Assessment of the Heterogeneity of the Treatment Effect among Subgroups by Detecting Qualitative Interactions

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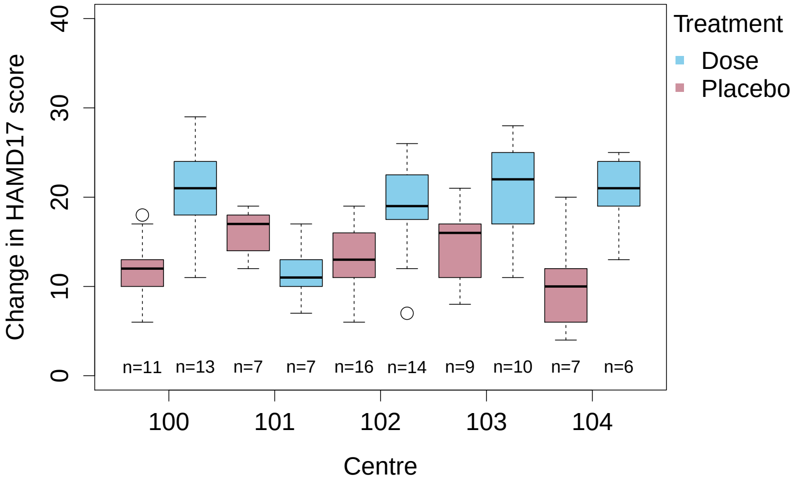
Subgroup analysis of clinical trials

Data are separated into various specific subgroups of subjects:

- Gender (male, female)
- Race (Asian, Black, White)
- Initial health status (blood pressure, severity of disease)
- Age ($<$50 years, $\geq$50 years)
- Centre (multi-centre trial)

Motivating Example - multi-centre clinical trial

Example based on "Analysis of Clinical Trials using SAS: A Practical Guide" (Dmitrienko et al., 2005)



Detection of heterogeneity of treatment effects in subgroups

ICH guidance "Statistical principles for clinical trials" (1998)

"Marked heterogeneity may be identified by graphical display of the results of individual centres or by analytical methods, such as a significance test of the treatment-by-centre interaction"

Several terms

- treatment-by-centre interaction
- treatment-by-clinic interaction
- treatment-by-stratum interaction
- heterogeneity of treatment effects

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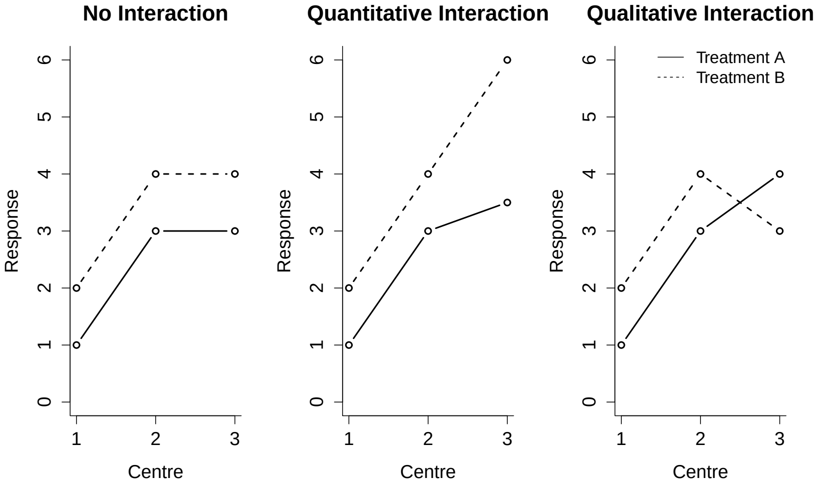
Types of interactions



The model

ANOVA model

$$Y_{ijk} = \mu + \alpha_i + \beta_j + (\alpha\beta)_{ij} + \epsilon_{ijk} \quad , \textit{where} \quad \epsilon_{ijk} \sim N(0, \sigma^2)$$

Cell means model

$$Y_{ijk} = \mu_{ij} + \epsilon_{ijk}$$

- main effect A: $\alpha_i = \mu_{i.} - \mu_{..}$
- main effect B: $\beta_j = \mu_{.j} - \mu_{..}$
- interaction effect: $(\alpha\beta)_{ij} = (\mu_{ij} - \mu_{..}) - (\mu_{i.} - \mu_{..}) - (\mu_{.j} - \mu_{..}) = \mu_{ij} - \mu_{i.} - \mu_{.j} + \mu_{..}$

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Interaction contrasts - multi-centre clinical trial

product type interaction contrast as a direct (Kronecker) product of the two one-way contrasts ($\boldsymbol{C_{AB}} = \boldsymbol{C_B} \otimes \boldsymbol{C_A}$).

Example for a balanced design with $I = 2$ and $J = 5$:

Define: $\mu = (\mu_{Dose(1)}, \mu_{Placebo(1)}, \mu_{Dose(2)}, \mu_{Placebo(2)}, \cdots, \mu_{Dose(5)}, \mu_{Placebo(5)})$

$$\boldsymbol{C_{Treatment}} = \begin{pmatrix} 1 & -1 \end{pmatrix} \qquad \boldsymbol{C_{Centre}} = \begin{pmatrix} 0.8 & -0.2 & -0.2 & -0.2 & -0.2 \\ -0.2 & 0.8 & -0.2 & -0.2 & -0.2 \\ -0.2 & -0.2 & 0.8 & -0.2 & -0.2 \\ -0.2 & -0.2 & -0.2 & 0.8 & -0.2 \\ -0.2 & -0.2 & -0.2 & -0.2 & 0.8 \end{pmatrix},$$

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Each contrast compares a centre with the grand mean of all centres.

$\Rightarrow$ No distinction between quantitative and qualitative interaction

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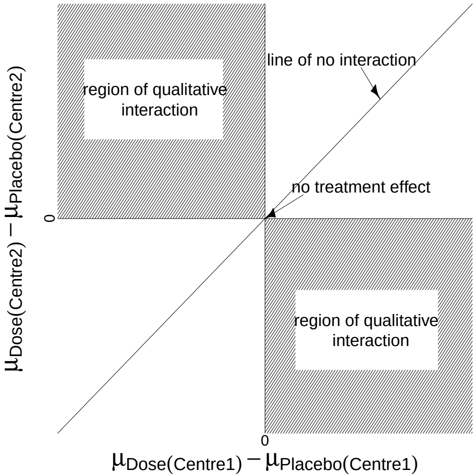
Parameter space for treatment effects



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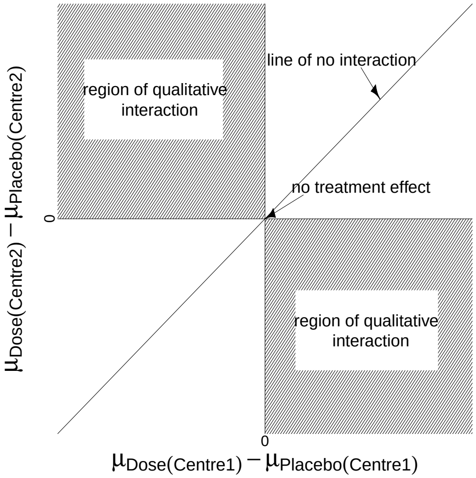

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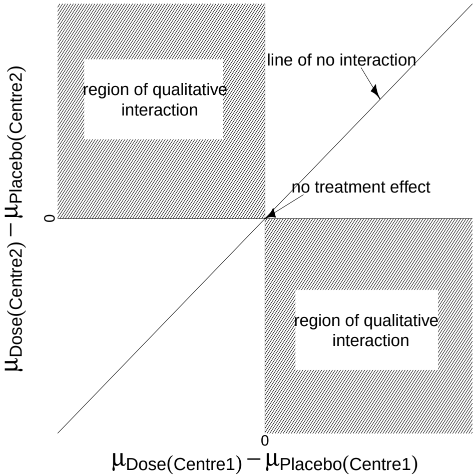

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Simultaneous inference to test for qualitative interaction

Interest is in simultaneous estimation of $l = 1, \ldots, L$ ratios of treatment effects

$$\gamma_l = \frac{\mathbf{n_l'}\boldsymbol{\mu}}{\mathbf{d_l'}\boldsymbol{\mu}}$$

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$\mathbf{n_l'}$ and $\mathbf{d_l'}$ user defined contrast vectors.

The goal is to simultaneous test the L hypotheses:

$$H_{0_l} : \gamma_l \geq 0 \qquad H_{A_l} : \gamma_l < 0$$

Methods for adjusted p-values and simultaneous confidence intervals are given in Dilba et al. (2006) and are implemented in the R package `mratios`.

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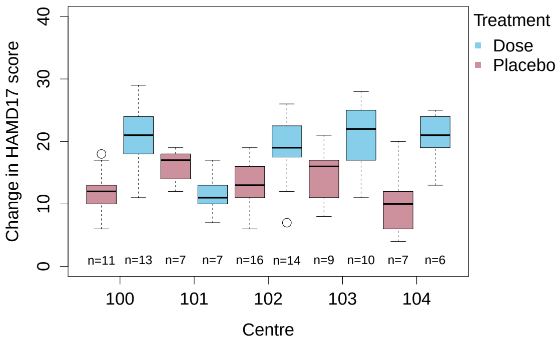
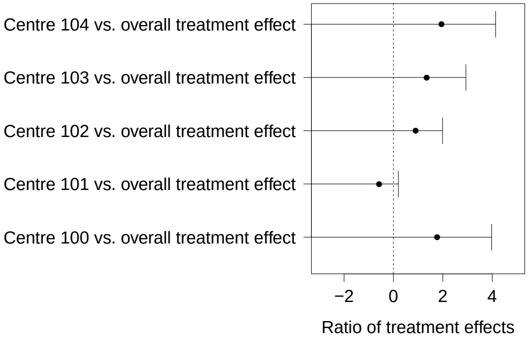
Example - Results



	Df	Sum Sq	Mean Sq	F value	Pr(>F)
DRUG	1	888.04	888.04	40.07	<.0001
CENTER	4	87.14	21.78	0.98	0.4209
DRUG:CENTER	4	507.45	126.86	5.72	0.0004
Residuals	90	1994.38	22.16		

Evaluated example using ratios of differences

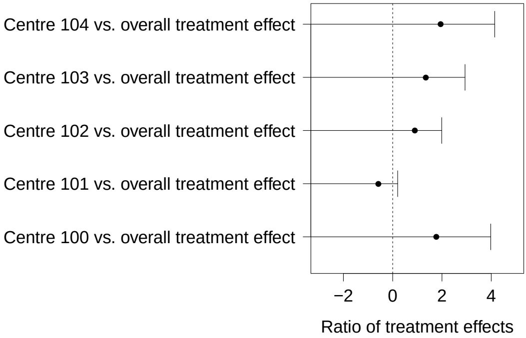
Hypothesis	Estimate	adj. p-value
Centre 100 treatment effect/Overall treatment effect < 0	1.77	1
Centre 101 treatment effect/Overall treatment effect < 0	-0.58	0.187
Centre 102 treatment effect/Overall treatment effect < 0	0.90	1
Centre 103 treatment effect/Overall treatment effect < 0	1.35	1
Centre 104 treatment effect/Overall treatment effect < 0	1.95	1



⇒ No significant qualitative interaction

Evaluated example using ratios of differences

Hypothesis	Estimate	adj. p-value
Centre 100 treatment effect/Overall treatment effect < 0	1.77	1
Centre 101 treatment effect/Overall treatment effect < 0	-0.58	0.187
Centre 102 treatment effect/Overall treatment effect < 0	0.90	1
Centre 103 treatment effect/Overall treatment effect < 0	1.35	1
Centre 104 treatment effect/Overall treatment effect < 0	1.95	1



$\Rightarrow$ No significant qualitative interaction

Summary

Using interaction contrasts provides:

- detection of the source of interaction
- taking the experimental structure into account
- simultaneous confidence intervals to evaluate the direction and magnitude of an interaction
- distinction between **quantitative** and **qualitative** interactions using ratios of differences

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