Multilevel network meta-regression for population adjustment based on individual and aggregate level data

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Overview

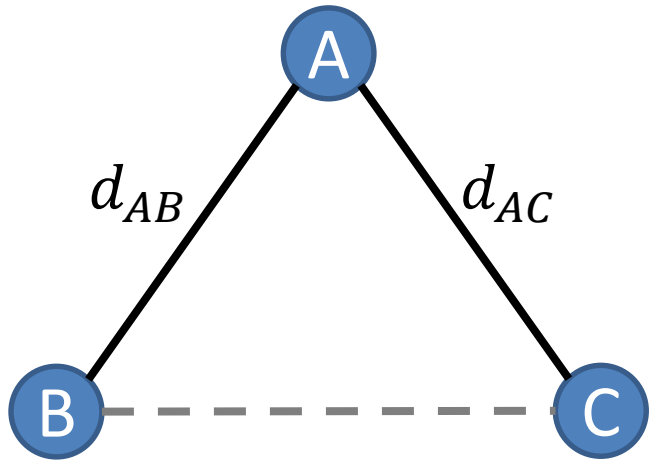
- Background
- Multilevel Network Meta-Regression
- Example – plaque psoriasis
- Conclusions and discussion

Background

We wish to compare multiple treatments, but not all are studied in the same trial

Standard methods using aggregate data:

- Indirect comparison: $d_{BC} = d_{AC} - d_{AB}$
- Network meta-analysis (NMA)



- Assume constancy of relative effects:

$$d_{AB(AB)} = d_{AB(AC)}$$

- Biased if there are differences in effect modifiers between studies

Background

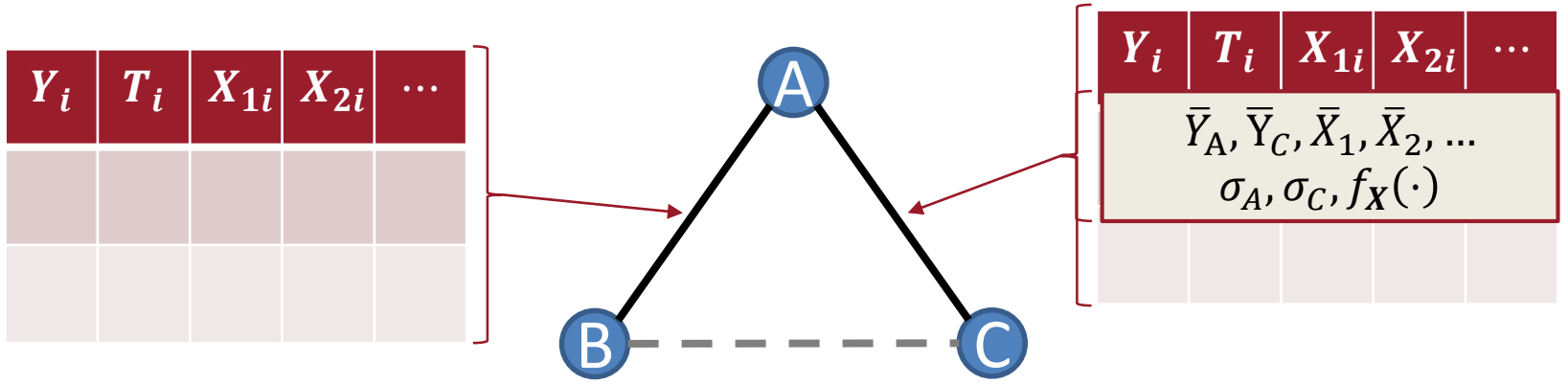
Population adjustment methods make use of available IPD to adjust for effect modifiers

Ideal scenario: full IPD

- "Gold standard" is IPD meta-regression

Common scenario: limited IPD

- Several recent methods make use of mixed data



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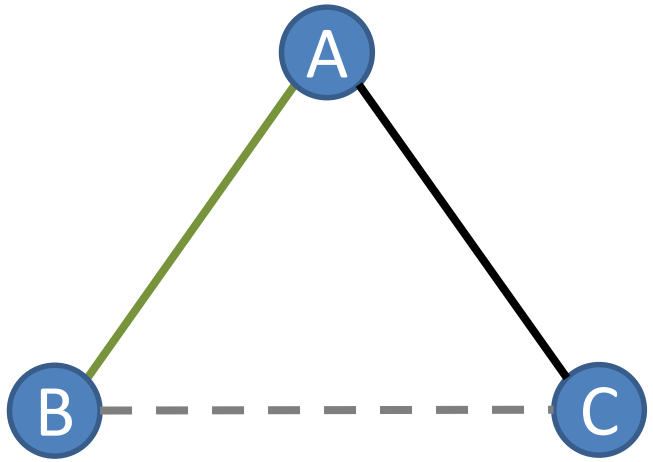
Population adjustment: MAIC and STC

Matching-**A**djusted **I**ndirect **C**omparison	**S**imulated **T**reatment **C**omparison
• Population reweighting method	• Outcome regression method
• Weight AB individuals to balance covariate distribution with AC trial	• Fit regression model in AB trial
• Estimate outcomes on A and B in AC trial using weights	• Estimate outcomes on A and B in AC trial using regression model



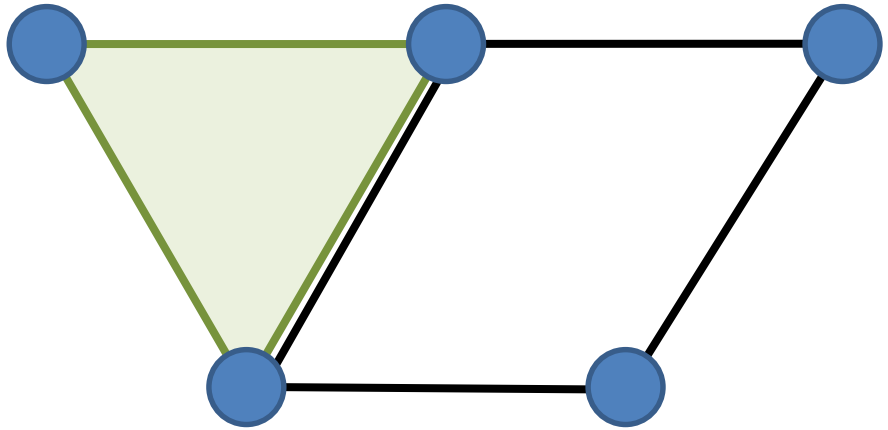
Limitations

- Limited to pairwise indirect comparisons
- Comparisons stuck in aggregate (AC) population

Population adjustment: larger networks

Meta-regression with “split” effects

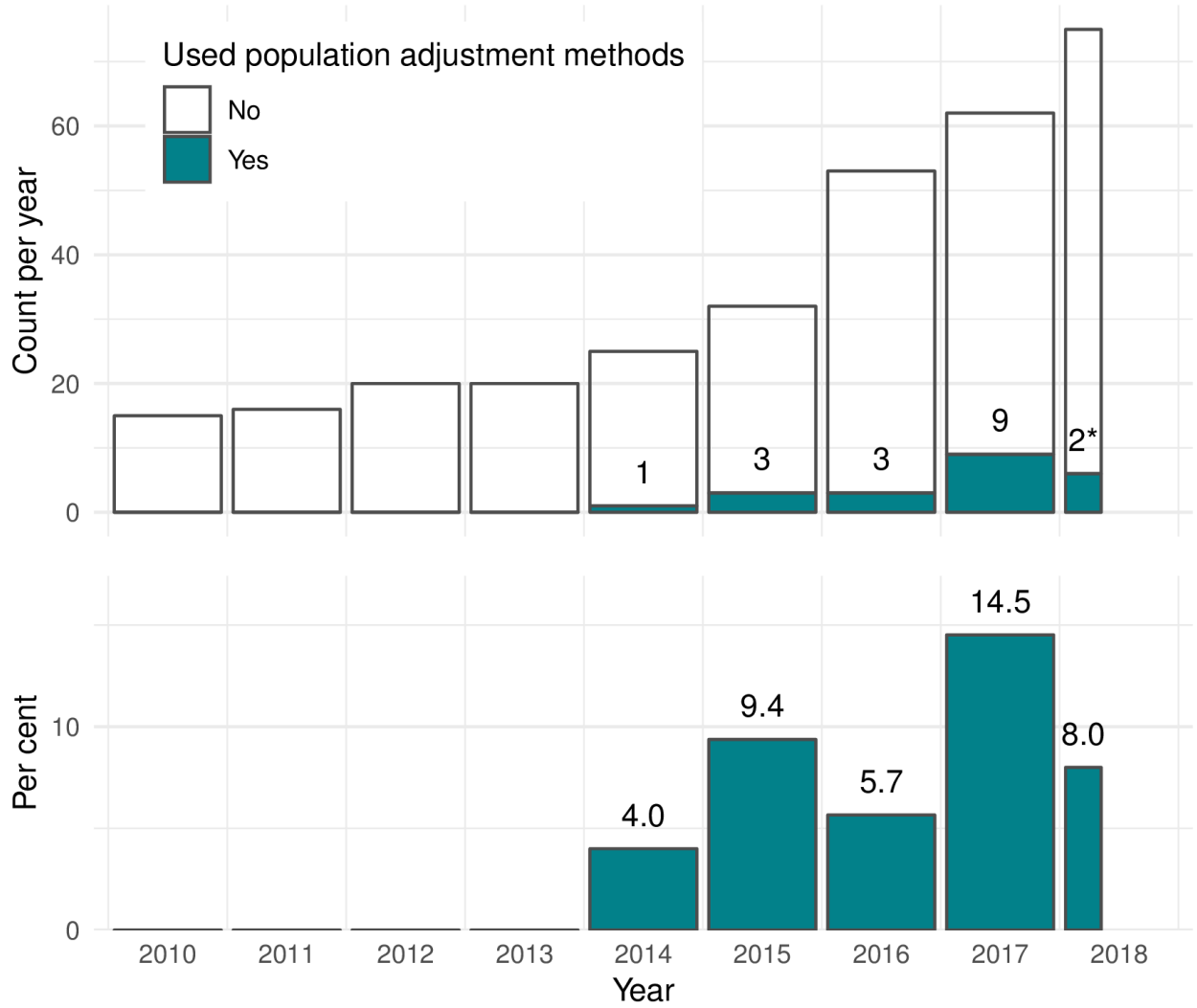
- Extends network meta-analysis framework
- Account for aggregation bias with split (between and within study) interaction terms



Limitations

- Less interpretable
- Not identifiable in small networks

Population adjustment in NICE Technology Appraisals



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Motivation

We require a population adjustment method that:

- Is applicable in networks of all sizes
- Avoids aggregation bias
- Produces estimates in any target population
- Extends the standard network meta-analysis (NMA) framework, reducing to:
  - IPD network meta-regression with full IPD
  - Standard NMA with no IPD and no adjustment

Multilevel Network Meta-Regression (ML-NMR)

Multilevel Network Meta-Regression

1. Define an individual-level regression model
   - IPD network meta-regression
2. Average (integrate) this over the aggregate population(s) to form the aggregate-level model

Individual:

$$y_{ijk} \sim \pi_{\text{Ind}}\left(\theta_{ijk}\right)$$

$$g\left(\theta_{ijk}\right) = \eta_{jk}\left(\boldsymbol{x}_{ijk}\right) = \mu_j + \boldsymbol{x}_{ijk}^T\left(\boldsymbol{\beta}_1 + \boldsymbol{\beta}_{2,k}\right) + \gamma_k$$

Aggregate:

1 $$y_{\cdot jk} \sim \pi_{\text{Agg}}\left(\theta_{\cdot jk}\right)$$

2 $$\theta_{\cdot jk} = \int_{X} g^{-1}\left(\eta_{jk}\left(\boldsymbol{x}\right)\right) f_{jk}\left(\boldsymbol{x}\right) d\boldsymbol{x}$$

ML-NMR

1. From individual to aggregate likelihood

$$y_{ijk} \sim \pi_{\text{Ind}}\left(\theta_{ijk}\right) \longrightarrow y_{\bullet jk} \sim \pi_{\text{Agg}}\left(\theta_{\bullet jk}\right)$$

- Straightforward in many cases
  - E.g. sum of Normal or Poisson outcomes
- Sum of independent binary outcomes with different event probabilities is Poisson Binomial
  - Approximate with first or second order Binomial

ML-NMR

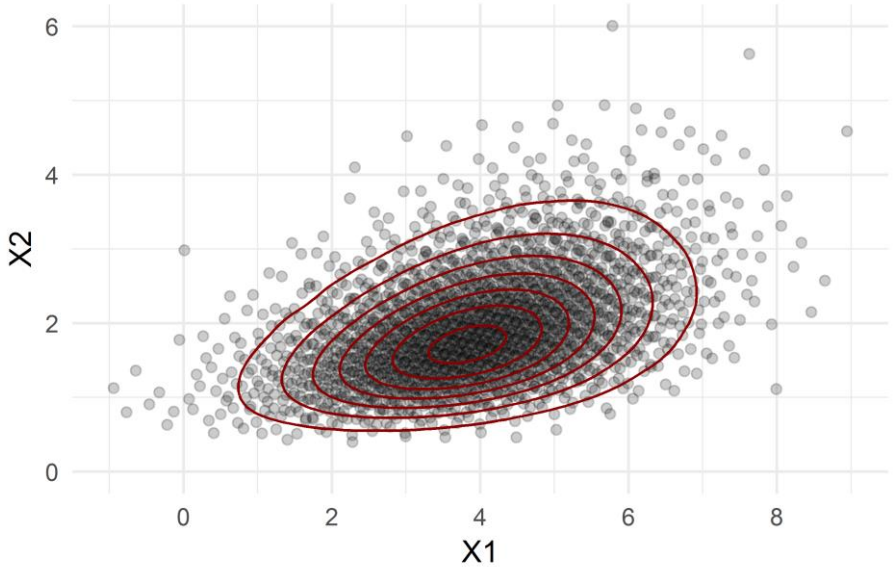
2. Integration over a population

$$\theta_{\bullet jk} = \int_{X} g^{-1}\left(\eta_{jk}\left(\boldsymbol{x}\right)\right) f_{jk}\left(\boldsymbol{x}\right) d\boldsymbol{x}$$

- Straightforward if
  - Link function is identity – plug in mean covariate values
  - Covariates are discrete – integration becomes summation
- Possible if covariates are Normal
- In general, use numerical integration

ML-NMR using Quasi Monte Carlo integration

1. Generate quasi-random points from the joint distribution in the aggregate population
   - Assume form of marginal distributions match those in the IPD
   - Impute correlation structure from IPD using copulae



2. Evaluate the integrand at these points and take the mean

$$\frac{1}{\tilde{N}}\sum_{i=1}^{\tilde{N}} g^{-1}\left(\eta_{jk}\left(\tilde{\boldsymbol{x}}\right)\right) \quad \square \quad \int_{\mathrm{X}} g^{-1}\left(\eta_{jk}\left(\boldsymbol{x}\right)\right) f_{jk}\left(\boldsymbol{x}\right) d\boldsymbol{x}$$

Predictions for a target population

The target population could be represented by

- A randomised trial
- An observational study
- A registry dataset
- …

With IPD covariate information

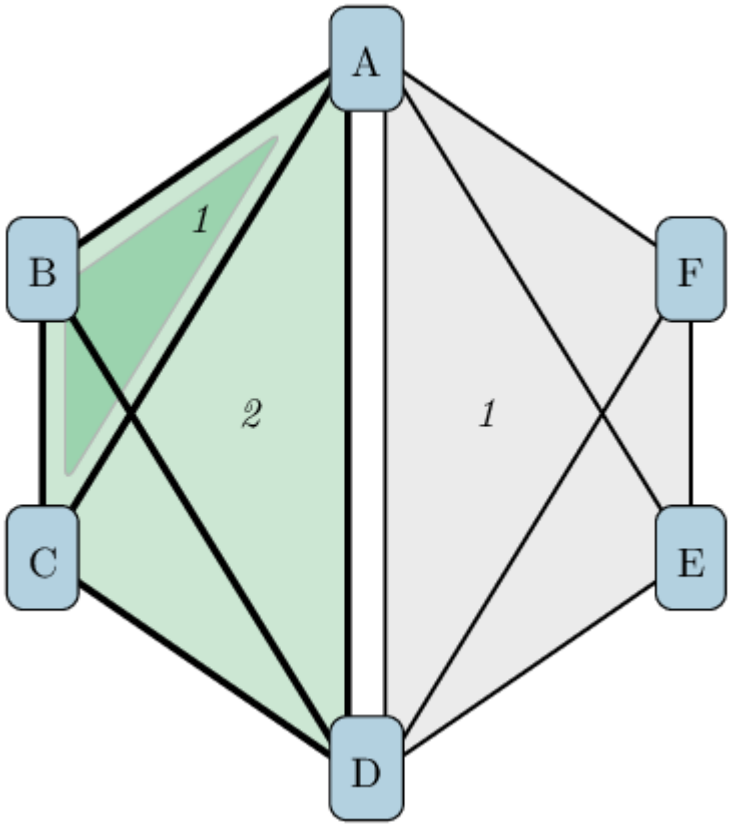
1. Make predictions for each individual
2. Summarise these for the population

With summary statistics

1. Generate integration points from joint covariate distribution
2. Integrate over the target population

When working on the linear predictor scale, both are equivalent to "plugging-in" mean covariate values.

Example: Plaque Psoriasis



- Six treatments for plaque psoriasis
- Three **IPD** studies
- One **AgD** study
- Outcomes are binary response on PASI scale (75%, 90%, 100%)
- Five potential effect modifiers to adjust for
  - Previous systemic treatment
  - Duration of psoriasis
  - Body surface area
  - Weight
  - Psoriatic arthritis

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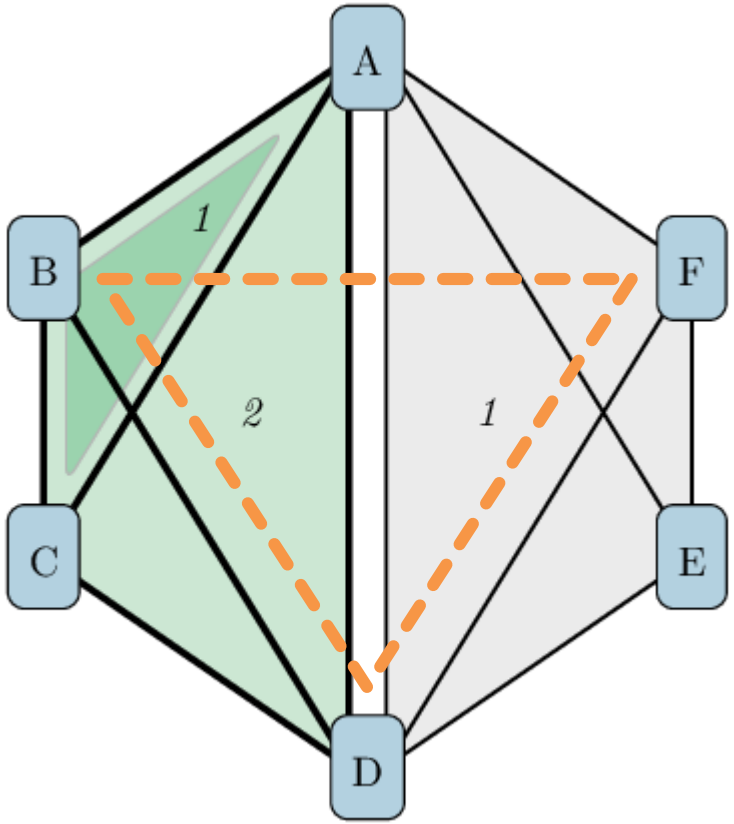
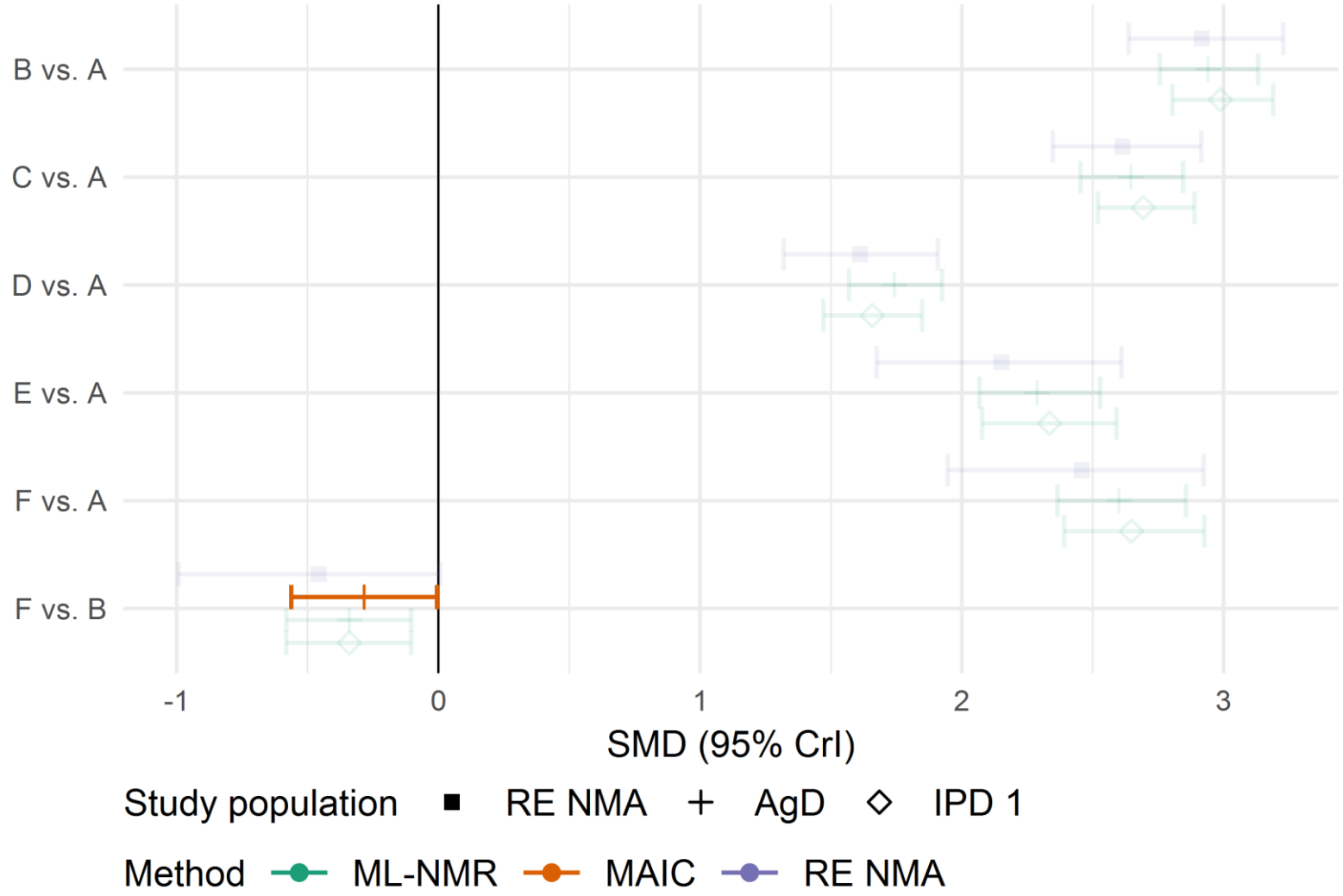
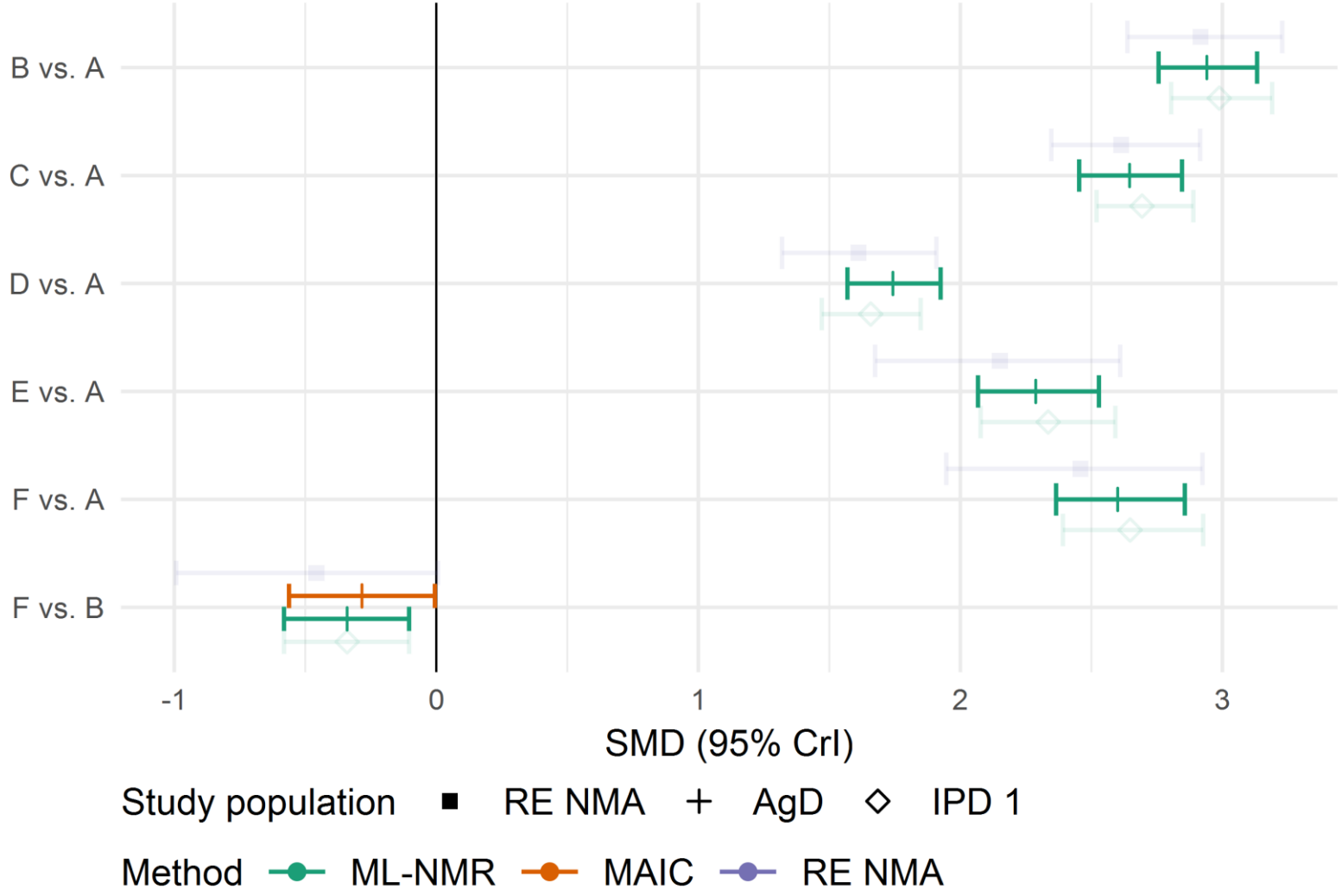
Example: Plaque Psoriasis



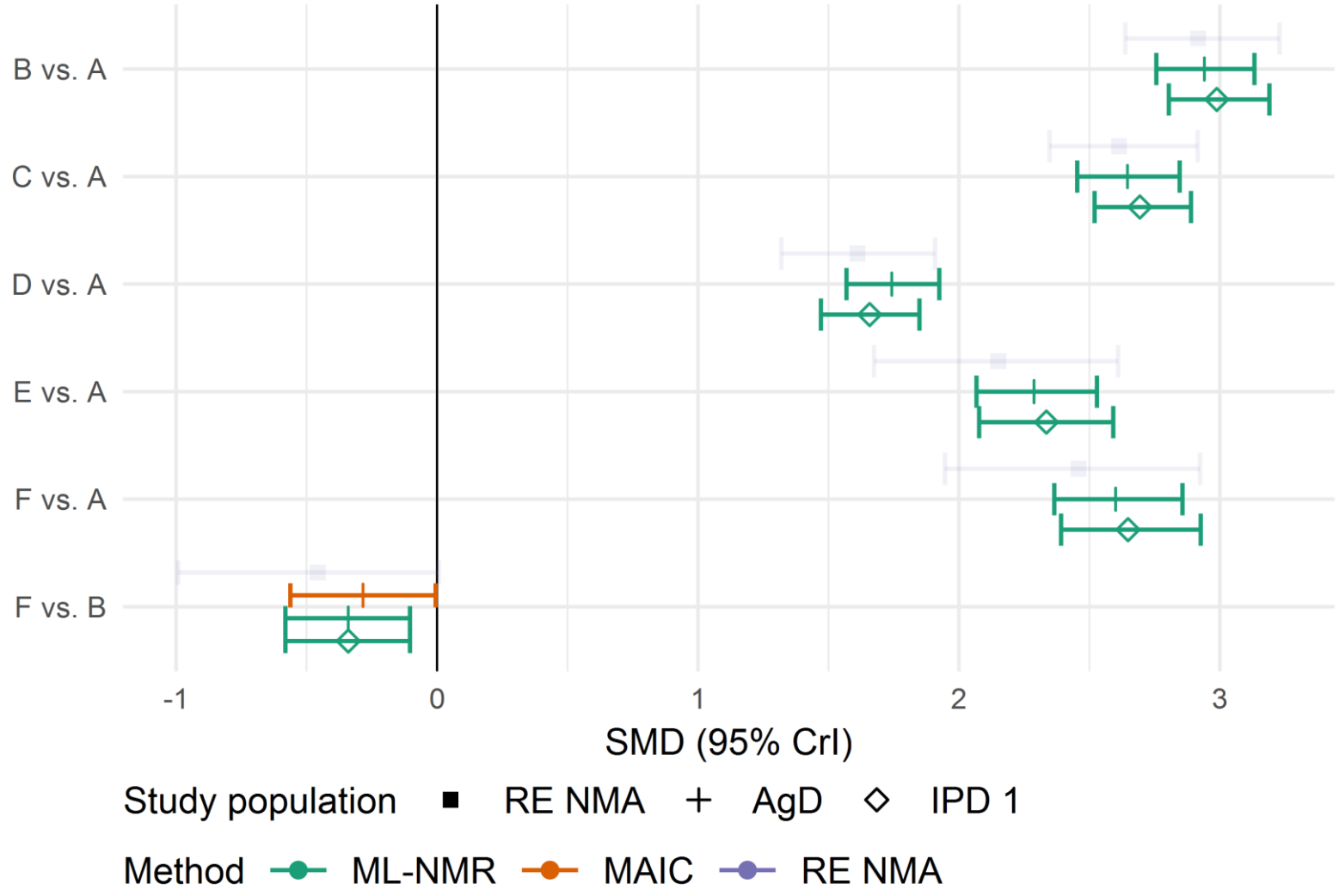
Previous MAIC compared treatments B and F via D

- Could have used common comparator A instead
- Threw away all information from one IPD study with no D arm
- Estimates only in aggregate population
- Unable to obtain a coherent set of effect estimates for all treatments

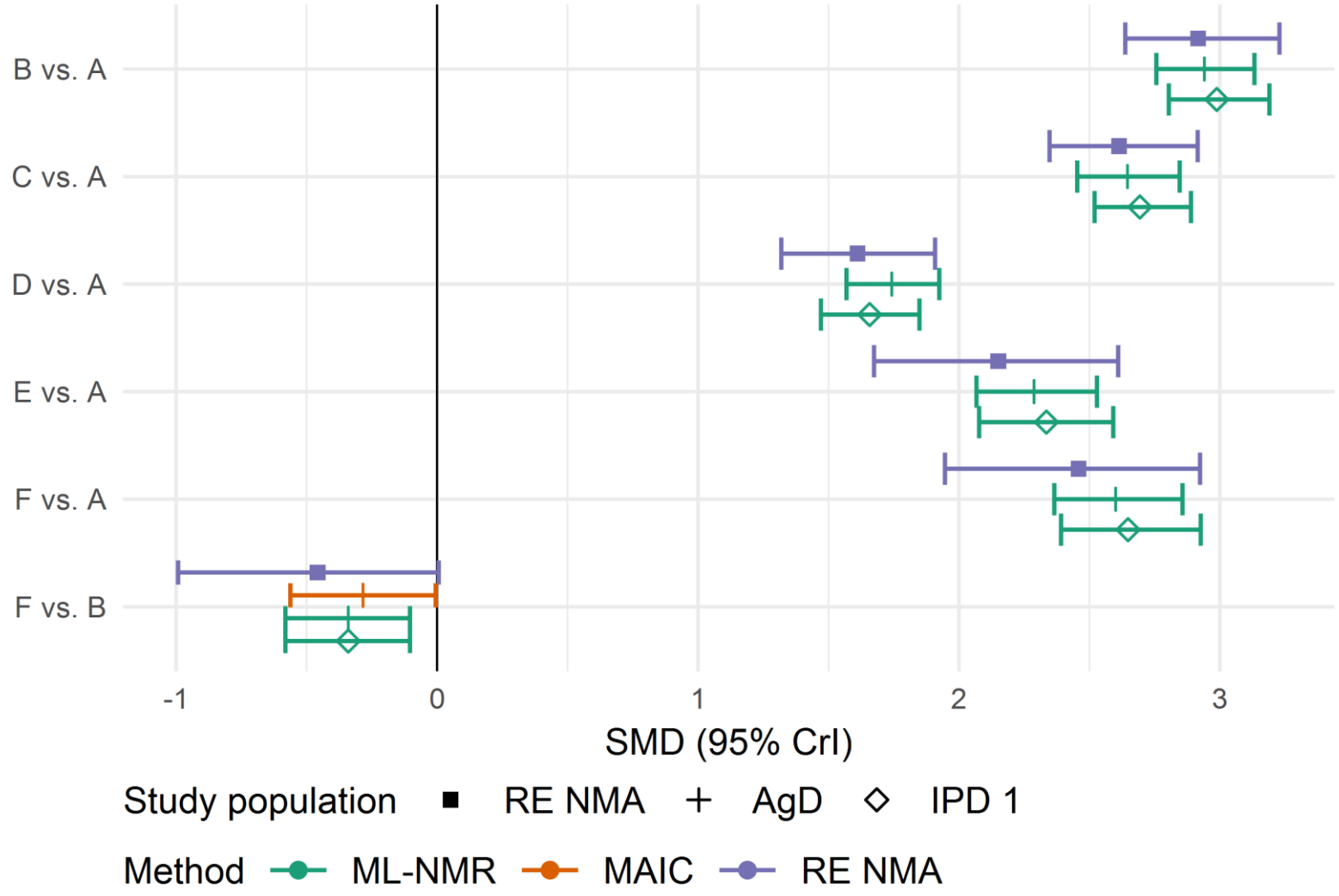

B vs. A
C vs. A
D vs. A
E vs. A
F vs. A
F vs. B
-1
0
1
2
3
SMD (95% CrI)
Study population
RE NMA
AgD
IPD 1
Method
ML-NMR
MAIC
RE NMA



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

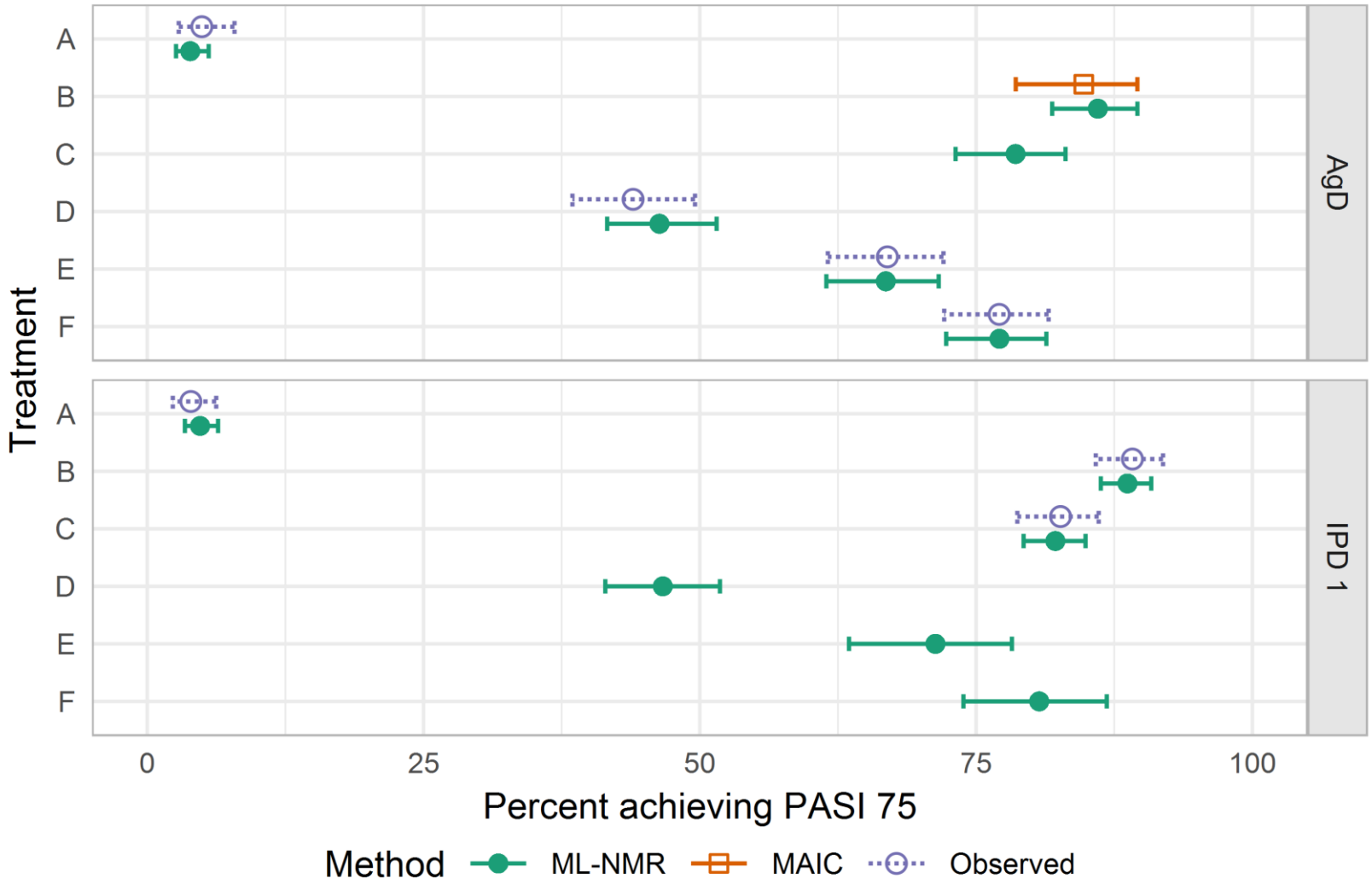


- Produce a full set of coherent estimates - in any target population
- Reduced uncertainty compared to MAIC



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

Example: Plaque Psoriasis – proportion achieving PASI 75



Conclusions

- ML-NMR is a flexible and general method for synthesising evidence from mixtures of individual and aggregate level data in networks of all sizes
- The use of numerical integration allows for easy implementation regardless of model form or complexity
- Decision making is aided by the production of effect estimates relevant to the decision target population
- Future work will extend ML-NMR to handle general likelihoods, including for survival analysis

Thank you

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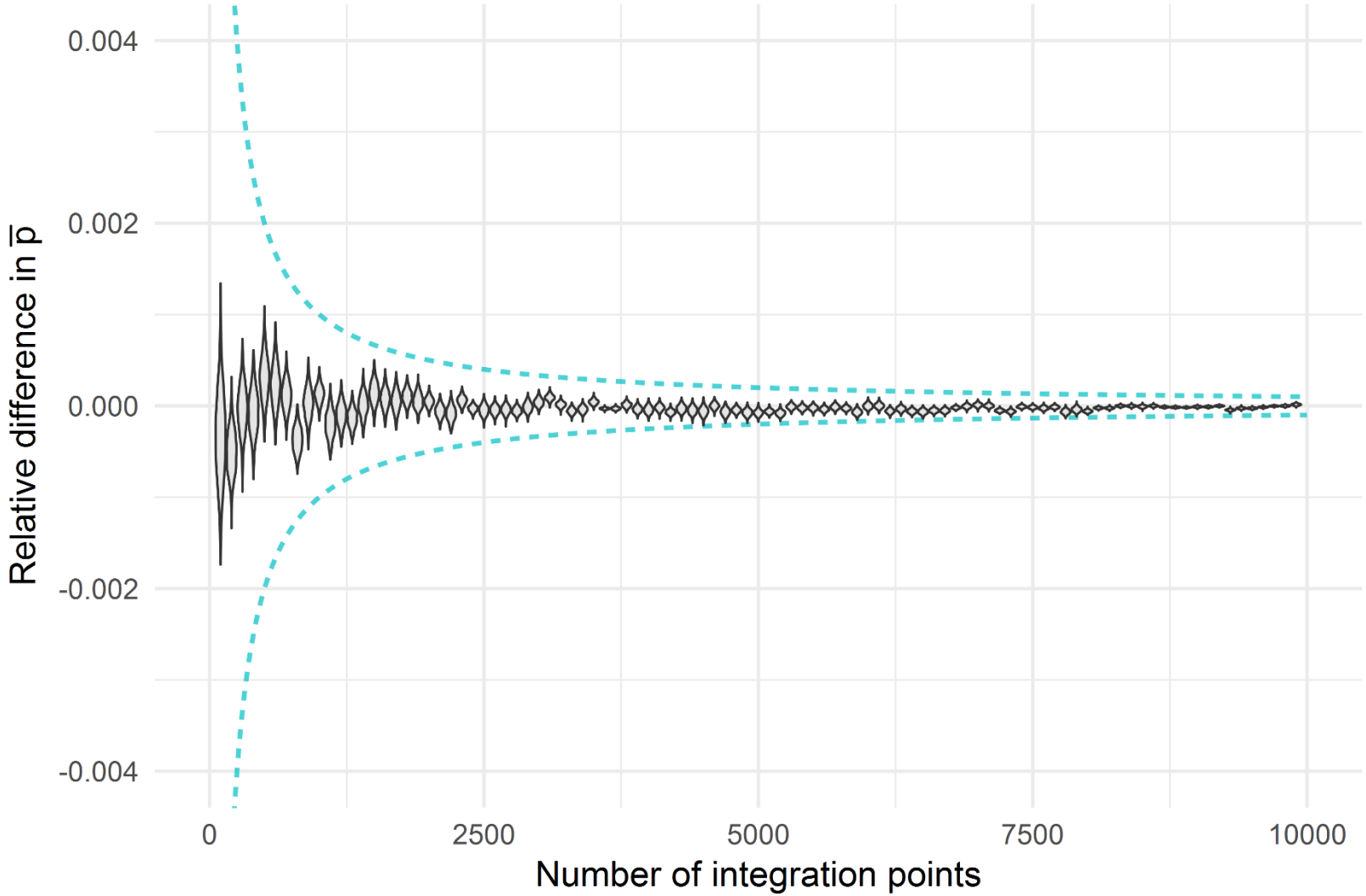
Example: Plaque Psoriasis – QMC integration convergence



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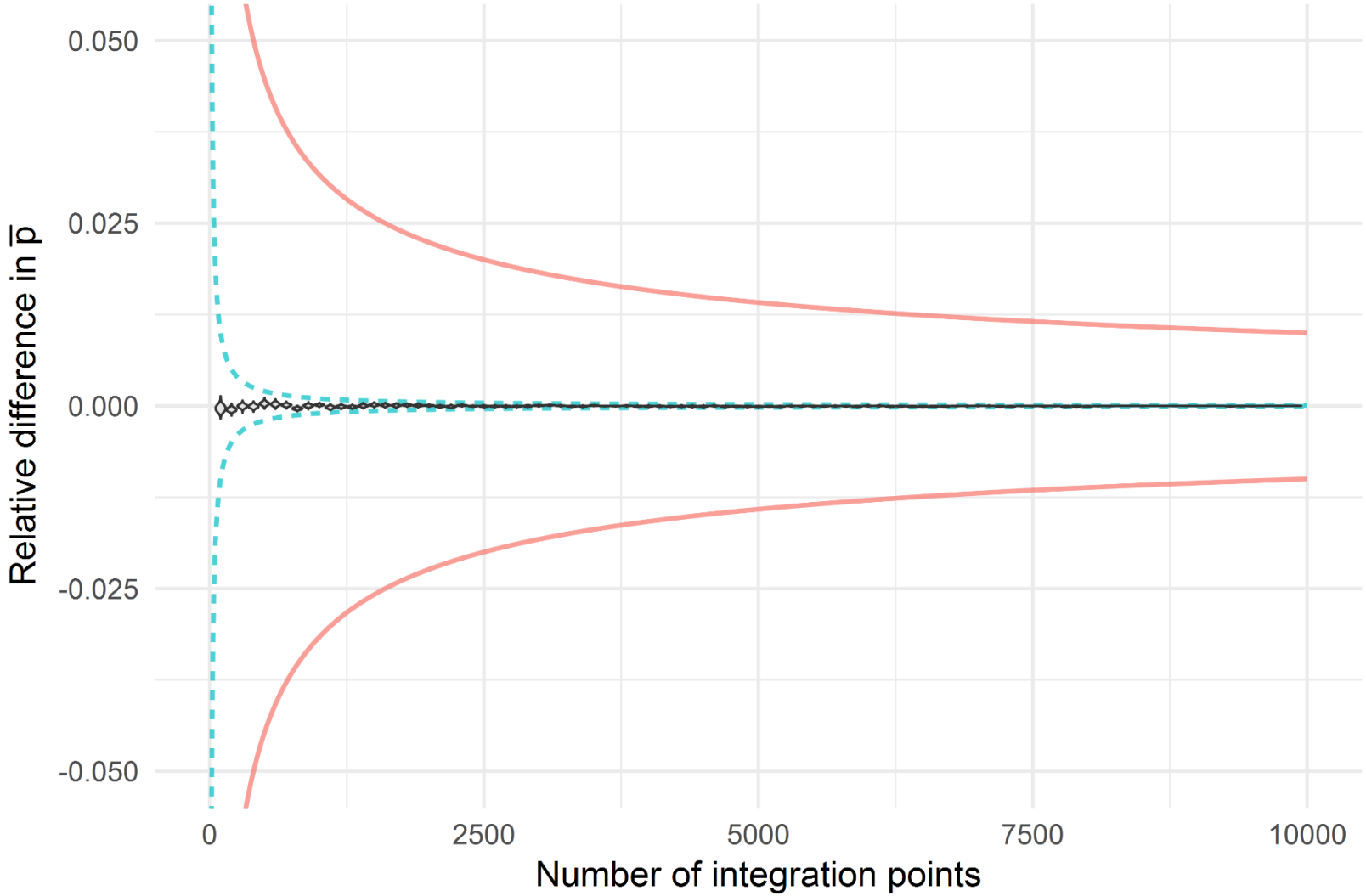
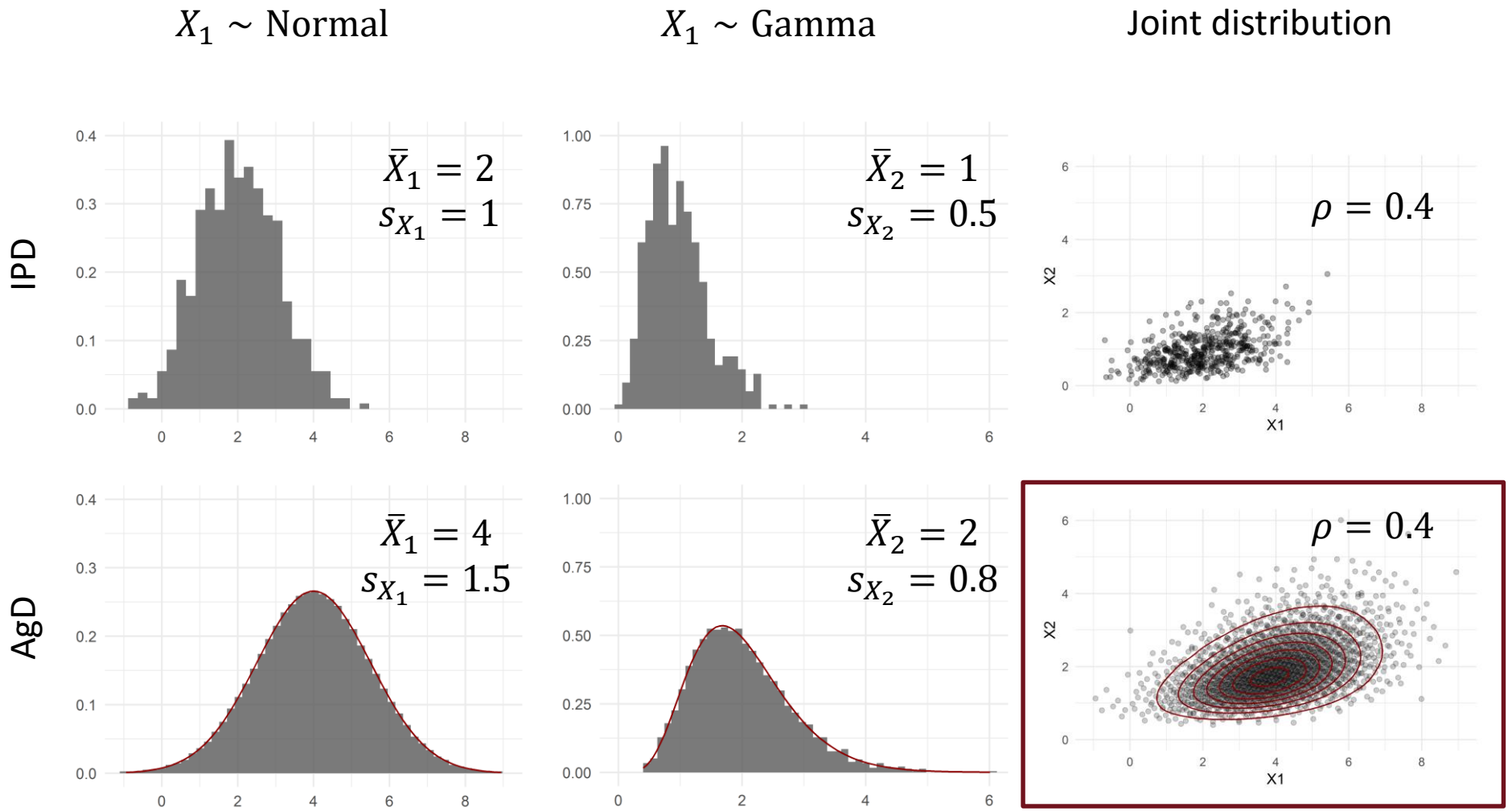
Example: Plaque Psoriasis – QMC integration convergence



ML-NMR: (Quasi) Monte Carlo integration



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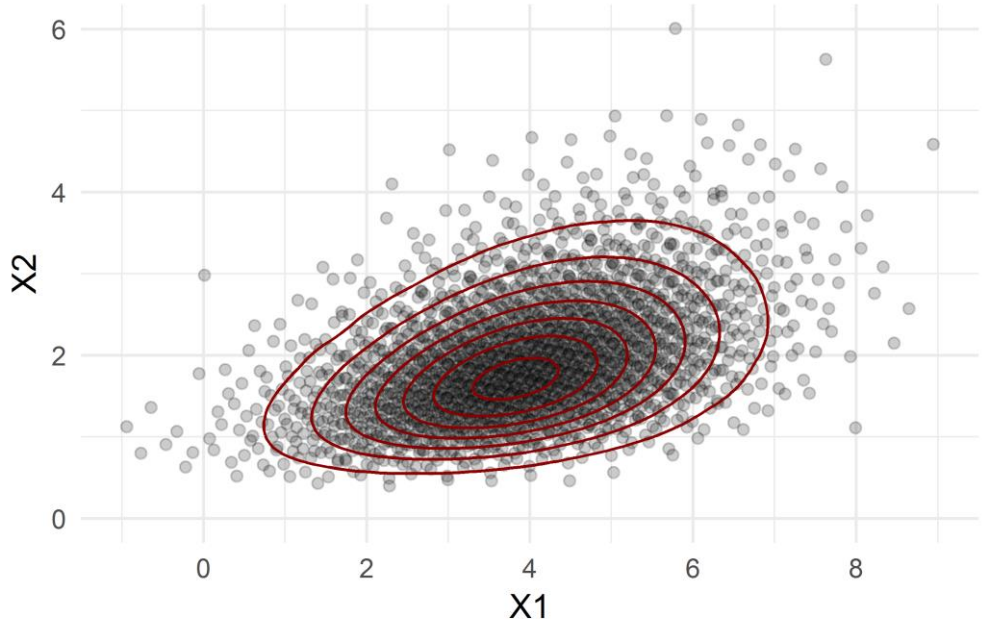
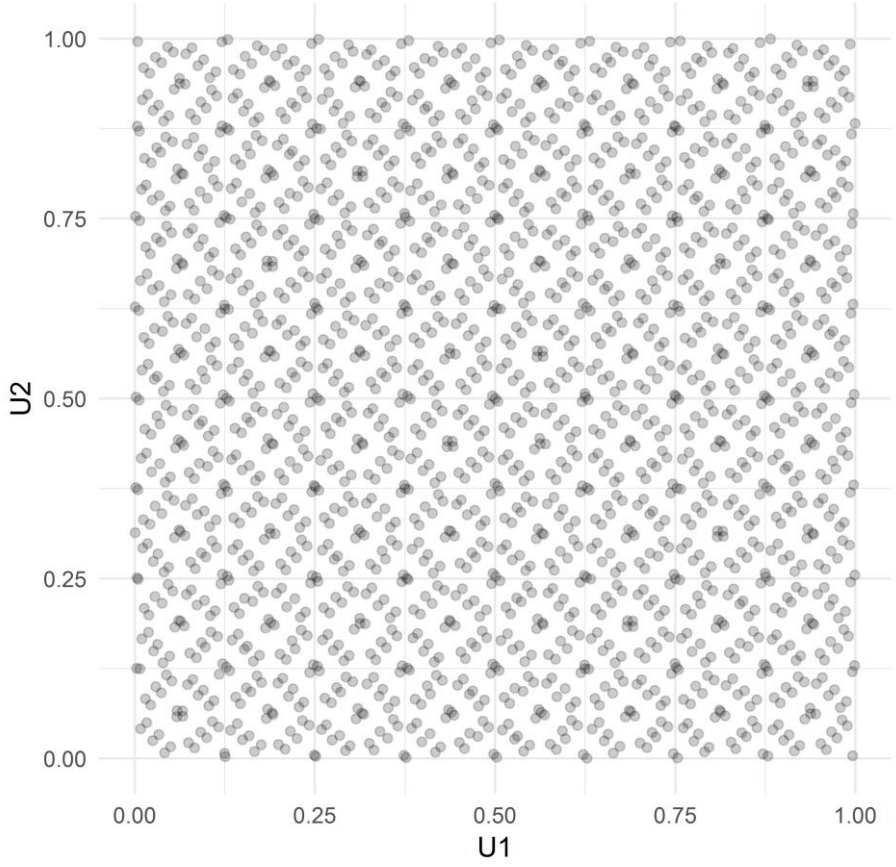
ML-NMR: (Quasi) Monte Carlo integration



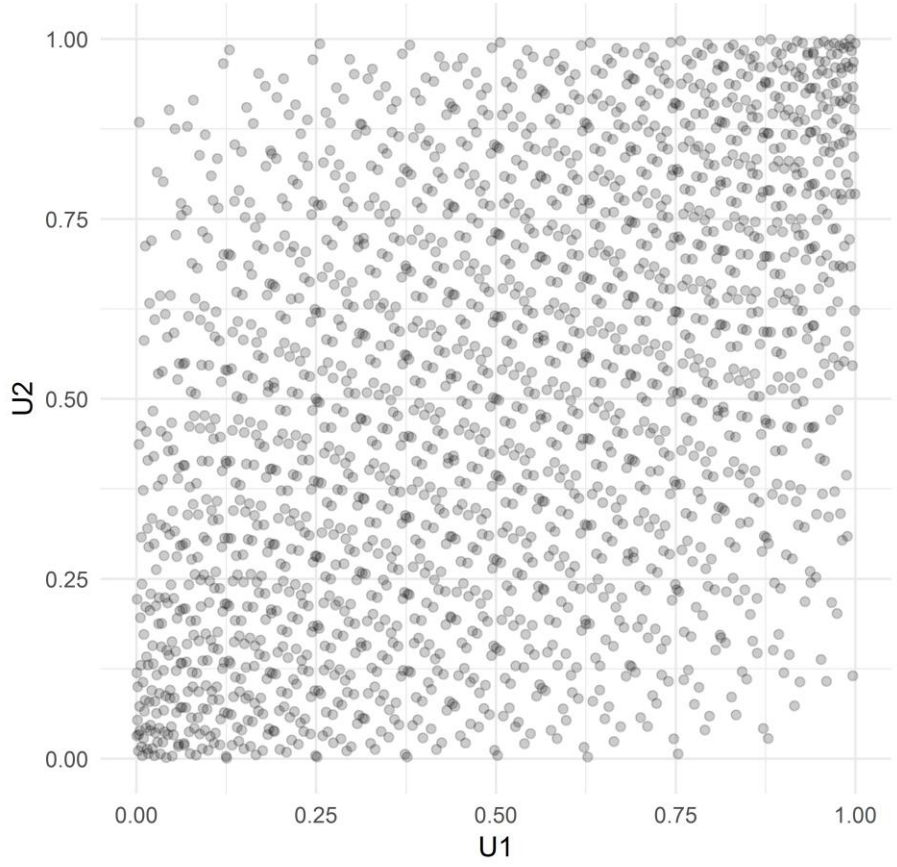
$$\frac{1}{\tilde{N}}\sum_{i=1}^{\tilde{N}} g^{-1}\left(\eta_{jk}\left(\tilde{\boldsymbol{x}}\right)\right) \quad \square \quad \int_{\mathrm{X}} g^{-1}\left(\eta_{jk}\left(\boldsymbol{x}\right)\right) f_{jk}\left(\boldsymbol{x}\right) d\boldsymbol{x}$$

Correlation structures with copulae

$\boldsymbol{U}$



$\widetilde{\boldsymbol{U}} = \Phi\left(\Phi_{\Sigma}^{-1}(\boldsymbol{U})\right)$



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