
A Nonlinear Hierarchical Model for Evidence Synthesis of Safety Data

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Outline

- background: drug development, safety analyses, guidelines
- example
- hierarchical model: ML vs. Bayesian approach
- sensitivity analyses
- discussion

Background

- **drug development**: highly regulated environment
- **marketing authorisation**
 - portfolio of studies
 - assessment of benefit-risk ratio
- **“risk”**: drug safety, adverse event profile
 - side effects (= adverse events)
 - evidence summarized across studies

Adverse Event Data

- often dealt with as **binary**
 - patient had an adverse event during follow-up: yes / no
- **time to event** of interest when period of drug intake varies
 - e.g. drug used for acute and chronic condition
- if based on lab data, **discrete event times** through visit schedule
- **censoring**: patients drop out

How to combine safety data across studies? International Guidelines (McEntegart 2000)

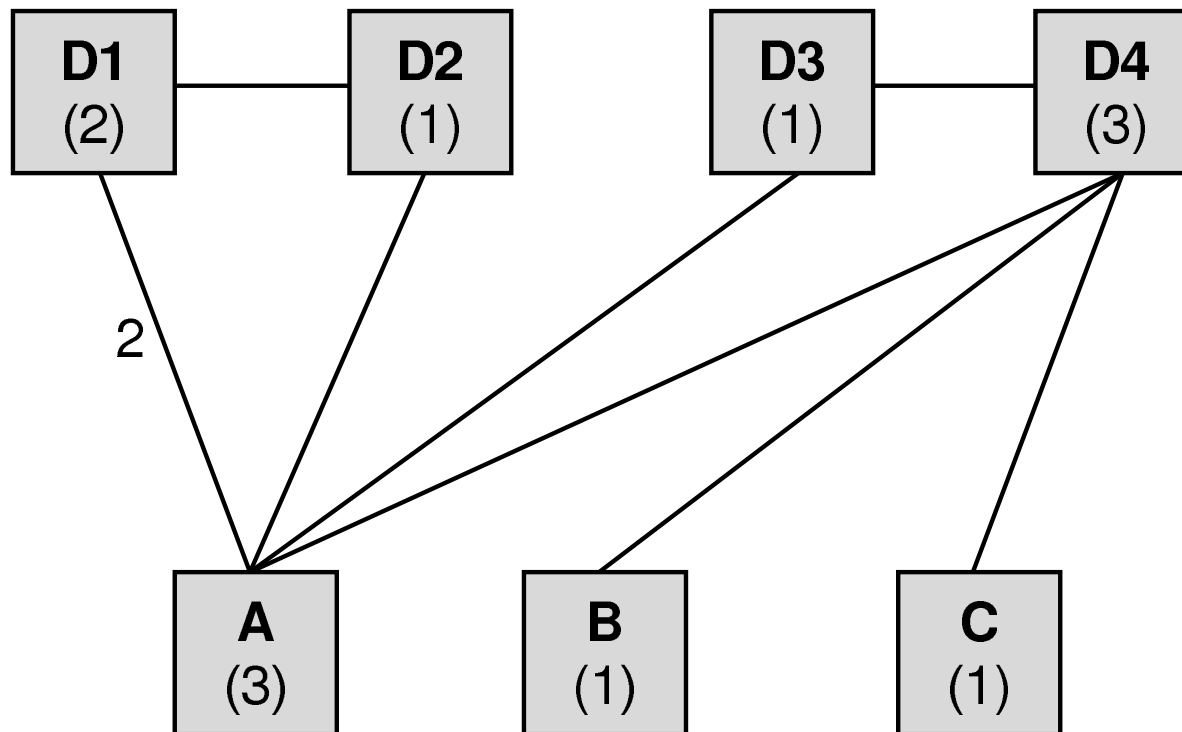
- **US Food and Drug Administration (FDA) Reviewer Guide**

“ . . . some consideration should be given to how the pooling is to be accomplished. It is probably most common to simply combine the numerator events and the denominators for the selected studies.”

- **International Conference on Harmonization (ICH) E9**

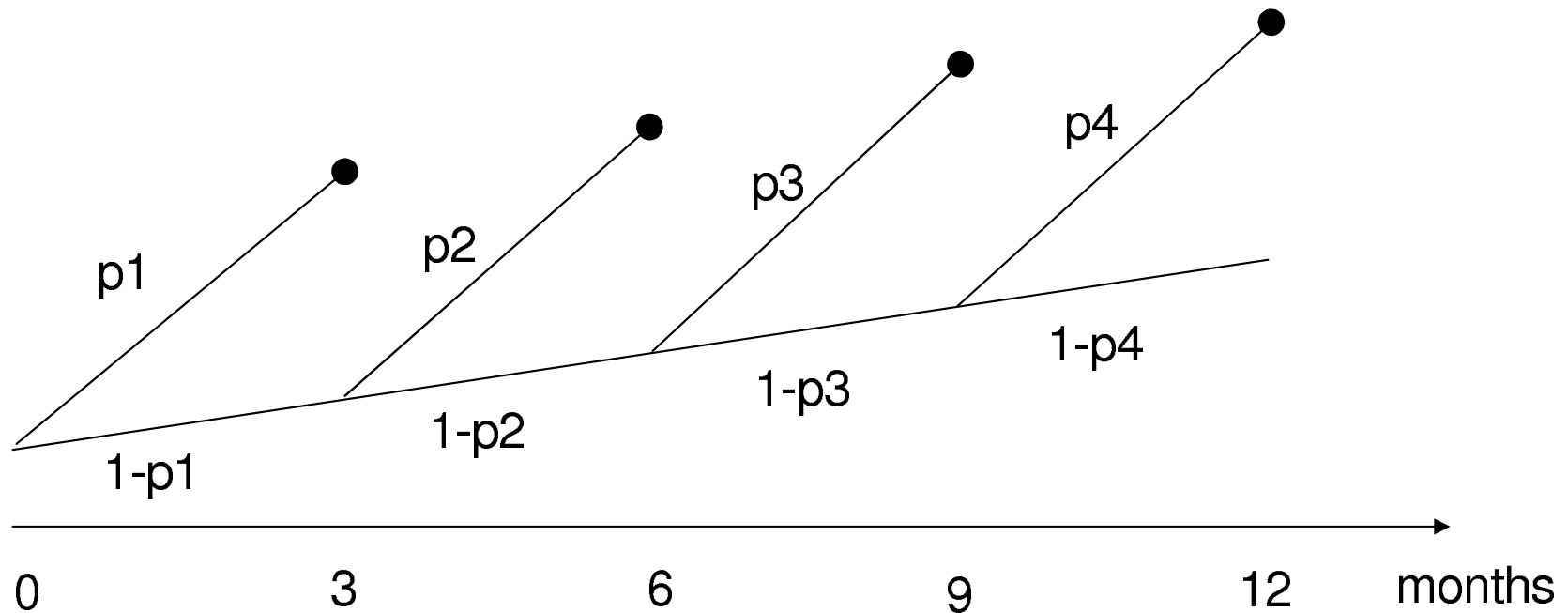
“ . . . any statistical procedures used to combine data across trials should be described in detail” and “. . . attention should be paid . . . to the proper modelling of the various sources of variation.”

Example: “Comparison Network”



- 5 **studies** with more than 24,000 patients in total
- 7 **treatments**
 - experimental: 4 doses (D1-D4)
 - 3 active comparators (A-C)
- “**network meta-analysis**” (Lumley 2002)

Model for Discrete Time-to-Event Data (e.g. Clayton & Hills 1993)



Between-Study Variation

- **causes** of between-study variation
 - study population, centres, trial design, methods of assessment, follow-up, ...
- **interpretation** of between-study variation (Spiegelhalter et al 2004, p 169-170)

Between-study SD σ	Heterogeneity
0.1 – 0.5	reasonable
0.5 – 1	fairly high
above 1	extreme

Hierarchical Model

- logistic model with interval specific treatment dependent hazards and normally distributed study effects

- number of events $x_{jtk} \sim \text{bin}(\pi_{jtk}, n_{jtk})$ with

$$\text{logit}(\pi_{jtk}) = \theta_{jt} + \eta_k \quad \text{and} \quad \eta_k \sim N(0, \sigma^2)$$

- ML estimation (SAS/NLMixed)

Confidence Intervals for Functions of Estimated Parameters

- for instance: 1 year survival probability
- Δ rule gives standard error
- Wald type confidence intervals
 - small number of studies: large sample approx. might not work
 - Follmann & Proschan (1999) suggested use of t-quantile with $k - 1$ df for random effects meta-analysis
- convenient in SAS Proc NLMixed

Example: Hierarchical Model

1 year event probabilities

- ML approach
- **more than 6,000 adverse events** (of type AE1)
- **between-study SD (SE):**

$$\hat{\sigma} = 0.175 (0.064)$$

Trt	Est.	(SE)	95% CI
D1	.33	(.028)	(.28, .39)
D2	.32	(.029)	(.26, .37)
D3	.34	(.033)	(.27, .40)
D4	.35	(.026)	(.30, .41)
A	.30	(.024)	(.25, .35)
B	.36	(.029)	(.30, .42)
C	.33	(.026)	(.28, .38)

Example: What if between-study variation is ignored?

Trt	With Study RE			Without Study RE		
	Est.	(SE)	95% CI	Est.	(SE)	95% CI
D1	.33	(.028)	(.28, .39)	.35	(.013)	(.32, .37)
D2	.32	(.029)	(.26, .37)	.38	(.015)	(.36, .41)
D3	.34	(.033)	(.27, .40)	.35	(.024)	(.30, .39)
D4	.35	(.026)	(.30, .41)	.33	(.005)	(.32, .34)
A	.30	(.024)	(.25, .35)	.32	(.012)	(.30, .35)
B	.36	(.029)	(.30, .42)	.29	(.007)	(.28, .31)
C	.33	(.026)	(.28, .38)	.34	(.008)	(.33, .36)

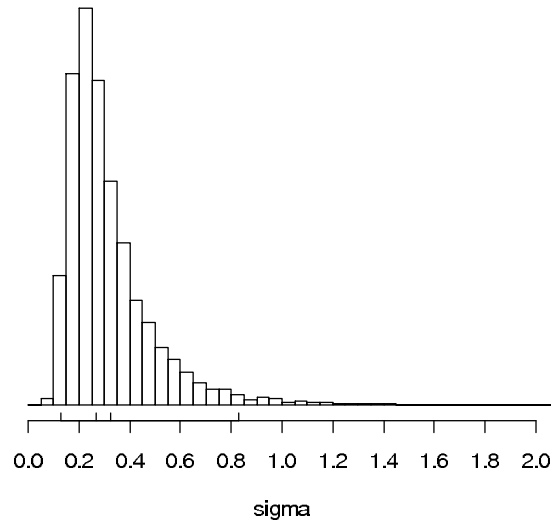
Bayesian Hierarchical Model

- “uninformative” prior for hazard θ_{jt} (Normal(0, 10^6))
- priors for between-study variation σ (sensitivity analysis)
 - uniform(0,10)
 - half-normal(0,1)
 - exponential(1)
- fitted in WinBUGS

Posterior Distributions of σ

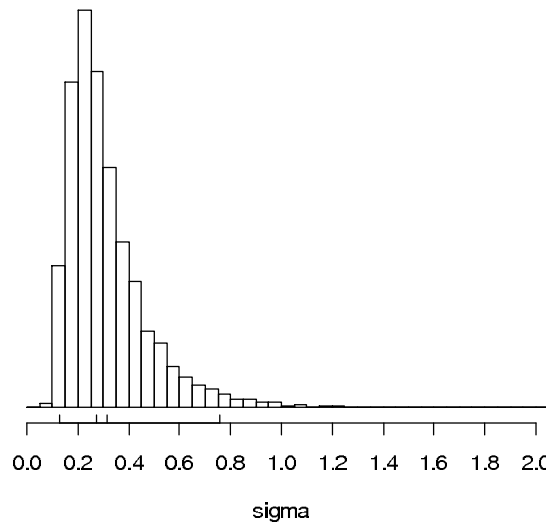
Uniform

between-trial SD (posterior)



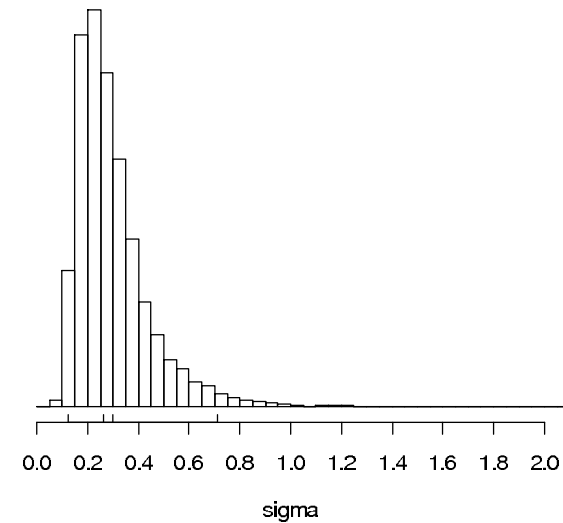
Half-normal

between-trial SD (posterior)



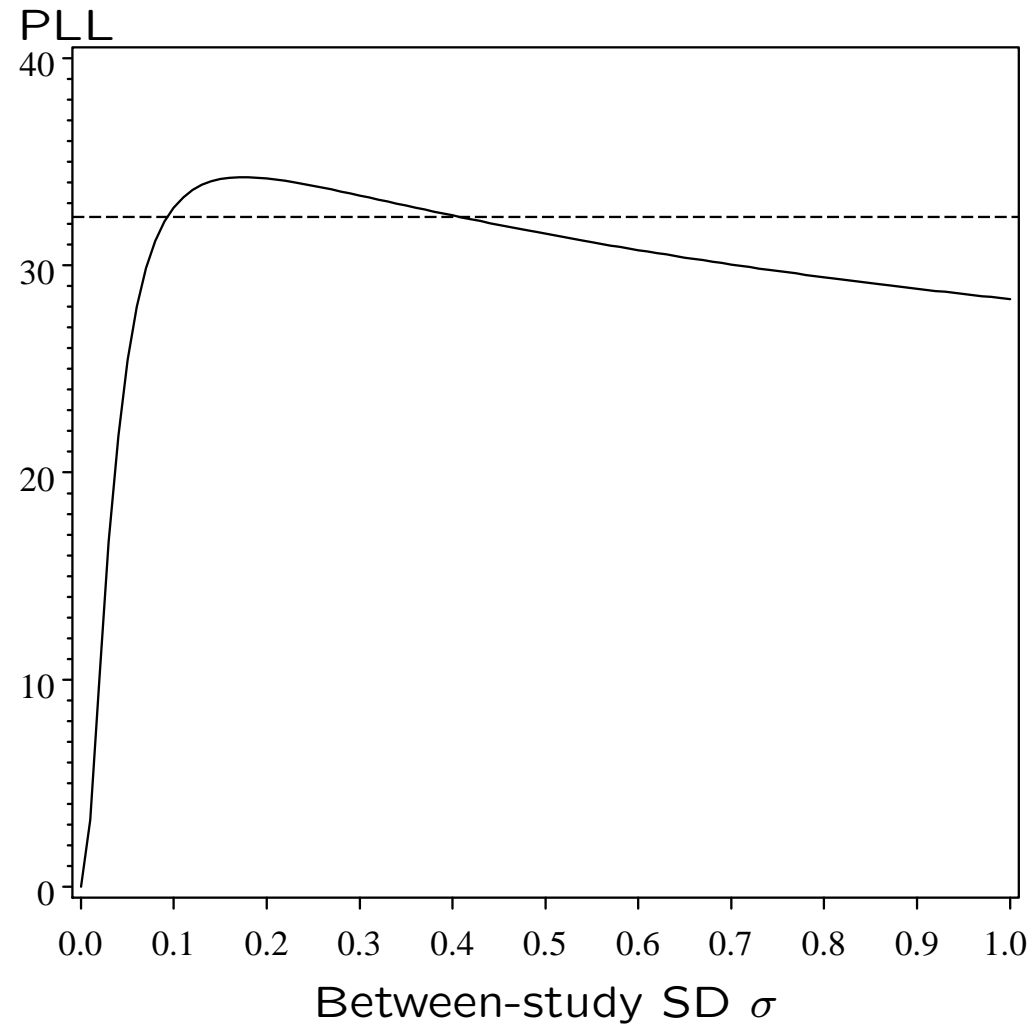
Exponential

between-trial SD (posterior)

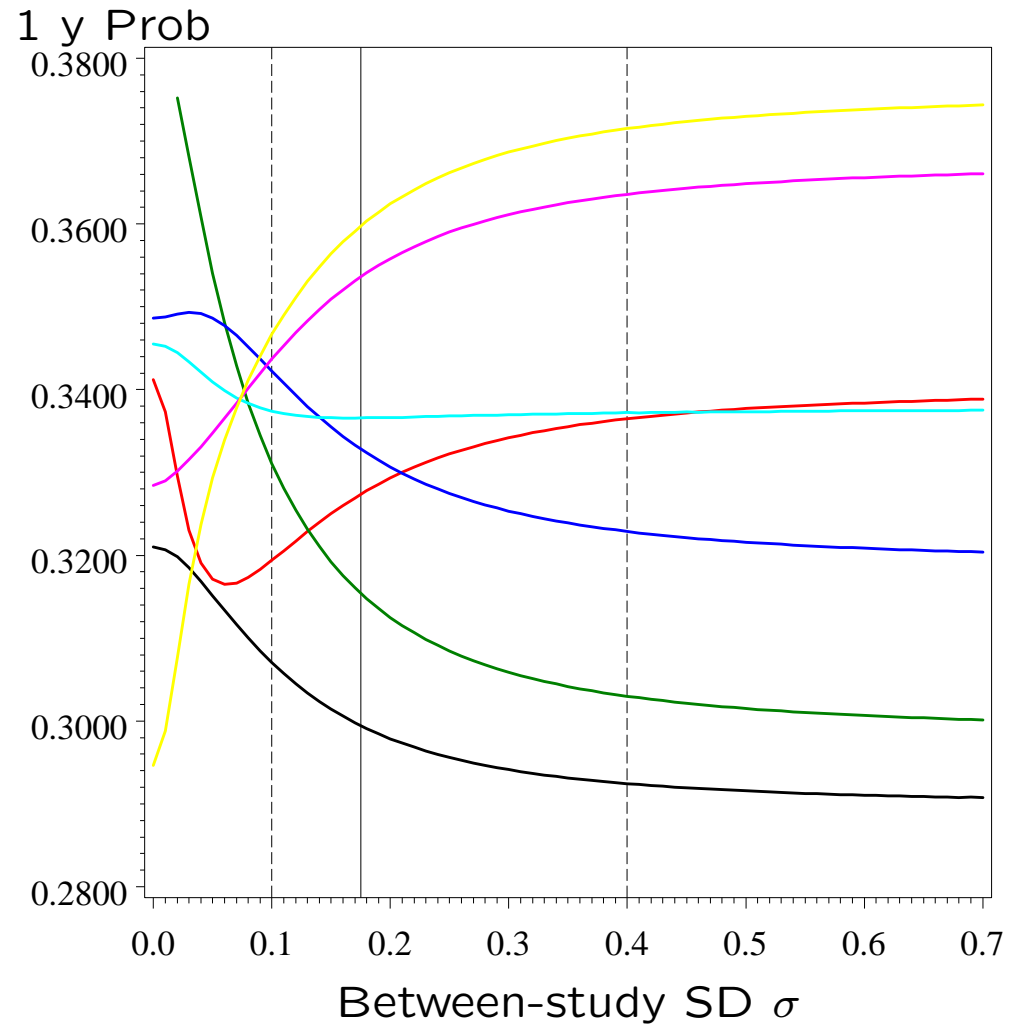


Prior	Mean	SD	2.5%	50%	97.5%
Uniform	0.344	0.255	0.131	0.278	0.938
Half-normal	0.340	0.203	0.128	0.285	0.883
Exponential	0.301	0.155	0.123	0.265	0.709

Sensitivity Analysis: Profile Likelihood



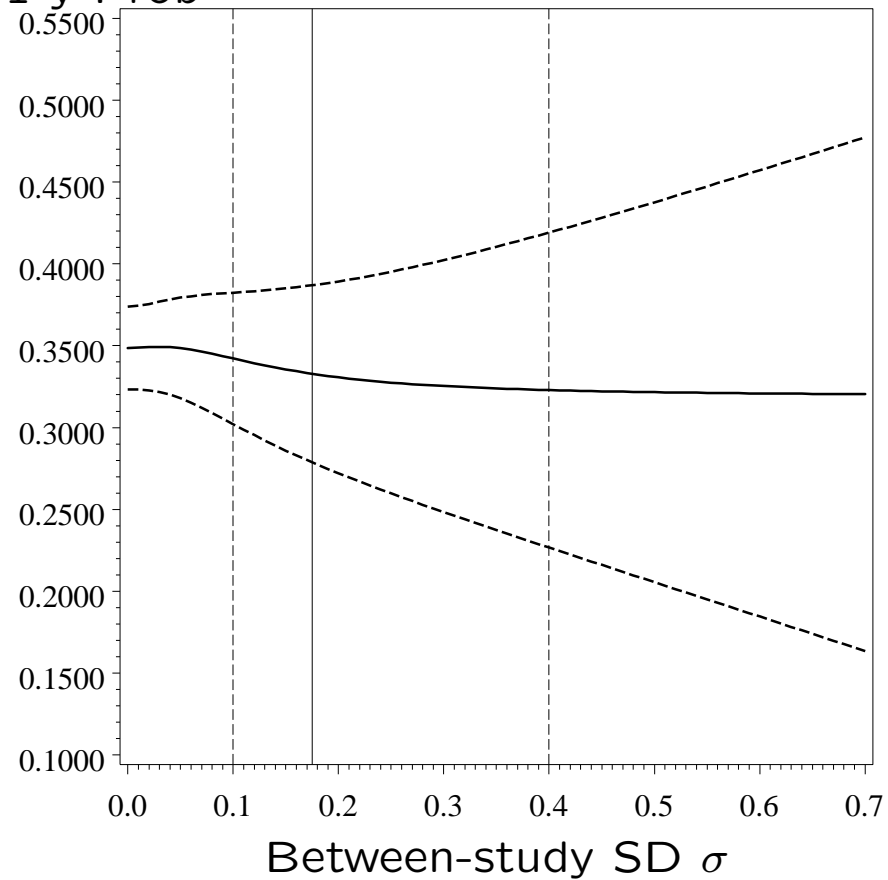
Sensitivity Analysis



Sensitivity Analysis

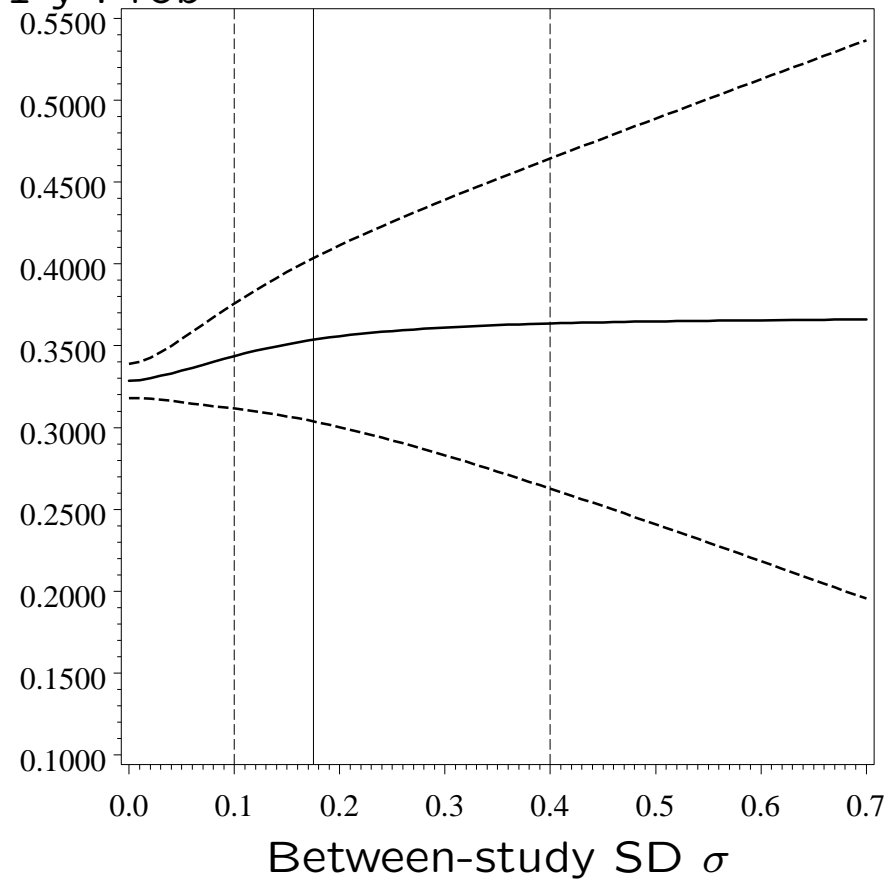
D1

1 y Prob



D4

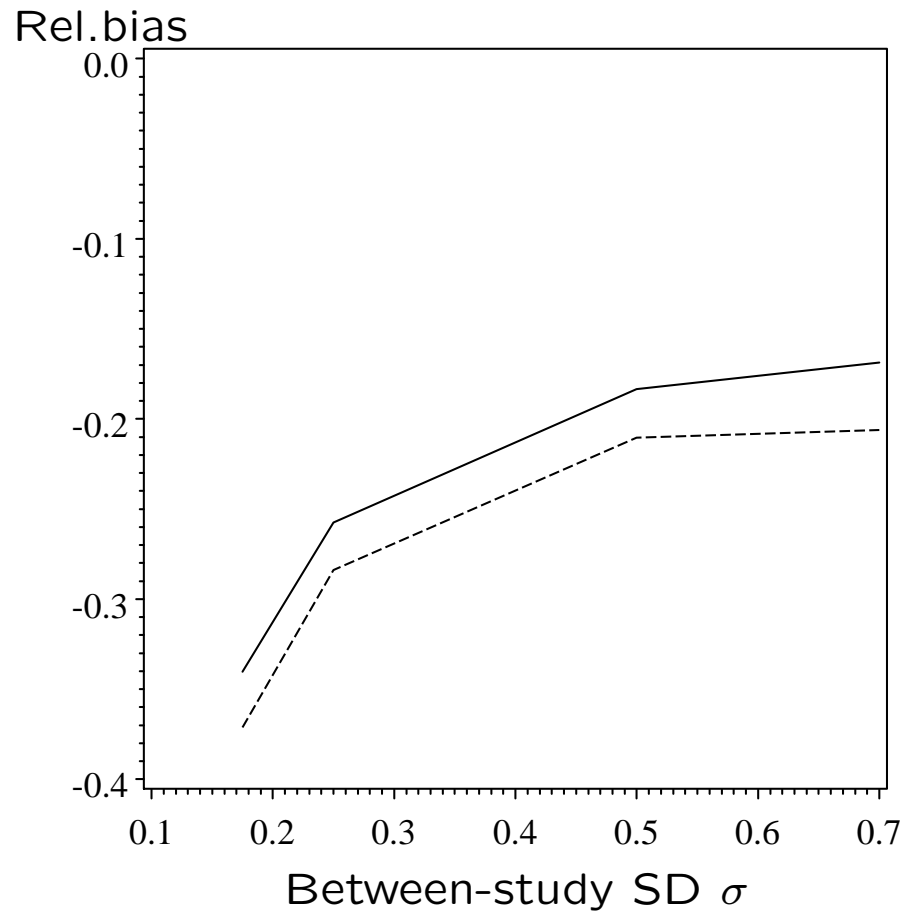
1 y Prob



Simulation Study

- **simulation based on the example data**
 - (only) 5 studies
 - number of patients at risk per interval and study arm
 - parameters as estimated (by ML approach)
 - (only) 100 replications per scenario
- **between-study SD:** $\sigma = 0.175, 0.25, 0.5, 0.7$
- **analysis:** ML approach (using SAS Proc NLMixed)

Simulation Study: Between-Study SD Estimates



σ	Mean	25%	Median	75%
0.175	0.12	0.07	0.11	0.16
0.25	0.19	0.13	0.18	0.25
0.5	0.41	0.30	0.39	0.50
0.7	0.58	0.40	0.56	0.73

- relative mean (solid) and median (dashed) bias
- about 75% of estimates below true value

Coverage Probability of Confidence Intervals

$$\sigma = 0.175$$

Treatment	Coverage probability	
	normal	t_4
D1	.83	.93
D2	.86	.92
D3	.90	1.00
D4	.84	.92
A	.88	.93
B	.85	.93
C	.88	.95
All	.86	.94

only 100 replications (SE about .03)

Rare Events

- 1 year probabilities of about 1 %
- could not fit the model neither with ML nor Bayesian approach
- constant hazards across time intervals assumed (trtmnt specific)
- example: ML fit resulted in between-study SD of virtually 0

Prior	Mean	SD	2.5%	50%	97.5%
Uniform	0.486	0.533	0.018	0.334	1.854
Half-normal	0.354	0.295	0.018	0.280	1.144
Exponential	0.326	0.278	0.018	0.259	1.023

Discussion

- **between-study variation**
 - natural, needs to be taken into account;
but difficult to estimate if number of studies small
- **sensitivity analyses**: in Bayesian and likelihood framework
- **effect measures**: risk differences vs. odds ratio
- **centre effects**: ignored here, additional hierarchy level
- **patient level data**: incorporating covariates

References

- Clayton D, Hills M (1993) Statistical models in epidemiology. Oxford University Press, Oxford. Chapter 4.
- Follmann DA, Proschan MA (1999) Valid inference in random effects meta-analysis. *Biometrics* 55: 732–737.
- Lumley T (2002) Network meta-analysis for indirect treatment comparison. *Statistics in Medicine* 21: 2313–2324.
- Spiegelhalter D, Abrams KR, Myles JP (2004) Bayesian approaches to clinical trials and health-care evaluation. Wiley, Chichester.