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Subgroup comparisons within and across studies in meta-analysis

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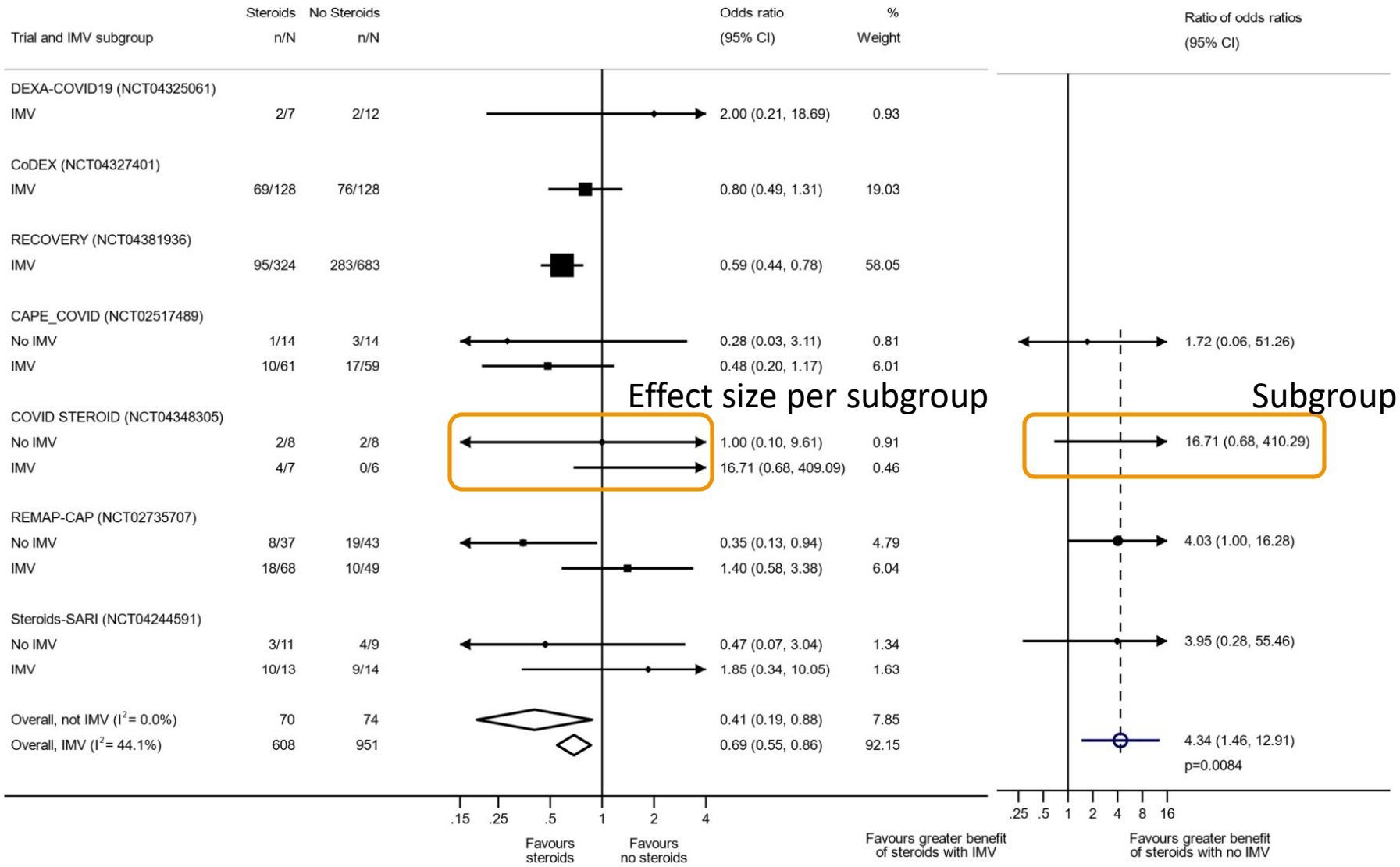
EXAMPLE: Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19

- **Population**: Critically ill COVID-19 patients.
- **Intervention**: Systemic (rather than targeted) corticosteroids administration. Reduce inflammation and modulate the immune response.
- **Comparison**: Standard care.
- **Outcome**:
  - Overall: Association between corticosteroids administration (treatment effect) and the reduction of 28-day all-cause **mortality**.
  - Subgroup-specific: Association between corticosteroids administration (treatment effect) and the reduction of 28-day all-cause **mortality in the presence of mechanic ventilation**.

Effect of Corticosteroids in 28-day all-cause mortality

Forest plot displaying heterogeneity



Effect size per subgroup

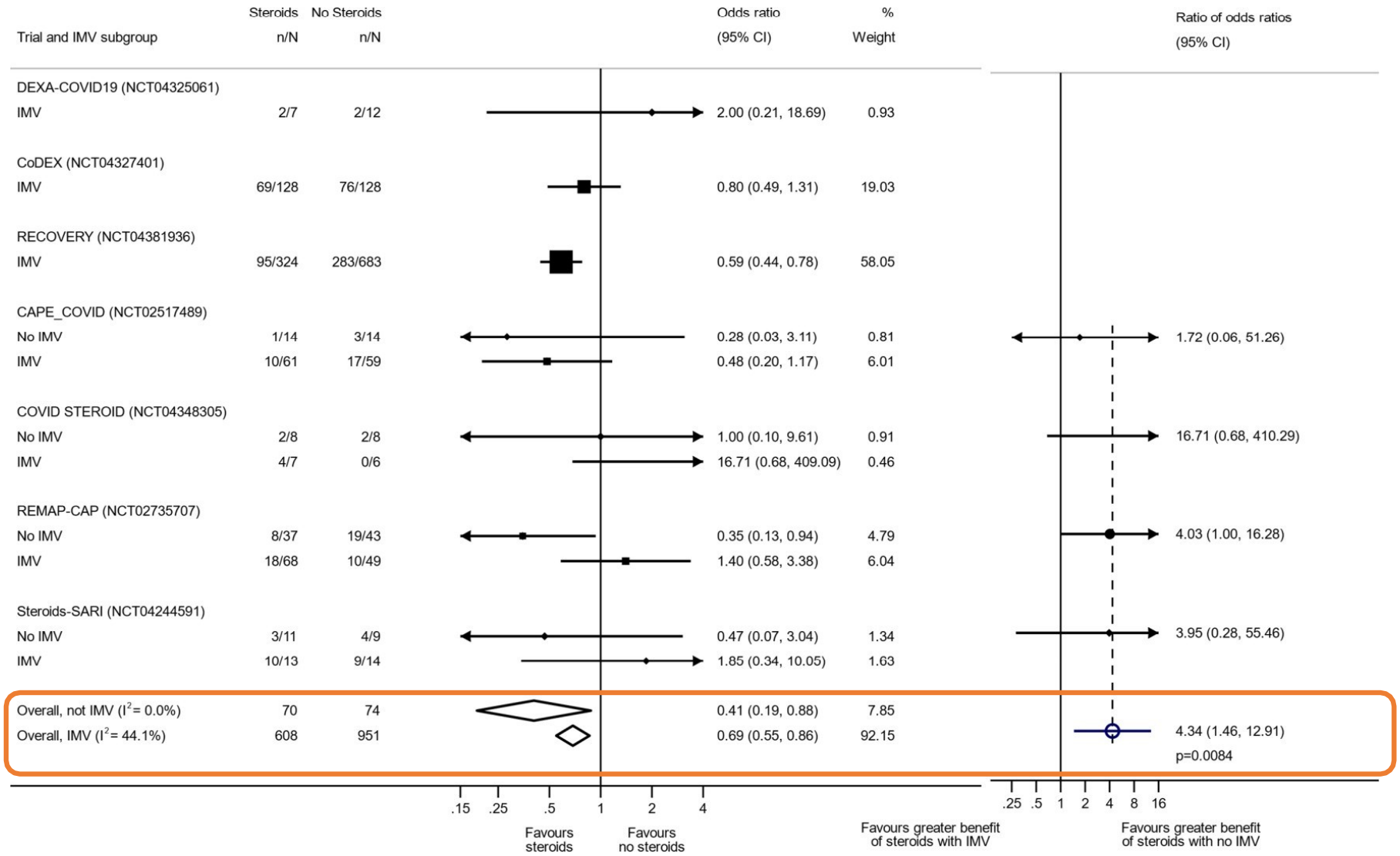
Subgroup interaction IV/NIV

Treatment effects in subgroups

Treatment-by-subgroup interaction

Problem: Unmatched Estimation

Forest plot displaying heterogeneity



BUT, 0.69 / 0.41 = 1.68…
and **NOT** 4.34

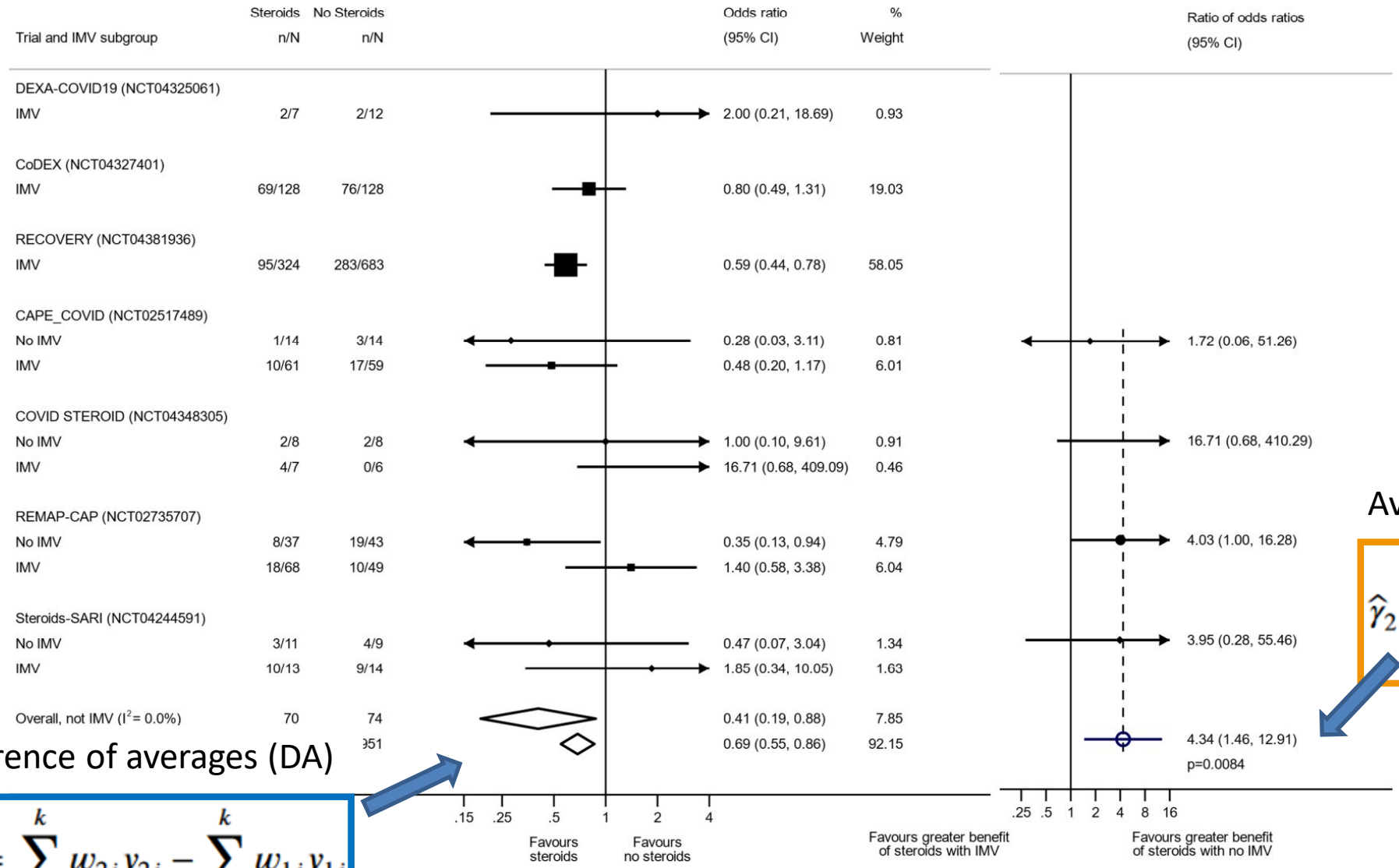
? ? ?

Treatment effects in subgroups

Treatment-by-subgroup interaction

Problem: Unmatched Estimation

Forest plot displaying heterogeneity



Average difference (AD)

$$\hat{\gamma}_2 = \sum_{j=1}^{k} w_j (y_{2j} - y_{1j})$$

Difference of averages (DA)

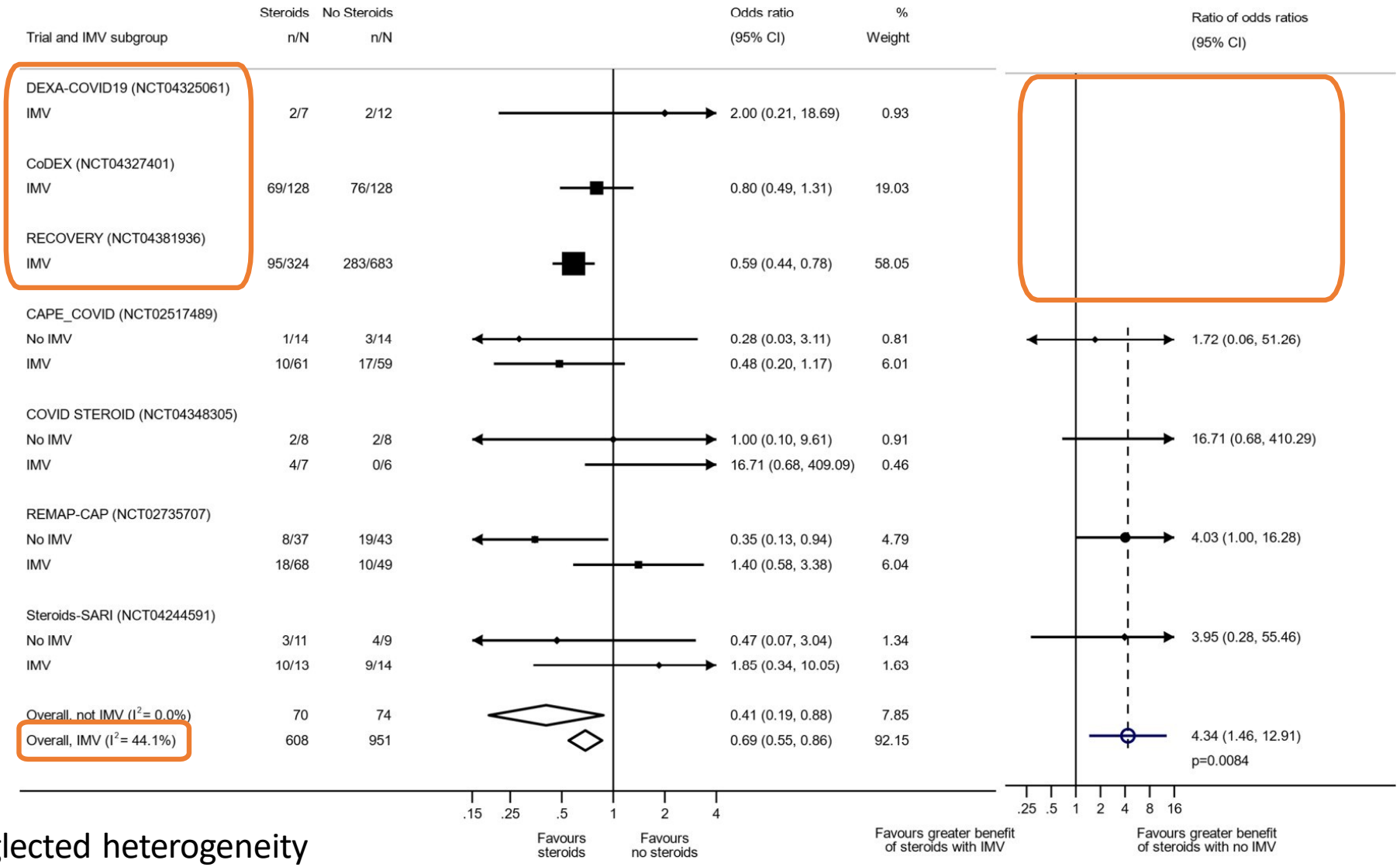
$$\hat{\gamma}_1 = \sum_{j=1}^{k} w_{2j} y_{2j} - \sum_{j=1}^{k} w_{1j} y_{1j}$$

eatment effects in subgroups

Treatment-by-subgroup interaction

Problem: Unmatched Estimation

Forest plot displaying heterogeneity



Data on IV only, therefore no interactions

Small number of studies (k = 4)

Heterogeneity underestimation

Neglected heterogeneity >25%

Treatment effects in subgroups

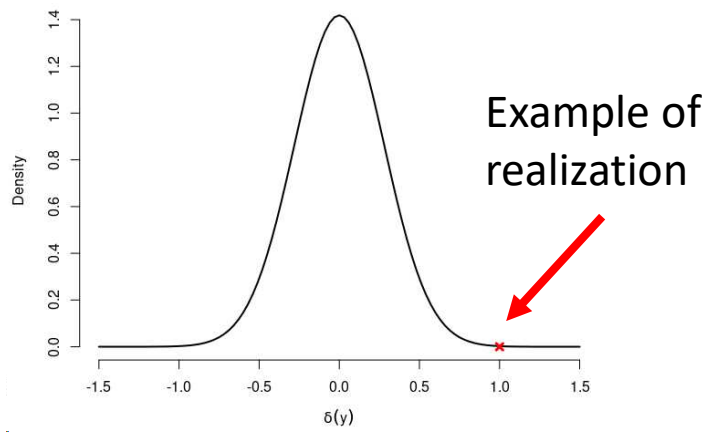
Treatment-by-subgroup interaction

Condition for matching estimates

- Condition: Any weighting scheme that satisfies $w_j = w_{1j} = w_{2j}$ will ensure identity between DA and AD. However, this does not narrow down the problem (infinite solutions).
- In general, the difference between projections has positive variance (and zero mean).

$$\begin{aligned}\delta(y) &= \hat{\gamma}_1 - \hat{\gamma}_2 \\ &= (\hat{\beta}_2 - \hat{\beta}_1) - \hat{\gamma} \\ &= CH_1 y - H_2 I_{k/2} \otimes Cy \\ &= Dy,\end{aligned}$$

where $\delta \sim \text{Normal}(0, DSD')$



Particular cases

- **Convex** weights
  - Assuming **proportional unnormalized weights** across subgroups is a sufficient condition for the agreement between estimates.

$$w_{2j} = \frac{a_{1j}p}{\sum_{j=1}^{k} a_{1j}p} = w_{1j}$$

- **Inverse-variances** weights (a type of convex weights)
  - Assuming **proportional subgroup variances** (or subgroup prevalence) is sufficient.

$$\hat{\gamma}_2 = \frac{\sum_{j=1}^{k} \frac{y_{2j}}{s_{2j}^2(1+s_{1j}^2/s_{2j}^2)}}{\sum_{j=1}^{k} \frac{1}{s_{2j}^2(1+s_{1j}^2/s_{2j}^2)}} = \frac{\sum_{j=1}^{k} \frac{y_{1j}}{s_{1j}^2(1+p^{-1})}}{\sum_{j=1}^{k} \frac{1}{s_{1j}^2(1+p^{-1})}} - \frac{\sum_{j=1}^{k} \frac{y_{2j}}{s_{2j}^2(1+p)}}{\sum_{j=1}^{k} \frac{1}{s_{2j}^2(1+p)}} = \hat{\gamma}_1$$

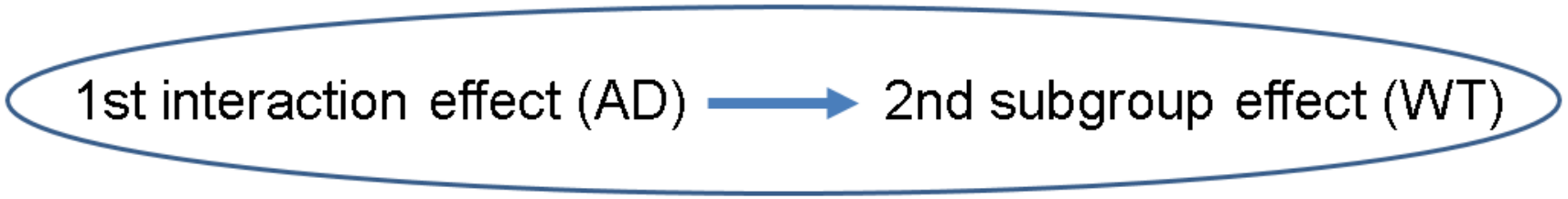
  - Proportional subgroup prevalences are special case where estimates always match.

Reconciling interaction estimates: weighted averages

- Standard weighting: Several schemes can enforce matching estimates by using **common weights for all three estimates**.
  - Equal-weights for all studies $\frac{1}{k}$
  - Inverse-variance weights based on contrast estimates $\frac{(n_{1j}^{-1}+n_{2j}^{-1})^{-1}}{\sum_{i=1}^{k}(n_{1i}^{-1}+n_{2i}^{-1})^{-1}}$
  - Weights proportional to studies` sample size $\frac{n_j}{\sum_{j=1}^{k} n_j}$
  - Weights proportional to the smaller of the subgroups $\frac{\min(n_{1j},n_{2j})}{\sum_{j=1}^{k}\min(n_{1j},n_{2j})}$
  - Minimum of three RE-weights $\frac{\min(n_{1j}^{-1},n_{2j}^{-1},(n_{1j}^{-1}+n_{2j}^{-1})^{-1})}{\sum_{i=1}^{k}\min(n_{1i}^{-1},n_{2i}^{-1},(n_{1i}^{-1}+n_{2i}^{-1})^{-1})}$
  - (D-)optimal weights given by the D-optimality criterion

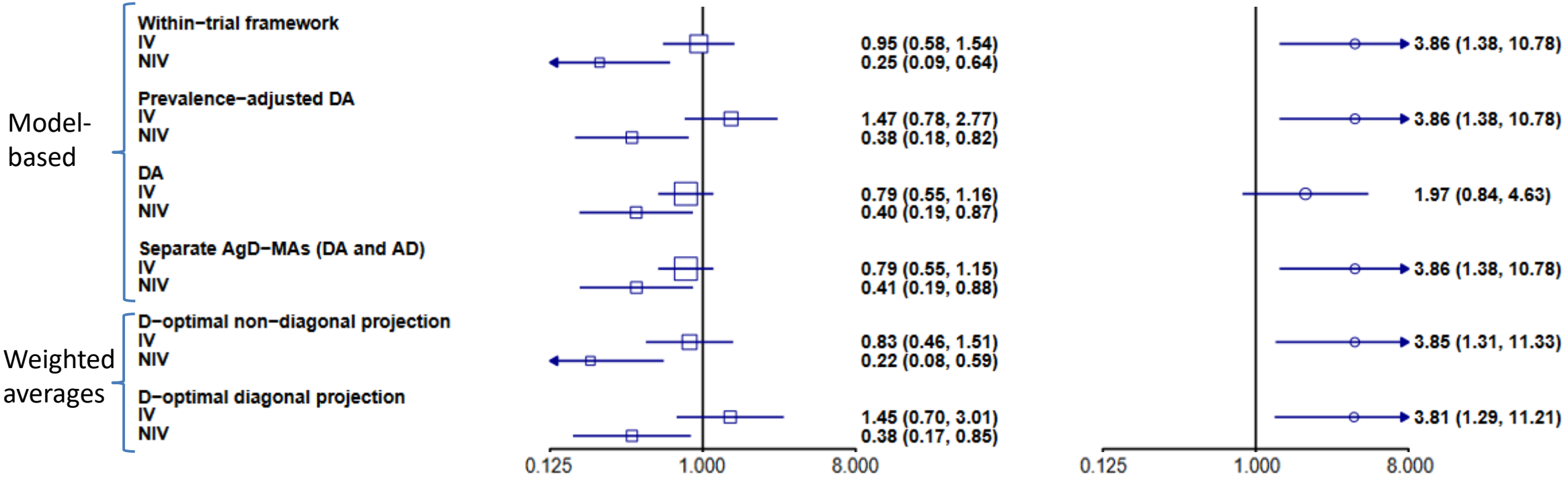
Model-based approaches

- The van Houwelingen's [2] ,,bivariate" MA (DA including correlation).
- Within-trial framework (AD/WT) [3] : Prioritizing the interaction estimate, by **conditioning subgroup estimation** on interaction estimation (including the heterogeneity part).

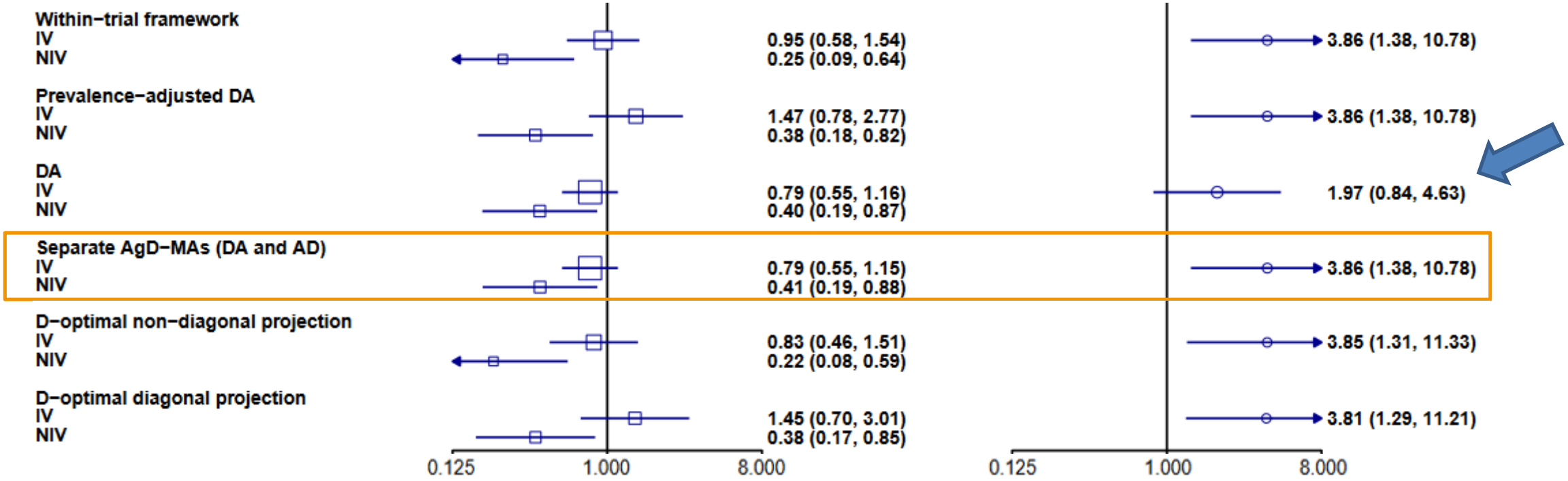


- Consider prevalence as covariable [4] in van Houwelingen's model.

Results for COVID-19 example



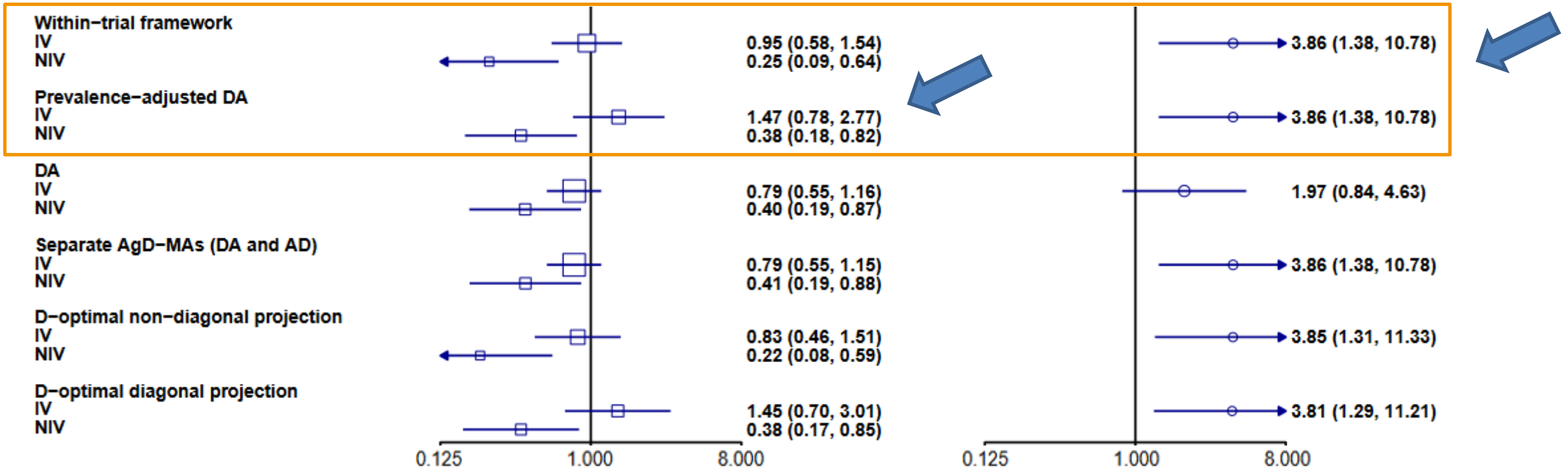
Results for COVID-19 example



Even when considering the RE assumption
0.79 / 0.41 = 1.97…
and **NOT** 3.86

The DA is the corresponding joint analysis

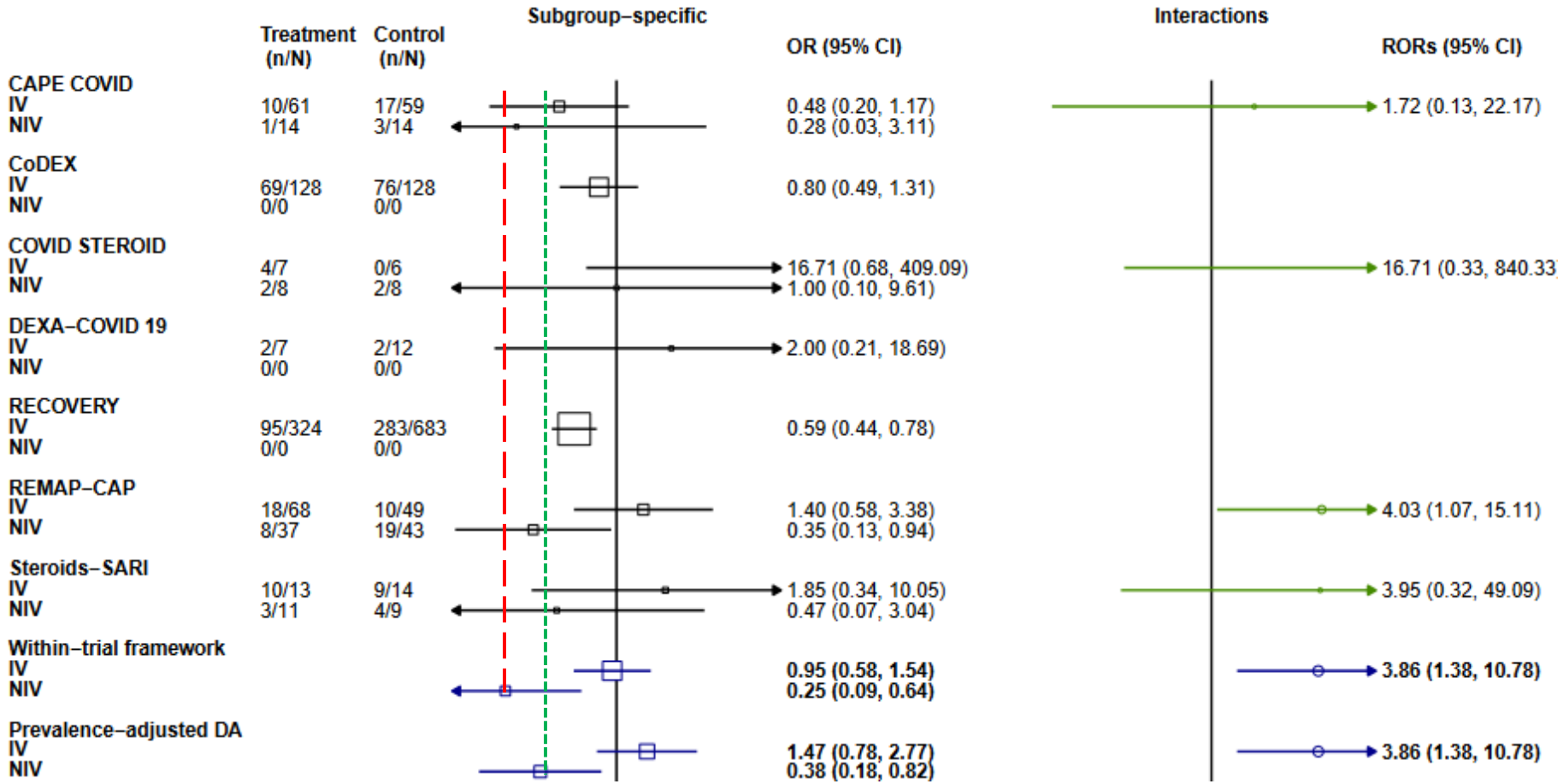
Results for COVID-19 example



- The prevalence-adjusted case of DA **prioritizes the interaction estimation** just as the Within-trial framework at the cost of having **wider subgroup intervals**.

Alignment with effect sizes

WT estimates do not align with effect sizes in some cases



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Simulation study

- The data generator model in an IPD model[5] that yields the following predictor when aggregated

$$E\left[y_{1j} \mid \beta_{1j}, \beta_{2j}, \tau_1, \tau_2\right] = \begin{cases} \beta_{2j} + \gamma_j(0 - \bar{z}_j), & \text{for the effect size of subgroup 1,} \\ \beta_{2j} + \gamma_j(1 - \bar{z}_j), & \text{for the effect size of subgroup 2.} \end{cases}$$

$$\text{where} \quad \beta_{2j} \sim \text{Normal}(\varphi + \gamma_\Lambda \bar{z}_j, \tau_1^2) \quad \text{and} \quad \gamma_{W_i} \sim \text{Normal}(\gamma_W, \tau_2^2),$$

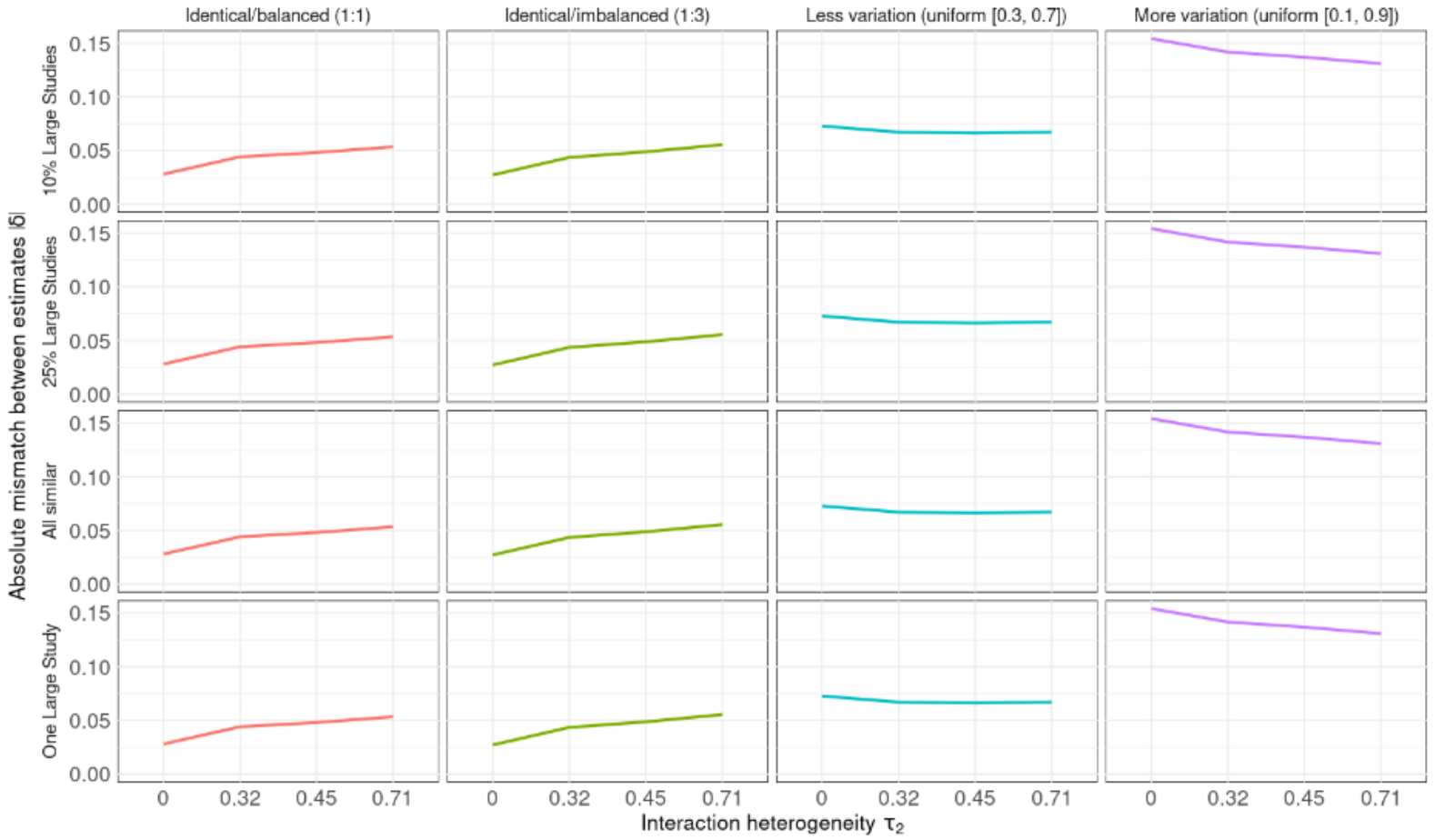
Subgroup-specific random effect

Subgroup prevalence

Interaction random effect

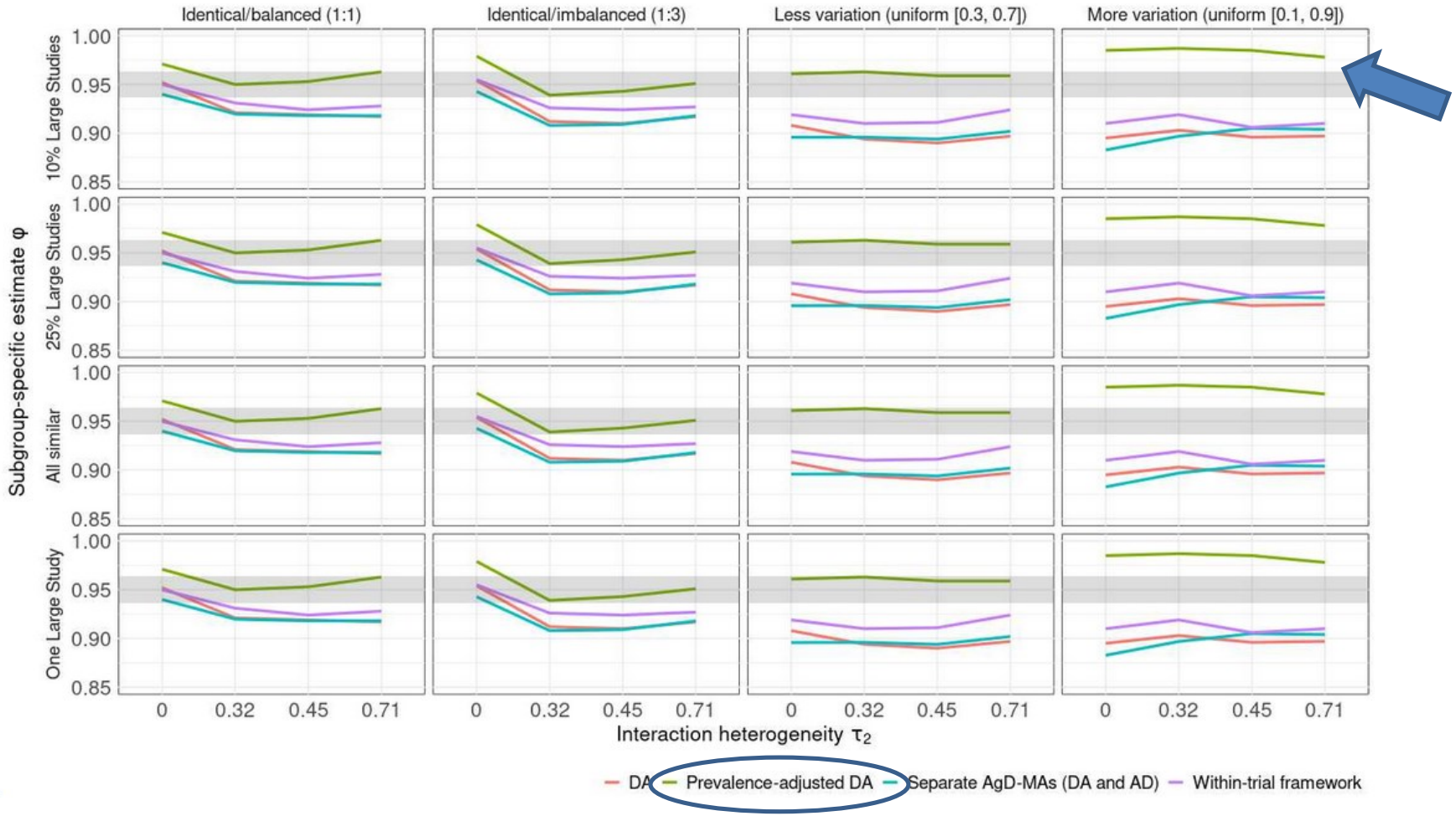
- We vary study sizes, heterogeneities and subgroup prevalences.
- We evaluate coverage for interaction and subgroup estimates.

Simulation study – Separate AgD MAs (DA and AD) Mismatch



Simulation study – Subgroup coverage

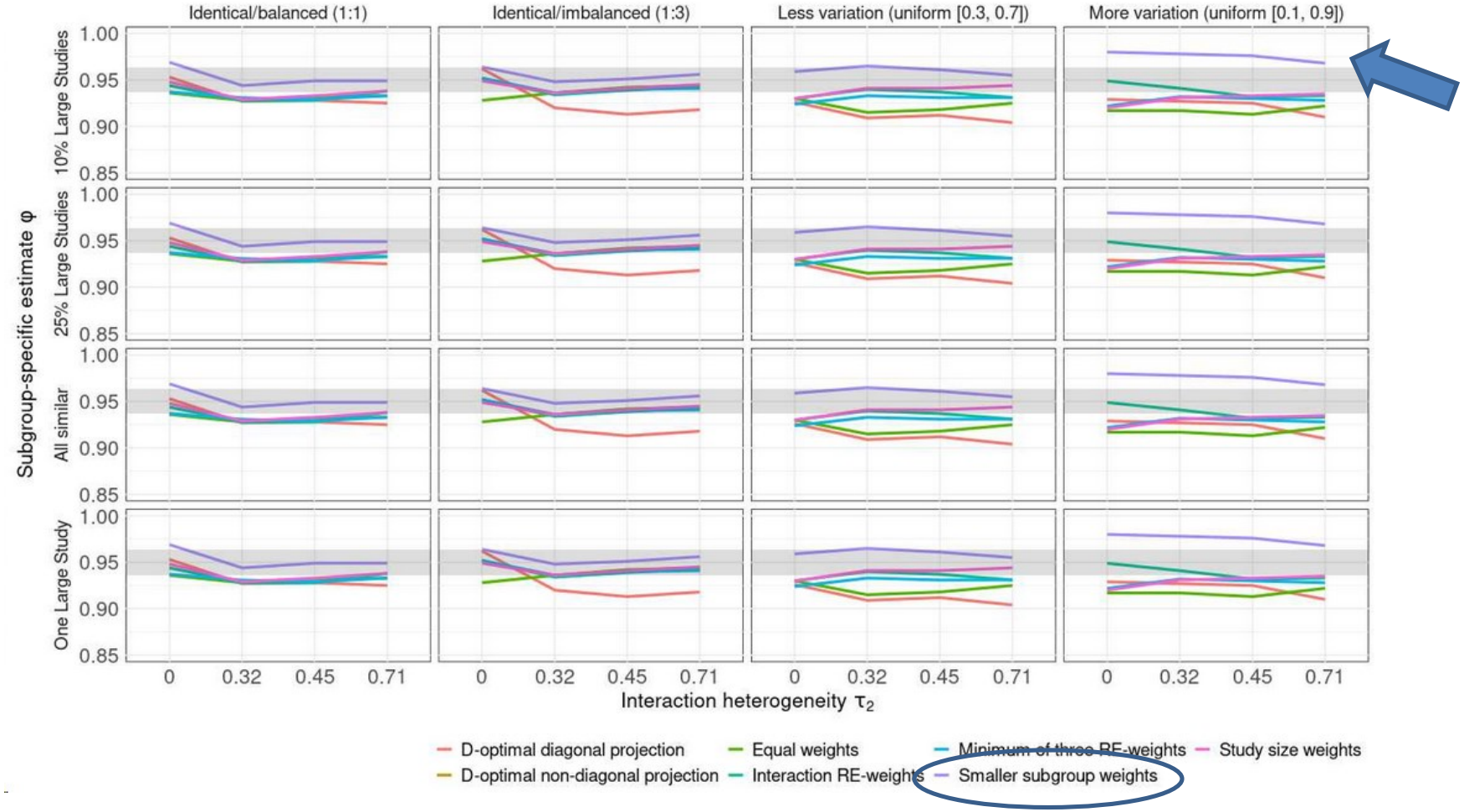
Weighted averages



- Prevalence adjusted DA holds coverage close to the nominal level when there is **little or no variation** and tends to **conservative estimation otherwise**.

Simulation study – Subgroup coverage

Model-based methods



- Smaller of the subgroup weights scheme holds coverage close to the nominal level when there is **little or no** subgroup-prevalence variation and tends to **conservative estimation otherwise**.

Summary and future investigation

- Although different, all the estimators for subgroups and interaction effects are (asymptotically) unbiased.
- Appropriate choice of weights guarantees agreement between contrast and subgroup estimates.
- Sometimes such weights result naturally e.g. with constant subgroup-prevalence across trials.
- Future work might include the improvement of heterogeneity matrices estimation and the case of few studies[6] in a Bayesian framework.[7]

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References

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2. Van Houwelingen, H. C., et al. "Advanced methods in meta-analysis: multivariate approach and meta-regression." Statistics in Medicine 21.4 (2002): 589-624.

3. Godolphin, P. J., et al. "Estimating interactions and subgroup-specific treatment effects in meta-analysis without aggregation bias: A within-trial framework." Research Synthesis Methods 14.1 (2023): 68-78.

4. Sørensen, A. L., et al. "Linear mixed models for investigating effect modification in subgroup meta-analysis." Statistical Methods in Medical Research 32.5 (2023): 994-1009.

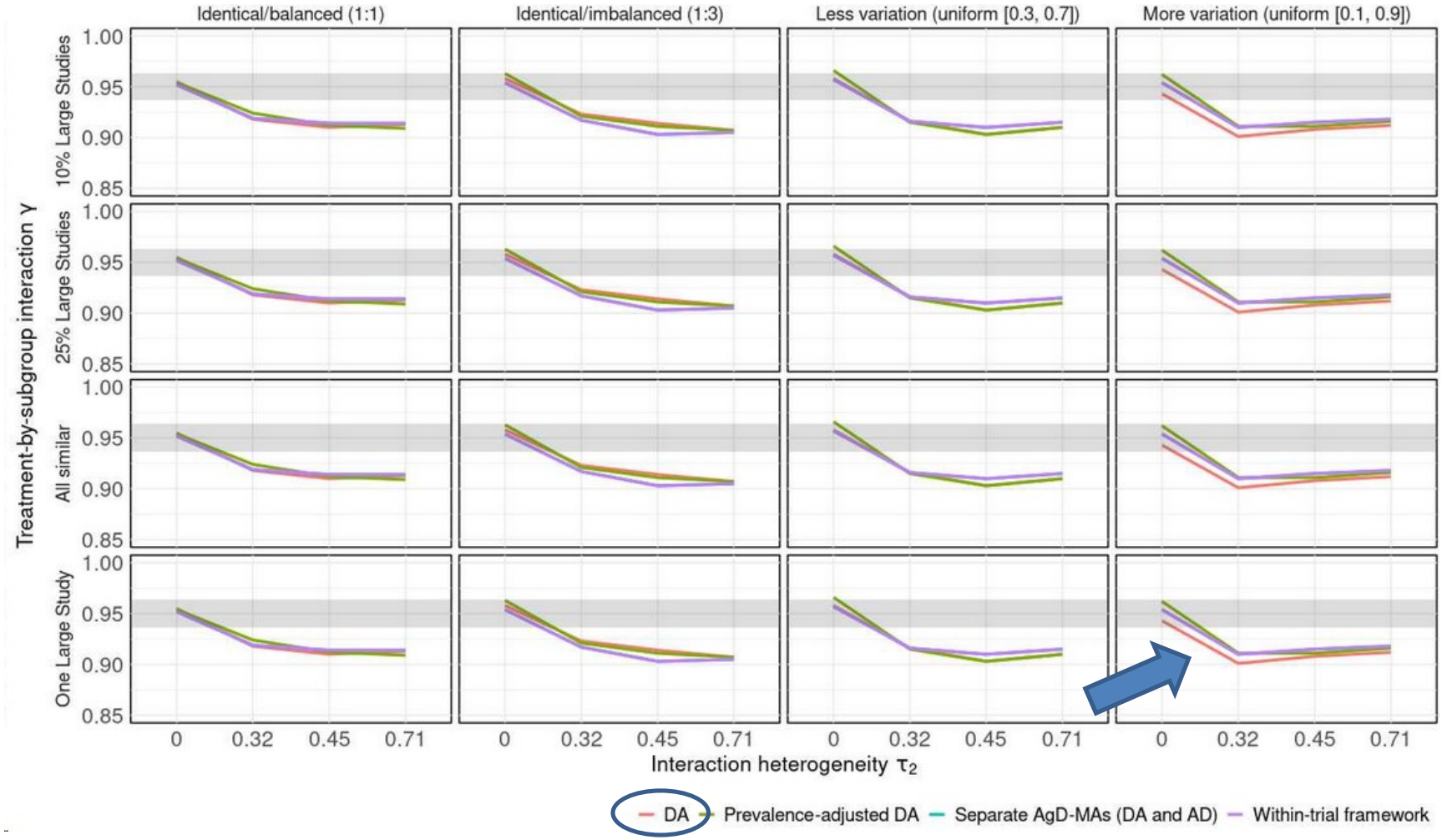
5. Hua, H., et al. "One-stage individual participant data meta-analysis models: estimation of treatment-covariate interactions must avoid ecological bias by separating out within-trial and across-trial information." Statistics in Medicine 36.5 (2017): 772-789.

6. Bender, R., et al. "Methods for evidence synthesis in the case of very few studies." Research Synthesis Methods 9.3 (2018): 382-392.

7. Friede, T., et al. "Meta-analysis of few small studies in orphan diseases." Research Synthesis Methods 8.1 (2017): 79-91.

Simulation study – Interaction coverage

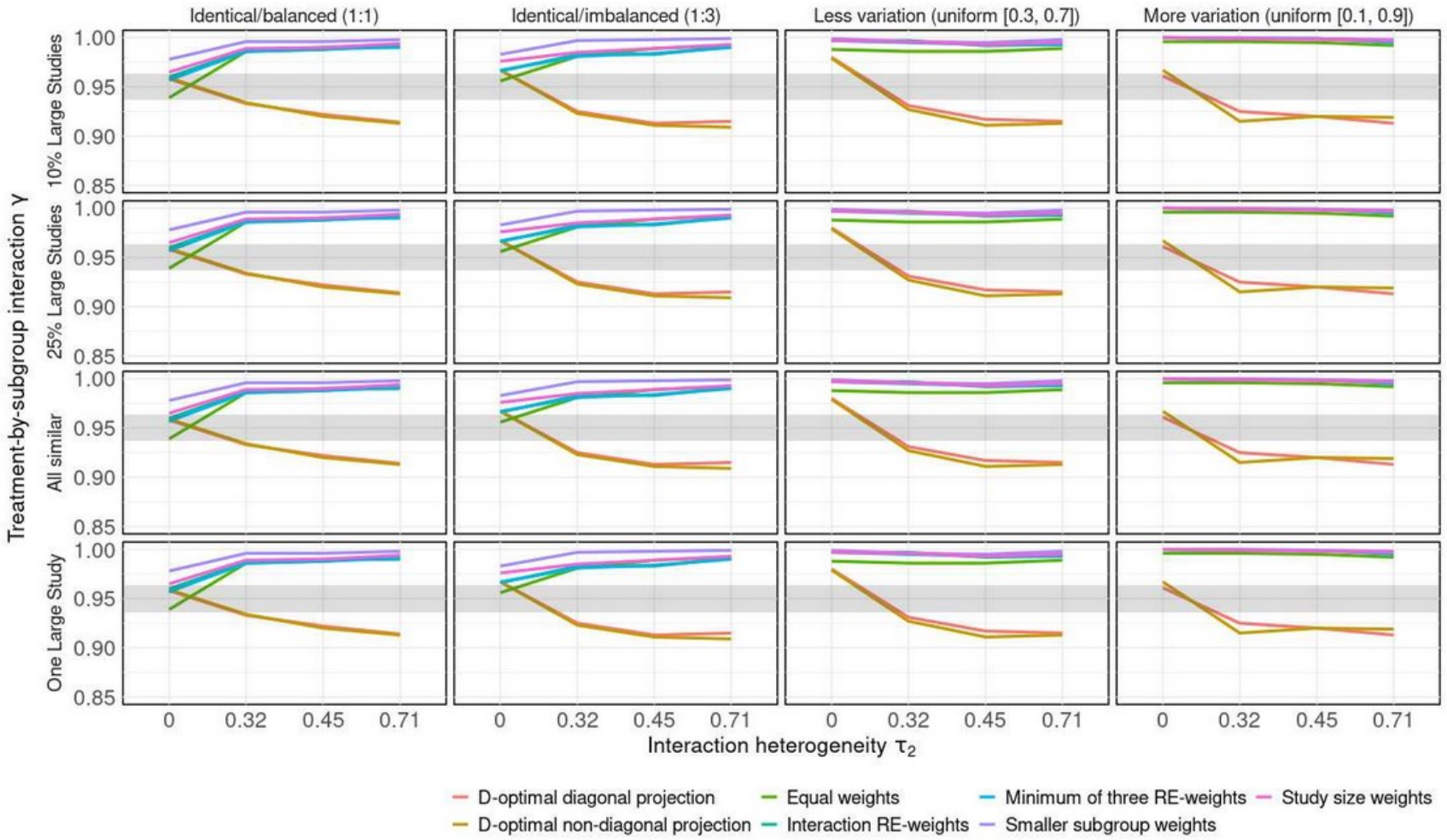
Model-based methods



- The Difference of averages (DA) has the lowest coverage **when subgroup prevalence varies** across studies.

Simulation study – Interaction coverage

Weighted averages



- Apart from D-optimal estimates, standard weighting methods provide **conservative** estimation of **interactions.**