

# A Bayesian two-stage dose-response meta-analysis model

Presented by: Tasnim Hamza

Authors: Tasnim Hamza, Toshi Furukawa, Andrea Cipriani, Nicola Orsini and Georgia Salanti

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## Dose-Response meta-analysis outline

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Dose-response model within a study

Dose-response meta-analysis:  
Frequentist approach

Dose-response meta-analysis:  
Bayesian approach

Compare

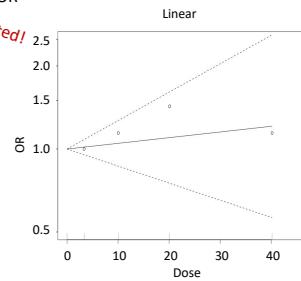
## Dose-Response models within a study

Linear model

Linear model fitted in each non-referral logOR  
*No intercept!* *Correlated!*

$$\log OR_j = \beta \times dose_j + e_j$$

dose	OR	logOR	se(logOR)
0	1.00	0.00	NA
3.35	1.00	$\log OR_1 = 0.00$	0.47
10.05	1.14	$\log OR_2 = 0.13$	0.45
20.1	1.43	$\log OR_3 = 0.36$	0.42
40.2	1.14	$\log OR_4 = 0.13$	0.45



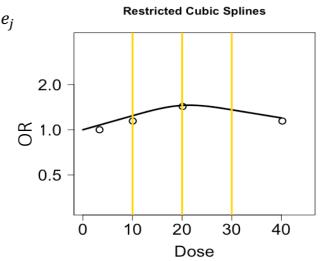
## Dose-Response models within a study

Restricted cubic spline model

Restricted cubic spline model fitted in each non-referral logOR

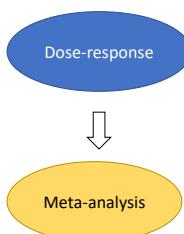
$$\log OR_j = \beta_1 \times dose_j + \beta_2 \times f(dose_j) + e_j$$

dose	OR	logOR	se(logOR)
0	1.00	0.00	NA
3.35	1.00	$\log OR_1 = 0.00$	0.47
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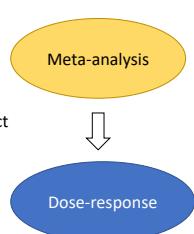


## Frequentist: Dose-Response Meta-analysis models

### Two-stage model



### One-stage model



Fixed and random effect models.

## Limitations in frequentist approach

Restricted cubic spline

$$\log OR_j = \beta_1 \times dose_j + \beta_2 \times f(dose_j) + e_j$$

**Two-stage**  
Studies with only two doses levels will be discarded (because one cannot estimate 2 parameters)

**One-stage**  
Heterogeneity can be addressed but not estimated.

- Bayesian**
- Studies with only two doses contribute some information and they borrow strength from other studies to estimate  $\beta_1$  and  $\beta_2$ .
  - Heterogeneity is estimated.

## Bayesian approach: Dose-Response meta-analysis

Two-stage model

- Step 1: Model dose-response associations within each study.

➤ Likelihood of the observed data

- ✓ Normal likelihood
- ✓ Binomial likelihood

➤ Dose-response transformation

- ✓ Linear model
- ✓ Restricted cubic spline (RCS)

- Step 2: Synthesize the dose-response associations across studies.

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## Bayesian approach: Dose-Response meta-analysis

within each study: Normal likelihood

- In a study  $i$  with dose  $j$ , let  $X_{ij}$  be the observed dose with relative effect  $Y_{ij}$ .
- Denote  $Y_i = (Y_{i1}, Y_{i2}, \dots, Y_{i\text{nd}_i})$ , where  $\text{nd}_i$  is the total number of non-referent dose. Then  $Y_i$  can be assumed to follow a multivariate normal distribution

$$Y_i \sim MVN(\Delta_i, C_i)$$

Where  $\Delta_i$  is the vector of the underlying relative effects  $\delta_{ij}$  and  $C_i$  is the approximated variance-covariance matrix.

## Bayesian approach: Dose-Response meta-analysis

within each study: Binomial likelihood

- Assume a binomial distribution for the observed events  $r_{ij}$  with probability  $p_{ij}$  and total number of observations  $n_{ij}$ .

$$r_{ij} \sim Bin(n_{ij}, p_{ij})$$

- Logistic transformation can be assumed

$$\text{logit}(p_{ij}) = \delta_{ij}$$

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## Bayesian approach: Dose-Response meta-analysis

within each study: dose transformations

- Now we can relate the dose and the relative effects by various transformation  $f$

$$\delta_{ij} = f(X_{ij}; \beta_i) - f(X_{i0}; \beta_i)$$

- Where  $f$  can be set as

➤ Linear model

$$\delta_{ij} = \beta_i(X_{ij} - X_{i0})$$

➤ Restricted Cubic Spline (RCS) with  $k$  knots.

$$\delta_{ij} = \beta_{i(1)}(X_{ij} - X_{i0}) + \dots + \beta_{i(k-1)}(f_{(k-1)}(X_{i(k-1)}) - f_{(k)}(X_{i0}))$$

## Bayesian approach: Dose-Response meta-analysis

across studies

Each one of the regression parameters can be synthesised under various assumptions. For the  $p^{\text{th}}$  regression coefficient

- Fixed-effect model

$$\beta_{i(p)} = B_{(p)}$$

Through the assumption of exchangeability, studies with only 2 doses can contribute to the estimation of more than 2 shape parameters!

- Random-effect model

$$\beta_{i(p)} \sim N(B_{(p)}, \tau^2)$$

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## Compare the three approaches

Simulation studies: Data generating mechanisms

- A dataset of 20 studies is generated, where each study has 3 doses  $X_{ij}$ .

$$X_{ij} \sim Unif(1, 10)$$

- The regression coefficients  $\beta_i$ 's are generated assuming normal random effect model with different mean and heterogeneity.

$$\beta_{i(p)} \sim N(B_{(p)}, \tau^2)$$

- The observed events  $r_{ij}$

$$r_{ij} \sim Bin(n_{ij}, p_{ij})$$

Where  $n_{ij} \sim Unif(180, 220)$  and  $p_0 = 0.1$

## Compare the three approaches

Simulation studies

- Compare the estimates of the **dose-response regression coefficients**  $B_{(p)}$  from
  - Two-stage Frequentist
  - Two-stage Bayesian with normal likelihood
  - Two-stage Bayesian with binomial likelihood
- Dose-response transformations: linear and restricted cubic splines
- Performance measure
  - For  $B_{(p)} = 0$ , absolute bias =  $|E(\beta_{(p)}^{pooled}) - B_{(p)}|$
  - For  $B_{(p)} \neq 0$ , absolute relative bias =  $\frac{|bias|}{B_{(p)}}$
  - Mean squared error, MSE =  $bias^2 + V(B_{(p)})$

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## Compare the three approaches

Results: Restricted cubic spline

### Simulated data parameters

$\beta_1$	$\beta_2$	$\tau$
0.02	0.02	0.001
0.03	0.05	0.001
0.03	0.2	0.001
0.05	0	0.001
0.2	0.03	0.001
0.02	0.02	0.05
0.03	0.05	0.05
0.03	0.2	0.05
0.05	0	0.05
0.2	0.03	0.03

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## Compare the three approaches

Results: Restricted cubic spline

Simulated data parameters			Absolute (relative) Bias $\beta_1$			Absolute (relative) Bias $\beta_2$		
$\beta_1$	$\beta_2$	$\tau$	Bayesian Normal	Bayesian Binomial	Frequentist	Bayesian Normal	Bayesian Binomial	Frequentist
0.02	0.02	0.001	22%	4%	23%	39%	12%	44%
0.03	0.05	0.001	25%	2%	22%	68%	0%	64%
0.03	0.2	0.001	33%	10%	37%	19%	2%	22%
0.05	0	0.001	12%	2%	12%	2%	0%	1%
0.2	0.03	0.001	3%	1%	3%	35%	1%	15%
0.02	0.02	0.05	50%	34%	42%	192%	34%	143%
0.03	0.05	0.05	28%	18%	25%	56%	3%	41%
0.03	0.2	0.01	24%	10%	25%	9%	2%	10%
0.05	0	0.05	15%	3%	15%	4%	0%	5%
0.2	0.03	0.01	2%	1%	2%	32%	12%	2%

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## Compare the three approaches

Results: Restricted cubic spline

Simulated data parameters			Absolute (relative) Bias $\beta_1$			Absolute (relative) Bias $\beta_2$		
$\beta_1$	$\beta_2$	$\tau$	Bayesian Normal	Bayesian Binomial	Frequentist	Bayesian Normal	Bayesian Binomial	Frequentist
0.02	0.02	0.001	22%	4%	23%	39%	12%	44%
0.03	0.05	0.001	25%	2%	22%	68%	0%	64%
0.03	0.2	0.001	33%	10%	37%	19%	2%	22%
0.05	0	0.001	12%	2%	12%	12%	2%	1%
0.2	0.03	0.001	3%	1%	3%	3%	35%	15%
0.02	0.02	0.05	50%	34%	42%	192%	34%	143%
0.03	0.05	0.05	28%	18%	25%	56%	3%	41%
0.03	0.2	0.01	24%	10%	25%	9%	2%	10%
0.05	0	0.05	15%	3%	15%	4%	0%	5%
0.2	0.03	0.01	2%	1%	2%	32%	12%	2%

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## Compare the three approaches

Results: Restricted cubic spline

Simulated data parameters			Absolute (relative) Bias $\beta_1$			Absolute (relative) Bias $\beta_2$		
$\beta_1$	$\beta_2$	$\tau$	Bayesian Normal	Bayesian Binomial	Frequentist	Bayesian Normal	Bayesian Binomial	Frequentist
0.02	0.02	0.001	22%	4%	23%	39%	12%	44%
0.03	0.05	0.001	25%	2%	22%	68%	0%	64%
0.03	0.2	0.001	33%	10%	37%	19%	2%	22%
0.05	0	0.001	12%	2%	12%	2%	0%	1%
0.2	0.03	0.001	3%	1%	3%	35%	1%	15%
0.02	0.02	0.05	50%	34%	42%	192%	34%	143%
0.03	0.05	0.05	28%	18%	25%	56%	3%	41%
0.03	0.2	0.01	24%	10%	25%	9%	2%	10%
0.05	0	0.05	15%	3%	15%	4%	0%	5%
0.2	0.03	0.01	2%	1%	2%	32%	12%	2%

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## Compare the three approaches

Results: Linear model

Simulated data parameters			Absolute Relative Bias $\beta$					
$\beta$	$\tau$		Bayesian Normal	Bayesian Binomial	Frequentist	Bayesian Normal	Bayesian Binomial	Frequentist
0.02	0.001		23%	12%	24%	7%	8%	7%
0.03	0.001		7%	2%	8%	2%	2%	2%
0.05	0.001		7%	3%	7%	3%	3%	3%
0.2	0.001		0%	0%	0%	0%	0%	0%
0.02	0.01		11%	1%	12%	8%	8%	8%
0.03	0.05		8%	0%	8%	9%	2%	10%
0.05	0.01		4%	1%	5%	4%	5%	5%
0.2	0.01		1%	1%	1%	1%	1%	1%

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## Compare the three approaches

Results: Absolute bias for  $B_{(p)} = 0$

Simulated data parameters			Absolute Bias $\beta_1$		Absolute Bias $\beta_2$			
$\beta_1$	$\beta_2$	$\tau$	Bayesian Normal	Bayesian Binomial	Frequentist	Bayesian Normal	Bayesian Binomial	Frequentist
0	0	0.001	0.000	0.002	0.010	0.001	0.000	0.026
0	0	0.05	0.007	0.004	0.006	0.012	0.000	0.009
0		0.001	0.000	0.000	0.000			
0		0.01	0.000	0.000	0.000			

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## Conclusions

- Bayesian approach is able to overcome the shortcomings in the frequentist approach.
  - Include all studies with 'less' information.
  - Estimate the heterogeneity
- The binomial approach is not applicable in frequentist settings.
- Binomial Bayesian gives less bias than normal Bayesian and frequentist approaches.
- Normal Bayesian and frequentist approaches agree.

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