Models of binary outcomes with 3-level data: A comparison of some options within SAS

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Designs

I. Cluster Randomized Trial

Cluster structure **20**/10/5

. 20 level-3 units: clusters to be randomized

. 10 level-2 units per level-3 unit (e.g., 200 people within clusters)

.   5 level-1 units per level-2 unit (e.g., 5 assessments per person)

. 1000 total level-1 units

Other cluster structure: **10**/20/5

Level-3 units (clusters) were the units of randomization, with equal allocation

Binary Y with ICC, ρ_y, ranging from = 0 to .7 by .1,

1000 replicate samples for each level of ρ_y (8 levels)

An Aside: *ICC in a 3-level sample*

. Given a 3-level sample there are different ICC estimates

. Denote $\sigma^2_{y.2}$ and $\sigma^2_{y.3}$ as the variance components for random intercepts at levels 2 and 3, respectively, and σ^2_{ε} as the residual variance.

Then the ICC at level-3 equals

$$\frac{\sigma^2_{y.3}}{\sigma^2_{y.3} + \sigma^2_{y.2} + \sigma^2_{\varepsilon}} \qquad (1)$$

And, the ICC at levels 2 *and* 3 equals

$$\frac{\sigma^2_{y.3} + \sigma^2_{y.2}}{\sigma^2_{y.3} + \sigma^2_{y.2} + \sigma^2_{\varepsilon}} \qquad (2)$$

For this simulation,

. ρ_y represents the ICC at levels 2 *and* 3 (pooled), i.e., Eq. 2,

. $\sigma^2_{y.2} = \sigma^2_{y.3}$, and

. $.5\rho_y$ represents the ICC at level 3, i.e., Eq. 1

Designs

II. MultiCenter Randomized Trial

Cluster structure **20**/10/5

. 20 level-3 units: e.g., 'centers'

. 10 level-2 units per level-3 unit (e.g.,. 200 people within 20 centers)

. 5 level-1 units per level-2 unit (e.g., 5 assessments per person)

. 1000 total level-1 units

Other cluster structures: **10**/20/5, **4**/50/5

Level-2 units (people) were the units of randomization.
Within each level-3 unit, subordinate level-2 units were equally allocated to intervention groups

Binary Y with ICC at levels 2 + 3, ρ_y, ranging from = 0 to .7 by .1,
and the ICC at level-3 equaled $0.5\rho_y$

1000 replicate samples for each level of ρ_y (8 levels)

Designs

III. Observational Study with Stochastic X variables

Cluster Structure **20**/10/5

. 20 level-3 units

. 10 level-2 units within each level-3 unit (i.e., 200 level-2 units)

. 5 level-1 units within each level-2 unit (i.e., 1000 level-1 units)

. 1000 total level-1 units

Other cluster structures: **10**/20/5, **4**/50/5

Binary Y with ICC at levels 2 + 3, ρ_y, ranging from 0 to .7 by .1, and the ICC at level-3 equal to $0.5\rho_y$

Continuous level-1 and level-2 X variables, each with ICC values, ρ_x, ranging from 0 to .9, by .1

1000 replicate samples for each combination of ρ_y and ρ_x (80 combinations)

Simulation Details for all 3 Designs

General

. N=1000;   Cluster Structure: **20**/10/5, **10**/20/5, and **4**/50/5; R=1000

. $y \sim B(0.50)$

. ρ_y = 0 to .7 by .1

I. Cluster RCT and II. MultiCenter RCT

. $Tx \sim B(0.50)$

. b = 0.3

. Note: $\rho_{Tx} = 1$ for a Cluster RCT and $\rho_{Tx} < 0$ for a MultiCenter RCT

III. Observational Study with Stochastic X

. $x1, x2 \sim N(0, 1)$

. $b_{x1} = b_{x2} = 0.2$

. $\rho_{x1} = \rho_{x2} = \rho_x$ = 0 to .9 by .1

Simulation Details: Population Models

Generate normally distributed y^* with constant variance and exchangeable correlation structure for each appropriate combination of ρ_y and ρ_x

I. Cluster RCT

$$y^*_{ijk} = Tx_i b + u_i + v_{ij} + e_{ijk}$$

II. MultiCenter RCT

$$y^*_{ijk} = Tx_{ij} b + u_i + v_{ij} + e_{ijk},$$

III. Observational study with Stochastic X

$$y^*_{ijk} = x1_{ijk} b_1 + x2_{ij} b_2 + u_i + v_{ij} + e_{ijk}$$

where u_i, v_{ij}, and e_{ijk} are level-3, -2 and -1 residuals

. e_{ijk} ~ Logistic(0,π^2/3)

. $\mathrm{VAR}(u_i) = \mathrm{VAR}(v_{ij}) = \sigma^2$, and

. σ^2 values chosen for specific ρ_y values

If y^*_{ijk} >0 then y_{ijk} = 1; else y_{ijk} = 0

Outcomes

Bias of standard error estimates

. Consider the mean standard error estimate across replicate samples, $\overline{se}$

. Across replicate samples, the standard deviation of a parameter estimate, σ_b, provides an unbiased estimate of its standard error.

. %bias = $100 \times \left(\overline{se} - \sigma_b \right) / \sigma_b$

Bias of parameter estimates (not reported)

. *Unit-specific* (mixed) population models were used for data generation

. Many *population-average* models used for analysis (Naïve, GEE, ALR)

. Uncertain of the corresponding *population-average* parameter values

. However, parameter estimates from *unit-specific* models were unbiased, as were parameter estimates from *population-average* models when $\rho_y = 0$

Relative power (not reported)

. Considered comparing relative power across modeling frameworks

. However, when standard error estimates were reasonably unbiased—or were similarly biased—across 2 or more competitors, then relative power was also roughly equivalent.

Modeling Frameworks

. Naïve (ignore cluster structure)
  I.e., a plain logistic regression with model-based standard error estimates

. GEE logistic regression with fixed effects of level-3 clusters:
  model-based and empirical standard error estimates

. Alternating Logistic Regressions (ALR):
  model-based and empirical standard error estimates

. Mixed Logistic Model via Laplace method:
  model-based and empirical standard error estimates

Modeling Frameworks: Naïve Logistic Regression

I. Cluster RCT / II. MultiCenter RCT

```
PROC GENMOD DATA= my_data ;

  CLASS group_indicator ;

  MODEL  outcome  =  group_indicator  /  DIST=BIN ;

RUN ;
```

III. Observational Study with Stochastic Xs

```
PROC GENMOD DATA= my_data ;

  MODEL  outcome  =  x1   x2  /  DIST=BIN ;

RUN ;
```

Modeling Frameworks: GEE Logistic w/ fixed effects @ level-3

General Idea

Model the level-3 cluster indicator as a fixed effect and
allow GEE to estimate exchangeable outcome response correlation within level-2 clusters

I. Cluster RCT

. Note: fixed effects of level-3 clusters & group indicator are at the same level.

. Technically, this model can be fit for a cluster RCT design, but the results with model SEs would be identical to the Naïve model

. You can obtain empirical SEs, but to what end?

Modeling Frameworks: GEE Logistic w/ fixed effects @ level-3

II. MultiCenter RCT

```
PROC GENMOD  DATA= my_data ;
  CLASS  level3_ID   level2_ID   group_indicator ;
   MODEL  outcome  = level3_ID   group_indicator  /  DIST=BIN ;
   REPEATED  SUBJECT =  level2_ID(level3_ID)  /  TYPE=EXCH  MODELSE ;
RUN ;
```

III. Observational Study with Stochastic Xs

```
PROC GENMOD  DATA= my_data ;
   CLASS  level3_ID   level2_ID ;
   MODEL  outcome =  x1   x2   level3_ID   /  DIST=BIN ;
   REPEATED  SUBJECT=  level2_ID(level3_ID)  /  TYPE=EXCH  MODELSE ;
RUN ;
```

Modeling Frameworks: Alternating Logistic Regressions (ALR)

. ALR is an alternative to GEE logistic regression.
ALR represents intra-cluster associations via log odds ratios.
I.e., pairwise log ORs of outcome response within the same cluster

. ALR allows for inferences about intra-cluster associations.
Some authors consider ALR to be part of the GEE2 family

. ALR algorithm alternates between
a regular GEE1 step to update the model for the mean and
a logistic regression step to update the log odds ratio model.

. SAS has a 3-level ALR option that estimates two log odds ratios:
one for patients within the same level-3 cluster and
another for patents within the same level-2 cluster

Modeling Frameworks: Alternating Logistic Regressions

I. Cluster RCT / II. MultiCenter RCT

```
PROC GENMOD  DATA=  my_data ;
  CLASS  level3_ID  level2_ID  group_indicator ;
  MODEL  outcome  =  group_indicator  /  DIST=BIN ;
  REPEATED SUBJECT=  level3_ID  /  LOGOR= NEST1
                                   SUBCLUSTER=  level2_ID
                                   MODELSE  /* for model-based SEs */ ;
RUN ;
```

III. Observational Study with Stochastic Xs

```
PROC GENMOD DATA=  my_data ;
  CLASS  level3_ID  level2_ID ;
  MODEL  outcome  =  x1  x2  /  DIST=BIN ;
  REPEATED  SUBJECT= level3_ID  /  LOGOR=NEST1
                                   SUBCLUSTER=  level2_ID
                                   MODELSE  /* for model-based SEs */ ;
RUN ;
```

Modeling Approaches: Mixed Logistic Model (MLM)

With random intercepts at levels 2 and 3; via Laplace estimation

Random effects models can be fit by maximizing the marginal likelihood after integrating out the random effects

Usually numerical approximations are needed, e.g., Gaussian Quadrature

Laplace = Adaptive Gaussian quadrature with a single quadrature point

Modeling Approaches: Mixed Logistic Model (MLM)

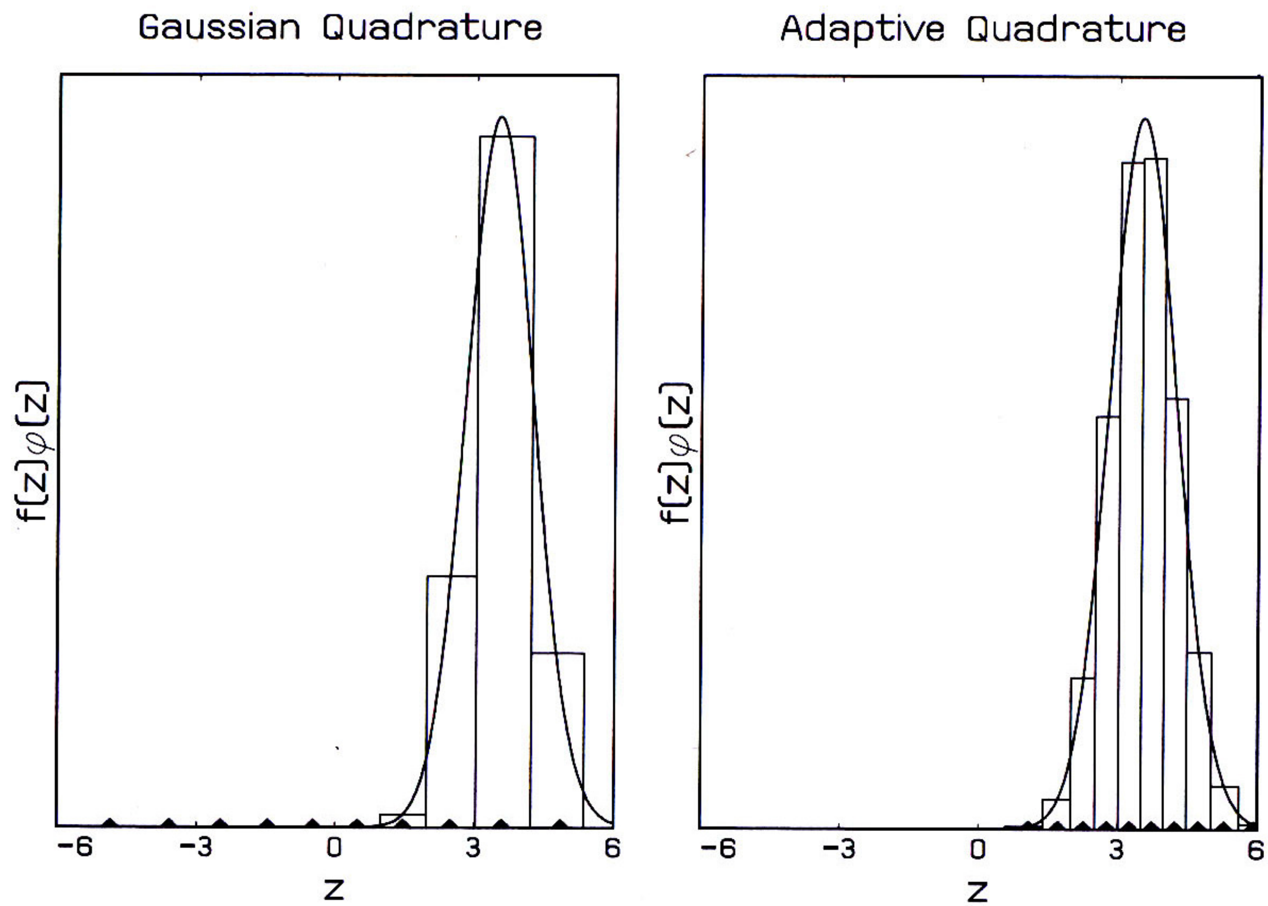

FIGURE 14.1. *Graphical illustration of Gaussian (left window) and adaptive Gaussian (right window) quadrature of order $Q = 10$. The black triangles indicate the position of the quadrature points, and the rectangles indicate the contribution of each point to the integral.*

Molenberghs & Verbeke (2005). *Models for Discrete Longitudinal Data*. Springer. (p. 274)

Modeling Approaches: Mixed Logistic Model (MLM)

I. Cluster RCT / II. MultiCenter RCT

```
PROC GLIMMIX  DATA= my_data
                    METHOD= LAPLACE
                    EMPIRICAL= CLASSICAL  /* if you want empirical SEs */ ;

  CLASS  level3_ID  level2_ID  group_indicator;

  MODEL  outcome  =  group_indicator  / DIST= BINARY  S ;

  RANDOM  INTERCEPT  /  SUBJECT=  level3_ID                 TYPE= CHOL ;

  RANDOM  INTERCEPT  /  SUBJECT=  level2_ID(level3_ID)  TYPE=CHOL ;

  NLOPTIONS  TECH=  QUANEW ;

 RUN ;
```

Modeling Approaches: Mixed Logistic Model (MLM)

III. Observational Study with Stochastic Xs

```
PROC GLIMMIX  DATA=  my_data
                     METHOD= LAPLACE
                     EMPIRICAL= CLASSICAL  /* if you want empirical SEs */ ;

   CLASS  level3_ID  level2_ID ;

   MODEL  outcome  =  x1  x2  / DIST=BINARY  S ;

   RANDOM  INTERCEPT  /  SUBJECT=  level3_ID                 TYPE= CHOL ;

   RANDOM  INTERCEPT  /  SUBJECT=  level2_ID(level3_ID)  TYPE=CHOL ;

   NLOPTIONS  TECH=  QUANEW ;

 RUN ;
```

Results Overview

Summarize the bias of standard error estimates for each noted combination of design and cluster structure

design	*cluster structure*		
	20/10/5	**10**/20/5	**5**/40/5
I. Cluster RCT	yes	yes	no
II. MultiCenter RCT	yes	yes	yes
III. Observational Study with Stochastic Xs	yes	yes	yes

Results: I. Cluster RCT: **20**/10/5

SE estimate bias summary

	Rank: ABS(SE %bias)			SE bias %			ABS(SE bias)†	
	mean	min	max	mean	min	max	≥10%	≥5%
Naive	5.9	5	6	-54%	-73%	4%	88%	88%
GEE emp	4.6	2	5	-50%	-62%	-2%	88%	88%
ALR mod	2.4	2	4	-6%	-7%	-2%	0%	63%
ALR emp	2.9	2	3	-6%	-8%	-2%	0%	75%
MLM mod	4.3	4	6	-5%	-9%	9%	0%	88%
MLM emp	1.0	1	1	-4%	-7%	2%	0%	38%

† percentage of N=8 experimental conditions (defined by ρ_y) with ABS(SE %bias) ≥ 10% and ≥ 5%

Results: I. Cluster RCT: **20**/10/5

Conditions with ≥ 5% ABS SE bias

	ρ_y							
	0	0.1	0.2	0.3	0.4	0.5	0.6	0.7
Naïve		X	X	X	X	X	X	X
GEE emp		X	X	X	X	X	X	X
ALR mod		X		X	X	X	X	
ALR emp		X		X	X	X	X	X
MLM mod	X	X		X	X	X	X	X
MLM emp				X	X	X		

Results: I. Cluster RCT: **10**/20/5

SE estimate bias summary

	Rank: ABS(SE bias)			SE bias %			ABS(SE bias)†	
	mean	min	max	mean	min	max	≥10%	≥5%
Naive	5.4	1	6	-63%	-81%	1%	88%	88%
GEE emp	4.6	2	5	-59%	-72%	1%	88%	88%
ALR mod	2.3	1	5	-13%	-14%	-10%	100%	100%
ALR emp	3.3	2	6	-13%	-14%	-11%	100%	100%
MLM mod	4.0	4	4	-11%	-16%	8%	88%	100%
MLM emp	1.5	1	3	-11%	-14%	-1%	75%	88%

† percentage of N=8 experimental conditions (defined by ρ_y) with ABS(SE %bias) ≥ 10% and ≥ 5%

Summary of Findings: I. Cluster RCT

Within the confines of this simulation and analysis of data from a Cluster Randomized Trial…

% Bias of Standard Error Estimates: Average (min, max): Top 2 performers

	Cluster Structure	
rank: model (se type)	**20**/10/5	**10**/20/5
#1: MLM (empirical)	-4% (-7%, +2%)	-11% (-14%, -1%)
#2: ALR (model-based)	-6% (-7%, -2%)	-13% (-14%, -10%)

With 10 level-3 clusters, performance of standard error estimates left something to be desired.

Results: II. MultiCenter RCT **20**/10/5

SE estimate bias summary

	Rank: ABS(SE bias)			SE bias %			ABS(SE bias)†	
	mean	min	max	mean	min	max	≥10%	≥5%
Naïve	6.0	1	7	-15%	-30%	0%	75%	75%
GEE mod	5.8	5	7	-6%	-9%	-3%	0%	63%
GEE emp	4.6	2	6	-5%	-8%	-2%	0%	50%
ALR mod	2.4	1	6	0%	-2%	5%	0%	0%
ALR emp	3.3	2	4	-3%	-6%	1%	0%	25%
MLM mod	2.5	1	6	-2%	-8%	3%	0%	25%
MLM emp	3.5	2	7	0%	-6%	18%	13%	38%

† percentage of N=8 experimental conditions (defined by ρ_y)
with ABS(SE %bias) ≥ 10% and ≥ 5%

Results: II. MultiCenter RCT **20**/10/5

Conditions with ≥ 5% ABS SE bias

	ρ_y							
	0	0.1	0.2	0.3	0.4	0.5	0.6	0.7
Naïve			X	X	X	X	X	X
GEE mod	X		X	X		X		X
GEE emp	X		X	X		X		
ALR mod								
ALR emp						X		X
MLM mod						X		X
MLM emp	X					X		X

Results: II. MultiCenter RCT **10**/20/5

SE estimate bias summary

	Rank: ABS(SE bias)			SE bias %			ABS(SE bias)†	
	mean	min	max	mean	min	max	≥10%	≥5%
Naive	6.4	4	7	-15%	-29%	4%	75%	88%
GEE mod	3.5	2	4	-3%	-6%	1%	0%	25%
GEE emp	2.0	1	3	-3%	-6%	1%	0%	13%
ALR mod	2.0	1	4	0%	-3%	3%	0%	0%
ALR emp	5.9	5	7	-8%	-10%	-5%	13%	88%
MLM mod	2.8	1	6	-2%	-6%	7%	0%	25%
MLM emp	5.5	5	7	-3%	-10%	30%	13%	88%

† percentage of N=8 experimental conditions (defined by ρ_y) with ABS(SE %bias) ≥ 10% and ≥ 5%

Results: II. MultiCenter RCT **10**/20/5

Conditions with ≥ 5% ABS SE bias

	ρ_y							
	0	0.1	0.2	0.3	0.4	0.5	0.6	0.7
Naïve		X	X	X	X	X	X	X
GEE mod		X						X
GEE emp		X						
ALR mod								
ALR emp		X	X	X	X	X	X	X
MLM mod	X							X
MLM emp	X	X	X	X	X	X		X

Results: II. MultiCenter RCT **4**/50/5

MLM not considered: Ranks from 1 to 5

SE estimate bias summary

	Rank: ABS(SE bias)			SE bias %			ABS(SE bias)†	
	mean	min	max	mean	min	max	≥10%	≥5%
Naive	4.0	1	5	-17%	-30%	-4%	63%	88%
GEE mod	2.4	1	3	-2%	-5%	1%	0%	25%
GEE emp	2.0	1	4	-2%	-5%	2%	0%	13%
ALR mod	2.0	1	3	0%	-4%	3%	0%	0%
ALR emp	4.63	4	5	-21%	-23%	-15%	100%	100%

† percentage of N=8 experimental conditions (defined by ρ_y) with ABS(SE %bias) ≥ 10% and ≥ 5%

Results: II. MultiCenter RCT **4**/50/5

Conditions with ≥ 5% ABS SE bias

	ρ_y							
	0	0.1	0.2	0.3	0.4	0.5	0.6	0.7
Naïve		X	X	X	X	X	X	X
GEE mod	X			X				X
GEE emp	X							
ALR mod								
ALR emp	X	X	X	X	X	X	X	X

Summary of Findings: II. MultiCenter RCT

Within the confines of this simulation and analysis of data from a MultiCenter RCT…

% Bias of Standard Error Estimates: Average (min, max): Top 3 performers

	Cluster Structure		
rank: model (se)	**20**/10/5	**10**/20/5	**4**/50/5
#1: ALR (model)	0% (-2%, +5%)	0% (-3%, +3%)	0% (-4%, +3%)
#2: MLM (model)	-2% (-8%, +3%)	-2% (-6%, +7%)	n/a
#3: GEE (empirical)	-5% (-8%, -2%)	-3% (-6%, +1%)	-2% (-5%, +2%)

Under the simulated circumstances, ALR produced standard error estimates that were generally unbiased

Results: III. Observational Study with Stochastic X: **20**/10/5

X1: SE estimate bias summary

	Rank: ABS(SE bias)			SE bias %			ABS(SE bias)†	
	mean	min	max	mean	min	max	≥10%	≥5%
Naïve	5.8	1	7	-15%	-41%	2%	58%	74%
GEE mod	3.7	1	7	-3%	-12%	7%	1%	34%
ALR mod	2.3	1	6	-1%	-7%	4%	0%	5%
MLM mod	2.2	1	6	-1%	-9%	3%	0%	6%

X2: SE estimate bias summary

Naïve	6.4	1	7	-43%	-72%	4%	88%	88%
GEE mod	4.7	1	7	-7%	-16%	3%	10%	76%
ALR mod	1.9	1	6	-3%	-10%	7%	0%	31%
MLM mod	2.5	1	7	-4%	-11%	7%	3%	43%

† percentage of N=80 experimental conditions (defined by ρ_y and ρ_x) with ABS(SE %bias) ≥ 10% and ≥ 5%

Results: III. Observational Study with Stochastic X1: **20**/10/5: Model-based ABS(SE) ≥5% bias

ρ_x	ρ_y								counts
	0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	
0			G A M					G	2 1 1
0.1	G		G						2 0 0
0.2	G			G			G		4 0 0
0.3						G			1 0 0
0.4	G								1 0 0
0.5	G			G	G				2 0 0
0.6		G	G M		G M	G			4 0 2
0.7		G	G	G			G		4 0 0
0.8				G	G				2 0 0
0.9		G A M		G		G	G	G A M	5 2 2
counts	4 0 0	3 1 1	4 1 2	5 0 0	3 0 1	3 0 0	3 0 0	2 1 1	27 3 5

Perhaps some improvement w/ GEE as $\rho_y \to 1$ and some worsening as $\rho_x \to 1$

Results: III. Observational Study with Stochastic X2: **20**/10/5: Model-based ABS(SE) ≥5% bias

ρ_x	ρ_y								counts
	0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	
0	G	G		G	G M	G M		G M	6 0 3
0.1	G		G M	G	G	G	G	G	7 0 1
0.2		G	G	G M	G		G A M	G	6 1 2
0.3	G	G		A M	G	G	G M	G M	6 1 3
0.4	M	G A	G	G A M		G	G M	G M	6 2 4
0.5	A	G		G A M	G	G	G	G M	6 2 2
0.6	G A	G A M			G A M	G A M	G	G M	6 4 4
0.7	M	G A			M	G A M	G A M	G A M	4 4 5
0.8	A	G	A M	G	G A M	G	G M	G M	6 3 4
0.9	G A	A M	G A M	G A M	G A M	G A M	G A M	G A M	7 8 7
counts	5 4 2	8 4 2	4 2 3	7 4 5	8 3 5	9 3 4	9 3 6	10 2 8	60 25 35

. GEE and MLM worsened as $\rho_y \to 1$

. ALR and MLM worsened as $\rho_x \to 1$

Results: III. Observational Study with Stochastic X: **10**/20/5

MLM not considered: Ranks from 1 to 5

X1: SE estimate bias summary

	Rank: ABS(SE bias)			SE bias %			ABS(SE bias)†	
	mean	min	max	mean	min	max	≥10%	≥5%
Naïve	4.3	1	5	-14%	-40%	8%	55%	76%
GEE mod	2.2	1	4	-2%	-9%	4%	0%	11%
ALR mod	1.5	1	4	-1%	-7%	6%	0%	6%

X2: SE estimate bias summary

Naïve	4.6	1	5	-50%	-80%	1%	88%	88%
GEE mod	2.0	1	3	-4%	-10%	2%	0%	26%
ALR mod	2.3	1	4	-5%	-17%	3%	19%	44%

† percentage of N=80 experimental conditions (defined by ρ_y and ρ_x) with ABS(SE %bias) ≥ 10% and ≥ 5%

Results: III. Observational Study with Stochastic X1: **10**/20/5: Model-based ABS(SE)≥5% bias

ρ_x	ρ_y 0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	counts
0					**A**				**0 1**
0.1							**A**		**0 1**
0.2									**0 0**
0.3				**A**					**0 1**
0.4									**0 0**
0.5									**0 0**
0.6									**0 0**
0.7			**G A**		**G**	**G A**		**G**	**4 2**
0.8			**G**		**G**		**G**		**3 0**
0.9							**G**	**G**	**2 0**
counts	**0 0**	**0 0**	**2 1**	**0 1**	**2 1**	**1 1**	**2 1**	**2 0**	**9 5**

%bias of GEE SE estimates worsened as $\rho_x \to 1$

Results: III. Observational Study with Stochastic X2: **10**/20/5: Model-based ABS(SE) ≥5% bias

ρ_x	ρ_y 0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	counts
0	G						G	G	3 0
0.1							G		1 0
0.2							G		1 0
0.3	A							G	1 1
0.4	G A			A		G A		G	3 3
0.5	A	A	A				G		1 3
0.6	A	A		G A		G	A		2 4
0.7	A	A	G A	A	A	A	A	A	1 8
0.8	A	A	A	A	A	G A	G A	G A	3 8
0.9	A	A	A	G A	A	A	A	G A	2 8
counts	1 7	0 5	1 4	2 5	0 3	3 4	6 4	5 3	18 35

%bias of ALR SE estimates improved as $\rho_y \to 1$; worsened as $\rho_x \to 1$

Results: III. Observational Study with Stochastic X: **4**/50/5

MLM not considered (Ranks range from 1 to 5)

X1: SE estimate bias summary

	Rank: ABS(SE bias)			SE bias %			ABS(SE bias)†	
	mean	min	max	mean	min	max	≥10%	≥5%
Naïve	3.9	1	5	-14%	-39%	4%	58	71
GEE mod	2.0	1	4	-1%	-7%	5%	0%	6%
ALR mod	2.0	1	4	-1%	-6%	6%	0%	8%

X2: SE estimate bias summary

Naïve	4.6	1	5	-56%	-86%	6%	86%	89%
GEE mod	1.7	1	3	-2%	-8%	3%	0%	9%
ALR mod	2.8	1	4	-11%	-38%	3%	44%	64%

† percentage of N=80 experimental conditions (defined by ρ_y and ρ_x) with ABS(SE %bias) ≥ 10% and ≥ 5%

Results: III. Observational Study with Stochastic X1: **4**/50/5: Model-based ABS(SE) ≥5% bias

ρ_x	ρ_y 0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	counts
0									0 0
0.1									0 0
0.2								G	1 0
0.3	A					A			0 2
0.4	A		G						1 1
0.5									0 0
0.6									0 0
0.7						G A			1 1
0.8								G A	1 1
0.9	A					G			1 1
counts	0 3	0 0	1 0	0 0	0 0	2 2	0 0	2 1	5 6

Both ALR and GEE produced reasonable SE estimates for effects of level-1 X

Results: III. Observational Study with Stochastic X2: **4**/50/5: Model-based ABS(SE) ≥5% bias

ρ_x	ρ_y								counts
	0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	
0									0 0
0.1	A								0 1
0.2	A	A				G A			1 3
0.3	A	A	A				G A		1 4
0.4	A	A	A				A	G A	1 5
0.5	A	A	A	A	A		G A		1 6
0.6	G A	A	A	A	A	G A	A	A	2 8
0.7	A	A	A	A	A	A	A	A	0 8
0.8	A	A	A	A	A	A	A	A	0 8
0.9	A	A	A	A	G A	A	A	A	1 8
counts	1 9	0 8	0 7	0 5	1 5	2 5	2 7	1 5	7 51

%bias of ALR SE estimates improved as $\rho_y \rightarrow 1$; worsened as $\rho_x \rightarrow 1$

Summary: III. Observational Study with Stochastic X

Within each model type, model-based SEs generally performed the best

level-1 Stochastic X: % Bias of Standard Error Estimates: Average (min, max)

rank: model (se)	Cluster Structure		
	20/10/5	**10**/20/5	**4**/50/5
#1: ALR (model)	-1% (-7%, +4%)	-1% (-7%, +6%)	-1% (-6%, +6%)
#2: MLM (model)	-1% (-9%, +3%)	n/a	n/a
#3: GEE (model)	-3% (-12%, +7%)	-2% (-7%, +4%)	-1% (-7%, +5%)

level-2 Stochastic X: % Bias of Standard Error Estimates: Average (min, max)

rank: model (se)	Cluster Structure		
	20/10/5	**10**/20/5	**4**/50/5
#?: ALR (model)	-3% (-10%, +7%)	-5% (-17%, +3%)	-11% (-38%, +3%)
#?: MLM (model)	-4% (-11%, +7%)	n/a	n/a
#?: GEE (model)	-7% (-16%, +3%)	-4% (-10%, +2%)	-2% (-8%, +3%)

Summary: III. Observational Study with Stochastic X

Level-1 Stochastic X

%bias of SE estimates for effect of the level-1 X variable was reasonable

ALR tended to perform as well or better than GEE

Level-2 Stochastic X

%bias of SE estimates for the effect of the level-2 X variable was variable

ALR bested GEE with higher numbers of level-3 clusters

The %bias of ALR SEs tended to increase as $\rho_x \to 1$

GEE bested ALR with lower numbers of level-3 clusters

The %bias of GEE SEs tended to increase as $\rho_y \to 1$

Conclusions: Caution

Very limited simulations!

All samples had N=1000

All samples had n=200 level-2 clusters

All samples had level-2 clusters of size 5

Computational burden prohibited use of MLM for some cluster structures

Conclusions: Other (unreported) Findings

Parameter estimates

appeared reasonable for

. MLM models and

. population-average models when $\rho_y = 0$

Relative statistical power

Comparable across modeling frameworks, conditional on SE bias

Conclusions: %bias of standard error estimates

Cluster RCT

With 20 level-3 clusters ALR and MLM did a pretty good job

With 10 level-3 clusters, not such a good job

MultiCenter RCT

ALR, MLM, and GEE seemed to perform well, especially ALR

Observational Study with Stochastic X

ALR, MLM, & GEE did a good job estimating SEs of level-1 effects

For SEs of level-2 stochastic X effects
the performance of ALR and GEE modeling frameworks
was moderated by the number of level-3 clusters.

Conclusions: Due Diligence

. In some cases, you can fit 3-level MLM with 2 or more quadrature points
    Give it a try: it should produce better results than Laplace

. Use a naïve cluster bootstrap procedure for estimating SEs?
    I have not tried this in the context of 3-level data

Consider conducting a simulation study prior to substantive modeling
    using empirically informed inputs (N, cluster structure, ICC, effect size)

    Especially for
        . Cluster RCTs with low-ish number of level-3 clusters and
        . Observational studies with stochastic Xs

END