Consistent Bayesian random-effects meta-analysis on subgroup-specific effects and interactions

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Content

Introduction

Why subgroup analyses matter

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- RCTs are often **underpowered** to detect differences in subgroups [2, 8].
- Subgroup comparisons motivated careful meta-analytic methods for treatment–covariate interactions [5, 6, 1, 7, 15].

Why meta-analysis becomes difficult

- Subgroup-MA estimates effects **within subgroups**; interaction-MA estimates **within-trial** effect **differences**.

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- Different analyses may therefore yield *seemingly contradictory estimates*.
- Subgroup-specific meta-analysis is appropriate as long as viewed in *isolation*.

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What is already known and what this work adds

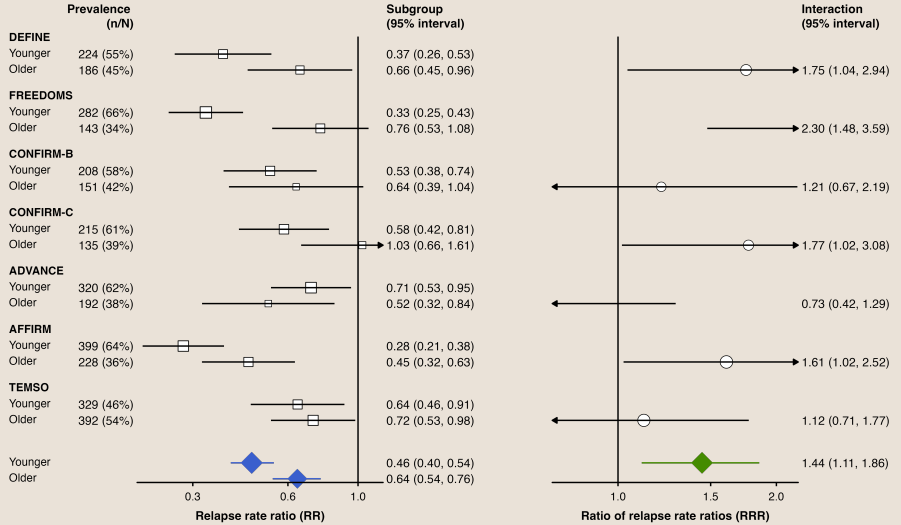
Already known

- Estimates align when subgroup prevalences are similar.
- Estimators may ensure algebraic matching [7, 10]

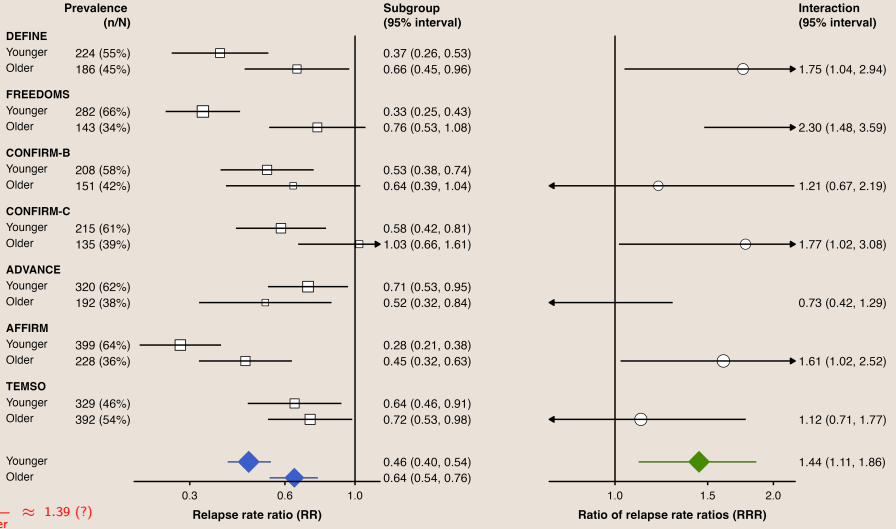
New in this work

- A new data model.
- Inference on interactions using subgroup-specific data.
- Transparent reporting of subgroup-specific effects.

Relapse rate reduction by age and disability score subgroups



Age < 40 vs. age ≥ 40 years: subgroup-specific RRs and interaction RRRs.



$\frac{RR_{Older}}{RR_{Younger}} \approx 1.39$ (?)

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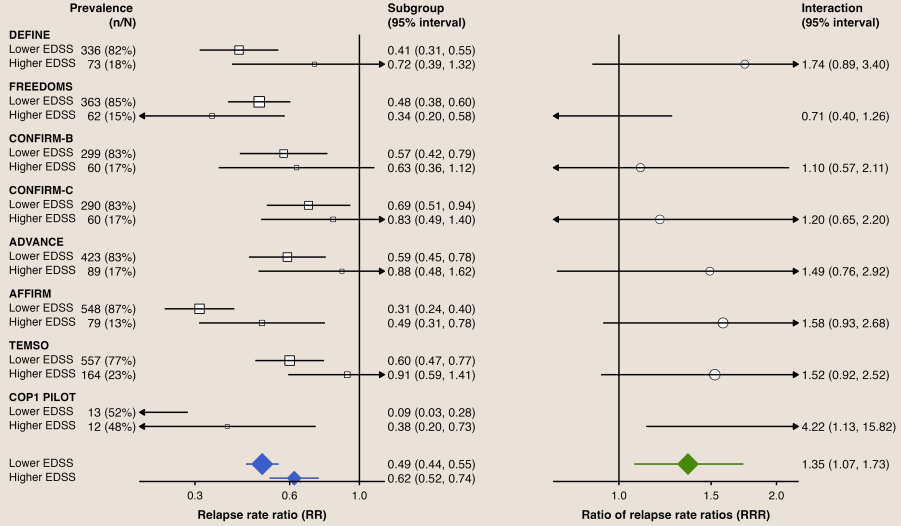
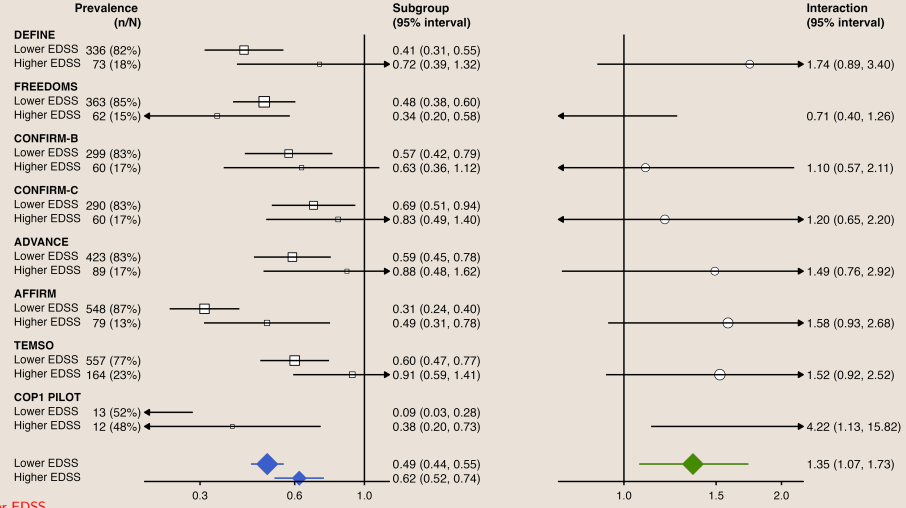


EDSS[2] ≤ 3.5 vs. EDSS > 3.5: subgroup-specific RRs and interaction RRRs.

[2]EDSS: Expanded Disability Status Scale (3.5 = "no walking impairment")



$\frac{RR_{\text{Higher EDSS}}}{RR_{\text{Lower EDSS}}} \approx 1.26$ (?)

EDSS[3] ≤ 3.5 vs. EDSS > 3.5: subgroup-specific RRs and interaction RRRs.

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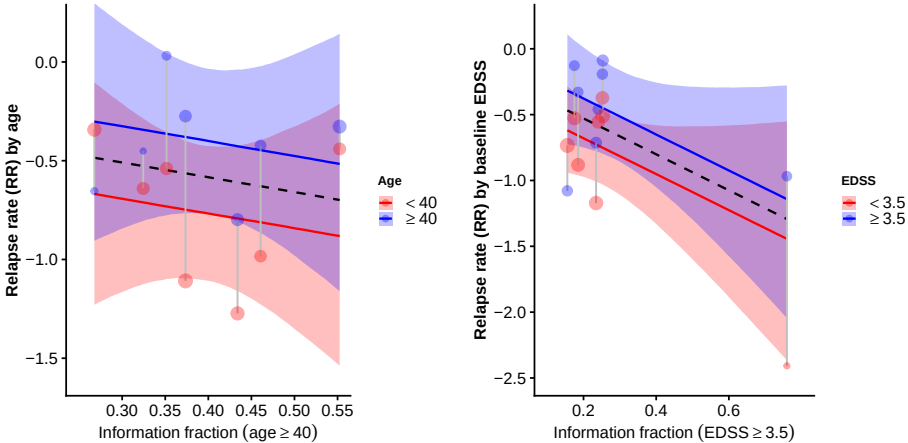
The problem of varying study contributions



Bubble plots show subgroup-specific effects by information fraction. The ecological slope can mix within-trial subgroup differences with between-trial case-mix variation.

Contribution-adjusted meta-analysis by subgroup (CAMS)

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CAMS is a contribution-centered model that includes the ecological slope:

$$y_{ij} = \alpha_j + \beta\,\pi_j + \gamma_j\left(x_{ij} - \pi_j\right) + \varepsilon_{ij},$$
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Motivated by treatment–covariate interactions in individual participant data (IPD) [11].

Equivalence of Interaction-MA and CAMS

With the **information fraction** $\pi_j = \frac{\sigma_{Bj}^{-2}}{\sigma_{Aj}^{-2}+\sigma_{Bj}^{-2}}$, the (rotated) likelihood factorizes as:

$$\begin{pmatrix} g_j \\ m_j \end{pmatrix} \sim \text{Normal}\left[\begin{pmatrix} \gamma \\ \alpha + \beta\pi_j \end{pmatrix}, \begin{pmatrix} \tau_\gamma^2 + \sigma_{Aj}^2 + \sigma_{Bj}^2 & 0 \\ 0 & \tau^2 + (1-\pi_j)^2\sigma_{Aj}^2 + \pi_j^2\sigma_{Bj}^2 \end{pmatrix}\right].$$

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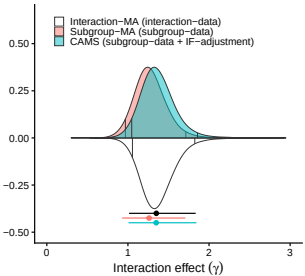
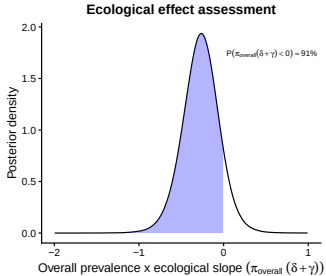
- Separates out interaction **and** treatment effect information.
- $m_j := \pi_j y_{Aj} + (1-\pi_j) y_{Bj}$: overall treatment effect (combined population).
- Prevalences (p_j) coincide with information fractions (π_j) [13] under the unit-information standard deviation (UISD) [12] assumption

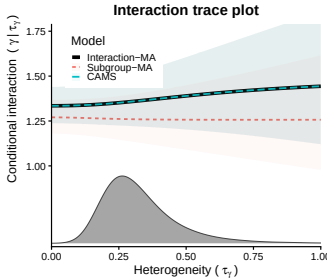
$$\pi_j \approx \frac{n_{Bj}/\sigma_u^2}{n_{Aj}/\sigma_u^2 + n_{Bj}/\sigma_u^2} = \frac{n_{Bj}}{n_{Aj}+n_{Bj}} = p_j,$$

Results

Interaction inference

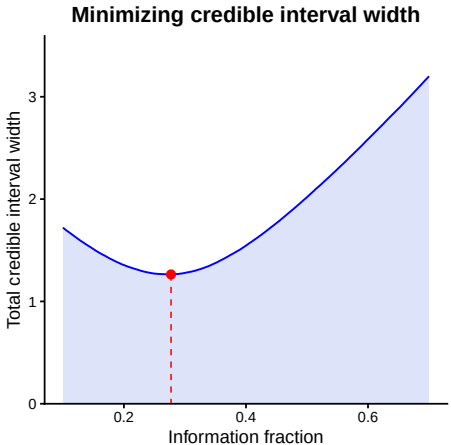


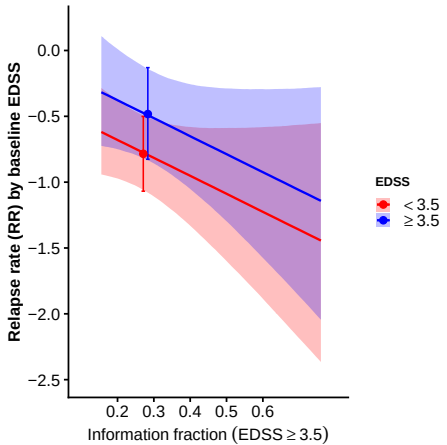




Contribution adjustment recovers interaction-MA inference in the presence of subgroup contribution variation.

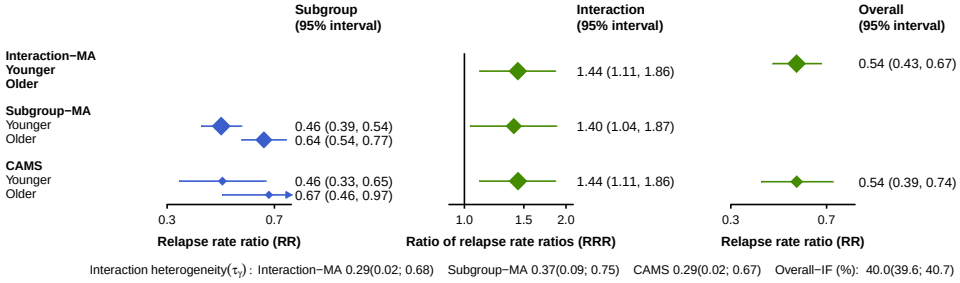
Dependence of estimates on the information fraction





The shortest interval may be statistically efficient, but can be optimistic and sensitive to observed trial composition.

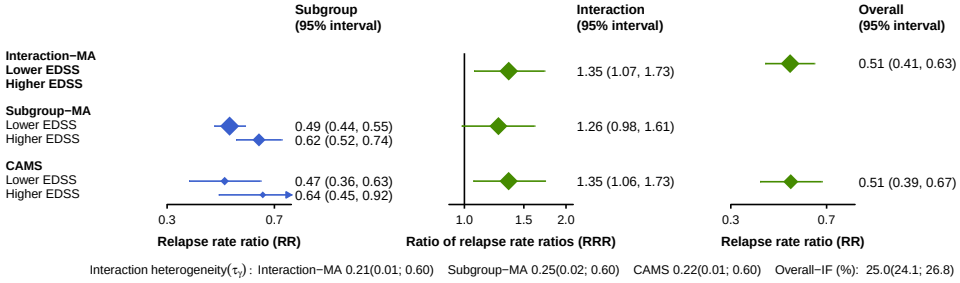
Age example



- The *overall information fraction* (overall-IF) is given by

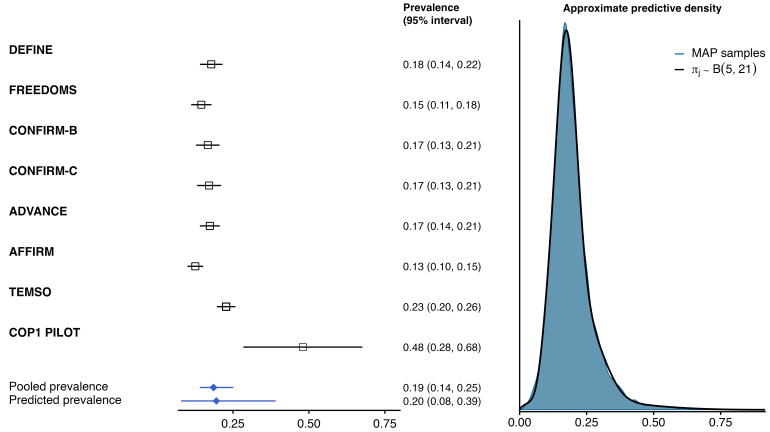
$$\tilde{\pi} = \frac{\sum_j w_j \pi_j}{\sum_j w_j}, \quad \text{where} \quad w_j = \frac{1}{\tau^2 + (1-\pi_j)^2 \sigma_{Aj}^2 + \pi_j^2 \sigma_{Bj}^2} \approx \frac{1}{\tau^2 + \frac{\sigma_u^2}{n_j}},$$

EDSS example



- COP PILOT 1 has little weight overall but high leverage in the interaction analysis.

Uncertainty propagation



Predictive prevalence for a new trial is approximated by a Beta distribution and can be propagated into subgroup-effect uncertainty.

Conclusions

Take-home messages

- Varying subgroup contributions can make subgroup-MA and interaction-MA disagree.
- After contribution adjustment, subgroup-data inference is equivalent to interaction-MA, including the interaction heterogeneity τ_γ.
- Subgroup-specific and overall effects can still be reported, but depend on a reported information fraction.
- Uncertainty propagation is especially useful to rule out a non-representative subgroup case mix.

Extensions and implementation

- CAMS can be used with Bayesian, likelihood, or frequentist formulations.
- Implementation is straightforward using standard R packages such as `brms` [3] and `metafor` [14].
- Extensions to multi-arm and network meta-analysis settings are natural future directions.
- Prior specification remains important when only a small number of trials are available.

Thank you for your attention

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Pre-prints on arXiv

Renato Panaro, Christian Röver **and** Tim Friede. "Subgroup comparisons within and across studies in meta-analysis". **in***arXiv preprint arXiv:2508.15531*: (2025)

Renato Panaro, Christian Röver **and** Tim Friede. "Consistent Bayesian meta-analysis on subgroup specific effects and interactions". **in***arXiv preprint arXiv:2512.18785*: (2025)

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