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Network Meta-epidemiology:
assessing the various impacts on the relative treatment effects and ranking of competing treatments

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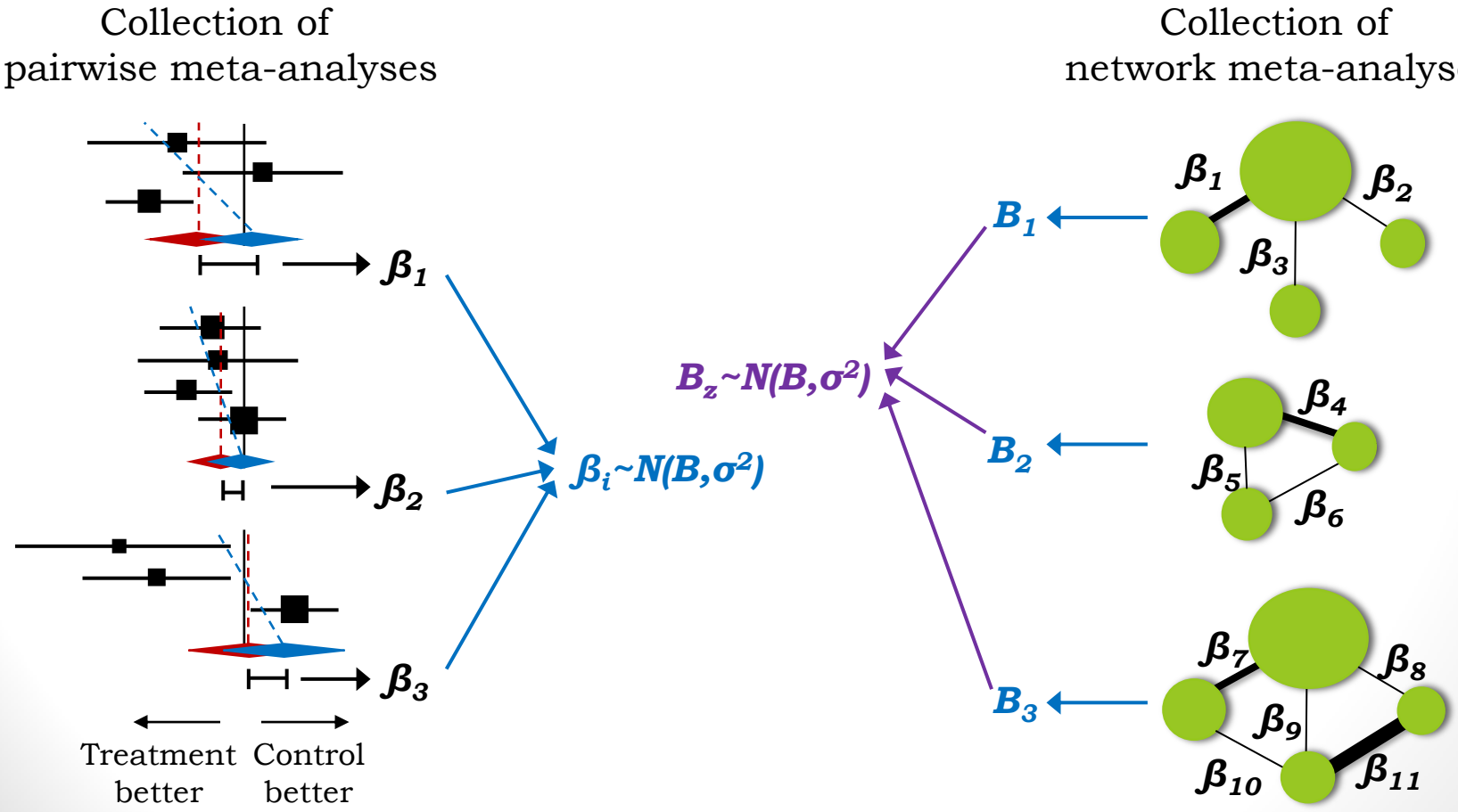
Outline

- Extending conventional meta-epidemiology to network meta-epidemiology
- Description of a database of 186 published networks
- Empirical studies using networks of interventions:
  1. Prevalence of statistical inconsistency [40 networks]
  2. Impact of four risk of bias items [32 networks]
  3. Impact of study precision [32 networks]
  4. Effect of differences in control group risk [32 networks]
  5. Effect of differences in study publication year [32 networks]
  6. Impact of novel agents effects [31 networks]

Extending conventional meta-epidemiology to network meta-epidemiology

Do non-blinded studies give different results from blinded studies??



Extending conventional meta-epidemiology to network meta-epidemiology

Do non-blinded studies give different results from blinded studies??

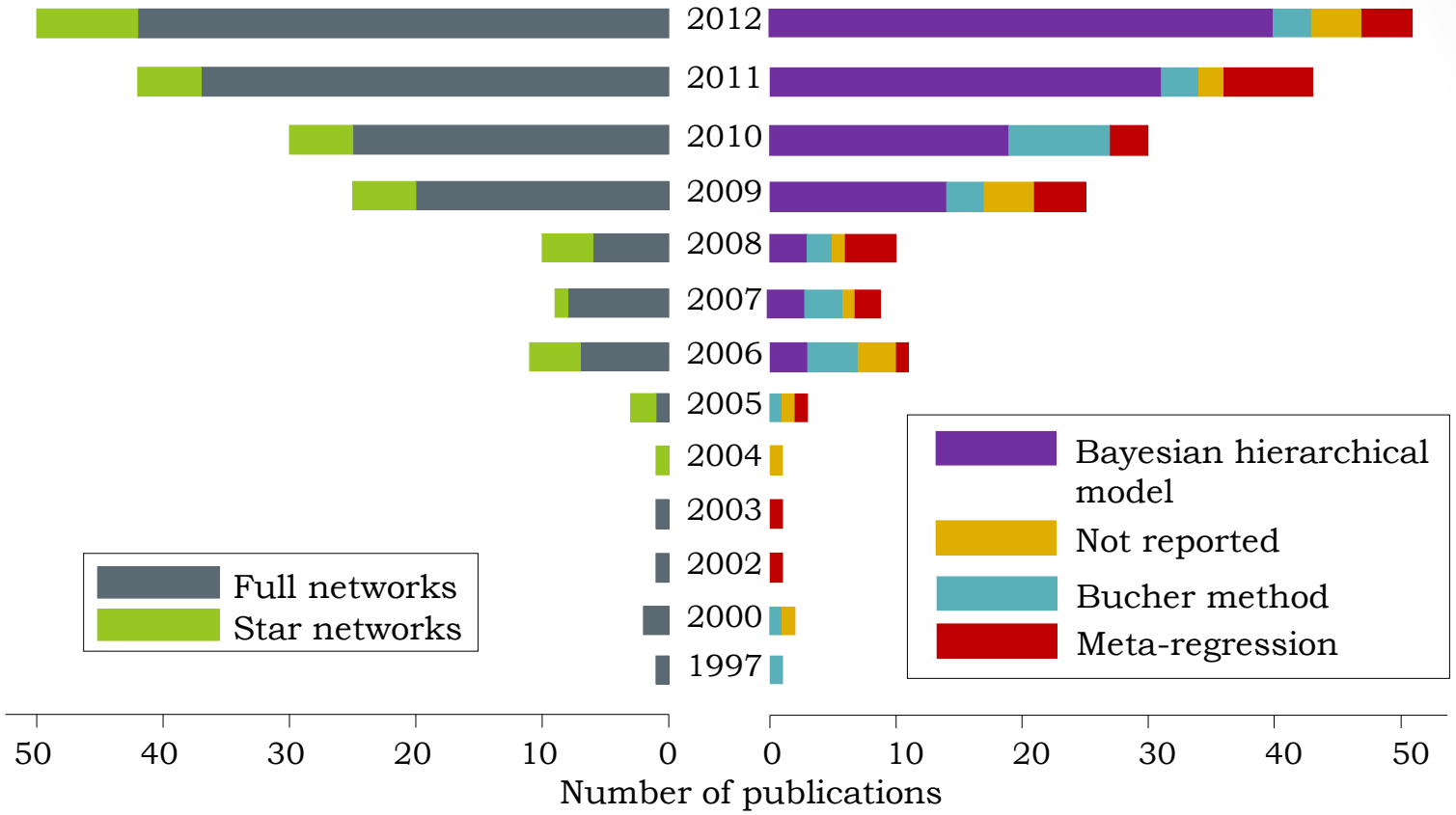
Collection of pairwise meta-analyses

- ***Comparability of the bias parameters across meta-analyses from different clinical fields – questionable***
- ***Small number of trials in most meta-analyses – low power***

Collection of network meta-analyses

- ***Exploits the assumption that bias parameters are more similar across comparisons within networks than across networks***
- ***Improves precision of the bias parameters within each network***

Database of 186 networks



- Median number of studies per network: 21(13-40)
- Median number of treatments per network: 6(5-9)
- Median number of studies per comparison: 2(1-4) [88 networks]

Nikolakopoulou et al. 2013 [under review]

Database of 186 networks

Type of outcome[1]	
Objective	36 (19%)
Semi-objective	72 (39%)
Subjective	78 (42%)

[1]*Turner et al 2012*

Outcome measured as	
Dichotomous	111 (60%)
Continuous	53 (28%)
Survival	17 (9%)
Rate	5 (3%)

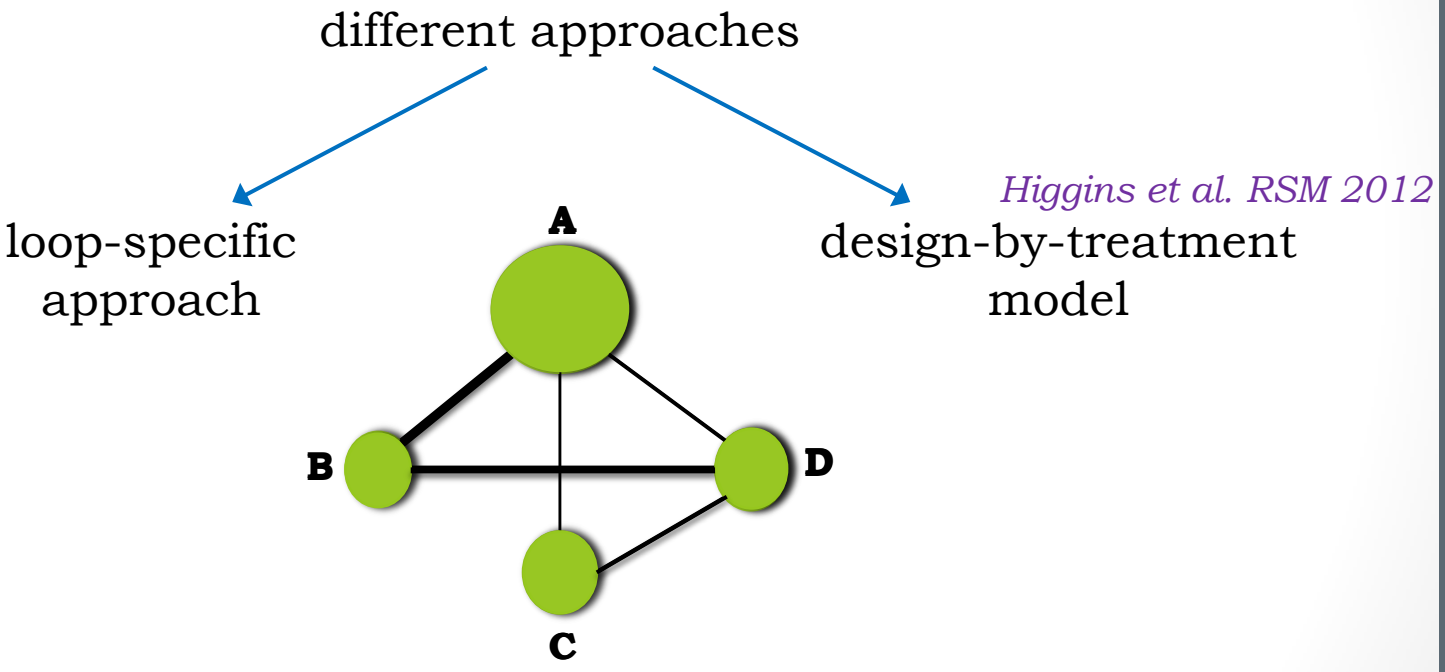
Effect size	
OR	66 (35%)
RR	44 (23%)
OR RR RD	1 (1%)
HR	17 (9%)
Rate ratio	5 (3%)
MD	43 (23%)
SMD	9 (5%)
Ratio of Means	1 (1%)

Similar findings by Trinquart et al. BMJ 2013

Nikolakopoulou et al. 2013 [under review]

Prevalence of statistical inconsistency

Estimation of inconsistency in 40 full networks (i.e. with at least one closed loop) with fully extracted dichotomous data



Veroniki et al. IJE 2013

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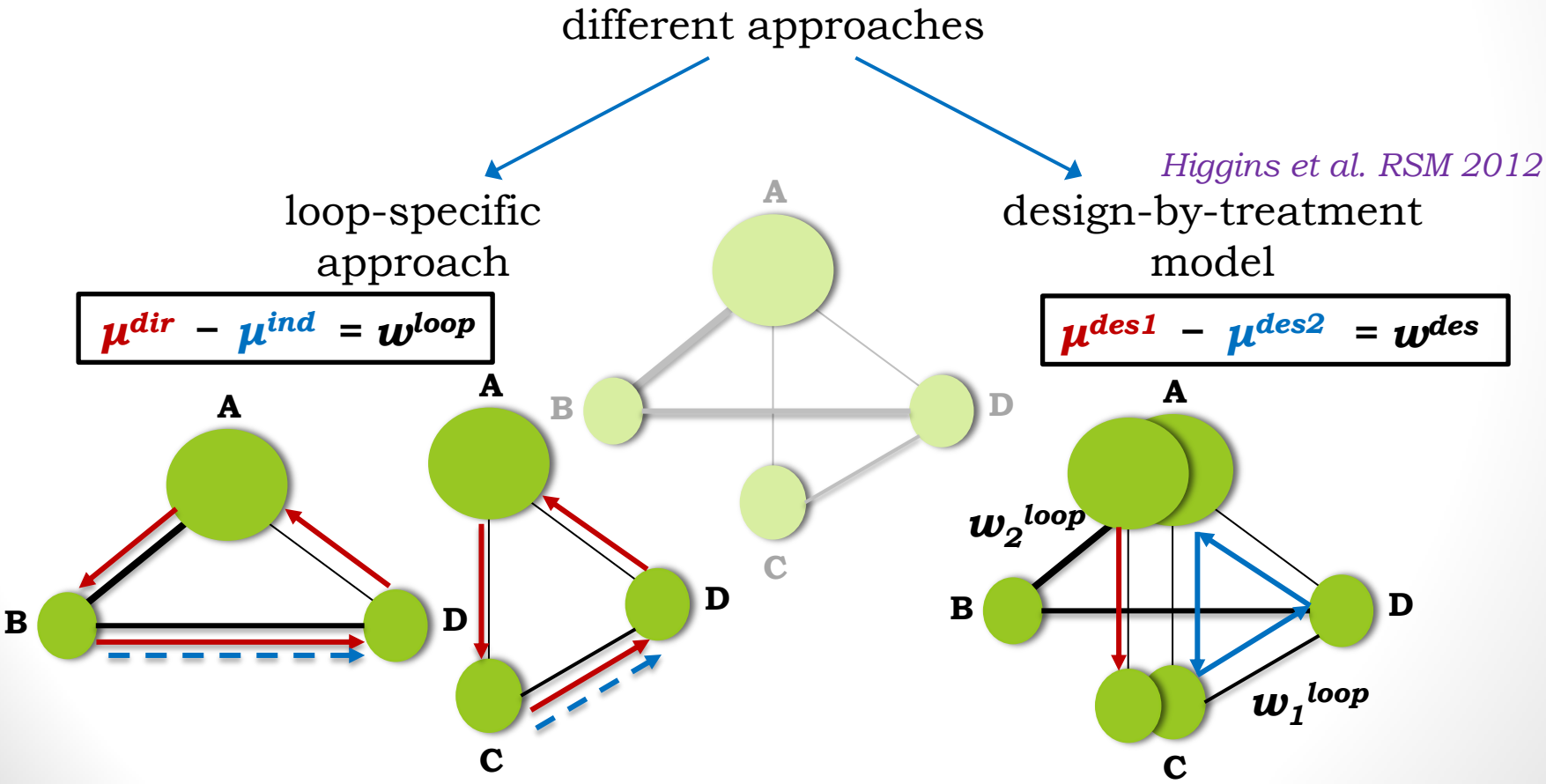


Higgins et al. RSM 2012

Veroniki et al. IJE 2013

Prevalence of statistical inconsistency

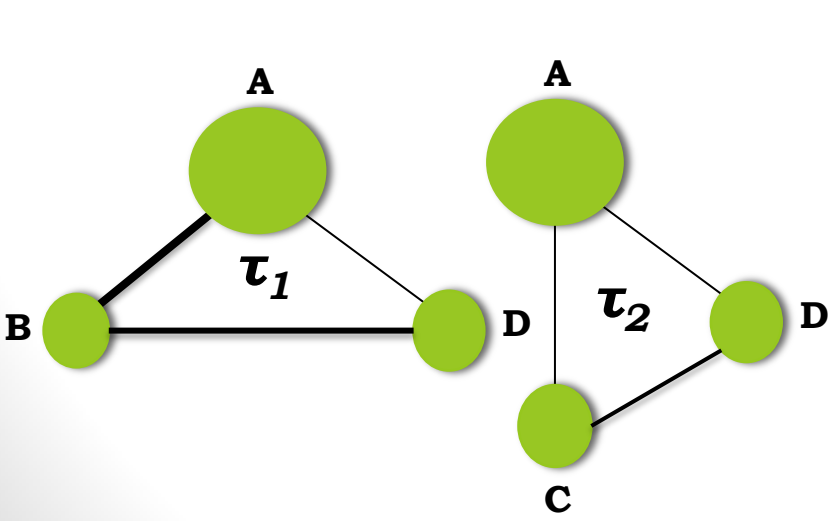
different approaches

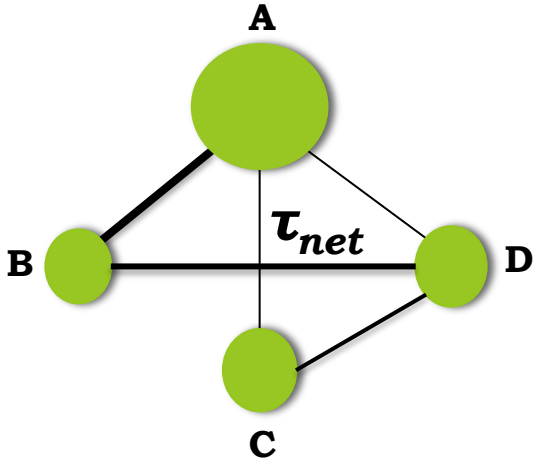
loop-specific approach

design-by-treatment model

loop-specific heterogeneities

network-specific heterogeneity





Veroniki et al. IJE 2013

Prevalence of statistical inconsistency

Inconsistent loops with the loop-specific approach

303 loops in total

	Loop-specific heterogeneities	Network-specific heterogeneity
OR	8%	5%
RRbeneficial	10%	6%
RRharmful	9%	6%
RD	10%	5%

Inconsistent networks with the design-by-treatment model

40 networks in total

13%-17% depending on the effect measure

Veroniki et al. IJE 2013

Prevalence of statistical inconsistency

Note that

- ***"For 35% of the networks we could not find any indication in the published articles that the authors evaluated the assumption of consistency"***

In the entire database

- ***In 24% of the networks the authors used inappropriate methods to evaluate inconsistency.***
- ***In 44% of the networks the authors did not report the method they used to evaluate inconsistency.***

Nikolakopoulou et al. 2013 [under review]

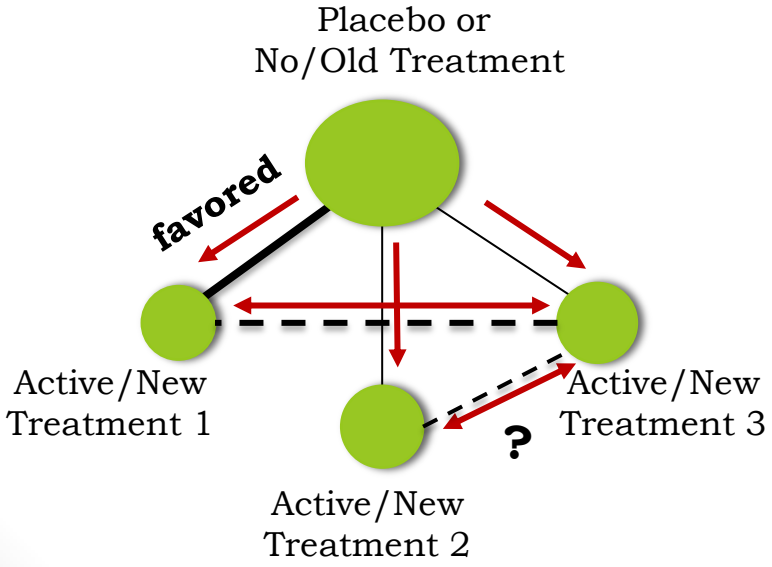
Veroniki et al. IJE 2013

Impact of risk of bias items

Use of network meta-epidemiology to evaluate the impact of

- *generation of allocation sequence*
- *allocation concealment*
- *blinding of patients*
- *blinding of outcome assessors*

Network meta-regression in 32 star-shaped networks with fully extracted data

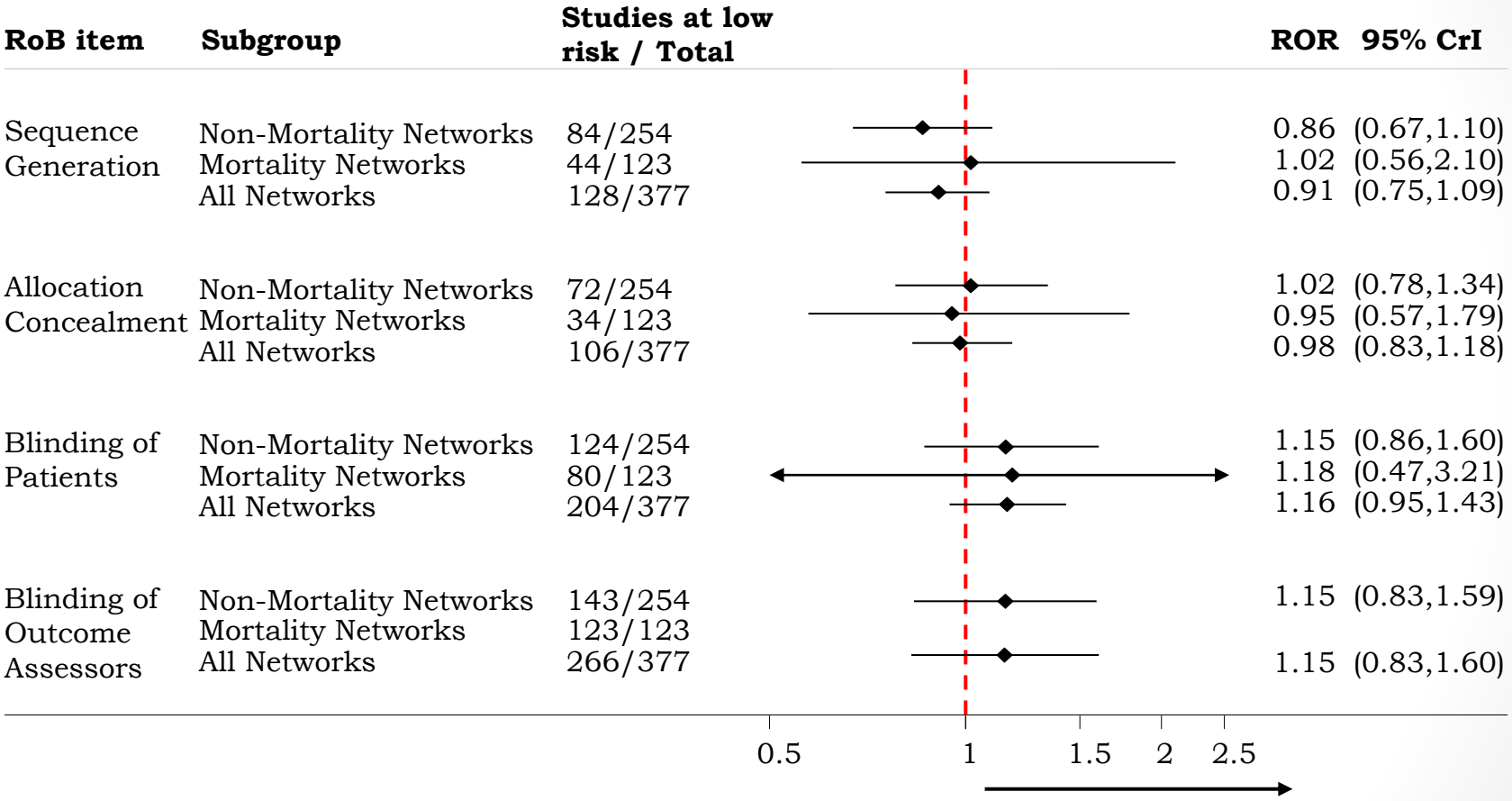


Adjustment took place:

- *within each network with ≥10 studies*
- *across all networks with dichotomous data*

Chaimani et al. IJE 2013

Impact of risk of bias items



unclear/high risk studies give larger effects for active treatments

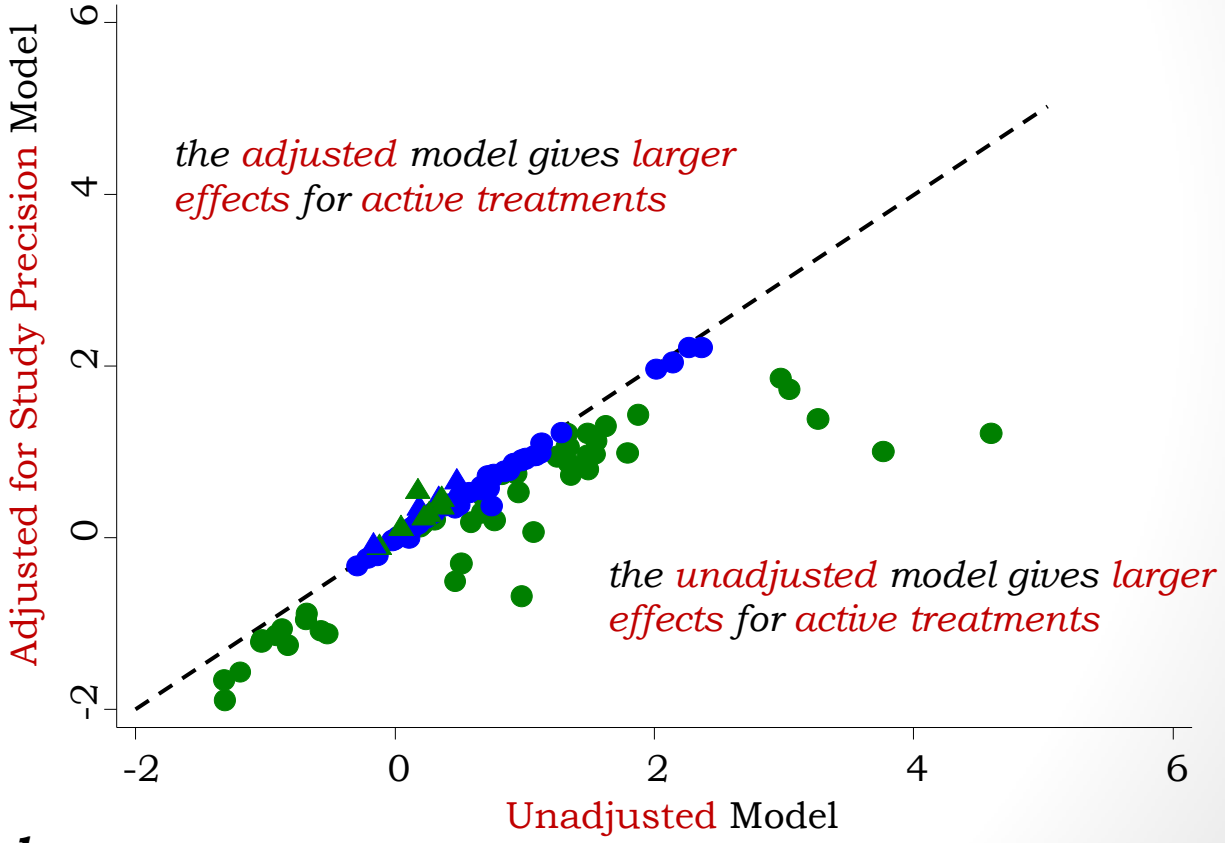
Adjustment across all networks with dichotomous data

Chaimani et al. IJE 2013

Impact of study precision

NMA summary effect sizes of every active treatment vs. the common comparator intervention of each network

study variance as explanatory variable

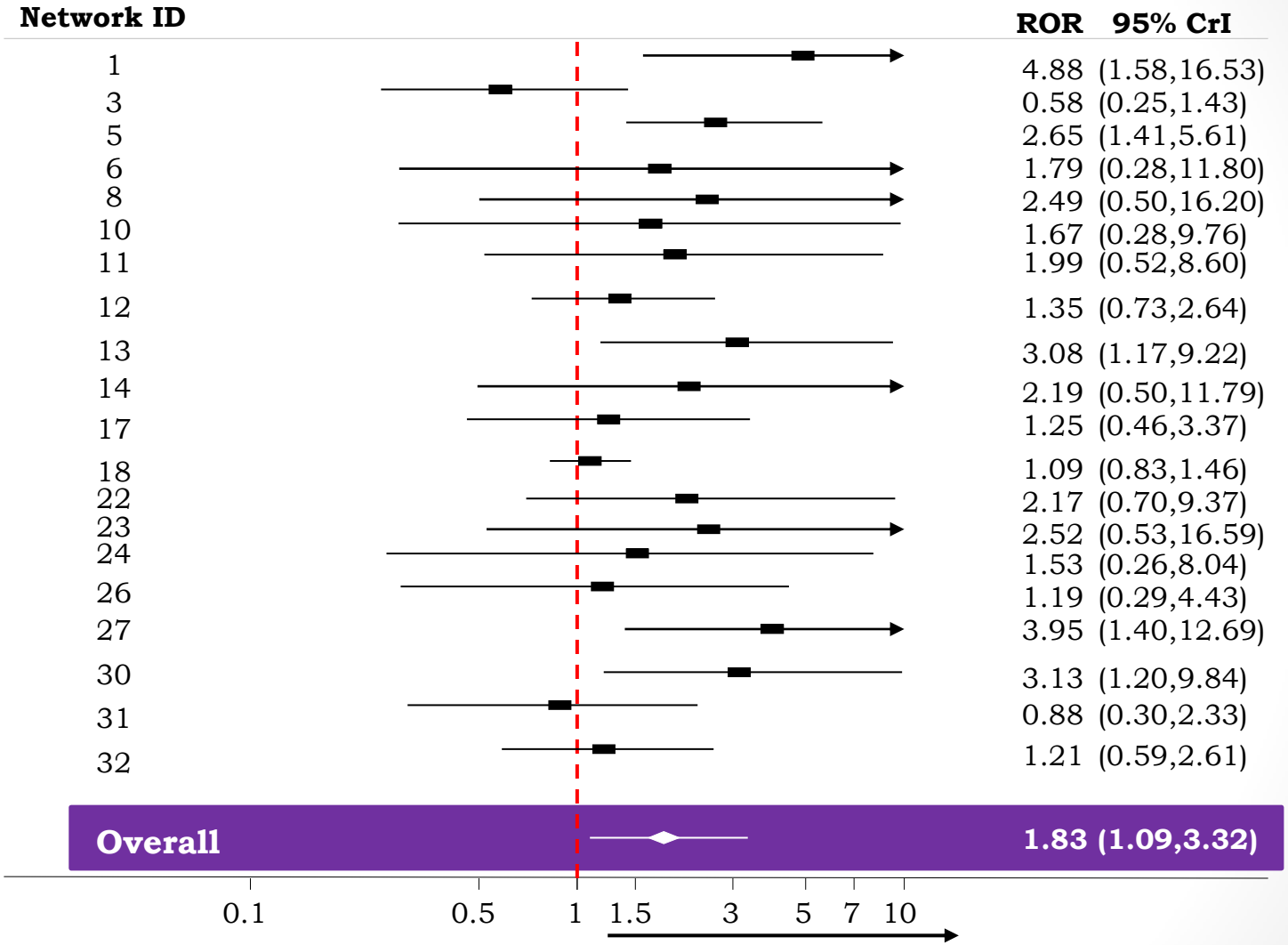


Coefficients	
Significant	●
Non-Significant	●

Adjustment within each network with ≥10 studies

Chaimani et al. IJE 2013

Impact of study precision



Adjustment across all networks with dichotomous data

Chaimani et al. IJE 2013

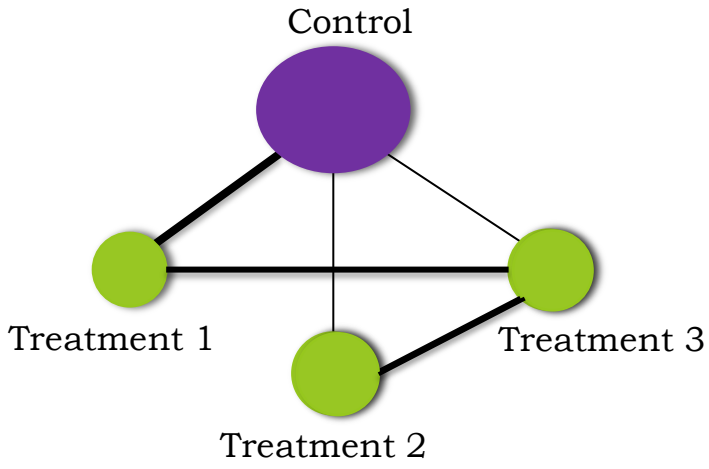
Effect of differences in control group risk

A wide range of CGRs within a meta-analysis are required

Network meta-regression in 32 networks including an 'obvious' control intervention with fully extracted dichotomous data

The control intervention is missing at random from the studies that do not include a control arm

Achana et al. Stat Med 2013



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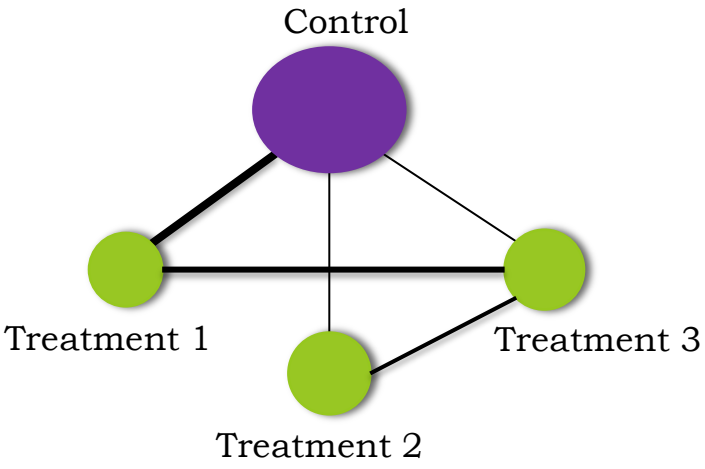

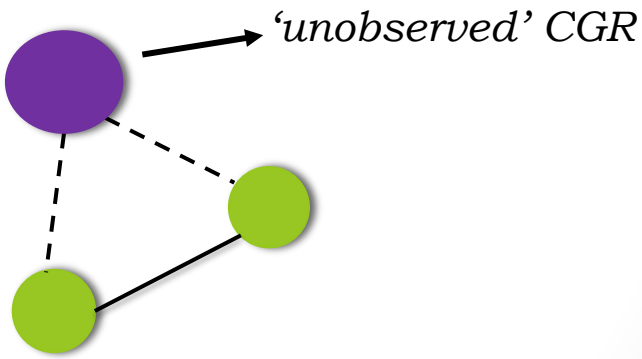

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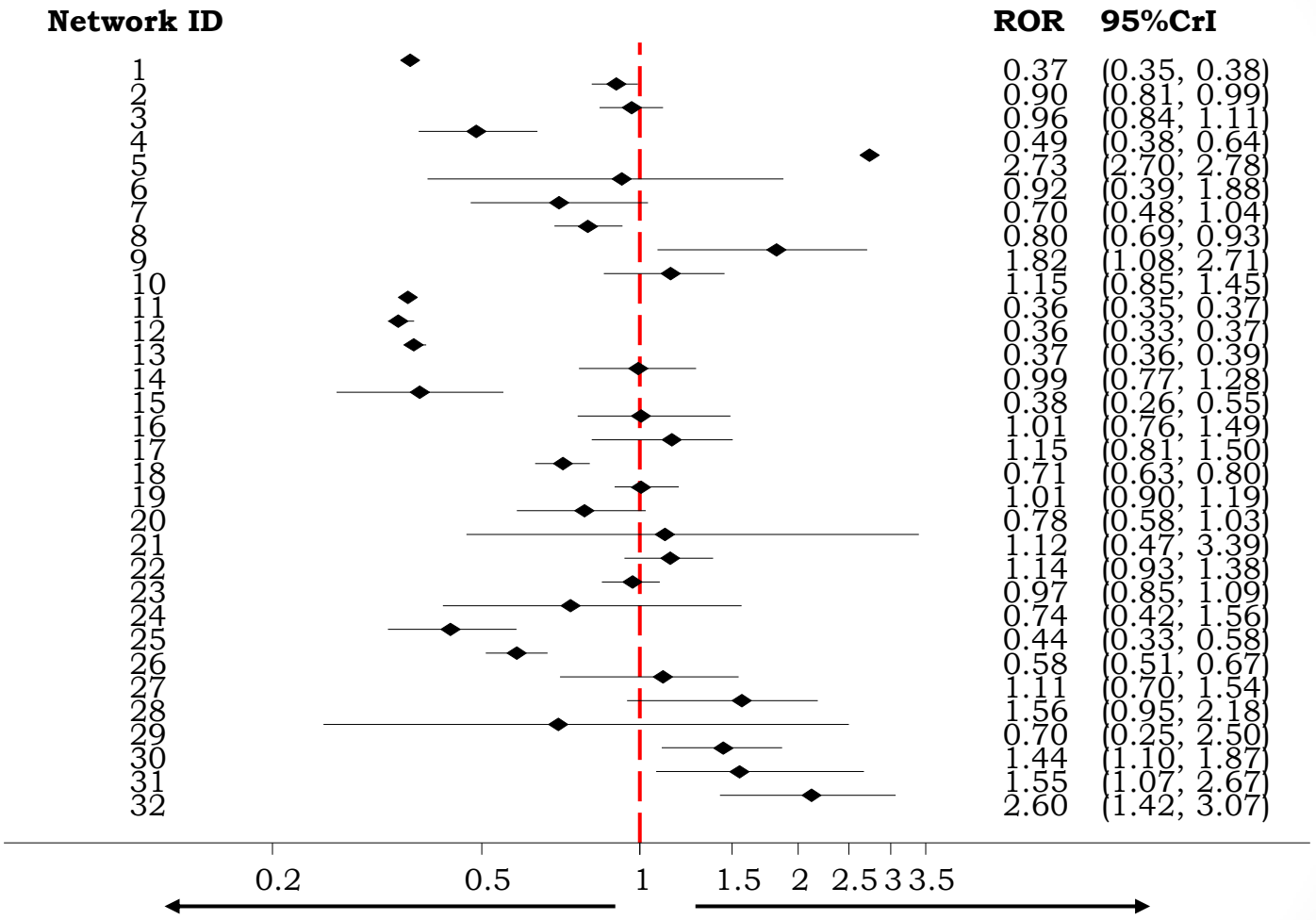


Chaimani et al. 2013 [under review]

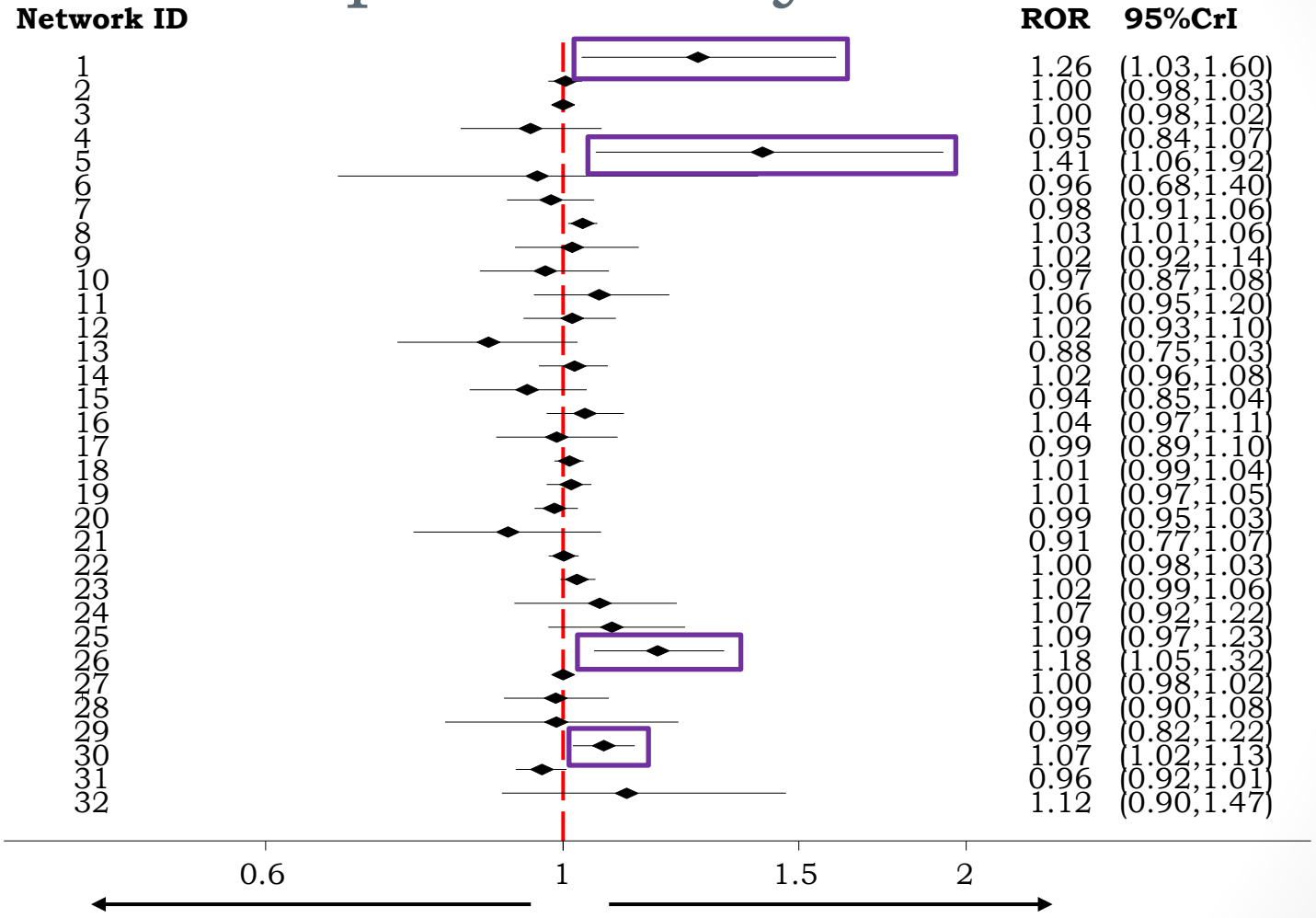
Effect of differences in control group risk

After the adjustment

- *17 (53%) networks with changes in relative treatment ranking*
- *30/209* ⬆ *in more favorable rank*
- *28/209* ⬇ *in less favorable rank*

Chaimani et al. 2013 [under review]

Effect of differences in study publication year



Chaimani et al. 2013 [under review]

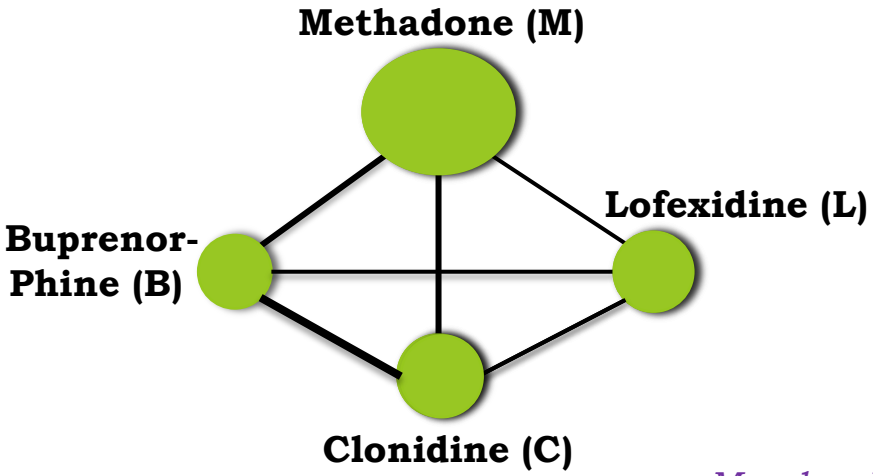
Impact of novel agents effects

- *Studies possibly tend to exaggerate the effect of newer treatments*
- In pairwise meta-analysis each treatment is always the newer or the older in all studies

Advantage of networks of interventions

Licensed from the FDA	
M	1947
C	1974
L	1992
B	2002

Opioid detoxification



Meader, Drug Alcohol Depend 2010

Dimitrakopoulou et al. [in progress]

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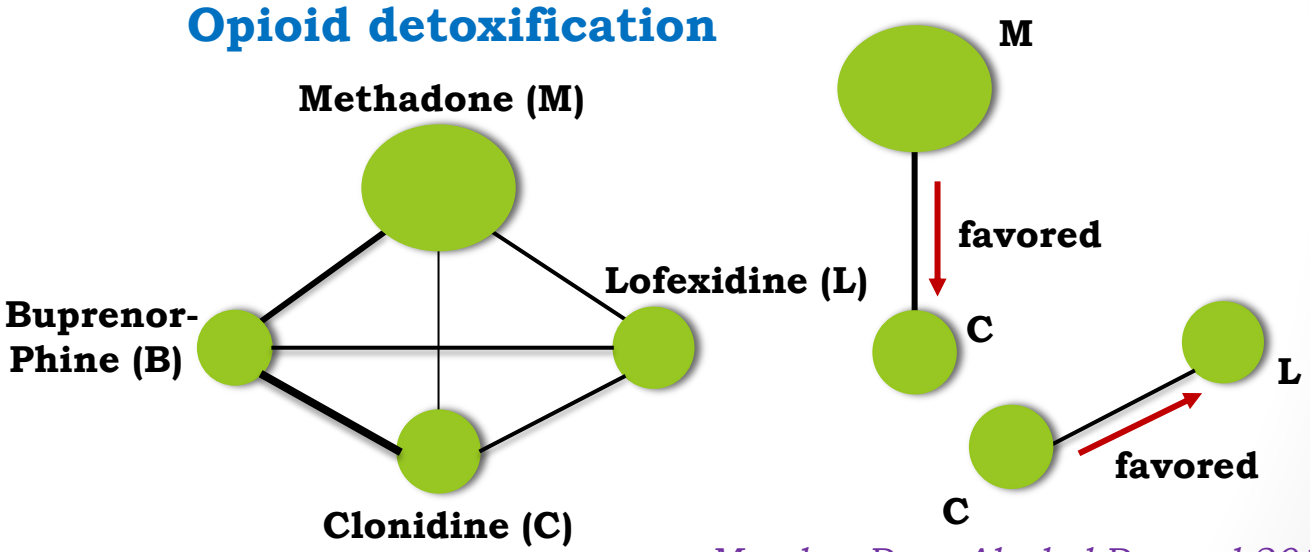

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Network meta-regression in 31 networks with data on treatments' licensing and with fully extracted dichotomous data

Dimitrakopoulou et al. [in progress]

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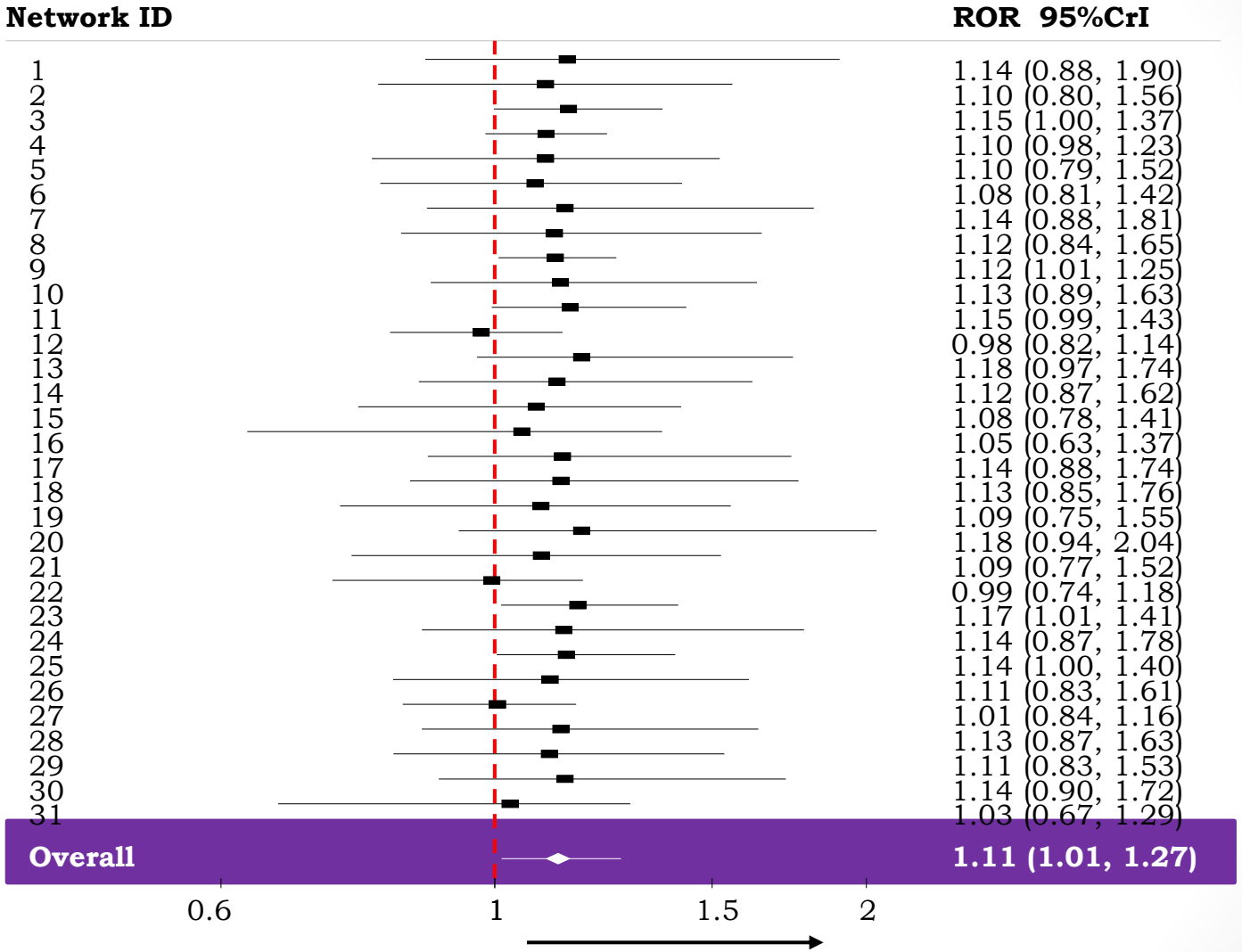
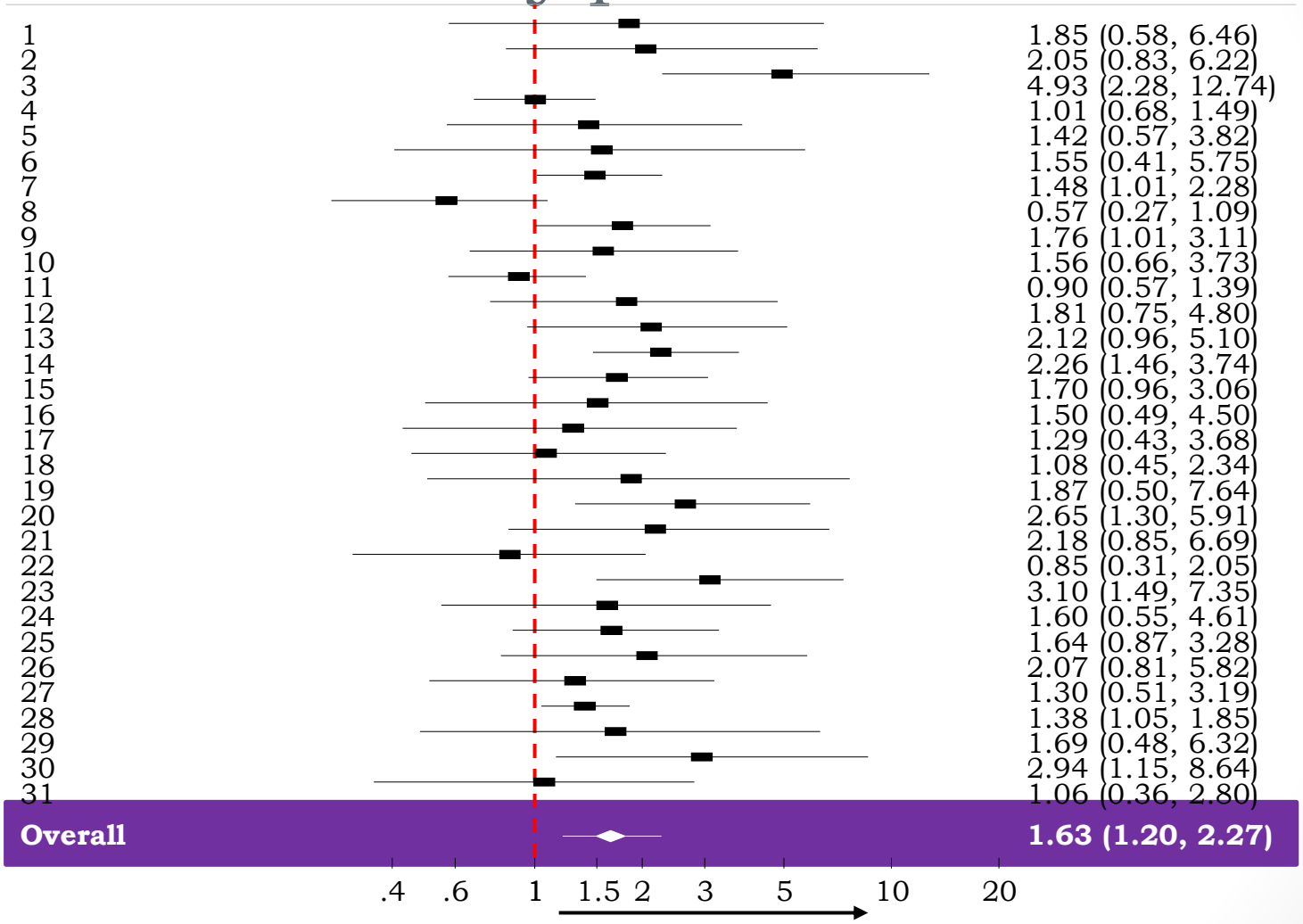


Adjustment across all networks

Dimitrakopoulou et al. [in progress]

Impact of novel agents effects × study precision



Adjustment across all networks

Dimitrakopoulou et al. [in progress]

Conclusions

- Publications of network meta-analyses are increasing rapidly over time
- About 1 in 8 networks might be subject of statistical inconsistency
- The inadequate conduct of the four risk of bias items might not affect substantially the NMA results
- Less precise studies possibly give larger effects for active treatments than more precise studies
- Differences in CGR can materially affect the relative treatment effects and relative ranking
- Differences in study publication year possibly do not impact on NMA results
- Studies and particularly less precise studies may tend to favor the newer treatments

Discussion

- Network meta-epidemiology is a new tool to investigate
  1. the impact of study characteristics on treatment effect estimates and
  2. the possible effect modifiers in networks of interventions

- More meta-epidemiological studies are necessary using also continuous data

- Enriching the database is important for the conduct of more representative empirical studies with increased power

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