Improving efficiency in composite endpoint analysis

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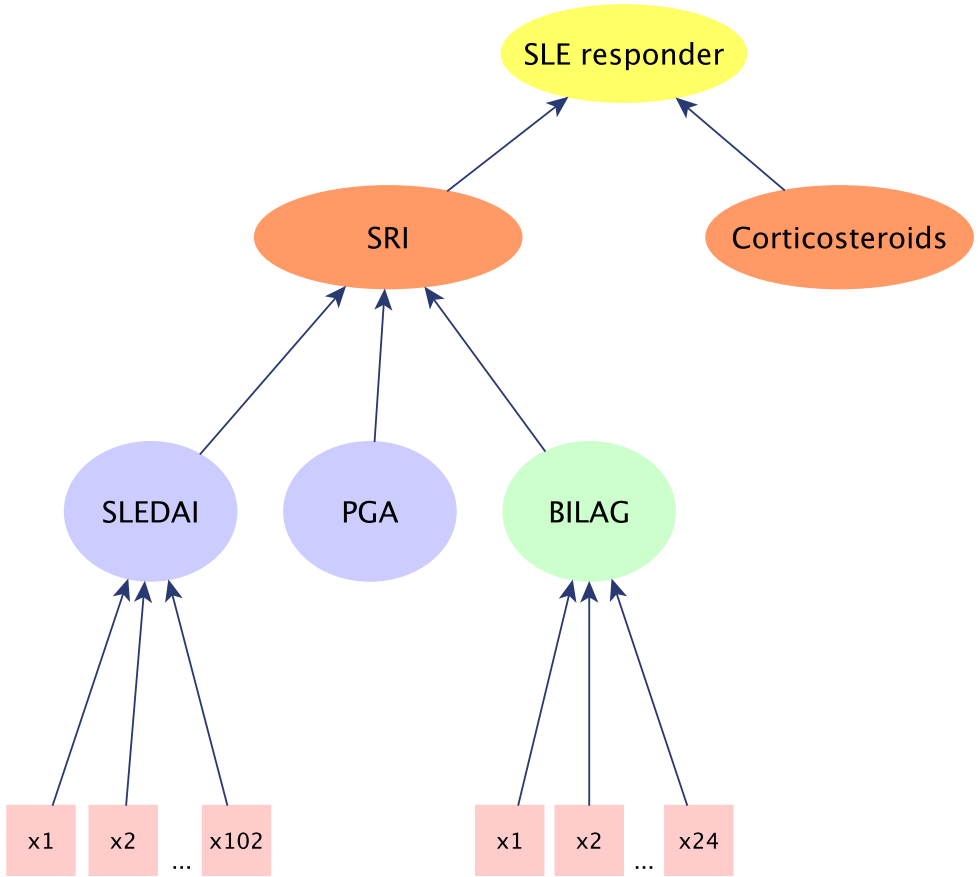
Motivation

- Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease
- Leads to significant morbidity and shortened lifespan
- Treatment is challenging because of limited efficacy and poor tolerability of standard therapy



Motivation

- **Standard binary method**

$$logit(Pr(S_i = 1|T_i, z_{i10}) = \alpha + \beta T_i + \gamma z_{i10}$$

- **Augmented binary method** (Wason & Seaman 2013)

$$Z_{i1} = \delta_0 + \delta_1 Ti + \delta_2 z_{i10} + \varepsilon_i$$

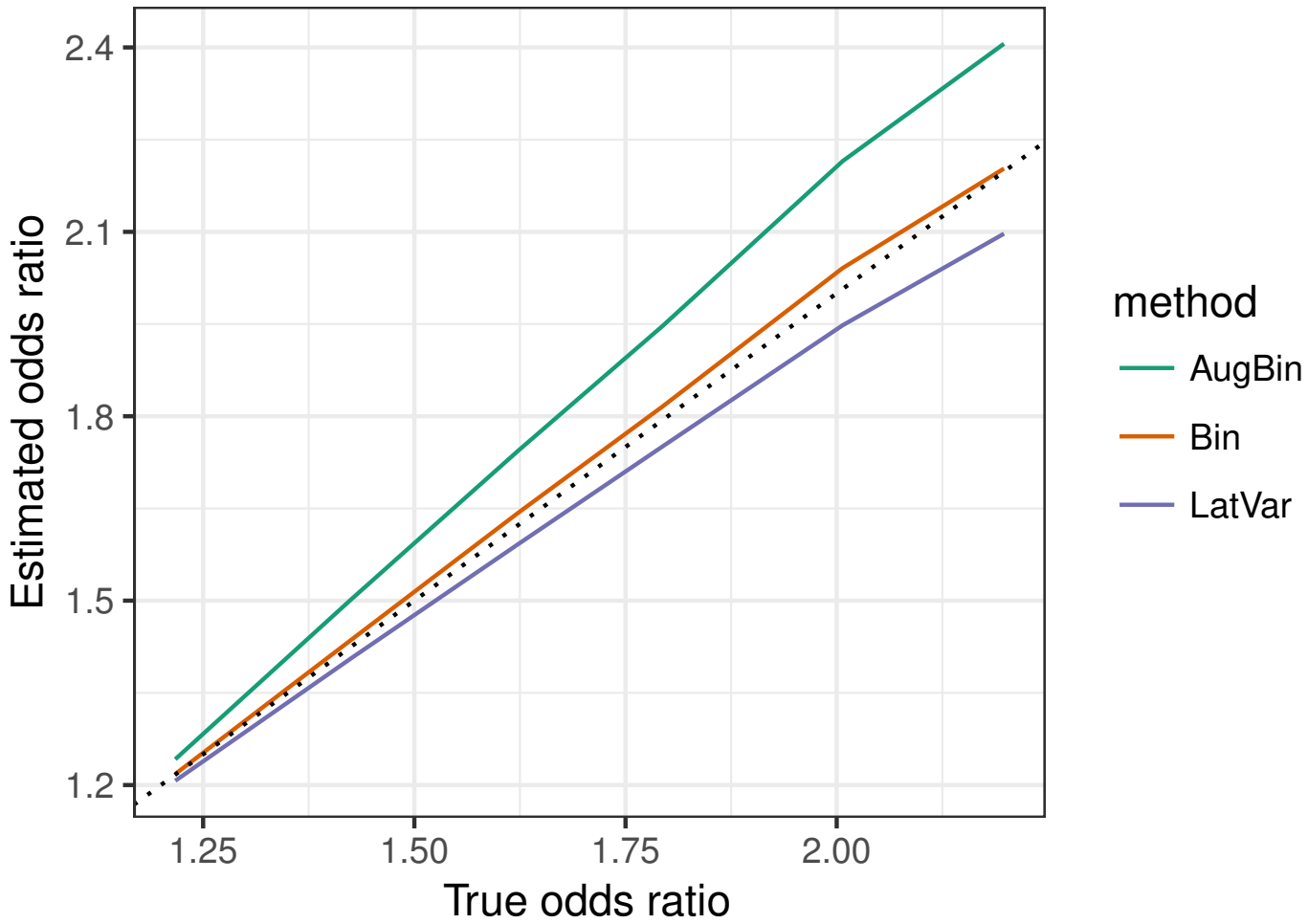
$$logit(Pr(F_i = 1|T_i, z_{i10}) = \alpha_F + \beta_F T_i + \gamma_F z_{i10}$$

Latent variable model

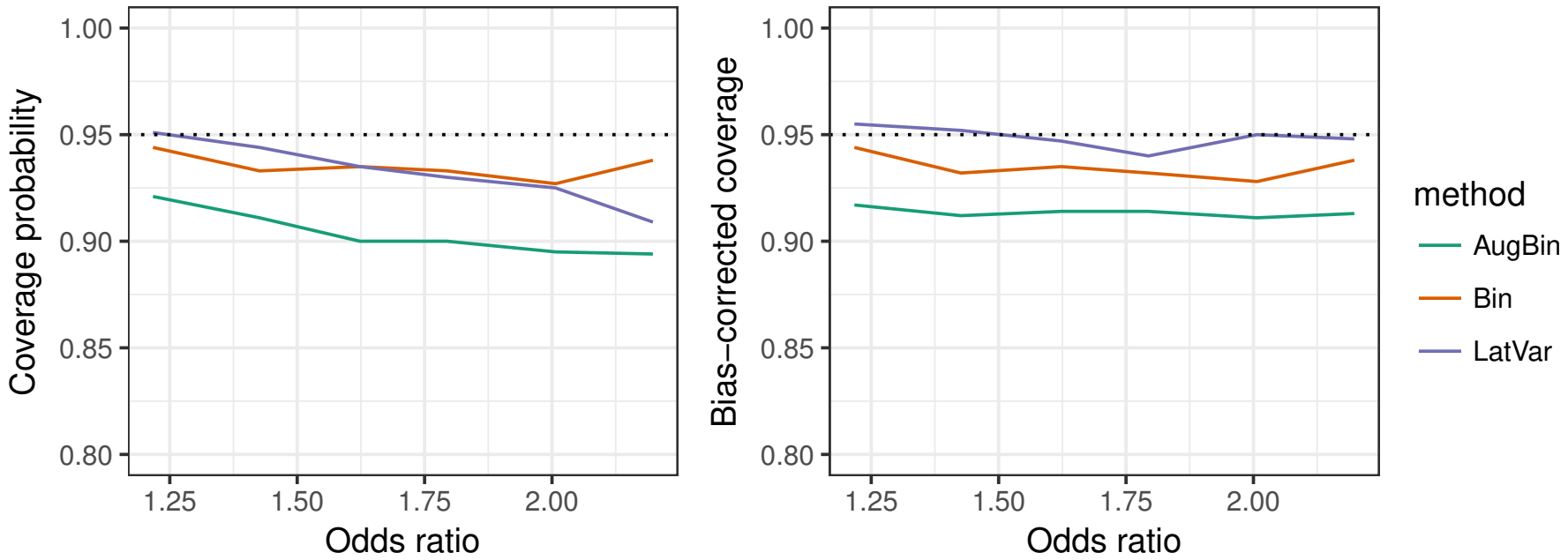
- Z_{i1}, Z_{i2} observed continuous variables SLEDAI and PGA
- Z_{i3} denotes BILAG, the observed ordinal manifestation of latent Z^*_{i3}
- Z_{i4} taper variable, the observed binary realisation of latent Z^*_{i4}

$$Z_{i3} = \begin{cases} \text{Grade E} & \text{if } \tau_{03} < Z^*_{i3} \leq \tau_{13}, \\ \text{Grade D} & \text{if } \tau_{13} < Z^*_{i3} \leq \tau_{23}, \\ \text{Grade C} & \text{if } \tau_{23} < Z^*_{i3} \leq \tau_{33}, \\ \text{Grade B} & \text{if } \tau_{33} < Z^*_{i3} \leq \tau_{43}, \\ \text{Grade A} & \text{if } \tau_{43} < Z^*_{i3} \leq \tau_{53} \end{cases} \qquad Z_{i4} = \begin{cases} 0 & \text{if } \tau_{04} < Z^*_{i4} \leq \tau_{14}, \\ 1 & \text{if } \tau_{14} < Z^*_{i4} \leq \tau_{24} \end{cases}$$

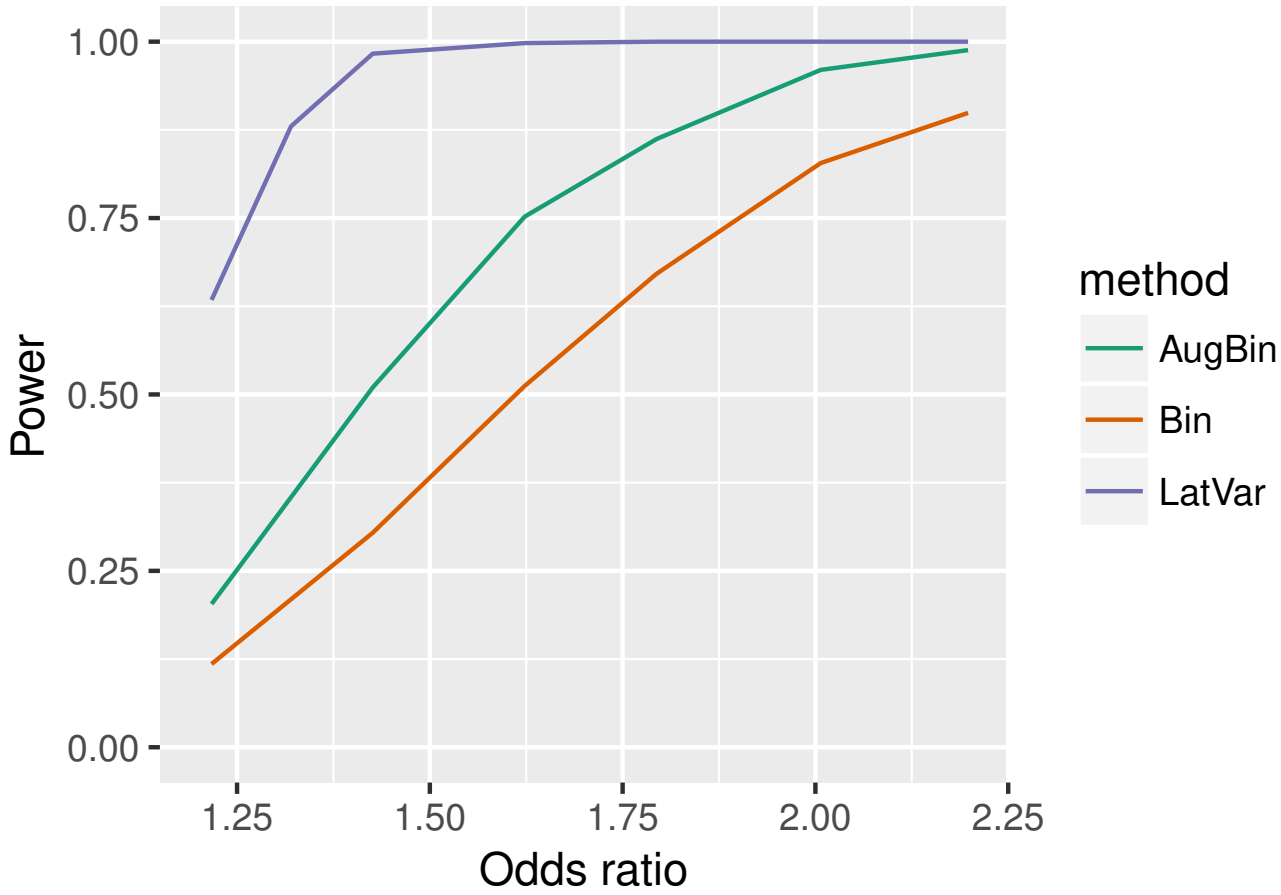
Treatment effect - bias



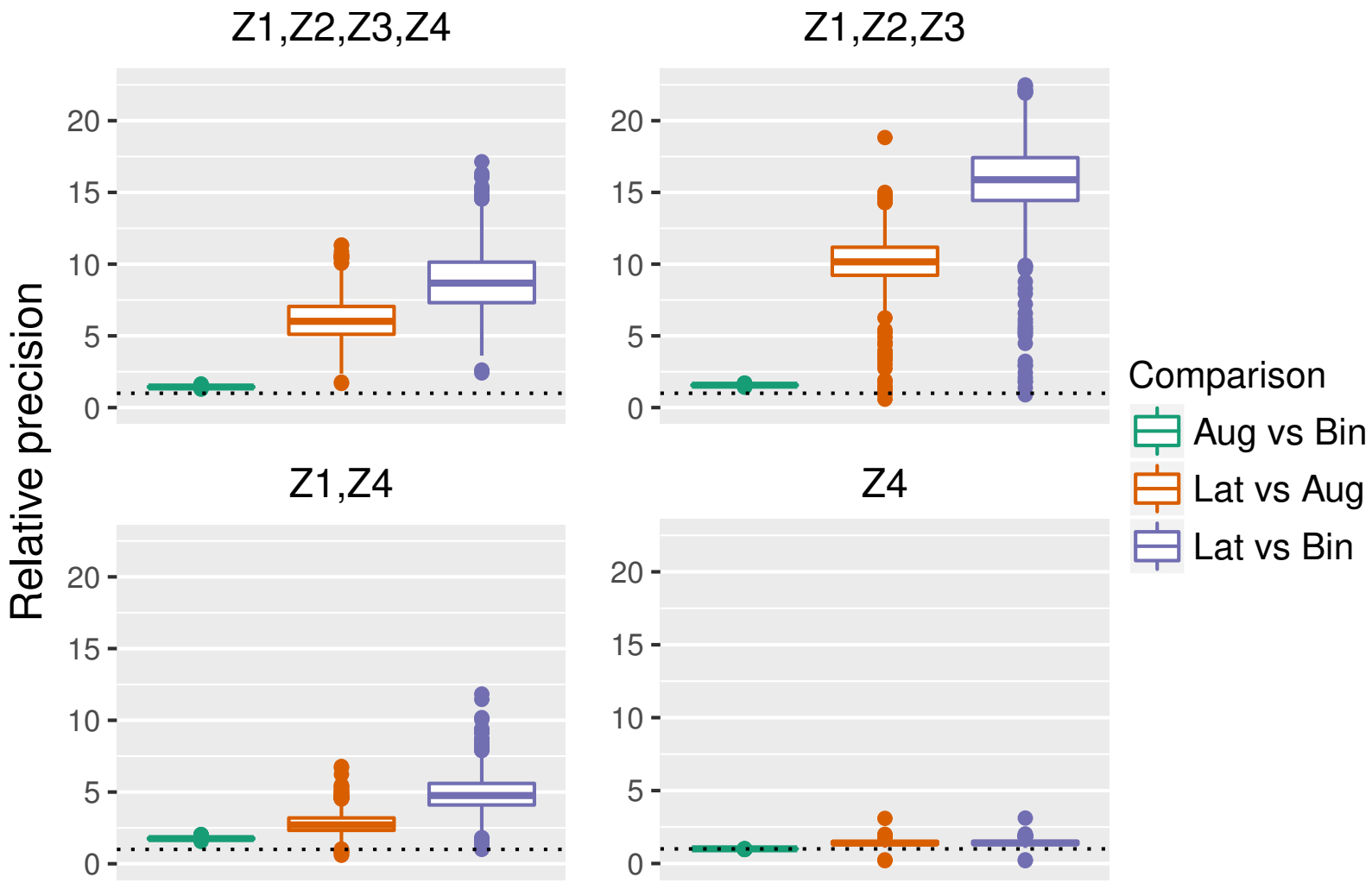
Treatment effect - Coverage



Treatment effect - power



Contributing components - precision



Sensitivity analyses summary

- Latent Variable method sensitive to joint normality assumption
- Introduces bias causing under-coverage (80%)
- Type I error rate approximately nominal
- Bootstrap?

Conclusion

- Can reduce required sample size by 60%+
- Applicable for many endpoints e.g. frailty
- Ongoing work to improve properties when assumptions not satisfied
- Employ as a secondary analysis method

References

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