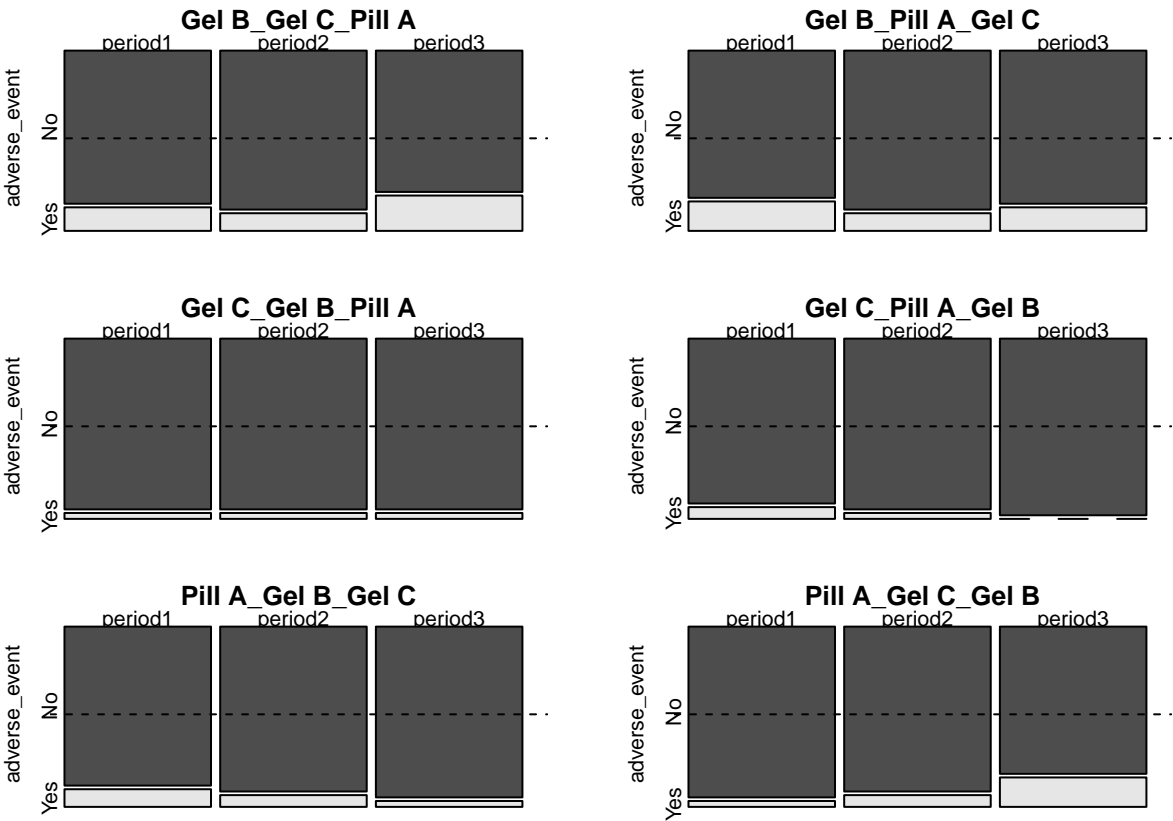# Chhiring_Analysis.Rmd

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2026-02-03

Objective: The primary goal of this trial is to compare the safety profiles of Pill A, GelB and GelC, i.e. whether the medications are sage for patients

###import and clean data

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

Notation:

$$k : \text{subject}, k = 1, ..., 180$$
$$j : \text{sequence}, j = 0, 1, 2$$
$$i : \text{period}, i = 1, 2, 3$$
$$h : \text{week}, h = 1, 2, 3, 4$$
$$\pi : \text{period effect}$$
$$\tau : \text{treatment effect}$$
$$\alpha : \text{grouped treatment effects}$$
$$\beta : \text{demographic effects}$$
$$\lambda : \text{sequence/carryover effect}$$
$$\gamma : \text{week effect}$$
$$b : \text{subject-specific intercepts}$$
$$\mu : \text{fixed-effect intercept}$$
$$\varepsilon : \text{residual error}$$

Logistic Regression

Model Results

```
## Data: endpoint_clean_dat
## Models:
## glmm2: adverse_event ~ treatment + period + seq + age + gender + race + (1 | ptid)
## glmm1: adverse_event ~ treatment * period + seq + age + gender + race + (1 | ptid)
##       npar    AIC    BIC  logLik -2*log(L)  Chisq Df Pr(>Chisq)
## glmm2   12 278.67 330.17 -127.34    254.67
## glmm1   16 281.34 350.01 -124.67    249.34 5.3313  4      0.255

## Data: endpoint_clean_dat
## Models:
## glmm3: adverse_event ~ treatment + period + seq + age + (1 | ptid)
## glmm2: adverse_event ~ treatment + period + seq + age + gender + race + (1 | ptid)
##       npar    AIC    BIC  logLik -2*log(L)  Chisq Df Pr(>Chisq)
## glmm3    9 274.39 313.01 -128.19    256.39
## glmm2   12 278.67 330.17 -127.34    254.67 1.7161  3      0.6334

## Generalized linear mixed model fit by maximum likelihood (Adaptive
##   Gauss-Hermite Quadrature, nAGQ = 0) [glmerMod]
##  Family: binomial  ( logit )
## Formula: adverse_event ~ treatment + period + seq + age + (1 | ptid)
##    Data: endpoint_clean_dat
##
##       AIC       BIC   logLik -2*log(L)  df.resid
##     274.4     313.0   -128.2     256.4       531
```

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	0.85	0.37, 1.93	0.7
Period			
period1	—	—	
period2	0.72	0.31, 1.65	0.4
period3	1.13	0.52, 2.46	0.8
Treatment Sequence			
ABC or BAC	—	—	
CAB or ACB	0.67	0.26, 1.72	0.4
BCA or CBA	0.92	0.39, 2.21	0.9
age	1.19	1.11, 1.27	**<0.001**

Abbreviations: CI = Confidence Interval, OR = Odds Ratio

```
## 
## Scaled residuals:
##     Min     1Q  Median     3Q     Max 
## -0.9223 -0.3122 -0.1725 -0.0964  4.1408 
## 
## Random effects:
##  Groups Name        Variance Std.Dev.
##  ptid   (Intercept) 0.8203   0.9057  
## Number of obs: 540, groups:  ptid, 180
## 
## Fixed effects:
##               Estimate Std. Error z value      Pr(>|z|)    
## (Intercept)   -8.41721    1.35576  -6.208 0.000000000535 ***
## treatmentGel B  0.18360    0.40078   0.458          0.647    
## treatmentGel C -0.16827    0.42246  -0.398          0.690    
## periodperiod2  -0.33173    0.42455  -0.781          0.435    
## periodperiod3   0.12185    0.39738   0.307          0.759    
## seq1          -0.40093    0.48197  -0.832          0.405    
## seq2          -0.08047    0.44529  -0.181          0.857    
## age            0.17332    0.03374   5.136 0.000000280531 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
## 
## Correlation of Fixed Effects:
##            (Intr) trtmGB trtmGC prdpr2 prdpr3 seq1   seq2 
## treatmntGlB -0.177                                          
## treatmntGlC -0.141  0.490                                   
## periodperd2 -0.120  0.005 -0.050                            
## periodperd3 -0.153  0.084 -0.055  0.479                     
## seq1        -0.188 -0.042  0.030  0.003 -0.063              
## seq2        -0.158  0.023  0.060  0.004 -0.027  0.450       
## age         -0.943  0.015 -0.005 -0.017  0.008  0.052 -0.007
```

Choosing the final model with treatment, period, sequence and age as predictors. Model is:

$$\widehat{logit}(P(AE_{ijk} = 1)) = b_{ik} + \mu + \tau_{ij} + \pi_i + \lambda_j + \beta a_k,$$
$$i = 1, 2, 3, \ j = 0, 1, 2, \ k = (1, 2, \ldots, 180),$$
$$b_{ik} \sim N(0, \sigma^2_b)$$

Table 2: random effects variances

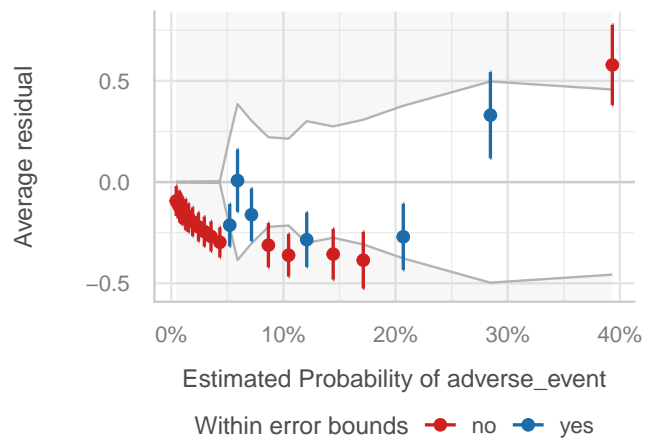| Groups	Name	Std.Dev.
ptid	(Intercept)	0.90571

Table 3: Fixed effects

	Estimate	Std. Error	z value	Pr($>$|z|)
(Intercept)	-8.417	1.356	-6.208	0.000
treatmentGel B	0.184	0.401	0.458	0.647
treatmentGel C	-0.168	0.422	-0.398	0.690
periodperiod2	-0.332	0.425	-0.781	0.435
periodperiod3	0.122	0.397	0.307	0.759
seq1	-0.401	0.482	-0.832	0.405
seq2	-0.080	0.445	-0.181	0.857
age	0.173	0.034	5.136	0.000

Posterior Predictive Check

Model−predicted intervals should include observed data points

Counts vs adverse_event

Legend: Observed data, Model−predicted data
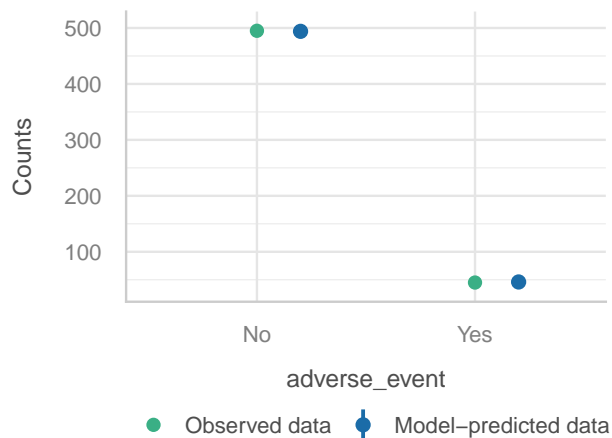
Binned Residuals

Points should be within error bounds

Average residual vs Estimated Probability of adverse_event

Within error bounds: no, yes

Influential Observations

Points should be inside the contour lines

Std. Residuals vs Leverage (h_{ii})
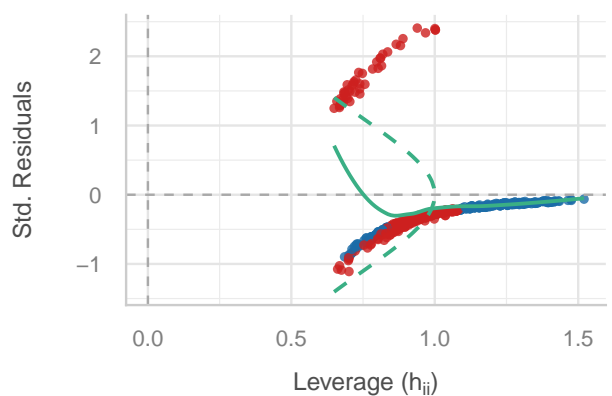
Collinearity

High collinearity (VIF) may inflate parameter uncertainty

Variance Inflation Factor (VIF, log−scaled) vs age, period, seq, treatment

Low (< 5)
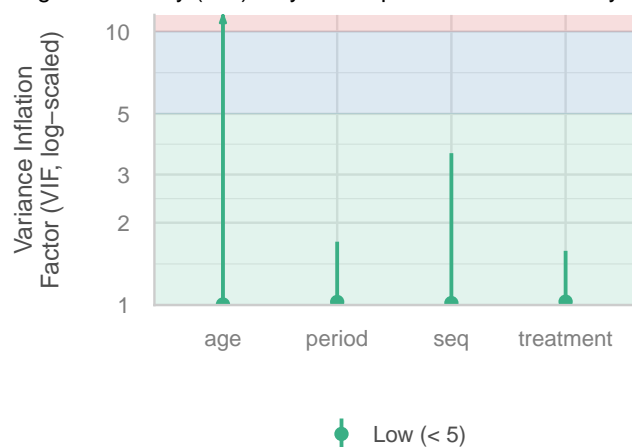
Distribution of Quantile Residuals

Dots should fall along the line

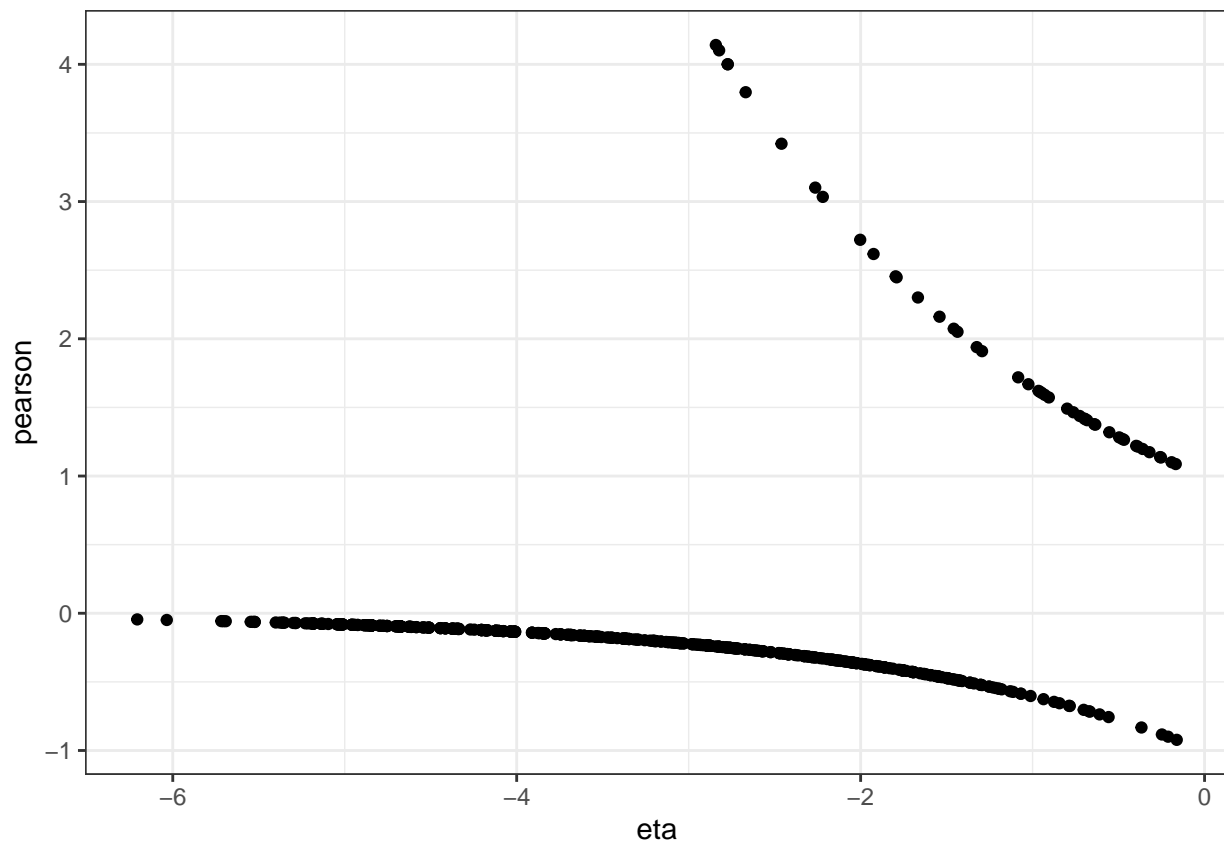Sample Quantiles vs Standard Uniform Distribution Quantiles
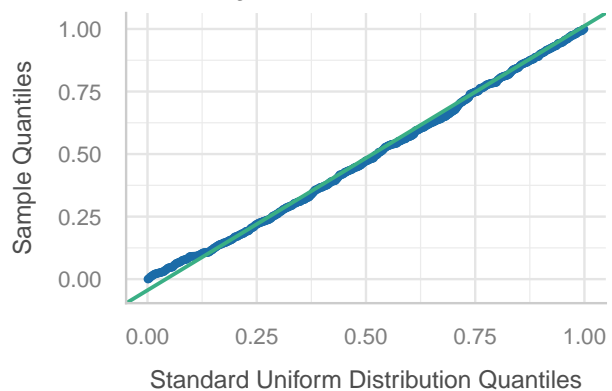
Normality of Random Effects (ptid)

Dots should be plotted along the line

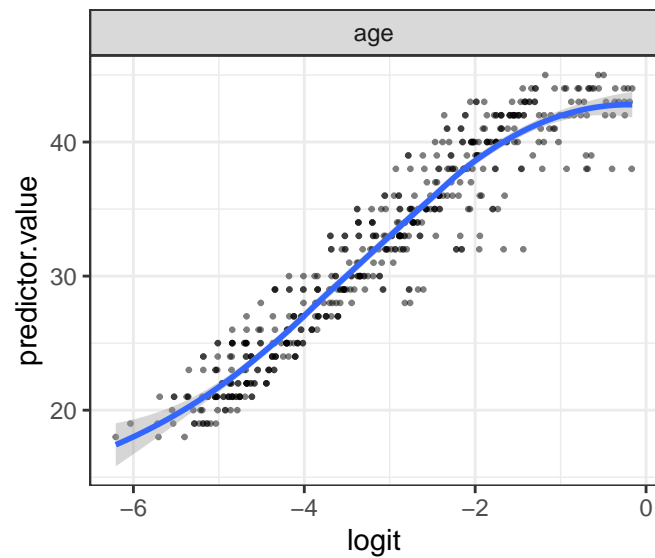RE Quantiles vs Theoretical Quantiles
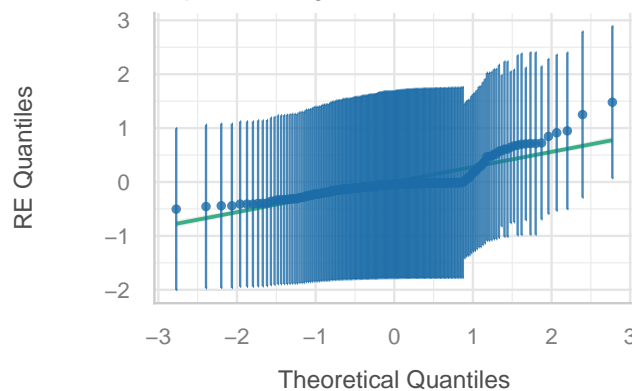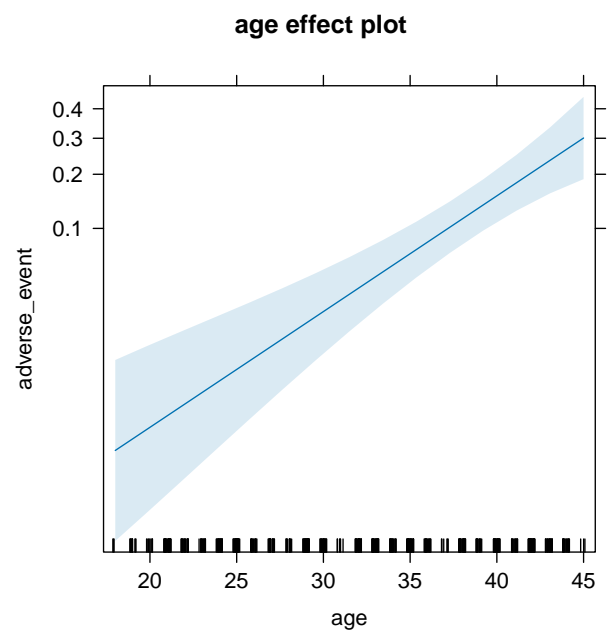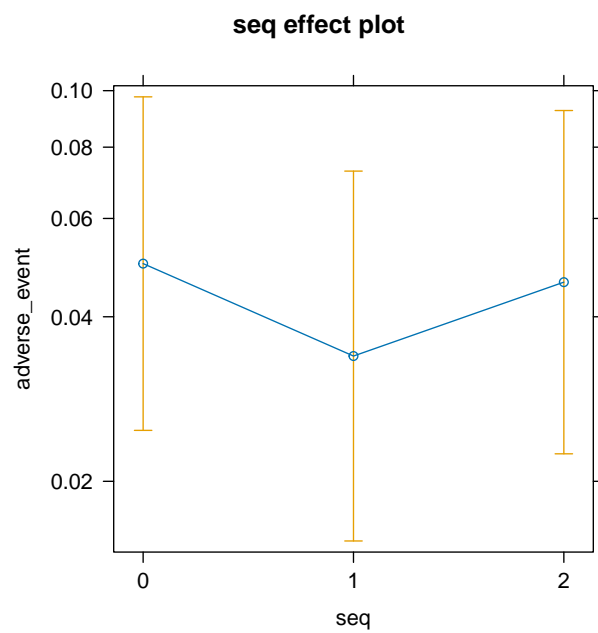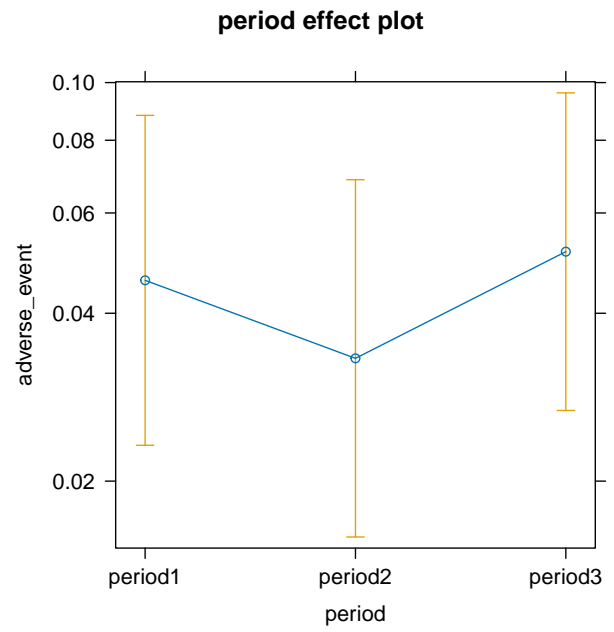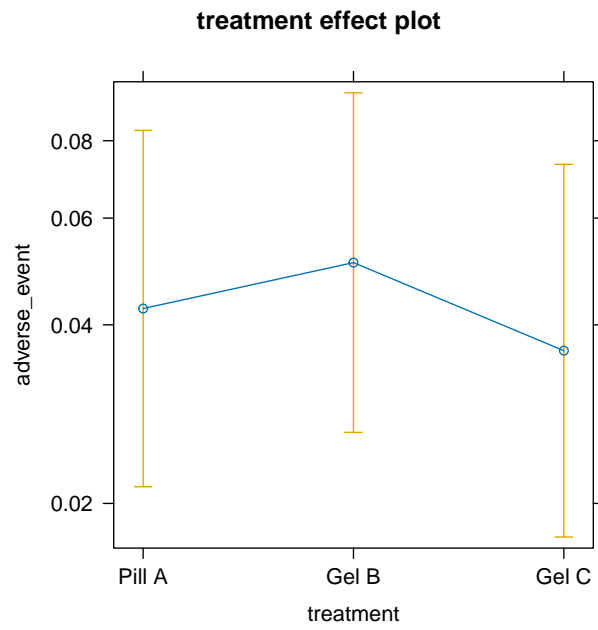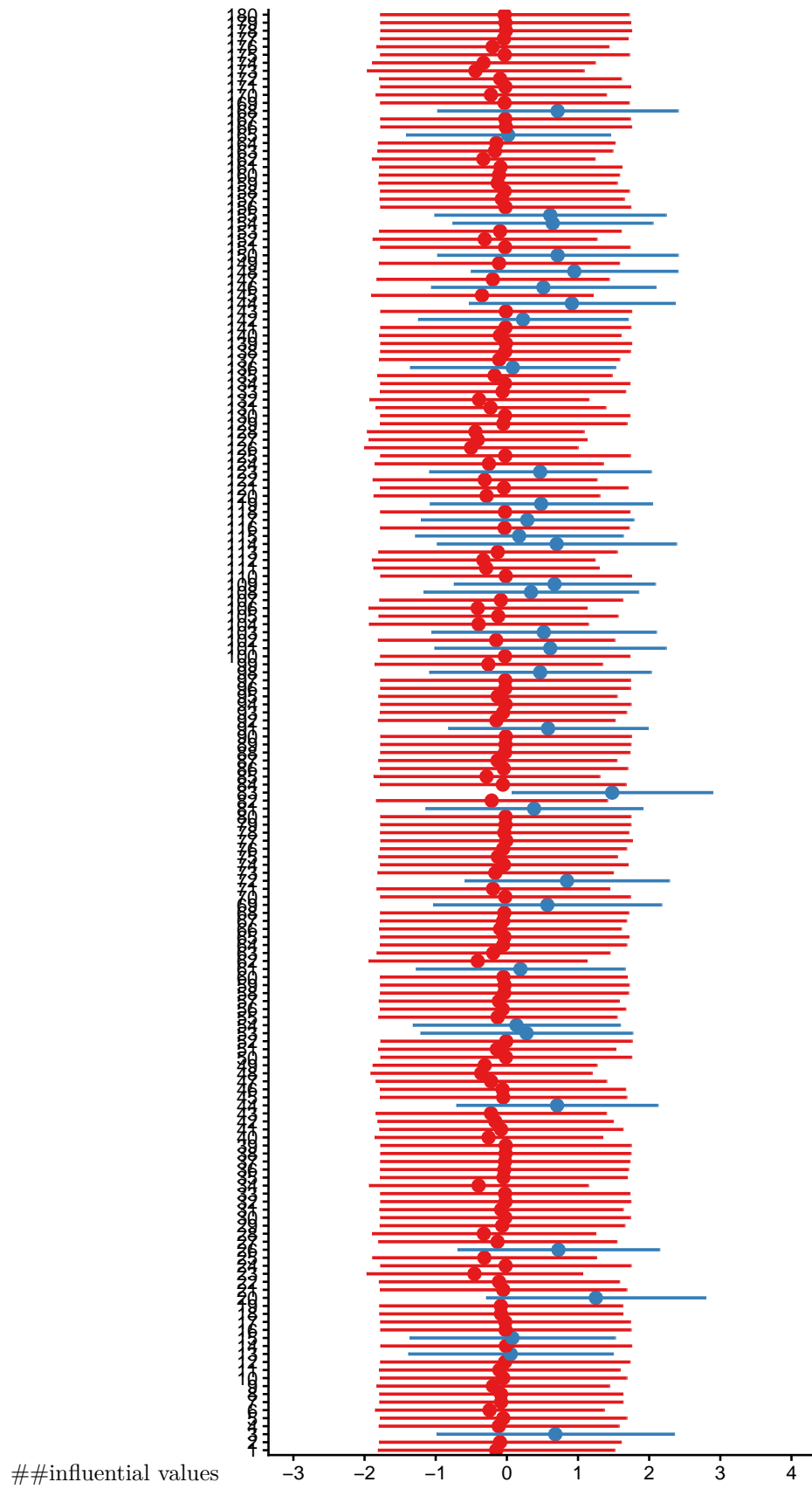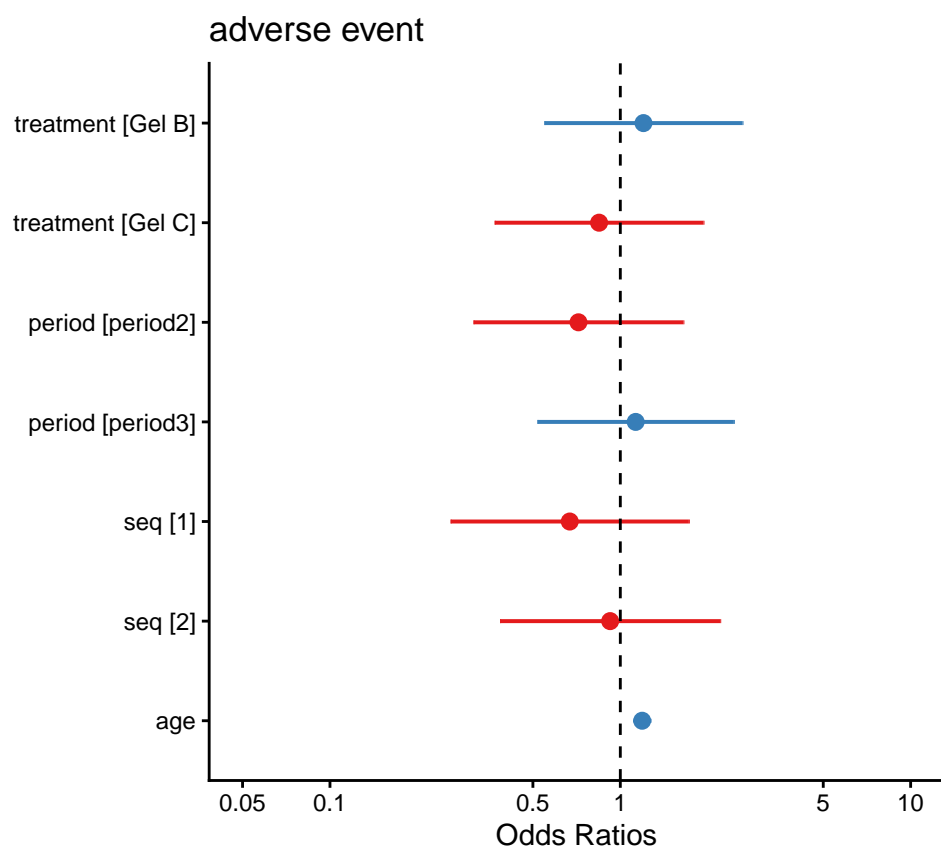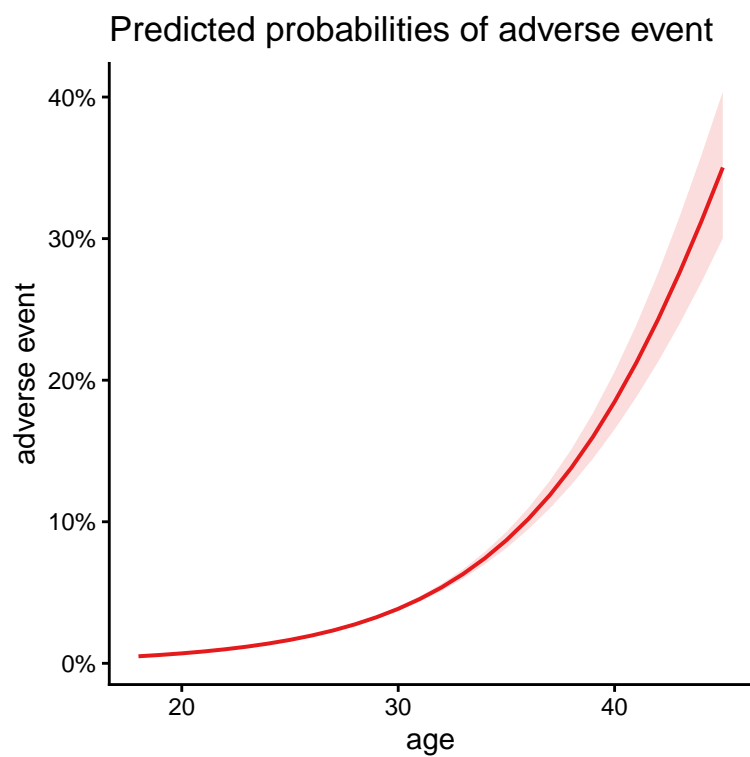
```
##        1       2       3       4       5       6
## "neg"   "neg"   "neg"   "neg"   "neg"   "neg"
```

##linearity

Random effects

Predicted probabilities of adverse event

adverse event

Characteristic	OR	95% CI	p-value
Treatment			
Pill A	—	—	
Gel B	1.20	0.55, 2.64	0.6
Gel C	0.85	0.37, 1.93	0.7
Period			
period1	—	—	
period2	0.72	0.31, 1.65	0.4
period3	1.13	0.52, 2.46	0.8
Treatment Sequence			
0	—	—	
1	0.67	0.26, 1.72	0.4
2	0.92	0.39, 2.21	0.9
Age	1.19	1.11, 1.27	**<0.001**

Abbreviations: CI = Confidence Interval, OR = Odds Ratio

Distribution of OR for Adverse Events
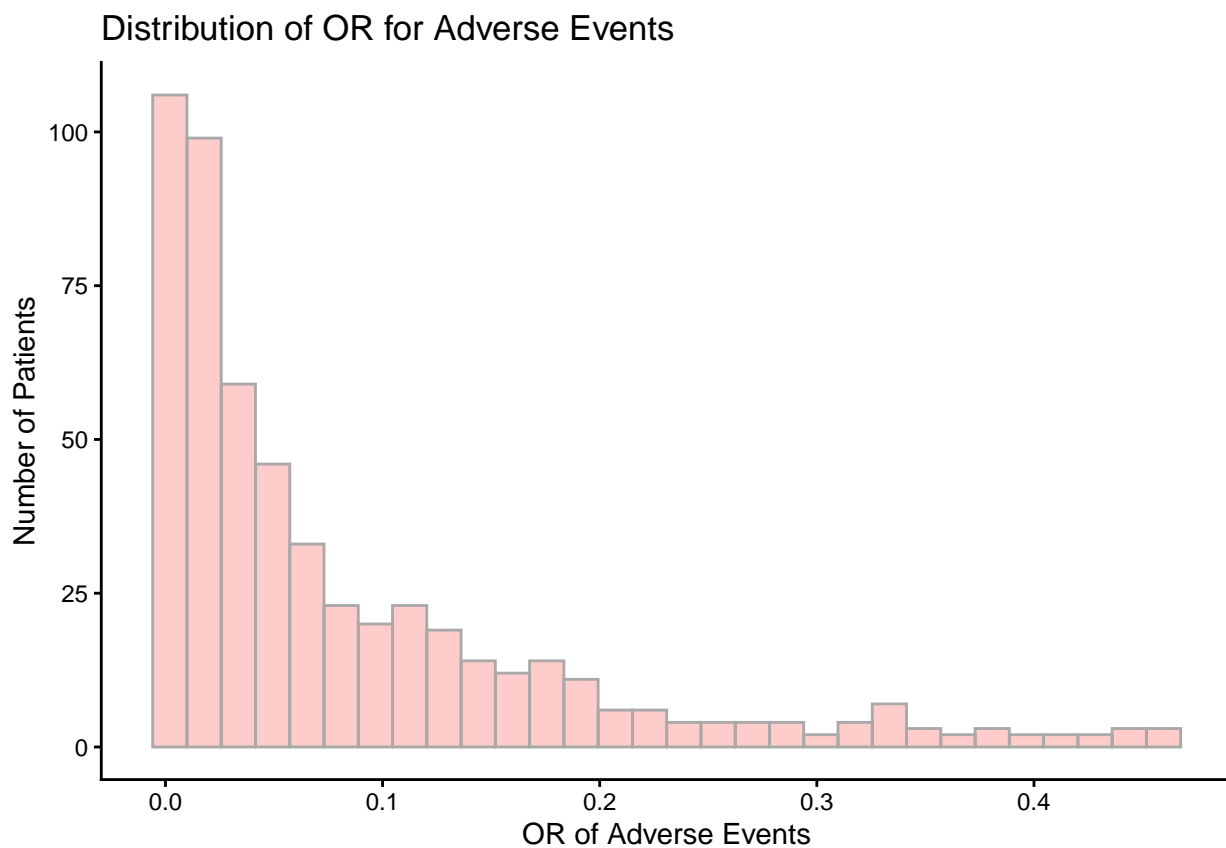
##run LR test with a model with main effects ##try another model without sequence (and compare the models), also with and without demographic variables ## test assumptions

Not significant change in log OR between GelB and GelC, and Pill A and Gel C. The probability of an adverse event for gel B after accounting for age and carryover effect is 0.0002