Choice of priors in rare events meta-analysis

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Outline :

- The problem
  - Rare events meta-analysis
  - Possible solutions
- Bayesian approach
  - Choice of priors
    - Fixed effect Meta-analysis
    - Random effects Meta-analysis
  - Simulation scenarios
  - Example of Rosiglitazone

Meta-analysis

- Meta-analysis (MA) combines statistical information across related studies
- MA has been widely utilized to combine data from clinical studies in order to summarize treatment efficacy
- Has also been used to assess drug safety. However, because adverse events are typically rare, standard methods may not work well in this setting.

The Problem

- Meta-analysis (MA) on adverse events often include randomized controlled trials (RCTs) in which zero events have been observed in one or both arms
- In MA of rare events RCTs, where computation may involve zero cells, effect measures, like odds ratio (OR) or relative risk (RR), are difficult to calculate
- When the events are rare, but not all zeros, the variance estimates for these methods are not robust which may lead to unreliable statistical inferences

Example: Risoglitazone

- Rosiglitazone was used to treat patients with Type II diabetes melitus
- RCTs of Rosiglitazone were designed to study cardiovascular morbidity and mortality
- For myocardial infarction (MI) out of 48 trials
  - 28 trials had zero in one arm
  - 8 trials with zero in both arms

Part of Rosiglitazone trials used in (Lane, 2013)

	Rosiglitazone		Comparator		
Trial	N	MI	N	MI	Duration (weeks)
011	357	2	176	0	24
020	391	2	207	1	52
024	774	1	185	1	26
093	213	0	109	1	26
094	232	1	116	0	26
684	43	0	47	1	52
143	121	1	124	0	24
211	110	5	114	2	52
284	382	1	384	0	24
008	284	1	135	0	48
264	294	0	302	1	52
185	563	2	142	0	32
334	278	2	279	1	52
347	418	2	212	0	24
015	395	2	198	1	24
079	203	1	106	1	26
080	104	1	99	2	156
082	212	2	107	0	26
085	138	3	139	1	26
095	196	0	96	0	26
097	122	0	120	1	156

Possible approaches

- Excluding trials with zero events in both arms
  - Which makes it more likely that the magnitude of the pooled treatment effect will be inflated
- Using a continuity correction
  - Allows the log-odds ratio or log-risk ratio to be estimated even when zero events are observed
  - The standard value of continuity correction is k = 0.5
    - Possible biases, specially in trials not having 1 : 1 randomization

Other approaches

- Various statistical methods were proposed for using information from trials with no events
  - (Cai et al., 2010) proposed a method using Poisson regression modeling that uses the idea of conjugacy in the same way as beta-binomial model
  - (Kuss, 2015) used beta-binomial regression methods to make inference about OR, RR and risk difference (RD)
  - (Böhning et al., 2015) proposed a Poisson model for random effects (REs)

Another approach to MA of rare events is to use fully probabilistic (Bayesian) methods

Bayesian approach

- $Y \rightarrow observed\ data$

$\theta \rightarrow unknown\ parameter(s)$

- $Prior \rightarrow p(\theta)$
- $Likelihood \rightarrow p(Y|\theta)$
- $Posterior \rightarrow p(\theta|Y)$

$$\boldsymbol{Posterior} \propto \boldsymbol{Prior} \times \boldsymbol{Likelihood}$$

$$p(\theta|Y) \propto p(\theta) \times p(Y|\theta)$$

Formulation for Bayesian methods

- Our outcome of interest is binary, so for each study i control group c and treatment group t
  - $x_{ic} \sim Binomial(p_{ic,}\, n_{ic})$
  - $x_{it} \sim Binomial(p_{it,}\, n_{it})$ where $i = 1,2, \ldots, n$
- Odds ratio (OR) is our target effect measure
  - $OR_i = (\frac{p_{it}}{1-p_{it}} / \frac{p_{ic}}{1-p_{ic}})$

- For FE MA, Assuming a common OR across studies in a Bayesian framework
  - $logit(p_{it}) = log(\text{OR}) + logit(p_{ic})$

    Where $logit(p_{it}) = \log(\frac{p_{it}}{1-p_{it}})$
- For REs MA
  - $\log(OR_i) \sim normal(\log(OR), \tau)$
    - τ is statistical heterogeneity

Prior distribution for

$$log(\text{OR}) \sim \text{Normal}(0, 10)$$

Prior distributions

- In an MA context, prior distributions could include expert beliefs of health professionals
- Priors can be derived from information from studies not explicitly included in the MA
- Necessity to explore sensitivity to choice of prior distributions
  - Risk in control group (p_{ic})
  - heterogeneity (τ), in case of REs MA

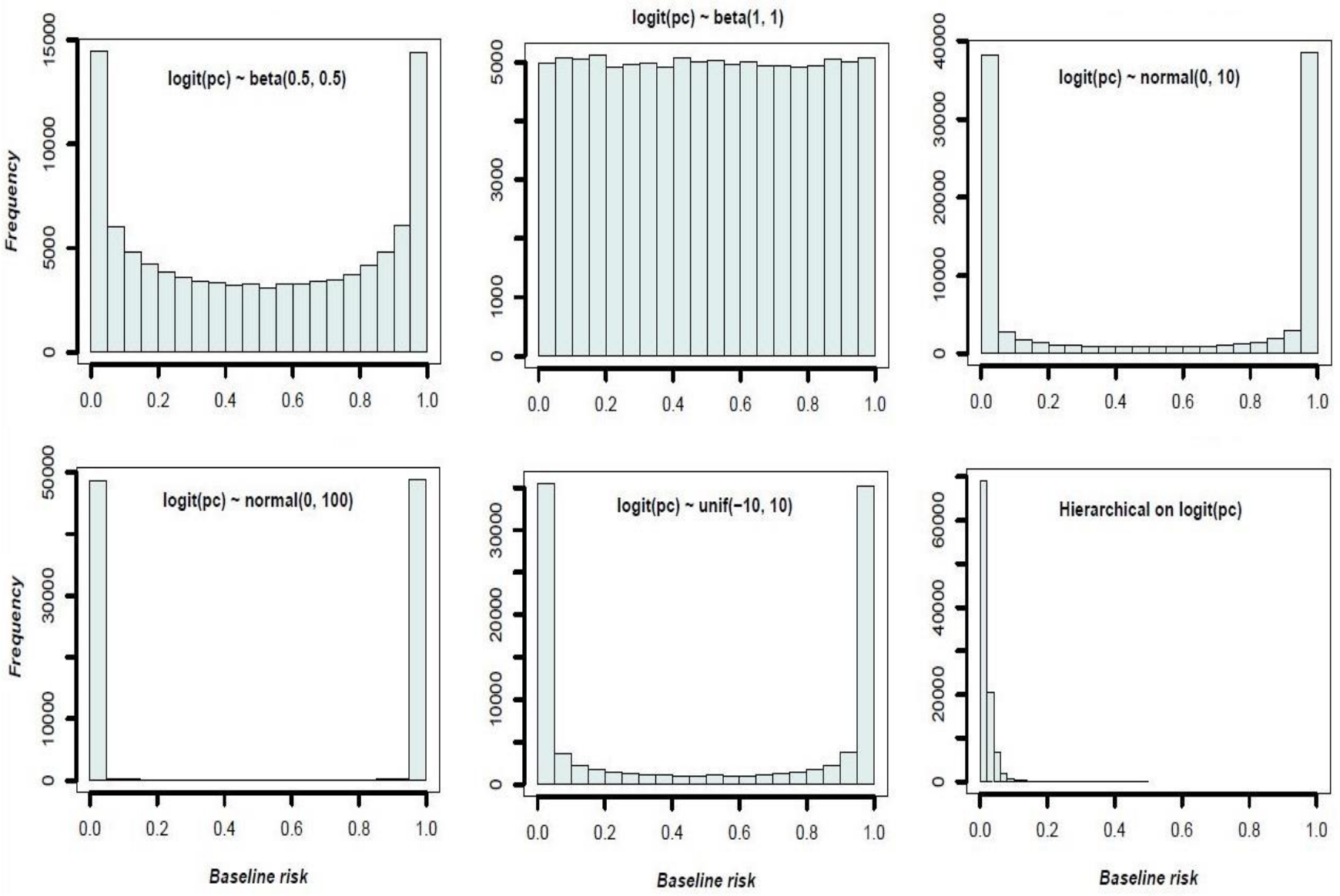
- For FE models we used several sets of priors on risk of control group (p_{ic})

Table I. List of prior distributions for p_{ic}

Parameter	Prior distribution
a. $\boldsymbol{p_{ic}}$	$beta(1,1)$
	$beta(0.5,0.5)$
a. $\boldsymbol{logit(p_{ic})}$	$unif(-10,10)$
	$normal(0,10)$
	$normal(0,100)$
a. $\boldsymbol{logit(p_{ic})}$*	$normal(\mu,\sigma)$ where
μ is bounded away from zero (0.0025, 0.048)	$\mu \sim unif(-6,-3)$
	$\sigma \sim unif(0,1)$

* hierarchical structure on $logit(p_{ic})$, $i = 1,2,\dots,n$

Figure I. Histograms of different priors for $logit(p_{ic})$



- In REs models
  - For τ

Table II. List of prior distributions for τ

Parameter	Prior distribution	Mean
τ	$exp(2)$	0.5
	$unif(0, 2)$	1
	half-normal	0.5

  - For p_{ic}
    - $logit(p_{ic}) \sim$ Normal$(0, 10)$
    - $logit(p_{ic}) \sim$ Normal$(0, 100)$
    - $logit(p_{ic}) \sim$ Hierarchical

Table III. Parameter values used in the simulation of MA data sets

FE scenarios	
$\log(OR)$	0 or 0.69
Number of patients in treatment group (n_{it})	[20, 60]
Risk of control group (p_{ic})	[0.001, 0.04]
Number of trials in each MA	10, 20 or 50
RE scenarios	
$\log(OR_i)^*$	
$\log(OR)$	0 or 0.69
Random effects standard deviation (τ)	0.2 or 0.5
Number of patients in treatment group (n_{it})	[10, 60]
Risk of control group (p_{ic})	[0.001, 0.035]
Number of trials in each MA	20 or 50
Both FE & REs scenarios	
Ratio of group sizes**	1:1, 1:2 or 1:4
Number of simulated MA data sets	1000

* follows a normal distribution with specified characteristics

** We assigned treatment vs. control group for the ratio of group sizes

Simulation steps

R :

- Data simulation (144)
- Linking R to JAGS
- Collect JAGS result
  - MeanlogOR(s)
  - 95% credible interval(s)

JAGS :

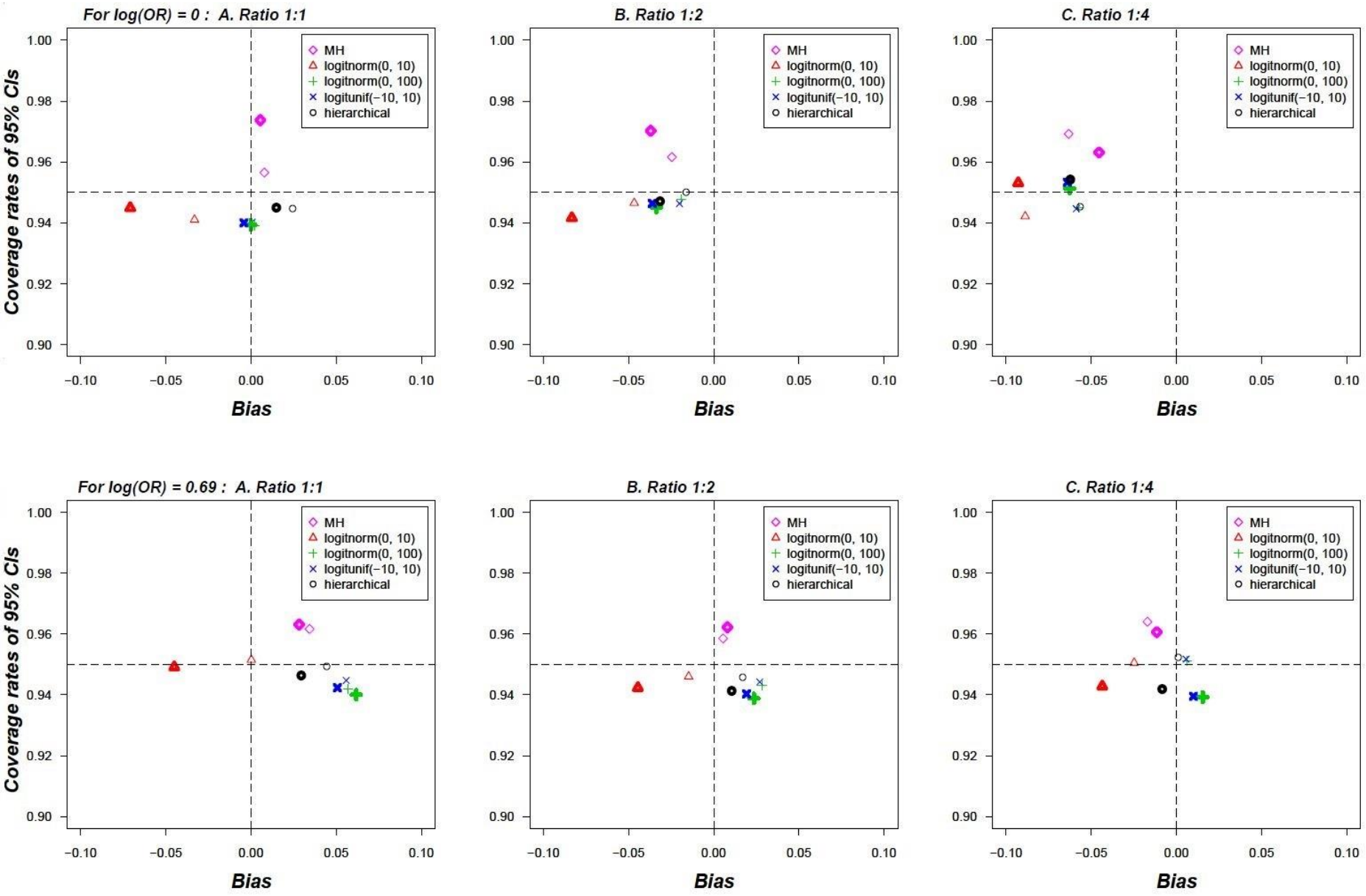
- MCMC
  - Number of Markov chians = 4
  - Number of iterations = 15000
  - Length of burn in = 5000

We used result of JAGS to calculate

- 95% coverage probability
- bias = True log(OR) – median log(OR)

Results of FE
Bayesian methods

Figure II. Results for FE Bayesian methods -- DL = FALSE



Results of REs
Bayesian methods

Figure III. Results for REs methods for log(OR) = 0 with different SDs -- DL=FALSE

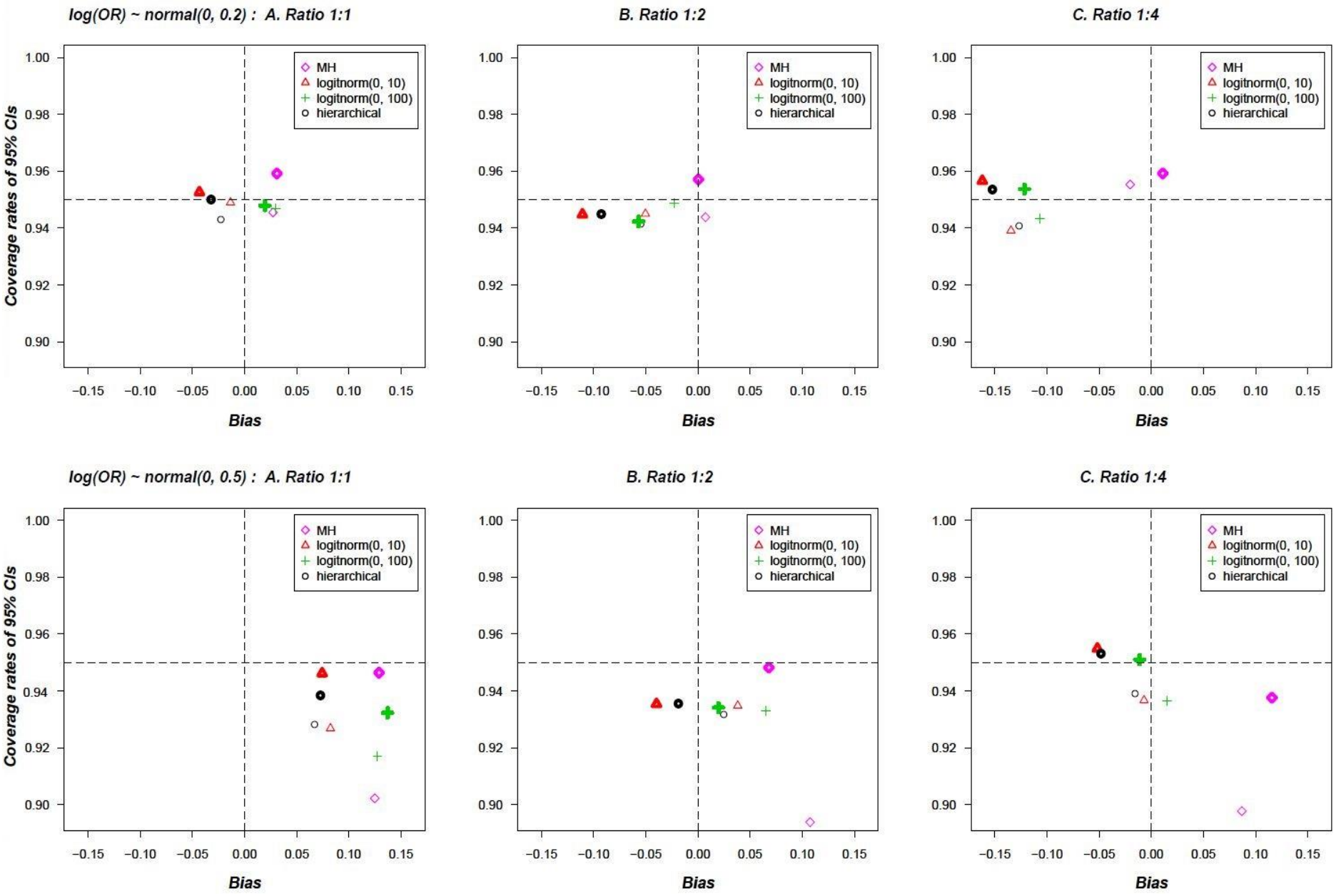
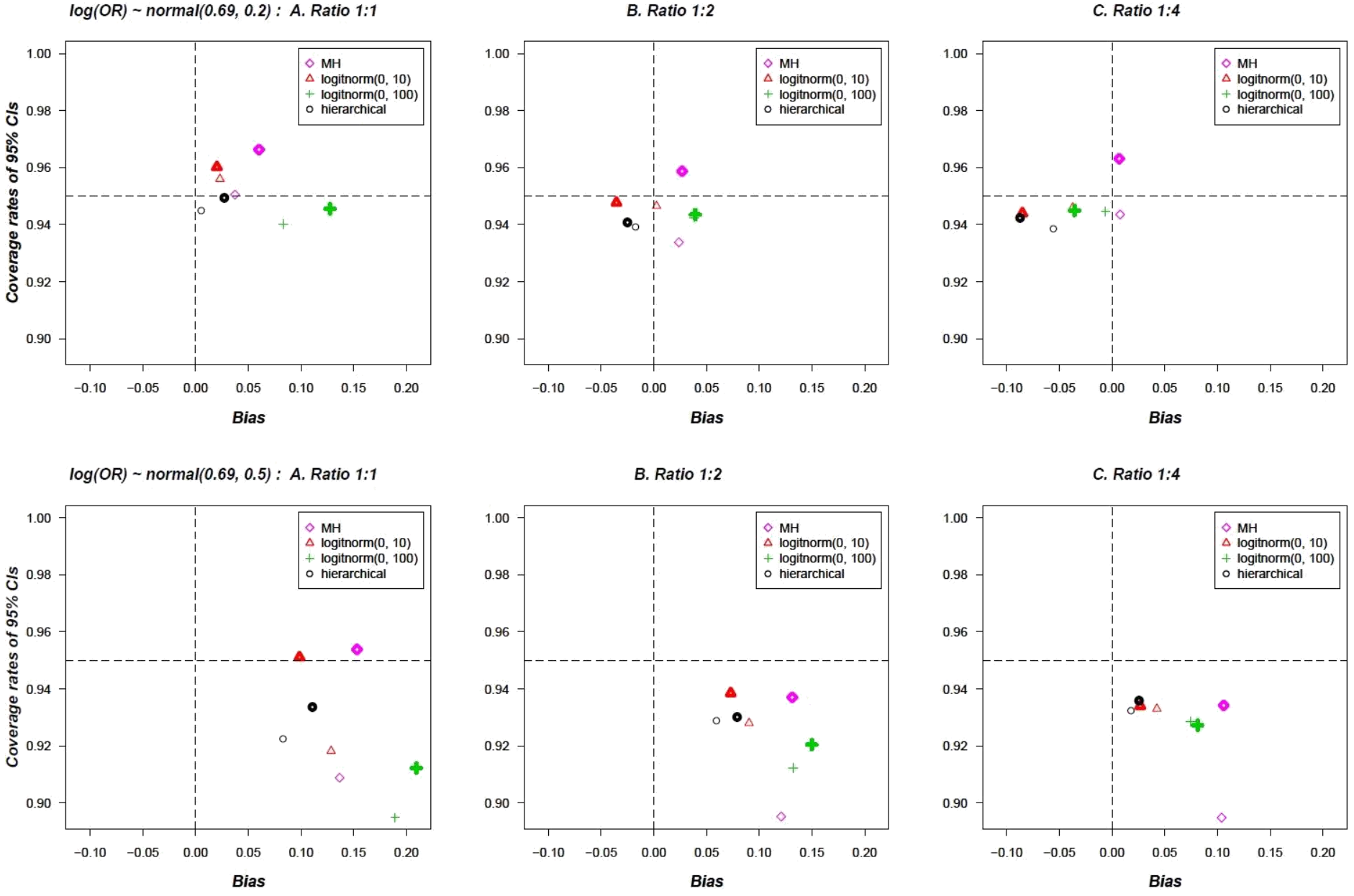


Figure IV. Results for REs methods for log(OR) = 0.69 with different SDs -- DL=FALSE



Summary of the results I

- When we used different prior distributions for meta-analytical approaches, we found that our Bayesian methods returned similar interval statements for log(OR), and matched the MH calculation method
- For FE
  - The conjugate Beta distributions calculation method did not provide good coverage or a precise mean estimate
  - Weakly informative and hierarchical priors provided coverage similar to the MH without CCs

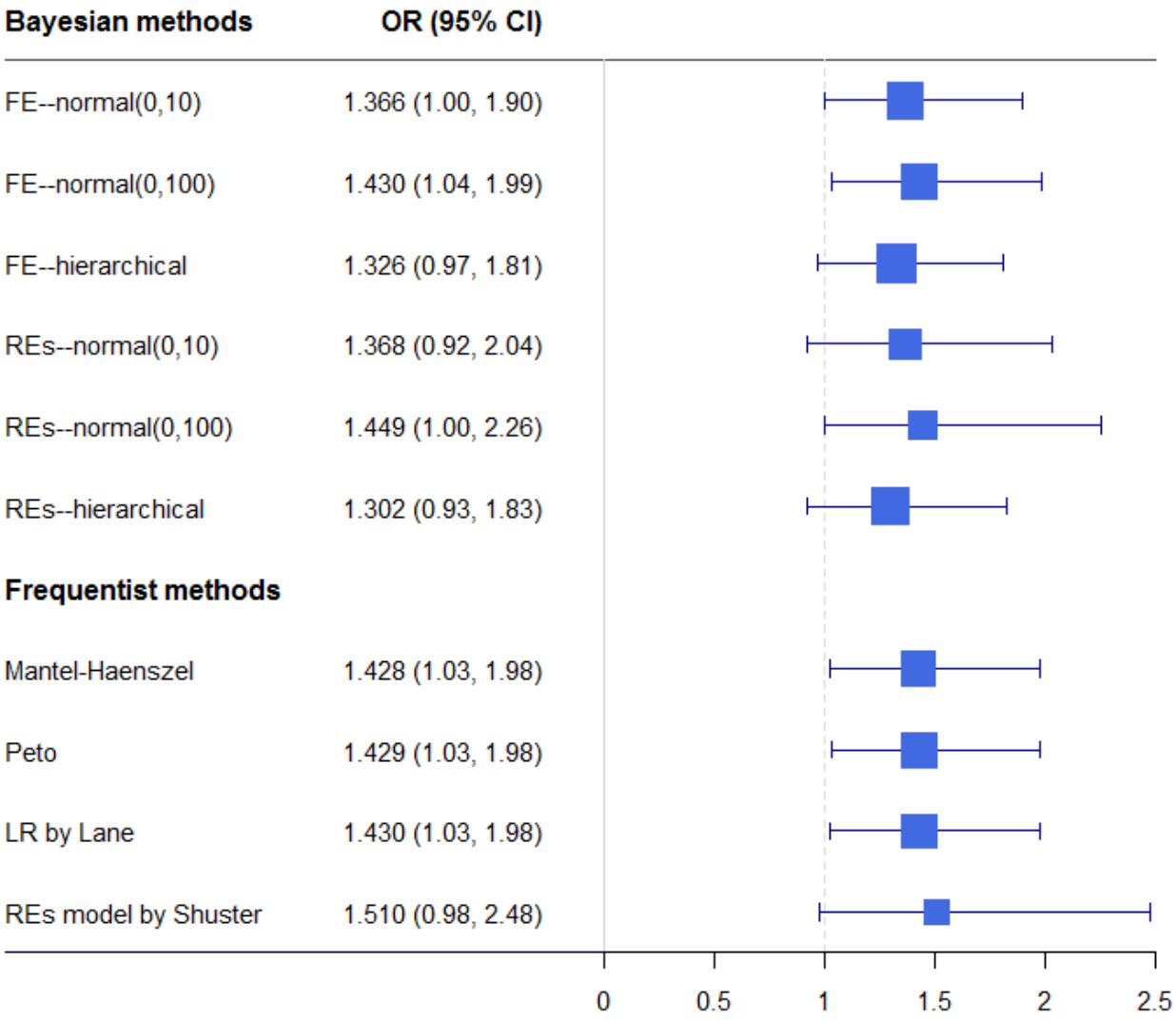
Summary of the results II

- For REs
  - In summary, results showed that uniform is a poor choice to account for τ in REs MA due to high bias from true log(OR) and low 95% coverage [results not shown today]
  - For τ, halfnormal and exp(2) with mean 0.5 performed very similar in all aspects

For both FE & REs Bayesian methods in different scenarios, results were almost identical when studies with no events were included or excluded.

Illustration : Risoglitazone Case

Figure V. Forest plot of an MA of Rosiglitazone for MI



Conclusion

- Our results demonstrate that calculations of coverage are very sensitive to the specification of the prior for p_{ic} and for τ
- In MA of rare events, the performance of the Bayesian CIs and log(OR) were not affected by excluding studies with no events in both arms
- In MA of rare events, one might be really carful interpreting the result since the results are highly method dependent

Thank you

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