

Ensaio clínico randomizado: efeito da droga vegetal de *Eclipta prostrata* (L.) L. (Asteraceae) no ângulo de fase em adultos com obesidade grau I

Análise de dados

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1 Bibliotecas e Dados

2 Estratégia Analítica Geral

Todas as análises foram conduzidas utilizando modelos lineares mistos (LMM), com intercepto aleatório por participante para considerar a estrutura longitudinal dos dados. A variável dependente em cada modelo foi analisada de forma individual, tendo como variáveis explicativas fixas o grupo de alocação, o tempo (visita) e a interação entre ambos. As covariáveis incluídas foram as mesmas em todos os modelos.

Variáveis com distribuição assimétrica à direita foram transformadas por logaritmo natural com deslocamento (+1), conforme apropriado, a fim de aproximar a normalidade dos resíduos. As demais variáveis foram mantidas em sua forma original. Para cada desfecho, os modelos foram ajustados aos dados completos e, adicionalmente, foi realizada uma análise de sensibilidade com exclusão de observações influentes, identificadas com base em medidas diagnósticas específicas.

As médias marginais estimadas (Estimated Marginal Means – EMMs) foram calculadas a partir dos modelos ajustados, com o objetivo de estimar os valores médios ajustados para cada grupo em cada ponto temporal. As comparações pareadas entre grupos em cada visita e entre visitas dentro de cada grupo foram realizadas com correção para múltiplas comparações pelo método de Bonferroni.

Esse procedimento foi replicado de forma consistente para todas as variáveis contínuas incluídas na análise.

3 Variáveis coletadas nas três visitas clínicas

Variáveis:

- labs_ast
- labs_alt
- labs_ggt
- labs_alkp
- labs_cholesterol
- labs_ldl
- labs_hdl
- labs_triglycerides
- labs_glucose
- labs_hba1c
- labs_insulin
- labs_homa_ir
- labs_quick_index
- abdomen
- bmi
- mean_bp_mean
- evs_score

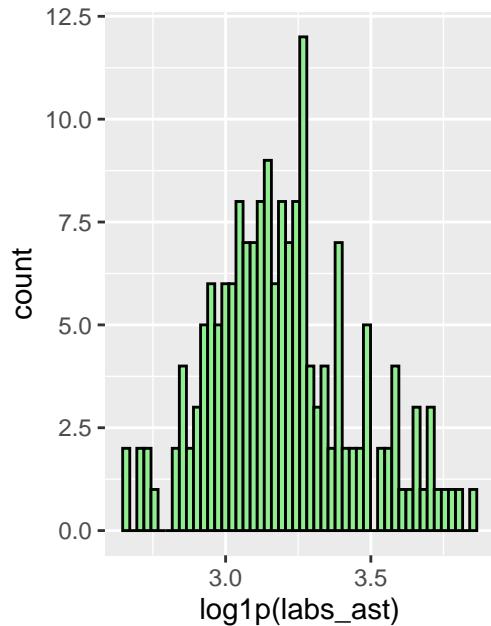
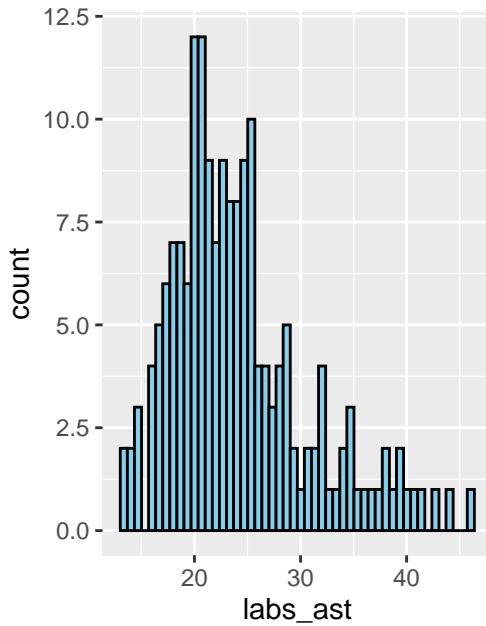
3.1 Aspartato Aminotransferase

Variável: labs_ast

```
# Plot 1: Raw data
labs_ast_hist_1 <- data_model %>%
  filter(
    labs_ast < 300
  ) %>%
  ggplot(aes(x = labs_ast)) +
  geom_histogram(bins = 50, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
labs_ast_hist_2 <- data_model %>%
  filter(
    labs_ast < 300
  ) %>%
  ggplot(aes(x = log1p(labs_ast))) +
  geom_histogram(bins = 50, fill = "lightgreen", color = "black")

# Combine side by side
labs_ast_hist_1 + labs_ast_hist_2 # library(patchwork)
```



```
# LMM

labs_ast_model <- lmer(log1p(labs_ast) ~ allocation_group * visit +
(1 | record_id), data = data_model)

check_collinearity(labs_ast_model)

# Check for Multicollinearity
```

Low Correlation

Term	VIF	VIF 95% CI	Increased SE	Tolerance
allocation_group	1.39	[1.21, 1.74]	1.18	0.72
visit	3.53	[2.81, 4.54]	1.88	0.28
allocation_group:visit	4.18	[3.30, 5.39]	2.04	0.24
Tolerance 95% CI				
	[0.57, 0.83]			
	[0.22, 0.36]			
	[0.19, 0.30]			

```
# Sensitivity analysis

labs_ast_model_check <- sensitivity_check_lmer(
  model = labs_ast_model,
  id_var = "record_id",
  top_n = 5)

# LMM Sensitivity

labs_ast_model_sens <- update(object = labs_ast_model,
                                subset = !(record_id %in%
                                labs_ast_model_check$influential_ids))

# Influential IDS

labs_ast_model_check$influential_ids

[1] "4"  "14" "33" "61" "16"
```

3.1.1 Resumo dos modelos

```
# Model comparison

summary(labs_ast_model)

Linear mixed model fit by REML. t-tests use Satterthwaite's method [
lmerModLmerTest]
```

Formula: log1p(labs_ast) ~ allocation_group * visit + (1 | record_id)

Data: data_model

REML criterion at convergence: 5.8

Scaled residuals:

Min	1Q	Median	3Q	Max
-2.72864	-0.55023	-0.04259	0.56429	2.70480

Random effects:

Groups	Name	Variance	Std.Dev.
record_id	(Intercept)	0.03007	0.1734
Residual		0.03385	0.1840

Number of obs: 179, groups: record_id, 75

Fixed effects:

	Estimate	Std. Error	df	t value
(Intercept)	3.211717	0.041563	126.794430	77.273
allocation_group	-0.020671	0.058392	126.794430	-0.354
visit2	-0.008428	0.045718	106.361849	-0.184
visit3	-0.009289	0.049356	109.412475	-0.188
allocation_group:visit2	-0.015833	0.066802	109.278386	-0.237
allocation_group:visit3	0.025422	0.071565	111.735957	0.355

	Pr(> t)
(Intercept)	<2e-16 ***
allocation_group	0.724
visit2	0.854
visit3	0.851
allocation_group:visit2	0.813
allocation_group:visit3	0.723

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

(Intr)	all_GB	visit2	visit3	a_GB:2
allctn_grGB	-0.712			

```

visit2      -0.481  0.343
visit3      -0.446  0.317  0.442
allctn_GB:2  0.330 -0.463 -0.684 -0.303
allctn_GB:3  0.308 -0.432 -0.305 -0.690  0.424

```

```
summary(labs_ast_model_sens)
```

```

Linear mixed model fit by REML. t-tests use Satterthwaite's method [
lmerModLmerTest]

```

```
Formula: log1p(labs_ast) ~ allocation_group * visit + (1 | record_id)
```

```
Data: data_model
```

```
Subset: !(record_id %in% labs_ast_model_check$influential_ids)
```

```
REML criterion at convergence: -33.2
```

Scaled residuals:

Min	1Q	Median	3Q	Max
-1.91122	-0.53274	-0.03816	0.58631	1.89195

Random effects:

Groups	Name	Variance	Std.Dev.
record_id	(Intercept)	0.03382	0.1839
Residual		0.02259	0.1503

```
Number of obs: 166, groups: record_id, 70
```

Fixed effects:

	Estimate	Std. Error	df	t value	Pr(> t)
(Intercept)	3.22105	0.04015	100.92953	80.229	<2e-16
allocation_groupGrupo B	-0.04417	0.05678	100.92953	-0.778	0.438
visit2	-0.01756	0.03879	95.56884	-0.453	0.652
visit3	-0.03571	0.04157	97.13735	-0.859	0.392
allocation_groupGrupo B:visit2	-0.02157	0.05710	97.80899	-0.378	0.706
allocation_groupGrupo B:visit3	0.06882	0.06184	99.31712	1.113	0.268

```
(Intercept) ***
```

```
allocation_groupGrupo B
```

```
visit2
```

```
visit3
```

```

allocation_groupGrupo B:visit2
allocation_groupGrupo B:visit3
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```

Correlation of Fixed Effects:

	(Intr)	all_GB	visit2	visit3	a_GB:2
allctn_grGB	-0.707				
visit2	-0.414	0.293			
visit3	-0.387	0.274	0.450		
allctn_GB:2	0.282	-0.398	-0.679	-0.306	
allctn_GB:3	0.260	-0.368	-0.302	-0.672	0.430

```

labs_ast_3performance <- performance::compare_performance(
  labs_ast_model,
  labs_ast_model_sens)

```

When comparing models, please note that probably not all models were fit from same data.

```

labs_ast_3performance
# Comparison of Model Performance Indices

```

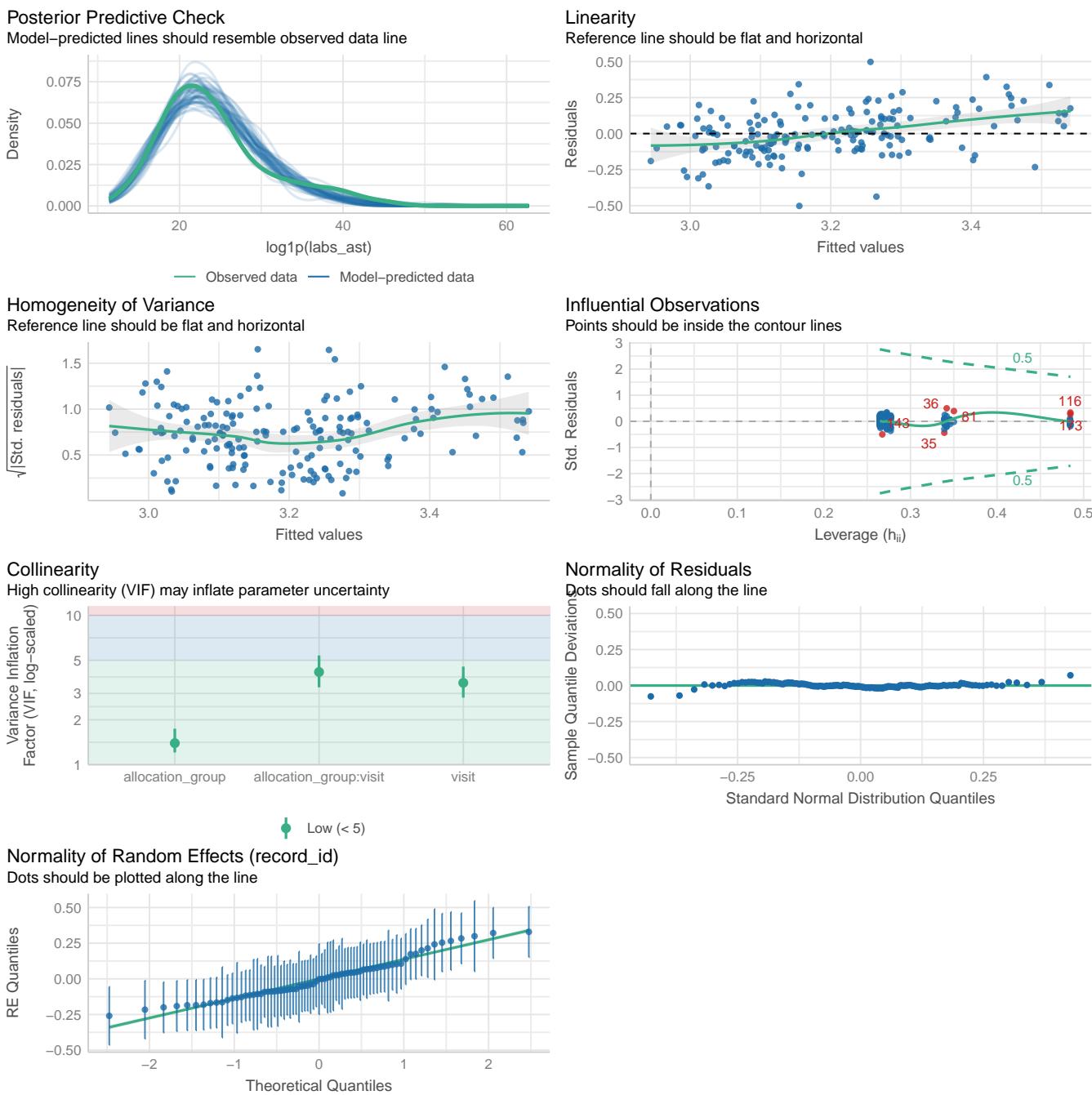
Name		Model		AIC (weights)		AICc (weights)

labs_ast_model		lmerModLmerTest		1139.5 (<.001)		1140.3 (<.001)
labs_ast_model_sens		lmerModLmerTest		1014.1 (>.999)		1015.0 (>.999)

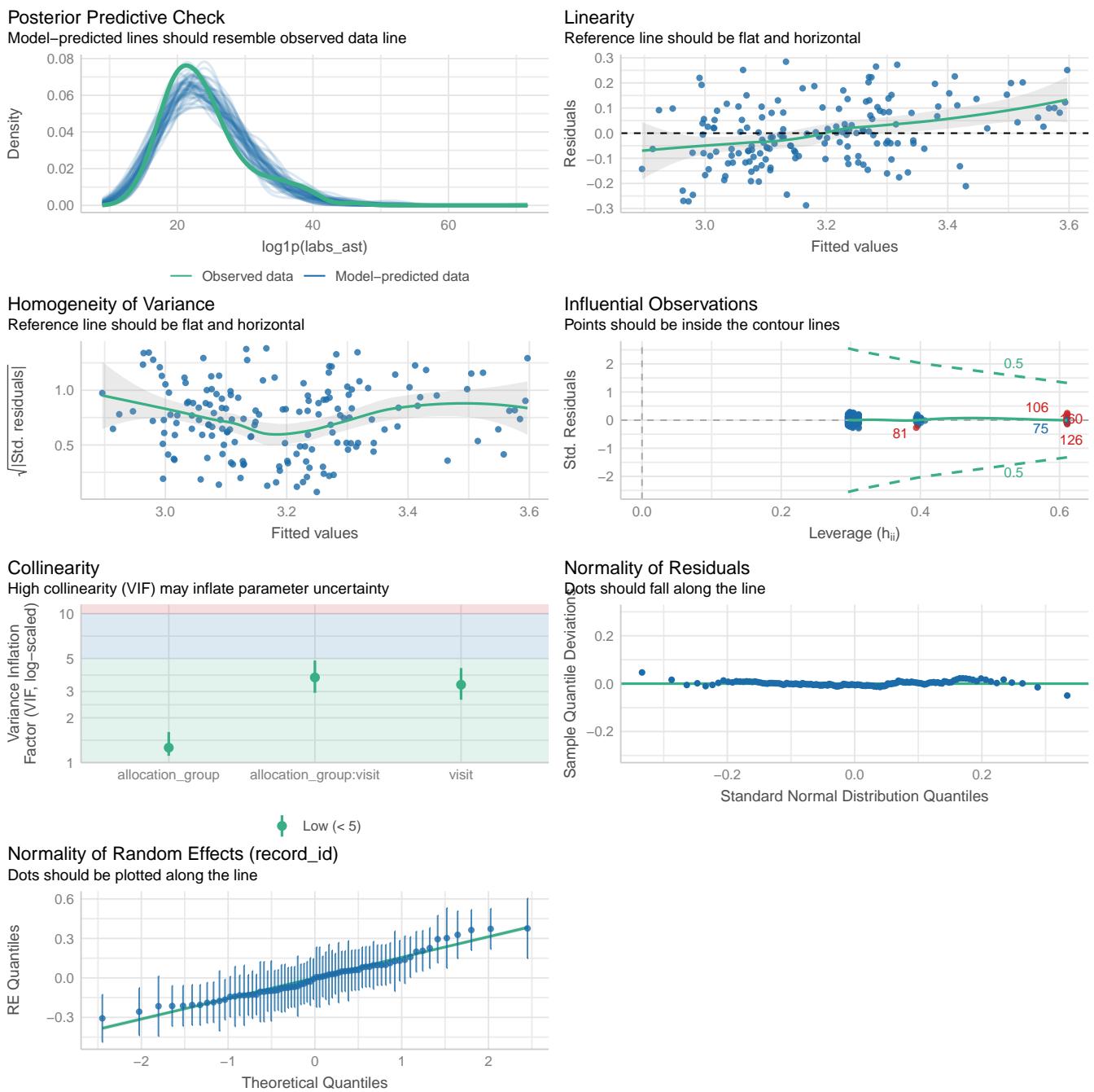
Name		BIC (weights)		R2 (cond.)		R2 (marg.)		ICC		RMSE		Sigma

labs_ast_model		1165.0 (<.001)		0.472		0.003		0.470		0.154		0.184
labs_ast_model_sens		1039.0 (>.999)		0.605		0.013		0.600		0.122		0.150

```
performance::check_model(labs_ast_model)
```



```
performance::check_model(labs_ast_model_sens)
```



3.1.2 Médias Marginais Estimadas

3.1.2.1 Todos os dados

```
# Get EMMs for each group at each visit (All data)
labs_ast_raw_emm <- emmeans::emmeans(
  labs_ast_model,
  ~ allocation_group * visit
```

```

)

labs_ast_raw_emm <- regrid(labs_ast_raw_emm)

# Table of marginal means
# labs_ast_raw_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(labs_ast_raw_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

visit = 1:
  contrast      estimate   SE  df lower.CL upper.CL t.ratio p.value
  Grupo A - Grupo B    0.508 1.43 128     -2.33      3.35   0.354  0.7240

visit = 2:
  contrast      estimate   SE  df lower.CL upper.CL t.ratio p.value
  Grupo A - Grupo B    0.882 1.58 142     -2.24      4.00   0.559  0.5771

visit = 3:
  contrast      estimate   SE  df lower.CL upper.CL t.ratio p.value
  Grupo A - Grupo B   -0.117 1.73 157     -3.54      3.31  -0.068  0.9462

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95

# Pairwise comparisons: Changes over time within each group
emmeans::contrast(labs_ast_raw_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

allocation_group = Grupo A:
  contrast      estimate   SE  df lower.CL upper.CL t.ratio p.value
  visit1 - visit2   0.2083 1.13 128     -2.53      2.95   0.184  1.0000
  visit1 - visit3   0.2295 1.22 128     -2.73      3.19   0.188  1.0000
  visit2 - visit3   0.0212 1.24 142     -2.98      3.02   0.017  1.0000

```

```

allocation_group = Grupo B:

contrast      estimate   SE  df lower.CL upper.CL t.ratio p.value
visit1 - visit2  0.5828 1.17 128     -2.25      3.42    0.499  1.0000
visit1 - visit3 -0.3954 1.28 128     -3.49      2.70   -0.310  1.0000
visit2 - visit3 -0.9782 1.33 155     -4.20      2.24   -0.735  1.0000

```

Degrees-of-freedom method: inherited from kenward-roger when re-gridding

Confidence level used: 0.95

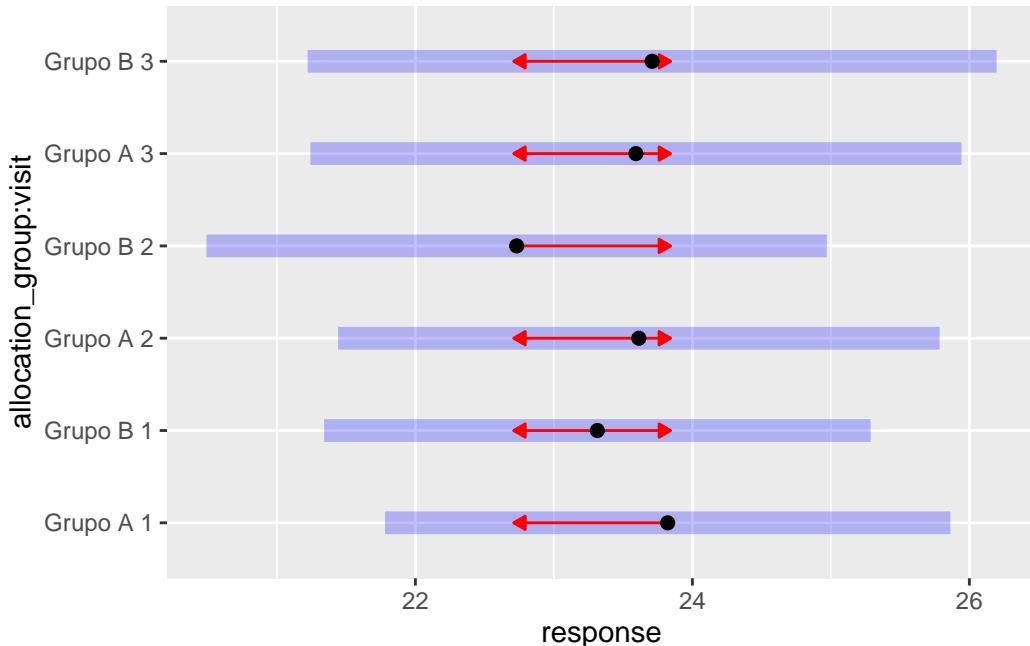
Conf-level adjustment: bonferroni method for 3 estimates

P value adjustment: bonferroni method for 3 tests

```

# Plot of marginal means
plot(labs_ast_raw_emm, comparisons = TRUE)

```



3.1.2.2 Análise de sensibilidade

```

# Get EMMs for each group at each visit (Sensitivity Analysis)
labs_ast_emm <- emmeans::emmeans(
  labs_ast_model_sens,
  ~ allocation_group * visit
)

labs_ast_emm <- regrid(labs_ast_emm)

```

```

# Table of marginal means
# labs_ast_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(labs_ast_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

visit = 1:
  contrast      estimate   SE  df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    1.083 1.39 104     -1.68      3.84   0.778  0.4386

visit = 2:
  contrast      estimate   SE  df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    1.566 1.49 118     -1.38      4.51   1.052  0.2948

visit = 3:
  contrast      estimate   SE  df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B   -0.603 1.64 132     -3.85      2.64  -0.368  0.7136

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95

# Pairwise comparisons: Changes over time within each group
emmeans::contrast(labs_ast_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

allocation_group = Grupo A:
  contrast      estimate   SE  df lower.CL upper.CL t.ratio p.value
visit1 - visit2    0.436 0.963 104     -1.91      2.78   0.453  1.0000
visit1 - visit3    0.879 1.020 104     -1.60      3.36   0.861  1.0000
visit2 - visit3    0.443 1.030 118     -2.06      2.94   0.430  1.0000

allocation_group = Grupo B:
  contrast      estimate   SE  df lower.CL upper.CL t.ratio p.value
visit1 - visit2    0.920 0.983 104     -1.47      3.31   0.936  1.0000
visit1 - visit3   -0.807 1.130 104     -3.55      1.93  -0.716  1.0000

```

```
visit2 - visit3 -1.727 1.150 131 -4.51 1.06 -1.505 0.4043
```

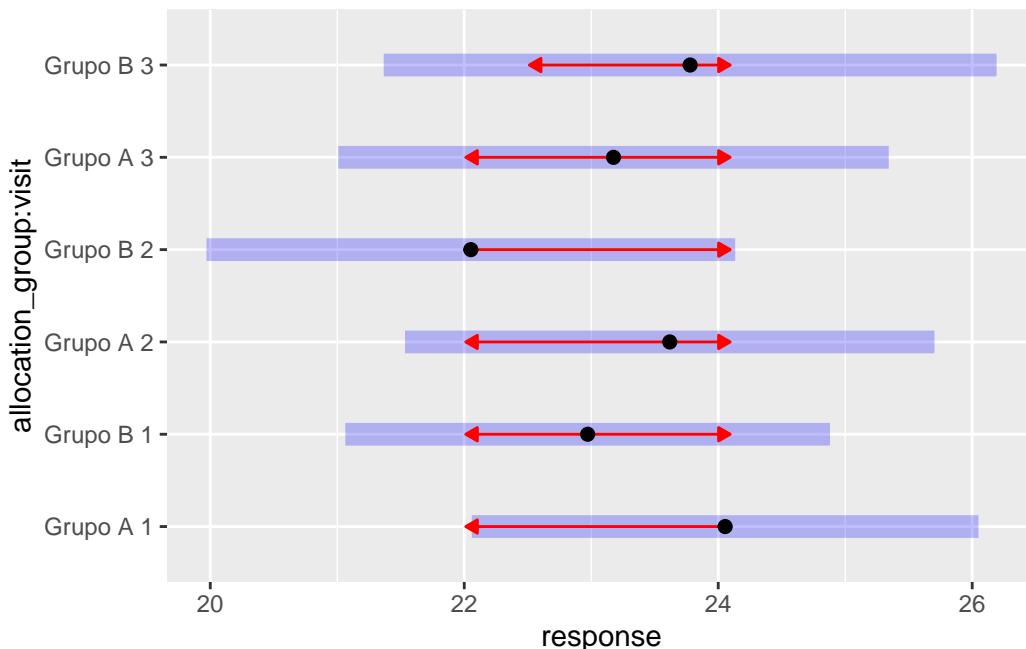
Degrees-of-freedom method: inherited from kenward-roger when re-gridding

Confidence level used: 0.95

Conf-level adjustment: bonferroni method for 3 estimates

P value adjustment: bonferroni method for 3 tests

```
# Plot of marginal means
plot(labs_ast_emm, comparisons = TRUE)
```



3.1.3 Resultado

No modelo ajustado para os níveis de AST, não foram observadas diferenças estatisticamente significativas entre os grupos em nenhum dos três momentos avaliados. Da mesma forma, não houve mudanças significativas ao longo do tempo dentro de cada grupo. A análise de sensibilidade não alterou substancialmente os resultados. As estimativas permaneceram estáveis e as diferenças entre os grupos e ao longo do tempo continuaram não significativas. As estimativas, intervalos de confiança de 95% e valores de p estão apresentados na Tabela 1.

Tabela 1: Diferenças estimadas dos níveis de Aspartato Aminotransferase (AST) entre os grupos de alocação (placebo vs Eclipta) e entre visitas dentro de cada grupo

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 1	0,51	[-2,33 ; 3,35]	0,724
Entre grupos	Visita 2	0,88	[-2,24 ; 4,00]	0,577

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 3	-0,12	[-3,54 ; 3,31]	0,946
Grupo Placebo	Visita 1 - Visita 2	0,21	[-2,53 ; 2,95]	1,000
Grupo Placebo	Visita 1 - Visita 3	0,23	[-2,73 ; 3,19]	1,000
Grupo Placebo	Visita 2 - Visita 3	0,02	[-2,98 ; 3,02]	1,000
Grupo Eclipta	Visita 1 - Visita 2	0,58	[-2,25 ; 3,42]	1,000
Grupo Eclipta	Visita 1 - Visita 3	-0,40	[-3,49 ; 2,70]	1,000
Grupo Eclipta	Visita 2 - Visita 3	-0,98	[-4,20 ; 2,24]	1,000

```

ggplot(
  data = data_model,
  aes(
    x = as.factor(visit),
    y = labs_ast,
    group = record_id,
  )
) +
  geom_line(alpha = 0.5) +
  geom_point(alpha = 0.7) +
  geom_smooth(
    aes(group = allocation_group),
    method = "lm",
    se = TRUE,
    linewidth = 1
  ) +
  labs(title = "All data") +
  facet_wrap(~ allocation_group)

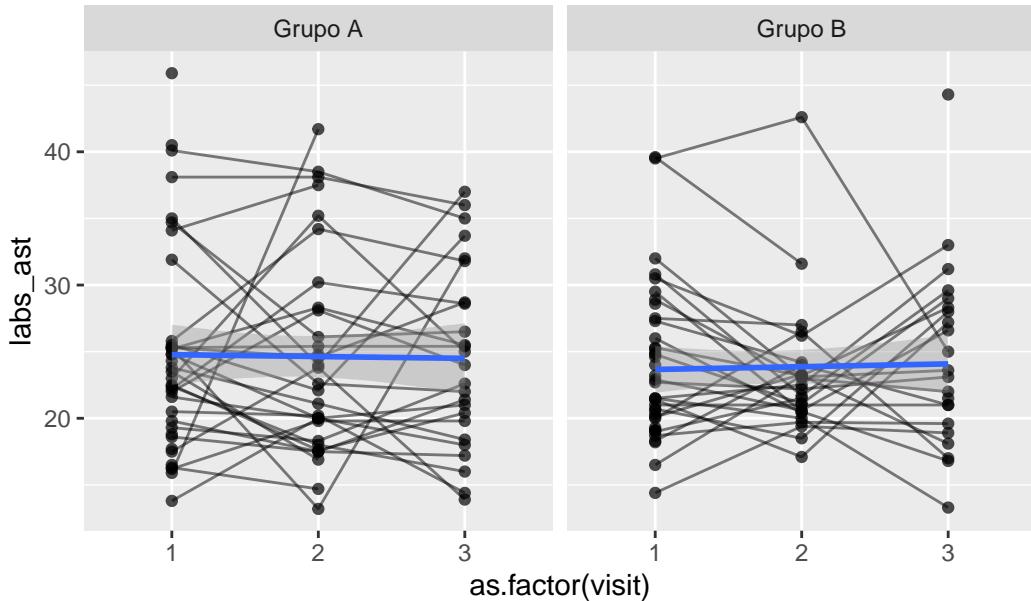
```

```

`geom_smooth()` using formula = 'y ~ x'
Warning: Removed 10 rows containing non-finite outside the scale range
(`stat_smooth()`).
Warning: Removed 8 rows containing missing values or values outside the scale range
(`geom_line()`).
Warning: Removed 10 rows containing missing values or values outside the scale range
(`geom_point()`).

```

All data



```
data_model %>%
  filter(
    !(record_id %in%
      labs_ast_model_check$influential_ids)
  ) %>%
  ggplot(
    aes(
      x = as.factor(visit),
      y = labs_ast,
      group = record_id,
    )
  ) +
  geom_line(alpha = 0.5) +
  geom_point(alpha = 0.7) +
  geom_smooth(
    aes(group = allocation_group),
    method = "lm",
    se = TRUE,
    linewidth = 1
  ) +
  labs(title = "Sensitivity analysis") +
```

```

facet_wrap(~ allocation_group)

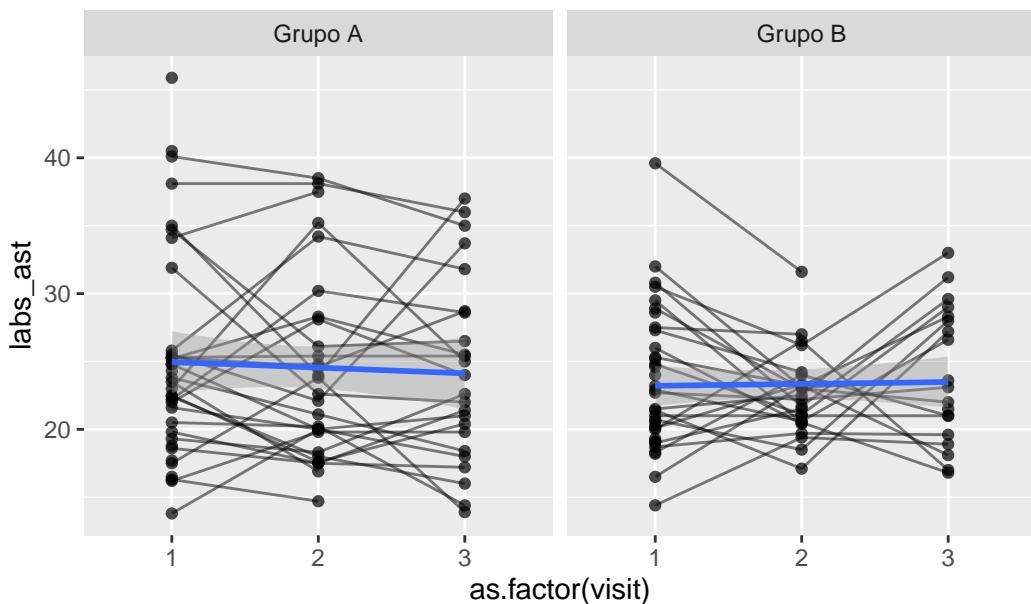
`geom_smooth()` using formula = 'y ~ x'
Warning: Removed 9 rows containing non-finite outside the scale range
(`stat_smooth()`).

Warning: Removed 8 rows containing missing values or values outside the scale range
(`geom_line()`).

Warning: Removed 9 rows containing missing values or values outside the scale range
(`geom_point()`).

```

Sensitivity analysis



3.2 Alanina Aminotransferase

```

# Plot 1: Raw data
labs_alt_hist_1 <- data_model %>%
  #filter(
  #  labs_alt < 300
  #) %>%
  ggplot(aes(x = labs_alt)) +
  geom_histogram(bins = 50, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
labs_alt_hist_2 <- data_model %>%
  #filter(

```

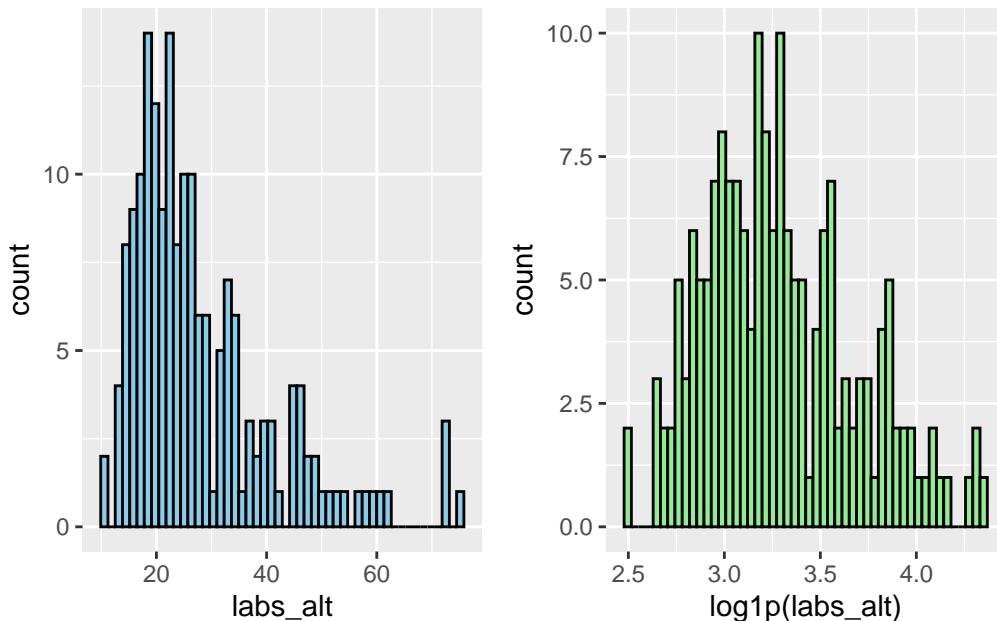
```

#     labs_alt < 300
#) %>%
ggplot(aes(x = log1p(labs_alt))) +
  geom_histogram(bins = 50, fill = "lightgreen", color = "black")

# Combine side by side
labs_alt_hist_1 + labs_alt_hist_2 # library(patchwork)

```

Warning: Removed 10 rows containing non-finite outside the scale range (`stat_bin()`).
 Removed 10 rows containing non-finite outside the scale range (`stat_bin()`).



```

# LMM
labs_alt_model <- lmer(log1p(labs_alt) ~ allocation_group * visit +
(1 | record_id), data = data_model)
check_collinearity(labs_alt_model)

# Check for Multicollinearity

```

Low Correlation

Term	VIF	VIF 95% CI	Increased SE	Tolerance
allocation_group	1.21	[1.08, 1.54]	1.10	0.83
visit	3.50	[2.79, 4.49]	1.87	0.29
allocation_group:visit	3.84	[3.04, 4.94]	1.96	0.26

```

Tolerance 95% CI
[0.65, 0.92]
[0.22, 0.36]
[0.20, 0.33]

# Sensitivity analysis
labs_alt_model_check <- sensitivity_check_lmer(
  model = labs_alt_model,
  id_var = "record_id",
  top_n = 5)

# LMM Sensitivity
labs_alt_model_sens <- update(object = labs_alt_model,
                                subset = !(record_id %in%
                                labs_alt_model_check$influential_ids))

# Influential IDS
labs_alt_model_check$influential_ids
[1] "33" "75" "5"   "58" "63"

```

3.2.1 Resumo dos modelos

```

# Model comparison
summary(labs_alt_model)

Linear mixed model fit by REML. t-tests use Satterthwaite's method [
lmerModLmerTest]
Formula: log1p(labs_alt) ~ allocation_group * visit + (1 | record_id)
Data: data_model

REML criterion at convergence: 132.2

```

Scaled residuals:

Min	1Q	Median	3Q	Max
-2.28166	-0.55027	-0.05275	0.54015	2.15582

Random effects:

Groups	Name	Variance	Std.Dev.
record_id	(Intercept)	0.10863	0.3296

```
Residual          0.05485  0.2342  
Number of obs: 179, groups: record_id, 75
```

Fixed effects:

	Estimate	Std. Error	df	t value	Pr(> t)
(Intercept)	3.34045	0.06647	102.44387	50.254	<2e-16
allocation_groupGrupo B	-0.10187	0.09338	102.44387	-1.091	0.278
visit2	-0.07956	0.05867	103.85033	-1.356	0.178
visit3	-0.03364	0.06353	105.34376	-0.529	0.598
allocation_groupGrupo B:visit2	0.06143	0.08602	105.75034	0.714	0.477
allocation_groupGrupo B:visit3	0.07920	0.09237	106.88087	0.857	0.393

```
(Intercept) ***  
allocation_groupGrupo B  
visit2  
visit3  
allocation_groupGrupo B:visit2  
allocation_groupGrupo B:visit3  
---  
Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

Correlation of Fixed Effects:

```
(Intr) all_GB visit2 visit3 a_GB:2  
allctn_grGB -0.712  
visit2     -0.380  0.271  
visit3     -0.351  0.250  0.449  
allctn_GB:2  0.259 -0.364 -0.682 -0.306  
allctn_GB:3  0.241 -0.339 -0.309 -0.688  0.432
```

```
summary(labs_alt_model_sens)
```

```
Linear mixed model fit by REML. t-tests use Satterthwaite's method [  
lmerModLmerTest]  
Formula: log1p(labs_alt) ~ allocation_group * visit + (1 | record_id)  
Data: data_model  
Subset: !(record_id %in% labs_alt_model_check$influential_ids)
```

REML criterion at convergence: 88.4

Scaled residuals:

Min	1Q	Median	3Q	Max
-1.98911	-0.51655	-0.03328	0.57521	2.21076

Random effects:

Groups	Name	Variance	Std.Dev.
record_id	(Intercept)	0.09385	0.3063
Residual		0.04238	0.2059

Number of obs: 165, groups: record_id, 70

Fixed effects:

	Estimate	Std. Error	df	t value	Pr(> t)
(Intercept)	3.249918	0.064250	90.966334	50.582	<2e-16
allocation_group	-0.013075	0.088373	90.966334	-0.148	0.883
visit2	-0.021536	0.055231	93.405160	-0.390	0.697
visit3	-0.035422	0.060679	94.750397	-0.584	0.561
allocation_group:visit2	-0.009275	0.078377	94.689442	-0.118	0.906
allocation_group:visit3	0.043535	0.085567	95.767451	0.509	0.612

(Intercept) ***

allocation_group

visit2

visit3

allocation_group:visit2

allocation_group:visit3

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

(Intr)	all_GB	visit2	visit3	a_GB:2	
allctn_grGB	-0.727				
visit2	-0.362	0.263			
visit3	-0.329	0.239	0.442		
allctn_GB:2	0.255	-0.351	-0.705	-0.311	
allctn_GB:3	0.234	-0.321	-0.313	-0.709	0.434

```
performance::compare_performance(  
  labs_alt_model,  
  labs_alt_model_sens)
```

When comparing models, please note that probably not all models were fit
from same data.

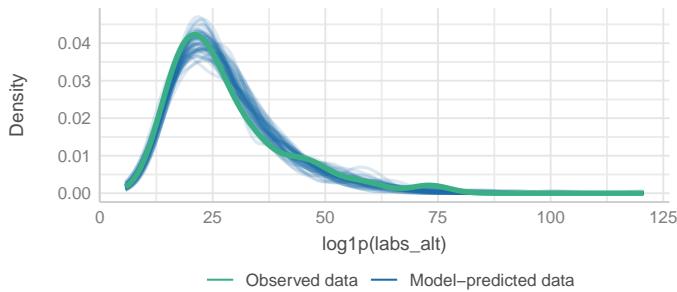
```
# Comparison of Model Performance Indices
```

Name	Model	AIC (weights)	AICc (weights)
labs_alt_model	lmerModLmerTest	1302.9 (<.001)	1303.8 (<.001)
labs_alt_model_sens	lmerModLmerTest	1150.5 (>.999)	1151.4 (>.999)

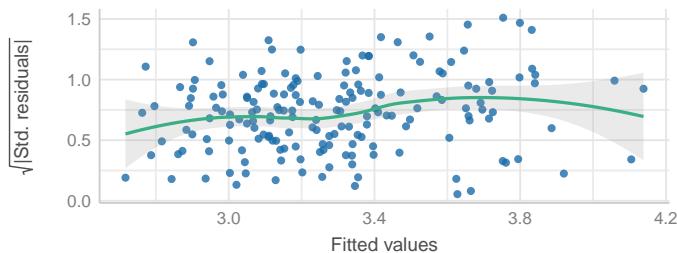
Name	BIC (weights)	R2 (cond.)	R2 (marg.)	ICC	RMSE	Sigma
labs_alt_model	1328.4 (<.001)	0.668	0.011	0.664	0.187	0.234
labs_alt_model_sens	1175.3 (>.999)	0.689	0.002	0.689	0.163	0.206

```
performance::check_model(labs_alt_model)
```

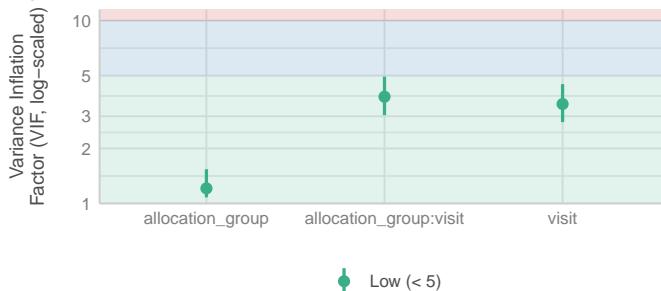
Posterior Predictive Check
Model-predicted lines should resemble observed data line



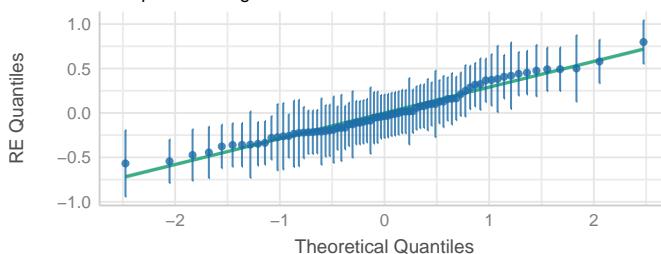
Homogeneity of Variance
Reference line should be flat and horizontal



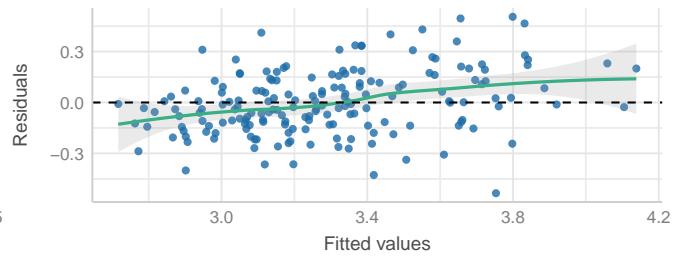
Collinearity
High collinearity (VIF) may inflate parameter uncertainty



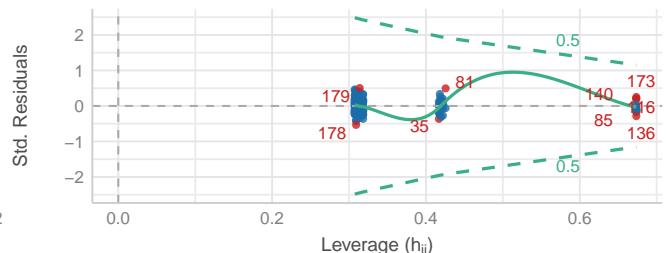
Normality of Random Effects (record_id)
Dots should be plotted along the line



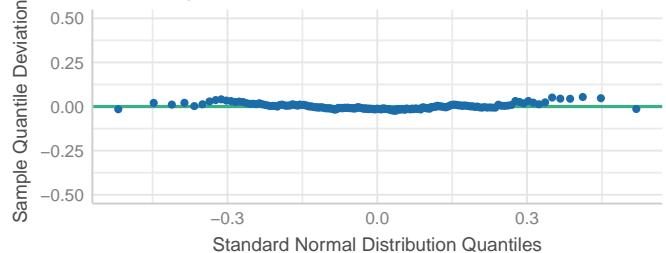
Linearity
Reference line should be flat and horizontal



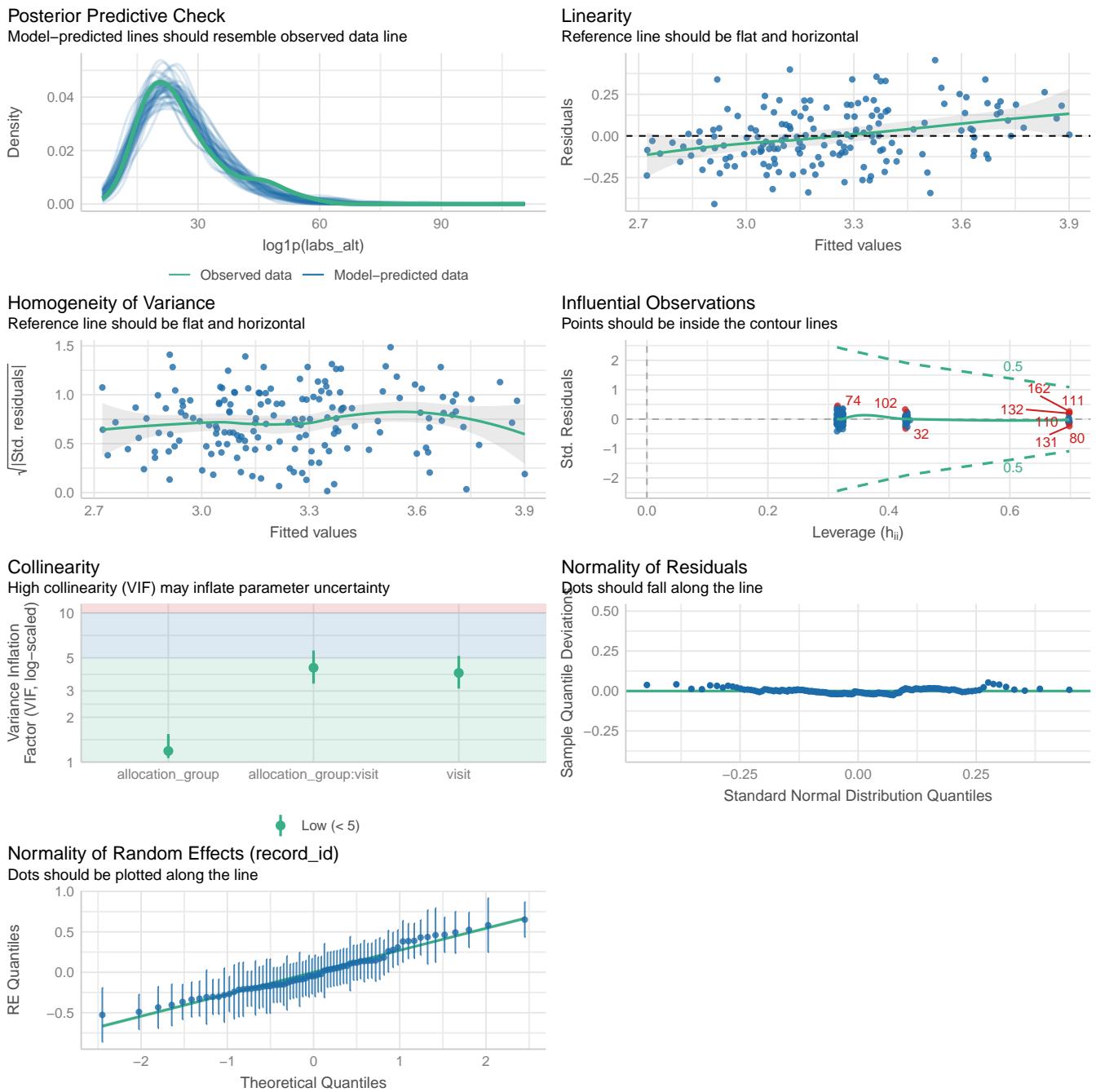
Influential Observations
Points should be inside the contour lines



Normality of Residuals
Dots should fall along the line



```
performance::check_model(labs_alt_model_sens)
```



3.2.2 Médias Marginais Estimadas

3.2.2.1 Todos os dados

```
# Get EMMs for each group at each visit
labs_alt_raw_emm <- emmeans::emmeans(
  labs_alt_model,
  ~ allocation_group * visit
```

```

)

labs_alt_raw_emm <- regrid(labs_alt_raw_emm)

# Table of marginal means
# labs_alt_raw_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(labs_alt_raw_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

visit = 1:
  contrast      estimate   SE  df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    2.734 2.51 104     -2.25     7.72    1.088  0.2792

visit = 2:
  contrast      estimate   SE  df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    1.033 2.59 118     -4.10     6.16    0.399  0.6907

visit = 3:
  contrast      estimate   SE  df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    0.612 2.88 134     -5.09     6.32    0.212  0.8324

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95

# Pairwise comparisons: Changes over time within each group
emmeans::contrast(labs_alt_raw_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

allocation_group = Grupo A:
  contrast      estimate   SE  df lower.CL upper.CL t.ratio p.value
visit1 - visit2    2.159 1.59 104     -1.71     6.03    1.357  0.5332
visit1 - visit3    0.934 1.76 104     -3.35     5.21    0.531  1.0000
visit2 - visit3   -1.225 1.72 118     -5.41     2.96   -0.711  1.0000

```

```

allocation_group = Grupo B:

contrast      estimate   SE  df lower.CL upper.CL t.ratio p.value
visit1 - visit2    0.458 1.59 104     -3.41      4.32   0.288  1.0000
visit1 - visit3   -1.189 1.77 104     -5.49      3.11  -0.672  1.0000
visit2 - visit3   -1.647 1.83 134     -6.07      2.78  -0.902  1.0000

```

Degrees-of-freedom method: inherited from kenward-roger when re-gridding

Confidence level used: 0.95

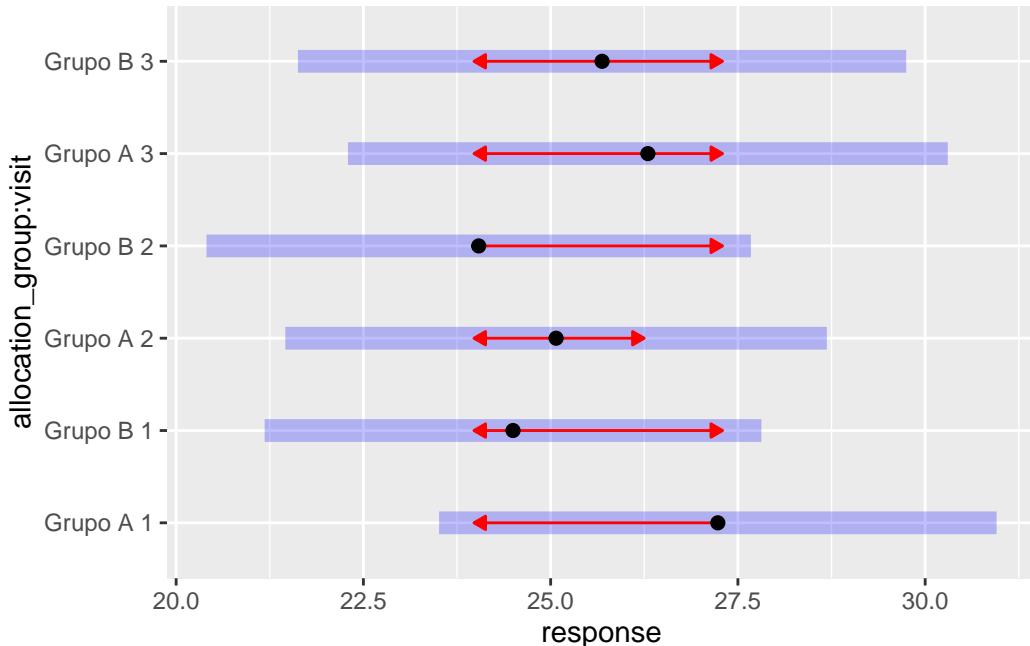
Conf-level adjustment: bonferroni method for 3 estimates

P value adjustment: bonferroni method for 3 tests

```

# Plot of marginal means
plot(labs_alt_raw_emm, comparisons = TRUE)

```



3.2.2.2 Análise de sensibilidade

```

# Get EMMs for each group at each visit (Sensitivity Analysis)
labs_alt_emm <- emmeans::emmeans(
  labs_alt_model_sens,
  ~ allocation_group * visit
)

labs_alt_emm <- regrid(labs_alt_emm)

```

```

# Table of marginal means
# labs_alt_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(labs_alt_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

visit = 1:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B     0.335 2.27  93.7     -4.16      4.83   0.148  0.8827

visit = 2:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B     0.558 2.38 107.7     -4.17      5.28   0.234  0.8153

visit = 3:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    -0.770 2.56 125.2     -5.84      4.31  -0.300  0.7645

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95

# Pairwise comparisons: Changes over time within each group
emmeans::contrast(labs_alt_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

allocation_group = Grupo A:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit2     0.549 1.41  93.7     -2.88      3.98   0.390  1.0000
visit1 - visit3     0.897 1.53  93.7     -2.84      4.63   0.586  1.0000
visit2 - visit3     0.348 1.54 107.7     -3.39      4.09   0.226  1.0000

allocation_group = Grupo B:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit2     0.772 1.39  93.7     -2.62      4.16   0.555  1.0000
visit1 - visit3    -0.207 1.55  93.7     -3.98      3.56  -0.134  1.0000

```

```
visit2 - visit3 -0.980 1.57 118.5 -4.80 2.84 -0.622 1.0000
```

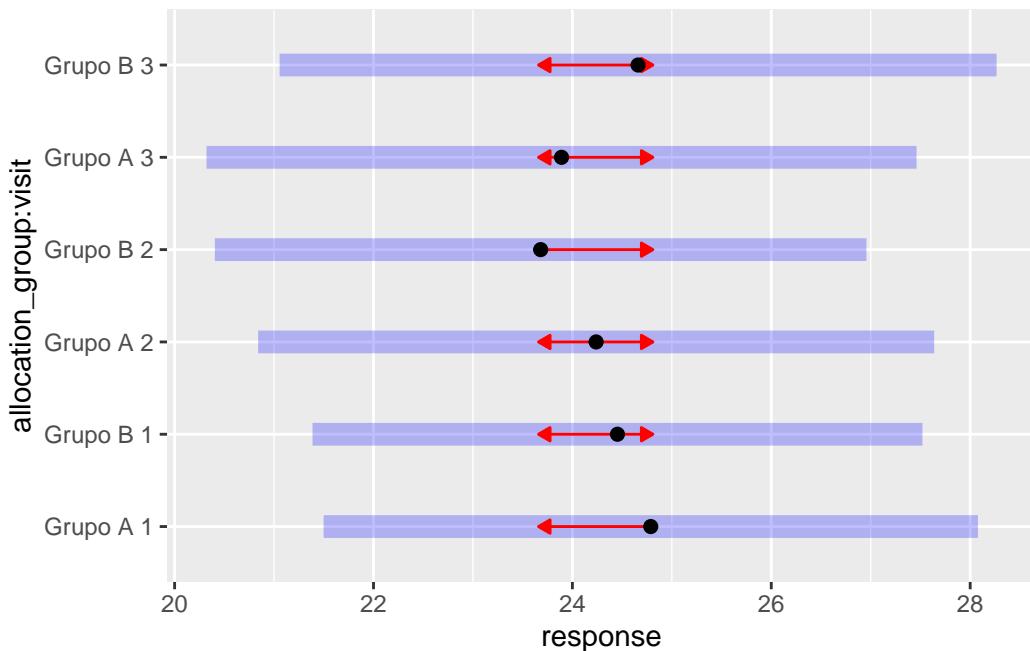
Degrees-of-freedom method: inherited from kenward-roger when re-gridding

Confidence level used: 0.95

Conf-level adjustment: bonferroni method for 3 estimates

P value adjustment: bonferroni method for 3 tests

```
# Plot of marginal means
plot(labs_alt_emm, comparisons = TRUE)
```



3.2.3 Resultado

No modelo ajustado para os níveis de ALT, não foram observadas diferenças estatisticamente significativas entre os grupos em nenhum dos três momentos avaliados. Da mesma forma, não houve mudanças significativas ao longo do tempo dentro de cada grupo. A análise de sensibilidade, realizada com a exclusão das observações influentes, confirmou esses achados. As estimativas permaneceram estáveis e todas as comparações entre os grupos e ao longo do tempo mantiveram-se não significativas. As estimativas, intervalos de confiança de 95% e valores de p estão apresentados na Tabela 2.

Tabela 2: Diferenças estimadas dos níveis de Alanina Aminotransferase (ALT) entre os grupos de alocação (placebo vs Eclipta) e entre visitas dentro de cada grupo

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 1	2,73	[-2,25 ; 7,72]	0,279
Entre grupos	Visita 2	1,03	[-4,10 ; 6,16]	0,691

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 3	0,61	[-5,09 ; 6,32]	0,832
Grupo Placebo	Visita 1 - Visita 2	2,16	[-1,71 ; 6,03]	0,533
Grupo Placebo	Visita 1 - Visita 3	0,93	[-3,35 ; 5,21]	1,000
Grupo Placebo	Visita 2 - Visita 3	-1,23	[-5,41 ; 2,96]	1,000
Grupo Eclipta	Visita 1 - Visita 2	0,46	[-3,41 ; 4,32]	1,000
Grupo Eclipta	Visita 1 - Visita 3	-1,19	[-5,49 ; 3,11]	1,000
Grupo Eclipta	Visita 2 - Visita 3	-1,65	[-6,07 ; 2,78]	1,000

```

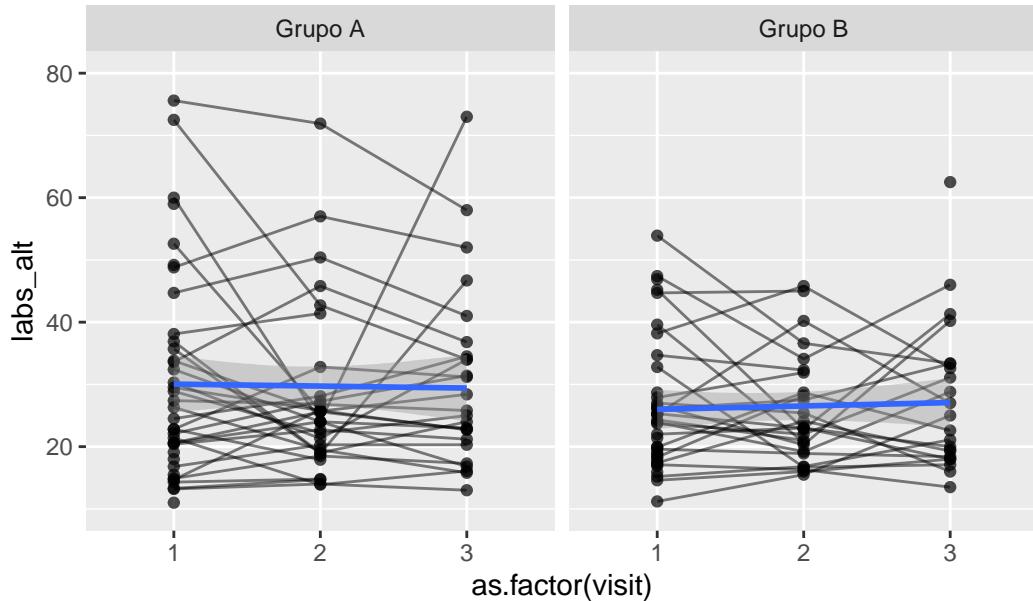
ggplot(
  data = data_model,
  aes(
    x = as.factor(visit),
    y = labs_alt,
    group = record_id,
  )
) +
  geom_line(alpha = 0.5) +
  geom_point(alpha = 0.7) +
  geom_smooth(
    aes(group = allocation_group),
    method = "lm",
    se = TRUE,
    linewidth = 1
  ) +
  labs(title = "All data") +
  facet_wrap(~ allocation_group) +
  coord_cartesian(ylim = c(10, 80))

`geom_smooth()` using formula = 'y ~ x'
Warning: Removed 10 rows containing non-finite outside the scale range
(`stat_smooth()`).
Warning: Removed 8 rows containing missing values or values outside the scale range
(`geom_line()`).

Warning: Removed 10 rows containing missing values or values outside the scale range
(`geom_point()`).

```

All data



```
data_model %>%
  filter(
    !(record_id %in%
      labs_alt_model_check$influential_ids)
  ) %>%
  ggplot(
    aes(
      x = as.factor(visit),
      y = labs_alt,
      group = record_id,
    )
  ) +
  geom_line(alpha = 0.5) +
  geom_point(alpha = 0.7) +
  geom_smooth(
    aes(group = allocation_group),
    method = "lm",
    se = TRUE,
    linewidth = 1
  ) +
  labs(title = "Sensitivity analysis") +
```

```

facet_wrap(~ allocation_group) +
coord_cartesian(ylim = c(10, 80))

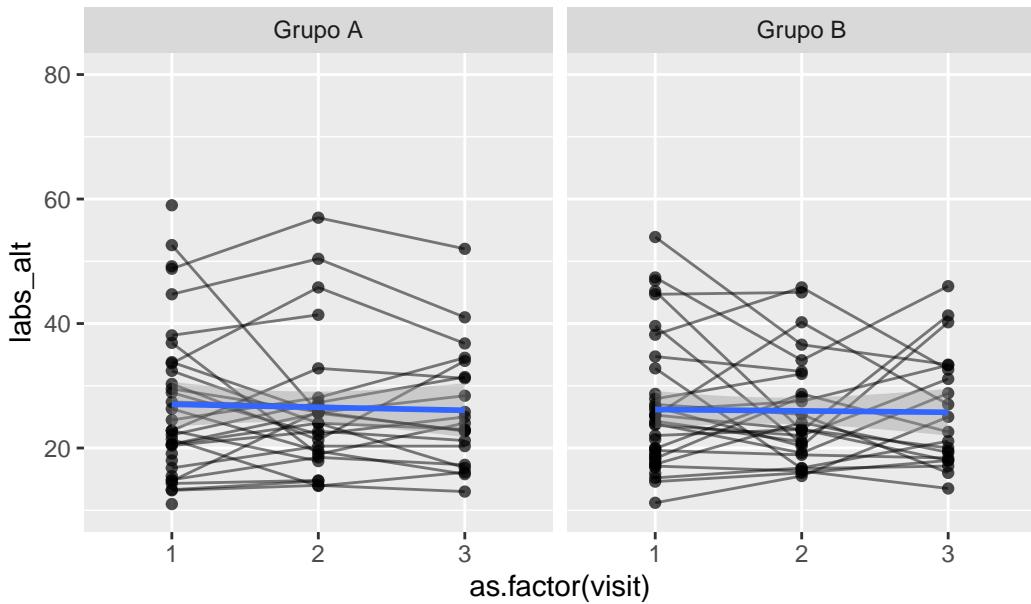
`geom_smooth()` using formula = 'y ~ x'
Warning: Removed 9 rows containing non-finite outside the scale range
(`stat_smooth()`).

Warning: Removed 8 rows containing missing values or values outside the scale range
(`geom_line()`).

Warning: Removed 9 rows containing missing values or values outside the scale range
(`geom_point()`).

```

Sensitivity analysis



3.3 Gama Glutamil-transferase

Variável: labs_ggt

```

# Plot 1: Raw data
labs_ggt_hist_1 <- data_model %>%
  filter(
    labs_ggt < 300
  ) %>%
  ggplot(aes(x = labs_ggt)) +
  geom_histogram(bins = 50, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data

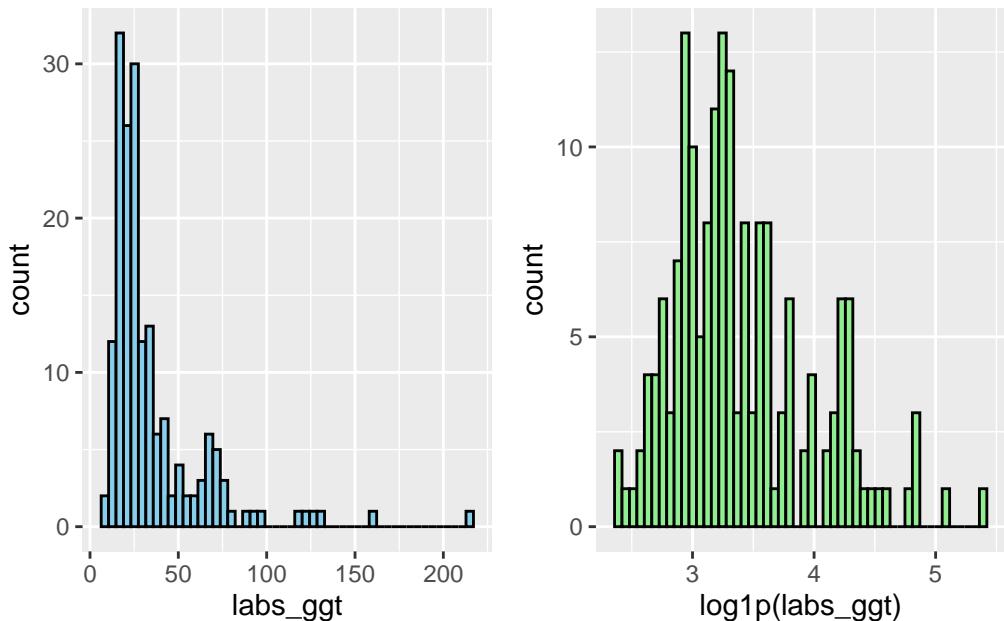
```

```

labs_ggt_hist_2 <- data_model %>%
  filter(
    labs_ggt < 300
  ) %>%
  ggplot(aes(x = log1p(labs_ggt))) +
  geom_histogram(bins = 50, fill = "lightgreen", color = "black")

# Combine side by side
labs_ggt_hist_1 + labs_ggt_hist_2 # library(patchwork)

```



```

# LMM
labs_ggt_model <- lmer(log1p(labs_ggt) ~ allocation_group * visit +
(1 | record_id), data = data_model)
check_collinearity(labs_ggt_model)

# Check for Multicollinearity

```

Low Correlation

	Term	VIF	VIF 95%	CI	Increased SE	Tolerance
	allocation_group	1.08	[1.01,	1.64]	1.04	0.93
	visit	3.40	[2.71,	4.36]	1.84	0.29
	allocation_group:visit	3.51	[2.79,	4.51]	1.87	0.28

```

Tolerance 95% CI
[0.61, 0.99]
[0.23, 0.37]
[0.22, 0.36]

# Sensitivity analysis
labs_ggt_model_check <- sensitivity_check_lmer(
  model = labs_ggt_model,
  id_var = "record_id",
  top_n = 7)

# LMM Sensitivity
labs_ggt_model_sens <- update(object = labs_ggt_model,
                                 subset = !(record_id %in%
                                             labs_ggt_model_check$influential_ids))

# Influential IDS
labs_ggt_model_check$influential_ids

[1] "13" "46" "49" "58" "22" "34" "41"

```

3.3.1 Resumo dos modelos

```

# Model comparison
summary(labs_ggt_model)

Linear mixed model fit by REML. t-tests use Satterthwaite's method [
lmerModLmerTest]

Formula: log1p(labs_ggt) ~ allocation_group * visit + (1 | record_id)

Data: data_model

```

REML criterion at convergence: 214.3

Scaled residuals:

Min	1Q	Median	3Q	Max
-1.98517	-0.41941	-0.02504	0.42332	2.68048

Random effects:

Groups	Name	Variance	Std.Dev.
record_id	(Intercept)	0.35840	0.5987

```

Residual          0.05825  0.2413
Number of obs: 178, groups: record_id, 75

Fixed effects:

              Estimate Std. Error      df t value Pr(>|t|)
(Intercept)      3.36365   0.10612 81.55575 31.697 <2e-16
allocation_group Grupo B    0.05279   0.14908 81.55575  0.354  0.724
visit2           -0.02673   0.06095 98.79849 -0.439  0.662
visit3            0.01219   0.06614 99.26017  0.184  0.854
allocation_group Grupo B:visit2  0.04689   0.08964 99.59537  0.523  0.602
allocation_group Grupo B:visit3  0.02698   0.09736 99.95801  0.277  0.782

```

```

(Intercept)          ***
allocation_group Grupo B
visit2
visit3
allocation_group Grupo B:visit2
allocation_group Grupo B:visit3
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```

Correlation of Fixed Effects:

```

(Intr) all_Gb visit2 visit3 a_Gb:2
allctn_grGB -0.712
visit2      -0.243  0.173
visit3      -0.224  0.160  0.455
allctn_Gb:2  0.166 -0.233 -0.680 -0.310
allctn_Gb:3  0.152 -0.214 -0.309 -0.679  0.436

```

```
summary(labs_ggt_model_sens)
```

```

Linear mixed model fit by REML. t-tests use Satterthwaite's method [
lmerModLmerTest]

Formula: log1p(labs_ggt) ~ allocation_group * visit + (1 | record_id)

Data: data_model

Subset: !(record_id %in% labs_ggt_model_check$influential_ids)

```

REML criterion at convergence: 129.2

Scaled residuals:

Min	1Q	Median	3Q	Max
-2.06521	-0.44956	-0.01804	0.45494	1.81501

Random effects:

Groups	Name	Variance	Std.Dev.
record_id	(Intercept)	0.2520	0.5020
Residual		0.0364	0.1908

Number of obs: 160, groups: record_id, 68

Fixed effects:

	Estimate	Std. Error	df	t value	Pr(> t)
(Intercept)	3.21202	0.09349	74.25204	34.357	<2e-16
allocation_group	0.14499	0.13031	74.25204	1.113	0.269
visit2	-0.01105	0.05075	89.14440	-0.218	0.828
visit3	0.03893	0.05564	89.56439	0.700	0.486
allocation_group:visit2	0.06129	0.07498	89.97944	0.817	0.416
allocation_group:visit3	0.01693	0.08145	90.24696	0.208	0.836

(Intercept) ***

allocation_group

visit2

visit3

allocation_group:visit2

allocation_group:visit3

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

(Intr)	all_GB	visit2	visit3	a_GB:2
allctn_grGB	-0.717			
visit2	-0.233	0.167		
visit3	-0.212	0.152	0.452	
allctn_GB:2	0.157	-0.219	-0.677	-0.306
allctn_GB:3	0.145	-0.202	-0.309	-0.683
				0.434

```
performance::compare_performance(  
  labs_ggt_model,  
  labs_ggt_model_sens)
```

When comparing models, please note that probably not all models were fit from same data.

```
# Comparison of Model Performance Indices
```

Name	Model	AIC (weights)	AICc (weights)

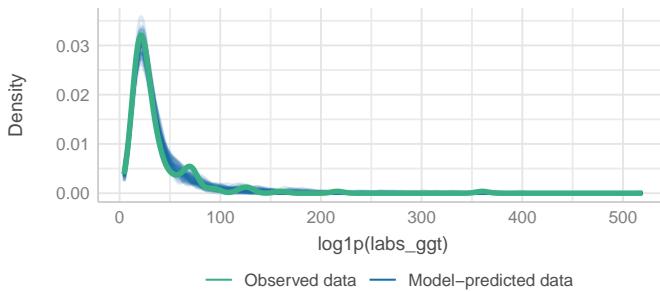
labs_ggt_model	lmerModLmerTest	1425.1 (<.001)	1426.0 (<.001)
labs_ggt_model_sens	lmerModLmerTest	1189.5 (>.999)	1190.4 (>.999)

Name	BIC (weights)	R2 (cond.)	R2 (marg.)	ICC	RMSE	Sigma

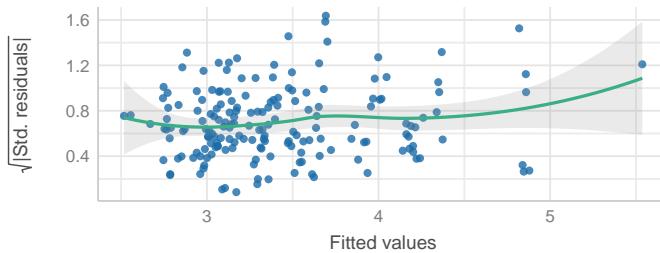
labs_ggt_model	1450.6 (<.001)	0.861	0.004	0.860	0.185	0.241
labs_ggt_model_sens	1214.1 (>.999)	0.877	0.026	0.874	0.145	0.191

```
performance::check_model(labs_ggt_model)
```

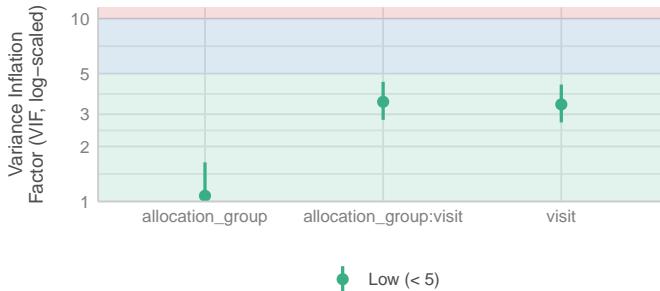
Posterior Predictive Check
Model-predicted lines should resemble observed data line



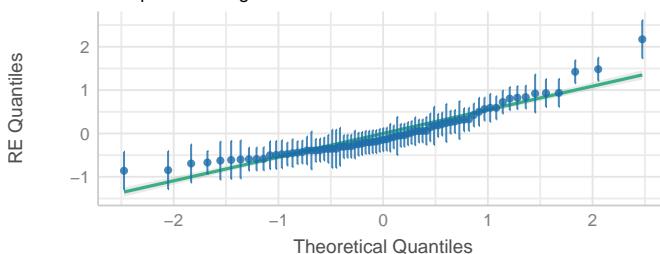
Homogeneity of Variance
Reference line should be flat and horizontal



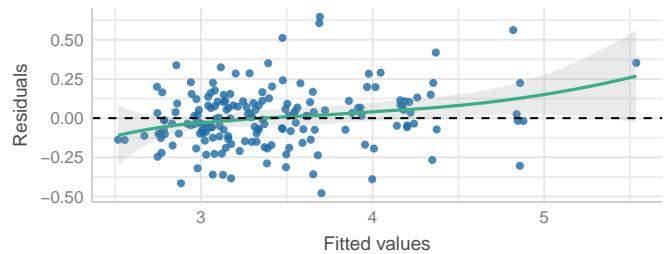
Collinearity
High collinearity (VIF) may inflate parameter uncertainty



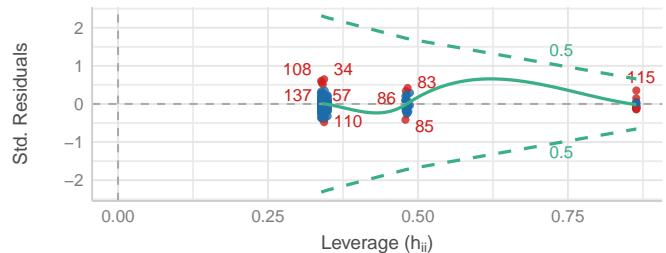
Normality of Random Effects (record_id)
Dots should be plotted along the line



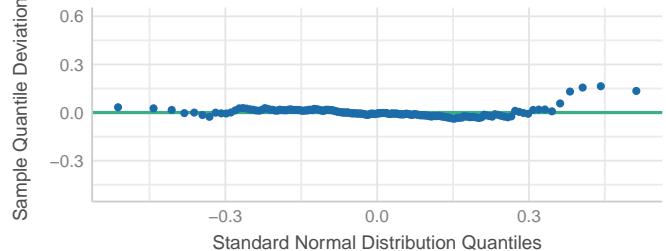
Linearity
Reference line should be flat and horizontal



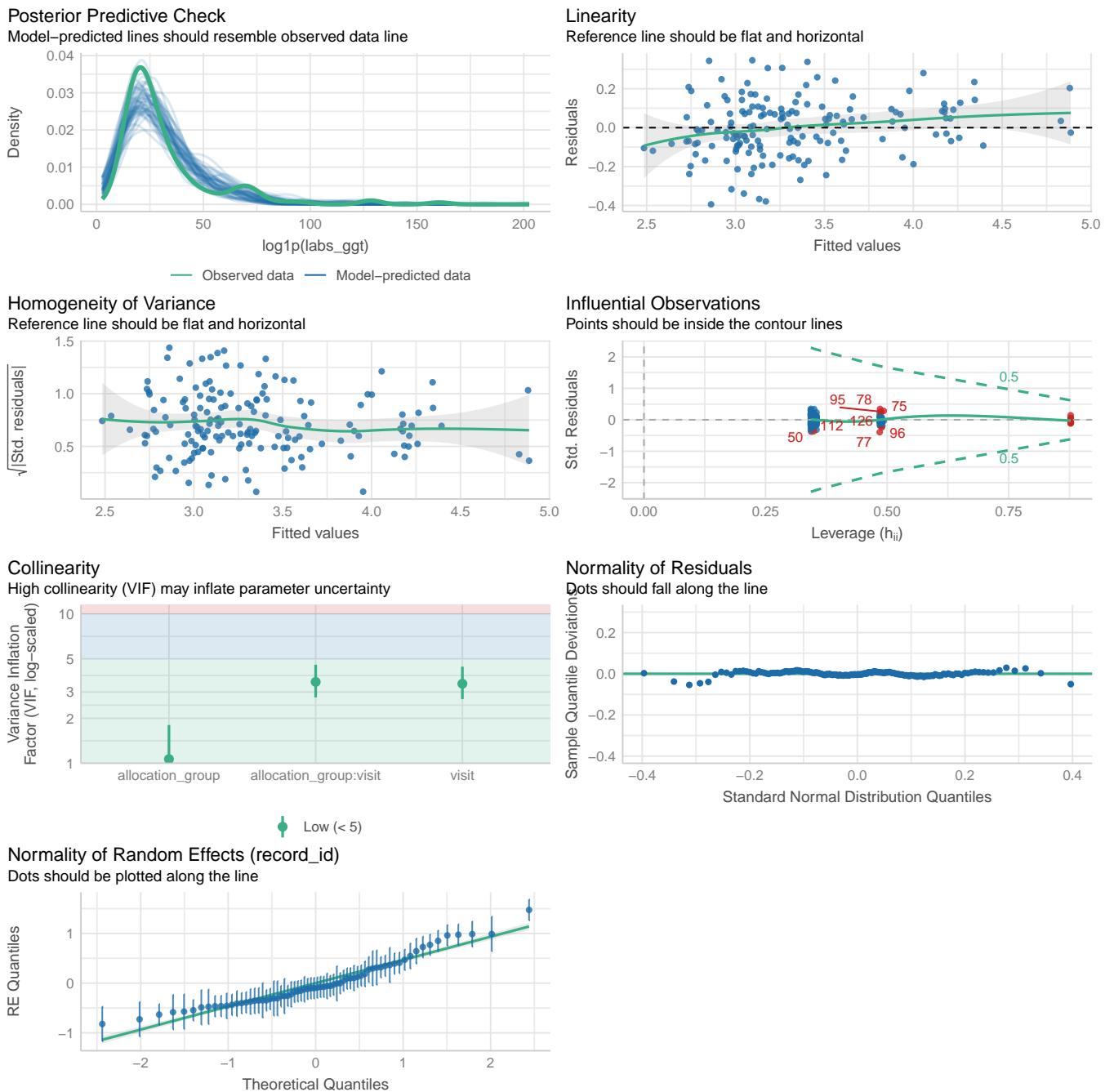
Influential Observations
Points should be inside the contour lines



Normality of Residuals
Dots should fall along the line



```
performance::check_model(labs_ggt_model_sens)
```



3.3.2 Médias Marginais Estimadas

3.3.2.1 Todos os dados

```
# Get EMMs for each group at each visit
labs_ggt_raw_emm <- emmeans::emmeans(
  labs_ggt_model,
  ~ allocation_group * visit
```

```

)

labs_ggt_raw_emm <- regrid(labs_ggt_raw_emm)

# Table of marginal means
# labs_ggt_raw_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(labs_ggt_raw_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

visit = 1:
  contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
  Grupo A - Grupo B    -1.57 4.42  84.1     -10.4      7.23  -0.354  0.7242

visit = 2:
  contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
  Grupo A - Grupo B    -2.95 4.60  91.4     -12.1      6.19  -0.641  0.5232

visit = 3:
  contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
  Grupo A - Grupo B    -2.43 4.87 100.1     -12.1      7.24  -0.498  0.6193

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95

# Pairwise comparisons: Changes over time within each group
emmeans::contrast(labs_ggt_raw_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

allocation_group = Grupo A:
  contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
  visit1 - visit2    0.762 1.74  84.1     -3.48      5.01  0.439  1.0000
  visit1 - visit3   -0.354 1.93  84.1     -5.06      4.35  -0.184  1.0000
  visit2 - visit3   -1.116 1.92  91.4     -5.79      3.56  -0.583  1.0000

```

```

allocation_group = Grupo B:

contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit2   -0.620 2.03  84.1     -5.58      4.34  -0.305  1.0000
visit1 - visit3   -1.217 2.24  84.1     -6.69      4.26  -0.543  1.0000
visit2 - visit3   -0.596 2.33 100.6     -6.27      5.08  -0.256  1.0000

```

Degrees-of-freedom method: inherited from kenward-roger when re-gridding

Confidence level used: 0.95

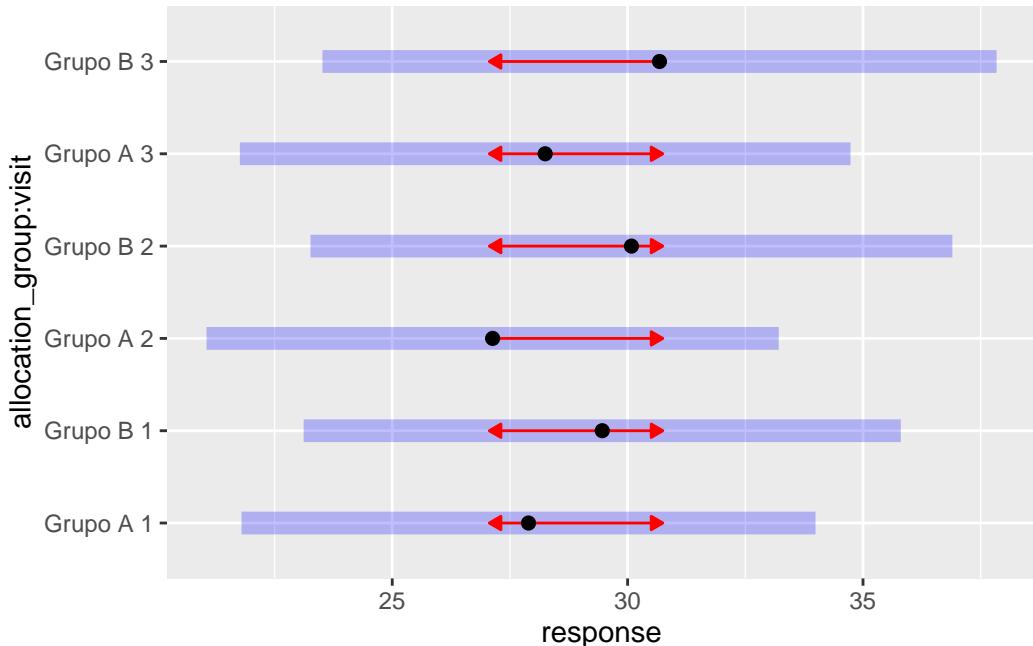
Conf-level adjustment: bonferroni method for 3 estimates

P value adjustment: bonferroni method for 3 tests

```

# Plot of marginal means
plot(labs_ggt_raw_emm, comparisons = TRUE)

```



3.3.2.2 Análise de sensibilidade

```

# Get EMMs for each group at each visit (Sensitivity Analysis)
labs_ggt_emm <- emmeans::emmeans(
  labs_ggt_model_sens,
  ~ allocation_group * visit
)

labs_ggt_emm <- regrid(labs_ggt_emm)

```

```

# Table of marginal means

# labs_ggt_emm

# Pairwise comparisons: Between groups at each visit

emmeans::contrast(labs_ggt_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

visit = 1:

contrast estimate SE df lower.CL upper.CL t.ratio p.value
Grupo A - Grupo B -3.87 3.49 74.8 -10.8 3.08 -1.110 0.2705

```

```

visit = 2:

contrast estimate SE df lower.CL upper.CL t.ratio p.value
Grupo A - Grupo B -5.63 3.73 80.4 -13.0 1.79 -1.510 0.1351

```

```

visit = 3:

contrast estimate SE df lower.CL upper.CL t.ratio p.value
Grupo A - Grupo B -4.54 3.92 88.4 -12.3 3.25 -1.158 0.2501

```

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
 Confidence level used: 0.95

```

# Pairwise comparisons: Changes over time within each group

emmeans::contrast(labs_ggt_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

allocation_group = Grupo A:

contrast estimate SE df lower.CL upper.CL t.ratio p.value
visit1 - visit2 0.273 1.25 74.8 -2.80 3.34 0.218 1.0000
visit1 - visit3 -0.986 1.42 74.8 -4.46 2.49 -0.694 1.0000
visit2 - visit3 -1.259 1.42 80.4 -4.73 2.21 -0.888 1.0000

```

```

allocation_group = Grupo B:

contrast estimate SE df lower.CL upper.CL t.ratio p.value
visit1 - visit2 -1.479 1.64 74.8 -5.51 2.55 -0.899 1.0000
visit1 - visit3 -1.649 1.78 74.8 -6.02 2.72 -0.924 1.0000

```

```
visit2 - visit3 -0.170 1.88 90.1 -4.74 4.40 -0.091 1.0000
```

Degrees-of-freedom method: inherited from kenward-roger when re-gridding

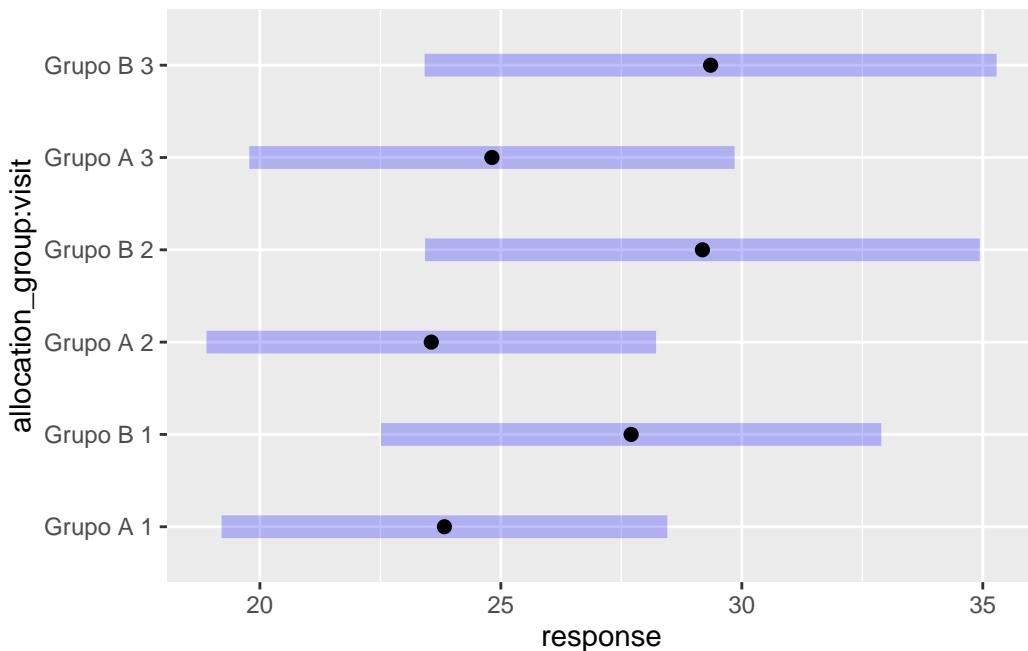
Confidence level used: 0.95

Conf-level adjustment: bonferroni method for 3 estimates

P value adjustment: bonferroni method for 3 tests

```
# Plot of marginal means
```

```
plot(labs_ggt_emm)
```



3.3.3 Resultado

No modelo ajustado para os níveis de Gama Glutamiltransferase (GGT), não foram observadas diferenças estatisticamente significativas entre os grupos em nenhum dos três momentos avaliados. Também não foram identificadas mudanças significativas ao longo do tempo dentro de cada grupo. A análise de sensibilidade, com exclusão das observações influentes, não alterou substancialmente os resultados. As estimativas permaneceram similares, reforçando a ausência de diferenças significativas entre os grupos ou de variações temporais relevantes. As estimativas, intervalos de confiança de 95% e valores de p estão apresentados na Tabela 3.

Tabela 3: Diferenças estimadas dos níveis de Gama Glutamiltransferase (GGT) entre os grupos de alocação (placebo vs Eclipta) e entre visitas dentro de cada grupo

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 1	-1,57	[-10,4 ; 7,23]	0,724

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 2	-2,95	[-12,1 ; 6,19]	0,523
Entre grupos	Visita 3	-2,43	[-12,1 ; 7,24]	0,619
Grupo Placebo	Visita 1 - Visita 2	0,76	[-3,48 ; 5,01]	1,000
Grupo Placebo	Visita 1 - Visita 3	-0,35	[-5,06 ; 4,35]	1,000
Grupo Placebo	Visita 2 - Visita 3	-1,12	[-5,79 ; 3,56]	1,000
Grupo Eclipta	Visita 1 - Visita 2	-0,62	[-5,58 ; 4,34]	1,000
Grupo Eclipta	Visita 1 - Visita 3	-1,22	[-6,69 ; 4,26]	1,000
Grupo Eclipta	Visita 2 - Visita 3	-0,60	[-6,27 ; 5,08]	1,000

```

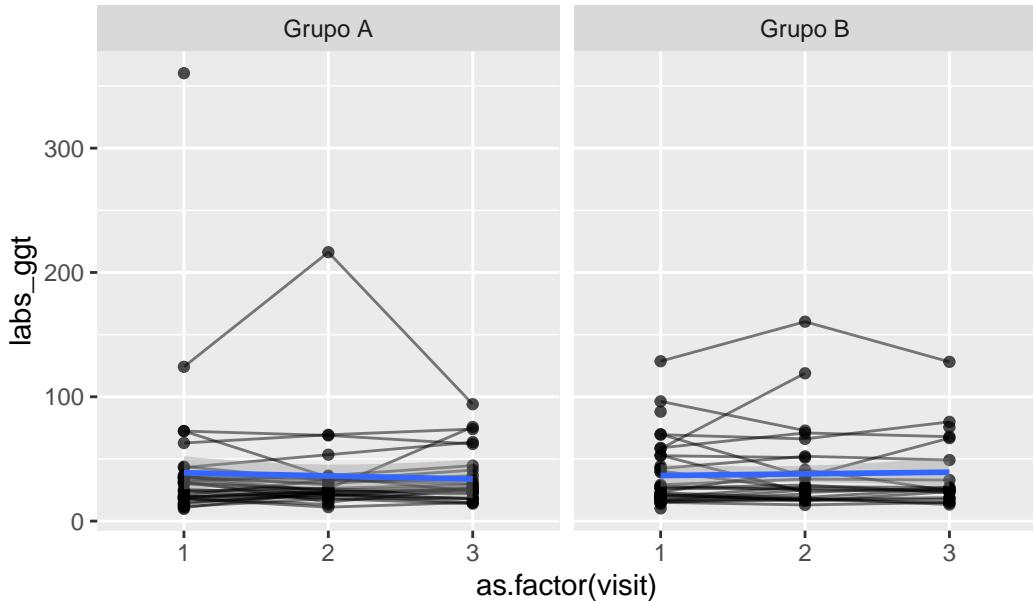
ggplot(
  data = data_model,
  aes(
    x = as.factor(visit),
    y = labs_ggt,
    group = record_id,
  )
) +
  geom_line(alpha = 0.5) +
  geom_point(alpha = 0.7) +
  geom_smooth(
    aes(group = allocation_group),
    method = "lm",
    se = TRUE,
    linewidth = 1
  ) +
  labs(title = "All data") +
  facet_wrap(~ allocation_group)

`geom_smooth()` using formula = 'y ~ x'
Warning: Removed 11 rows containing non-finite outside the scale range
(`stat_smooth()`).
Warning: Removed 9 rows containing missing values or values outside the scale range
(`geom_line()`).

Warning: Removed 11 rows containing missing values or values outside the scale range
(`geom_point()`).

```

All data



```
#coord_cartesian(ylim = c(10, 150))

data_model %>%
  filter(
    !(record_id %in%
      labs_ggt_model_check$influential_ids)
  ) %>%
  ggplot(
    aes(
      x = as.factor(visit),
      y = labs_ggt,
      group = record_id,
    )
  ) +
  geom_line(alpha = 0.5) +
  geom_point(alpha = 0.7) +
  geom_smooth(
    aes(group = allocation_group),
    method = "lm",
    se = TRUE,
    linewidth = 1
  )
```

```

) +
  labs(title = "Sensitivity analysis") +
  facet_wrap(~ allocation_group)

`geom_smooth()` using formula = 'y ~ x'

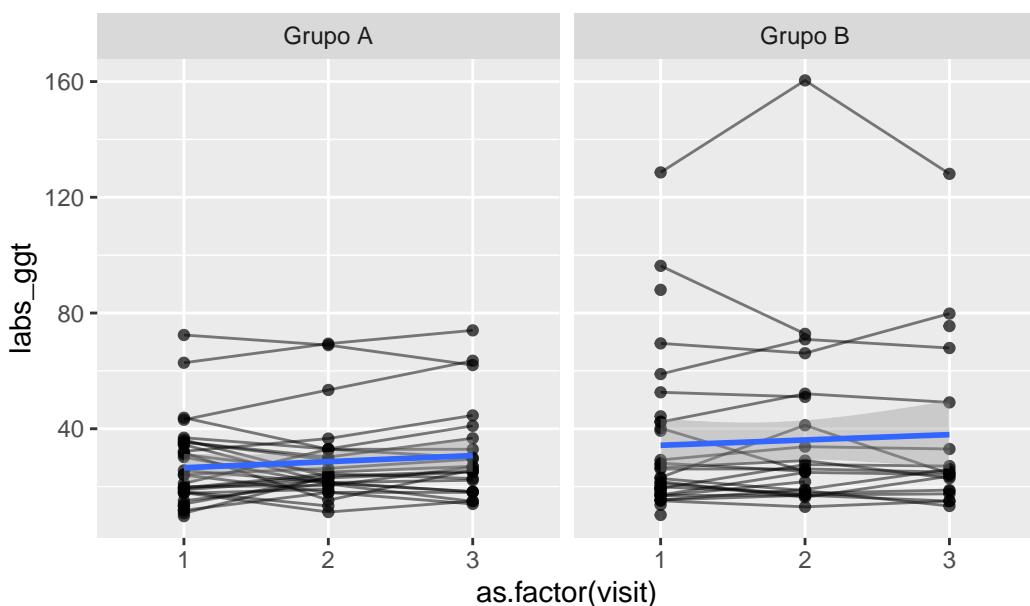
Warning: Removed 10 rows containing non-finite outside the scale range
(`stat_smooth()`).

Warning: Removed 8 rows containing missing values or values outside the scale range
(`geom_line()`).

Warning: Removed 10 rows containing missing values or values outside the scale range
(`geom_point()`).

```

Sensitivity analysis



```
#coord_cartesian(ylim = c(10, 150))
```

3.4 Fosfatase Alcalina

Variável: labs_alkp

```

# Plot 1: Raw data
labs_alkp_hist_1 <- data_model %>%
  #filter(
  #  labs_alkp < 300
  #) %>%
  ggplot(aes(x = labs_alkp)) +

```

```

geom_histogram(bins = 50, fill = "skyblue", color = "black")

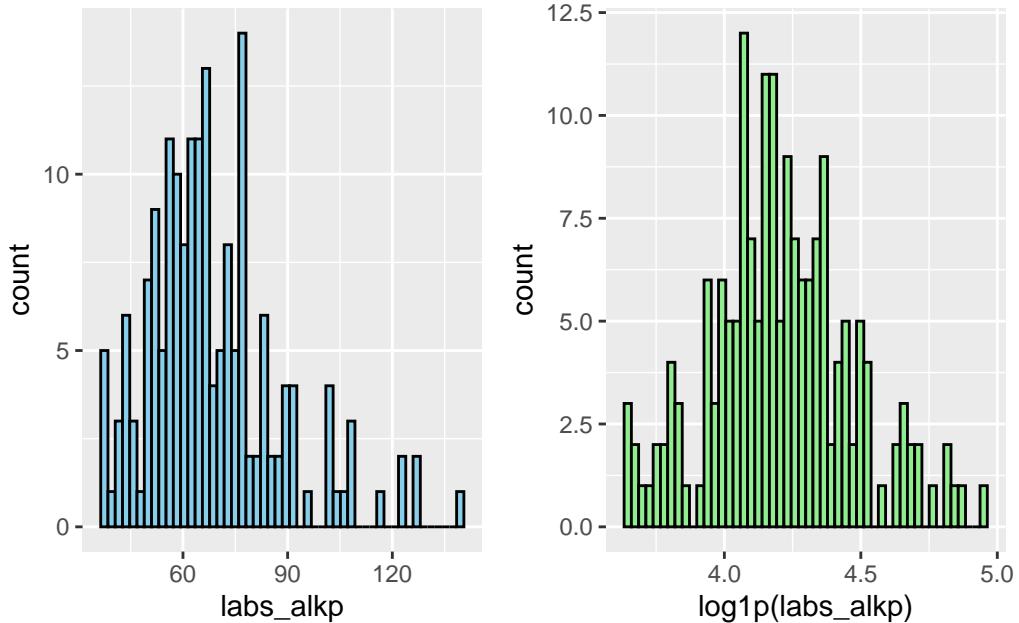
# Plot 2: Log-transformed data
labs_alkp_hist_2 <- data_model %>%
  #filter(
  #  labs_alkp < 300
  #) %>%
  ggplot(aes(x = log1p(labs_alkp))) +
  geom_histogram(bins = 50, fill = "lightgreen", color = "black")

# Combine side by side
labs_alkp_hist_1 + labs_alkp_hist_2 # library(patchwork)

```

Warning: Removed 11 rows containing non-finite outside the scale range (`stat_bin()`).

Removed 11 rows containing non-finite outside the scale range (`stat_bin()`).



```

# LMM
labs_alkp_model <- lmer(log1p(labs_alkp) ~ allocation_group * visit +
(1 | record_id), data = data_model)
check_collinearity(labs_alkp_model)

# Check for Multicollinearity

```

Low Correlation

Term	VIF	VIF 95% CI	Increased SE	Tolerance
allocation_group	1.08	[1.01, 1.62]	1.04	0.93
visit	3.40	[2.71, 4.36]	1.84	0.29
allocation_group:visit	3.52	[2.80, 4.52]	1.88	0.28
Tolerance 95% CI				
	[0.62, 0.99]			
	[0.23, 0.37]			
	[0.22, 0.36]			

```

# Sensitivity analysis
labs_alkp_model_check <- sensitivity_check_lmer(
  model = labs_alkp_model,
  id_var = "record_id",
  top_n = 4)

# LMM Sensitivity
labs_alkp_model_sens <- update(object = labs_alkp_model,
  subset = !(record_id %in%
  labs_alkp_model_check$influential_ids))

# Influential IDS
labs_alkp_model_check$influential_ids
```

[1] "56" "75" "53" "3"

3.4.1 Resumo dos modelos

```

# Model comparison
summary(labs_alkp_model)

Linear mixed model fit by REML. t-tests use Satterthwaite's method [
lmerModLmerTest]

Formula: log1p(labs_alkp) ~ allocation_group * visit + (1 | record_id)

Data: data_model

REML criterion at convergence: -87.9
```

Scaled residuals:

Min	1Q	Median	3Q	Max
-----	----	--------	----	-----

```
-2.02732 -0.46612  0.01043  0.43200  2.62132
```

Random effects:

Groups	Name	Variance	Std.Dev.
record_id	(Intercept)	0.06041	0.2458
Residual		0.01021	0.1010

Number of obs: 178, groups: record_id, 75

Fixed effects:

	Estimate	Std. Error	df	t value
(Intercept)	4.210088	0.043688	84.150015	96.367
allocation_group	0.033160	0.061377	84.150015	0.540
visit2	-0.046856	0.025510	100.999520	-1.837
visit3	-0.030253	0.027680	101.476417	-1.093
allocation_group:visit2	0.018421	0.037511	101.816342	0.491
allocation_group:visit3	0.004182	0.040741	102.191761	0.103
	Pr(> t)			
(Intercept)	<2e-16	***		
allocation_group	0.5904			
visit2	0.0692	.		
visit3	0.2770			
allocation_group:visit2	0.6244			
allocation_group:visit3	0.9184			

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1				

Correlation of Fixed Effects:

	(Intr)	all_GB	visit2	visit3	a_GB:2
allctn_gr	-0.712				
visit2	-0.248	0.176			
visit3	-0.228	0.162	0.455		
allctn_GB:2	0.168	-0.236	-0.680	-0.310	
allctn_GB:3	0.155	-0.218	-0.309	-0.679	0.436

```
summary(labs_alkp_model_sens)
```

```
Linear mixed model fit by REML. t-tests use Satterthwaite's method [lmerModLmerTest]
```

Formula: log1p(labs_alkp) ~ allocation_group * visit + (1 | record_id)
Data: data_model
Subset: !(record_id %in% labs_alkp_model_check\$influential_ids)

REML criterion at convergence: -118.6

Scaled residuals:

Min	1Q	Median	3Q	Max
-1.95508	-0.49130	0.04228	0.50567	1.80928

Random effects:

Groups	Name	Variance	Std.Dev.
record_id	(Intercept)	0.06287	0.25073
Residual		0.00669	0.08179

Number of obs: 167, groups: record_id, 71

Fixed effects:

	Estimate	Std. Error	df	t value	Pr(> t)
(Intercept)	4.198426	0.044579	75.550975	94.179	<2e-16
allocation_group	0.071738	0.062605	75.550975	1.146	0.255
visit2	-0.021391	0.021391	93.237481	-1.000	0.320
visit3	-0.002867	0.023373	93.517548	-0.123	0.903
allocation_group:visit2	-0.020052	0.031577	93.770609	-0.635	0.527
allocation_group:visit3	-0.052680	0.034183	93.954152	-1.541	0.127

(Intercept) ***

allocation_group

visit2

visit3

allocation_group:visit2

allocation_group:visit3

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

(Intr) all_GB visit2 visit3 a_GB:2

```

allctn_grGB -0.712
visit2      -0.200  0.143
visit3      -0.183  0.131  0.454
allctn_GB:2  0.136 -0.191 -0.677 -0.307
allctn_GB:3  0.125 -0.176 -0.310 -0.684  0.438

performance::compare_performance(
  labs_alkp_model,
  labs_alkp_model_sens)

```

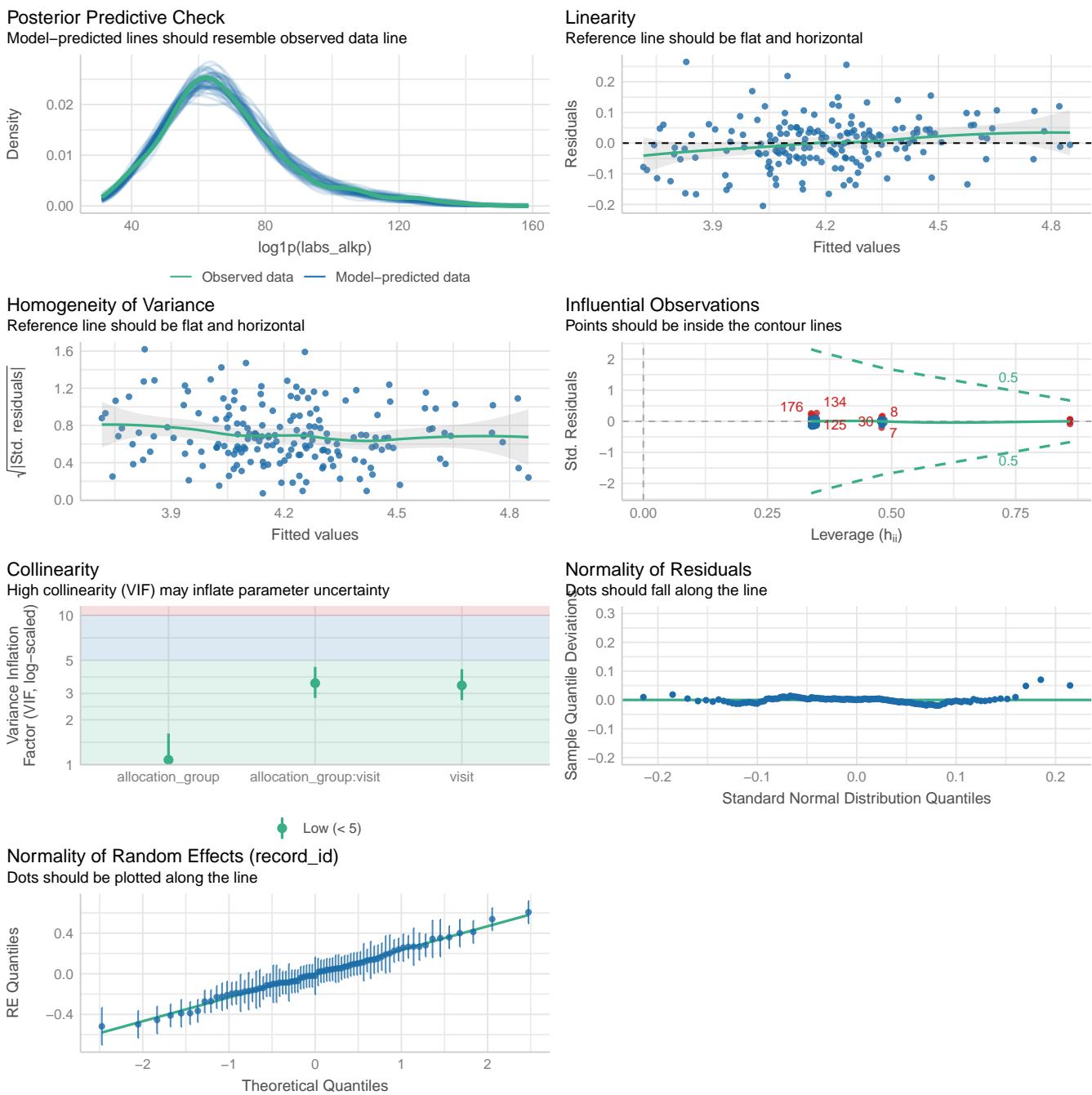
When comparing models, please note that probably not all models were fit from same data.

```
# Comparison of Model Performance Indices
```

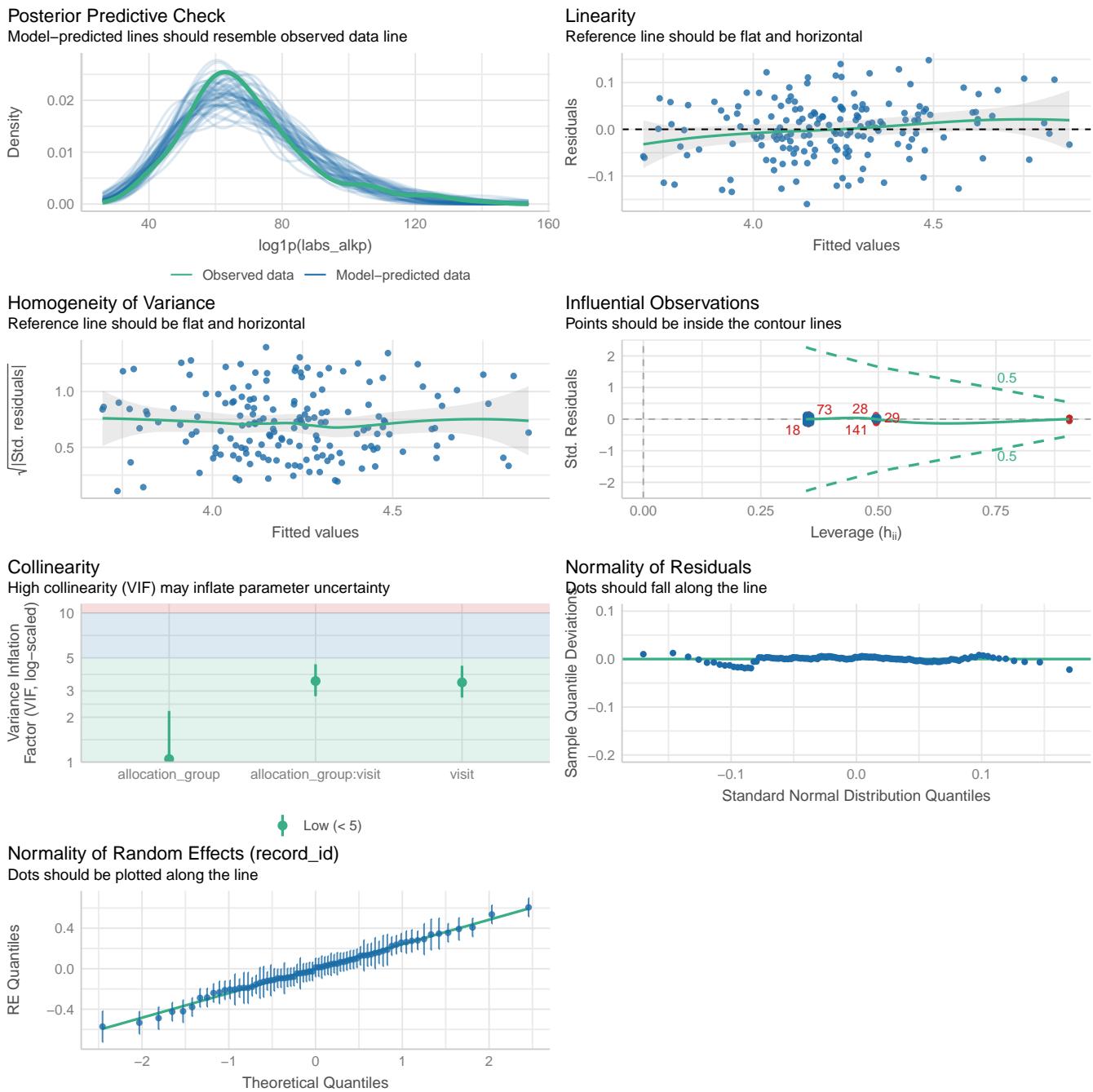
Name	Model	AIC (weights)	AICc (weights)
labs_alkp_model	lmerModLmerTest	1394.9 (<.001)	1395.7 (<.001)
labs_alkp_model_sens	lmerModLmerTest	1274.2 (>.999)	1275.1 (>.999)

Name	BIC (weights)	R2 (cond.)	R2 (marg.)	ICC	RMSE	Sigma
labs_alkp_model	1420.3 (<.001)	0.857	0.010	0.855	0.077	0.101
labs_alkp_model_sens	1299.1 (>.999)	0.905	0.015	0.904	0.062	0.082

```
performance::check_model(labs_alkp_model)
```



```
performance::check_model(labs_alkp_model_sens)
```



3.4.2 Médias Marginais Estimadas

3.4.2.1 Todos os dados

```
# Get EMMs for each group at each visit
labs_alkp_raw_emm <- emmeans::emmeans(
  labs_alkp_model,
  ~ allocation_group * visit
```

```

)

labs_alkp_raw_emm <- regrid(labs_alkp_raw_emm)

# Table of marginal means
# labs_alkp_raw_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(labs_alkp_raw_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

visit = 1:
  contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
  Grupo A - Grupo B    -2.27 4.20  84.5     -10.6      6.09  -0.540  0.5904

visit = 2:
  contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
  Grupo A - Grupo B    -3.40 4.22  92.0     -11.8      4.98  -0.806  0.4223

visit = 3:
  contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
  Grupo A - Grupo B    -2.49 4.39 101.0     -11.2      6.22  -0.566  0.5724

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95

# Pairwise comparisons: Changes over time within each group
emmeans::contrast(labs_alkp_raw_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

allocation_group = Grupo A:
  contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
  visit1 - visit2    3.08 1.68  84.5     -1.02      7.18   1.837  0.2094
  visit1 - visit3    2.01 1.83  84.5     -2.47      6.48   1.096  0.8290
  visit2 - visit3   -1.08 1.81  92.0     -5.48      3.33  -0.596  1.0000

```

```

allocation_group = Grupo B:

contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit2     1.95 1.88  84.5     -2.65     6.55   1.036  0.9090
visit1 - visit3     1.79 2.05  84.5     -3.21     6.79   0.875  1.0000
visit2 - visit3    -0.16 2.10 101.5     -5.28     4.96  -0.076  1.0000

```

Degrees-of-freedom method: inherited from kenward-roger when re-gridding

Confidence level used: 0.95

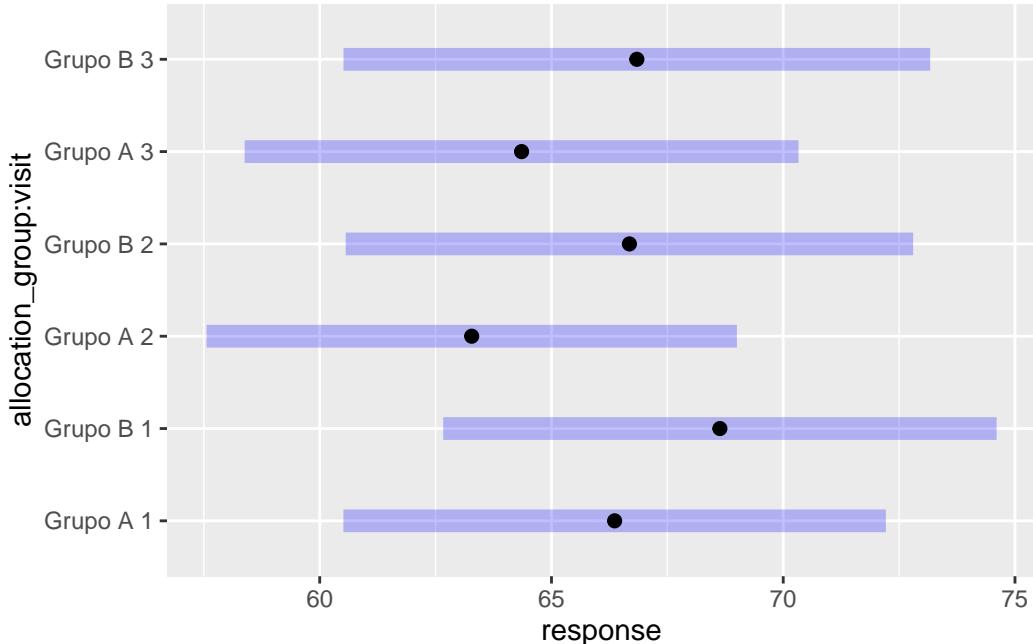
Conf-level adjustment: bonferroni method for 3 estimates

P value adjustment: bonferroni method for 3 tests

```

# Plot of marginal means
plot(labs_alkp_raw_emm)

```



3.4.2.2 Análise de sensibilidade

```

# Get EMMs for each group at each visit (Sensitivity Analysis)
labs_alkp_emm <- emmeans::emmeans(
  labs_alkp_model_sens,
  ~ allocation_group * visit
)

# Table of marginal means

```

```

# labs_alkp_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(labs_alkp_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

visit = 1:
contrast estimate SE df lower.CL upper.CL t.ratio p.value
Grupo A - Grupo B -0.0717 0.0626 75.8 -0.196 0.0530 -1.146 0.2554

visit = 2:
contrast estimate SE df lower.CL upper.CL t.ratio p.value
Grupo A - Grupo B -0.0517 0.0645 84.4 -0.180 0.0766 -0.801 0.4254

visit = 3:
contrast estimate SE df lower.CL upper.CL t.ratio p.value
Grupo A - Grupo B -0.0191 0.0658 90.6 -0.150 0.1117 -0.289 0.7729

```

Note: contrasts are still on the log1p scale. Consider using
`regrid()` if you want contrasts of back-transformed estimates.

Degrees-of-freedom method: kenward-roger

Confidence level used: 0.95

```

# Pairwise comparisons: Changes over time within each group
emmeans::contrast(labs_alkp_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

allocation_group = Grupo A:
contrast estimate SE df lower.CL upper.CL t.ratio p.value
visit1 - visit2 0.02139 0.0214 93.5 -0.03077 0.0736 1.000 0.9602
visit1 - visit3 0.00287 0.0234 93.8 -0.05413 0.0599 0.123 1.0000
visit2 - visit3 -0.01852 0.0235 92.6 -0.07572 0.0387 -0.790 1.0000

allocation_group = Grupo B:
contrast estimate SE df lower.CL upper.CL t.ratio p.value
visit1 - visit2 0.04144 0.0232 94.5 -0.01521 0.0981 1.783 0.2333

```

```

visit1 - visit3  0.05555  0.0250  94.6 -0.00529   0.1164    2.225  0.0853
visit2 - visit3  0.01410  0.0259  92.9 -0.04902   0.0772    0.545  1.0000

```

Note: contrasts are still on the log1p scale. Consider using
regrid() if you want contrasts of back-transformed estimates.

Degrees-of-freedom method: kenward-roger

Confidence level used: 0.95

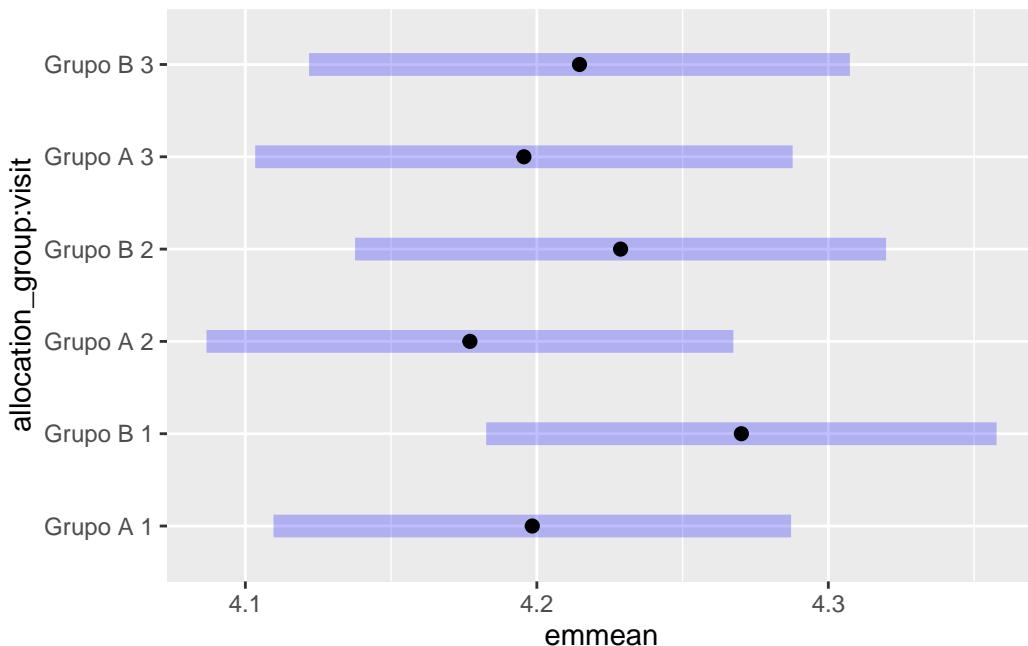
Conf-level adjustment: bonferroni method for 3 estimates

P value adjustment: bonferroni method for 3 tests

```

# Plot of marginal means
plot(labs_alkp_emm)

```



3.4.3 Resultado

No modelo ajustado para os níveis de Fosfatase Alcalina (ALP), não foram observadas diferenças estatisticamente significativas entre os grupos em nenhum dos três momentos avaliados. Da mesma forma, as comparações intragrupo ao longo do tempo não indicaram variações significativas. A análise de sensibilidade, realizada com exclusão das observações influentes, manteve os resultados essencialmente inalterados, com estimativas semelhantes e ausência de significância estatística nas comparações entre grupos e entre visitas. As estimativas, intervalos de confiança de 95% e valores de p estão apresentados na Tabela 4.

Tabela 4: Diferenças estimadas dos níveis de Fosfatase Alcalina (ALP) entre os grupos de alocação (placebo vs Eclipta) e entre visitas dentro de cada grupo

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 1	-2,27	[-10,6 ; 6,09]	0,590
Entre grupos	Visita 2	-3,40	[-11,8 ; 4,98]	0,422
Entre grupos	Visita 3	-2,49	[-11,2 ; 6,22]	0,572
Grupo Placebo	Visita 1 - Visita 2	3,08	[-1,02 ; 7,18]	0,209
Grupo Placebo	Visita 1 - Visita 3	2,01	[-2,47 ; 6,48]	0,829
Grupo Placebo	Visita 2 - Visita 3	-1,08	[-5,48 ; 3,33]	1,000
Grupo Eclipta	Visita 1 - Visita 2	1,95	[-2,65 ; 6,55]	0,909
Grupo Eclipta	Visita 1 - Visita 3	1,79	[-3,21 ; 6,79]	1,000
Grupo Eclipta	Visita 2 - Visita 3	-0,16	[-5,28 ; 4,96]	1,000

```

ggplot(
  data = data_model,
  aes(
    x = as.factor(visit),
    y = labs_alkp,
    group = record_id,
  )
) +
  geom_line(alpha = 0.5) +
  geom_point(alpha = 0.7) +
  geom_smooth(
    aes(group = allocation_group),
    method = "lm",
    se = TRUE,
    linewidth = 1
) +
  labs(title = "All data") +
  facet_wrap(~ allocation_group)

```

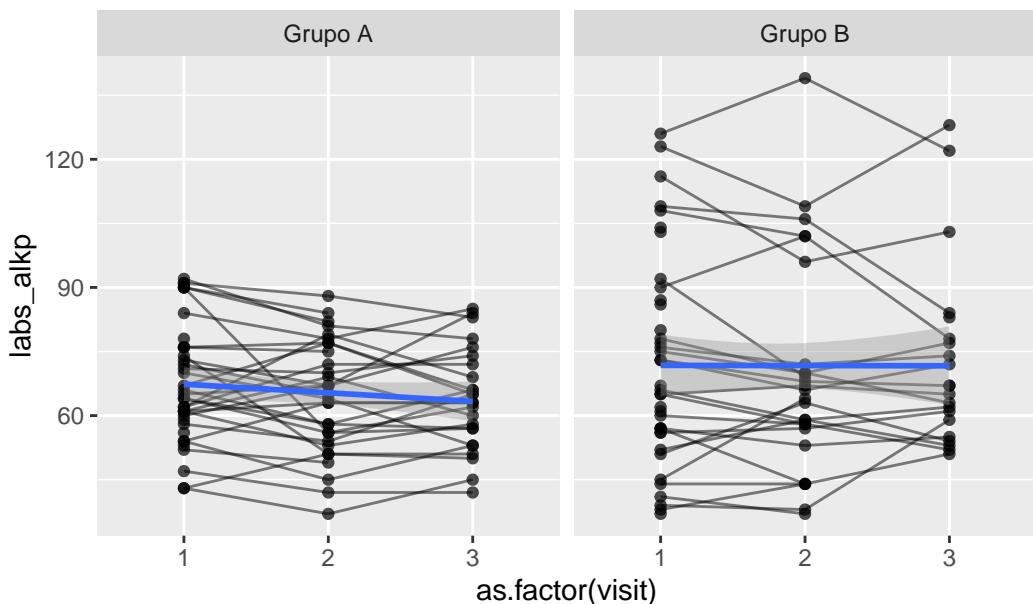
```
`geom_smooth()` using formula = 'y ~ x'
```

```
Warning: Removed 11 rows containing non-finite outside the scale range
(`stat_smooth()`).
```

```
Warning: Removed 9 rows containing missing values or values outside the scale range
```

```
(`geom_line()`).
Warning: Removed 11 rows containing missing values or values outside the scale range
(`geom_point()`).
```

All data



```
#coord_cartesian(ylim = c(10, 150))

data_model %>%
  filter(
    !(record_id %in%
      labs_alkp_model_check$influential_ids)
  ) %>%
  ggplot(
    aes(
      x = as.factor(visit),
      y = labs_alkp,
      group = record_id,
    )
  ) +
  geom_line(alpha = 0.5) +
  geom_point(alpha = 0.7) +
  geom_smooth(
    aes(group = allocation_group),
    method = "lm",
  )
```

```

    se = TRUE,
    linewidth = 1
) +
  labs(title = "Sensitivity analysis") +
  facet_wrap(~ allocation_group)

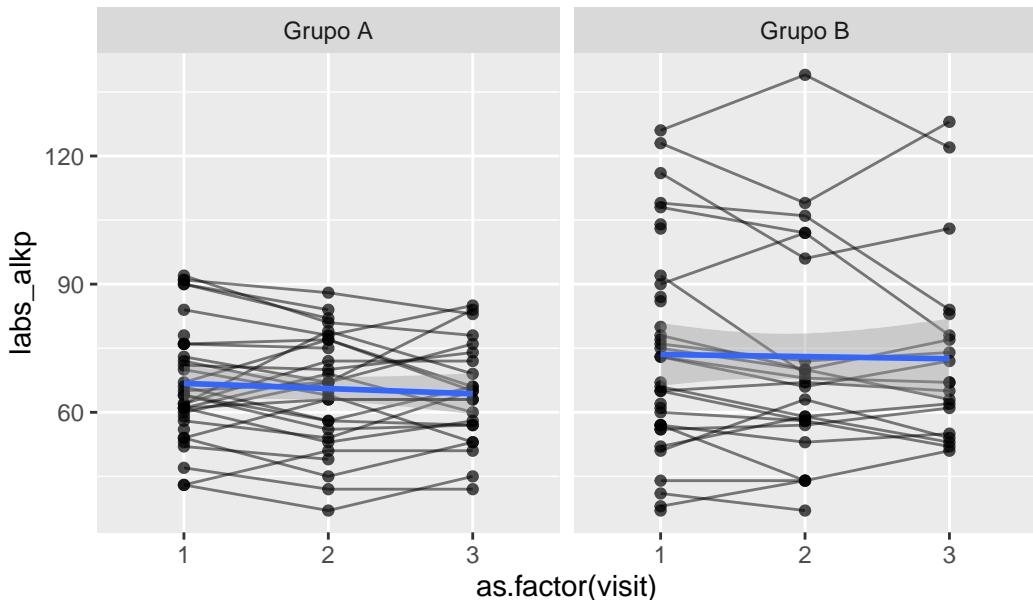
`geom_smooth()` using formula = 'y ~ x'
Warning: Removed 11 rows containing non-finite outside the scale range
(`stat_smooth()`).

Warning: Removed 9 rows containing missing values or values outside the scale range
(`geom_line()`).

Warning: Removed 11 rows containing missing values or values outside the scale range
(`geom_point()`).

```

Sensitivity analysis



```
#coord_cartesian(ylim = c(10, 150))
```

3.5 Colesterol Total

Variável: labs_cholesterol

```

# Plot 1: Raw data
labs_cholesterol_hist_1 <- data_model %>%
  #filter(
  #  labs_cholesterol < 300

```

```

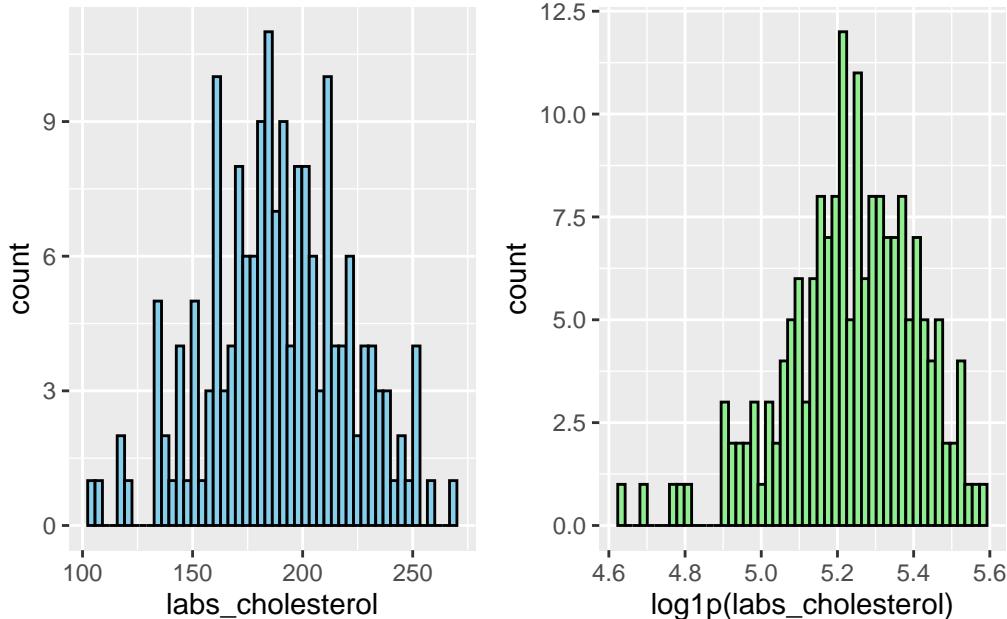
#) %>%
ggplot(aes(x = labs_cholesterol)) +
  geom_histogram(bins = 50, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
labs_cholesterol_hist_2 <- data_model %>%
  #filter(
  #  labs_cholesterol < 300
  #) %>%
  ggplot(aes(x = log1p(labs_cholesterol))) +
  geom_histogram(bins = 50, fill = "lightgreen", color = "black")

# Combine side by side
labs_cholesterol_hist_1 + labs_cholesterol_hist_2 # library(patchwork)

```

Warning: Removed 10 rows containing non-finite outside the scale range (`stat_bin()`).
 Removed 10 rows containing non-finite outside the scale range (`stat_bin()`).



```

# LMM
labs_cholesterol_model <- lmer(labs_cholesterol ~ allocation_group * visit +
  (1 | record_id), data = data_model)
check_collinearity(labs_cholesterol_model)

# Check for Multicollinearity

```

Low Correlation

Term	VIF	VIF 95% CI	Increased SE	Tolerance
allocation_group	1.15	[1.05, 1.50]	1.07	0.87
visit	3.49	[2.78, 4.48]	1.87	0.29
allocation_group:visit	3.73	[2.96, 4.80]	1.93	0.27

Tolerance 95% CI

[0.67, 0.96]
[0.22, 0.36]
[0.21, 0.34]

```
# Sensitivity analysis
labs_cholesterol_model_check <- sensitivity_check_lmer(
  model = labs_cholesterol_model,
  id_var = "record_id",
  top_n = 5)

# LMM Sensitivity
labs_cholesterol_model_sens <- update(object = labs_cholesterol_model,
                                         subset = !(record_id %in%
                                         labs_cholesterol_model_check$influential_ids))

# Influential IDs
labs_cholesterol_model_check$influential_ids

[1] "17" "37" "56" "61" "13"
```

3.5.1 Resumo dos modelos

```
# Model comparison
summary(labs_cholesterol_model)

Linear mixed model fit by REML. t-tests use Satterthwaite's method [
lmerModLmerTest]

Formula: labs_cholesterol ~ allocation_group * visit + (1 | record_id)

Data: data_model

REML criterion at convergence: 1617.3
```

Scaled residuals:

Min	1Q	Median	3Q	Max
-3.2546	-0.4103	0.0145	0.4447	2.5046

Random effects:

Groups	Name	Variance	Std.Dev.
record_id	(Intercept)	743.1	27.26
Residual		257.0	16.03

Number of obs: 179, groups: record_id, 75

Fixed effects:

	Estimate	Std. Error	df	t value	Pr(> t)
(Intercept)	191.2270	5.1990	96.6933	36.782	<2e-16
allocation_group	-0.7165	7.3039	96.6933	-0.098	0.922
visit2	-5.9068	4.0291	105.4088	-1.466	0.146
visit3	-0.3796	4.3671	106.4164	-0.087	0.931
allocation_group:visit2	-0.1153	5.9143	106.8530	-0.019	0.984
allocation_group:visit3	-7.7590	6.3553	107.5905	-1.221	0.225

(Intercept) ***

allocation_group

visit2

visit3

allocation_group:visit2

allocation_group:visit3

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

(Intr)	all_GB	visit2	visit3	a_GB:2	
allctn_grGB	-0.712				
visit2	-0.332	0.236			
visit3	-0.306	0.218	0.451		
allctn_GB:2	0.226	-0.317	-0.681	-0.308	
allctn_GB:3	0.210	-0.295	-0.310	-0.687	0.436

```

summary(labs_cholesterol_model_sens)

Linear mixed model fit by REML. t-tests use Satterthwaite's method [
lmerModLmerTest]

Formula: labs_cholesterol ~ allocation_group * visit + (1 | record_id)

Data: data_model

Subset: !(record_id %in% labs_cholesterol_model_check$influential_ids)

```

REML criterion at convergence: 1418.7

Scaled residuals:

Min	1Q	Median	3Q	Max
-2.44867	-0.52709	0.01502	0.52817	2.19955

Random effects:

Groups	Name	Variance	Std.Dev.
record_id	(Intercept)	728.2	26.98
	Residual	139.8	11.82

Number of obs: 164, groups: record_id, 70

Fixed effects:

	Estimate	Std. Error	df	t value	Pr(> t)
(Intercept)	191.1697	5.1285	80.3020	37.276	<2e-16
allocation_group	-0.6778	7.0540	80.3020	-0.096	0.9237
visit2	-5.9843	3.1939	93.1276	-1.874	0.0641
visit3	-3.9379	3.5150	93.6547	-1.120	0.2654
allocation_group:visit2	-1.5573	4.5754	93.8263	-0.340	0.7343
allocation_group:visit3	-2.1290	4.9645	94.1891	-0.429	0.6690

(Intercept) ***

allocation_group

visit2 .

visit3

allocation_group:visit2

allocation_group:visit3

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

```
(Intr) all_GB visit2 visit3 a_GB:2  
allctn_grGB -0.727  
visit2      -0.259  0.188  
visit3      -0.235  0.171  0.448  
allctn_GB:2  0.180 -0.248 -0.698 -0.312  
allctn_GB:3  0.166 -0.229 -0.317 -0.708  0.436
```

```
performance::compare_performance(  
  labs_cholesterol_model,  
  labs_cholesterol_model_sens)
```

When comparing models, please note that probably not all models were fit from same data.

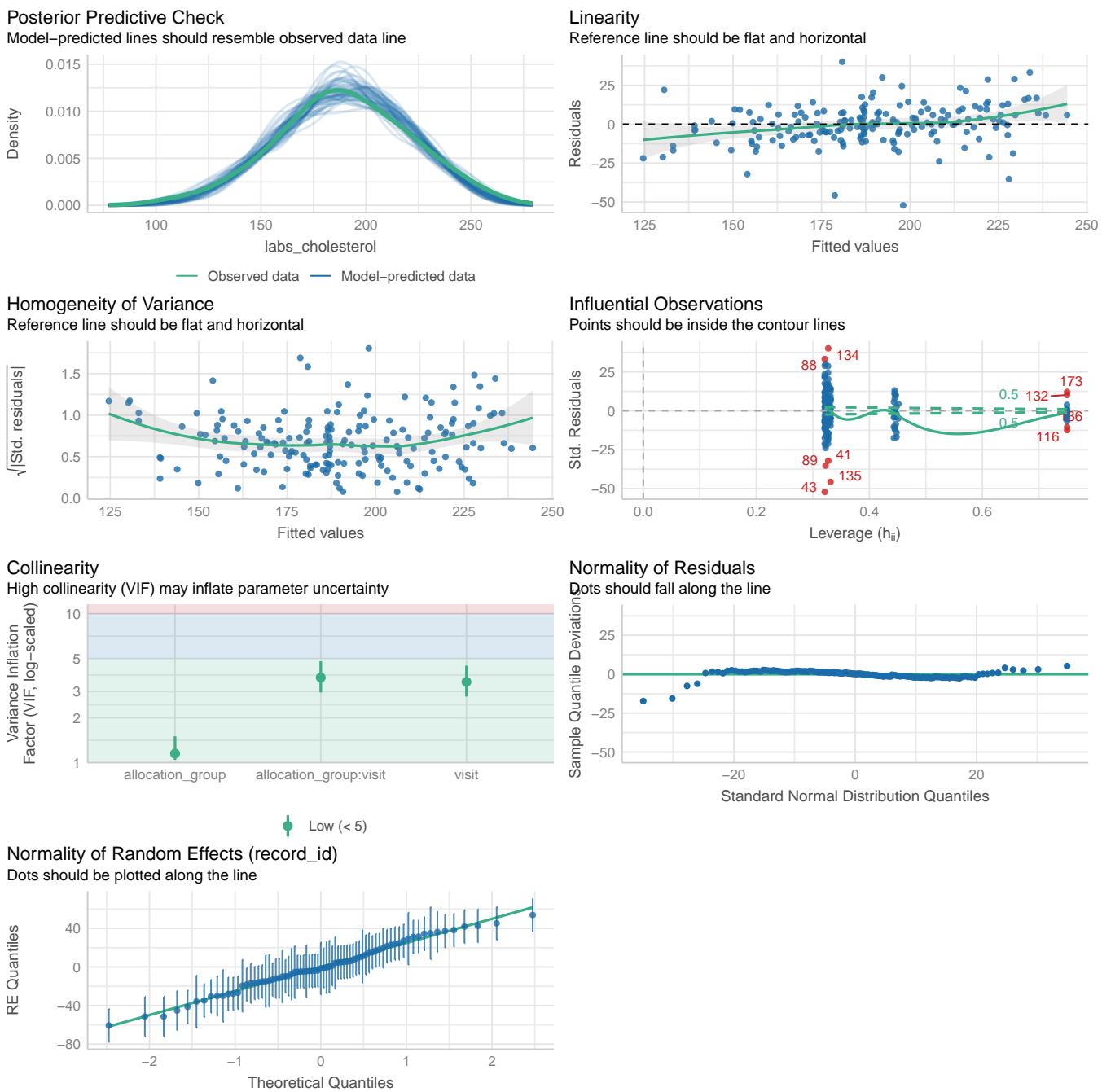
```
# Comparison of Model Performance Indices
```

Name	Model	AIC (weights)	AICc (weights)
labs_cholesterol_model	lmerModLmerTest	1661.8 (<.001)	1662.7 (<.001)
labs_cholesterol_model_sens	lmerModLmerTest	1461.2 (>.999)	1462.1 (>.999)

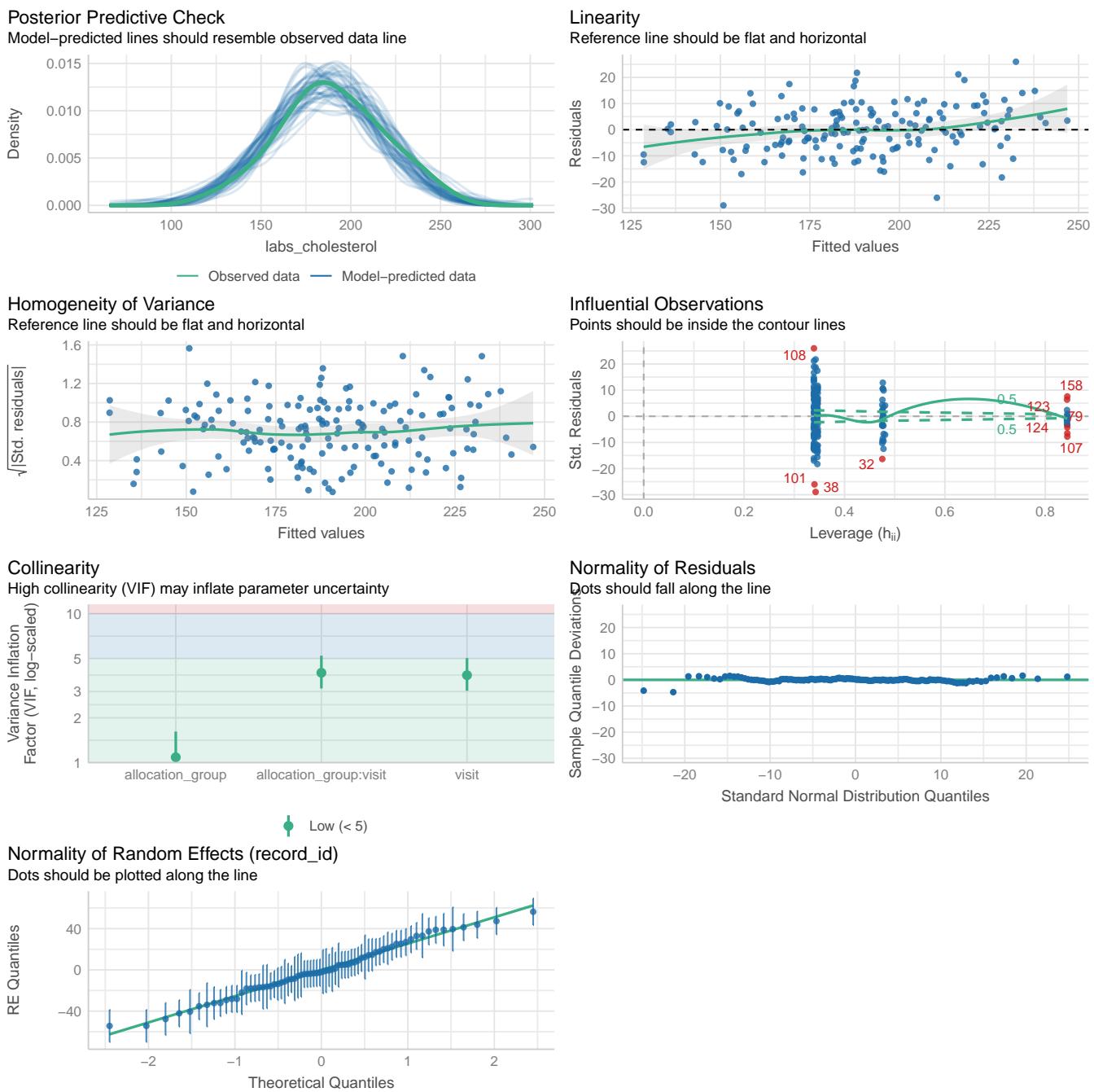
Name	BIC (weights)	R2 (cond.)	R2 (marg.)	ICC
labs_cholesterol_model	1687.3 (<.001)	0.746	0.011	0.743
labs_cholesterol_model_sens	1486.0 (>.999)	0.841	0.011	0.839

Name	RMSE	Sigma
labs_cholesterol_model	12.602	16.030
labs_cholesterol_model_sens	9.049	11.822

```
performance::check_model(labs_cholesterol_model)
```



```
performance::check_model(labs_cholesterol_model_sens)
```



3.5.2 Médias Marginais Estimadas

3.5.2.1 Todos os dados

```
# Get EMMs for each group at each visit
labs_cholesterol_raw_emm <- emmeans::emmeans(
  labs_cholesterol_model,
  ~ allocation_group * visit
```

```

)

labs_cholesterol_raw_emm <- regrid(labs_cholesterol_raw_emm)

# Table of marginal means
# labs_cholesterol_raw_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(labs_cholesterol_raw_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

visit = 1:
  contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
  Grupo A - Grupo B    0.717 7.30  95.4   -13.78     15.2    0.098  0.9221

visit = 2:
  contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
  Grupo A - Grupo B    0.832 7.81 107.2   -14.65     16.3    0.107  0.9154

visit = 3:
  contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
  Grupo A - Grupo B    8.476 8.15 121.8    -7.66     24.6    1.040  0.3004

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95

# Pairwise comparisons: Changes over time within each group
emmeans::contrast(labs_cholesterol_raw_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

allocation_group = Grupo A:
  contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
  visit1 - visit2    5.91 4.03  95.4    -3.92     15.73    1.465  0.4387
  visit1 - visit3    0.38 4.37  95.4   -10.27     11.03    0.087  1.0000
  visit2 - visit3   -5.53 4.41 107.2   -16.25     5.19   -1.254  0.6378

```

```

allocation_group = Grupo B:

contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit2     6.02 4.34  95.4     -4.54    16.59    1.389  0.5041
visit1 - visit3     8.14 4.62  95.4     -3.13    19.41    1.760  0.2448
visit2 - visit3     2.12 4.82 121.6     -9.58    13.81    0.439  1.0000

```

Degrees-of-freedom method: inherited from kenward-roger when re-gridding

Confidence level used: 0.95

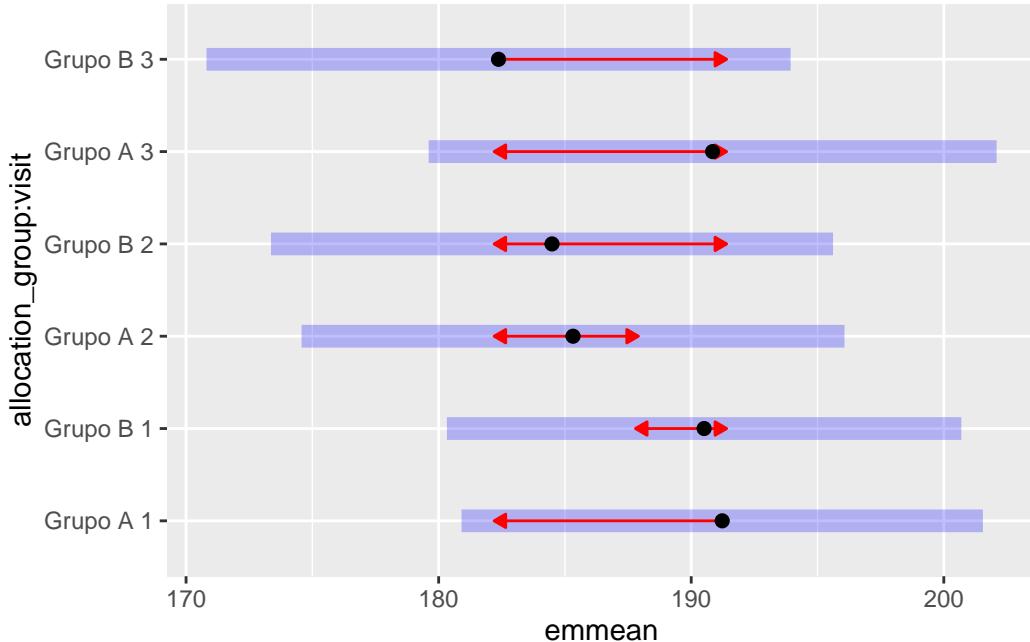
Conf-level adjustment: bonferroni method for 3 estimates

P value adjustment: bonferroni method for 3 tests

```

# Plot of marginal means
plot(labs_cholesterol_raw_emm, comparisons = TRUE)

```



3.5.2.2 Análise de sensibilidade

```

# Get EMMs for each group at each visit (Sensitivity Analysis)
labs_cholesterol_emm <- emmeans::emmeans(
  labs_cholesterol_model_sens,
  ~ allocation_group * visit
)

labs_cholesterol_emm <- regrid(labs_cholesterol_emm)

```

```

# Table of marginal means
# labs_cholesterol_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(labs_cholesterol_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

visit = 1:
  contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    0.678 7.05 79.8     -13.4     14.7    0.096  0.9237

visit = 2:
  contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    2.235 7.40 88.6     -12.5     16.9    0.302  0.7632

visit = 3:
  contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    2.807 7.64 99.7     -12.4     18.0    0.367  0.7142

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95

# Pairwise comparisons: Changes over time within each group
emmeans::contrast(labs_cholesterol_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

allocation_group = Grupo A:
  contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit2     5.98 3.20 79.8    -1.832    13.80    1.872  0.1944
visit1 - visit3     3.94 3.52 79.8    -4.665    12.54    1.119  0.7990
visit2 - visit3    -2.05 3.54 88.6   -10.679     6.59   -0.579  1.0000

allocation_group = Grupo B:
  contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit2     7.54 3.28 79.8    -0.478    15.56    2.300  0.0723
visit1 - visit3     6.07 3.51 79.8    -2.516    14.65    1.729  0.2632

```

```
visit2 - visit3      -1.47 3.65 97.7  -10.355      7.41  -0.404  1.0000
```

Degrees-of-freedom method: inherited from kenward-roger when re-gridding

Confidence level used: 0.95

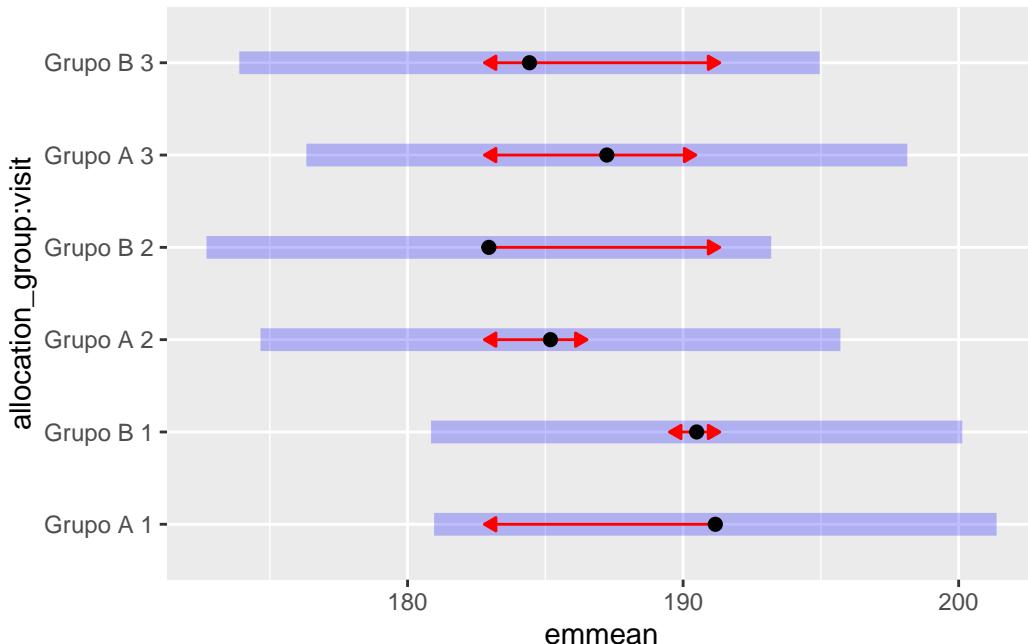
Conf-level adjustment: bonferroni method for 3 estimates

P value adjustment: bonferroni method for 3 tests

```
# Plot of marginal means  
plot(labs_cholesterol_emm, comparisons = TRUE)
```

Warning: Comparison discrepancy in group "1", Grupo B visit1 - Grupo A visit2:

Target overlap = 0.7468, overlap on graph = -1.2872



3.5.3 Resultado

No modelo ajustado para os níveis de colesterol total, não foram observadas diferenças estatisticamente significativas entre os grupos em nenhum dos três momentos avaliados. As comparações intragrupo ao longo do tempo também não indicaram alterações significativas em nenhum dos grupos. A análise de sensibilidade, realizada com a exclusão de observações influentes, confirmou esses achados. As estimativas se mantiveram estáveis e as diferenças permaneceram não significativas. As estimativas, intervalos de confiança de 95% e valores de p estão apresentados na Tabela 5.

Tabela 5: Diferenças estimadas dos níveis de Colesterol Total entre os grupos de alocação (placebo vs Eclipta) e entre visitas dentro de cada grupo

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 1	0,72	[-13,78 ; 15,21]	0,922
Entre grupos	Visita 2	0,83	[-14,65 ; 16,30]	0,915
Entre grupos	Visita 3	8,48	[-7,66 ; 24,61]	0,300
Grupo Placebo	Visita 1 - Visita 2	5,91	[-3,92 ; 15,73]	0,439
Grupo Placebo	Visita 1 - Visita 3	0,38	[-10,27 ; 11,03]	1,000
Grupo Placebo	Visita 2 - Visita 3	-5,53	[-16,25 ; 5,19]	0,638
Grupo Eclipta	Visita 1 - Visita 2	6,02	[-4,54 ; 16,59]	0,504
Grupo Eclipta	Visita 1 - Visita 3	8,14	[-3,13 ; 19,41]	0,245
Grupo Eclipta	Visita 2 - Visita 3	2,12	[-9,58 ; 13,81]	1,000

```

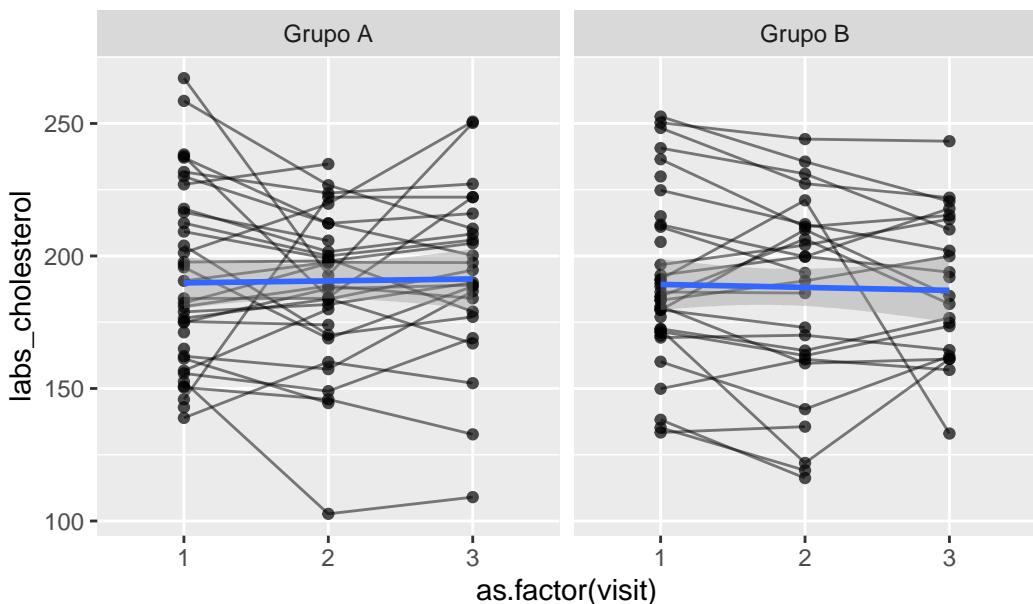
ggplot(
  data = data_model,
  aes(
    x = as.factor(visit),
    y = labs_cholesterol,
    group = record_id,
  )
) +
  geom_line(alpha = 0.5) +
  geom_point(alpha = 0.7) +
  geom_smooth(
    aes(group = allocation_group),
    method = "lm",
    se = TRUE,
    linewidth = 1
  ) +
  labs(title = "All data") +
  facet_wrap(~ allocation_group)

`geom_smooth()` using formula = 'y ~ x'
Warning: Removed 10 rows containing non-finite outside the scale range
(`stat_smooth()`).
Warning: Removed 8 rows containing missing values or values outside the scale range

```

```
(`geom_line()`).
Warning: Removed 10 rows containing missing values or values outside the scale range
(`geom_point()`).
```

All data



```
#coord_cartesian(ylim = c(10, 150))

data_model %>%
  filter(
    !(record_id %in%
      labs_cholesterol_model_check$influential_ids)
  ) %>%
  ggplot(
    aes(
      x = as.factor(visit),
      y = labs_cholesterol,
      group = record_id,
    )
  ) +
  geom_line(alpha = 0.5) +
  geom_point(alpha = 0.7) +
  geom_smooth(
    aes(group = allocation_group),
    method = "lm",
  )
```

```

    se = TRUE,
    linewidth = 1
) +
  labs(title = "Sensitivity analysis") +
  facet_wrap(~ allocation_group)

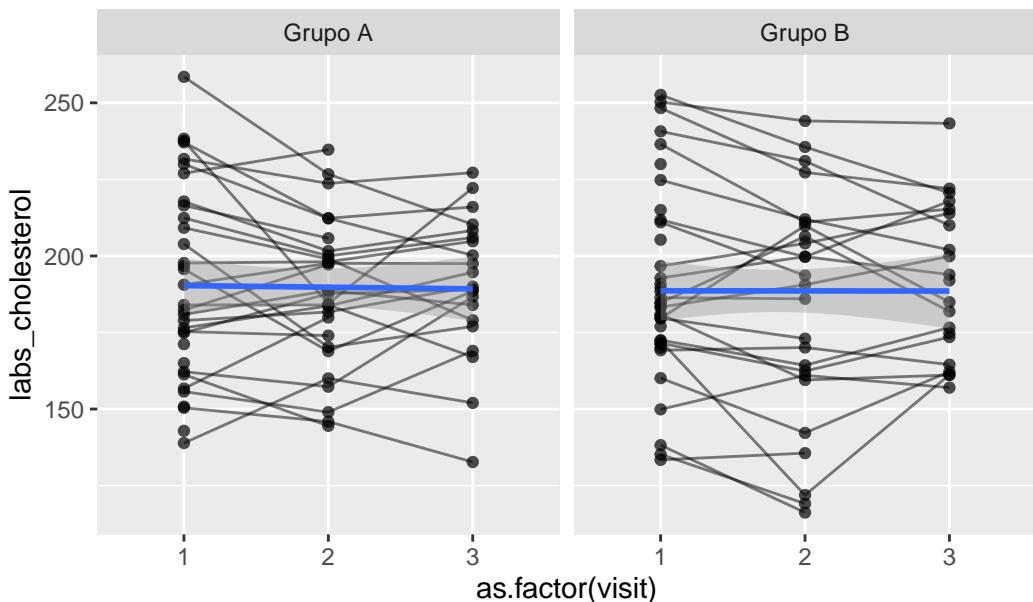
`geom_smooth()` using formula = 'y ~ x'
Warning: Removed 10 rows containing non-finite outside the scale range
(`stat_smooth()`).

Warning: Removed 8 rows containing missing values or values outside the scale range
(`geom_line()`).

Warning: Removed 10 rows containing missing values or values outside the scale range
(`geom_point()`).

```

Sensitivity analysis



```
#coord_cartesian(ylim = c(10, 150))
```

3.6 LDL Colesterol

Variável: `labs_ldl`

```

# Plot 1: Raw data
labs_ldl_hist_1 <- data_model %>%
  #filter(
  #  labs_ldl < 300

```

```

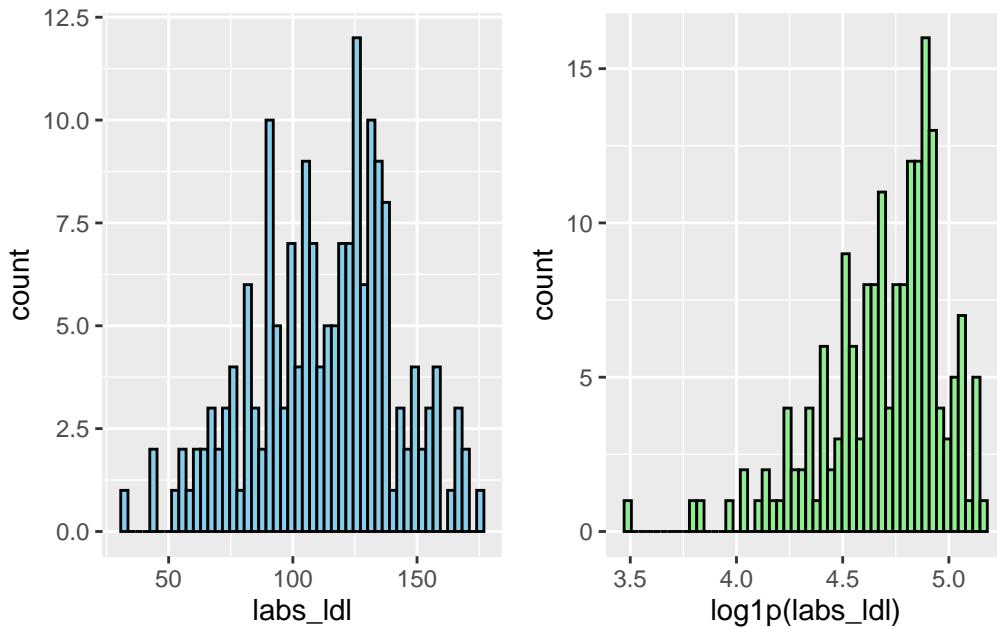
#) %>%
ggplot(aes(x = labs_ldl)) +
  geom_histogram(bins = 50, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
labs_ldl_hist_2 <- data_model %>%
  #filter(
  #  labs_ldl < 300
  #) %>%
  ggplot(aes(x = log1p(labs_ldl))) +
  geom_histogram(bins = 50, fill = "lightgreen", color = "black")

# Combine side by side
labs_ldl_hist_1 + labs_ldl_hist_2 # library(patchwork)

```

Warning: Removed 10 rows containing non-finite outside the scale range (`stat_bin()`).
 Removed 10 rows containing non-finite outside the scale range (`stat_bin()`).



```

# LMM
labs_ldl_model <- lmer(labs_ldl ~ allocation_group * visit +
(1 | record_id), data = data_model)
check_collinearity(labs_ldl_model)

# Check for Multicollinearity

```

Low Correlation

Term	VIF	VIF 95% CI	Increased SE	Tolerance
allocation_group	1.18	[1.06, 1.52]	1.08	0.85
visit	3.49	[2.78, 4.49]	1.87	0.29
allocation_group:visit	3.77	[3.00, 4.86]	1.94	0.26

Tolerance 95% CI

[0.66, 0.94]
[0.22, 0.36]
[0.21, 0.33]

```
# Sensitivity analysis
labs_ldl_model_check <- sensitivity_check_lmer(
  model = labs_ldl_model,
  id_var = "record_id",
  top_n = 7)

# LMM Sensitivity
labs_ldl_model_sens <- update(object = labs_ldl_model,
                                 subset = !(record_id %in%
                                labs_ldl_model_check$influential_ids))

# Influential IDs
labs_ldl_model_check$influential_ids

[1] "16" "17" "56" "37" "50" "61" "75"
```

3.6.1 Resumo dos modelos

```
# Model comparison
summary(labs_ldl_model)

Linear mixed model fit by REML. t-tests use Satterthwaite's method [
lmerModLmerTest]

Formula: labs_ldl ~ allocation_group * visit + (1 | record_id)

Data: data_model

REML criterion at convergence: 1601.5
```

Scaled residuals:

Min	1Q	Median	3Q	Max
-2.9892	-0.3229	-0.0296	0.3610	2.5195

Random effects:

Groups	Name	Variance	Std.Dev.
record_id	(Intercept)	605.7	24.61
Residual		249.7	15.80

Number of obs: 179, groups: record_id, 75

Fixed effects:

	Estimate	Std. Error	df	t value	Pr(> t)	
(Intercept)	115.4919	4.8081	98.3445	24.020	<2e-16	
allocation_group	Grupo B	-3.7735	6.7548	98.3445	-0.559	0.578
visit2		-5.5925	3.9659	103.9503	-1.410	0.161
visit3		-0.0205	4.2968	105.1671	-0.005	0.996
allocation_group	Grupo B:visit2	1.9191	5.8182	105.6037	0.330	0.742
allocation_group	Grupo B:visit3	-5.9060	6.2502	106.5086	-0.945	0.347

(Intercept) ***

allocation_group

visit2

visit3

allocation_group

Grupo B:visit2

allocation_group

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

(Intr)	all_GB	visit2	visit3	a_GB:2
allctn_grGB	-0.712			
visit2	-0.354	0.252		
visit3	-0.327	0.233	0.450	
allctn_GB:2	0.241	-0.339	-0.682	-0.307
allctn_GB:3	0.225	-0.315	-0.310	-0.687
				0.434

```

summary(labs_ldl_model_sens)

Linear mixed model fit by REML. t-tests use Satterthwaite's method [
lmerModLmerTest]

Formula: labs_ldl ~ allocation_group * visit + (1 | record_id)

Data: data_model

Subset: !(record_id %in% labs_ldl_model_check$influential_ids)

REML criterion at convergence: 1338.9

Scaled residuals:
    Min      1Q  Median      3Q     Max 
-1.83006 -0.44200 -0.05731  0.40788  2.36163 

Random effects:
Groups   Name        Variance Std.Dev.
record_id (Intercept) 650.2     25.50
Residual           111.8     10.57
Number of obs: 158, groups: record_id, 68

Fixed effects:
            Estimate Std. Error       df t value Pr(>|t|)    
(Intercept) 115.8687  4.8799 75.3685 23.744 <2e-16  
allocation_groupGrupo B -3.8299  6.7068 75.3685 -0.571  0.5697 
visit2       -5.1922  2.9125 87.5739 -1.783  0.0781 
visit3       0.6698  3.2198 88.0305  0.208  0.8357 
allocation_groupGrupo B:visit2  1.8681  4.1755 88.1990  0.447  0.6557 
allocation_groupGrupo B:visit3 -5.5726  4.5483 88.5080 -1.225  0.2237 

(Intercept) *** 
allocation_groupGrupo B
visit2       .
visit3       .
allocation_groupGrupo B:visit2
allocation_groupGrupo B:visit3
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```

Correlation of Fixed Effects:

```
(Intr) all_GB visit2 visit3 a_GB:2  
allctn_grGB -0.728  
visit2      -0.246  0.179  
visit3      -0.222  0.162  0.446  
allctn_GB:2  0.171 -0.236 -0.698 -0.311  
allctn_GB:3  0.157 -0.216 -0.316 -0.708  0.434
```

```
performance::compare_performance(  
  labs_ldl_model,  
  labs_ldl_model_sens)
```

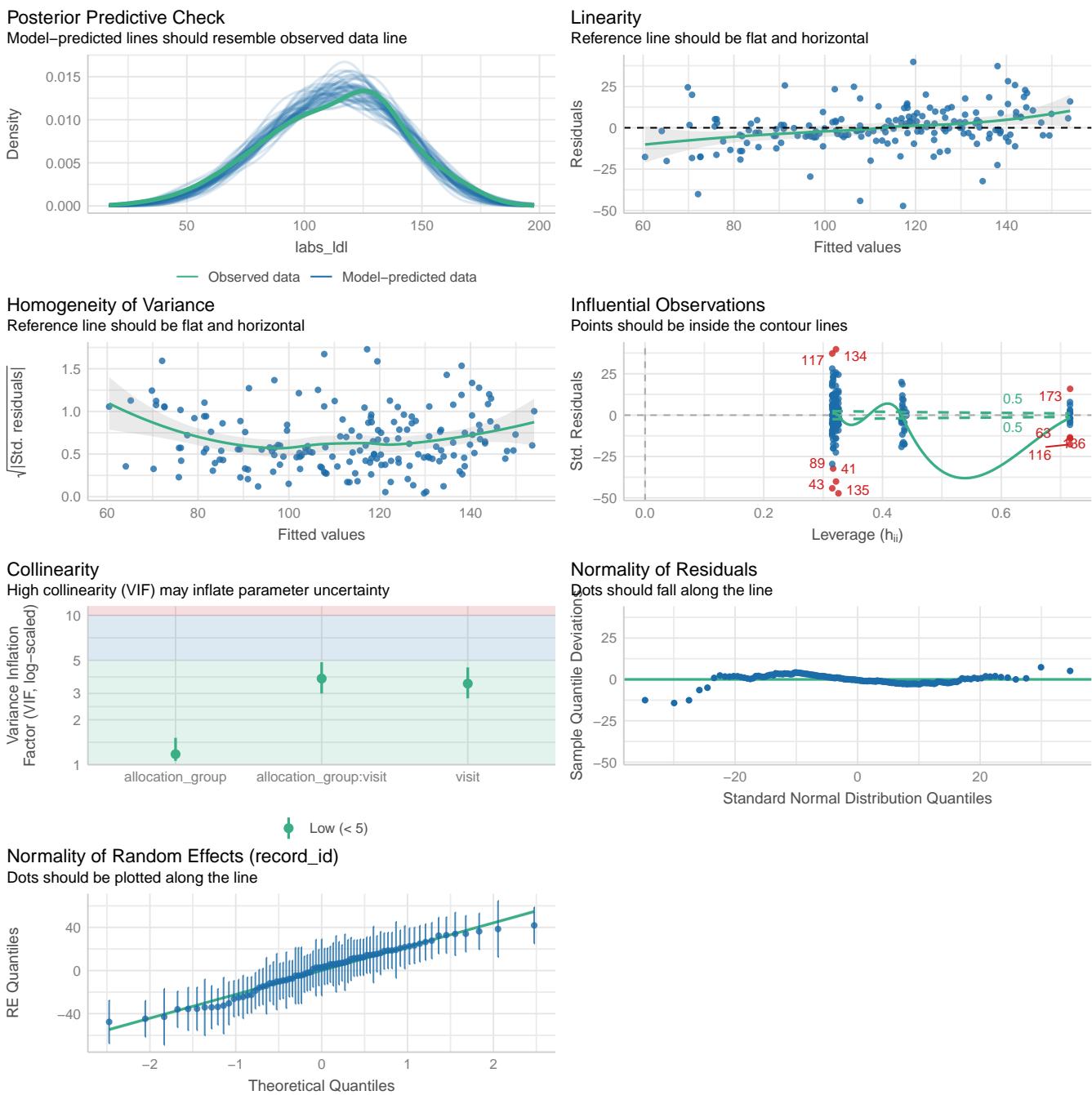
When comparing models, please note that probably not all models were fit from same data.

```
# Comparison of Model Performance Indices
```

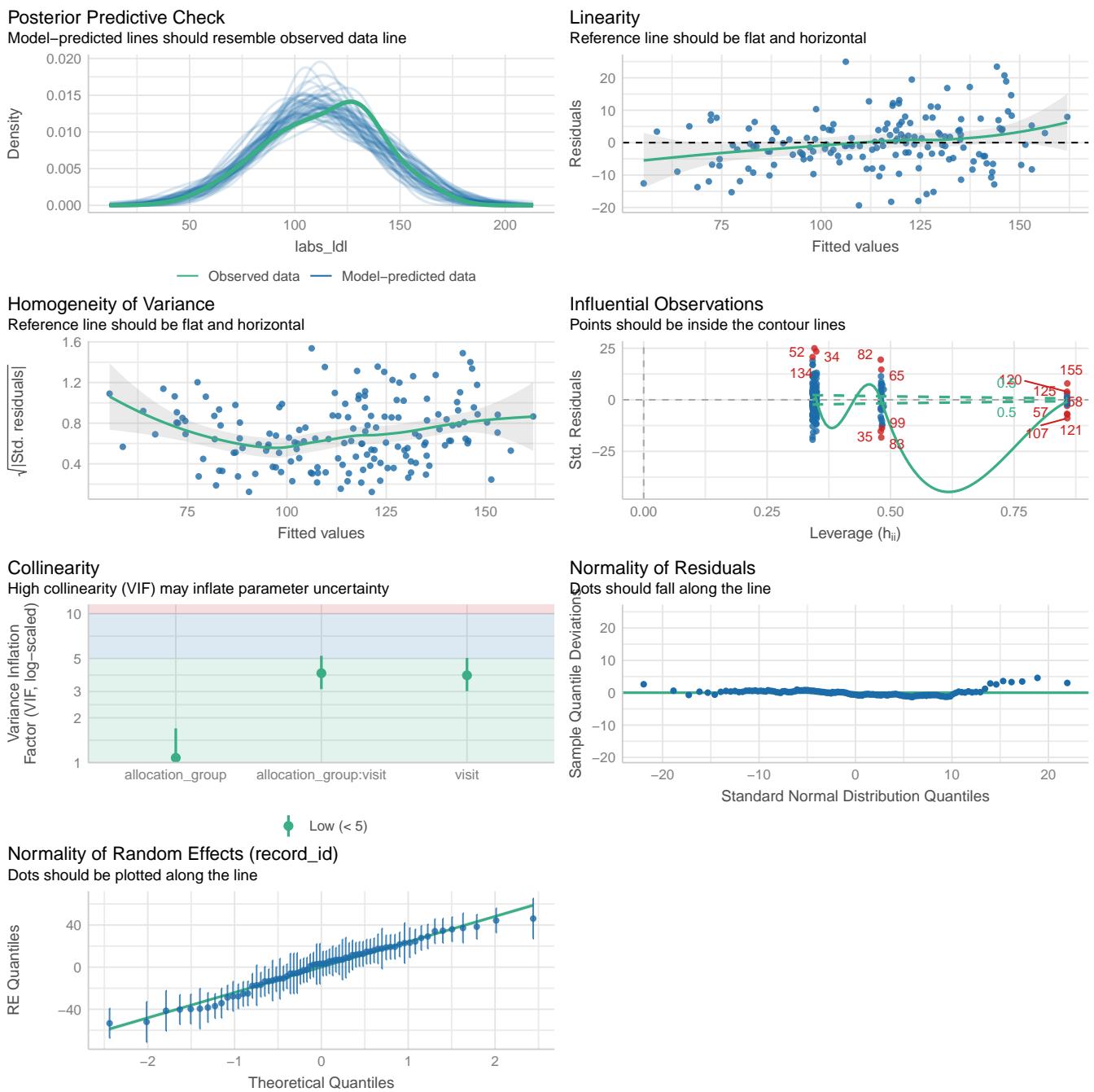
Name	Model	AIC (weights)	AICc (weights)
labs_ldl_model	lmerModLmerTest	1645.5 (<.001)	1646.4 (<.001)
labs_ldl_model_sens	lmerModLmerTest	1380.5 (>.999)	1381.5 (>.999)

Name	BIC (weights)	R2 (cond.)	R2 (marg.)	ICC	RMSE	Sigma
labs_ldl_model	1671.0 (<.001)	0.712	0.014	0.708	12.514	15.802
labs_ldl_model_sens	1405.0 (>.999)	0.855	0.014	0.853	8.043	10.574

```
performance::check_model(labs_ldl_model)
```



```
performance::check_model(labs_ldl_model_sens)
```



3.6.2 Médias Marginais Estimadas

3.6.2.1 Todos os dados

```
# Get EMMs for each group at each visit
labs_ldl_raw_emm <- emmeans::emmeans(
  labs_ldl_model,
  ~ allocation_group * visit
```

```

)

labs_ldl_raw_emm <- regrid(labs_ldl_raw_emm)

# Table of marginal means
# labs_ldl_raw_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(labs_ldl_raw_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

visit = 1:
  contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
  Grupo A - Grupo B     3.77 6.75 99.1    -9.63     17.2   0.559  0.5777

visit = 2:
  contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
  Grupo A - Grupo B     1.85 7.27 111.9   -12.56     16.3   0.255  0.7993

visit = 3:
  contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
  Grupo A - Grupo B     9.68 7.63 127.7    -5.41     24.8   1.269  0.2067

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95

# Pairwise comparisons: Changes over time within each group
emmeans::contrast(labs_ldl_raw_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

allocation_group = Grupo A:
  contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
  visit1 - visit2  5.5925 3.97 99.1    -4.07    15.26   1.409  0.4859
  visit1 - visit3  0.0205 4.30 99.1   -10.46    10.50   0.005  1.0000
  visit2 - visit3 -5.5720 4.34 111.9   -16.13     4.98  -1.283  0.6064

```

```

allocation_group = Grupo B:

contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit2  3.6734 4.26 99.1     -6.71    14.06  0.862 1.0000
visit1 - visit3  5.9265 4.55 99.1     -5.15    17.00  1.304 0.5862
visit2 - visit3  2.2531 4.74 127.2     -9.26   13.76  0.475 1.0000

```

Degrees-of-freedom method: inherited from kenward-roger when re-gridding

Confidence level used: 0.95

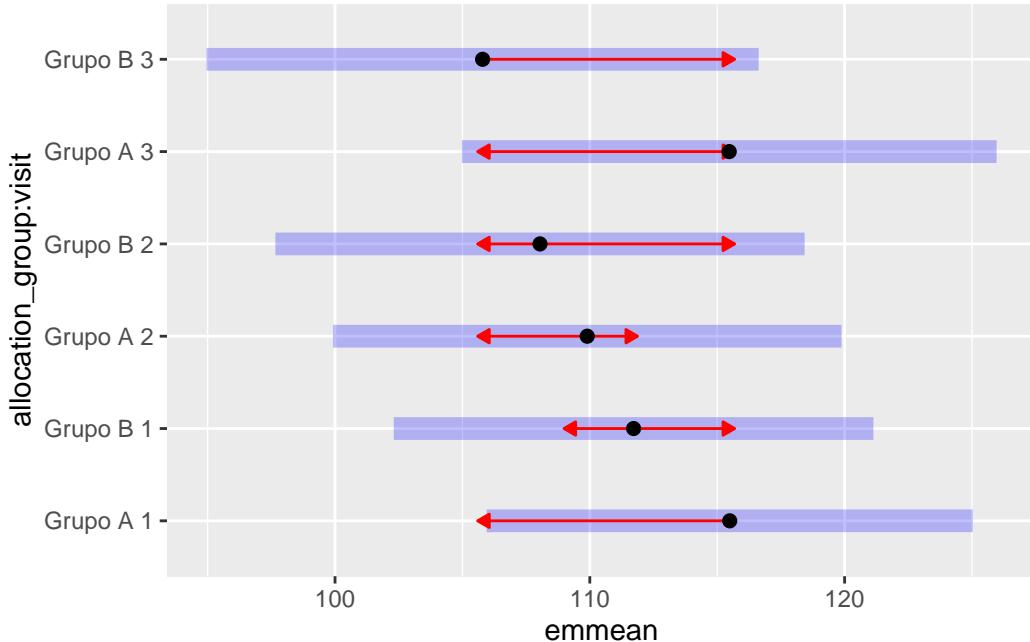
Conf-level adjustment: bonferroni method for 3 estimates

P value adjustment: bonferroni method for 3 tests

```

# Plot of marginal means
plot(labs_ldl_raw_emm, comparisons = TRUE)

```



3.6.2.2 Análise de sensibilidade

```

# Get EMMs for each group at each visit (Sensitivity Analysis)
labs_ldl_emm <- emmeans::emmeans(
  labs_ldl_model_sens,
  ~ allocation_group * visit
)

labs_ldl_emm <- regrid(labs_ldl_emm)

```

```

# Table of marginal means

# labs_ldl_emm

# Pairwise comparisons: Between groups at each visit

emmeans::contrast(labs_ldl_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

visit = 1:

contrast estimate SE df lower.CL upper.CL t.ratio p.value
Grupo A - Grupo B 3.83 6.71 76.2 -9.53 17.2 0.571 0.5697

```

```

visit = 2:

contrast estimate SE df lower.CL upper.CL t.ratio p.value
Grupo A - Grupo B 1.96 7.02 84.3 -11.99 15.9 0.280 0.7805

```

```

visit = 3:

contrast estimate SE df lower.CL upper.CL t.ratio p.value
Grupo A - Grupo B 9.40 7.25 94.8 -4.98 23.8 1.298 0.1976

```

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
 Confidence level used: 0.95

```

# Pairwise comparisons: Changes over time within each group

emmeans::contrast(labs_ldl_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

allocation_group = Grupo A:

contrast estimate SE df lower.CL upper.CL t.ratio p.value
visit1 - visit2 5.19 2.91 76.2 -1.94 12.33 1.782 0.2364
visit1 - visit3 -0.67 3.22 76.2 -8.56 7.22 -0.208 1.0000
visit2 - visit3 -5.86 3.24 84.3 -13.77 2.05 -1.810 0.2217

```

```

allocation_group = Grupo B:

contrast estimate SE df lower.CL upper.CL t.ratio p.value
visit1 - visit2 3.32 2.99 76.2 -4.01 10.66 1.110 0.8116
visit1 - visit3 4.90 3.22 76.2 -2.97 12.78 1.525 0.3945

```

```
visit2 - visit3      1.58 3.34 92.9     -6.57      9.73   0.472  1.0000
```

Degrees-of-freedom method: inherited from kenward-roger when re-gridding

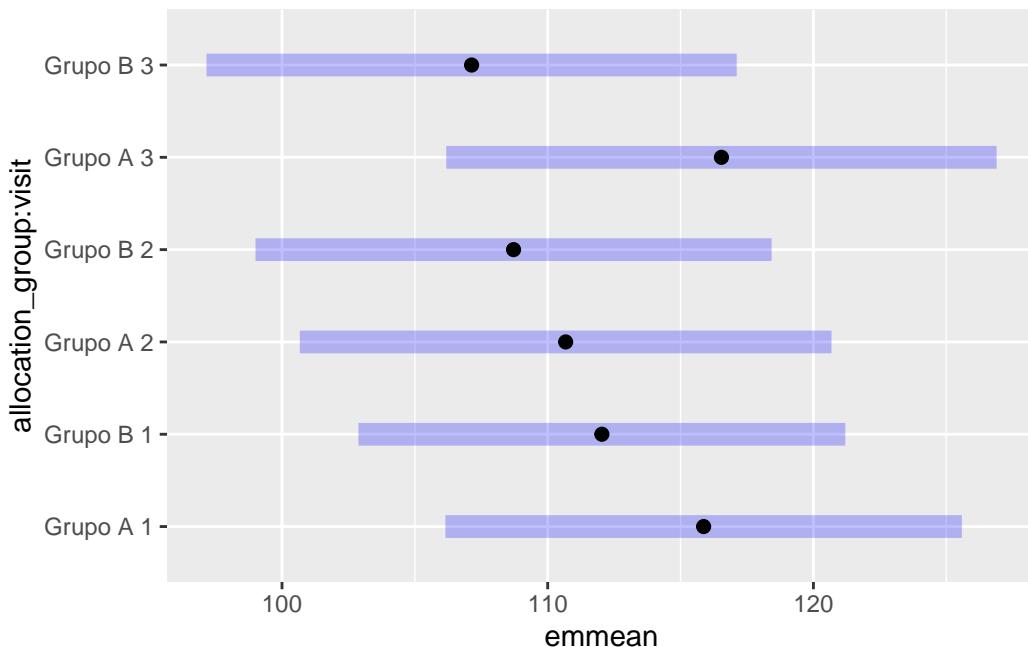
Confidence level used: 0.95

Conf-level adjustment: bonferroni method for 3 estimates

P value adjustment: bonferroni method for 3 tests

```
# Plot of marginal means
```

```
plot(labs_ldl_emm)
```



3.6.3 Resultado

No modelo ajustado para os níveis de LDL-colesterol, não foram observadas diferenças estatisticamente significativas entre os grupos em nenhum dos três momentos avaliados. Da mesma forma, as comparações dentro de cada grupo ao longo do tempo não indicaram alterações significativas. A análise de sensibilidade, com exclusão das observações influentes, não modificou substancialmente os achados: as estimativas permaneceram estáveis e todas as comparações continuaram não significativas. As estimativas, intervalos de confiança de 95% e valores de p estão apresentados na Tabela 6.

Tabela 6: Diferenças estimadas dos níveis de LDL-colesterol entre os grupos de alocação (placebo vs Eclipta) e entre visitas dentro de cada grupo

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 1	3,77	[-9,63 ; 17,17]	0,578
Entre grupos	Visita 2	1,85	[-12,56 ; 16,26]	0,799

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 3	9,68	[-5,41 ; 24,78]	0,207
Grupo Placebo	Visita 1 - Visita 2	5,59	[-4,07 ; 15,26]	0,486
Grupo Placebo	Visita 1 - Visita 3	0,02	[-10,46 ; 10,50]	1,000
Grupo Placebo	Visita 2 - Visita 3	-5,57	[-16,13 ; 4,98]	0,606
Grupo Eclipta	Visita 1 - Visita 2	3,67	[-6,71 ; 14,06]	1,000
Grupo Eclipta	Visita 1 - Visita 3	5,93	[-5,15 ; 17,00]	0,586
Grupo Eclipta	Visita 2 - Visita 3	2,25	[-9,26 ; 13,76]	1,000

```

ggplot(
  data = data_model,
  aes(
    x = as.factor(visit),
    y = labs_ldl,
    group = record_id,
  )
) +
  geom_line(alpha = 0.5) +
  geom_point(alpha = 0.7) +
  geom_smooth(
    aes(group = allocation_group),
    method = "lm",
    se = TRUE,
    linewidth = 1
  ) +
  labs(title = "All data") +
  facet_wrap(~ allocation_group)

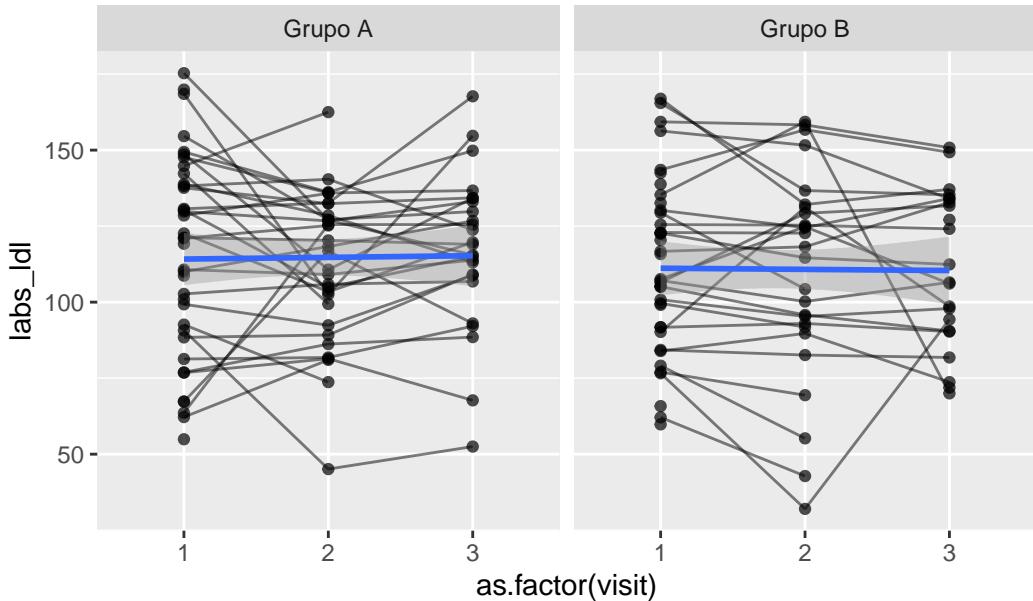
```

```

`geom_smooth()` using formula = 'y ~ x'
Warning: Removed 10 rows containing non-finite outside the scale range
(`stat_smooth()`).
Warning: Removed 8 rows containing missing values or values outside the scale range
(`geom_line()`).
Warning: Removed 10 rows containing missing values or values outside the scale range
(`geom_point()`).

```

All data



```
#coord_cartesian(ylim = c(10, 150))

data_model %>%
  filter(
    !(record_id %in%
      labs_ldl_model_check$influential_ids)
  ) %>%
  ggplot(
    aes(
      x = as.factor(visit),
      y = labs_ldl,
      group = record_id,
    )
  ) +
  geom_line(alpha = 0.5) +
  geom_point(alpha = 0.7) +
  geom_smooth(
    aes(group = allocation_group),
    method = "lm",
    se = TRUE,
    linewidth = 1
  )
```

```

) +
  labs(title = "Sensitivity analysis") +
  facet_wrap(~ allocation_group)

`geom_smooth()` using formula = 'y ~ x'

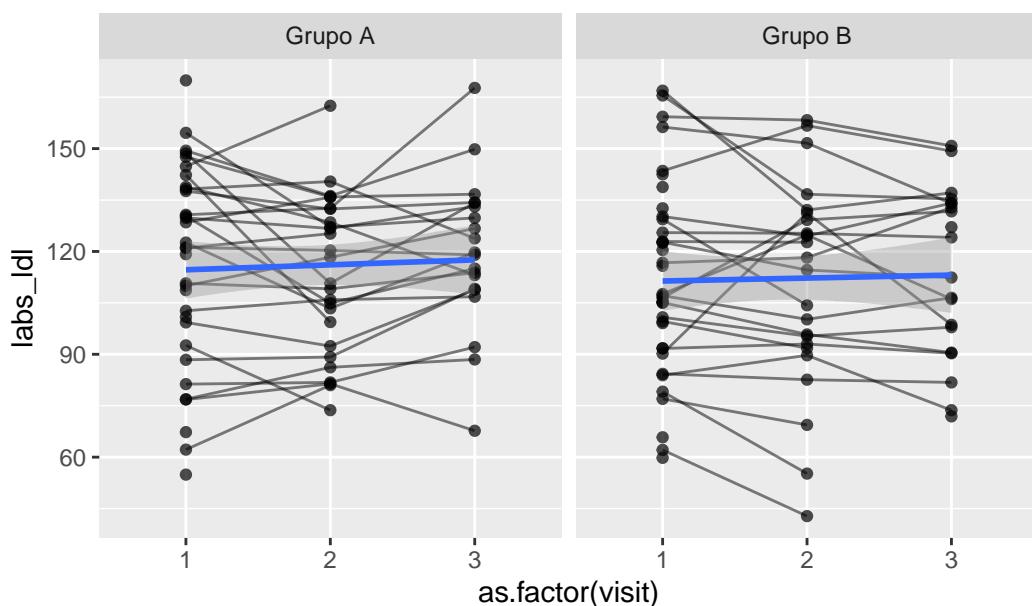
Warning: Removed 10 rows containing non-finite outside the scale range
(`stat_smooth()`).

Warning: Removed 8 rows containing missing values or values outside the scale range
(`geom_line()`).

Warning: Removed 10 rows containing missing values or values outside the scale range
(`geom_point()`).

```

Sensitivity analysis



```
#coord_cartesian(ylim = c(10, 150))
```

3.7 HDL Colesterol

Variável: labs_hdl

```

# Plot 1: Raw data
labs_hdl_hist_1 <- data_model %>%
  #filter(
  #  labs_hdl < 300
  #) %>%
  ggplot(aes(x = labs_hdl)) +

```

```

geom_histogram(bins = 50, fill = "skyblue", color = "black")

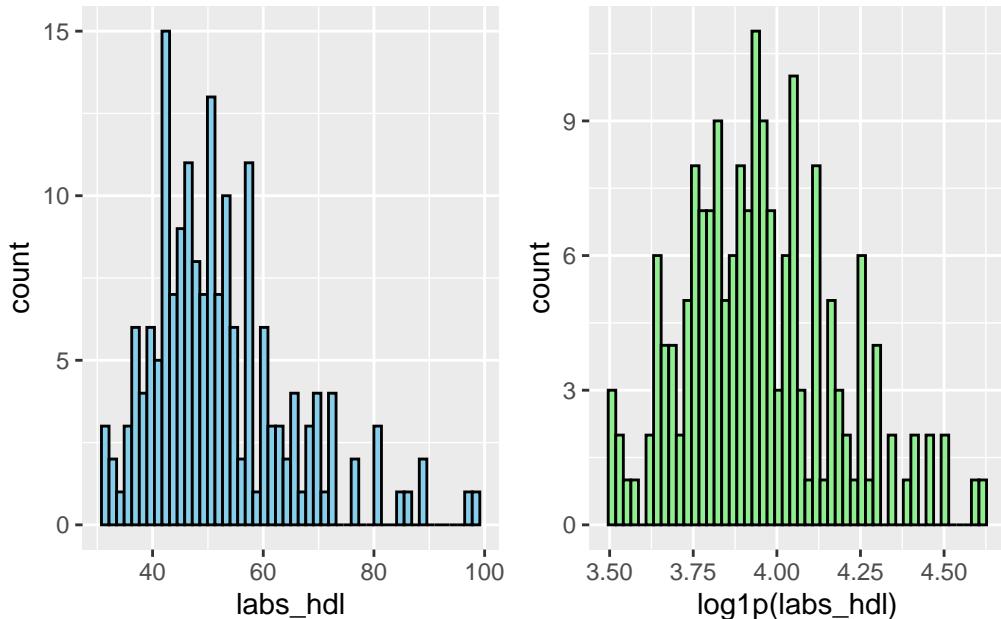
# Plot 2: Log-transformed data
labs_hdl_hist_2 <- data_model %>%
  #filter(
  #  labs_hdl < 300
  #) %>%
  ggplot(aes(x = log1p(labs_hdl))) +
  geom_histogram(bins = 50, fill = "lightgreen", color = "black")

# Combine side by side
labs_hdl_hist_1 + labs_hdl_hist_2 # library(patchwork)

```

Warning: Removed 10 rows containing non-finite outside the scale range (`stat_bin()`).

Removed 10 rows containing non-finite outside the scale range (`stat_bin()`).



```

# LMM
labs_hdl_model <- lmer(log1p(labs_hdl) ~ allocation_group * visit +
(1 | record_id), data = data_model)

check_collinearity(labs_hdl_model)

# Check for Multicollinearity

```

Low Correlation

Term	VIF	VIF 95% CI	Increased SE	Tolerance
allocation_group	1.16	[1.05, 1.51]	1.08	0.86
visit	3.49	[2.78, 4.48]	1.87	0.29
allocation_group:visit	3.74	[2.97, 4.81]	1.93	0.27
Tolerance 95% CI				
	[0.66, 0.95]			
	[0.22, 0.36]			
	[0.21, 0.34]			

```

# Sensitivity analysis
labs_hdl_model_check <- sensitivity_check_lmer(
  model = labs_hdl_model,
  id_var = "record_id",
  top_n = 5)

# LMM Sensitivity
labs_hdl_model_sens <- update(object = labs_hdl_model,
  subset = !(record_id %in%
  labs_hdl_model_check$influential_ids))

# Influential IDS
labs_hdl_model_check$influential_ids
[1] "16" "75" "38" "42" "26"

```

3.7.1 Resumo dos modelos

```

# Model comparison
summary(labs_hdl_model)

Linear mixed model fit by REML. t-tests use Satterthwaite's method [
lmerModLmerTest]

Formula: log1p(labs_hdl) ~ allocation_group * visit + (1 | record_id)
Data: data_model

REML criterion at convergence: -79.8

```

Scaled residuals:

Min	1Q	Median	3Q	Max
-----	----	--------	----	-----

```
-2.4161 -0.4907 -0.0289  0.4389  3.0395
```

Random effects:

Groups	Name	Variance	Std.Dev.
record_id	(Intercept)	0.03949	0.1987
Residual		0.01437	0.1199

Number of obs: 179, groups: record_id, 75

Fixed effects:

	Estimate	Std. Error	df	t value	Pr(> t)
(Intercept)	3.94481	0.03815	94.81644	103.399	<2e-16
allocation_group	0.06500	0.05360	94.81644	1.213	0.228
visit2	-0.01725	0.03011	102.74671	-0.573	0.568
visit3	-0.01928	0.03264	103.82312	-0.591	0.556
allocation_group:visit2	-0.02214	0.04420	104.26672	-0.501	0.618
allocation_group:visit3	-0.03185	0.04749	105.05887	-0.671	0.504

(Intercept) ***
allocation_group
visit2
visit3
allocation_group:visit2
allocation_group:visit3

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

(Intr)	all_GB	visit2	visit3	a_GB:2	
allctn_grGB	-0.712				
visit2	-0.338	0.241			
visit3	-0.312	0.222	0.451		
allctn_GB:2	0.230	-0.324	-0.681	-0.307	
allctn_GB:3	0.214	-0.301	-0.310	-0.687	0.435

```
summary(labs_hdl_model_sens)
```

```
Linear mixed model fit by REML. t-tests use Satterthwaite's method [  
lmerModLmerTest]
```

```
Formula: log1p(labs_hdl) ~ allocation_group * visit + (1 | record_id)

Data: data_model

Subset: !(record_id %in% labs_hdl_model_check$influential_ids)
```

REML criterion at convergence: -109.5

Scaled residuals:

Min	1Q	Median	3Q	Max
-1.93721	-0.52772	-0.00876	0.50466	2.04629

Random effects:

Groups	Name	Variance	Std.Dev.
record_id	(Intercept)	0.03870	0.1967
Residual		0.01007	0.1004

Number of obs: 166, groups: record_id, 70

Fixed effects:

	Estimate	Std. Error	df	t value	Pr(> t)
(Intercept)	3.92823	0.03733	82.44138	105.230	<2e-16
allocation_group	0.06708	0.05279	82.44138	1.271	0.207
visit2	-0.01029	0.02612	93.87428	-0.394	0.695
visit3	-0.01338	0.02805	94.47459	-0.477	0.635
allocation_group:visit2	-0.02943	0.03859	95.06373	-0.763	0.448
allocation_group:visit3	-0.03861	0.04187	95.58326	-0.922	0.359

(Intercept) ***

allocation_group

visit2

visit3

allocation_group:visit2

allocation_group:visit3

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

(Intr) all_GB visit2 visit3 a_GB:2

```

allctn_grGB -0.707
visit2      -0.295  0.209
visit3      -0.275  0.194  0.457
allctn_GB:2  0.200 -0.283 -0.677 -0.310
allctn_GB:3  0.184 -0.260 -0.306 -0.670  0.440

performance::compare_performance(
  labs_hdl_model,
  labs_hdl_model_sens)

```

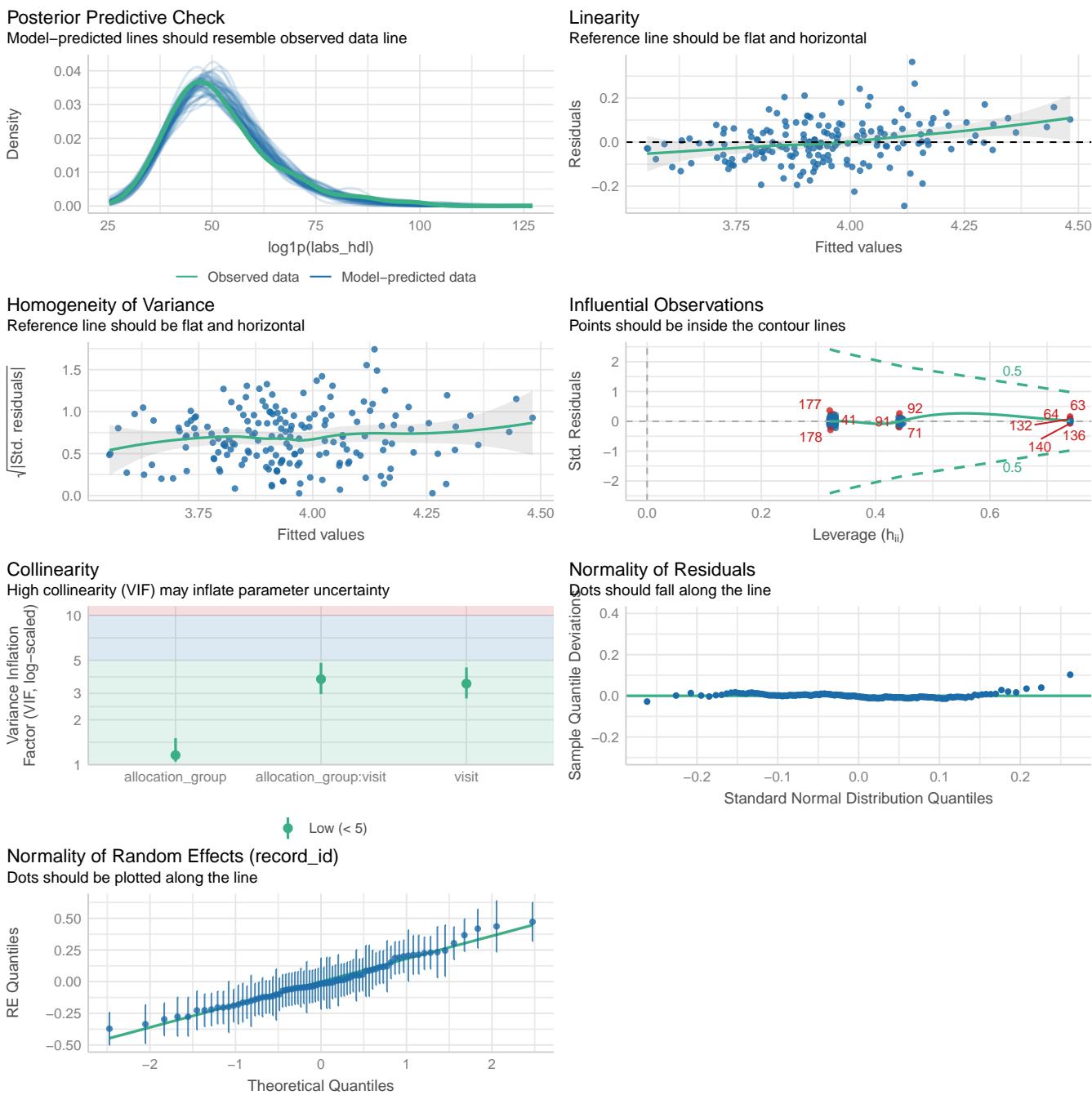
When comparing models, please note that probably not all models were fit from same data.

```
# Comparison of Model Performance Indices
```

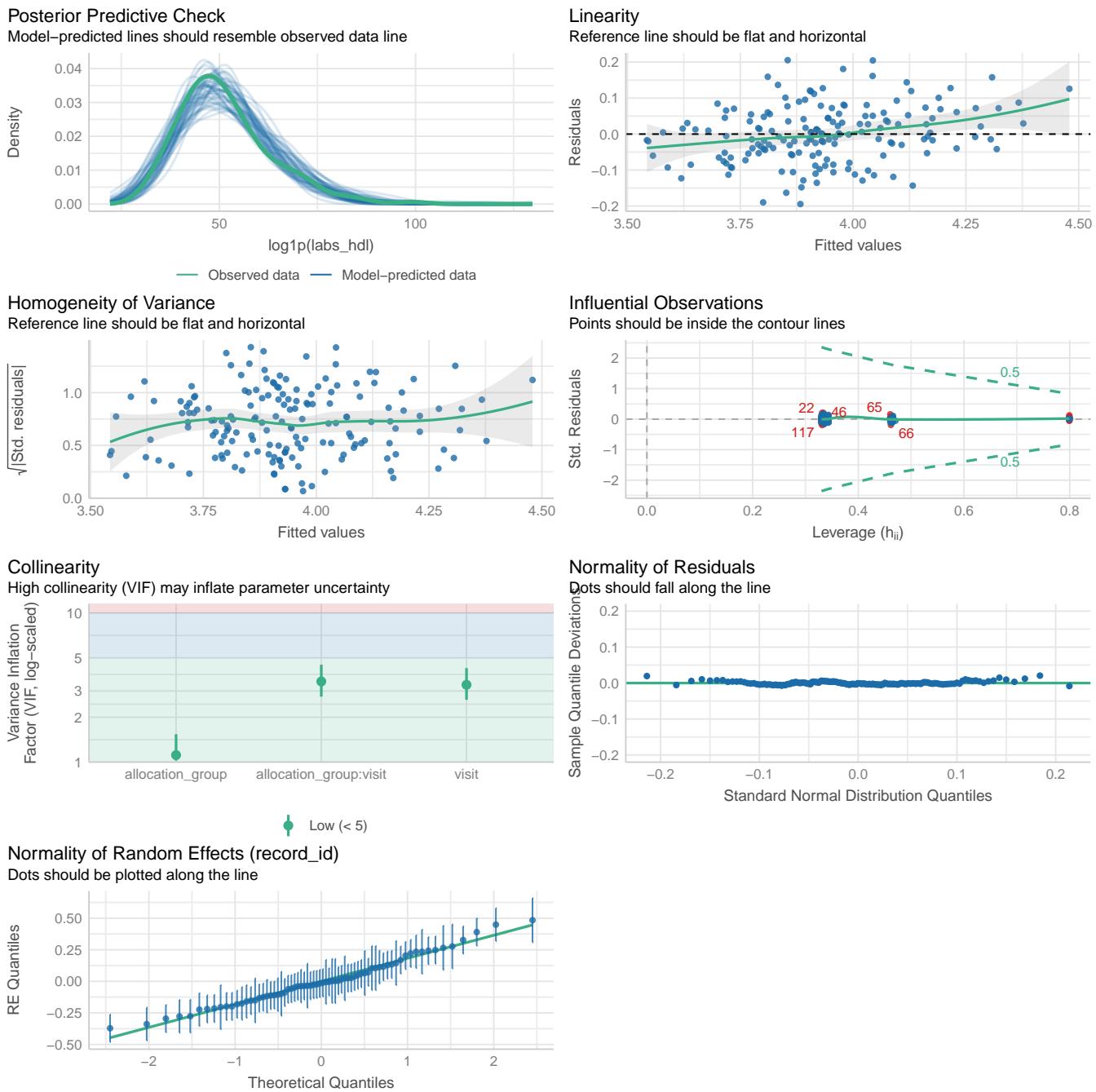
Name	Model	AIC (weights)	AICc (weights)
labs_hdl_model	lmerModLmerTest	1319.8 (<.001)	1320.7 (<.001)
labs_hdl_model_sens	lmerModLmerTest	1181.6 (>.999)	1182.5 (>.999)

Name	BIC (weights)	R2 (cond.)	R2 (marg.)	ICC	RMSE	Sigma
labs_hdl_model	1345.3 (<.001)	0.738	0.017	0.733	0.094	0.120
labs_hdl_model_sens	1206.5 (>.999)	0.797	0.018	0.793	0.078	0.100

```
performance::check_model(labs_hdl_model)
```



```
performance::check_model(labs_hdl_model_sens)
```



3.7.2 Médias Marginais Estimadas

3.7.2.1 Todos os dados

```
# Get EMMs for each group at each visit
labs_hdl_raw_emm <- emmeans::emmeans(
  labs_hdl_model,
  ~ allocation_group * visit
```

```

)

labs_hdl_raw_emm <- regrid(labs_hdl_raw_emm)

# Table of marginal means
# labs_hdl_raw_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(labs_hdl_raw_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

visit = 1:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
  Grupo A - Grupo B     -3.47 2.86 96.4     -9.15     2.21  -1.212  0.2284

visit = 2:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
  Grupo A - Grupo B     -2.22 2.98 108.6    -8.14     3.69  -0.746  0.4576

visit = 3:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
  Grupo A - Grupo B     -1.71 3.09 123.5    -7.83     4.42  -0.552  0.5819

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95

# Pairwise comparisons: Changes over time within each group
emmeans::contrast(labs_hdl_raw_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

allocation_group = Grupo A:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
  visit1 - visit2     0.883 1.54 96.4     -2.87     4.64   0.573  1.0000
  visit1 - visit3     0.986 1.67 96.4     -3.08     5.05   0.591  1.0000
  visit2 - visit3     0.103 1.67 108.6    -3.96     4.17   0.062  1.0000

```

```

allocation_group = Grupo B:

contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit2    2.129 1.74  96.4     -2.12     6.38   1.221  0.6751
visit1 - visit3    2.748 1.84  96.4     -1.74     7.24   1.491  0.4175
visit2 - visit3    0.619 1.90 123.2     -3.99     5.22   0.326  1.0000

```

Degrees-of-freedom method: inherited from kenward-roger when re-gridding

Confidence level used: 0.95

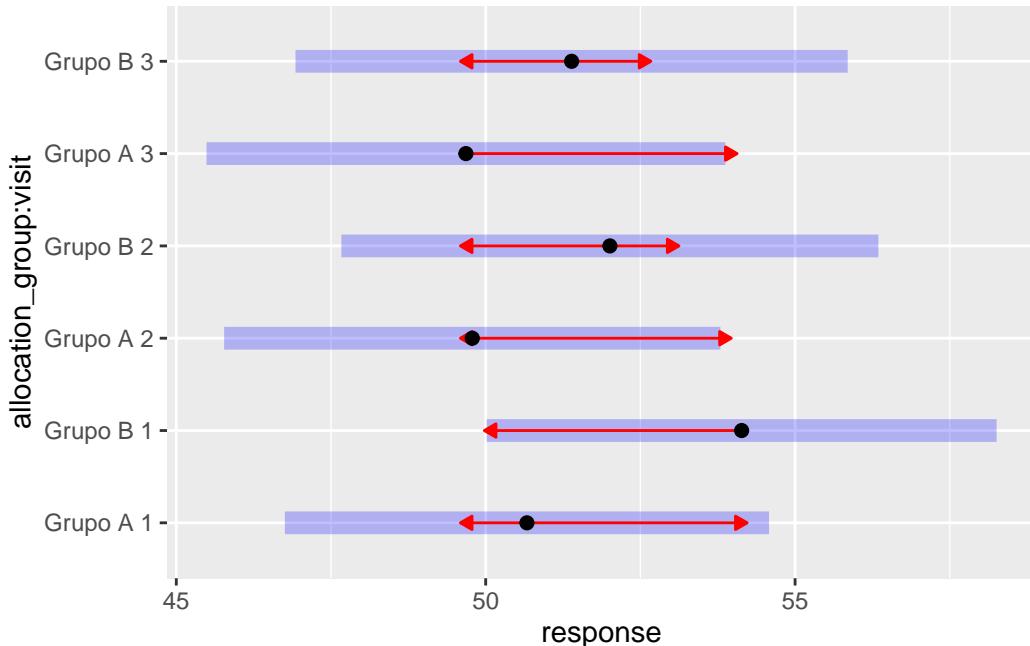
Conf-level adjustment: bonferroni method for 3 estimates

P value adjustment: bonferroni method for 3 tests

```

# Plot of marginal means
plot(labs_hdl_raw_emm, comparisons = TRUE)

```



3.7.2.2 Análise de sensibilidade

```

# Get EMMs for each group at each visit (Sensitivity Analysis)
labs_hdl_emm <- emmeans::emmeans(
  labs_hdl_model_sens,
  ~ allocation_group * visit
)

labs_hdl_emm <- regrid(labs_hdl_emm)

```

```

# Table of marginal means
# labs_hdl_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(labs_hdl_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

visit = 1:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B     -3.53 2.78  83.9     -9.05     2.00  -1.269  0.2078

visit = 2:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B     -1.93 2.87  93.9     -7.63     3.77  -0.672  0.5029

visit = 3:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B     -1.45 2.97 104.0     -7.33     4.43  -0.488  0.6264

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95

# Pairwise comparisons: Changes over time within each group
emmeans::contrast(labs_hdl_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

allocation_group = Grupo A:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit2     0.520 1.32  83.9     -2.71     3.75  0.394  1.0000
visit1 - visit3     0.675 1.41  83.9     -2.78     4.13  0.477  1.0000
visit2 - visit3     0.155 1.42  93.9     -3.31     3.62  0.109  1.0000

allocation_group = Grupo B:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit2     2.116 1.51  83.9     -1.57     5.80  1.403  0.4931
visit1 - visit3     2.753 1.63  83.9     -1.24     6.75  1.684  0.2874

```

```
visit2 - visit3      0.637 1.66 105.0     -3.40      4.67    0.384 1.0000
```

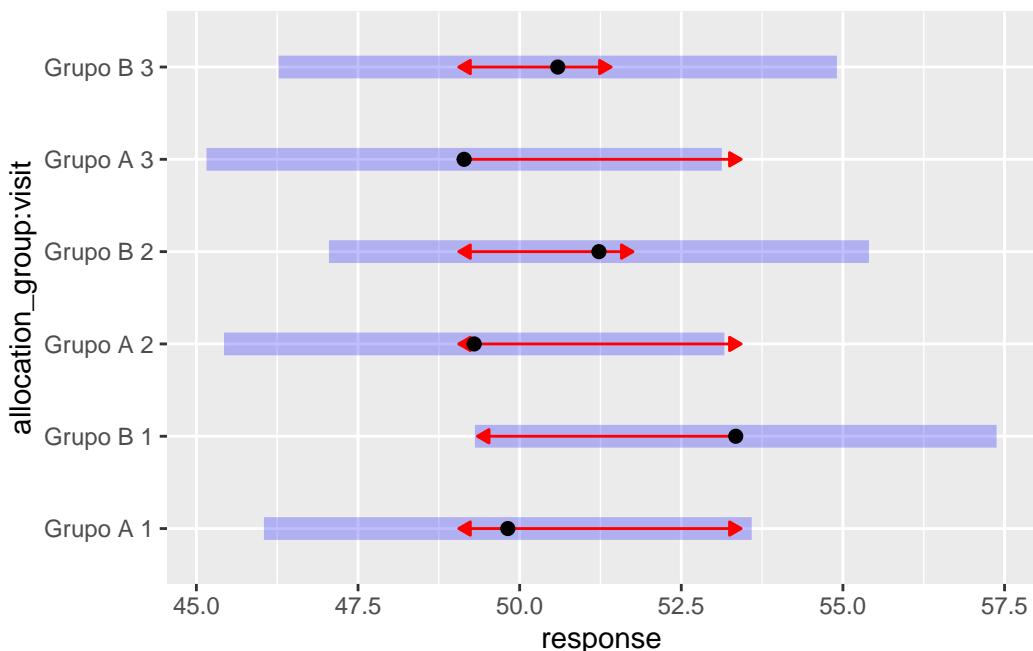
Degrees-of-freedom method: inherited from kenward-roger when re-gridding

Confidence level used: 0.95

Conf-level adjustment: bonferroni method for 3 estimates

P value adjustment: bonferroni method for 3 tests

```
# Plot of marginal means
plot(labs_hdl_emm, comparisons = TRUE)
```



3.7.3 Resultado

No modelo ajustado para os níveis de HDL-colesterol, não foram observadas diferenças estatisticamente significativas entre os grupos em nenhum dos três momentos avaliados. Também não houve mudanças significativas ao longo do tempo dentro de cada grupo. A análise de sensibilidade, conduzida com a exclusão das observações influentes, não alterou substancialmente os resultados. As estimativas permaneceram consistentes e as comparações entre grupos e ao longo do tempo continuaram não significativas. As estimativas, intervalos de confiança de 95% e valores de p estão apresentados na Tabela 7.

Tabela 7: Diferenças estimadas dos níveis de HDL-colesterol entre os grupos de alocação (placebo vs Eclipta) e entre visitas dentro de cada grupo

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 1	-3,47	[-9,15 ; 2,21]	0,228
Entre grupos	Visita 2	-2,22	[-8,14 ; 3,69]	0,458

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 3	-1,71	[-7,83 ; 4,42]	0,582
Grupo Placebo	Visita 1 - Visita 2	0,88	[-2,87 ; 4,64]	1,000
Grupo Placebo	Visita 1 - Visita 3	0,99	[-3,08 ; 5,05]	1,000
Grupo Placebo	Visita 2 - Visita 3	0,10	[-3,96 ; 4,17]	1,000
Grupo Eclipta	Visita 1 - Visita 2	2,13	[-2,12 ; 6,38]	0,675
Grupo Eclipta	Visita 1 - Visita 3	2,75	[-1,74 ; 7,24]	0,418
Grupo Eclipta	Visita 2 - Visita 3	0,62	[-3,99 ; 5,22]	1,000

```

ggplot(
  data = data_model,
  aes(
    x = as.factor(visit),
    y = labs_hdl,
    group = record_id,
  )
) +
  geom_line(alpha = 0.5) +
  geom_point(alpha = 0.7) +
  geom_smooth(
    aes(group = allocation_group),
    method = "lm",
    se = TRUE,
    linewidth = 1
  ) +
  labs(title = "All data") +
  facet_wrap(~ allocation_group)

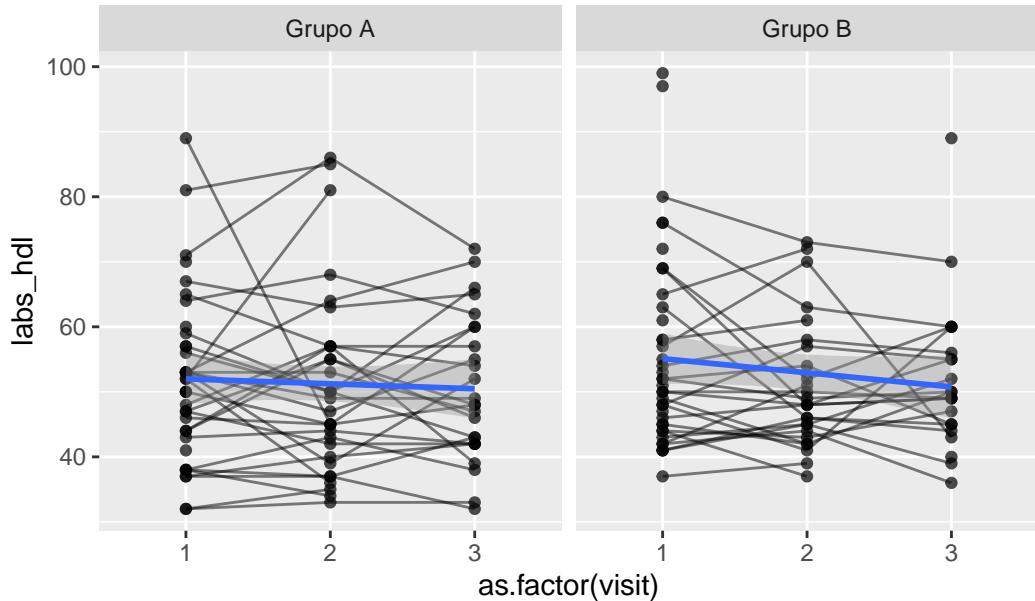
```

```

`geom_smooth()` using formula = 'y ~ x'
Warning: Removed 10 rows containing non-finite outside the scale range
(`stat_smooth()`).
Warning: Removed 8 rows containing missing values or values outside the scale range
(`geom_line()`).
Warning: Removed 10 rows containing missing values or values outside the scale range
(`geom_point()`).

```

All data



```
#coord_cartesian(ylim = c(10, 150))

data_model %>%
  filter(
    !(record_id %in%
      labs_hdl_model_check$influential_ids)
  ) %>%
  ggplot(
    aes(
      x = as.factor(visit),
      y = labs_hdl,
      group = record_id,
    )
  ) +
  geom_line(alpha = 0.5) +
  geom_point(alpha = 0.7) +
  geom_smooth(
    aes(group = allocation_group),
    method = "lm",
    se = TRUE,
    linewidth = 1
  )
```

```

) +
  labs(title = "Sensitivity analysis") +
  facet_wrap(~ allocation_group)

`geom_smooth()` using formula = 'y ~ x'

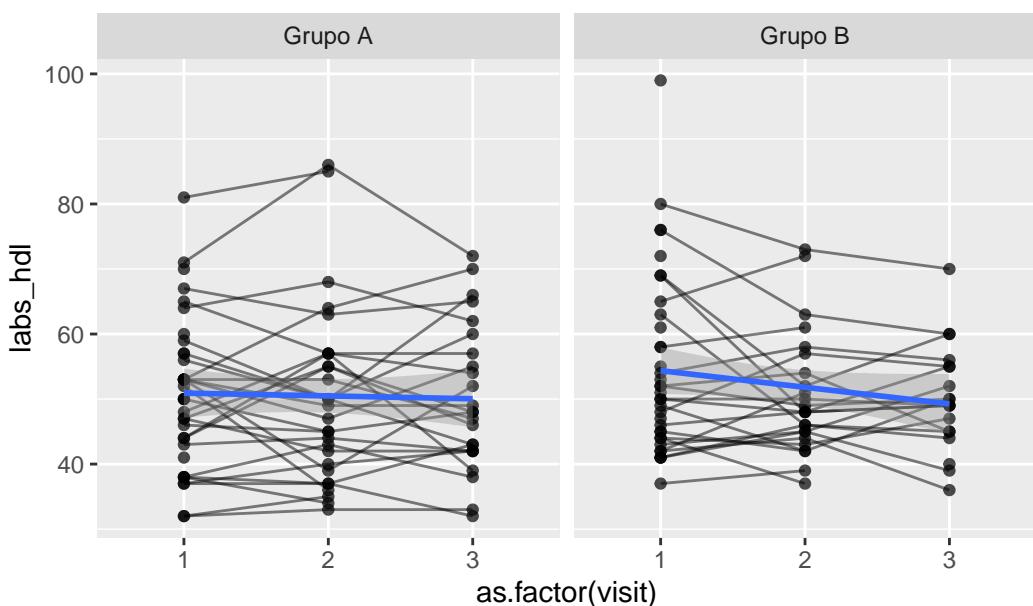
Warning: Removed 8 rows containing non-finite outside the scale range
(`stat_smooth()`).

Warning: Removed 7 rows containing missing values or values outside the scale range
(`geom_line()`).

Warning: Removed 8 rows containing missing values or values outside the scale range
(`geom_point()`).

```

Sensitivity analysis



```
#coord_cartesian(ylim = c(10, 150))
```

3.8 Triglicerídeos

Variável: labs_triglycerides

```

# Plot 1: Raw data
labs_triglycerides_hist_1 <- data_model %>%
  #filter(
  #  labs_triglycerides < 300
  #) %>%
  ggplot(aes(x = labs_triglycerides)) +

```

```

geom_histogram(bins = 50, fill = "skyblue", color = "black")

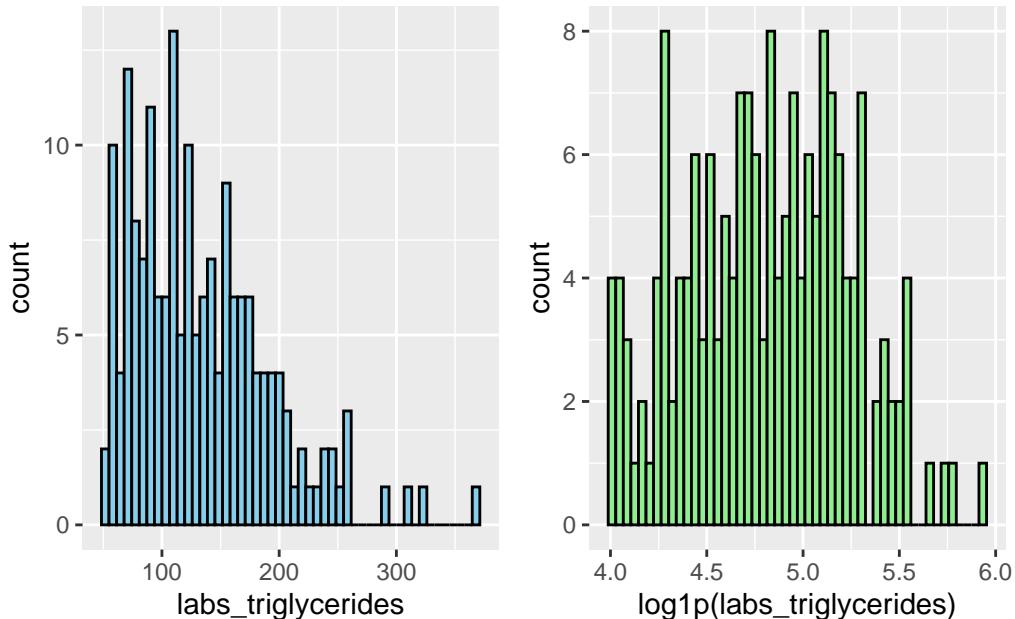
# Plot 2: Log-transformed data
labs_triglycerides_hist_2 <- data_model %>%
  #filter(
  #  labs_triglycerides < 300
  #) %>%
  ggplot(aes(x = log1p(labs_triglycerides))) +
  geom_histogram(bins = 50, fill = "lightgreen", color = "black")

# Combine side by side
labs_triglycerides_hist_1 + labs_triglycerides_hist_2 # library(patchwork)

```

Warning: Removed 10 rows containing non-finite outside the scale range (`stat_bin()`).

Removed 10 rows containing non-finite outside the scale range (`stat_bin()`).



```

# LMM
labs_triglycerides_model <- lmer(log1p(labs_triglycerides) ~ allocation_group * visit +
(1 | record_id), data = data_model)

check_collinearity(labs_triglycerides_model)

```

Check for Multicollinearity

Low Correlation

Term	VIF	VIF 95% CI	Increased SE	Tolerance
allocation_group	1.20	[1.08, 1.53]	1.10	0.83
visit	3.50	[2.79, 4.49]	1.87	0.29
allocation_group:visit	3.82	[3.03, 4.92]	1.95	0.26
Tolerance 95% CI				
	[0.65, 0.93]			
	[0.22, 0.36]			
	[0.20, 0.33]			

```
# Sensitivity analysis
labs_triglycerides_model_check <- sensitivity_check_lmer(
  model = labs_triglycerides_model,
  id_var = "record_id",
  top_n = 5)

# LMM Sensitivity
labs_triglycerides_model_sens <- update(object = labs_triglycerides_model,
  subset = !(record_id %in%
  labs_triglycerides_model_check$influential_ids))

# Influential IDS
labs_triglycerides_model_check$influential_ids
```

[1] "16" "17" "1" "2" "20"

3.8.1 Resumo dos modelos

```
# Model comparison
summary(labs_triglycerides_model)

Linear mixed model fit by REML. t-tests use Satterthwaite's method [
lmerModLmerTest]

Formula: log1p(labs_triglycerides) ~ allocation_group * visit + (1 | record_id)
Data: data_model

REML criterion at convergence: 156.5
```

Scaled residuals:

Min	1Q	Median	3Q	Max
-----	----	--------	----	-----

-2.48575 -0.55624 -0.06875 0.50582 2.77617

Random effects:

Groups	Name	Variance	Std.Dev.
record_id	(Intercept)	0.12894	0.3591
Residual		0.06212	0.2492

Number of obs: 179, groups: record_id, 75

Fixed effects:

	Estimate	Std. Error	df	t value	Pr(> t)	
(Intercept)	4.76585	0.07186	100.80805	66.322	<2e-16	
allocation_group	Grupo B	-0.02118	0.10095	100.80805	-0.210	0.834
visit2		0.05652	0.06246	103.24903	0.905	0.368
visit3		0.00822	0.06765	104.67836	0.122	0.904
allocation_group	Grupo B:visit2	-0.05643	0.09159	105.09618	-0.616	0.539
allocation_group	Grupo B:visit3	0.04983	0.09836	106.17407	0.507	0.614

(Intercept) ***
allocation_group

Grupo B
visit2
visit3
allocation_group

Grupo B:visit2
allocation_group

Grupo B:visit3

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

(Intr) all_GB visit2 visit3 a_GB:2
allctn_grGB -0.712
visit2 -0.374 0.266
visit3 -0.345 0.246 0.449
allctn_GB:2 0.255 -0.358 -0.682 -0.306
allctn_GB:3 0.238 -0.334 -0.309 -0.688 0.433

summary(labs_triglycerides_model_sens)

Linear mixed model fit by REML. t-tests use Satterthwaite's method [
lmerModLmerTest]

```

Formula: log1p(labs_triglycerides) ~ allocation_group * visit + (1 | record_id)

Data: data_model

Subset: !(record_id %in% labs_triglycerides_model_check$influential_ids)

REML criterion at convergence: 110.8

```

Scaled residuals:

Min	1Q	Median	3Q	Max
-1.56781	-0.62311	-0.09172	0.57450	2.18137

Random effects:

Groups	Name	Variance	Std.Dev.
record_id	(Intercept)	0.12547	0.3542
Residual		0.04498	0.2121

Number of obs: 164, groups: record_id, 70

Fixed effects:

	Estimate	Std. Error	df	t value	Pr(> t)
(Intercept)	4.74183	0.07187	86.86729	65.980	<2e-16
allocation_group	-0.02502	0.09885	86.86729	-0.253	0.8008
visit2	0.04807	0.05702	92.31050	0.843	0.4014
visit3	-0.09539	0.06269	93.35327	-1.522	0.1314
allocation_group:visit2	-0.01744	0.08158	93.47289	-0.214	0.8312
allocation_group:visit3	0.17857	0.08845	94.22579	2.019	0.0463

(Intercept) ***
 allocation_group
 visit2
 visit3
 allocation_group:visit2
 allocation_group:visit3 *

 Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

(Intr)	all_GB	visit2	visit3	a_GB:2
--------	--------	--------	--------	--------

```

allctn_grGB -0.727
visit2      -0.333  0.242
visit3      -0.303  0.220  0.444
allctn_GB:2  0.232 -0.320 -0.699 -0.310
allctn_GB:3  0.214 -0.295 -0.314 -0.709  0.431

performance::compare_performance(
  labs_triglycerides_model,
  labs_triglycerides_model_sens)

```

When comparing models, please note that probably not all models were fit from same data.

```
# Comparison of Model Performance Indices
```

Name	Model	AIC (weights)
------	-------	---------------

labs_triglycerides_model	lmerModLmerTest	1873.1 (<.001)
labs_triglycerides_model_sens	lmerModLmerTest	1671.7 (>.999)

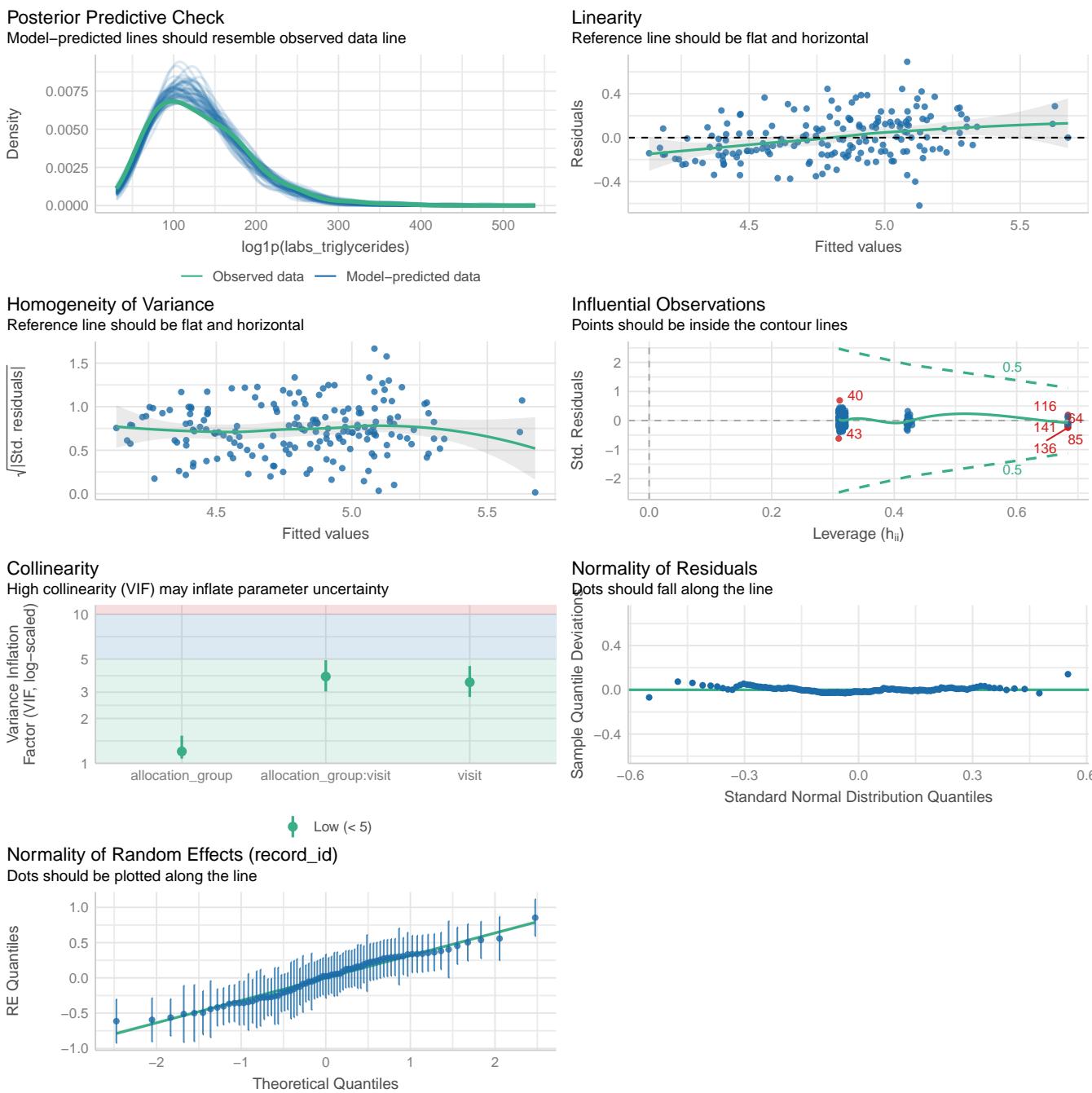
Name	AICc (weights)	BIC (weights)	R2 (cond.)
------	----------------	---------------	------------

labs_triglycerides_model	1873.9 (<.001)	1898.6 (<.001)	0.676
labs_triglycerides_model_sens	1672.6 (>.999)	1696.5 (>.999)	0.739

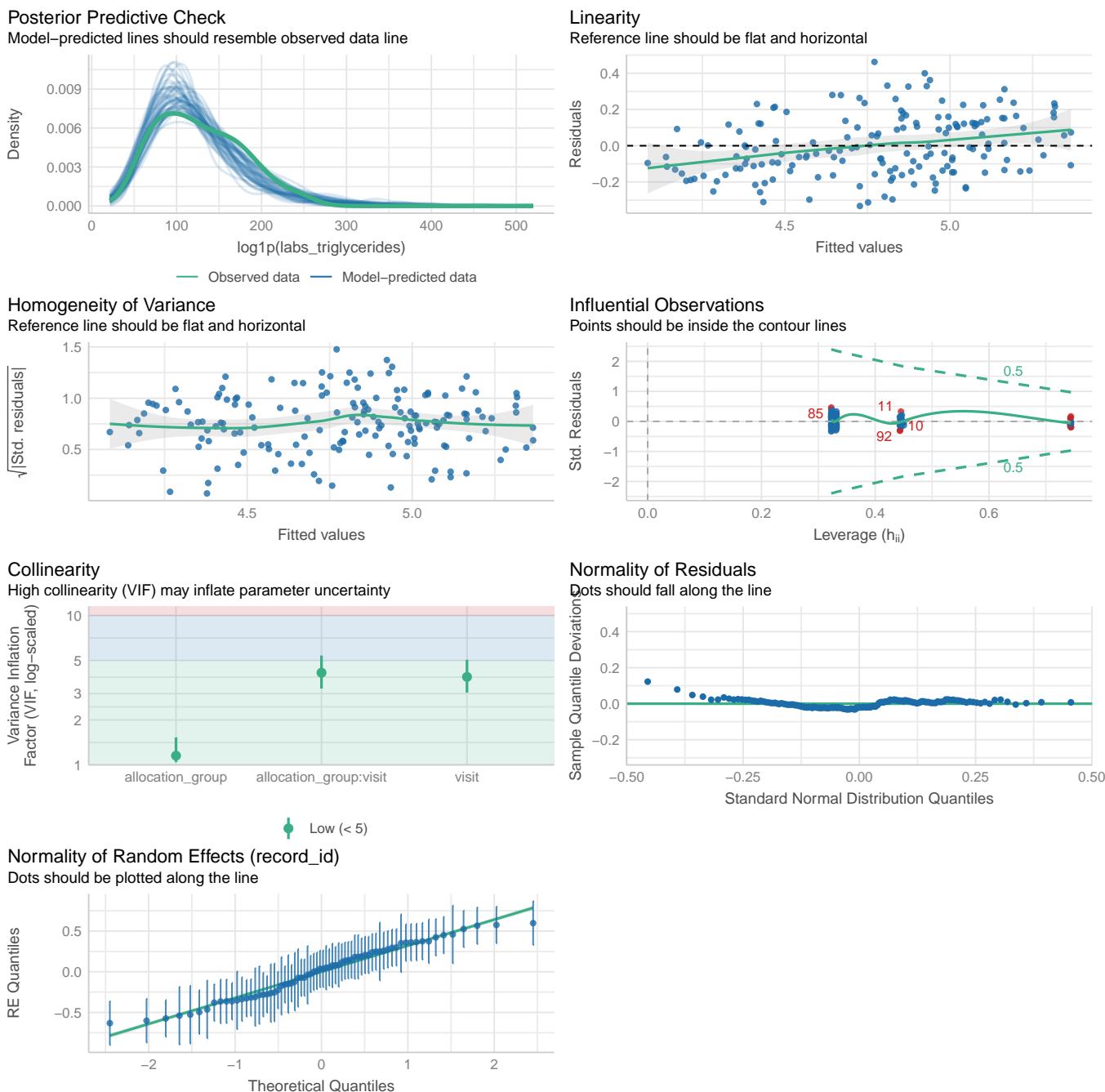
Name	R2 (marg.)	ICC	RMSE	Sigma
------	------------	-----	------	-------

labs_triglycerides_model	0.004	0.675	0.199	0.249
labs_triglycerides_model_sens	0.012	0.736	0.166	0.212

```
performance::check_model(labs_triglycerides_model)
```



```
performance::check_model(labs_triglycerides_model_sens)
```



3.8.2 Médias Marginais Estimadas

3.8.2.1 Todos os dados

```
# Get EMMs for each group at each visit
labs_triglycerides_raw_emm <- emmeans::emmeans(
  labs_triglycerides_model,
  ~ allocation_group * visit
```

```

)

labs_triglycerides_raw_emm <- regrid(labs_triglycerides_raw_emm)

# Table of marginal means
# labs_triglycerides_raw_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(labs_triglycerides_raw_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

visit = 1:
  contrast      estimate   SE  df lower.CL upper.CL t.ratio p.value
  Grupo A - Grupo B     2.46 11.7 103    -20.8     25.7   0.210  0.8343

visit = 2:
  contrast      estimate   SE  df lower.CL upper.CL t.ratio p.value
  Grupo A - Grupo B     9.28 13.1 116    -16.6     35.2   0.710  0.4793

visit = 3:
  contrast      estimate   SE  df lower.CL upper.CL t.ratio p.value
  Grupo A - Grupo B    -3.44 13.8 133    -30.8     23.9  -0.249  0.8041

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95

# Pairwise comparisons: Changes over time within each group
emmeans::contrast(labs_triglycerides_raw_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

allocation_group = Grupo A:
  contrast      estimate   SE  df lower.CL upper.CL t.ratio p.value
  visit1 - visit2 -6.82768 7.60 103    -25.3     11.7  -0.899  1.0000
  visit1 - visit3 -0.96930 8.00 103    -20.4     18.5  -0.121  1.0000
  visit2 - visit3  5.85838 8.29 116    -14.3     26.0   0.707  1.0000

```

```

allocation_group = Grupo B:

contrast      estimate   SE  df lower.CL upper.CL t.ratio p.value
visit1 - visit2 -0.00919 7.71 103     -18.8      18.8 -0.001 1.0000
visit1 - visit3 -6.87130 8.57 103     -27.7      14.0 -0.802 1.0000
visit2 - visit3 -6.86211 8.90 132     -28.4      14.7 -0.771 1.0000

```

Degrees-of-freedom method: inherited from kenward-roger when re-gridding

Confidence level used: 0.95

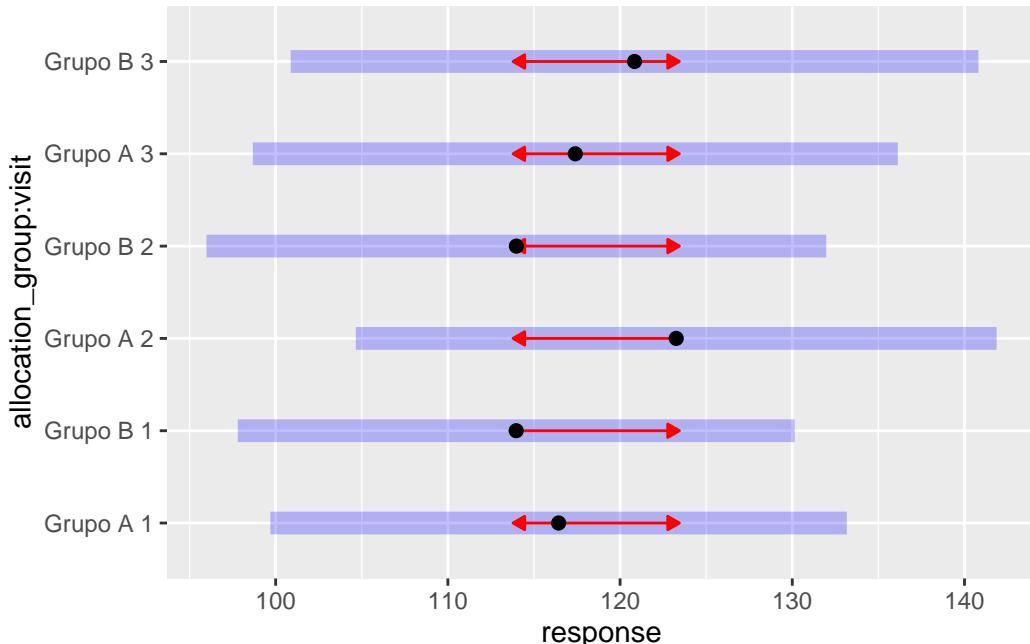
Conf-level adjustment: bonferroni method for 3 estimates

P value adjustment: bonferroni method for 3 tests

```

# Plot of marginal means
plot(labs_triglycerides_raw_emm, comparisons = TRUE)

```



3.8.2.2 Análise de sensibilidade

```

# Get EMMs for each group at each visit (Sensitivity Analysis)
labs_triglycerides_emm <- emmeans::emmeans(
  labs_triglycerides_model_sens,
  ~ allocation_group * visit
)

labs_triglycerides_emm <- regrid(labs_triglycerides_emm)

```

```

# Table of marginal means
# labs_triglycerides_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(labs_triglycerides_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

visit = 1:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B     2.83 11.2  88.9    -19.4     25.09   0.253  0.8010

visit = 2:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B     5.00 12.5 101.6    -19.8     29.83   0.399  0.6904

visit = 3:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B   -17.30 12.6 117.7    -42.3      7.68  -1.371  0.1729

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95

# Pairwise comparisons: Changes over time within each group
emmeans::contrast(labs_triglycerides_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

allocation_group = Grupo A:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit2    -5.65 6.74  88.9    -22.10     10.81  -0.837  1.0000
visit1 - visit3    10.43 6.81  88.9     -6.17     27.04   1.533  0.3866
visit2 - visit3   16.08 7.12 101.6     -1.25     33.40   2.259  0.0780

allocation_group = Grupo B:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit2    -3.48 6.67  88.9    -19.75     12.79  -0.522  1.0000
visit1 - visit3    -9.70 7.43  88.9    -27.83     8.44  -1.305  0.5861

```

```
visit2 - visit3      -6.22 7.76 114.3   -25.07    12.63  -0.802  1.0000
```

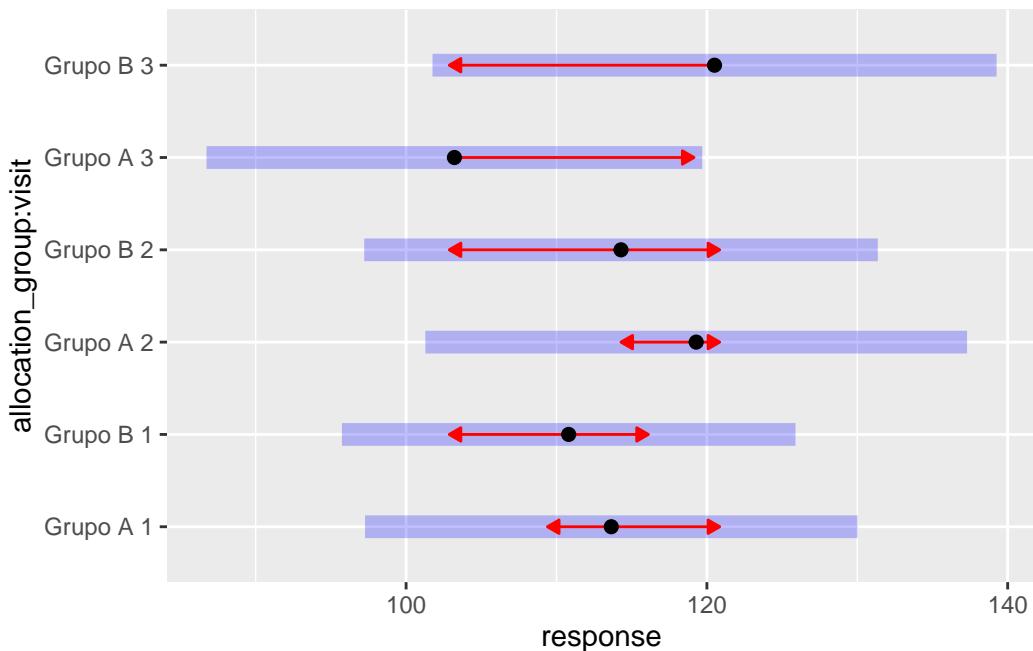
Degrees-of-freedom method: inherited from kenward-roger when re-gridding

Confidence level used: 0.95

Conf-level adjustment: bonferroni method for 3 estimates

P value adjustment: bonferroni method for 3 tests

```
# Plot of marginal means  
plot(labs_triglycerides_emm, comparisons = TRUE)
```



3.8.3 Resultado

No modelo ajustado para os níveis de triglicerídeos, não foram observadas diferenças estatisticamente significativas entre os grupos em nenhum dos três momentos avaliados. As estimativas entre grupos foram próximas de zero e os intervalos de confiança incluíram o valor nulo, com valores de p superiores a 0,47 em todas as comparações. Da mesma forma, as comparações intragrupo ao longo do tempo não revelaram mudanças significativas em nenhum dos grupos, embora tenha havido uma tendência não significativa de aumento entre a visita 2 e a visita 3 no grupo A ($p = 0,078$).

A análise de sensibilidade, realizada após a exclusão de observações influentes, manteve os resultados essencialmente inalterados. As estimativas permaneceram próximas das observadas no modelo completo e não houve modificações relevantes nas interpretações. As estimativas, intervalos de confiança de 95% e valores de p estão apresentados na Tabela 8.

Tabela 8: Diferenças estimadas dos níveis de triglicerídeos entre os grupos de alocação (placebo vs Eclipta) e entre visitas dentro de cada grupo

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 1	2,46	[-20,8 ; 25,7]	0,834
Entre grupos	Visita 2	9,28	[-16,6 ; 35,2]	0,479
Entre grupos	Visita 3	-3,44	[-30,8 ; 23,9]	0,804
Grupo Placebo	Visita 1 - Visita 2	-6,83	[-25,3 ; 11,7]	1,000
Grupo Placebo	Visita 1 - Visita 3	-0,97	[-20,4 ; 18,5]	1,000
Grupo Placebo	Visita 2 - Visita 3	5,86	[-14,3 ; 26,0]	1,000
Grupo Eclipta	Visita 1 - Visita 2	-0,01	[-18,8 ; 18,8]	1,000
Grupo Eclipta	Visita 1 - Visita 3	-6,87	[-27,7 ; 14,0]	1,000
Grupo Eclipta	Visita 2 - Visita 3	-6,86	[-28,4 ; 14,7]	1,000

```

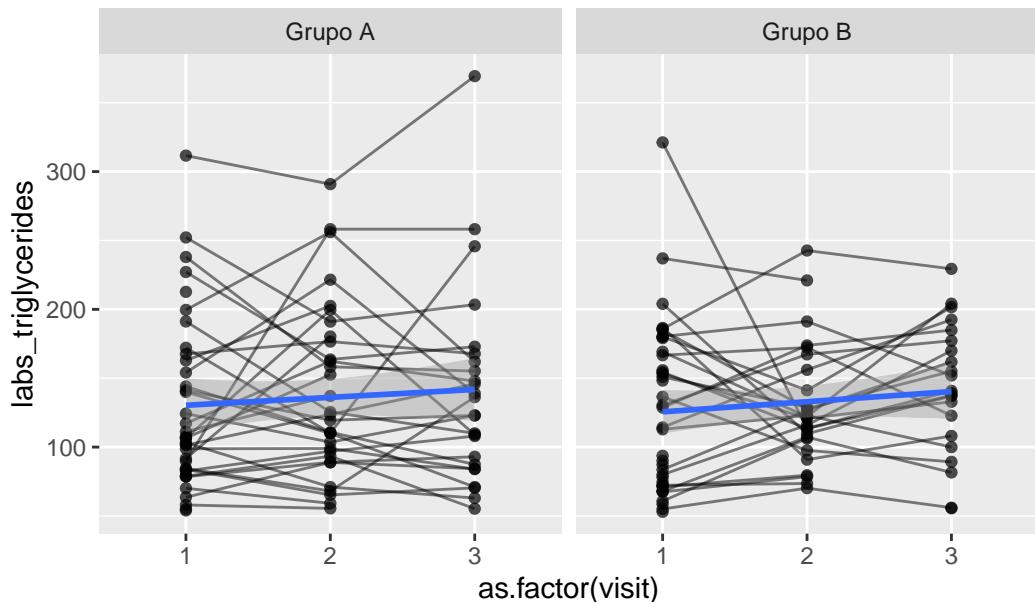
ggplot(
  data = data_model,
  aes(
    x = as.factor(visit),
    y = labs_triglycerides,
    group = record_id,
  )
) +
  geom_line(alpha = 0.5) +
  geom_point(alpha = 0.7) +
  geom_smooth(
    aes(group = allocation_group),
    method = "lm",
    se = TRUE,
    linewidth = 1
  ) +
  labs(title = "All data") +
  facet_wrap(~ allocation_group)

`geom_smooth()` using formula = 'y ~ x'
Warning: Removed 10 rows containing non-finite outside the scale range
(`stat_smooth()`).
Warning: Removed 8 rows containing missing values or values outside the scale range

```

```
(`geom_line()`).
Warning: Removed 10 rows containing missing values or values outside the scale range
(`geom_point()`).
```

All data



```
#coord_cartesian(ylim = c(10, 150))

data_model %>%
  filter(
    !(record_id %in%
      labs_triglycerides_model_check$influential_ids)
  ) %>%
  ggplot(
    aes(
      x = as.factor(visit),
      y = labs_triglycerides,
      group = record_id,
    )
  ) +
  geom_line(alpha = 0.5) +
  geom_point(alpha = 0.7) +
  geom_smooth(
    aes(group = allocation_group),
    method = "lm",
  )
```

```

    se = TRUE,
    linewidth = 1
) +
  labs(title = "Sensitivity analysis") +
  facet_wrap(~ allocation_group)

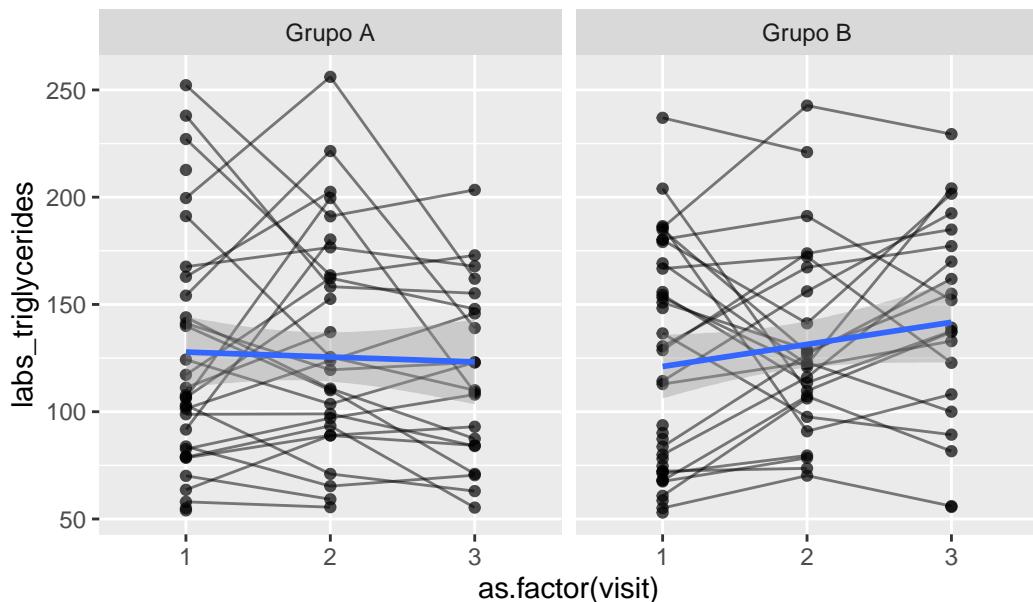
`geom_smooth()` using formula = 'y ~ x'
Warning: Removed 10 rows containing non-finite outside the scale range
(`stat_smooth()`).

Warning: Removed 8 rows containing missing values or values outside the scale range
(`geom_line()`).

Warning: Removed 10 rows containing missing values or values outside the scale range
(`geom_point()`).

```

Sensitivity analysis



```
#coord_cartesian(ylim = c(10, 150))
```

3.9 Glicemia de jejum

Variável: `labs_glucose`

```

# Plot 1: Raw data
labs_glucose_hist_1 <- data_model %>%
  #filter(
  #  labs_glucose < 140

```

```

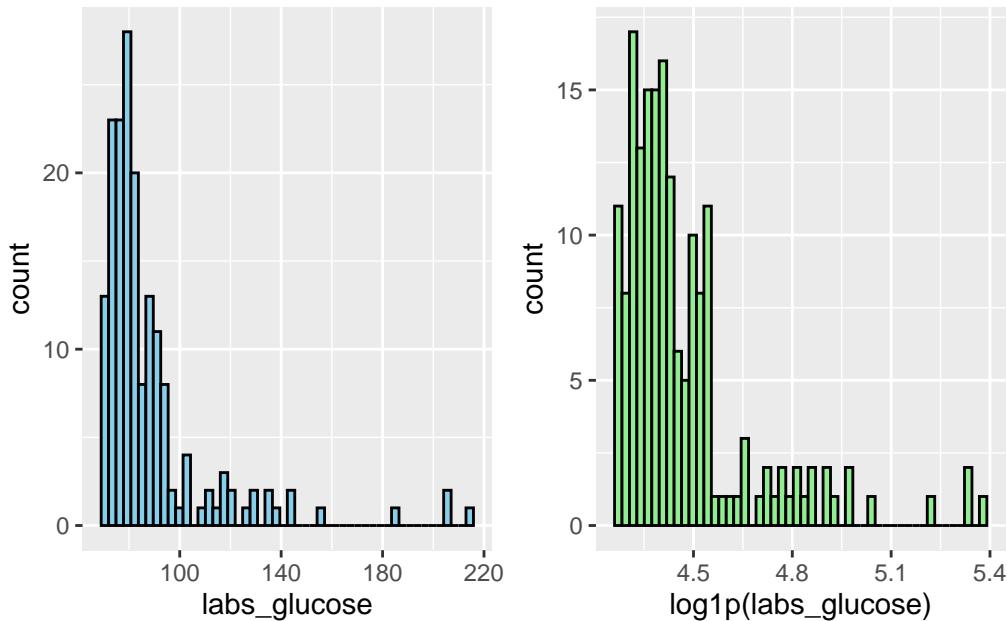
#) %>%
ggplot(aes(x = labs_glucose)) +
  geom_histogram(bins = 50, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
labs_glucose_hist_2 <- data_model %>%
  #filter(
  #  labs_glucose < 140
  #) %>%
  ggplot(aes(x = log1p(labs_glucose))) +
  geom_histogram(bins = 50, fill = "lightgreen", color = "black")

# Combine side by side
labs_glucose_hist_1 + labs_glucose_hist_2 # library(patchwork)

```

Warning: Removed 13 rows containing non-finite outside the scale range (`stat_bin()`).
 Removed 13 rows containing non-finite outside the scale range (`stat_bin()`).



```

# LMM
labs_glucose_model <- lmer(log1p(labs_glucose) ~ allocation_group * visit +
(1 | record_id), data = data_model)
check_collinearity(labs_glucose_model)

# Check for Multicollinearity

```

Low Correlation

Term	VIF	VIF 95% CI	Increased SE	Tolerance
allocation_group	1.13	[1.03, 1.51]	1.06	0.89
visit	3.47	[2.76, 4.47]	1.86	0.29
allocation_group:visit	3.69	[2.93, 4.75]	1.92	0.27

Tolerance 95% CI

[0.66, 0.97]
[0.22, 0.36]
[0.21, 0.34]

```
# Sensitivity analysis
labs_glucose_model_check <- sensitivity_check_lmer(
  model = labs_glucose_model,
  id_var = "record_id",
  top_n = 5)

# LMM Sensitivity
labs_glucose_model_sens <- update(object = labs_glucose_model,
                                     subset = !(record_id %in%
                                     labs_glucose_model_check$influential_ids))
# Influential IDs
labs_glucose_model_check$influential_ids

[1] "2"  "16" "17" "56" "13"
```

3.9.1 Resumo dos modelos

```
# Model comparison
summary(labs_glucose_model)

Linear mixed model fit by REML. t-tests use Satterthwaite's method [
lmerModLmerTest]

Formula: log1p(labs_glucose) ~ allocation_group * visit + (1 | record_id)
Data: data_model

REML criterion at convergence: -153
```

Scaled residuals:

Min	1Q	Median	3Q	Max
-2.0712	-0.5250	-0.1192	0.4737	3.4423

Random effects:

Groups	Name	Variance	Std.Dev.
record_id	(Intercept)	0.030440	0.17447
Residual		0.008319	0.09121

Number of obs: 176, groups: record_id, 74

Fixed effects:

	Estimate	Std. Error	df	t value
(Intercept)	4.445812	0.032366	92.773372	137.362
allocation_group	0.002937	0.045895	93.526588	0.064
visit2	0.009144	0.023244	104.438133	0.393
visit3	0.035792	0.024905	105.095812	1.437
allocation_group:visit2	-0.019077	0.034014	105.360265	-0.561
allocation_group:visit3	-0.007509	0.036617	106.709642	-0.205
	Pr(> t)			
(Intercept)	<2e-16	***		
allocation_group	0.949			
visit2	0.695			
visit3	0.154			
allocation_group:visit2	0.576			
allocation_group:visit3	0.838			

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

(Intr)	all_GB	visit2	visit3	a_GB:2
allctn_grGB	-0.705			
visit2	-0.299	0.211		
visit3	-0.279	0.197	0.445	
allctn_GB:2	0.204	-0.293	-0.683	-0.304
allctn_GB:3	0.190	-0.278	-0.303	-0.680
				0.439

```
summary(labs_glucose_model_sens)
```

Linear mixed model fit by REML. t-tests use Satterthwaite's method [
lmerModLmerTest]

Formula: log1p(labs_glucose) ~ allocation_group * visit + (1 | record_id)

Data: data_model

Subset: !(record_id %in% labs_glucose_model_check\$influential_ids)

REML criterion at convergence: -224.4

Scaled residuals:

Min	1Q	Median	3Q	Max
-1.9874	-0.5692	-0.1200	0.5703	1.9303

Random effects:

Groups	Name	Variance	Std.Dev.
record_id	(Intercept)	0.011973	0.10942
Residual		0.005831	0.07636

Number of obs: 161, groups: record_id, 69

Fixed effects:

	Estimate	Std. Error	df	t value
(Intercept)	4.4198168	0.0228838	96.3391006	193.142
allocation_group	-0.0005277	0.0322590	97.2962023	-0.016
visit2	-0.0018470	0.0203795	96.0503867	-0.091
visit3	0.0190546	0.0220059	97.1965932	0.866
allocation_group:visit2	-0.0022058	0.0295835	97.2662772	-0.075
allocation_group:visit3	0.0099619	0.0320363	99.3466017	0.311

	Pr(> t)
(Intercept)	<2e-16 ***
allocation_group	0.987
visit2	0.928
visit3	0.389
allocation_group:visit2	0.941
allocation_group:visit3	0.756

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

```
(Intr) all_GB visit2 visit3 a_GB:2  
allctn_grGB -0.709  
visit2      -0.368  0.261  
visit3      -0.341  0.242  0.435  
allctn_GB:2  0.253 -0.360 -0.689 -0.300  
allctn_GB:3  0.234 -0.339 -0.299 -0.687  0.428
```

```
performance::compare_performance(  
  labs_glucose_model,  
  labs_glucose_model_sens)
```

When comparing models, please note that probably not all models were fit from same data.

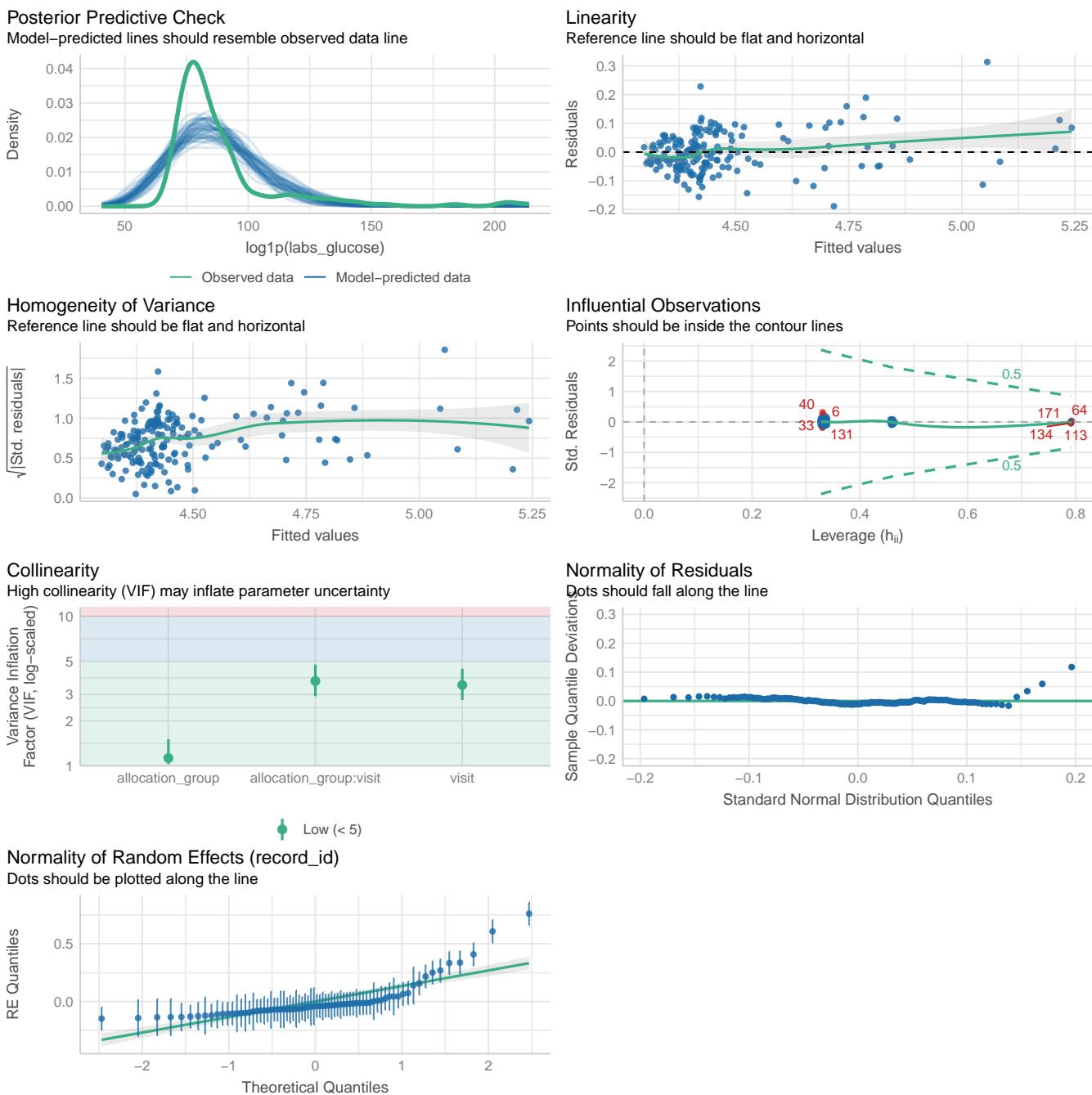
```
# Comparison of Model Performance Indices
```

Name	Model	AIC (weights)	AICc (weights)
labs_glucose_model	lmerModLmerTest	1404.0 (<.001)	1404.9 (<.001)
labs_glucose_model_sens	lmerModLmerTest	1183.8 (>.999)	1184.7 (>.999)

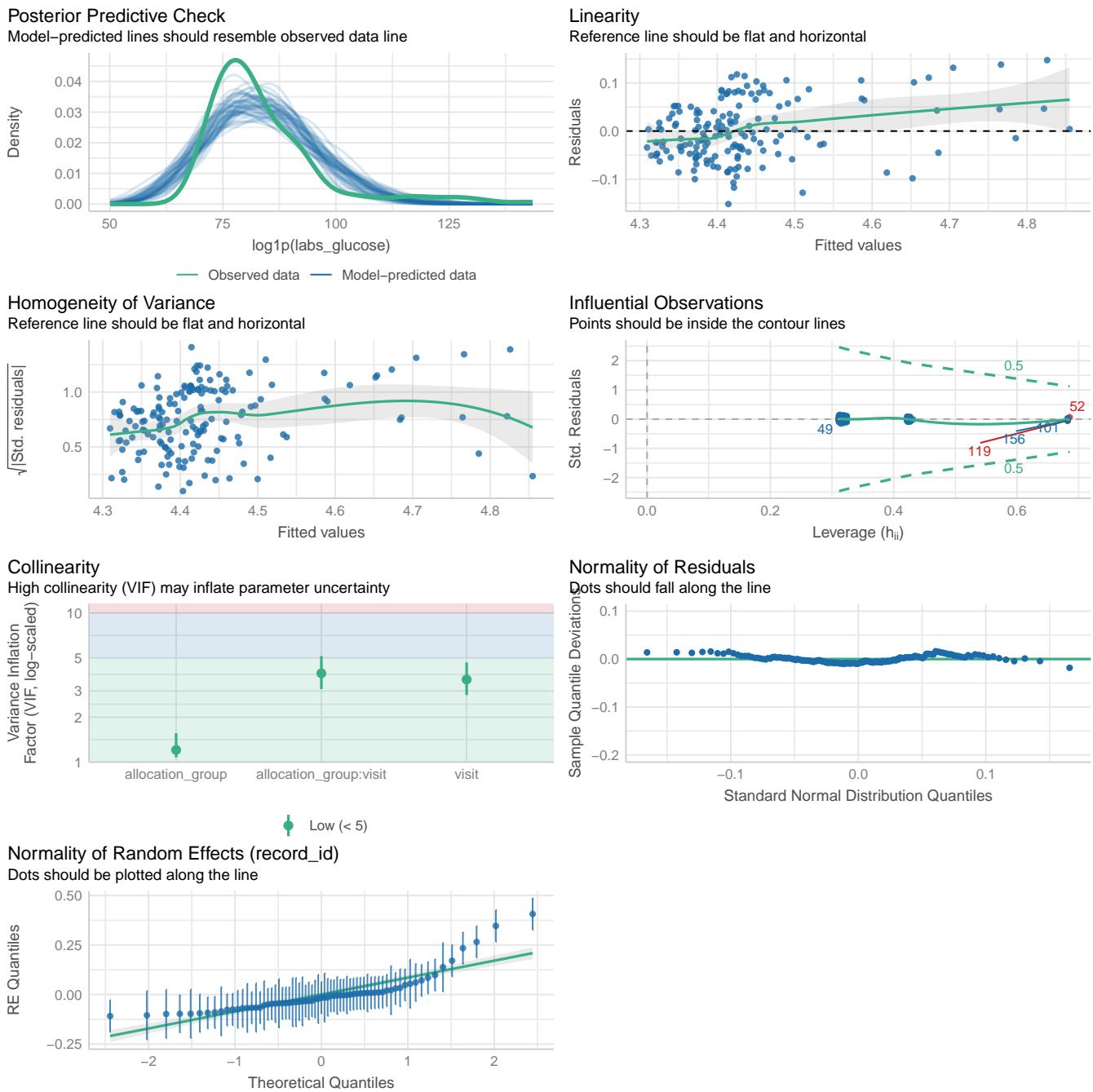
Name	BIC (weights)	R2 (cond.)	R2 (marg.)	ICC
labs_glucose_model	1429.4 (<.001)	0.787	0.006	0.785
labs_glucose_model_sens	1208.4 (>.999)	0.675	0.007	0.672

Name	RMSE	Sigma
labs_glucose_model	0.071	0.091
labs_glucose_model_sens	0.061	0.076

```
performance::check_model(labs_glucose_model)
```



```
performance::check_model(labs_glucose_model_sens)
```



3.9.2 Médias Marginais Estimadas

3.9.2.1 Todos os dados

```
# Get EMMs for each group at each visit
labs_glucose_raw_emm <- emmeans::emmeans(
  labs_glucose_model,
  ~ allocation_group * visit
```

```

)

labs_glucose_raw_emm <- regrid(labs_glucose_raw_emm)

# Table of marginal means
# labs_glucose_raw_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(labs_glucose_raw_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

visit = 1:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B   -0.251 3.92  89.7    -8.04     7.54  -0.064  0.9491

visit = 2:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    1.378 4.14 101.8    -6.83     9.59   0.333  0.7399

visit = 3:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    0.403 4.42 112.6    -8.36     9.17   0.091  0.9276

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95

# Pairwise comparisons: Changes over time within each group
emmeans::contrast(labs_glucose_raw_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

allocation_group = Grupo A:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit2   -0.783 1.99  89.7    -5.65     4.08  -0.393  1.0000
visit1 - visit3   -3.107 2.18  89.7    -8.42     2.20  -1.427  0.4709
visit2 - visit3   -2.324 2.22 101.8    -7.73     3.08  -1.046  0.8937

```

```

allocation_group = Grupo B:

contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit2    0.845 2.11  91.2     -4.31      6.00  0.400  1.0000
visit1 - visit3   -2.453 2.34  91.2     -8.17      3.26 -1.047  0.8942
visit2 - visit3   -3.299 2.39 111.0     -9.10      2.51 -1.381  0.5102

```

Degrees-of-freedom method: inherited from kenward-roger when re-gridding

Confidence level used: 0.95

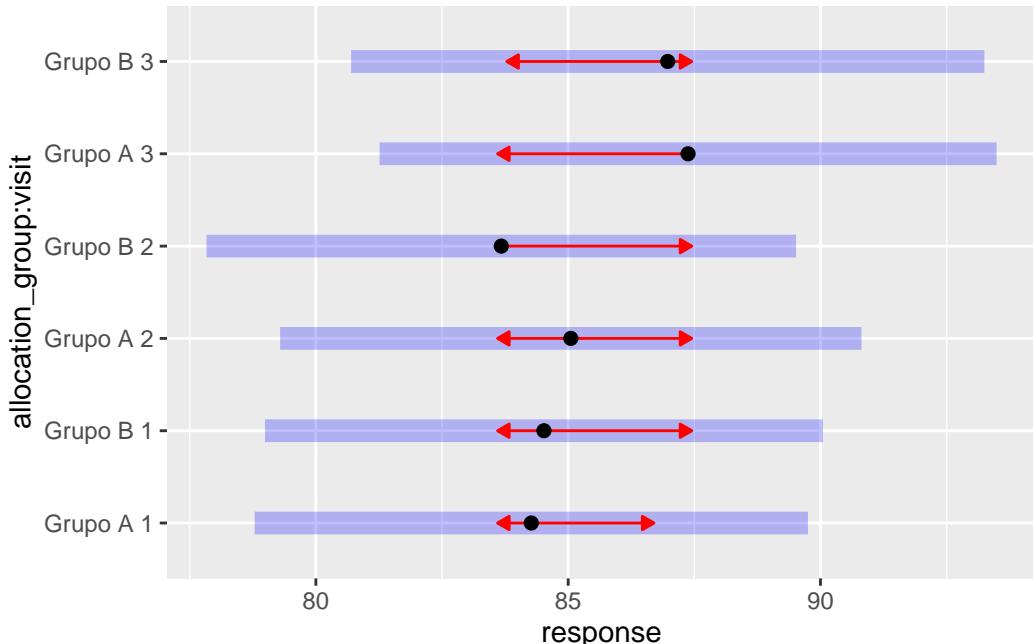
Conf-level adjustment: bonferroni method for 3 estimates

P value adjustment: bonferroni method for 3 tests

```

# Plot of marginal means
plot(labs_glucose_raw_emm, comparisons = TRUE)

```



3.9.2.2 Análise de sensibilidade

```

# Get EMMs for each group at each visit (Sensitivity Analysis)
labs_glucose_emm <- emmeans::emmeans(
  labs_glucose_model_sens,
  ~ allocation_group * visit
)

labs_glucose_emm <- regrid(labs_glucose_emm)

```

```

# Table of marginal means

# labs_glucose_emm

# Pairwise comparisons: Between groups at each visit

emmeans::contrast(labs_glucose_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

visit = 1:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B  0.0438 2.68  93.6    -5.28     5.36  0.016  0.9870

visit = 2:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B  0.2264 2.91 109.6    -5.53     5.98  0.078  0.9380

visit = 3:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B -0.8027 3.15 123.8    -7.04     5.43 -0.255  0.7993

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95

# Pairwise comparisons: Changes over time within each group

emmeans::contrast(labs_glucose_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

allocation_group = Grupo A:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit2  0.153 1.69  93.6    -3.97     4.28  0.091  1.0000
visit1 - visit3 -1.598 1.85  93.6    -6.12     2.92 -0.862  1.0000
visit2 - visit3 -1.752 1.90 109.6    -6.36     2.86 -0.924  1.0000

allocation_group = Grupo B:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit2  0.336 1.78  95.5    -4.00     4.67  0.189  1.0000
visit1 - visit3 -2.445 1.98  95.5    -7.26     2.37 -1.237  0.6578

```

```
visit2 - visit3 -2.781 2.03 120.0 -7.72 2.16 -1.367 0.5226
```

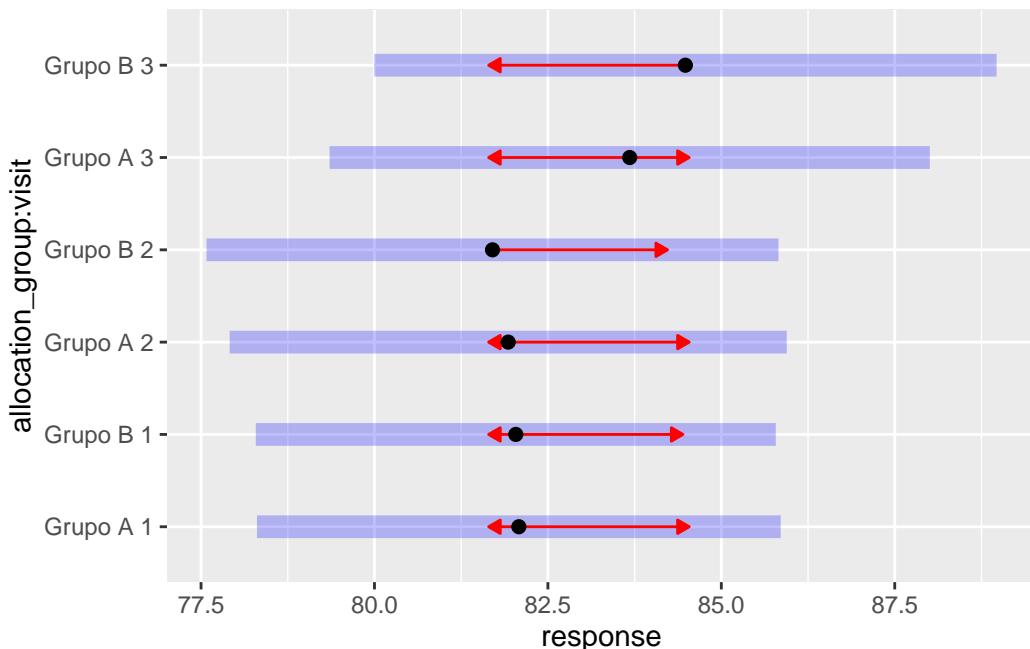
Degrees-of-freedom method: inherited from kenward-roger when re-gridding

Confidence level used: 0.95

Conf-level adjustment: bonferroni method for 3 estimates

P value adjustment: bonferroni method for 3 tests

```
# Plot of marginal means
plot(labs_glucose_emm, comparisons = TRUE)
```



3.9.3 Resultado

No modelo ajustado para os níveis de glicose, não foram observadas diferenças estatisticamente significativas entre os grupos em nenhum dos três momentos avaliados. Da mesma forma, não houve mudanças significativas ao longo do tempo dentro de cada grupo. A análise de sensibilidade, conduzida após a exclusão de observações influentes, não alterou substancialmente os resultados. As estimativas permaneceram estáveis e as diferenças entre os grupos e ao longo do tempo continuaram não significativas. As estimativas, intervalos de confiança de 95% e valores de p estão apresentados na Tabela 9.

Tabela 9: Diferenças estimadas dos níveis de glicose entre os grupos de alocação (placebo vs Eclipta) e entre visitas dentro de cada grupo

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 1	-0,25	[-8,04 ; 7,54]	0,949
Entre grupos	Visita 2	1,38	[-6,83 ; 9,59]	0,740

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 3	0,40	[-8,36 ; 9,17]	0,928
Grupo Placebo	Visita 1 - Visita 2	-0,78	[-5,65 ; 4,08]	1,000
Grupo Placebo	Visita 1 - Visita 3	-3,11	[-8,42 ; 2,20]	0,471
Grupo Placebo	Visita 2 - Visita 3	-2,32	[-7,73 ; 3,08]	0,894
Grupo Eclipta	Visita 1 - Visita 2	0,85	[-4,31 ; 6,00]	1,000
Grupo Eclipta	Visita 1 - Visita 3	-2,45	[-8,17 ; 3,26]	0,894
Grupo Eclipta	Visita 2 - Visita 3	-3,30	[-9,10 ; 2,51]	0,510

```

ggplot(
  data = data_model,
  aes(
    x = as.factor(visit),
    y = labs_glucose,
    group = record_id,
  )
) +
  geom_line(alpha = 0.5) +
  geom_point(alpha = 0.7) +
  geom_smooth(
    aes(group = allocation_group),
    method = "lm",
    se = TRUE,
    linewidth = 1
  ) +
  labs(title = "All data") +
  facet_wrap(~ allocation_group)

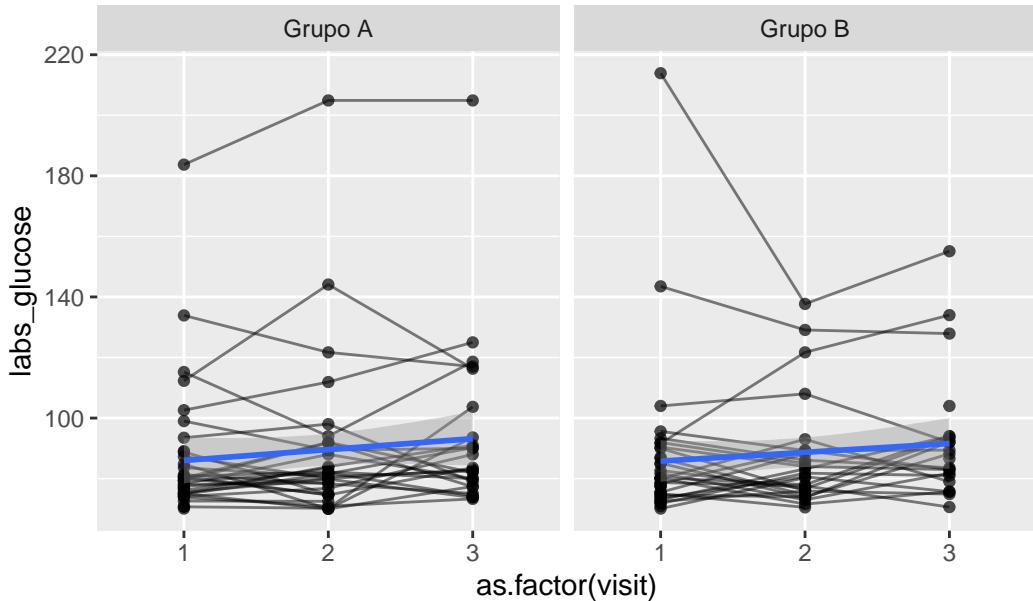
```

```

`geom_smooth()` using formula = 'y ~ x'
Warning: Removed 13 rows containing non-finite outside the scale range
(`stat_smooth()`).
Warning: Removed 11 rows containing missing values or values outside the scale range
(`geom_line()`).
Warning: Removed 13 rows containing missing values or values outside the scale range
(`geom_point()`).

```

All data



```
#coord_cartesian(ylim = c(10, 150))
```

```
data_model %>%
  filter(
    !(record_id %in%
      labs_glucose_model_check$influential_ids)
  ) %>%
  ggplot(
    aes(
      x = as.factor(visit),
      y = labs_glucose,
      group = record_id,
    )
  ) +
  geom_line(alpha = 0.5) +
  geom_point(alpha = 0.7) +
  geom_smooth(
    aes(group = allocation_group),
    method = "lm",
    se = TRUE,
    linewidth = 1
```

```

) +
  labs(title = "Sensitivity analysis") +
  facet_wrap(~ allocation_group)

`geom_smooth()` using formula = 'y ~ x'

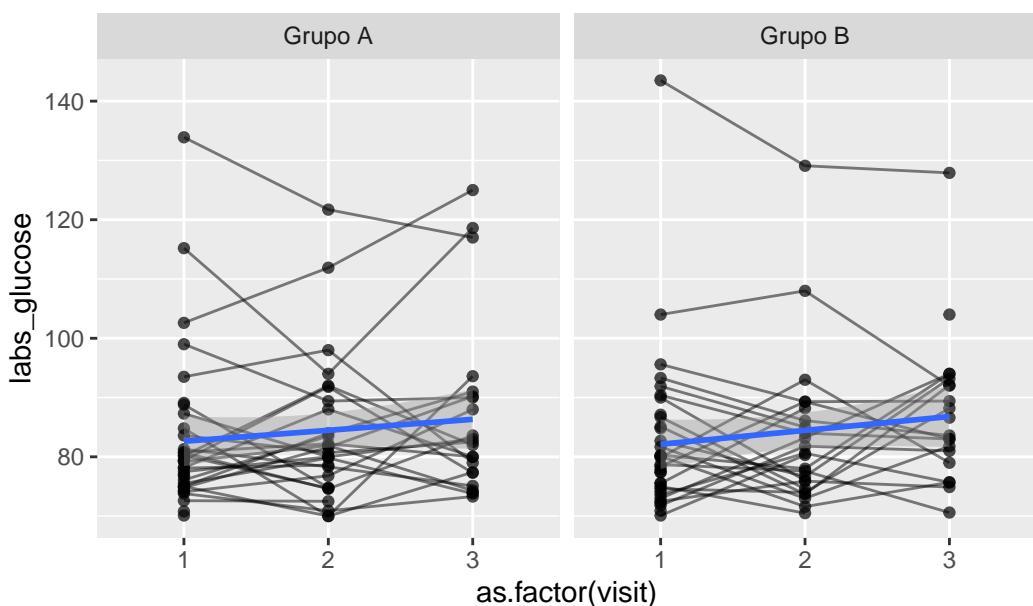
Warning: Removed 13 rows containing non-finite outside the scale range
(`stat_smooth()`).

Warning: Removed 11 rows containing missing values or values outside the scale range
(`geom_line()`).

Warning: Removed 13 rows containing missing values or values outside the scale range
(`geom_point()`).

```

Sensitivity analysis



```
#coord_cartesian(ylim = c(10, 150))
```

3.10 Hemoglobina Glicosilada

Variável: labs_hba1c

```

# Plot 1: Raw data
labs_hba1c_hist_1 <- data_model %>%
  #filter(
  #  labs_hba1c < 300
  #) %>%
  ggplot(aes(x = labs_hba1c)) +

```

```

geom_histogram(bins = 50, fill = "skyblue", color = "black")

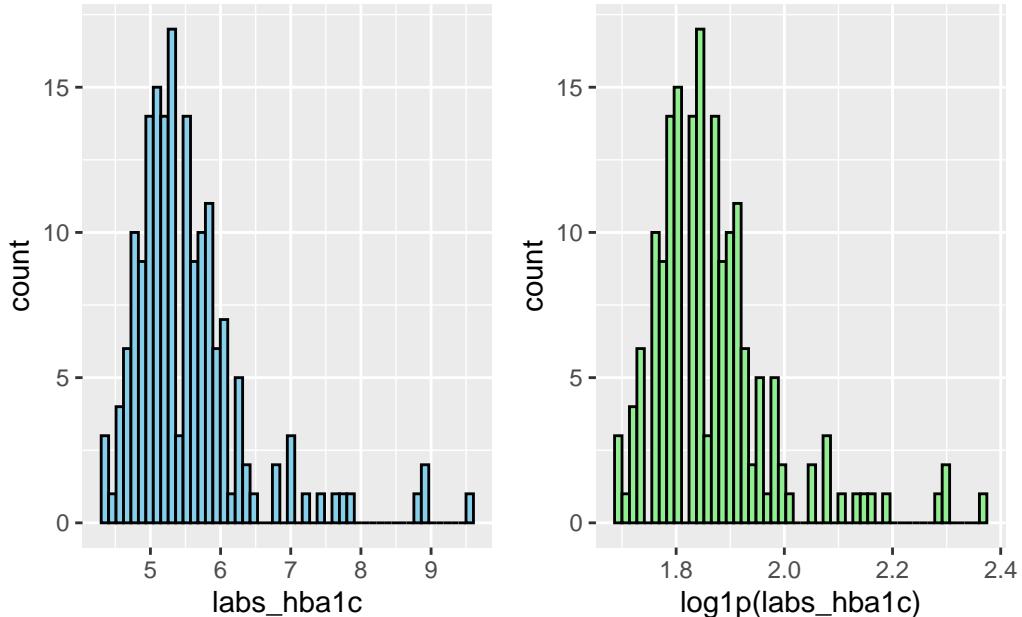
# Plot 2: Log-transformed data
labs_hba1c_hist_2 <- data_model %>%
  #filter(
  #  labs_hba1c < 300
  #) %>%
  ggplot(aes(x = log1p(labs_hba1c))) +
  geom_histogram(bins = 50, fill = "lightgreen", color = "black")

# Combine side by side
labs_hba1c_hist_1 + labs_hba1c_hist_2 # library(patchwork)

```

Warning: Removed 13 rows containing non-finite outside the scale range (`stat_bin()`).

Removed 13 rows containing non-finite outside the scale range (`stat_bin()`).



```

# LMM
labs_hba1c_model <- lmer(log1p(labs_hba1c) ~ allocation_group * visit +
(1 | record_id), data = data_model)
check_collinearity(labs_hba1c_model)

# Check for Multicollinearity

```

Low Correlation

```

Term   VIF    VIF 95% CI Increased SE Tolerance
allocation_group 1.06 [1.00, 1.93]      1.03      0.95
visit            3.65 [2.89, 4.70]      1.91      0.27
allocation_group:visit 3.74 [2.96, 4.82] 1.93      0.27
Tolerance 95% CI
[0.52, 1.00]
[0.21, 0.35]
[0.21, 0.34]

# Sensitivity analysis
labs_hba1c_model_check <- sensitivity_check_lmer(
  model = labs_hba1c_model,
  id_var = "record_id",
  top_n = 5)

# LMM Sensitivity
labs_hba1c_model_sens <- update(object = labs_hba1c_model,
                                    subset = !(record_id %in%
                                    labs_hba1c_model_check$influential_ids))

# Influential IDS
labs_hba1c_model_check$influential_ids
[1] "16" "17" "34" "56" "52"

```

3.10.1 Resumo dos modelos

```

# Model comparison
summary(labs_hba1c_model)

Linear mixed model fit by REML. t-tests use Satterthwaite's method [
lmerModLmerTest]

Formula: log1p(labs_hba1c) ~ allocation_group * visit + (1 | record_id)
Data: data_model

REML criterion at convergence: -411.1

```

Scaled residuals:

Min	1Q	Median	3Q	Max
-----	----	--------	----	-----

```
-3.3899 -0.3924 -0.0647  0.3801  3.3624
```

Random effects:

Groups	Name	Variance	Std.Dev.
record_id	(Intercept)	0.011000	0.10488
Residual		0.001301	0.03607

Number of obs: 176, groups: record_id, 75

Fixed effects:

	Estimate	Std. Error	df	t value							
(Intercept)	1.869e+00	1.823e-02	8.210e+01	102.481							
allocation_group	-1.949e-02	2.562e-02	8.210e+01	-0.761							
visit2	4.593e-04	9.355e-03	9.978e+01	0.049							
visit3	1.390e-02	1.007e-02	1.001e+02	1.381							
allocation_group:visit2	-4.818e-03	1.358e-02	1.003e+02	-0.355							
allocation_group:visit3	-2.942e-03	1.455e-02	1.005e+02	-0.202							
	Pr(> t)										
(Intercept)	<2e-16	***									
allocation_group	0.449										
visit2	0.961										
visit3	0.170										
allocation_group:visit2	0.724										
allocation_group:visit3	0.840										

Signif. codes:	0	'***'	0.001	'**'	0.01	'*'	0.05	'. '	0.1	' '	1

Correlation of Fixed Effects:

(Intr)	all_GB	visit2	visit3	a_GB:2	
allctn_grGB	-0.712				
visit2	-0.206	0.147			
visit3	-0.192	0.136	0.432		
allctn_GB:2	0.142	-0.200	-0.689	-0.297	
allctn_GB:3	0.133	-0.186	-0.299	-0.692	0.431

```
summary(labs_hba1c_model_sens)
```

```
Linear mixed model fit by REML. t-tests use Satterthwaite's method [  
lmerModLmerTest]
```

Formula: log1p(labs_hba1c) ~ allocation_group * visit + (1 | record_id)
Data: data_model
Subset: !(record_id %in% labs_hba1c_model_check\$influential_ids)

REML criterion at convergence: -468.7

Scaled residuals:

Min	1Q	Median	3Q	Max
-1.75531	-0.51316	-0.01487	0.45407	2.35285

Random effects:

Groups	Name	Variance	Std.Dev.
record_id	(Intercept)	0.0063862	0.07991
Residual		0.0006516	0.02553

Number of obs: 161, groups: record_id, 70

Fixed effects:

	Estimate	Std. Error	df	t value
(Intercept)	1.860e+00	1.398e-02	7.444e+01	133.059
allocation_group	-3.287e-02	2.006e-02	7.444e+01	-1.639
visit2	-4.313e-03	6.739e-03	8.855e+01	-0.640
visit3	8.905e-03	7.274e-03	8.877e+01	1.224
allocation_group:visit2	-3.267e-05	1.013e-02	8.909e+01	-0.003
allocation_group:visit3	3.675e-03	1.095e-02	8.925e+01	0.336

	Pr(> t)
(Intercept)	<2e-16 ***
allocation_group	0.106
visit2	0.524
visit3	0.224
allocation_group:visit2	0.997
allocation_group:visit3	0.738

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

(Intr) all_GB visit2 visit3 a_GB:2

```

allctn_grGB -0.697
visit2      -0.192  0.134
visit3      -0.178  0.124  0.430
allctn_GB:2  0.128 -0.183 -0.665 -0.286
allctn_GB:3  0.118 -0.170 -0.285 -0.664  0.423

performance::compare_performance(
  labs_hba1c_model,
  labs_hba1c_model_sens)

```

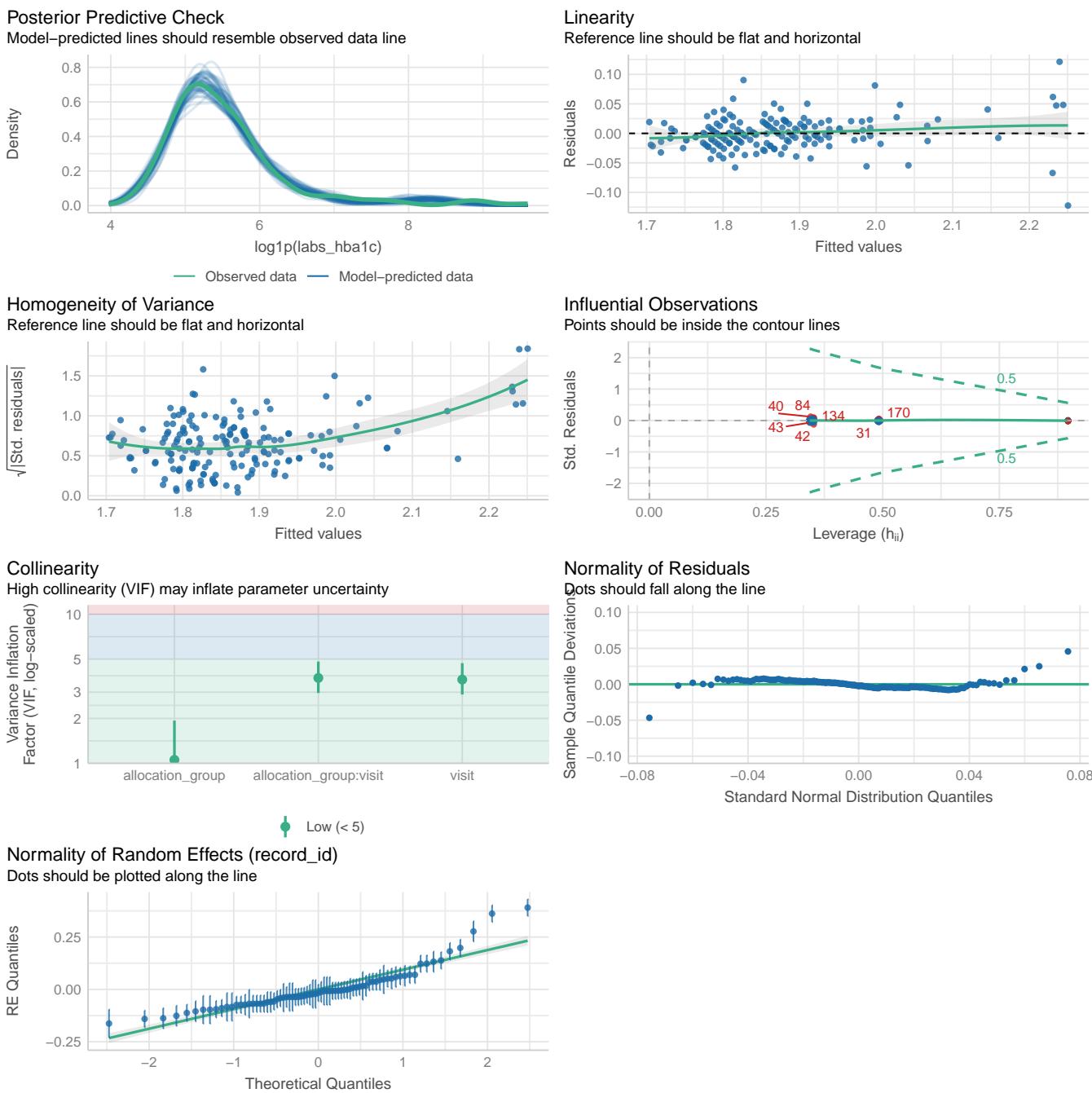
When comparing models, please note that probably not all models were fit from same data.

```
# Comparison of Model Performance Indices
```

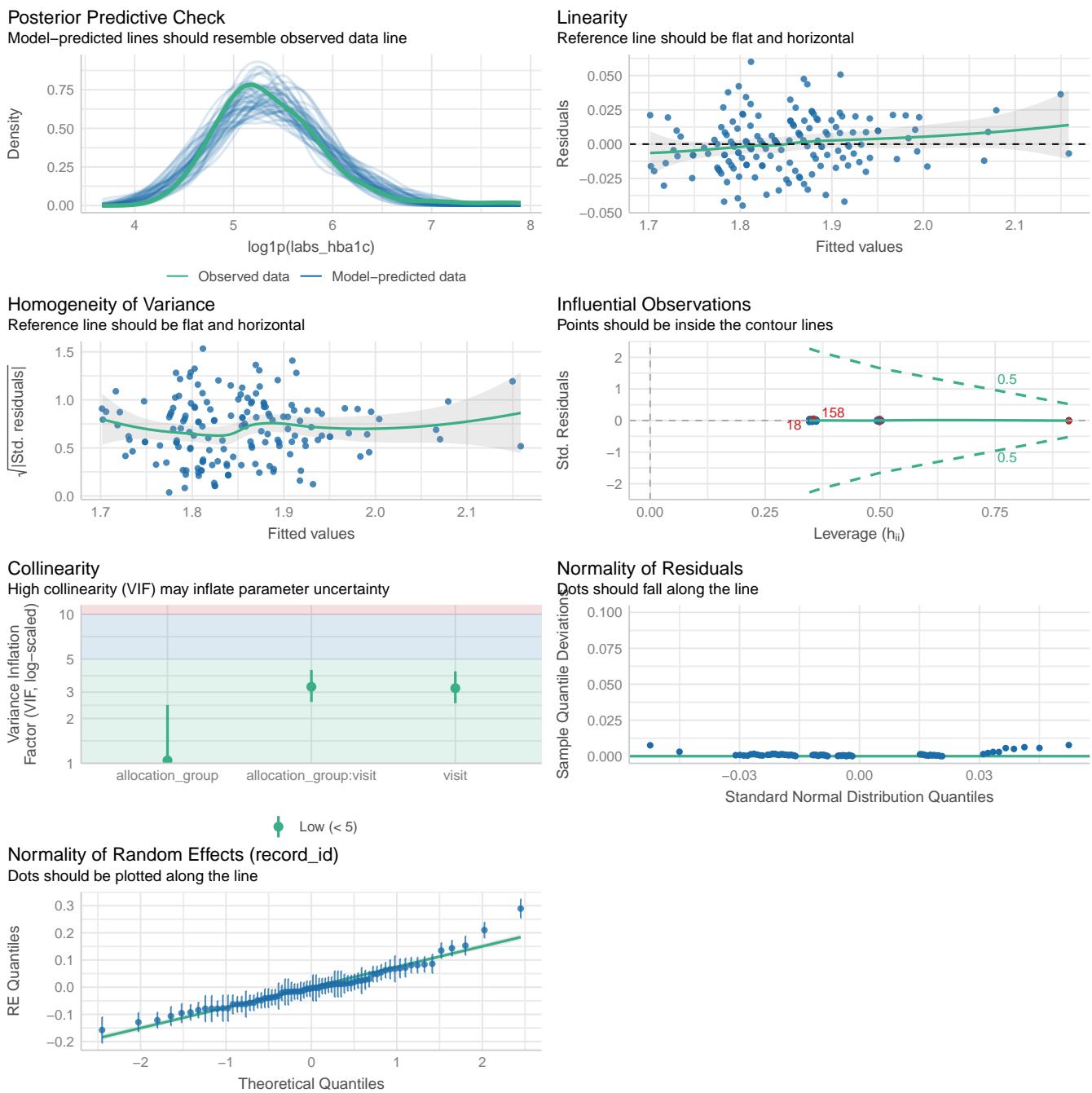
Name	Model	AIC (weights)	AICc (weights)
labs_hba1c_model	lmerModLmerTest	220.5 (<.001)	221.4 (<.001)
labs_hba1c_model_sens	lmerModLmerTest	97.5 (>.999)	98.5 (>.999)

Name	BIC (weights)	R2 (cond.)	R2 (marg.)	ICC	RMSE	Sigma
labs_hba1c_model	245.9 (<.001)	0.896	0.013	0.894	0.027	0.036
labs_hba1c_model_sens	122.2 (>.999)	0.911	0.040	0.907	0.019	0.026

```
performance::check_model(labs_hba1c_model)
```



```
performance::check_model(labs_hba1c_model_sens)
```



3.10.2 Médias Marginais Estimadas

3.10.2.1 Todos os dados

```
# Get EMMs for each group at each visit
labs_hba1c_raw_emm <- emmeans::emmeans(
  labs_hba1c_model,
  ~ allocation_group * visit
```

```

)

labs_hba1c_raw_emm <- regrid(labs_hba1c_raw_emm)

# Table of marginal means
# labs_hba1c_raw_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(labs_hba1c_raw_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

visit = 1:
  contrast      estimate      SE   df lower.CL upper.CL t.ratio p.value
  Grupo A - Grupo B    0.125 0.164 81.1    -0.202     0.452    0.761  0.4490

visit = 2:
  contrast      estimate      SE   df lower.CL upper.CL t.ratio p.value
  Grupo A - Grupo B    0.156 0.170 88.7    -0.181     0.493    0.918  0.3614

visit = 3:
  contrast      estimate      SE   df lower.CL upper.CL t.ratio p.value
  Grupo A - Grupo B    0.146 0.175 94.9    -0.203     0.494    0.831  0.4082

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95

# Pairwise comparisons: Changes over time within each group
emmeans::contrast(labs_hba1c_raw_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

allocation_group = Grupo A:
  contrast      estimate      SE   df lower.CL upper.CL t.ratio p.value
  visit1 - visit2 -0.00298 0.0607 81.1    -0.151    0.1453   -0.049  1.0000
  visit1 - visit3 -0.09069 0.0659 81.1    -0.252    0.0703   -1.377  0.5171
  visit2 - visit3 -0.08772 0.0678 88.7    -0.253    0.0776   -1.294  0.5966

```

```

allocation_group = Grupo B:
contrast      estimate      SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit2  0.02764 0.0624 81.1    -0.125   0.1803   0.443  1.0000
visit1 - visit3 -0.07002 0.0673 81.1    -0.235   0.0946  -1.040  0.9044
visit2 - visit3 -0.09765 0.0695 93.9    -0.267   0.0717  -1.406  0.4891

```

Degrees-of-freedom method: inherited from kenward-roger when re-gridding

Confidence level used: 0.95

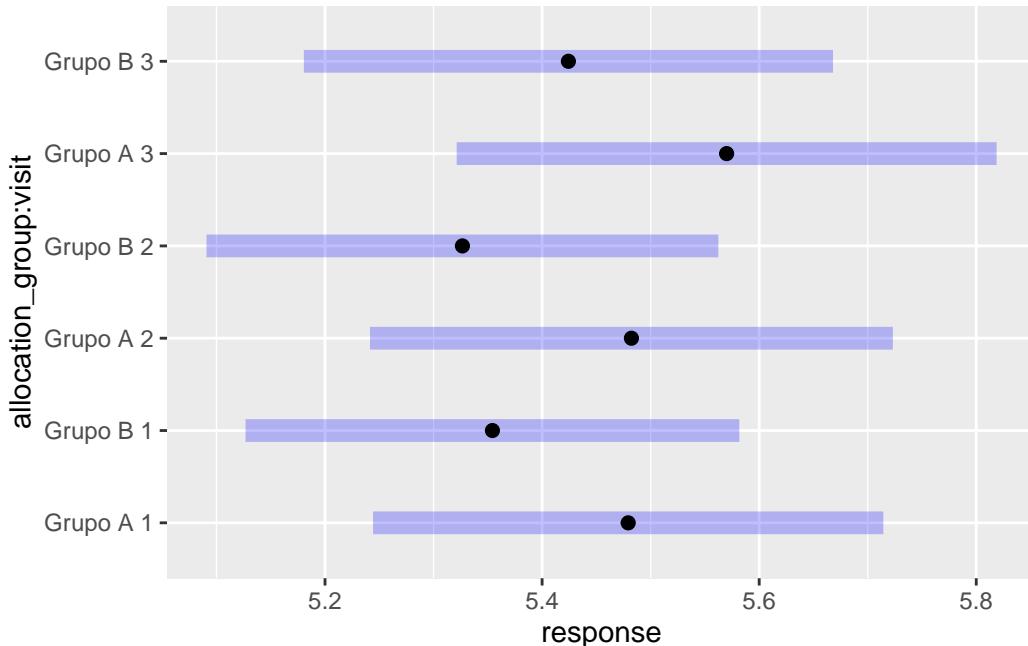
Conf-level adjustment: bonferroni method for 3 estimates

P value adjustment: bonferroni method for 3 tests

```

# Plot of marginal means
plot(labs_hba1c_raw_emm)

```



3.10.2.2 Análise de sensibilidade

```

# Get EMMs for each group at each visit (Sensitivity Analysis)
labs_hba1c_emm <- emmeans::emmeans(
  labs_hba1c_model_sens,
  ~ allocation_group * visit
)

# Table of marginal means

```

```

# labs_hba1c_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(labs_hba1c_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

visit = 1:
  contrast      estimate      SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B  0.0329 0.0201 74.3 -0.00710  0.0728   1.639  0.1055

visit = 2:
  contrast      estimate      SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B  0.0329 0.0208 83.8 -0.00837  0.0742   1.586  0.1166

visit = 3:
  contrast      estimate      SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B  0.0292 0.0212 89.7 -0.01286  0.0713   1.379  0.1712

```

Note: contrasts are still on the log1p scale. Consider using
`regrid()` if you want contrasts of back-transformed estimates.

Degrees-of-freedom method: kenward-roger

Confidence level used: 0.95

```

# Pairwise comparisons: Changes over time within each group
emmeans::contrast(labs_hba1c_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

allocation_group = Grupo A:
  contrast      estimate      SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit2  0.00431 0.00674 88.4  -0.0121  0.02076   0.640  1.0000
visit1 - visit3 -0.00890 0.00728 88.7  -0.0267  0.00885  -1.224  0.6731
visit2 - visit3 -0.01322 0.00750 87.8  -0.0315  0.00509  -1.763  0.2444

allocation_group = Grupo B:
  contrast      estimate      SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit2  0.00435 0.00757 89.4  -0.0141  0.02282   0.574  1.0000

```

```

visit1 - visit3 -0.01258 0.00819 89.5 -0.0326 0.00741 -1.536 0.3845
visit2 - visit3 -0.01693 0.00852 87.9 -0.0377 0.00387 -1.986 0.1504

```

Note: contrasts are still on the log1p scale. Consider using
regrid() if you want contrasts of back-transformed estimates.

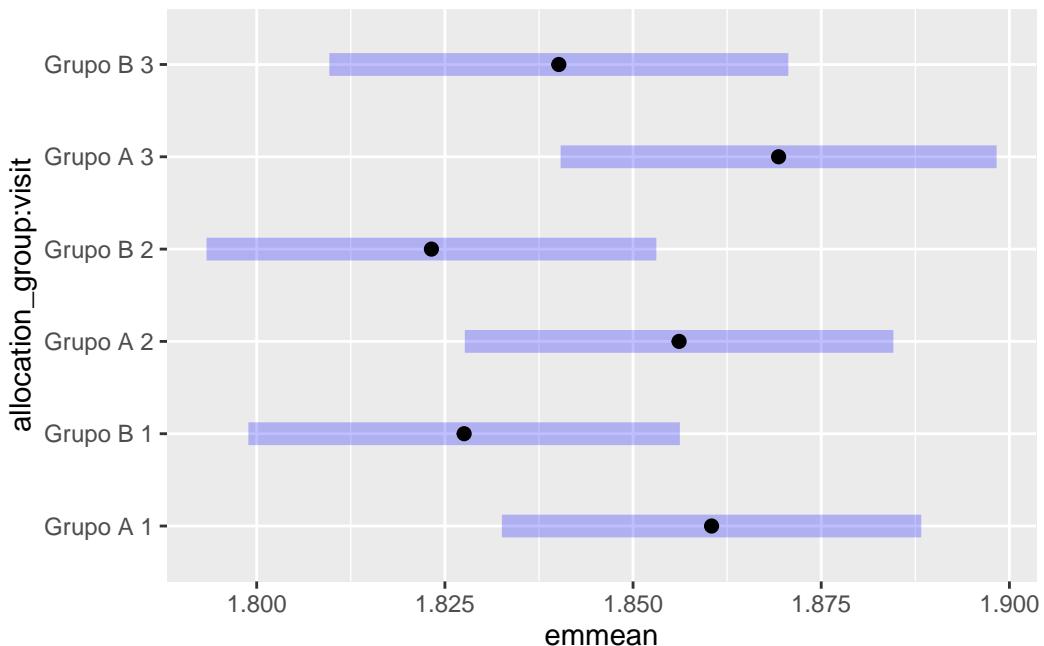
Degrees-of-freedom method: kenward-roger

Confidence level used: 0.95

Conf-level adjustment: bonferroni method for 3 estimates

P value adjustment: bonferroni method for 3 tests

```
# Plot of marginal means
plot(labs_hba1c_emm)
```



3.10.3 Resultado

No modelo ajustado para os níveis de hemoglobina glicada (HbA1c), não foram observadas diferenças estatisticamente significativas entre os grupos em nenhum dos três momentos avaliados. Da mesma forma, não houve mudanças significativas ao longo do tempo dentro de cada grupo. A análise de sensibilidade, realizada após a exclusão de observações influentes, confirmou a estabilidade das estimativas. As diferenças entre os grupos e entre as visitas permaneceram não significativas. As estimativas, intervalos de confiança de 95% e valores de p estão apresentados na Tabela 10.

Tabela 10: Diferenças estimadas dos níveis de hemoglobina glicada (HbA1c) entre os grupos de alocação (placebo vs Eclipta) e entre visitas dentro de cada grupo

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 1	0,13	[-0,20 ; 0,45]	0,449
Entre grupos	Visita 2	0,16	[-0,18 ; 0,49]	0,361
Entre grupos	Visita 3	0,15	[-0,20 ; 0,49]	0,408
Grupo Placebo	Visita 1 - Visita 2	0,00	[-0,15 ; 0,15]	1,000
Grupo Placebo	Visita 1 - Visita 3	-0,09	[-0,25 ; 0,07]	0,517
Grupo Placebo	Visita 2 - Visita 3	-0,09	[-0,25 ; 0,08]	0,597
Grupo Eclipta	Visita 1 - Visita 2	0,03	[-0,13 ; 0,18]	1,000
Grupo Eclipta	Visita 1 - Visita 3	-0,07	[-0,24 ; 0,09]	0,904
Grupo Eclipta	Visita 2 - Visita 3	-0,10	[-0,27 ; 0,07]	0,489

```

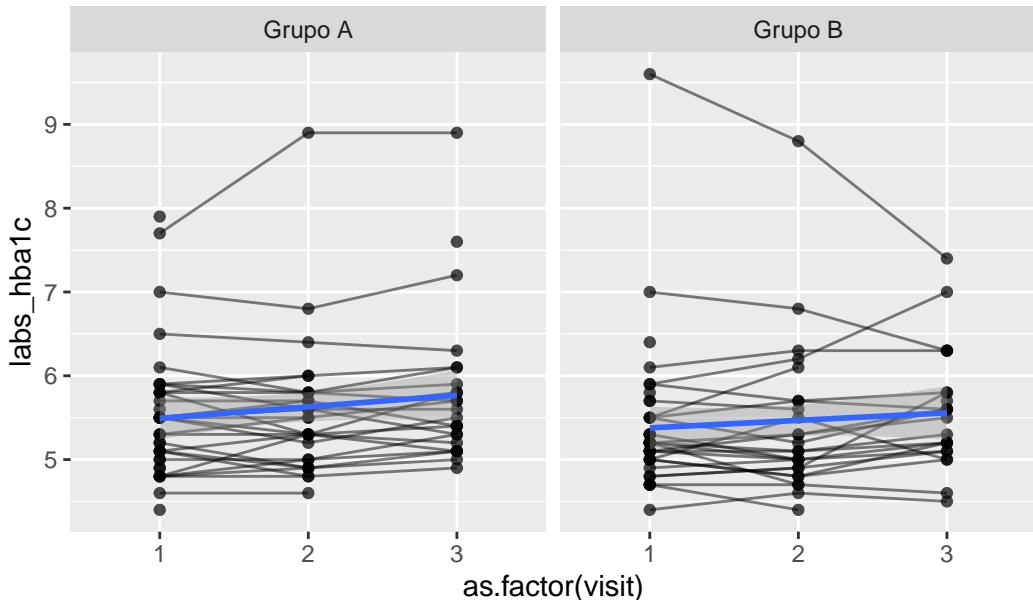
ggplot(
  data = data_model,
  aes(
    x = as.factor(visit),
    y = labs_hb1c,
    group = record_id,
  )
) +
  geom_line(alpha = 0.5) +
  geom_point(alpha = 0.7) +
  geom_smooth(
    aes(group = allocation_group),
    method = "lm",
    se = TRUE,
    linewidth = 1
  ) +
  labs(title = "All data") +
  facet_wrap(~ allocation_group)

`geom_smooth()` using formula = 'y ~ x'
Warning: Removed 13 rows containing non-finite outside the scale range
(`stat_smooth()`).
Warning: Removed 9 rows containing missing values or values outside the scale range

```

```
(`geom_line()`).
Warning: Removed 13 rows containing missing values or values outside the scale range
(`geom_point()`).
```

All data



```
#coord_cartesian(ylim = c(10, 150))

data_model %>%
  filter(
    !(record_id %in%
      labs_hba1c_model_check$influential_ids)
  ) %>%
  ggplot(
    aes(
      x = as.factor(visit),
      y = labs_hba1c,
      group = record_id,
    )
  ) +
  geom_line(alpha = 0.5) +
  geom_point(alpha = 0.7) +
  geom_smooth(
    aes(group = allocation_group),
    method = "lm",
  )
```

```

    se = TRUE,
    linewidth = 1
) +
  labs(title = "Sensitivity analysis") +
  facet_wrap(~ allocation_group)

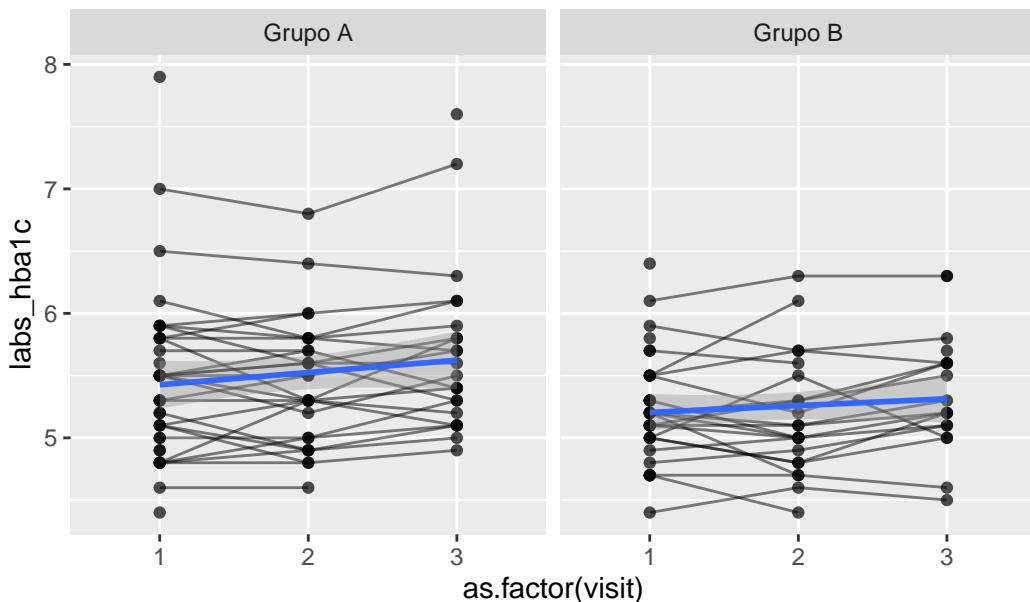
`geom_smooth()` using formula = 'y ~ x'
Warning: Removed 13 rows containing non-finite outside the scale range
(`stat_smooth()`).

Warning: Removed 9 rows containing missing values or values outside the scale range
(`geom_line()`).

Warning: Removed 13 rows containing missing values or values outside the scale range
(`geom_point()`).

```

Sensitivity analysis



```
#coord_cartesian(ylim = c(10, 150))
```

3.11 Insulina

Variável: labs_insulin

```

# Plot 1: Raw data
labs_insulin_hist_1 <- data_model %>%
  #filter(
  #  labs_insulin < 300

```

```

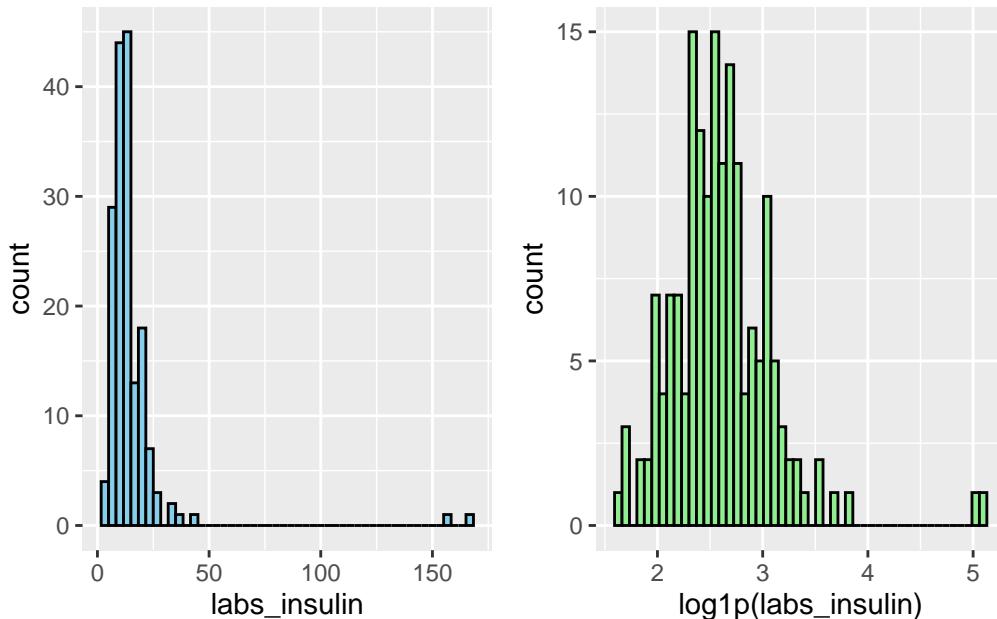
#) %>%
ggplot(aes(x = labs_insulin)) +
  geom_histogram(bins = 50, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
labs_insulin_hist_2 <- data_model %>%
  #filter(
  #  labs_insulin < 300
  #) %>%
  ggplot(aes(x = log1p(labs_insulin))) +
  geom_histogram(bins = 50, fill = "lightgreen", color = "black")

# Combine side by side
labs_insulin_hist_1 + labs_insulin_hist_2 # library(patchwork)

```

Warning: Removed 20 rows containing non-finite outside the scale range (`stat_bin()`).
 Removed 20 rows containing non-finite outside the scale range (`stat_bin()`).



```

# LMM
labs_insulin_model <- lmer(log1p(labs_insulin) ~ allocation_group * visit +
(1 | record_id), data = data_model)
check_collinearity(labs_insulin_model)

# Check for Multicollinearity

```

Low Correlation

Term	VIF	VIF 95% CI	Increased SE	Tolerance
allocation_group	1.22	[1.09, 1.56]	1.10	0.82
visit	3.48	[2.75, 4.49]	1.86	0.29
allocation_group:visit	3.83	[3.02, 4.97]	1.96	0.26

Tolerance 95% CI

[0.64, 0.92]
[0.22, 0.36]
[0.20, 0.33]

```
# Sensitivity analysis
labs_insulin_model_check <- sensitivity_check_lmer(
  model = labs_insulin_model,
  id_var = "record_id",
  top_n = 5)

# LMM Sensitivity
labs_insulin_model_sens <- update(object = labs_insulin_model,
                                     subset = !(record_id %in%
                                     labs_insulin_model_check$influential_ids))

# Influential IDs
labs_insulin_model_check$influential_ids

[1] "2"  "11" "19" "16" "4"
```

3.11.1 Resumo dos modelos

```
# Model comparison
summary(labs_insulin_model)

Linear mixed model fit by REML. t-tests use Satterthwaite's method [
lmerModLmerTest]

Formula: log1p(labs_insulin) ~ allocation_group * visit + (1 | record_id)

Data: data_model

REML criterion at convergence: 187.4
```

Scaled residuals:

Min	1Q	Median	3Q	Max
-1.96281	-0.57160	-0.06048	0.44965	2.54304

Random effects:

Groups	Name	Variance	Std.Dev.
record_id	(Intercept)	0.14686	0.3832
Residual		0.08142	0.2853

Number of obs: 169, groups: record_id, 74

Fixed effects:

	Estimate	Std. Error	df	t value	Pr(> t)
(Intercept)	2.64624	0.07855	107.03898	33.689	<2e-16
allocation_group	-0.03170	0.11108	107.03898	-0.285	0.7759
visit2	-0.16405	0.07413	100.79694	-2.213	0.0291
visit3	-0.03592	0.07987	102.16292	-0.450	0.6538
allocation_group:visit2	0.08449	0.10664	101.86854	0.792	0.4300
allocation_group:visit3	0.06963	0.11919	103.64642	0.584	0.5603

(Intercept) ***

allocation_group

visit2 *

visit3

allocation_group:visit2

allocation_group:visit3

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

(Intr)	all_GB	visit2	visit3	a_GB:2
allctn_grGB	-0.707			
visit2	-0.378	0.267		
visit3	-0.351	0.248	0.409	
allctn_GB:2	0.263	-0.372	-0.695	-0.284
allctn_GB:3	0.235	-0.332	-0.274	-0.670
				0.394

```
summary(labs_insulin_model_sens)
```

Linear mixed model fit by REML. t-tests use Satterthwaite's method [
lmerModLmerTest]

Formula: log1p(labs_insulin) ~ allocation_group * visit + (1 | record_id)

Data: data_model

Subset: !(record_id %in% labs_insulin_model_check\$influential_ids)

REML criterion at convergence: 115.2

Scaled residuals:

Min	1Q	Median	3Q	Max
-1.80008	-0.61531	-0.03624	0.53209	1.86528

Random effects:

Groups	Name	Variance	Std.Dev.
record_id	(Intercept)	0.08728	0.2954
Residual		0.05932	0.2436

Number of obs: 154, groups: record_id, 69

Fixed effects:

	Estimate	Std. Error	df	t value	Pr(> t)
(Intercept)	2.57731	0.06381	101.20590	40.388	<2e-16
allocation_group	0.04862	0.09228	101.20590	0.527	0.599
visit2	-0.12539	0.06422	88.77727	-1.952	0.054
visit3	-0.05126	0.06938	90.33134	-0.739	0.462
allocation_group:visit2	0.06302	0.09543	90.36785	0.660	0.511
allocation_group:visit3	0.05725	0.10923	92.66742	0.524	0.601

(Intercept) ***

allocation_group

visit2 .

visit3

allocation_group:visit2

allocation_group:visit3

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```
Correlation of Fixed Effects:
```

```
(Intr) all_GB visit2 visit3 a_GB:2  
allctn_grGB -0.692  
visit2      -0.402  0.278  
visit3      -0.372  0.257  0.405  
allctn_GB:2  0.271 -0.391 -0.673 -0.272  
allctn_GB:3  0.236 -0.342 -0.257 -0.635  0.376
```

```
performance::compare_performance(  
  labs_insulin_model,  
  labs_insulin_model_sens)
```

When comparing models, please note that probably not all models were fit from same data.

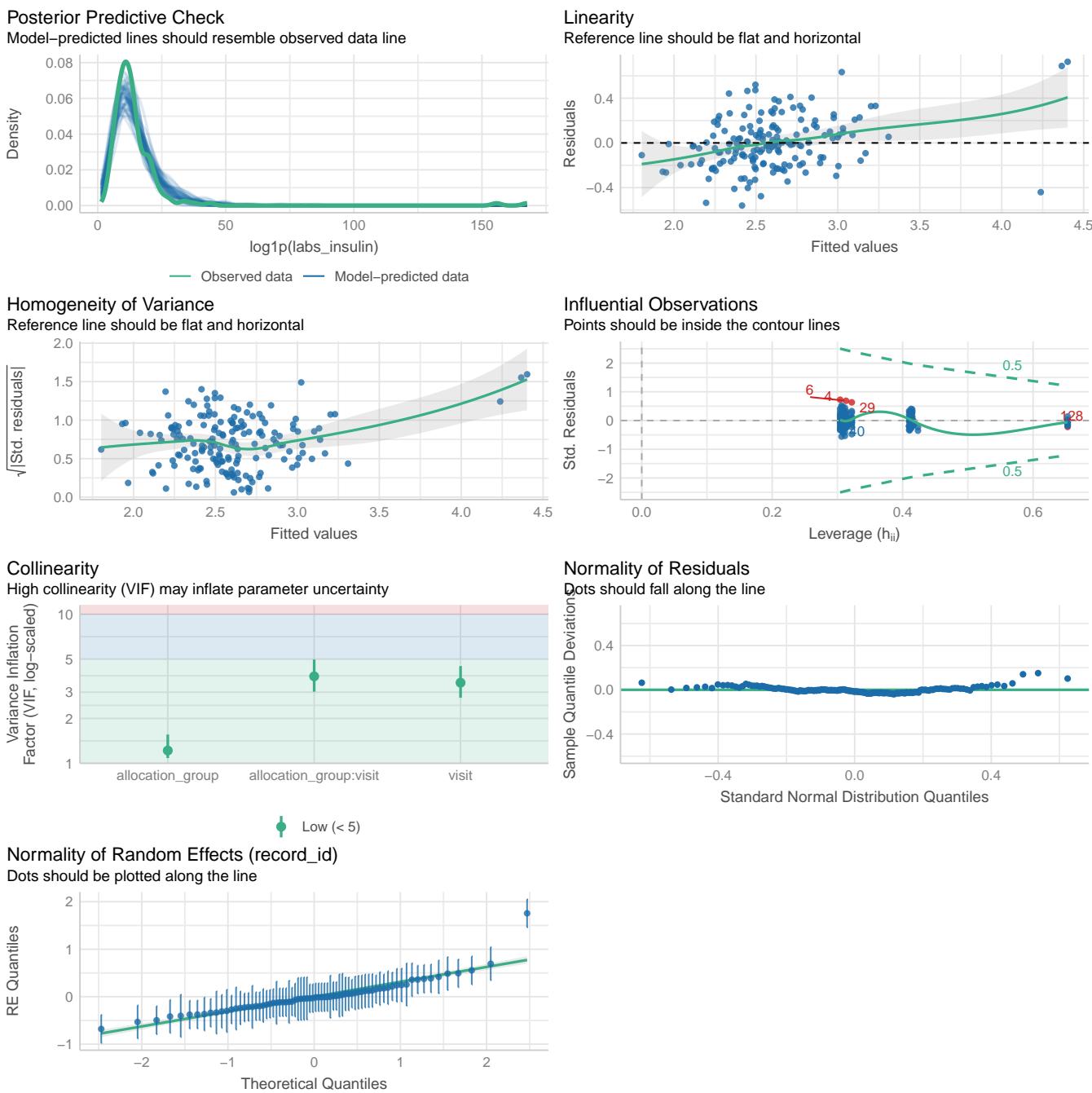
```
# Comparison of Model Performance Indices
```

Name	Model	AIC (weights)	AICc (weights)
labs_insulin_model	lmerModLmerTest	1062.1 (<.001)	1063.0 (<.001)
labs_insulin_model_sens	lmerModLmerTest	900.0 (>.999)	901.0 (>.999)

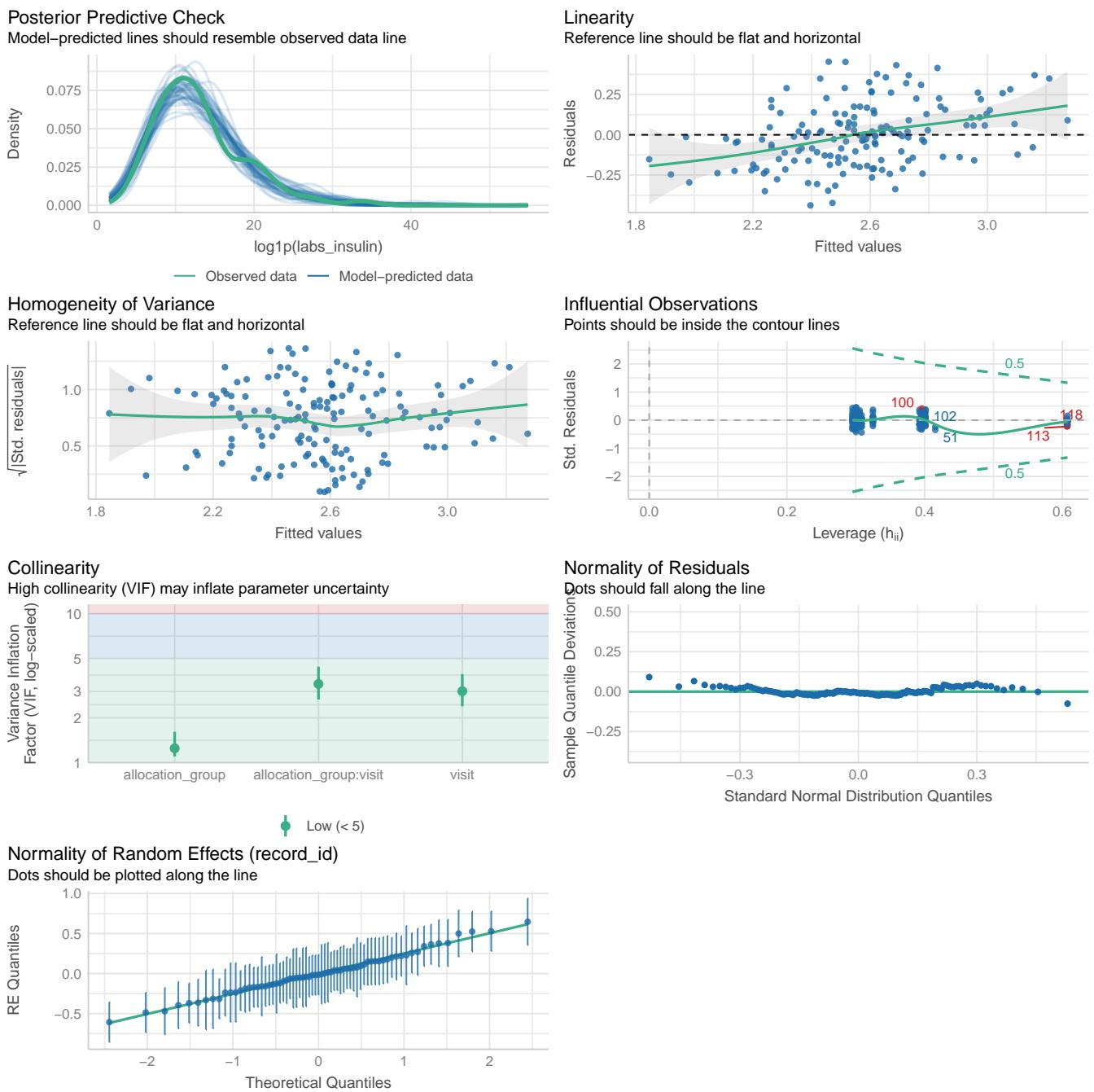
Name	BIC (weights)	R2 (cond.)	R2 (marg.)	ICC
labs_insulin_model	1087.2 (<.001)	0.649	0.016	0.643
labs_insulin_model_sens	924.3 (>.999)	0.605	0.025	0.595

Name	RMSE	Sigma
labs_insulin_model	0.227	0.285
labs_insulin_model_sens	0.195	0.244

```
performance::check_model(labs_insulin_model)
```



```
performance::check_model(labs_insulin_model_sens)
```



3.11.2 Médias Marginais Estimadas

3.11.2.1 Todos os dados

```
# Get EMMs for each group at each visit
labs_insulin_raw_emm <- emmeans::emmeans(
  labs_insulin_model,
  ~ allocation_group * visit
```

```

)

labs_insulin_raw_emm <- regrid(labs_insulin_raw_emm)

# Table of marginal means
# labs_insulin_raw_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(labs_insulin_raw_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

visit = 1:
  contrast      estimate   SE  df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    0.440 1.54 103     -2.62      3.50   0.285  0.7760

visit = 2:
  contrast      estimate   SE  df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B   -0.649 1.50 125     -3.63      2.33  -0.431  0.6669

visit = 3:
  contrast      estimate   SE  df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B   -0.526 1.85 139     -4.19      3.14  -0.284  0.7770

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95

# Pairwise comparisons: Changes over time within each group
emmeans::contrast(labs_insulin_raw_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

allocation_group = Grupo A:
  contrast      estimate   SE  df lower.CL upper.CL t.ratio p.value
visit1 - visit2    2.133 0.964 103    -0.213     4.48   2.213  0.0873
visit1 - visit3    0.498 1.100 103    -2.186     3.18   0.451  1.0000
visit2 - visit3   -1.636 1.090 125    -4.280     1.01  -1.502  0.4072

```

```

allocation_group = Grupo B:

contrast      estimate     SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit2    1.045 1.000 103    -1.393      3.48    1.043  0.8981
visit1 - visit3   -0.468 1.240 103    -3.490      2.55   -0.377  1.0000
visit2 - visit3   -1.513 1.260 130    -4.566      1.54   -1.202  0.6945

```

Degrees-of-freedom method: inherited from kenward-roger when re-gridding

Confidence level used: 0.95

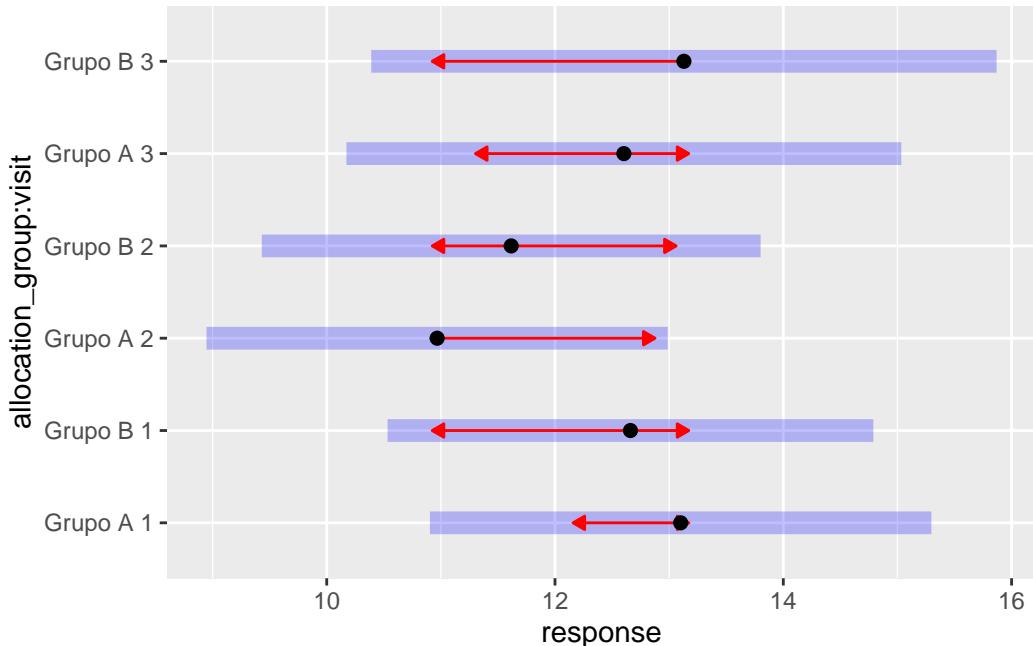
Conf-level adjustment: bonferroni method for 3 estimates

P value adjustment: bonferroni method for 3 tests

```

# Plot of marginal means
plot(labs_insulin_raw_emm, comparisons = TRUE)

```



3.11.2.2 Análise de sensibilidade

```

# Get EMMs for each group at each visit (Sensitivity Analysis)
labs_insulin_emm <- emmeans::emmeans(
  labs_insulin_model_sens,
  ~ allocation_group * visit
)

labs_insulin_emm <- regrid(labs_insulin_emm)

```

```

# Table of marginal means

# labs_insulin_emm

# Pairwise comparisons: Between groups at each visit

emmeans::contrast(labs_insulin_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

visit = 1:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B   -0.656 1.25 99.9    -3.13     1.82  -0.526  0.6000

visit = 2:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B   -1.371 1.28 120.3    -3.91     1.17  -1.068  0.2876

visit = 3:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B   -1.396 1.56 133.2    -4.48     1.68  -0.897  0.3714

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95

# Pairwise comparisons: Changes over time within each group

emmeans::contrast(labs_insulin_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

allocation_group = Grupo A:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit2    1.551 0.792 99.9    -0.377     3.48   1.959  0.1586
visit1 - visit3    0.658 0.886 99.9    -1.499     2.81   0.743  1.0000
visit2 - visit3   -0.893 0.888 120.3    -3.049     1.26  -1.006  0.9490

allocation_group = Grupo B:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit2    0.835 0.941 99.9    -1.456     3.13   0.888  1.0000
visit1 - visit3   -0.083 1.170 99.9    -2.943     2.78  -0.071  1.0000

```

```
visit2 - visit3 -0.919 1.210 127.6 -3.848 2.01 -0.761 1.0000
```

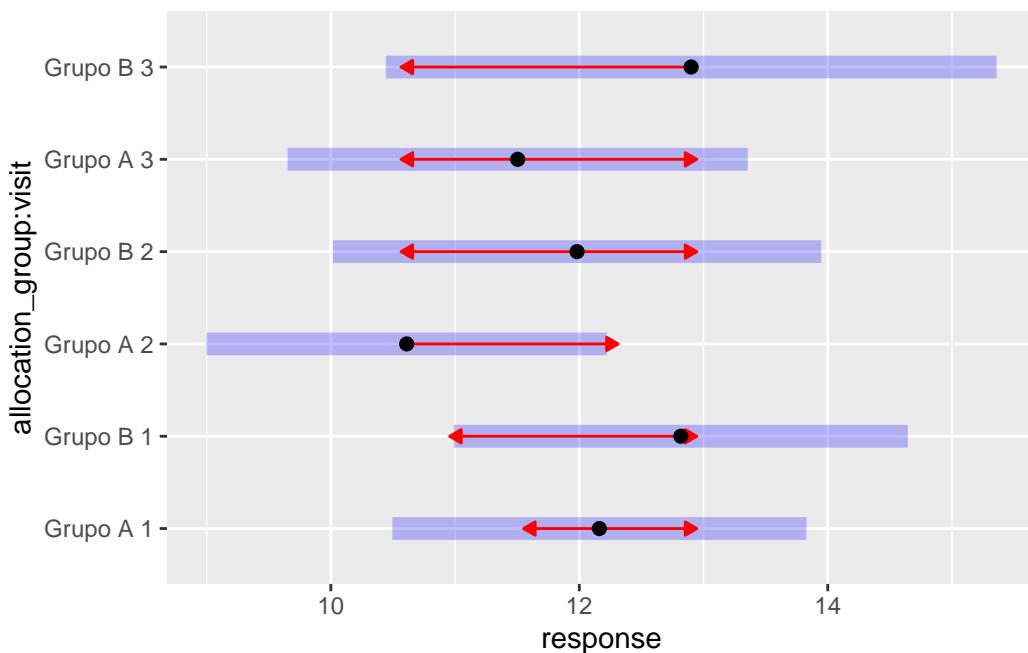
Degrees-of-freedom method: inherited from kenward-roger when re-gridding

Confidence level used: 0.95

Conf-level adjustment: bonferroni method for 3 estimates

P value adjustment: bonferroni method for 3 tests

```
# Plot of marginal means  
plot(labs_insulin_emm, comparisons = TRUE)
```



3.11.3 Resultado

No modelo ajustado para os níveis de insulina, não foram observadas diferenças estatisticamente significativas entre os grupos em nenhum dos três momentos avaliados. Também não foram encontradas mudanças significativas ao longo do tempo dentro de cada grupo. A análise de sensibilidade, realizada com a exclusão das observações influentes, confirmou a ausência de diferenças significativas entre os grupos e ao longo das visitas, com estimativas semelhantes às observadas na análise principal. As estimativas, intervalos de confiança de 95% e valores de p estão apresentados na Tabela 11.

Tabela 11: Diferenças estimadas dos níveis de insulina entre os grupos de alocação (placebo vs Eclipta) e entre visitas dentro de cada grupo

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 1	0,44	[-2,62 ; 3,50]	0,776
Entre grupos	Visita 2	-0,65	[-3,63 ; 2,33]	0,667

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 3	-0,53	[-4,19 ; 3,14]	0,777
Grupo Placebo	Visita 1 - Visita 2	2,13	[-0,21 ; 4,48]	0,087
Grupo Placebo	Visita 1 - Visita 3	0,50	[-2,19 ; 3,18]	1,000
Grupo Placebo	Visita 2 - Visita 3	-1,64	[-4,28 ; 1,01]	0,407
Grupo Eclipta	Visita 1 - Visita 2	1,05	[-1,39 ; 3,48]	0,898
Grupo Eclipta	Visita 1 - Visita 3	-0,47	[-3,49 ; 2,55]	1,000
Grupo Eclipta	Visita 2 - Visita 3	-1,51	[-4,57 ; 1,54]	0,695

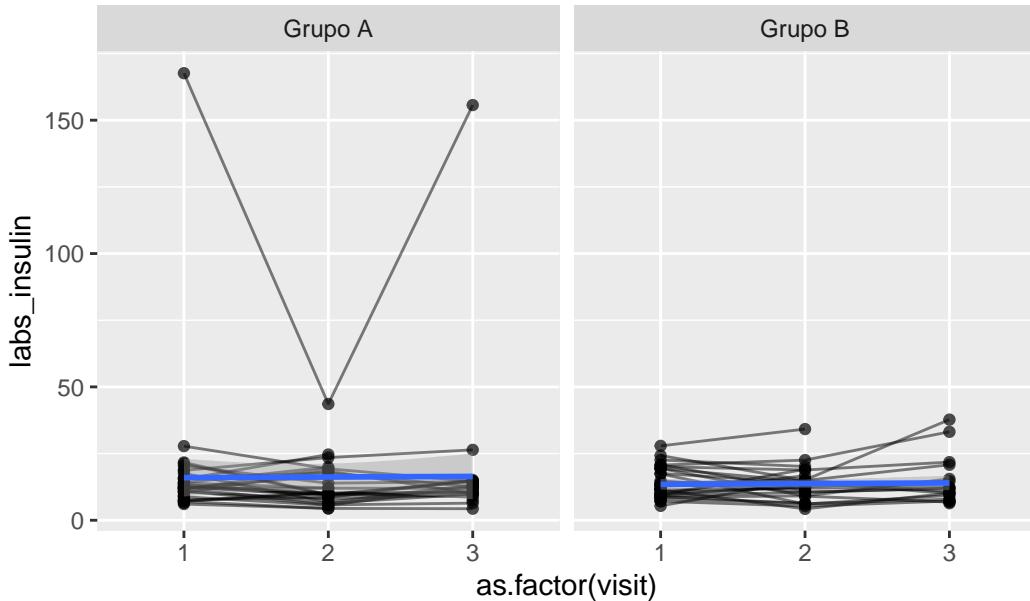
```

ggplot(
  data = data_model,
  aes(
    x = as.factor(visit),
    y = labs_insulin,
    group = record_id,
  )
) +
  geom_line(alpha = 0.5) +
  geom_point(alpha = 0.7) +
  geom_smooth(
    aes(group = allocation_group),
    method = "lm",
    se = TRUE,
    linewidth = 1
  ) +
  labs(title = "All data") +
  facet_wrap(~ allocation_group)

`geom_smooth()` using formula = 'y ~ x'
Warning: Removed 20 rows containing non-finite outside the scale range
(`stat_smooth()`).
Warning: Removed 15 rows containing missing values or values outside the scale range
(`geom_line()`).
Warning: Removed 20 rows containing missing values or values outside the scale range
(`geom_point()`).

```

All data



```
#coord_cartesian(ylim = c(10, 150))

data_model %>%
  filter(
    !(record_id %in%
      labs_insulin_model_check$influential_ids)
  ) %>%
  ggplot(
    aes(
      x = as.factor(visit),
      y = labs_insulin,
      group = record_id,
    )
  ) +
  geom_line(alpha = 0.5) +
  geom_point(alpha = 0.7) +
  geom_smooth(
    aes(group = allocation_group),
    method = "lm",
    se = TRUE,
    linewidth = 1
```

```

) +
  labs(title = "Sensitivity analysis") +
  facet_wrap(~ allocation_group)

`geom_smooth()` using formula = 'y ~ x'

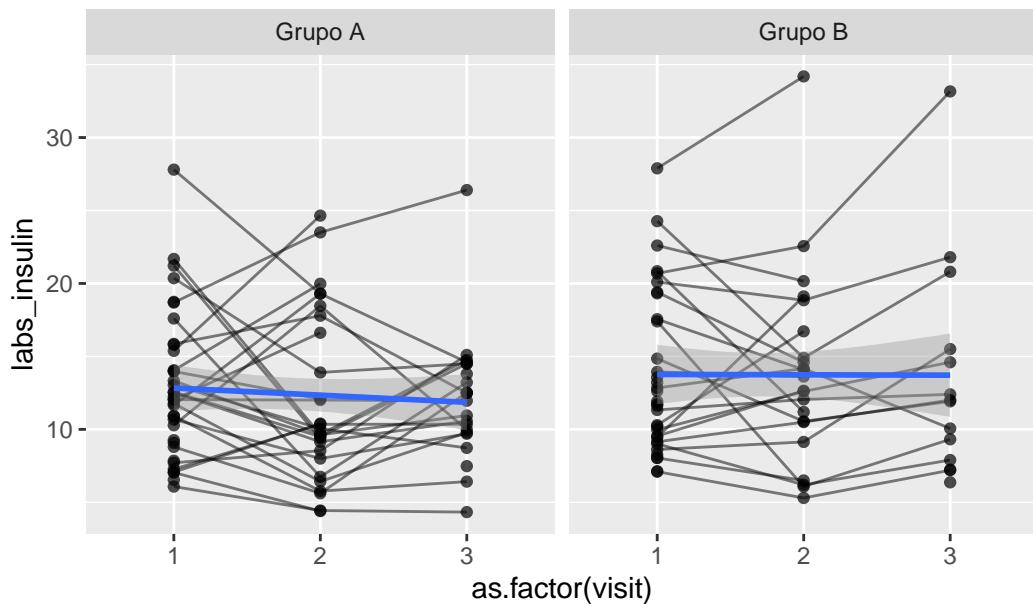
Warning: Removed 20 rows containing non-finite outside the scale range
(`stat_smooth()`).

Warning: Removed 15 rows containing missing values or values outside the scale range
(`geom_line()`).

Warning: Removed 20 rows containing missing values or values outside the scale range
(`geom_point()`).

```

Sensitivity analysis



```
#coord_cartesian(ylim = c(10, 150))
```

3.12 HOMA-IR

Variável: labs_homa_ir

```
# Plot 1: Raw data
labs_homa_ir_hist_1 <- data_model %>%
  #filter(
  #  labs_homa_ir < 300
  #) %>%
  ggplot(aes(x = labs_homa_ir)) +
```

```

geom_histogram(bins = 50, fill = "skyblue", color = "black")

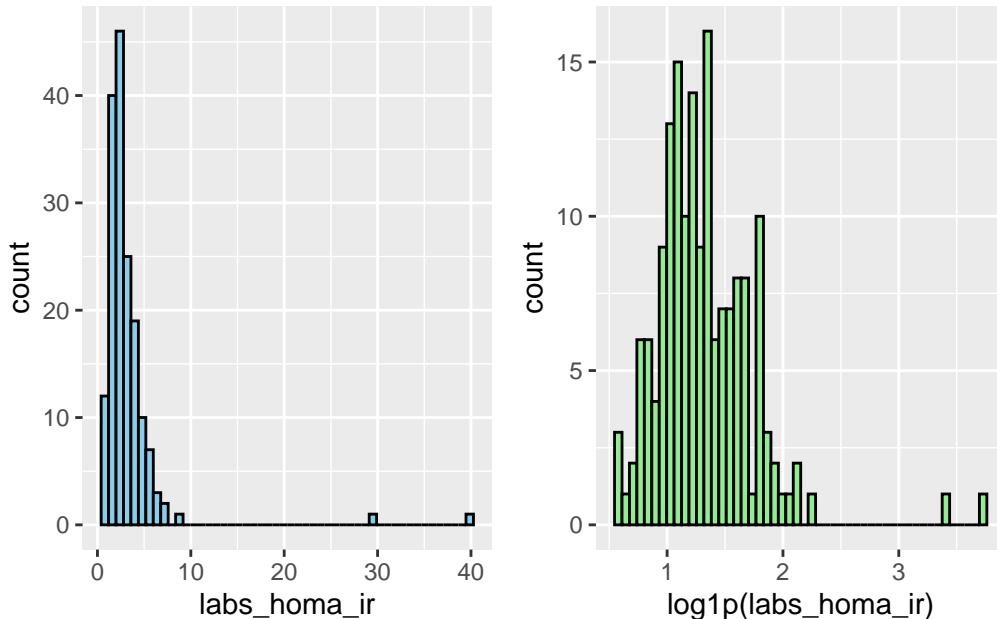
# Plot 2: Log-transformed data
labs_homa_ir_hist_2 <- data_model %>%
  #filter(
  #  labs_homa_ir < 300
  #) %>%
  ggplot(aes(x = log1p(labs_homa_ir))) +
  geom_histogram(bins = 50, fill = "lightgreen", color = "black")

# Combine side by side
labs_homa_ir_hist_1 + labs_homa_ir_hist_2 # library(patchwork)

```

Warning: Removed 22 rows containing non-finite outside the scale range (`stat_bin()`).

Removed 22 rows containing non-finite outside the scale range (`stat_bin()`).



```

# LMM
labs_homa_ir_model <- lmer(log1p(labs_homa_ir) ~ allocation_group * visit +
(1 | record_id), data = data_model)

check_collinearity(labs_homa_ir_model)

# Check for Multicollinearity

```

Low Correlation

Term	VIF	VIF 95% CI	Increased SE	Tolerance
allocation_group	1.24	[1.10, 1.58]	1.11	0.81
visit	3.42	[2.71, 4.42]	1.85	0.29
allocation_group:visit	3.83	[3.02, 4.97]	1.96	0.26
Tolerance 95% CI				
	[0.63, 0.91]			
	[0.23, 0.37]			
	[0.20, 0.33]			

```
# Sensitivity analysis
labs_homa_ir_model_check <- sensitivity_check_lmer(
  model = labs_homa_ir_model,
  id_var = "record_id",
  top_n = 5)

# LMM Sensitivity
labs_homa_ir_model_sens <- update(object = labs_homa_ir_model,
  subset = !(record_id %in%
  labs_homa_ir_model_check$influential_ids))

# Influential IDS
labs_homa_ir_model_check$influential_ids
```

[1] "2" "11" "19" "27" "56"

3.12.1 Resumo dos modelos

```
# Model comparison
summary(labs_homa_ir_model)

Linear mixed model fit by REML. t-tests use Satterthwaite's method [
lmerModLmerTest]

Formula: log1p(labs_homa_ir) ~ allocation_group * visit + (1 | record_id)
Data: data_model

REML criterion at convergence: 144.6
```

Scaled residuals:

Min	1Q	Median	3Q	Max
-----	----	--------	----	-----

```
-2.2411 -0.5509 -0.0823  0.4113  3.4196
```

Random effects:

Groups	Name	Variance	Std.Dev.
record_id	(Intercept)	0.10984	0.3314
Residual		0.06459	0.2541

Number of obs: 167, groups: record_id, 73

Fixed effects:

	Estimate	Std. Error	df	t value
(Intercept)	1.336898	0.068660	106.824873	19.471
allocation_group	-0.041261	0.098203	107.871628	-0.420
visit2	-0.114741	0.065977	99.749814	-1.739
visit3	0.009875	0.071078	101.178973	0.139
allocation_group:visit2	0.062435	0.095196	100.497655	0.656
allocation_group:visit3	0.056616	0.107100	103.972738	0.529
	Pr(> t)			
(Intercept)	<2e-16 ***			
allocation_group	0.6752			
visit2	0.0851 .			
visit3	0.8898			
allocation_group:visit2	0.5134			
allocation_group:visit3	0.5982			

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1				

Correlation of Fixed Effects:

	(Intr)	all_GB	visit2	visit3	a_GB:2
allctn_gr	-0.699				
visit2	-0.385	0.269			
visit3	-0.358	0.250	0.409		
allctn_GB:2	0.267	-0.385	-0.693	-0.283	
allctn_GB:3	0.237	-0.349	-0.271	-0.664	0.399

```
summary(labs_homa_ir_model_sens)
```

```
Linear mixed model fit by REML. t-tests use Satterthwaite's method [lmerModLmerTest]
```

Formula: log1p(labs_homa_ir) ~ allocation_group * visit + (1 | record_id)
Data: data_model
Subset: !(record_id %in% labs_homa_ir_model_check\$influential_ids)

REML criterion at convergence: 73

Scaled residuals:

Min	1Q	Median	3Q	Max
-1.91572	-0.58345	-0.06265	0.42749	2.17496

Random effects:

Groups	Name	Variance	Std.Dev.
record_id	(Intercept)	0.07069	0.2659
Residual		0.04329	0.2081

Number of obs: 152, groups: record_id, 68

Fixed effects:

	Estimate	Std. Error	df	t value	Pr(> t)
(Intercept)	1.284413	0.057067	97.408593	22.507	<2e-16
allocation_group	0.008783	0.082328	98.496265	0.107	0.9153
visit2	-0.100160	0.055929	87.585394	-1.791	0.0768
visit3	-0.013517	0.060661	89.023495	-0.223	0.8242
allocation_group:visit2	0.053800	0.081686	88.465703	0.659	0.5119
allocation_group:visit3	0.025914	0.093706	92.342897	0.277	0.7827

(Intercept) ***
allocation_group
visit2 .
visit3
allocation_group:visit2
allocation_group:visit3

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

(Intr) all_GB visit2 visit3 a_GB:2

```

allctn_grGB -0.693
visit2      -0.388  0.269
visit3      -0.357  0.248  0.401
allctn_GB:2  0.265 -0.386 -0.685 -0.275
allctn_GB:3  0.231 -0.345 -0.260 -0.647  0.386

performance::compare_performance(
  labs_homa_ir_model,
  labs_homa_ir_model_sens)

```

When comparing models, please note that probably not all models were fit from same data.

```
# Comparison of Model Performance Indices
```

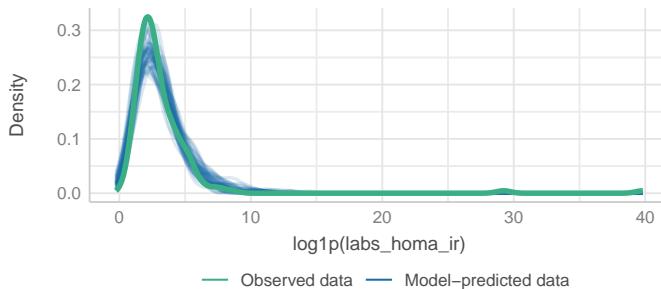
Name	Model	AIC (weights)	AICc (weights)
labs_homa_ir_model	lmerModLmerTest	579.2 (<.001)	580.1 (<.001)
labs_homa_ir_model_sens	lmerModLmerTest	454.2 (>.999)	455.2 (>.999)

Name	BIC (weights)	R2 (cond.)	R2 (marg.)	ICC
labs_homa_ir_model	604.1 (<.001)	0.635	0.014	0.630
labs_homa_ir_model_sens	478.4 (>.999)	0.625	0.014	0.620

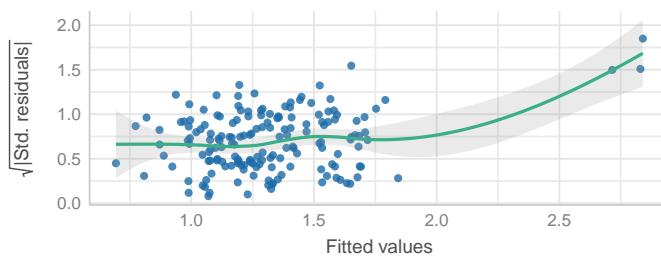
Name	RMSE	Sigma
labs_homa_ir_model	0.203	0.254
labs_homa_ir_model_sens	0.165	0.208

```
performance::check_model(labs_homa_ir_model)
```

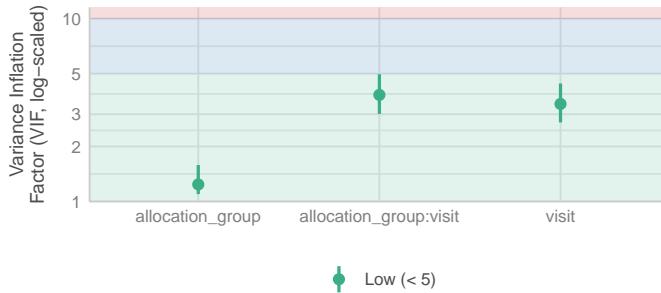
Posterior Predictive Check
Model-predicted lines should resemble observed data line



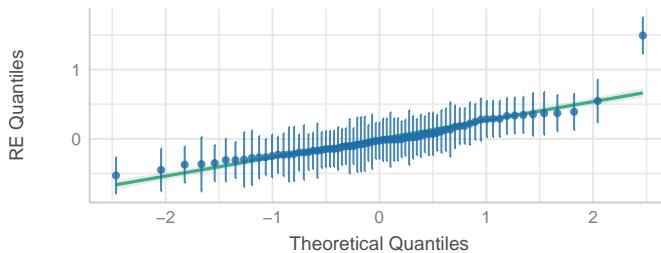
Homogeneity of Variance
Reference line should be flat and horizontal



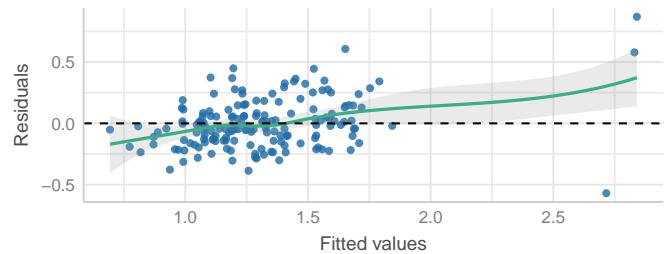
Collinearity
High collinearity (VIF) may inflate parameter uncertainty



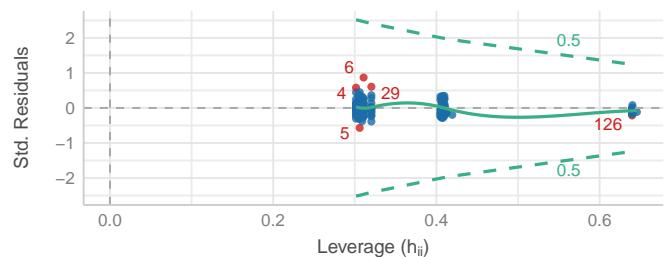
Normality of Random Effects (record_id)
Dots should be plotted along the line



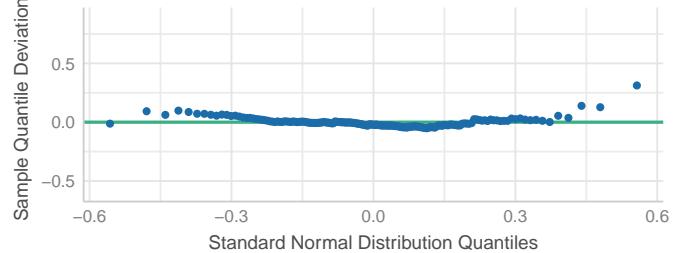
Linearity
Reference line should be flat and horizontal



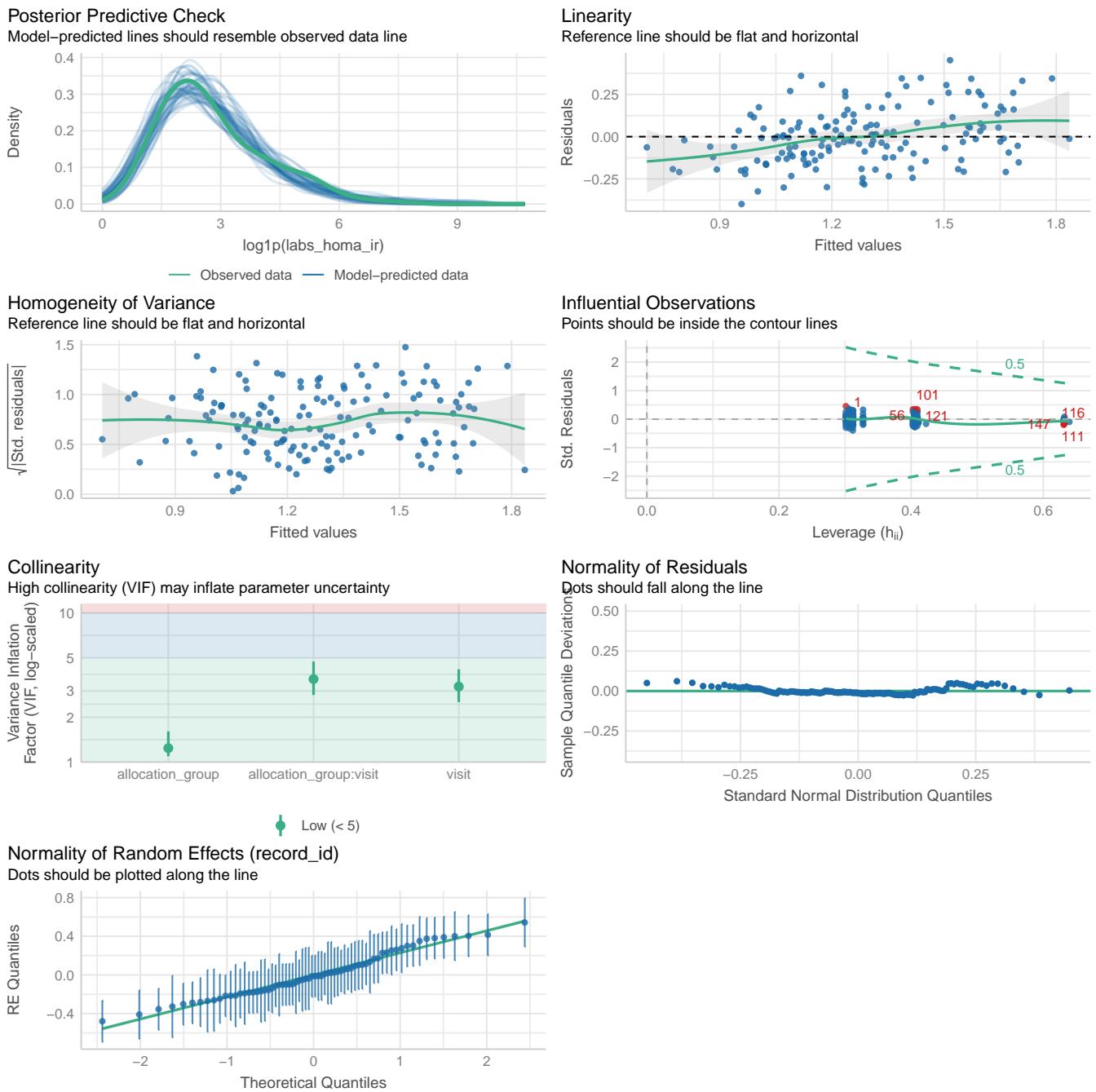
Influential Observations
Points should be inside the contour lines



Normality of Residuals
Dots should fall along the line



```
performance::check_model(labs_homa_ir_model_sens)
```



3.12.2 Médias Marginais Estimadas

3.12.2.1 Todos os dados

```
# Get EMMs for each group at each visit
labs_homa_ir_raw_emm <- emmeans::emmeans(
  labs_homa_ir_model,
  ~ allocation_group * visit
```

```

)

labs_homa_ir_raw_emm <- regrid(labs_homa_ir_raw_emm)

# Table of marginal means
# labs_homa_ir_raw_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(labs_homa_ir_raw_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

visit = 1:

```

contrast	estimate	SE	df	lower.CL	upper.CL	t.ratio	p.value
Grupo A - Grupo B	0.1539	0.366	103	-0.572	0.880	0.420	0.6752

```
visit = 2:
```

contrast	estimate	SE	df	lower.CL	upper.CL	t.ratio	p.value
Grupo A - Grupo B	-0.0726	0.369	125	-0.802	0.657	-0.197	0.8441

```
visit = 3:
```

contrast	estimate	SE	df	lower.CL	upper.CL	t.ratio	p.value
Grupo A - Grupo B	-0.0595	0.456	139	-0.961	0.842	-0.131	0.8963

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
 Confidence level used: 0.95

```
# Pairwise comparisons: Changes over time within each group
emmeans::contrast(labs_homa_ir_raw_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
allocation_group = Grupo A:
```

contrast	estimate	SE	df	lower.CL	upper.CL	t.ratio	p.value
visit1 - visit2	0.4127	0.237	103	-0.163	0.988	1.744	0.2522
visit1 - visit3	-0.0378	0.273	103	-0.702	0.626	-0.138	1.0000
visit2 - visit3	-0.4505	0.274	125	-1.116	0.215	-1.642	0.3093

```

allocation_group = Grupo B:
contrast      estimate     SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit2  0.1862 0.244 106   -0.406    0.779    0.764  1.0000
visit1 - visit3 -0.2512 0.308 106   -1.001    0.498   -0.815  1.0000
visit2 - visit3 -0.4374 0.311 128   -1.191    0.316   -1.408  0.4849

```

Degrees-of-freedom method: inherited from kenward-roger when re-gridding

Confidence level used: 0.95

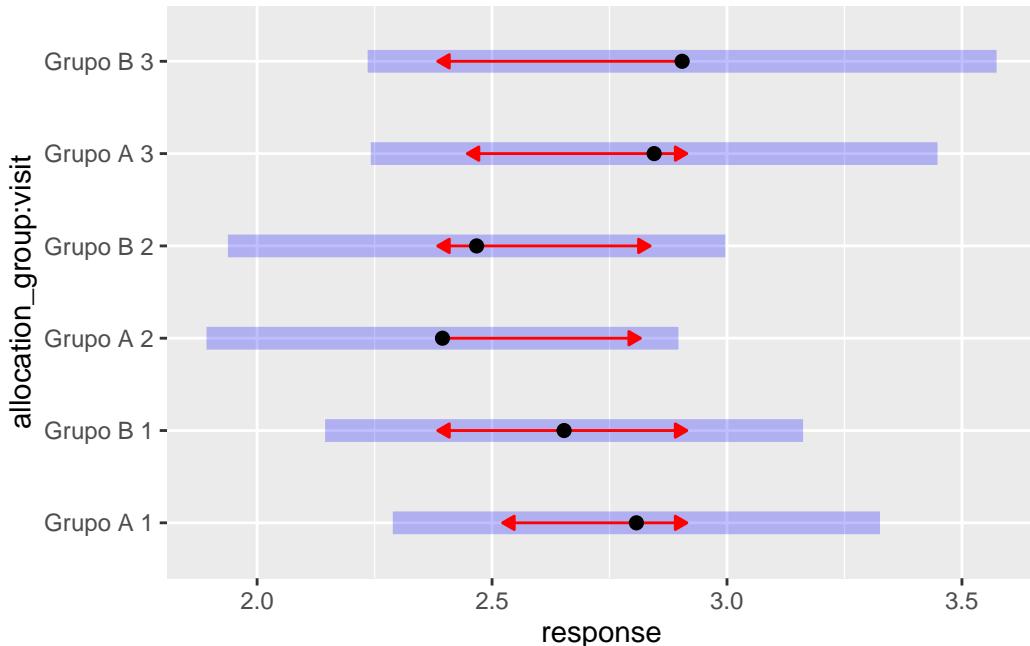
Conf-level adjustment: bonferroni method for 3 estimates

P value adjustment: bonferroni method for 3 tests

```

# Plot of marginal means
plot(labs_homa_ir_raw_emm, comparisons = TRUE)

```



3.12.2.2 Análise de sensibilidade

```

# Get EMMs for each group at each visit (Sensitivity Analysis)
labs_homa_ir_emm <- emmeans::emmeans(
  labs_homa_ir_model_sens,
  ~ allocation_group * visit
)

labs_homa_ir_emm <- regrid(labs_homa_ir_emm)

```

```

# Table of marginal means

# labs_homa_ir_emm

# Pairwise comparisons: Between groups at each visit

emmeans::contrast(labs_homa_ir_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

visit = 1:

contrast estimate SE df lower.CL upper.CL t.ratio p.value
Grupo A - Grupo B -0.0319 0.299 96 -0.625 0.561 -0.107 0.9153

```

```

visit = 2:

contrast estimate SE df lower.CL upper.CL t.ratio p.value
Grupo A - Grupo B -0.2111 0.308 117 -0.821 0.398 -0.686 0.4942

```

```

visit = 3:

contrast estimate SE df lower.CL upper.CL t.ratio p.value
Grupo A - Grupo B -0.1258 0.369 130 -0.855 0.603 -0.341 0.7334

```

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
 Confidence level used: 0.95

```

# Pairwise comparisons: Changes over time within each group

emmeans::contrast(labs_homa_ir_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

allocation_group = Grupo A:

contrast estimate SE df lower.CL upper.CL t.ratio p.value
visit1 - visit2 0.3443 0.192 96.0 -0.122 0.811 1.798 0.2261
visit1 - visit3 0.0485 0.218 96.0 -0.482 0.579 0.223 1.0000
visit2 - visit3 -0.2958 0.221 116.6 -0.832 0.240 -1.341 0.5479

```

```

allocation_group = Grupo B:

contrast estimate SE df lower.CL upper.CL t.ratio p.value
visit1 - visit2 0.1651 0.211 98.1 -0.350 0.680 0.781 1.0000
visit1 - visit3 -0.0455 0.264 98.1 -0.687 0.596 -0.173 1.0000

```

```
visit2 - visit3 -0.2106 0.268 120.7 -0.861 0.440 -0.786 1.0000
```

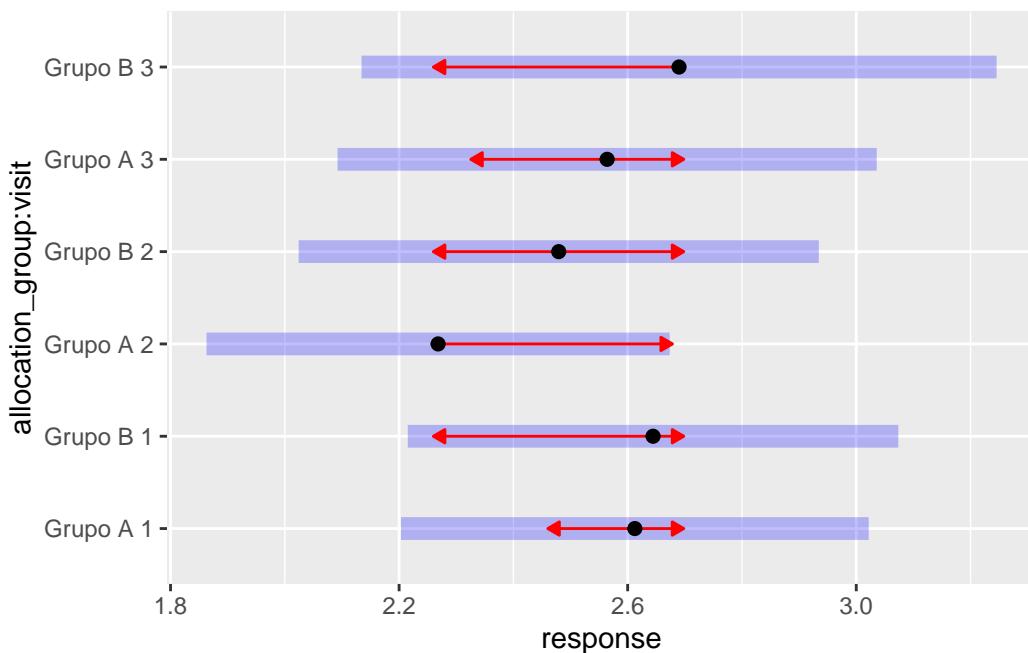
Degrees-of-freedom method: inherited from kenward-roger when re-gridding

Confidence level used: 0.95

Conf-level adjustment: bonferroni method for 3 estimates

P value adjustment: bonferroni method for 3 tests

```
# Plot of marginal means
plot(labs_homa_ir_emm, comparisons = TRUE)
```



3.12.3 Resultado

No modelo ajustado para os níveis de HOMA-IR, não foram observadas diferenças estatisticamente significativas entre os grupos em nenhum dos três momentos avaliados. Além disso, as comparações dentro de cada grupo ao longo do tempo não revelaram mudanças significativas. A análise de sensibilidade, realizada com a exclusão de observações influentes, confirmou a robustez dos achados, com estimativas semelhantes e ausência de diferenças significativas entre os grupos ou ao longo das visitas. As estimativas, intervalos de confiança de 95% e valores de p estão apresentados na Tabela 12.

Tabela 12: Diferenças estimadas dos níveis de HOMA-IR entre os grupos de alocação (placebo vs Eclipta) e entre visitas dentro de cada grupo

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 1	0,15	[-0,57 ; 0,88]	0,675
Entre grupos	Visita 2	-0,07	[-0,80 ; 0,66]	0,844

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 3	-0,06	[-0,96 ; 0,84]	0,896
Grupo Placebo	Visita 1 - Visita 2	0,41	[-0,16 ; 0,99]	0,252
Grupo Placebo	Visita 1 - Visita 3	-0,04	[-0,70 ; 0,63]	1,000
Grupo Placebo	Visita 2 - Visita 3	-0,45	[-1,12 ; 0,22]	0,309
Grupo Eclipta	Visita 1 - Visita 2	0,19	[-0,41 ; 0,78]	1,000
Grupo Eclipta	Visita 1 - Visita 3	-0,25	[-1,00 ; 0,50]	1,000
Grupo Eclipta	Visita 2 - Visita 3	-0,44	[-1,19 ; 0,32]	0,485

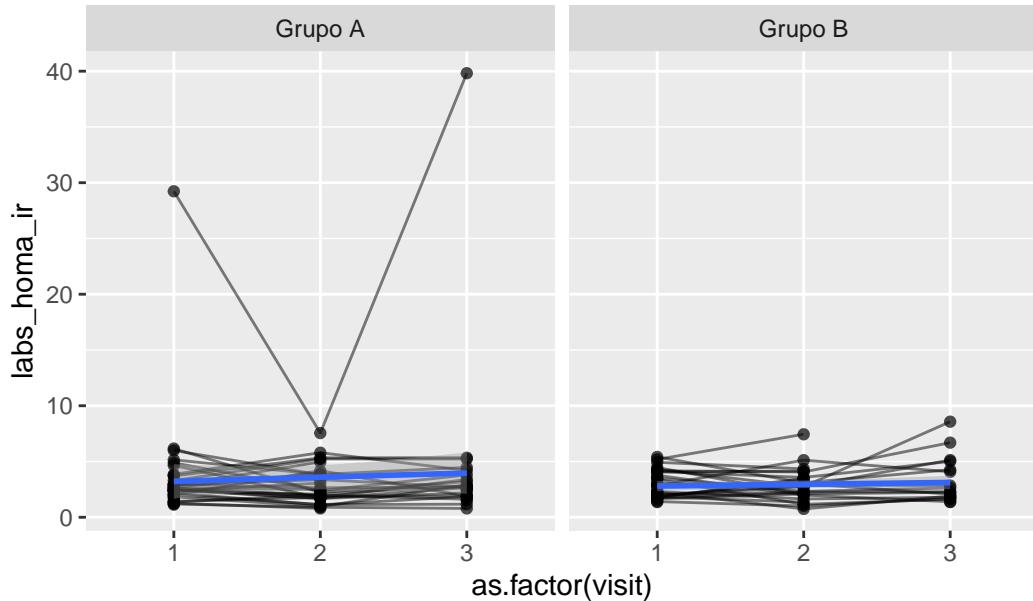
```

ggplot(
  data = data_model,
  aes(
    x = as.factor(visit),
    y = labs_homa_ir,
    group = record_id,
  )
) +
  geom_line(alpha = 0.5) +
  geom_point(alpha = 0.7) +
  geom_smooth(
    aes(group = allocation_group),
    method = "lm",
    se = TRUE,
    linewidth = 1
  ) +
  labs(title = "All data") +
  facet_wrap(~ allocation_group)

`geom_smooth()` using formula = 'y ~ x'
Warning: Removed 22 rows containing non-finite outside the scale range
(`stat_smooth()`).
Warning: Removed 18 rows containing missing values or values outside the scale range
(`geom_line()`).
Warning: Removed 22 rows containing missing values or values outside the scale range
(`geom_point()`).

```

All data



```
#coord_cartesian(ylim = c(10, 150))

data_model %>%
  filter(
    !(record_id %in%
      labs_homa_ir_model_check$influential_ids)
  ) %>%
  ggplot(
    aes(
      x = as.factor(visit),
      y = labs_homa_ir,
      group = record_id,
    )
  ) +
  geom_line(alpha = 0.5) +
  geom_point(alpha = 0.7) +
  geom_smooth(
    aes(group = allocation_group),
    method = "lm",
    se = TRUE,
    linewidth = 1
```

```

) +
  labs(title = "Sensitivity analysis") +
  facet_wrap(~ allocation_group)

`geom_smooth()` using formula = 'y ~ x'

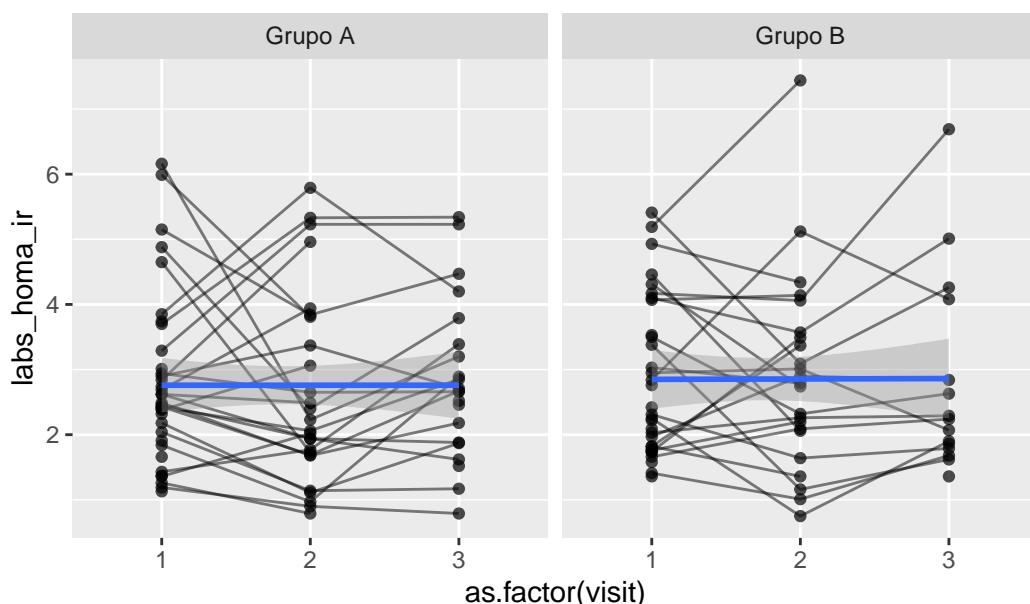
Warning: Removed 22 rows containing non-finite outside the scale range
(`stat_smooth()`).

Warning: Removed 18 rows containing missing values or values outside the scale range
(`geom_line()`).

Warning: Removed 22 rows containing missing values or values outside the scale range
(`geom_point()`).

```

Sensitivity analysis



```
#coord_cartesian(ylim = c(10, 150))
```

3.13 Índice QUICK

Variável: labs_quick_index

```

# Plot 1: Raw data
labs_quick_index_hist_1 <- data_model %>%
  #filter(
  #  labs_quick_index < 300
  #) %>%
  ggplot(aes(x = labs_quick_index)) +

```

```

geom_histogram(bins = 50, fill = "skyblue", color = "black")

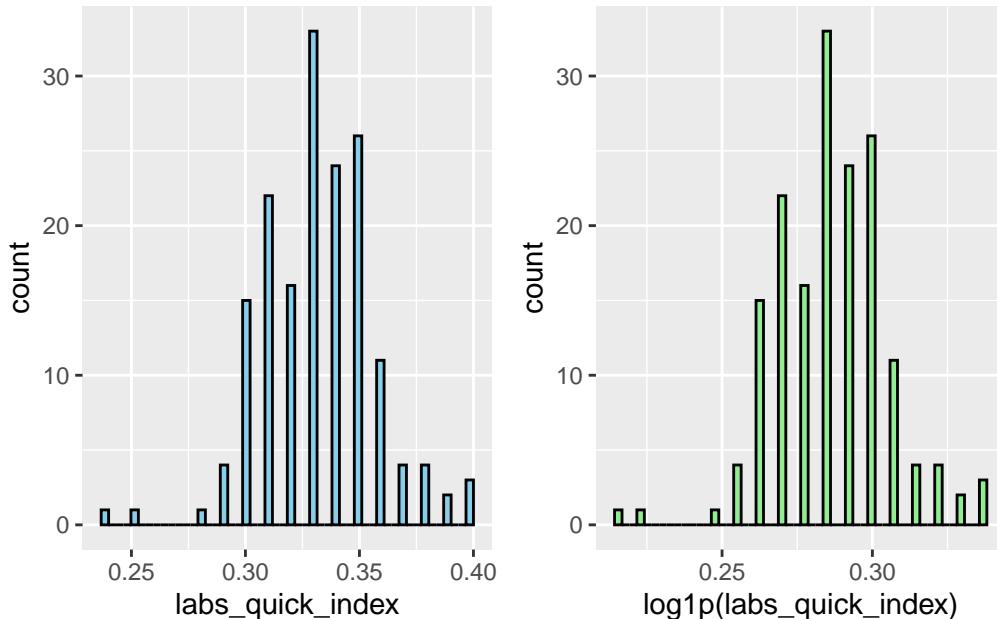
# Plot 2: Log-transformed data
labs_quick_index_hist_2 <- data_model %>%
  #filter(
  #  labs_quick_index < 300
  #) %>%
  ggplot(aes(x = log1p(labs_quick_index))) +
  geom_histogram(bins = 50, fill = "lightgreen", color = "black")

# Combine side by side
labs_quick_index_hist_1 + labs_quick_index_hist_2 # library(patchwork)

```

Warning: Removed 22 rows containing non-finite outside the scale range (`stat_bin()`).

Removed 22 rows containing non-finite outside the scale range (`stat_bin()`).



```

# LMM
labs_quick_index_model <- lmer(labs_quick_index ~ allocation_group * visit +
(1 | record_id), data = data_model)
check_collinearity(labs_quick_index_model)

# Check for Multicollinearity

```

Low Correlation

```

Term  VIF    VIF 95% CI Increased SE Tolerance
allocation_group 1.25 [1.11, 1.60]      1.12      0.80
visit 3.42 [2.71, 4.42]      1.85      0.29
allocation_group:visit 3.85 [3.03, 5.00]      1.96      0.26
Tolerance 95% CI
[0.63, 0.90]
[0.23, 0.37]
[0.20, 0.33]

# Sensitivity analysis
labs_quick_index_model_check <- sensitivity_check_lmer(
  model = labs_quick_index_model,
  id_var = "record_id",
  top_n = 5)

# LMM Sensitivity
labs_quick_index_model_sens <- update(object = labs_quick_index_model,
                                         subset = !(record_id %in%
                                         labs_quick_index_model_check$influential_ids))
# Influential IDS
labs_quick_index_model_check$influential_ids
[1] "2"   "4"   "11"  "19"  "8"

```

3.13.1 Resumo dos modelos

```

# Model comparison
summary(labs_quick_index_model)

Linear mixed model fit by REML. t-tests use Satterthwaite's method [
lmerModLmerTest]

Formula: labs_quick_index ~ allocation_group * visit + (1 | record_id)
Data: data_model

REML criterion at convergence: -754.1

```

Scaled residuals:

Min	1Q	Median	3Q	Max
-----	----	--------	----	-----

```
-2.0927 -0.4844  0.0304  0.5467  2.4024
```

Random effects:

Groups	Name	Variance	Std.Dev.
record_id	(Intercept)	0.0003959	0.01990
Residual		0.0002488	0.01577

Number of obs: 167, groups: record_id, 73

Fixed effects:

	Estimate	Std. Error	df	t value
(Intercept)	0.330541	0.004174	107.176150	79.186
allocation_group	0.001261	0.005971	108.248173	0.211
visit2	0.008362	0.004092	98.621725	2.044
visit3	0.002322	0.004407	100.155478	0.527
allocation_group:visit2	-0.003691	0.005903	99.395689	-0.625
allocation_group:visit3	-0.005408	0.006638	103.075477	-0.815

Pr(>|t|)

(Intercept)	<2e-16 ***
allocation_group	0.8331
visit2	0.0436 *
visit3	0.5994
allocation_group:visit2	0.5332
allocation_group:visit3	0.4171

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

(Intr)	all_GB	visit2	visit3	a_GB:2
allctn_grGB	-0.699			
visit2	-0.394	0.275		
visit3	-0.366	0.256	0.408	
allctn_GB:2	0.273	-0.393	-0.693	-0.283
allctn_GB:3	0.243	-0.357	-0.271	-0.664
				0.399

```
summary(labs_quick_index_model_sens)
```

```
Linear mixed model fit by REML. t-tests use Satterthwaite's method [  
lmerModLmerTest]
```

```

Formula: labs_quick_index ~ allocation_group * visit + (1 | record_id)

Data: data_model

Subset: !(record_id %in% labs_quick_index_model_check$influential_ids)

```

REML criterion at convergence: -714.5

Scaled residuals:

Min	1Q	Median	3Q	Max
-1.8870	-0.4995	0.0244	0.5783	2.3369

Random effects:

Groups	Name	Variance	Std.Dev.
record_id	(Intercept)	0.0002799	0.01673
Residual		0.0002110	0.01452

Number of obs: 152, groups: record_id, 68

Fixed effects:

	Estimate	Std. Error	df	t value
(Intercept)	3.317e-01	3.745e-03	1.010e+02	88.573
allocation_group	5.364e-04	5.405e-03	1.021e+02	0.099
visit2	6.683e-03	3.894e-03	8.696e+01	1.716
visit3	1.888e-03	4.221e-03	8.872e+01	0.447
allocation_group:visit2	-5.420e-03	5.685e-03	8.792e+01	-0.953
allocation_group:visit3	-5.218e-03	6.509e-03	9.243e+01	-0.802
	Pr(> t)			
(Intercept)	<2e-16 ***			
allocation_group	0.9212			
visit2	0.0897 .			
visit3	0.6558			
allocation_group:visit2	0.3430			
allocation_group:visit3	0.4248			

Signif. codes:	0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1			

Correlation of Fixed Effects:

(Intr)	all_GB	visit2	visit3	a_GB:2
--------	--------	--------	--------	--------

```

allctn_grGB -0.693
visit2      -0.413  0.286
visit3      -0.381  0.264  0.400
allctn_GB:2  0.283 -0.411 -0.685 -0.274
allctn_GB:3  0.247 -0.368 -0.260 -0.648  0.385

performance::compare_performance(
  labs_quick_index_model,
  labs_quick_index_model_sens)

```

When comparing models, please note that probably not all models were fit from same data.

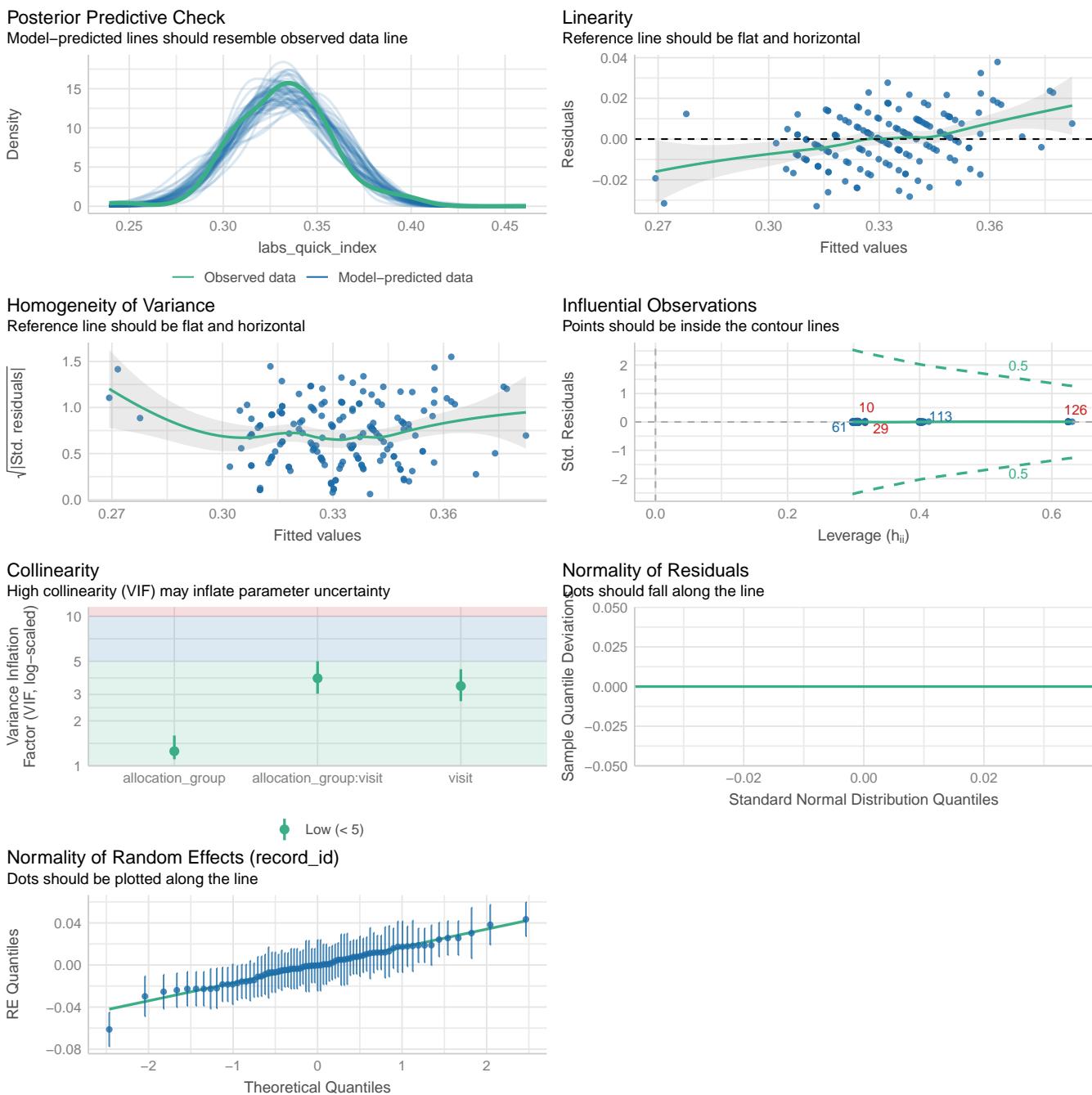
```
# Comparison of Model Performance Indices
```

Name	Model	AIC (weights)	AICc (weights)
labs_quick_index_model	lmerModLmerTest	-793.2 (>.999)	-792.3 (>.999)
labs_quick_index_model_sens	lmerModLmerTest	-754.3 (<.001)	-753.3 (<.001)

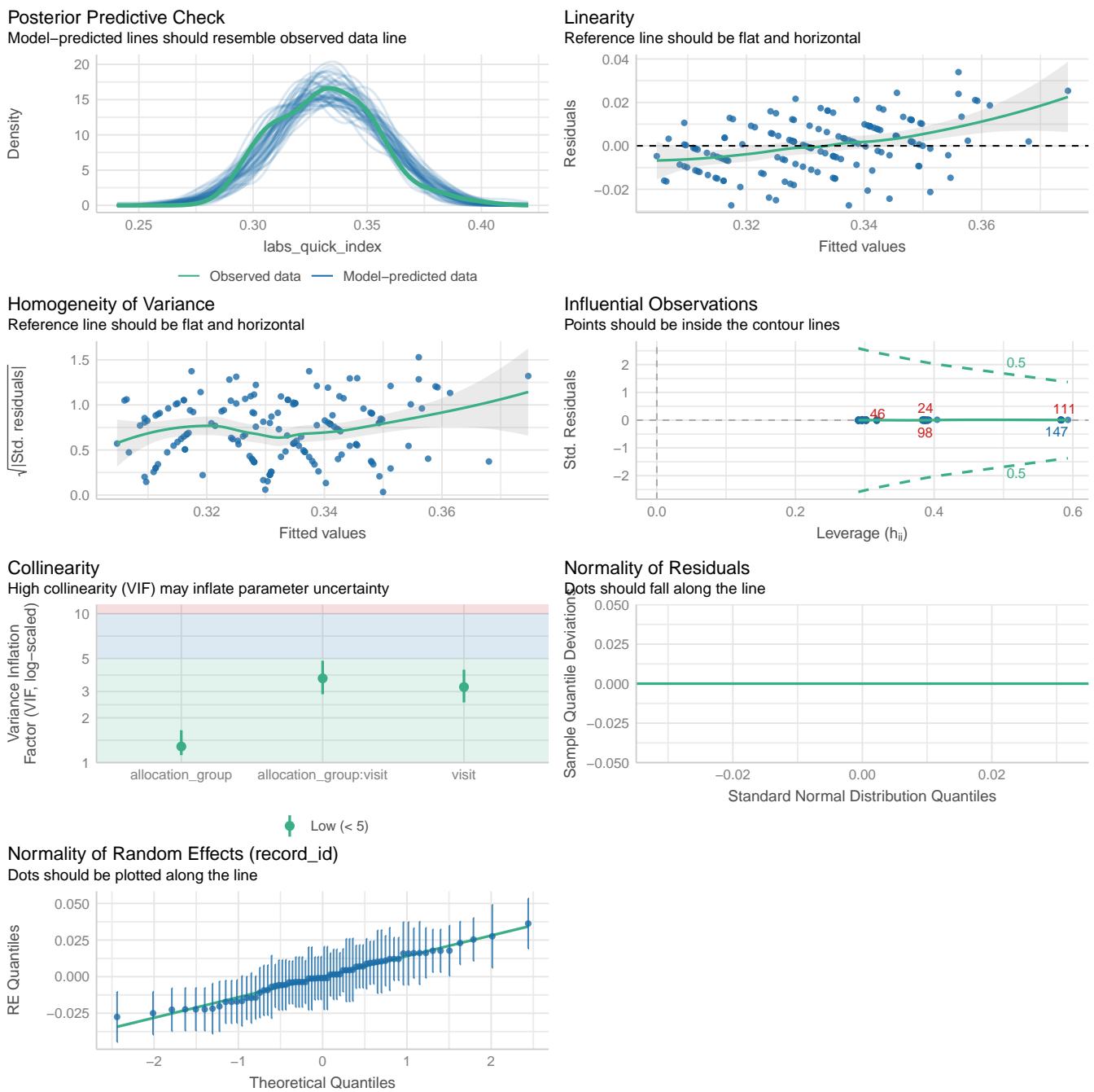
Name	BIC (weights)	R2 (cond.)	R2 (marg.)	ICC
labs_quick_index_model	-768.3 (>.999)	0.621	0.017	0.614
labs_quick_index_model_sens	-730.1 (<.001)	0.576	0.014	0.570

Name	RMSE	Sigma
labs_quick_index_model	0.013	0.016
labs_quick_index_model_sens	0.012	0.015

```
performance::check_model(labs_quick_index_model)
```



```
performance::check_model(labs_quick_index_model_sens)
```



3.13.2 Médias Marginais Estimadas

3.13.2.1 Todos os dados

```
# Get EMMs for each group at each visit
labs_quick_index_raw_emm <- emmeans::emmeans(
  labs_quick_index_model,
  ~ allocation_group * visit
```

```

)

labs_quick_index_raw_emm <- regrid(labs_quick_index_raw_emm)

# Table of marginal means
# labs_quick_index_raw_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(labs_quick_index_raw_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

visit = 1:
  contrast      estimate      SE  df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B -0.00126 0.00597 105  -0.0131   0.0106  -0.211  0.8331

visit = 2:
  contrast      estimate      SE  df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B  0.00243 0.00655 126  -0.0105   0.0154   0.371  0.7113

visit = 3:
  contrast      estimate      SE  df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B  0.00415 0.00719 140  -0.0101   0.0184   0.577  0.5648

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95

# Pairwise comparisons: Changes over time within each group
emmeans::contrast(labs_quick_index_raw_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

allocation_group = Grupo A:
  contrast      estimate      SE  df lower.CL upper.CL t.ratio p.value
visit1 - visit2 -0.00836 0.00410 105 -0.01833  0.00160  -2.041  0.1312
visit1 - visit3 -0.00232 0.00441 105 -0.01306  0.00842  -0.526  1.0000
visit2 - visit3  0.00604 0.00464 126 -0.00521  0.01729   1.303  0.5848

```

```

allocation_group = Grupo B:
contrast      estimate      SE  df lower.CL upper.CL t.ratio p.value
visit1 - visit2 -0.00467 0.00426 107 -0.01504  0.00569 -1.096  0.8263
visit1 - visit3  0.00309 0.00498 107 -0.00902  0.01519  0.620  1.0000
visit2 - visit3  0.00776 0.00513 130 -0.00469  0.02020  1.512  0.3989

```

Degrees-of-freedom method: inherited from kenward-roger when re-gridding

Confidence level used: 0.95

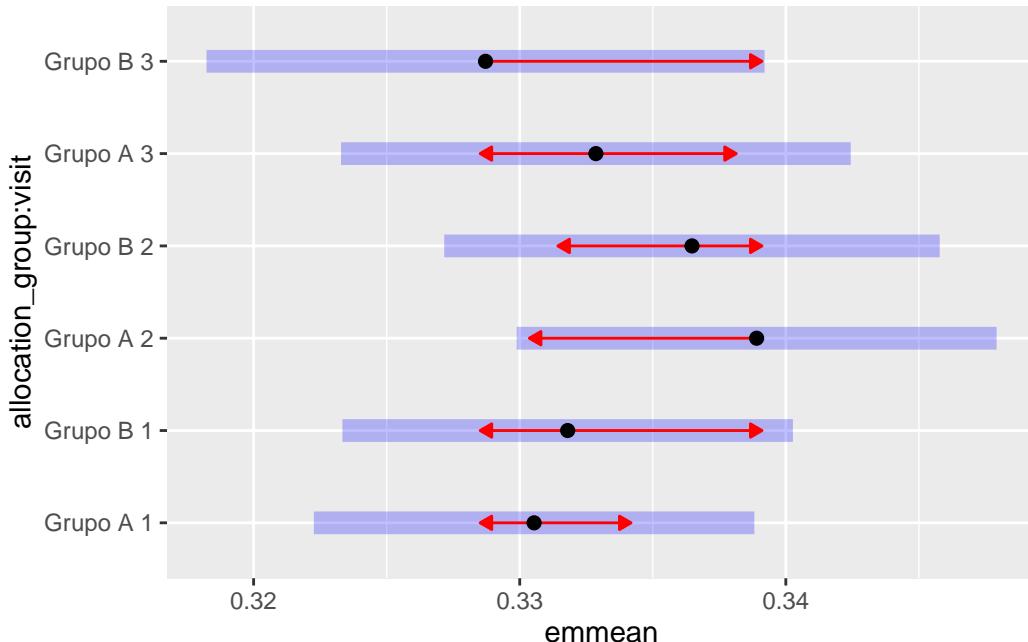
Conf-level adjustment: bonferroni method for 3 estimates

P value adjustment: bonferroni method for 3 tests

```

# Plot of marginal means
plot(labs_quick_index_raw_emm, comparisons = TRUE)

```



3.13.2.2 Análise de sensibilidade

```

# Get EMMs for each group at each visit (Sensitivity Analysis)
labs_quick_index_emm <- emmeans::emmeans(
  labs_quick_index_model_sens,
  ~ allocation_group * visit
)

labs_quick_index_emm <- regrid(labs_quick_index_emm)

```

```

# Table of marginal means
# labs_quick_index_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(labs_quick_index_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

visit = 1:
  contrast      estimate      SE  df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B -0.000536 0.00541 101 -0.01126   0.0102  -0.099  0.9212

visit = 2:
  contrast      estimate      SE  df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B  0.004884 0.00603 122 -0.00706   0.0168   0.810  0.4197

visit = 3:
  contrast      estimate      SE  df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B  0.004682 0.00678 134 -0.00873   0.0181   0.691  0.4910

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95

# Pairwise comparisons: Changes over time within each group
emmeans::contrast(labs_quick_index_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

allocation_group = Grupo A:
  contrast      estimate      SE  df lower.CL upper.CL t.ratio p.value
visit1 - visit2 -0.00668 0.00390 101 -0.01618  0.00281  -1.713  0.2691
visit1 - visit3 -0.00189 0.00423 101 -0.01219  0.00841  -0.446  1.0000
visit2 - visit3  0.00480 0.00446 122 -0.00603  0.01562   1.075  0.8531

allocation_group = Grupo B:
  contrast      estimate      SE  df lower.CL upper.CL t.ratio p.value
visit1 - visit2 -0.00126 0.00415 103 -0.01136  0.00884  -0.304  1.0000
visit1 - visit3  0.00333 0.00497 103 -0.00878  0.01544   0.670  1.0000

```

```
visit2 - visit3  0.00459 0.00515 125 -0.00790  0.01709    0.892  1.0000
```

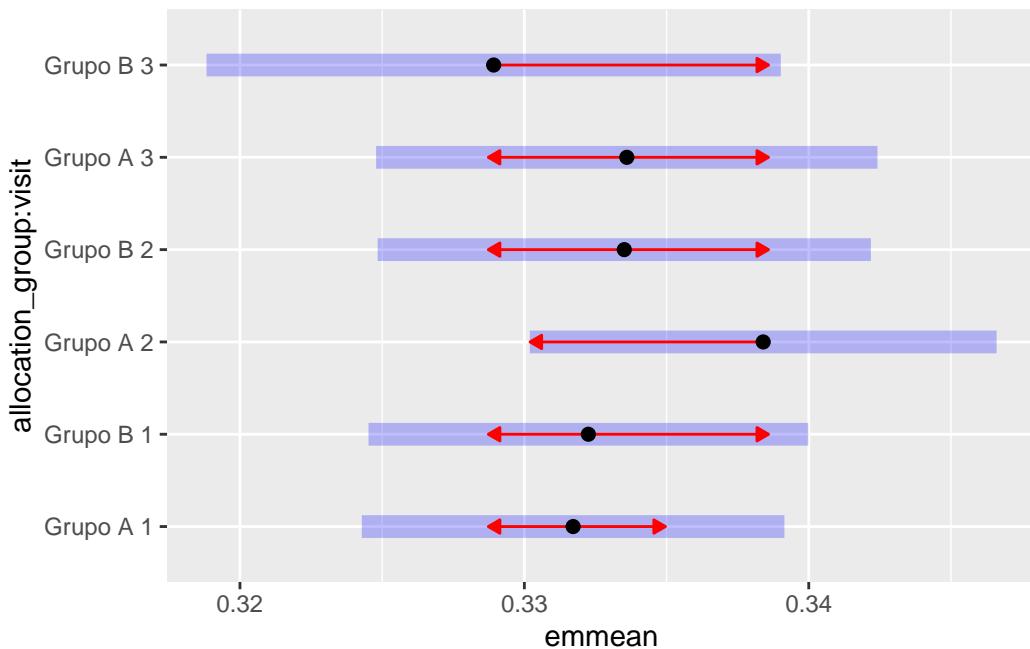
Degrees-of-freedom method: inherited from kenward-roger when re-gridding

Confidence level used: 0.95

Conf-level adjustment: bonferroni method for 3 estimates

P value adjustment: bonferroni method for 3 tests

```
# Plot of marginal means  
plot(labs_quick_index_emm, comparisons = TRUE)
```



3.13.3 Resultado

No modelo ajustado para o índice de sensibilidade à insulina (Quick Index), não foram observadas diferenças estatisticamente significativas entre os grupos em nenhum dos três momentos avaliados. Da mesma forma, as comparações ao longo do tempo dentro de cada grupo também não mostraram variações significativas. A análise de sensibilidade, realizada com a exclusão das observações influentes, confirmou os achados da análise principal. As estimativas permaneceram consistentes, sem diferenças estatisticamente significativas entre os grupos ou ao longo do tempo. As estimativas, intervalos de confiança de 95% e valores de p estão apresentados na Tabela 13.

Tabela 13: Diferenças estimadas do índice Quick entre os grupos de alocação (placebo vs Eclipta) e entre visitas dentro de cada grupo

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 1	-0,001	[-0,013 ; 0,011]	0,833

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 2	0,002	[-0,011 ; 0,015]	0,711
Entre grupos	Visita 3	0,004	[-0,010 ; 0,018]	0,565
Grupo Placebo	Visita 1 - Visita 2	-0,008	[-0,018 ; 0,002]	0,131
Grupo Placebo	Visita 1 - Visita 3	-0,002	[-0,013 ; 0,008]	1,000
Grupo Placebo	Visita 2 - Visita 3	0,006	[-0,005 ; 0,017]	0,585
Grupo Eclipta	Visita 1 - Visita 2	-0,005	[-0,015 ; 0,006]	0,826
Grupo Eclipta	Visita 1 - Visita 3	0,003	[-0,009 ; 0,015]	1,000
Grupo Eclipta	Visita 2 - Visita 3	0,008	[-0,005 ; 0,020]	0,399

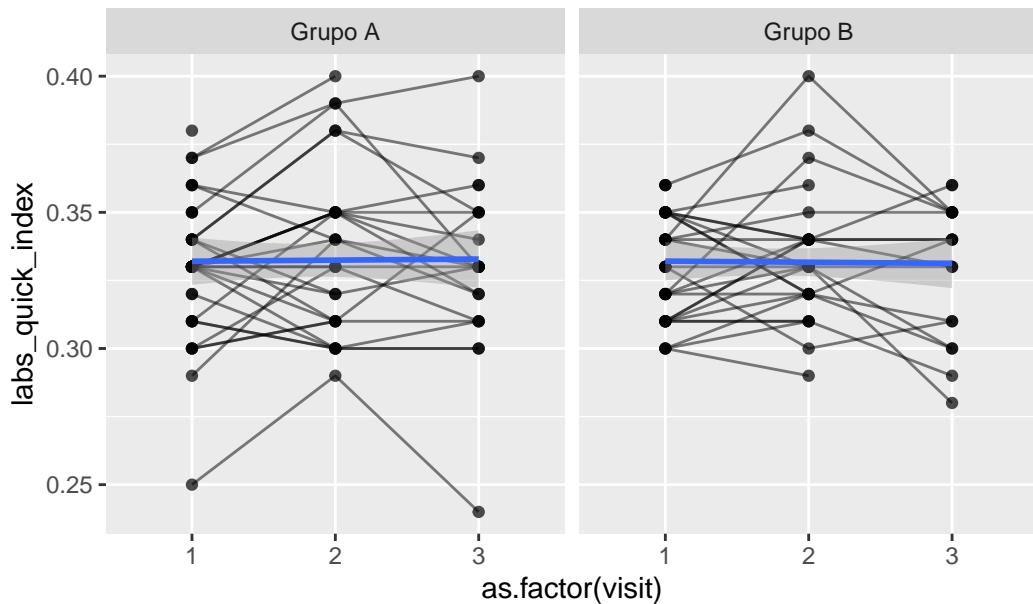
```

ggplot(
  data = data_model,
  aes(
    x = as.factor(visit),
    y = labs_quick_index,
    group = record_id,
  )
) +
  geom_line(alpha = 0.5) +
  geom_point(alpha = 0.7) +
  geom_smooth(
    aes(group = allocation_group),
    method = "lm",
    se = TRUE,
    linewidth = 1
  ) +
  labs(title = "All data") +
  facet_wrap(~ allocation_group)

`geom_smooth()` using formula = 'y ~ x'
Warning: Removed 22 rows containing non-finite outside the scale range
(`stat_smooth()`).
Warning: Removed 18 rows containing missing values or values outside the scale range
(`geom_line()`).
Warning: Removed 22 rows containing missing values or values outside the scale range
(`geom_point()`).

```

All data



```
#coord_cartesian(ylim = c(10, 150))

data_model %>%
  filter(
    !(record_id %in%
      labs_quick_index_model_check$influential_ids)
  ) %>%
  ggplot(
    aes(
      x = as.factor(visit),
      y = labs_quick_index,
      group = record_id,
    )
  ) +
  geom_line(alpha = 0.5) +
  geom_point(alpha = 0.7) +
  geom_smooth(
    aes(group = allocation_group),
    method = "lm",
    se = TRUE,
    linewidth = 1
  )
```

```

) +
  labs(title = "Sensitivity analysis") +
  facet_wrap(~ allocation_group)

`geom_smooth()` using formula = 'y ~ x'

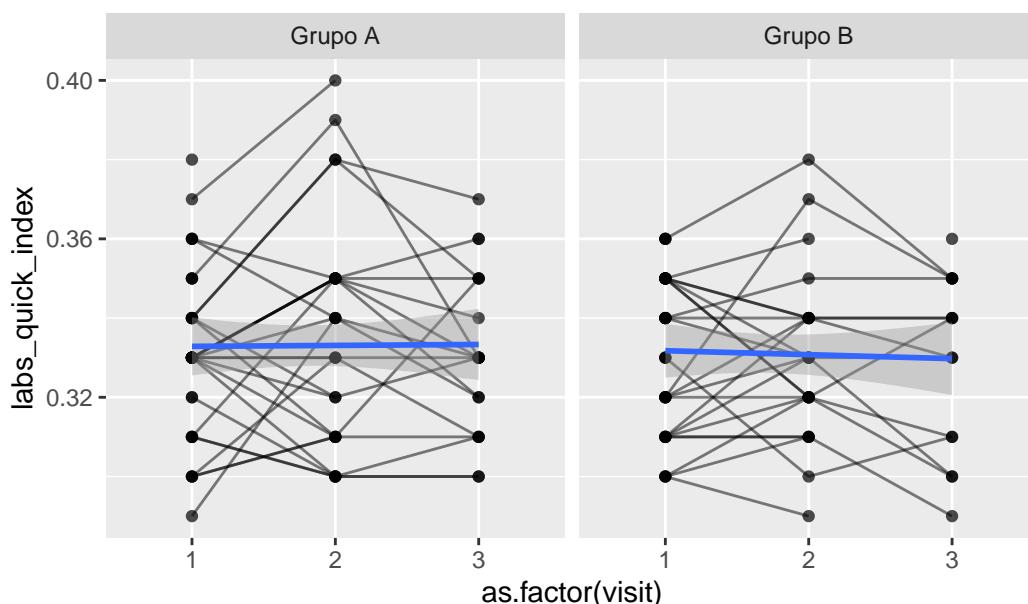
Warning: Removed 22 rows containing non-finite outside the scale range
(`stat_smooth()`).

Warning: Removed 18 rows containing missing values or values outside the scale range
(`geom_line()`).

Warning: Removed 22 rows containing missing values or values outside the scale range
(`geom_point()`).

```

Sensitivity analysis



```
#coord_cartesian(ylim = c(10, 150))
```

3.14 Circunferência abdominal

Variável: abdomen

```

# Plot 1: Raw data
abdomen_hist_1 <- data_model %>%
  #filter(
  #  abdomen < 300
  #) %>%
  ggplot(aes(x = abdomen)) +

```

```

geom_histogram(bins = 50, fill = "skyblue", color = "black")

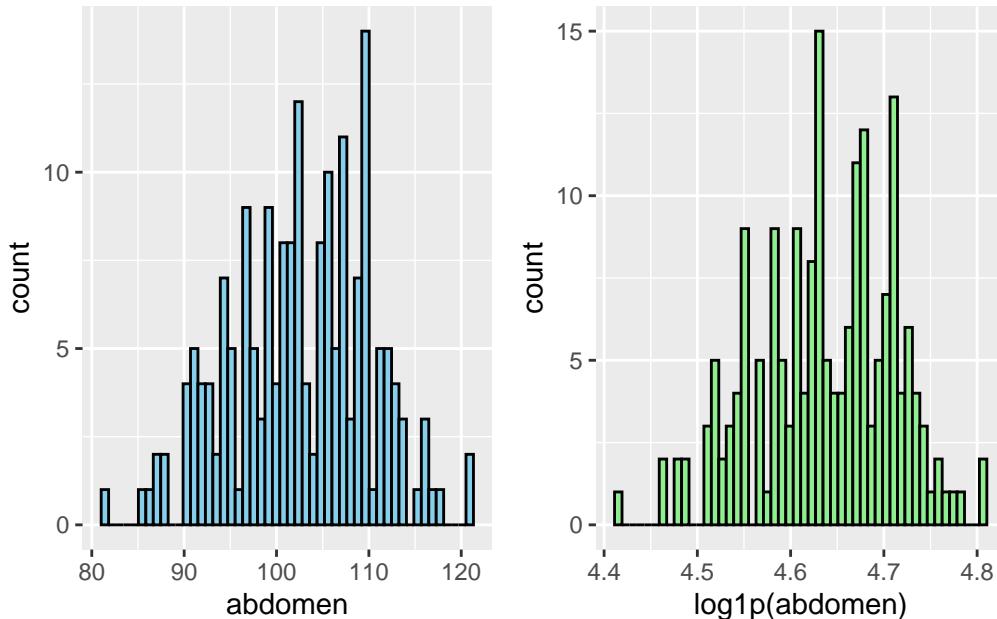
# Plot 2: Log-transformed data
abdomen_hist_2 <- data_model %>%
  #filter(
  #  abdomen < 300
  #) %>%
  ggplot(aes(x = log1p(abdomen))) +
  geom_histogram(bins = 50, fill = "lightgreen", color = "black")

# Combine side by side
abdomen_hist_1 + abdomen_hist_2 # library(patchwork)

```

Warning: Removed 2 rows containing non-finite outside the scale range (`stat_bin()`).

Removed 2 rows containing non-finite outside the scale range (`stat_bin()`).



```

# LMM
abdomen_model <- lmer(log1p(abdomen) ~ allocation_group * visit +
(1 | record_id), data = data_model)
check_collinearity(abdomen_model)

# Check for Multicollinearity

```

Low Correlation

Term	VIF	VIF 95% CI	Increased SE	Tolerance
allocation_group	1.08	[1.01, 1.60]	1.04	0.93
visit	3.74	[2.98, 4.79]	1.93	0.27
allocation_group:visit	3.87	[3.08, 4.96]	1.97	0.26
Tolerance 95% CI				
	[0.62, 0.99]			
	[0.21, 0.34]			
	[0.20, 0.32]			

```

# Sensitivity analysis
abdomen_model_check <- sensitivity_check_lmer(
  model = abdomen_model,
  id_var = "record_id",
  top_n = 5)

# LMM Sensitivity
abdomen_model_sens <- update(object = abdomen_model,
  subset = !(record_id %in%
  abdomen_model_check$influential_ids))

# Influential IDS
abdomen_model_check$influential_ids
```

[1] "8" "42" "47" "53" "63"

3.14.1 Resumo dos modelos

```

# Model comparison
summary(abdomen_model)

Linear mixed model fit by REML. t-tests use Satterthwaite's method [
lmerModLmerTest]

Formula: log1p(abdomen) ~ allocation_group * visit + (1 | record_id)
Data: data_model

REML criterion at convergence: -568.7
```

Scaled residuals:

Min	1Q	Median	3Q	Max
-----	----	--------	----	-----

```
-2.23622 -0.44732 0.00364 0.48062 2.42979
```

Random effects:

Groups	Name	Variance	Std.Dev.
record_id	(Intercept)	0.0047493	0.06892
Residual		0.0007424	0.02725

Number of obs: 187, groups: record_id, 75

Fixed effects:

	Estimate	Std. Error	df	t value
(Intercept)	4.646300	0.012183	84.898832	381.378
allocation_group	-0.015067	0.017116	84.898832	-0.880
visit2	-0.008742	0.006883	110.950474	-1.270
visit3	-0.016017	0.007250	111.261323	-2.209
allocation_group:visit2	0.006622	0.009887	111.494381	0.670
allocation_group:visit3	0.022973	0.010437	111.762586	2.201

Pr(>|t|)

(Intercept)	<2e-16 ***
allocation_group	0.3812
visit2	0.2067
visit3	0.0292 *
allocation_group:visit2	0.5044
allocation_group:visit3	0.0298 *

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

(Intr)	all_GB	visit2	visit3	a_GB:2	
allctn_grGB	-0.712				
visit2	-0.239	0.170			
visit3	-0.227	0.162	0.469		
allctn_GB:2	0.167	-0.234	-0.696	-0.327	
allctn_GB:3	0.158	-0.222	-0.326	-0.695	0.467

```
summary(abdomen_model_sens)
```

```
Linear mixed model fit by REML. t-tests use Satterthwaite's method [lmerModLmerTest]
```

Formula: log1p(abdomen) ~ allocation_group * visit + (1 | record_id)

Data: data_model

Subset: !(record_id %in% abdomen_model_check\$influential_ids)

REML criterion at convergence: -552.6

Scaled residuals:

Min	1Q	Median	3Q	Max
-2.17405	-0.44945	0.00727	0.51473	1.83706

Random effects:

Groups	Name	Variance	Std.Dev.
record_id	(Intercept)	0.004706	0.06860
Residual		0.000536	0.02315

Number of obs: 172, groups: record_id, 70

Fixed effects:

	Estimate	Std. Error	df	t value
(Intercept)	4.646664	0.012604	75.952119	368.673
allocation_group	-0.016907	0.017336	75.952119	-0.975
visit2	-0.001980	0.006272	100.199396	-0.316
visit3	-0.009382	0.006665	100.412373	-1.408
allocation_group:visit2	0.001495	0.008783	100.495350	0.170
allocation_group:visit3	0.020633	0.009324	100.671803	2.213

	Pr(> t)
(Intercept)	<2e-16 ***
allocation_group	0.3325
visit2	0.7529
visit3	0.1623
allocation_group:visit2	0.8652
allocation_group:visit3	0.0292 *

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

(Intr) all_GB visit2 visit3 a_GB:2

```

allctn_grGB -0.727
visit2      -0.205  0.149
visit3      -0.193  0.141  0.466
allctn_GB:2  0.147 -0.202 -0.714 -0.333
allctn_GB:3  0.138 -0.190 -0.333 -0.715  0.466

performance::compare_performance(
  abdomen_model,
  abdomen_model_sens)

```

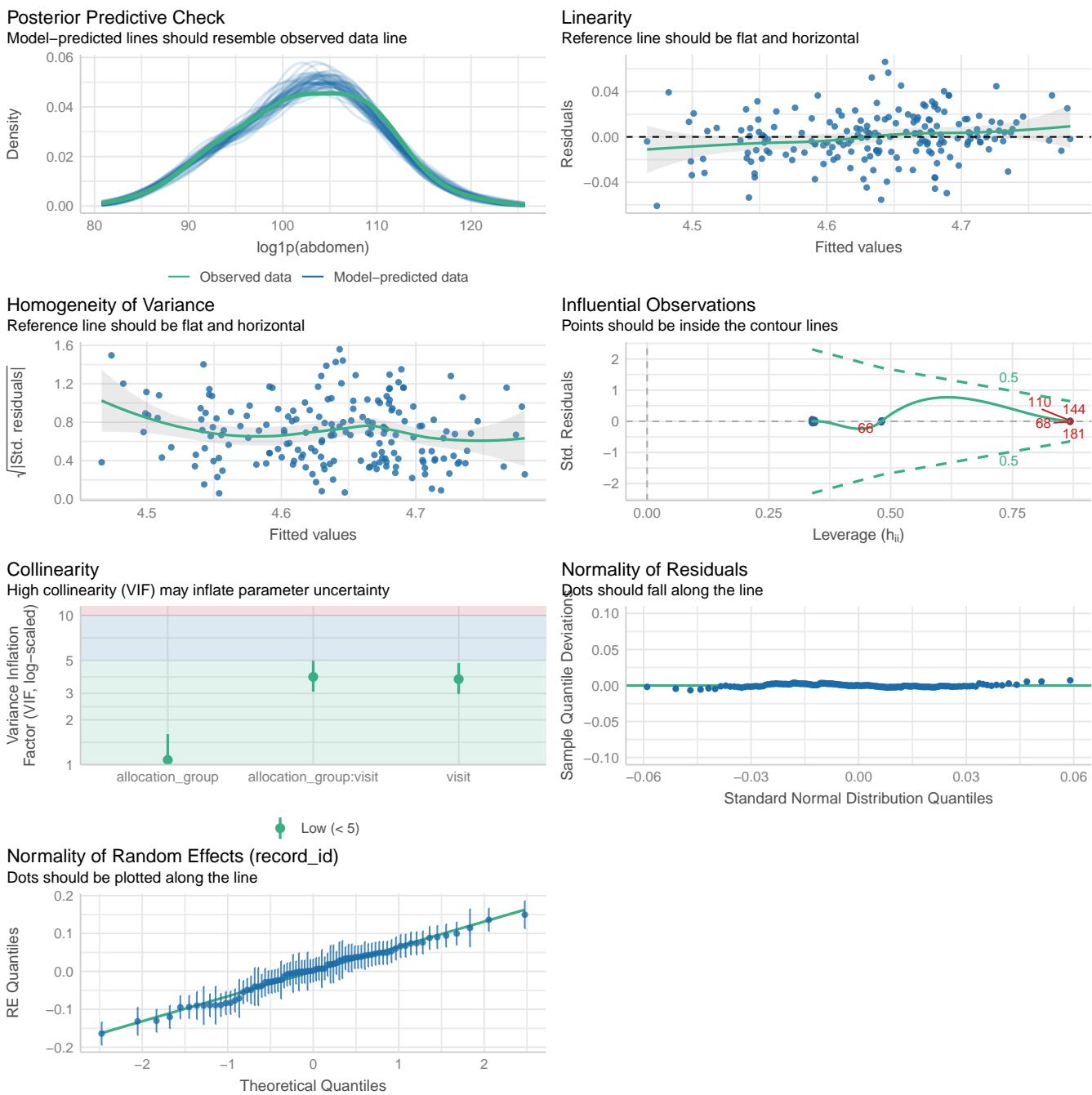
When comparing models, please note that probably not all models were fit from same data.

```
# Comparison of Model Performance Indices
```

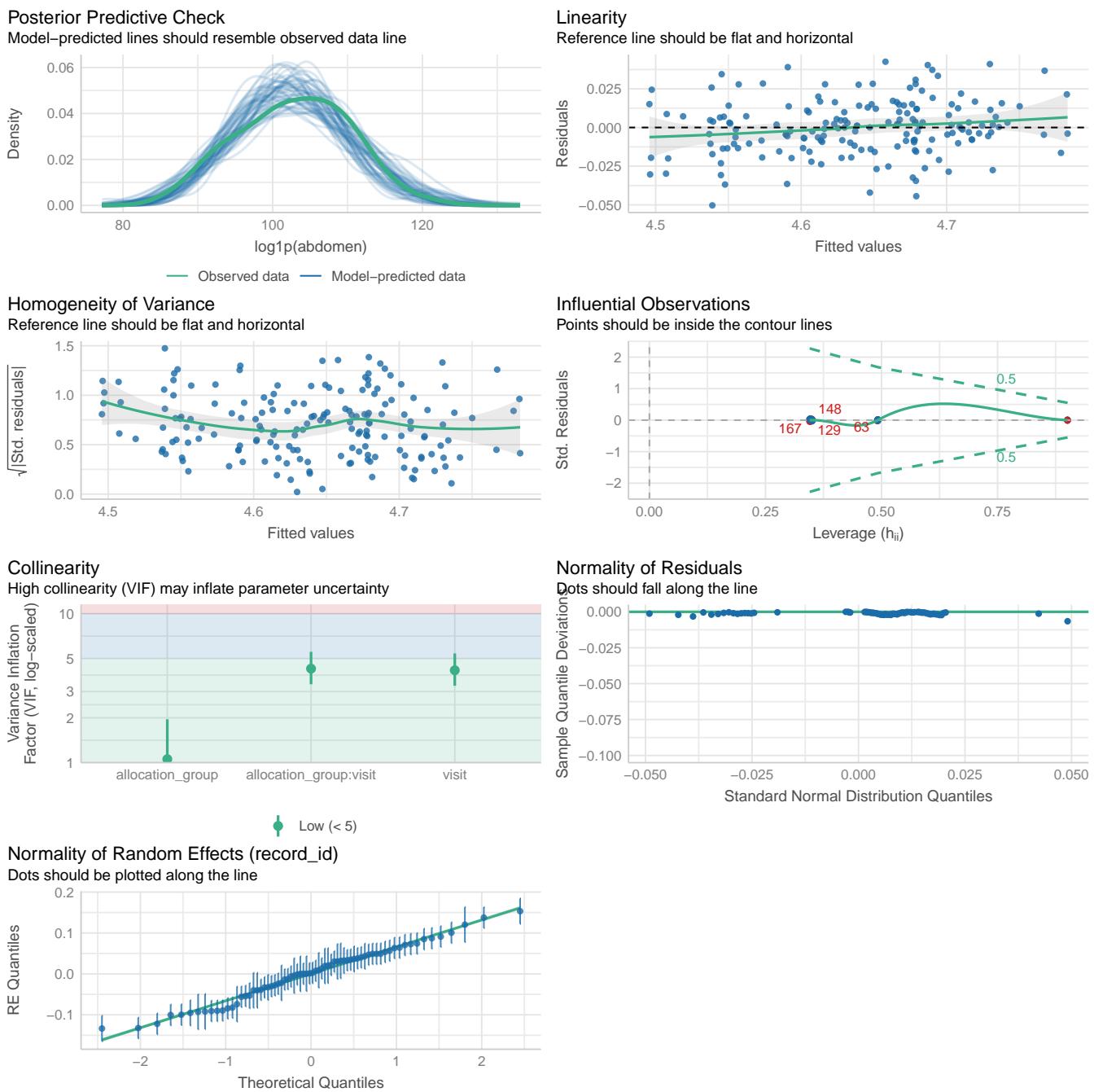
Name	Model	AIC (weights)	AICc (weights)
abdomen_model	lmerModLmerTest	1134.8 (<.001)	1135.6 (<.001)
abdomen_model_sens	lmerModLmerTest	1011.7 (>.999)	1012.6 (>.999)

Name	BIC (weights)	R2 (cond.)	R2 (marg.)	ICC	RMSE	Sigma
abdomen_model	1160.7 (<.001)	0.866	0.007	0.865	0.021	0.027
abdomen_model_sens	1036.9 (>.999)	0.899	0.009	0.898	0.018	0.023

```
performance::check_model(abdomen_model)
```



```
performance::check_model(abdomen_model_sens)
```



3.14.2 Médias Marginais Estimadas

3.14.2.1 Todos os dados

```
# Get EMMs for each group at each visit
abdomen_raw_emm <- emmeans::emmeans(
  abdomen_model,
  ~ allocation_group * visit
```

```

)

abdomen_raw_emm <- regrid(abdomen_raw_emm)

# Table of marginal means
# abdomen_raw_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(abdomen_raw_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

visit = 1:

```

contrast	estimate	SE	df	lower.CL	upper.CL	t.ratio	p.value
Grupo A - Grupo B	1.558	1.77	84.3	-1.96	5.08	0.880	0.3813

```
visit = 2:
```

contrast	estimate	SE	df	lower.CL	upper.CL	t.ratio	p.value
Grupo A - Grupo B	0.869	1.82	91.4	-2.74	4.47	0.478	0.6335

```
visit = 3:
```

contrast	estimate	SE	df	lower.CL	upper.CL	t.ratio	p.value
Grupo A - Grupo B	-0.814	1.85	96.8	-4.49	2.86	-0.440	0.6609

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
 Confidence level used: 0.95

```
# Pairwise comparisons: Changes over time within each group
emmeans::contrast(abdomen_raw_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
allocation_group = Grupo A:
```

contrast	estimate	SE	df	lower.CL	upper.CL	t.ratio	p.value
visit1 - visit2	0.907	0.714	84.3	-0.837	2.651	1.270	0.6225
visit1 - visit3	1.656	0.749	84.3	-0.173	3.484	2.212	0.0891
visit2 - visit3	0.749	0.750	91.4	-1.080	2.577	0.999	0.9617

```

allocation_group = Grupo B:
contrast      estimate     SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit2    0.217 0.728 84.3    -1.561     1.996   0.298  1.0000
visit1 - visit3   -0.716 0.775 84.3    -2.609     1.176  -0.925  1.0000
visit2 - visit3   -0.934 0.779 95.7    -2.831     0.964  -1.199  0.7002

```

Degrees-of-freedom method: inherited from kenward-roger when re-gridding

Confidence level used: 0.95

Conf-level adjustment: bonferroni method for 3 estimates

P value adjustment: bonferroni method for 3 tests

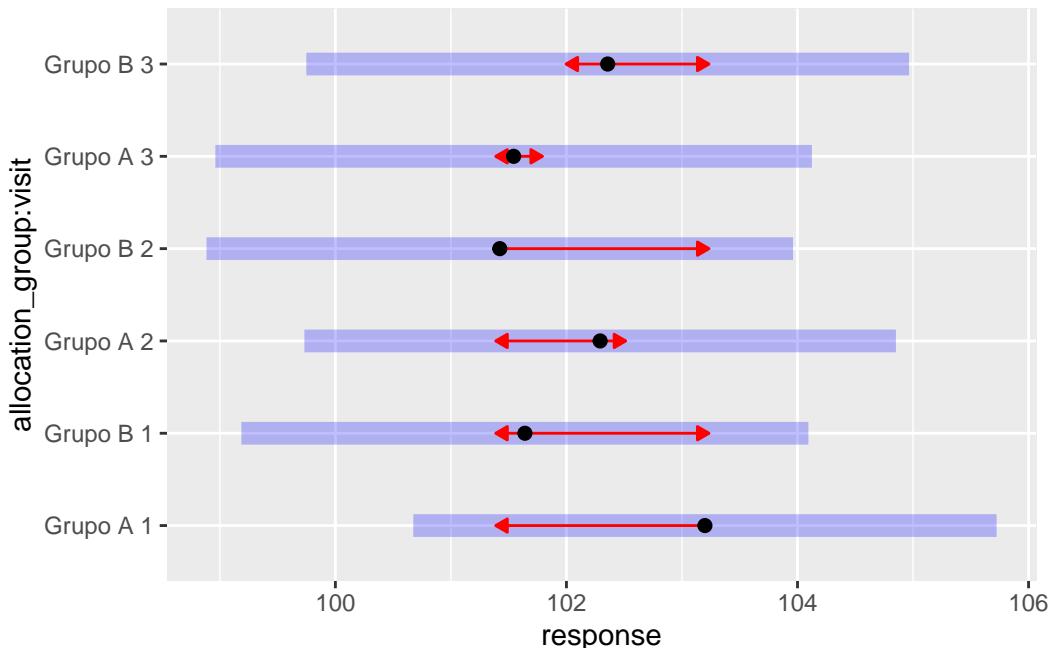
```

# Plot of marginal means
plot(abdomen_raw_emm, comparisons = TRUE)

```

Warning: Comparison discrepancy in group "1", Grupo A visit3 - Grupo B visit3:

Target overlap = 0.8487, overlap on graph = -0.3329



3.14.2.2 Análise de sensibilidade

```

# Get EMMs for each group at each visit (Sensitivity Analysis)
abdomen_emm <- emmeans::emmeans(
  abdomen_model_sens,
  ~ allocation_group * visit
)

```

```

abdomen_emm <- regrid(abdomen_emm)

# Table of marginal means
# abdomen_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(abdomen_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

visit = 1:
  contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
  Grupo A - Grupo B    1.747 1.79 75.5     -1.82      5.32   0.975  0.3328

```

```

visit = 2:
  contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
  Grupo A - Grupo B    1.591 1.84 81.5     -2.06      5.25   0.866  0.3889

visit = 3:
  contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
  Grupo A - Grupo B   -0.386 1.87 86.0     -4.10      3.33  -0.206  0.8370

```

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
 Confidence level used: 0.95

```

# Pairwise comparisons: Changes over time within each group
emmeans::contrast(abdomen_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

```

```

allocation_group = Grupo A:
  contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
  visit1 - visit2   0.2062 0.653 75.5     -1.393     1.806   0.316  1.0000
  visit1 - visit3   0.9734 0.691 75.5     -0.719     2.665   1.409  0.4892
  visit2 - visit3   0.7672 0.693 81.5     -0.928     2.462   1.106  0.8156

```

```

allocation_group = Grupo B:
  contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value

```

```

visit1 - visit2  0.0497 0.630 75.5   -1.494    1.593   0.079  1.0000
visit1 - visit3 -1.1596 0.674 75.5   -2.809    0.490   -1.721  0.2679
visit2 - visit3 -1.2094 0.676 84.1   -2.861    0.443   -1.788  0.2319

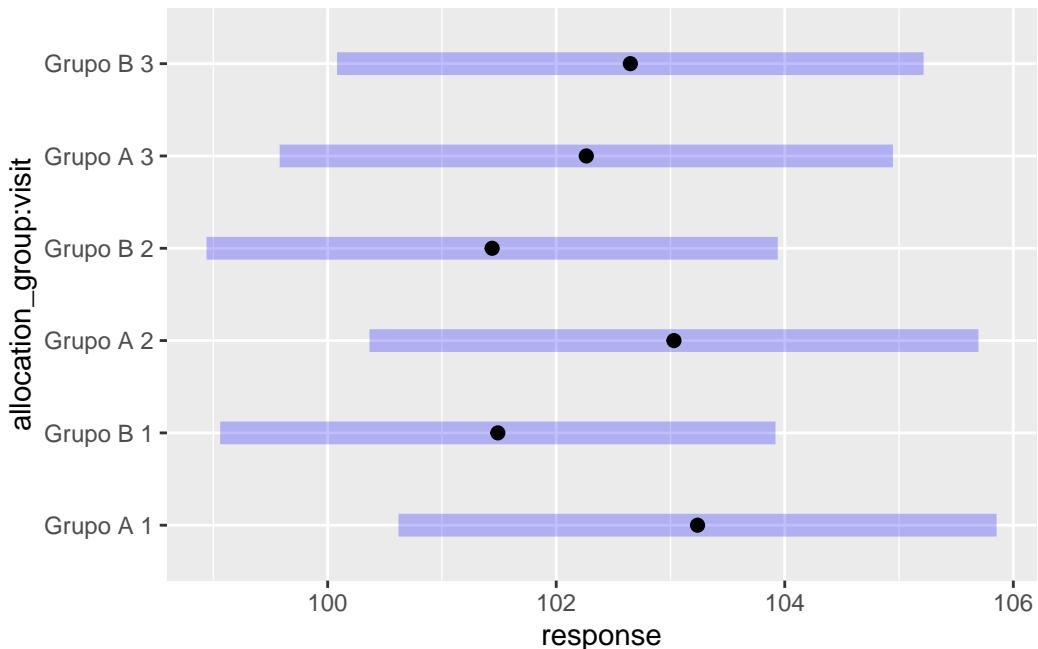
```

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
 Confidence level used: 0.95
 Conf-level adjustment: bonferroni method for 3 estimates
 P value adjustment: bonferroni method for 3 tests

```

# Plot of marginal means
plot(abdomen_emm)

```



3.14.3 Resultado

No modelo ajustado para a circunferência abdominal, não foram observadas diferenças estatisticamente significativas entre os grupos em nenhum dos três momentos avaliados. As comparações dentro dos grupos ao longo do tempo também não revelaram mudanças significativas. Embora a diferença entre as visitas 1 e 3 no grupo placebo tenha se aproximado da significância ($p = 0,089$), essa tendência não foi confirmada na análise de sensibilidade. Após a exclusão das observações influentes, os resultados permaneceram estáveis, sem diferenças estatisticamente significativas entre os grupos ou ao longo do tempo. As estimativas, intervalos de confiança de 95% e valores de p estão apresentados na Tabela 14.

Tabela 14: Diferenças estimadas da circunferência abdominal entre os grupos de alocação (placebo vs Eclipta) e entre visitas dentro de cada grupo

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 1	1,56	[-1,96 ; 5,08]	0,381
Entre grupos	Visita 2	0,87	[-2,74 ; 4,47]	0,634
Entre grupos	Visita 3	-0,81	[-4,49 ; 2,86]	0,661
Grupo Placebo	Visita 1 - Visita 2	0,91	[-0,84 ; 2,65]	0,623
Grupo Placebo	Visita 1 - Visita 3	1,66	[-0,17 ; 3,48]	0,089
Grupo Placebo	Visita 2 - Visita 3	0,75	[-1,08 ; 2,58]	0,962
Grupo Eclipta	Visita 1 - Visita 2	0,22	[-1,56 ; 2,00]	1,000
Grupo Eclipta	Visita 1 - Visita 3	-0,72	[-2,61 ; 1,18]	1,000
Grupo Eclipta	Visita 2 - Visita 3	-0,93	[-2,83 ; 0,96]	0,700

```

ggplot(
  data = data_model,
  aes(
    x = as.factor(visit),
    y = abdomen,
    group = record_id,
  )
) +
  geom_line(alpha = 0.5) +
  geom_point(alpha = 0.7) +
  geom_smooth(
    aes(group = allocation_group),
    method = "lm",
    se = TRUE,
    linewidth = 1
) +
  labs(title = "All data") +
  facet_wrap(~ allocation_group)

```

```
`geom_smooth()` using formula = 'y ~ x'
```

```
Warning: Removed 2 rows containing non-finite outside the scale range
```

```
(`stat_smooth()`).
```

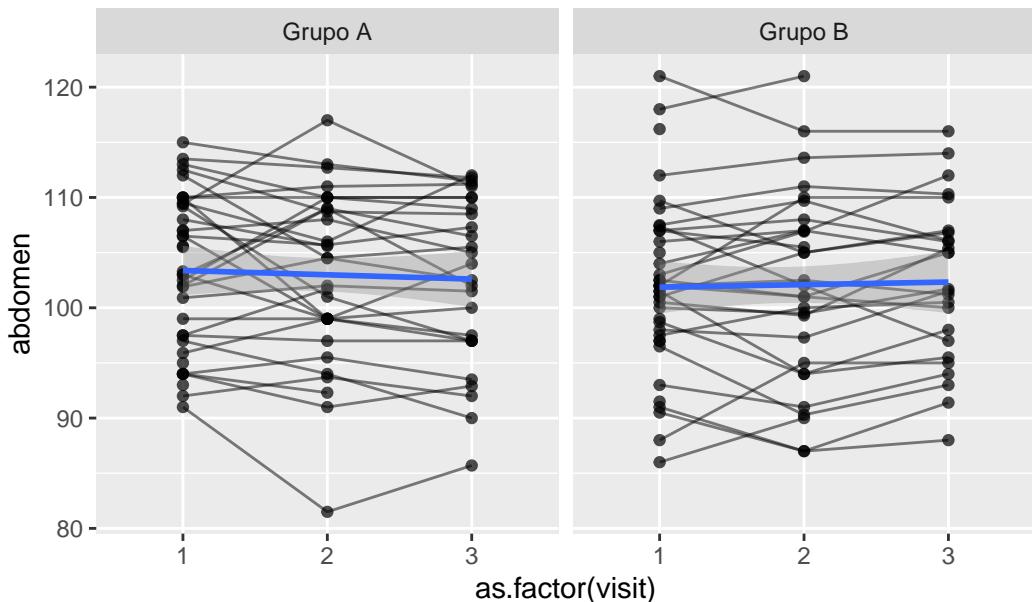
```
Warning: Removed 2 rows containing missing values or values outside the scale range
```

```
(`geom_line()`).
```

```
Warning: Removed 2 rows containing missing values or values outside the scale range
```

```
(`geom_point()`).
```

All data



```
#coord_cartesian(ylim = c(10, 150))
```

```
data_model %>%
  filter(
    !(record_id %in%
      abdomen_model_check$influential_ids)
  ) %>%
  ggplot(
    aes(
      x = as.factor(visit),
      y = abdomen,
      group = record_id,
    )
  ) +
  geom_line(alpha = 0.5) +
  geom_point(alpha = 0.7) +
  geom_smooth(
    aes(group = allocation_group),
    method = "lm",
```

```

    se = TRUE,
    linewidth = 1
) +
  labs(title = "Sensitivity analysis") +
  facet_wrap(~ allocation_group)

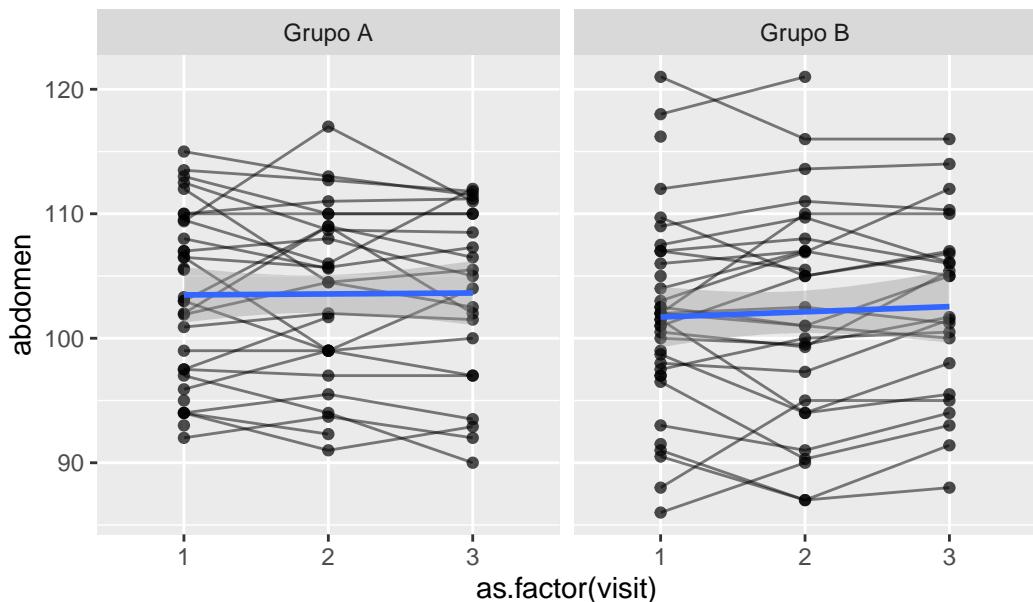
`geom_smooth()` using formula = 'y ~ x'
Warning: Removed 2 rows containing non-finite outside the scale range
(`stat_smooth()`).

Warning: Removed 2 rows containing missing values or values outside the scale range
(`geom_line()`).

Warning: Removed 2 rows containing missing values or values outside the scale range
(`geom_point()`).

```

Sensitivity analysis



3.15 Índice de Massa Corporal

Variável: bmi

```

# Plot 1: Raw data
bmi_hist_1 <- data_model %>%
  #filter(
  #  bmi < 300

```

```

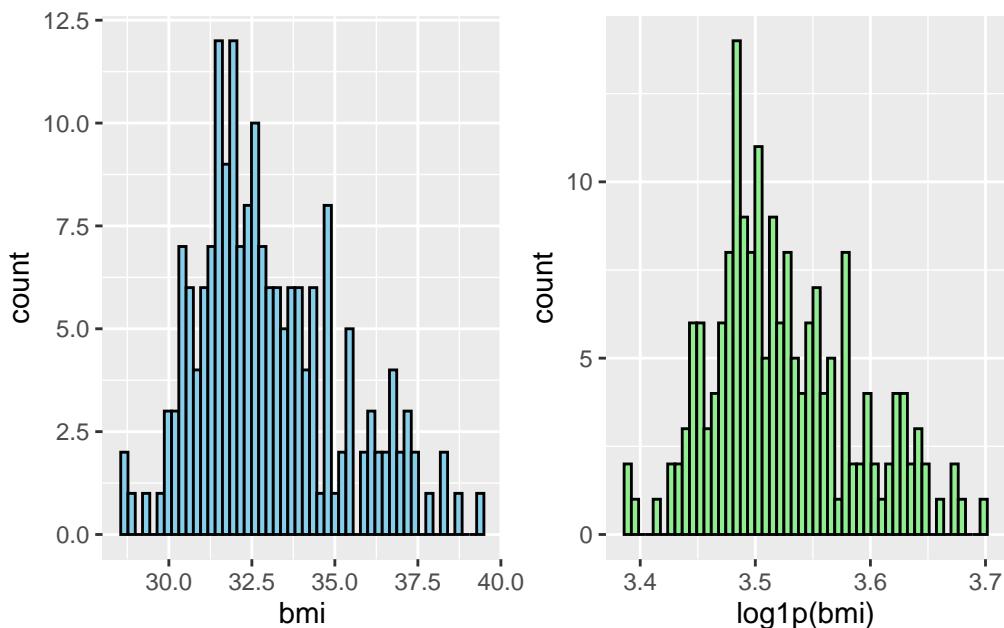
#) %>%
ggplot(aes(x = bmi)) +
  geom_histogram(bins = 50, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
bmi_hist_2 <- data_model %>%
  #filter(
  #  bmi < 300
  #) %>%
  ggplot(aes(x = log1p(bmi))) +
  geom_histogram(bins = 50, fill = "lightgreen", color = "black")

# Combine side by side
bmi_hist_1 + bmi_hist_2 # library(patchwork)

```

Warning: Removed 2 rows containing non-finite outside the scale range (`stat_bin()`).
 Removed 2 rows containing non-finite outside the scale range (`stat_bin()`).



```

# LMM
bmi_model <- lmer(bmi ~ allocation_group * visit +
(1 | record_id), data = data_model)
check_collinearity(bmi_model)

# Check for Multicollinearity

```

Low Correlation

Term	VIF	VIF 95% CI	Increased SE	Tolerance
allocation_group	1.05	[1.00, 1.88]	1.03	0.95
visit	3.74	[2.98, 4.78]	1.93	0.27
allocation_group:visit	3.83	[3.05, 4.91]	1.96	0.26

Tolerance 95% CI

[0.53, 1.00]
[0.21, 0.34]
[0.20, 0.33]

```
# Sensitivity analysis
bmi_model_check <- sensitivity_check_lmer(
  model = bmi_model,
  id_var = "record_id",
  top_n = 5)

# LMM Sensitivity
bmi_model_sens <- update(object = bmi_model,
                           subset = !(record_id %in%
                           bmi_model_check$influential_ids))

# Influential IDS
bmi_model_check$influential_ids

[1] "8"   "50"  "53"  "74"  "32"
```

3.15.1 Resumo dos modelos

```
# Model comparison
summary(bmi_model)

Linear mixed model fit by REML. t-tests use Satterthwaite's method [
lmerModLmerTest]

Formula: bmi ~ allocation_group * visit + (1 | record_id)

Data: data_model

REML criterion at convergence: 615.9
```

Scaled residuals:

Min	1Q	Median	3Q	Max
-3.4029	-0.4671	-0.0177	0.4841	3.3103

Random effects:

Groups	Name	Variance	Std.Dev.
record_id	(Intercept)	4.1025	2.0255
Residual		0.4525	0.6727

Number of obs: 187, groups: record_id, 75

Fixed effects:

	Estimate	Std. Error	df	t value	Pr(> t)
(Intercept)	32.9678	0.3509	81.3398	93.961	< 2e-16
allocation_group	0.3598	0.4929	81.3398	0.730	0.46754
visit2	-0.3263	0.1702	110.0171	-1.917	0.05782
visit3	-0.5740	0.1793	110.2335	-3.201	0.00179
allocation_group:visit2	0.3364	0.2445	110.4215	1.375	0.17179
allocation_group:visit3	0.5709	0.2582	110.6050	2.211	0.02910

(Intercept) ***

allocation_group

visit2 .

visit3 **

allocation_group:visit2

allocation_group:visit3 *

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

(Intr)	all_GB	visit2	visit3	a_GB:2
allctn_grGB	-0.712			
visit2	-0.205	0.146		
visit3	-0.194	0.138	0.471	
allctn_GB:2	0.143	-0.200	-0.696	-0.328
allctn_GB:3	0.135	-0.190	-0.327	-0.694
				0.469

```
summary(bmi_model_sens)
```

Linear mixed model fit by REML. t-tests use Satterthwaite's method [
lmerModLmerTest]

Formula: bmi ~ allocation_group * visit + (1 | record_id)

Data: data_model

Subset: !(record_id %in% bmi_model_check\$influential_ids)

REML criterion at convergence: 508.5

Scaled residuals:

Min	1Q	Median	3Q	Max
-2.08439	-0.51935	0.00596	0.47882	2.16447

Random effects:

Groups	Name	Variance	Std.Dev.
record_id	(Intercept)	3.6273	1.9045
Residual		0.2717	0.5213

Number of obs: 172, groups: record_id, 70

Fixed effects:

	Estimate	Std. Error	df	t value	Pr(> t)
(Intercept)	32.6952	0.3437	73.0061	95.118	<2e-16 ***
allocation_group	0.5473	0.4728	73.0061	1.158	0.2508
visit2	-0.1738	0.1414	99.2311	-1.229	0.2221
visit3	-0.2725	0.1503	99.3680	-1.813	0.0729 .
allocation_group:visit2	0.1222	0.1981	99.4346	0.617	0.5388
allocation_group:visit3	0.2026	0.2103	99.5464	0.963	0.3378

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

	(Intr)	all_GB	visit2	visit3	a_GB:2
allctn_gr	GB	-0.727			
visit2		-0.169	0.123		
visit3		-0.159	0.116	0.467	
allctn_GB:2		0.121	-0.166	-0.714	-0.334

```
allctn_GB:3 0.114 -0.157 -0.334 -0.715 0.467
```

```
performance::compare_performance(  
  bmi_model,  
  bmi_model_sens)
```

When comparing models, please note that probably not all models were fit from same data.

```
# Comparison of Model Performance Indices
```

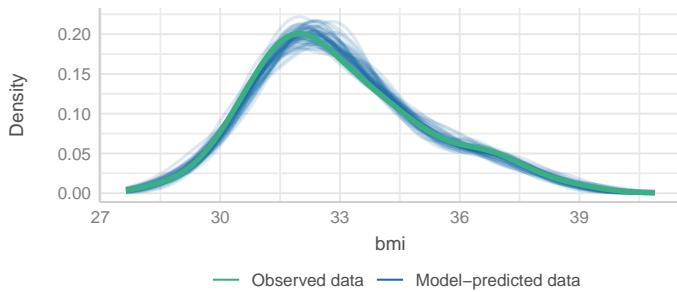
Name	Model	AIC (weights)	AICc (weights)
bmi_model	lmerModLmerTest	624.2 (<.001)	625.0 (<.001)
bmi_model_sens	lmerModLmerTest	515.0 (>.999)	515.9 (>.999)

Name	BIC (weights)	R2 (cond.)	R2 (marg.)	ICC	RMSE	Sigma
bmi_model	650.1 (<.001)	0.903	0.027	0.901	0.520	0.673
bmi_model_sens	540.2 (>.999)	0.932	0.028	0.930	0.398	0.521

```
performance::check_model(bmi_model)
```

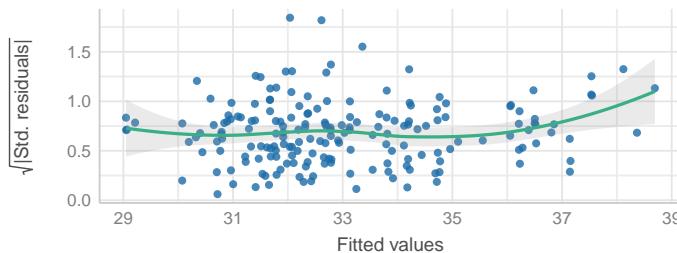
Posterior Predictive Check

Model-predicted lines should resemble observed data line



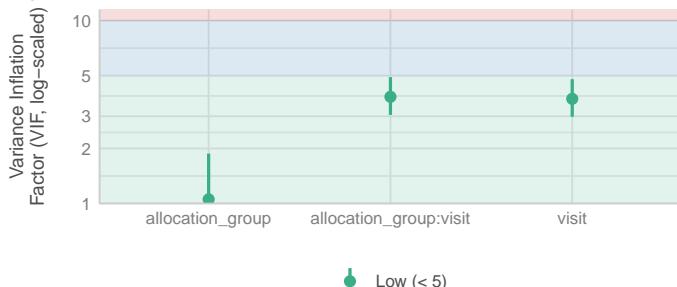
Homogeneity of Variance

Reference line should be flat and horizontal



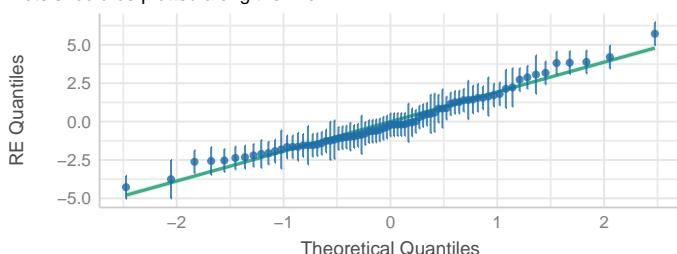
Collinearity

High collinearity (VIF) may inflate parameter uncertainty



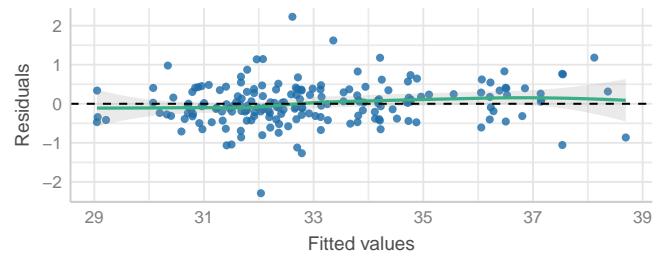
Normality of Random Effects (record_id)

Dots should be plotted along the line



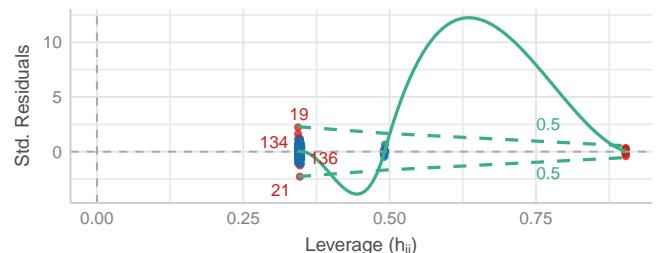
Linearity

Reference line should be flat and horizontal



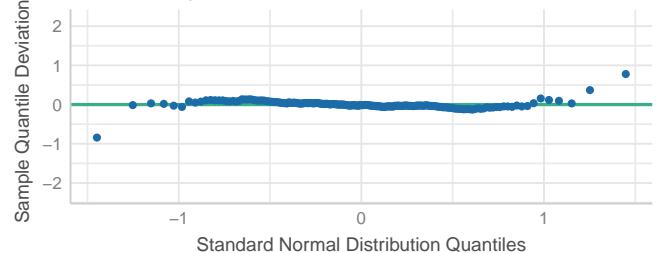
Influential Observations

Points should be inside the contour lines

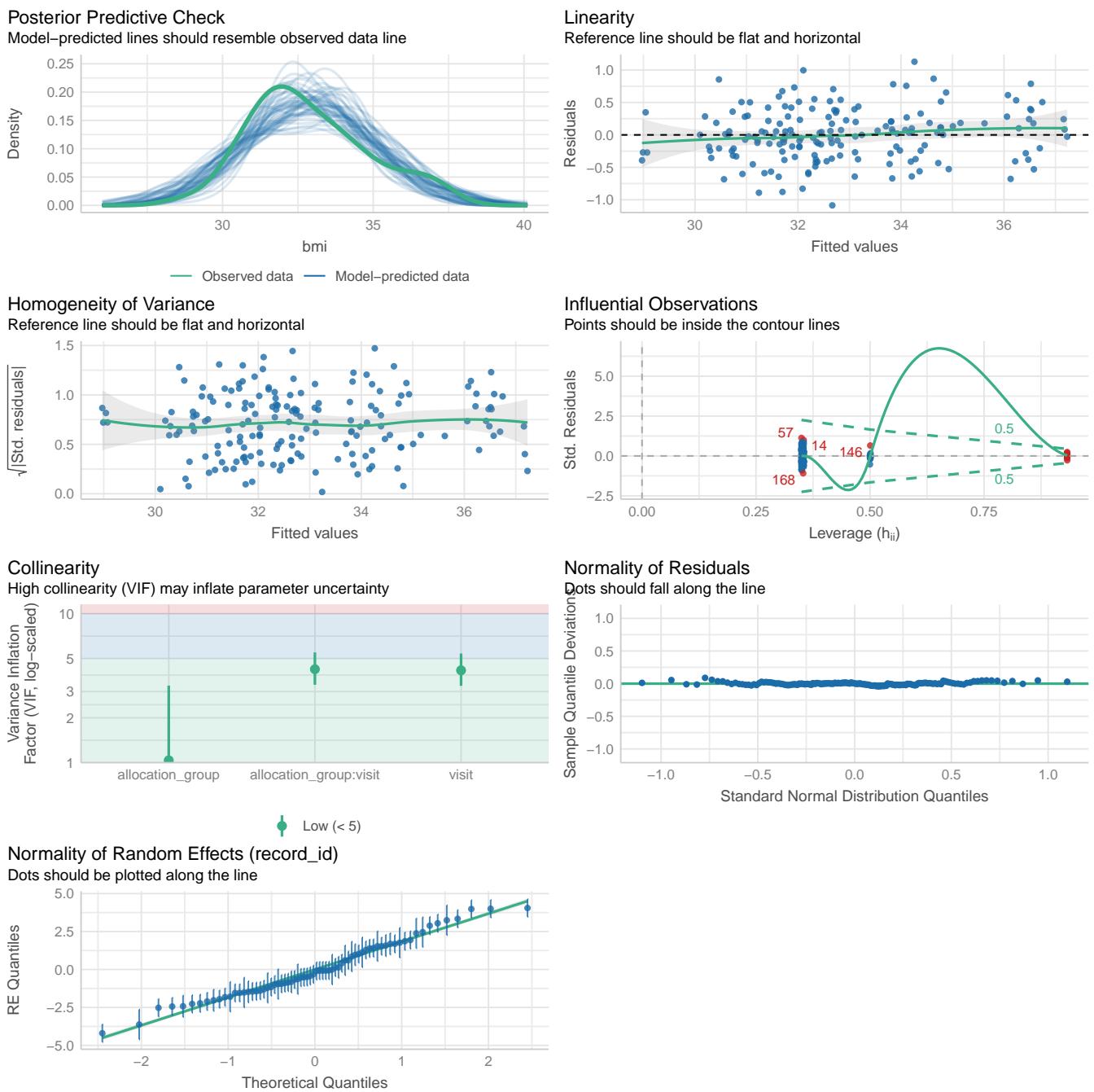


Normality of Residuals

Dots should fall along the line



```
performance::check_model(bmi_model_sens)
```



3.15.2 Médias Marginais Estimadas

3.15.2.1 Todos os dados

```
# Get EMMs for each group at each visit
bmi_raw_emm <- emmeans::emmeans(
  bmi_model,
  ~ allocation_group * visit
```

```

)

bmi_raw_emm <- regrid(bmi_raw_emm)

# Table of marginal means
# bmi_raw_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(bmi_raw_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

visit = 1:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B   -0.360 0.493 81.0    -1.34    0.6210  -0.730  0.4675

visit = 2:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B   -0.696 0.505 86.4    -1.70    0.3068  -1.380  0.1712

visit = 3:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B   -0.931 0.511 90.4    -1.95    0.0851  -1.820  0.0720

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95

# Pairwise comparisons: Changes over time within each group
emmeans::contrast(bmi_raw_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

allocation_group = Grupo A:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit2  0.32626 0.170 81.0   -0.0899    0.742   1.916  0.1765
visit1 - visit3  0.57397 0.179 81.0    0.1355    1.012   3.200  0.0059
visit2 - visit3  0.24771 0.180 86.4   -0.1917    0.687   1.376  0.5167

```

```

allocation_group = Grupo B:

contrast      estimate     SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit2 -0.01010 0.176 81.0  -0.4396    0.419  -0.057  1.0000
visit1 - visit3  0.00309 0.186 81.0  -0.4514    0.458   0.017  1.0000
visit2 - visit3  0.01319 0.187 89.7  -0.4426    0.469   0.071  1.0000

```

Degrees-of-freedom method: inherited from kenward-roger when re-gridding

Confidence level used: 0.95

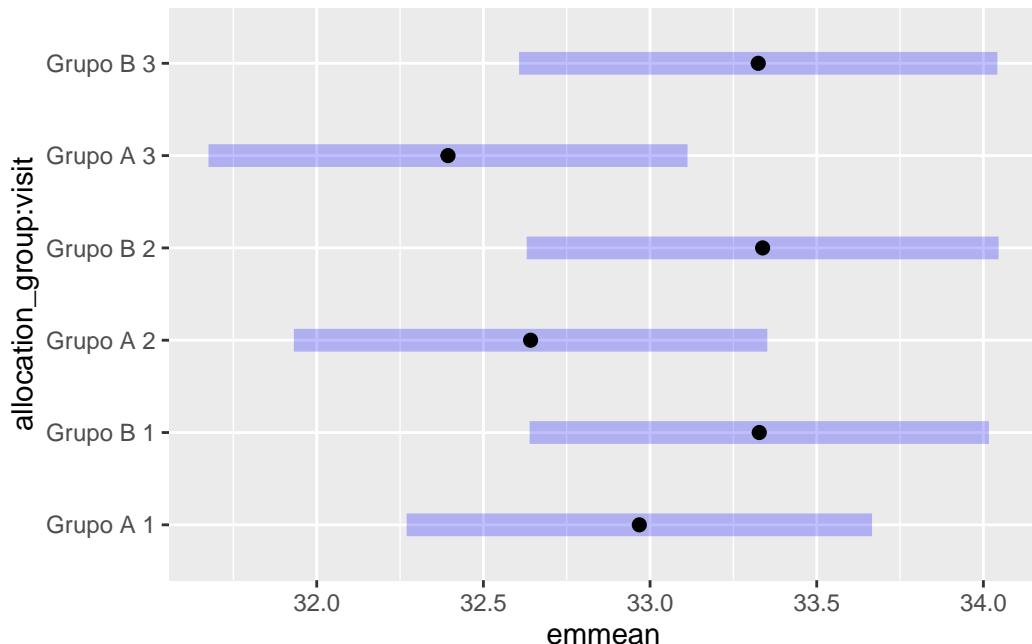
Conf-level adjustment: bonferroni method for 3 estimates

P value adjustment: bonferroni method for 3 tests

```

# Plot of marginal means
plot(bmi_raw_emm)

```



3.15.2.2 Análise de sensibilidade

```

# Get EMMs for each group at each visit (Sensitivity Analysis)
bmi_emm <- emmeans::emmeans(
  bmi_model_sens,
  ~ allocation_group * visit
)

bmi_emm <- regrid(bmi_emm)

```

```

# Table of marginal means
# bmi_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(bmi_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

visit = 1:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B   -0.547 0.473 73.0    -1.49     0.395  -1.158  0.2508

visit = 2:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B   -0.669 0.481 77.1    -1.63     0.289  -1.391  0.1682

visit = 3:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B   -0.750 0.486 80.2    -1.72     0.218  -1.541  0.1271

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95

# Pairwise comparisons: Changes over time within each group
emmeans::contrast(bmi_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

allocation_group = Grupo A:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit2   0.1738 0.141 73.0    -0.173     0.520   1.228  0.6699
visit1 - visit3   0.2725 0.150 73.0    -0.096     0.641   1.812  0.2222
visit2 - visit3   0.0987 0.151 77.1    -0.270     0.468   0.655  1.0000

allocation_group = Grupo B:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit2   0.0516 0.139 73.0    -0.288     0.392   0.372  1.0000
visit1 - visit3   0.0699 0.147 73.0    -0.291     0.431   0.475  1.0000

```

```
visit2 - visit3  0.0184 0.148 78.9   -0.343     0.380   0.124  1.0000
```

Degrees-of-freedom method: inherited from kenward-roger when re-gridding

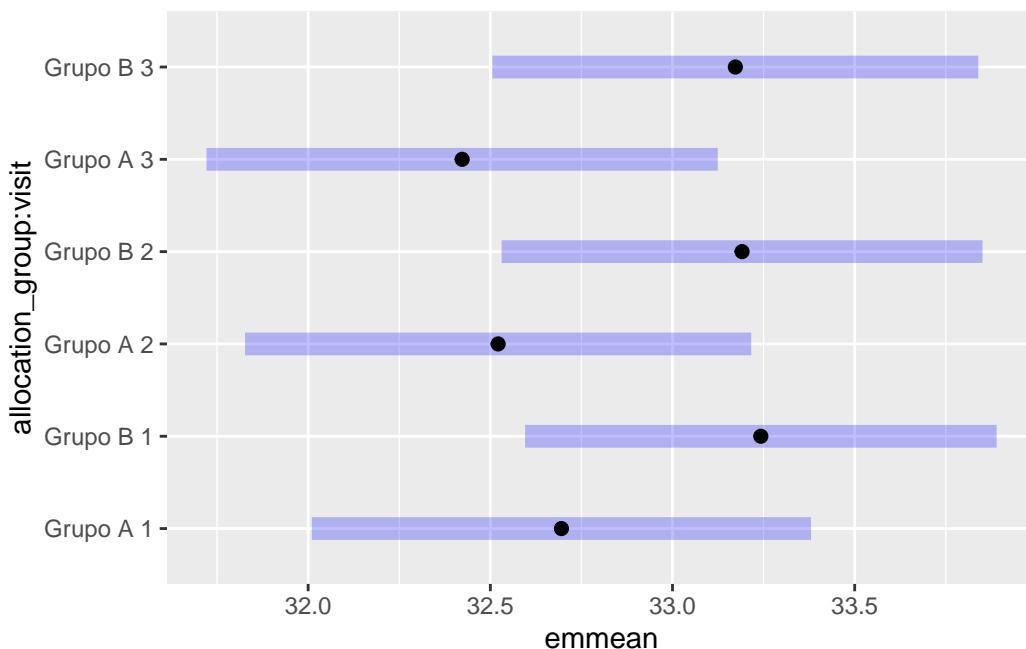
Confidence level used: 0.95

Conf-level adjustment: bonferroni method for 3 estimates

P value adjustment: bonferroni method for 3 tests

```
# Plot of marginal means
```

```
plot(bmi_emm)
```



3.15.3 Resultado

No modelo ajustado para o índice de massa corporal (IMC), não foram observadas diferenças estatisticamente significativas entre os grupos em nenhum dos três momentos avaliados. No entanto, dentro do grupo placebo, observou-se uma redução estatisticamente significativa entre as visitas 1 e 3 ($p = 0,0059$). Para investigar a robustez desse achado, foi realizada uma análise de sensibilidade com exclusão das cinco observações mais influentes (IDs: 8, 50, 53, 74 e 32). Após a exclusão, a diferença intra grupo placebo deixou de ser significativa ($p = 0,222$), sugerindo que o resultado original foi influenciado por outliers.

As figuras de diagnóstico do modelo indicaram leve heterocedasticidade e presença de observações influentes, justificando a realização da análise de sensibilidade. A comparação entre os modelos mostrou melhora nos índices de ajuste após a exclusão dos dados influentes (AIC e BIC consideravelmente menores e RMSE reduzido), além de maior normalidade dos resíduos e aleatoriedade nos efeitos aleatórios.

As estimativas, intervalos de confiança de 95% e valores de p estão apresentados na Tabela 15. As estimativas, intervalos de confiança de 95% e valores de p da análise de sensibilidade estão apresentadas na Tabela 16.

Tabela 15: Diferenças estimadas do índice de massa corporal (IMC) entre os grupos de alocação (placebo vs Eclipta) e entre visitas dentro de cada grupo

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 1	-0,36	[-1,34 ; 0,62]	0,468
Entre grupos	Visita 2	-0,70	[-1,70 ; 0,31]	0,171
Entre grupos	Visita 3	-0,93	[-1,95 ; 0,09]	0,072
Grupo Placebo	Visita 1 - Visita 2	0,33	[-0,09 ; 0,74]	0,177
Grupo Placebo	Visita 1 - Visita 3	0,57	[0,14 ; 1,01]	0,006
Grupo Placebo	Visita 2 - Visita 3	0,25	[-0,19 ; 0,69]	0,517
Grupo Eclipta	Visita 1 - Visita 2	-0,01	[-0,44 ; 0,42]	1,000
Grupo Eclipta	Visita 1 - Visita 3	0,00	[-0,45 ; 0,46]	1,000
Grupo Eclipta	Visita 2 - Visita 3	0,01	[-0,44 ; 0,47]	1,000

Tabela 16: Diferenças estimadas do índice de massa corporal (IMC) entre os grupos de alocação (placebo vs Eclipta) e entre visitas dentro de cada grupo – Análise de sensibilidade

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 1	-0,55	[-1,49 ; 0,39]	0,251
Entre grupos	Visita 2	-0,67	[-1,63 ; 0,29]	0,168
Entre grupos	Visita 3	-0,75	[-1,72 ; 0,22]	0,127
Grupo Placebo	Visita 1 - Visita 2	0,17	[-0,17 ; 0,52]	0,670
Grupo Placebo	Visita 1 - Visita 3	0,27	[-0,10 ; 0,64]	0,222
Grupo Placebo	Visita 2 - Visita 3	0,10	[-0,27 ; 0,47]	1,000
Grupo Eclipta	Visita 1 - Visita 2	0,05	[-0,29 ; 0,39]	1,000
Grupo Eclipta	Visita 1 - Visita 3	0,07	[-0,29 ; 0,43]	1,000
Grupo Eclipta	Visita 2 - Visita 3	0,02	[-0,34 ; 0,38]	1,000

```
ggplot(
  data = data_model,
  aes(
    x = as.factor(visit),
    y = bmi,
    group = record_id,
  )
) +
```

```

geom_line(alpha = 0.5) +
geom_point(alpha = 0.7) +
geom_smooth(
  aes(group = allocation_group),
  method = "lm",
  se = TRUE,
  linewidth = 1
) +
labs(title = "All data") +
facet_wrap(~ allocation_group)

`geom_smooth()` using formula = 'y ~ x'

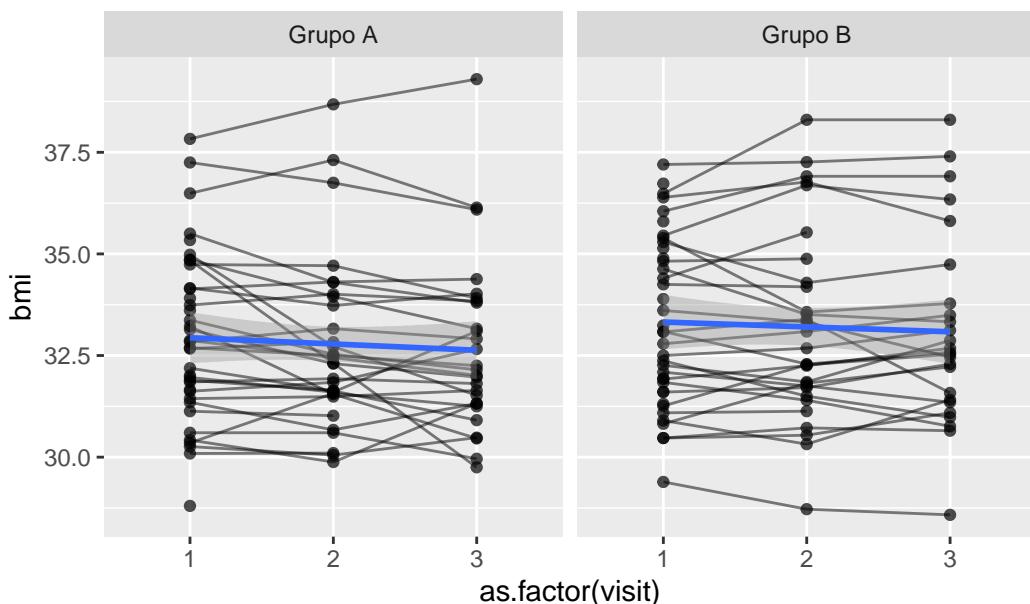
Warning: Removed 2 rows containing non-finite outside the scale range
(`stat_smooth()`).

Warning: Removed 2 rows containing missing values or values outside the scale range
(`geom_line()`).

Warning: Removed 2 rows containing missing values or values outside the scale range
(`geom_point()`).

```

All data



```

#coord_cartesian(ylim = c(10, 150))

data_model %>%
  filter(
    visit == 1 &
      !is.na(bmi) &
      !is.na(allocation_group)
  )

```

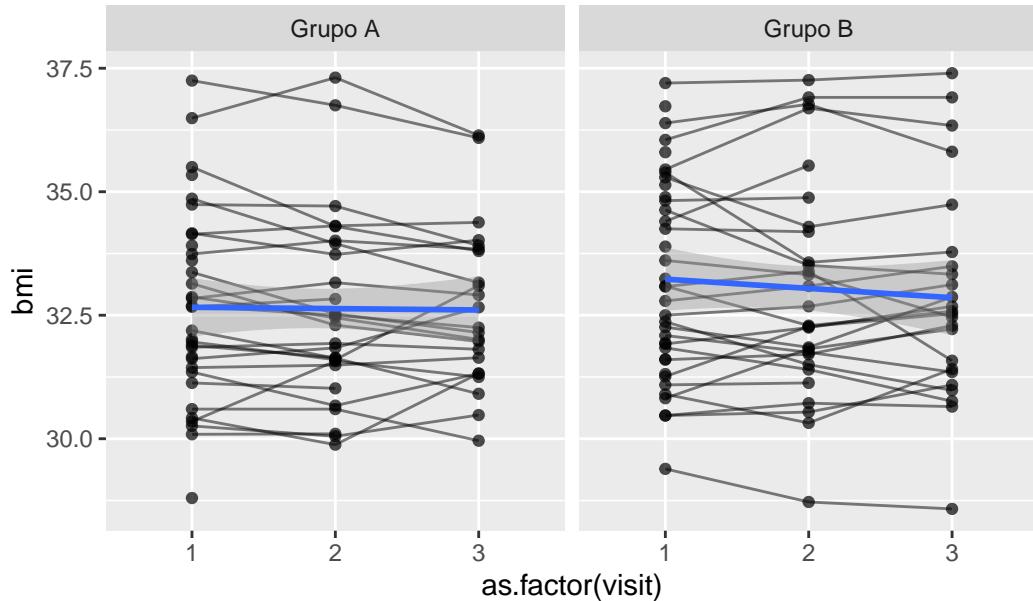
```

!(record_id %in%
bmi_model_check$influential_ids)
) %>%
ggplot(
  aes(
    x = as.factor(visit),
    y = bmi,
    group = record_id,
  )
) +
geom_line(alpha = 0.5) +
geom_point(alpha = 0.7) +
geom_smooth(
  aes(group = allocation_group),
  method = "lm",
  se = TRUE,
  linewidth = 1
) +
labs(title = "Sensitivity analysis") +
facet_wrap(~ allocation_group)

`geom_smooth()` using formula = 'y ~ x'
Warning: Removed 2 rows containing non-finite outside the scale range
(`stat_smooth()`).
Warning: Removed 2 rows containing missing values or values outside the scale range
(`geom_line()`).
Warning: Removed 2 rows containing missing values or values outside the scale range
(`geom_point()`).

```

Sensitivity analysis



```
#coord_cartesian(ylim = c(10, 150))
```

3.16 Pressão Arterial Média

Variável: mean_bp_mean

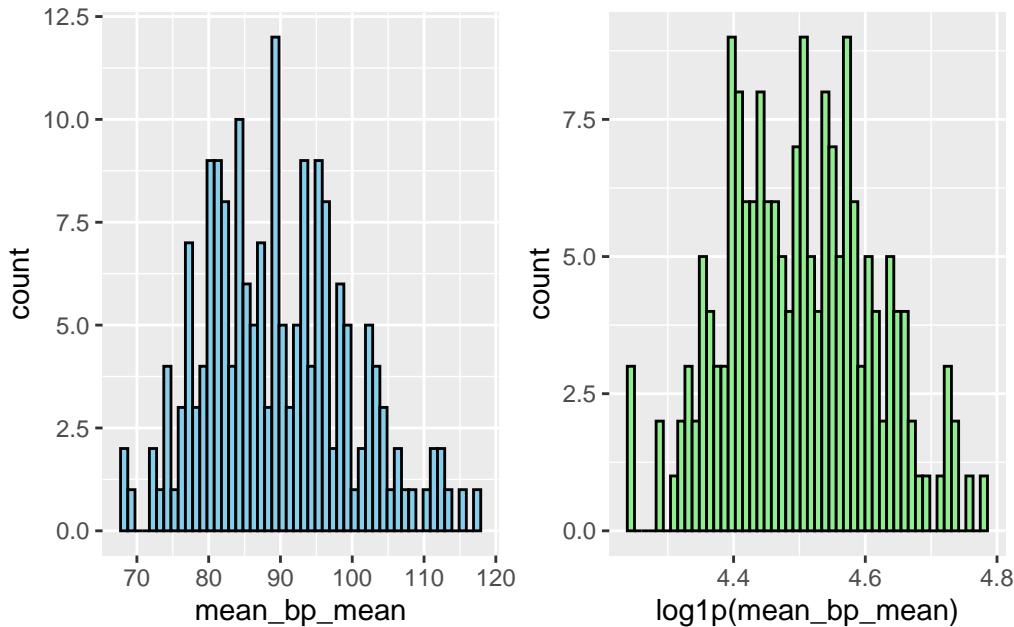
```
# Plot 1: Raw data
mean_bp_mean_hist_1 <- data_model %>%
  #filter(
  #  mean_bp_mean < 300
  #) %>%
  ggplot(aes(x = mean_bp_mean)) +
  geom_histogram(bins = 50, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
mean_bp_mean_hist_2 <- data_model %>%
  #filter(
  #  mean_bp_mean < 300
  #) %>%
  ggplot(aes(x = log1p(mean_bp_mean))) +
  geom_histogram(bins = 50, fill = "lightgreen", color = "black")

# Combine side by side
```

```
mean_bp_mean_hist_1 + mean_bp_mean_hist_2 # library(patchwork)

Warning: Removed 4 rows containing non-finite outside the scale range (`stat_bin()`).
Removed 4 rows containing non-finite outside the scale range (`stat_bin()`).
```



```
# LMM
mean_bp_mean_model <- lmer(mean_bp_mean ~ allocation_group * visit +
(1 | record_id), data = data_model)
check_collinearity(mean_bp_mean_model)

# Check for Multicollinearity
```

Low Correlation

Term	VIF	VIF 95% CI	Increased SE	Tolerance
allocation_group	1.22	[1.09, 1.54]	1.10	0.82
visit	3.88	[3.09, 4.98]	1.97	0.26
allocation_group:visit	4.29	[3.39, 5.51]	2.07	0.23

Tolerance 95% CI

- [0.65, 0.92]
- [0.20, 0.32]
- [0.18, 0.29]

```

# Sensitivity analysis
mean_bp_mean_model_check <- sensitivity_check_lmer(
  model = mean_bp_mean_model,
  id_var = "record_id",
  top_n = 5)

# LMM Sensitivity
mean_bp_mean_model_sens <- update(object = mean_bp_mean_model,
                                     subset = !(record_id %in%
                                     mean_bp_mean_model_check$influential_ids))

# Influential IDS
mean_bp_mean_model_check$influential_ids

```

[1] "46" "17" "45" "27" "50"

3.16.1 Resumo dos modelos

```

# Model comparison
summary(mean_bp_mean_model)

Linear mixed model fit by REML. t-tests use Satterthwaite's method [
lmerModLmerTest]

Formula: mean_bp_mean ~ allocation_group * visit + (1 | record_id)

Data: data_model

REML criterion at convergence: 1286.9

```

Scaled residuals:

Min	1Q	Median	3Q	Max
-2.62758	-0.53598	-0.01067	0.48135	3.02975

Random effects:

Groups	Name	Variance	Std.Dev.
record_id	(Intercept)	67.94	8.243
	Residual	34.36	5.862

Number of obs: 185, groups: record_id, 75

Fixed effects:

	Estimate	Std. Error	df	t value	Pr(> t)
(Intercept)	89.595	1.663	104.881	53.882	<2e-16 ***
allocation_groupGrupo B	2.775	2.336	104.881	1.188	0.2375
visit2	-1.208	1.504	111.576	-0.803	0.4238
visit3	-3.713	1.545	112.106	-2.403	0.0179 *
allocation_groupGrupo B:visit2	-2.813	2.130	112.538	-1.321	0.1893
allocation_groupGrupo B:visit3	1.435	2.220	113.267	0.647	0.5192

Signif. codes:	0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1				

Correlation of Fixed Effects:

```
(Intr) all_GB visit2 visit3 a_GB:2
allctn_grGB -0.712
visit2      -0.371  0.264
visit3      -0.362  0.257  0.448
allctn_GB:2  0.262 -0.368 -0.706 -0.317
allctn_GB:3  0.252 -0.353 -0.312 -0.696  0.451
```

```
summary(mean_bp_mean_model_sens)
```

```
Linear mixed model fit by REML. t-tests use Satterthwaite's method [lmerModLmerTest]
Formula: mean_bp_mean ~ allocation_group * visit + (1 | record_id)
Data: data_model
Subset: !(record_id %in% mean_bp_mean_model_check$influential_ids)
```

REML criterion at convergence: 1154

Scaled residuals:

Min	1Q	Median	3Q	Max
-1.93844	-0.57618	-0.01579	0.55161	1.94113

Random effects:

Groups	Name	Variance	Std.Dev.
record_id	(Intercept)	66.38	8.147
	Residual	25.49	5.049

Number of obs: 171, groups: record_id, 70

Fixed effects:

	Estimate	Std. Error	df	t value	Pr(> t)
(Intercept)	88.940	1.668	90.996	53.307	< 2e-16 ***
allocation_groupGrupo B	3.765	2.295	90.996	1.641	0.10434
visit2	-2.137	1.375	101.567	-1.554	0.12337
visit3	-4.528	1.440	102.162	-3.144	0.00218 **
allocation_groupGrupo B:visit2	-2.666	1.911	102.226	-1.395	0.16591
allocation_groupGrupo B:visit3	1.794	2.012	102.825	0.892	0.37455

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

(Intr)	all_GB	visit2	visit3	a_GB:2
allctn_grGB	-0.727			
visit2	-0.337	0.245		
visit3	-0.321	0.234	0.451	
allctn_GB:2	0.242	-0.333	-0.720	-0.324
allctn_GB:3	0.230	-0.316	-0.323	-0.716
				0.453

```
performance::compare_performance(  
  mean_bp_mean_model,  
  mean_bp_mean_model_sens)
```

When comparing models, please note that probably not all models were fit
from same data.

Comparison of Model Performance Indices

Name		Model	AIC (weights) AICc (weights)	

mean_bp_mean_model	lmerModLmerTest	1318.4 (<.001) 1319.2 (<.001)		
mean_bp_mean_model_sens	lmerModLmerTest	1184.7 (>.999) 1185.6 (>.999)		

Name		BIC (weights)	R2 (cond.) R2 (marg.) ICC	

mean_bp_mean_model	1344.2 (<.001)	0.677	0.038 0.664	
mean_bp_mean_model_sens	1209.8 (>.999)	0.742	0.070 0.723	

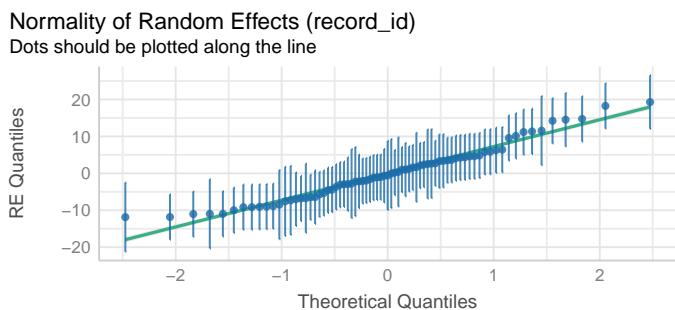
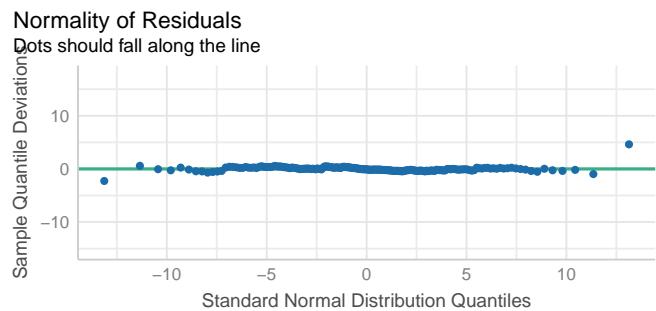
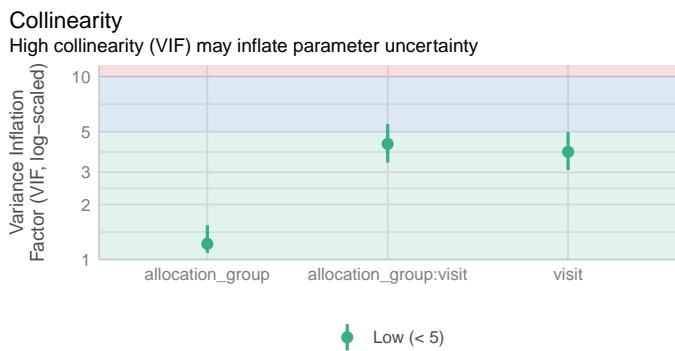
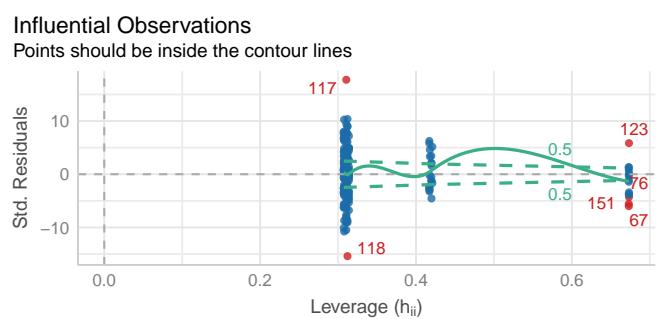
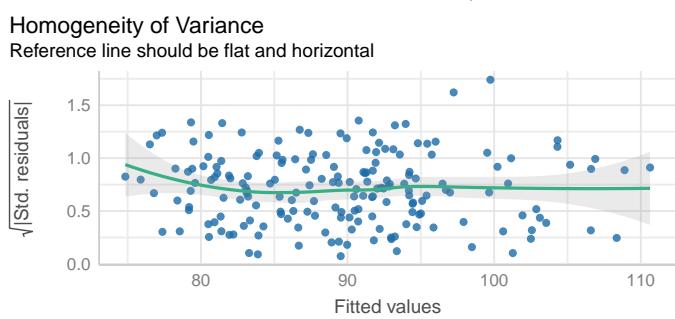
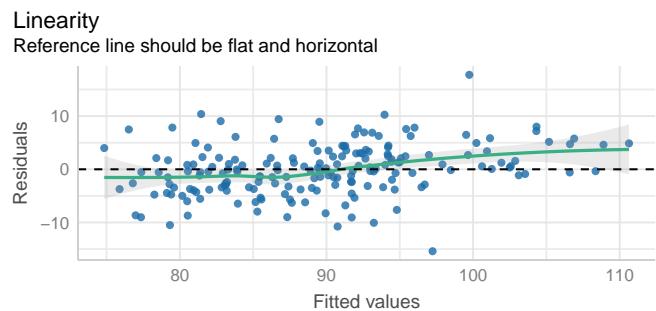
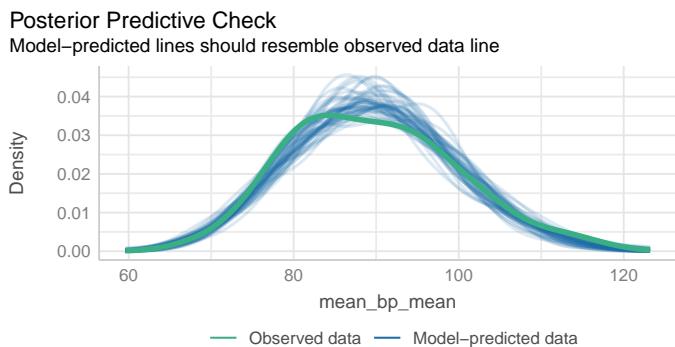
Name | RMSE | Sigma

```

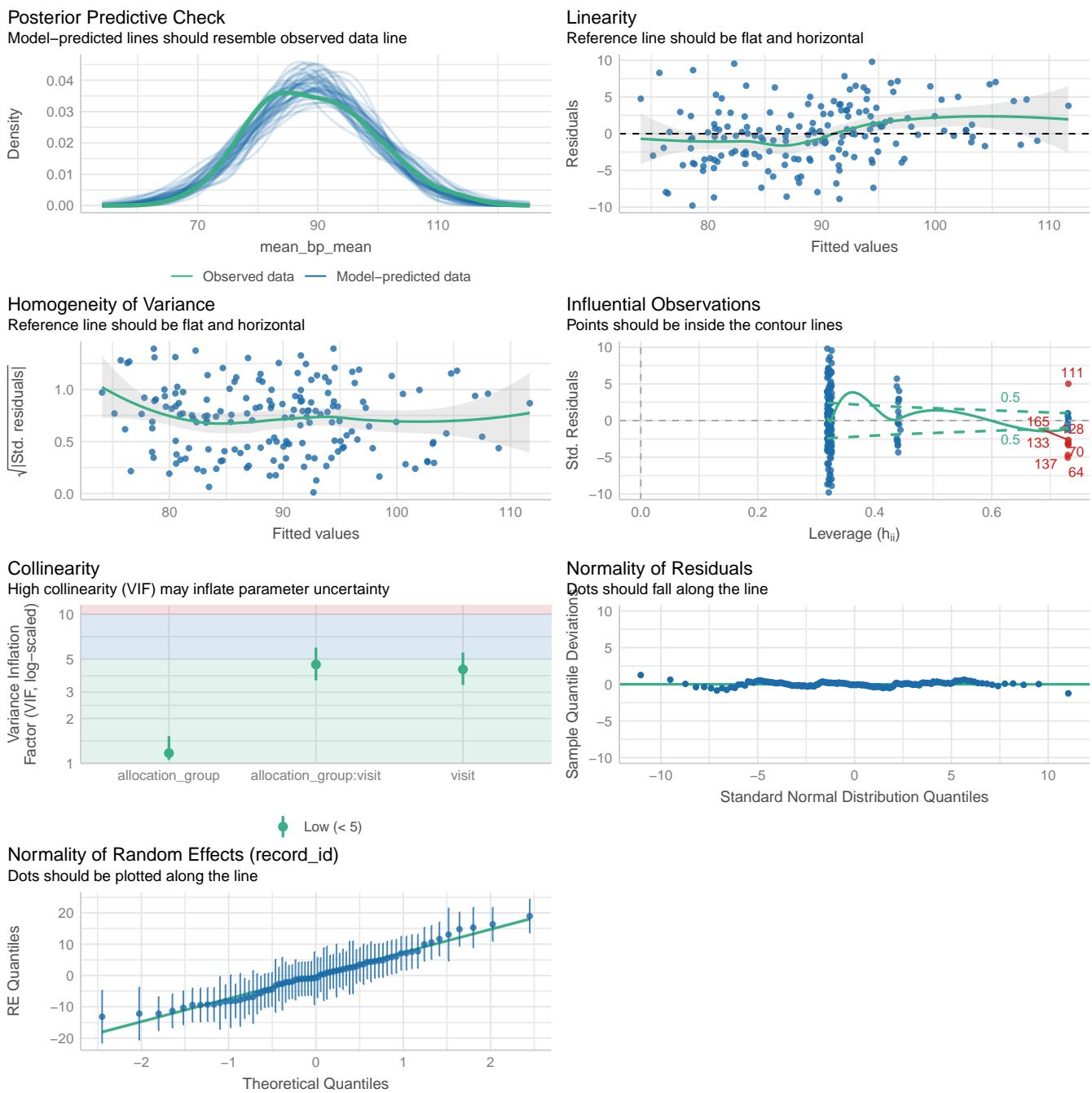
mean_bp_mean_model | 4.720 | 5.862
mean_bp_mean_model_sens | 4.005 | 5.049

performance::check_model(mean_bp_mean_model)

```



```
performance::check_model(mean_bp_mean_model_sens)
```



3.16.2 Médias Marginais Estimadas

3.16.2.1 Todos os dados

```
# Get EMMs for each group at each visit
mean_bp_mean_raw_emm <- emmeans::emmeans(
  mean_bp_mean_model,
  ~ allocation_group * visit
```

```

)
mean_bp_mean_raw_emm <- regrid(mean_bp_mean_raw_emm)

# Table of marginal means
# mean_bp_mean_raw_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(mean_bp_mean_raw_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

```

```

visit = 1:
contrast      estimate   SE  df lower.CL upper.CL t.ratio p.value
Grupo A - Grupo B -2.7754 2.34 105    -7.41     1.856 -1.188  0.2375

```

```

visit = 2:
contrast      estimate   SE  df lower.CL upper.CL t.ratio p.value
Grupo A - Grupo B  0.0381 2.52 125    -4.95     5.022  0.015  0.9880

```

```

visit = 3:
contrast      estimate   SE  df lower.CL upper.CL t.ratio p.value
Grupo A - Grupo B -4.2106 2.59 131    -9.34     0.922 -1.623  0.1070

```

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
 Confidence level used: 0.95

```

# Pairwise comparisons: Changes over time within each group
emmeans::contrast(mean_bp_mean_raw_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

```

```

allocation_group = Grupo A:
contrast      estimate   SE  df lower.CL upper.CL t.ratio p.value
visit1 - visit2  1.21 1.51 105  -2.4559     4.87    0.802  1.0000
visit1 - visit3  3.71 1.55 105  -0.0494     7.48    2.401  0.0543
visit2 - visit3  2.51 1.60 125  -1.3844     6.39    1.563  0.3618

```

```

allocation_group = Grupo B:

contrast      estimate   SE  df lower.CL upper.CL t.ratio p.value
visit1 - visit2     4.02 1.51 105    0.3469     7.70    2.662  0.0269
visit1 - visit3     2.28 1.60 105   -1.6056     6.16    1.427  0.4697
visit2 - visit3    -1.74 1.62 127   -5.6828     2.20   -1.074  0.8549

```

Degrees-of-freedom method: inherited from kenward-roger when re-gridding

Confidence level used: 0.95

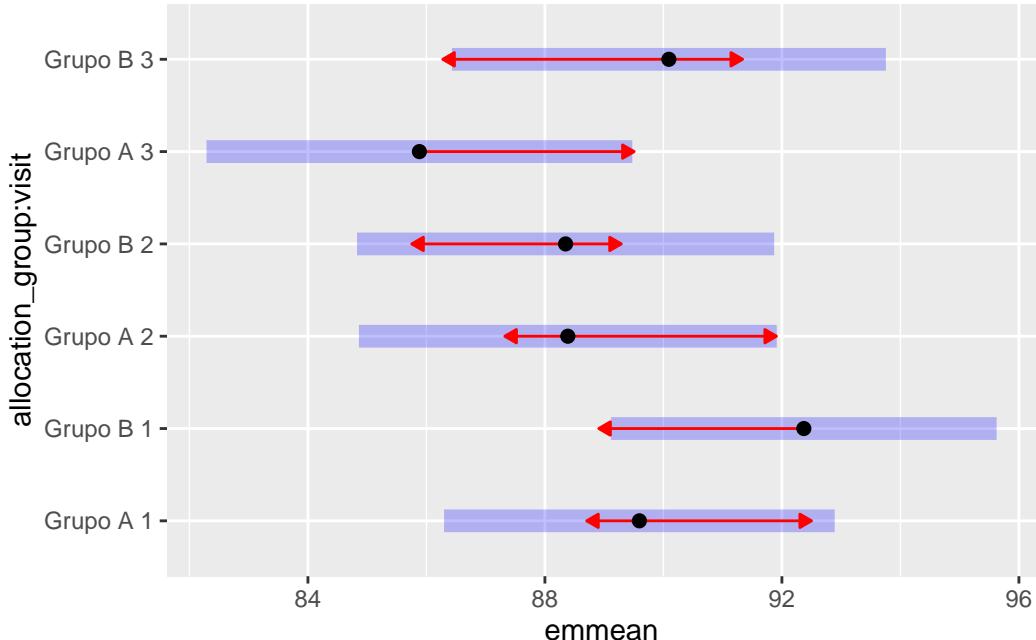
Conf-level adjustment: bonferroni method for 3 estimates

P value adjustment: bonferroni method for 3 tests

```

# Plot of marginal means
plot(mean_bp_mean_raw_emm, comparisons = TRUE)

```



3.16.2.2 Análise de sensibilidade

```

# Get EMMs for each group at each visit (Sensitivity Analysis)
mean_bp_mean_emm <- emmeans::emmeans(
  mean_bp_mean_model_sens,
  ~ allocation_group * visit
)

mean_bp_mean_emm <- regrid(mean_bp_mean_emm)

```

```

# Table of marginal means
# mean_bp_mean_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(mean_bp_mean_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

visit = 1:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B     -3.76  2.29  91.4     -8.32     0.793  -1.641  0.1043

visit = 2:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B     -1.10  2.45 107.3     -5.96     3.758  -0.448  0.6548

visit = 3:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B     -5.56  2.53 115.6    -10.57    -0.548  -2.197  0.0300

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95

# Pairwise comparisons: Changes over time within each group
emmeans::contrast(mean_bp_mean_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

allocation_group = Grupo A:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit2     2.14  1.38  91.4    -1.221     5.49   1.552  0.3722
visit1 - visit3     4.53  1.44  91.4     1.012     8.04   3.141  0.0068
visit2 - visit3     2.39  1.48 107.3    -1.202     5.98   1.619  0.3254

allocation_group = Grupo B:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit2     4.80  1.33  91.4     1.565     8.04   3.617  0.0015
visit1 - visit3     2.73  1.41  91.4    -0.698     6.17   1.943  0.1654

```

```
visit2 - visit3      -2.07 1.43 110.3     -5.540      1.40   -1.450  0.4495
```

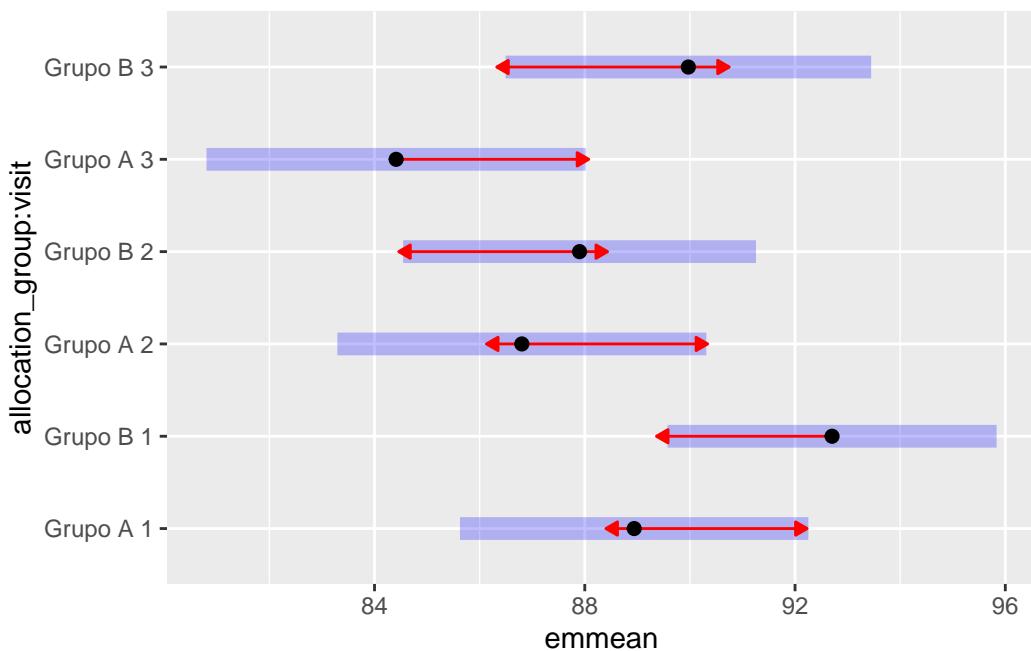
Degrees-of-freedom method: inherited from kenward-roger when re-gridding

Confidence level used: 0.95

Conf-level adjustment: bonferroni method for 3 estimates

P value adjustment: bonferroni method for 3 tests

```
# Plot of marginal means  
plot(mean_bp_mean_emm, comparisons = TRUE)
```



3.16.3 Resultado

No modelo ajustado para a média da pressão arterial, não foram observadas diferenças estatisticamente significativas entre os grupos em nenhum dos três momentos avaliados. No entanto, observou-se uma redução da pressão arterial entre as visitas 1 e 2 no grupo Eclipta (diferença média de 4,02 mmHg; IC 95%: 0,35 a 7,70), e uma tendência à redução entre as visitas 1 e 3 no grupo placebo (diferença média de 3,71 mmHg; IC 95%: -0,05 a 7,48).

Na análise de sensibilidade, realizada com exclusão das observações mais influentes, foi identificada uma diferença significativa entre os grupos na visita 3, com o grupo Eclipta apresentando pressão arterial média 5,56 mmHg inferior ao grupo placebo (IC 95%: -10,57 a -0,55). A redução entre as visitas 1 e 3 no grupo placebo tornou-se significativa e mais pronunciada, com diferença de 4,53 mmHg (IC 95%: 1,01 a 8,04), e a diferença entre as visitas 1 e 2 no grupo Eclipta foi mantida (diferença de 4,80 mmHg; IC 95%: 1,57 a 8,04). Essas mudanças foram acompanhadas por melhora nos indicadores de ajuste do modelo. As melhorias nos indicadores de ajuste (AIC, BIC, RMSE e R²) reforçam a adequação do modelo sensível.

As estimativas, intervalos de confiança de 95% e valores de p estão apresentadas nas Tabelas Tabela 19 e Tabela 20.

Tabela 17: Diferenças estimadas da pressão arterial média entre os grupos de alocação (placebo vs Eclipta) e entre visitas dentro de cada grupo – Todos os dados

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 1	-2,78	[-7,41 ; 1,86]	0,238
Entre grupos	Visita 2	0,04	[-4,95 ; 5,02]	0,988
Entre grupos	Visita 3	-4,21	[-9,34 ; 0,92]	0,107
Grupo Placebo	Visita 1 - Visita 2	1,21	[-2,46 ; 4,87]	1,000
Grupo Placebo	Visita 1 - Visita 3	3,71	[-0,05 ; 7,48]	0,054
Grupo Placebo	Visita 2 - Visita 3	2,51	[-1,38 ; 6,39]	0,362
Grupo Eclipta	Visita 1 - Visita 2	4,02	[0,35 ; 7,70]	0,027
Grupo Eclipta	Visita 1 - Visita 3	2,28	[-1,61 ; 6,16]	0,470
Grupo Eclipta	Visita 2 - Visita 3	-1,74	[-5,68 ; 2,20]	0,855

Tabela 18: Diferenças estimadas da pressão arterial média entre os grupos de alocação (placebo vs Eclipta) e entre visitas dentro de cada grupo – Análise de sensibilidade

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 1	-3,76	[-8,32 ; 0,79]	0,104
Entre grupos	Visita 2	-1,10	[-5,96 ; 3,76]	0,655
Entre grupos	Visita 3	-5,56	[-10,57 ; -0,55]	0,030
Grupo Placebo	Visita 1 - Visita 2	2,14	[-1,22 ; 5,49]	0,372
Grupo Placebo	Visita 1 - Visita 3	4,53	[1,01 ; 8,04]	0,007
Grupo Placebo	Visita 2 - Visita 3	2,39	[-1,20 ; 5,98]	0,325
Grupo Eclipta	Visita 1 - Visita 2	4,80	[1,57 ; 8,04]	0,002
Grupo Eclipta	Visita 1 - Visita 3	2,73	[-0,70 ; 6,17]	0,165
Grupo Eclipta	Visita 2 - Visita 3	-2,07	[-5,54 ; 1,40]	0,450

```
ggplot(
  data = data_model,
  aes(
    x = as.factor(visit),
    y = mean_bp_mean,
    group = record_id,
  )
) +
```

```

geom_line(alpha = 0.5) +
geom_point(alpha = 0.7) +
geom_smooth(
  aes(group = allocation_group),
  method = "lm",
  se = TRUE,
  linewidth = 1
) +
labs(title = "All data") +
facet_wrap(~ allocation_group)

`geom_smooth()` using formula = 'y ~ x'

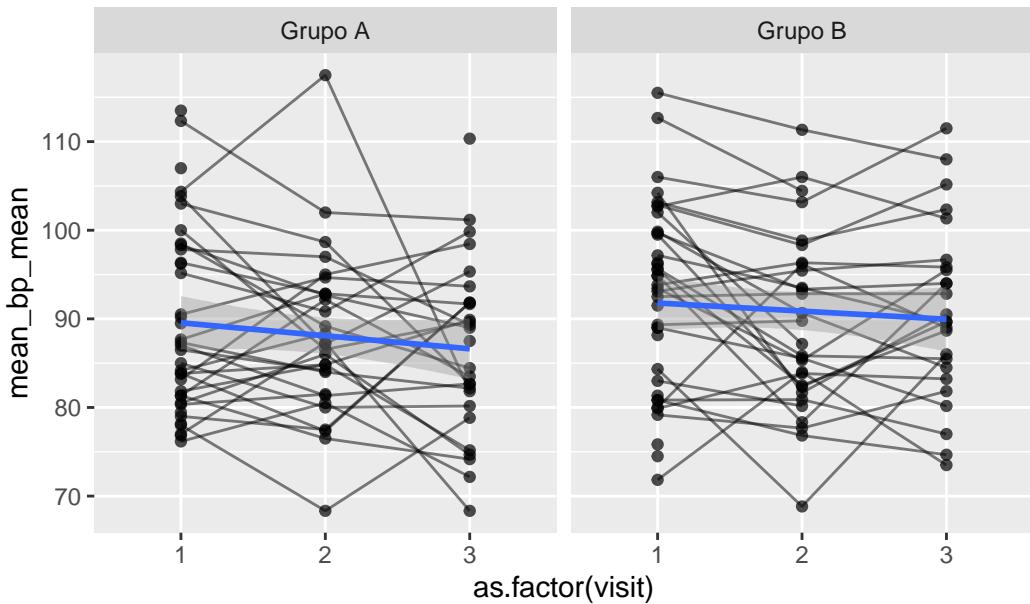
Warning: Removed 4 rows containing non-finite outside the scale range
(`stat_smooth()`).

Warning: Removed 2 rows containing missing values or values outside the scale range
(`geom_line()`).

Warning: Removed 4 rows containing missing values or values outside the scale range
(`geom_point()`).

```

All data



```

#coord_cartesian(ylim = c(10, 150))

data_model %>%
  filter(
    ...
  )

```

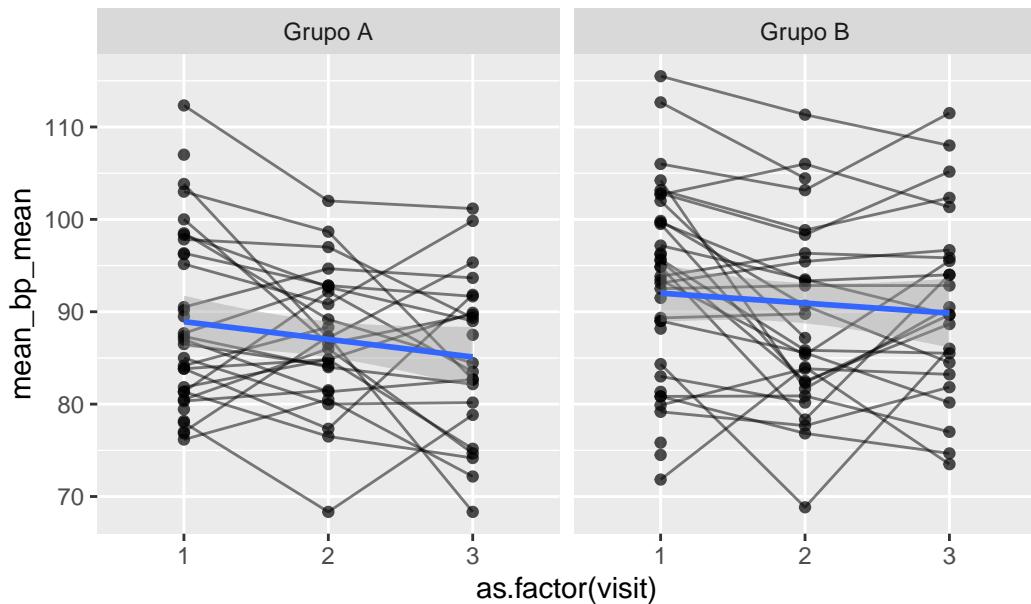
```

!(record_id %in%
  mean_bp_mean_model_check$influential_ids)
) %>%
ggplot(
  aes(
    x = as.factor(visit),
    y = mean_bp_mean,
    group = record_id,
  )
) +
geom_line(alpha = 0.5) +
geom_point(alpha = 0.7) +
geom_smooth(
  aes(group = allocation_group),
  method = "lm",
  se = TRUE,
  linewidth = 1
) +
labs(title = "Sensitivity analysis") +
facet_wrap(~ allocation_group)

`geom_smooth()` using formula = 'y ~ x'
Warning: Removed 3 rows containing non-finite outside the scale range
(`stat_smooth()`).
Warning: Removed 2 rows containing missing values or values outside the scale range
(`geom_line()`).
Warning: Removed 3 rows containing missing values or values outside the scale range
(`geom_point()`).

```

Sensitivity analysis



```
#coord_cartesian(ylim = c(10, 150))
```

3.17 PRESSÃO ARTERIAL

Importante destacar que, ao invés de resumir cada visita em um único valor, incorporamos ao modelo todas as leituras realizadas em cada participante em cada ponto de avaliação (2 a 3 medidas por visita). Essa estratégia aumentou o número total de observações disponíveis para os modelos lineares mistos. O intercepto aleatório por participante continuou a controlar a correlação entre medidas repetidas do mesmo indivíduo, permitindo capturar tanto a variabilidade intraindividual (entre as 2–3 leituras de cada visita) quanto a variabilidade interindividual, sem prejuízo à robustez dos resultados.

```
data_bp_long <- readRDS('local_files/Data_processed/data_bp_long.rds') %>%
  mutate(
    visit = as.factor(visit)
  )
```

3.17.1 Pressão Arterial Média

Variável: bp_mean

```
# Plot 1: Raw data
bp_mean_hist_1 <- data_bp_long %>%
  #filter(
  #  bp_mean < 300
  #) %>%
```

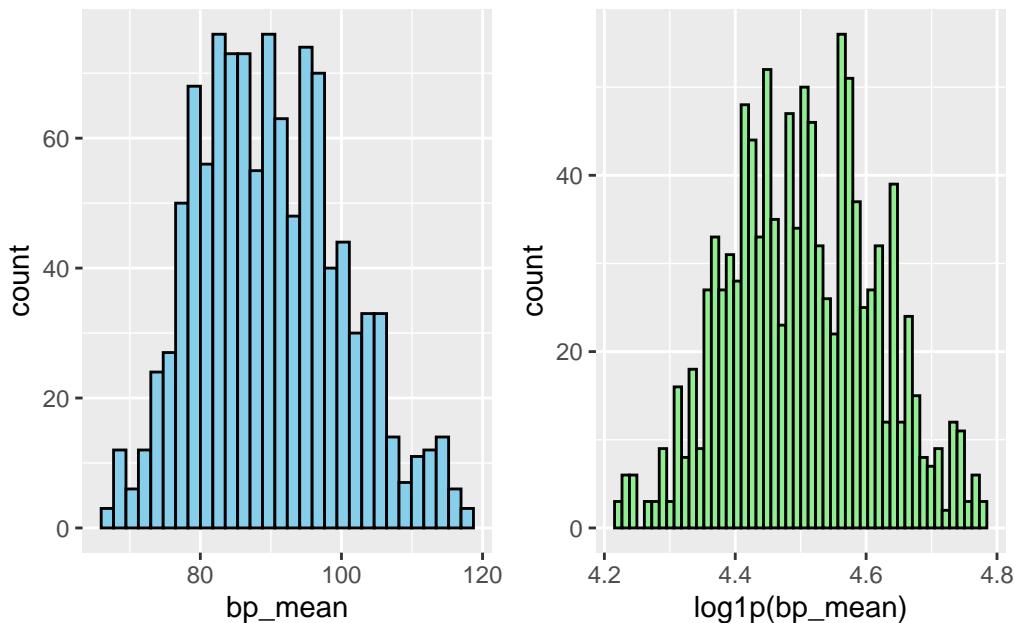
```

ggplot(aes(x = bp_mean)) +
  geom_histogram(bins = 30, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
bp_mean_hist_2 <- data_bp_long %>%
  #filter(
  #  bp_mean < 300
  #) %>%
  ggplot(aes(x = log1p(bp_mean))) +
  geom_histogram(bins = 50, fill = "lightgreen", color = "black")

# Combine side by side
bp_mean_hist_1 + bp_mean_hist_2 # library(patchwork)

```



```

# LMM
bp_mean_model <- lmer(bp_mean ~ allocation_group * visit +
(1 | record_id), data = data_bp_long)
check_collinearity(bp_mean_model)

# Check for Multicollinearity

```

Low Correlation

```

Term   VIF   VIF 95% CI Increased SE Tolerance
allocation_group 1.03 [1.00, 1.28]      1.01      0.98
visit 3.83 [3.47, 4.24]      1.96      0.26
allocation_group:visit 3.87 [3.51, 4.30]      1.97      0.26

Tolerance 95% CI
[0.78, 1.00]
[0.24, 0.29]
[0.23, 0.29]

# Sensitivity analysis
bp_mean_model_check <- sensitivity_check_lmer(
  model = bp_mean_model,
  id_var = "record_id",
  top_n = 5)

Warning in checkConv(attr(opt, "derivs")), opt$par, ctrl = control$checkConv, :
Model failed to converge with max|grad| = 0.00564557 (tol = 0.002, component 1)

# LMM Sensitivity
bp_mean_model_sens <- update(object = bp_mean_model,
                                subset = !(record_id %in%
                                bp_mean_model_check$influential_ids))

# Influential IDS
bp_mean_model_check$influential_ids

[1] "1"  "4"  "10" "13" "17" "18" "19" "22" "23" "26" "27" "31" "32" "34" "37"
[16] "38" "39" "45" "46" "47" "51" "52" "53" "54" "58" "63" "64" "69" "71"

```

3.17.1.1 Resumo dos modelos

```

summary(bp_mean_model)

Linear mixed model fit by REML. t-tests use Satterthwaite's method [
lmerModLmerTest]

Formula: bp_mean ~ allocation_group * visit + (1 | record_id)

Data: data_bp_long

```

REML criterion at convergence: 7010.5

Scaled residuals:

Min	1Q	Median	3Q	Max
-----	----	--------	----	-----

```
-3.4686 -0.5899 -0.0157  0.5536  3.3685
```

Random effects:

Groups	Name	Variance	Std.Dev.
record_id	(Intercept)	81.26	9.014
Residual		25.19	5.019

```
Number of obs: 1113, groups: record_id, 75
```

Fixed effects:

	Estimate	Std. Error	df	t value	Pr(> t)
(Intercept)	89.8090	1.5300	76.2999	58.700	< 2e-16
allocation_groupGrupo B	2.7084	2.1518	76.6090	1.259	0.211973
visit2	-1.6710	0.5224	1041.0211	-3.199	0.001422
visit3	-4.0199	0.5299	1042.2597	-7.586	7.28e-14
allocation_groupGrupo B:visit2	-2.8069	0.7391	1042.5621	-3.798	0.000154
allocation_groupGrupo B:visit3	1.3575	0.7631	1043.1895	1.779	0.075531

(Intercept) ***

allocation_groupGrupo B

visit2 **

visit3 ***

allocation_groupGrupo B:visit2 ***

allocation_groupGrupo B:visit3 .

```
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

Correlation of Fixed Effects:

	(Intr)	all_GB	visit2	visit3	a_GB:2
allctn_grGB	-0.711				
visit2	-0.142	0.101			
visit3	-0.137	0.097	0.479		
allctn_GB:2	0.100	-0.139	-0.707	-0.338	
allctn_GB:3	0.095	-0.131	-0.332	-0.694	0.472

```
summary(bp_mean_model_sens)
```

```
Linear mixed model fit by REML. t-tests use Satterthwaite's method [lmerModLmerTest]
```

Formula: bp_mean ~ allocation_group * visit + (1 | record_id)
Data: data_bp_long
Subset: !(record_id %in% bp_mean_model_check\$influential_ids)

REML criterion at convergence: 2871.8

Scaled residuals:

Min	1Q	Median	3Q	Max
-2.17909	-0.65916	-0.03621	0.63690	2.49223

Random effects:

Groups	Name	Variance	Std.Dev.
record_id	(Intercept)	94.529	9.723
Residual		7.816	2.796

Number of obs: 546, groups: record_id, 46

Fixed effects:

	Estimate	Std. Error	df	t value	Pr(> t)
(Intercept)	88.9393	2.0946	44.4582	42.462	< 2e-16
allocation_group	3.1831	2.9015	44.5612	1.097	0.278508
visit2	-1.5490	0.4163	497.8714	-3.721	0.000221
visit3	-5.1020	0.4403	497.9669	-11.588	< 2e-16
allocation_group:visit2	-2.3391	0.5917	498.3073	-3.953	8.82e-05
allocation_group:visit3	1.6228	0.6284	498.2316	2.582	0.010097

(Intercept) ***

allocation_group

visit2 ***

visit3 ***

allocation_group:visit2 ***

allocation_group:visit3 *

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

(Intr) all_GB visit2 visit3 a_GB:2

```

allctn_grGB -0.722
visit2      -0.071  0.051
visit3      -0.063  0.046  0.450
allctn_GB:2  0.050 -0.069 -0.704 -0.317
allctn_GB:3  0.044 -0.062 -0.315 -0.701  0.459

performance::compare_performance(
  bp_mean_model,
  bp_mean_model_sens)

```

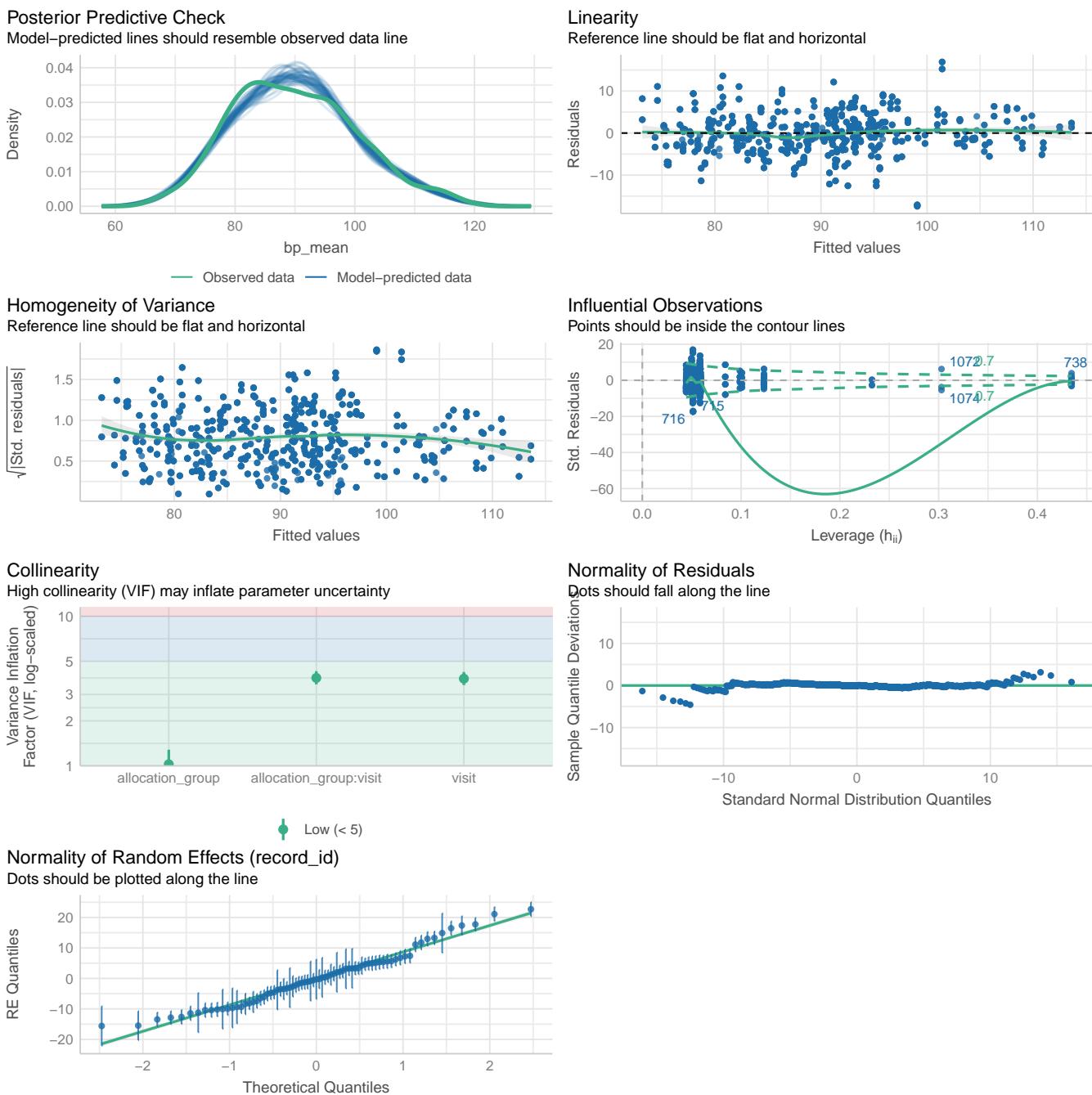
When comparing models, please note that probably not all models were fit from same data.

```
# Comparison of Model Performance Indices
```

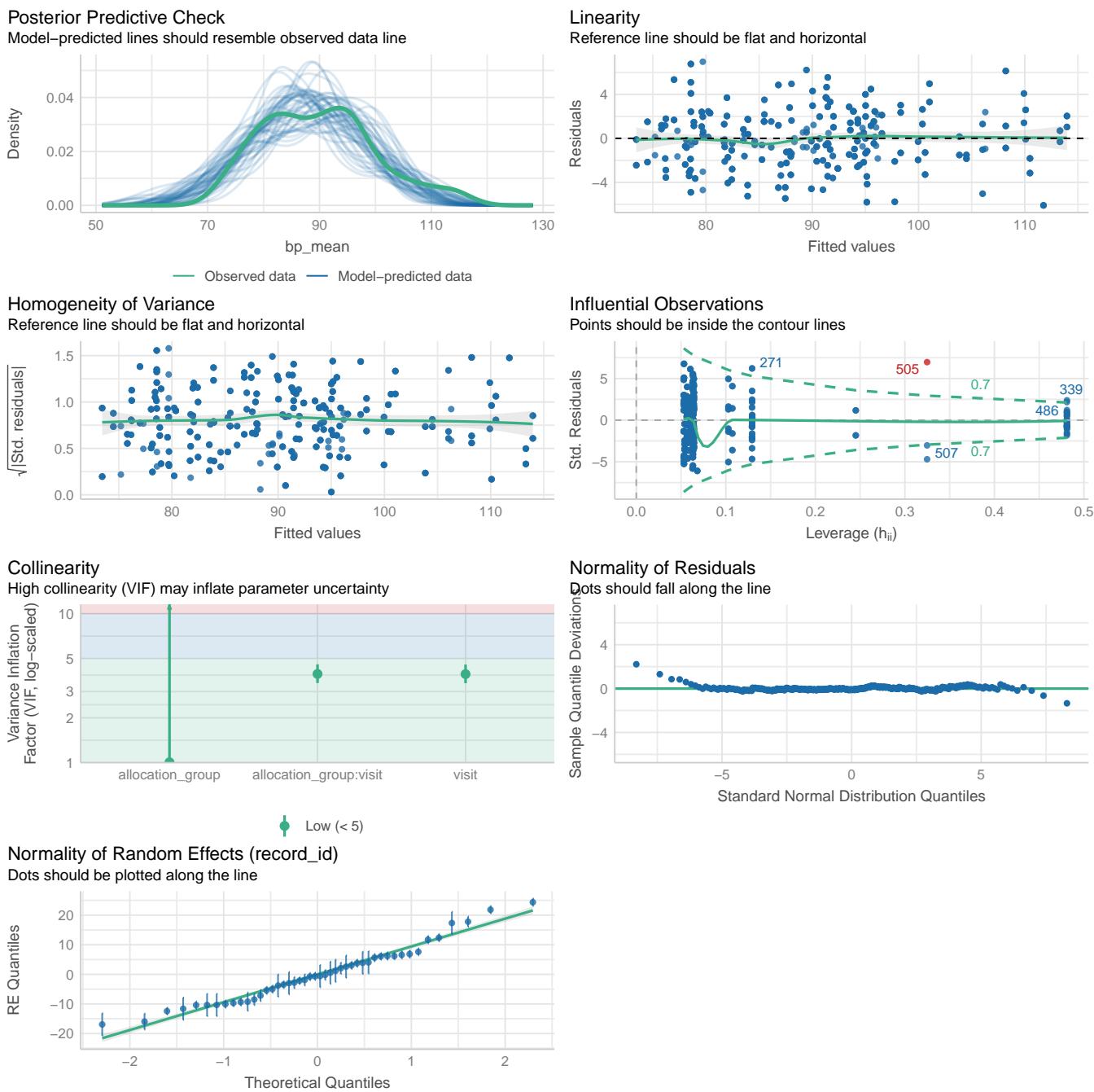
Name	Model	AIC (weights)	AICc (weights)
bp_mean_model	lmerModLmerTest	7033.6 (<.001)	7033.7 (<.001)
bp_mean_model_sens	lmerModLmerTest	2894.5 (>.999)	2894.8 (>.999)

Name	BIC (weights)	R2 (cond.)	R2 (marg.)	ICC	RMSE	Sigma
bp_mean_model	7073.7 (<.001)	0.773	0.040	0.763	4.845	5.019
bp_mean_model_sens	2928.9 (>.999)	0.928	0.055	0.924	2.667	2.796

```
performance::check_model(bp_mean_model)
```



```
performance::check_model(bp_mean_model_sens)
```



3.17.1.2 Médias Marginais Estimadas

3.17.1.2.1 Todos os dados

```
# Get EMMs for each group at each visit
bp_mean_raw_emm <- emmeans::emmeans(
  bp_mean_model,
```

```

~ allocation_group * visit
)

bp_mean_raw_emm <- regrid(bp_mean_raw_emm)

# Table of marginal means
# bp_mean_raw_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(bp_mean_raw_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

visit = 1:

```

contrast	estimate	SE	df	lower.CL	upper.CL	t.ratio	p.value
Grupo A - Grupo B	-2.7084	2.15	76.4	-6.99	1.577	-1.259	0.2120

```

visit = 2:

```

contrast	estimate	SE	df	lower.CL	upper.CL	t.ratio	p.value
Grupo A - Grupo B	0.0985	2.18	79.1	-4.23	4.430	0.045	0.9640

```

visit = 3:

```

contrast	estimate	SE	df	lower.CL	upper.CL	t.ratio	p.value
Grupo A - Grupo B	-4.0659	2.19	80.0	-8.42	0.286	-1.859	0.0667

Degrees-of-freedom method: inherited from kenward-roger when re-gridding

Confidence level used: 0.95

```

# Pairwise comparisons: Changes over time within each group
emmeans::contrast(bp_mean_raw_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

allocation_group = Grupo A:

```

contrast	estimate	SE	df	lower.CL	upper.CL	t.ratio	p.value
visit1 - visit2	1.67	0.522	76.4	0.392	2.950	3.198	0.0060
visit1 - visit3	4.02	0.530	76.4	2.723	5.317	7.585	<.0001
visit2 - visit3	2.35	0.537	79.1	1.035	3.663	4.372	0.0001

```

allocation_group = Grupo B:

contrast      estimate     SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit2    4.48 0.523 77.0     3.198    5.758    8.563 <.0001
visit1 - visit3    2.66 0.549 77.0     1.318    4.006    4.848 <.0001
visit2 - visit3   -1.82 0.555 80.7    -3.172   -0.459   -3.272  0.0047

```

Degrees-of-freedom method: inherited from kenward-roger when re-gridding

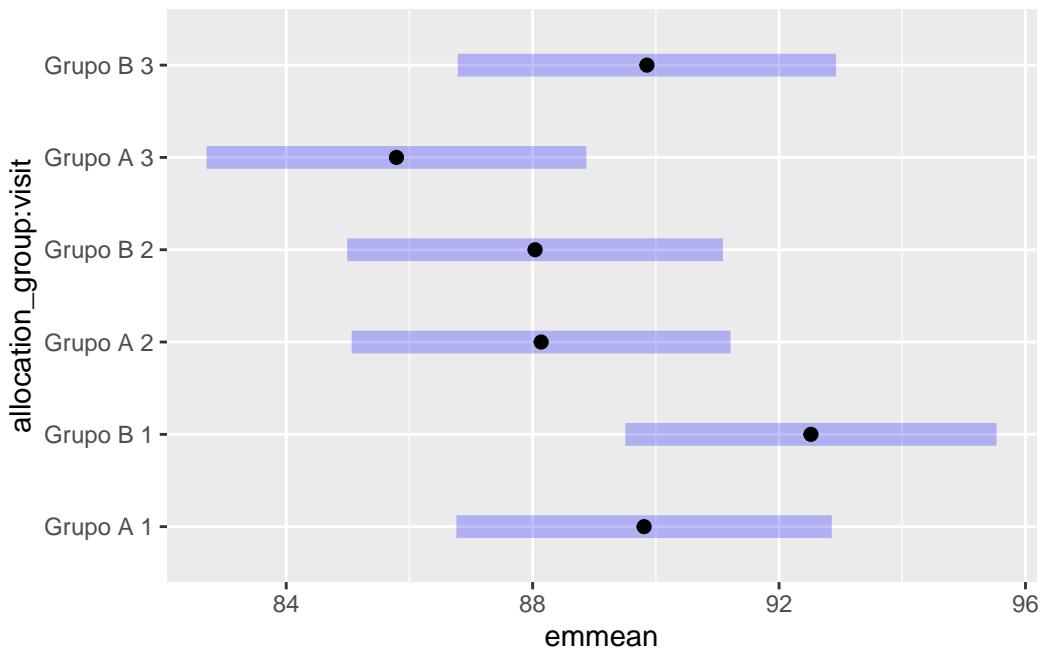
Confidence level used: 0.95

Conf-level adjustment: bonferroni method for 3 estimates

P value adjustment: bonferroni method for 3 tests

```
# Plot of marginal means
```

```
plot(bp_mean_raw_emm)
```



3.17.1.2.2 Análise de sensibilidade

```

# Get EMMs for each group at each visit (Sensitivity Analysis)
bp_mean_emm <- emmeans::emmeans(
  bp_mean_model_sens,
  ~ allocation_group * visit
)

```

```

bp_mean_emm <- regrid(bp_mean_emm)

# Table of marginal means
# bp_mean_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(bp_mean_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

visit = 1:

```

contrast	estimate	SE	df	lower.CL	upper.CL	t.ratio	p.value
Grupo A - Grupo B	-3.183	2.90	44.4	-9.03	2.66	-1.097	0.2785

```
visit = 2:
```

contrast	estimate	SE	df	lower.CL	upper.CL	t.ratio	p.value
Grupo A - Grupo B	-0.844	2.92	45.4	-6.73	5.04	-0.289	0.7739

```
visit = 3:
```

contrast	estimate	SE	df	lower.CL	upper.CL	t.ratio	p.value
Grupo A - Grupo B	-4.806	2.93	45.9	-10.70	1.09	-1.640	0.1078

Degrees-of-freedom method: inherited from kenward-roger when re-gridding

Confidence level used: 0.95

```

# Pairwise comparisons: Changes over time within each group
emmeans::contrast(bp_mean_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

```

```
allocation_group = Grupo A:
```

contrast	estimate	SE	df	lower.CL	upper.CL	t.ratio	p.value
visit1 - visit2	1.549	0.416	44.4	0.513	2.585	3.721	0.0017
visit1 - visit3	5.102	0.440	44.4	4.006	6.198	11.587	<.0001
visit2 - visit3	3.553	0.450	45.4	2.435	4.671	7.901	<.0001

```
allocation_group = Grupo B:
```

contrast	estimate	SE	df	lower.CL	upper.CL	t.ratio	p.value
----------	----------	----	----	----------	----------	---------	---------

```

visit1 - visit2    3.888 0.421 44.6    2.842    4.934   9.245 <.0001
visit1 - visit3    3.479 0.448 44.6    2.364    4.595   7.759 <.0001
visit2 - visit3   -0.409 0.449 46.0   -1.524    0.706  -0.911  1.0000

```

Degrees-of-freedom method: inherited from kenward-roger when re-gridding

Confidence level used: 0.95

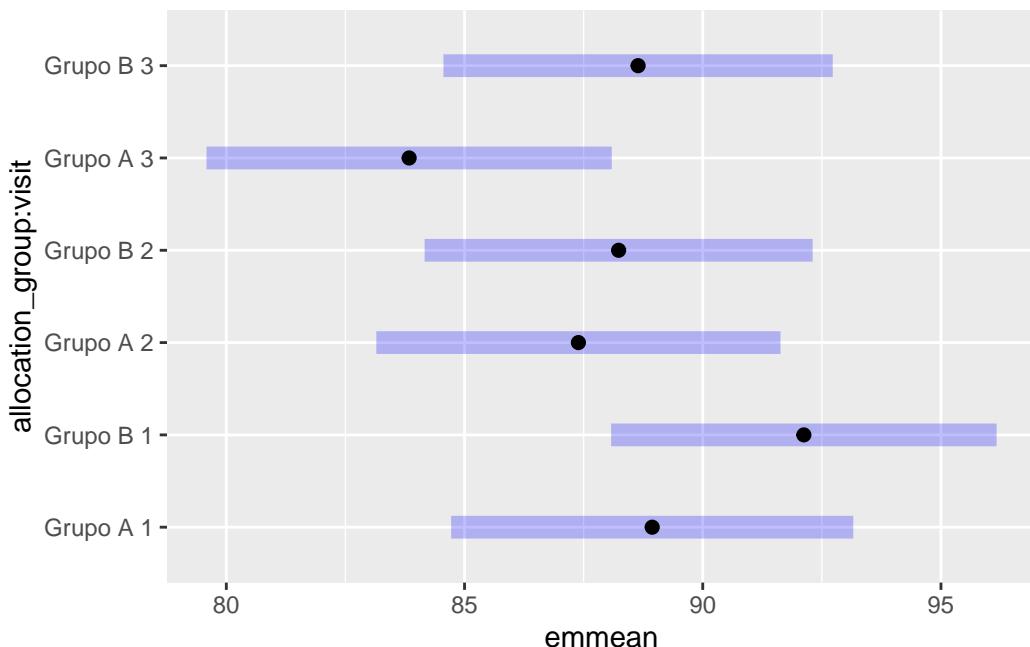
Conf-level adjustment: bonferroni method for 3 estimates

P value adjustment: bonferroni method for 3 tests

```

# Plot of marginal means
plot(bp_mean_emm)

```



3.17.1.3 Resultado

No modelo ajustado para a pressão arterial média não foram observadas diferenças estatisticamente significativas entre os grupos em nenhum dos três momentos avaliados (visita 1: estimativa = -2,71 mmHg; IC 95%: -6,99 a 1,58; p = 0,212; visita 2: estimativa = 0,10 mmHg; IC 95%: -4,23 a 4,43; p = 0,964; visita 3: estimativa = -4,07 mmHg; IC 95%: -8,42 a 0,29; p = 0,067).

Ambos os grupos apresentaram redução significativa da pressão arterial entre as visitas 1 e 2 (placebo: -1,67 mmHg; IC 95%: -2,95 a -0,39; p = 0,006; eclipta: -4,48 mmHg; IC 95%: -5,76 a -3,20; p < 0,001) e entre as visitas 1 e 3 (placebo: -4,02 mmHg; IC 95%: -5,32 a -2,72; p < 0,001; eclipta: -2,66 mmHg; IC 95%: -4,01 a -1,32; p < 0,001). No grupo placebo houve ainda redução entre as visitas 2 e 3 (-2,35 mmHg; IC 95%: -3,66 a -1,04; p = 0,0001), enquanto no grupo eclipta essa redução entre a visita 2 e a 3 foi significativa apenas no modelo completo.

Na análise de sensibilidade, as reduções entre as visitas 1 e 2 e entre as visitas 1 e 3 mantiveram-se significativas em

ambos os grupos. Porém, a redução entre as visitas 2 e 3 no grupo eclipta deixou de ser significativa ($-0,41$ mmHg; IC 95%: $-1,52$ a $0,71$; $p = 1,000$).

Tabelas com estimativas, IC 95% e p-valores:

Tabela 19: Diferenças estimadas da pressão arterial média entre grupos (placebo vs eclipta) e entre visitas – Todos os dados

Grupo de comparação	Comparação	Estimativa (mmHg)	IC 95%	p-valor
Entre grupos	Visita 1	-2,71	[-6,99; 1,58]	0,212
Entre grupos	Visita 2	0,10	[-4,23; 4,43]	0,964
Entre grupos	Visita 3	-4,07	[-8,42; 0,29]	0,067
Grupo Placebo	Visita 1 – Visita 2	-1,67	[-2,95; -0,39]	0,006
Grupo Placebo	Visita 1 – Visita 3	-4,02	[-5,32; -2,72]	< 0,001
Grupo Placebo	Visita 2 – Visita 3	-2,35	[-3,66; -1,04]	0,0001
Grupo Eclipta	Visita 1 – Visita 2	-4,48	[-5,76; -3,20]	< 0,001
Grupo Eclipta	Visita 1 – Visita 3	-2,66	[-4,01; -1,32]	< 0,001
Grupo Eclipta	Visita 2 – Visita 3	1,82	[0,46; 3,17]	0,005

Tabela 20: Diferenças estimadas da pressão arterial média – Análise de sensibilidade

Grupo de comparação	Comparação	Estimativa (mmHg)	IC 95%	p-valor
Entre grupos	Visita 1	-3,18	[-9,03; 2,66]	0,279
Entre grupos	Visita 2	-0,84	[-6,73; 5,04]	0,774
Entre grupos	Visita 3	-4,81	[-10,70; 1,09]	0,108
Grupo Placebo	Visita 1 – Visita 2	-1,55	[-2,59; -0,51]	0,002
Grupo Placebo	Visita 1 – Visita 3	-5,10	[-6,20; -4,01]	< 0,001
Grupo Placebo	Visita 2 – Visita 3	-3,55	[-4,67; -2,44]	< 0,001
Grupo Eclipta	Visita 1 – Visita 2	-3,89	[-4,93; -2,84]	< 0,001
Grupo Eclipta	Visita 1 – Visita 3	-3,48	[-4,60; -2,36]	< 0,001
Grupo Eclipta	Visita 2 – Visita 3	0,41	[-1,52; 0,71]	1,000

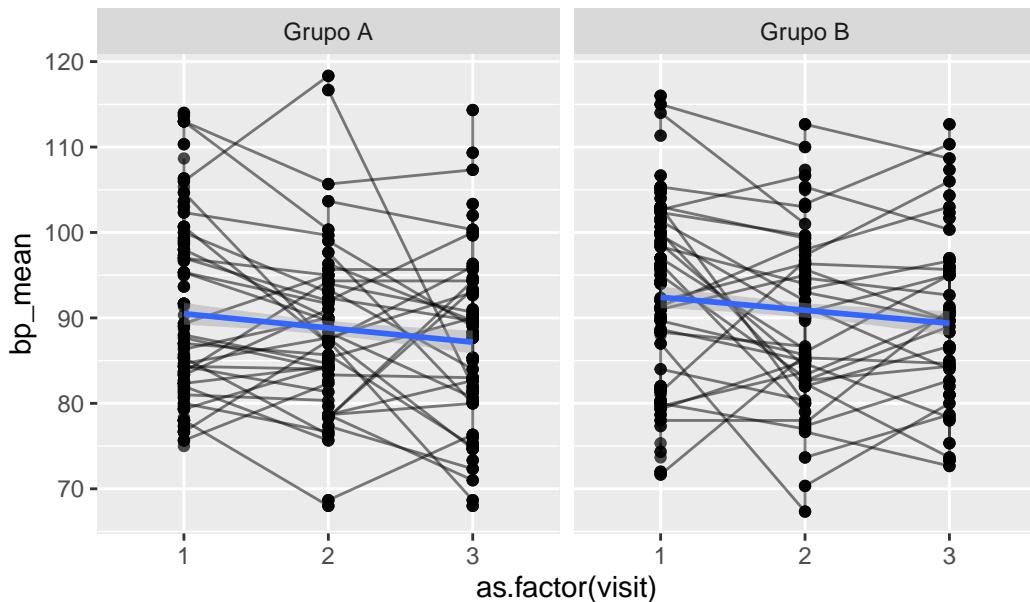
```
ggplot(
  data = data_bp_long,
  aes(
    x = as.factor(visit),
    y = bp_mean,
    group = record_id,
```

```

)
) +
  geom_line(alpha = 0.5) +
  geom_point(alpha = 0.7) +
  geom_smooth(
    aes(group = allocation_group),
    method = "lm",
    se = TRUE,
    linewidth = 1
  ) +
  labs(title = "All data") +
  facet_wrap(~ allocation_group)
`geom_smooth()` using formula = 'y ~ x'

```

All data



```

data_bp_long %>%
  filter(
    !(record_id %in%
      bp_mean_model_check$influential_ids)
  ) %>%
  ggplot(
    aes(
      x = as.factor(visit),

```

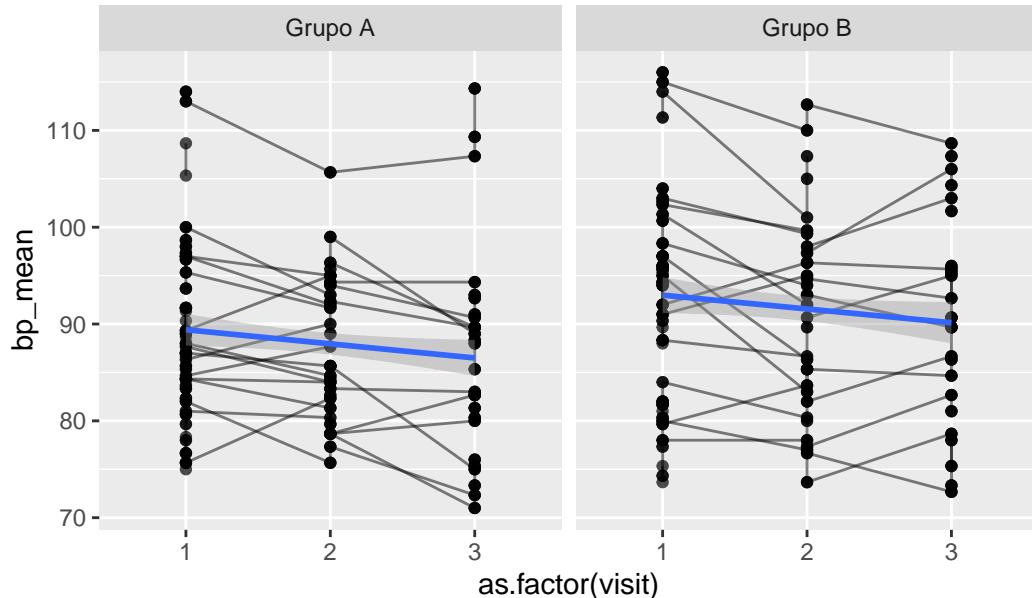
```

y = bp_mean,
group = record_id,
)
) +
geom_line(alpha = 0.5) +
geom_point(alpha = 0.7) +
geom_smooth(
  aes(group = allocation_group),
  method = "lm",
  se = TRUE,
  linewidth = 1
) +
labs(title = "Sensitivity analysis") +
facet_wrap(~ allocation_group)

```

`geom_smooth()` using formula = 'y ~ x'

Sensitivity analysis



3.17.2 Pressão Arterial Sistólica

Variável: systolic

```

# Plot 1: Raw data
systolic_hist_1 <- data_bp_long %>%
  #filter(

```

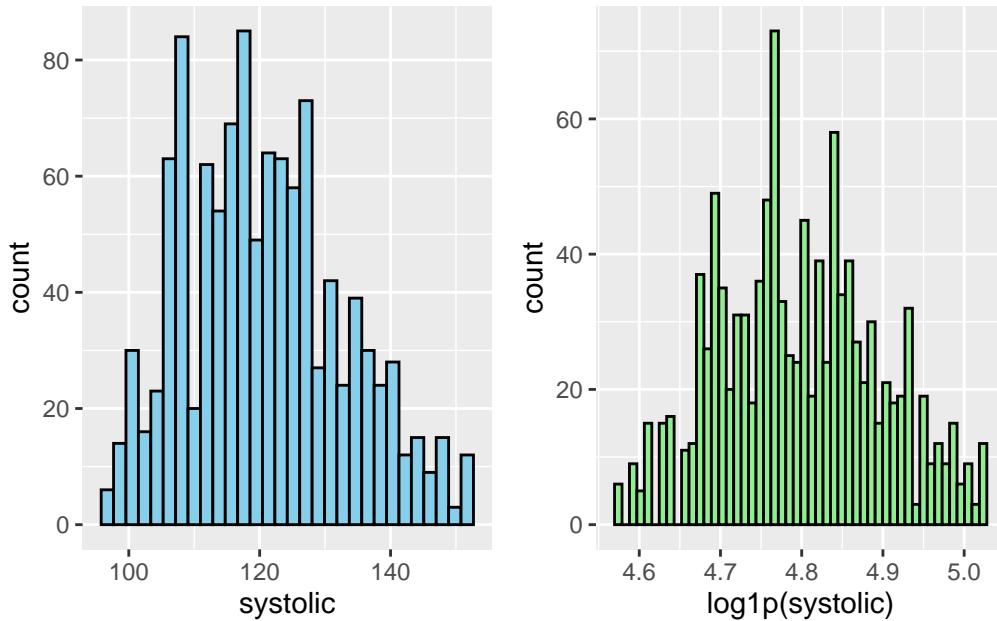
```

#     systolic < 300
#) %>%
ggplot(aes(x = systolic)) +
geom_histogram(bins = 30, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
systolic_hist_2 <- data_bp_long %>%
  #filter(
#     systolic < 300
#) %>%
  ggplot(aes(x = log1p(systolic))) +
  geom_histogram(bins = 50, fill = "lightgreen", color = "black")

# Combine side by side
systolic_hist_1 + systolic_hist_2 # library(patchwork)

```



```

# LMM
systolic_model <- lmer(log1p(systolic) ~ allocation_group * visit +
(1 | record_id), data = data_bp_long)
check_collinearity(systolic_model)

# Check for Multicollinearity

```

Low Correlation

Term	VIF	VIF 95% CI	Increased SE	Tolerance
allocation_group	1.03	[1.00, 1.22]	1.02	0.97
visit	3.83	[3.47, 4.25]	1.96	0.26
allocation_group:visit	3.89	[3.52, 4.31]	1.97	0.26

Tolerance 95% CI

[0.82, 1.00]
[0.24, 0.29]
[0.23, 0.28]

```
# Sensitivity analysis
systolic_model_check <- sensitivity_check_lmer(
  model = systolic_model,
  id_var = "record_id",
  top_n = 5)

# LMM Sensitivity
systolic_model_sens <- update(object = systolic_model,
  subset = !(record_id %in%
  systolic_model_check$influential_ids))

# Influential IDS
systolic_model_check$influential_ids
```

[1] "1" "4" "10" "12" "13" "16" "17" "18" "19" "22" "23" "26" "27" "31" "32"
[16] "34" "37" "38" "39" "41" "45" "46" "47" "52" "53" "54" "58" "61" "63" "65"
[31] "69" "71" "72" "74"

3.17.2.1 Resumo dos modelos

```
summary(systolic_model)

Linear mixed model fit by REML. t-tests use Satterthwaite's method [
lmerModLmerTest]

Formula: log1p(systolic) ~ allocation_group * visit + (1 | record_id)

Data: data_bp_long

REML criterion at convergence: -3077.1
```

Scaled residuals:

Min	1Q	Median	3Q	Max
-3.06595	-0.61196	-0.01167	0.62427	2.83791

Random effects:

Groups	Name	Variance	Std.Dev.
record_id	(Intercept)	0.007252	0.08516
Residual		0.002818	0.05308

Number of obs: 1113, groups: record_id, 75

Fixed effects:

	Estimate	Std. Error	df	t value							
(Intercept)	4.792e+00	1.456e-02	7.756e+01	329.002							
allocation_group	2.609e-02	2.049e-02	7.792e+01	1.273							
visit2	-1.520e-02	5.523e-03	1.043e+03	-2.753							
visit3	-4.020e-02	5.601e-03	1.044e+03	-7.178							
allocation_group:visit2	-2.193e-02	7.813e-03	1.045e+03	-2.807							
allocation_group:visit3	1.666e-02	8.066e-03	1.045e+03	2.066							
	Pr(> t)										
(Intercept)	< 2e-16	***									
allocation_group	0.20664										
visit2	0.00601	**									
visit3	1.34e-12	***									
allocation_group:visit2	0.00510	**									
allocation_group:visit3	0.03911	*									

Signif. codes:	0	'***'	0.001	'**'	0.01	'*'	0.05	'. '	0.1	' '	1

Correlation of Fixed Effects:

(Intr)	all_GB	visit2	visit3	a_GB:2	
allctn_grGB	-0.711				
visit2	-0.158	0.113			
visit3	-0.153	0.109	0.478		
allctn_GB:2	0.112	-0.155	-0.707	-0.338	
allctn_GB:3	0.106	-0.146	-0.332	-0.694	0.471

```

summary(systolic_model_sens)

Linear mixed model fit by REML. t-tests use Satterthwaite's method [
lmerModLmerTest]

Formula: log1p(systolic) ~ allocation_group * visit + (1 | record_id)
Data: data_bp_long
Subset: !(record_id %in% systolic_model_check$influential_ids)

REML criterion at convergence: -1653.2

Scaled residuals:
    Min      1Q  Median      3Q     Max 
-2.42310 -0.70717 -0.04306  0.62788  2.21616 

Random effects:
Groups      Name        Variance Std.Dev.
record_id (Intercept) 0.0080365 0.08965
Residual            0.0008443 0.02906
Number of obs: 441, groups: record_id, 41

Fixed effects:
            Estimate Std. Error       df t value
(Intercept) 4.771322  0.019826 39.496588 240.654
allocation_groupGrupo B 0.041052  0.028424 39.701164   1.444
visit2       -0.010491  0.004477 398.072789  -2.343
visit3       -0.036465  0.004803 398.110452  -7.592
allocation_groupGrupo B:visit2 -0.022957  0.006840 398.846655  -3.356
allocation_groupGrupo B:visit3  0.018660  0.007688 398.549816   2.427
Pr(>|t|)    
(Intercept) < 2e-16 ***
allocation_groupGrupo B 0.156511
visit2       0.019601 *
visit3       2.27e-13 ***
allocation_groupGrupo B:visit2 0.000866 ***
allocation_groupGrupo B:visit3 0.015665 *
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```

Correlation of Fixed Effects:

```
(Intr) all_GB visit2 visit3 a_GB:2  
allctn_grGB -0.698  
visit2      -0.079  0.055  
visit3      -0.070  0.048  0.441  
allctn_GB:2  0.052 -0.075 -0.655 -0.289  
allctn_GB:3  0.043 -0.063 -0.275 -0.625  0.426
```

```
performance::compare_performance(  
  systolic_model,  
  systolic_model_sens)
```

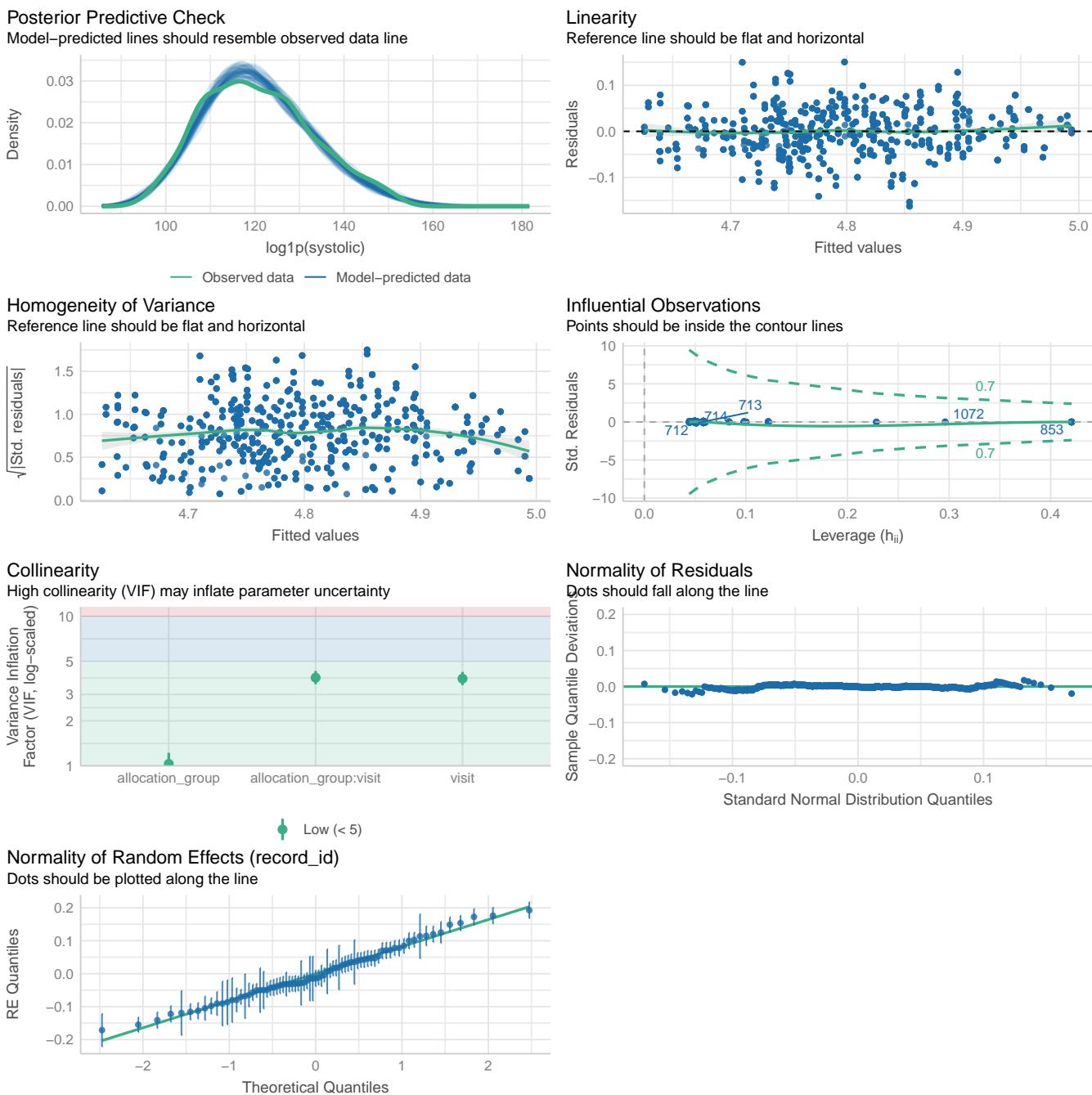
When comparing models, please note that probably not all models were fit from same data.

```
# Comparison of Model Performance Indices
```

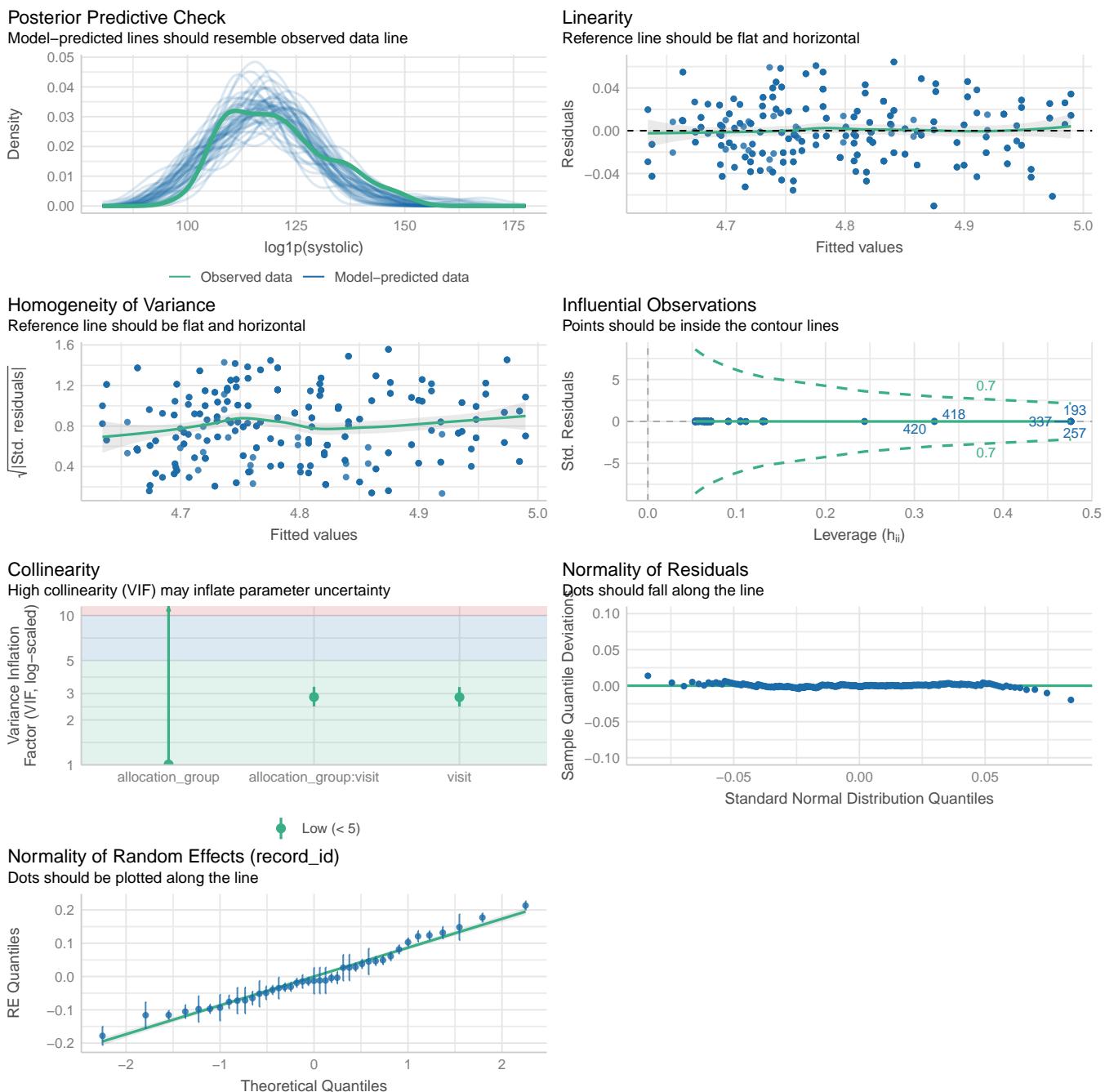
Name	Model	AIC (weights)	AICc (weights)
systolic_model	lmerModLmerTest	7568.9 (<.001)	7569.0 (<.001)
systolic_model_sens	lmerModLmerTest	2545.4 (>.999)	2545.7 (>.999)

Name	BIC (weights)	R2 (cond.)	R2 (marg.)	ICC	RMSE	Sigma
systolic_model	7609.0 (<.001)	0.731	0.040	0.720	0.051	0.053
systolic_model_sens	2578.1 (>.999)	0.911	0.063	0.905	0.028	0.029

```
performance::check_model(systolic_model)
```



```
performance::check_model(systolic_model_sens)
```



3.17.2.2 Médias Marginais Estimadas

3.17.2.2.1 Todos os dados

```
# Get EMMs for each group at each visit
systolic_raw_emm <- emmeans::emmeans(
  systolic_model,
```

```

~ allocation_group * visit
)

systolic_raw_emm <- regrid(systolic_raw_emm)

# Table of marginal means
# systolic_raw_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(systolic_raw_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

visit = 1:

```

contrast	estimate	SE	df	lower.CL	upper.CL	t.ratio	p.value
Grupo A - Grupo B	-3.185	2.50	77.3	-8.16	1.795	-1.273	0.2067

```

visit = 2:

```

contrast	estimate	SE	df	lower.CL	upper.CL	t.ratio	p.value
Grupo A - Grupo B	-0.495	2.47	80.6	-5.41	4.420	-0.200	0.8417

```

visit = 3:

```

contrast	estimate	SE	df	lower.CL	upper.CL	t.ratio	p.value
Grupo A - Grupo B	-5.055	2.47	81.6	-9.97	-0.138	-2.045	0.0440

Degrees-of-freedom method: inherited from kenward-roger when re-gridding

Confidence level used: 0.95

```

# Pairwise comparisons: Changes over time within each group
emmeans::contrast(systolic_raw_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

```

```

allocation_group = Grupo A:

```

contrast	estimate	SE	df	lower.CL	upper.CL	t.ratio	p.value
visit1 - visit2	1.82	0.660	77.3	0.202	3.4332	2.754	0.0220
visit1 - visit3	4.75	0.662	77.3	3.127	6.3691	7.167	<.0001
visit2 - visit3	2.93	0.667	80.6	1.300	4.5607	4.394	0.0001

```

allocation_group = Grupo B:

contrast      estimate     SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit2    4.51 0.672 78.0     2.865   6.1507   6.713 <.0001
visit1 - visit3    2.88 0.708 78.0     1.145   4.6103   4.064  0.0003
visit2 - visit3   -1.63 0.705 82.4    -3.353   0.0925  -2.313  0.0697

```

Degrees-of-freedom method: inherited from kenward-roger when re-gridding

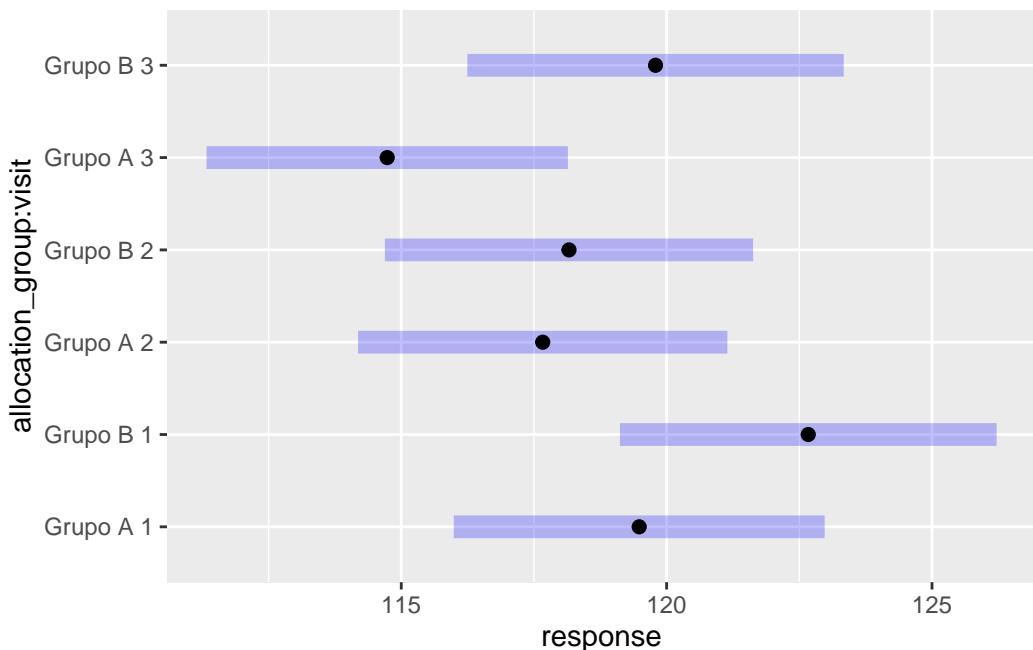
Confidence level used: 0.95

Conf-level adjustment: bonferroni method for 3 estimates

P value adjustment: bonferroni method for 3 tests

```
# Plot of marginal means
```

```
plot(systolic_raw_emm)
```



3.17.2.2.2 Análise de sensibilidade

```

# Get EMMs for each group at each visit (Sensitivity Analysis)
systolic_emm <- emmeans::emmeans(
  systolic_model_sens,
  ~ allocation_group * visit
)

```

```

systolic_emm <- regrid(systolic_emm)

# Table of marginal means
# systolic_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(systolic_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

visit = 1:

```

contrast	estimate	SE	df	lower.CL	upper.CL	t.ratio	p.value
Grupo A - Grupo B	-4.95	3.43	39.3	-11.88	1.986	-1.443	0.1570

```
visit = 2:
```

contrast	estimate	SE	df	lower.CL	upper.CL	t.ratio	p.value
Grupo A - Grupo B	-2.13	3.39	40.5	-8.98	4.713	-0.630	0.5325

```
visit = 3:
```

contrast	estimate	SE	df	lower.CL	upper.CL	t.ratio	p.value
Grupo A - Grupo B	-7.01	3.41	41.3	-13.88	-0.128	-2.057	0.0461

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
 Confidence level used: 0.95

```

# Pairwise comparisons: Changes over time within each group
emmeans::contrast(systolic_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

```

```
allocation_group = Grupo A:
```

contrast	estimate	SE	df	lower.CL	upper.CL	t.ratio	p.value
visit1 - visit2	1.23	0.526	39.3	-0.0822	2.5468	2.344	0.0726
visit1 - visit3	4.23	0.559	39.3	2.8301	5.6260	7.563	<.0001
visit2 - visit3	3.00	0.569	40.5	1.5750	4.4166	5.266	<.0001

```
allocation_group = Grupo B:
```

contrast	estimate	SE	df	lower.CL	upper.CL	t.ratio	p.value
----------	----------	----	----	----------	----------	---------	---------

```

visit1 - visit2      4.05 0.627 39.7    2.4801   5.6135   6.456 <.0001
visit1 - visit3     2.17 0.730 39.7    0.3474   3.9946   2.976  0.0149
visit2 - visit3    -1.88 0.731 41.9   -3.7000  -0.0516  -2.564  0.0420

```

Degrees-of-freedom method: inherited from kenward-roger when re-gridding

Confidence level used: 0.95

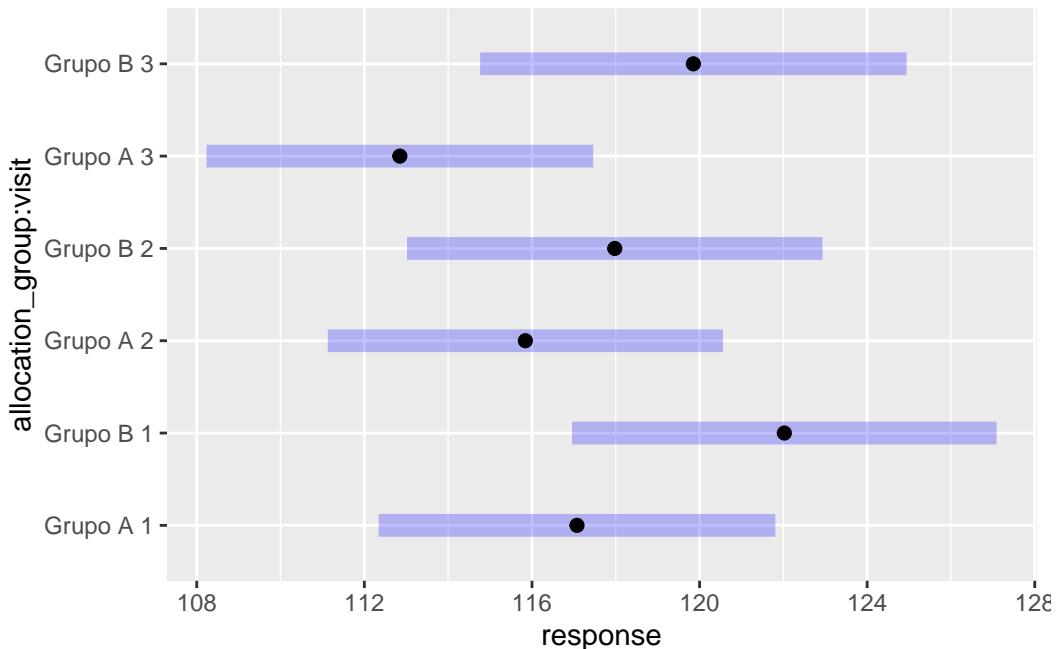
Conf-level adjustment: bonferroni method for 3 estimates

P value adjustment: bonferroni method for 3 tests

```

# Plot of marginal means
plot(systolic_emm)

```



3.17.2.3 Resultado

No modelo ajustado para pressão arterial sistólica, não houve diferença significativa entre os grupos nas visitas 1 (estimativa = -3,19 mmHg; IC 95%: -8,16 a 1,80; p = 0,207) e 2 (estimativa = -0,50 mmHg; IC 95%: -5,41 a 4,42; p = 0,842). Na visita 3, a pressão sistólica no grupo placebo foi em média 5,06 mmHg inferior ao grupo Eclipta (estimativa = -5,06 mmHg; IC 95%: -9,97 a -0,14; p = 0,044).

Ao longo do tempo, ambos os grupos exibiram redução significativa da pressão sistólica: - **Grupo Placebo**: redução de 1,82 mmHg entre visita 1 e 2 (IC 95%: 0,20 a 3,43; p = 0,022), de 4,75 mmHg entre visita 1 e 3 (IC 95%: 3,13 a 6,37; p < 0,001) e de 2,93 mmHg entre visita 2 e 3 (IC 95%: 1,30 a 4,56; p < 0,001). - **Grupo Eclipta**: redução de 4,51 mmHg entre visita 1 e 2 (IC 95%: 2,87 a 6,15; p < 0,001) e de 2,88 mmHg entre visita 1 e 3 (IC 95%: 1,15 a 4,61; p = 0,0003); não houve redução significativa entre visita 2 e 3 (-1,63 mmHg; IC 95%: -3,35 a 0,09; p = 0,070).

Na análise de sensibilidade, o contraste entre grupos na visita 3 permaneceu significativo (estimativa = -7,01 mmHg; IC

95%: -13,88 a -0,13; $p = 0,046$). As reduções dentro de cada grupo entre visita 1 e 3 mantiveram-se (placebo: -5,10 mmHg; IC 95%: -6,20 a -4,01; $p < 0,001$; eclipta: -3,48 mmHg; IC 95%: -4,60 a -2,36; $p < 0,001$), e a redução entre visita 2 e 3 no grupo eclipta continuou significativa (-1,88 mmHg; IC 95%: -3,70 a -0,05; $p = 0,042$), enquanto a redução entre visita 1 e 2 no placebo deixou de ser significativa (-1,55 mmHg; IC 95%: -2,59 a -0,51; $p = 0,073$).

Tabela 21: Diferenças estimadas da pressão arterial sistólica entre grupos e entre visitas – Todos os dados

Grupo de comparação	Comparação	Estimativa (mmHg)	IC 95%	p-valor
Entre grupos	Visita 1	-3,19	[-8,16; 1,80]	0,207
Entre grupos	Visita 2	-0,50	[-5,41; 4,42]	0,842
Entre grupos	Visita 3	-5,06	[-9,97; -0,14]	0,044
Grupo Placebo	Visita 1–Visita 2	-1,82	[0,20; 3,43]	0,022
Grupo Placebo	Visita 1–Visita 3	-4,75	[3,13; 6,37]	< 0,001
Grupo Placebo	Visita 2–Visita 3	-2,93	[1,30; 4,56]	< 0,001
Grupo Eclipta	Visita 1–Visita 2	-4,51	[2,87; 6,15]	< 0,001
Grupo Eclipta	Visita 1–Visita 3	-2,88	[1,15; 4,61]	0,0003
Grupo Eclipta	Visita 2–Visita 3	-1,63	[-3,35; 0,09]	0,070

Tabela 22: Diferenças estimadas da pressão arterial sistólica – Análise de sensibilidade

Grupo de comparação	Comparação	Estimativa (mmHg)	IC 95%	p-valor
Entre grupos	Visita 1	-4,95	[-11,88; 1,99]	0,157
Entre grupos	Visita 2	-2,13	[-8,98; 4,71]	0,533
Entre grupos	Visita 3	-7,01	[-13,88; -0,13]	0,046
Grupo Placebo	Visita 1–Visita 2	-1,55	[-2,59; -0,51]	0,073
Grupo Placebo	Visita 1–Visita 3	-5,10	[-6,20; -4,01]	< 0,001
Grupo Placebo	Visita 2–Visita 3	-3,55	[-4,67; -2,44]	< 0,001
Grupo Eclipta	Visita 1–Visita 2	-3,89	[-4,93; -2,84]	< 0,001
Grupo Eclipta	Visita 1–Visita 3	-3,48	[-4,60; -2,36]	< 0,001
Grupo Eclipta	Visita 2–Visita 3	-1,88	[-3,70; -0,05]	0,042

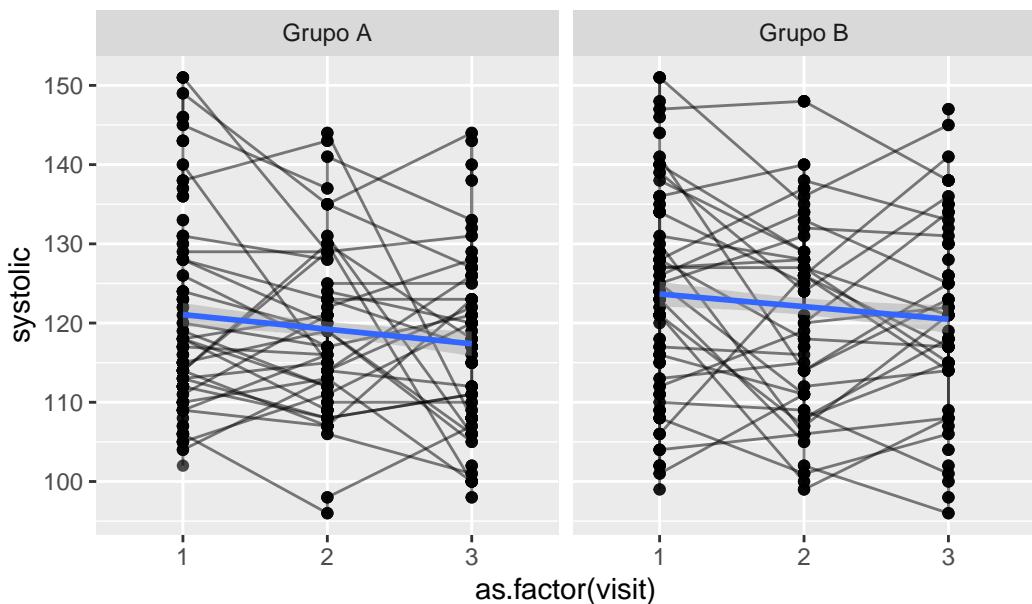
```
ggplot(
  data = data_bp_long,
  aes(
    x = as.factor(visit),
    y = systolic,
```

```

        group = record_id,
    )
) +
  geom_line(alpha = 0.5) +
  geom_point(alpha = 0.7) +
  geom_smooth(
    aes(group = allocation_group),
    method = "lm",
    se = TRUE,
    linewidth = 1
) +
  labs(title = "All data") +
  facet_wrap(~ allocation_group)
`geom_smooth()` using formula = 'y ~ x'

```

All data



```

data_bp_long %>%
  filter(
    !(record_id %in%
      systolic_model_check$influential_ids)
  ) %>%
  ggplot(
    aes(

```

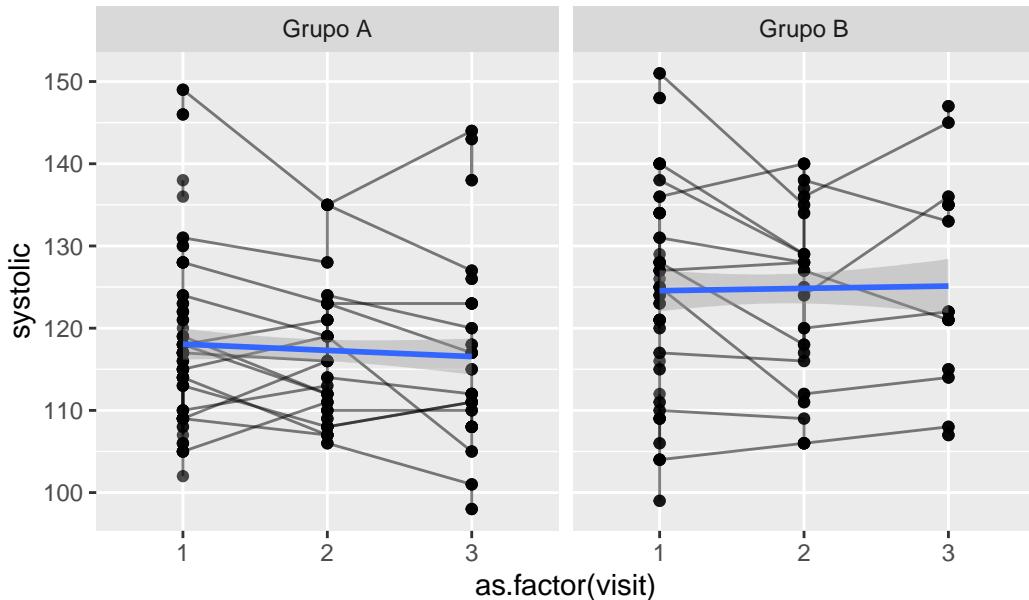
```

    x = as.factor(visit),
    y = systolic,
    group = record_id,
)
) +
geom_line(alpha = 0.5) +
geom_point(alpha = 0.7) +
geom_smooth(
  aes(group = allocation_group),
  method = "lm",
  se = TRUE,
  linewidth = 1
) +
labs(title = "Sensitivity analysis") +
facet_wrap(~ allocation_group)

```

`geom_smooth()` using formula = 'y ~ x'

Sensitivity analysis



3.17.3 Pressão Arterial Diastólica

Variável: diastolic

```

# Plot 1: Raw data
diastolic_hist_1 <- data_bp_long %>%

```

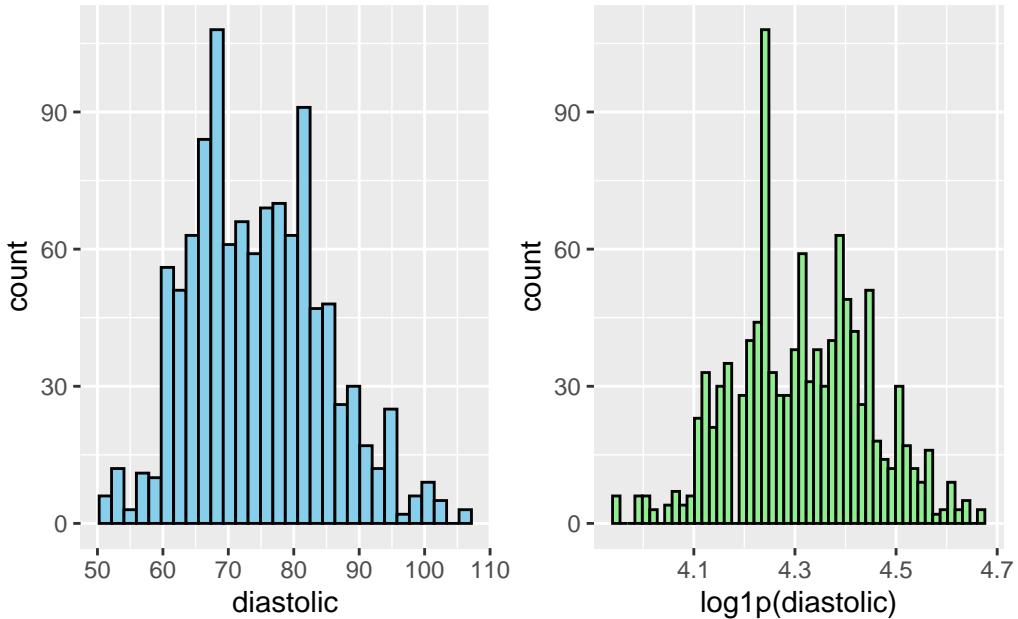
```

#filter(
  #  diastolic < 300
  #) %>%
  ggplot(aes(x = diastolic)) +
  geom_histogram(bins = 30, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
diastolic_hist_2 <- data_bp_long %>%
  #filter(
  #  diastolic < 300
  #) %>%
  ggplot(aes(x = log1p(diastolic))) +
  geom_histogram(bins = 50, fill = "lightgreen", color = "black")

# Combine side by side
diastolic_hist_1 + diastolic_hist_2 # library(patchwork)

```



```

# LMM
diastolic_model <- lmer(log1p(diastolic) ~ allocation_group * visit +
(1 | record_id), data = data_bp_long)
check_collinearity(diastolic_model)

# Check for Multicollinearity

```

Low Correlation

Term	VIF	VIF 95% CI	Increased SE	Tolerance
allocation_group	1.02	[1.00, 1.29]	1.01	0.98
visit	3.83	[3.47, 4.24]	1.96	0.26
allocation_group:visit	3.87	[3.51, 4.29]	1.97	0.26

Tolerance 95% CI

[0.77, 1.00]
[0.24, 0.29]
[0.23, 0.29]

```
# Sensitivity analysis
diastolic_model_check <- sensitivity_check_lmer(
  model = diastolic_model,
  id_var = "record_id",
  top_n = 5)

# LMM Sensitivity
diastolic_model_sens <- update(object = diastolic_model,
                                   subset = !(record_id %in%
                                   diastolic_model_check$influential_ids))

# Influential IDs
diastolic_model_check$influential_ids

[1] "1"   "4"   "9"   "10"  "13"  "17"  "18"  "19"  "20"  "21"  "22"  "23"  "26"  "27"  "32"
[16] "34"  "37"  "38"  "39"  "45"  "46"  "47"  "52"  "54"  "56"  "58"  "63"  "64"  "69"  "71"
[31] "75"
```

3.17.3.1 Resumo dos modelos

```
summary(diastolic_model)

Linear mixed model fit by REML. t-tests use Satterthwaite's method [
lmerModLmerTest]

Formula: log1p(diastolic) ~ allocation_group * visit + (1 | record_id)

Data: data_bp_long

REML criterion at convergence: -2610.1
```

Scaled residuals:

Min	1Q	Median	3Q	Max
-3.0300	-0.5971	0.0085	0.5673	3.2997

Random effects:

Groups	Name	Variance	Std.Dev.
--------	------	----------	----------

record_id	(Intercept)	0.013982	0.11825
-----------	-------------	----------	---------

Residual		0.004229	0.06503
----------	--	----------	---------

Number of obs: 1113, groups: record_id, 75

Fixed effects:

	Estimate	Std. Error	df	t value							
(Intercept)	4.317e+00	2.005e-02	7.593e+01	215.282							
allocation_group	3.222e-02	2.821e-02	7.623e+01	1.142							
visit2	-2.013e-02	6.769e-03	1.041e+03	-2.973							
visit3	-4.721e-02	6.866e-03	1.042e+03	-6.876							
allocation_group:visit2	-3.683e-02	9.577e-03	1.042e+03	-3.846							
allocation_group:visit3	1.627e-02	9.887e-03	1.043e+03	1.645							
	Pr(> t)										
(Intercept)	< 2e-16	***									
allocation_group	0.256880										
visit2	0.003013	**									
visit3	1.06e-11	***									
allocation_group:visit2	0.000127	***									
allocation_group:visit3	0.100214										

Signif. codes:	0	'***'	0.001	'**'	0.01	'*'	0.05	'. '	0.1	' '	1

Correlation of Fixed Effects:

(Intr)	all_GB	visit2	visit3	a_GB:2	
allctn_grGB	-0.711				
visit2	-0.140	0.100			
visit3	-0.135	0.096	0.479		
allctn_GB:2	0.099	-0.137	-0.707	-0.338	
allctn_GB:3	0.094	-0.130	-0.332	-0.694	0.472

```
summary(diastolic_model_sens)

Linear mixed model fit by REML. t-tests use Satterthwaite's method [
lmerModLmerTest]

Formula: log1p(diastolic) ~ allocation_group * visit + (1 | record_id)

Data: data_bp_long

Subset: !(record_id %in% diastolic_model_check$influential_ids)
```

REML criterion at convergence: -1677.8

Scaled residuals:

Min	1Q	Median	3Q	Max
-2.71801	-0.66604	-0.03126	0.65483	2.92478

Random effects:

Groups	Name	Variance	Std.Dev.
record_id	(Intercept)	0.017286	0.13148
	Residual	0.001356	0.03682

Number of obs: 510, groups: record_id, 44

Fixed effects:

	Estimate	Std. Error	df	t value							
(Intercept)	4.331558	0.030479	42.381568	142.116							
allocation_group	0.018610	0.040443	42.413113	0.460							
visit2	-0.018719	0.006188	463.802406	-3.025							
visit3	-0.056333	0.006591	463.886716	-8.547							
allocation_group:visit2	-0.025477	0.008163	464.002361	-3.121							
allocation_group:visit3	0.016096	0.008706	463.957521	1.849							
	Pr(> t)										
(Intercept)	< 2e-16	***									
allocation_group	0.64775										
visit2	0.00262	**									
visit3	< 2e-16	***									
allocation_group:visit2	0.00191	**									
allocation_group:visit3	0.06513	.									

Signif. codes:	0	'***'	0.001	'**'	0.01	'*'	0.05	'. '	0.1	' '	1

Correlation of Fixed Effects:

```
(Intr) all_GB visit2 visit3 a_GB:2  
allctn_grGB -0.754  
visit2      -0.066  0.050  
visit3      -0.058  0.044  0.429  
allctn_GB:2  0.050 -0.067 -0.758 -0.325  
allctn_GB:3  0.044 -0.059 -0.325 -0.757  0.448
```

```
performance::compare_performance(  
  diastolic_model,  
  diastolic_model_sens)
```

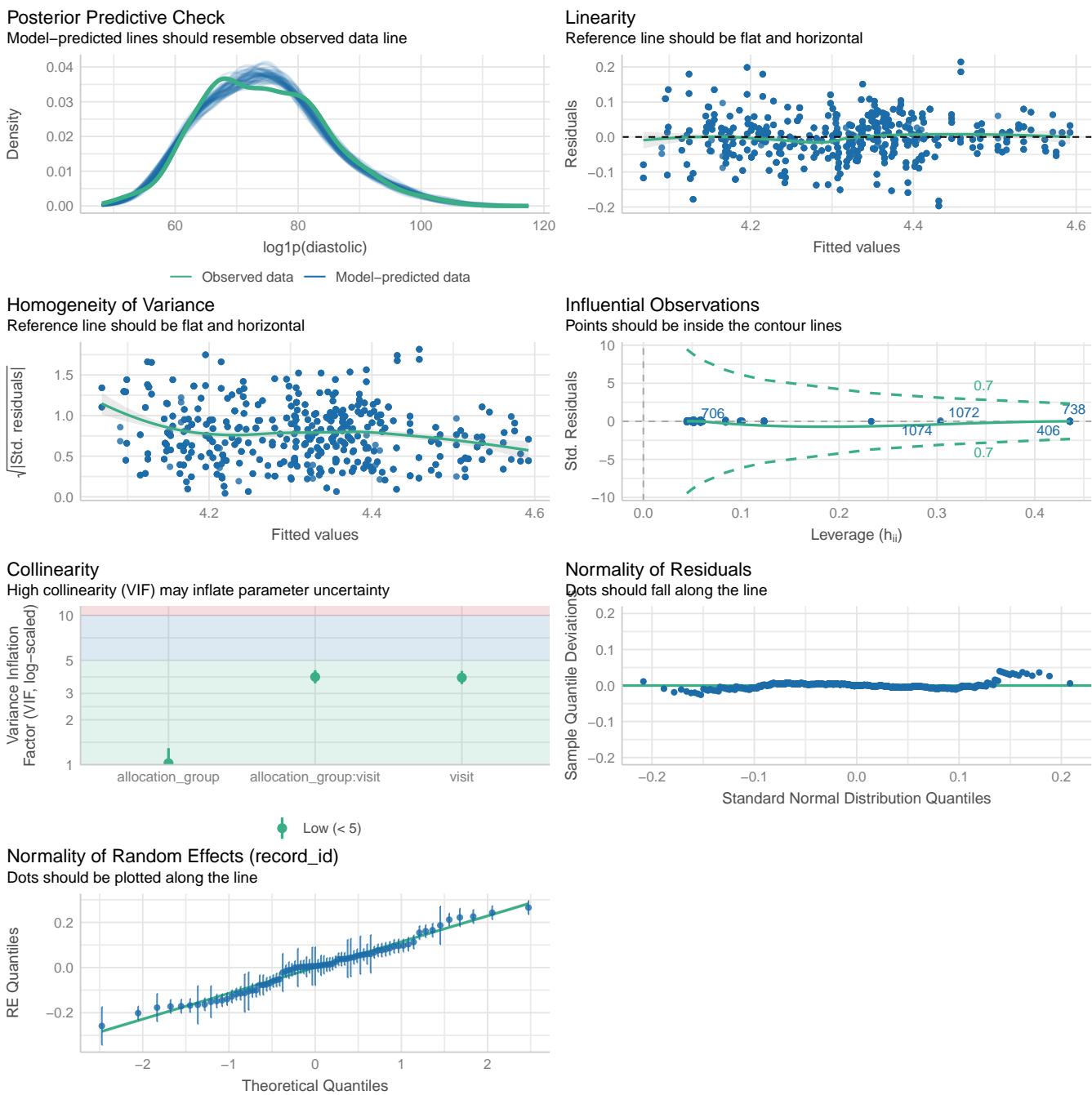
When comparing models, please note that probably not all models were fit from same data.

```
# Comparison of Model Performance Indices
```

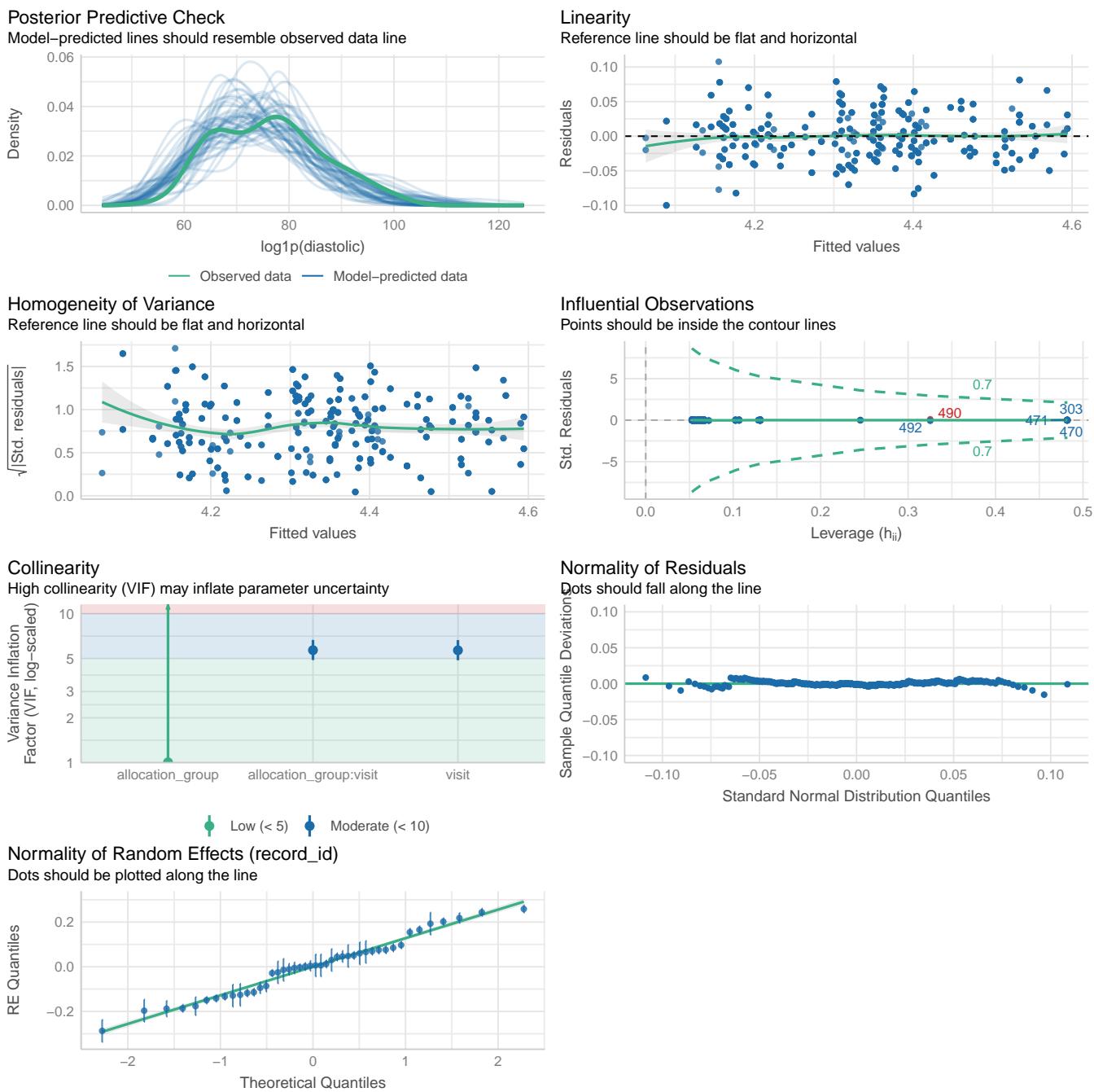
Name	Model	AIC (weights)	AICc (weights)
diastolic_model	lmerModLmerTest	6968.0 (<.001)	6968.2 (<.001)
diastolic_model_sens	lmerModLmerTest	2718.9 (>.999)	2719.1 (>.999)

Name	BIC (weights)	R2 (cond.)	R2 (marg.)	ICC	RMSE	Sigma
diastolic_model	7008.1 (<.001)	0.776	0.034	0.768	0.063	0.065
diastolic_model_sens	2752.7 (>.999)	0.929	0.027	0.927	0.035	0.037

```
performance::check_model(diastolic_model)
```



```
performance::check_model(diastolic_model_sens)
```



3.17.3.2 Médias Marginais Estimadas

3.17.3.2.1 Todos os dados

```
# Get EMMs for each group at each visit
diastolic_raw_emm <- emmeans::emmeans(
  diastolic_model,
```

```

~ allocation_group * visit
)

diastolic_raw_emm <- regrid(diastolic_raw_emm)

# Table of marginal means
# diastolic_raw_emm

# Pairwise comparisons: Between groups at each visit
emmmeans::contrast(diastolic_raw_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

visit = 1:

```

contrast	estimate	SE	df	lower.CL	upper.CL	t.ratio	p.value
Grupo A - Grupo B	-2.456	2.15	76.3	-6.74	1.826	-1.142	0.2569

```

visit = 2:

```

contrast	estimate	SE	df	lower.CL	upper.CL	t.ratio	p.value
Grupo A - Grupo B	0.338	2.09	79.0	-3.82	4.501	0.162	0.8719

```

visit = 3:

```

contrast	estimate	SE	df	lower.CL	upper.CL	t.ratio	p.value
Grupo A - Grupo B	-3.554	2.10	79.8	-7.74	0.628	-1.691	0.0947

Degrees-of-freedom method: inherited from kenward-roger when re-gridding

Confidence level used: 0.95

```

# Pairwise comparisons: Changes over time within each group
emmmeans::contrast(diastolic_raw_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

```

```

allocation_group = Grupo A:

```

contrast	estimate	SE	df	lower.CL	upper.CL	t.ratio	p.value
visit1 - visit2	1.49	0.503	76.3	0.264	2.72	2.973	0.0118
visit1 - visit3	3.46	0.505	76.3	2.221	4.69	6.844	<.0001
visit2 - visit3	1.96	0.506	79.0	0.726	3.20	3.881	0.0006

```

allocation_group = Grupo B:

contrast      estimate     SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit2    4.29 0.514 76.9     3.030     5.55    8.343 <.0001
visit1 - visit3    2.36 0.542 76.9     1.033     3.69    4.353  0.0001
visit2 - visit3   -1.93 0.535 80.5    -3.237    -0.62   -3.605  0.0016

```

Degrees-of-freedom method: inherited from kenward-roger when re-gridding

Confidence level used: 0.95

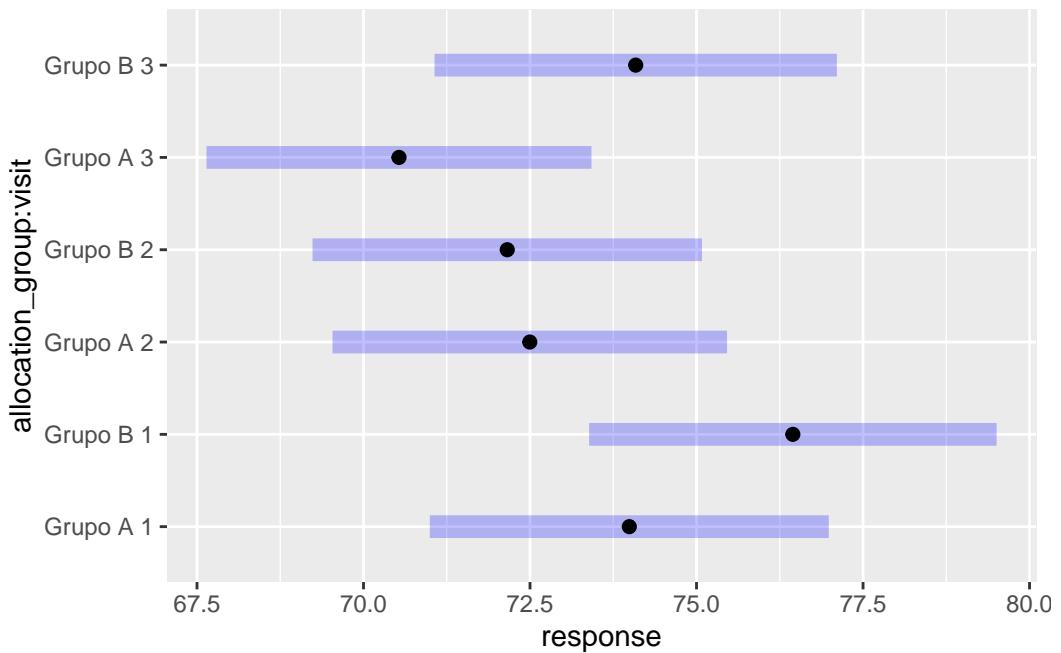
Conf-level adjustment: bonferroni method for 3 estimates

P value adjustment: bonferroni method for 3 tests

```

# Plot of marginal means
plot(diastolic_raw_emm)

```



3.17.3.2.2 Análise de sensibilidade

```

# Get EMMs for each group at each visit (Sensitivity Analysis)
diastolic_emm <- emmeans::emmeans(
  diastolic_model_sens,
  ~ allocation_group * visit
)

```

```

diastolic_emm <- regrid(diastolic_emm)

# Table of marginal means
# diastolic_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(diastolic_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

visit = 1:
  contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
  Grupo A - Grupo B    -1.429 3.10 42.4     -7.69     4.83  -0.461  0.6474

visit = 2:
  contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
  Grupo A - Grupo B     0.511 3.03 43.6     -5.60     6.62   0.169  0.8669

visit = 3:
  contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
  Grupo A - Grupo B    -2.539 2.98 44.2     -8.55     3.47  -0.851  0.3993

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95

# Pairwise comparisons: Changes over time within each group
emmeans::contrast(diastolic_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

allocation_group = Grupo A:
  contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
  visit1 - visit2    1.411 0.467 42.4     0.247    2.574   3.022  0.0127
  visit1 - visit3    4.166 0.498 42.4     2.926    5.407   8.371 <.0001
  visit2 - visit3    2.756 0.507 43.6     1.495    4.017   5.440 <.0001

allocation_group = Grupo B:
  contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value

```

```

visit1 - visit2    3.350 0.410 42.5      2.327    4.373   8.162 <.0001
visit1 - visit3    3.056 0.436 42.5      1.969    4.143   7.009 <.0001
visit2 - visit3   -0.294 0.420 43.6     -1.341    0.752   -0.700  1.0000

```

Degrees-of-freedom method: inherited from kenward-roger when re-gridding

Confidence level used: 0.95

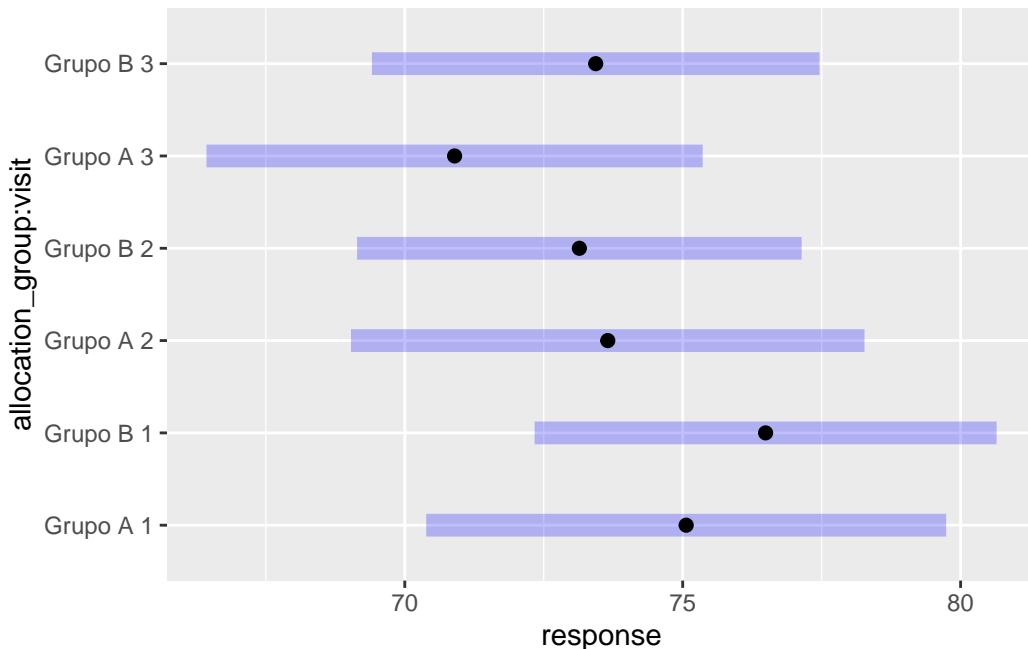
Conf-level adjustment: bonferroni method for 3 estimates

P value adjustment: bonferroni method for 3 tests

```

# Plot of marginal means
plot(diastolic_emm)

```



3.17.3.3 Resultado

No modelo ajustado para a pressão arterial diastólica, não houve diferenças estatisticamente significativas entre os grupos em nenhum dos três momentos avaliados (visita 1: estimativa = -2,46 mmHg; IC 95%: -6,74 a 1,83; p = 0,257; visita 2: estimativa = 0,34 mmHg; IC 95%: -3,82 a 4,50; p = 0,872; visita 3: estimativa = -3,55 mmHg; IC 95%: -7,74 a 0,63; p = 0,095).

Contudo, ambos os grupos apresentaram redução significativa da pressão diastólica ao longo do tempo: - **Grupo Placebo**: redução média de 1,49 mmHg entre visita 1 e 2 (IC 95%: 0,26 a 2,72; p = 0,012), de 3,46 mmHg entre visita 1 e 3 (IC 95%: 2,22 a 4,69; p < 0,001) e de 1,96 mmHg entre visita 2 e 3 (IC 95%: 0,73 a 3,20; p = 0,001). - **Grupo Eclipta**: redução média de 4,29 mmHg entre visita 1 e 2 (IC 95%: 3,03 a 5,55; p < 0,001), de 2,36 mmHg entre visita 1 e 3 (IC 95%: 1,03 a 3,69; p < 0,001) e de 1,93 mmHg entre visita 2 e 3 (IC 95%: 1,24 a 3,23; p = 0,002).

Na análise de sensibilidade, as reduções entre visita 1 e 2 e entre visita 1 e 3 mantiveram-se significativas em ambos os grupos. Já a redução entre visita 2 e 3 no grupo Eclipta deixou de ser significativa (-0,29 mmHg; IC 95%: -1,34 a 0,75; p =

1,000).

Tabela 23: Diferenças estimadas da pressão diastólica entre grupos e ao longo do tempo – Modelo completo

Grupo de comparação	Comparação	Estimativa (mmHg)	IC 95%	p-valor
Entre grupos	Visita 1	-2,46	[-6,74; 1,83]	0,257
Entre grupos	Visita 2	0,34	[-3,82; 4,50]	0,872
Entre grupos	Visita 3	-3,55	[-7,74; 0,63]	0,095
Grupo Placebo	Visita 1 – Visita 2	-1,49	[0,26; 2,72]	0,012
Grupo Placebo	Visita 1 – Visita 3	-3,46	[2,22; 4,69]	< 0,001
Grupo Placebo	Visita 2 – Visita 3	-1,96	[0,73; 3,20]	0,001
Grupo Eclipta	Visita 1 – Visita 2	-4,29	[3,03; 5,55]	< 0,001
Grupo Eclipta	Visita 1 – Visita 3	-2,36	[1,03; 3,69]	< 0,001
Grupo Eclipta	Visita 2 – Visita 3	-1,93	[1,24; 3,23]	0,002

Tabela 24: Diferenças estimadas da pressão diastólica – Análise de sensibilidade

Grupo de comparação	Comparação	Estimativa (mmHg)	IC 95%	p-valor
Entre grupos	Visita 1	-1,43	[-7,69; 4,83]	0,647
Entre grupos	Visita 2	0,51	[-5,60; 6,62]	0,867
Entre grupos	Visita 3	-2,54	[-8,55; 3,47]	0,399
Grupo Placebo	Visita 1 – Visita 2	-1,41	[0,25; 2,57]	0,013
Grupo Placebo	Visita 1 – Visita 3	-4,17	[2,93; 5,41]	< 0,001
Grupo Placebo	Visita 2 – Visita 3	-2,76	[1,50; 4,02]	< 0,001
Grupo Eclipta	Visita 1 – Visita 2	-3,35	[2,33; 4,37]	< 0,001
Grupo Eclipta	Visita 1 – Visita 3	-3,06	[1,97; 4,14]	< 0,001
Grupo Eclipta	Visita 2 – Visita 3	-0,29	[-1,34; 0,75]	1,000

```
ggplot(
  data = data_bp_long,
  aes(
    x = as.factor(visit),
    y = diastolic,
    group = record_id,
  )
) +
```

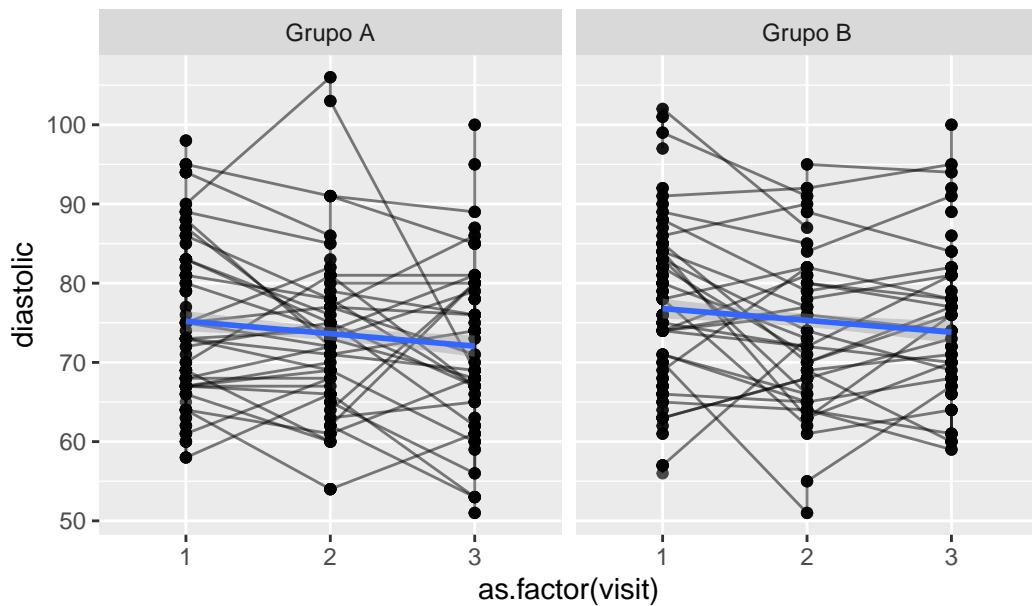
```

geom_line(alpha = 0.5) +
geom_point(alpha = 0.7) +
geom_smooth(
  aes(group = allocation_group),
  method = "lm",
  se = TRUE,
  linewidth = 1
) +
labs(title = "All data") +
facet_wrap(~ allocation_group)

```

`geom_smooth()` using formula = 'y ~ x'

All data



```

data_bp_long %>%
  filter(
    !(record_id %in%
      diastolic_model_check$influential_ids)
  ) %>%
  ggplot(
    aes(
      x = as.factor(visit),
      y = diastolic,
      group = record_id,

```

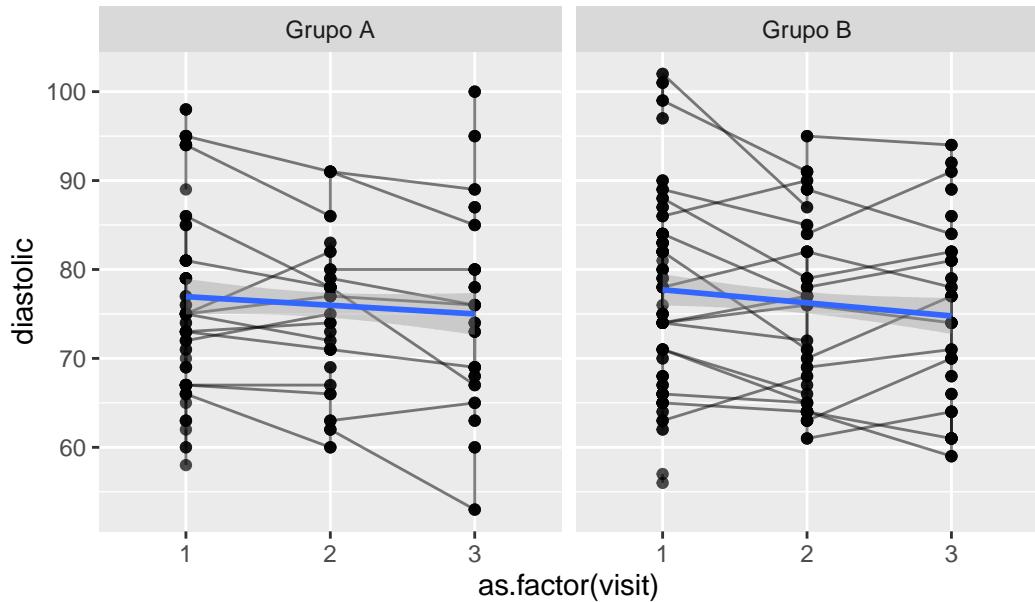
```

)
) +
geom_line(alpha = 0.5) +
geom_point(alpha = 0.7) +
geom_smooth(
  aes(group = allocation_group),
  method = "lm",
  se = TRUE,
  linewidth = 1
) +
labs(title = "Sensitivity analysis") +
facet_wrap(~ allocation_group)

`geom_smooth()` using formula = 'y ~ x'

```

Sensitivity analysis



3.18 Escore EVS

Variável: evs_score

```

# Plot 1: Raw data
evs_score_hist_1 <- data_model %>%
  filter(
    evs_score >0
  ) %>%

```

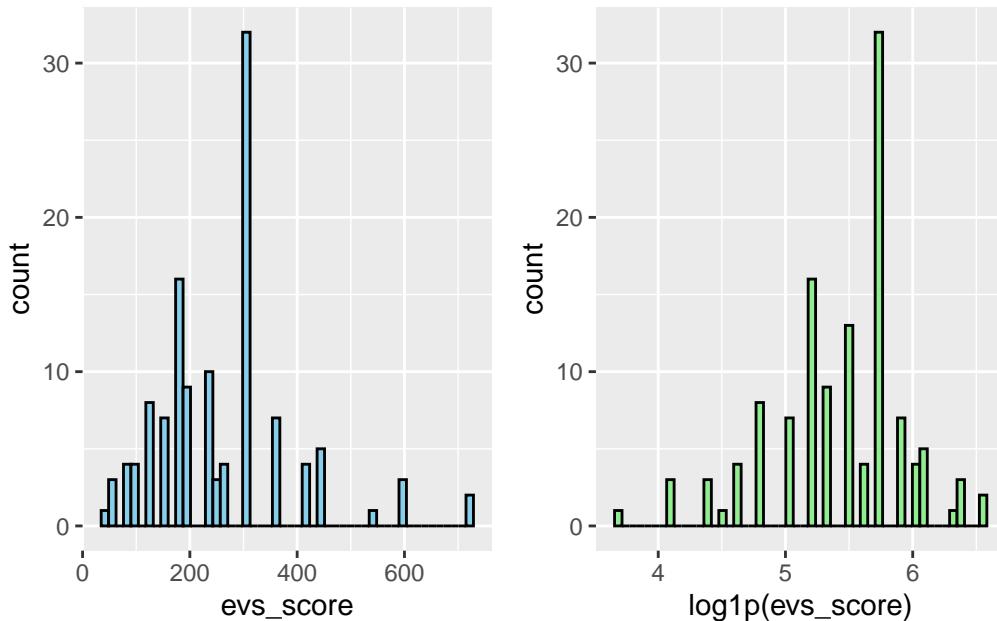
```

ggplot(aes(x = evs_score)) +
  geom_histogram(bins = 50, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
evs_score_hist_2 <- data_model %>%
  filter(
    evs_score >0
  ) %>%
  ggplot(aes(x = log1p(evs_score))) +
  geom_histogram(bins = 50, fill = "lightgreen", color = "black")

# Combine side by side
evs_score_hist_1 + evs_score_hist_2 # library(patchwork)

```



```

# LMM

data_model_evs <- data_model %>%
  filter(evs_score > 0)

evs_score_model <- lmer(log1p(evs_score) ~ allocation_group * visit +
(1 | record_id), data = data_model_evs)
check_collinearity(evs_score_model)

```

```
# Check for Multicollinearity
```

Low Correlation

	Term	VIF	VIF 95% CI	Increased SE	Tolerance	Tolerance 95% CI
allocation_group	2.02	[1.62, 2.66]	1.42	0.50	[0.38, 0.62]	
visit	3.96	[3.02, 5.35]	1.99	0.25	[0.19, 0.33]	

Moderate Correlation

	Term	VIF	VIF 95% CI	Increased SE	Tolerance
allocation_group:visit	5.59	[4.18, 7.61]	2.36	0.18	
Tolerance 95% CI		[0.13, 0.24]			

```
# Sensitivity analysis
evs_score_model_check <- sensitivity_check_lmer(
  model = evs_score_model,
  id_var = "record_id",
  top_n = 5)

# LMM Sensitivity
evs_score_model_sens <- update(object = evs_score_model,
  subset = !(record_id %in%
  evs_score_model_check$influential_ids))

# Influential IDS
evs_score_model_check$influential_ids

[1] "18" "44" "68" "50" "12"
```

3.18.1 Resumo dos modelos

```
# Model comparison
summary(evs_score_model)

Linear mixed model fit by REML. t-tests use Satterthwaite's method [
lmerModLmerTest]
Formula: log1p(evs_score) ~ allocation_group * visit + (1 | record_id)
Data: data_model_evs
```

REML criterion at convergence: 196.5

Scaled residuals:

Min	1Q	Median	3Q	Max
-2.5002	-0.4282	0.1341	0.4983	1.9054

Random effects:

Groups	Name	Variance	Std.Dev.
record_id	(Intercept)	0.1002	0.3166
Residual		0.1919	0.4380

Number of obs: 123, groups: record_id, 56

Fixed effects:

	Estimate	Std. Error	df	t value	Pr(> t)
(Intercept)	5.45023	0.12407	113.97017	43.927	<2e-16
allocation_group	-0.07889	0.16813	112.03406	-0.469	0.640
visit2	-0.06127	0.14094	79.06500	-0.435	0.665
visit3	0.09117	0.14936	76.96426	0.610	0.543
allocation_group:visit2	0.12742	0.19735	80.22191	0.646	0.520
allocation_group:visit3	-0.01678	0.20995	78.03049	-0.080	0.937

(Intercept) ***

allocation_group

visit2

visit3

allocation_group:visit2

allocation_group:visit3

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

(Intr)	all_GB	visit2	visit3	a_GB:2
allctn_grGB	-0.738			
visit2	-0.678	0.501		
visit3	-0.621	0.458	0.554	

```

allctn_GB:2  0.484 -0.644 -0.714 -0.396
allctn_GB:3  0.442 -0.587 -0.394 -0.711  0.520

summary(evs_score_model_sens)

Linear mixed model fit by REML. t-tests use Satterthwaite's method [
lmerModLmerTest]

Formula: log1p(evs_score) ~ allocation_group * visit + (1 | record_id)

Data: data_model_evs

Subset: !(record_id %in% evs_score_model_check$influential_ids)

```

REML criterion at convergence: 136.4

Scaled residuals:

Min	1Q	Median	3Q	Max
-2.47567	-0.51463	0.07711	0.49472	2.15838

Random effects:

Groups	Name	Variance	Std.Dev.
record_id	(Intercept)	0.06004	0.2450
Residual		0.13788	0.3713

Number of obs: 109, groups: record_id, 51

Fixed effects:

	Estimate	Std. Error	df	t value	Pr(> t)
(Intercept)	5.57355	0.10898	100.91854	51.145	<2e-16
allocation_group	-0.12141	0.14669	99.63237	-0.828	0.410
visit2	-0.12042	0.12666	66.59739	-0.951	0.345
visit3	0.06011	0.13576	64.41769	0.443	0.659
allocation_group:visit2	0.09871	0.17636	68.03387	0.560	0.578
allocation_group:visit3	-0.05185	0.18957	65.91159	-0.274	0.785

(Intercept) ***
allocation_group
visit2
visit3
allocation_group:visit2
allocation_group:visit3

```
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

Correlation of Fixed Effects:

	(Intr)	all_GB	visit2	visit3	a_GB:2
allctn_grGB	-0.743				
visit2	-0.689	0.512			
visit3	-0.623	0.463	0.543		
allctn_GB:2	0.495	-0.658	-0.718	-0.390	
allctn_GB:3	0.446	-0.594	-0.389	-0.716	0.513

```
performance::compare_performance(
  evs_score_model,
  evs_score_model_sens)
```

When comparing models, please note that probably not all models were fit from same data.

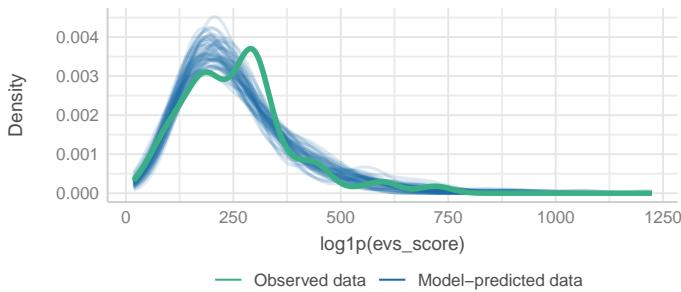
```
# Comparison of Model Performance Indices
```

Name	Model	AIC (weights)	AICc (weights)
evs_score_model	lmerModLmerTest	1532.6 (<.001)	1533.9 (<.001)
evs_score_model_sens	lmerModLmerTest	1332.9 (>.999)	1334.3 (>.999)

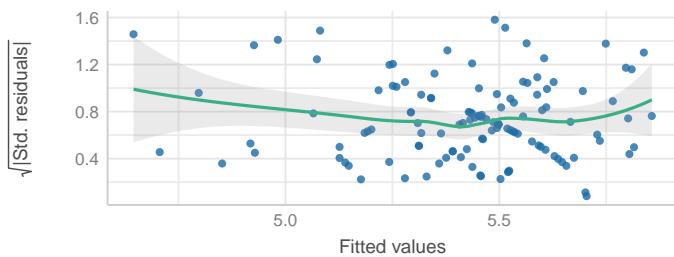
Name	BIC (weights)	R2 (cond.)	R2 (marg.)	ICC	RMSE	Sigma
evs_score_model	1555.1 (<.001)	0.350	0.010	0.343	0.374	0.438
evs_score_model_sens	1354.4 (>.999)	0.322	0.027	0.303	0.319	0.371

```
performance::check_model(evs_score_model)
```

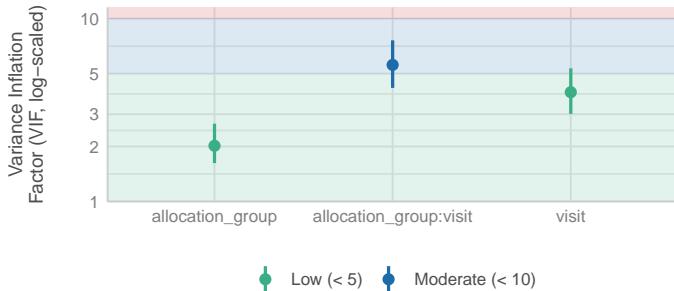
Posterior Predictive Check
Model-predicted lines should resemble observed data line



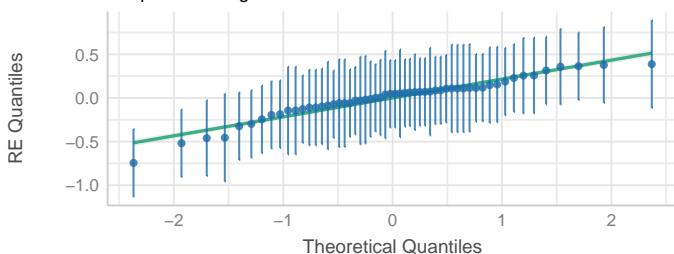
Homogeneity of Variance
Reference line should be flat and horizontal



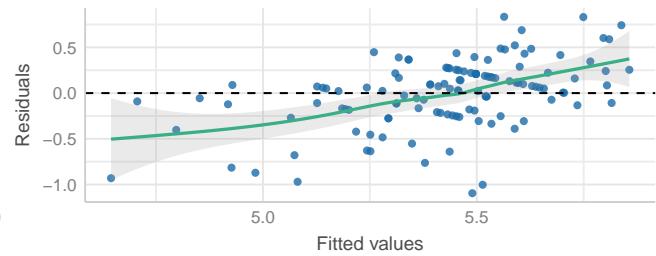
Collinearity
High collinearity (VIF) may inflate parameter uncertainty



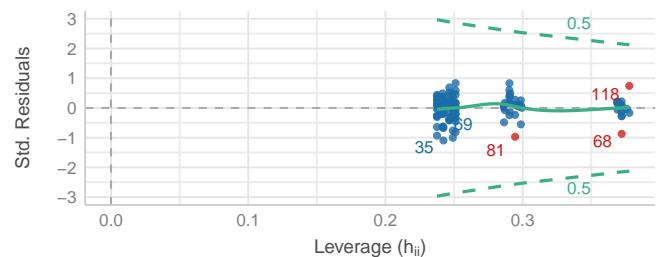
Normality of Random Effects (record_id)
Dots should be plotted along the line



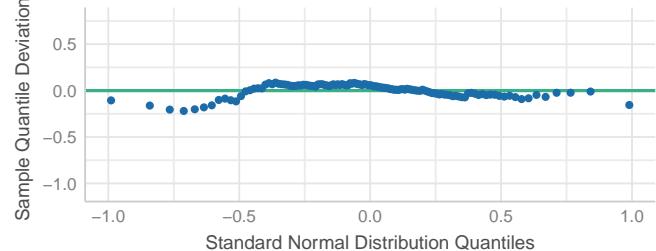
Linearity
Reference line should be flat and horizontal



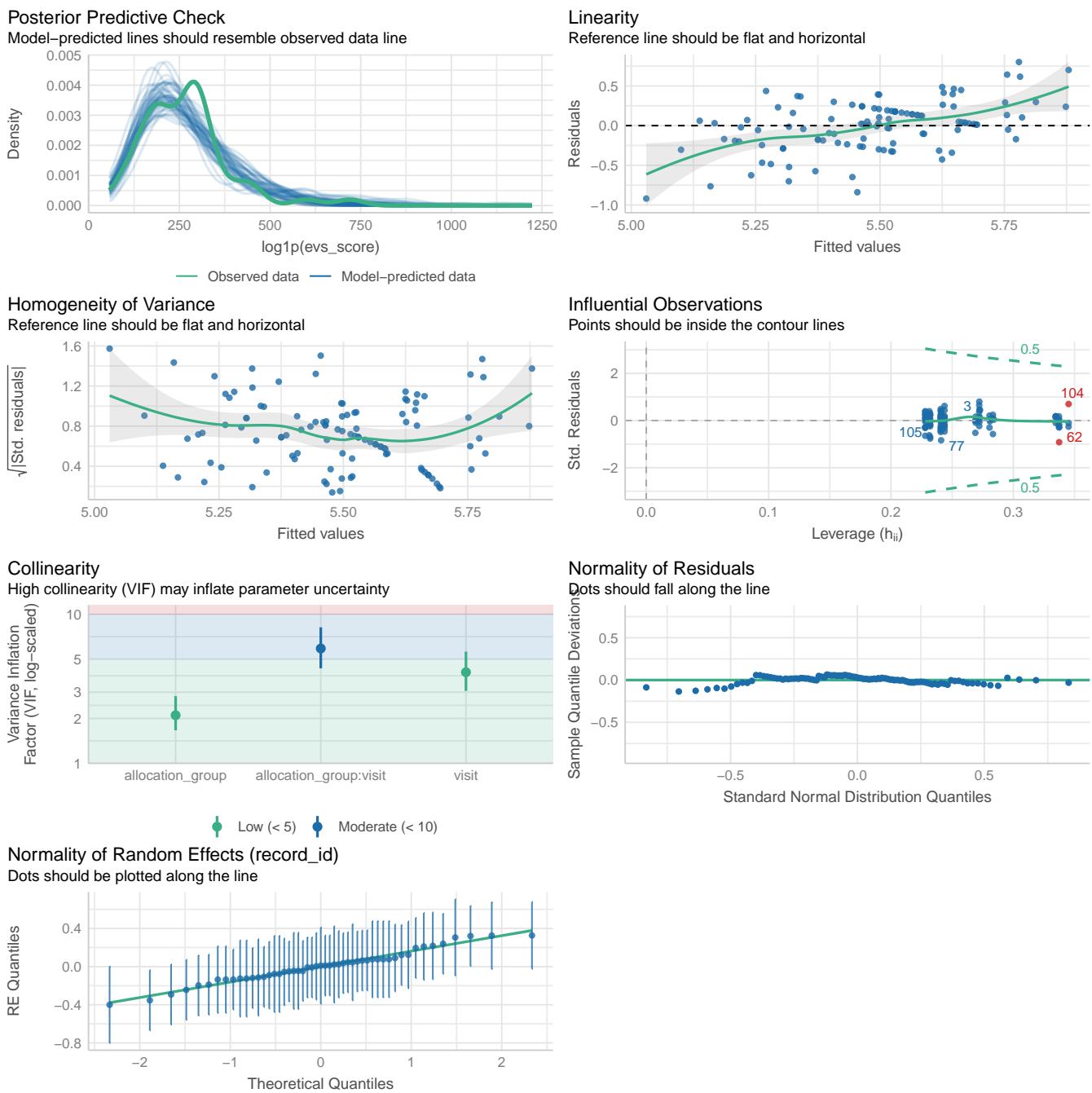
Influential Observations
Points should be inside the contour lines



Normality of Residuals
Dots should fall along the line



```
performance::check_model(evs_score_model_sens)
```



3.18.2 Médias Marginais Estimadas

3.18.2.1 Todos os dados

```
# Get EMMs for each group at each visit
evs_score_raw_emm <- emmeans::emmeans(
  evs_score_model,
  ~ allocation_group * visit
```

```

)
evs_score_raw_emm <- regrid(evs_score_raw_emm)

# Table of marginal means
# evs_score_raw_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(evs_score_raw_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

```

visit = 1:

contrast	estimate	SE	df	lower.CL	upper.CL	t.ratio	p.value
Grupo A - Grupo B	17.7	38.0	109	-57.6	92.9	0.465	0.6426

visit = 2:

contrast	estimate	SE	df	lower.CL	upper.CL	t.ratio	p.value
Grupo A - Grupo B	-10.9	35.2	104	-80.8	59.0	-0.309	0.7579

visit = 3:

contrast	estimate	SE	df	lower.CL	upper.CL	t.ratio	p.value
Grupo A - Grupo B	23.3	42.9	113	-61.8	108.3	0.542	0.5889

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
 Confidence level used: 0.95

```

# Pairwise comparisons: Changes over time within each group
emmeans::contrast(evs_score_raw_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

```

allocation_group = Grupo A:

contrast	estimate	SE	df	lower.CL	upper.CL	t.ratio	p.value
visit1 - visit2	13.8	32.2	104	-64.5	92.2	0.430	1.0000
visit1 - visit3	-22.2	36.6	113	-111.1	66.7	-0.607	1.0000
visit2 - visit3	-36.1	33.2	104	-116.9	44.7	-1.086	0.8402

```

allocation_group = Grupo B:

contrast      estimate   SE  df lower.CL upper.CL t.ratio p.value
visit1 - visit2    -14.7 30.9 108     -89.9      60.4  -0.476  1.0000
visit1 - visit3    -16.6 33.4 109     -97.7      64.5  -0.498  1.0000
visit2 - visit3     -1.9 33.6 108     -83.7      79.9  -0.057  1.0000

```

Degrees-of-freedom method: inherited from kenward-roger when re-gridding

Confidence level used: 0.95

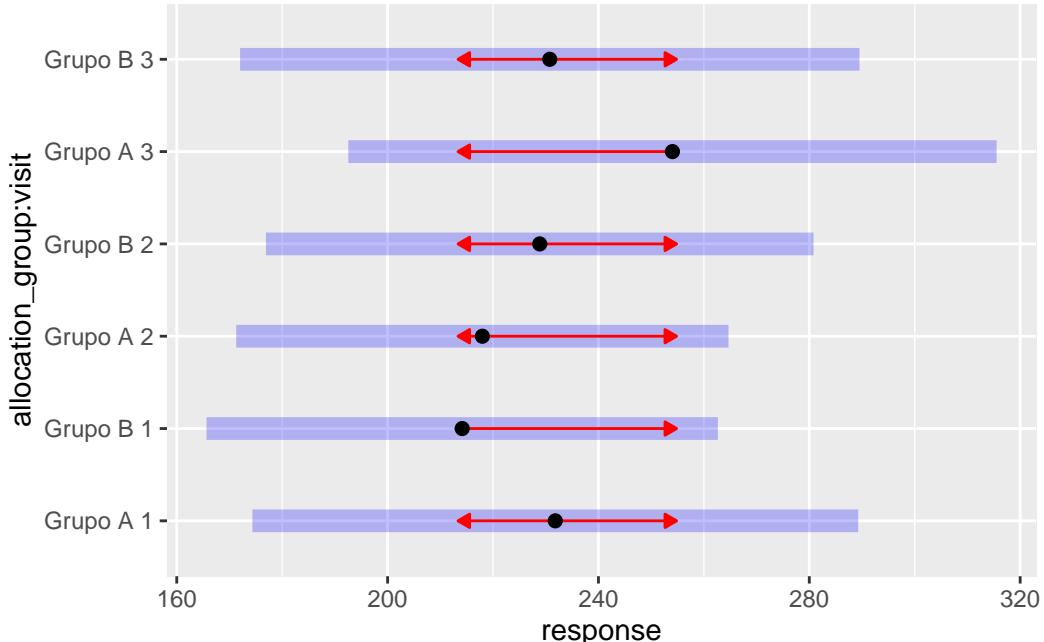
Conf-level adjustment: bonferroni method for 3 estimates

P value adjustment: bonferroni method for 3 tests

```

# Plot of marginal means
plot(evs_score_raw_emm, comparisons = TRUE)

```



3.18.2.2 Análise de sensibilidade

```

# Get EMMs for each group at each visit (Sensitivity Analysis)
evs_score_emm <- emmeans::emmeans(
  evs_score_model_sens,
  ~ allocation_group * visit
)

evs_score_emm <- regrid(evs_score_emm)

```

```

# Table of marginal means

# evs_score_emm

# Pairwise comparisons: Between groups at each visit

emmeans::contrast(evs_score_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

visit = 1:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B     30.11 36.9  98.3     -43.1     103.3    0.816  0.4163

visit = 2:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B      5.24 31.5  94.7     -57.4      67.8    0.166  0.8684

visit = 3:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B     44.49 40.5 101.1     -35.9     124.9    1.098  0.2750

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95

# Pairwise comparisons: Changes over time within each group

emmeans::contrast(evs_score_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

allocation_group = Grupo A:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit2     29.88 32.1  94.7     -48.3     108.0    0.932  1.0000
visit1 - visit3    -16.32 37.1 101.1    -106.6      73.9   -0.440  1.0000
visit2 - visit3    -46.20 33.1  94.7    -127.0      34.6   -1.394  0.5001

allocation_group = Grupo B:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit2      5.01 28.5  97.7     -64.4      74.4    0.176  1.0000
visit1 - visit3     -1.93 31.2  98.3     -77.9      74.0   -0.062  1.0000

```

```
visit2 - visit3      -6.95 30.4  97.7     -80.9      67.0  -0.229  1.0000
```

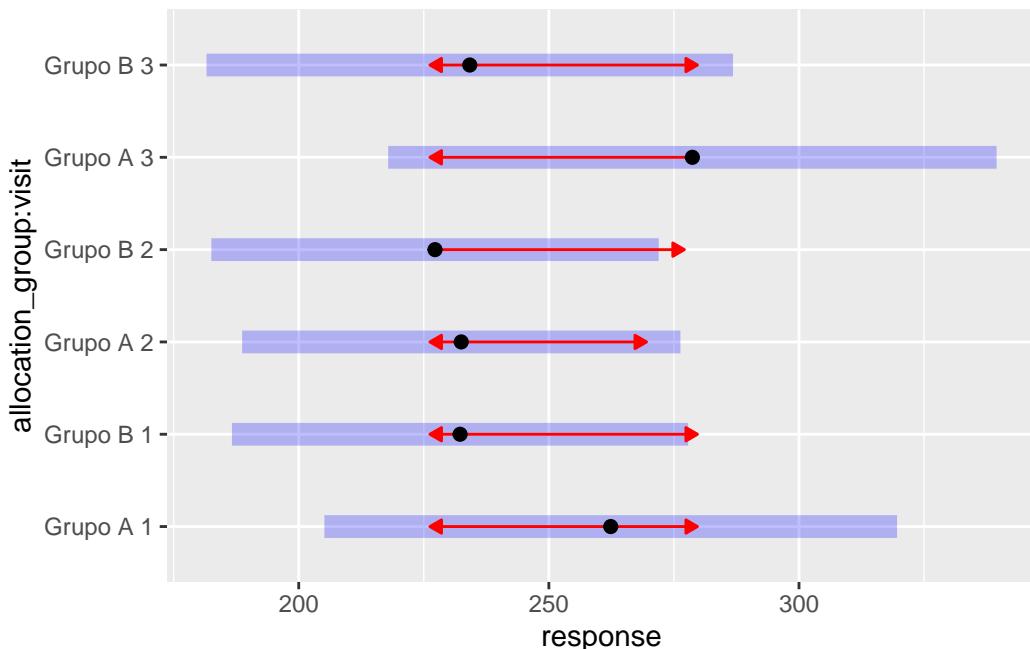
Degrees-of-freedom method: inherited from kenward-roger when re-gridding

Confidence level used: 0.95

Conf-level adjustment: bonferroni method for 3 estimates

P value adjustment: bonferroni method for 3 tests

```
# Plot of marginal means
plot(evs_score_emm, comparisons = TRUE)
```



```
ggplot(
  data = data_model_evs,
  aes(
    x = as.factor(visit),
    y = evs_score,
    group = record_id,
  )
) +
  geom_line(alpha = 0.5) +
  geom_point(alpha = 0.7) +
  geom_smooth(
    aes(group = allocation_group),
    method = "lm",
  )
```

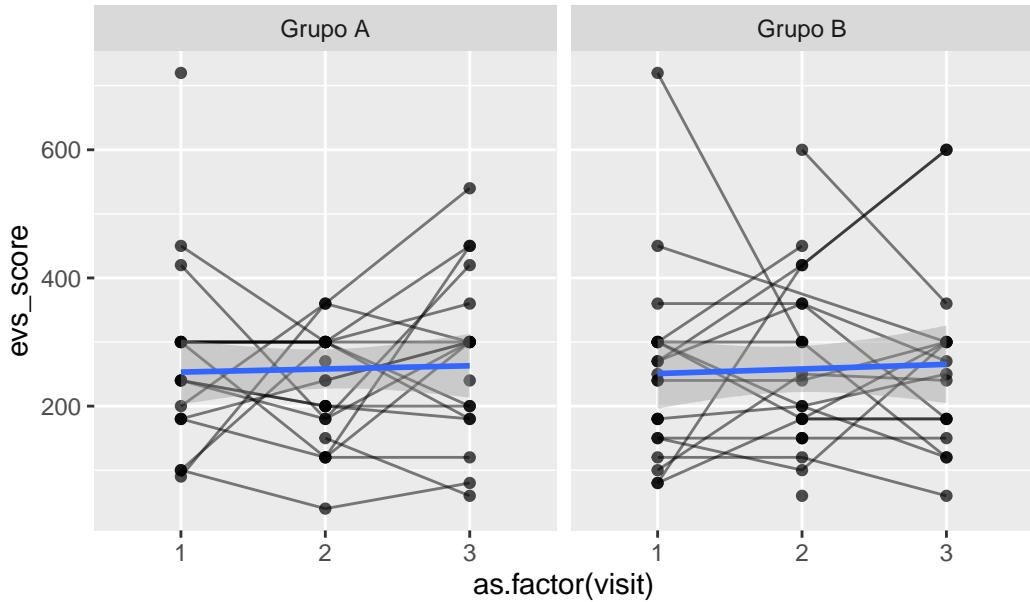
```

    se = TRUE,
    linewidth = 1
) +
labs(title = "All data") +
facet_wrap(~ allocation_group)

`geom_smooth()` using formula = 'y ~ x'

```

All data



```

#coord_cartesian(ylim = c(10, 150))

data_model_evs %>%
  filter(
    !(record_id %in%
      evs_score_model_check$influential_ids)
  ) %>%
  ggplot(
    aes(
      x = as.factor(visit),
      y = evs_score,
      group = record_id,
    )
  ) +
  geom_line(alpha = 0.5) +

```

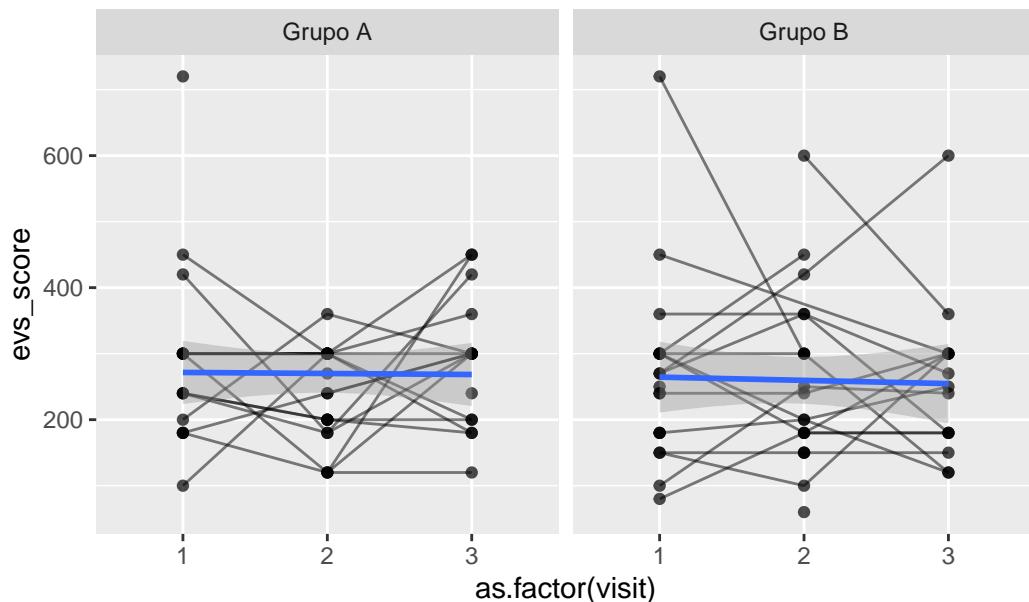
```

geom_point(alpha = 0.7) +
geom_smooth(
  aes(group = allocation_group),
  method = "lm",
  se = TRUE,
  linewidth = 1
) +
labs(title = "Sensitivity analysis") +
facet_wrap(~ allocation_group)

`geom_smooth()` using formula = 'y ~ x'

```

Sensitivity analysis



```
#coord_cartesian(ylim = c(10, 150))
```

3.18.3 EVS - modelo em 2 partes

```

data_model_evs <- data_model %>%
  mutate(
    exercised = if_else(evs_score > 0, 1, 0)
  )

model_part1 <- glmer(
  exercised ~ allocation_group * visit + (1 | record_id),

```

```

  data = data_model_evs,
  family = binomial
)

summary(model_part1)

```

What factors are associated with whether someone exercises at all during the week? Generalized linear mixed

What factors are associated with whether someone exercises at all during the week? Approximation) [glmer

What factors are associated with whether someone exercises at all during the week? Family: binomial (lo

What factors are associated with whether someone exercises at all during the week? Formula: exercised ~ al

What factors are associated with whether someone exercises at all during the week? Data: data_model_evs

What factors are associated with whether someone exercises at all during the week?

What factors are associated with whether someone exercises at all during the week? AIC BIC

What factors are associated with whether someone exercises at all during the week? 209.4 232.0

What factors are associated with whether someone exercises at all during the week?

What factors are associated with whether someone exercises at all during the week? Scaled residuals:

What factors are associated with whether someone exercises at all during the week? Min 1Q Median

What factors are associated with whether someone exercises at all during the week? -2.3438 -0.3319 0.1545

What factors are associated with whether someone exercises at all during the week?

What factors are associated with whether someone exercises at all during the week? Random effects:

What factors are associated with whether someone exercises at all during the week? Groups Name

What factors are associated with whether someone exercises at all during the week? record_id (Intercept)

What factors are associated with whether someone exercises at all during the week? Number of obs: 187, gro

What factors are associated with whether someone exercises at all during the week?

What factors are associated with whether someone exercises at all during the week? Fixed effects:

What factors are associated with whether someone exercises at all during the week?

What factors are associated with whether someone exercises at all during the week? (Intercept)

What factors are associated with whether someone exercises at all during the week? allocation_groupGrupo B

What factors are associated with whether someone exercises at all during the week? visit2

What factors are associated with whether someone exercises at all during the week? visit3

What factors are associated with whether someone exercises at all during the week? allocation_groupGrupo B

What factors are associated with whether someone exercises at all during the week? allocation_groupGrupo B

What factors are associated with whether someone exercises at all during the week? ---

What factors are associated with whether someone exercises at all during the week? Signif. codes: 0 '***'

What factors are associated with whether someone exercises at all during the week?

What factors are associated with whether someone exercises at all during the week? Correlation of Fixed Eff

What factors are associated with whether someone exercises at all during the week? (Intr) all_

```
What factors are associated with whether someone exercises at all during the week? allctn_grGB -0.675
What factors are associated with whether someone exercises at all during the week? visit2      -0.331  0.30
What factors are associated with whether someone exercises at all during the week? visit3      -0.379  0.30
What factors are associated with whether someone exercises at all during the week? allctn_GB:2  0.282 -0.40
What factors are associated with whether someone exercises at all during the week? allctn_GB:3  0.284 -0.40

data_model_evs_active <- data_model_evs %>%
  filter(evs_score > 0)

model_part2 <- lmer(
  log(evs_score) ~ allocation_group * visit + (1 | record_id),
  data = data_model_evs_active
)
summary(model_part2)
```

3.18.3.1 Resultado

Para analisar o escore de atividade física semanal (`evs_score`), que representa o produto entre os dias por semana e os minutos por dia de exercício relatados por cada participante, foi adotado um modelo em dois estágios. Esta abordagem se mostrou mais adequada devido à presença de 33.9% de valores iguais a zero (pacientes inativos) e à distribuição assimétrica dos valores positivos (pacientes ativos).

No primeiro estágio, foi ajustado um modelo de regressão logística mista com intercepto aleatório por participante para estimar a probabilidade de o participante relatar qualquer atividade física (`evs_score > 0`). Observou-se que, independentemente do grupo, a chance de relatar exercício aumentou significativamente na visita 2 ($OR \approx 24$, $p = 0,002$) e, em menor grau, na visita 3 ($p = 0,046$) em comparação à visita 1. No entanto, não houve efeito significativo do grupo de intervenção (Grupo B) nem interações significativas entre grupo e visita, indicando que o aumento da atividade física ao longo do tempo pode estar relacionado a outros fatores (por exemplo, efeito de acompanhamento ou motivação decorrente da participação no estudo).

No segundo estágio, foi ajustado um modelo linear misto com intercepto aleatório por participante, incluindo apenas os participantes que relataram `evs_score > 0`, utilizando a transformação logarítmica dos minutos semanais de exercício como variável dependente. Neste modelo, nenhuma diferença significativa foi observada entre os grupos ou ao longo do tempo em relação à quantidade de exercício realizada entre os participantes ativos. Ou seja, embora mais participantes tenham relatado

prática de atividade física nas visitas seguintes, a duração total semanal entre aqueles que se exercitavam permaneceu estável.

Esses resultados sugerem que o efeito observado ao longo do tempo se concentrou em uma maior adesão à prática de atividade física, mas não em um aumento da quantidade entre os que já praticavam.

4 Variáveis coletadas na primeira e terceira visitas

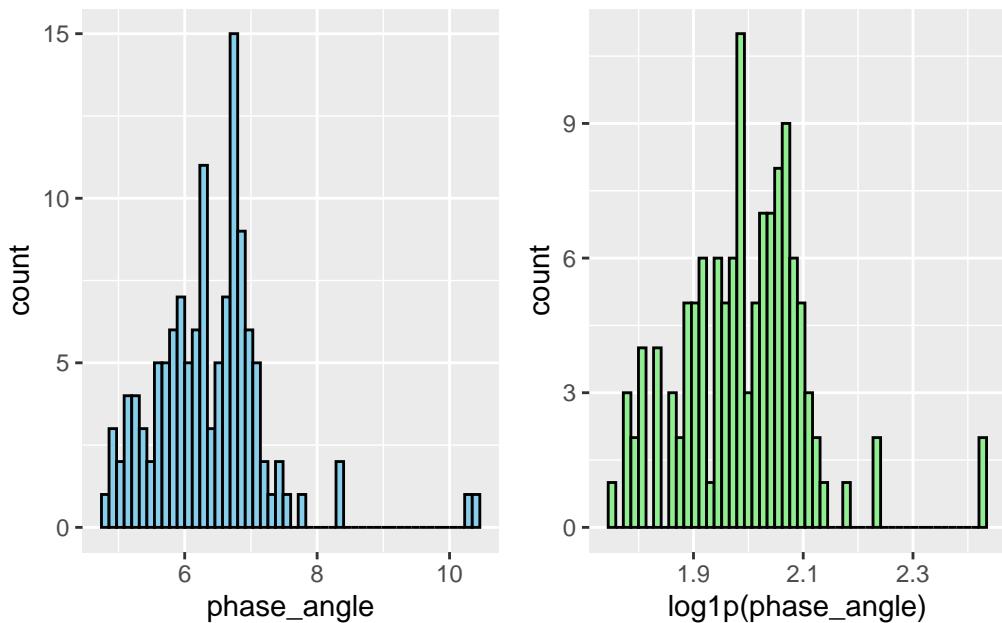
4.1 Ângulo de Fase

Variável: phase_angle

```
# Plot 1: Raw data
phase_angle_hist_1 <- data_model_V1V3 %>%
  filter(
    phase_angle < 300
  ) %>%
  ggplot(aes(x = phase_angle)) +
  geom_histogram(bins = 50, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
phase_angle_hist_2 <- data_model_V1V3 %>%
  filter(
    phase_angle < 300
  ) %>%
  ggplot(aes(x = log1p(phase_angle))) +
  geom_histogram(bins = 50, fill = "lightgreen", color = "black")

# Combine side by side
phase_angle_hist_1 + phase_angle_hist_2 # library(patchwork)
```



```
# LMM
phase_angle_model <- lmer(log1p(phase_angle) ~ allocation_group * visit +
(1 | record_id), data = data_model_V1V3)
check_collinearity(phase_angle_model)

# Check for Multicollinearity
```

Low Correlation

Term	VIF	VIF 95% CI	Increased SE	Tolerance
allocation_group	1.07	[1.01, 1.97]	1.04	0.93
visit	1.86	[1.51, 2.46]	1.37	0.54
allocation_group:visit	1.93	[1.55, 2.54]	1.39	0.52

Tolerance 95% CI

[0.51, 0.99]

[0.41, 0.66]

[0.39, 0.64]

```
# Sensitivity analysis
phase_angle_model_check <- sensitivity_check_lmer(
  model = phase_angle_model,
  id_var = "record_id",
  top_n = 5)
```

```

# LMM Sensitivity
phase_angle_model_sens <- update(object = phase_angle_model,
                                    subset = !(record_id %in%
                                                phase_angle_model_check$influential_ids))
# Influential IDS
phase_angle_model_check$influential_ids

```

[1] "38" "46" "50" "74" "58"

4.1.1 Resumo dos modelos

```

# Model comparison
summary(phase_angle_model)

Linear mixed model fit by REML. t-tests use Satterthwaite's method [
lmerModLmerTest]

Formula: log1p(phase_angle) ~ allocation_group * visit + (1 | record_id)
Data: data_model_V1V3

```

REML criterion at convergence: -221.5

Scaled residuals:

Min	1Q	Median	3Q	Max
-2.3340	-0.3586	0.0353	0.3389	3.5151

Random effects:

Groups	Name	Variance	Std.Dev.
record_id	(Intercept)	0.010030	0.10015
Residual		0.002521	0.05021

Number of obs: 125, groups: record_id, 75

Fixed effects:

	Estimate	Std. Error	df	t value	Pr(> t)
(Intercept)	2.021165	0.018418	82.634225	109.738	<2e-16
allocation_group	-0.045637	0.025875	82.634225	-1.764	0.0815
visit3	-0.011701	0.013479	49.678850	-0.868	0.3895
allocation_group:visit3	0.007182	0.019804	50.362921	0.363	0.7184

```

(Intercept) ***  

allocation_groupGrupo B .  

visit3  

allocation_groupGrupo B:visit3  

---  

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```

Correlation of Fixed Effects:

```

(Intr) all_GB visit3  

allctn_grGB -0.712  

visit3      -0.274  0.195  

allctn_GB:3  0.187 -0.262 -0.681

```

```
summary(phase_angle_model_sens)
```

```

Linear mixed model fit by REML. t-tests use Satterthwaite's method [  

lmerModLmerTest]  

Formula: log1p(phase_angle) ~ allocation_group * visit + (1 | record_id)  

Data: data_model_V1V3  

Subset: !(record_id %in% phase_angle_model_check$influential_ids)

```

REML criterion at convergence: -274.5

Scaled residuals:

Min	1Q	Median	3Q	Max
-1.89890	-0.42265	0.07545	0.42996	1.44461

Random effects:

Groups	Name	Variance	Std.Dev.
record_id	(Intercept)	0.006874	0.08291
Residual		0.001001	0.03163

Number of obs: 116, groups: record_id, 70

Fixed effects:

	Estimate	Std. Error	df	t value	Pr(> t)
(Intercept)	2.008697	0.015448	74.173320	130.033	<2e-16
allocation_groupGrupo B	-0.045312	0.021248	74.173320	-2.133	0.0363

```

visit3                  -0.018047   0.009238 46.006589 -1.954   0.0569
allocation_groupGrupo B:visit3  0.017523   0.013049 46.227426  1.343   0.1859

(Intercept)          ***
allocation_groupGrupo B      *
visit3                 .
allocation_groupGrupo B:visit3

---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```

Correlation of Fixed Effects:

```

(Intr) all_GB visit3
allctn_grGB -0.727
visit3     -0.212  0.154
allctn_GB:3  0.150 -0.207 -0.708

```

```

performance::compare_performance(
  phase_angle_model,
  phase_angle_model_sens)

```

When comparing models, please note that probably not all models were fit from same data.

Comparison of Model Performance Indices

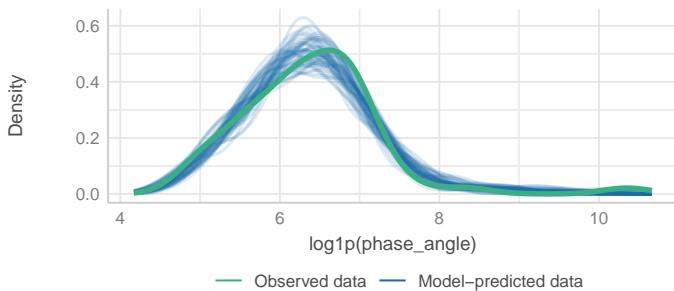
Name		Model	AIC (weights)	AICc (weights)
phase_angle_model	lmerModLmerTest	262.3 (<.001)	263.0 (<.001)	
phase_angle_model_sens	lmerModLmerTest	168.0 (>.999)	168.8 (>.999)	

Name		BIC (weights)	R2 (cond.)	R2 (marg.)	ICC
phase_angle_model	279.3 (<.001)	0.806	0.036	0.799	
phase_angle_model_sens	184.5 (>.999)	0.879	0.049	0.873	

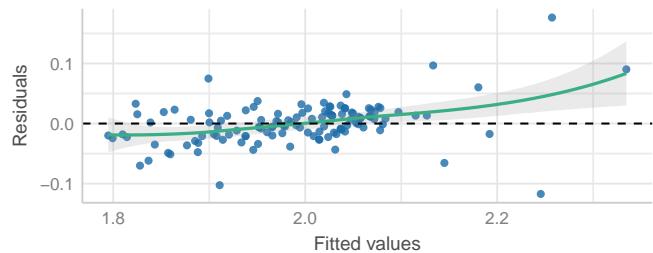
Name		RMSE	Sigma
phase_angle_model	0.034	0.050	
phase_angle_model_sens	0.021	0.032	

```
performance::check_model(phase_angle_model)
```

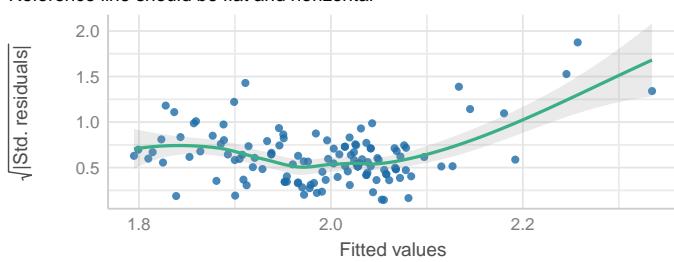
Posterior Predictive Check
Model-predicted lines should resemble observed data line



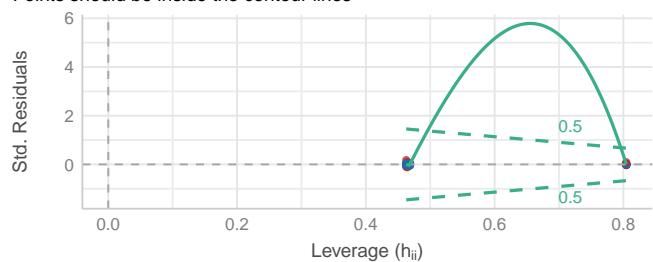
Linearity
Reference line should be flat and horizontal



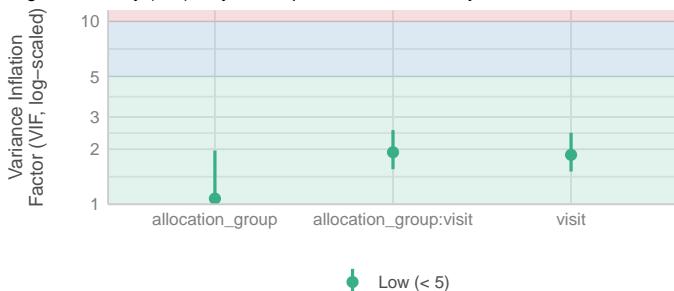
Homogeneity of Variance
Reference line should be flat and horizontal



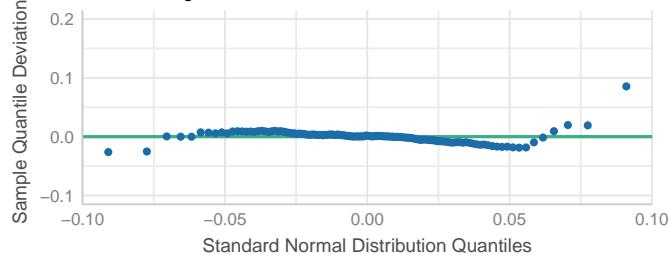
Influential Observations
Points should be inside the contour lines



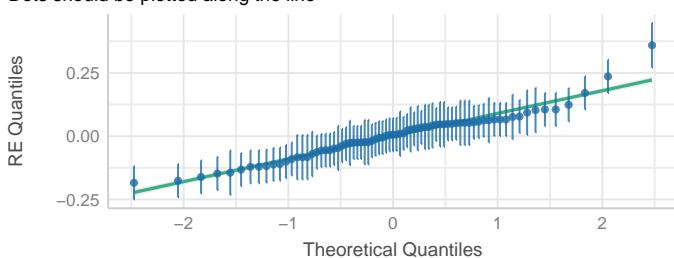
Collinearity
High collinearity (VIF) may inflate parameter uncertainty



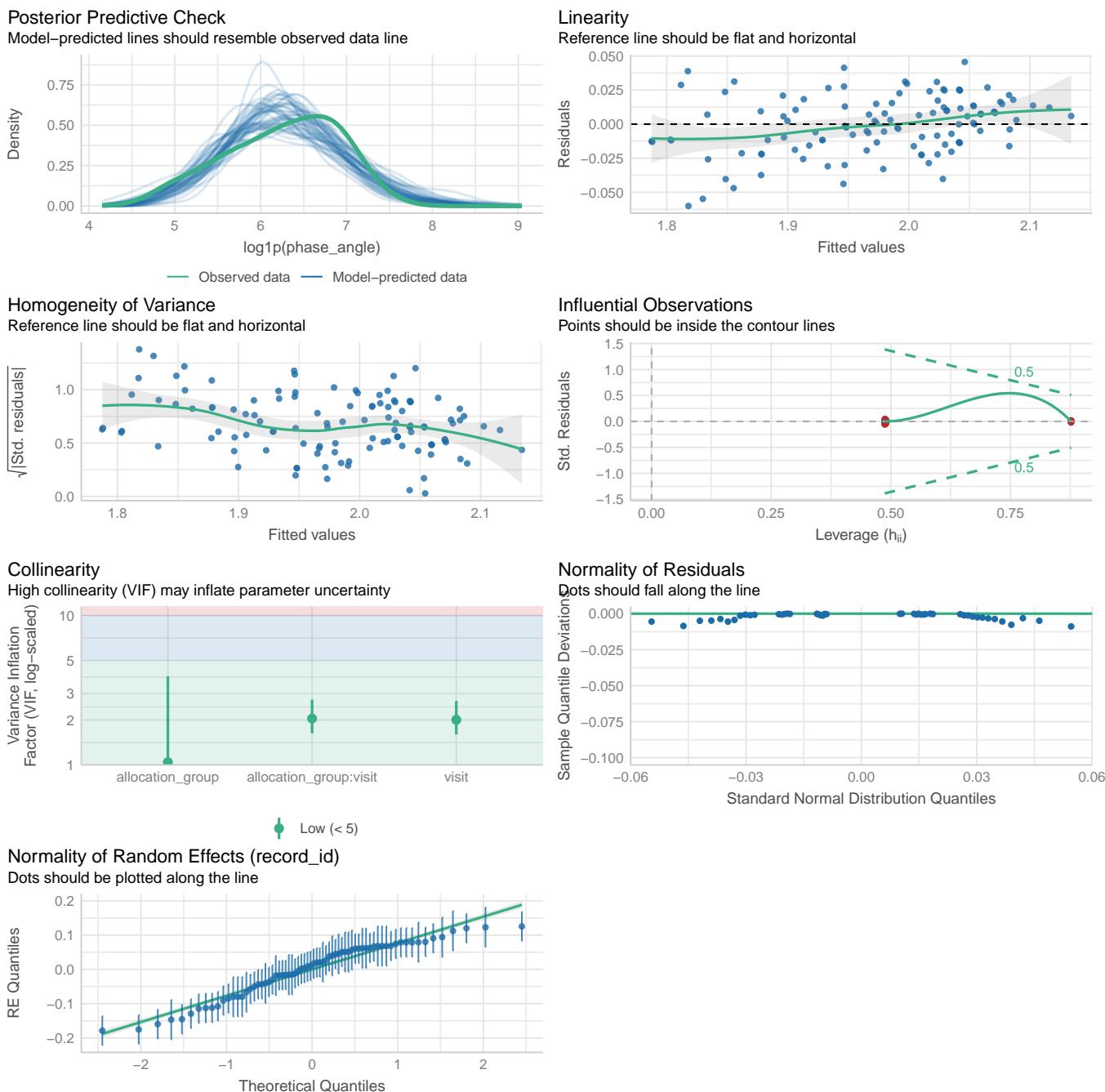
Normality of Residuals
Dots should fall along the line



Normality of Random Effects (record_id)
Dots should be plotted along the line



```
performance::check_model(phase_angle_model_sens)
```



4.1.2 Médias Marginais Estimadas

4.1.2.1 Todos os dados

```
# Get EMMs for each group at each visit
phase_angle_raw_emm <- emmeans::emmeans(
  phase_angle_model,
  ~ allocation_group * visit
```

```

)

phase_angle_raw_emm <- regrid(phase_angle_raw_emm)

# Table of marginal means
# phase_angle_raw_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(phase_angle_raw_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

visit = 1:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B     0.337 0.191 83.6   -0.0432     0.717    1.762  0.0817

visit = 3:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B     0.281 0.206 99.1   -0.1277     0.691    1.365  0.1754

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95

# Pairwise comparisons: Changes over time within each group
emmeans::contrast(phase_angle_raw_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

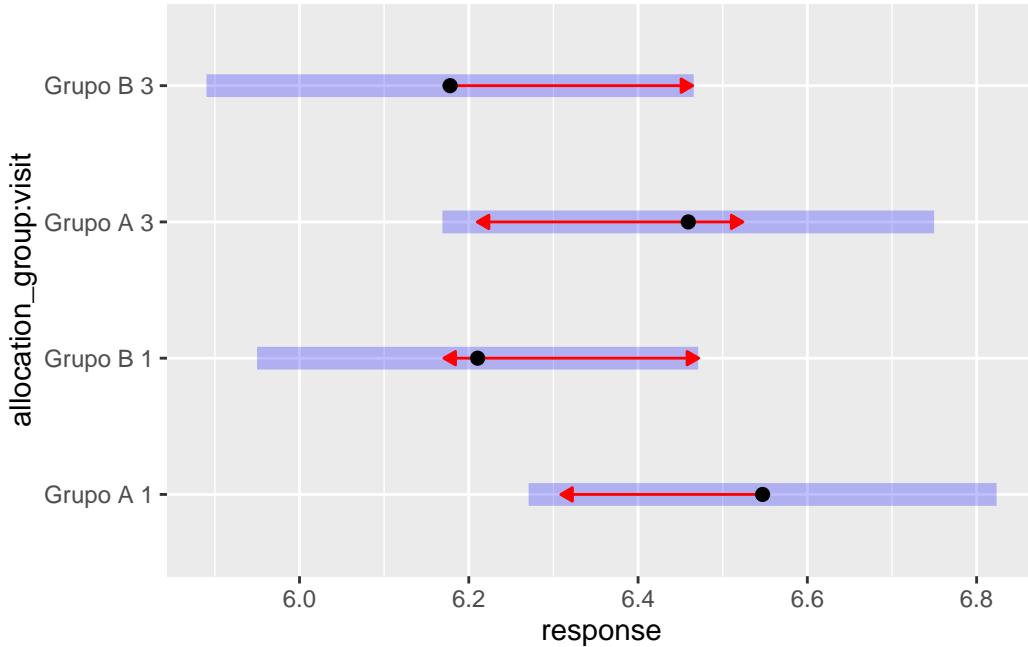
allocation_group = Grupo A:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
 visit1 - visit3   0.0878 0.101 83.6   -0.113     0.289    0.868  0.3880

allocation_group = Grupo B:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
 visit1 - visit3   0.0325 0.105 83.6   -0.175     0.240    0.311  0.7566

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95

```

```
# Plot of marginal means
plot(phase_angle_raw_emm, comparisons = TRUE)
```



4.1.2.2 Análise de sensibilidade

```
# Get EMMs for each group at each visit (Sensitivity Analysis)
phase_angle_emm <- emmeans::emmeans(
  phase_angle_model_sens,
  ~ allocation_group * visit
)

phase_angle_emm <- regrid(phase_angle_emm)

# Table of marginal means
# phase_angle_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(phase_angle_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

visit = 1:
  contrast      estimate      SE   df lower.CL upper.CL t.ratio p.value

```

```
Grupo A - Grupo B      0.330 0.155 73.9    0.0211     0.639    2.129   0.0366
```

```
visit = 3:
```

contrast	estimate	SE	df	lower.CL	upper.CL	t.ratio	p.value
Grupo A - Grupo B	0.201	0.163	86.3	-0.1229	0.524	1.233	0.2210

Degrees-of-freedom method: inherited from kenward-roger when re-gridding

Confidence level used: 0.95

```
# Pairwise comparisons: Changes over time within each group  
emmeans::contrast(phase_angle_emm,  
method = "pairwise", by = "allocation_group",  
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
allocation_group = Grupo A:
```

contrast	estimate	SE	df	lower.CL	upper.CL	t.ratio	p.value
visit1 - visit3	0.13331	0.0682	73.9	-0.00255	0.269	1.955	0.0543

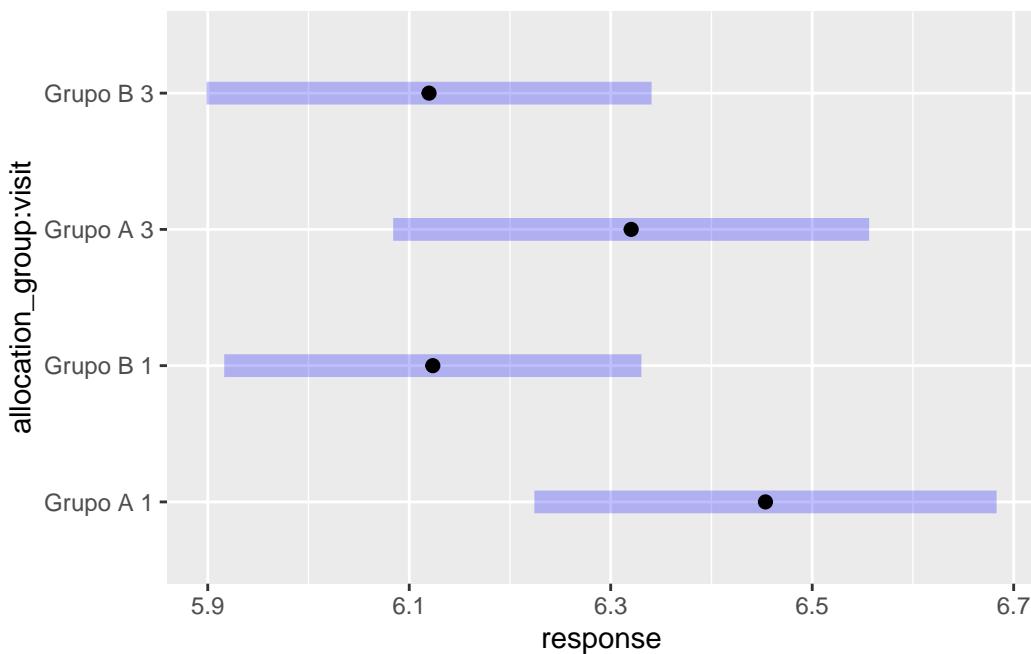
```
allocation_group = Grupo B:
```

contrast	estimate	SE	df	lower.CL	upper.CL	t.ratio	p.value
visit1 - visit3	0.00373	0.0657	73.9	-0.12725	0.135	0.057	0.9549

Degrees-of-freedom method: inherited from kenward-roger when re-gridding

Confidence level used: 0.95

```
# Plot of marginal means  
plot(phase_angle_emm)
```



4.1.3 Resultado

No modelo ajustado para o desfecho primário do estudo, o ângulo de fase, observou-se uma tendência à diferença entre os grupos na visita 1 (estimativa = 0,34; IC 95% [-0,04 ; 0,72]), embora sem significância estatística. Na visita 3, as médias estimadas também foram semelhantes entre os grupos (estimativa = 0,28; IC 95% [-0,13 ; 0,69]). Dentro de cada grupo, não foram detectadas mudanças significativas ao longo do tempo.

A análise de sensibilidade, com exclusão de observações influentes, revelou um aumento da magnitude do efeito entre os grupos na visita 1, com significância estatística (estimativa = 0,33; IC 95% [0,02 ; 0,64]), sugerindo que o grupo placebo apresentou valores de ângulo de fase ligeiramente superiores no início do estudo. As demais comparações permaneceram não significativas, e as estimativas dentro dos grupos ao longo do tempo se mantiveram estáveis.

As estimativas, intervalos de confiança de 95% e valores de p estão apresentados na Tabela 25 e Tabela 26

Tabela 25: Diferenças estimadas do ângulo de fase entre os grupos de alocação (placebo vs Eclipta) e entre visitas dentro de cada grupo (todos os dados)

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 1	0,34	[-0,04 ; 0,72]	0,082
Entre grupos	Visita 3	0,28	[-0,13 ; 0,69]	0,175
Grupo Placebo	Visita 1 - Visita 3	0,09	[-0,11 ; 0,29]	0,388
Grupo Eclipta	Visita 1 - Visita 3	0,03	[-0,18 ; 0,24]	0,757

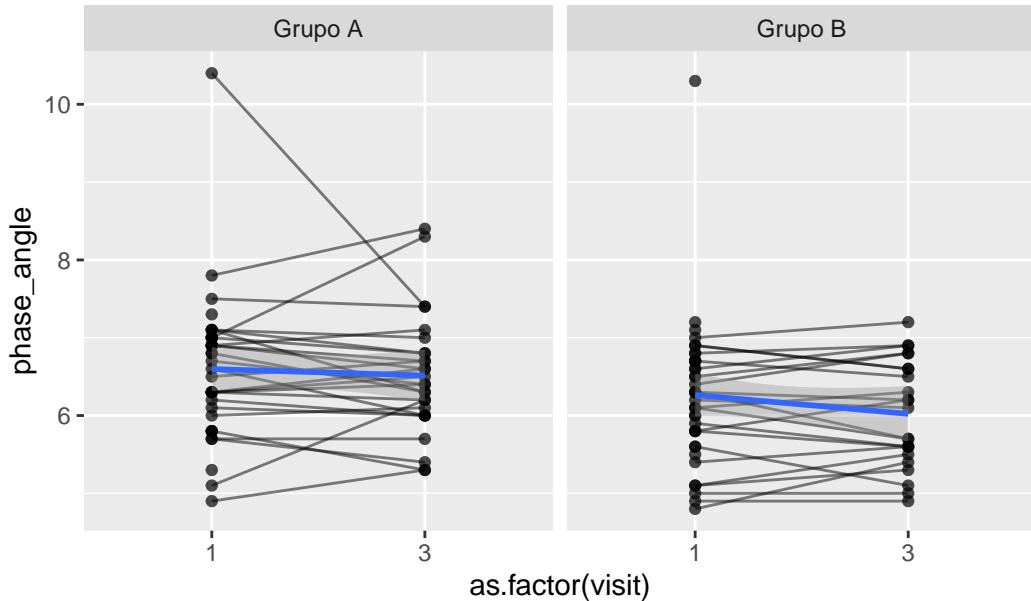
Tabela 26: Diferenças estimadas do ângulo de fase entre os grupos de alocação (placebo vs Eclipta) e entre visitas dentro de cada grupo (Análise de sensibilidade)

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 1	0,33	[0,02 ; 0,64]	0,037
Entre grupos	Visita 3	0,20	[-0,12 ; 0,52]	0,221
Grupo Placebo	Visita 1 - Visita 3	0,13	[-0,00 ; 0,27]	0,054
Grupo Eclipta	Visita 1 - Visita 3	0,00	[-0,13 ; 0,14]	0,955

```
ggplot(
  data = data_model_V1V3,
  aes(
    x = as.factor(visit),
    y = phase_angle,
    group = record_id,
  )
) +
  geom_line(alpha = 0.5) +
  geom_point(alpha = 0.7) +
  geom_smooth(
    aes(group = allocation_group),
    method = "lm",
    se = TRUE,
    linewidth = 1
) +
  labs(title = "All data") +
  facet_wrap(~ allocation_group)
```

```
`geom_smooth()` using formula = 'y ~ x'
Warning: Removed 3 rows containing non-finite outside the scale range
(`stat_smooth()`).
Warning: Removed 3 rows containing missing values or values outside the scale range
(`geom_line()`).
Warning: Removed 3 rows containing missing values or values outside the scale range
(`geom_point()`).
```

All data



```

data_model_V1V3 %>%
  filter(
    !(record_id %in%
      phase_angle_model_check$influential_ids)
  ) %>%
  ggplot(
    aes(
      x = as.factor(visit),
      y = phase_angle,
      group = record_id,
    )
  ) +
  geom_line(alpha = 0.5) +
  geom_point(alpha = 0.7) +
  geom_smooth(
    aes(group = allocation_group),
    method = "lm",
    se = TRUE,
    linewidth = 1
  ) +
  labs(title = "Sensitivity analysis") +

```

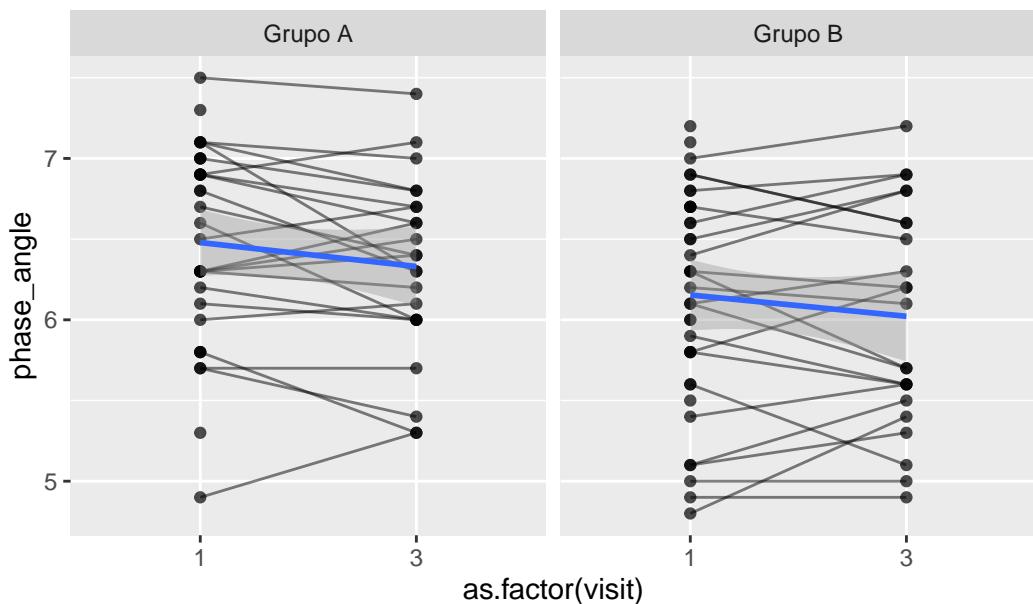
```

facet_wrap(~ allocation_group)

`geom_smooth()` using formula = 'y ~ x'
Warning: Removed 2 rows containing non-finite outside the scale range
(`stat_smooth()`).
Warning: Removed 2 rows containing missing values or values outside the scale range
(`geom_line()`).
Warning: Removed 2 rows containing missing values or values outside the scale range
(`geom_point()`).

```

Sensitivity analysis



4.2 Reatância

Variável: reactance

```

# Plot 1: Raw data
reactance_hist_1 <- data_model_V1V3 %>%
  #filter(
  #  reactance < 300
  #) %>%
  ggplot(aes(x = reactance)) +
  geom_histogram(bins = 50, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
reactance_hist_2 <- data_model_V1V3 %>%

```

```

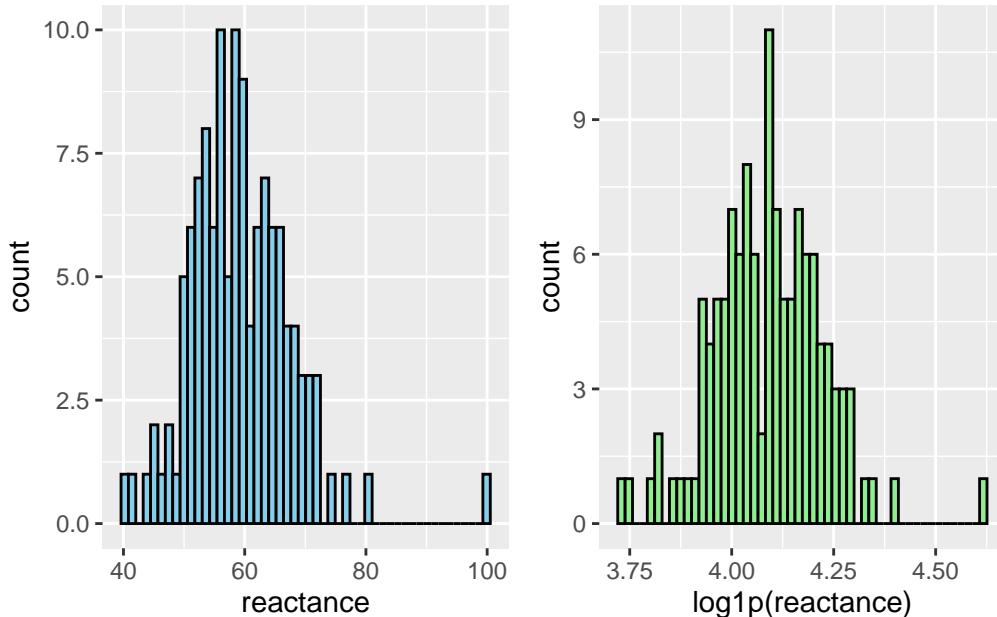
#filter(
  #   reactance < 300
  #) %>%
  ggplot(aes(x = log1p(reactance))) +
  geom_histogram(bins = 50, fill = "lightgreen", color = "black")

# Combine side by side
reactance_hist_1 + reactance_hist_2 # library(patchwork)

```

Warning: Removed 3 rows containing non-finite outside the scale range (`stat_bin()`).

Removed 3 rows containing non-finite outside the scale range (`stat_bin()`).



```

# LMM
reactance_model <- lmer(log1p(reactance) ~ allocation_group * visit +
(1 | record_id), data = data_model_V1V3)
check_collinearity(reactance_model)

# Check for Multicollinearity

```

Low Correlation

Term	VIF	VIF 95% CI	Increased SE	Tolerance
allocation_group	1.12	[1.02, 1.68]	1.06	0.90
visit	1.87	[1.52, 2.47]	1.37	0.53

```

allocation_group:visit 1.97 [1.58, 2.60]           1.40      0.51
Tolerance 95% CI
[0.60, 0.98]
[0.41, 0.66]
[0.38, 0.63]

# Sensitivity analysis
reactance_model_check <- sensitivity_check_lmer(
  model = reactance_model,
  id_var = "record_id",
  top_n = 5)

# LMM Sensitivity
reactance_model_sens <- update(object = reactance_model,
                                 subset = !(record_id %in%
                                             reactance_model_check$influential_ids))

# Influential IDS
reactance_model_check$influential_ids
[1] "22" "50" "74" "1"   "31"

```

4.2.1 Resumo dos modelos

```

# Model comparison
summary(reactance_model)

Linear mixed model fit by REML. t-tests use Satterthwaite's method [
lmerModLmerTest]

Formula: log1p(reactance) ~ allocation_group * visit + (1 | record_id)
Data: data_model_V1V3

REML criterion at convergence: -154.5

```

Scaled residuals:

Min	1Q	Median	3Q	Max
-2.01721	-0.46574	0.01052	0.54712	2.07167

Random effects:

Groups	Name	Variance	Std.Dev.
--------	------	----------	----------

```
record_id (Intercept) 0.013481 0.11611  
Residual 0.005657 0.07522  
Number of obs: 125, groups: record_id, 75
```

Fixed effects:

	Estimate	Std. Error	df	t value	Pr(> t)
(Intercept)	4.10499	0.02274	86.69858	180.493	<2e-16
allocation_groupGrupo B	-0.01206	0.03195	86.69858	-0.377	0.707
visit3	-0.01119	0.02006	49.12966	-0.558	0.579
allocation_groupGrupo B:visit3	0.01600	0.02942	50.14982	0.544	0.589

```
(Intercept) ***  
allocation_groupGrupo B  
visit3  
allocation_groupGrupo B:visit3  
---  
Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

Correlation of Fixed Effects:

```
(Intr) all_GB visit3  
allctn_grGB -0.712  
visit3 -0.335 0.239  
allctn_GB:3 0.229 -0.321 -0.682
```

```
summary(reactance_model_sens)
```

```
Linear mixed model fit by REML. t-tests use Satterthwaite's method [  
lmerModLmerTest]  
Formula: log1p(reactance) ~ allocation_group * visit + (1 | record_id)  
Data: data_model_V1V3  
Subset: !(record_id %in% reactance_model_check$influential_ids)
```

REML criterion at convergence: -179.8

Scaled residuals:

Min	1Q	Median	3Q	Max
-1.59721	-0.57888	0.01363	0.51723	1.65081

Random effects:

Groups	Name	Variance	Std.Dev.
record_id	(Intercept)	0.008423	0.09177
Residual		0.004527	0.06728

Number of obs: 116, groups: record_id, 70

Fixed effects:

	Estimate	Std. Error	df	t value	Pr(> t)
(Intercept)	4.12073	0.01924	85.06056	214.231	<2e-16
allocation_groupGrup0 B	-0.02913	0.02720	85.06056	-1.071	0.287
visit3	-0.01607	0.01855	47.78854	-0.866	0.391
allocation_groupGrup0 B:visit3	0.02453	0.02730	48.84683	0.899	0.373

(Intercept) ***

allocation_groupGrup0 B

visit3

allocation_groupGrup0 B:visit3

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

(Intr) all_GB visit3
allctn_grGB -0.707
visit3 -0.363 0.256
allctn_GB:3 0.246 -0.348 -0.680

```
performance::compare_performance(  
  reactance_model,  
  reactance_model_sens)
```

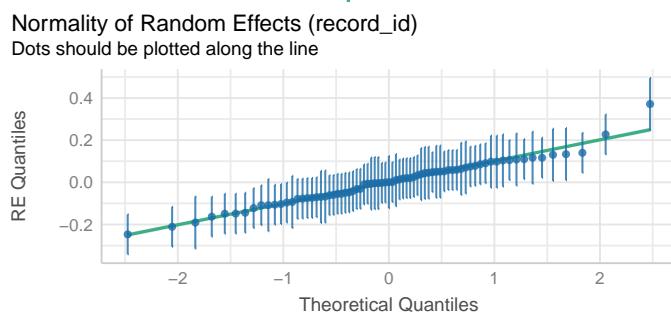
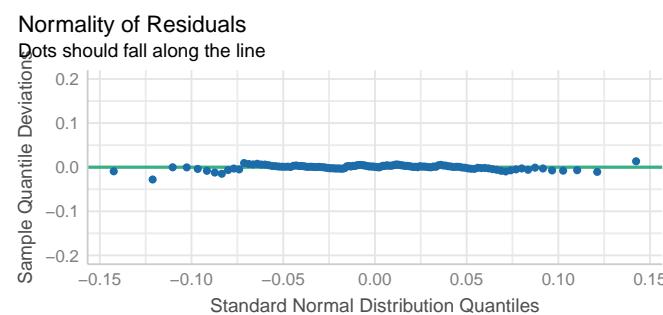
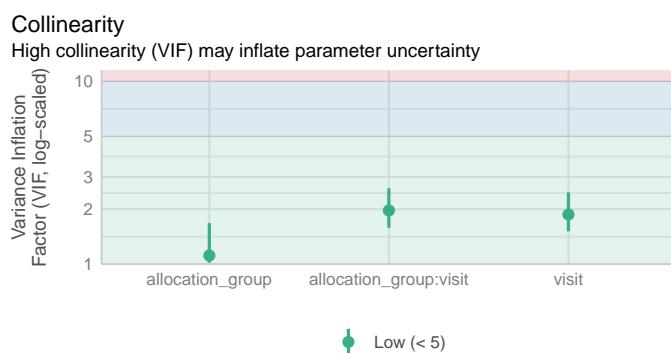
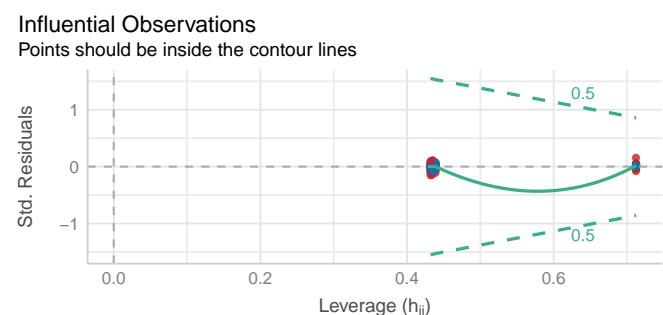
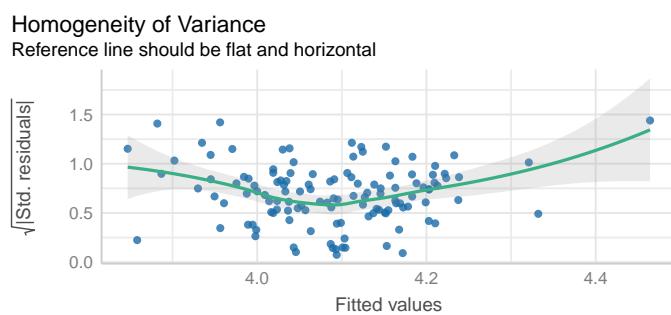
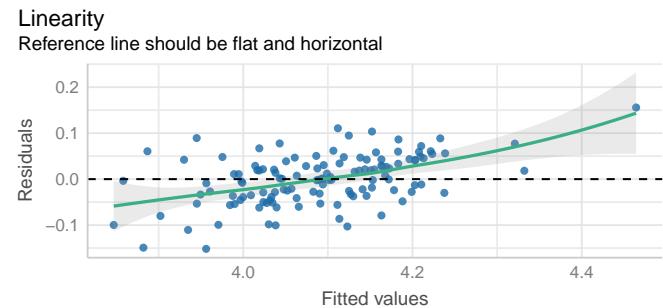
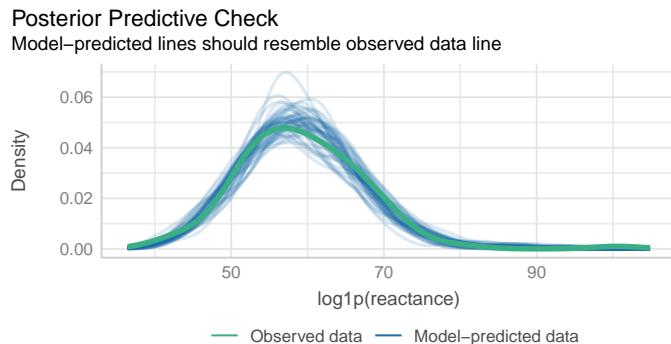
When comparing models, please note that probably not all models were fit
from same data.

Comparison of Model Performance Indices

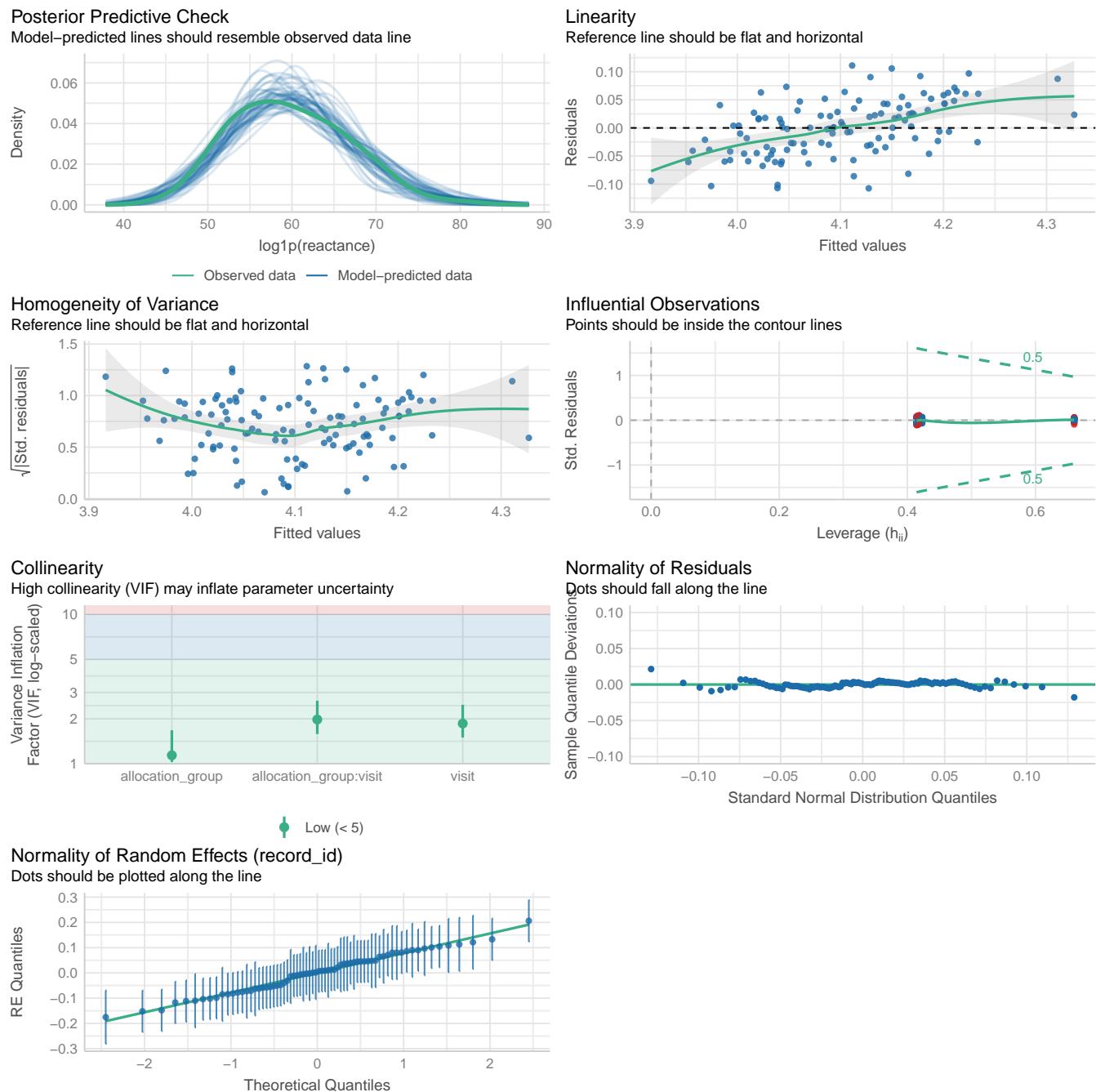
Name		Model	AIC (weights)	AICc (weights)
reactance_model	lmerModLmerTest	856.3 (<.001)	857.0 (<.001)	
reactance_model_sens	lmerModLmerTest	758.9 (>.999)	759.7 (>.999)	

Name	BIC (weights)	R2 (cond.)	R2 (marg.)	ICC	RMSE	Sigma
reactance_model	873.3 (<.001)	0.705	0.001	0.704	0.054	0.075
reactance_model_sens	775.5 (>.999)	0.654	0.010	0.650	0.049	0.067

```
performance::check_model(reactance_model)
```



```
performance::check_model(reactance_model_sens)
```



4.2.2 Médias Marginais Estimadas

4.2.2.1 Todos os dados

```
# Get EMMs for each group at each visit
reactance_raw_emm <- emmeans::emmeans(
  reactance_model,
```

```

~ allocation_group * visit
)

reactance_raw_emm <- regrid(reactance_raw_emm)

# Table of marginal means
# reactance_raw_emm

# Pairwise comparisons: Between groups at each visit
emmmeans::contrast(reactance_raw_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

visit = 1:
  contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    0.727 1.93  89.2     -3.10     4.55   0.377  0.7068

visit = 3:
  contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B   -0.237 2.16 107.1     -4.51     4.04  -0.110  0.9128

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95

# Pairwise comparisons: Changes over time within each group
emmmeans::contrast(reactance_raw_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

allocation_group = Grupo A:
  contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
 visit1 - visit3    0.675 1.21  89.2     -1.73     3.08   0.558  0.5785

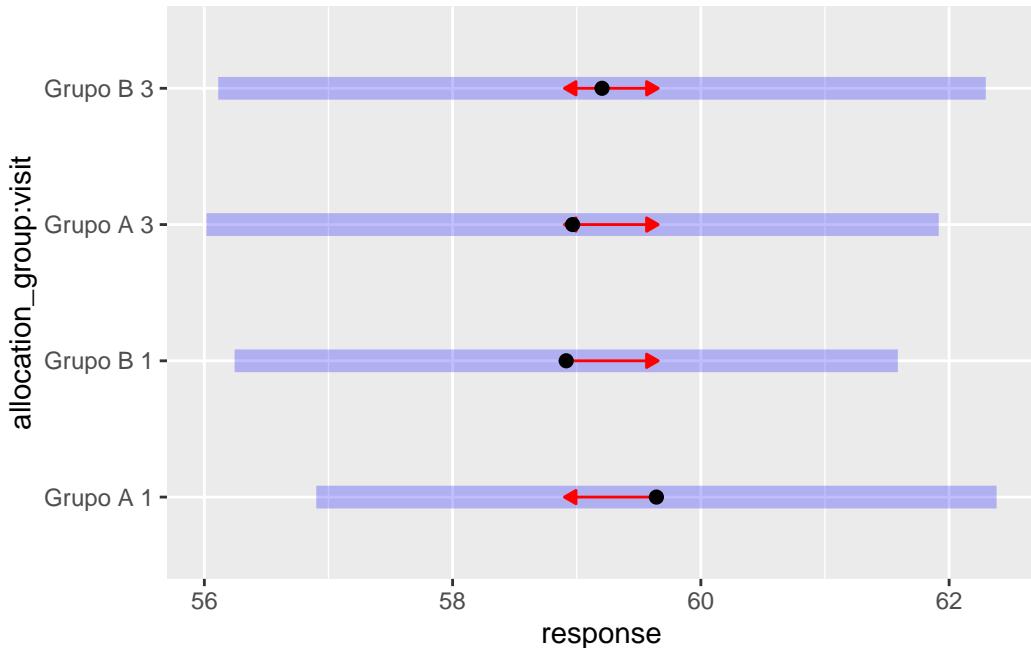
allocation_group = Grupo B:
  contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
 visit1 - visit3   -0.288 1.30  89.2     -2.87     2.29  -0.222  0.8247

Degrees-of-freedom method: inherited from kenward-roger when re-gridding

```

Confidence level used: 0.95

```
# Plot of marginal means  
plot(reactance_raw_emm, comparisons = TRUE)
```



4.2.2.2 Análise de sensibilidade

```
# Get EMMs for each group at each visit (Sensitivity Analysis)  
reactance_emm <- emmeans::emmeans(  
  reactance_model_sens,  
  ~ allocation_group * visit  
)  
  
reactance_emm <- regrid(reactance_emm)  
  
# Table of marginal means  
# reactance_emm  
  
# Pairwise comparisons: Between groups at each visit  
emmeans::contrast(reactance_emm,  
  method = "pairwise", by = "visit",  
  adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))  
  
visit = 1:
```

```
contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
Grupo A - Grupo B    1.769 1.65  85.8    -1.52     5.05   1.071  0.2874
```

```
visit = 3:
```

```
contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
Grupo A - Grupo B    0.278 1.89 103.4    -3.46     4.02   0.147  0.8830
```

Degrees-of-freedom method: inherited from kenward-roger when re-gridding

Confidence level used: 0.95

```
# Pairwise comparisons: Changes over time within each group
```

```
emmeans::contrast(reactance_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
allocation_group = Grupo A:
```

```
contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit3    0.982 1.13  85.8    -1.27     3.24   0.865  0.3892
```

```
allocation_group = Grupo B:
```

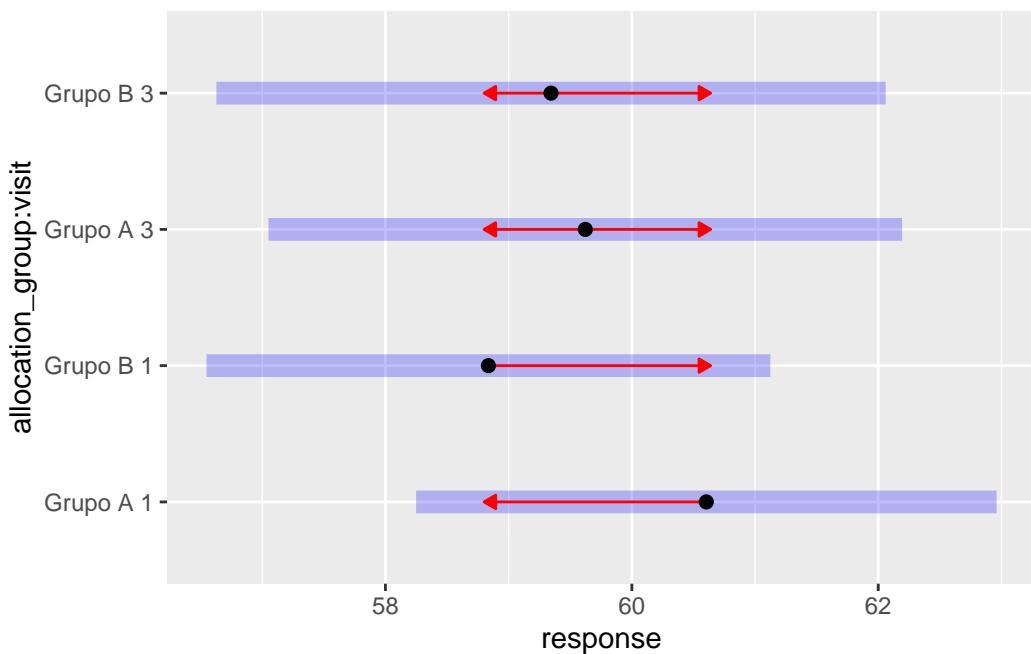
```
contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit3   -0.508 1.21  85.8    -2.91     1.90  -0.420  0.6756
```

Degrees-of-freedom method: inherited from kenward-roger when re-gridding

Confidence level used: 0.95

```
# Plot of marginal means
```

```
plot(reactance_emm, comparisons = TRUE)
```



4.2.3 Resultado

No modelo ajustado para os valores de reatância, não foram observadas diferenças estatisticamente significativas entre os grupos em nenhum dos momentos avaliados. As estimativas de diferença entre os grupos na visita 1 (estimativa = 0,73; IC 95% [-3,10 ; 4,55]) e na visita 3 (estimativa = -0,24; IC 95% [-4,51 ; 4,04]) apresentaram ampla sobreposição dos intervalos de confiança com zero. Da mesma forma, não foram identificadas mudanças significativas ao longo do tempo dentro de cada grupo.

A análise de sensibilidade não alterou substancialmente os resultados. Embora tenha havido um leve aumento da estimativa de diferença entre os grupos na visita 1 (estimativa = 1,77; IC 95% [-1,52 ; 5,05]), essa diferença continuou não significativa. As demais comparações permaneceram estáveis, sem alterações relevantes nas conclusões.

As estimativas, intervalos de confiança de 95% e valores de p estão apresentados na Tabela 27.

Tabela 27: Diferenças estimadas da reatância entre os grupos de alocação (placebo vs Eclipta) e entre visitas dentro de cada grupo

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 1	0,73	[-3,10 ; 4,55]	0,707
Entre grupos	Visita 3	-0,24	[-4,51 ; 4,04]	0,913
Grupo Placebo	Visita 1 - Visita 3	0,68	[-1,73 ; 3,08]	0,579
Grupo Eclipta	Visita 1 - Visita 3	-0,29	[-2,87 ; 2,29]	0,825

```
ggplot(
  data = data_model_V1V3,
  aes(
    # your code here
  )
)
```

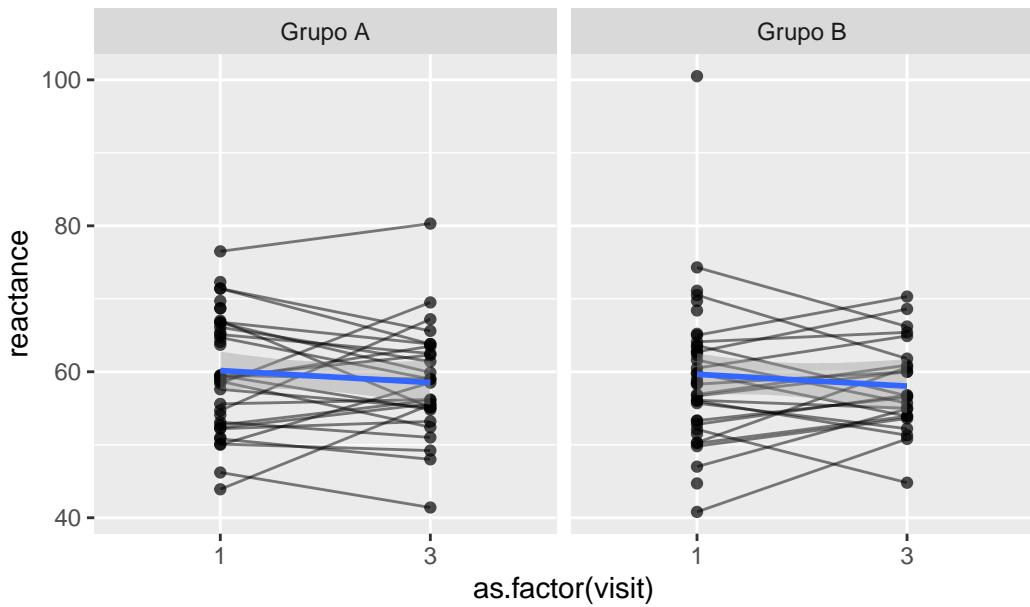
```

x = as.factor(visit),
y = reactance,
group = record_id,
)
) +
geom_line(alpha = 0.5) +
geom_point(alpha = 0.7) +
geom_smooth(
  aes(group = allocation_group),
  method = "lm",
  se = TRUE,
  linewidth = 1
) +
labs(title = "All data") +
facet_wrap(~ allocation_group)

`geom_smooth()` using formula = 'y ~ x'
Warning: Removed 3 rows containing non-finite outside the scale range
(`stat_smooth()`).
Warning: Removed 3 rows containing missing values or values outside the scale range
(`geom_line()`).
Warning: Removed 3 rows containing missing values or values outside the scale range
(`geom_point()`).

```

All data



```
data_model_V1V3 %>%
  filter(
    !(record_id %in%
      reactance_model_check$influential_ids)
  ) %>%
  ggplot(
    aes(
      x = as.factor(visit),
      y = reactance,
      group = record_id,
    )
  ) +
  geom_line(alpha = 0.5) +
  geom_point(alpha = 0.7) +
  geom_smooth(
    aes(group = allocation_group),
    method = "lm",
    se = TRUE,
    linewidth = 1
  ) +
  labs(title = "Sensitivity analysis") +
```

```

facet_wrap(~ allocation_group)

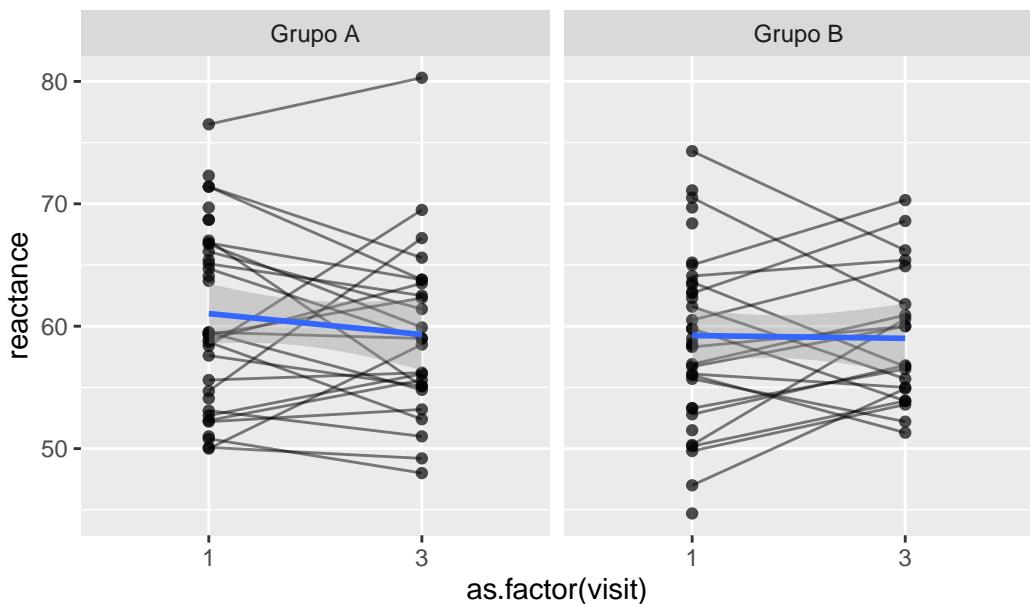
`geom_smooth()` using formula = 'y ~ x'
Warning: Removed 2 rows containing non-finite outside the scale range
(`stat_smooth()`).

Warning: Removed 2 rows containing missing values or values outside the scale range
(`geom_line()`).

Warning: Removed 2 rows containing missing values or values outside the scale range
(`geom_point()`).

```

Sensitivity analysis



4.3 Resistência

Variável: resistance

```

# Plot 1: Raw data
resistance_hist_1 <- data_model_V1V3 %>%
  #filter(
  #  resistance < 300
  #) %>%
  ggplot(aes(x = resistance)) +
  geom_histogram(bins = 50, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
resistance_hist_2 <- data_model_V1V3 %>%

```

```

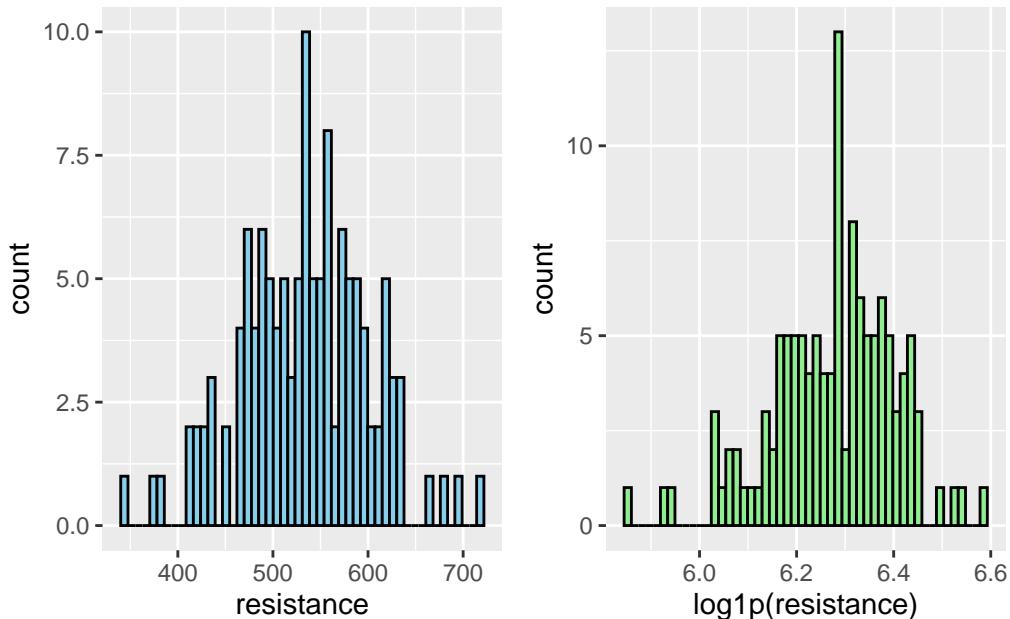
#filter(
  #  resistance < 300
  #) %>%
  ggplot(aes(x = log1p(resistance))) +
  geom_histogram(bins = 50, fill = "lightgreen", color = "black")

# Combine side by side
resistance_hist_1 + resistance_hist_2 # library(patchwork)

```

Warning: Removed 3 rows containing non-finite outside the scale range (`stat_bin()`).

Removed 3 rows containing non-finite outside the scale range (`stat_bin()`).



```

# LMM

resistance_model <- lmer(resistance ~ allocation_group * visit +
(1 | record_id), data = data_model_V1V3)
check_collinearity(resistance_model)

# Check for Multicollinearity

```

Low Correlation

	Term	VIF	VIF 95% CI	Increased SE	Tolerance
	allocation_group	1.09	[1.01, 1.82]	1.04	0.92
	visit	1.87	[1.51, 2.46]	1.37	0.54

```

allocation_group:visit 1.94 [1.56, 2.56]           1.39      0.52
Tolerance 95% CI
[0.55, 0.99]
[0.41, 0.66]
[0.39, 0.64]

# Sensitivity analysis
resistance_model_check <- sensitivity_check_lmer(
  model = resistance_model,
  id_var = "record_id",
  top_n = 5)

# LMM Sensitivity
resistance_model_sens <- update(object = resistance_model,
                                   subset = !(record_id %in%
                                   resistance_model_check$influential_ids))

# Influential IDS
resistance_model_check$influential_ids
[1] "1"  "34" "46" "64" "4"

```

4.3.1 Resumo dos modelos

```

# Model comparison
summary(resistance_model)

Linear mixed model fit by REML. t-tests use Satterthwaite's method [
lmerModLmerTest]

Formula: resistance ~ allocation_group * visit + (1 | record_id)
Data: data_model_V1V3

REML criterion at convergence: 1326.5

```

Scaled residuals:

Min	1Q	Median	3Q	Max
-3.15014	-0.38120	0.03119	0.40613	3.07461

Random effects:

Groups	Name	Variance	Std.Dev.
--------	------	----------	----------

```
record_id (Intercept) 3316.7   57.59  
Residual             992.1   31.50  
Number of obs: 125, groups: record_id, 75
```

Fixed effects:

	Estimate	Std. Error	df	t value	Pr(> t)
(Intercept)	524.476	10.791	85.554	48.601	<2e-16 ***
allocation_group	20.506	15.161	85.554	1.353	0.180
visit3	2.234	8.438	51.500	0.265	0.792
allocation_group:visit3	4.651	12.392	52.296	0.375	0.709

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

	(Intr)	all_GB	visit3
allctn_gr	-0.712		
visit3	-0.294	0.210	
allctn_GB:3	0.201	-0.282	-0.681

```
summary(resistance_model_sens)
```

```
Linear mixed model fit by REML. t-tests use Satterthwaite's method [  
lmerModLmerTest]  
Formula: resistance ~ allocation_group * visit + (1 | record_id)  
Data: data_model_V1V3  
Subset: !(record_id %in% resistance_model_check$influential_ids)
```

REML criterion at convergence: 1182.7

Scaled residuals:

Min	1Q	Median	3Q	Max
-1.70853	-0.47972	0.04526	0.42531	1.76454

Random effects:

Groups	Name	Variance	Std.Dev.
record_id	(Intercept)	2489.5	49.90
Residual		572.8	23.93

Number of obs: 116, groups: record_id, 70

Fixed effects:

	Estimate	Std. Error	df	t value	Pr(> t)
(Intercept)	531.866	9.354	77.137	56.860	<2e-16 ***
allocation_groupGrupo B	9.586	13.228	77.137	0.725	0.471
visit3	-3.225	6.679	46.655	-0.483	0.631
allocation_groupGrupo B:visit3	10.852	9.855	47.200	1.101	0.276

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

```
(Intr) all_GB visit3  
allctn_grGB -0.707  
visit3      -0.262  0.185  
allctn_GB:3  0.178 -0.251 -0.678
```

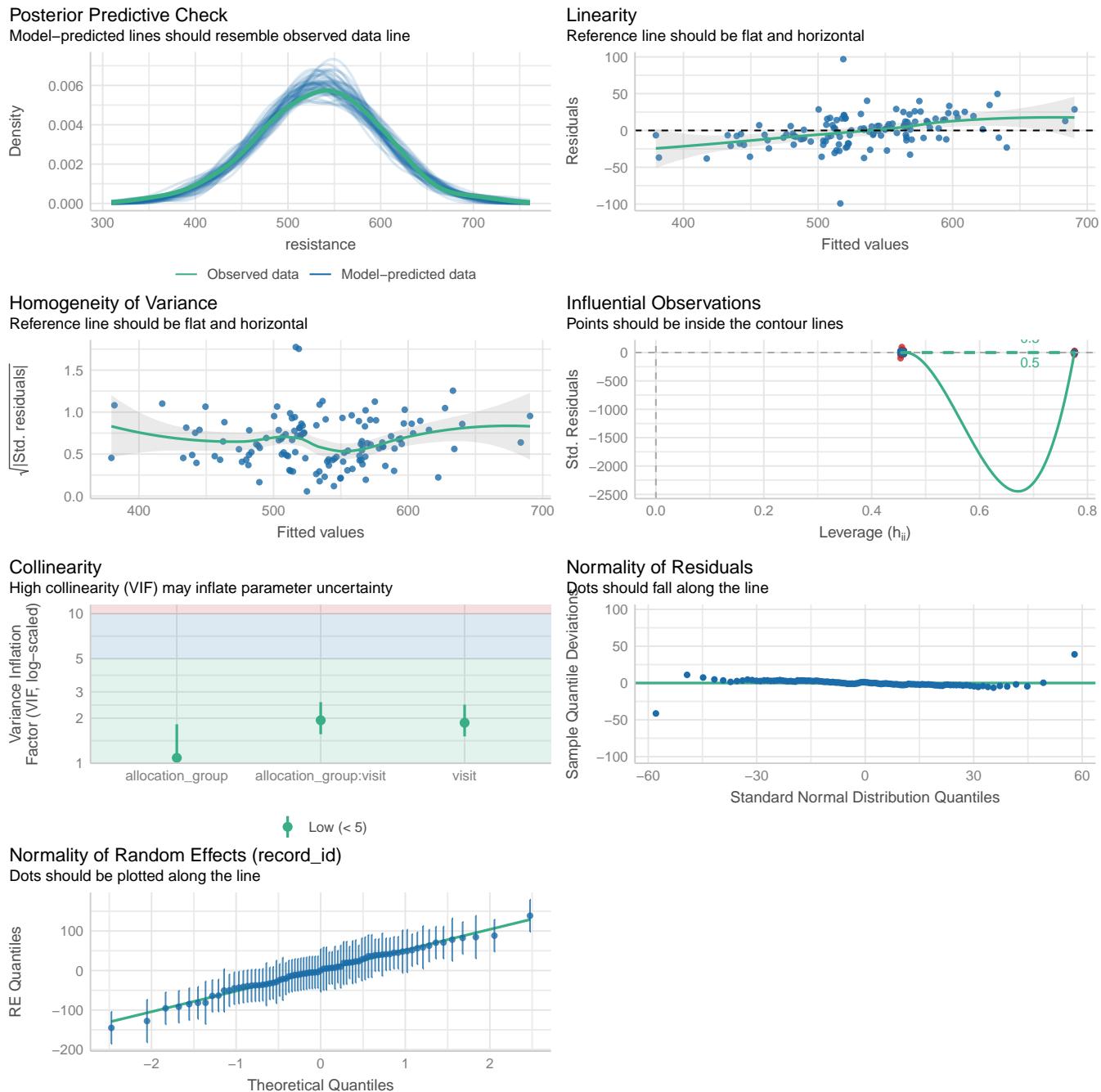
```
performance::compare_performance(  
  resistance_model,  
  resistance_model_sens)
```

When comparing models, please note that probably not all models were fit from same data.

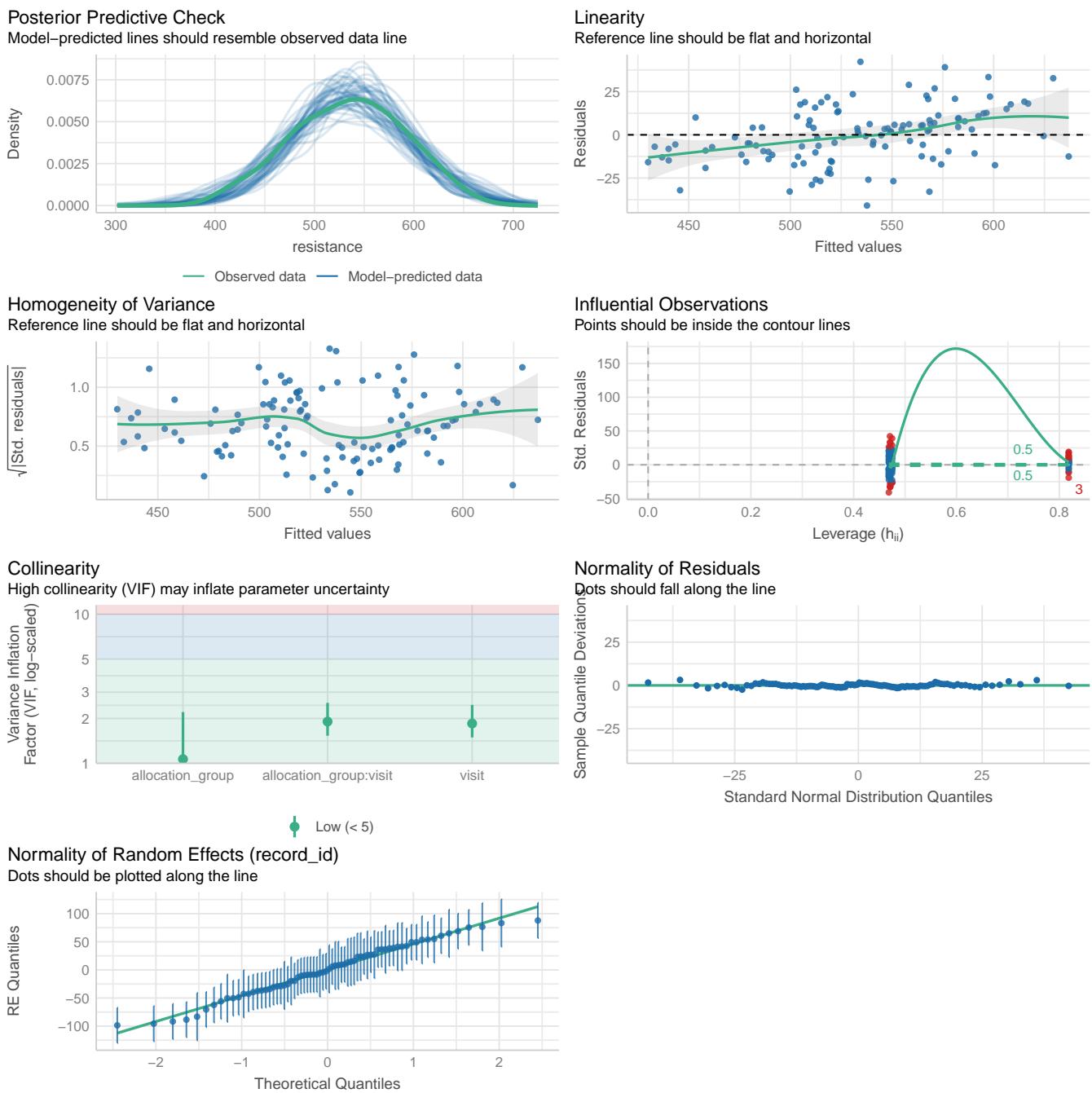
Comparison of Model Performance Indices

Name		Model	AIC (weights)	AICc (weights)	
<hr/>					
resistance_model	lmerModLmerTest	1363.8 (<.001)	1364.5 (<.001)		
resistance_model_sens	lmerModLmerTest	1218.5 (>.999)	1219.3 (>.999)		
<hr/>					
Name		BIC (weights)	R2 (cond.)	R2 (marg.)	ICC
<hr/>					
resistance_model	1380.8 (<.001)	0.776	0.029	0.770	
resistance_model_sens	1235.0 (>.999)	0.816	0.018	0.813	
<hr/>					
Name		RMSE	Sigma		
<hr/>					
resistance_model	21.823	31.498			
resistance_model_sens	16.183	23.934			

```
performance::check_model(resistance_model)
```



```
performance::check_model(resistance_model_sens)
```



4.3.2 Médias Marginais Estimadas

4.3.2.1 Todos os dados

```
# Get EMMs for each group at each visit
resistance_raw_emm <- emmeans::emmeans(
  resistance_model,
  ~ allocation_group * visit
```

```

)

resistance_raw_emm <- regrid(resistance_raw_emm)

# Table of marginal means
# resistance_raw_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(resistance_raw_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

visit = 1:

contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
Grupo A - Grupo B    -20.5 15.2  85.3     -50.6      9.64  -1.353  0.1798
```

```

visit = 3:

contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
Grupo A - Grupo B    -25.2 16.7 101.9     -58.2      7.93  -1.508  0.1346
```

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
 Confidence level used: 0.95

```

# Pairwise comparisons: Changes over time within each group
emmeans::contrast(resistance_raw_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```

allocation_group = Grupo A:

contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit3    -2.23 8.45  85.3       -19      14.6  -0.264  0.7922
```

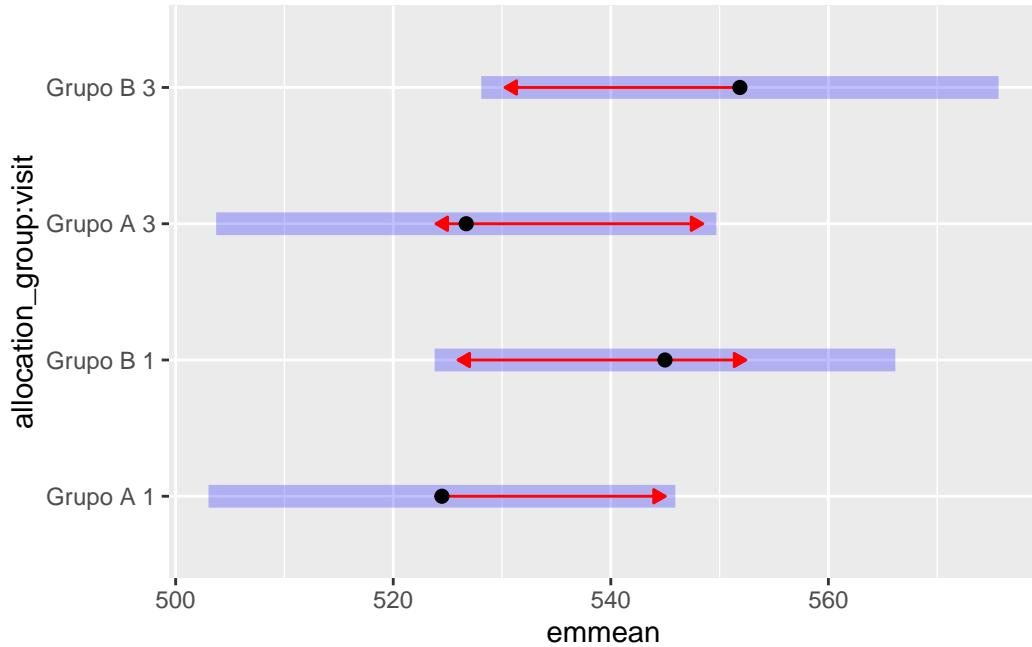
```

allocation_group = Grupo B:

contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit3    -6.88 9.10  85.3       -25      11.2  -0.757  0.4514
```

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
 Confidence level used: 0.95

```
# Plot of marginal means
plot(resistance_raw_emm, comparisons = TRUE)
```



4.3.2.2 Análise de sensibilidade

```
# Get EMMs for each group at each visit (Sensitivity Analysis)
resistance_emm <- emmeans::emmeans(
  resistance_model_sens,
  ~ allocation_group * visit
)

resistance_emm <- regrid(resistance_emm)

# Table of marginal means
# resistance_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(resistance_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

visit = 1:
  contrast      estimate     SE    df lower.CL upper.CL t.ratio p.value

```

```
Grupo A - Grupo B      -9.59 13.2 77.0      -35.9     16.76  -0.725  0.4709
```

visit = 3:

contrast	estimate	SE	df	lower.CL	upper.CL	t.ratio	p.value
Grupo A - Grupo B	-20.44	14.4	91.8	-49.0	8.14	-1.420	0.1589

Degrees-of-freedom method: inherited from kenward-roger when re-gridding

Confidence level used: 0.95

```
# Pairwise comparisons: Changes over time within each group  
emmeans::contrast(resistance_emm,  
method = "pairwise", by = "allocation_group",  
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

allocation_group = Grupo A:

contrast	estimate	SE	df	lower.CL	upper.CL	t.ratio	p.value
visit1 - visit3	3.22	6.69	77	-10.1	16.55	0.482	0.6312

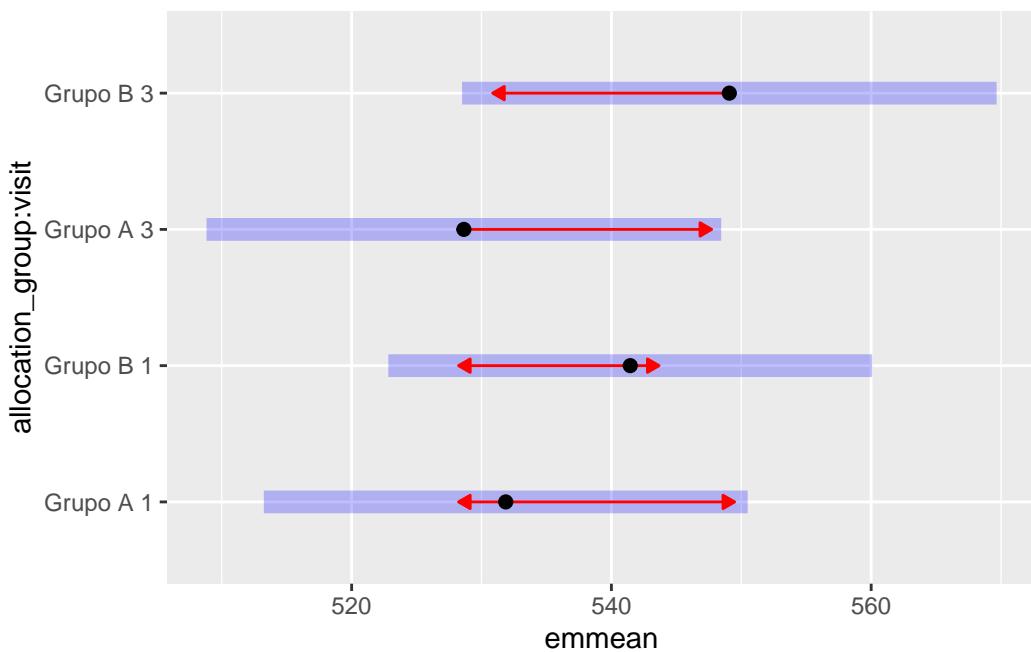
allocation_group = Grupo B:

contrast	estimate	SE	df	lower.CL	upper.CL	t.ratio	p.value
visit1 - visit3	-7.63	7.27	77	-22.1	6.84	-1.050	0.2970

Degrees-of-freedom method: inherited from kenward-roger when re-gridding

Confidence level used: 0.95

```
# Plot of marginal means  
plot(resistance_emm, comparisons = TRUE)
```



4.3.3 Resultado

No modelo ajustado para os valores de resistência bioelétrica corporal, não foram observadas diferenças estatisticamente significativas entre os grupos em nenhum dos momentos avaliados. As estimativas de diferença entre os grupos foram de -20,5 ohms (IC 95%: -50,6 a 9,6) na visita 1 e -25,2 ohms (IC 95%: -58,2 a 7,9) na visita 3. Tampouco foram observadas mudanças significativas ao longo do tempo dentro de cada grupo.

A análise de sensibilidade, com exclusão das observações mais influentes, não alterou substancialmente os resultados. As estimativas permaneceram similares, com diferença entre os grupos de -9,6 ohms (IC 95%: -35,9 a 16,8) na visita 1 e -20,4 ohms (IC 95%: -49,0 a 8,1) na visita 3, também sem significância estatística. Da mesma forma, não houve mudanças significativas entre as visitas dentro de cada grupo. As estimativas e intervalos de confiança de 95% estão apresentados na Tabela Tabela 28.

Tabela 28: Diferenças estimadas nos valores de resistência elétrica entre os grupos de alocação (placebo vs Eclipta) e entre visitas dentro de cada grupo – Todos os dados

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 1	-20,5	[-50,6 ; 9,6]	0,180
Entre grupos	Visita 3	-25,2	[-58,2 ; 7,9]	0,135
Grupo Placebo	Visita 1 - Visita 3	-2,23	[-19,0 ; 14,6]	0,792
Grupo Eclipta	Visita 1 - Visita 3	-6,88	[-25,0 ; 11,2]	0,451

```
ggplot(
  data = data_model_V1V3,
```

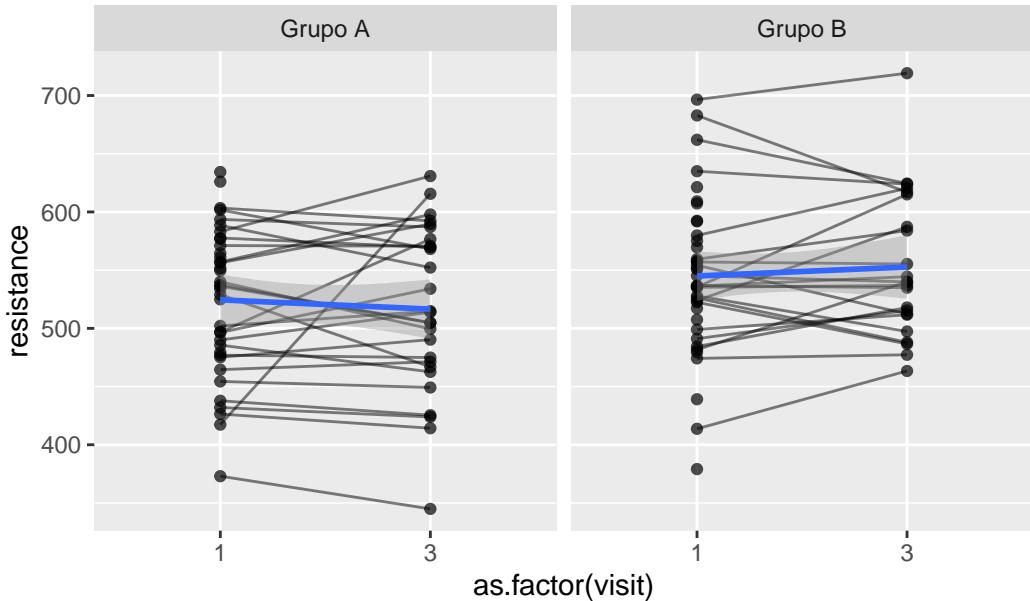
```

aes(
  x = as.factor(visit),
  y = resistance,
  group = record_id,
)
) +
  geom_line(alpha = 0.5) +
  geom_point(alpha = 0.7) +
  geom_smooth(
    aes(group = allocation_group),
    method = "lm",
    se = TRUE,
    linewidth = 1
) +
  labs(title = "All data") +
  facet_wrap(~ allocation_group)

`geom_smooth()` using formula = 'y ~ x'
Warning: Removed 3 rows containing non-finite outside the scale range
(`stat_smooth()`).
Warning: Removed 3 rows containing missing values or values outside the scale range
(`geom_line()`).
Warning: Removed 3 rows containing missing values or values outside the scale range
(`geom_point()`).

```

All data



```
data_model_V1V3 %>%
  filter(
    !(record_id %in%
      resistance_model_check$influential_ids)
  ) %>%
  ggplot(
    aes(
      x = as.factor(visit),
      y = resistance,
      group = record_id,
    )
  ) +
  geom_line(alpha = 0.5) +
  geom_point(alpha = 0.7) +
  geom_smooth(
    aes(group = allocation_group),
    method = "lm",
    se = TRUE,
    linewidth = 1
  ) +
  labs(title = "Sensitivity analysis") +
```

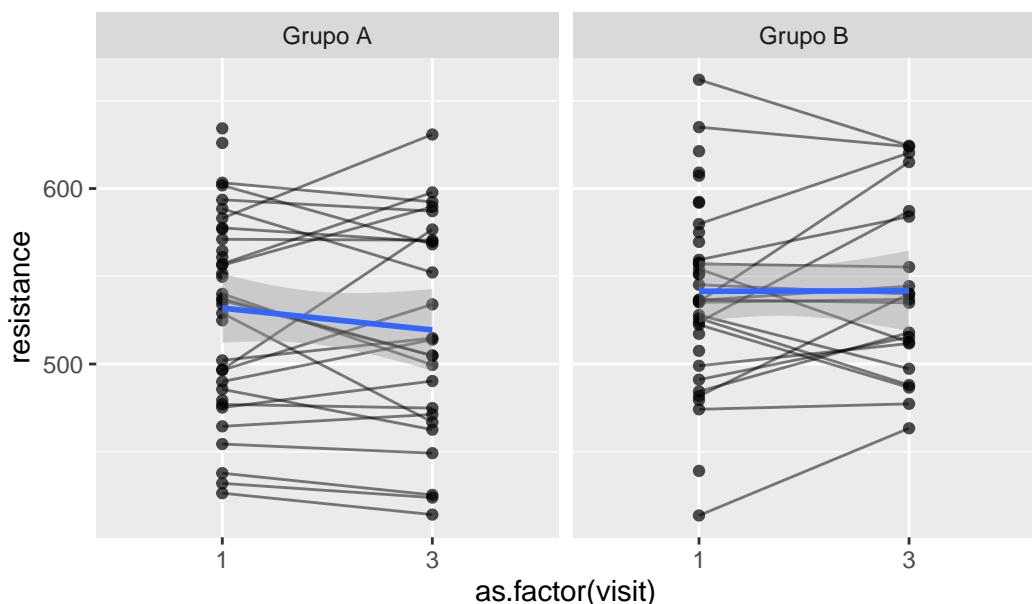
```

facet_wrap(~ allocation_group)

`geom_smooth()` using formula = 'y ~ x'
Warning: Removed 2 rows containing non-finite outside the scale range
(`stat_smooth()`).
Warning: Removed 2 rows containing missing values or values outside the scale range
(`geom_line()`).
Warning: Removed 2 rows containing missing values or values outside the scale range
(`geom_point()`).

```

Sensitivity analysis



4.4 Força de Prensão Palmar

Variável: handgrip

```

# Plot 1: Raw data
handgrip_hist_1 <- data_model_V1V3 %>%
  #filter(
  #  handgrip < 300
  #) %>%
  ggplot(aes(x = handgrip)) +
  geom_histogram(bins = 50, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
handgrip_hist_2 <- data_model_V1V3 %>%

```

```

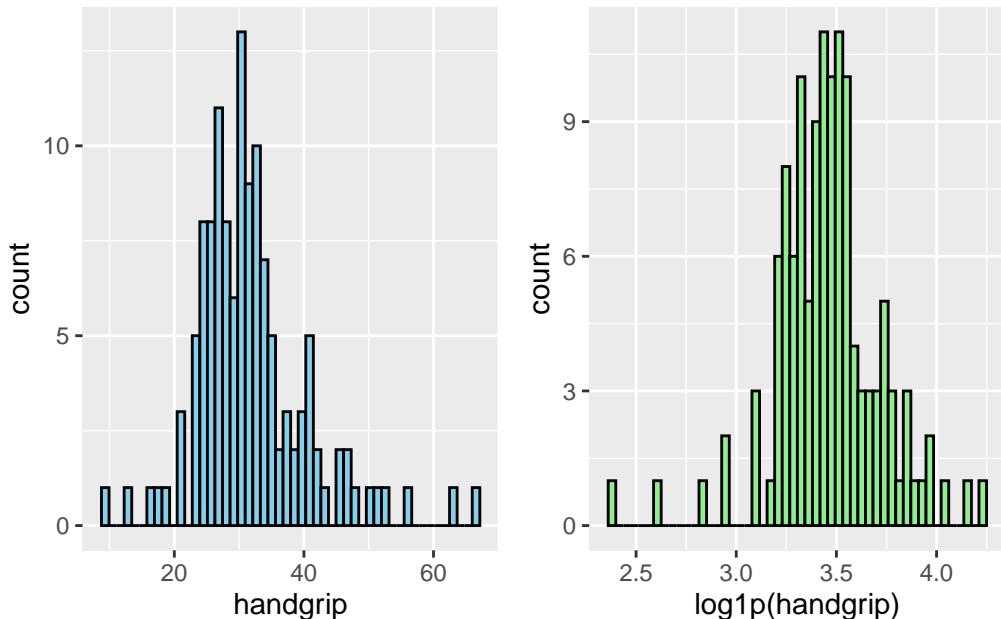
#filter(
  #  handgrip < 300
  #) %>%
  ggplot(aes(x = log1p(handgrip))) +
  geom_histogram(bins = 50, fill = "lightgreen", color = "black")

# Combine side by side
handgrip_hist_1 + handgrip_hist_2 # library(patchwork)

```

Warning: Removed 1 row containing non-finite outside the scale range (`stat_bin()`).

Removed 1 row containing non-finite outside the scale range (`stat_bin()`).



```

# LMM
handgrip_model <- lmer(log1p(handgrip) ~ allocation_group * visit +
(1 | record_id), data = data_model_V1V3)
check_collinearity(handgrip_model)

# Check for Multicollinearity

```

Low Correlation

	Term	VIF	VIF 95% CI	Increased SE	Tolerance
	allocation_group	1.06	[1.00, 2.22]	1.03	0.94
	visit	1.93	[1.56, 2.55]	1.39	0.52

```

allocation_group:visit 1.99 [1.60, 2.62]           1.41      0.50
Tolerance 95% CI
[0.45, 1.00]
[0.39, 0.64]
[0.38, 0.62]

# Sensitivity analysis
handgrip_model_check <- sensitivity_check_lmer(
  model = handgrip_model,
  id_var = "record_id",
  top_n = 5)

# LMM Sensitivity
handgrip_model_sens <- update(object = handgrip_model,
                                subset = !(record_id %in%
                               handgrip_model_check$influential_ids))

# Influential IDS
handgrip_model_check$influential_ids

[1] "16" "23" "31" "72" "56"

```

4.4.1 Resumo dos modelos

```

# Model comparison
summary(handgrip_model)

Linear mixed model fit by REML. t-tests use Satterthwaite's method [
lmerModLmerTest]

Formula: log1p(handgrip) ~ allocation_group * visit + (1 | record_id)
Data: data_model_V1V3

REML criterion at convergence: -36.3

```

Scaled residuals:

Min	1Q	Median	3Q	Max
-3.2121	-0.2737	0.0096	0.3023	2.3599

Random effects:

Groups	Name	Variance	Std.Dev.
--------	------	----------	----------

```
record_id (Intercept) 0.05291 0.2300  
Residual 0.01046 0.1023  
Number of obs: 127, groups: record_id, 75
```

Fixed effects:

	Estimate	Std. Error	df	t value	Pr(> t)
(Intercept)	3.51478	0.04138	81.97737	84.934	<2e-16
allocation_groupGrupo B	-0.09908	0.05814	81.97737	-1.704	0.0921
visit3	0.02794	0.02752	52.37961	1.015	0.3146
allocation_groupGrupo B:visit3	-0.07741	0.03962	52.70060	-1.954	0.0561

(Intercept) ***
allocation_groupGrupo B .
visit3
allocation_groupGrupo B:visit3 .

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

(Intr)	all_GB	visit3
allctn_grGB	-0.712	
visit3	-0.248	0.177
allctn_GB:3	0.172	-0.242
		-0.694

```
summary(handgrip_model_sens)
```

```
Linear mixed model fit by REML. t-tests use Satterthwaite's method [  
lmerModLmerTest]  
Formula: log1p(handgrip) ~ allocation_group * visit + (1 | record_id)  
Data: data_model_V1V3  
Subset: !(record_id %in% handgrip_model_check$influential_ids)
```

REML criterion at convergence: -112.4

Scaled residuals:

Min	1Q	Median	3Q	Max
-2.07607	-0.35838	0.02018	0.31173	2.01345

```

Random effects:

Groups      Name        Variance Std.Dev.
record_id (Intercept) 0.037729 0.19424
Residual            0.003193 0.05651

Number of obs: 117, groups: record_id, 70

```

Fixed effects:

	Estimate	Std. Error	df	t value	Pr(> t)
(Intercept)	3.49708	0.03372	70.87133	103.723	<2e-16
allocation_groupGrupo B	-0.06327	0.04838	70.87133	-1.308	0.195
visit3	0.02342	0.01559	45.19417	1.503	0.140
allocation_groupGrupo B:visit3	-0.01675	0.02329	45.40129	-0.719	0.476
(Intercept)	***				
allocation_groupGrupo B					
visit3					
allocation_groupGrupo B:visit3					

Signif. codes:	0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1				

Correlation of Fixed Effects:

(Intr)	all_GB	visit3
allctn_grGB	-0.697	
visit3	-0.169	0.118
allctn_GB:3	0.113	-0.162
		-0.669

```

performance::compare_performance(
  handgrip_model,
  handgrip_model_sens)

```

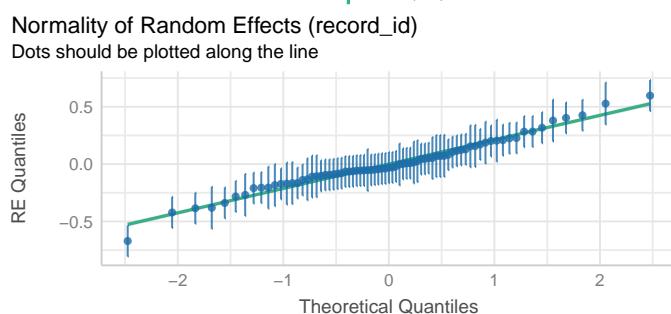
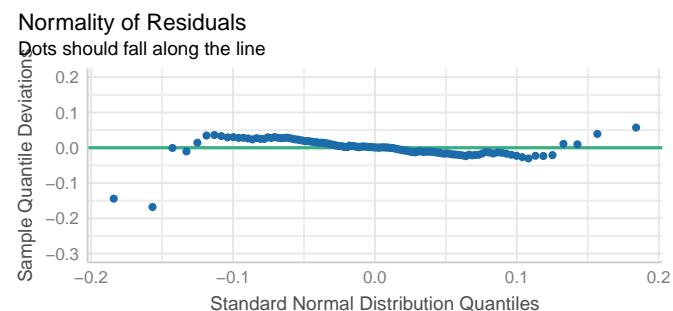
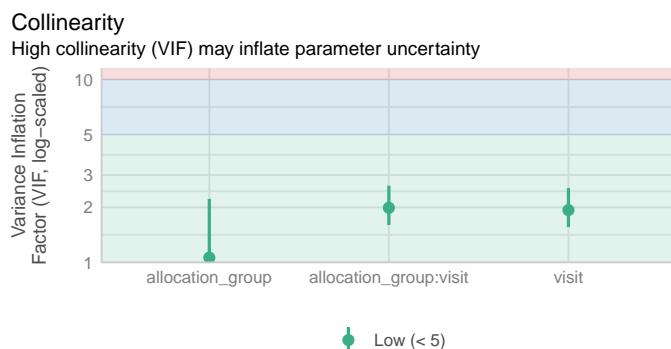
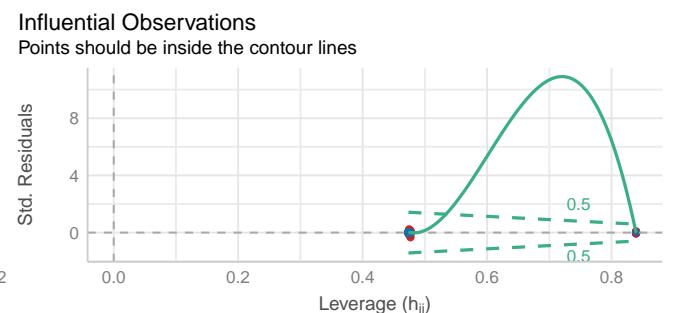
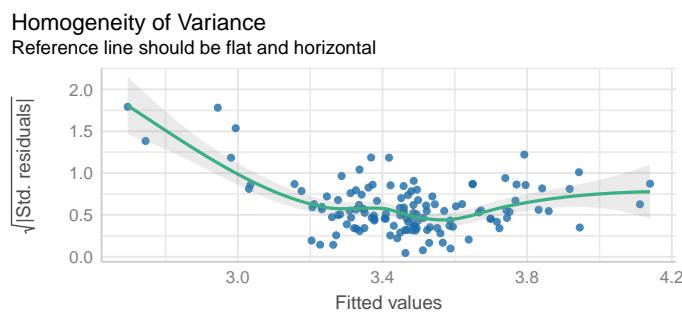
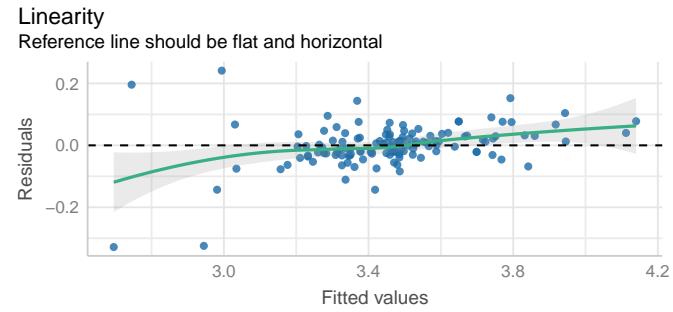
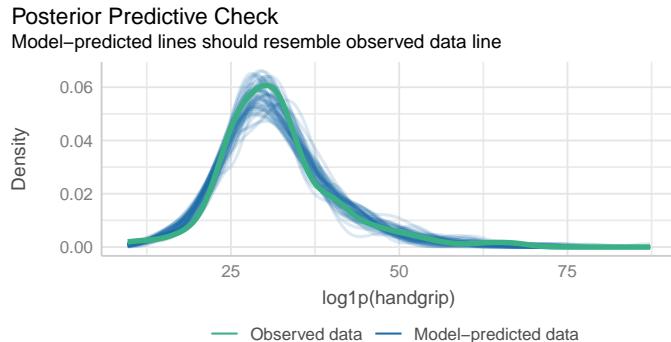
When comparing models, please note that probably not all models were fit from same data.

```
# Comparison of Model Performance Indices
```

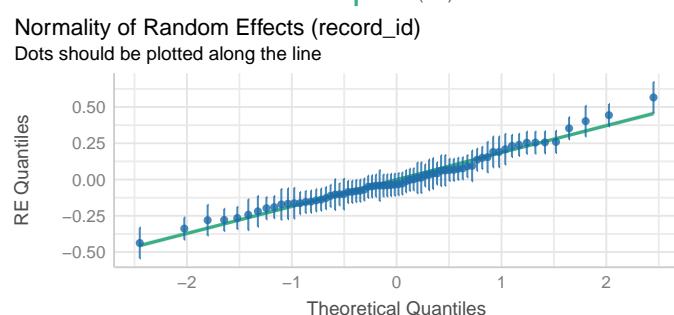
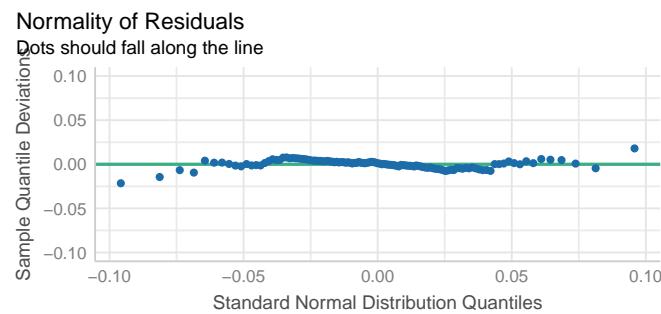
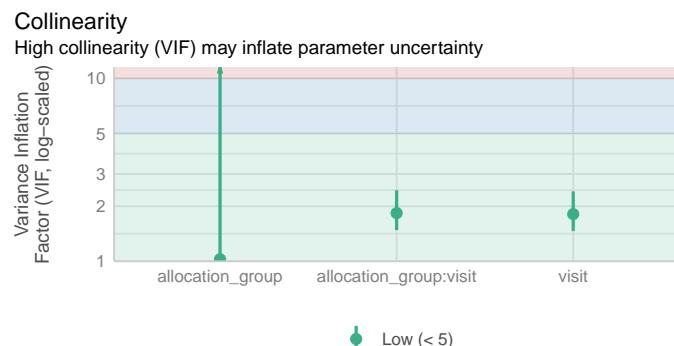
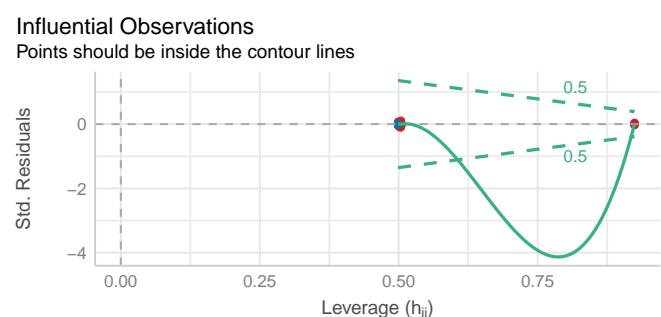
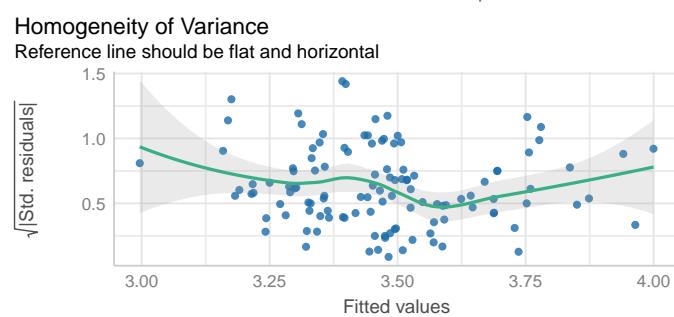
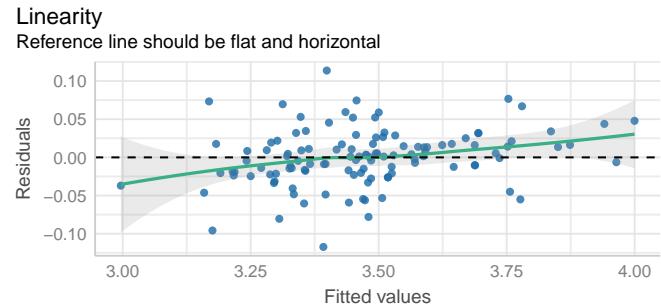
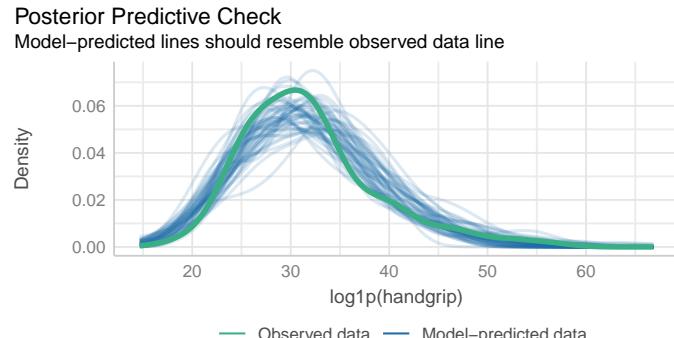
Name		Model	AIC (weights)	AICc (weights)
handgrip_model	lmerModLmerTest	834.9 (<.001)	835.6 (<.001)	
handgrip_model_sens	lmerModLmerTest	689.5 (>.999)	690.3 (>.999)	

Name	BIC (weights)	R2 (cond.)	R2 (marg.)	ICC	RMSE	Sigma
<hr/>						
handgrip_model	851.9 (<.001)	0.846	0.069	0.835	0.069	0.102
handgrip_model_sens	706.1 (>.999)	0.924	0.031	0.922	0.036	0.057

```
performance::check_model(handgrip_model)
```



```
performance::check_model(handgrip_model_sens)
```



4.4.2 Médias Marginais Estimadas

4.4.2.1 Todos os dados

```
# Get EMMs for each group at each visit
handgrip_raw_emm <- emmeans::emmeans(
  handgrip_model,
```

```

~ allocation_group * visit
)

handgrip_raw_emm <- regrid(handgrip_raw_emm)

# Table of marginal means
# handgrip_raw_emm

# Pairwise comparisons: Between groups at each visit
emmmeans::contrast(handgrip_raw_emm,
method = "pairwise", by = "visit",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

visit = 1:
  contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B     3.17 1.87 81.9    -0.541     6.88    1.700  0.0930

visit = 3:
  contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B     5.59 1.97 95.8     1.672     9.51    2.832  0.0056

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95

# Pairwise comparisons: Changes over time within each group
emmmeans::contrast(handgrip_raw_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

allocation_group = Grupo A:
  contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
 visit1 - visit3   -0.952 0.943 81.9    -2.829     0.924   -1.009  0.3157

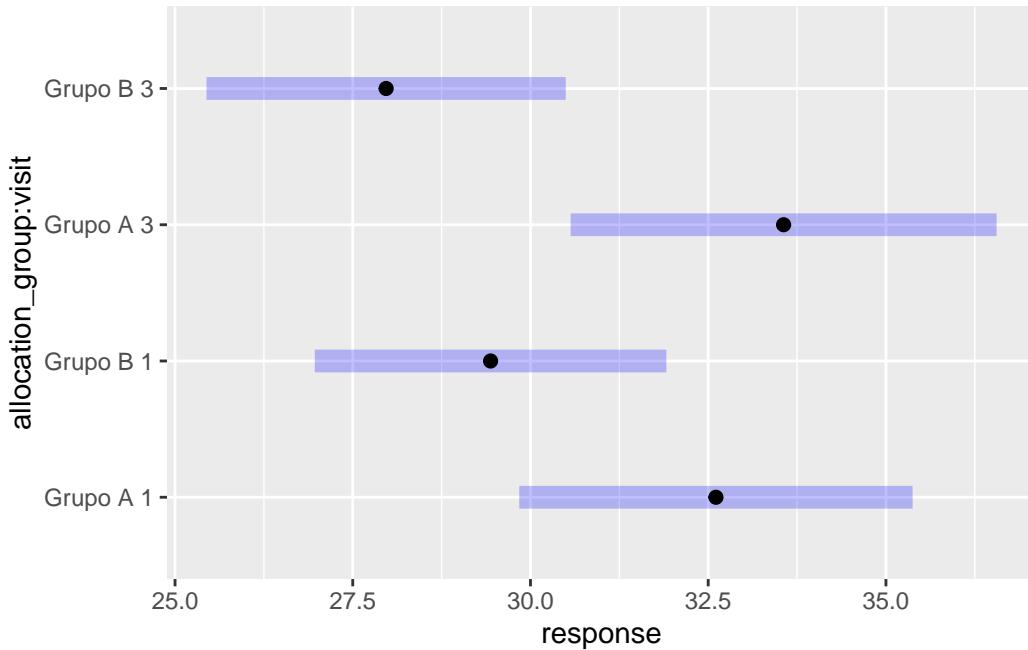
allocation_group = Grupo B:
  contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
 visit1 - visit3    1.469 0.844 81.9    -0.209     3.147    1.742  0.0853

Degrees-of-freedom method: inherited from kenward-roger when re-gridding

```

Confidence level used: 0.95

```
# Plot of marginal means  
plot(handgrip_raw_emm)
```



4.4.2.2 Análise de sensibilidade

```
# Get EMMs for each group at each visit (Sensitivity Analysis)  
handgrip_emm <- emmeans::emmeans(  
  handgrip_model_sens,  
  ~ allocation_group * visit  
)  
  
handgrip_emm <- regrid(handgrip_emm)  
  
# Table of marginal means  
# handgrip_emm  
  
# Pairwise comparisons: Between groups at each visit  
emmeans::contrast(handgrip_emm,  
  method = "pairwise", by = "visit",  
  adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))  
  
visit = 1:
```

```
contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
Grupo A - Grupo B     2.02 1.55 71.7    -1.061      5.11   1.308  0.1951
```

```
visit = 3:
```

```
contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
Grupo A - Grupo B     2.60 1.63 79.0    -0.644      5.84   1.595  0.1147
```

Degrees-of-freedom method: inherited from kenward-roger when re-gridding

Confidence level used: 0.95

```
# Pairwise comparisons: Changes over time within each group
```

```
emmeans::contrast(handgrip_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
allocation_group = Grupo A:
```

```
contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit3   -0.782 0.523 71.7    -1.83      0.261  -1.495  0.1394
```

```
allocation_group = Grupo B:
```

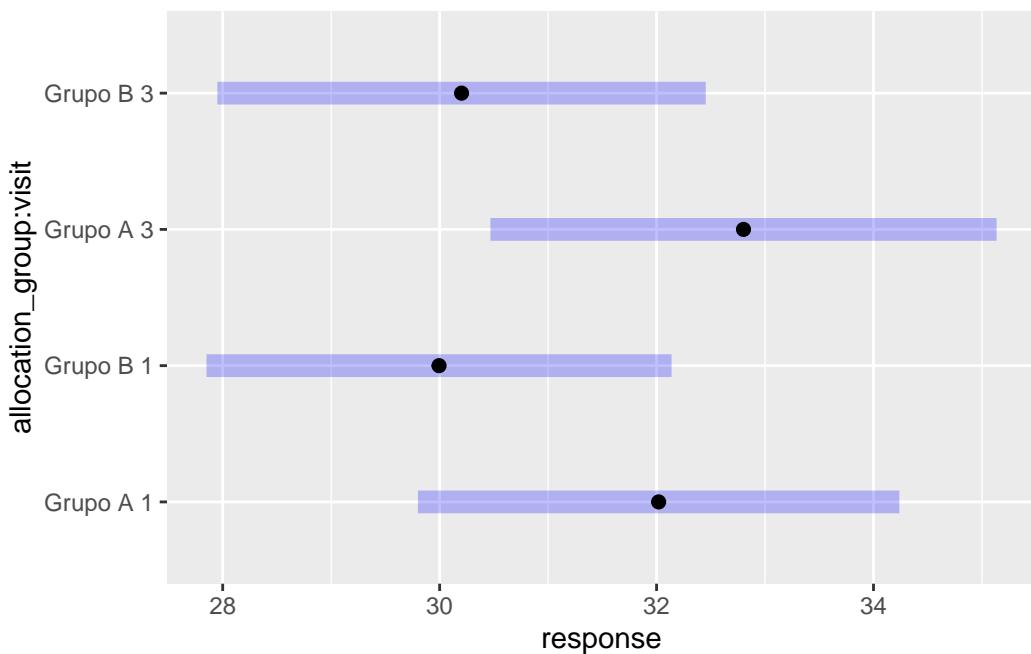
```
contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit3   -0.208 0.540 71.7    -1.28      0.868  -0.385  0.7017
```

Degrees-of-freedom method: inherited from kenward-roger when re-gridding

Confidence level used: 0.95

```
# Plot of marginal means
```

```
plot(handgrip_emm)
```



4.4.3 Resultado

No modelo ajustado para a força de preensão manual, observou-se uma diferença estatisticamente significativa entre os grupos na visita 3, com o grupo placebo apresentando força média 5,59 kgf superior ao grupo Eclipta (IC 95%: 1,67 a 9,51). Na visita 1, a diferença entre os grupos foi de 3,17 kgf (IC 95%: -0,54 a 6,88), sem alcançar significância estatística. Dentro de cada grupo, não foram observadas mudanças significativas ao longo do tempo.

Na análise de sensibilidade, os efeitos observados foram atenuados e perderam significância estatística. A diferença entre os grupos na visita 3 reduziu-se para 2,60 kgf (IC 95%: -0,64 a 5,84), e na visita 1 para 2,02 kgf (IC 95%: -1,06 a 5,11). Também não houve mudanças significativas entre as visitas dentro de cada grupo. Esses achados sugerem que os resultados observados no modelo completo podem ter sido influenciados por observações com alto impacto.

As estimativas, intervalos de confiança de 95% e valores de p estão apresentadas nas Tabelas Tabela 29 e Tabela 30.

Tabela 29: Diferenças estimadas da força de preensão manual entre os grupos de alocação (placebo vs Eclipta) e entre visitas dentro de cada grupo – Todos os dados

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 1	3,17	[-0,54 ; 6,88]	0,093
Entre grupos	Visita 3	5,59	[1,67 ; 9,51]	0,006
Grupo Placebo	Visita 1 - Visita 3	-0,95	[-2,83 ; 0,92]	0,316
Grupo Eclipta	Visita 1 - Visita 3	1,47	[-0,21 ; 3,15]	0,085

Tabela 30: Diferenças estimadas da força de preensão manual entre os grupos de alocação (placebo vs Eclipta) e entre visitas dentro de cada grupo – Análise de sensibilidade

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 1	2,02	[-1,06 ; 5,11]	0,195
Entre grupos	Visita 3	2,60	[-0,64 ; 5,84]	0,115
Grupo Placebo	Visita 1 - Visita 3	-0,78	[-1,83 ; 0,26]	0,139
Grupo Eclipta	Visita 1 - Visita 3	-0,21	[-1,28 ; 0,87]	0,702

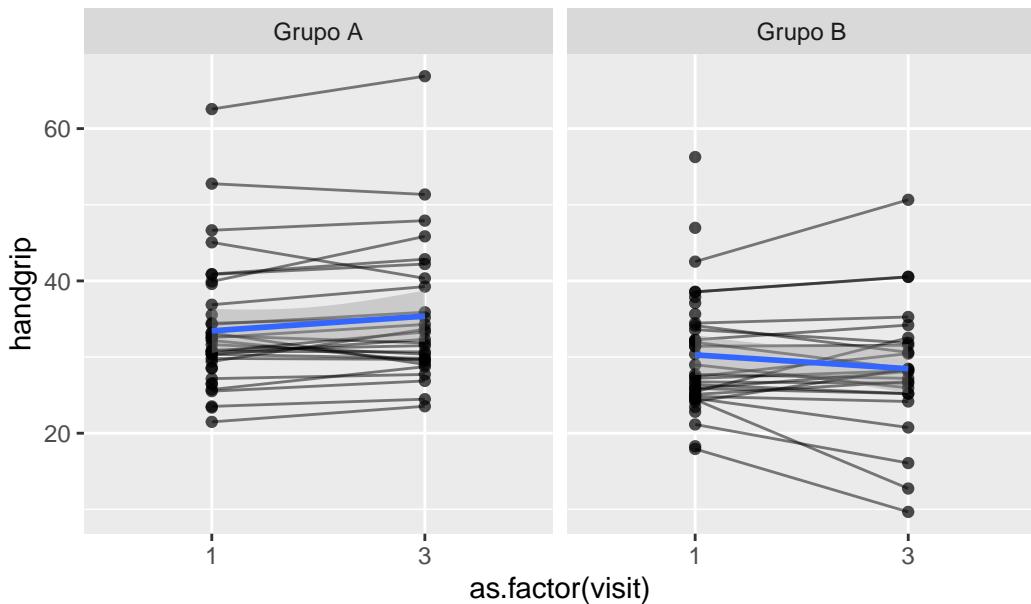
```

ggplot(
  data = data_model_V1V3,
  aes(
    x = as.factor(visit),
    y = handgrip,
    group = record_id,
  )
) +
  geom_line(alpha = 0.5) +
  geom_point(alpha = 0.7) +
  geom_smooth(
    aes(group = allocation_group),
    method = "lm",
    se = TRUE,
    linewidth = 1
  ) +
  labs(title = "All data") +
  facet_wrap(~ allocation_group)

`geom_smooth()` using formula = 'y ~ x'
Warning: Removed 1 row containing non-finite outside the scale range
(`stat_smooth()`).
Warning: Removed 1 row containing missing values or values outside the scale range
(`geom_line()`).
Warning: Removed 1 row containing missing values or values outside the scale range
(`geom_point()`).

```

All data



```
data_model_V1V3 %>%
  filter(
    !(record_id %in%
      handgrip_model_check$influential_ids)
  ) %>%
  ggplot(
    aes(
      x = as.factor(visit),
      y = handgrip,
      group = record_id,
    )
  ) +
  geom_line(alpha = 0.5) +
  geom_point(alpha = 0.7) +
  geom_smooth(
    aes(group = allocation_group),
    method = "lm",
    se = TRUE,
    linewidth = 1
  ) +
  labs(title = "Sensitivity analysis") +
```

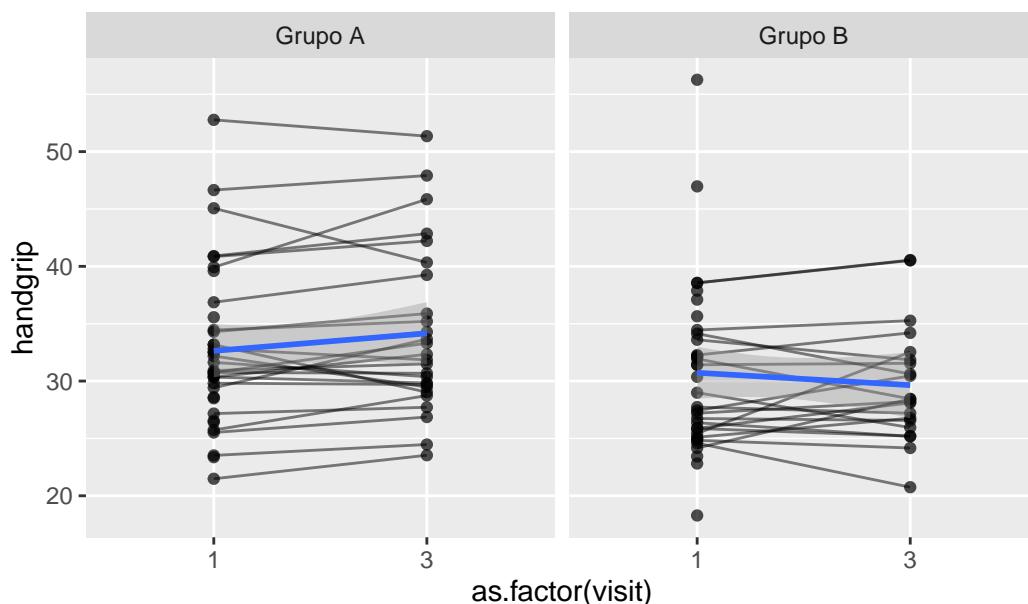
```

facet_wrap(~ allocation_group)

`geom_smooth()` using formula = 'y ~ x'
Warning: Removed 1 row containing non-finite outside the scale range
(`stat_smooth()`).
Warning: Removed 1 row containing missing values or values outside the scale range
(`geom_line()`).
Warning: Removed 1 row containing missing values or values outside the scale range
(`geom_point()`).

```

Sensitivity analysis



5 Informações da Sessão

```

sessionInfo()

R version 4.4.1 (2024-06-14)
Platform: aarch64-apple-darwin20
Running under: macOS 15.5

Matrix products: default
BLAS: /Library/Frameworks/R.framework/Versions/4.4-arm64/Resources/lib/libRblas.0.dylib
LAPACK: /Library/Frameworks/R.framework/Versions/4.4-arm64/Resources/lib/libRlapack.dylib; LAPACK version

locale:

```

```
[1] en_US.UTF-8/en_US.UTF-8/en_US.UTF-8/C/en_US.UTF-8/en_US.UTF-8
```

```
time zone: America/Sao_Paulo
```

```
tzcode source: internal
```

```
attached base packages:
```

```
[1] stats      graphics   grDevices utils      datasets  methods    base
```

```
other attached packages:
```

```
[1] broom.mixed_0.2.9.6 influence.ME_0.9-9  kableExtra_1.4.0.12  
[4] knitr_1.50            emmeans_1.11.1    patchwork_1.3.0  
[7] gt_1.0.0              performance_0.13.0 skimr_2.1.5  
[10] lmerTest_3.1-3       lme4_1.1-37      Matrix_1.7-0  
[13] here_1.0.1           readxl_1.4.3     lubridate_1.9.4  
[16] forcats_1.0.0        stringr_1.5.1    dplyr_1.1.4.9000  
[19] purrrr_1.0.4          readr_2.1.5      tidyverse_2.0.0  
[22] tibble_3.2.1         ggplot2_3.5.1    tidyverse_2.0.0
```

```
loaded via a namespace (and not attached):
```

```
[1] tidyselect_1.2.1    viridisLite_0.4.2  farver_2.1.2  
[4] fastmap_1.2.0     TH.data_1.1-3    bayestestR_0.15.3  
[7] digest_0.6.37     timechange_0.3.0  estimability_1.5.1  
[10] lifecycle_1.0.4   survival_3.7-0   magrittr_2.0.3  
[13] compiler_4.4.1    rlang_1.1.6     tools_4.4.1  
[16] yaml_2.3.10      labeling_0.4.3  xml2_1.3.8  
[19] repr_1.1.7       multcomp_1.4-28 withr_3.0.2  
[22] numDeriv_2016.8-1.1 datawizard_1.1.0 grid_4.4.1  
[25] future_1.34.0    xtable_1.8-4   colorspace_2.1-1  
[28] globals_0.16.3   scales_1.3.0   MASS_7.3-61  
[31] insight_1.2.0    cli_3.6.5     mvtnorm_1.3-3  
[34] rmarkdown_2.29    reformulas_0.4.1 generics_0.1.3  
[37] rstudioapi_0.17.1 tzdb_0.4.0    minqa_1.2.8  
[40] splines_4.4.1    parallel_4.4.1 cellranger_1.1.0  
[43] base64enc_0.1-3   vctrs_0.6.5    boot_1.3-31  
[46] sandwich_3.1-1   jsonlite_2.0.0  hms_1.1.3  
[49] pbkrtest_0.5.4   ggrepel_0.9.6   listenv_0.9.1
```

```
[52] systemfonts_1.2.3    see_0.11.0        parallelly_1.44.0
[55] glue_1.8.0          nloptr_2.2.1      codetools_0.2-20
[58] stringi_1.8.7       gtable_0.3.6      munsell_0.5.1
[61] furrr_0.3.1         pillar_1.10.2     htmltools_0.5.8.1
[64] R6_2.6.1            textshaping_0.4.0 Rdpack_2.6.4
[67] rprojroot_2.0.4     evaluate_1.0.3    lattice_0.22-6
[70] backports_1.5.0     rbibutils_2.3     broom_1.0.7
[73] Rcpp_1.0.14          svglite_2.2.1     coda_0.19-4.1
[76] nlme_3.1-166         mgcv_1.9-1       xfun_0.52
[79] zoo_1.8-14           pkgconfig_2.0.3
```