Analysis of Incomplete Non-Normal Longitudinal Lipid Data

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Outline

- Standard methods and Existing issues
- Case study (Merck trial)
- Proposed robust method
- Simulation results
- Conclusions

Standard Methods and Existing issues

- In lipid study, we often encounter
  - Non-normal parameters, such as Triglycerides, Lipoprotein (a) etc.
  - Outliers
  - Drop-out: not significant but still very common (10-15%)

Standard Methods and Existing issues

- Current standard Methods
  - LOCF (Last value carried forward) + Rank based analysis

    Do not utilize the longitudinal nature of the data;

    Biased estimation
  - Standard Longitudinal Data Analysis Method: Restricted Maximum Likelihood (REML) (Laird & Ware, 1982)

    Key Assumption: Multivariate normality of the residual vector

Standard Methods and Existing issues

- Alternative Methods
  - Generalized Estimating Equations (GEE) (Liang and Zeger 1986)

    Alternative to REML if normality is in question

    Missing data (if any) are missing completely at random (MCAR)
  - Weighted GEE (WGEE)

    Relaxes MCAR assumption to missing at random (MAR) by adding weights to GEE

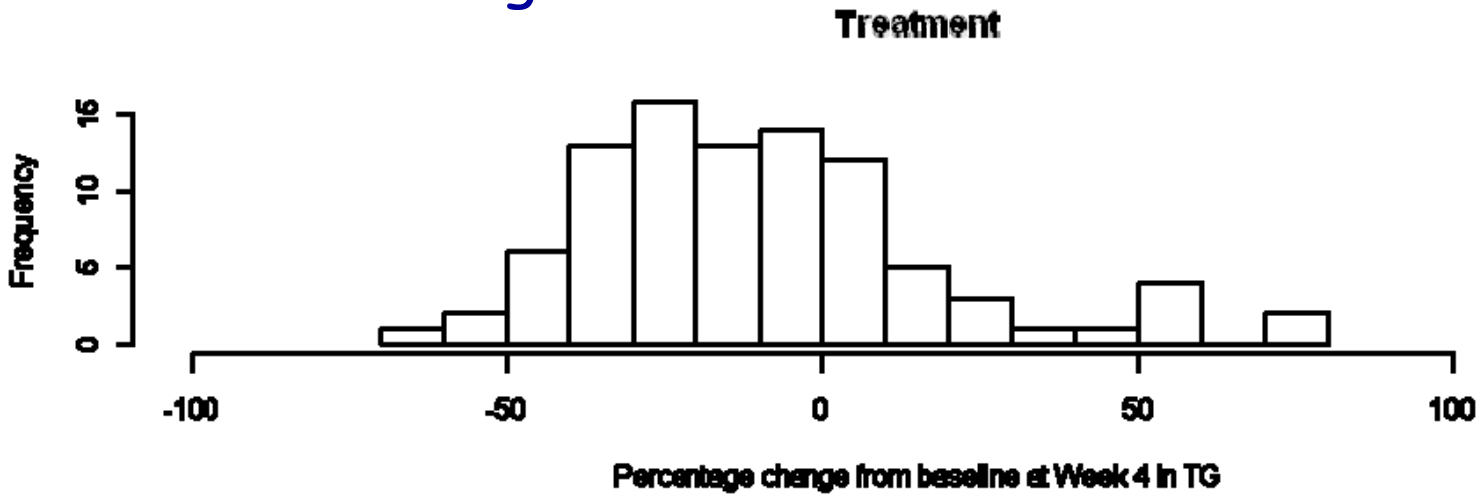
Case Study

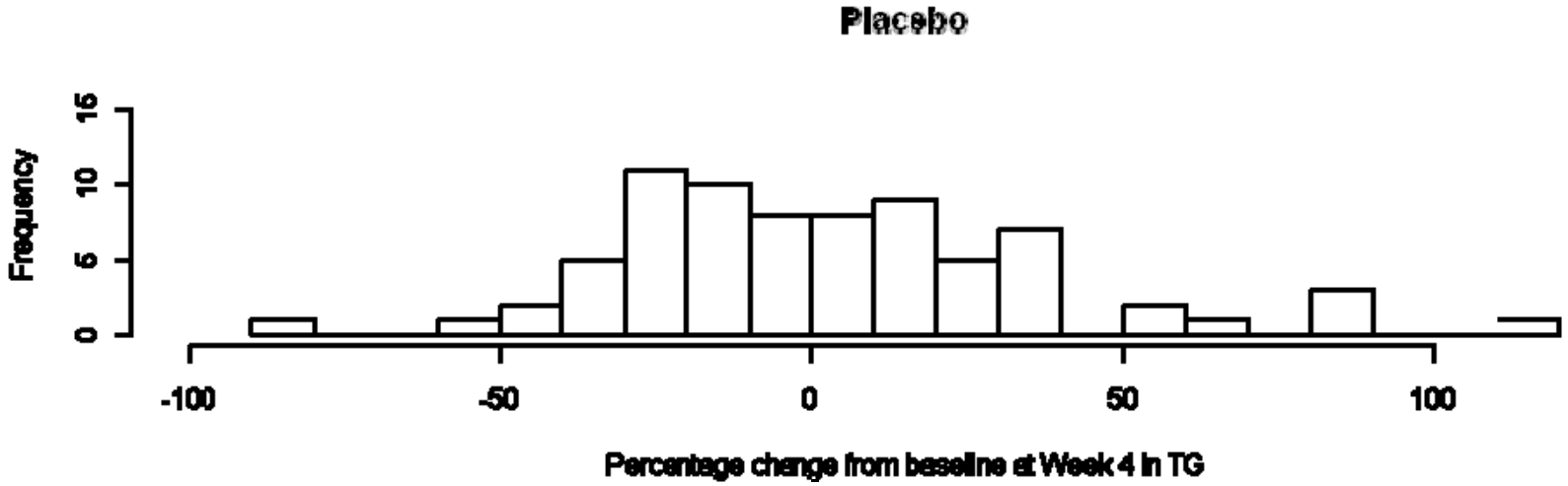
Drug (A) vs. placebo (B), 3:2 randomization

- Patients with Dyslipidemia
- Triglycerides (TG) measured at t = 0 (baseline), 2 and 4 weeks
- Y_{tjk} = % change from baseline (post-pre) for time t, trt j, subject k, and let $\mu_{tj} = E(Y_{tjk})$
- **Objectives:**
  - Estimation of treatment difference at time T
    $\delta = \mu_{TA} - \mu_{TB}$ (T = 4 weeks)
  - Hypothesis testing
    $H_0: \delta = 0$ **vs.** $H_1: \delta \neq 0$

Case Study (continued)

% Change from baseline at Week 4 in TG





The data has significant outliers.

Dropouts: Treatment 19/112=17%; Placebo 1/75=1%

Case Study (continued)

Standard LDA Methods: Results

METHOD	Estimate of δ	Standard Error	95 % CI for δ	2-tailed p-value
LOCF+Rank	-7.47	4.08	(-15.47, 0.52)	0.068
REML	-8.90	4.45	(-17.68, -0.12)	0.047
GEE	-8.80	4.52	(-17.66, 0.06)	0.052
WGEE	-8.83	4.57	(-17.80, 0.13)	0.053

LOCF+ Rank = Last value carry forward. Use turkey normalized ranks.
REML = mixed effects model with restricted maximum likelihood estimation (Laird & Ware, 1982)
GEE = generalized estimating equations (Liang & Zeger, 1986)
WGEE = weighted GEE (Robins, Rotnitzsky, & Zhao, 1995)
Covariance structures: UN for REML and AR(1) for GEE/WGEE
SAS implementation: PROC MIXED for REML and PROC GENMOD for GEE/WGEE

Is there a statistically significant drug effect?

Proposed Robust Method

- We propose a simple "adaptive" robust procedure: Mehrotra, Li, Liu, and Lu (submitted)
  Test for normality at .001 level
  Normality not rejected ⇒ use REML
  Normality rejected ⇒ use **MI → RR**

MI → RR

- Create C (=20) complete datasets using **multiple imputation** of missing values {SAS: PROC MI}
- Analyze each imputed dataset via **robust regression** for endpoint of interest (e.g., Y = % change from baseline at week 4) {SAS: PROC ROBUSTREG}
- Combine the C results for estimation/inference using a plug-in formula (Rubin, 1987)

Test for Normality

- Test is based on the mixed model residuals scaled by the inverse Cholesky root of the marginal variance-covariance matrix (**VCIRY** option).

- ```
  PROC MIXED DATA=a;
  CLASS trt time sub;
  MODEL resp=x trt time trt*time/OUTPM=b RESIDUAL VCIRY;
  REPEATED time/TYPE=UN SUBJECT=sub(trt);
  RUN;

  PROC UNIVARIATE DATA=b NORMAL;
  VAR scaledresid;
  OUTPUT OUT=mvntest PROBN=swprob; * Shapiro-Wilks (1965) test;
  RUN;
  ```
  ```

Robust Regression for a Single Imputed Dataset

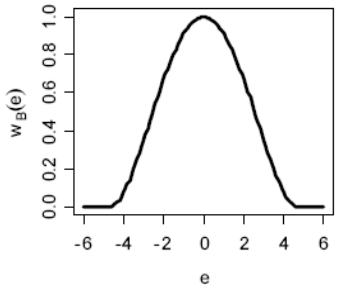
- Regression model:

$$Y = \beta_0 + \beta_1 Z + (\text{covariate terms}) + \varepsilon$$

$$E(\varepsilon) = 0,\ V(\varepsilon) = \sigma^2,\ Z = \begin{cases} 1 & \text{trt A} \\ 0 & \text{trt B} \end{cases}$$

$$\text{Null}: \beta_1 = 0 \quad \text{Alternative}: \beta_1 \neq 0 \quad \boxed{(\beta_1 \equiv \delta)}$$

- $\tilde{\beta}_1$ = **M-estimate** of β_1 with variance $V(\tilde{\beta}_1)$
  (obtained via SAS PROC ROBUSTREG default)
  M-estimation = weighted least squares (Huber 1973)



Default weight function for M-estimation;
outliers get automatically down-weighted!

Combining Results from Multiple Imputed Datasets

- Let $\widetilde{\beta}_{1i}\left(\equiv \widetilde{\delta}_i\right)$ be the M-estimate of $\beta_1\left(\equiv \delta\right)$ for i-th of **C** imputed (i.e., completed) datasets.

$$Z_{MI\to RR} = \frac{\frac{1}{C}\sum_i \widetilde{\delta}_i}{\sqrt{\frac{1}{C}\sum_i V\left(\widetilde{\delta}_i\right) + \left(\frac{C+1}{C}\right)\left(\frac{1}{C-1}\right)\sum_i \left(\widetilde{\delta}_i - \widetilde{\delta}\right)^2}} \equiv \frac{\widetilde{\delta}}{\sqrt{V\left(\widetilde{\delta}\right)}}$$

Rubin (1987) variance is used above. Robins & Wang [R-W] (2000) variance is "more accurate" but very complicated!

- p-value = $2\times P\left\{Z > \left|Z_{MI\to RR}\right|\right\}$
- Confidence interval = $\widetilde{\delta} \pm Z_{\alpha/2}\sqrt{V\left(\widetilde{\delta}\right)}$

Case Study Revisited

Analysis of % change from baseline in TG

METHOD	Estimate of δ	Standard Error	95 % CI For δ	2-tailed p-value
LOCF+Rank	-7.47	4.08	(-15.47, 0.52)	0.068
REML	-8.90	4.45	(-17.68, -0.12)	0.047
GEE	-8.80	4.52	(-17.66, 0.06)	0.052
WGEE	-8.83	4.57	(-17.80, 0.13)	0.053
MI → RR	-11.1	4.60	(-20.12, -2.08)	0.022
Adaptive*	-11.1	4.60	(-20.12, -2.08)	0.022

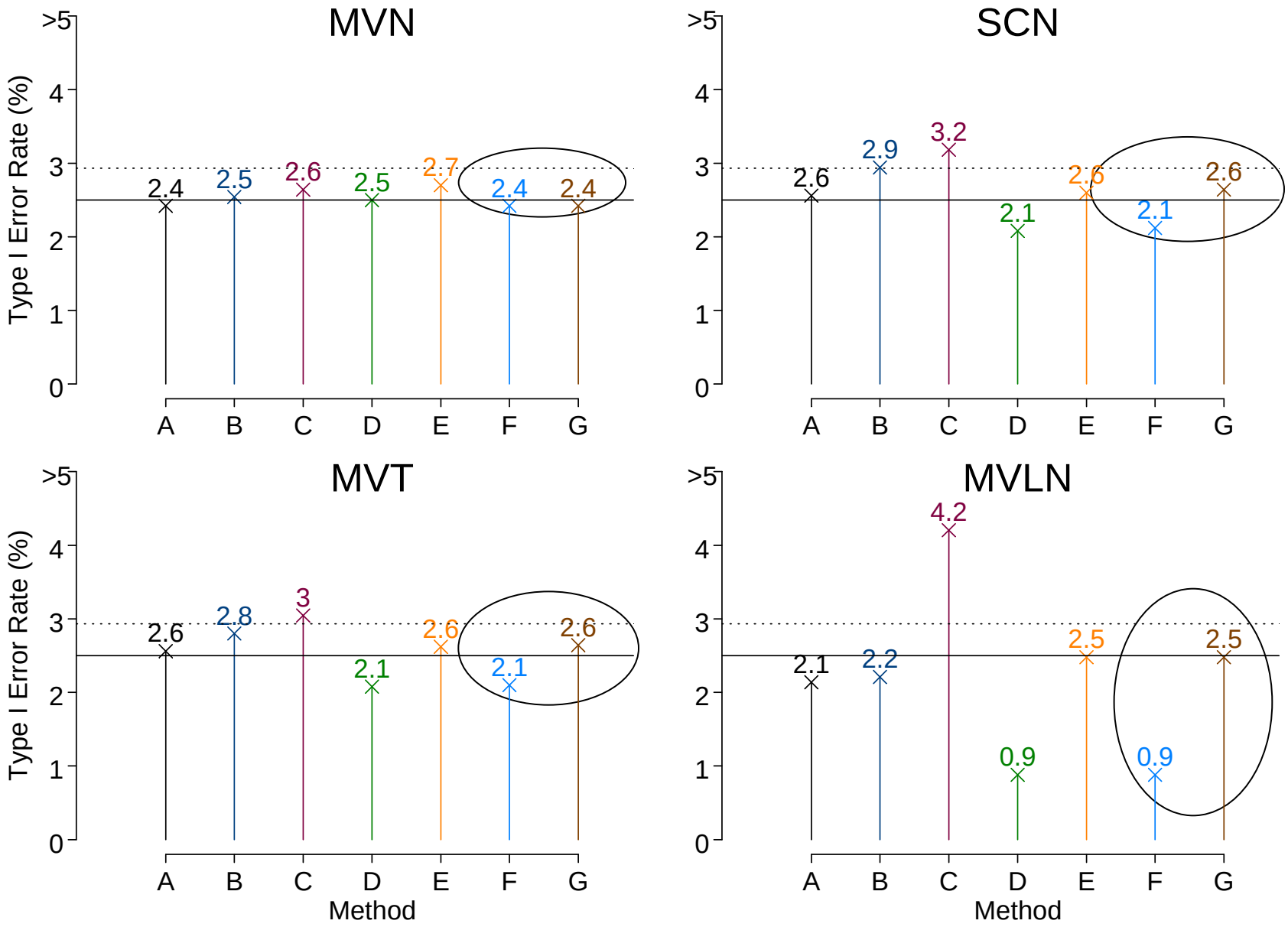
* MI → RR is chosen because normality is rejected at the .001 level

This is not an isolated example.

Simulations confirm that the proposed method:

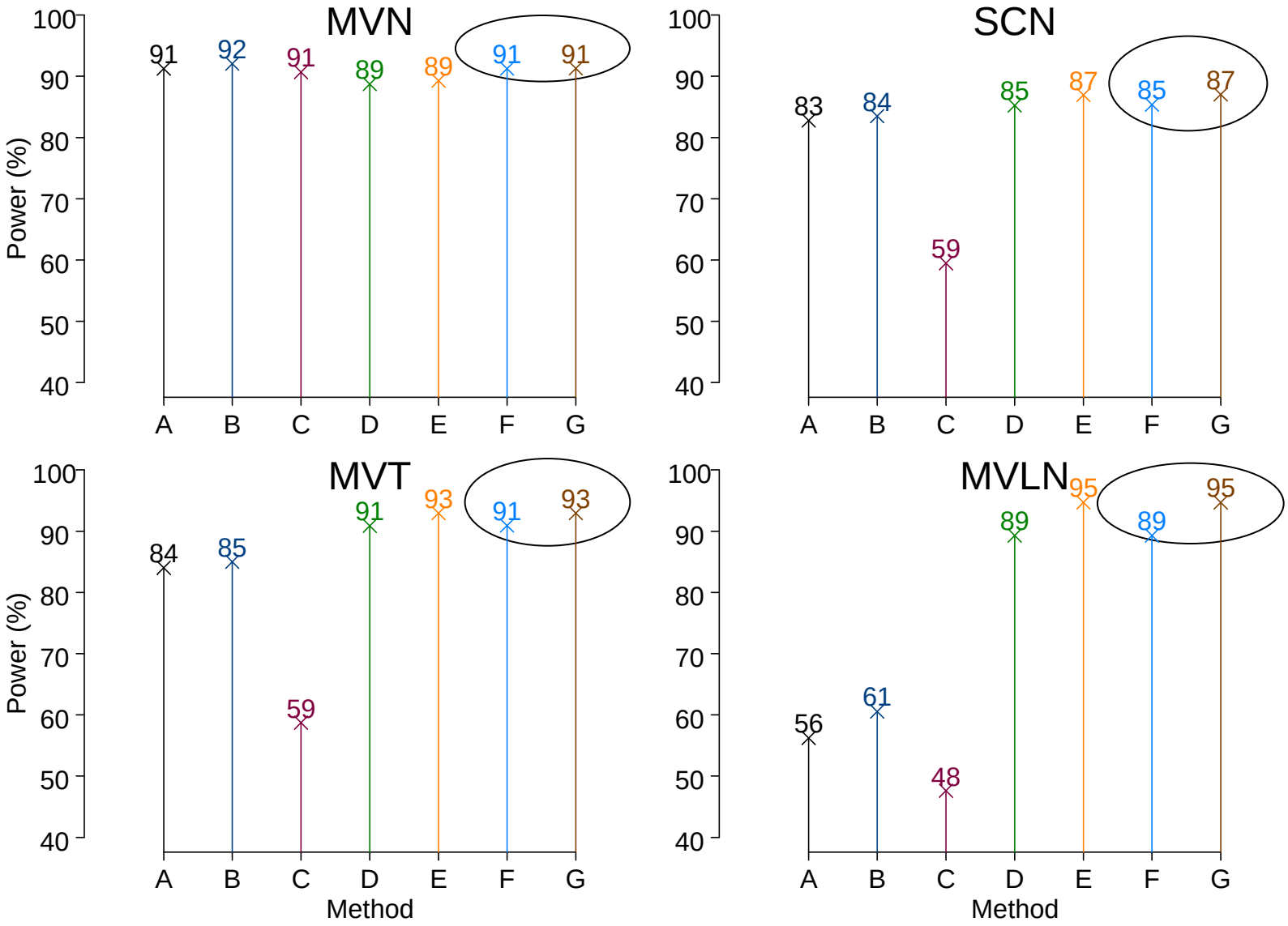
- Is as powerful as REML under normality.
- Is much more powerful than REML/GEE/WGEE under non-normality.
- Controls the type I error rate.

Type I Error Rate (α=2.5%) [80/group]



A-REML B-GEE C-WGEE D-MI/RReg E-MI/RReg(RW) F-Adap G-Adap(RW)

Power (%) [80/group]



Conclusions

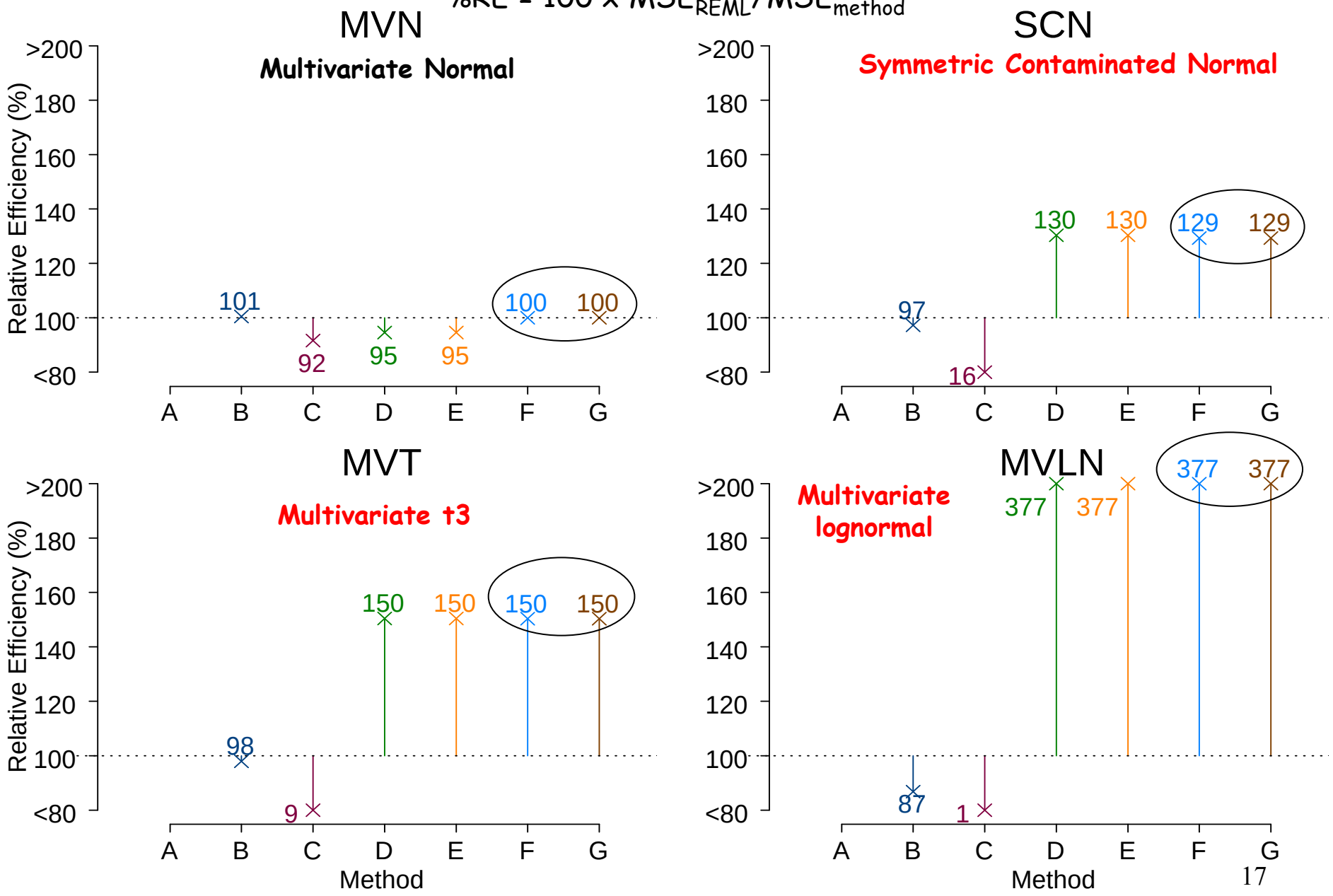
- Traditional analysis method on non-normal lipid data lacks robustness against its **non-normality/outliers,** which can increase the risk of erroneous conclusions.
- MI → RR is a robust, flexible, and easy-to-implement alternative to REML, GEE, and WGEE that simultaneously tackles the challenge of missing data and non-normality/outliers.

  Note: using the Robins & Wang (2000) [RW] variance can improve power compared with the Rubin (1987) variance, but the former is very complicated!

RECOMMENDATION: Adaptive method (choosing between REML and MI → RR based on a test of normality) is recommended for routine use.

% Relative Efficiency vs. REML [80/group]

%RE = 100 x MSE_{REML}/MSE_{method}



A-REML B-GEE C-WGEE D-MI/RReg E-MI/RReg(RW) F-Adap G-Adap(RW)