A critical review of methods for the assessment of interactions in individual patient data meta-analysis

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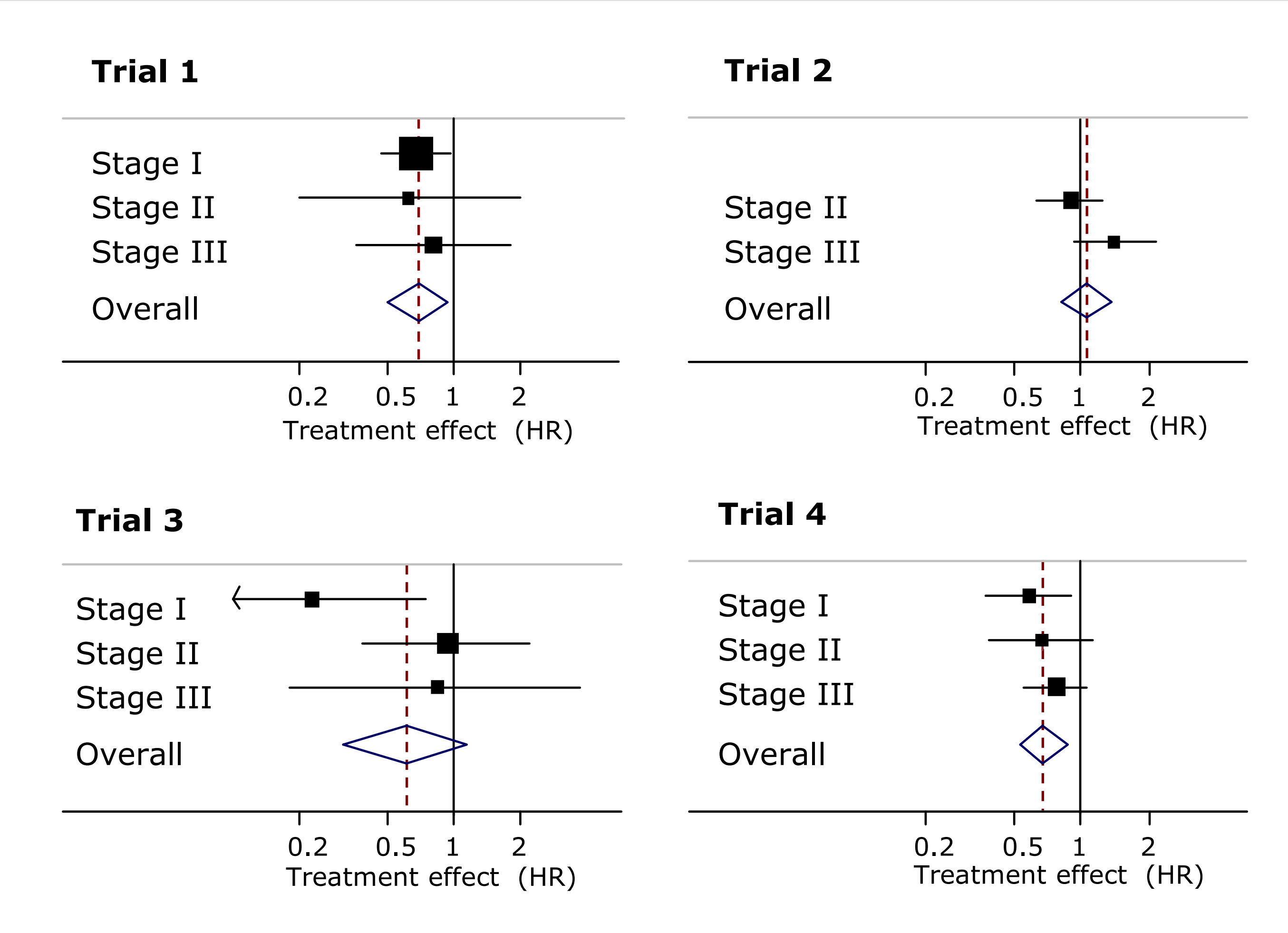
Objectives & methods

- Individual patient data (IPD) meta-analysis (MA)
  - Treatment, outcome and covariate known for each patient
    - $\Rightarrow$ Treatment-covariate interactions
    - $\Rightarrow$ Targeted treatment
- Research questions
  - How should treatment-covariate effects be analysed?
  - How should such analyses be presented?
- Methods & objectives
  - Literature search for existing approaches
  - Critical appraisal of identified approaches
  - Apply these approaches to existing IPD datasets
  - Develop guidance

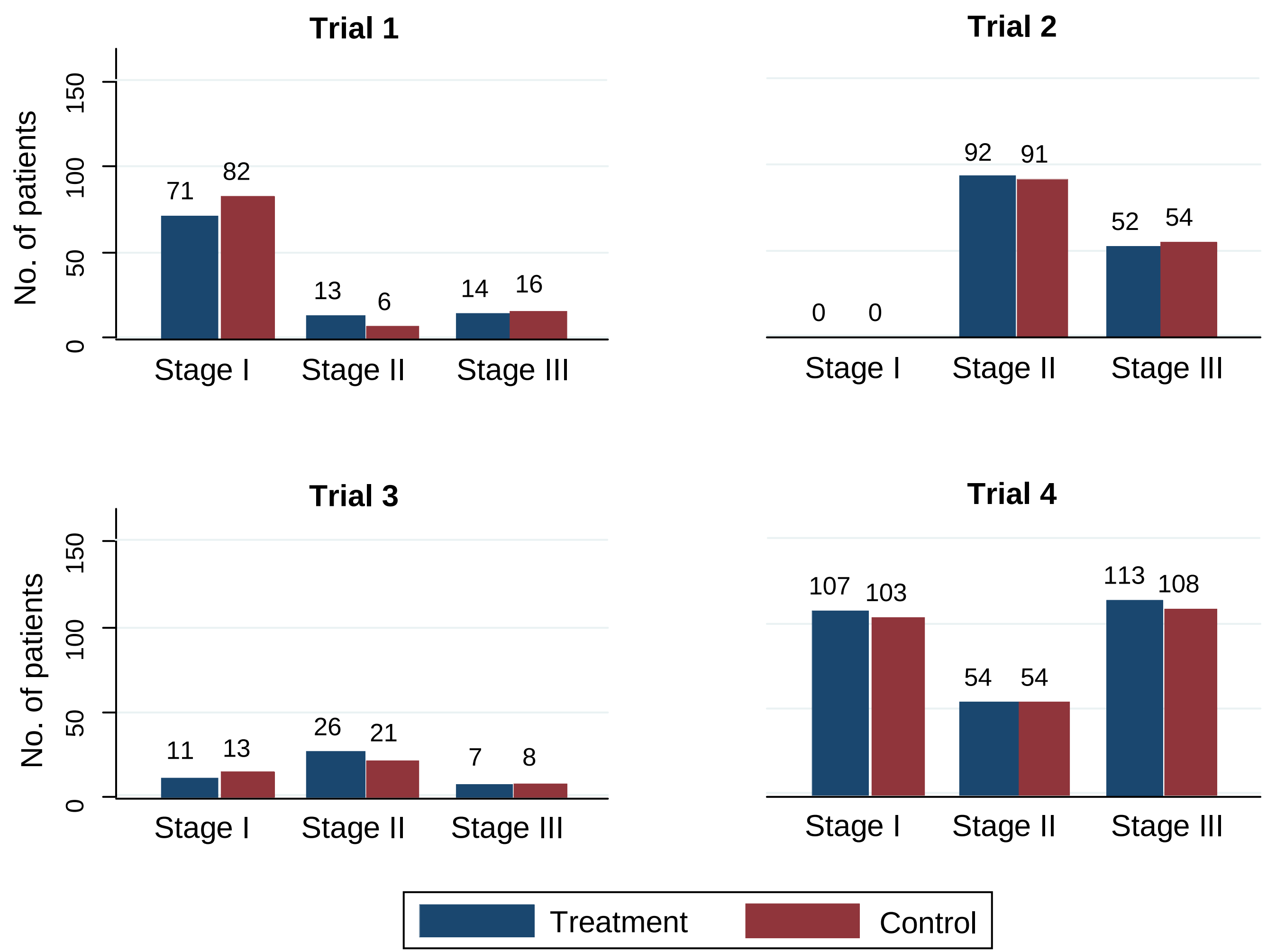
Treatment effect by trial and disease stage



- Post-op RT vs surgery alone in non-small-cell lung cancer
- Outcome is overall survival (time-to-event)

- Question: does trt effect differ by disease stage group?
- For simplicity, interaction measured using a linear slope fitted across subgroups

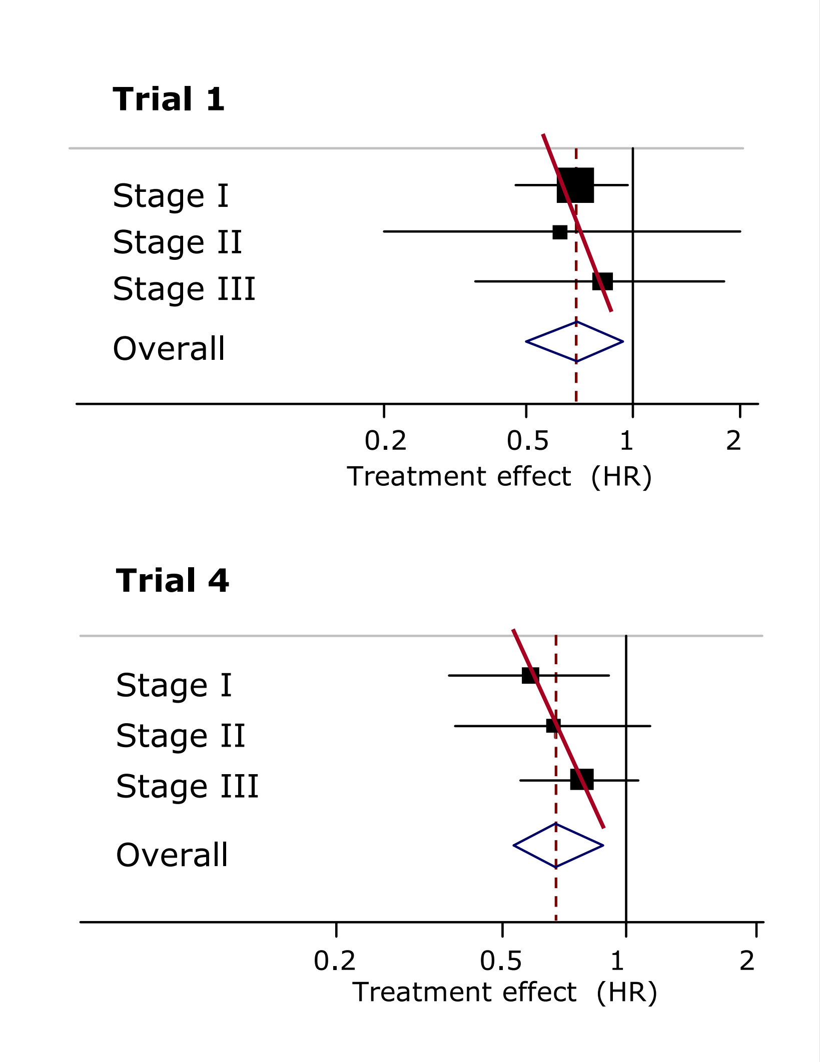
Distribution of disease stage



Within-trial effect

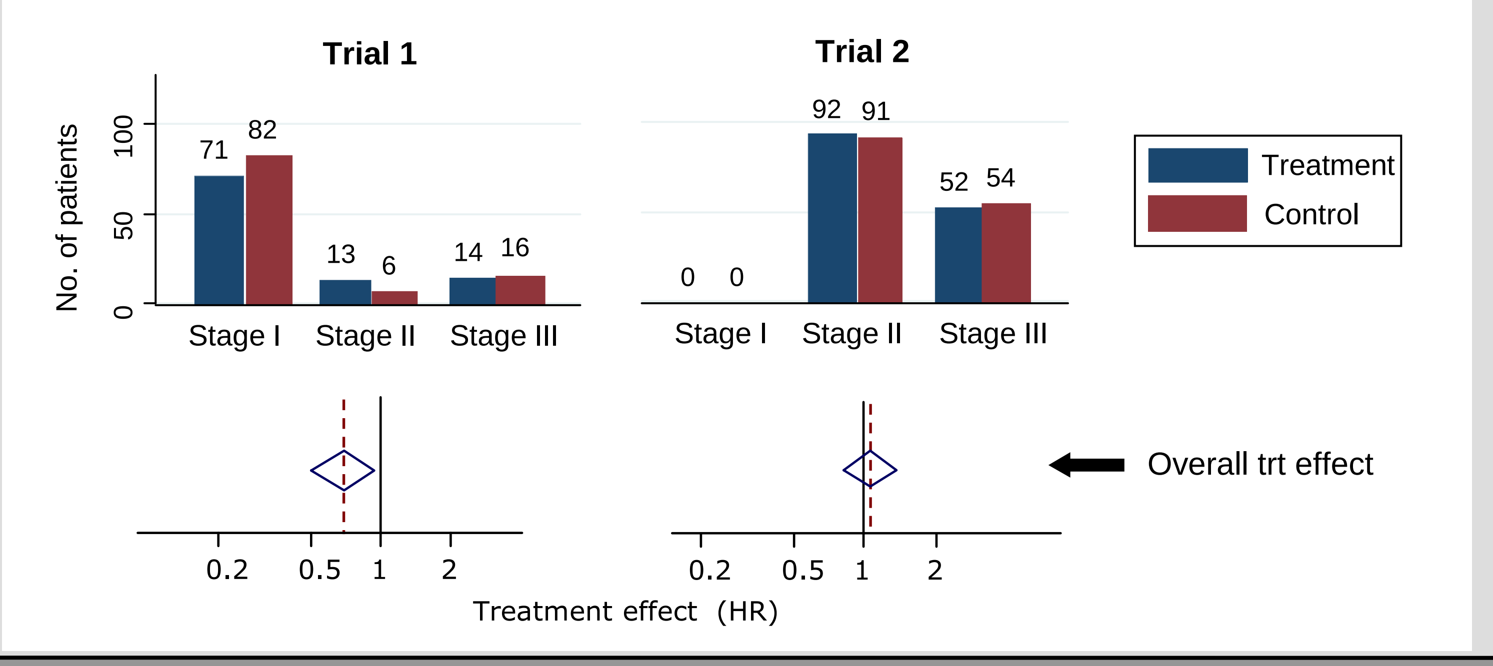
Within-trial (WT) effect

- Measures how disease stage affects treatment outcome for individual pts within an "average" trial
- Can be visualised as "average" slope
- Patients are randomised to trt arms within disease stage subgroups, all subject to the same trial protocol



Across-trial effect

- Across-trial (AT) effect
  - Measures how the "average" disease stage in a trial affects treatment outcome
  - Not randomised, and subject to "ecological bias"
    - Difference in "average" between trials may not be representative of differences between individuals



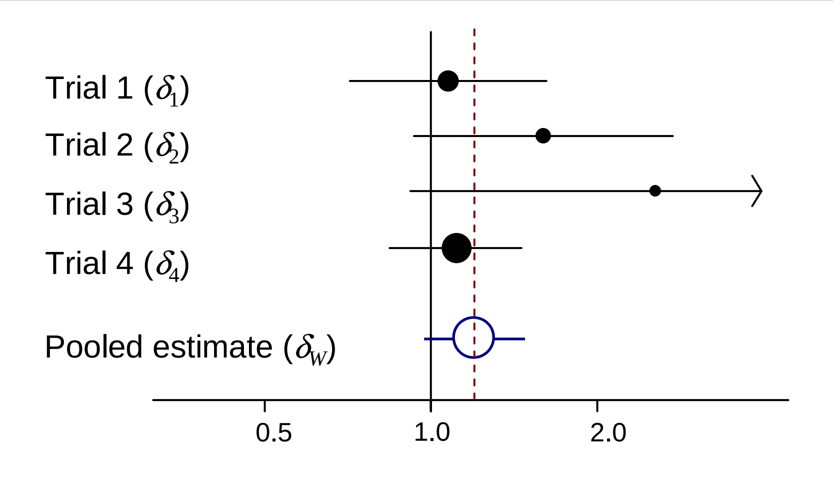
Why use across-trial information?

- WT info tells us how treatment effect differs between patients with different values of a covariate:– true interaction
- AT info might help when combined with WT if WT has low power and AT has greater power
  - Analogous with case for non-randomised studies (cohort/case-control) – providing extra evidence where RCT evidence is low
  - If analysis is exploratory, may wish to maximise power if risk of bias is considered acceptable

1. Pooling of Within-Trial covariate Interactions (WTI)

y = outcome; x = treatment; z = covariate (e.g. disease stage);
α = trial ("baseline") coeff.; β = treatment coeff.; γ = covariate coeff.; δ = interaction coeff.;
i = trial; j = patient

- "Two-step" pooling of within-trial covariate interactions
  - Step 1: Fit regression model with interaction term separately within each trial i: $g(y_{ij}) = \alpha_i + \beta_i x_{ij} + \gamma_i z_{ij} + \delta_i x_{ij} z_{ij}$
  - Step 2: Combine interaction coeffs δ_i using inverse-variance MA



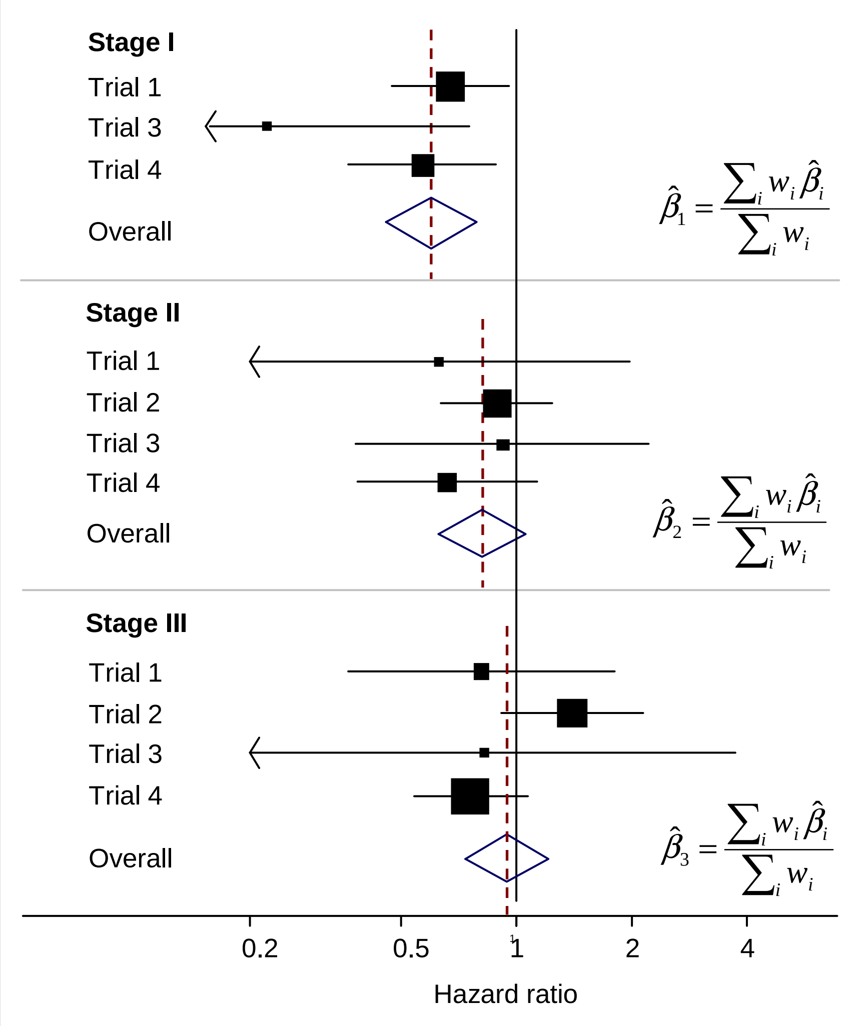
$$\hat{\delta}_W = \frac{\sum_i w_i \hat{\delta}_i}{\sum_i w_i} \qquad se(\hat{\delta}_W) = 1 \Big/ \sqrt{\sum_i w_i}$$

W = "within-trials"

Critique of WTI

- Within-trials effect only, so randomisation is retained
- Solid, simple approach for continuous and ordered categorical covariates (e.g. disease stage)
- BUT:
  - Trials with data in only one subgroup cannot be included
  - Unordered covariates cannot be analysed

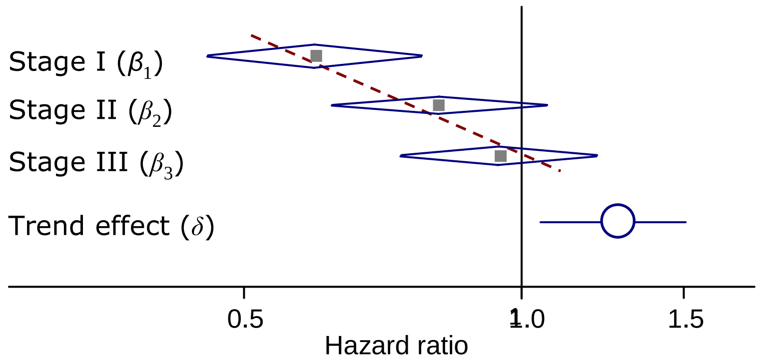
2. Across Covariate Subgroup effect (ACS)



Step 1: Split data into disease stage subgroups

Step 2: Carry out standard IPD MA for treatment effect β_k within each subgroup k

Step 3: Fit a trend line to the treatment estimates β_k to obtain estimate of interaction δ :



$$\hat{\beta}_k = \beta_0 + \delta k + \varepsilon_k, \quad \varepsilon_k \sim N\left(0, se\left(\hat{\beta}_k\right)^2\right)$$

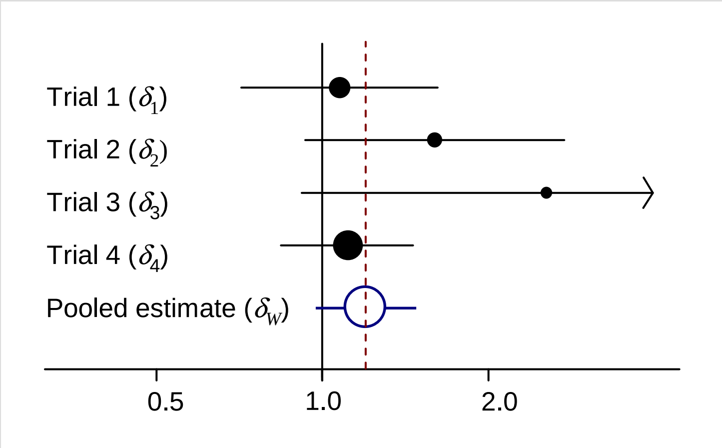
Critique of ACS

- Relatively simple
- Very commonly used (e.g. cancer)
- BUT:
  - Randomisation structure is broken
  - Within-trial correlations across covariate subgroups are unaccounted for
  - Mixture of within- and across-trials info, which cannot be separated: "black box"

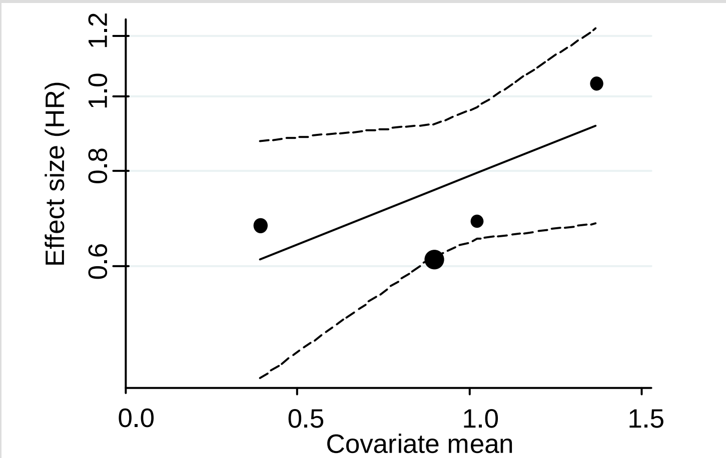
    $\Rightarrow$ no way to assess ecological bias

3. Combining Within- & Across-trials effects (CWA)

Pooled within-trials effect (WTI)



Meta-regression of disease stage means

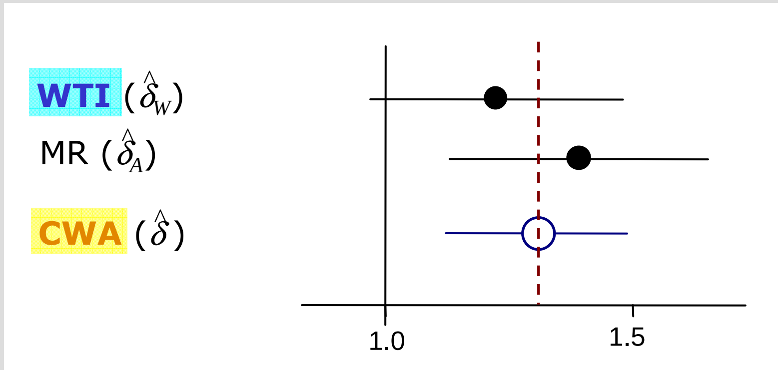


Step 1: Separately estimate within-trials effect δ_W using **WTI**, and across-trials effect δ_A using meta-regression (MR) on trial-level disease stage means

Step 2: Combine the two estimates in a further meta-analysis:

$$\hat{\delta} = \frac{w_W \hat{\delta}_W + w_A \hat{\delta}_A}{w_W + w_A}, \quad se\left(\hat{\delta}\right) = 1 \Big/ \sqrt{w_W + w_A}$$

where $w_W = 1 \big/ se\left(\hat{\delta}_W\right)^2$ and $w_A = 1 \big/ se\left(\hat{\delta}_A\right)^2$



Critique of CWA

- Relatively simple
- Can increase power over WTI in certain circumstances
- Allows WT & AT to be combined: pros & cons of this discussed later
- Transparency and user control
  - Each effect derived independently and combined manually by the analyst
- More open to bias and/or bad judgment?
  - Analyst could downweight unfavourable results

4. Mixed-Effects Models (MEM)

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- "One-step" mixed-effects model
  - Uses all available data in a single interaction model:

$$g(y_{ij}) = \alpha_i + \beta x_{ij} + \gamma z_{ij} + \delta x_{ij} z_{ij}$$

- Interaction term $\delta x_{ij} z_{ij}$ can also be parameterised so as to separate within- and across-trial effects:

$$g(y_{ij}) = \alpha_i + \beta x_{ij} + \gamma z_{ij} + \delta_W x_{ij} (z_{ij} - \bar{z}_i) + \delta_A x_{ij} \bar{z}_i$$

where $\bar{z}_i$ is the covariate mean value in trial i;
δ_W = within-trial effect; δ_A = across-trial effect.
Difference $\delta_A - \delta_W$ is a quantification of ecological bias.

Reference: Simmonds (2005)

Critique of MEM

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- Arguably 'gold standard' since other models are special cases
- Well-established in other study areas e.g. multi-centre trials
- Flexible & maximises power
  - Allows simultaneous estimation of multiple parameters, allowing non-linear interactions etc.
  - Can be parameterised to isolate WT & AT
- BUT:
  - Currently issues with random-effects with time-to-event data
  - Complex and computationally intensive; greater expertise & care required
- Allows WT & AT to be combined: pros & cons of this discussed later

Using across-trials information

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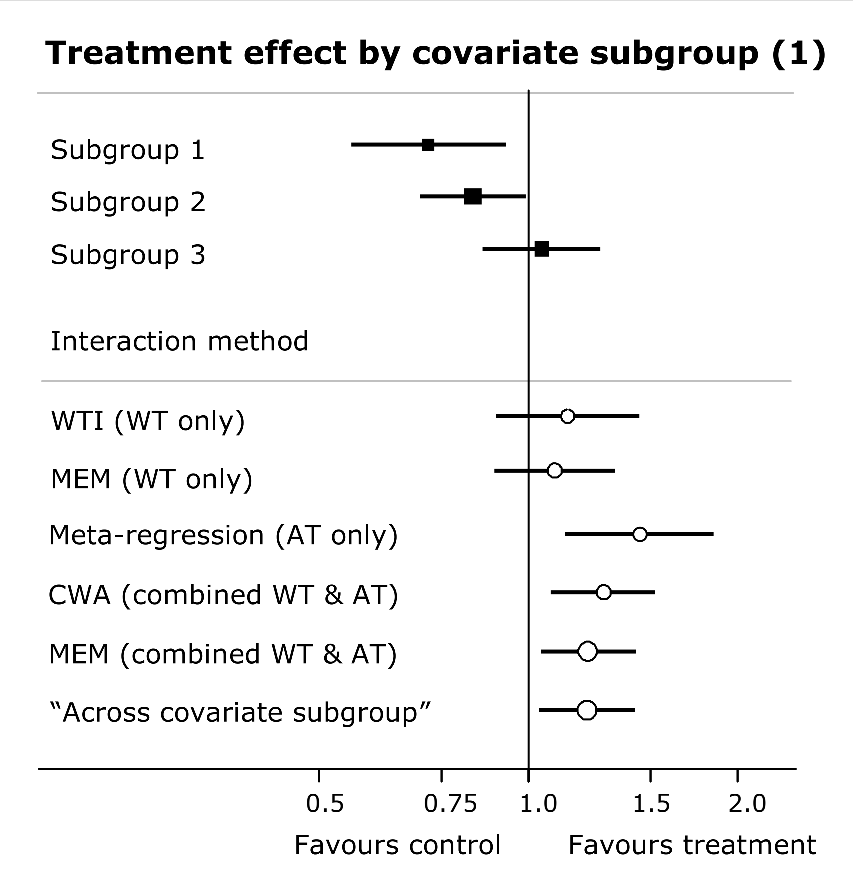
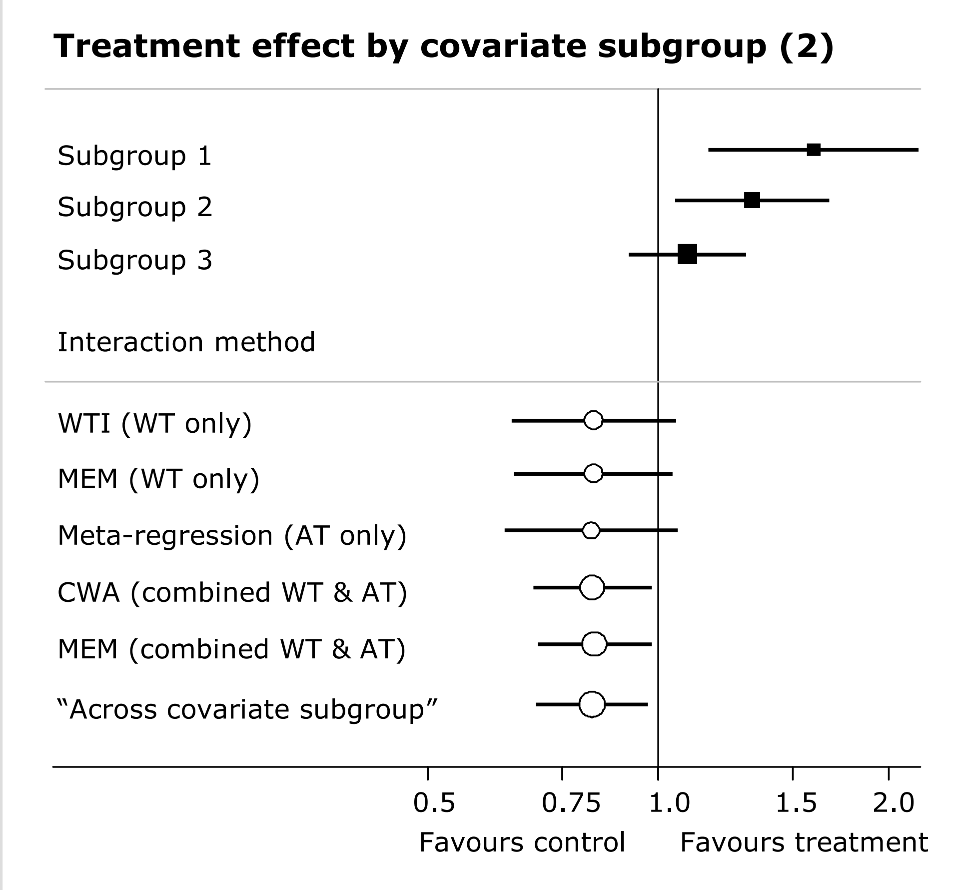
- Use of AT is controversial
  - Many analysts will never want to use it
  - Including it in the wrong circumstances risks ecological bias
  - Might be used if analysis is hypothesis generating, & more power is desired at the risk of increased bias
- In the event that AT info is under consideration, it is important to decide a priori:
  - Whether to consider it, with reasons
  - How to include it, with specific criteria
- Examples of criteria:
  - Estimates could differ by less than a pre-specified amount
  - Variance of the across-trial estimate could be increased by a factor before combining (CWA)

Examples





Using AT will introduce bias

AT might be included to increase power

Guidance

Proposed strategy:

1. Make an *a priori* decision whether or not to consider using across-trials info, together with criteria for inclusion
   - Most analysts will decide not to
2. WTI is recommended in many situations, especially if complex stats are unnecessary
3. If across-trials info is to be considered, fit a meta-regression and test results against the pre-specified criteria; if criteria are met, use CWA
4. For those with suitable expertise and resources, MEM is a powerful and versatile alternative, and can include or exclude across-trials info as desired
5. ACS is not recommended for patient-level covariates and should be avoided.

Děkuji!

Thankyou!