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Beyond Dichotomization: Efficient Estimation of Response Rates using Continuous Outcomes

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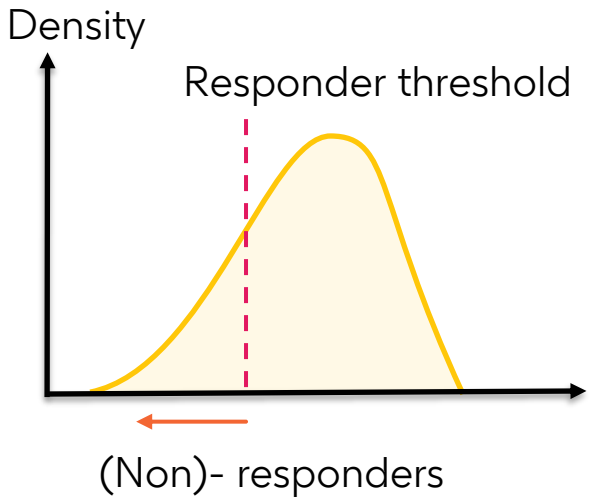
Responder endpoints are common across medical research

- Some examples:

Disease Area	Diagnostic / responder threshold
Diabetes	HbA1c < 7.0%
Respiratory	Patient Reported Outcomes, e.g. CAT, SGRQ, E-RS, ACQ6
Oncology	RECIST: ≥ 30% reduction in tumour size Myelofibrosis: ≥ 35% reduction in spleen volume
Rheumatology	ACR20 ≥ 20%
Hypertension	SBP ≥ 140mmHg, DBP ≥ 90mmHg



- Review of 21,435 RCTs found that 66% have a binary primary efficacy outcome[1]

1.. van Zwet EW, Harrell Jr FE, Senn SJ. An Empirical Assessment of the Cost of Dichotomization of the Outcome of Clinical Trials. *Statistics in Medicine*. 2026;45(3-5):e70402. doi:10.1002/sim.70402

Change the estimator, not the estimand

- An alternative to dichotomization is to focus on estimands for continuous data
  - e.g. Comparison of means of the underlying continuous outcome (ANCOVA)

- But despite limitations responder endpoints remain appealing due to
  - Familiarity (with clinicians, patients and regulators)
  - Interpretability
  - Comparability (with previous trials / studies)

- Estimate responder rates by modelling the continuous outcome and computing tail probabilities at the clinically meaningful threshold
  "Keeping clinical interpretability without throwing away information"

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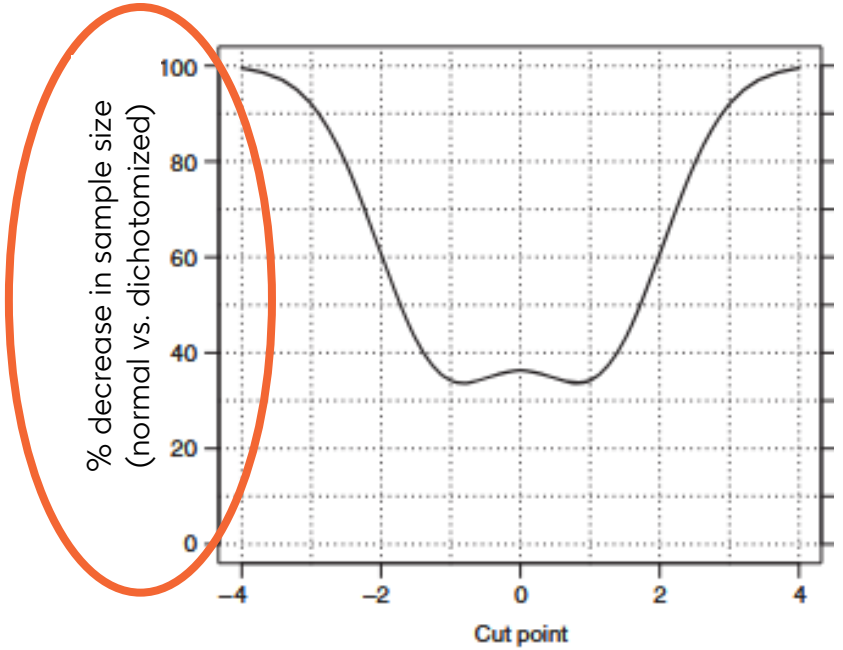
Large efficiency gains when model is correctly specified

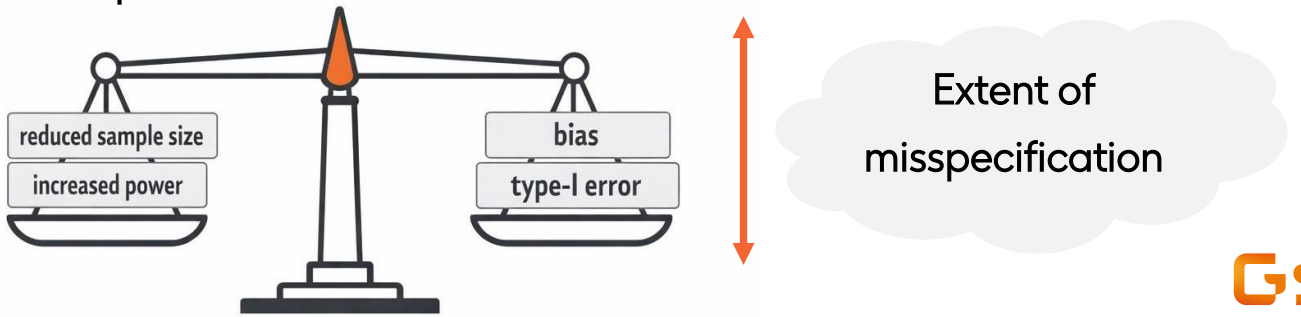
- If the **parametric model is correctly specified**
  - Consistency (asymptotically unbiased)
  - Maximum gain in efficiency
- Sample size improvement vs. dichotomization can be pronounced (AT LEAST 33% SMALLER!)[1]
- However, a **misspecified model** can result in
  - Bias in responder rates and treatment effects
  - Inflated Type-I error
- Critical to check distributional assumptions



Standard Normal Distribution

1. Fedorov V, Mannino F, Zhang R. Consequences of dichotomization. *Pharmaceutical Statistics.* 2009;8(1):50-61. doi:10.1002/pst.331

"Bias-Variance tradeoff"



Core Idea

Estimand of interest:

$$p(Y < c \,|T = t)$$

for endpoint Y, responder threshold c and treatment arm T

Parametric Estimator:

1. **Model** the distribution $(Y|X;\theta)$ separately by treatment arm
2. **Predict** response rate for each individual under each treatment $\hat{p}_{it} = F_t(c; X_i, \hat{\theta}_t)$
3. Obtain **marginal response rate** for each arm: $\hat{p}_t = \frac{1}{n}\sum_{i=1}^{n} \hat{p}_{it}$ using G-computation
4. Obtain **marginal treatment effect** of interest (risk difference, odds ratio, risk ratio)
5. **Calculate standard errors** via delta method or nonparametric bootstrap

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Methods investigated to protect against misspecification

- We have assessed several modelling choices, all **stratified by arm**:

Model	Details	Key assumption
Logistic regression	Benchmark dichotomized analysis	Binary indicator; binomial inference

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Yeo-Johnson (YJ) transformed linear regression	Transform full outcome data (extension of Box-Cox) Then linear regression	Normal residuals after Yeo-Johnson transformation

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Skew-t regression	Skew-t regression with covariates affecting location (4-parameters: location, scale, skewness, kurtosis)	Skew-t distributed residuals

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Case Study: PROs in COPD

- Patient Reported Outcomes in COPD studies (CAT, SGRQ, E-RS: COPD)
- PRO data from a Phase 3 COPD trial (N= ~800); 1:1 active vs. placebo
- Responder analyses based on a pre-determined improvement from baseline
  - SGRQ Total Score reduction of ≥ 4 points → Responder
  - E-RS: COPD Total Score reduction of ≥ 2 points → Responder
- We analysed the PROs using dichotomized and non-dichotomized transformation-based responder methods.

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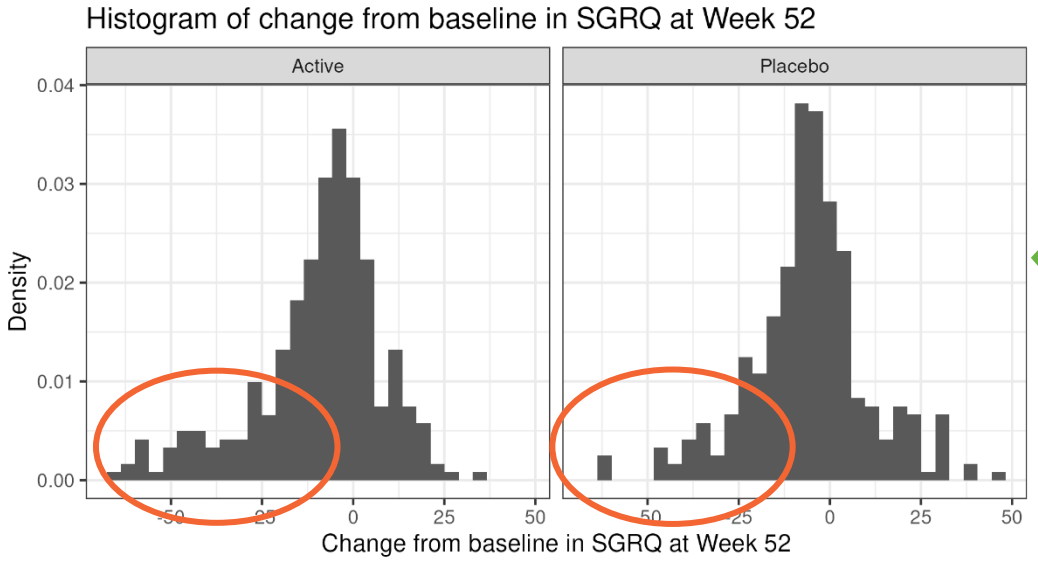
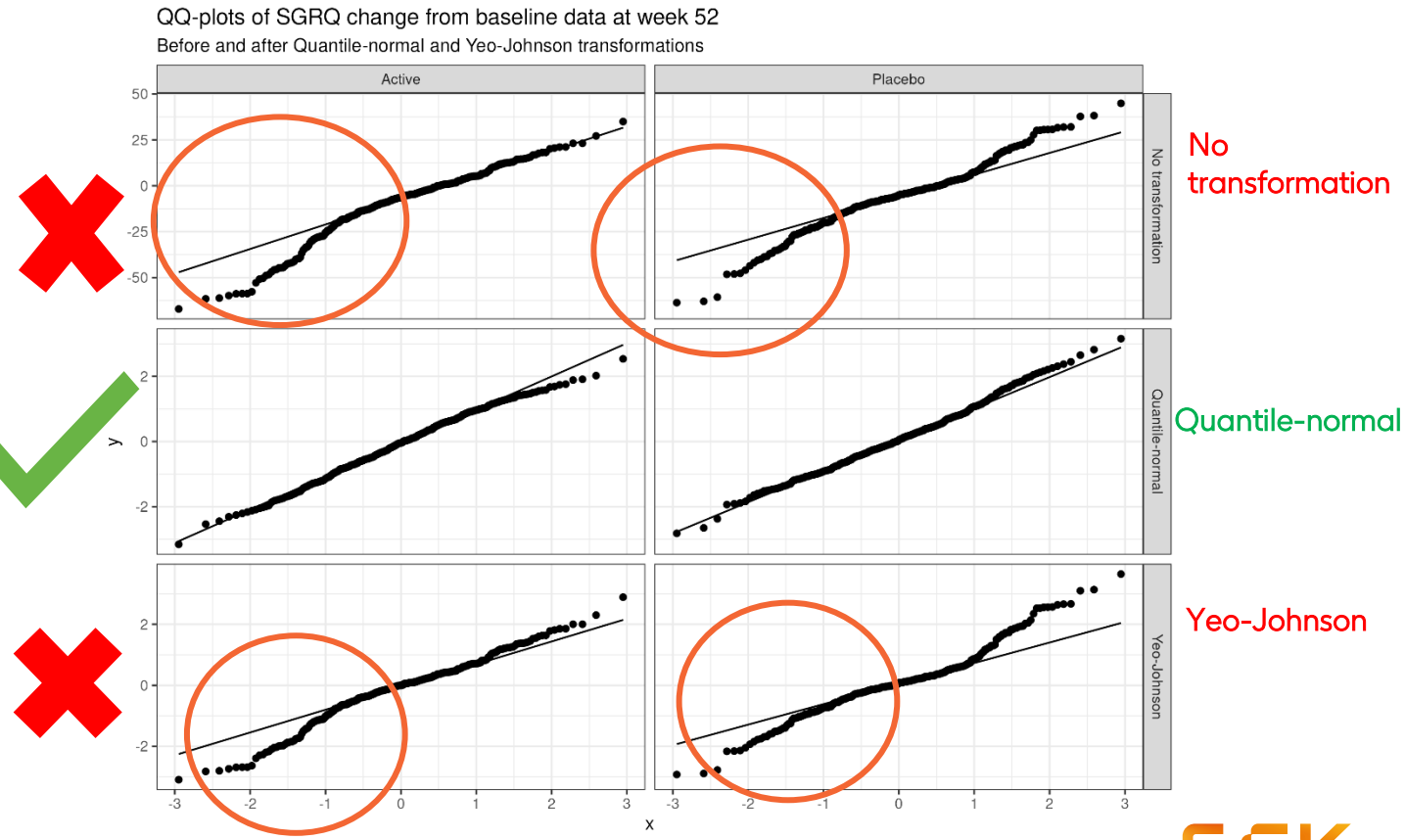
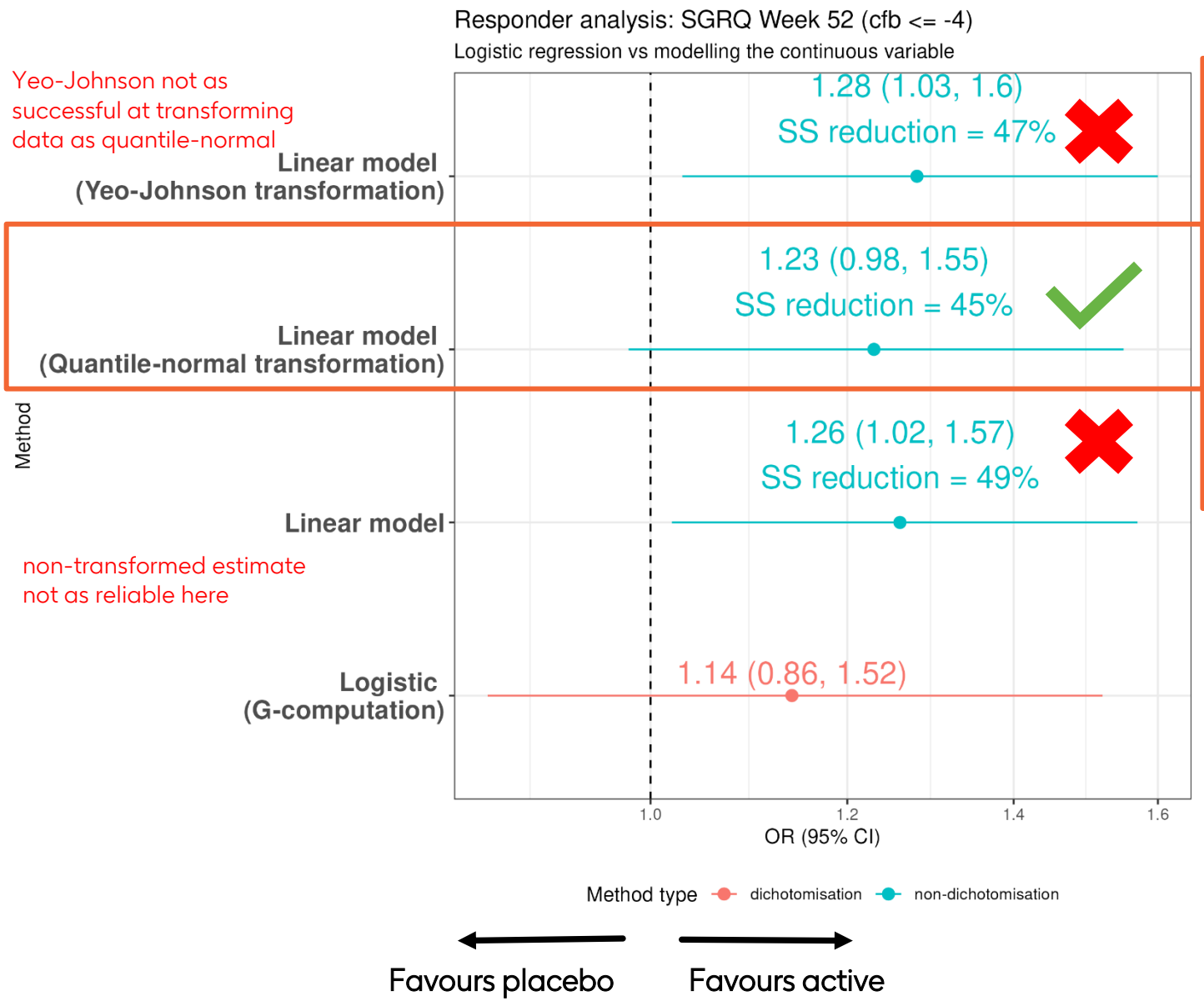
Handling deviations from the normality assumption

- Assessing Normality with diagnostic plots
- For SGRQ – there is some non-normality. Only quantile-normal reliably transformed the data here





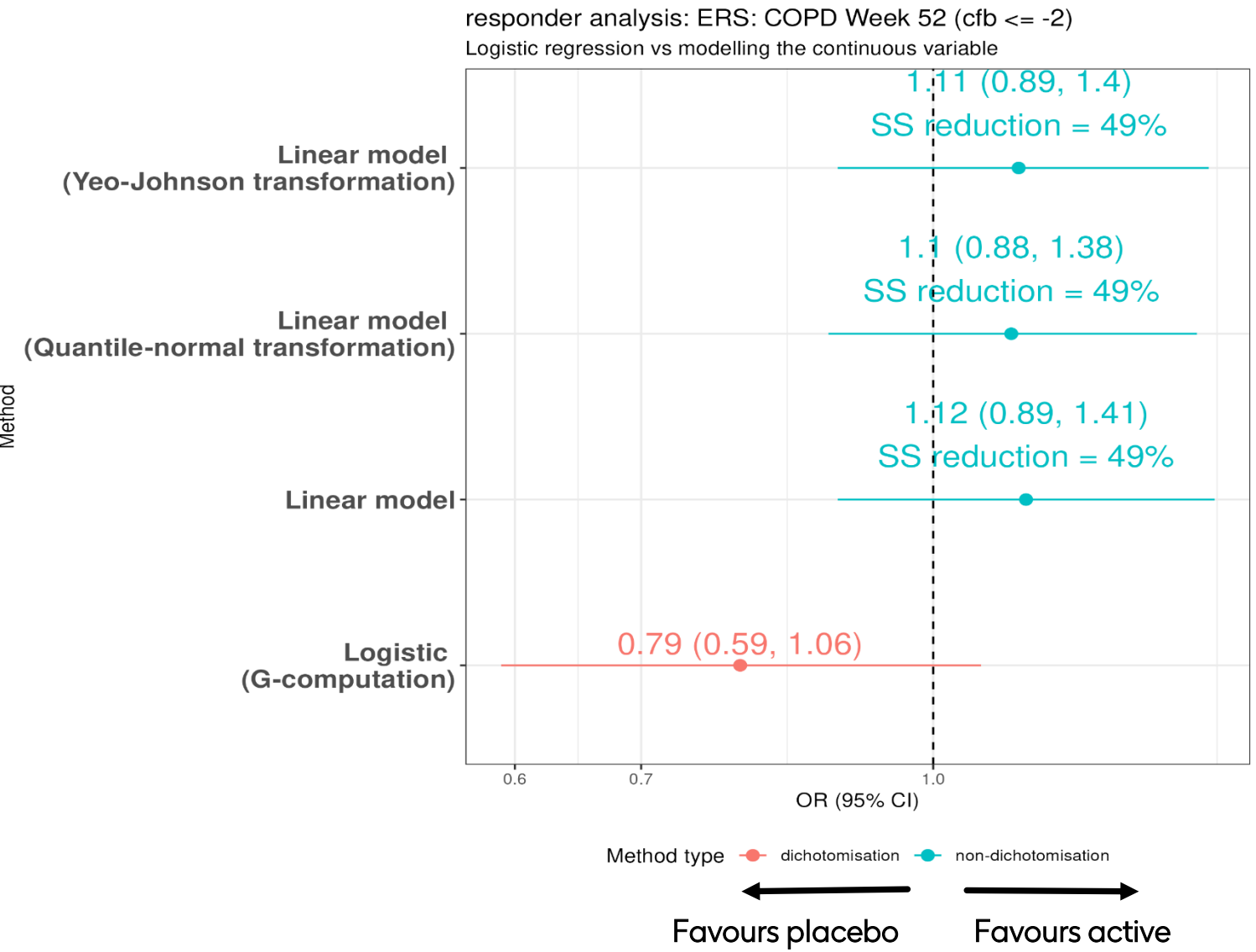
SGRQ responders



- ✓ Non-dichotomisation demonstrates substantial precision gain (45% reduction in sample size)
- ✓ Point estimates comparable to dichotomisation approach

E-RS: COPD results

Discrepancy between dichotomisation and non-dichotomisation approaches



Original results:

- Dichotomized responder analysis point estimate favoured placebo
- Continuous analysis (MMRM) point estimate favoured treatment:

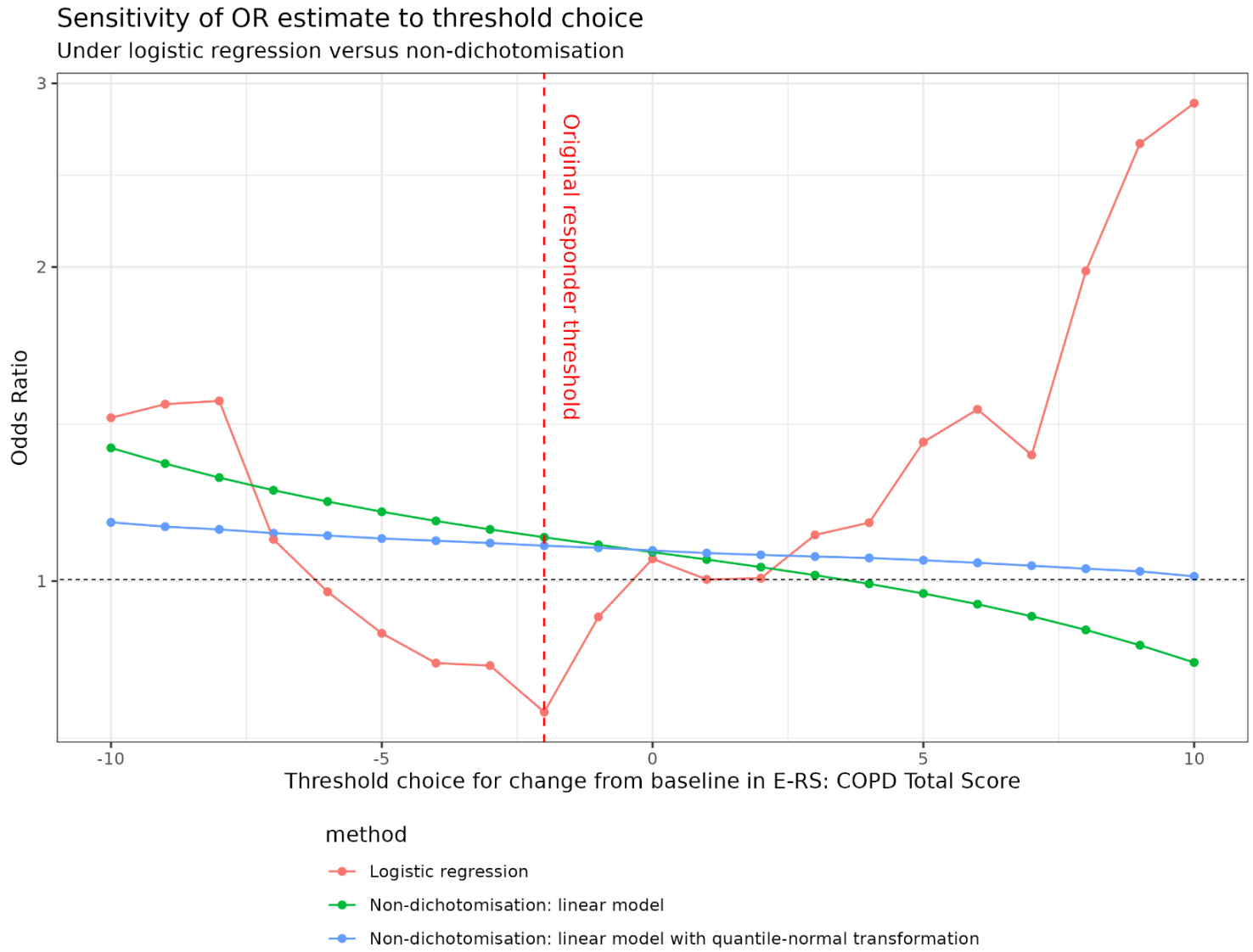
  Active vs Placebo mean difference:

  -0.2 (-1.00, 0.55)

- Non-dichotomized methods aligned with MMRM analysis

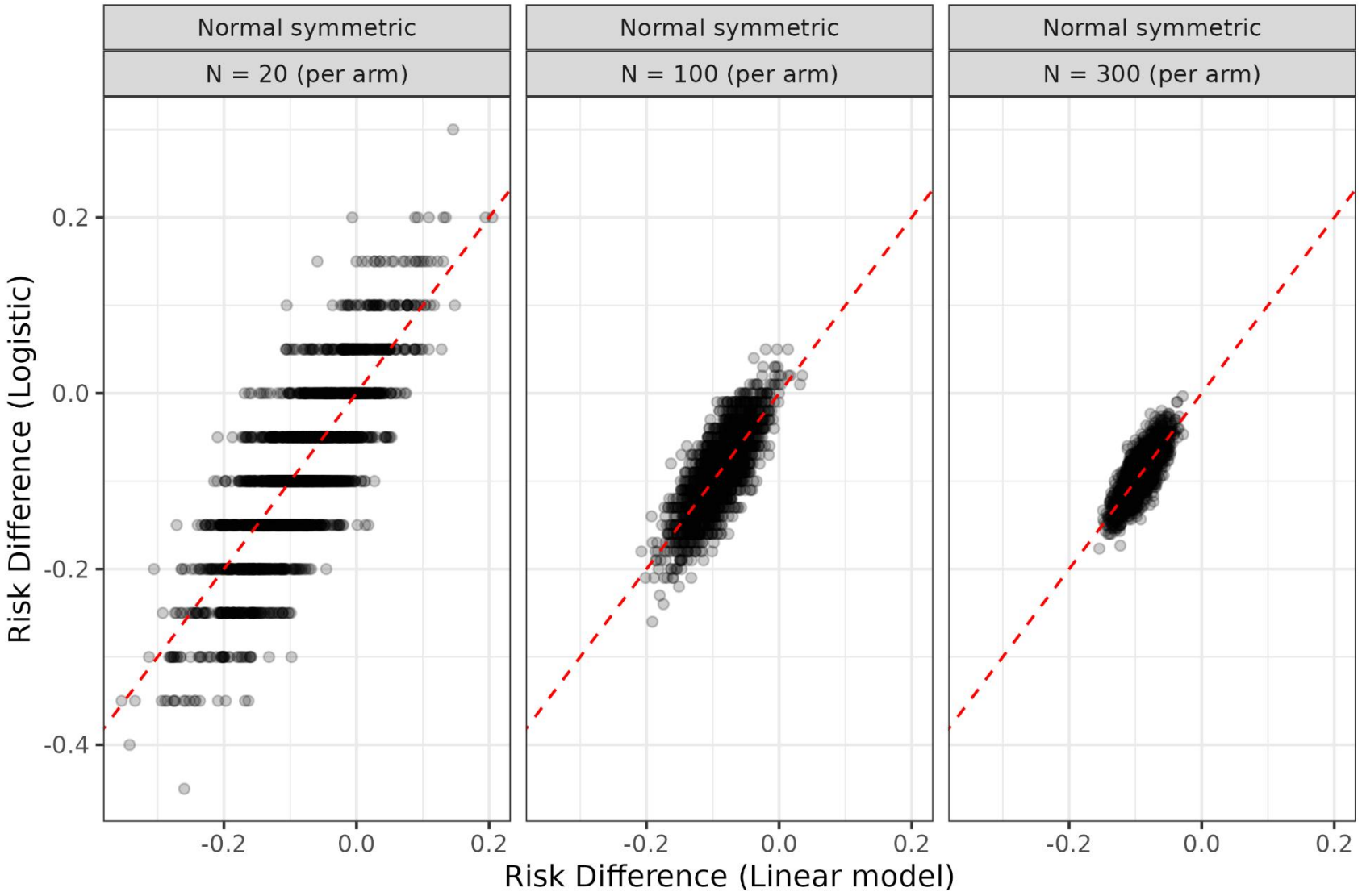
Dichotomized logistic ORs are highly sensitive to response thresholds

ORs estimated using non-dichotomized methods are more stable across response thresholds



Finite-sample differences even under correct specification

Linear model under Normal DGM



Finite-sample differences

- ✓ Between model-based (linear) and empirical (logistic) estimator
- ✓ Even under correct model specification
- ✓ Up to +/- 0.1 on RD scale for N=100 per arm

Handling intercurrent events / missing data

- The following often result in a non-responder classification:
  - Patients experiencing an intercurrent event handled using a composite strategy
  - Patients whose outcome cannot be ascertained due to missing data
- Non-dichotomisation methods require additional modelling in this setting

$$P(\text{Responder}) = P(\text{Responder}|\text{Evaluable})P(\text{Evaluable})$$

Non-dichotomization method on evaluable pts

Model (e.g. logistic)

where "Evaluable" data = No composite ICE and no missing data

- Robust approach but efficiency decreases as non-evaluable pts increase

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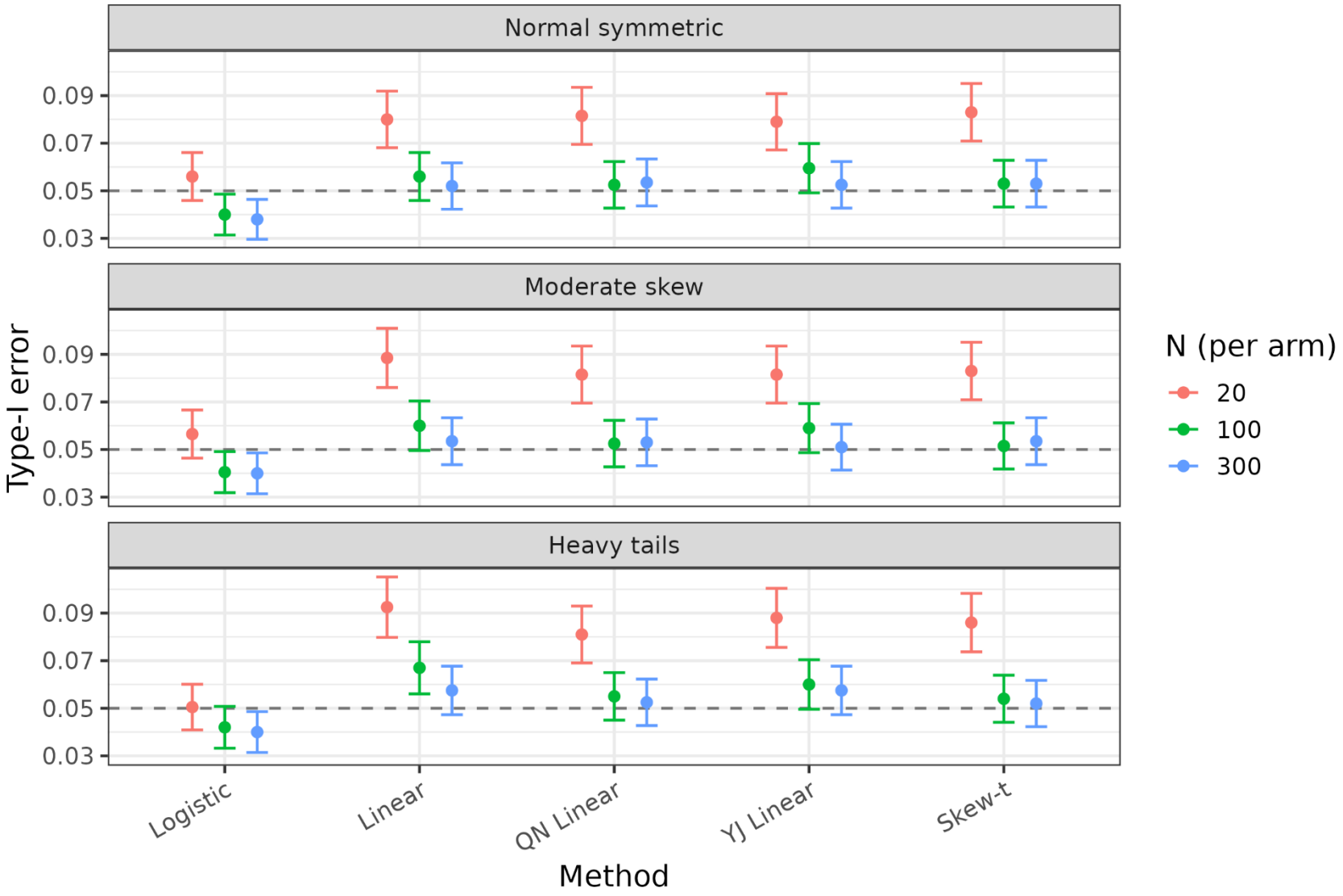
Type-I error rate by sample size (simulation study results)



Bootstrapped Type-I error

- ✓ Type-I error inflated for small “P2-type” trials
- ✓ For N > 100 most models control type-I even under misspecification

Conclusions

- Non-dichotomization methods can lead to substantial increase in efficiency
- However model misspecification can cause bias
- Composite ICEs / missing data require additional modelling but remain naturally accommodated within the framework
- Type-I error reasonably controlled for sample sizes >100 if bootstrap SEs/CIs used
- Differences are likely between empirical and model-based estimates
- Early regulatory engagement critical for justifying model-based responder analyses.
- Practical Recommendation:

QN-linear + G-computation + bootstrap SE/CI, with prespecified diagnostics/sensitivity; consider skew-t when heavy tails /skew suspected.

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Simulation Study: Data Generating Mechanisms

3 scenarios:

1. Normal Distribution
2. Moderate Negative Skew (same for both arms)
3. Skewness with Heavy Tails (same for both arms)

Null and alternative hypotheses

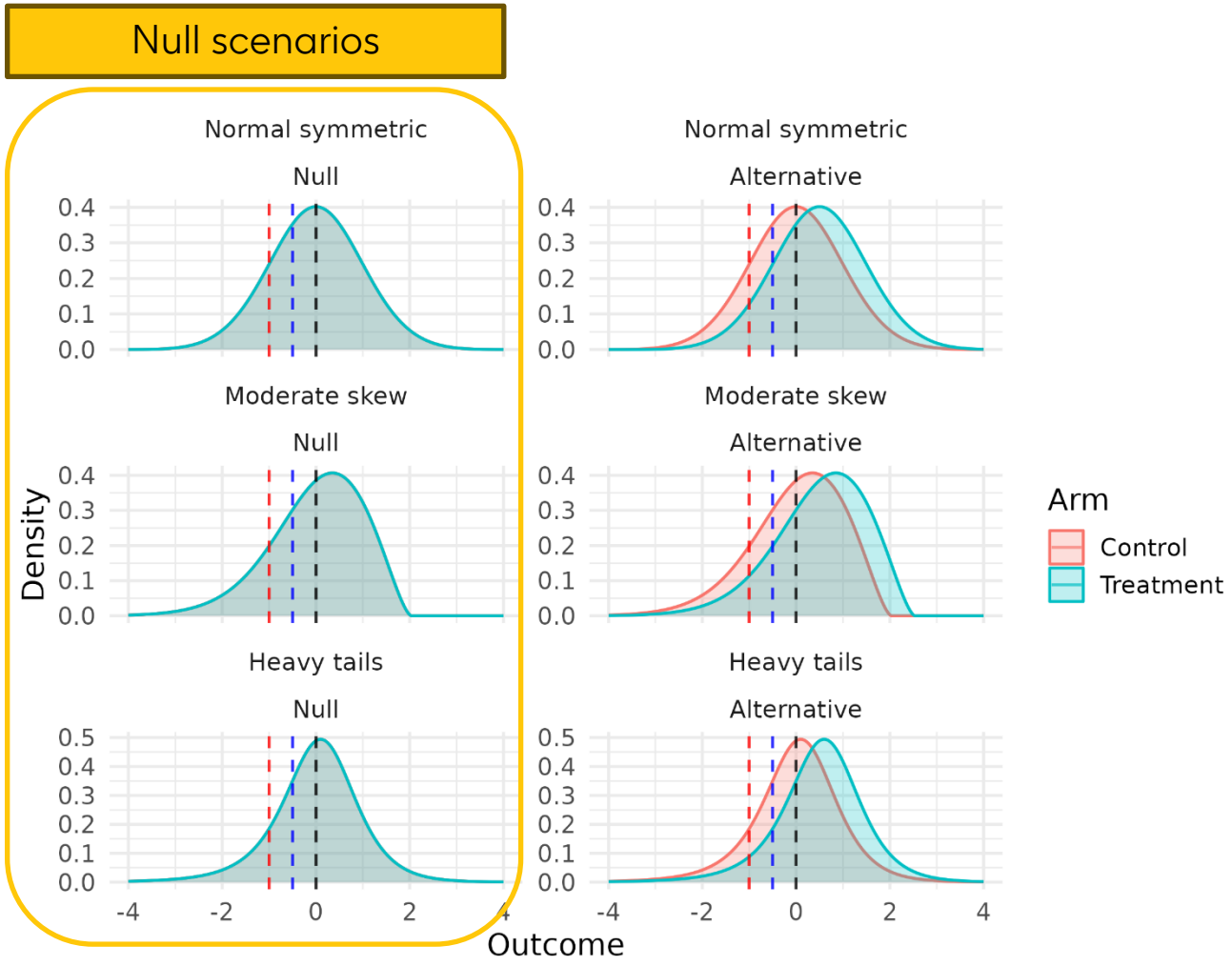
- **Null:** Zero location shift (treatment vs. control)
- **Alternative:** Treatment location shift = + 0.5

3 responder thresholds

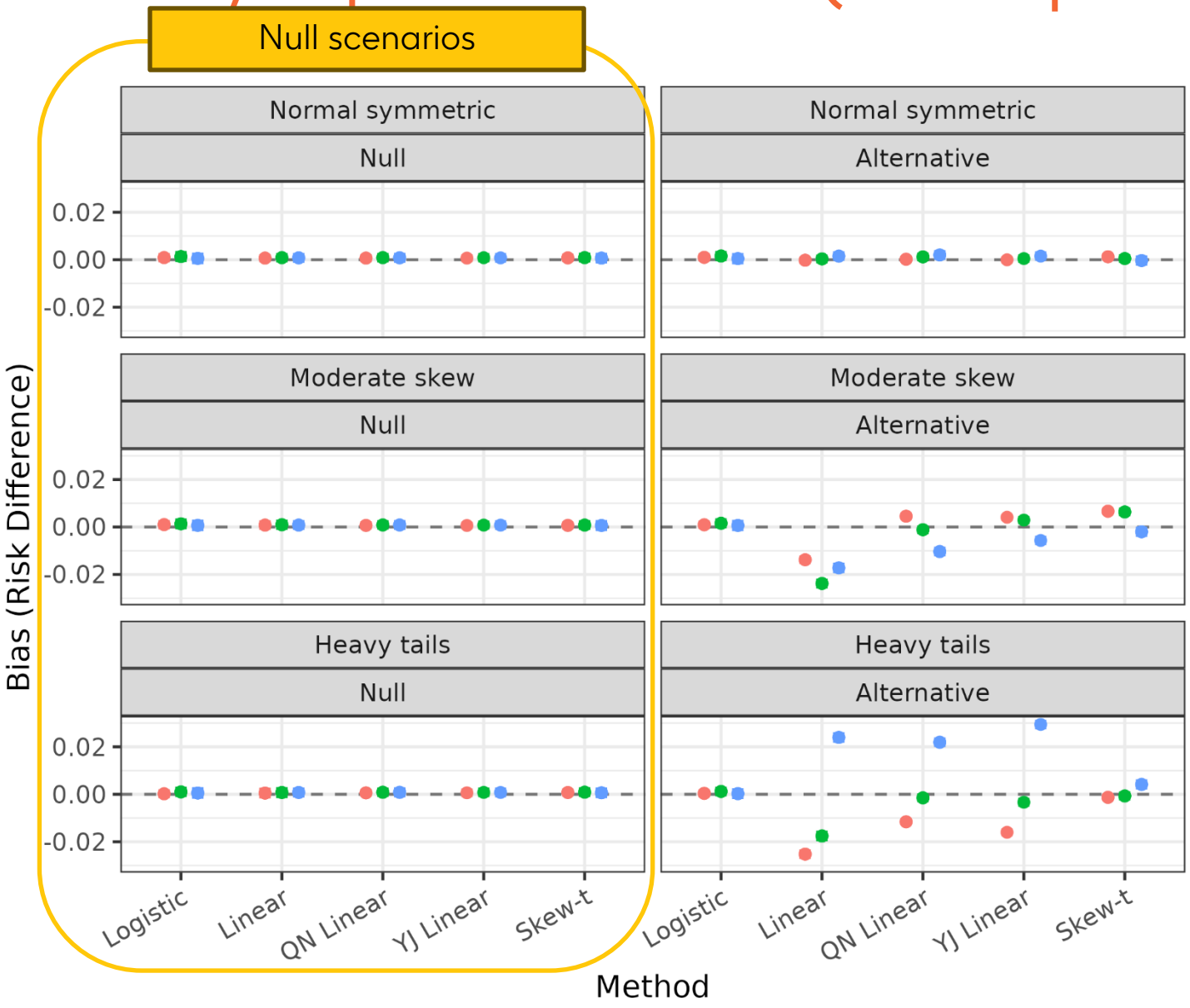
- Responder if ≤ -1, ≤ -0.5, ≤ 0

Sample Sizes

- 20, 100 & 300 per arm,



Bias by responder threshold (N=300 per arm)



- ✓ Little to no bias under null and Normal scenarios
- ✓ Linear method biased under non-normality
- ✓ Q-N and Y-J transform biased under heavy tails
- ✓ Skew-t performs reasonably well

2000 simulations

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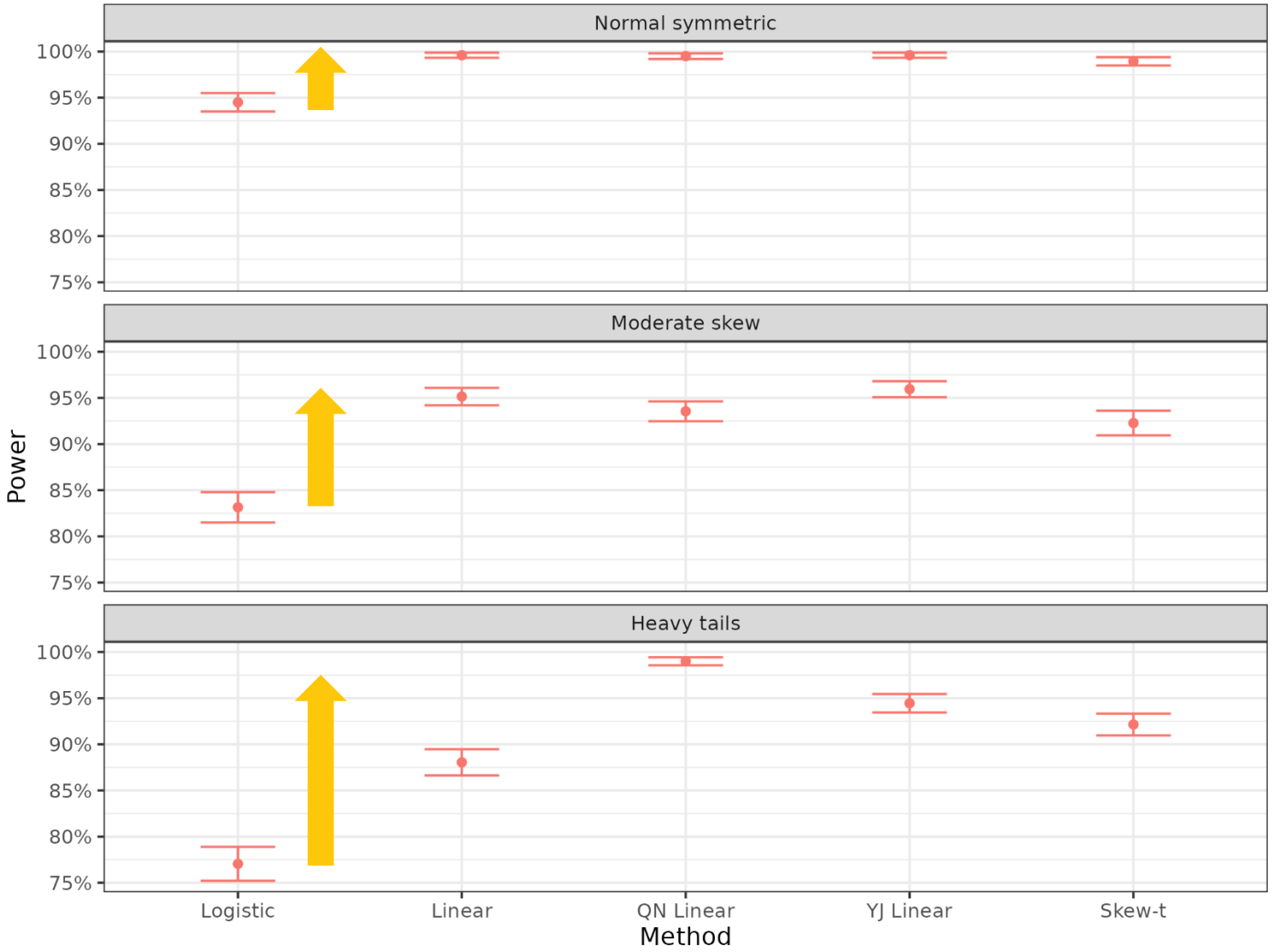
Power at threshold = -1 , N = 300 per arm



Power

- ✓ Substantial increase in power compared to logistic
- ✓ Results need to be interpreted in combination with bias

Example: Linear Regression

1. **Model:** $Y_i \sim N(\beta_t^T X_i, \sigma_t)$ for each treatment arm t separately
2. **Predict:** $\hat{p}_{it} = \Phi\left(\frac{c - \hat{\beta}_t^T X_i}{\hat{\sigma}_t}\right)$ from tail area of Normal distribution evaluated at c
3. **G-computation:** $\hat{p}_t = \frac{1}{n}\sum_{i=1}^{n} \hat{p}_{it}$
4. **Marginal Odds Ratio:** $\widehat{OR} = \frac{\hat{p}_1/(1-\hat{p}_1)}{\hat{p}_0/(1-\hat{p}_0)}$
5. **Calculate standard errors** via delta method or nonparametric bootstrap