3900
<http://dx.doi.org/10.1136/bmj.m3900>

 Check for updates

GRADE approach to drawing conclusions from a network meta-analysis using a partially contextualised framework

Romina Brignardello-Petersen,¹ Ariel Izcovich,² Bram Rochweg,¹ Ivan D Florez,^{1,3} Glen Hazlewood,⁴ Waleed Alhazanni,¹ Juan Yepes-Nuñez,⁵ Nancy Santesso,¹ Gordon H Guyatt,¹ Holger J Schünemann,^{1,6} on behalf of the GRADE working group

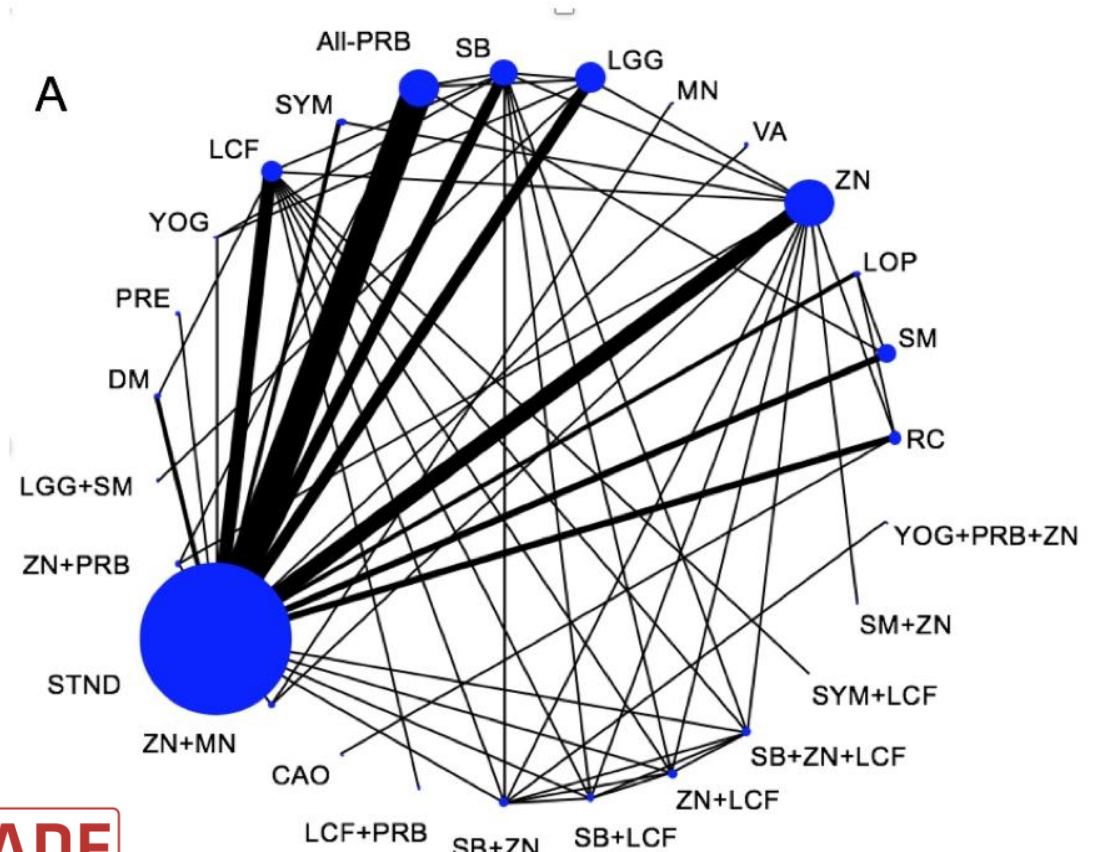
Cite this as: *BMJ* 2020;**371**:m3907
<http://dx.doi.org/10.1136/bmj.m3907>

Key messages

- Network meta-analysis (NMA) rarely establishes that, for a single outcome, one intervention is better than all others
- Classify in groups of interventions
 - MC: Most to least effective
 - PC: Large to trivial effect
- Consider estimates of effect, certainty of the evidence, and ranking

Conclusions: outcome level

- **NMA of the interventions for Acute Diarrhea and Gastroenteritis in Children** (Florez et al. 2019)
- 27 interventions
- 138 studies
- 20,256 participants
- 62 direct comparisons
- 351 pairwise comparisons



Certainty on the evidence	Classification	Intervention	Intervention vs. Standard/placebo MD (95%CrI)	SUCRA
High Certainty (Moderate- to High-quality evidence)	Category 2: Among the most effective	S. boulardii + Zinc	-39.45 (-52.5; -26.7)	0.92
		Smectite + Zinc	-35.63 (-57.6; -13.2)	0.88
	Category 1: Inferior to the most effective / superior to the least effective	Symbiotics	-26.26 (-36.1; -16.2)	0.77
		Zinc + LCF	-21.37 (-36.5; -6.1)	0.61
		Zinc (All)	-18.38 (-23.4; -13.5)	0.50
		Loperamide	-17.79; (-30.4; -5.7)	0.46
		Zinc + Micronutrients	-17.76 (-31.8; -4.1)	0.46
	Category 0: Among the least effective	Prebiotics	-15.32 (-42.8; 12.0)	0.38
Low Certainty (Low- to Very Low-quality evidence)	Category 2: May be among the most effective	LGG + Smectite	-51.08 (-64.3; -37.9)	1.00
		Zinc + Probiotics	-29.39 (-40.3; -18.6)	0.81
	Category 1: May be inferior to the most effective / superior than the least effective	Symbiotics + LCF	-32.11 (-53.0; -11.3)	0.85
		Smectite	-23.90 (-30.8; -17.0)	0.69
		LGG (All)	-22.74 (-28.8; -16.7)	0.65
		All Probiotics	-19.36 (-23.7; -15.1)	0.54
		Racecadotril	-17.19 (-24.7; -9.8)	0.46
		S. boulardii	-16.48 (-23.3; -9.7)	0.42
		LCF	-12.50 (-19.0; -6.0)	0.31
	Category 0: May be among the least effective	S. boulardii + Zinc + LCF	-16.74 (-36.1; 2.7)	0.42
		Yogurt	-16.43 (-30.5; -2.1)	0.42
		Yogurt + Probiotics + Zinc	-15.63 (-56.8; 26.6)	0.38
		LCF + Probiotics	-13.27 (-36.0; 9.2)	0.31
		S. boulardii + LCF	-12.32 (-30.0; 6.0)	0.27
		Vitamin A	-5.95 (-21.4; 9.3)	0.19
		Kaolin-Pectin	-5.32 (-33.8; 22.8)	0.15
Micronutrients		-0.68 (-33.3; 32.8)	0.08	
Standard treatment/placebo	--	0.08		
	Diluted milk	3.02 (-14.3; 8.4)	0.04	

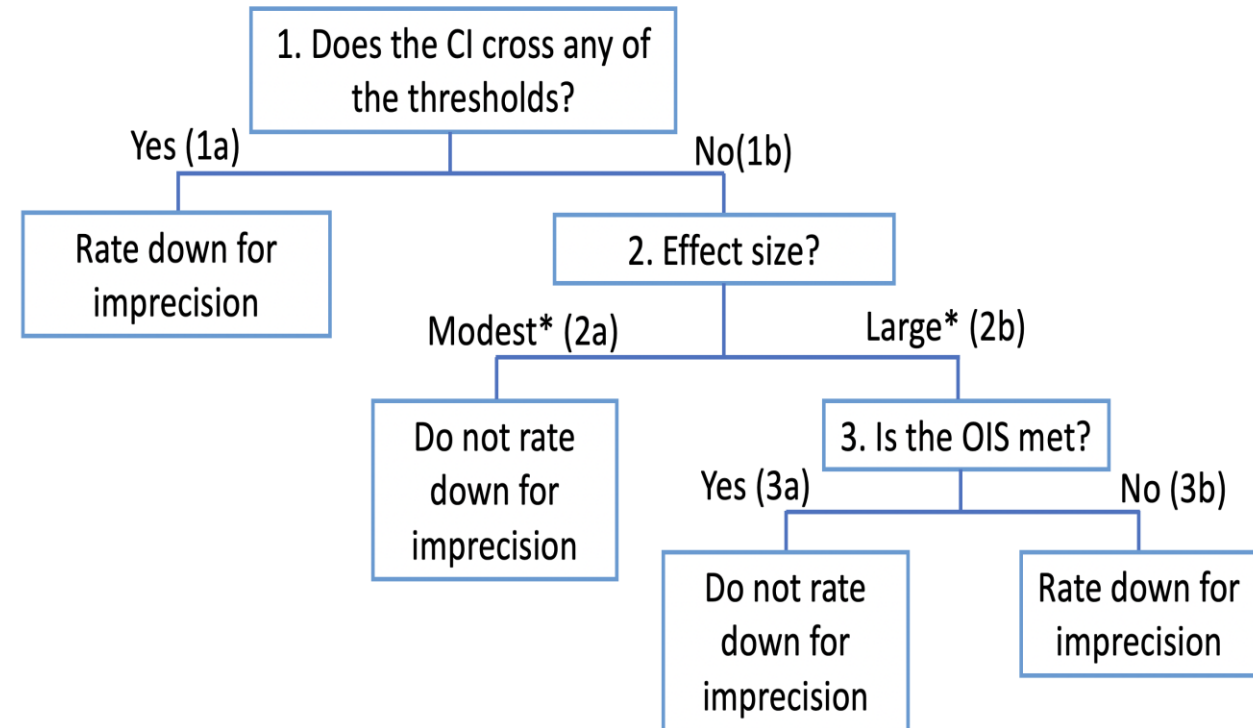
Classification	Intervention	Effect on hours of diarrhea duration, MD (95%CI)	Certainty
Large beneficial effect	LGG + Smectite	-51.08 (-64.30; -37.85)	VERY LOW
	S. boulardii + Zinc	-39.45 (-52.45; -26.73)	MODERATE
	Smectite + Zinc	-35.63 (-57.57; -13.16)	MODERATE
	Symbiotics + LCF	-32.11 (-53.01; -11.33)	VERY LOW
	Zinc + Probiotics	-29.39 (-40.26; -18.57)	LOW
	Symbiotics	-26.26 (-36.14; -16.22)	HIGH
Moderate beneficial effect	Smectite	-23.90 (-30.80; -16.96)	VERY LOW
	LGG (All)	-22.74 (-28.81; -16.68)	LOW
	Zinc + LCF	-21.37 (-36.54; -6.13)	MODERATE
	All Probiotics	-19.36 (-23.66; -15.09)	LOW
	Zinc (All)	-18.38 (-23.39; -13.45)	MODERATE
	Loperamide	-17.79; (-30.35; -5.65)	MODERATE
	Zinc + Micronutrients	-17.76 (-31.77; -4.13)	MODERATE
	Racecadotril	-17.19 (-24.65; -9.76)	LOW
	S. boulardii + Zinc + LCF	-16.74 (-36.05; 2.72)	LOW
	S. boulardii	-16.48 (-23.33; -9.69)	LOW
	Yogurt	-16.43 (-30.49; -2.05)	VERY LOW
	Yogurt + Probiotics + Zinc	-15.63 (-56.82; 26.63)	VERY LOW
	Prebiotics	-15.62 (-42.42; 11.28)	VERY LOW
	LCF + Probiotics	-13.27 (-35.96; 9.19)	VERY LOW
	LCF	-12.50 (-19.04; -5.99)	VERY LOW
S. boulardii + LCF	-12.32 (-30.01; 5.98)	VERY LOW	
Small beneficial effect	Vitamin A	-5.95 (-21.43; 9.32)	VERY LOW
	Kaolin-Pectin	-5.32 (-33.76; 22.83)	VERY LOW
Trivial to no effect	Micronutrients	-0.68 (-33.29; 32.79)	LOW
Small harmful effect	Diluted milk	3.02 (-14.32; 8.41)	VERY LOW

2. To be published, in the works

Imprecision, Intransitivity

Imprecision- Key messages

- Algorithm
- Relationship between CI and thresholds
- OIS
 - Guidance on how to assess it
 - Calculator



*In relation to the threshold chosen for the target of the certainty rating

Intransitivity

- Work has just started

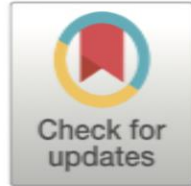
3. Other work

Spurious judgments of imprecision in sparse networks, SoFs for NMA, presentation formats across outcomes

Avoiding spurious judgments of imprecision



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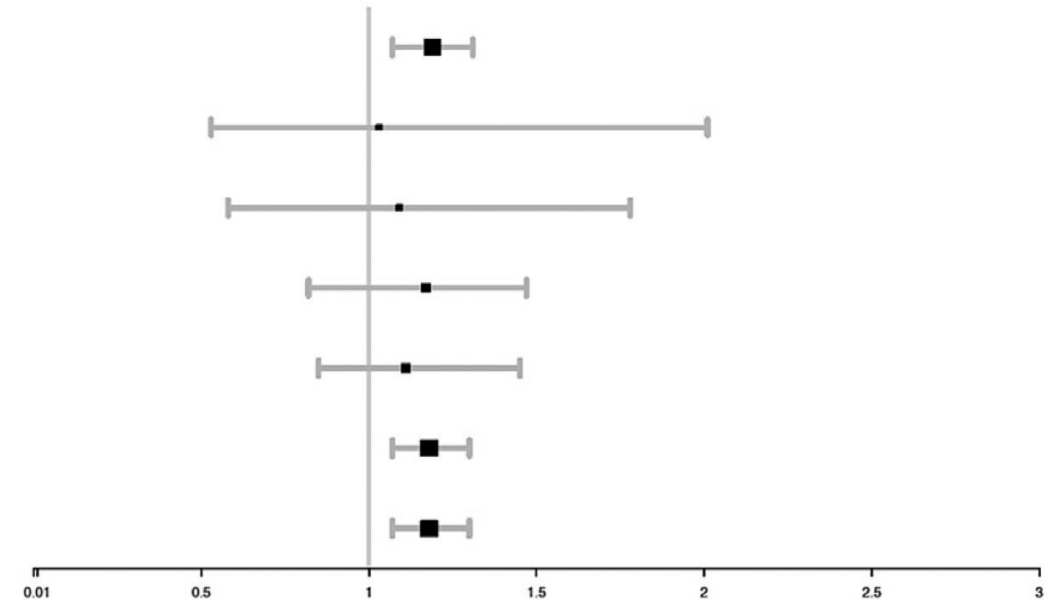
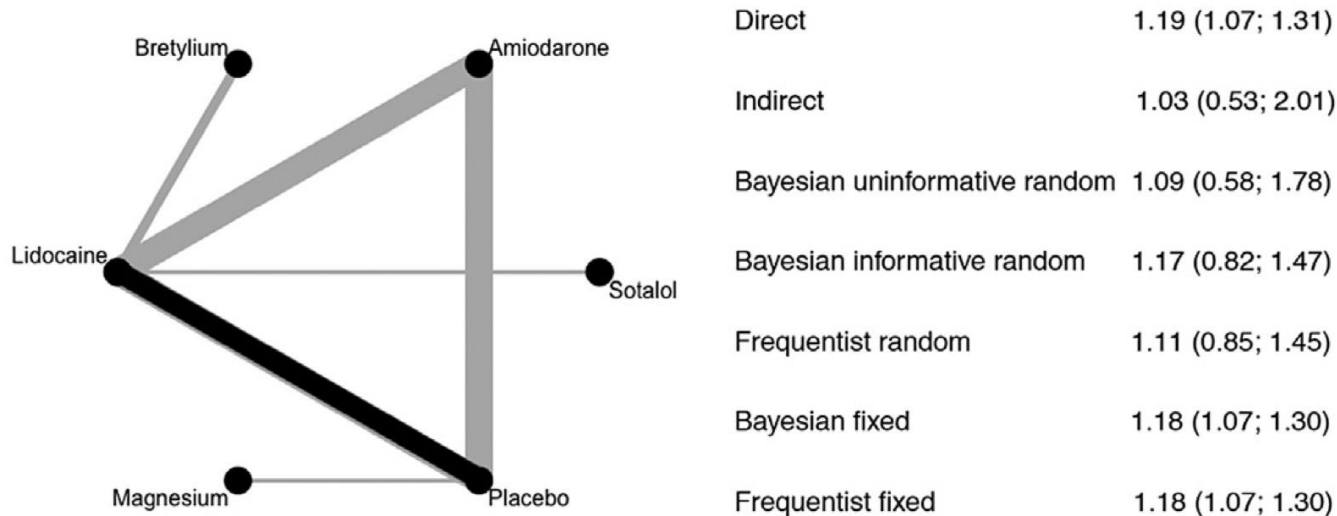
ORIGINAL ARTICLE

GRADE approach to rate the certainty from a network meta-analysis: avoiding spurious judgments of imprecision in sparse networks

Romina Brignardello-Petersen^a, M. Hassan Murad^{b,*}, Stephen D. Walter^a, Shelley McLeod^{a,c},
Alonso Carrasco-Labra^{a,d}, Bram Rochweg^{a,e}, Holger J. Schünemann^a, George Tomlinson^{f,g},
Gordon H. Guyatt^a, for the GRADE Working Group

Key message

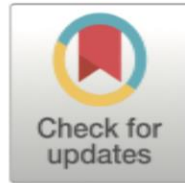
- In sparse networks, the choice of statistical model can lead to extremely wide, inappropriately imprecise CIs



Summary of findings tables



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Journal of Clinical Epidemiology 115 (2019) 1–13

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ORIGINAL ARTICLE

Development of the summary of findings table for network meta-analysis

Juan José Yepes-Nuñez^{a,b}, Shelly-Anne Li^c, Gordon Guyatt^{a,d}, Susan M. Jack^{a,e}, Jan L. Brozek^{a,d}, Joseph Beyene^a, M. Hassan Murad^f, Bram Rochwerg^{a,d}, Lawrence Mbuagbaw^a, Yuan Zhang^a, Ivan D. Flórez^{a,g}, Reed A. Siemieniuk^a, Behnam Sadeghirad^a, Reem Mustafa^{a,h}, Nancy Santesso^a, Holger J. Schünemann^{a,d,*}

Table 3. NMA-SoF table template for dichotomous outcomes

BENEFITS

Estimates of effects, credible intervals, and certainty of the evidence for chemoprevention of colorectal cancer in individuals with previous colorectal neoplasia

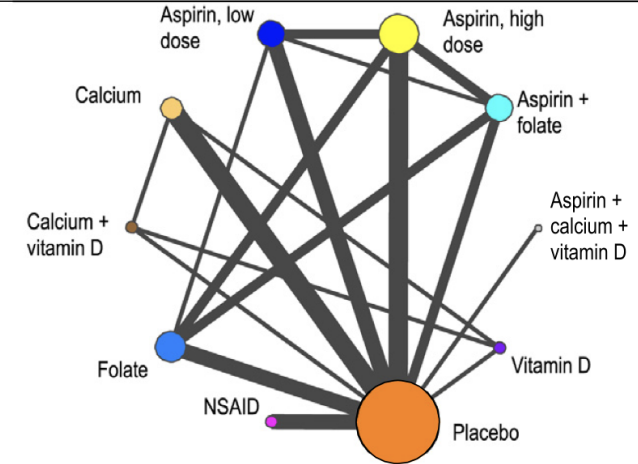
Patient or population: Individuals with previous colorectal neoplasia

Interventions: Low and high dose aspirin, nonaspirin non-steroidal anti-inflammatory drugs (NSAIDs), calcium, vitamin D, folic acid

Comparator (reference): Placebo

Outcome: Prevention of advanced neoplasia; range of follow up between three to five years

Setting: Outpatient



Total studies: 21 RCT Total Participants: 12088	Relative effect** (95% CrI)	Anticipated absolute effect*** (95% CrI)			Certainty of evidence	Ranking**** (95% CrI)	Interpretation of Findings
		Without intervention	With intervention	Difference			
● Aspirin + calcium + vitamin D (1 RCT; 427 participants)	OR 0.71 (0.18 to 2.49) Network estimate	74 per 1000 ¹	53 per 1000	21 fewer per 1000 (61 fewer to 110 more)	⊕⊕○○ Low Due to Imprecision ^{2,5}	3 (1 to 10)	-
● Calcium + vitamin D (1 RCT; 1028 participants)	OR 0.91 (0.52 to 1.63) Network estimate	74 per 1000 ¹	67 per 1000	7 fewer per 1000 (36 fewer to 47 more)	⊕⊕○○ Low Due to Imprecision ^{2,5}	6 (1 to 10)	-
● Aspirin + folate (2 RCT; 916 participants)	OR 0.73 (0.43 to 1.19) Network estimate	74 per 1000 ¹	54 per 1000	20 fewer per 1000 (42 fewer to 14 more)	⊕⊕○○ Low Due to Imprecision ^{2,5}	4 (2 to 8)	-
● Aspirin, high dose (3 RCT; 917 participants)	OR 0.81 (0.50 to 1.28) Network estimate	74 per 1000 ¹	60 per 1000	14 fewer per 1000 (37 fewer to 21 more)	⊕⊕○○ Low Due to Imprecision ^{2,5}	5 (2 to 9)	-



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GRADE

Network Meta-Analysis