

A case-study examining the use of Bayesian methods for subgroup analysis in Clinical Trials

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Outline

Motivation

- Background to subgroup analysis in clinical trials
- Review of previous approaches to subgroup analysis

Case-study and data analysis

- Introduction to case-study
- Analysis with Bayesian hierarchical model

Discussion

- Case-study conclusions
- Discussion on subgroup modelling

Background to subgroup analysis in clinical trials

- ▶ For biological reasons a treatment may well be more effective in some populations of patients than others
- ▶ Important variables may include baseline characteristics directly related to disease severity and a range of demographic factors
- ▶ Increased focus on tailored therapies has led to greater interest in sub-group analysis

Overview of Statistical approaches

- ▶ Statistical approaches can broadly be divided into two groups
- 1. Methods which attempt to **test** a large number of potential groups with the aim of identifying groups that are divergent from the rest of the population
- 2. **Modelling/ estimation** approaches which attempt to provide a summary of the variability among different groups

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Approaches based on testing

Simple testing approaches

- ▶ Subgroup analysis can be formulated (hypothesis) testing problem
- ▶ In a regulatory setting such an approach is unlikely to be acceptable unless a test for a particular subgroup is pre-planned

Post-hoc subgroup analysis

- ▶ Post-hoc analyses based on simple approaches to testing are difficult to interpret and can be very misleading (Pocock et al. 2002)
- ▶ More sophisticated methods such as mixture modelling and false discover rate have been developed in the context of data rich problems

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Approaches based on modelling and estimation

Motivation

- ▶ Can provide a better understanding of a patients benefit-risk profile leading to better informed treatment choices
- ▶ Helps motivate further studies in specific subgroups

Interaction terms

- ▶ Inevitably leads to models with treatment by subgroup interactions
- ▶ This motivates approaches which account for the (spatial) structure among sub-groups and provide some level of *shrinkage* (Dixon and Simon; 1991)

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meta-analysis

- ▶ "the statistical analysis of a large collection of analysis results from individual studies for the purpose of integrating the findings' Glass (1976)"
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Overview of models used in meta-analysis

		treatment effects/contrasts (trt vs. control)		
		C common	F unrelated unconstrained "fixed effects"	R related/similar constrained "random" effects
baseline	c common	complete pooling crude estimates (often done, not recommended)		
	f unrelated unconstrained "fixed baselines"	common effect or "fixed effects" analysis	full stratification (useful for data description)	random effects analysis
	r related/similar constrained "random" baselines	common effect analysis with random baselines (useful for rare events)		bivariate random-effects analysis

Case-study overview

- ▶ 7 studies comparing an active treatment ($n=4126$) with placebo ($n=2505$) the response variable was binary (responder=1, non-responder=0)
- ▶ Three important symptomatic baseline factors, denoted a b and c were identified
- ▶ Based on a clinical definition each variable was classified into two groups (0= lower burden of disease 1= higher burden of disease)
- ▶ Clinical team believed that the drug would be more effective in groups with a higher burden of disease

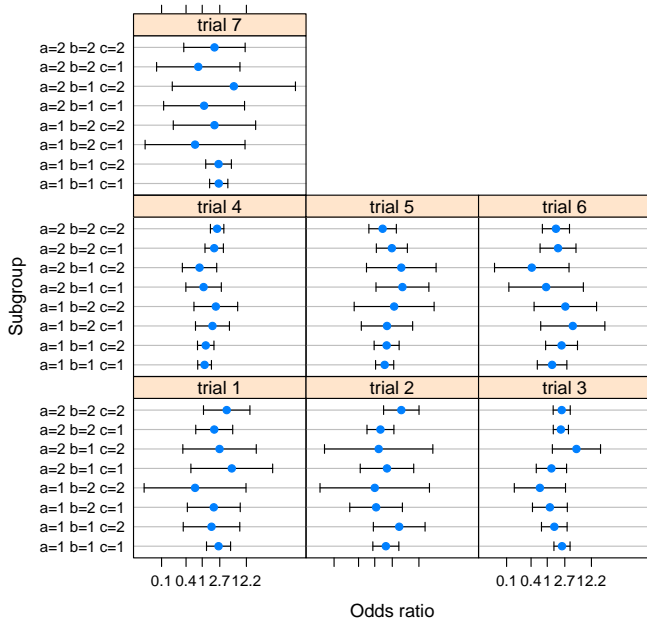


Figure: Subgroup effects for each trial on the odds ratio scale

Bayesian meta-analysis models

1. (rR) A general model for meta analysis is a the bivariate random effects model

$$\text{logit}(p_{i1}) = \mu_1 + \alpha_{1i}$$

$$\text{logit}(p_{i2}) = \mu_2 + \alpha_{2i}$$

$$(\alpha_{1,i}, \alpha_{2,i})' \sim N_2(\mathbf{0}, \Sigma)$$

2. (fR) Smith Spiegelhalter and Thomas (1995) random effects

$$\text{logit}(p_{i1}) = \mu_{0j} - 0.5\alpha_j$$

$$\text{logit}(p_{i2}) = \mu_{0j} + 0.5\alpha_j$$

$$\alpha_j \sim N(d, \sigma_{ST}^2)$$

3. (fC) The simplest approach is the **common** effect meta-analysis model. ie

$$\alpha_1 = \dots = \alpha_n = \alpha_{common}$$

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Models for subgroup effects

1. Exchangeable subgroups

$$\begin{aligned}\text{logit}(p_{i1}) &= \tau + \theta_{ji} \\ \theta_{j1} &\sim \mathbf{N}(\mathbf{0}, \sigma_{SG}^2)\end{aligned}$$

2. Dixon and Simon - First order interaction with shrinkage

$$\begin{aligned}\text{logit}(p_{i1}) &= \tau + \gamma_{j1}x_{ij1} + \gamma_{j2}x_{ij2} + \gamma_{j13}x_{ij1} \\ \gamma_{j1} &\sim \mathbf{N}(\mathbf{0}, \sigma_{DS}^2)\end{aligned}$$

3. Extension of Dixon and Simon to models with second or third order interactions with shrinkage

4. Hodges et al (2007) separate variance components for each factor

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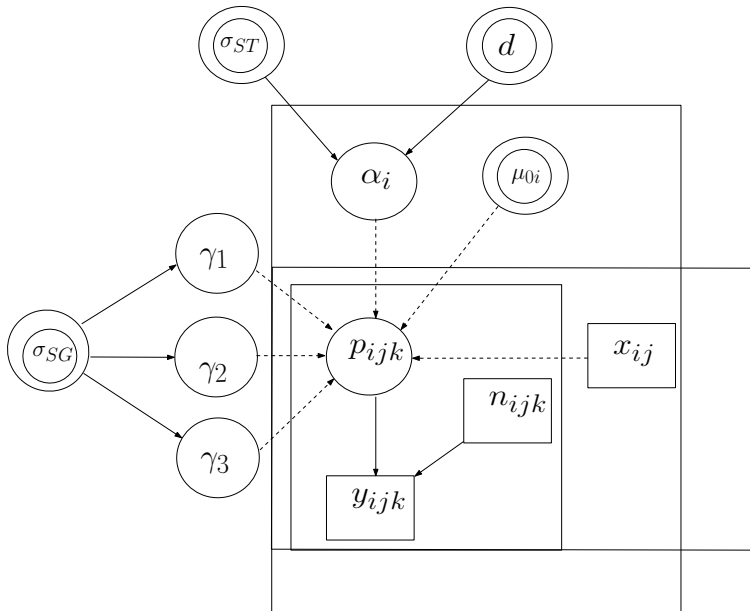
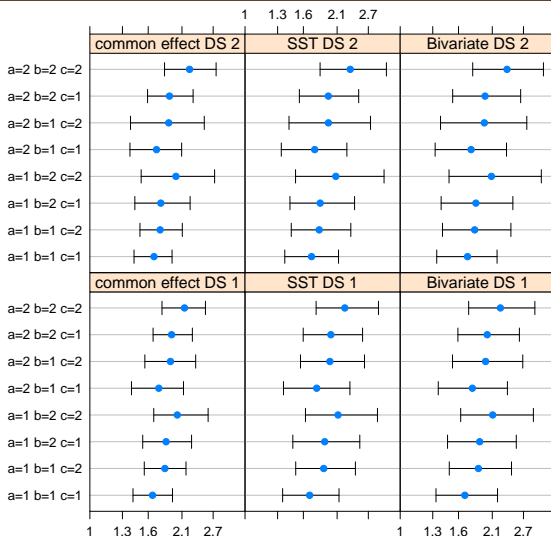


Figure: Directed acyclic graphical model

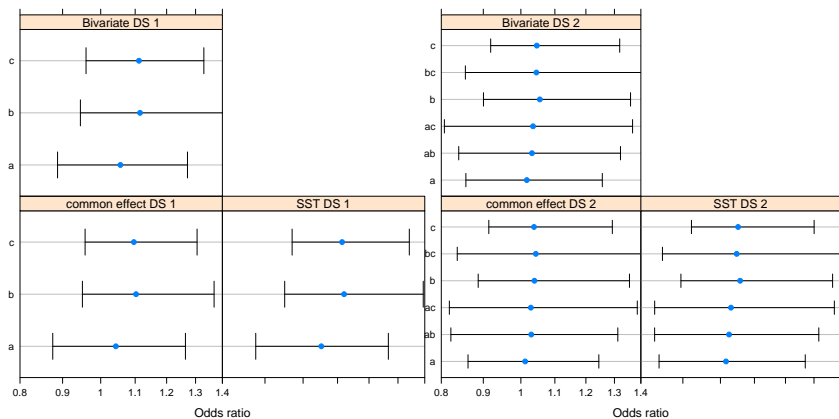
Results (1) model fit

meta-analysis model	Subgroup model	$D(\hat{\theta})$	$\overline{D(\theta)}$	P_d	DIC
Saturated	Saturated	0.0	114.4	114.4	228.8
Common (fC)	none	88.1	96.1	8.0	104.1
SST (fR)	none	85.2	95.8	10.6	106.4
Bivariate (rR)	none	85.0	95.6	10.7	106.3
Common (fC)	exchangeable	88.5	97.8	9.3	107.0
SST (fR)	exchangeable	85.0	97.1	12.1	109.2
Bivariate (rR)	exchangeable	84.2	97.1	12.9	109.9
Common (fC)	1st order DS	82.5	92.7	10.2	102.9
SST (fR)	1st order DS	83.4	94.5	11.1	105.6
Bivariate (rR)	1st order DS	77.5	91.0	13.4	104.4
Common (fC)	2nd order DS	78.4	92.4	14.0	106.3
SST (fR)	2nd order DS	76.9	90.5	13.6	104.1
Bivariate (rR)	2nd order DS	79.6	93.6	14.0	107.5

Summary of sub-group results



Dixon and Simon model: key parameter estimates



Model Diagnostics

- ▶ Model checking in hierarchical models has often been based on the ability of the model to predict the observed data or ideally an independent set of completely external data.
- ▶ We used the **conflict P-value** (Marshall and Spiegelhalter; 2007). to assess the compatibility of the data from different studies and subgroups
- ▶ The results showed no cause for concern in any of the well supported models

Case-study conclusions

- ▶ There was evidence of small to moderate variation across the study subgroups
- ▶ There was no evidence of divergent subgroups
- ▶ The well supported models which included subgroup modelling were consistent with the prior belief that the drug might have a greater effect in patients with a higher burden of disease
- ▶ Bayesian modelling allowed a wide range of structures to be considered

Discussion on subgroup modelling

- ▶ Modelling strategy to deal with model uncertainty (Complex model +shrinkage v's a range of models and DIC to assess inference robustness)
- ▶ Effect of parametrization and priors
- ▶ Extensions to autoregressive structures and more robust distributional assumptions
- ▶ Extensions to continuous baseline variables using splines

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