

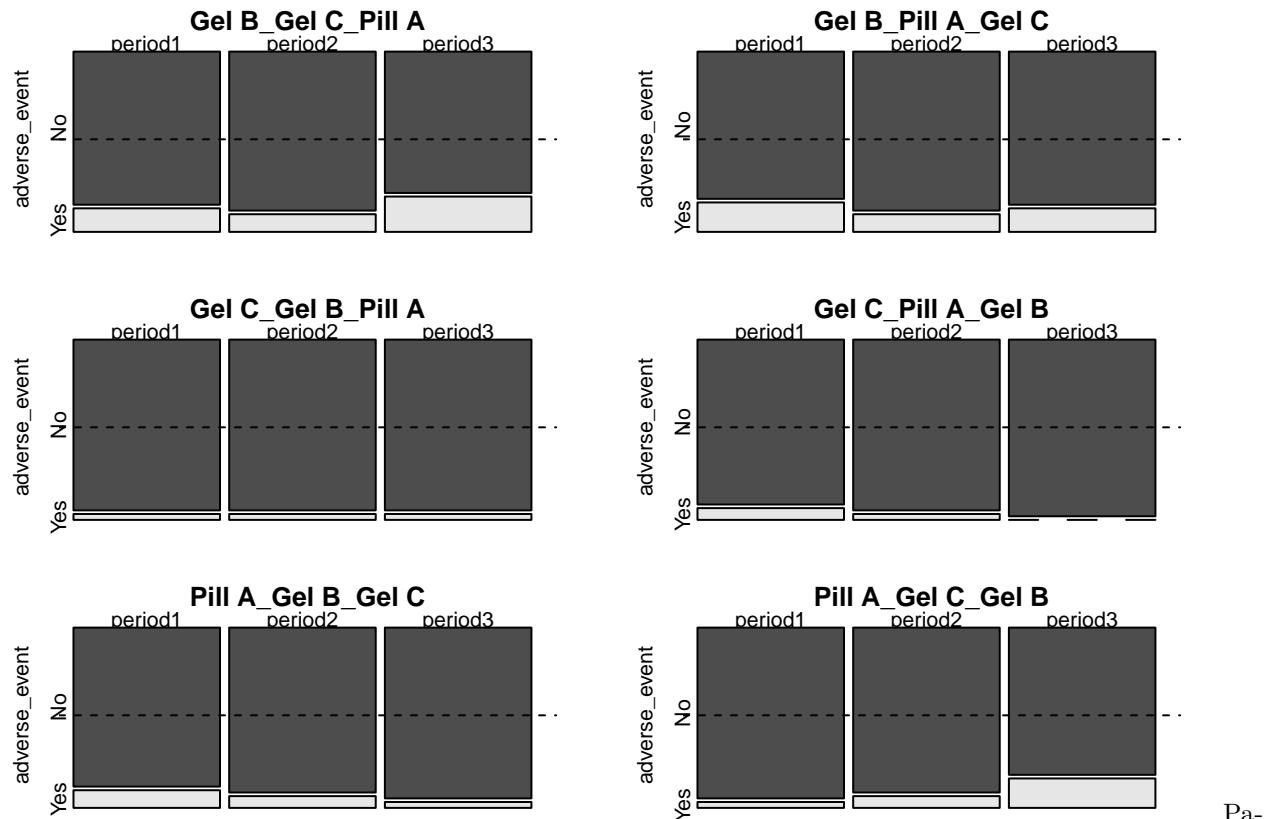
Chhiring_Analysis.Rmd

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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 safe 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 :subject, $k = 1, \dots, 180$
 j :Treatment, $j = 1, 2, 3$
 i :period, $i = 1, 2, 3$
 π_i :period effect
 β :Demographic effect
 τ_{ij} :treatment effect
 λ_j :sequence/carryover effect
 b_{ik} :subject-specific intercepts
 ε :error

k :subject, $k = 1, \dots, 180$
 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

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
##
## 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
## treatmntG1B -0.177
## treatmntG1C -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:

$$\widehat{\text{logit}}(P(AE_{ijk} = 1)) = b_{ik} + \mu + \tau_{ij} + \pi_i + \lambda_j + \beta a_k,$$

$$i = 1, 2, 3, j = 0, 1, 2, k = (1, 2, \dots, 180),$$

$$b_{ik} \sim N(0, \sigma^2_b)$$

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

Table 2: random effects variances

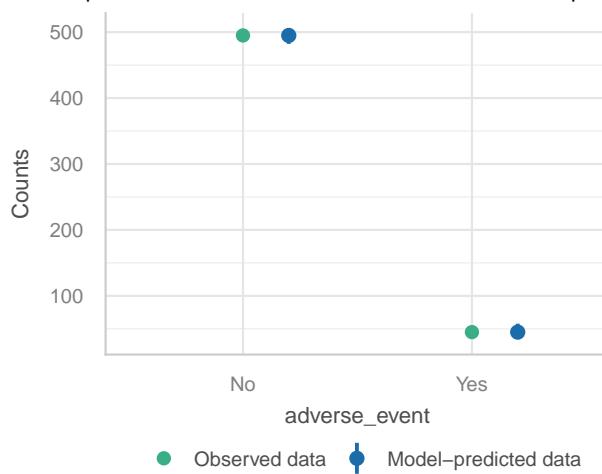
Groups	Name	Std.Dev.
ptid	(Intercept)	0.90571

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

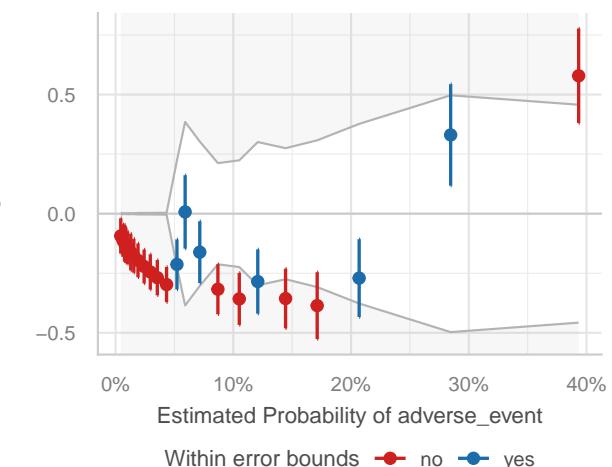
Posterior Predictive Check

Model-predicted intervals should include observed data points
Points should be within error bounds



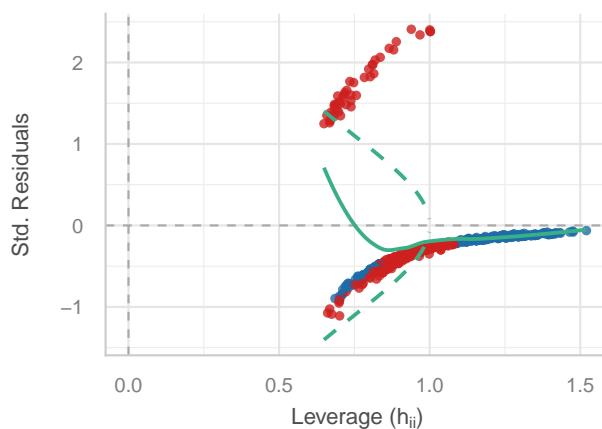
Binned Residuals

Model-predicted intervals should include observed data points
Points should be within error bounds



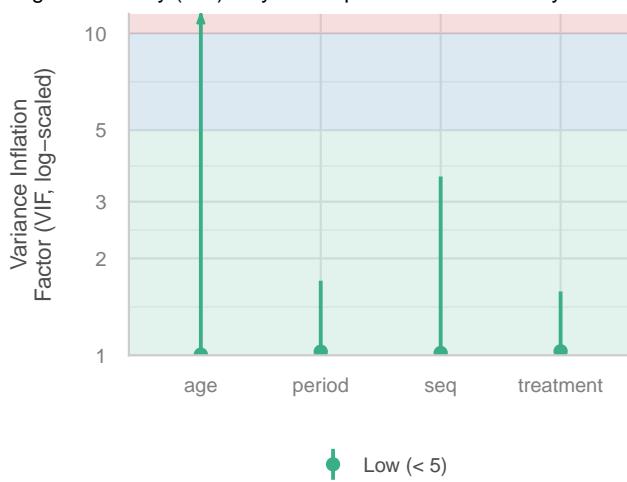
Influential Observations

Points should be inside the contour lines



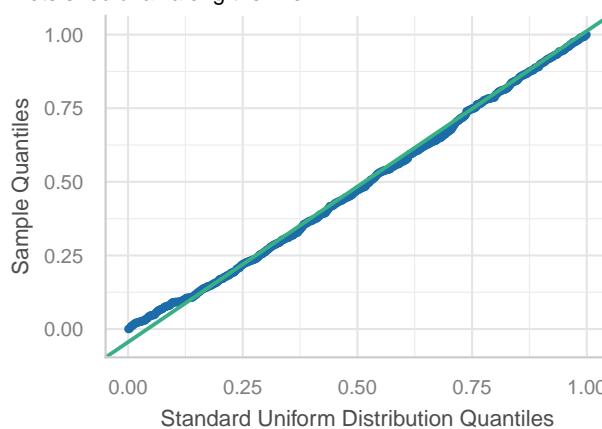
Collinearity

High collinearity (VIF) may inflate parameter uncertainty



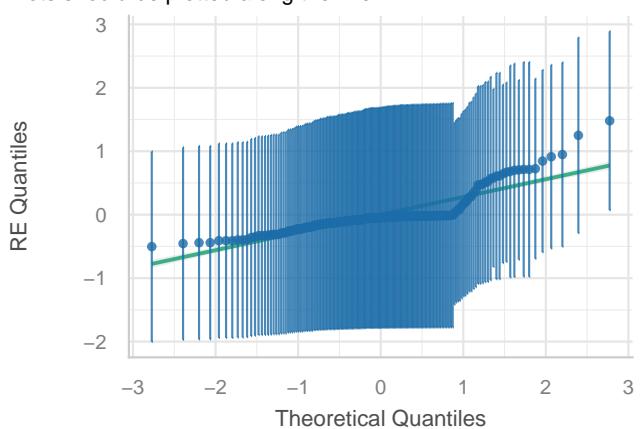
Distribution of Quantile Residuals

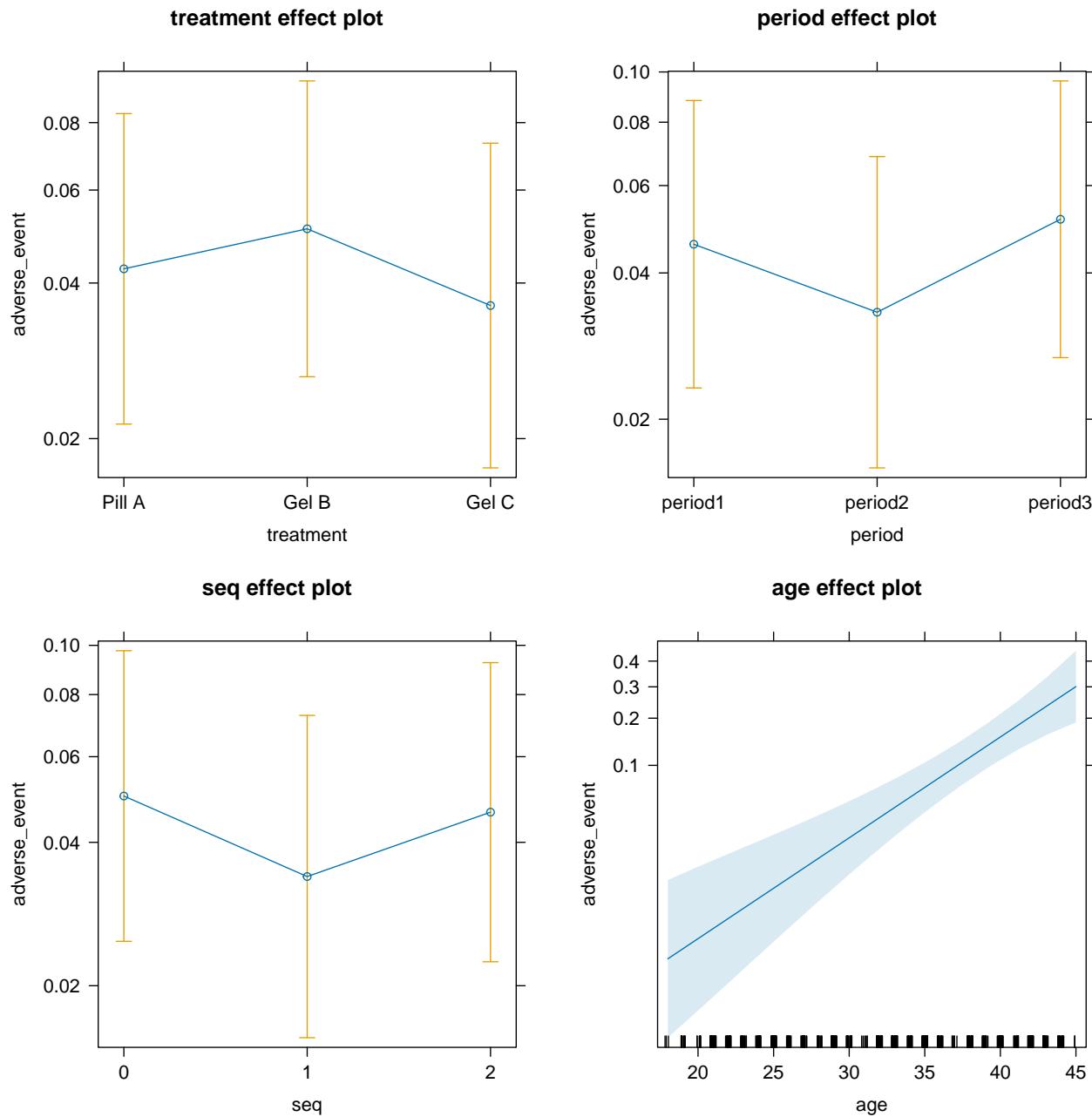
Dots should fall along the line

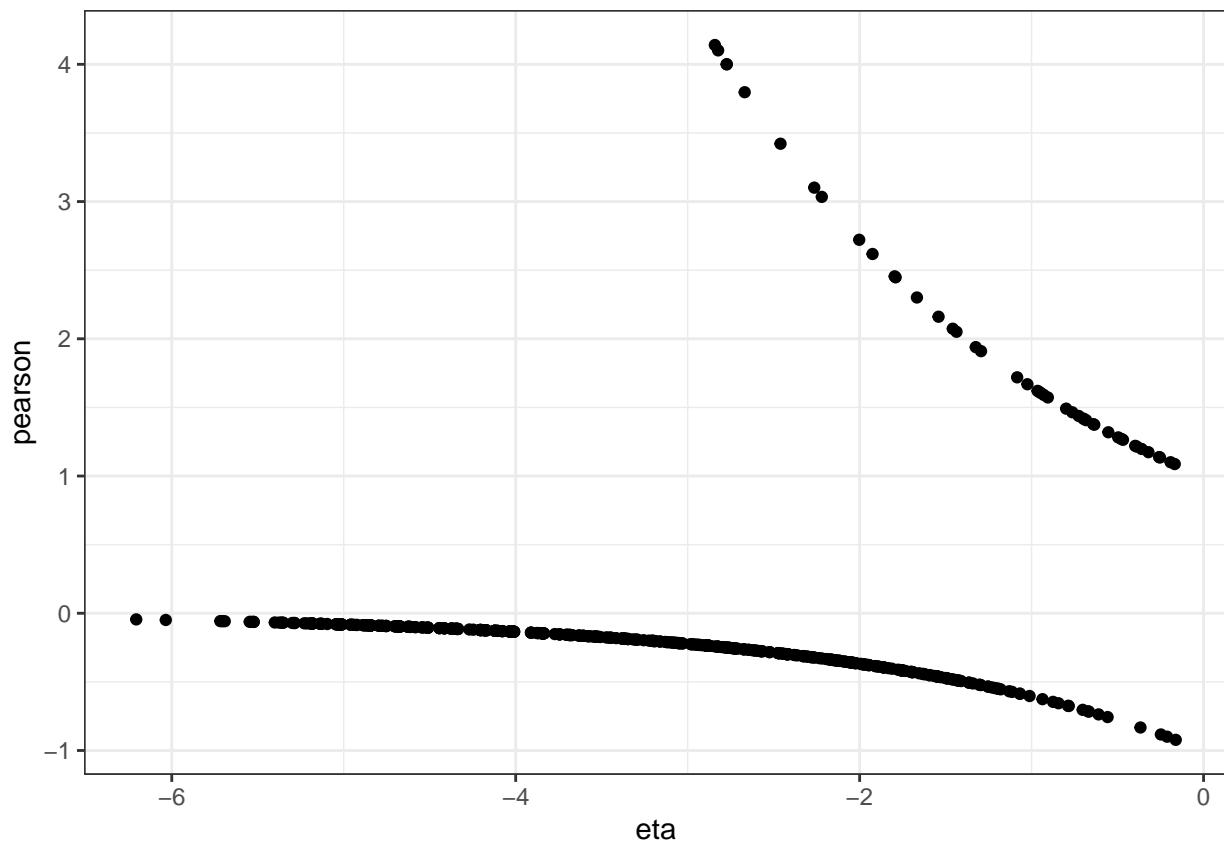


Normality of Random Effects (ptid)

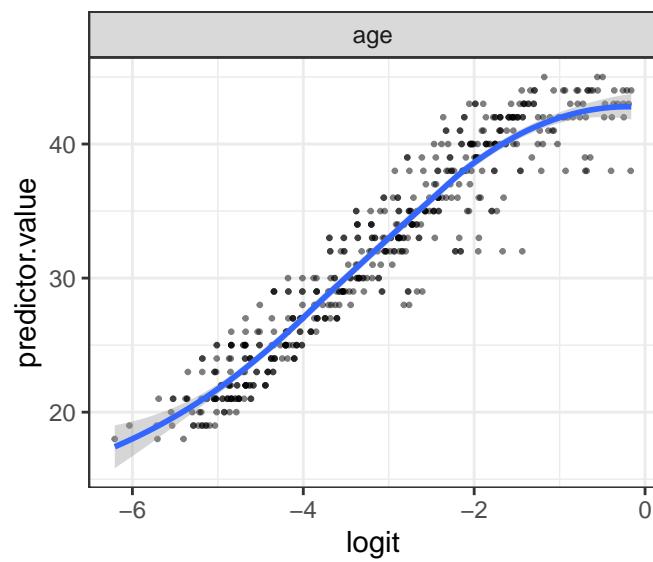
Dots should be plotted along the line



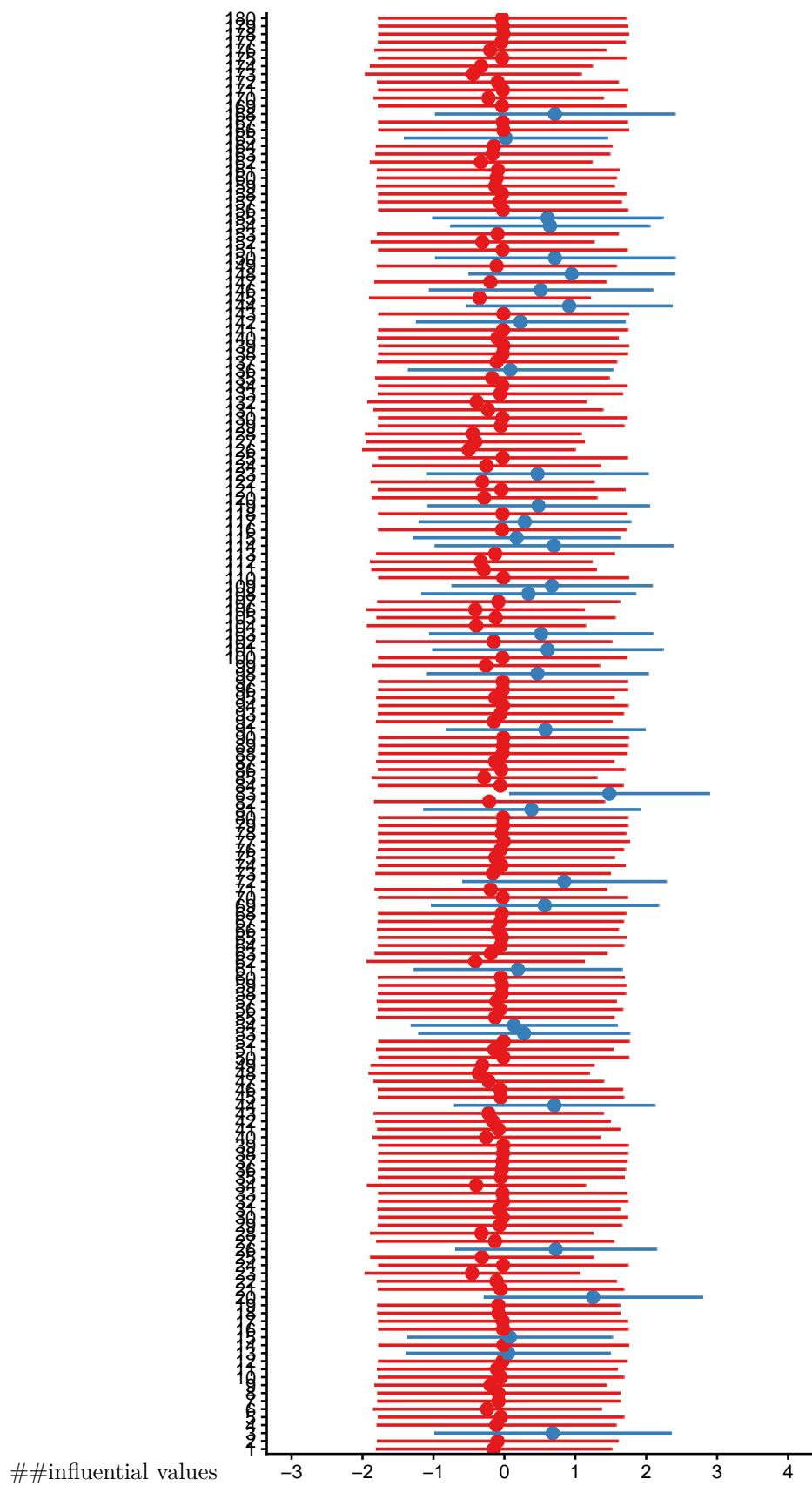


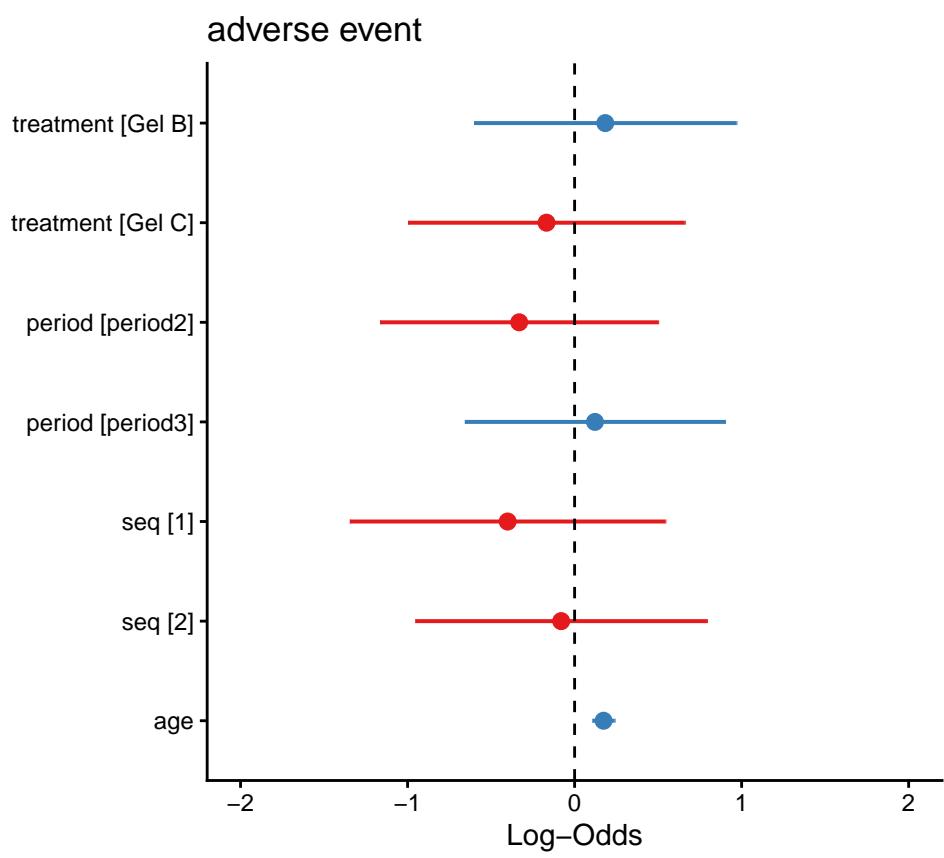
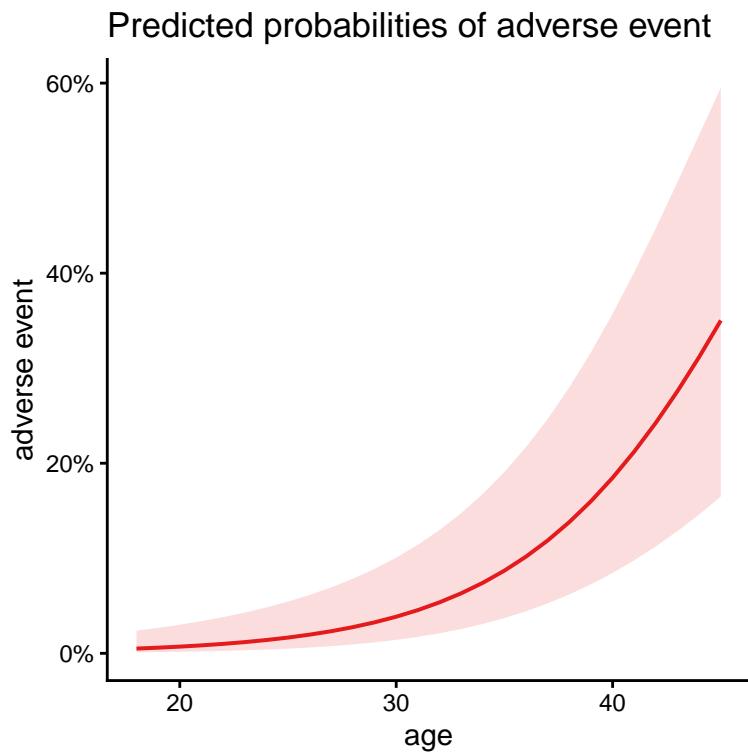


```
##      1   2   3   4   5   6
## "neg" "neg" "neg" "neg" "neg" "neg"
## #linearity
```



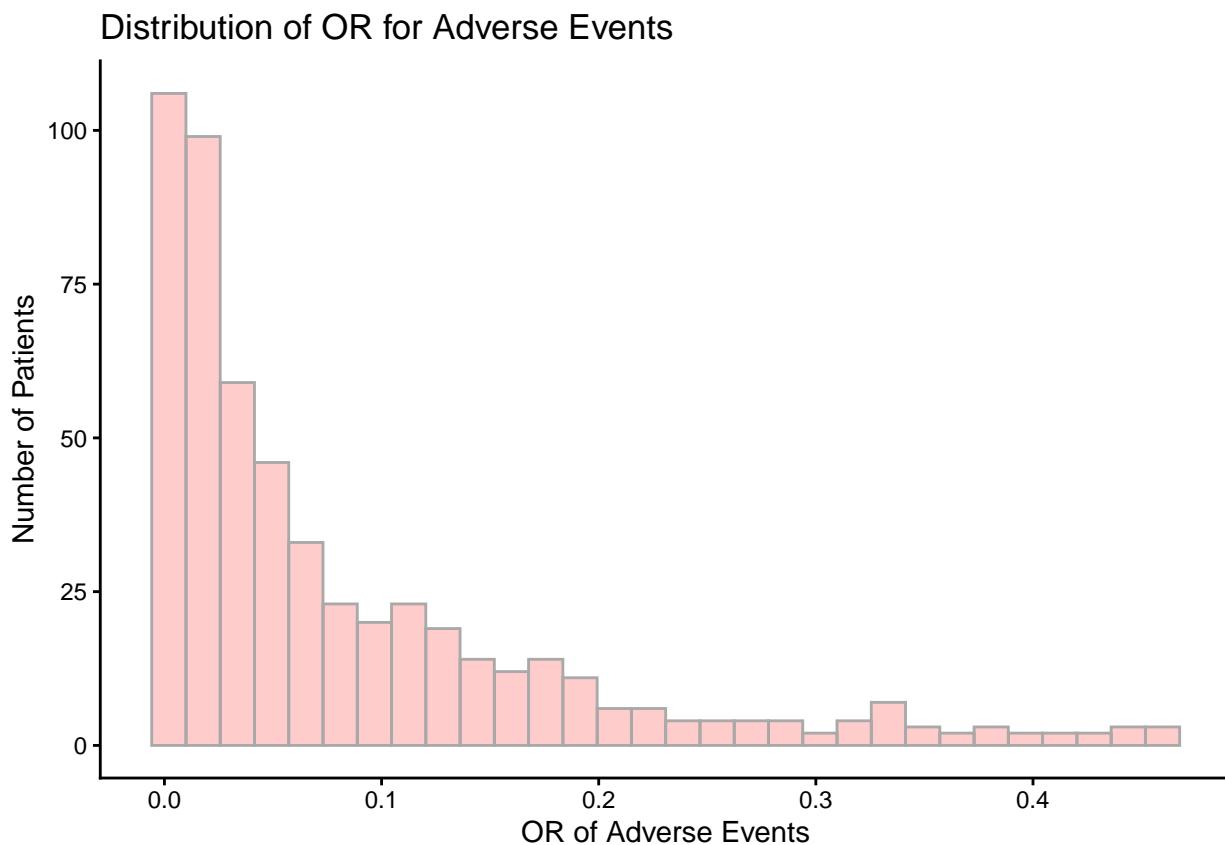
Random effects





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



```
##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