Network meta-analysis in an ANOVA framework

Hans-Peter Piepho

Biostatistics Unit
Universität Hohenheim
Germany

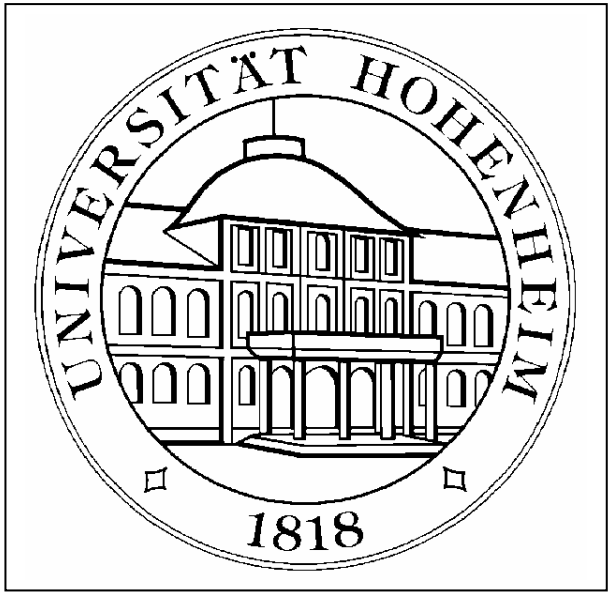


Table of contents

1. Introduction

Meta-analysis

- Combine results from several trials / studies
- Mostly clinical trials
- Individual patient data (IPD) or treatment summaries
- Two modelling approaches:

  (1) Model for contrasts with baseline treatment per trial

  (2) Two-way ANOVA model for trial × treatment classification
- Option (1) most common; but we think option (2) is much simpler

⇒ compare both modelling options

⇒ investigate when they are equivalent

1. Introduction

Table 1. Smoking Cessation Rates (r_{ik}/n_{ik}) (Hasselblad 1998)

Baseline	Study number	No contact (A)	Self-help (B)	Individual counseling (C)	Group counseling (D)
$G_{(A)}$	1	9/140		23/140	10/138
$G_{(B)}$	2		11/78	12/85	29/170
$G_{(A)}$	3	79/702	77/694		
	4	18/671	21/535		
	5	8/116	19/146		
	6	75/731		363/714	
	7	2/106		9/205	
	8	58/549		237/1,561	
	9	0/33		9/48	
	10	3/100		31/98	
	11	1/31		26/95	
	12	6/39		17/77	
	13	95/1,107		134/1,031	
	14	15/187		35/504	
	15	78/584		73/675	
	16	69/1,177		54/888	
	17	64/642		107/761	
	18	5/62		8/90	
	19	20/234		34/237	
	20	0/20			9/20
$G_{(B)}$	21		20/49	16/43	
	22		7/66		32/127
$G_{(C)}$	23			12/76	20/74
	24			9/55	3/26

Example 1:
Lu & Ades (2006) JASA

1. Introduction

Network meta-analysis

- More than two treatments tested in combined trials
- Need to combine direct and indirect evidence on treatment comparisons

Example 1:

- Direct comparison: Trials *A* vs *B*
- Indirect comparison: Trials *A* vs *C* and *B* vs *C*

- Other names:

  Mixed-treatment comparisons (MTC)

  Mixed-treatment meta-analysis (MTM)

1. Introduction

Table 1. Smoking Cessation Rates (r_{ik}/n_{ik}) (Hasselblad 1998)

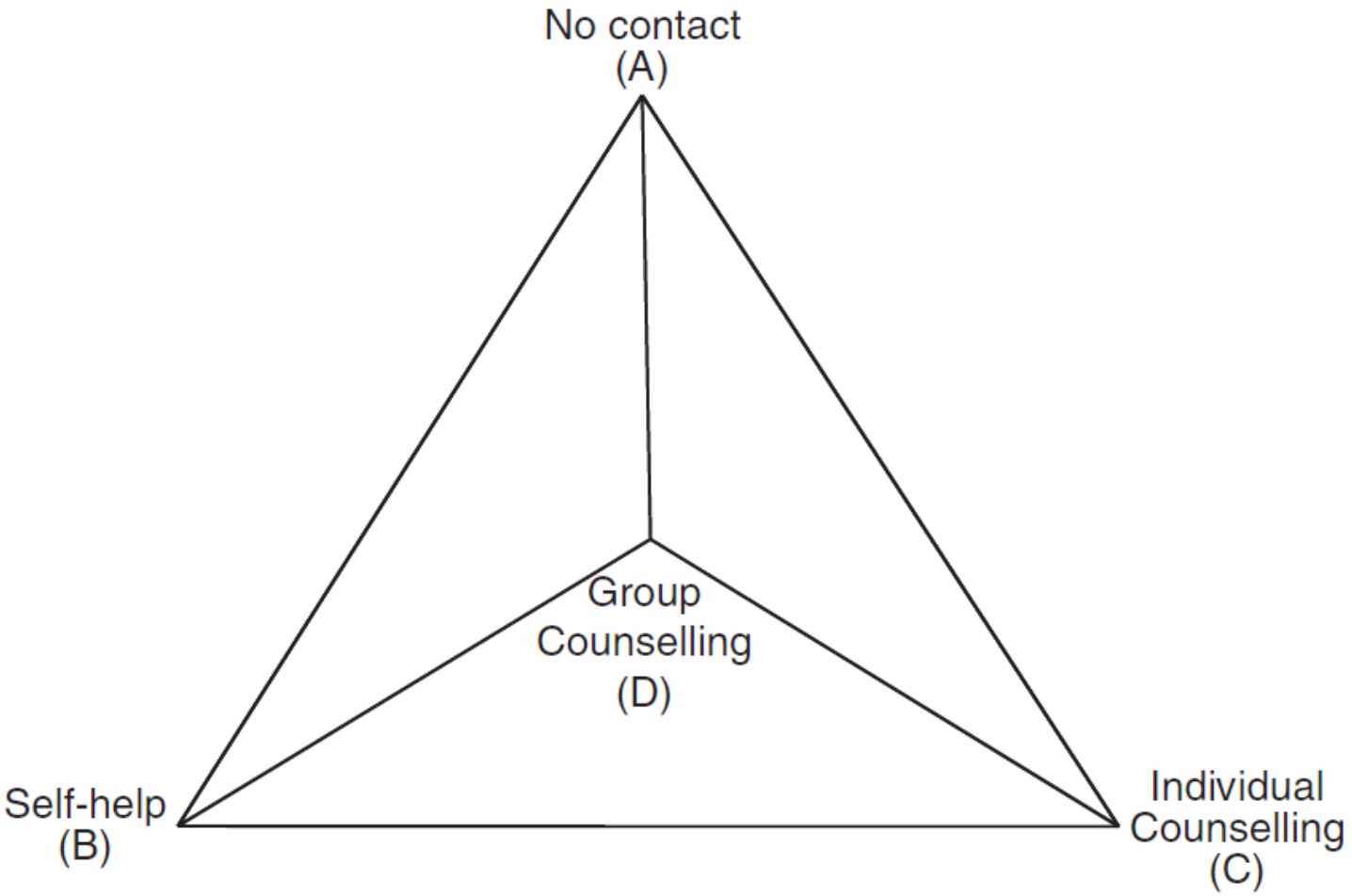
Baseline	Study number	No contact (A)	Self-help (B)	Individual counseling (C)	Group counseling (D)
$G_{(A)}$	1	9/140		23/140	10/138
$G_{(B)}$	2		11/78	12/85	29/170
$G_{(A)}$	3	79/702	77/694		
	4	18/671	21/535		
	5	8/116	19/146		
	6	75/731		363/714	
	7	2/106		9/205	
	8	58/549		237/1,561	
	9	0/33		9/48	
	10	3/100		31/98	
	11	1/31		26/95	
	12	6/39		17/77	
	13	95/1,107		134/1,031	
	14	15/187		35/504	
	15	78/584		73/675	
	16	69/1,177		54/888	
	17	64/642		107/761	
	18	5/62		8/90	
	19	20/234		34/237	
	20	0/20			9/20
$G_{(B)}$	21		20/49	16/43	
	22		7/66		32/127
$G_{(C)}$	23			12/76	20/74
	24			9/55	3/26

Direct comparison (A vs B)

Indirect comparison (via C)

Example 1:
Lu and Ades (2006)

1. Introduction

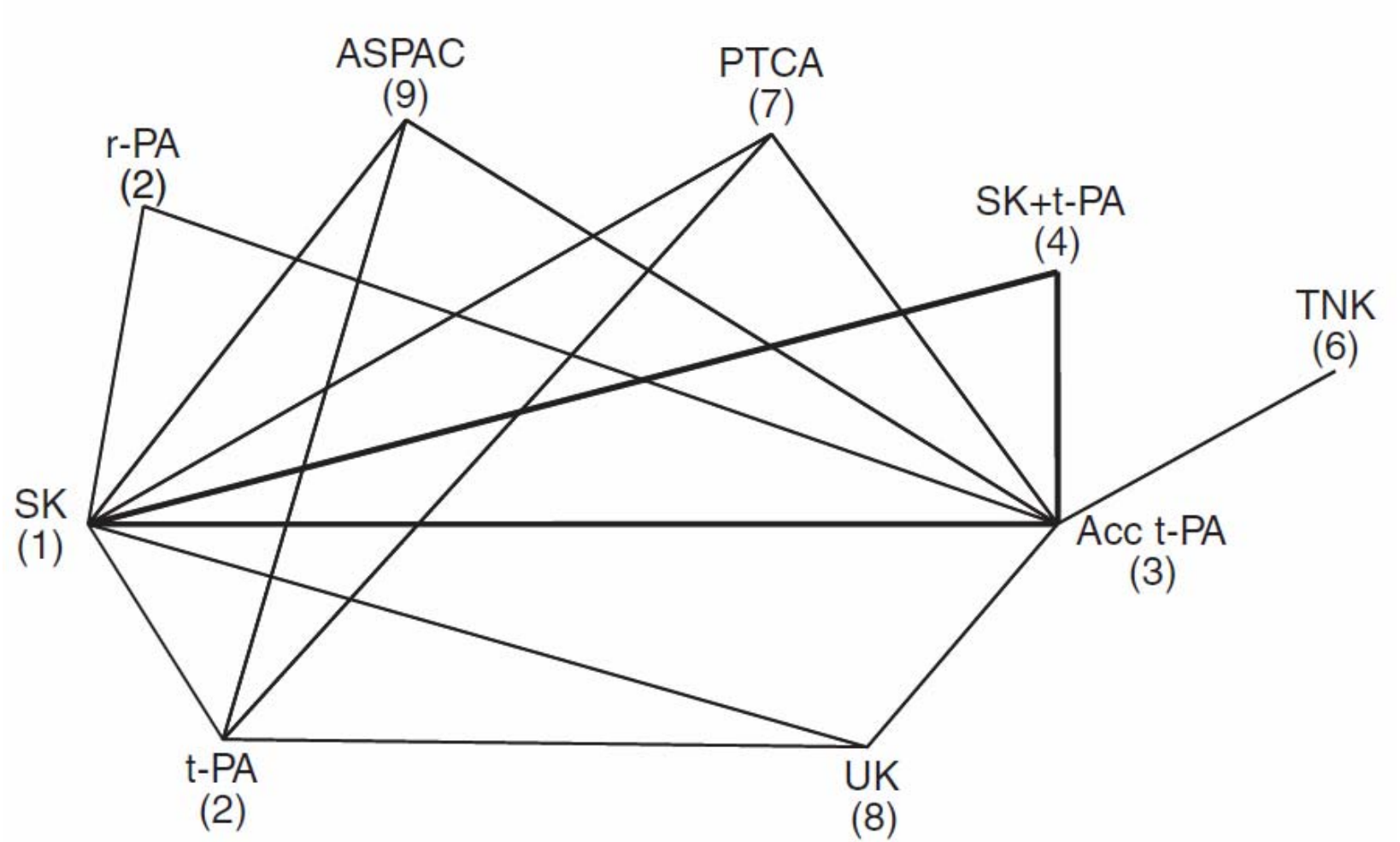


(Dias et al., 2010)

Undirected graph: Vertices = treatments

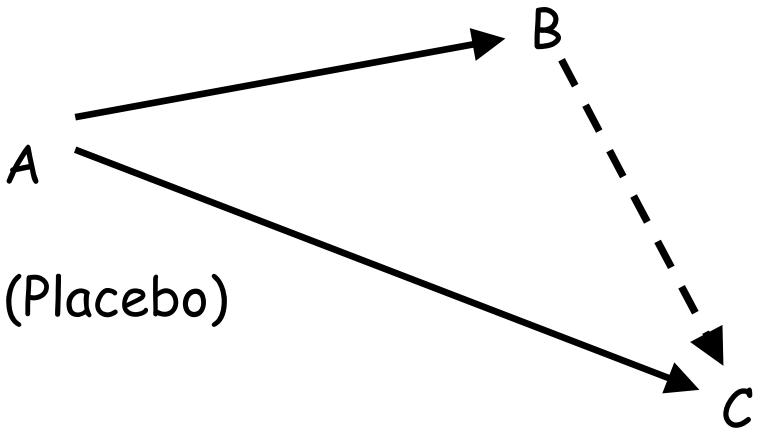
Edges = direct comparisons

1. Introduction



Example 2: Trombolytics data (Dias et al., 2010), nine treatments, 50 trials, response = mortalities (binomial)

1. Introduction



? Indirect comparison

Comparison	Mean difference (contrast)
B vs A	-0.34
C vs A	-0.19

$$MD_{BC} = MD_{BA} - MD_{CA} = -0.34 + 0.19 = -0.15$$

1. Introduction

Combining direct and indirect evidence

- Inverse variance method
- Each estimate of mean difference (MD) is 'weighted' by the inverse of its variance
- This leads to a 'mixed' result:

$$\text{'mixed } MD\text{'} = \frac{\frac{1}{\text{var}_{direct}} MD_{direct} + \frac{1}{\text{var}_{indirect}} MD_{indirect}}{\frac{1}{\text{var}_{direct}} + \frac{1}{\text{var}_{indirect}}}$$

(Georgia Salanti, Workshop Zurich 2011)

1. Introduction

Parallels with multi-environment trials (MET)

- Incomplete genotype × environment trials

  (treatments = genotypes, environments = trials, studies)

- Interested in genotype means across environments

- Heterogeneity between environments ⇒ genotype-environment interaction

- Modelling variance-covariance structure for heterogeneity
  ⇒ variance-covariance structures for genotype-environment interaction
  ⇒ variances and covariances not constant between genotypes
  ⇒ stability analysis, analysis of phenotypic stability

- Also similar to incomplete block designs

2. Modelling individual patient data

Two modelling approaches

(1) Contrast-based models

- relative treatment effects compared to baseline (log relative risk, log odds ratio, mean difference)
- Models for contrasts

(2) Arm-based models

- absolute treatment effects (log risk, log odds, treatment means)
- Analysis-of-variance (ANOVA) models for factors study and treatment

2. Modelling individual patient data

Linear predictors for two treatments *A* and *B*

A = baseline treatment

B = new medication

A: $\eta = \mu$

B: $\eta = \mu + d_{AB}$

μ = baseline effect for the trial

d_{AB} = effect of treatment *B* compared to baseline *A*

2. Modelling individual patient data

Linear predictors for three treatments A, B and C

(1) When A is baseline (A vs B and A vs C trials)

A: $\eta = \mu$

B: $\eta = \mu + d_{AB}$

C: $\eta = \mu + d_{AC}$

(2) When B is baseline (B vs C trials)

B: $\eta = \mu$

C: $\eta = \mu + d_{BC}$

2. Modelling individual patient data

Basic parameters and functional parameters

Basic parameters: d_{AB} , d_{AC}

Functional parameters: $d_{BC} = d_{AC} - d_{AB}$

(2) When B is baseline (B vs C trials)

B: $\eta = \mu$

C: $\eta = \mu + d_{AC} - d_{AB}$

2. Modelling individual patient data

The linear predictor for the k-th treatment in the i-th trial is given by

$$\eta_{ik} = \mu_i + U_{ik}\delta_{ib(i)k}$$

where

μ_i = baseline parameter in the i-th trial

= expected value of the baseline treatment $b(i)$ in the i-th trial

$\delta_{ib(i)k}$ = random effect of treatment k versus baseline $b(i)$ in the i-th trial

$$U_{ik} = \begin{cases} 1, & k \neq b(i) \\ 0, & k = b(i) \end{cases}$$

(Lu & Ades, 2006)

2. Modelling individual patient data

Random effects for baseline contrasts:

$$E\left(\delta_{ib(i)k}\right) = d_{b(i)k}$$

$d_{b(i)k}$ = treatment effects to be estimated across trials

Fixed effects-part of the model:

$$E\left(\eta_{ik}\right) = \mu_i + U_{ik} d_{b(i)k} \; .$$

2. Modelling individual patient data

Heterogeneity between trials

$\Rightarrow$ Variance-covariance structure for $\delta_{ib(i)k}$ in i-th trial, e.g.

$$\mathrm{var}\left\{\delta_{ib(i)k}\right\} = \left(I_{n(i)-1} + J_{n(i)-1}\right)\tau^2 / 2$$

where

I_n = n-dimensional identity matrix

J_n = $n \times n$ matrix of ones

τ^2 = a variance component for between-trial heterogeneity

$n(i)$ = number of treatments in the i-th trial

(Higgins & Whitehead, 1996; Lu & Ades, 2004)

2. Modelling individual patient data

Conditionally on the linear predictor, the observation y_{ijk} on the j-th individual in the i-th trial for the k-th treatment has expected value

$$E\left(y_{ijk} \mid \eta_{ib(i)k}\right) = g^{-1}\left(\eta_{ib(i)k}\right)$$

where $g(.)$ is a suitable link function

$\Rightarrow$ Generalized linear mixed model (GLMM)

$\Rightarrow$ use adaptive Gaussian quadrature (Pinheiro & Bates, 1995)

2. Modelling individual patient data

An alternative linear predictor

$$\eta_{ik} = \beta_i + \alpha_k + u_{ik}$$

where

β_i = fixed main effect of the i-th trial,

α_k = main effect of the k-th treatment, and

u_{ik} = random effect associated with η_{ik}

$$E(\eta_{ik}) = \beta_i + \alpha_k$$

2. Modelling individual patient data

Variance-covariance structure for heterogeneity

Let u_i = vector of random effects u_{ik} for the i-th trial

Then

$E(u_i) = 0$ and

$\text{var}(u_i) = \Sigma_i$

2. Modelling individual patient data

Relation between baseline contrast model and the two-way model

$$\eta_{ik} = \beta_i + \alpha_k + u_{ik}$$

$$\eta_{ik} = \underbrace{\beta_i + \alpha_{b(i)} + u_{ib(i)}}_{\mu_i} + \underbrace{\alpha_k - \alpha_{b(i)} + u_{ik} - u_{ib(i)}}_{\delta_{ib(i)k}} = \mu_i + U_{ik}\delta_{ib(i)k}$$

$$\mu_i = \beta_i + \alpha_{b(i)} + u_{ib(i)} \qquad \delta_{ib(i)k} = \alpha_k - \alpha_{b(i)} + \tilde{u}_{ik}$$

where

$\tilde{u}_{ik} = u_{ik} - u_{ib(i)}$ and $E\left(\delta_{ib(i)k}\right) = d_{b(i)k} = \alpha_k - \alpha_{b(i)}$

$b(i)$ = baseline treatment in *i*-th trial

2. Modelling individual patient data

Re-parameterized model has random effects:

$u_{ib(i)}$ and $\widetilde{u}_{ik} = u_{ik} - u_{ib(i)}$ $\left[k \neq b(i)\right]$

Transition from two-way model to baseline contrast model:

Conditioning on $u_{ib(i)}$!!

$\Rightarrow$ baseline treatment has no variance in i-th trial

2. Modelling individual patient data

Let

- u_i = vector of random effects u_{ik} for the i-th trial
- $\widetilde{u}_i$ = vector of random effects $\widetilde{u}_{ik}$ for the i-th trial
- $\mathrm{var}(u_i) = \Sigma_i$ and (without loss of generality) that $b(i) = 1$

Then

$$\mathrm{var}(\widetilde{u}_i) = \widetilde{\Sigma}_i = D_i \Sigma_i D_i^T$$

where $D_i = \begin{pmatrix} -1_{n(i)-1} & I_{n(i)-1} \end{pmatrix}$ is the matrix generating all contrasts relative to the baseline treatment in the i-th trial

2. Modelling individual patient data

Examples for variance-covariance structure of $\tilde{u}_i$

Constant variance model:

$$\Sigma_i = I_{n(i)}\sigma_u^2 \Rightarrow \tilde{\Sigma}_i = \left(I_{n(i)-1} + J_{n(i)-1}\right)\sigma_u^2$$

Diagonal model:

$$\Sigma_i = \mathrm{diag}\left(\sigma_1^2, \sigma_2^2, ..., \sigma_n^2\right) \Rightarrow \tilde{\Sigma}_i = \mathrm{diag}\left(\sigma_2^2, \sigma_3^2, ..., \sigma_n^2\right) + J_{n-1}\sigma_1^2$$

Factor-analytic model (one factor):

$\Sigma_i = \lambda\lambda^T$, where $\lambda^T = \left(\lambda_1, \lambda_2, ...\right) \Rightarrow \tilde{\Sigma}_i = \tilde{\lambda}\tilde{\lambda}^T$ with $\tilde{\lambda}^T = \left(\lambda_2 - \lambda_1, \lambda_3 - \lambda_1, ...\right)$

Unstructured model:

Maximum $n_i\left(n_i - 1\right)/2$ free parameters for $\tilde{\Sigma}_i$

2. Modelling individual patient data

Implement conditional model for $\widetilde{\Sigma}_i$ via unconditional model for Σ_i

$$\widetilde{u}_{ik} = u_{ik} - u_{ib(i)} \Rightarrow \widetilde{u}_{ik} = \sum_{k=1}^{n} x_{ik} u_{ik}$$

Example 1: Smoking cessation data

		Dummy variables			
Baseline treatment	Treatment	x_{i1}	x_{i2}	x_{i3}	x_{i4}
A	A	0	0	0	0
	B	–1	1	0	0
	C	–1	0	1	0
	D	–1	0	0	1

2. Modelling individual patient data

Baseline treatment	Treatment	Dummy variables x_{i1}	x_{i2}	x_{i3}	x_{i4}
B	A	1	–1	0	0
	B	0	0	0	0
	C	0	–1	1	0
	D	0	–1	0	1
C	A	1	0	–1	0
	B	0	1	–1	0
	C	0	0	0	0
	D	0	0	–1	1

2. Modelling individual patient data

Equivalence of conditional and unconditional model

Conditional model:

$\mathrm{var}(\eta_i \mid u_{i1}) = 0 \oplus \widetilde{\Sigma}_i$, where $\eta_i^T = (\eta_{i1}, \eta_{i2}, \ldots)$ and $b(i) = 1$

Unconditional model:

$\mathrm{var}(\eta_i) = \Sigma_i$

Both models are equivalent in the sense that for any contrast $c^T \eta_i$

$$\mathrm{var}(c^T \eta_i \mid u_{i1}) = c^T (0 \oplus \widetilde{\Sigma}_i) c = c^T \Sigma_i c = \mathrm{var}(c^T \eta_i)$$

2. Modelling individual patient data

Equivalence (continued)

$$\mathrm{var}\left(c^T \eta_i \mid u_{i1}\right) = c^T \left(0 \oplus \widetilde{\Sigma}_i\right) c = c^T \Sigma_i c = \mathrm{var}\left(c^T \eta_i\right)$$

To see this, let $c^T = \left(c_1, c_2^T\right)$, where c_1 is the first element of c and c_2 is the remainder. Then $c^T \left(0 \oplus \widetilde{\Sigma}_i\right) c = c_2^T \widetilde{\Sigma}_i c_2 = c_2^T D_i \Sigma_i D_i^T c_2 = \left(c_1, c_2^T\right) \Sigma_i \left(c_1, c_2^T\right)^T$.

2. Modelling individual patient data

Equivalence (continued)

- Models fully equivalent with identity link and normal distribution
- Models not equivalent with other link functions and distributions

Example 1:

- Smoking cessation data
- Changed baseline treatment in some trials
- Used adaptive Gaussian quadrature (GLIMMIX procedure of SAS)
- $\Sigma_i = I_{n(i)}\sigma_u^2 \Rightarrow \widetilde{\Sigma}_i = \left(I_{n(i)-1} + J_{n(i)-1}\right)\sigma_u^2$

2. Modelling individual patient data

Table 1: Smoking cessation data (Example 1)

	Estimate	Standard error
Baseline contrasts using original baseline treatments (*A*)		
d_{AB}	0.4192	0.2959
d_{AC}	0.7407	0.1738
d_{AD}	0.9484	0.3292
Baseline contrasts taking *B* as baseline treatment in trials 3-5		
d_{AB}	0.4415	0.2982
d_{AC}	0.7449	0.1751
d_{AD}	0.9580	0.3315

2. Modelling individual patient data

Table 1: Smoking cessation data (Example 1 continued)

	Estimate	Standard error
Baseline contrasts (2) taking *C* as baseline treatment in trials 6-15		
d_{AB}	0.4407	0.3154
d_{AC}	0.7773	0.1868
d_{AD}	0.9821	0.3493
Two-way model estimates		
$\alpha_B - \alpha_A$	0.3865	0.2387
$\alpha_C - \alpha_A$	0.7166	0.1374
$\alpha_D - \alpha_A$	0.9199	0.2720

2. Modelling individual patient data

Table 2: Smoking cessation data (Example 1 continued); constant variance model for u_{ij}

	Estimate	Standard error
Adjusted means $		
$\alpha_A + \overline{\beta}_\bullet$	-2.4235 a	0.1107
$\alpha_B + \overline{\beta}_\bullet$	-2.0366 ab	0.2106
$\alpha_C + \overline{\beta}_\bullet$	-1.7068 b	0.0971
$\alpha_D + \overline{\beta}_\bullet$	-1.5047 b	0.2273

$ Adjusted means (computed on the logit scale) followed by a common letter are not significantly different at $\alpha = 5\%$ according to a Wald-test.

2. Modelling individual patient data

Table 3: Analysis of smoking cessation data based on two-way model.

Parameter	Estimate	Standard error	AIC
Constant variance:			
σ_u^2	0.09068	0.02810	391.20
Diagonal (treatment-specific variance):			
$\sigma_{u(1)}^2$	0.5599	0.2626	365.91
$\sigma_{u(2)}^2$	0	-	
$\sigma_{u(3)}^2$	0	-	
$\sigma_{u(4)}^2$	0.1292	0.2411	

2. Modelling individual patient data

Table 4: Analysis of smoking cessation data based on two-way model.

Parameter	Estimate	Standard error	AIC
Constant variance:			
σ_u^2	0.09068	0.02810	391.20
Factor-analytic:			
λ_1	0.4969	0.1736	364.02
λ_2	0	-	
λ_3	-0.2423	0.1157	
λ_4	0.05856	0.1985	

2. Modelling individual patient data

Fitting the FA model with SAS

```
proc glimmix data=a maxopt=100
             method=quad(qpoints=6);
class study trt;
model m/n = study trt
                      / ddfm=none solution chisq;
random trt / sub=study type=fa1(1);
lsmeans trt / pdiff lines;
run;
```

2. Modelling individual patient data

Study effects fixed or random?

Study effects fixed

- Inference based on within-study information
- Inference Protected by randomization
- Obeys principle of concurrent control
- Can only assess relative treatment effects

Study effects random

- Recovery of inter-study information
- Need to assume that studies in NMA are random sample from some urne
- Can also assess absolute treatment effects

2. Modelling individual patient data

Recent discussion on arm-based (AB) versus contrast-based (CB) models

- The discussion focusses much on estimation of relative treatment effects (CB) versus absolute treatment effects (AB)
- I think this becomes a non-issue when a study main effect is included in the AB model
- The main issue is whether or not to recover the inter-study information, i.e. whether the study main effect is taken as fixed or random

Dias S, Ades AE 2016 Absolute or relative effects? Arm-based synthesis of trial data (Commentary). Research Synthesis Methods 7, 23-28.

Hong, H., Chu, H., Zhang, J., Carlin, B.P. 2016 Rejoinder to the discussion of "a Bayesian missing data framework for generalized multiple outcome mixed treatment comparisons," by S. Dias and A.E. Ades. Research Synthesis Methods 7, 29-33.

3. Treatment summaries and contrasts thereof

Notation for treatment summaries

- s_i = vector of treatment summaries in *i*-th trial (means, log odds, etc)
- sorted such that the baseline for the *i*-th trial is in the first position
- Pairwise contrasts of all treatments to baseline are computed by

$$z_i = D_i s_i ,$$

where $D_i = \left(-1_{n(i)-1} \quad I_{n(i)-1}\right)$ and $n(i)$ = number of treatments in *i*-th trial

- Stacking trials $i = 1,2,...,m$, we may write

$$z = Ds ,$$

where $z^T = \left(z_1^T, z_2^T, ..., z_m^T\right)$, $s^T = \left(s_1^T, s_2^T, ..., s_m^T\right)$ and $D = \bigoplus_{i=1}^{m} D_i$.

3. Treatment summaries and contrasts thereof

Basic model for treatment summaries

$$s = \eta + e \,,$$

where

$\eta^T = \left(\eta_1^T, \eta_2^T, ..., \eta_m^T\right)$ is a vector holding linear predictors η_{ik}

e = estimation errors associated with summary measures s

$$e \sim N\left(0, R\right)$$

$R = \bigoplus_{i=1}^{m} R_i$, where $R_i = \mathrm{var}\left(s_i \mid \eta_i\right)$

3. Treatment summaries and contrasts thereof

Two-way model for linear predictor vector

$$\eta = X_\beta \beta + X_\alpha \alpha + u \,,$$

where

β = fixed trial main effects with design matrix X_β

α = fixed treatment main effects with design matrix X_α

u = random between-trial effects with $u \sim N(0, \Sigma)$ and $\Sigma = \bigoplus_{i=1}^{m} \Sigma_i$

Hence,

$E(s) = E(\eta) = X_\beta \beta + X_\alpha \alpha$ and

$\mathrm{var}(s) = V = \Sigma + R$

3. Treatment summaries and contrasts thereof

Sweeping out trial main effects

$z^* = \overline{P}s$,

where $\overline{P} = I - P$ and $P = X_\beta \left(X_\beta^T X_\beta \right)^- X_\beta^T$

This is equivalent to computing contrasts to baseline per trial: $z = Ds$

$\Leftrightarrow \overline{P} = D^T \left(DD^T \right)^{-1} D$ and hence $z^* = D^T \left(DD^T \right)^{-1} z$

Normal equations for $z^* = \overline{P}s$ yield same solution for γ as those for s

Proof in De Hoog, Speed & Williams (1990)

3. Treatment summaries and contrasts thereof

Equivalence of REML estimates of variance components

REML

- operates on contrasts free of fixed effects
- is invariant to the choice of contrasts (Harville, 1977)

After sweeping out the trial effect β via $z = Ds$, the conditional and the unconditional variance-covariance models are identical:

$\mathrm{var}(z) = DVD^T = \widetilde{V}$, where $\widetilde{V} = \widetilde{\Sigma} + DRD^T$ and $\widetilde{\Sigma} = \bigoplus_{i=1}^{m} \widetilde{\Sigma}_i$.

$\Rightarrow$ **REML estimates of variance components coincide under both models**

3. Treatment summaries and contrasts thereof

Example 1 (continued)

- Empirical log-odds of treatment versus baseline

  $\Rightarrow$ baseline contrast on logit scale

- In case a treatment has no successes or failures, a correction factor of a half is added to both success and failure counts
- Compute error variance R of log-odds using GLM package
- Baseline treatment differs among trials
- Basic parameters d_{AB}, d_{AC} and d_{AD}
- Functional parameters $d_{BC} = d_{AC} - d_{AB}$, $d_{BD} = d_{AD} - d_{AB}$, $d_{CD} = d_{AD} - d_{AC}$

3. Treatment summaries and contrasts thereof

Test of global null hypothesis

- $H_0 : d_{AB} = d_{AC} = d_{AD} = 0 \Leftrightarrow H_0 : \gamma_A = \gamma_B = \gamma_C = \gamma_D$
- χ^2 = 4.62
- 3 numerator d.f.
- 21 denominator d.f.
- $p = 0.0124$

Both analyses identical!

3. Treatment summaries and contrasts thereof

Table 3: Summary measures analysis for smoking cessation data (REML). We assumed $\Sigma_i = I_{n(i)}\sigma_u^2$ for heterogeneity under the two-way model. This is equivalent to fitting $\widetilde{\Sigma}_i = \left(I_{n(i)-1} + J_{n(i)-1}\right)\sigma_u^2$ for the baseline-contrast model.

Contrast		Estimate	Standard error
Baseline contrasts §	Two-way model §		
d_{AB}	$\alpha_B - \alpha_A$	0.3978	0.3305
d_{AC}	$\alpha_C - \alpha_A$	0.7013	0.1972
d_{AD}	$\alpha_D - \alpha_A$	0.8642	0.3749

§ Results are identical for both analyses

3. Treatment summaries and contrasts thereof

Table 3 (continued)

Contrast		Estimate	Standard error
Baseline contrasts	Two-way model		
		Adjusted means $	
-	$\alpha_A + \overline{\beta}_\bullet$	-2.3792 a	0.1553
-	$\alpha_B + \overline{\beta}_\bullet$	-1.9815 ab	0.2886
-	$\alpha_C + \overline{\beta}_\bullet$	-1.6779 b	0.1352
-	$\alpha_D + \overline{\beta}_\bullet$	-1.5150 b	0.3100

$ Adjusted means followed by a common letter are not significantly different at $\alpha = 5\%$ according to a t-test using the Kenward-Roger (1997) method for degrees of freedom and variance adjustments

3. Treatment summaries and contrasts thereof

Take home message up to here

Compared:

- Baseline contrast model (conditional) $\eta_{ik} = \mu_i + U_{ik}\delta_{ib(i)k}$
- Two-way model (unconditional) $\eta_{ik} = \beta_i + \alpha_k + u_{ik}$

Full equivalence:

- Summary data
- Individual patient data with identity link and normal errors

Very similar results:

- All other cases
- But: Baseline contrast model is not invariant to choice of baseline!

4. Testing inconsistency

Example

- Trial network with three treatments (*A*, *B*, *C*)
- Three types of trial: *A* vs *B*, *A* vs *C* and *B* vs *C*
- Consider evidence on *B* vs *C*
- Need to combine direct and indirect evidence on treatment comparisons

  Direct comparison: Trials *B* vs *C*

  Indirect comparison: Trials *A* vs *B* and *A* vs *C*

- Inconsistency (incoherence):

  $\Rightarrow$ direct and indirect comparisons for *B* vs *C* do not agree

4. Testing inconsistency

Reasons for inconsistency

- A new drug may be tested on a population of patients, for which a standard drug did not show a satisfactory effect. The effect relative to a placebo in such a selected population may differ from the effect in a population that is not selected in this way.

- Inconsistency may also occur in open-label or imperfectly blinded trials (Lumley, 2002)

Other term

- Incoherence (Lumley, 2002)

4. Testing inconsistency

Inconsistency relation

- Assume that *B* is baseline treatment in trials *B* vs *C*
- Use functional parameter to model effect of *C* :

$$d_{BC} = d_{AC} - d_{AB}$$

- Modification in case of inconsistency :

$$d_{BC} = d_{AC} - d_{AB} + w_{ABC} \qquad \text{(inconsistency relation)}$$

$\Rightarrow$ use this for treatment C in trials where B is baseline

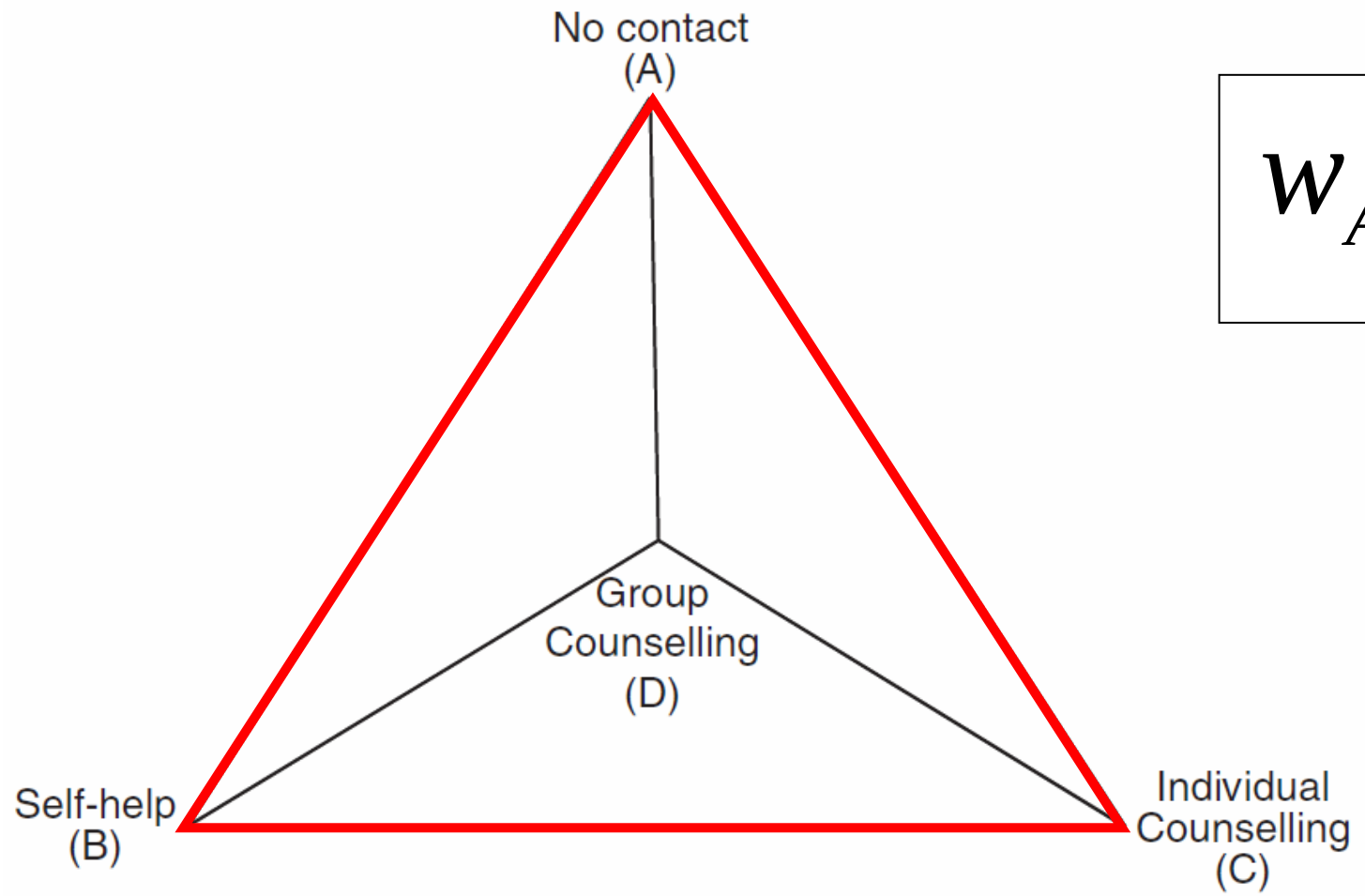
- If w_{ABC} is significant, inconsistency is established

4. Testing inconsistency

Loops

Network forms a closed loop between *A*, *B* and *C* in an undirected graph with vertices corresponding to treatments and edges representing direct comparisons between treatments (Lu and Ades, 2006)

4. Testing inconsistency



$$W_{ABC}$$

(Dias et al., 2010)

Undirected graph: Vertices = treatments

Edges = direct comparisons

4. Testing inconsistency

Using inconsistency factors is not easy!

- Modeling and interpretation of inconsistency become more difficult in the presence of multi-arm trials, and fitting the model may require careful programming
- The types of inconsistency that can be tested using inconsistency factors are not invariant to the choice of basic parameters
- "… we have not managed to find a general formula of a mechanical routine to count [the number of independent consistency relations]" (Lu & Ades, 2006)
- "In practice, an inconsistency model must be programmed very carefully, and the [number of independent inconsistencies] may have to be counted by hand." (Lu & Ades, 2006)

4. Testing inconsistency

Example:

- Structure {*A* vs *B*, *A* vs *C*, *A* vs *B* vs *C*}.
- This could be modeled by parameters (d_{AB}, d_{AC}), (d_{AB}, d_{BC}) , or (d_{AC}, d_{BC})
- The three parameterizations are essentially equivalent
- But: If (d_{AB}, d_{AC}) is chosen, then the inconsistency relation

  $d_{BC} = d_{AC} - d_{AB} + w_{ABC}$ cannot be used, because parameter d_{BC} is already implicitly defined by the parameterization of three-arm trial *A* vs *B* vs *C*.

(Lu & Ades, 2006)

4. Testing inconsistency

Here we keep it simple

- Node-splitting algorithm (Dias et al., 2010)

$\Rightarrow$ Use inconsistency factors one comparison at a time

$w_{AB} = 1$ for B when A & B in same trial

$w_{AB} = 0$ otherwise

(for details on more complex approaches see Lu & Ades, 2006)

4. Testing inconsistency

Table 4: Estimates for inconsistency factors (w_{AB}) when fitted one-at-a-time in two-way model trial-by-treatment for Thrombolytics data (Dias et al. 2010)

Treatments A	Treatments B	w_{AB}	Standard error	p-value	AIC§
1	2	-0.2038	0.2296	0.3749	593.79
1	3	0.09045	0.1040	0.3843	593.83
1	5	0.1206	0.1204	0.3164	593.58
1	7	-0.2678	0.2200	0.2235	593.09
1	8	-0.1799	0.5591	0.7476	594.48
1	9	-0.4050	0.2517	0.1076	591.94
2	7	-0.1291	0.3986	0.7461	594.48
2	8	-0.1352	0.4464	0.7619	594.49
2	9	-0.3005	0.3557	0.3983	593.87
3	4	-0.4568	0.6620	0.4902	594.10
3	5	-0.1206	0.1204	0.3164	593.58
3	7	0.2780	0.2091	0.1835	592.80
3	8	0.2559	0.4529	0.5720	594.26
3	9	1.1924	0.4094	0.0036	584.52

§ The two-way model without inconsistency factor has AIC = 592.59.

4. Testing inconsistency

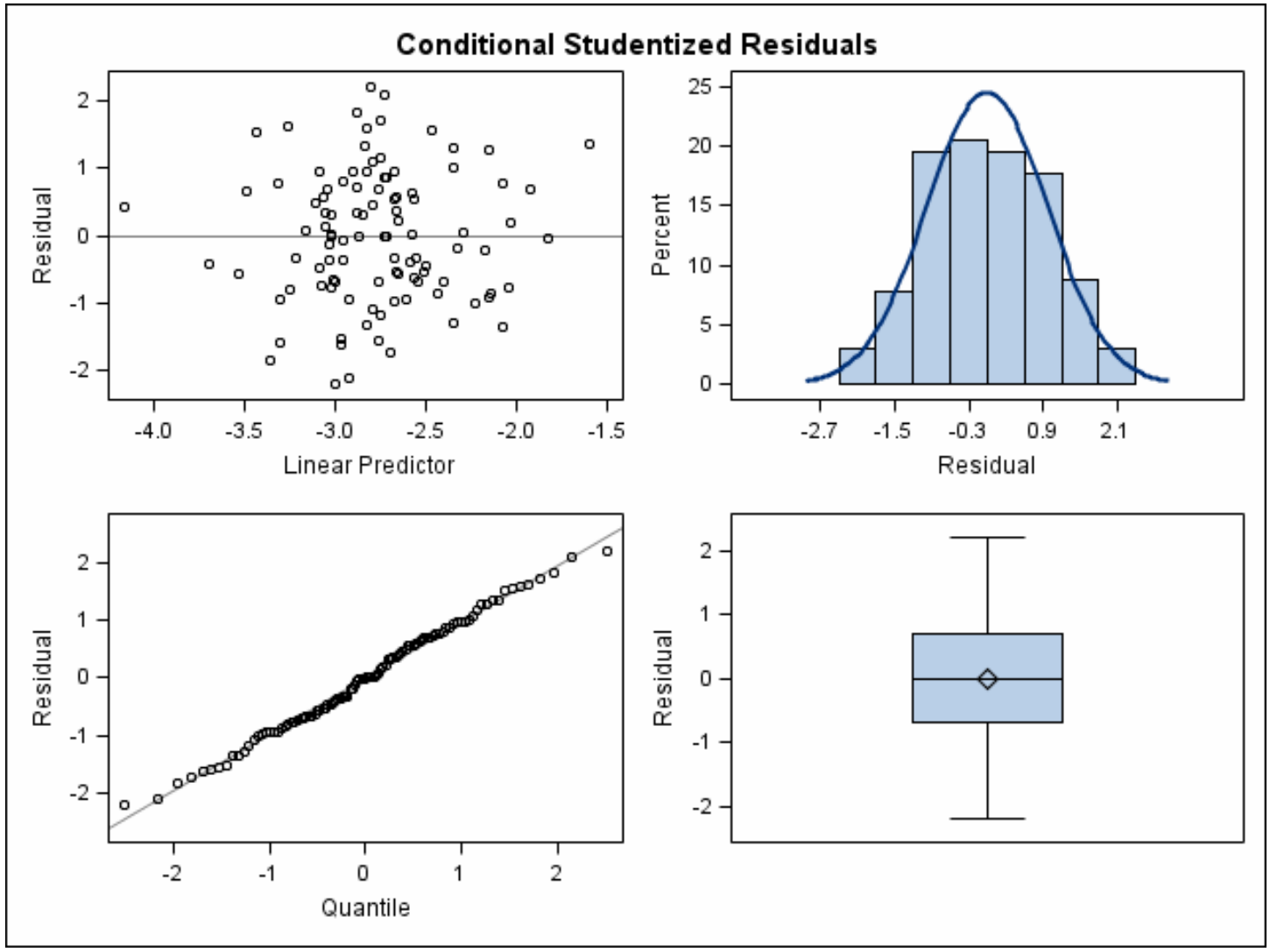


Fig. 1 Residual plots for two-way model (5) fitted to Thrombolytics data.

4. Testing inconsistency

Table 5: Observations with absolute studentized residuals > 2 in Thrombolytics data based on an additive model with main effects for trial and treatment.

Treatment	Trial	Cases	Sample size	Studentized residual
3	44	5	210	-2.20288
3	45	3	138	-2.09658
9	44	17	211	2.20280
9	45	13	147	2.09651

4. Testing inconsistency

Extending the notion of inconsistency

- Comparison of direct and indirect evidence on a contrast
- Presence of a new treatment in a trial may well modify the direct difference between *A* and *B* (Lu et al., 2011)

  $\Rightarrow$ need to compare direct comparisons from different types of trial

Idea

$\Rightarrow$ Test interaction in trial type $\times$ treatment classification

4. Testing inconsistency

	Treatment		
Trial type	*A*	*B*	*C*
1	X	X	
2	X		X
3		X	X

Fig. 2: Trial type × treatment classification for network {*A* vs *B*, *A* vs *C*, *B* vs *C*}.

- $n = 3$ treatments
- $m = 3$ trial types
- $c = 6$ cells filled

$\Rightarrow$ $c - n - m + 1 = 1$ d.f. for interaction trial type × treatment

4. Testing inconsistency

	Treatment		
Trial type	*A*	*B*	*C*
1	X	X	X
2	X	X	

Fig. 3: Trial type × treatment classification for network {*A* vs *B* vs *C*, *A* v. *B*}.

- $n = 3$ treatments
- $m = 2$ trial types
- $c = 5$ cells filled

$\Rightarrow \; c - n - m + 1 = 1$ d.f. for interaction trial type × treatment

4. Testing inconsistency

	Treatment		
Trial type	*A*	*B*	*C*
1	X	X	
2	X		X
3	X	X	X

Fig. 4: Trial type × treatment classification for network {*A* vs *B*, *A* vs *C*, *A* vs *B* vs *C*}.

- $n = 3$ treatments
- $m = 3$ trial types
- $c = 7$ cells filled

$\Rightarrow$ $c - n - m + 1 = 2$ d.f. for interaction trial type × treatment

4. Testing inconsistency

Model to test for inconsistency

$$\eta_{ijk} = \delta_j + \beta_{ij} + \alpha_k + (\alpha\delta)_{jk} + u_{ijk}$$

δ_j = fixed main effect for the j-th trial type

$(\alpha\delta)_{jk}$ = fixed effect for the interaction jk-th trial type $\times$ treatment

- Heterogeneity u_{ijk} can be separated from inconsistency $(\alpha\delta)_{jk}$ provided there are several trials per trial type (design)
- Heterogeneity is a property of variation among trials within the same trial type, while inconsistency affects variation between trial types

(Piepho, Madden and Williams, 2012, *Biometrics*)

4. Testing inconsistency

Example 2 (Thrombolytics data):

- Wald test for the trial type-treatment interaction in the
- $\chi^2 = 13.40$ on 10 d.f.; p = 0.2020
- Bonferroni-adjustment for test of inconsistency factor w_{39} : p = 0.0504
- In summary, there is overall good agreement between our analysis and that presented in Dias et al. (2010)

4. Testing inconsistency

Example 1 (Smoking cessation data):

- $c - n - m + 1 = 18 - 8 - 4 + 1 = 7$ degrees of freedom for inconsistency
- Adaptive Gaussian quadrature to fit a logit model by ML
- $\chi^2 = 5.81$ (p = 0.5627) with heterogeneity (u_{ik})
- $\chi^2 = 12.18$ (p = 0.0948) without heterogeneity

For comparison: Model with baseline contrasts (Lu et al., 2011)

- $\chi^2 = 4.71$ with heterogeneity
- $\chi^2 = 15.22$ without heterogeneity

4. Testing inconsistency

Example 3:

- Diabetes study of Senn et al. (2013)
- 26 trials
- 15 different designs (one three-arm trial)
- 10 treatments, mostly involving glucose-lowering agent added to baseline sulfonylurea treatment
- Continuous outcome: blood glucose change

4. Testing inconsistency

Factor symbol	Factor description
G	Group of trials, trial type, design
S	Study, trial
T	Treatment

Two-way ANOVA

$S \times T = S + T + S.T$

Model for inconsistency

$(G/S) \times T = G + G.S + T + G.T + G.S.T$

inconsistency heterogeneity

4. Testing inconsistency

Locating inconsistency by detachment of individual designs

Factor symbol	Factor description
D1	D1 = 1 for design 1, D1 = 0 otherwise
G	Group of trials, trial type, design
S	Study, trial
T	Treatment

$$(D1/G/S) \times T = D1 + D1.G + D1.G.S + T + D1.T + D1.G.T + D1.G.S.T$$

D1.T: detach design 1 — D1.G.T: inconsistency — D1.G.S.T: heterogeneity

4. Testing inconsistency

Design	Design no. (*k*)	No. of trials	D.f. for D*k*.T	Effect G.S.T fixed			
				D*k*.T		D*k*.G.T	
				Wald statistic	*p*-value	Wald statistic	*p*-value
acar:plac	1	1	1	0.09	0.7699	**22.45**	**0.0010**
acar:SUal	2	1	1	0.01	0.9091	**22.52**	**0.0010**
metf:plac	4	3	1	0.46	0.4976	**22.07**	**0.0012**
metf:acar:plac	5	1	2	0.15	0.9297	**22.39**	**0.0004**
metf:SUal	6	1	1	**15.02**	**0.0001**	7.52	0.2758
piog:plac	8	1	1	**5.28**	**0.0215**	**17.25**	**0.0084**
piog:metf	9	1	1	**5.40**	**0.0201**	**17.13**	**0.0088**
piog:rosi	10	1	1	0.05	0.8280	**22.49**	**0.0010**
rosi:plac	11	6	1	**6.24**	**0.0125**	**16.30**	**0.0122**
rosi:metf	12	2	1	0.01	0.9199	**22.52**	**0.0010**
rosi:SUal	13	1	1	**15.76**	**<0.0001**	6.77	0.3424

4. Testing inconsistency

Design	Design no. (*k*)	No. of trials	D.f. for D*k*.T	Effect G.S.T random			
				D*k*.T		D*k*.G.T	
				Wald statistic	*p*-value	Wald statistic	*p*-value
acar:plac	1	1	1	0.02	0.8889	2.25	0.8782
acar:SUal	2	1	1	0.01	0.9430	2.26	0.8765
metf:plac	4	3	1	0.04	0.8379	2.22	0.8814
metf:acar:plac	5	1	2	0.07	0.9634	2.18	0.8129
metf:SUal	6	1	1	1.63	0.2343	0.92	0.9835
piog:plac	8	1	1	0.43	0.5299	1.96	0.9062
piog:metf	9	1	1	0.43	0.5318	1.94	0.9081
piog:rosi	10	1	1	0.01	0.9065	2.27	0.8751
rosi:plac	11	6	1	0.74	0.4112	1.87	0.9168
rosi:metf	12	2	1	0.01	0.9276	2.25	0.8795
rosi:SUal	13	1	1	1.79	0.2146	0.66	0.9930

4. Testing inconsistency

Case-deletion plots and residual diagnostics

(1) Fit model (G/S) × T and compute G.T means

(2) Fit model G + T to G.T means

⇒ Drop a G.T mean and compute T means based on model G + T

⇒ Compute studentized residuals for G.T means from model G + T

4. Testing inconsistency

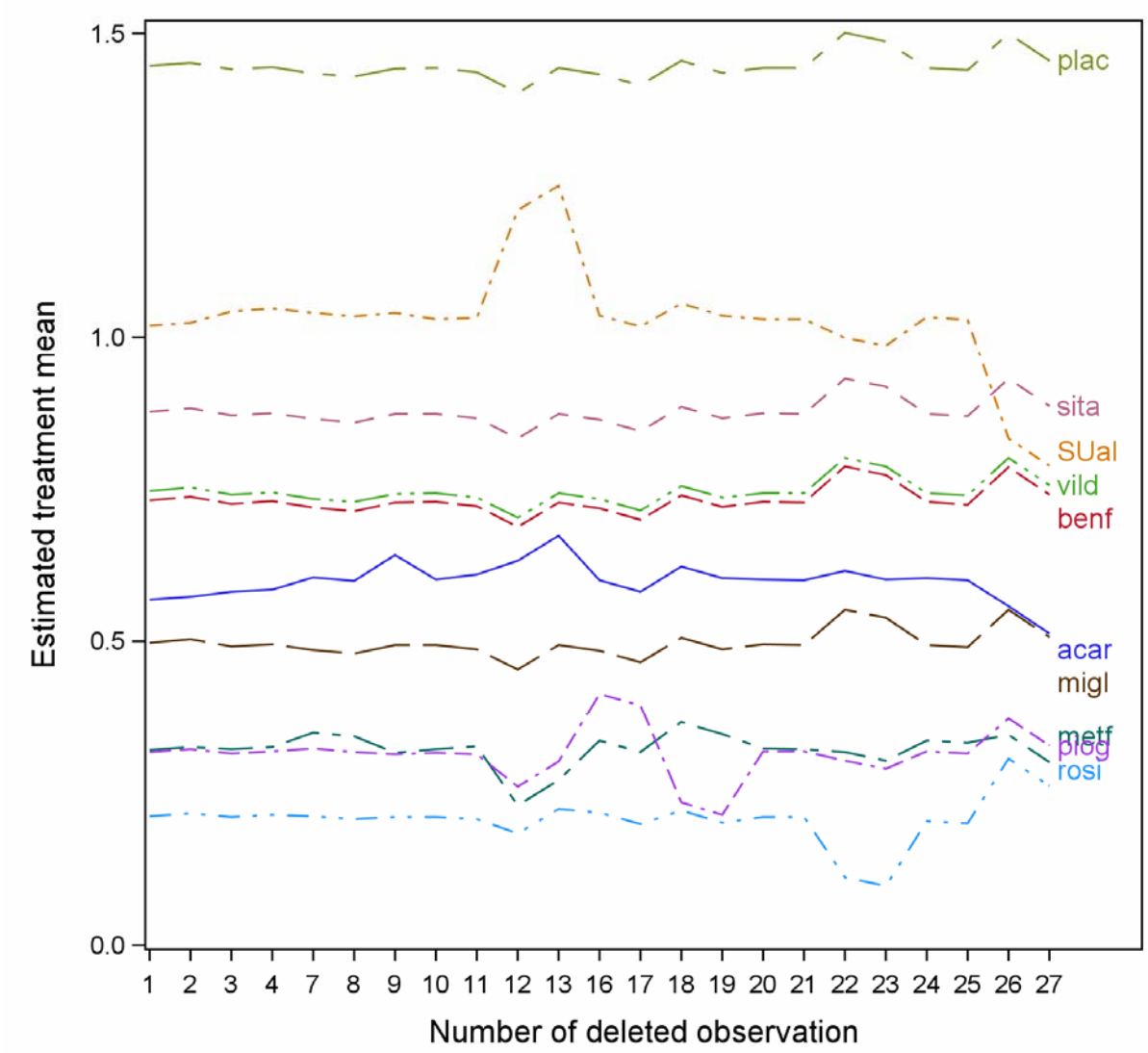


Fig. 1: Case-deletion plot of treatment means. Case-deletion means based on a fit of the model G + T using design × treatment mean estimates obtained from fitting model (2) taking heterogeneity G.S.T as random. To obtain diagnostics for treatment means (factor T), we prevented an intercept from being fitted and imposed a sum-to-zero restriction on the design effects G.

4. Testing inconsistency

Design	Observation	Treatment	G.S.T random	
			PRESS residual	Studentized res.
1	1	Acar	0.0785	0.1453
	2	plac	-0.0785	-0.1453
2	3	acar	0.0619	0.1056
	4	SUal	-0.0619	-0.1056
3	5	benf	.	.
	6	plac	.	.
4	7	metf	-0.0781	-0.2282
	8	plac	0.0781	0.2282
5	9	acar	-0.1507	-0.2601
	10	metf	0.0036	0.0075
	11	plac	0.1193	0.2273
6	**12**	**metf**	**0.6095**	**1.1614**
	13	**SUal**	**-0.6095**	**-1.1614**
7	14	migl	.	.
	15	plac	.	.

4. Testing inconsistency

Design	Observation	Treatment	G.S.T random	
			PRESS residual	Studentized res.
8	16	piog	-0.2802	-0.5585
	17	plac	0.2802	0.5585
9	18	metf	-0.2927	-0.5779
	19	piog	0.2927	0.5779
10	20	piog	-0.0073	-0.0141
	21	rosi	0.0073	0.0141
11	22	plac	-0.2100	-0.6391
	23	rosi	0.2100	0.6391
12	24	metf	-0.0616	-0.1610
	25	rosi	0.0616	0.1610
13	**26**	**rosi**	**-0.6733**	**-1.2693**
	27	**SUal**	**0.6733**	**1.2693**
14	28	plac	.	.
	29	sita	.	.
15	30	plac	.	.
	31	vild	.	.

5. Introducing multiplicative terms

Example 4:

- Sclerotherapy data in Sharp and Thompson (2000)
- 19 trials
- 2 treatments (control and treatment)
- Number of deaths and bleeds

5. Introducing multiplicative terms

Table I. Numbers of deaths and bleeds, and total numbers of patients, in 19 sclerotherapy trials, taken from Pagliaro [12].

Trial	Control group			Treatment group			Quality*	Duration†
	Deaths	Bleeds	Total	Deaths	Bleeds	Total		
1	14	22	36	2	3	35	6	24
2	29	30	53	12	5	56	38	35
3	6	6	18	6	5	16	31	36
4	6	9	22	4	3	23	0	19
5	34	31	46	30	11	49	38	44
6	14	9	60	13	19	53	52	13
7	27	26	60	15	17	53	75	24
8	26	29	69	16	10	71	71	13
9	19	14	41	10	12	41	81	36
10	2	3	20	0	0	21	63	17
11	18	13	41	18	9	42	75	24
12	21	14	35	20	13	33	71	61
13	23	23	138	46	31	143	68	22
14	24	19	51	19	20	55	58	24
15	14	13	72	18	13	73	83	15
16	4	12	16	2	3	13	NA	16
17	8	5	28	6	3	21	NA	30
18	6	0	19	7	4	18	NA	24
19	5	2	24	5	6	22	NA	16

* Quality is calculated as a percentage of the maximum possible score, based on a scoring system which took into account how various aspects of the trial were handled, such as randomization, compliance, sample size and withdrawals [12]. Higher scores indicate higher quality, NA = not available.

† Duration is the average length of follow-up in months.

5. Introducing multiplicative terms

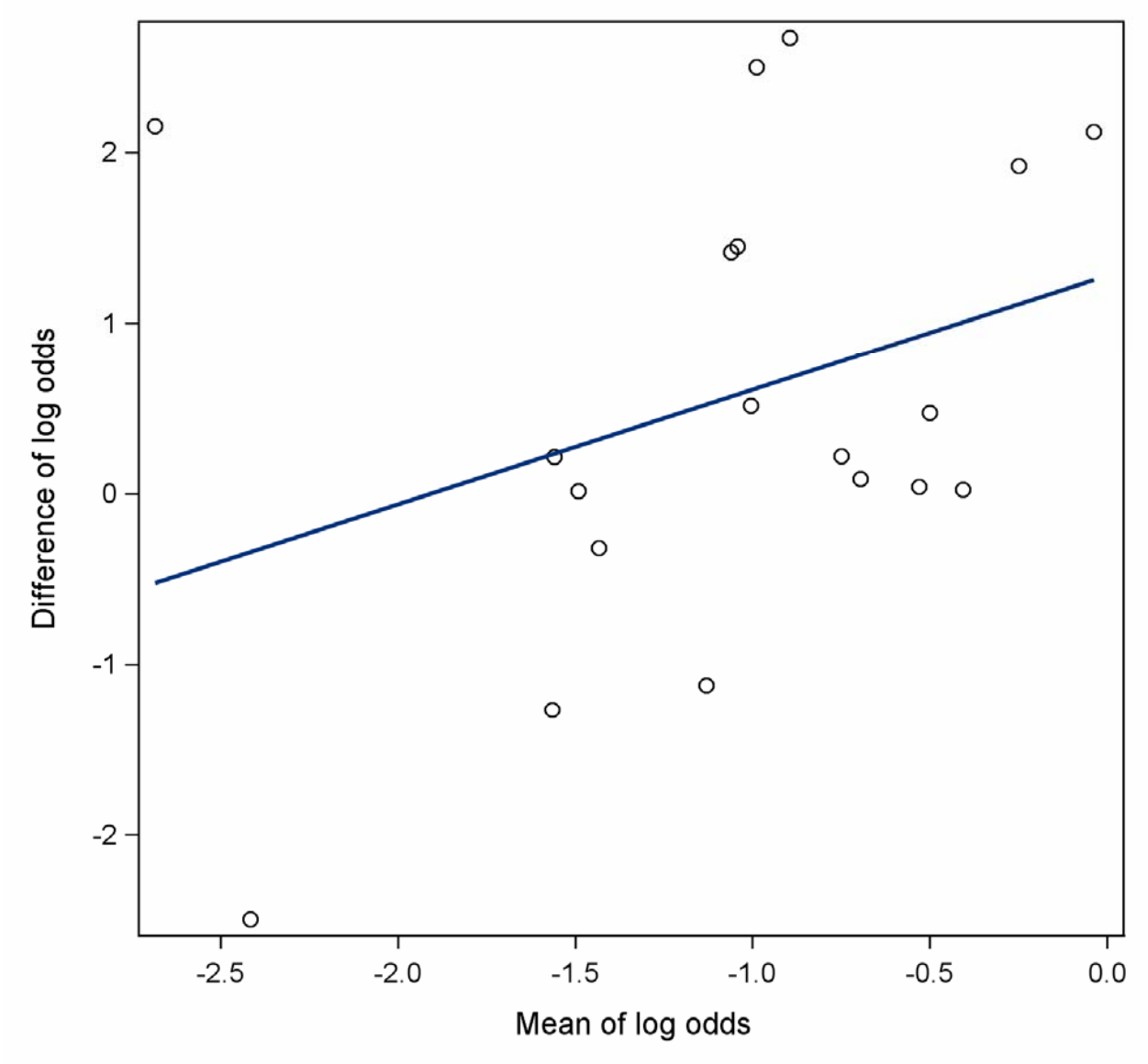


Fig: Difference of control and treatment vs. mean on log odds scale.

5. Introducing multiplicative terms

Regress expected treatment difference baseline treatment

$$\eta_{i2} - \eta_{i1} = \theta_0 + \theta_1 \eta_{i1} \Leftrightarrow \eta_{i2} = \theta_0 + (\theta_1 + 1)\eta_{i1}$$

η_{i1} = expected value of the baseline treatment in the *i*-th trial

η_{i2} = expected value of the new treatment

Schmid et al. (1998), Sharp & Thompson (2000)

Ignoring heterogeneity among the trials, this type of model is commensurate with a multiplicative model of the form …

5. Introducing multiplicative terms

A commensurate model (joint regression model)

$$\eta_{ik} = \alpha_k + \gamma_k \beta_i \quad ,$$

where α_k = intercept for *k*-th treatment

γ_k = slope for *k*-th treatment

β_i = effect (latent variable) for *i*-th trial (fixed!)

$\Rightarrow$ Finlay-Wilkinson (1963) regression in plant breeding!

Identifiability constraints $\sum_{k=1}^{n} \gamma_k = n$ and $\sum_{i=1}^{m} \beta_i = 0$ (Ng & Grunwald, 1997).

5. Introducing multiplicative terms

- With just two treatments, rearranging and comparing coefficients yields:

$$\theta_0 = \alpha_2 - \alpha_1\gamma_2/\gamma_1$$

$$\theta_1 = \gamma_2/\gamma_1 - 1$$

- With Finlay-Wilkinson model easy to extend to more than 2 treatments!

- Add random effect for heterogeneity:

$$\eta_{ik} = \alpha_k + \gamma_k\beta_i + u_{ik}$$

5. Introducing multiplicative terms

Interpretation of treatment effects more difficult

$$\eta_{i1} - \eta_{i2} = \alpha_1 - \alpha_2 + (\gamma_1 - \gamma_2)\beta_i$$

$\Rightarrow$ contrast depends on study

5. Introducing multiplicative terms

Factor-analytic model (β_i random!)

We may define the composite random term

$$f_{ik} = \gamma_k \beta_i + u_{ik}$$

and set the linear predictor equal to

$$\eta_{ik} = \alpha_k + f_{ik}$$

For identifiability, we require $\sigma^2_\beta = \mathrm{var}(\beta_i) = 1$, while γ_1 and γ_2 are unconstrained. Thus, we have for two treatments

$$\mathrm{var}\begin{pmatrix} f_{i1} \\ f_{i2} \end{pmatrix} = \gamma\gamma^T + I_2\sigma^2_u ,$$

where $\gamma^T = (\gamma_1, \gamma_2)$. (Piepho, 1997, *Biometrics*)

5. Introducing multiplicative terms

Table: Fit of joint regression model (sclerotherapy data).

	Fixed-effects model		Random-effects model	
Parameter	Estimate	Standard Error	Estimate	Standard Error
α_1 (control)	-0.927	0.261	-0.755	0.227
α_2 (new treatment)	-1.247	0.089	-1.305	0.145
γ_1	2.140	0.257	0.779	0.238
γ_2	-0.140	0.257	-0.106	0.186
σ_u^2	0.013	0.036	0.201	0.128
θ_0	-1.308	0.131	-1.408	0.235
θ_1	-1.065	0.112	-1.137	0.242
$\alpha_2 - \alpha_1$	-0.320	0.281	-0.550	0.286

5. Introducing multiplicative terms

Comparison with compound symmetry (CS) model (random model)

$\gamma_1 = \gamma_2 = 1$

$\Rightarrow$ CS model = two-way model with random study effects

Model	AIC
Factor-analytic	243.15
Compound symmetry	244.61

5. Introducing multiplicative terms

Example 5: Diabetes data

- Incidence of diabetes with various antihypertensive drugs
- Binomial response (cases/total counts)
- 6 treatments:
  ACE Inhibitor, ARB, CCB, Diuretic, Placebo, Beta-blocker
- 22 studies
- Treatment x trial classification very incomplete

(Elliot and Meyer, 2007, Lancet)

5. Introducing multiplicative terms

	Year	Duration (years)	Drug 1	New cases of diabetes/total	Drug 2	New cases of diabetes/total	Drug 3	New cases of diabetes/total
AASK[25]	2006	3·8	ACE inhibitor	45/410	β blocker	70/405	CCB	32/202
ALLHAT[26]	2002	4·0	ACE inhibitor	119/4096	CCB	154/3954	Diuretic	302/6766
ALPINE[27]	2003	1·0	ARB	1/196	Diuretic	8/196	..	..
ANBP-2[28]	2005	4·1	ACE inhibitor	138/2800	Diuretic	200/2826	..	..
ASCOT[28]	2005	5·5	β blocker	799/7040	CCB	567/7072	..	..
CAPPP[29]	1999	6·1	ACE inhibitor	337/5183	β blocker	380/5230	..	..
CHARM[30]	2003	~3·1	ARB	163/2715	Placebo	202/2721	..	..
DREAM[31]	2006	~3·0	ACE inhibitor	449/2623	Placebo	489/2646	..	..
EWPHE[32]	1991	4·7	Diuretic	29/416	Placebo	20/424	..	..
FEVER[20]	2005	3·3	CCB	177/4841	Placebo	154/4870	..	..
HAPPHY[33]	1987	3·8	β blocker	86/3297	Diuretic	75/3272	..	..
HOPE[34]	2001	4·5	ACE inhibitor	102/2837	Placebo	155/2883	..	..
INSIGHT[35]	2000	3·0	CCB	136/2508	Diuretic	176/2511	..	..
INVEST[36]	2003	4·0	β blocker	665/8078	CCB	569/8098	..	..
LIFE[37]	2002	4·8	ARB	242/4020	β blocker	320/3979	..	..
MRC-E[38]	1992	5·8	β blocker	37/1102	Diuretic	43/1081	Placebo	34/2213
NORDIL[39]	2000	4·5	β blocker or diuretic	251/5059	CCB	216/5095	..	..
PEACE[40]	2004	4·8	ACE inhibitor	335/3432	Placebo	399/3472	..	..
SCOPE[41]	2003	3·7	ARB	93/2167	Placebo	115/2175	..	..
SHEP[42]	1998	3·0	Diuretic	140/1631	Placebo	118/1578	..	..
STOP-2[43]	1999	4·0	ACE inhibitor	93/1970	β blocker or diuretic	97/1960	CCB	95/1965
VALUE[44]	2004	4·2	ARB	690/5087	CCB	845/5074	..	..

Table 1: **Summary of clinical trials of antihypertensive drugs that reported new cases of diabetes**

5. Introducing multiplicative terms

Factor-analytic model

$$\eta_{ik} = \alpha_k + f_{ik} \quad \text{with} \quad f_{ik} = \gamma_k \beta_i + u_{ik}$$

$$\text{var}(f_k) = \gamma\gamma^T + I_6\sigma_u^2 \quad \text{with } \gamma^T = (\gamma_1, \gamma_2, \ldots, \gamma_6) \text{ and } f_i^T = (f_{i1}, f_{i2}, \ldots, f_{i6})$$

$$\text{var}\begin{pmatrix} f_{i1} \\ f_{i2} \\ f_{i3} \\ f_{i4} \\ f_{i5} \\ f_{i6} \end{pmatrix} = \begin{pmatrix} \gamma_1^2 + \sigma_u^2 & \gamma_1\gamma_2 & \gamma_1\gamma_3 & \gamma_1\gamma_4 & \gamma_1\gamma_5 & \gamma_1\gamma_6 \\ \gamma_2\gamma_1 & \gamma_2^2 + \sigma_u^2 & \gamma_2\gamma_3 & \gamma_2\gamma_4 & \gamma_2\gamma_5 & \gamma_2\gamma_6 \\ \gamma_3\gamma_1 & \gamma_3\gamma_2 & \gamma_3^2 + \sigma_u^2 & \gamma_3\gamma_4 & \gamma_3\gamma_5 & \gamma_3\gamma_6 \\ \gamma_4\gamma_1 & \gamma_4\gamma_2 & \gamma_4\gamma_3 & \gamma_4^2 + \sigma_u^2 & \gamma_4\gamma_5 & \gamma_4\gamma_6 \\ \gamma_5\gamma_1 & \gamma_5\gamma_2 & \gamma_5\gamma_3 & \gamma_5\gamma_4 & \gamma_5^2 + \sigma_u^2 & \gamma_5\gamma_6 \\ \gamma_6\gamma_1 & \gamma_6\gamma_2 & \gamma_6\gamma_3 & \gamma_6\gamma_4 & \gamma_6\gamma_5 & \gamma_6^2 + \sigma_u^2 \end{pmatrix}$$

5. Introducing multiplicative terms

Table: Parameter estimates for joint regression model (diabetes data).

	Fixed-effects model		Random-effects model	
Parameter	Estimate	Standard Error	Estimate	Standard Error
α_1 (ACE inhibitor)	-2.852	0.046	-2.864	0.156
α_2 (ARB)	-2.907	0.061	-2.929	0.128
α_3 (CCB)	-2.793	0.034	-2.759	0.125
α_4 (Diuretic)	-2.492	0.069	-2.523	0.135
α_5 (Placebo)	-2.710	0.052	-2.743	0.162
α_6 (Beta-blocker)	-2.603	0.038	-2.572	0.136

5. Introducing multiplicative terms

Table: Parameter estimates for joint regression model (diabetes data).

	Fixed-effects model		Random-effects model	
Parameter	Estimate	Standard Error	Estimate	Standard Error
γ_1 (ACE inhibitor)	1.193	0.088	0.694	0.128
γ_2 (ARB)	0.738	0.083	0.533	0.132
γ_3 (CCB)	0.820	0.062	0.555	0.105
γ_4 (Diuretic)	1.039	0.116	0.586	0.124
γ_5 (Placebo)	1.198	0.084	0.723	0.130
γ_6 (Beta-blocker)	1.013	0.071	0.602	0.108
σ_u^2	0	-	0.0036	0.0042

5. Introducing multiplicative terms

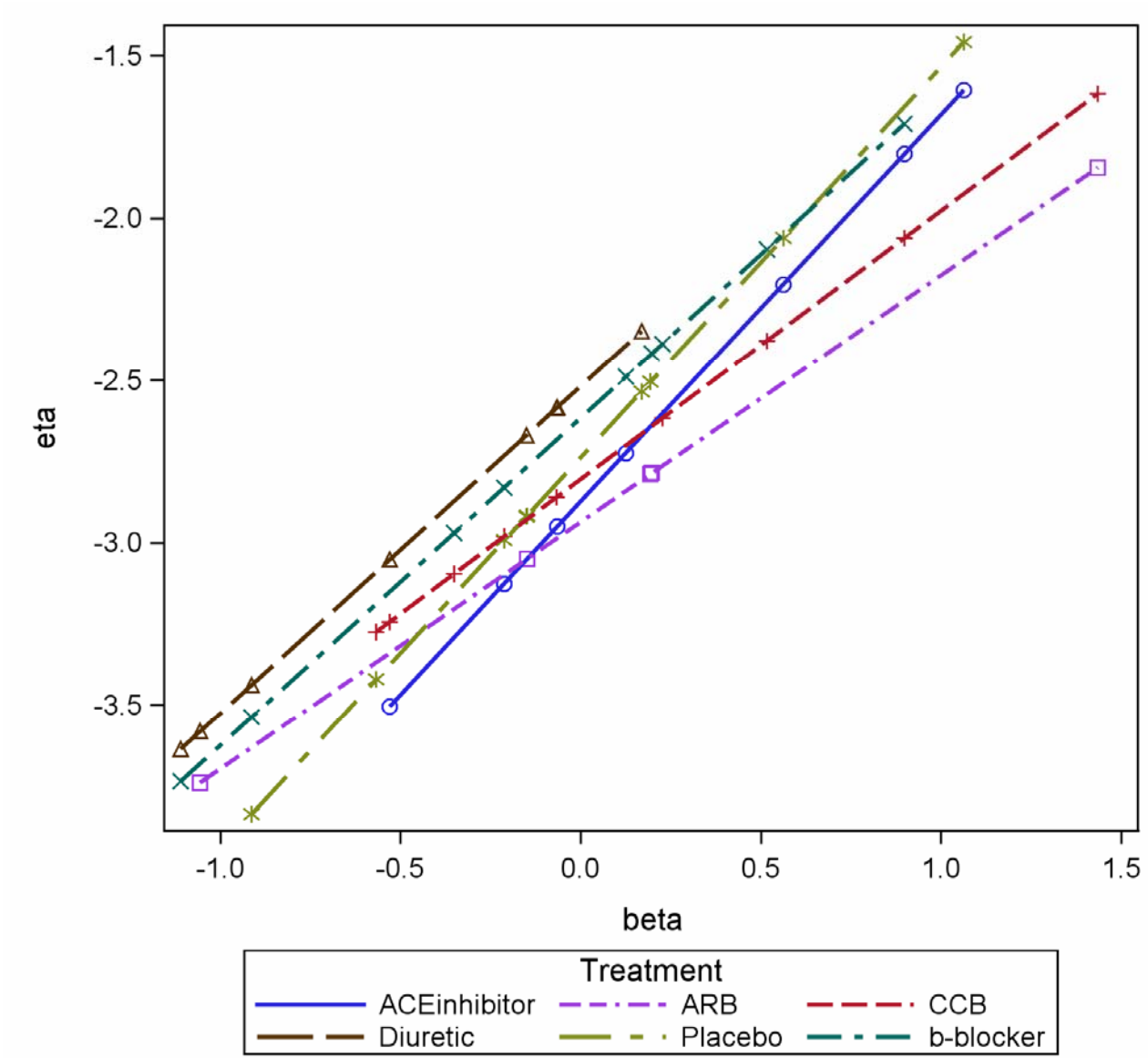


Fig. 2: Plot of fitted linear predictor (η_{ik}) versus estimated fixed trial effect (β_i) for the analysis of the diabetes example.

5. Introducing multiplicative terms

Modelling inconsistency

$$\eta_{ijk} = \delta_j + \beta_{ij} + \alpha_k + (\alpha\delta)_{jk} + u_{ijk}$$

δ_j = fixed main effect for the j-th trial type

$(\alpha\delta)_{jk}$ = fixed effect for the interaction jk-th trial type $\times$ treatment

(significant inconsistency at $P = 0.0021$)

Modelling inconsistency by multiplicative terms

$$(\alpha\delta)_{jk} = (\gamma_k - 1)\delta_j \quad \Rightarrow$$

$$\eta_{ijk} = \gamma_k\delta_j + \beta_{ij} + \alpha_k + u_{ijk}$$

5. Introducing multiplicative terms

Comparing models (1) and (2)

$$\chi^2 = 14.41 \quad (d.f. = 8, P = 0.0711)$$

$$AIC(1) = 417.8$$

$$AIC(2) = 418.2$$

$\Rightarrow$ Mild evidence that inconsistency well represented by multiplicative terms

5. Introducing multiplicative terms

Table VI. Parameter estimates for the multiplicative (joint regression) model for inconsistency (17) (diabetes data of Elliot and Meyer, 2007 [9]) based analysis for individual patient data (Example 2).

	Standard			Standard	
Parameter	Estimate	Error	Parameter	Estimate	Error
α_1 (ACE inhibitor)	−3.0064	0.0731	δ_1	1.4349	0.1429
α_2 (ARB)	−3.0774	0.0855	δ_2	0.0670	0.0770
α_3 (CCB)	−2.9337	0.0468	δ_3	−1.0530	0.3802
α_4 (Diuretic)	−2.6645	0.0619	δ_4	0.0874	0.0823
α_5 (Placebo)	−2.9621	0.0783	δ_5	−0.4126	0.0670
α_6 (Beta-blocker)	−2.6744	0.0383	δ_6	0.5708	0.0635
γ_1	1.1803	0.1230	δ_7	0.1801	0.0630
γ_2	0.8581	0.1259	δ_8	−0.3383	0.0726
γ_3	0.9190	0.0969	δ_9	0.1766	0.0831
γ_4	0.8545	0.1156	δ_{10}	0.2478	0.0582
γ_5	1.4187	0.1217	δ_{11}	0.3452	0.0714
γ_6	0.7694	0.0940	δ_{12}	0.2492	0.0486
σ_u^2	0	—	δ_{13}	0.4945	0.0660
			δ_{14}	−1.2521	0.1585
			δ_{15}	−0.7975	0.1010

ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blockers; CCB, calcium-channel blockers.

6. Summary

Inter-trial information: some remarks

- All models have fixed trial effect (some implicitly so)
- between-trial information on treatment effects is not recovered
- principle of concurrent control (Senn, 2000):
  $\Rightarrow$ effect of treatments should only be judged by within-trial comparisons because only these are protected by randomization, provided that individual trials are randomized, and only these are based on the same groups of units (e.g., patients, plots, etc.).
  $\Rightarrow$ By contrast, with a meta-analysis, there is usually no randomization between trials and groups of units for different trials may differ by important confounding factors.
- Approaches that exploit between-trial information (van Houwelingen et al., 2002; Dias and Ades, 2016) have been criticized by some authors.

6. Summary

- In practice, between-trial information is often low, so differences in analyses with fixed or random trial main effects are small, especially when the same set of treatments is tested in all trials.
- In complex multiple-treatment networks, however, between-trial information may be non-negligible.

6. Summary

Compared:

- Baseline contrast model (conditional) $\eta_{ik} = \mu_i + U_{ik}\delta_{ib(i)k}$
- Two-way model (unconditional) $\eta_{ik} = \beta_i + \alpha_k + u_{ik}$

Full equivalence:

- Summary data
- Individual patient data with identity link and normal errors

Very similar results:

- All other cases
- But: Baseline contrast model is not invariant to choice of baseline!

6. Summary

- Two-way model invariant to choice of baseline
- Two-way model much easier to fit using standard software
- Easy to fit two-way variance-covariance models for heterogeneity
- Joint regression model and factor-analytic models extend regression on baseline treatment when there are more than two treatments

  $\Rightarrow$ easy to implement with two-way model

Lesson for multi-environment variety trials:

- Consider inconsistency of trials

References:

Madden, L.V., Piepho, H.P., Paul, P.A. (2016): Models and methods for network meta-analysis. *Phytopathology* **106**, 792-806.

Piepho, H.P. (2014): Network-meta analysis made easy: Detection of inconsistency using factorial analysis-of-variance models. *BMC Medical Research Methodology* **14**, 61.

Piepho, H.P., Madden, L.V., Williams, E.R. (2015): Multiplicative interaction in network meta-analysis. *Statistics in Medicine* **34**, 582-594.

Piepho, H.P., Möhring, J., Schulz-Streeck, T., Ogutu, J.O. (2012): A stage-wise approach for analysis of multi-environment trials. *Biometrical Journal* **54**, 844-860.

Piepho, H.P., Williams, E.R., Madden, L.V. (2012): The use of two-way mixed models in multi-treatment meta-analysis. *Biometrics* **68**, 1269-1277.

Thanks!