P9185 Project 1: Protocol of a Phase II MATIK Trial

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Contents

I. Introduction

II. Methods

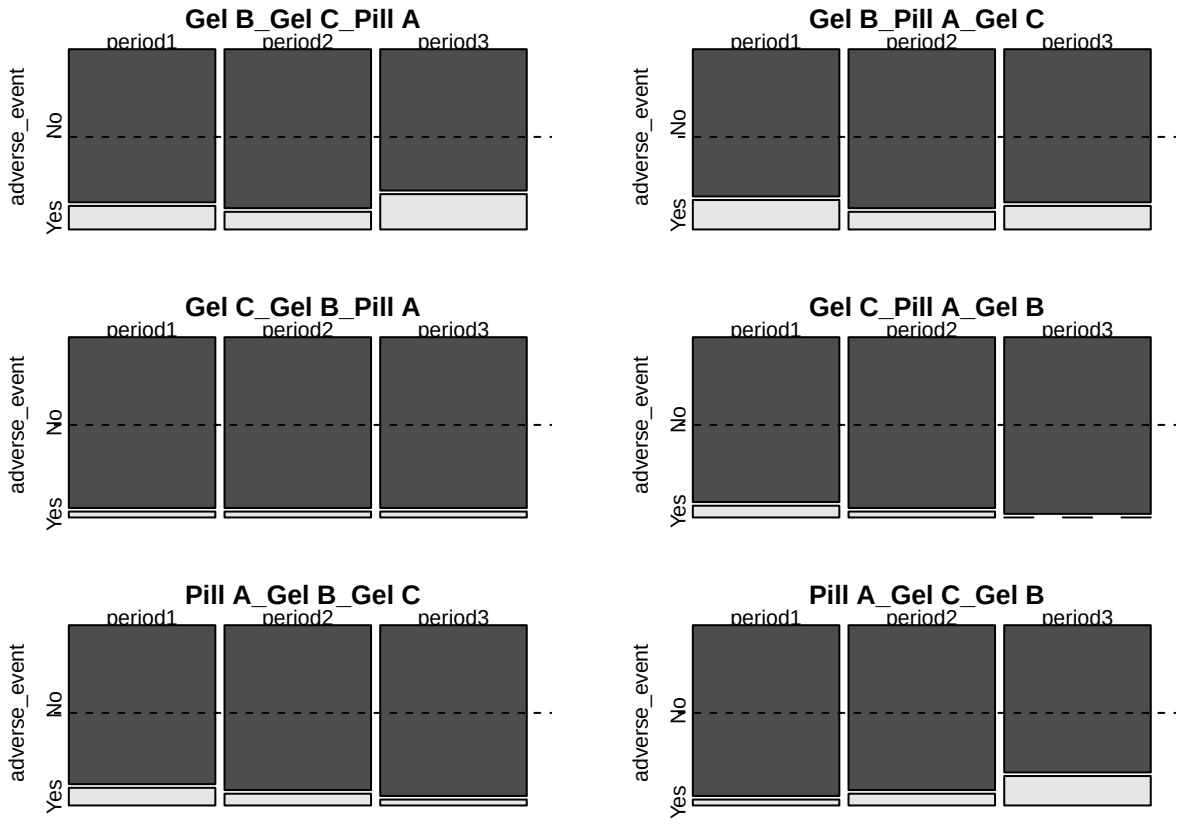
Notation:

k :subject, $k = 1, ..., 180$
j :sequence, $j = 0, 1, 2$
i :period, $i = 1, 2, 3$
h :week, $h = 1, 2, 3, 4$
π :period effect
τ :treatment effect
α :grouped treatment effects
β :demographic effects
λ :sequence/carryover effect
γ :week effect
b :subject-specific intercepts
μ :fixed-effect intercept
ε :residual error

III. Results

3.1 Primary Objective 1

Proportion of Adverse Events per period



Patient Distribution: 30 people in per treatment sequence Initial Observation: Most patients do not face adverse events over the course of 4 weeks in each of the consecutive periods.

add demographic data

demographic summary

Table 1: Distributional Summary of Predictor variables in the Study

Characteristic	period1			period2			period3		
	No N = 164	**Yes** N = 16	**p-value**	**No** N = 168	**Yes** N = 12	**p-value**	**No** N = 163	**Yes** N = 17	**p-value**
age	31 (25, 37)	42 (40, 44)	<0.001	32 (25, 38)	40 (37, 44)	<0.001	32 (25, 38)	38 (32, 42)	0.012

[1] Median (Q1, Q3)

[2] Wilcoxon rank sum test

Characteristic	**OR**	**95% CI**	**p-value**
(Intercept)	0.00	0.00, 0.00	**<0.001**
Treatment			
Pill A	—	—	
Gel B	1.20	0.55, 2.64	0.6
Gel C	0.84	0.37, 1.92	0.7
Period			
period1	—	—	
period2	0.71	0.31, 1.64	0.4
period3	1.13	0.52, 2.46	0.8
Treatment Sequence			
ABC or BAC	—	—	
CAB or ACB	0.61	0.23, 1.62	0.3
BCA or CBA	0.84	0.35, 2.02	0.7
age	1.19	1.11, 1.27	**<0.001**
gender			
Female	—	—	
Male	0.90	0.43, 1.89	0.8
race			
black	—	—	
others	1.55	0.61, 3.95	0.4
white	1.74	0.65, 4.68	0.3

Abbreviations: CI = Confidence Interval, OR = Odds Ratio

GLMM

Model Selection

Table 2: LRT Between Model w/ and w/o Interaction Between Tx and Period

term	npar	AIC	BIC	logLik	minus2logL	statistic	df	p.value
glmm2	12	278.67	330.17	-127.34	254.67	NA	NA	NA
glmm1	16	281.34	350.01	-124.67	249.34	5.33	4	0.25

Table 3: LRT Between Model w/ and w/o Race, Gender and Carryover Effect

term	npar	AIC	BIC	logLik	minus2logL	statistic	df	p.value
glmm3	7	271.25	301.29	-128.62	257.25	NA	NA	NA
glmm2	12	278.67	330.17	-127.34	254.67	2.57	5	0.77

Characteristic	OR	95% CI	p-value
(Intercept)	0.00	0.00, 0.00	**<0.001**
Treatment			
Pill A	—	—	
Gel B	1.18	0.54, 2.58	0.7
Gel C	0.85	0.37, 1.94	0.7
Period			
period1	—	—	
period2	0.72	0.31, 1.65	0.4
period3	1.11	0.51, 2.40	0.8
age	1.19	1.12, 1.27	**<0.001**

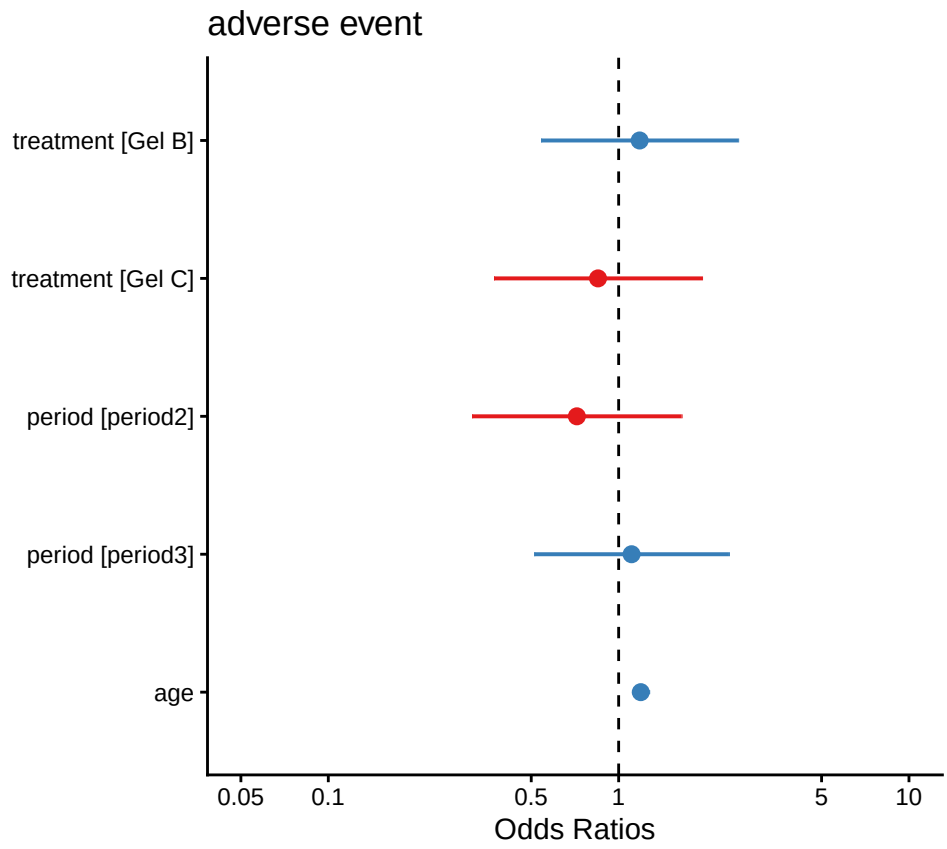
Abbreviations: CI = Confidence Interval, OR = Odds Ratio

Model Result (with Carryover Effect)

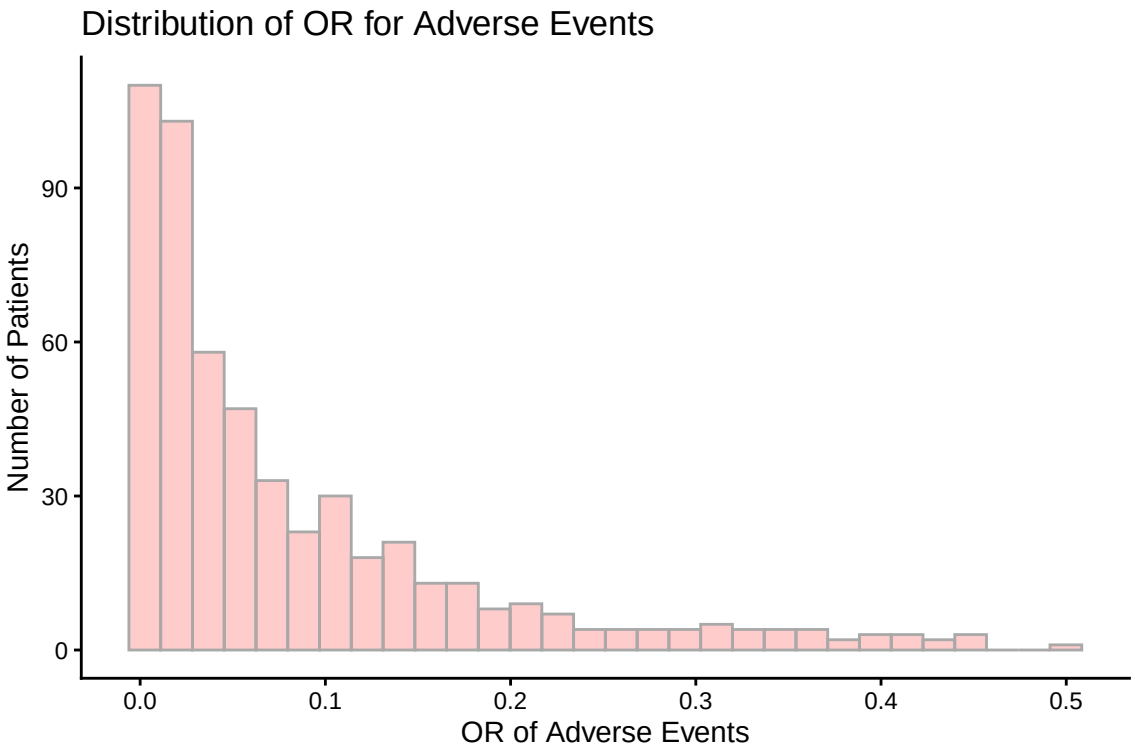
Final Model Result (without Carryover Effect)

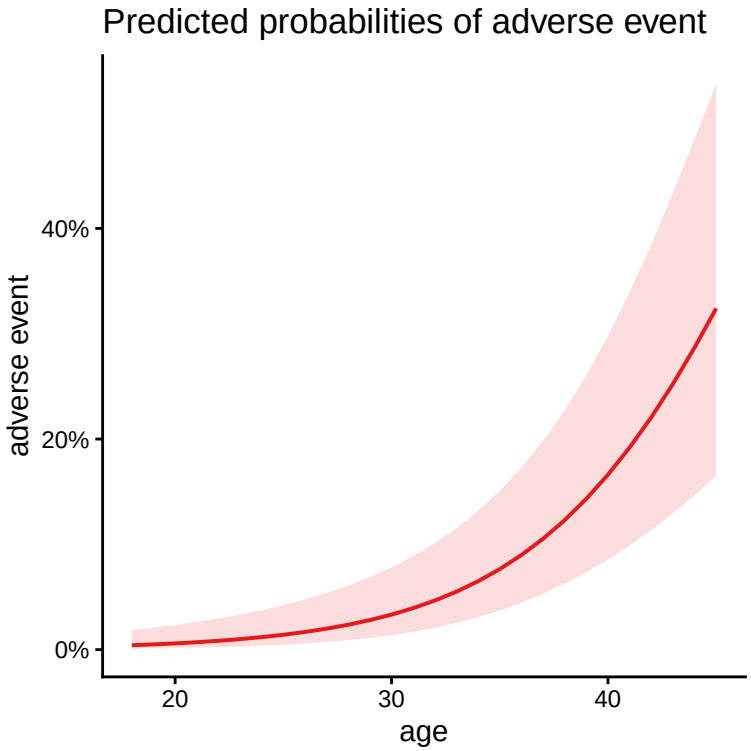
Notation:

$$\widehat{logit}(P(AE_{ijk}=1)) = b_k + \mu + \tau_i + \pi_j + \beta a_k,$$
$$i = 1,2,3,\ j = 1,2,3,\ k = (1,2,\ldots,180),$$
$$b_k \sim N(0, {\sigma^2}_b)$$



AE Prediction

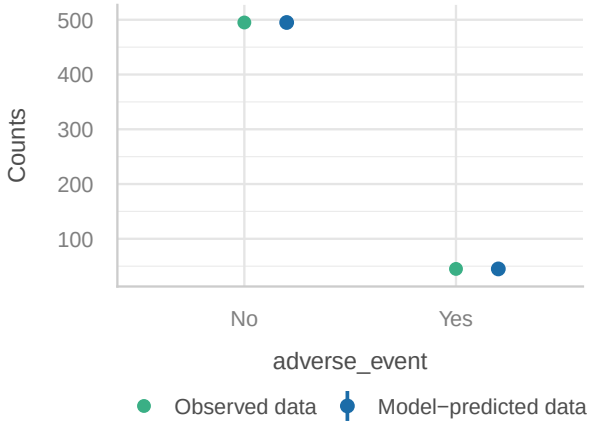




Model Diagnostics

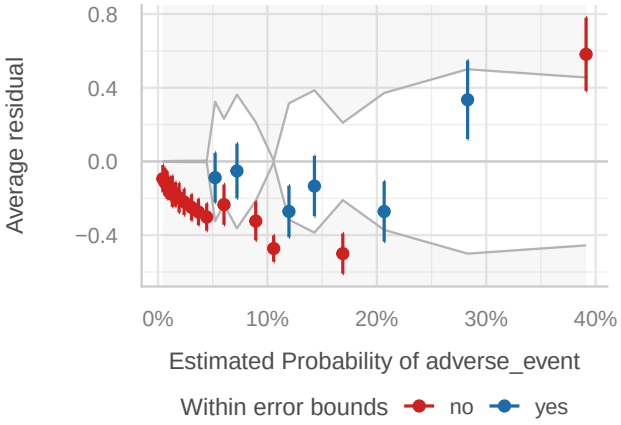
Posterior Predictive Check

Model−predicted intervals should include observed data points



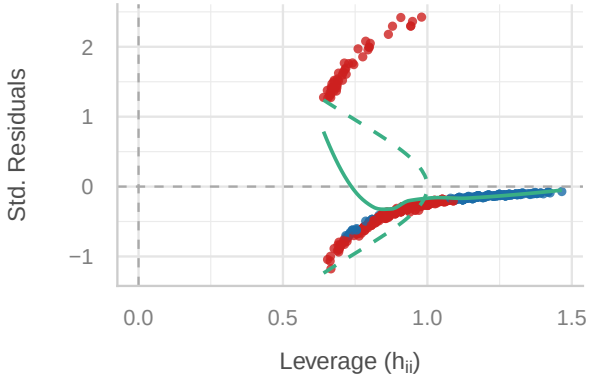
Binned Residuals

Points should be within error bounds



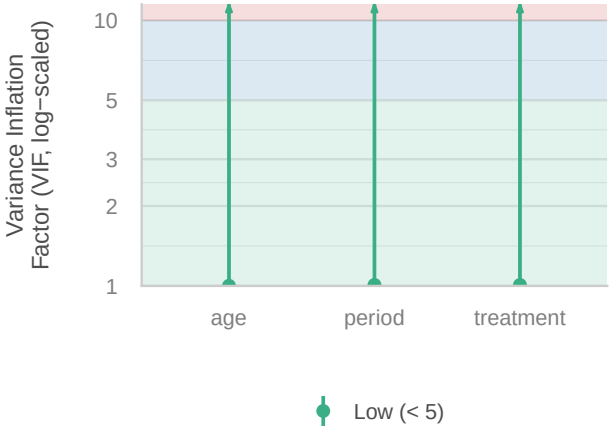
Influential Observations

Points should be inside the contour lines



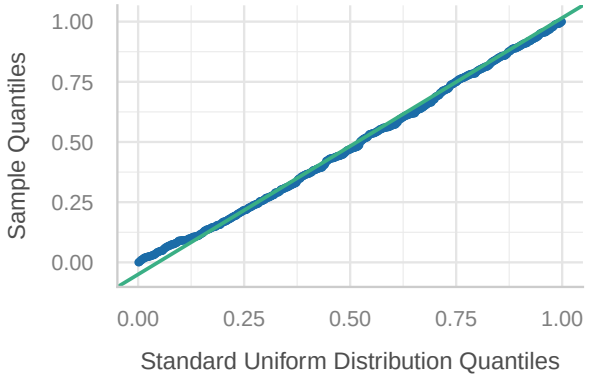
Collinearity

High collinearity (VIF) may inflate parameter uncertainty



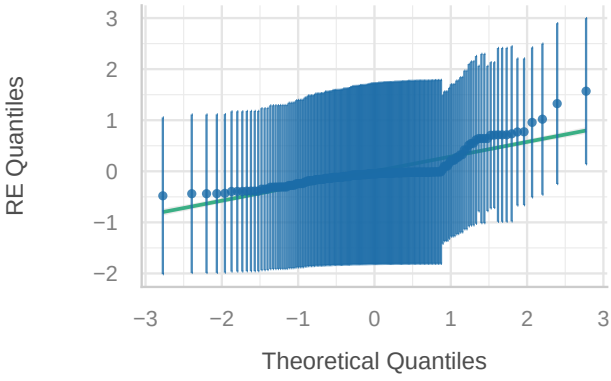
Distribution of Quantile Residuals

Dots should fall along the line

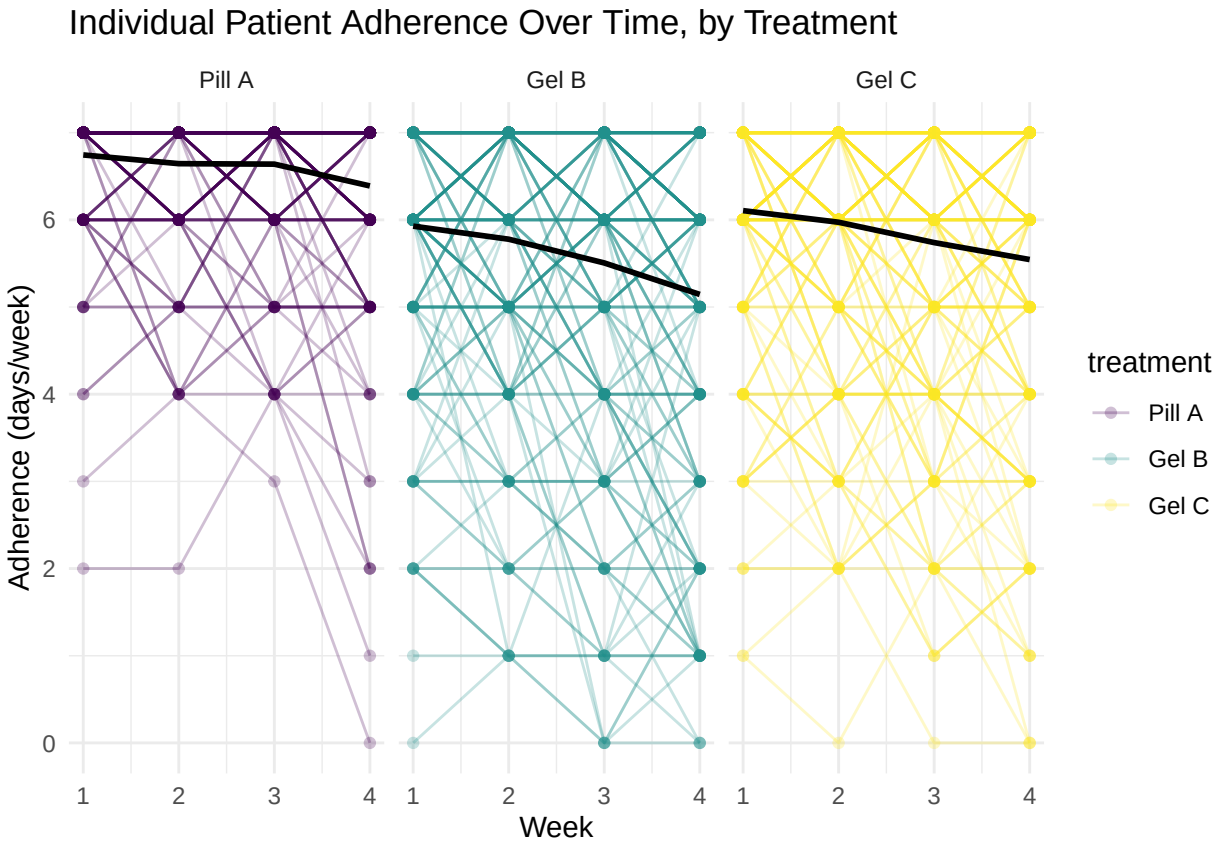


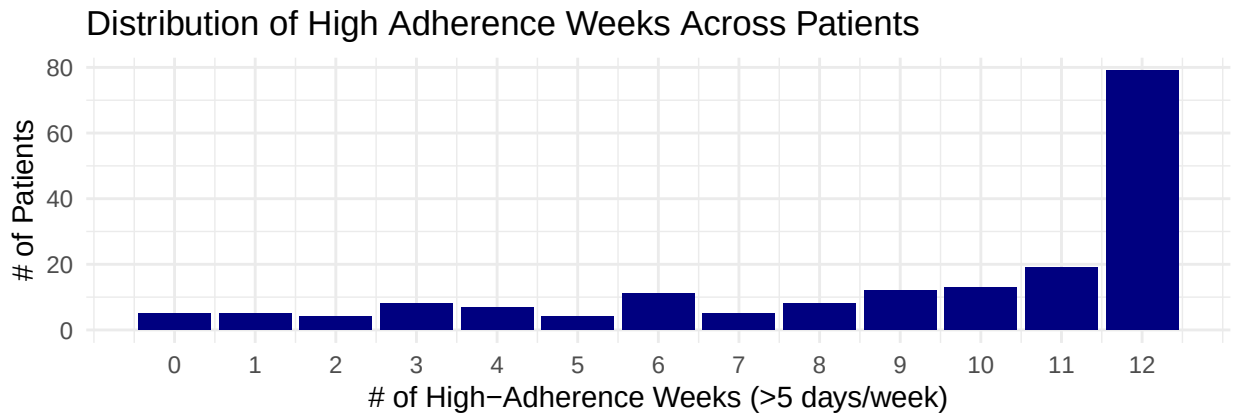
Normality of Random Effects (ptid)

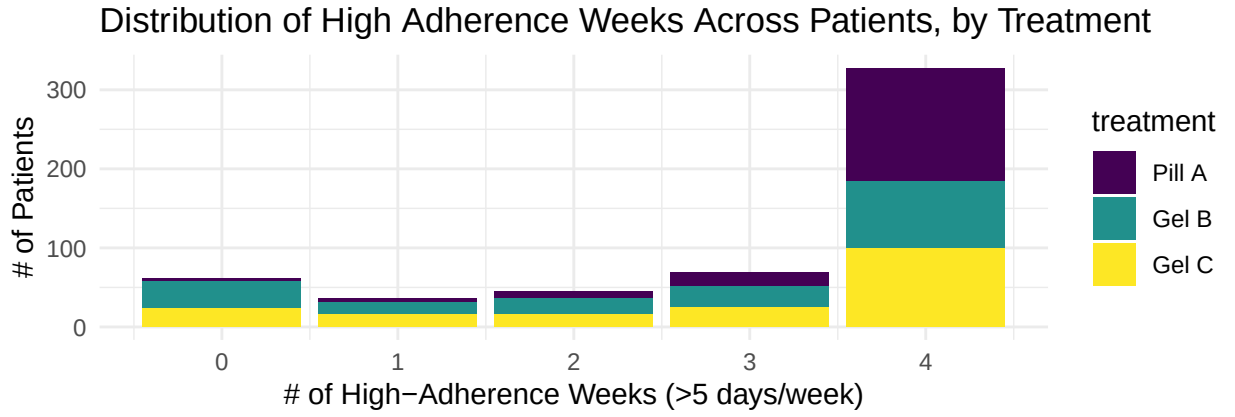
Dots should be plotted along the line



3.2 Primary Objective 2







Model

$$

$$Y_{hik} \sim \text{Binomial}\big(n = 7, p_{hik}\big), \tag{1}$$

$$\text{logit}(p_{hik}) = \mu + b_k + \pi_i + \tau_i + \lambda_j + \gamma * h, \tag{2}$$

$$b_k \sim \mathcal{N}(0, \sigma_b^2) \tag{3}$$

$$

Table 4: **GLMM Results of Treatment on Adherence**

Characteristic	**OR**	**95% CI**	**p-value**
Treatment			
Pill A	—	—	
Gel B	0.14	0.12, 0.17	**<0.001**
Gel C	0.21	0.17, 0.24	**<0.001**
Week	0.73	0.69, 0.76	**<0.001**
Period			
1	—	—	
2	1.15	1.00, 1.32	0.051
3	1.05	0.92, 1.20	0.5

Abbreviations: CI = Confidence Interval, OR = Odds Ratio

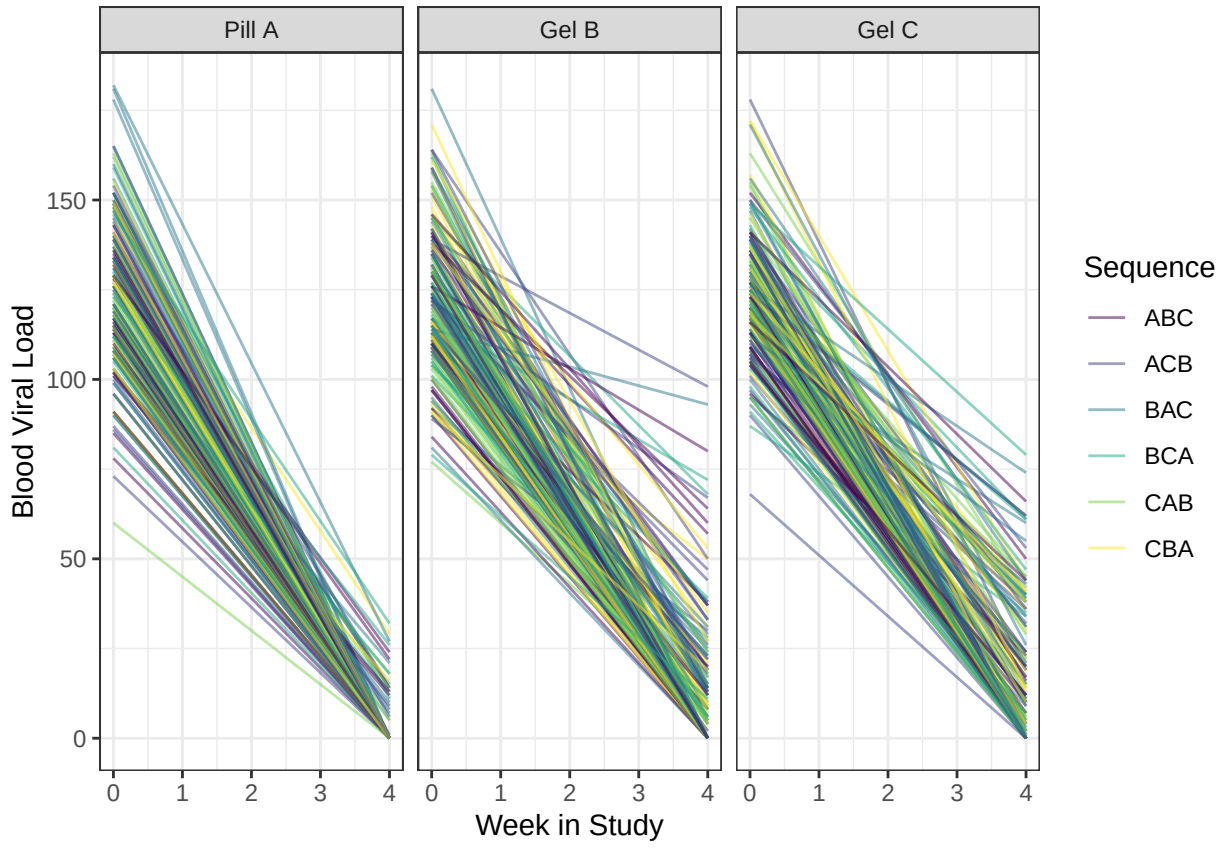
Table 5: **Baseline Characteristics**

Characteristic	**N = 180**[1]
Age (years)	32 (8) [18, 45]
Race	
Black	64 (36%)
White	52 (29%)
Other	64 (36%)
Female	81 (45%)

[1]Mean (SD) [Min, Max]; n (%)

3.3 Secondary Objective 1

EDA: Blood VL

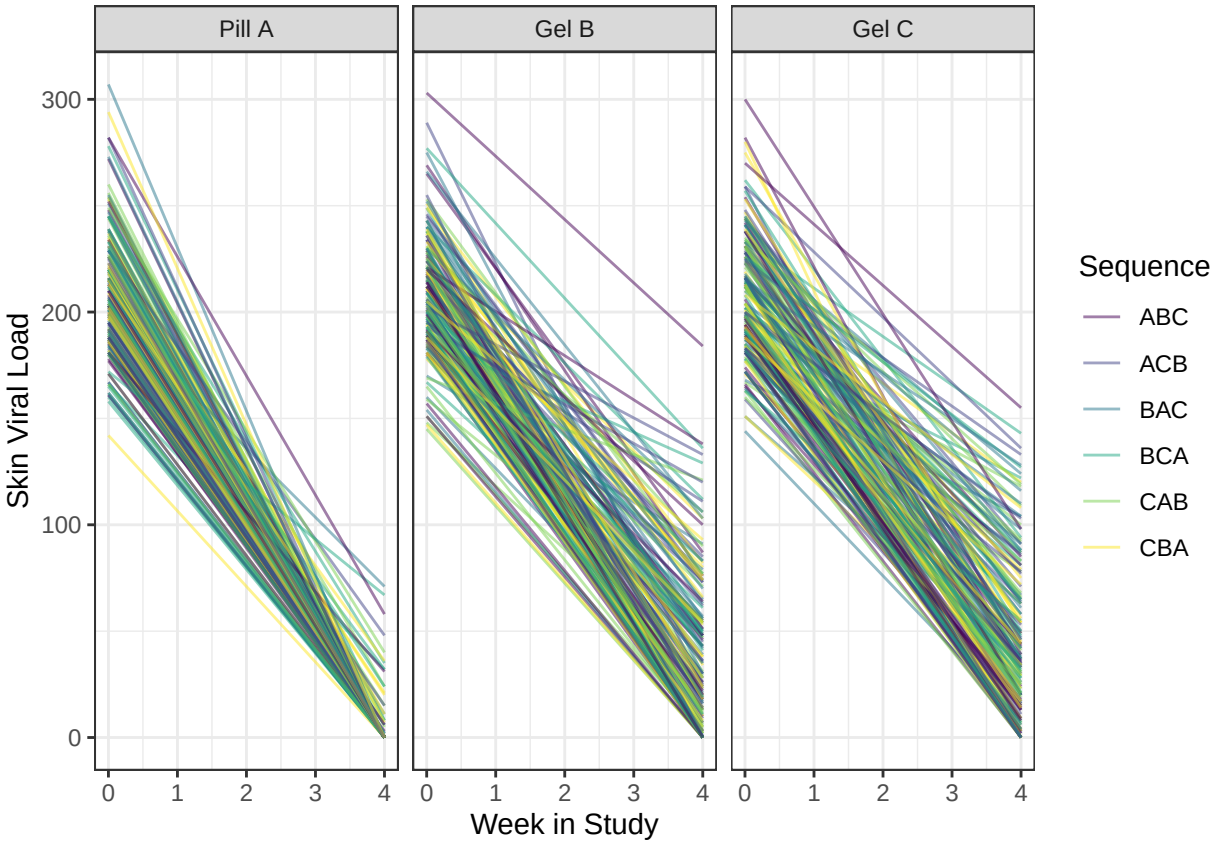

Pill A
Gel B
Gel C
Blood Viral Load
150
100
50
0
0
1
2
3
4
Week in Study
Sequence
ABC
ACB
BAC
BCA
CAB
CBA

EDA: Skin VL

Table 6: Linear mixed-effects model results examining change in blood and skin viral loads (baseline minus end of period) by treatment group, adverse event status, study period, and baseline viral load. Results show beta coefficients, 95% confidence intervals, and p-values for each predictor.

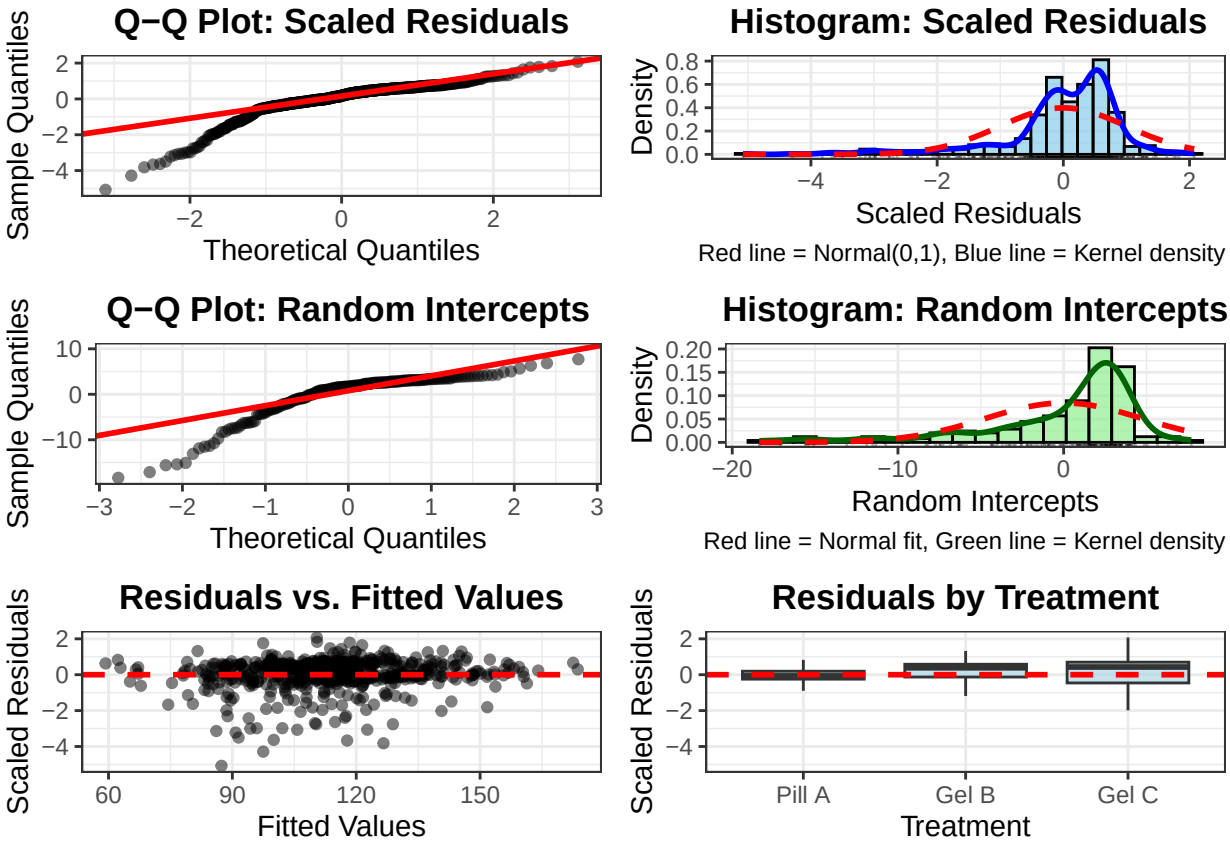
	Blood Viral Load			Skin Viral Load		
Comparison	**Beta**	**95% CI**	**p-value**	**Beta**	**95% CI**	**p-value**
Intercept	14.6	6.2, 23.1	**<0.001**	45.0	25.9, 64.0	**<0.001**
Treatment						
Gel B vs Pill A	-9.8	-12.5, -7.0	**<0.001**	-31.7	-36.9, -26.5	**<0.001**
Gel C vs Pill A	-12.1	-14.8, -9.4	**<0.001**	-41.5	-46.7, -36.3	**<0.001**
Adverse Event						
Adverse Event	-21.0	-25.6, -16.5	**<0.001**	-44.8	-53.5, -36.1	**<0.001**
Period						
Period 2 vs Period 1	-1.4	-4.1, 1.3	0.3	-1.0	-6.2, 4.3	0.7
Period 3 vs Period 1	-1.5	-4.2, 1.2	0.3	0.4	-4.8, 5.7	0.9
Baseline Blood VL	0.9	0.8, 1.0	**<0.001**			
Baseline Skin VL				0.8	0.7, 0.9	**<0.001**

Abbreviation: CI = Confidence Interval



Safety Mixed Models

Model Diagnostics: Blood VL

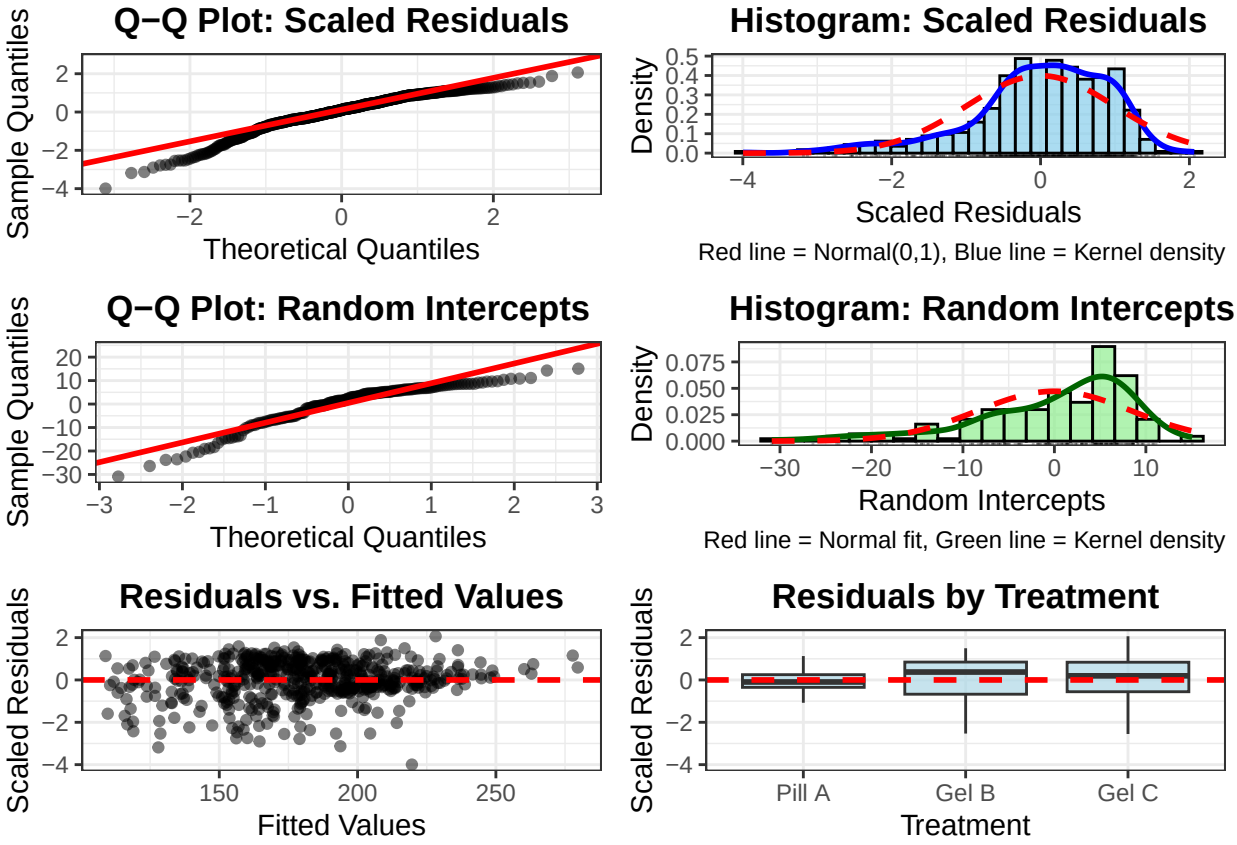


Model Diagnostics: Skin VL

Table 7: Linear mixed-effects model results examining change in blood and skin viral loads (baseline minus end of period) by treatment group, adverse event status, study period, and baseline viral load. Results show beta coefficients, 95% confidence intervals, and p-values for each predictor.

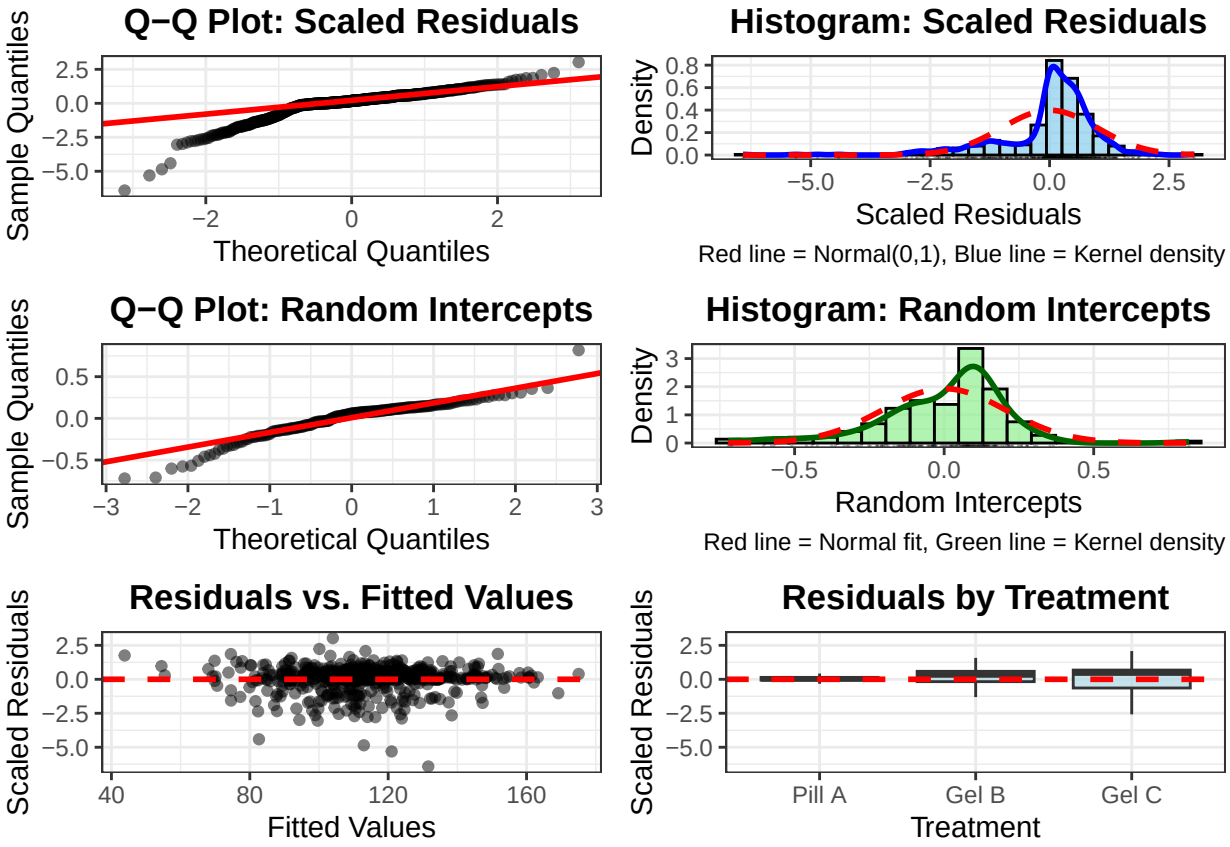
	Blood Viral Load			Skin Viral Load		
Comparison	**Beta**	**95% CI**	**p-value**	**Beta**	**95% CI**	**p-value**
Intercept	-31.8	-43.1, -20.5	**<0.001**	-45.7	-71.4, -20.1	**<0.001**
Treatment						
Gel B vs Pill A	-4.4	-7.5, -1.3	**0.005**	-22.0	-27.9, -16.1	**<0.001**
Gel C vs Pill A	-7.7	-10.7, -4.7	**<0.001**	-33.2	-39.0, -27.5	**<0.001**
Additional Day of Adherence	1.4	1.1, 1.6	**<0.001**	2.5	2.0, 3.0	**<0.001**
Period						
Period 2 vs Period 1	-1.2	-4.1, 1.7	0.4	-0.8	-6.4, 4.7	0.8
Period 3 vs Period 1	-1.6	-4.5, 1.3	0.3	0.1	-5.5, 5.7	>0.9
Baseline Blood VL	1.0	0.9, 1.0	**<0.001**			
Baseline Skin VL				0.9	0.8, 1.0	**<0.001**

Abbreviation: CI = Confidence Interval

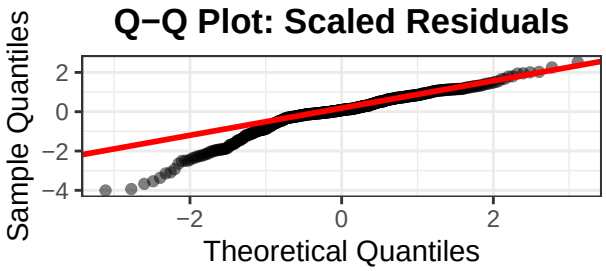


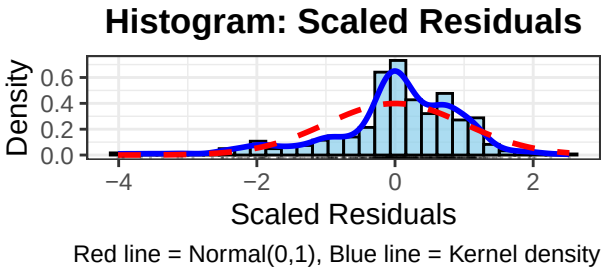
Adherence Mixed Models

Model Diagnostics: Blood VL

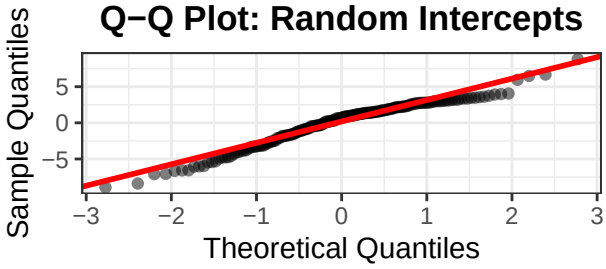


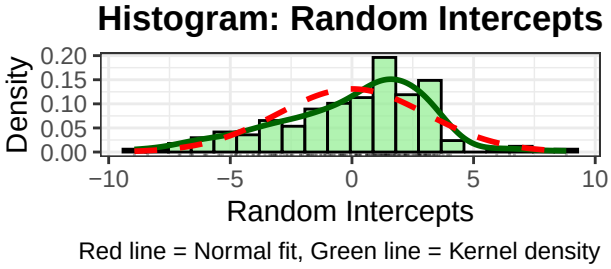
Model Diagnostics: Skin VL



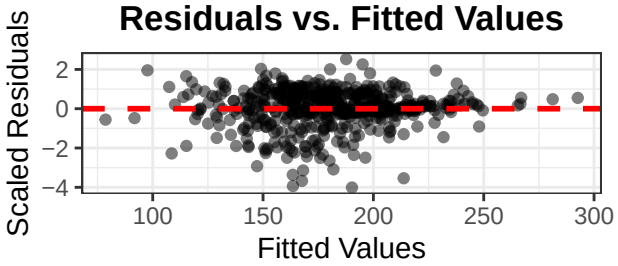


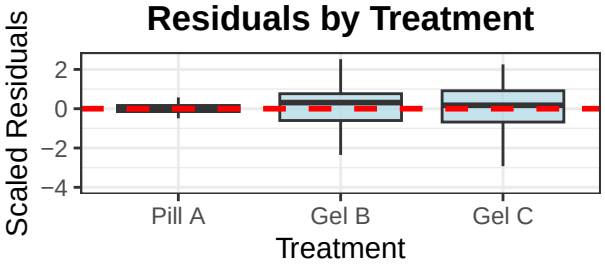
Red line = Normal(0,1), Blue line = Kernel density



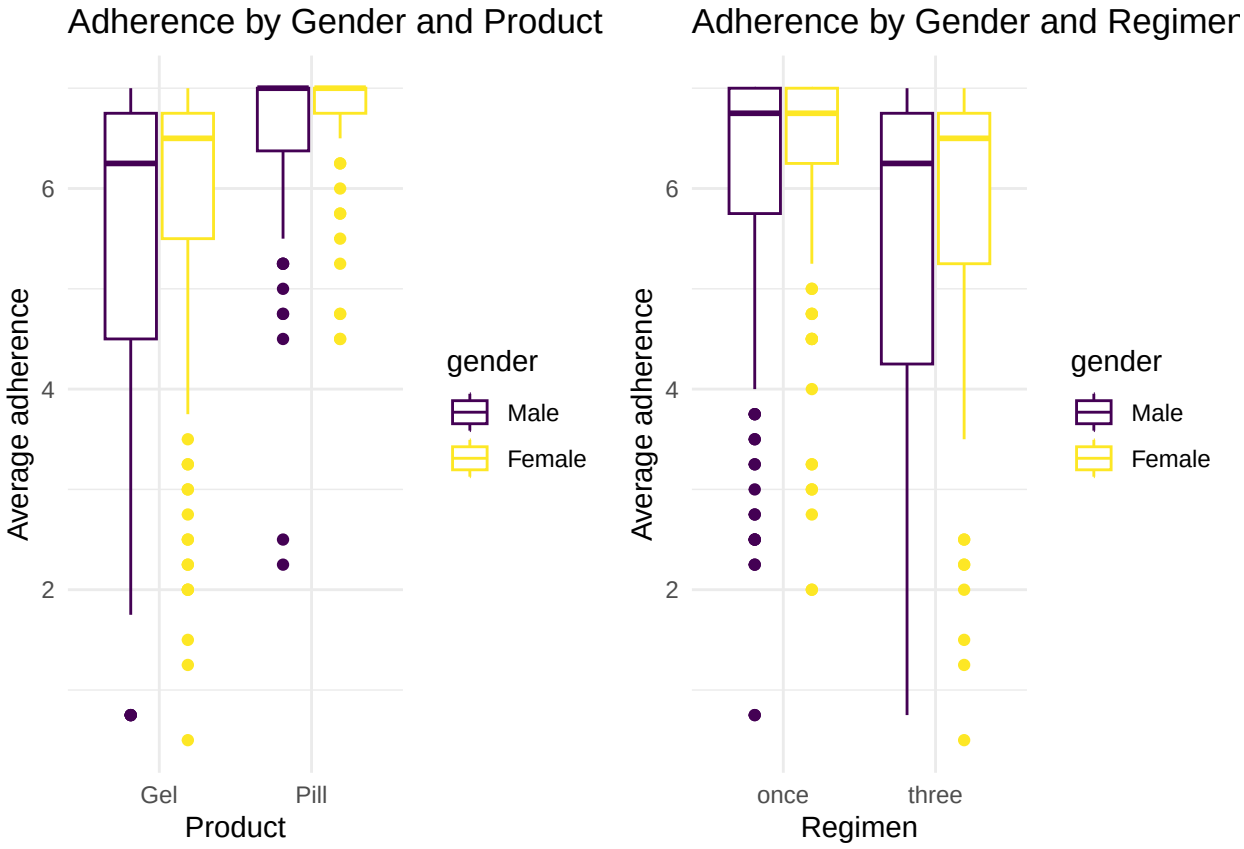


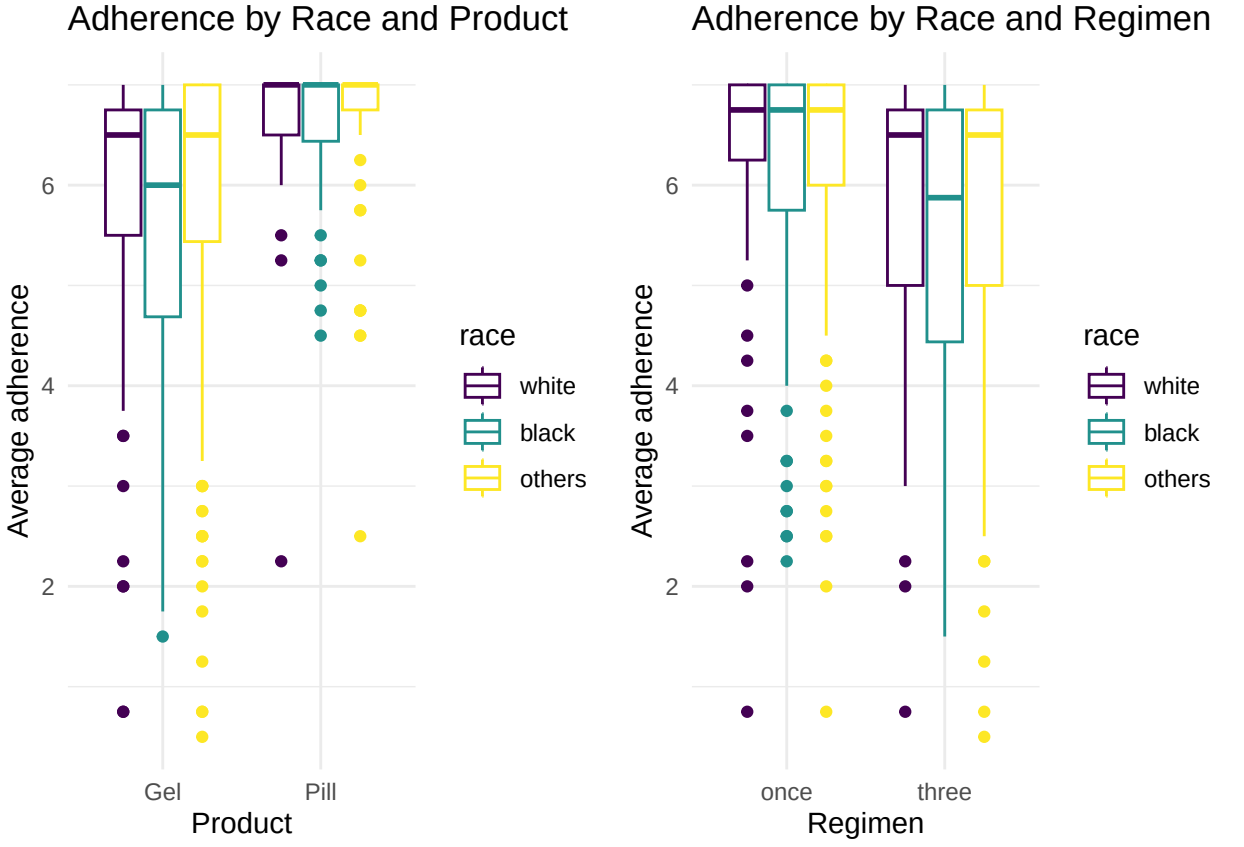
Red line = Normal fit, Green line = Kernel density

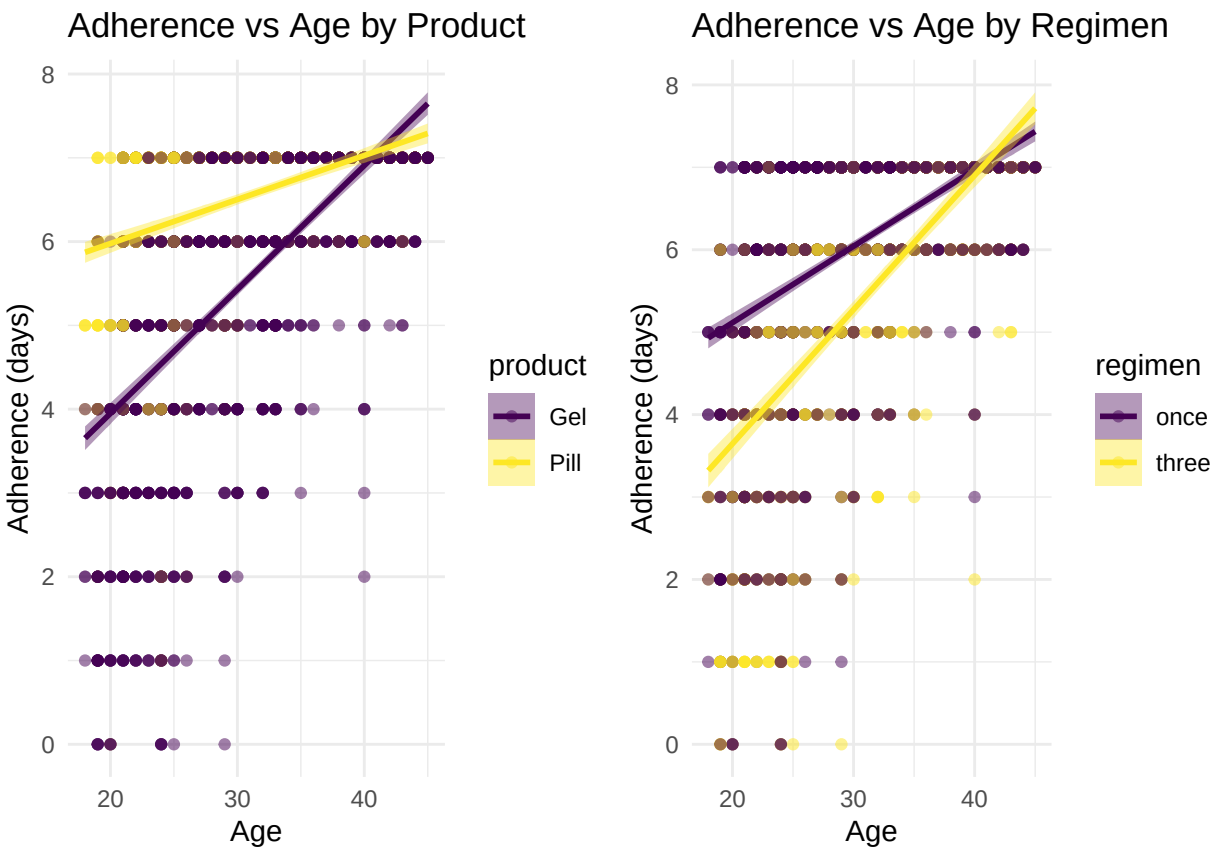




3.4 Secondary Objective 2







Model

$$

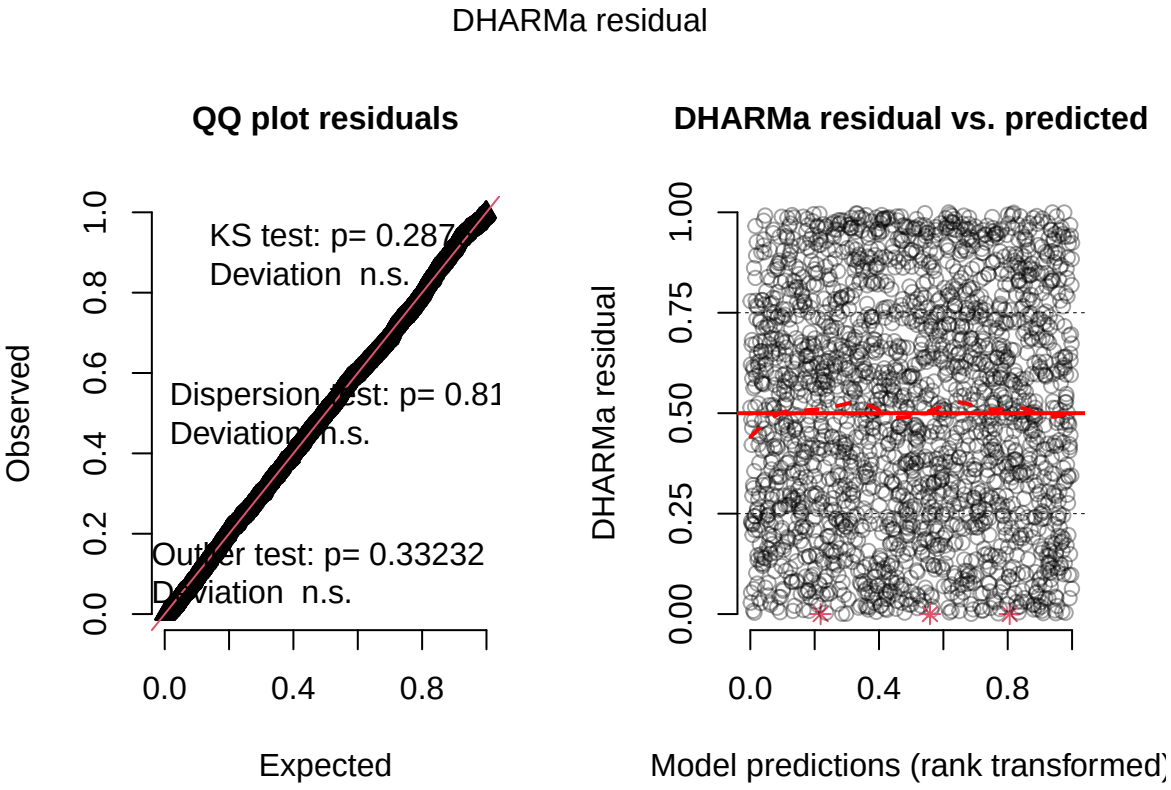
$$Y_{hik} \sim \text{Binomial}\big(n = 7, p_{hik}\big), \tag{4}$$

$$\text{logit}(p_{hik}) = \mu + b_k + \pi_i + \lambda_j + \gamma * h + \beta_d * d_k + \beta_r * regimen + \beta_p * product \tag{5}$$

$$+ \beta_{dr} * d_k * regimen + \beta_{dp} * d_k * product \tag{6}$$

$$b_k \sim \mathcal{N}(0, \sigma_b^2) \tag{7}$$

$$



IV. Discussion

V. Conclusion

VI. Appendix

Table 8: **Interaction Results of Demographic Variables on Adherence**

Characteristic	OR	95% CI	p-value
Age	1.21	1.18, 1.24	**<0.001**
Product			
Gel	—	—	
Pill	4.35	2.98, 6.35	**<0.001**
Gender			
Male	—	—	
Female	1.36	0.95, 1.95	0.10
Race			
white	—	—	
black	1.02	0.65, 1.60	>0.9
others	0.97	0.62, 1.53	0.9
Regimen			
once	—	—	
three	0.76	0.58, 1.00	**0.050**
Period			
1	—	—	
2	1.14	0.99, 1.32	0.073
3	1.03	0.89, 1.18	0.7
Week	0.73	0.69, 0.76	**<0.001**
Age * Product			
Age * Pill	1.00	0.97, 1.03	>0.9
Product * Gender			
Pill * Female	1.00	0.71, 1.40	>0.9
Product * Race			
Pill * black	1.23	0.81, 1.86	0.3
Pill * others	1.05	0.69, 1.61	0.8
Age * Regimen			
Age * three	1.02	1.00, 1.04	0.074
Gender * Regimen			
Female * three	0.89	0.69, 1.15	0.4
Race * Regimen			
black * three	1.14	0.84, 1.56	0.4
others * three	1.02	0.74, 1.41	0.9

Abbreviations: CI = Confidence Interval, OR = Odds Ratio

Table 9: **Main Effect Results of Demographic Variables on Adherence**

Characteristic	OR	95% CI	p-value
Age	1.22	1.19, 1.25	**<0.001**
Gender			
Male	—	—	
Female	1.29	0.92, 1.80	0.14
Race			
white	—	—	
black	1.11	0.73, 1.69	0.6
others	0.99	0.65, 1.50	>0.9
Regimen			
once	—	—	
three	0.71	0.63, 0.80	**<0.001**
Product			
Gel	—	—	
Pill	4.84	4.12, 5.70	**<0.001**
Period			
1	—	—	
2	1.14	0.99, 1.32	0.065
3	1.04	0.91, 1.20	0.6
Week	0.73	0.69, 0.76	**<0.001**

Abbreviations: CI = Confidence Interval, OR = Odds Ratio