To Adjust or Not to Adjust for Effect Modifiers in HTA Submissions; Considerations in Population-Adjusted Indirect Treatment Comparisons

Multi-Level Network Meta-Regression

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Thanks to: David Phillippo (University of Bristol)

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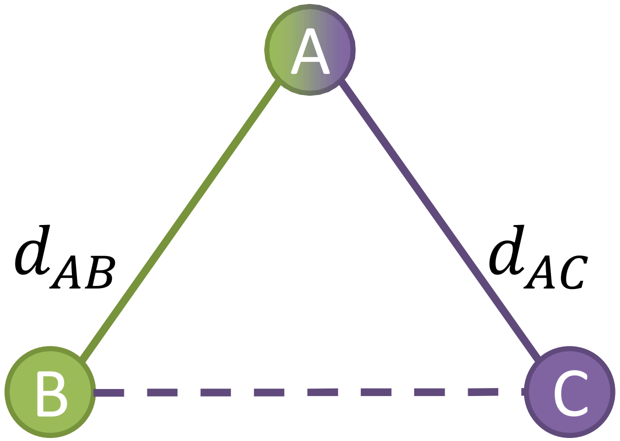
Indirect Comparisons: Assumption

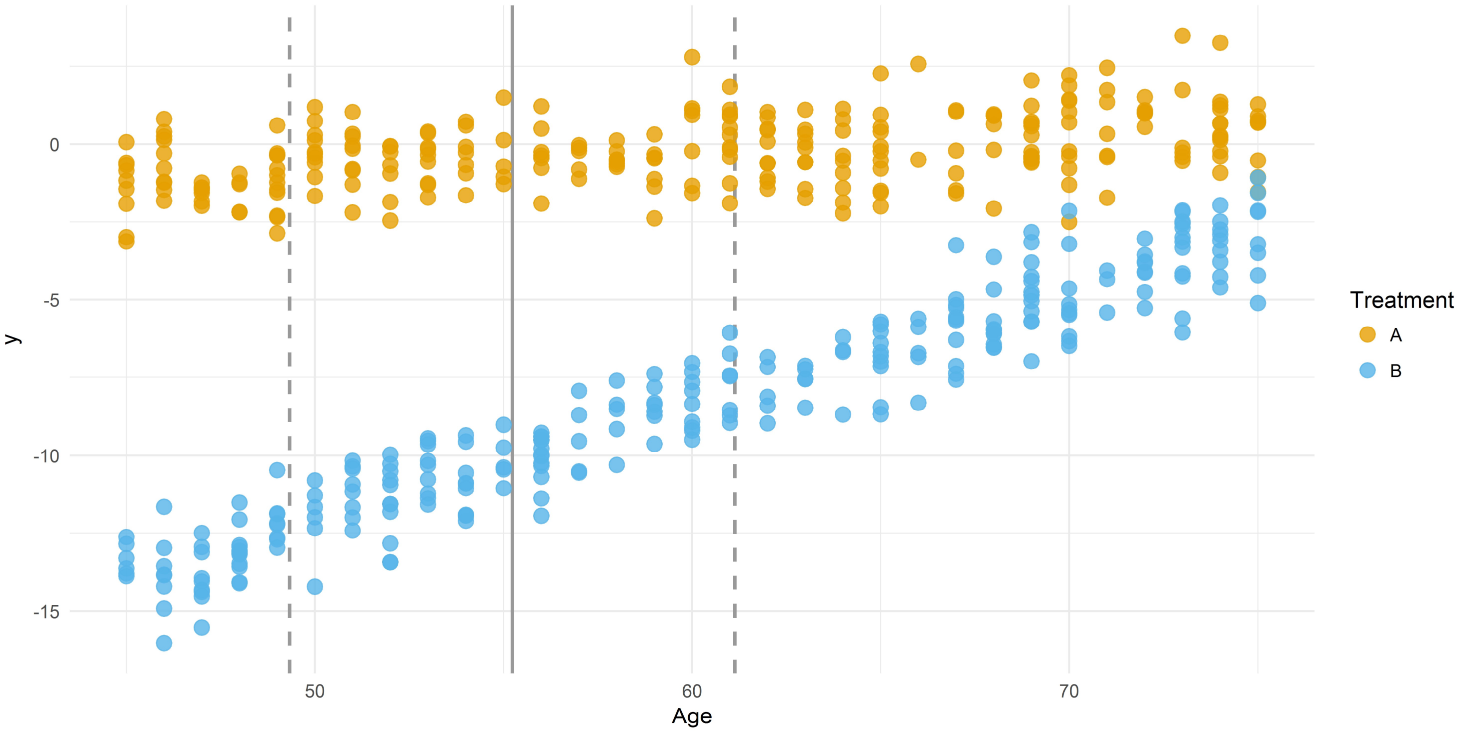


- Biased if there are imbalances in effect modifiers between AB and AC
- Population Adjusted Indirect Comparisons have been proposed to adjust for this
  - when there is IPD for AB study and aggregate data for the AC study

Matching-Adjusted Indirect Comparison (MAIC)

Signorovitch et al. (2010)

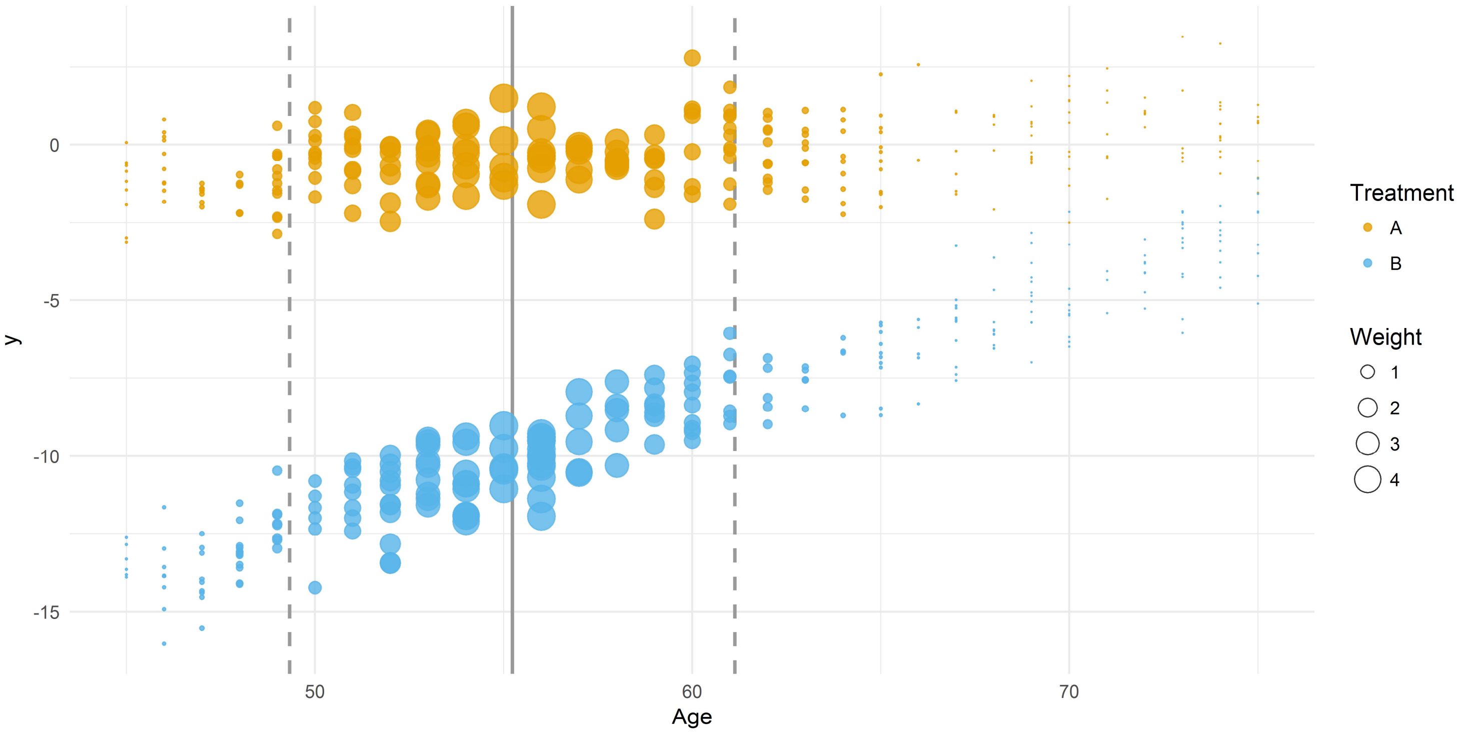
- Population reweighting method (similar to propensity score re-weighting)
- Weight AB individuals to balance covariate distribution with AC trial



Matching-Adjusted Indirect Comparison (MAIC)

Signorovitch et al. (2010)

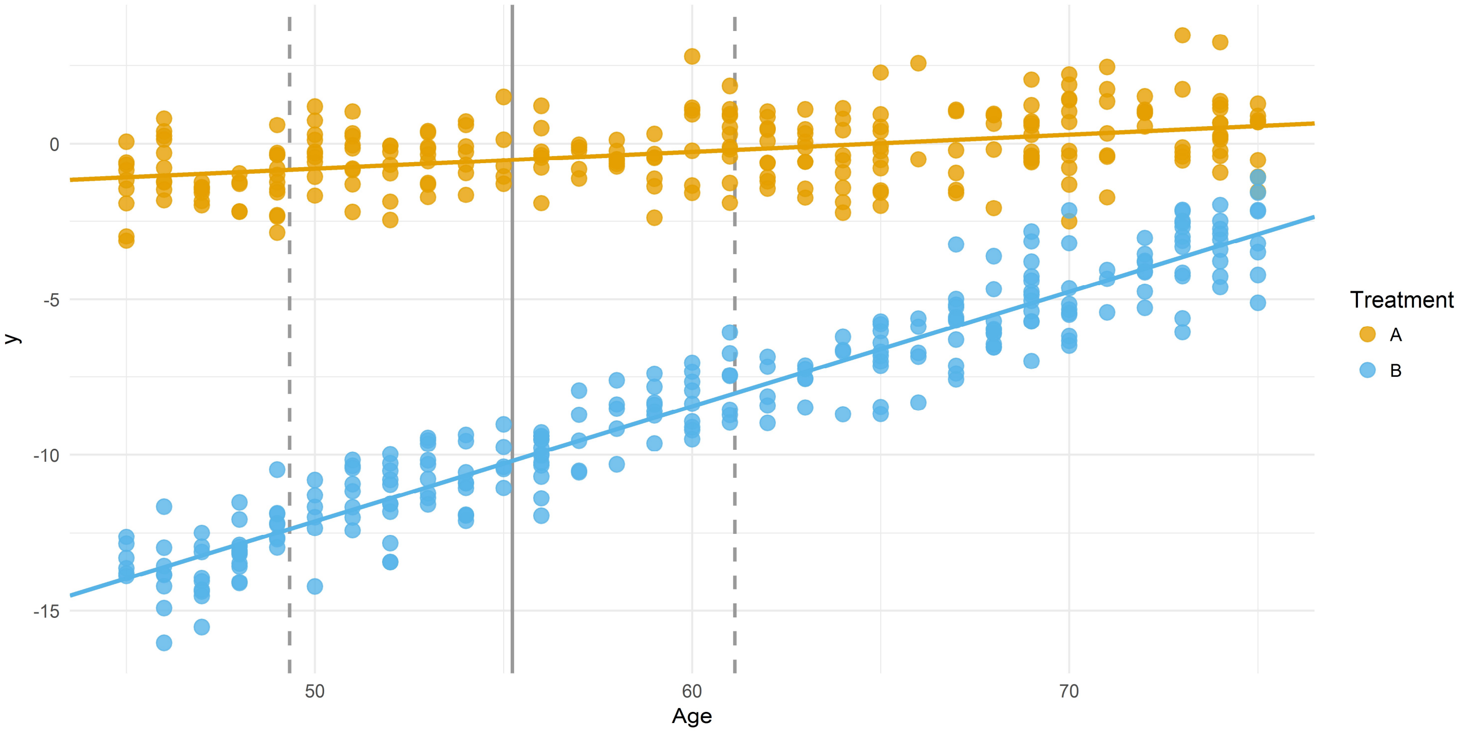
- Population reweighting method (similar to propensity score re-weighting)
- Weight AB individuals to balance covariate distribution with AC trial
- Requires AC population to be contained in the AB population
- Estimates are valid for the AC (Aggregate Data) population
- Cannot be used for networks of evidence



Simulated Treatment Comparisons (STC)

Ishak et al. (2015)

- Create an outcome regression model in the AB trial
- Use this to predict mean outcomes on treatments A and B in the AC trial population
- Can handle some lack of overlap, but relies on extrapolation
- Estimates are valid for the AC (Aggregate Data) population
- Vulnerable to aggregation bias
- Cannot be used for networks of evidence



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Multilevel Network Meta-Regression (ML-NMR)

Phillippo et al (2020)

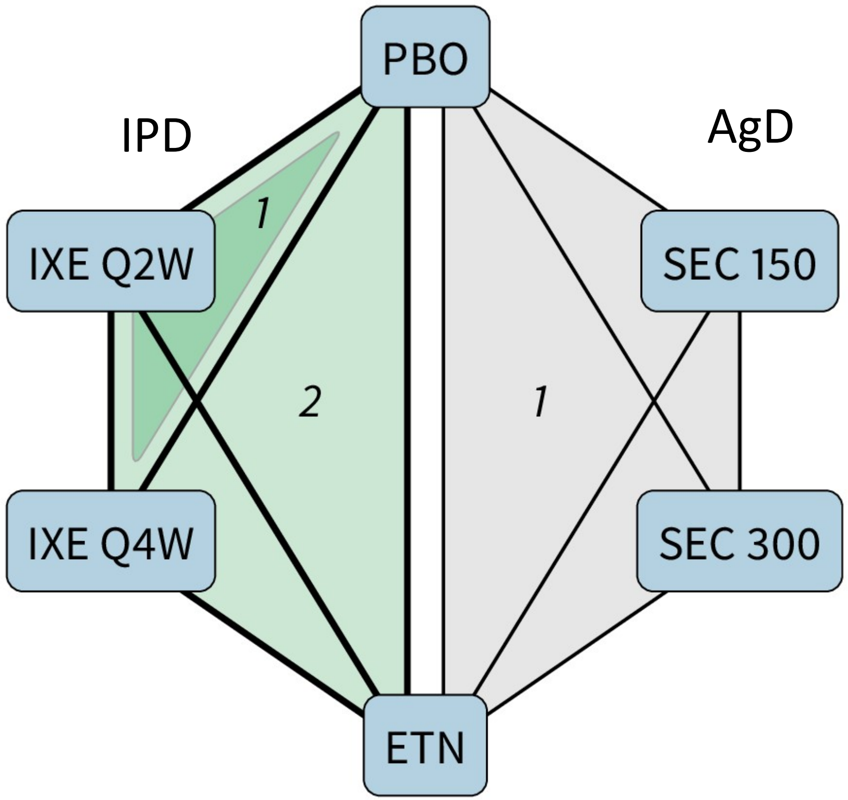
- Combines IPD and Aggregate Data
  - Using an individual-level regression model integrated over covariate distribution
- General framework
  - Builds on previous approaches
    - Jackson et al. (2006, 2008), Jansen (2012)
  - Special cases
    - Standard NMA with no adjustment
    - IPD network meta-regression with full IPD
- Can be used in networks of all sizes
- Produces estimates in any specified target population

ML-NMR: Assumptions about EM Interactions

- Common/shared EM interactions
  - May be justified for treatment classes
- Independent EM interactions
  - Requires IPD, or several AgD studies at different covariate values, on each treatment
- Exchangeable EM interactions
  - Similar data requirements to independent EM interactions
  - Hard to estimate in practice

Example: Plaque Psoriasis (ML-NMR)

- Two treatment classes (plus placebo)
  - IL blocker
  - anti-TNFa



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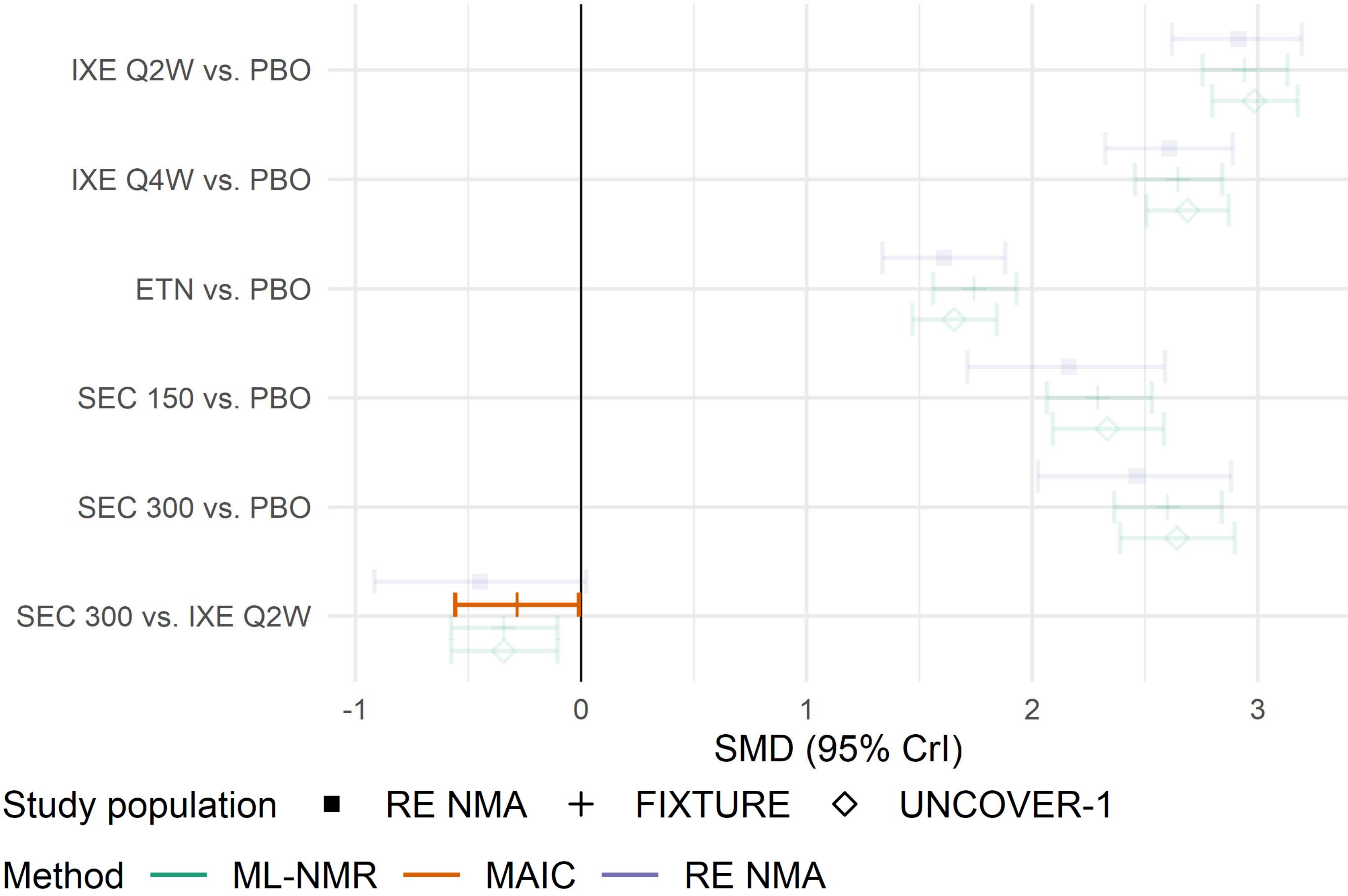
Identifying Important Covariates

- Based on individual patient data
  - Interaction tests / subgroup analyses / regression models ... but lack of power
- Expert clinical opinion / previous studies
- Need to be reported in all studies
  - omit individuals with missing covariates, or use imputation techniques
- Five covariates identified in psoriasis example
  - duration of psoriasis, body surface area, weight, previous systemic treatment, psoriatic arthritis
- Shared effect modifier assumption made for treatments within the same class



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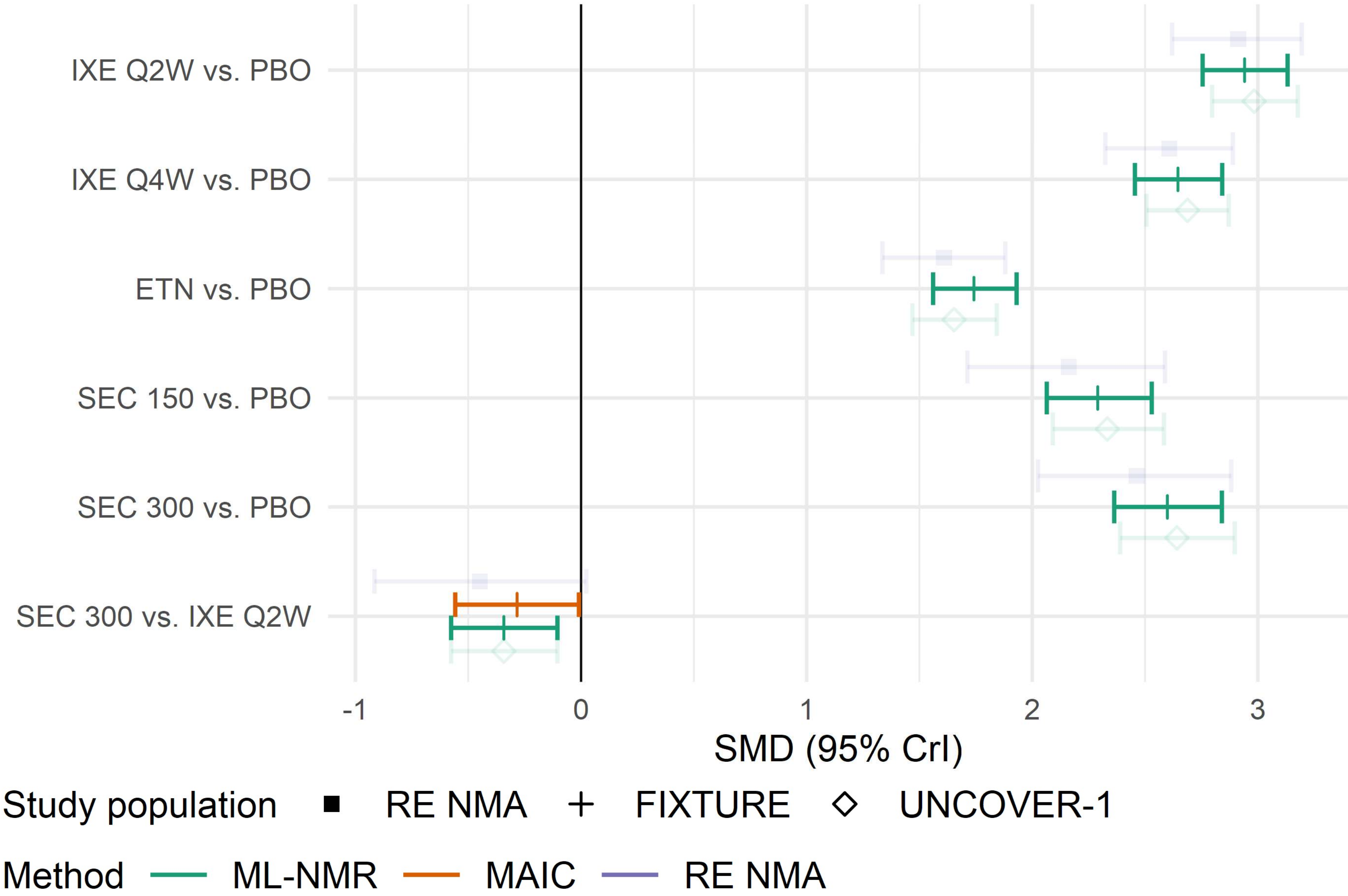

- Produce a full set of coherent estimates
- Reduced uncertainty compared to MAIC

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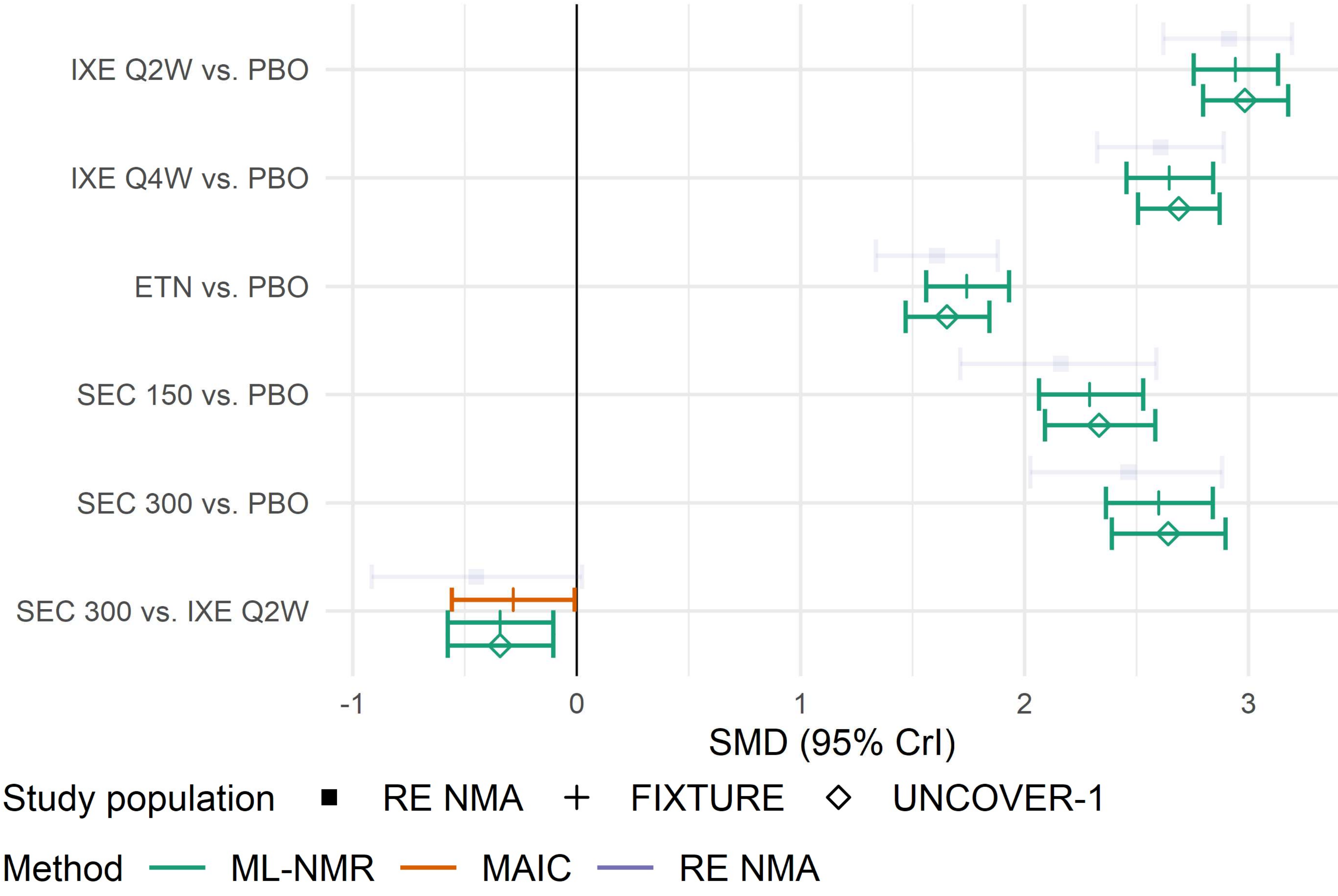
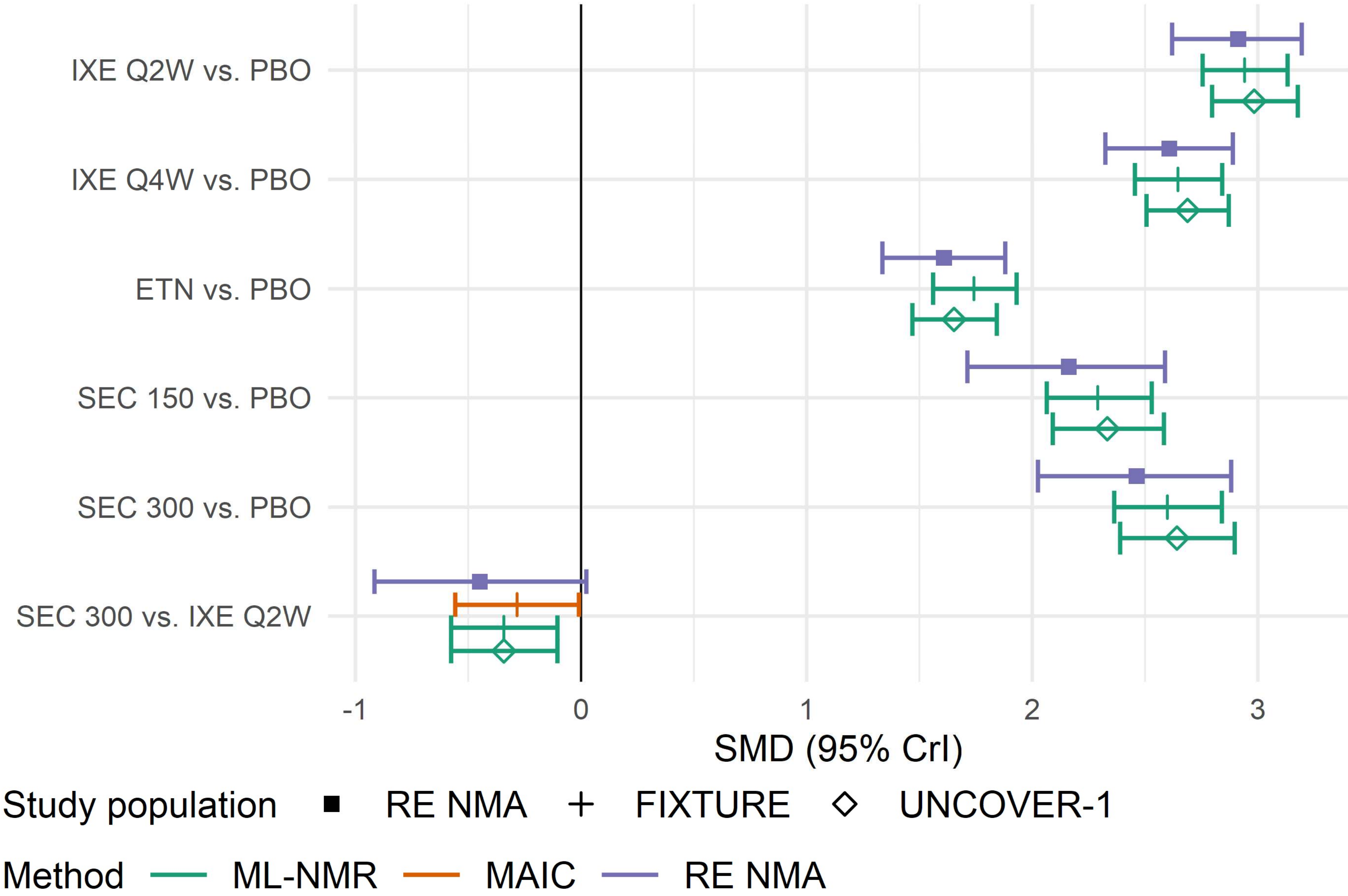


- Produce a full set of coherent estimates - in any target population
- Reduced uncertainty compared to MAIC



- Produce a full set of coherent estimates - in any target population
- Reduced uncertainty compared to MAIC
- Substantially reduced uncertainty compared to RE NMA

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Findings from a Simulation Study

Phillippo 2020

- ML-NMR and STC both performed similarly well throughout
  - Both incur bias when extrapolation or shared EM assumption invalid
  - ML-NMR not seen to be sensitive to additional assumptions regarding joint covariate distribution in AgD population
- MAIC performed poorly in almost all scenarios, in some cases even increasing bias compared to a standard Bucher IC
  - Especially with small sample sizes
  - Needs full overlap to be unbiased, and for stable estimation of SE
- All methods susceptible to bias (and resulting under-coverage) when missing any EMs
  - Highlights the need for careful, justified variable selection (TSD 18)

Recommendations for Practice

- Use regression methods (ML-NMR, STC) over weighting methods (MAIC) when populations do not fully overlap
  - i.e. when AgD study population not fully contained within IPD population
  - Important to examine covariate distributions, and ESS for MAIC
- Use network meta-analysis based methods (ML-NMR) when presented with more than 2 studies
  - Repeated MAIC/STC will not give coherent or compatible estimates
  - Standard heterogeneity and inconsistency checks can assess assumptions in connected networks

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