

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_hb1c
- labs_insulin
- labs_homa_ir
- labs_quick_index
- abdomen
- bmi
- mean_bp_mean
- evs_score

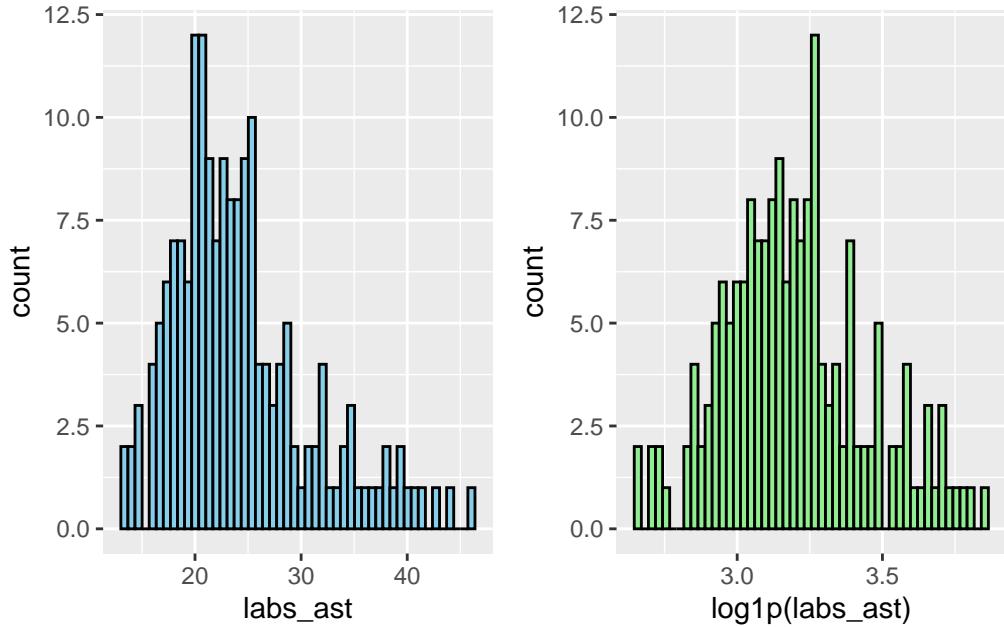
3.0.1 Aspartato Aminotransferase

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"

```

3.0.1.1 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_gr	GB	-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	9.2953	80.229 <2e-16
allocation_group	-0.04417	0.05678	100	9.2953	-0.778 0.438
visit2	-0.01756	0.03879	95	5.56884	-0.453 0.652
visit3	-0.03571	0.04157	97	1.13735	-0.859 0.392
allocation_group	-0.02157	0.05710	97	8.0899	-0.378 0.706
allocation_group	0.06882	0.06184	99	3.1712	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_model_check$comparison_table
```

A tibble: 16 x 6

Model	term	estimate	std.error	statistic	p.value
<chr>	<chr>	<dbl>	<dbl>	<dbl>	<dbl>
1 Original	(Intercept)	3.21	0.0416	77.3	1.64e-108
2 Sensitivity	(Intercept)	3.22	0.0401	80.2	3.09e- 93
3 Original	allocation_groupGrupo B	-0.0207	0.0584	-0.354	7.24e- 1
4 Sensitivity	allocation_groupGrupo B	-0.0442	0.0568	-0.778	4.38e- 1
5 Original	allocation_groupGrupo B:~	-0.0158	0.0668	-0.237	8.13e- 1
6 Sensitivity	allocation_groupGrupo B:~	-0.0216	0.0571	-0.378	7.06e- 1
7 Original	allocation_groupGrupo B:~	0.0254	0.0716	0.355	7.23e- 1
8 Sensitivity	allocation_groupGrupo B:~	0.0688	0.0618	1.11	2.68e- 1
9 Original	sd__(Intercept)	0.173	NA	NA	NA

```

10 Sensitivity sd__(Intercept)          0.184    NA      NA      NA
11 Original     sd__Observation       0.184    NA      NA      NA
12 Sensitivity sd__Observation       0.150    NA      NA      NA
13 Original     visit2              -0.00843   0.0457  -0.184  8.54e- 1
14 Sensitivity visit2              -0.0176   0.0388  -0.453  6.52e- 1
15 Original     visit3              -0.00929   0.0494  -0.188  8.51e- 1
16 Sensitivity visit3              -0.0357   0.0416  -0.859  3.92e- 1

```

```

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.

```

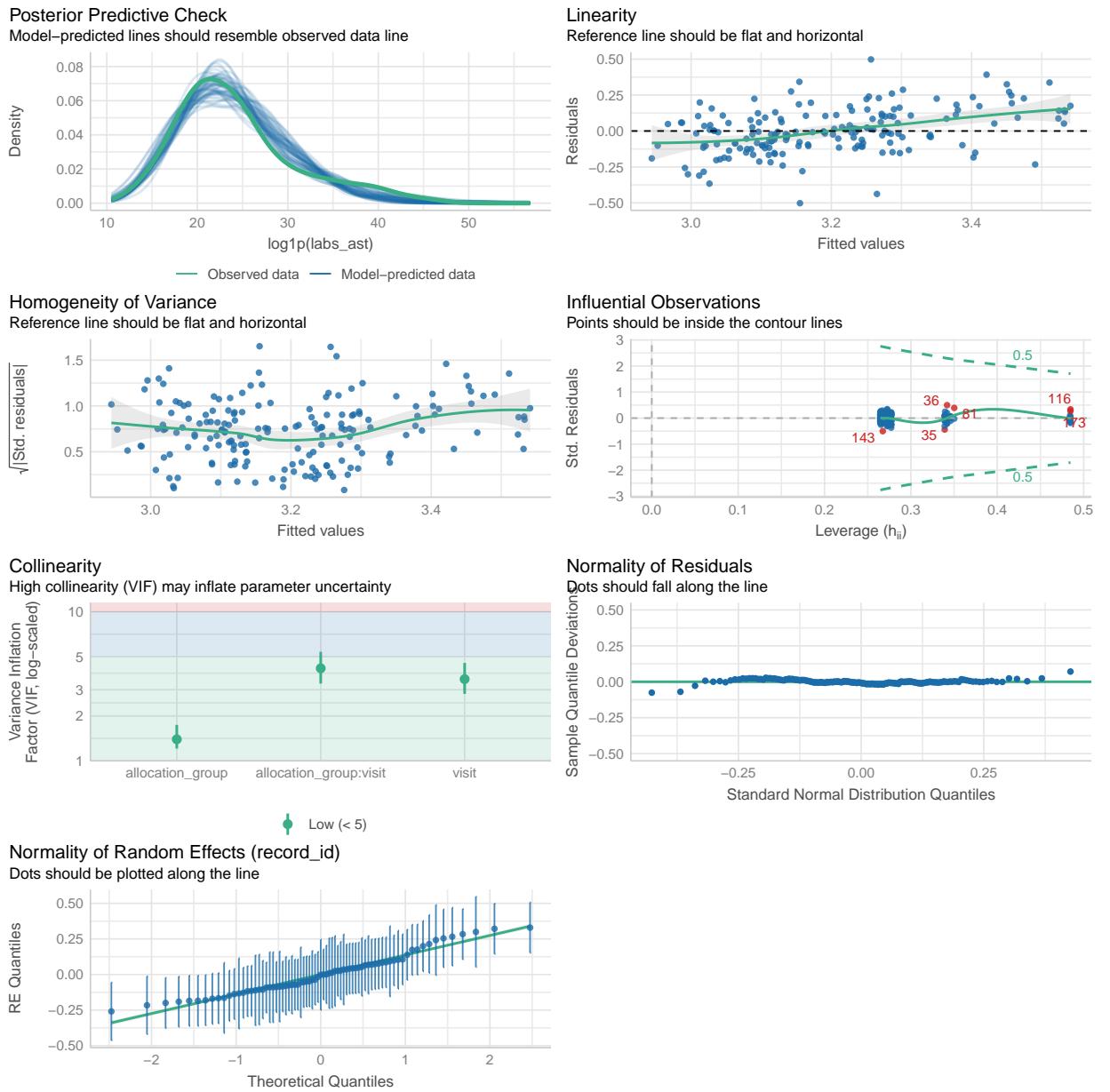
labs_ast_3performance
# Comparison of Model Performance Indices

```

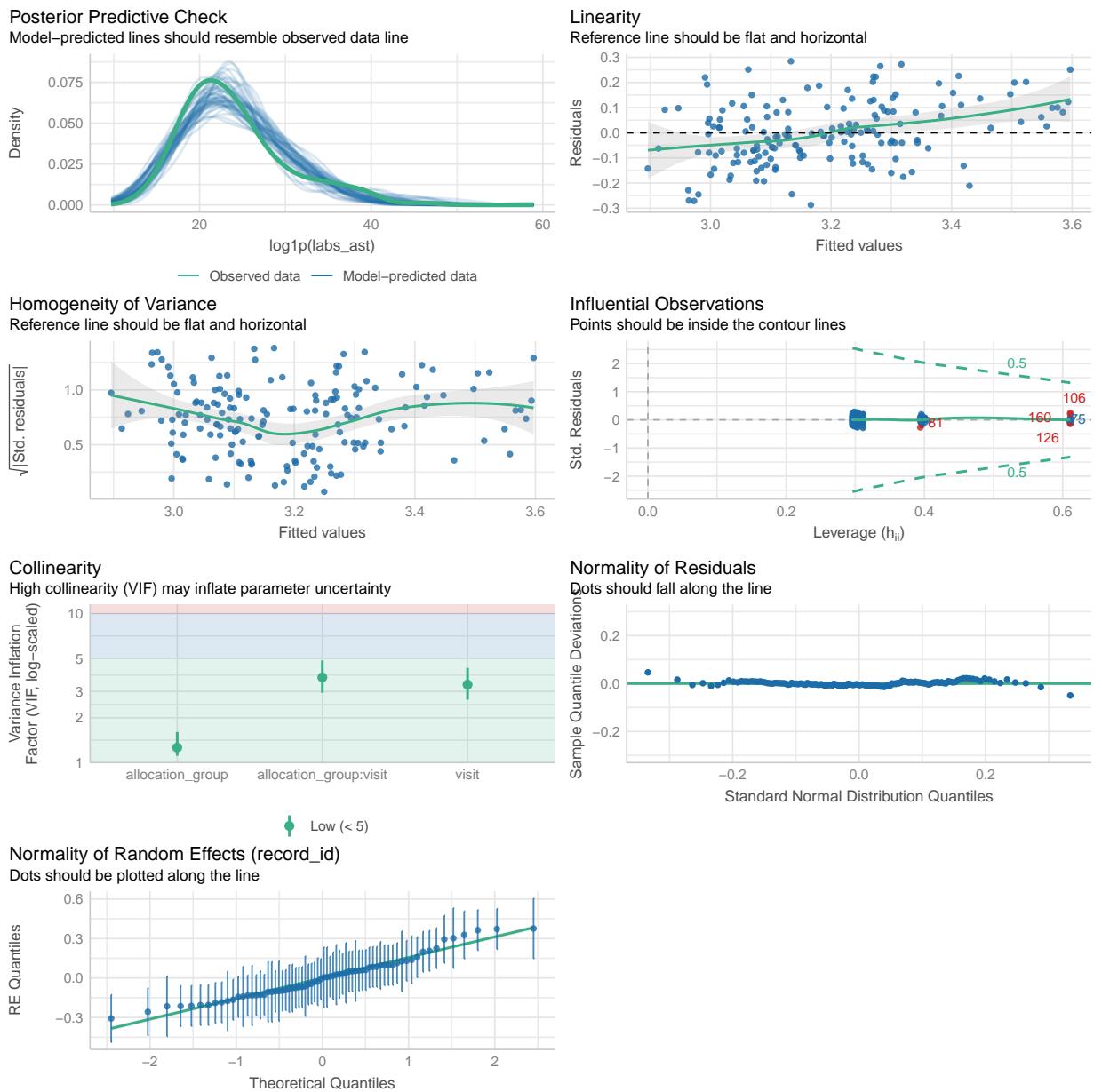
Name	Model	AIC (weights)	AICc (weights)
labs_ast_model	lmerModLmerTest	1139.5 (<.001)	1140.3 (<.001)
labs_ast_model_sens	lmerModLmerTest	1014.1 (>.999)	1015.0 (>.999)

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)
```



3.0.1.2 Médias Marginais Estimadas

3.0.1.2.1 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

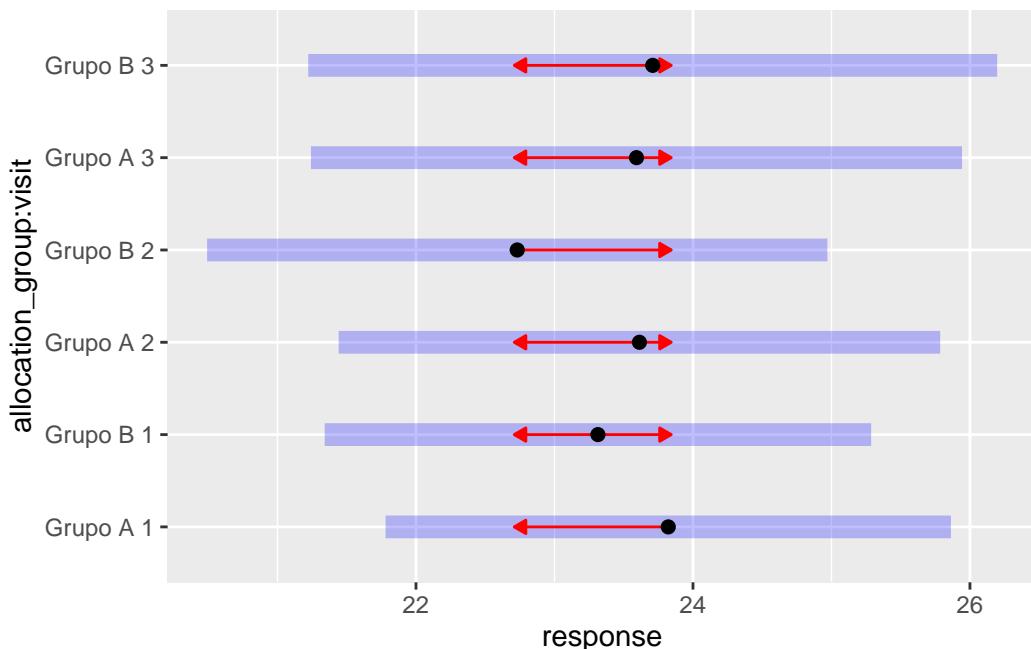
Conf-level adjustment: bonferroni method for 3 estimates

P value adjustment: bonferroni method for 3 tests

```

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

```



3.0.1.2.2 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  
emmmeans::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

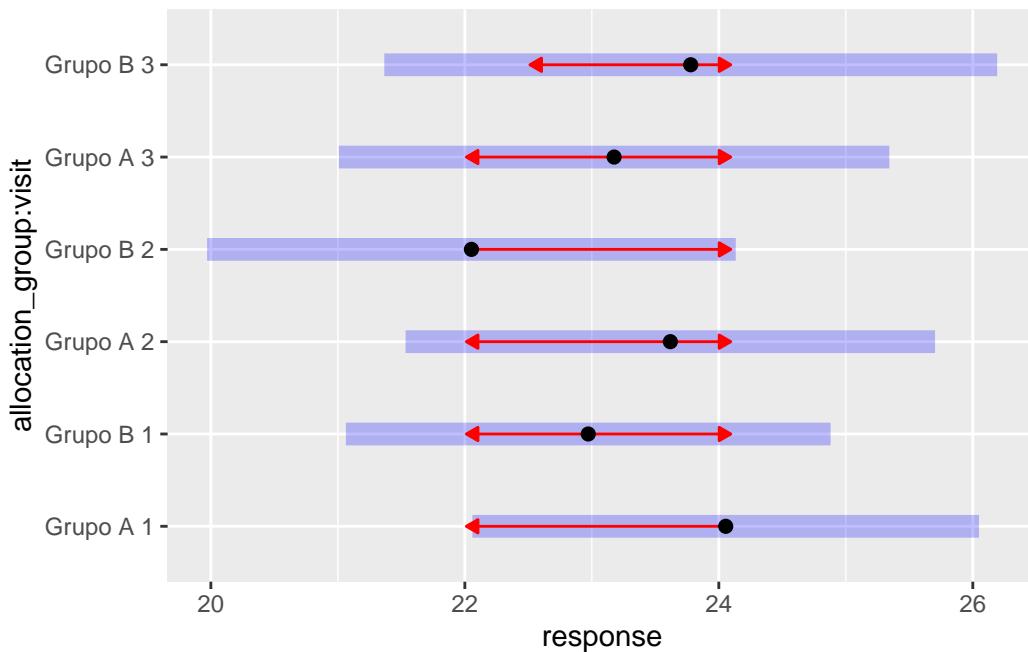
Degrees-of-freedom method: inherited from kenward-roger when re-gridding

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)
```



3.0.1.3 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
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 de comparação	Comparação	Estimativa	IC 95%	p-valor
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()`).

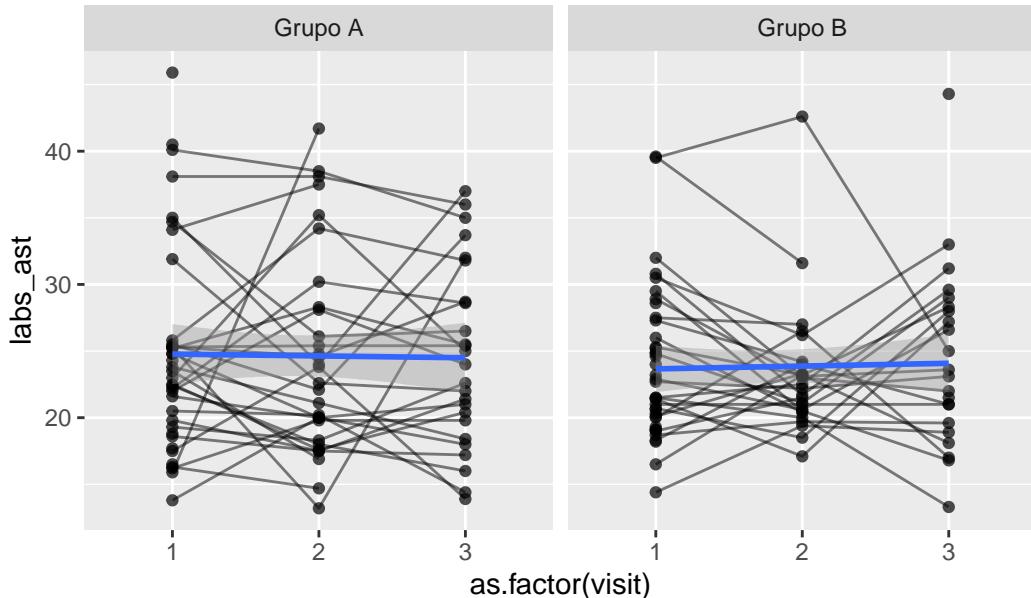
Warning: Removed 8 rows containing missing values or values outside the scale range

```

```
(`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(  
    method = "loess",  
    se = TRUE,  
    span = 0.5  
  )
```

```

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

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

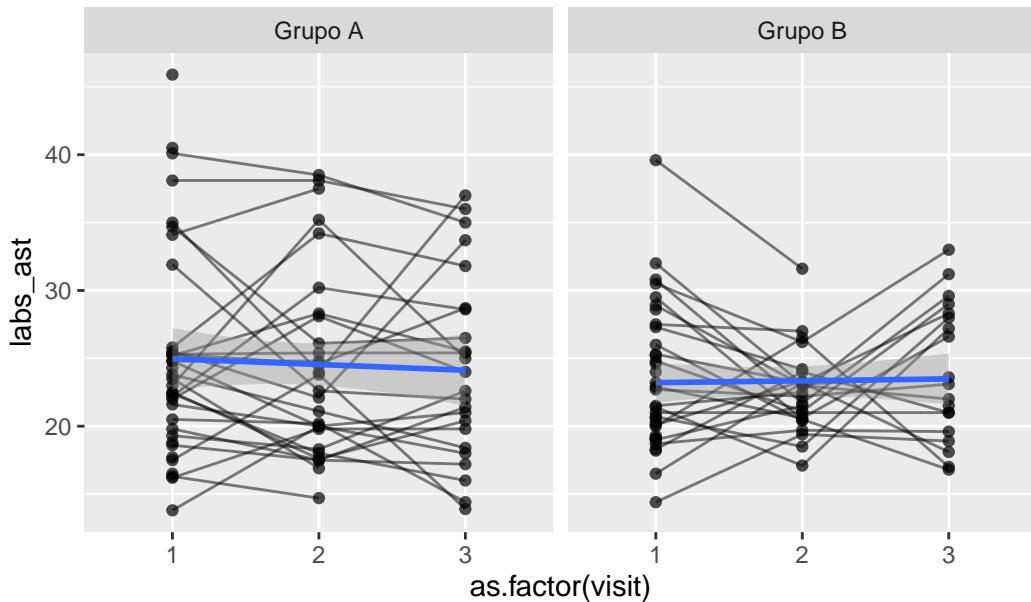
Warning: Removed 9 rows containing non-finite outside the scale range
(`stat_smooth()`).

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



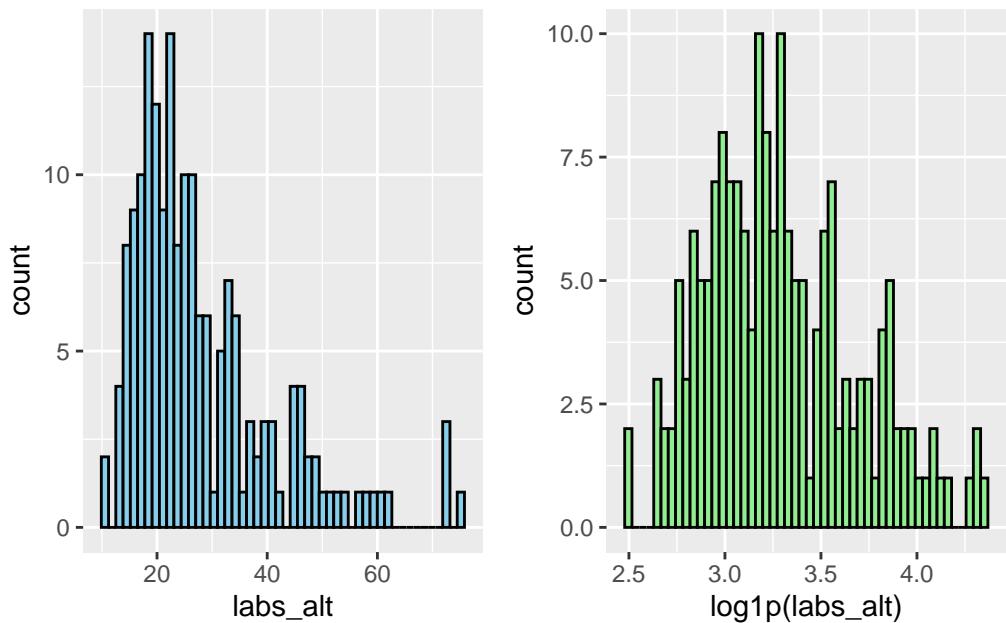
3.0.2 Alanina Aminotransferase

```
# 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"

```

3.0.2.1 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_group	-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_group:visit2	0.06143	0.08602	105.75034	0.714	0.477
allocation_group:visit3	0.07920	0.09237	106.88087	0.857	0.393

(Intercept)	***
allocation_group	Grupo B
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_gr	GB	-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	-0.009275	0.078377	94.689442	-0.118	0.906
allocation_group	0.043535	0.085567	95.767451	0.509	0.612

(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	-0.727				
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

```
labs_alt_model_check$comparison_table
```

A tibble: 16 x 6

Model	term	estimate	std.error	statistic	p.value
<chr>	<chr>	<dbl>	<dbl>	<dbl>	<dbl>
1 Original	(Intercept)	3.34	0.0665	50.3	5.32e-74
2 Sensitivity	(Intercept)	3.25	0.0642	50.6	2.13e-68
3 Original	allocation_groupGrupo B	-0.102	0.0934	-1.09	2.78e- 1
4 Sensitivity	allocation_groupGrupo B	-0.0131	0.0884	-0.148	8.83e- 1
5 Original	allocation_groupGrupo B:v~	0.0614	0.0860	0.714	4.77e- 1
6 Sensitivity	allocation_groupGrupo B:v~	-0.00928	0.0784	-0.118	9.06e- 1
7 Original	allocation_groupGrupo B:v~	0.0792	0.0924	0.857	3.93e- 1
8 Sensitivity	allocation_groupGrupo B:v~	0.0435	0.0856	0.509	6.12e- 1
9 Original	sd__(Intercept)	0.330	NA	NA	NA
10 Sensitivity	sd__(Intercept)	0.306	NA	NA	NA

```

11 Original    sd__Observation      0.234     NA      NA      NA
12 Sensitivity sd__Observation      0.206     NA      NA      NA
13 Original    visit2              -0.0796   0.0587  -1.36   1.78e- 1
14 Sensitivity visit2              -0.0215   0.0552  -0.390  6.97e- 1
15 Original    visit3              -0.0336   0.0635  -0.529  5.98e- 1
16 Sensitivity visit3              -0.0354   0.0607  -0.584  5.61e- 1

performance::compare_performance(
  labs_alt_model,
  labs_alt_model_sens)

```

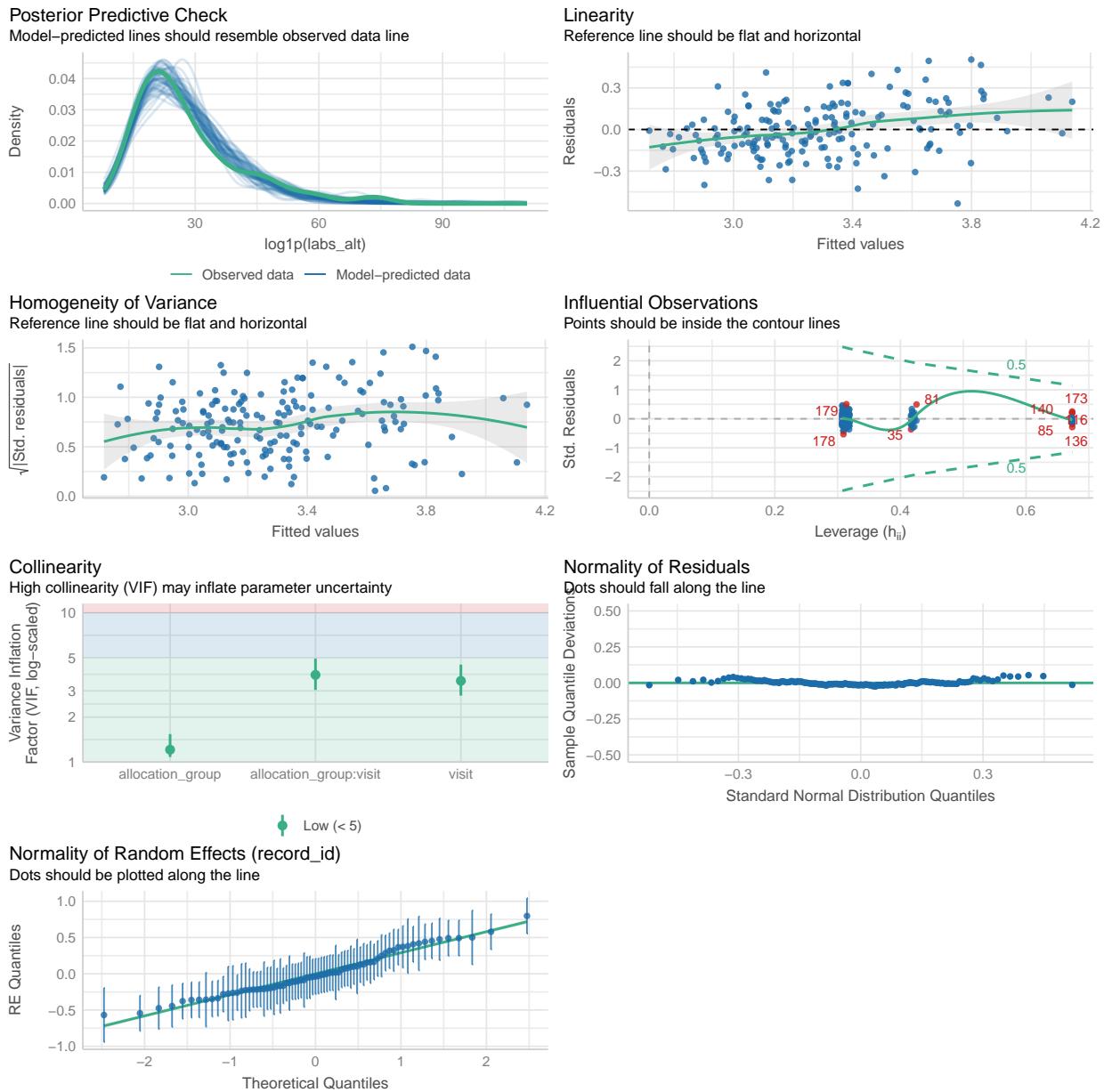
When comparing models, please note that probably not all models were fit from same data.

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

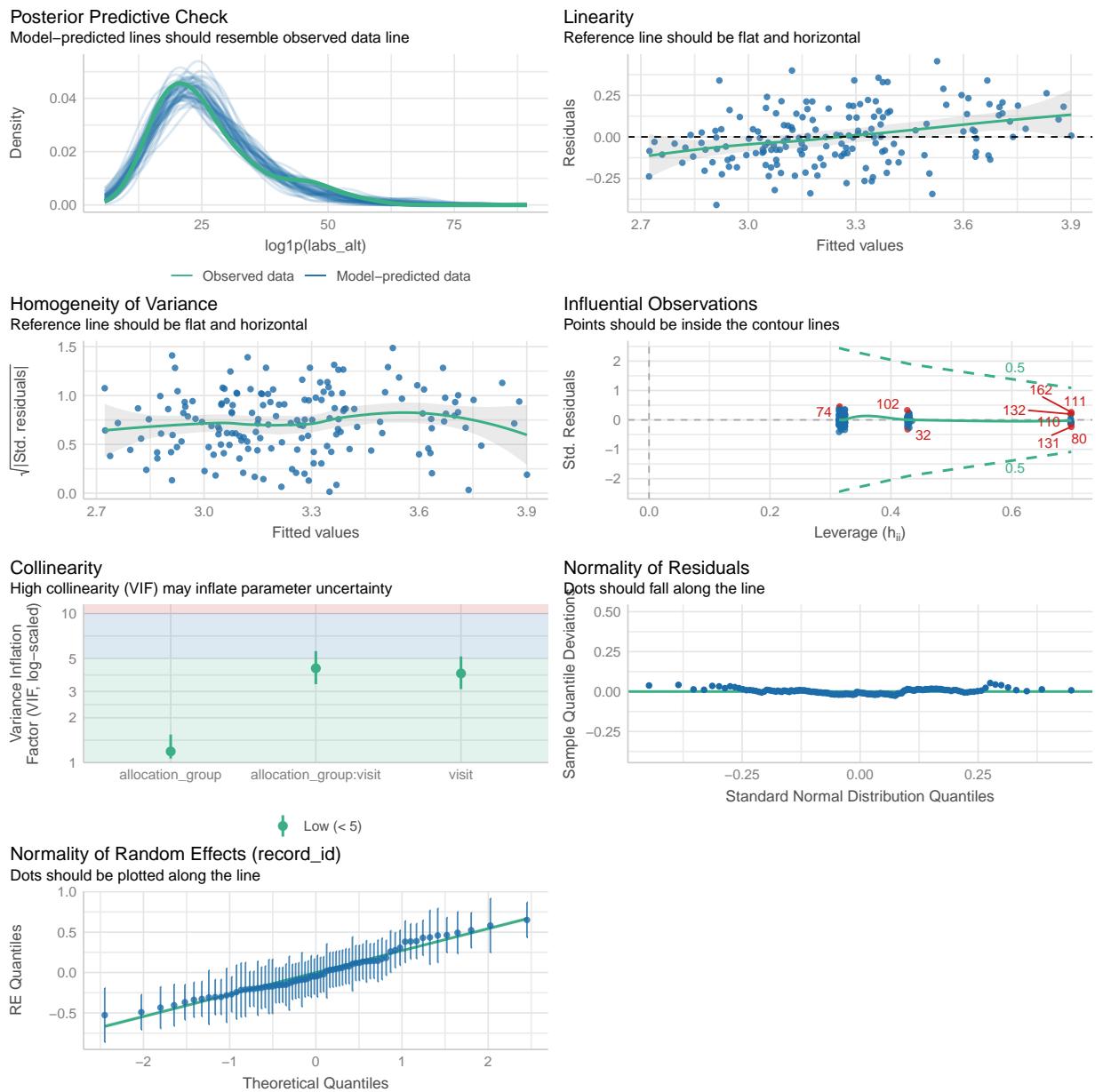
Name		Model	AIC (weights)	AICc (weights)
<hr/>				
labs_alt_model		lmerModLmerTest	1302.9 (<.001)	1303.8 (<.001)
labs_alt_model_sens		lmerModLmerTest	1150.5 (>.999)	1151.4 (>.999)

Name		BIC (weights)	R2 (cond.)	R2 (marg.)	ICC	RMSE	Sigma
<hr/>							
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)
```



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



3.0.2.2 Médias Marginais Estimadas

3.0.2.2.1 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

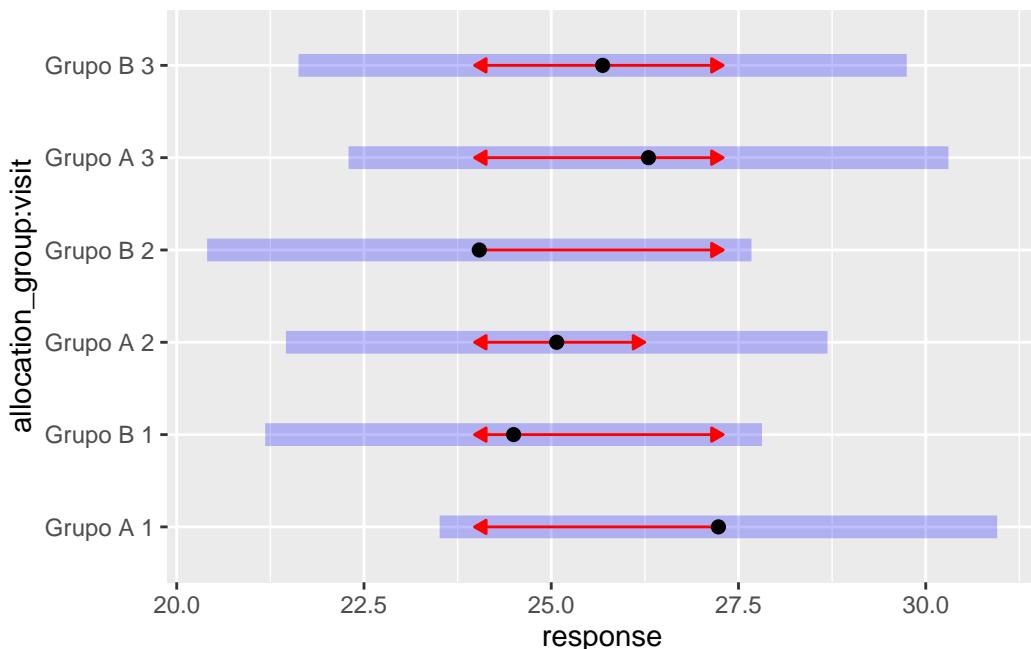
Conf-level adjustment: bonferroni method for 3 estimates

P value adjustment: bonferroni method for 3 tests

```

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

```



3.0.2.2.2 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  
emmmeans::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

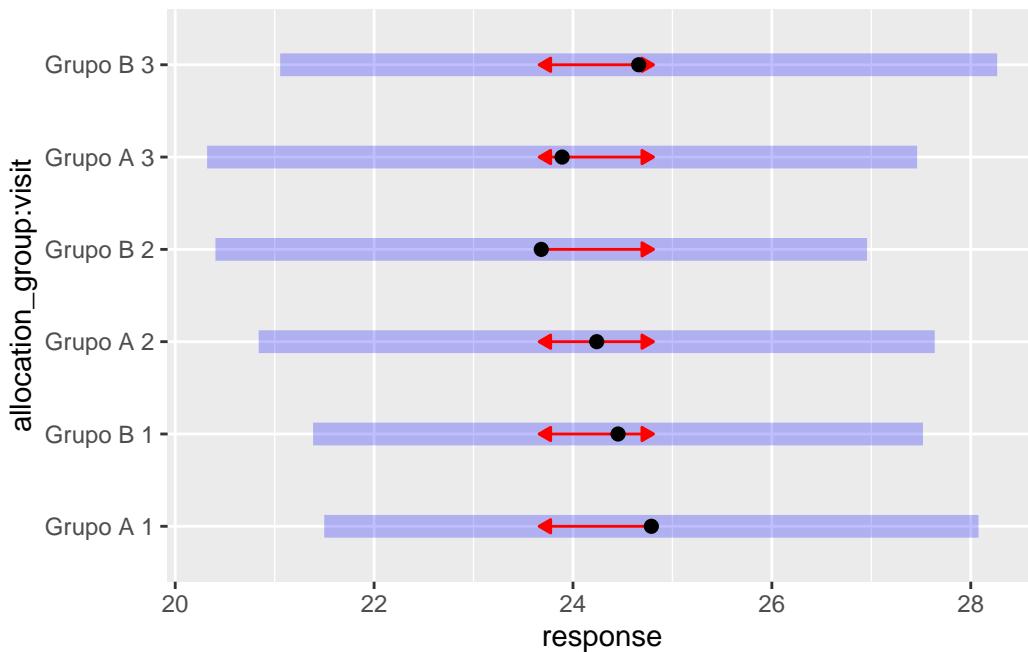
Degrees-of-freedom method: inherited from kenward-roger when re-gridding

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)
```



3.0.2.3 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
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 de comparação	Comparação	Estimativa	IC 95%	p-valor
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))

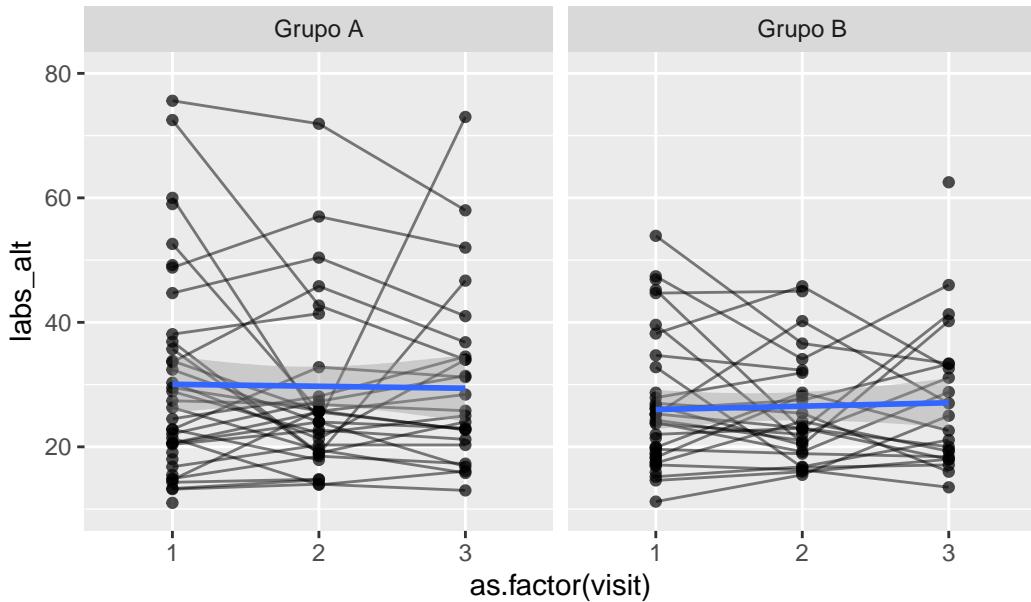
`geom_smooth()` using formula = 'y ~ x'
Warning: Removed 10 rows containing non-finite outside the scale range
(`stat_smooth()`).

```

```
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))

```

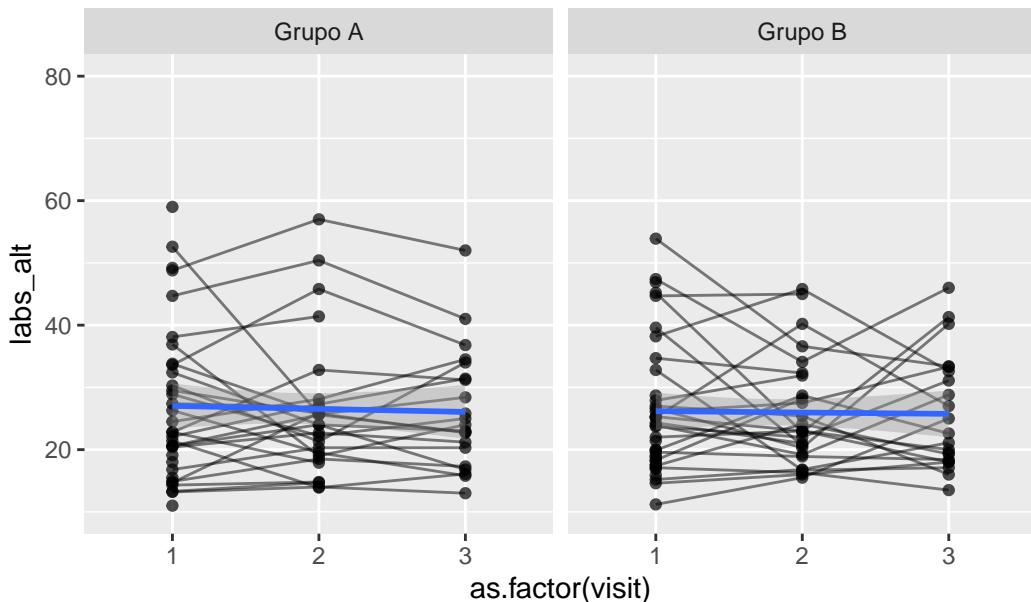
`geom_smooth()` using formula = 'y ~ x'

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



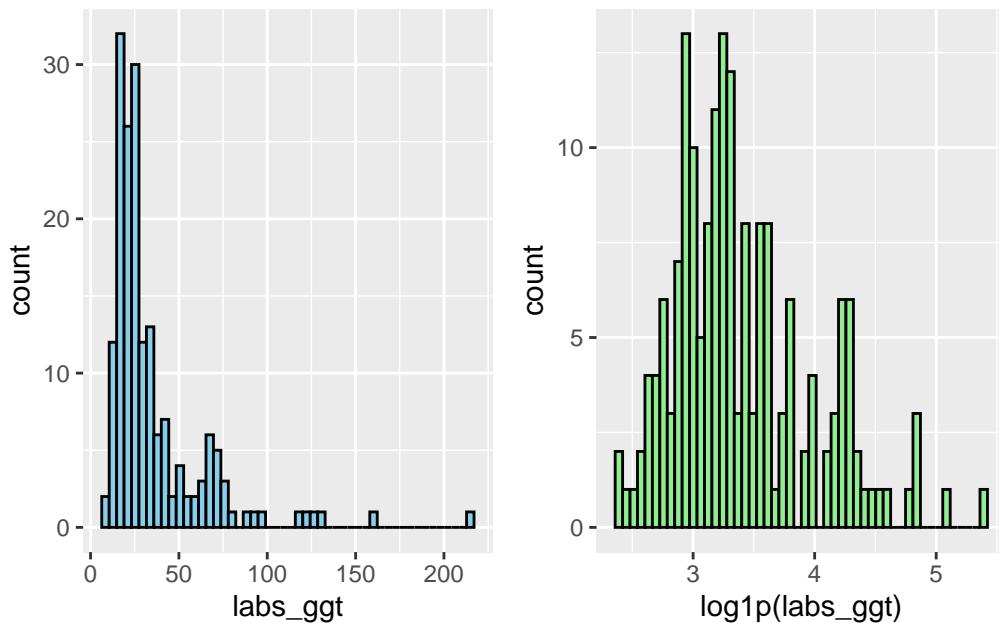
3.0.3 Gama Glutamil-transferase

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"

```

3.0.3.1 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	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:visit2	0.04689	0.08964	99.59537	0.523	0.602
allocation_group:visit3	0.02698	0.09736	99.95801	0.277	0.782

(Intercept)	***
allocation_group	Grupo B
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_gr	GB	-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_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	-0.717				
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

```
labs_ggt_model_check$comparison_table
```

```
# A tibble: 16 x 6
```

Model	term	estimate	std.error	statistic	p.value
<chr>	<chr>	<dbl>	<dbl>	<dbl>	<dbl>
1 Original	(Intercept)	3.36	0.106	31.7	1.28e-47
2 Sensitivity	(Intercept)	3.21	0.0935	34.4	2.48e-47
3 Original	allocation_groupGrupo B	0.0528	0.149	0.354	7.24e- 1
4 Sensitivity	allocation_groupGrupo B	0.145	0.130	1.11	2.69e- 1
5 Original	allocation_groupGrupo B:v~	0.0469	0.0896	0.523	6.02e- 1
6 Sensitivity	allocation_groupGrupo B:v~	0.0613	0.0750	0.817	4.16e- 1
7 Original	allocation_groupGrupo B:v~	0.0270	0.0974	0.277	7.82e- 1
8 Sensitivity	allocation_groupGrupo B:v~	0.0169	0.0814	0.208	8.36e- 1
9 Original	sd__(Intercept)	0.599	NA	NA	NA
10 Sensitivity	sd__(Intercept)	0.502	NA	NA	NA

```

11 Original      sd__Observation          0.241    NA        NA        NA
12 Sensitivity  sd__Observation          0.191    NA        NA        NA
13 Original      visit2                  -0.0267   0.0610   -0.439   6.62e- 1
14 Sensitivity  visit2                  -0.0110   0.0507   -0.218   8.28e- 1
15 Original      visit3                  0.0122   0.0661   0.184   8.54e- 1
16 Sensitivity  visit3                  0.0389   0.0556   0.700   4.86e- 1

performance::compare_performance(
  labs_ggt_model,
  labs_ggt_model_sens)

```

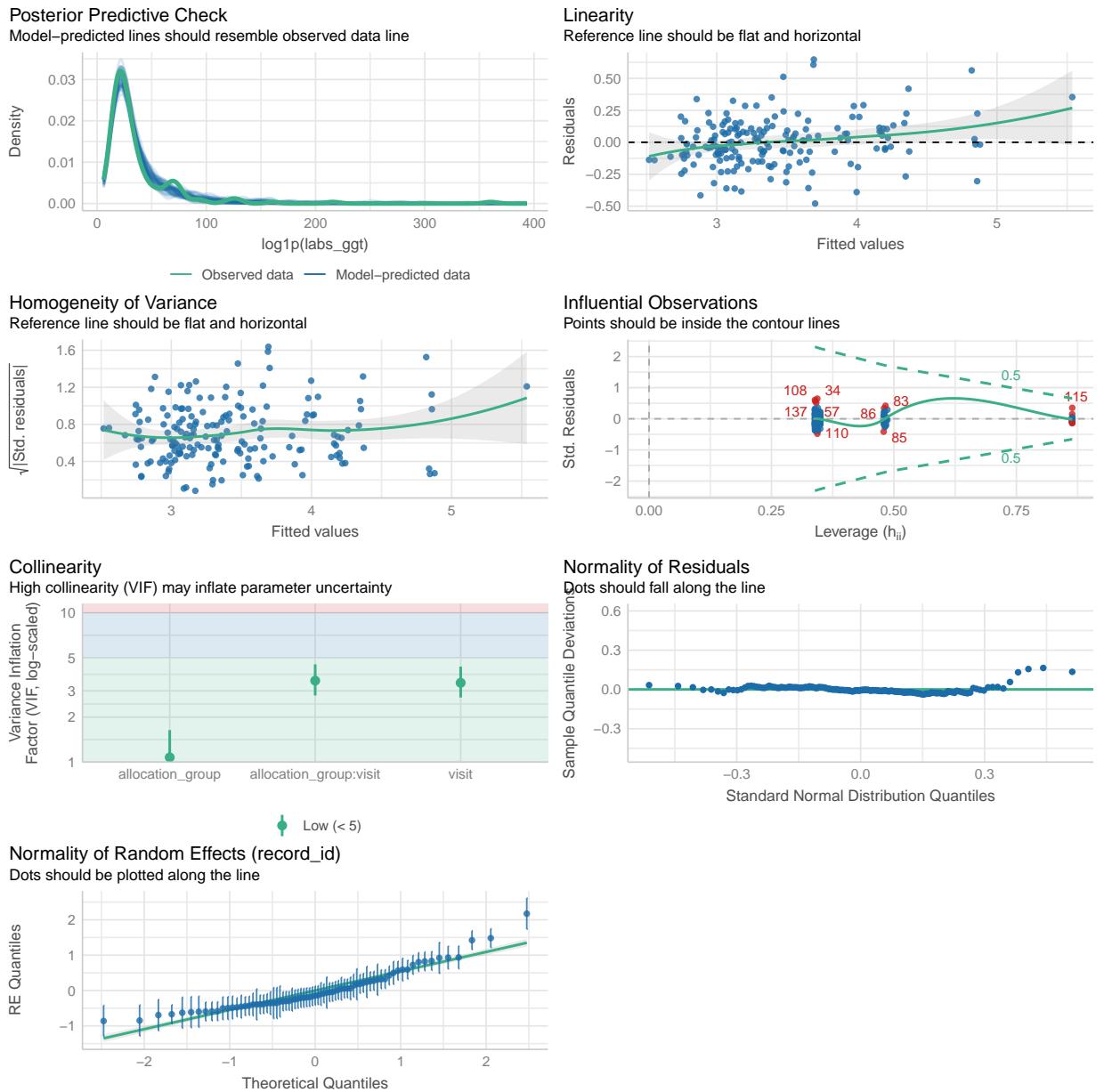
When comparing models, please note that probably not all models were fit from same data.

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

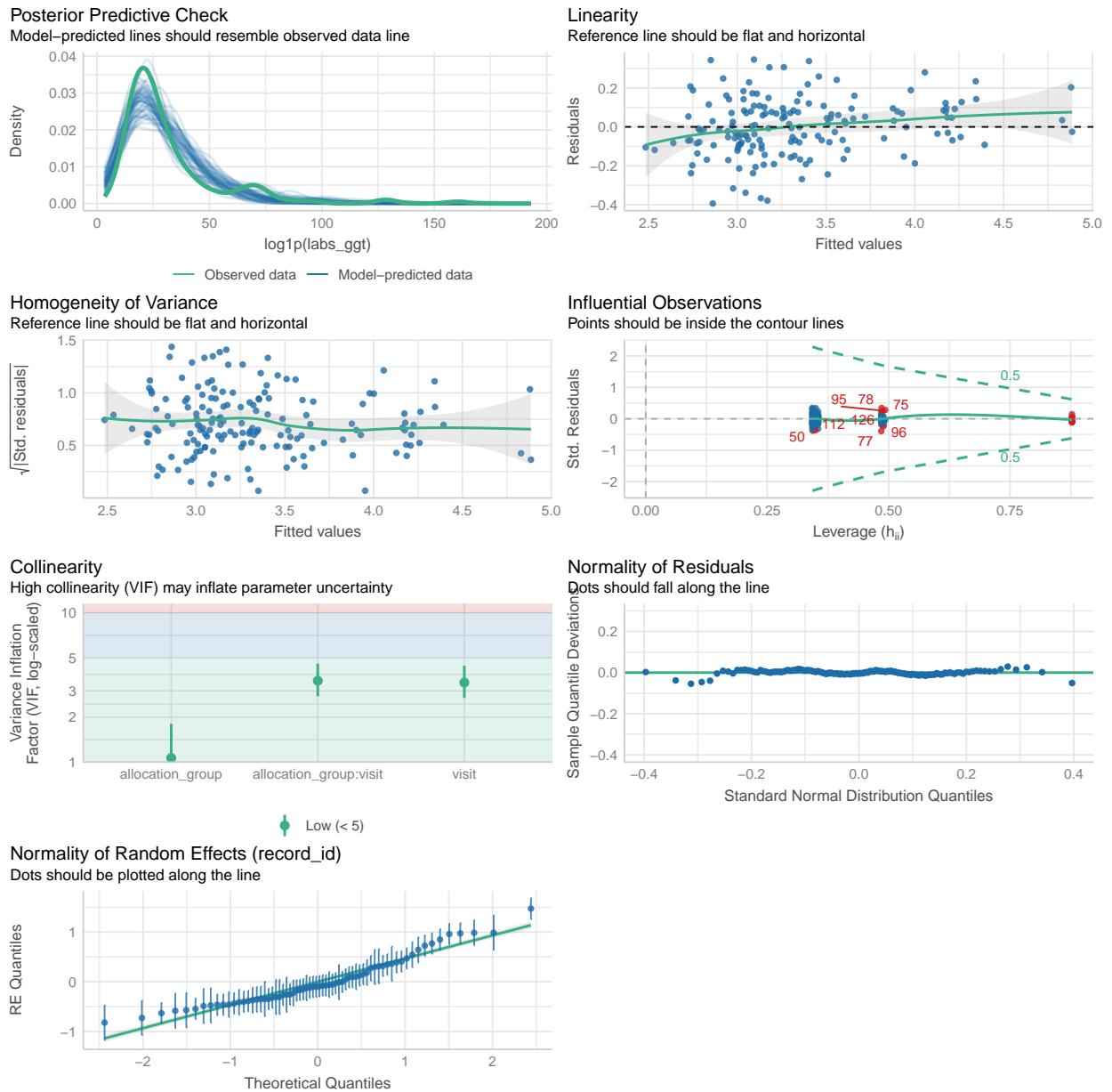
Name	Model	AIC (weights)	AICc (weights)
labs_ggt_model	lmerModLmerTest	1425.1 (<.001)	1426.0 (<.001)
labs_ggt_model_sens	lmerModLmerTest	1189.5 (>.999)	1190.4 (>.999)

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)
```



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



3.0.3.2 Médias Marginais Estimadas

3.0.3.2.1 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

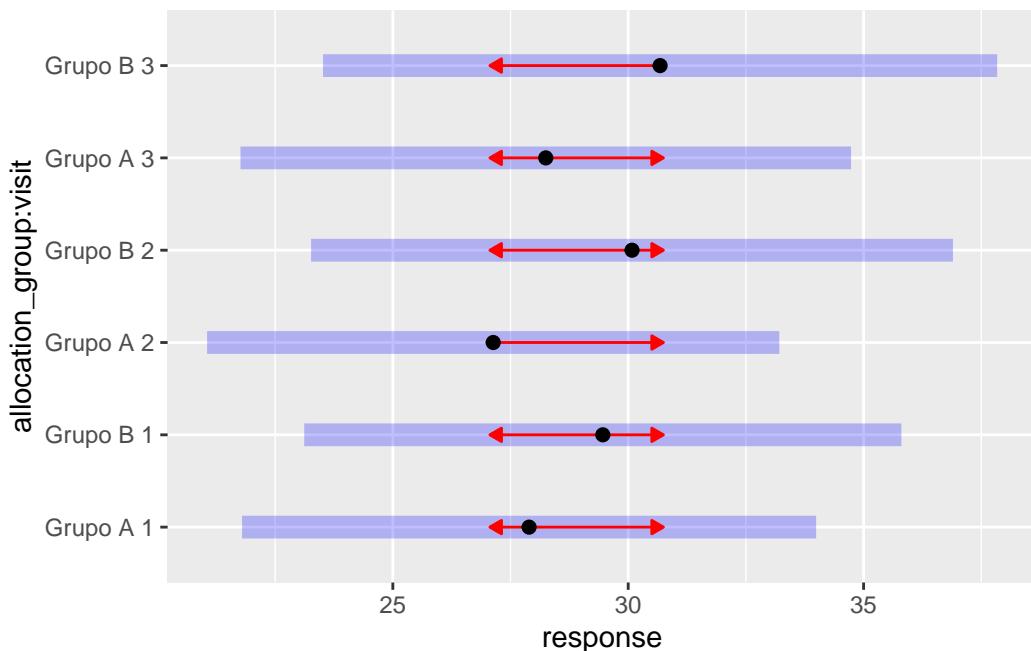
Conf-level adjustment: bonferroni method for 3 estimates

P value adjustment: bonferroni method for 3 tests

```

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

```



3.0.3.2.2 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  
emmmeans::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

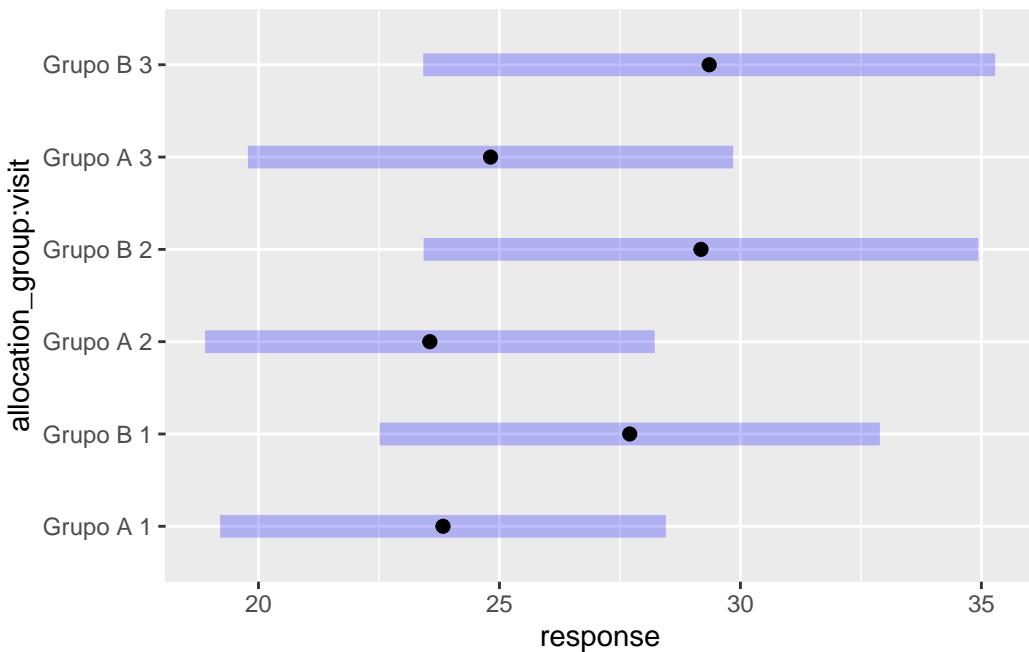
Degrees-of-freedom method: inherited from kenward-roger when re-gridding

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)
```



3.0.3.3 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
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 de

comparação	Comparação	Estimativa	IC 95%	p-valor
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)

```

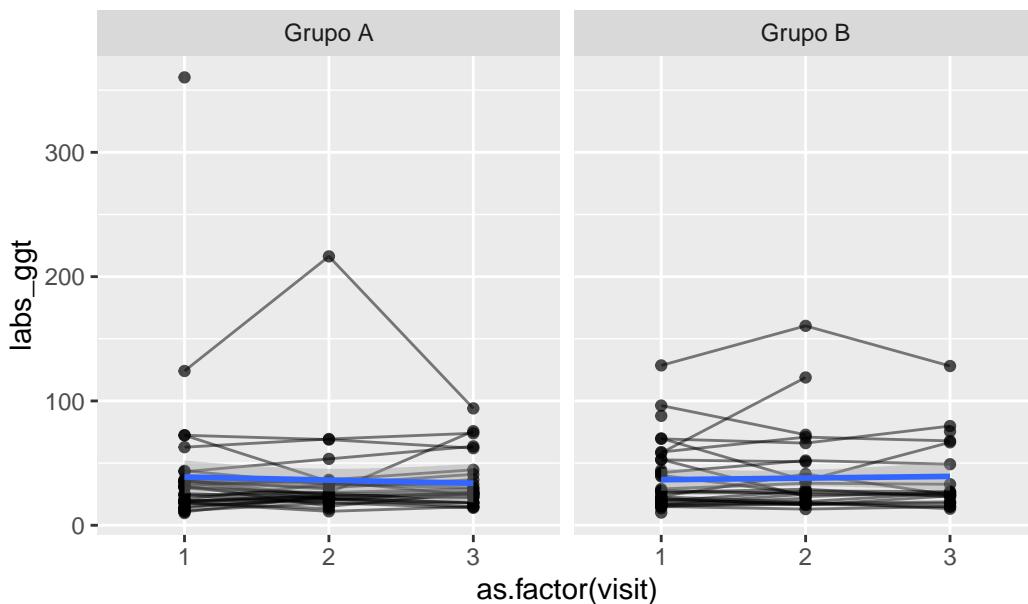
`geom_smooth()` using formula = 'y ~ x'

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)

```

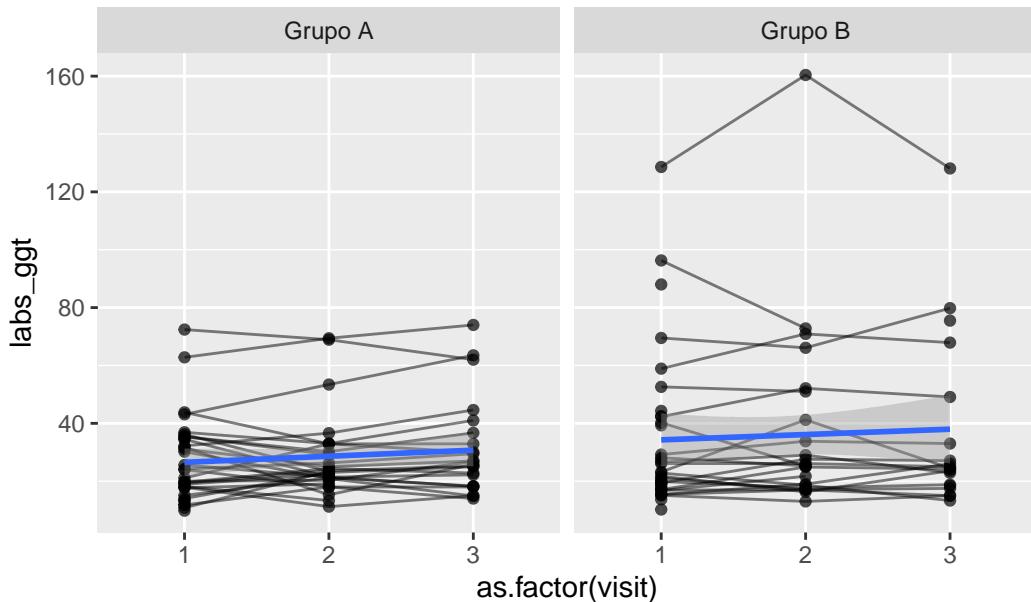
`geom_smooth()` using formula = 'y ~ x'

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))
```

3.0.4 Fosfatase Alcalina

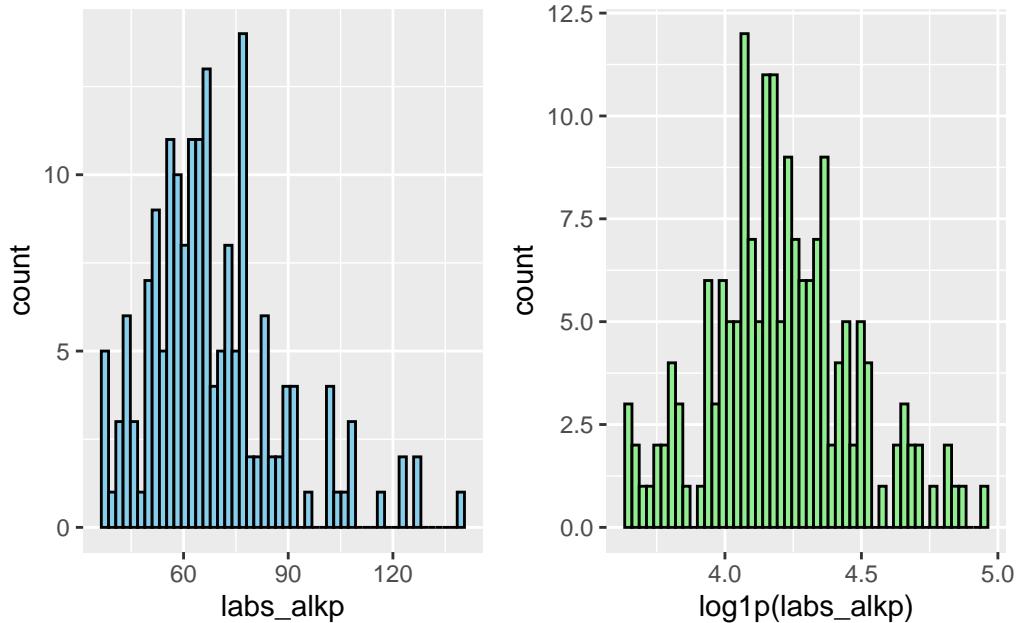
Variável: labs_alkp

```
# 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"

```

3.0.4.1 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			
<hr/>				
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	-0.020052	0.031577	93.770609	-0.635	0.527
allocation_group	-0.052680	0.034183	93.954152	-1.541	0.127

(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	-0.200	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

```
labs_alkp_model_check$comparison_table
```

```
# A tibble: 16 x 6
```

Model	term	estimate	std.error	statistic	p.value
<chr>	<chr>	<dbl>	<dbl>	<dbl>	<dbl>
1 Original	(Intercept)	4.21	0.0437	96.4	6.67e-88
2 Sensitivity	(Intercept)	4.20	0.0446	94.2	4.38e-80
3 Original	allocation_groupGrupo B	0.0332	0.0614	0.540	5.90e- 1
4 Sensitivity	allocation_groupGrupo B	0.0717	0.0626	1.15	2.55e- 1
5 Original	allocation_groupGrupo B:v~	0.0184	0.0375	0.491	6.24e- 1
6 Sensitivity	allocation_groupGrupo B:v~	-0.0201	0.0316	-0.635	5.27e- 1
7 Original	allocation_groupGrupo B:v~	0.00418	0.0407	0.103	9.18e- 1
8 Sensitivity	allocation_groupGrupo B:v~	-0.0527	0.0342	-1.54	1.27e- 1
9 Original	sd__(Intercept)	0.246	NA	NA	NA
10 Sensitivity	sd__(Intercept)	0.251	NA	NA	NA

```

11 Original    sd__Observation      0.101     NA      NA      NA
12 Sensitivity sd__Observation      0.0818    NA      NA      NA
13 Original    visit2              -0.0469    0.0255  -1.84   6.92e- 2
14 Sensitivity visit2              -0.0214    0.0214  -1.00   3.20e- 1
15 Original    visit3              -0.0303    0.0277  -1.09   2.77e- 1
16 Sensitivity visit3              -0.00287   0.0234  -0.123  9.03e- 1

performance::compare_performance(
  labs_alkp_model,
  labs_alkp_model_sens)

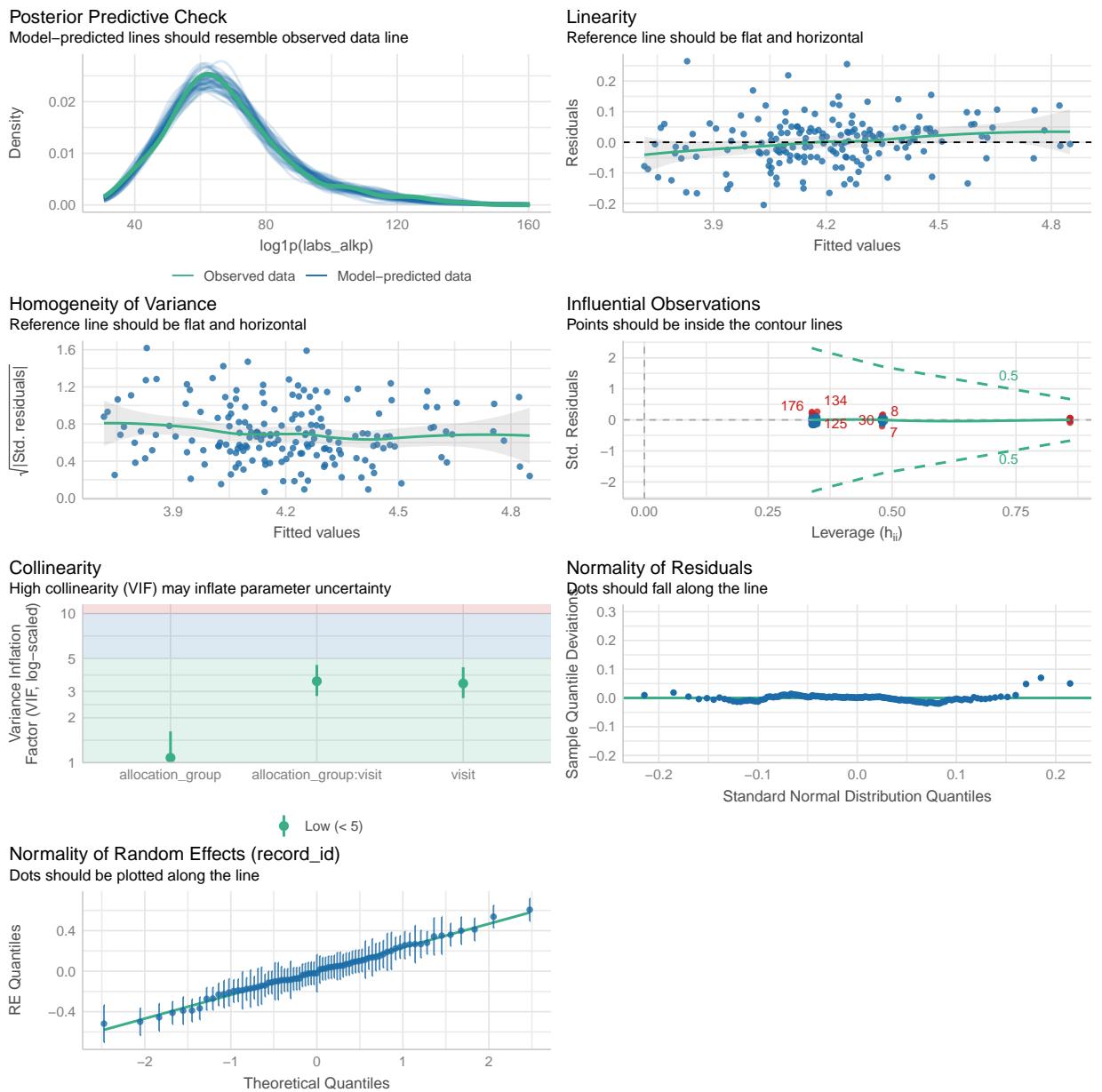
```

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

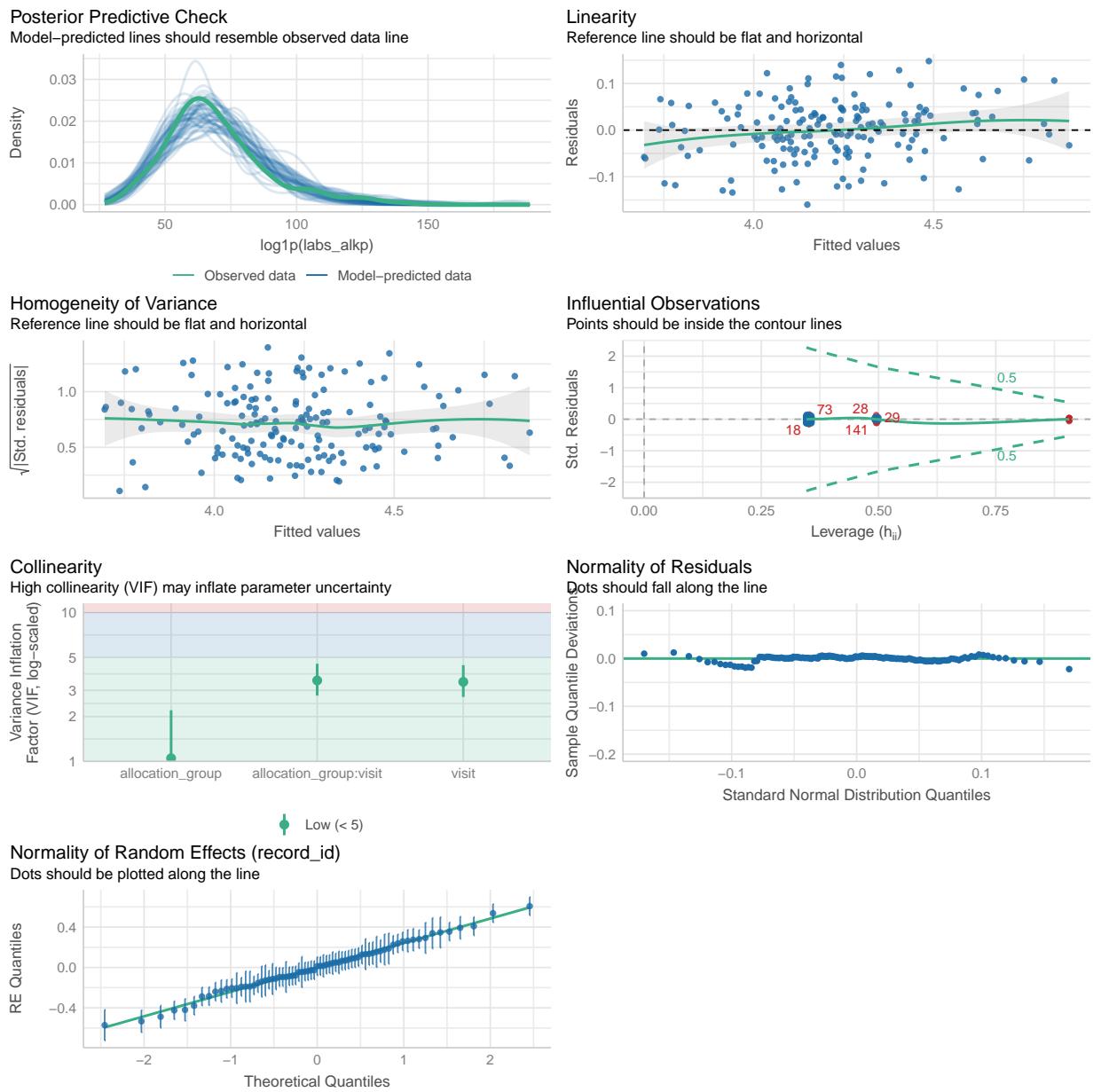
```
# Comparison of Model Performance Indices
```

Name		Model	AIC (weights)	AICc (weights)			
<hr/>							
labs_alkp_model		lmerModLmerTest	1394.9 (<.001)	1395.7 (<.001)			
labs_alkp_model_sens		lmerModLmerTest	1274.2 (>.999)	1275.1 (>.999)			
<hr/>							
Name		BIC (weights)	R2 (cond.)	R2 (marg.)	ICC	RMSE	Sigma
<hr/>					<hr/>		
labs_alkp_model		1420.3 (<.001)	0.857	0.010	0.855	0.077	0.100
labs_alkp_model_sens		1299.1 (>.999)	0.905	0.015	0.904	0.062	0.080

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



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



3.0.4.2 Médias Marginais Estimadas

3.0.4.2.1 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

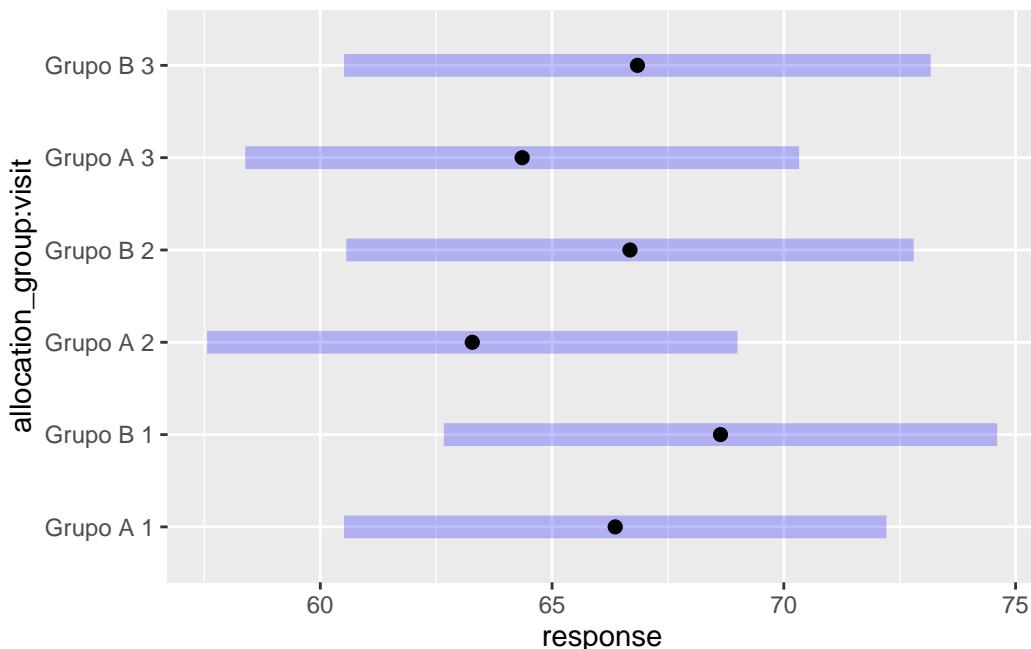
Conf-level adjustment: bonferroni method for 3 estimates

P value adjustment: bonferroni method for 3 tests

```

# Plot of marginal means
plot(labs_alkp_raw_emm)

```



3.0.4.2.2 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.

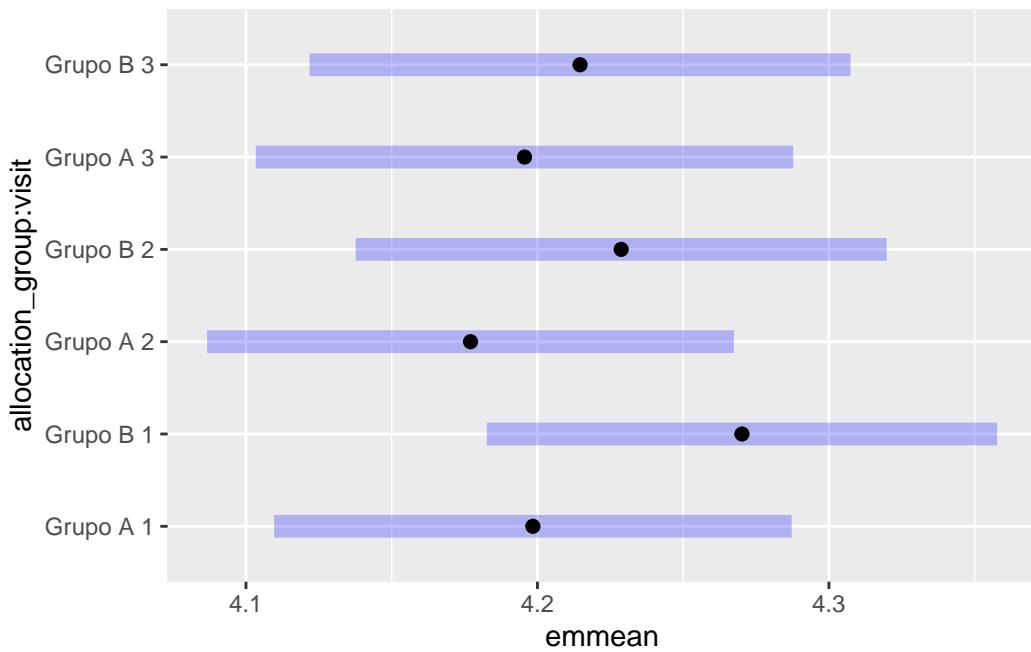
Degrees-of-freedom method: kenward-roger

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)
```



3.0.4.3 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 de comparação	Comparação	Estimativa	IC 95%	p-valor
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)

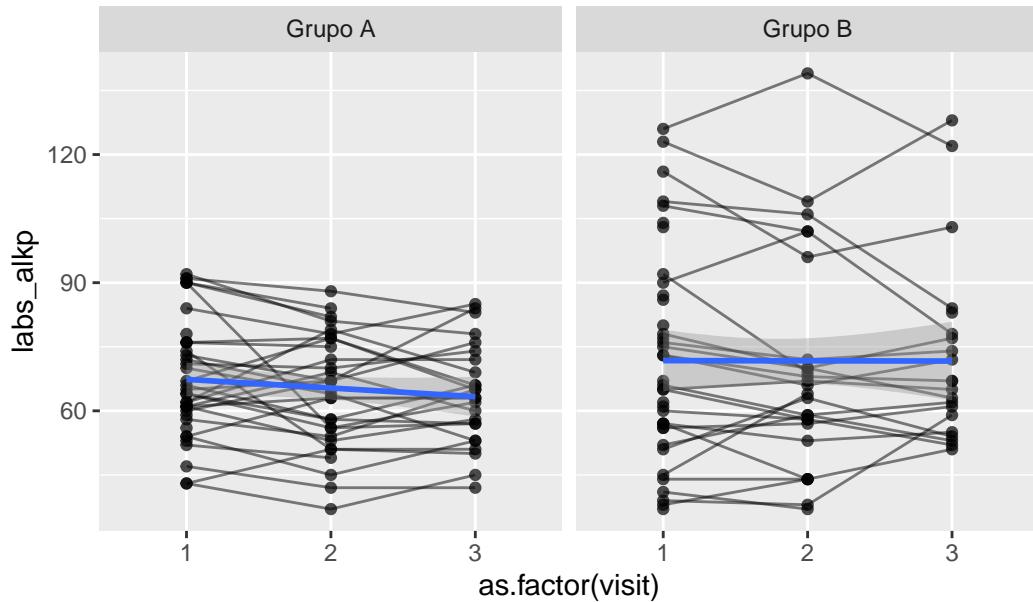
`geom_smooth()` using formula = 'y ~ x'
Warning: Removed 11 rows containing non-finite outside the scale range
(`stat_smooth()`).

```

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)

```

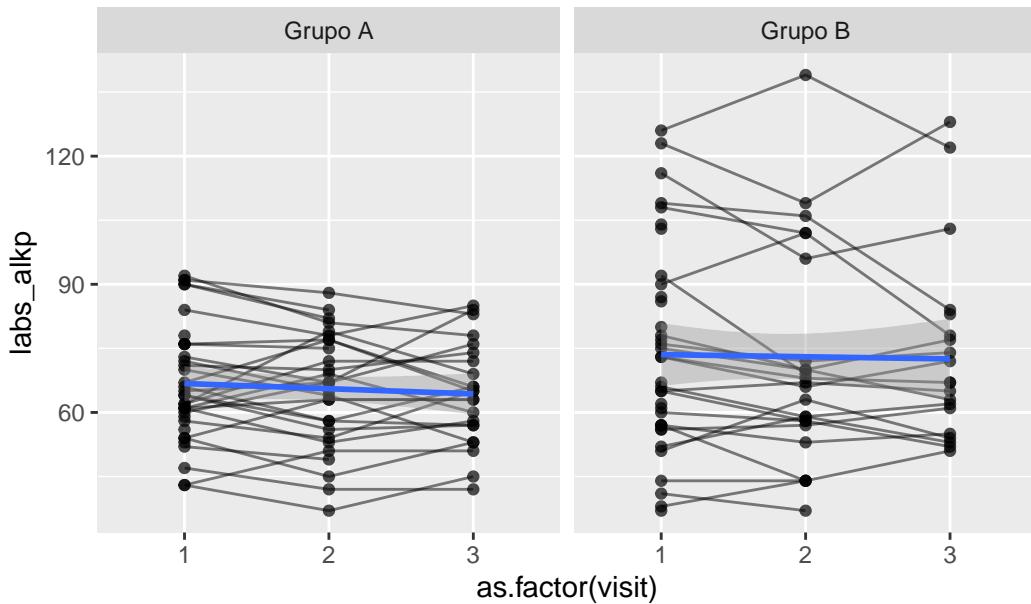
`geom_smooth()` using formula = 'y ~ x'

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))
```

3.0.5 Colesterol Total

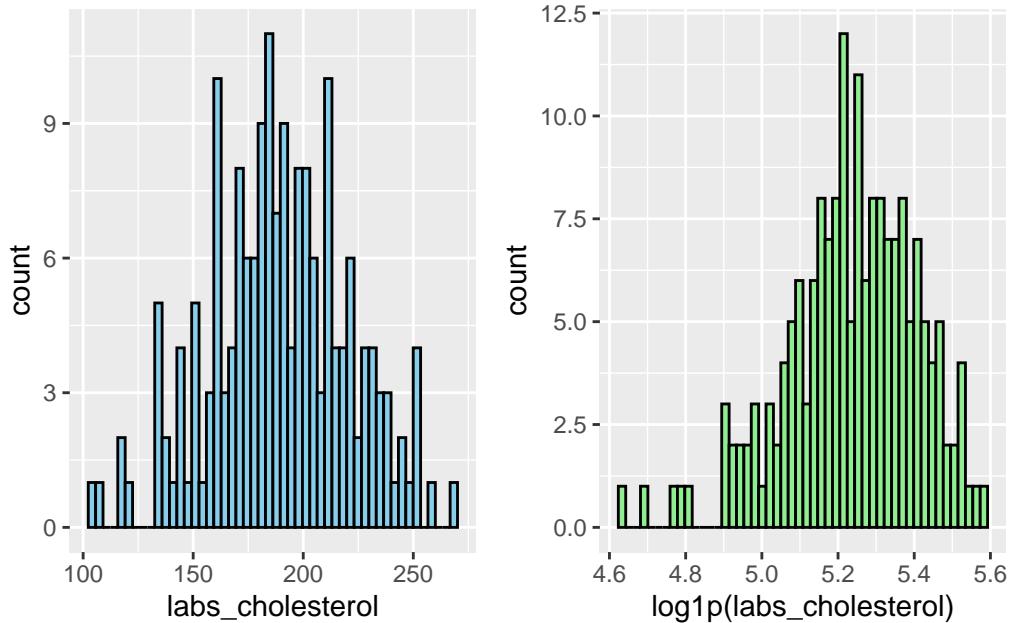
Variável: labs_cholesterol

```
# 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"

```

3.0.5.1 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_gr	GB	-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	-1.5573	4.5754	93.8263	-0.340	0.7343
allocation_group	-2.1290	4.9645	94.1891	-0.429	0.6690

(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	-0.727				
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

```
labs_cholesterol_model_check$comparison_table
```

```
# A tibble: 16 x 6
```

Model	term	estimate	std.error	statistic	p.value
<chr>	<chr>	<dbl>	<dbl>	<dbl>	<dbl>
1 Original	(Intercept)	191.	5.20	36.8	1.19e-58
2 Sensitivity	(Intercept)	191.	5.13	37.3	1.85e-52
3 Original	allocation_groupGrupo B	-0.717	7.30	-0.0981	9.22e- 1
4 Sensitivity	allocation_groupGrupo B	-0.678	7.05	-0.0961	9.24e- 1
5 Original	allocation_groupGrupo B:v~	-0.115	5.91	-0.0195	9.84e- 1
6 Sensitivity	allocation_groupGrupo B:v~	-1.56	4.58	-0.340	7.34e- 1
7 Original	allocation_groupGrupo B:v~	-7.76	6.36	-1.22	2.25e- 1
8 Sensitivity	allocation_groupGrupo B:v~	-2.13	4.96	-0.429	6.69e- 1
9 Original	sd__(Intercept)	27.3	NA	NA	NA
10 Sensitivity	sd__(Intercept)	27.0	NA	NA	NA

```

11 Original      sd__Observation          16.0       NA       NA       NA
12 Sensitivity  sd__Observation          11.8       NA       NA       NA
13 Original      visit2                  -5.91      4.03    -1.47   1.46e- 1
14 Sensitivity  visit2                  -5.98      3.19    -1.87   6.41e- 2
15 Original      visit3                  -0.380     4.37    -0.0869 9.31e- 1
16 Sensitivity  visit3                  -3.94      3.51    -1.12   2.65e- 1

```

```

  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.

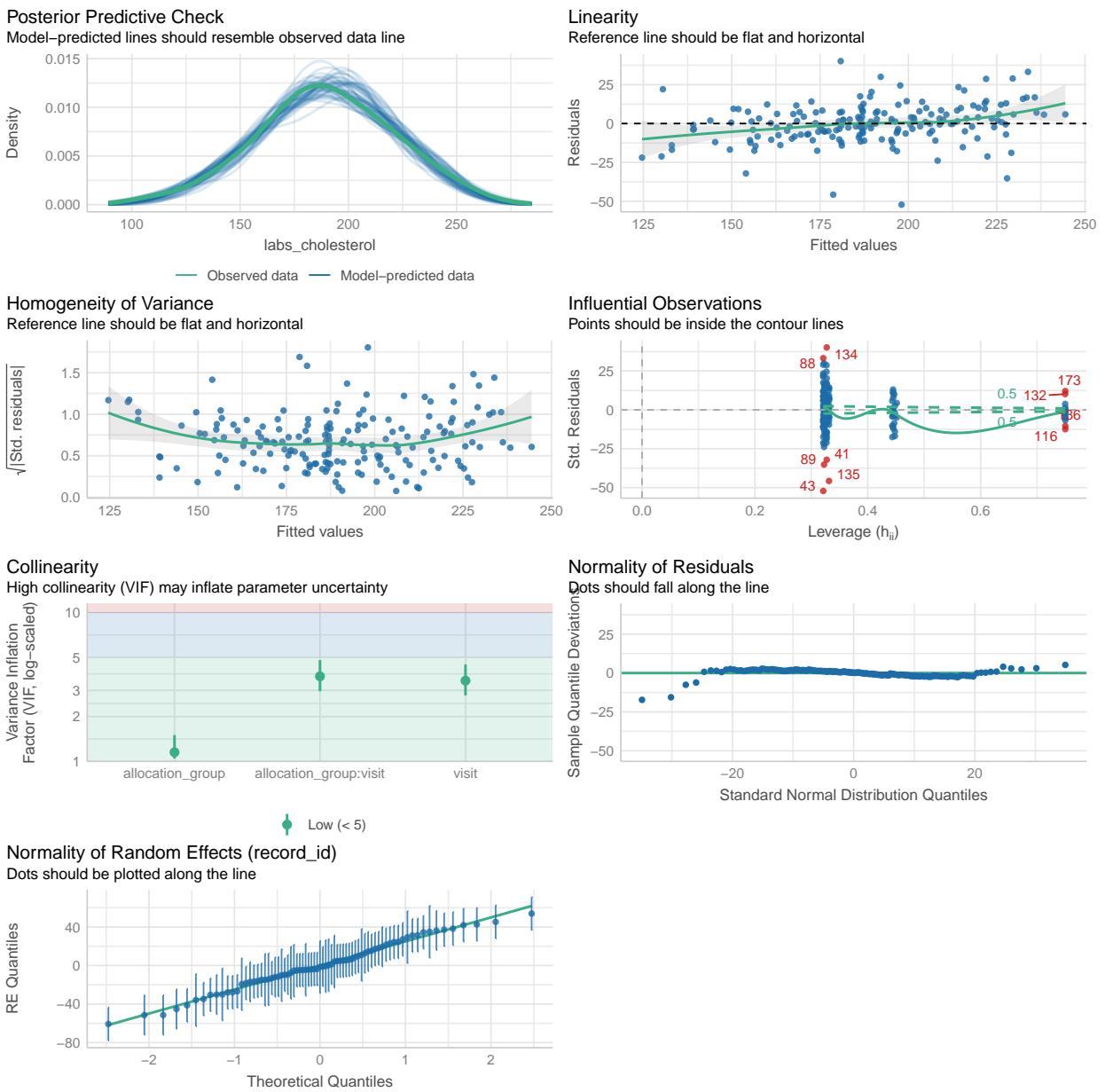
```
# Comparison of Model Performance Indices
```

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)

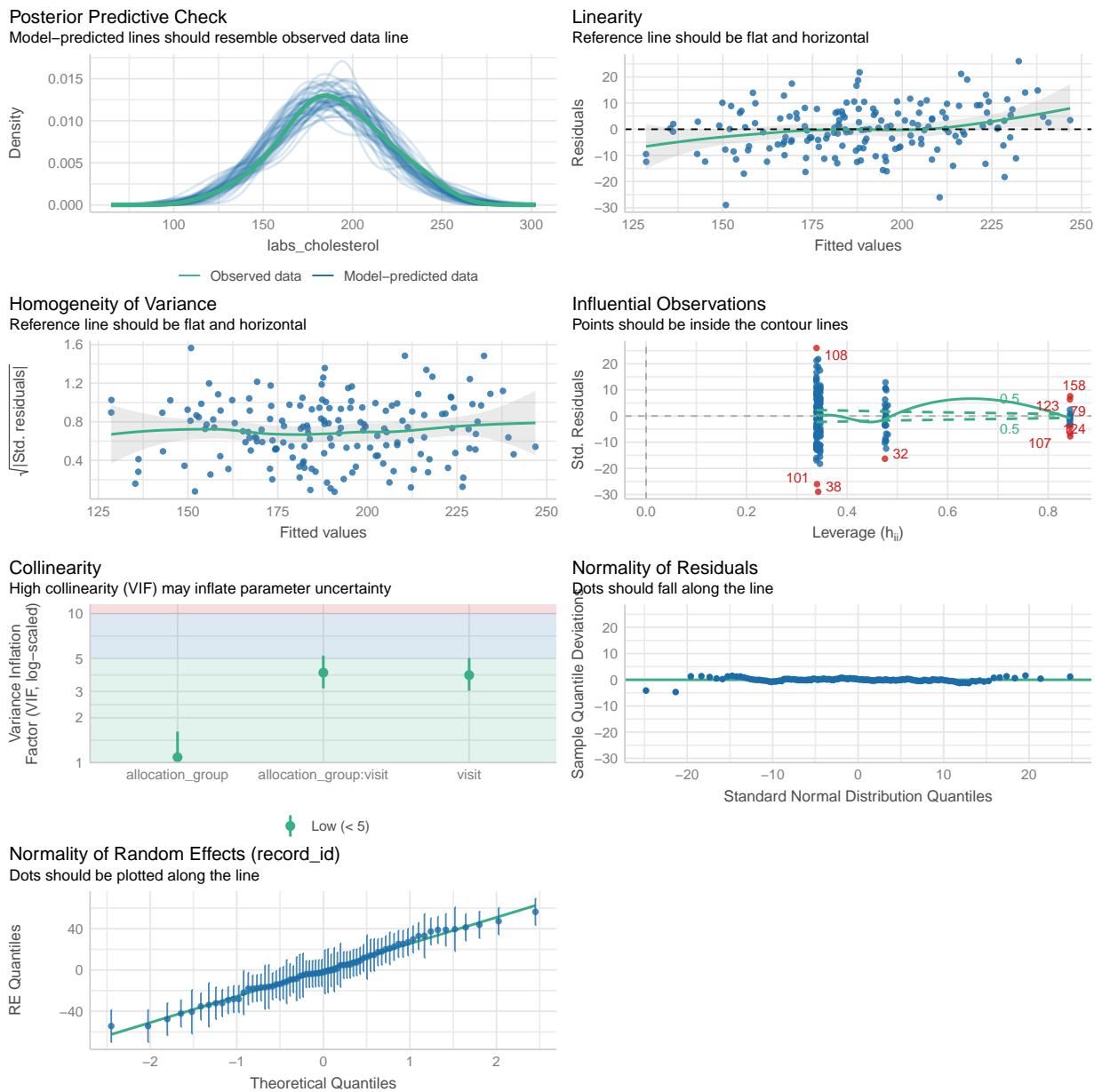
Name	BIC (weights)	R2 (cond.)	R2 (marg.)	ICC
labs_cholesterol_model	1687.3 (<.001)	0.746	0.011	0.743
labs_cholesterol_model_sens	1486.0 (>.999)	0.841	0.011	0.839

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)
```



3.0.5.2 Médias Marginais Estimadas

3.0.5.2.1 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

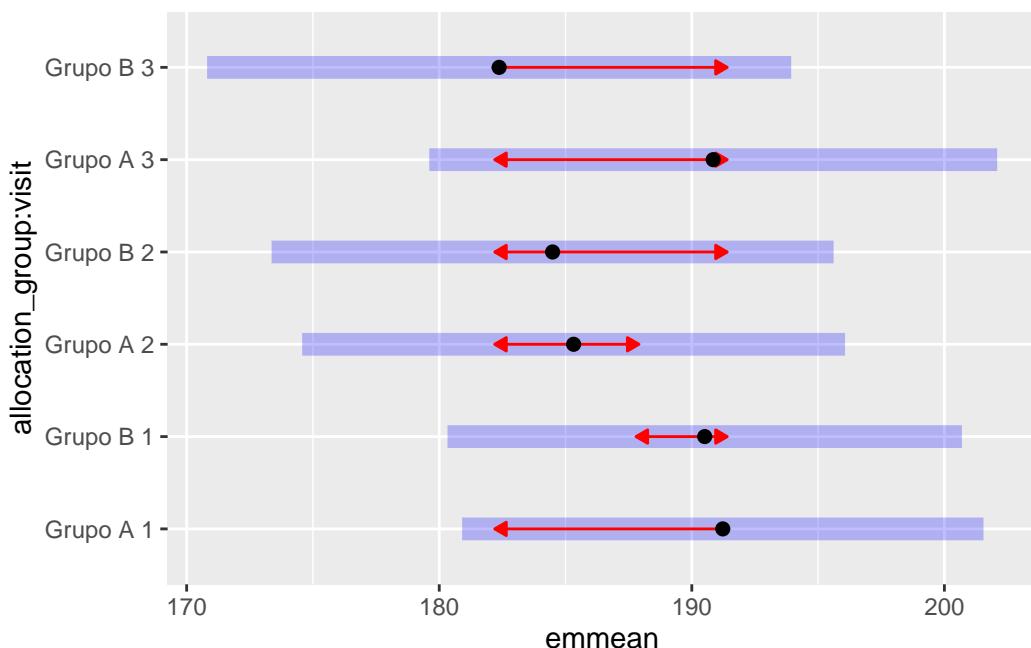
Conf-level adjustment: bonferroni method for 3 estimates

P value adjustment: bonferroni method for 3 tests

```

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

```



3.0.5.2.2 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

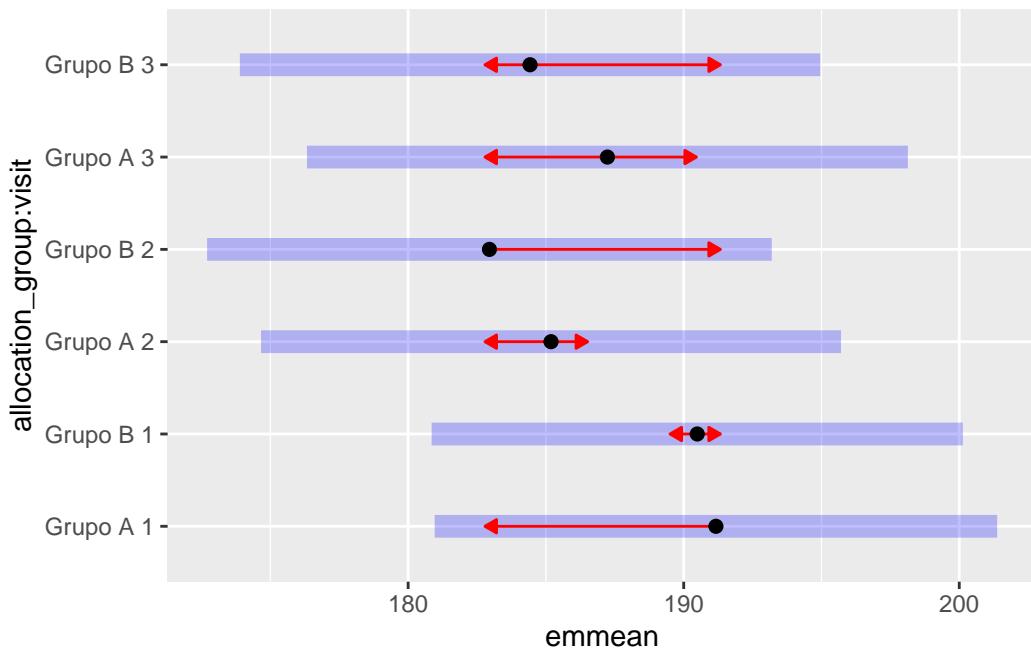
P value adjustment: bonferroni method for 3 tests

```
# 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



3.0.5.3 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 de comparação	Comparação	Estimativa	IC 95%	p-valor
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

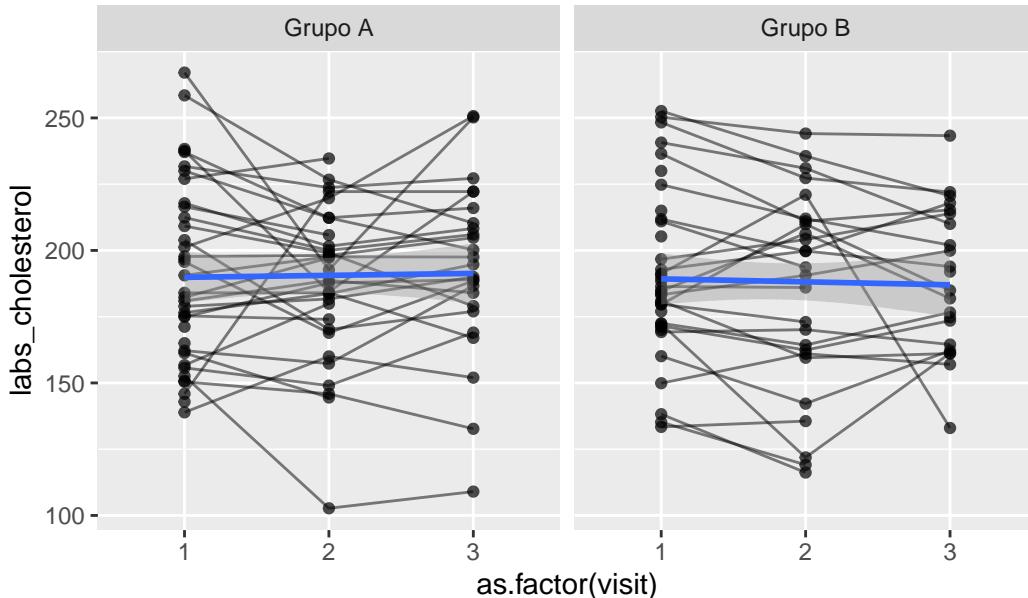
```

```
(`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)

```

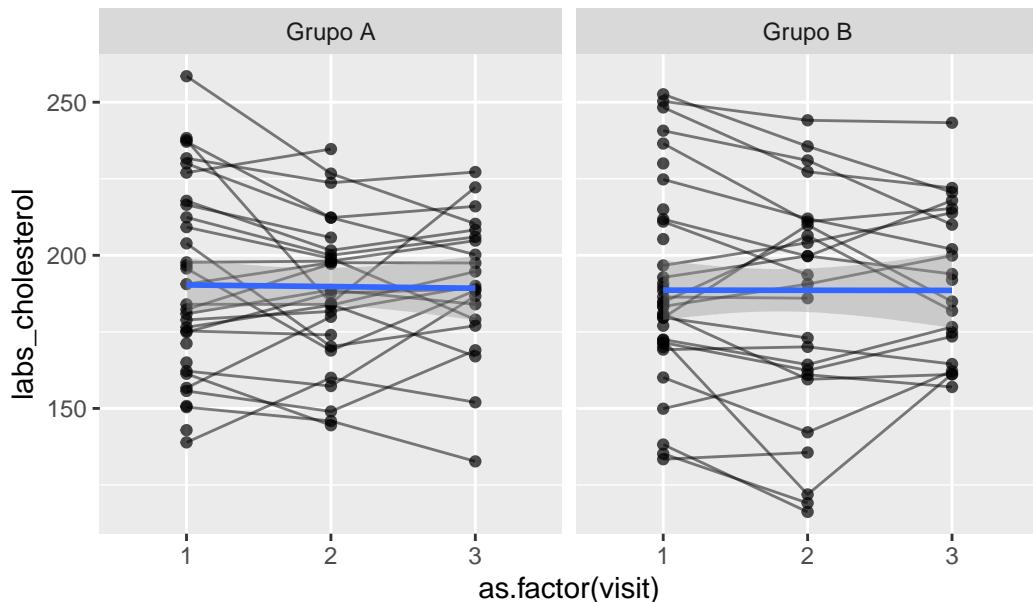
`geom_smooth()` using formula = 'y ~ x'

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))
```

3.0.6 LDL Colesterol

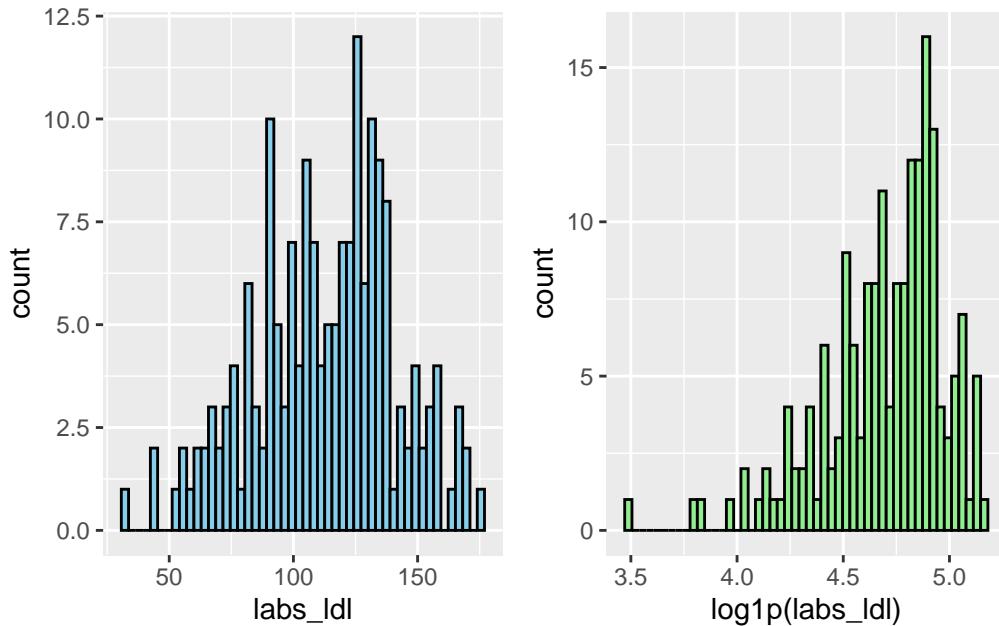
Variável: labs_ldl

```
# 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"

```

3.0.6.1 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	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_gr	GB	-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_group	-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_group:visit2	1.8681	4.1755	88.1990	0.447	0.6557
allocation_group: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

```
labs_ldl_model_check$comparison_table
```

A tibble: 16 x 6

Model	term	estimate	std.error	statistic	p.value
<chr>	<chr>	<dbl>	<dbl>	<dbl>	<dbl>
1 Original	(Intercept)	115.	4.81	24.0	6.20e-43
2 Sensitivity	(Intercept)	116.	4.88	23.7	1.00e-36
3 Original	allocation_groupGrupo B	-3.77	6.75	-0.559	5.78e- 1
4 Sensitivity	allocation_groupGrupo B	-3.83	6.71	-0.571	5.70e- 1
5 Original	allocation_groupGrupo B:v~	1.92	5.82	0.330	7.42e- 1
6 Sensitivity	allocation_groupGrupo B:v~	1.87	4.18	0.447	6.56e- 1
7 Original	allocation_groupGrupo B:v~	-5.91	6.25	-0.945	3.47e- 1
8 Sensitivity	allocation_groupGrupo B:v~	-5.57	4.55	-1.23	2.24e- 1
9 Original	sd__(Intercept)	24.6	NA	NA	NA
10 Sensitivity	sd__(Intercept)	25.5	NA	NA	NA

```

11 Original      sd__Observation          15.8       NA       NA       NA
12 Sensitivity  sd__Observation          10.6       NA       NA       NA
13 Original      visit2                  -5.59      3.97    -1.41   1.61e- 1
14 Sensitivity  visit2                  -5.19      2.91    -1.78   7.81e- 2
15 Original      visit3                  -0.0205    4.30    -0.00477 9.96e- 1
16 Sensitivity  visit3                  0.670     3.22     0.208   8.36e- 1

performance::compare_performance(
  labs_ldl_model,
  labs_ldl_model_sens)

```

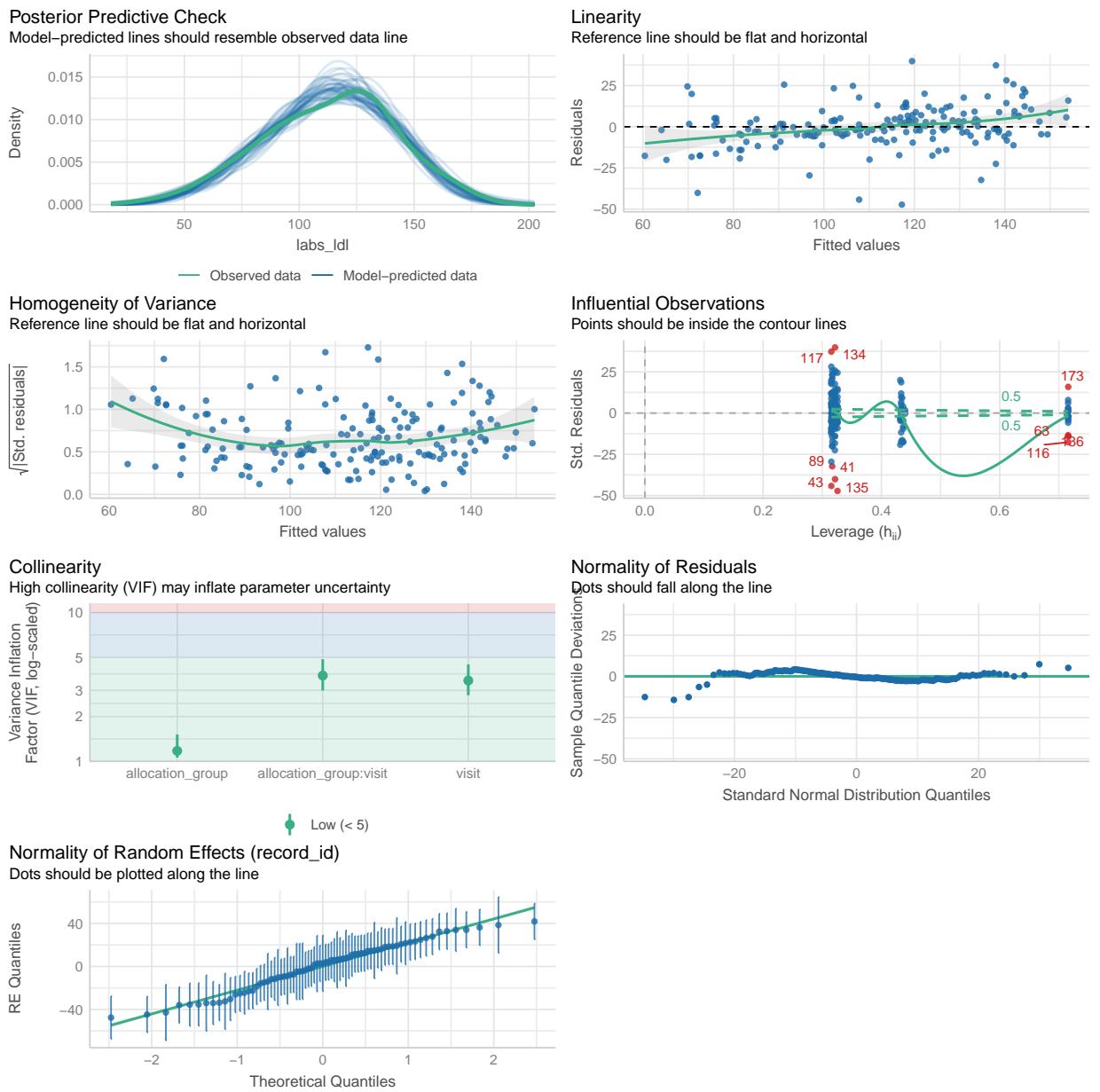
When comparing models, please note that probably not all models were fit from same data.

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

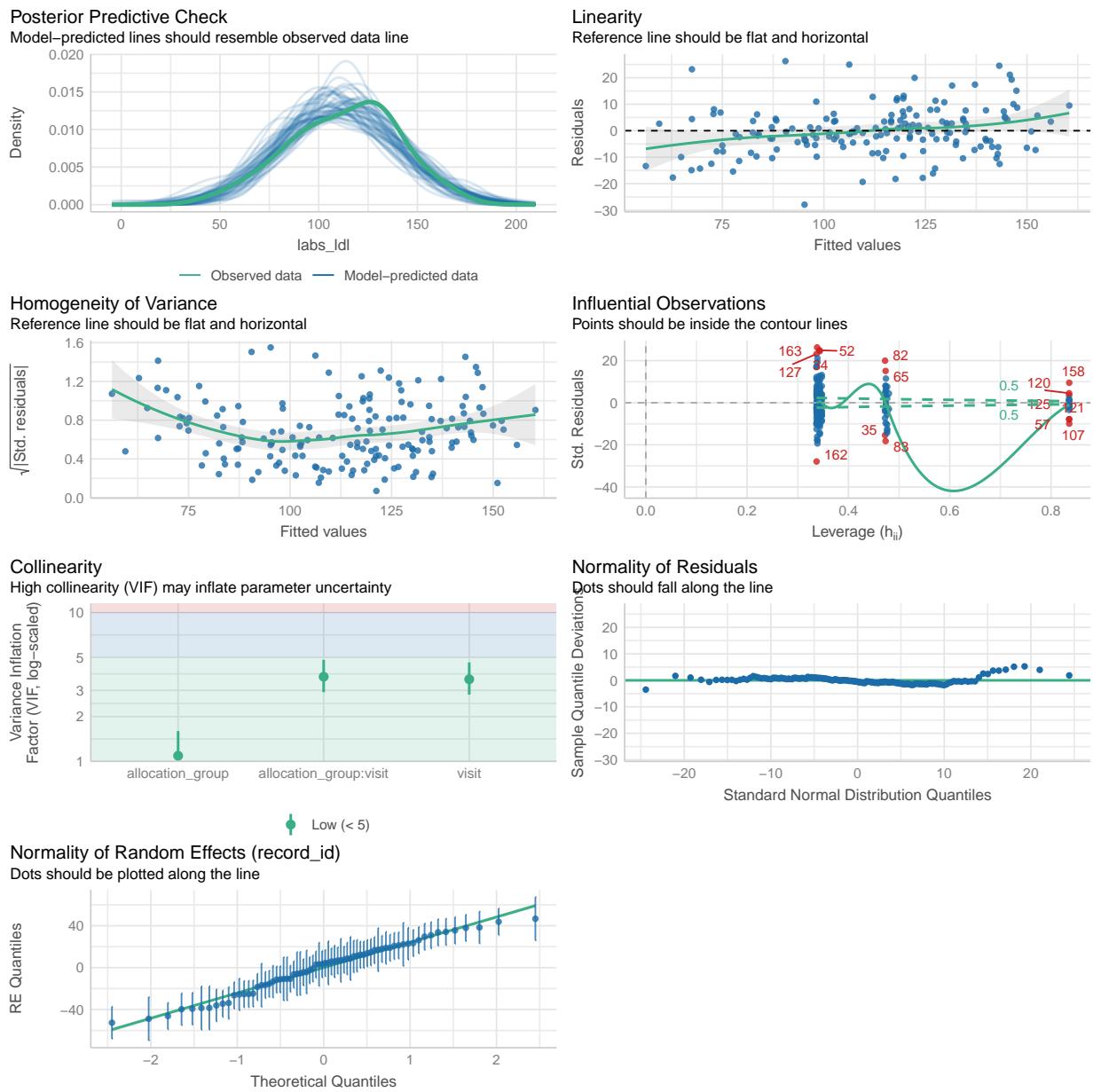
Name	Model	AIC (weights)	AICc (weights)
labs_ldl_model	lmerModLmerTest	1645.5 (<.001)	1646.4 (<.001)
labs_ldl_model_sens	lmerModLmerTest	1380.5 (>.999)	1381.5 (>.999)

Name	BIC (weights)	R2 (cond.)	R2 (marg.)	ICC	RMSE	Sig
labs_ldl_model	1671.0 (<.001)	0.712	0.014	0.708	12.514	15.8
labs_ldl_model_sens	1405.0 (>.999)	0.855	0.014	0.853	8.043	10.5

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



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



3.0.6.2 Médias Marginais Estimadas

3.0.6.2.1 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

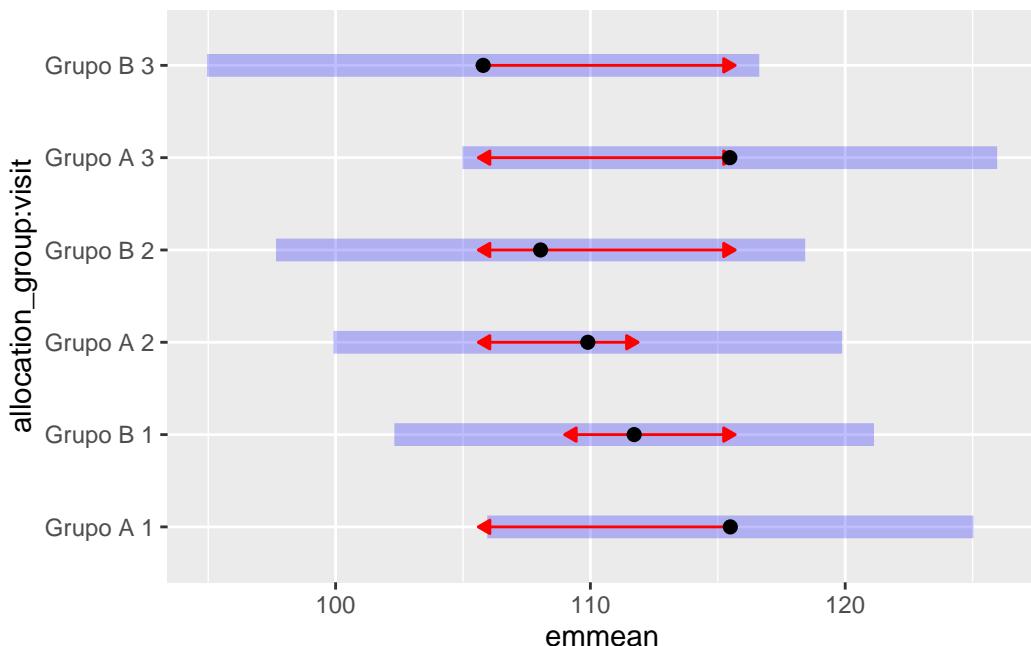
Conf-level adjustment: bonferroni method for 3 estimates

P value adjustment: bonferroni method for 3 tests

```

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

```



3.0.6.2.2 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  
emmmeans::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

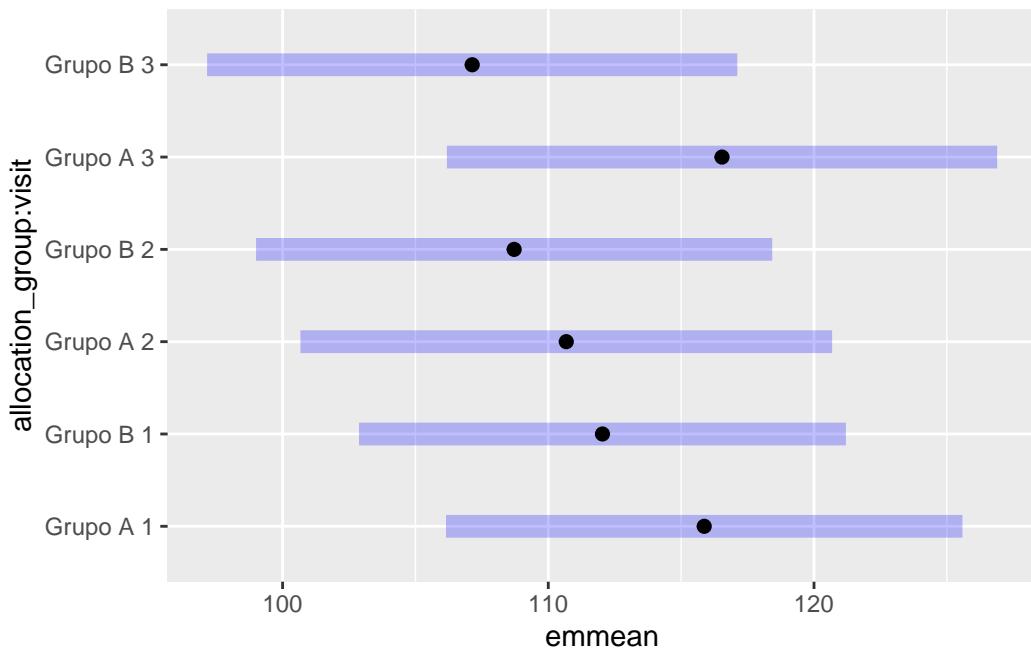
Degrees-of-freedom method: inherited from kenward-roger when re-gridding

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)
```



3.0.6.3 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
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 de comparação	Comparação	Estimativa	IC 95%	p-valor
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

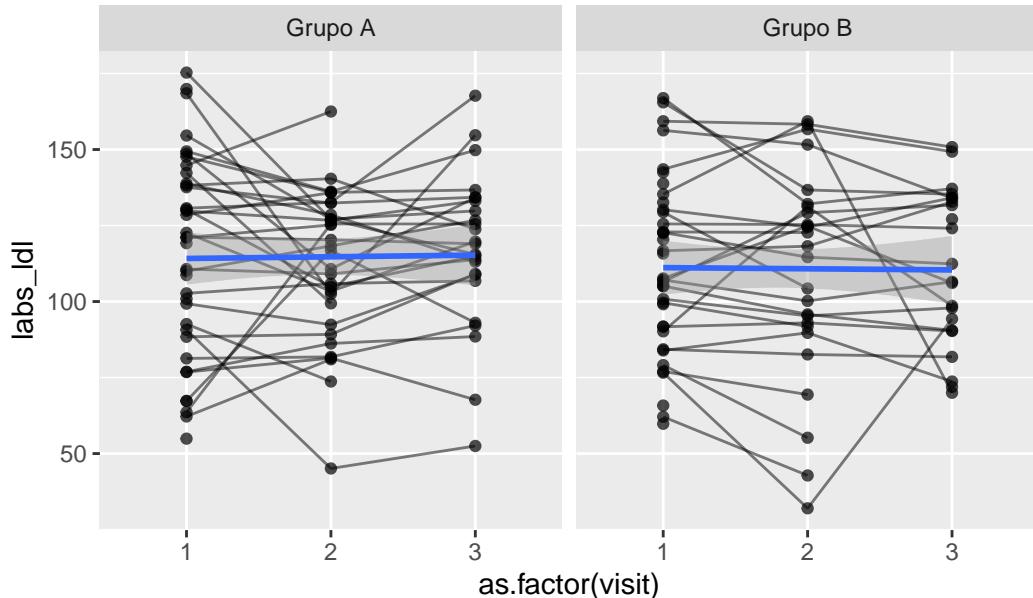
```

```
(`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)

```

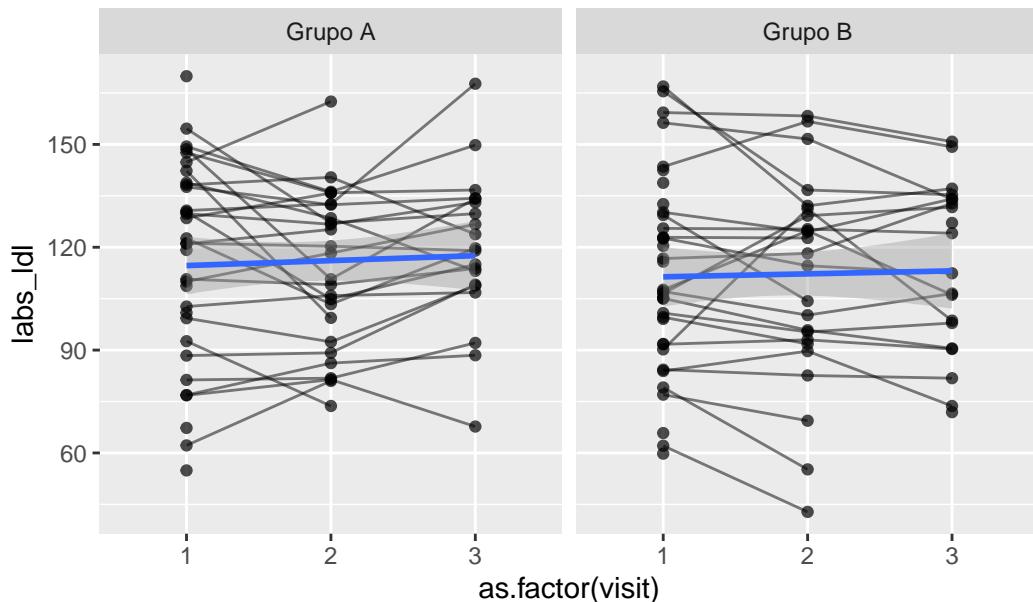
`geom_smooth()` using formula = 'y ~ x'

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))
```

3.0.7 HDL Colesterol

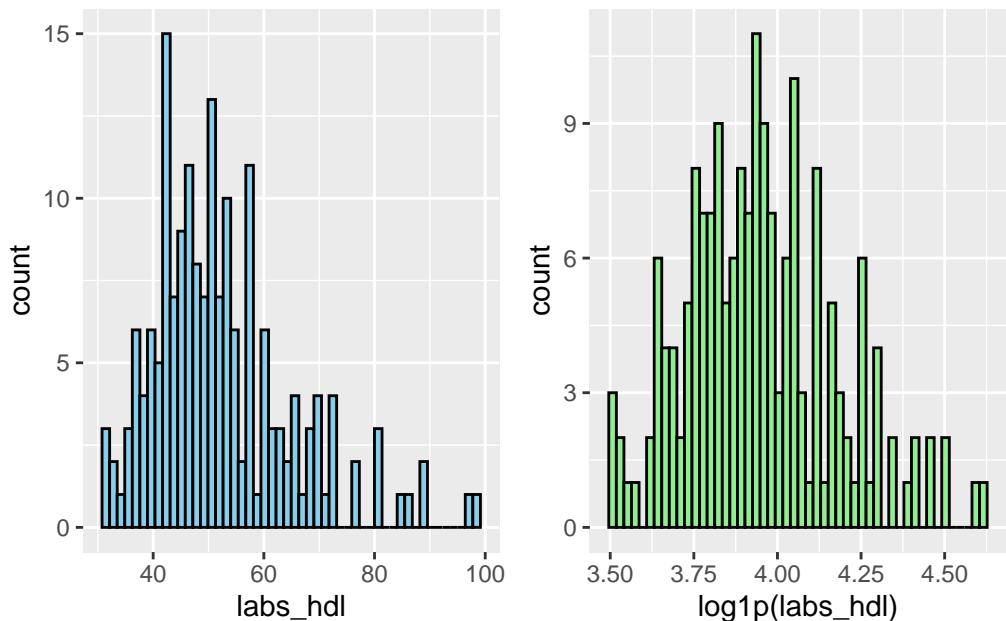
Variável: labs_hdl

```
# 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"

```

3.0.7.1 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	Grupo B
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_gr	GB	-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_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	-0.295	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

```
labs_hdl_model_check$comparison_table
```

A tibble: 16 x 6

Model	term	estimate	std.error	statistic	p.value
<chr>	<chr>	<dbl>	<dbl>	<dbl>	<dbl>
1 Original	(Intercept)	3.94	0.0382	103.	2.78e-99
2 Sensitivity	(Intercept)	3.93	0.0373	105.	1.23e-89
3 Original	allocation_groupGrupo B	0.0650	0.0536	1.21	2.28e- 1
4 Sensitivity	allocation_groupGrupo B	0.0671	0.0528	1.27	2.07e- 1
5 Original	allocation_groupGrupo B:v~	-0.0221	0.0442	-0.501	6.18e- 1
6 Sensitivity	allocation_groupGrupo B:v~	-0.0294	0.0386	-0.763	4.48e- 1
7 Original	allocation_groupGrupo B:v~	-0.0318	0.0475	-0.671	5.04e- 1
8 Sensitivity	allocation_groupGrupo B:v~	-0.0386	0.0419	-0.922	3.59e- 1
9 Original	sd__(Intercept)	0.199	NA	NA	NA
10 Sensitivity	sd__(Intercept)	0.197	NA	NA	NA

```

11 Original      sd__Observation          0.120    NA        NA        NA
12 Sensitivity  sd__Observation          0.100    NA        NA        NA
13 Original      visit2                  -0.0172   0.0301   -0.573   5.68e- 1
14 Sensitivity  visit2                  -0.0103   0.0261   -0.394   6.95e- 1
15 Original      visit3                  -0.0193   0.0326   -0.591   5.56e- 1
16 Sensitivity  visit3                  -0.0134   0.0281   -0.477   6.35e- 1

performance::compare_performance(
  labs_hdl_model,
  labs_hdl_model_sens)

```

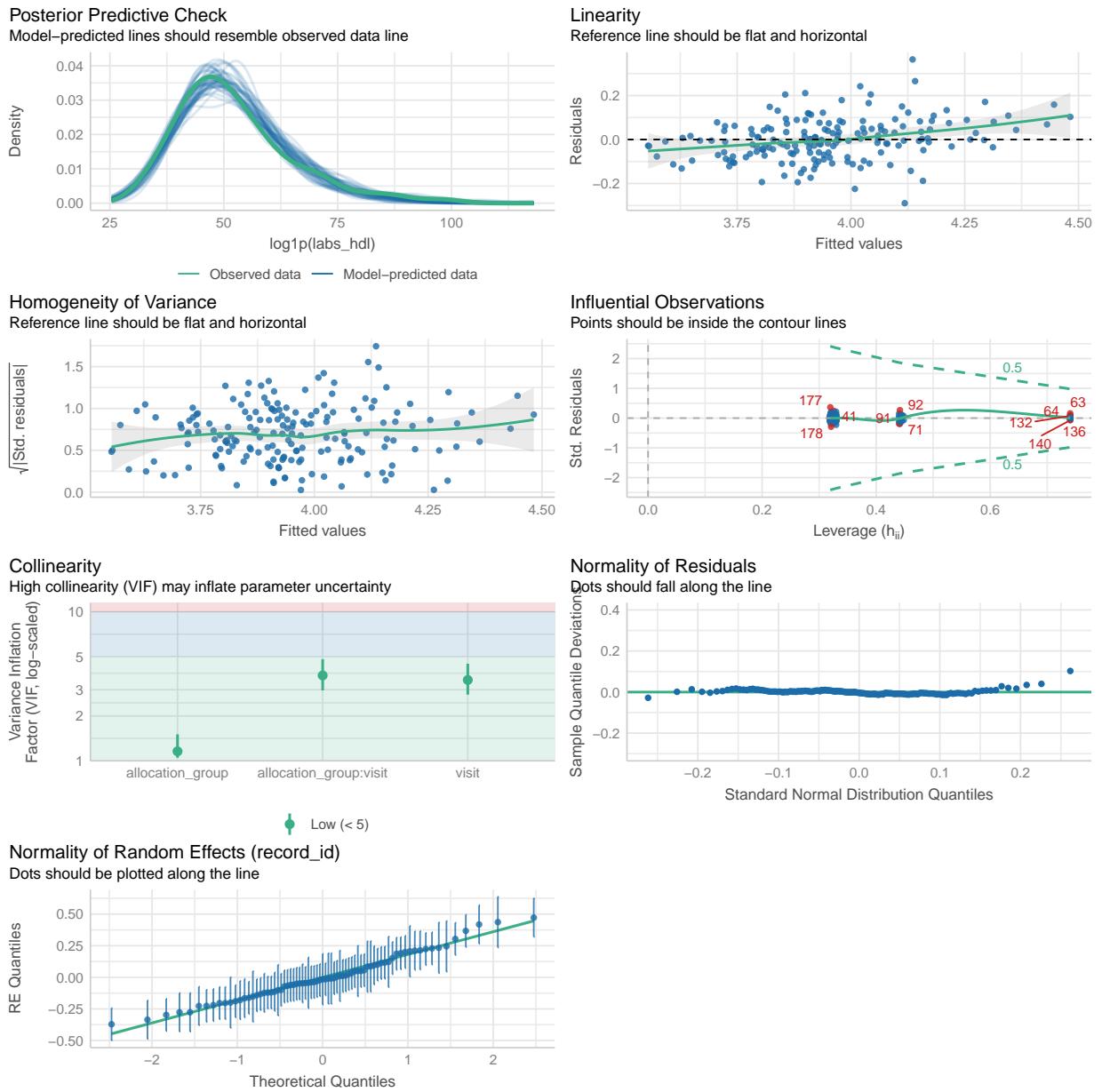
When comparing models, please note that probably not all models were fit from same data.

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

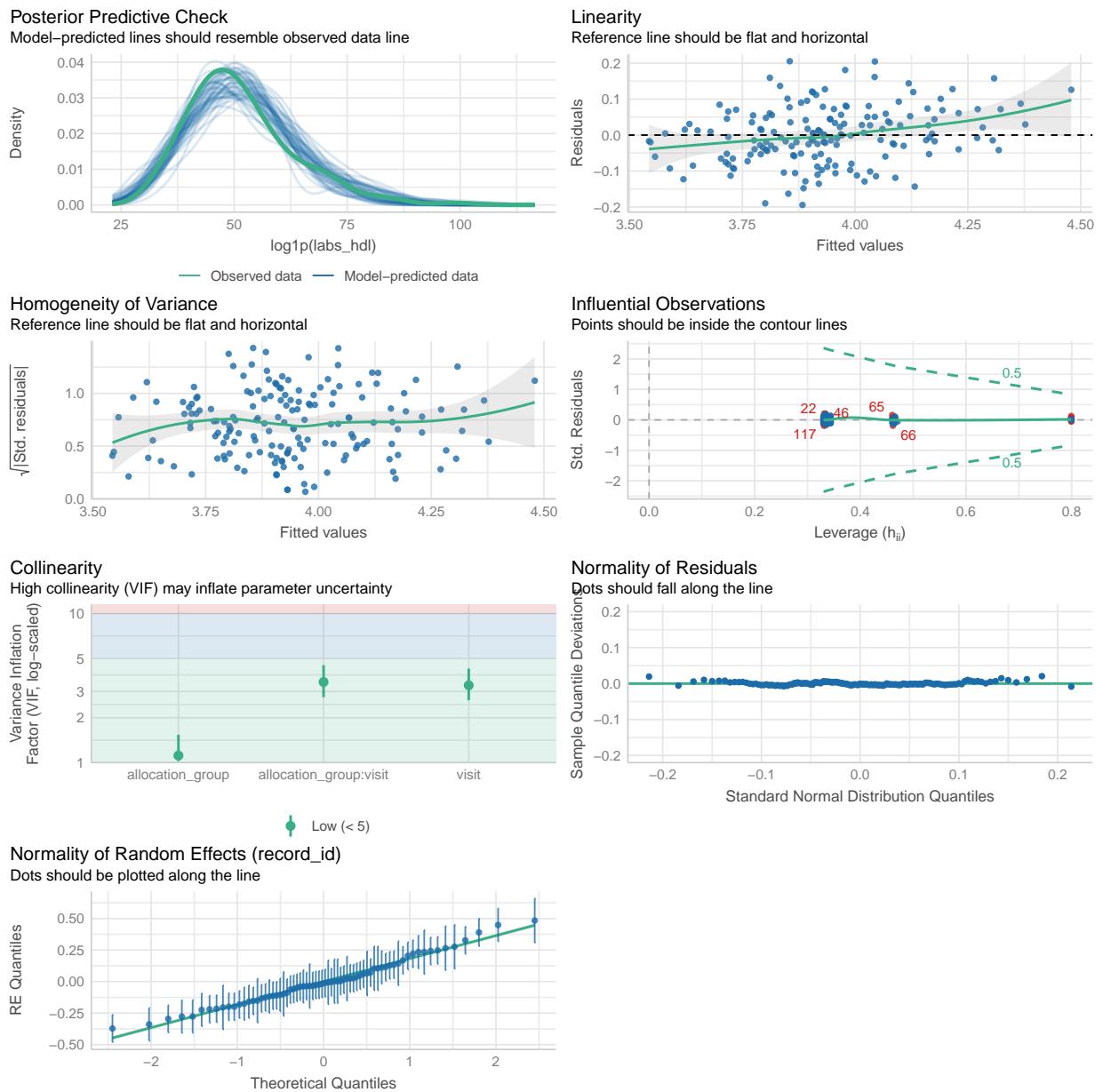
Name	Model	AIC (weights)	AICc (weights)
labs_hdl_model	lmerModLmerTest	1319.8 (<.001)	1320.7 (<.001)
labs_hdl_model_sens	lmerModLmerTest	1181.6 (>.999)	1182.5 (>.999)

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)
```



3.0.7.2 Médias Marginais Estimadas

3.0.7.2.1 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

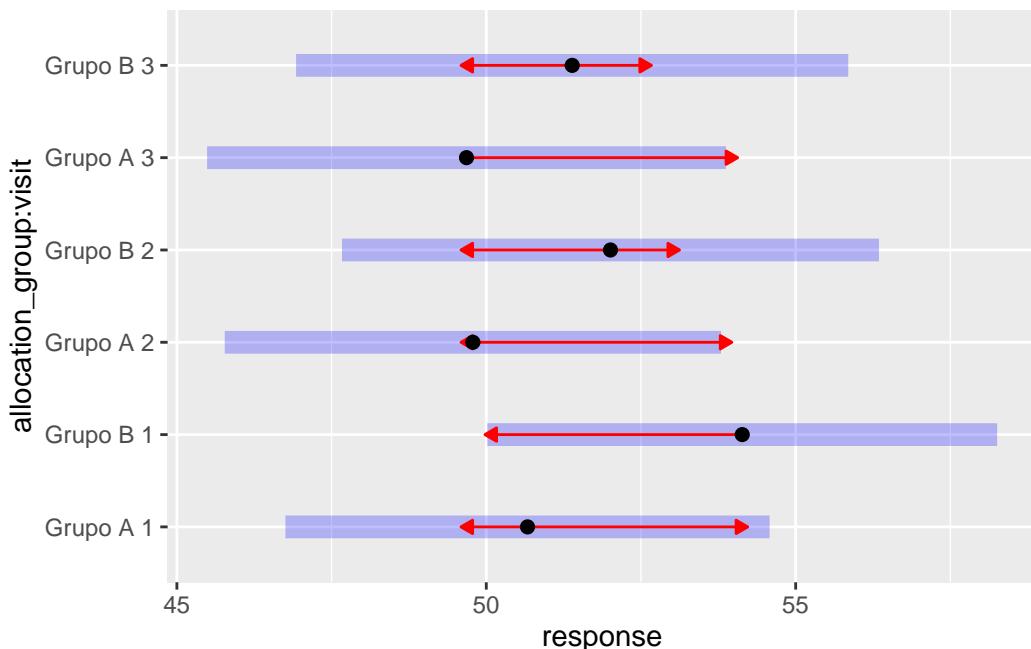
Conf-level adjustment: bonferroni method for 3 estimates

P value adjustment: bonferroni method for 3 tests

```

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

```



3.0.7.2.2 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  
emmmeans::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

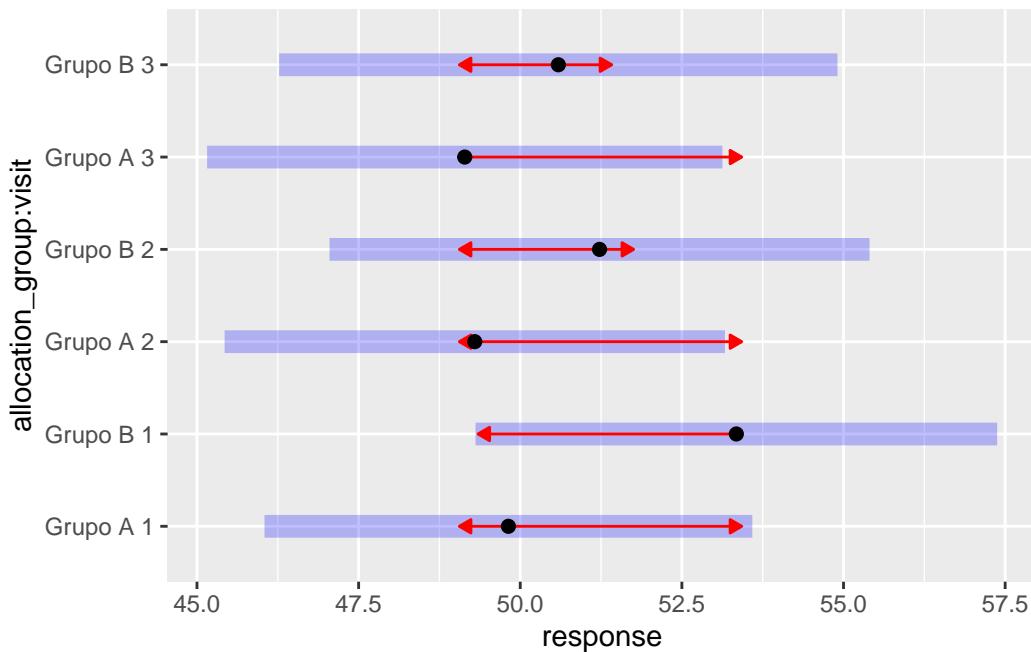
Degrees-of-freedom method: inherited from kenward-roger when re-gridding

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)
```



3.0.7.3 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
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 de comparação	Comparação	Estimativa	IC 95%	p-valor
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)

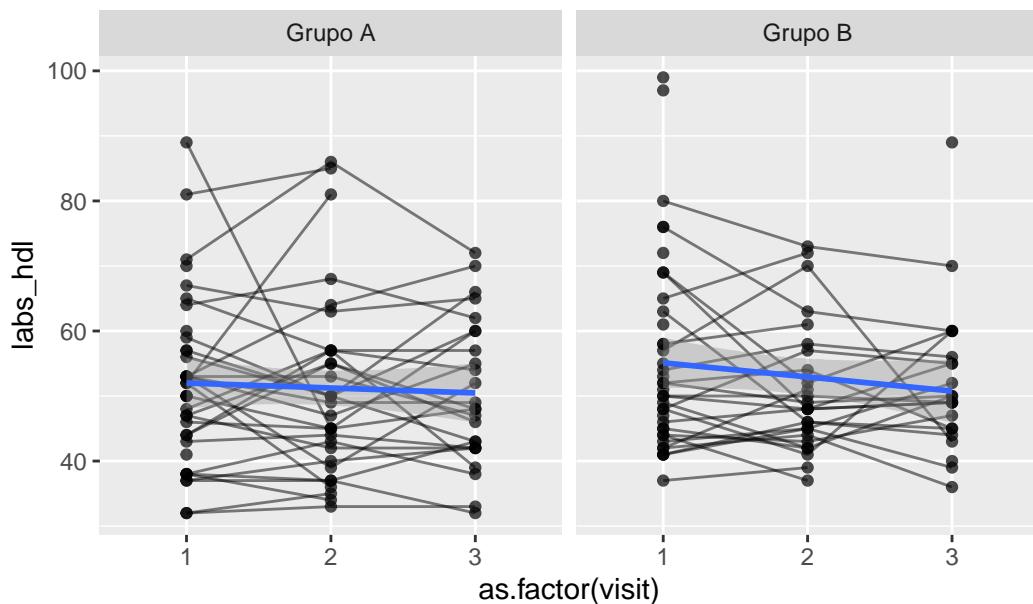
`geom_smooth()` using formula = 'y ~ x'
Warning: Removed 10 rows containing non-finite outside the scale range
(`stat_smooth()`).

```

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)

```

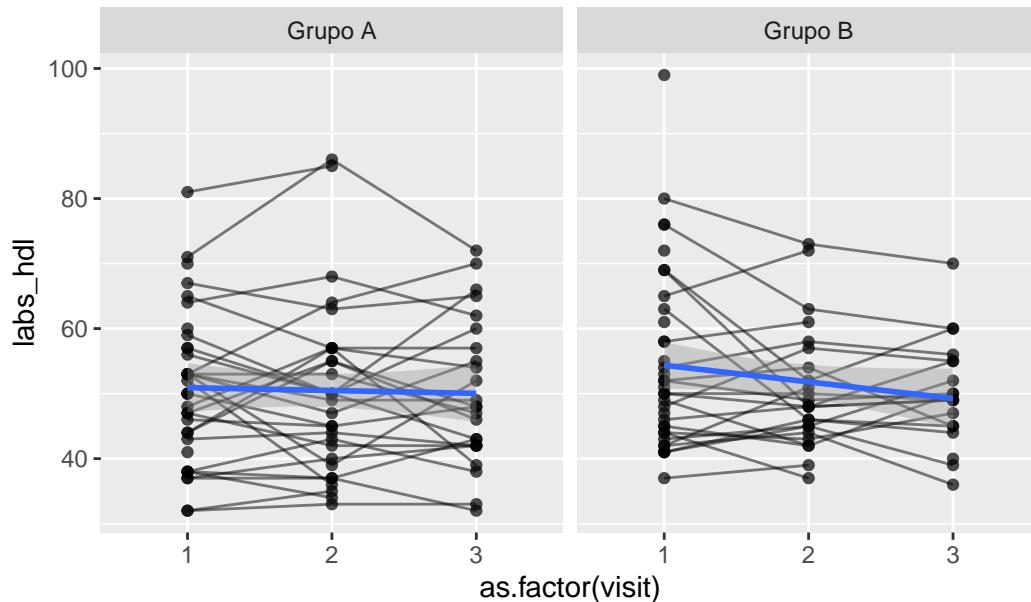
`geom_smooth()` using formula = 'y ~ x'

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))
```

3.0.8 Triglicerídeos

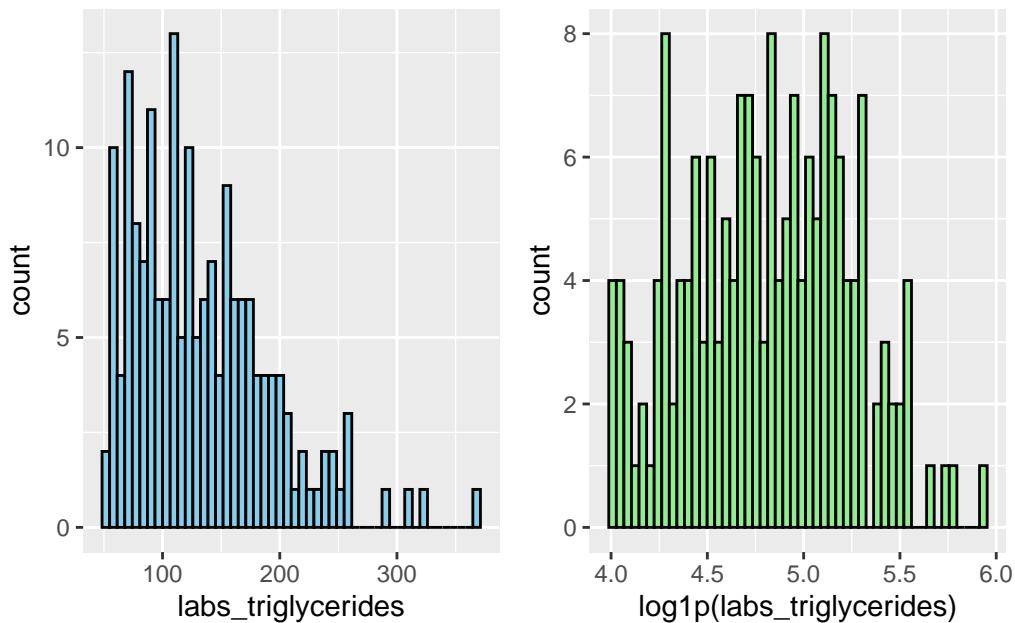
Variável: labs_triglycerides

```
# 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"

```

3.0.8.1 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	-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:visit2	-0.05643	0.09159	105.09618	-0.616	0.539
allocation_group:visit3	0.04983	0.09836	106.17407	0.507	0.614

(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_gr	GB	-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	-0.01744	0.08158	93.47289	-0.214	0.8312
allocation_group	0.17857	0.08845	94.22579	2.019	0.0463

(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	-0.727				
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

```
 labs_triglycerides_model_check$comparison_table
```

```
# A tibble: 16 x 6
```

Model	term	estimate	std.error	statistic	p.value
<chr>	<chr>	<dbl>	<dbl>	<dbl>	<dbl>
1 Original	(Intercept)	4.77	0.0719	66.3	5.68e-85
2 Sensitivity	(Intercept)	4.74	0.0719	66.0	5.34e-76
3 Original	allocation_groupGrupo B	-0.0212	0.101	-0.210	8.34e- 1
4 Sensitivity	allocation_groupGrupo B	-0.0250	0.0989	-0.253	8.01e- 1
5 Original	allocation_groupGrupo B:v~	-0.0564	0.0916	-0.616	5.39e- 1
6 Sensitivity	allocation_groupGrupo B:v~	-0.0174	0.0816	-0.214	8.31e- 1
7 Original	allocation_groupGrupo B:v~	0.0498	0.0984	0.507	6.14e- 1
8 Sensitivity	allocation_groupGrupo B:v~	0.179	0.0884	2.02	4.63e- 2
9 Original	sd__(Intercept)	0.359	NA	NA	NA
10 Sensitivity	sd__(Intercept)	0.354	NA	NA	NA

```

11 Original    sd__Observation      0.249     NA      NA      NA
12 Sensitivity sd__Observation      0.212     NA      NA      NA
13 Original    visit2              0.0565    0.0625   0.905   3.68e- 1
14 Sensitivity visit2              0.0481    0.0570   0.843   4.01e- 1
15 Original    visit3              0.00822   0.0677   0.122   9.04e- 1
16 Sensitivity visit3             -0.0954   0.0627  -1.52    1.31e- 1

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.

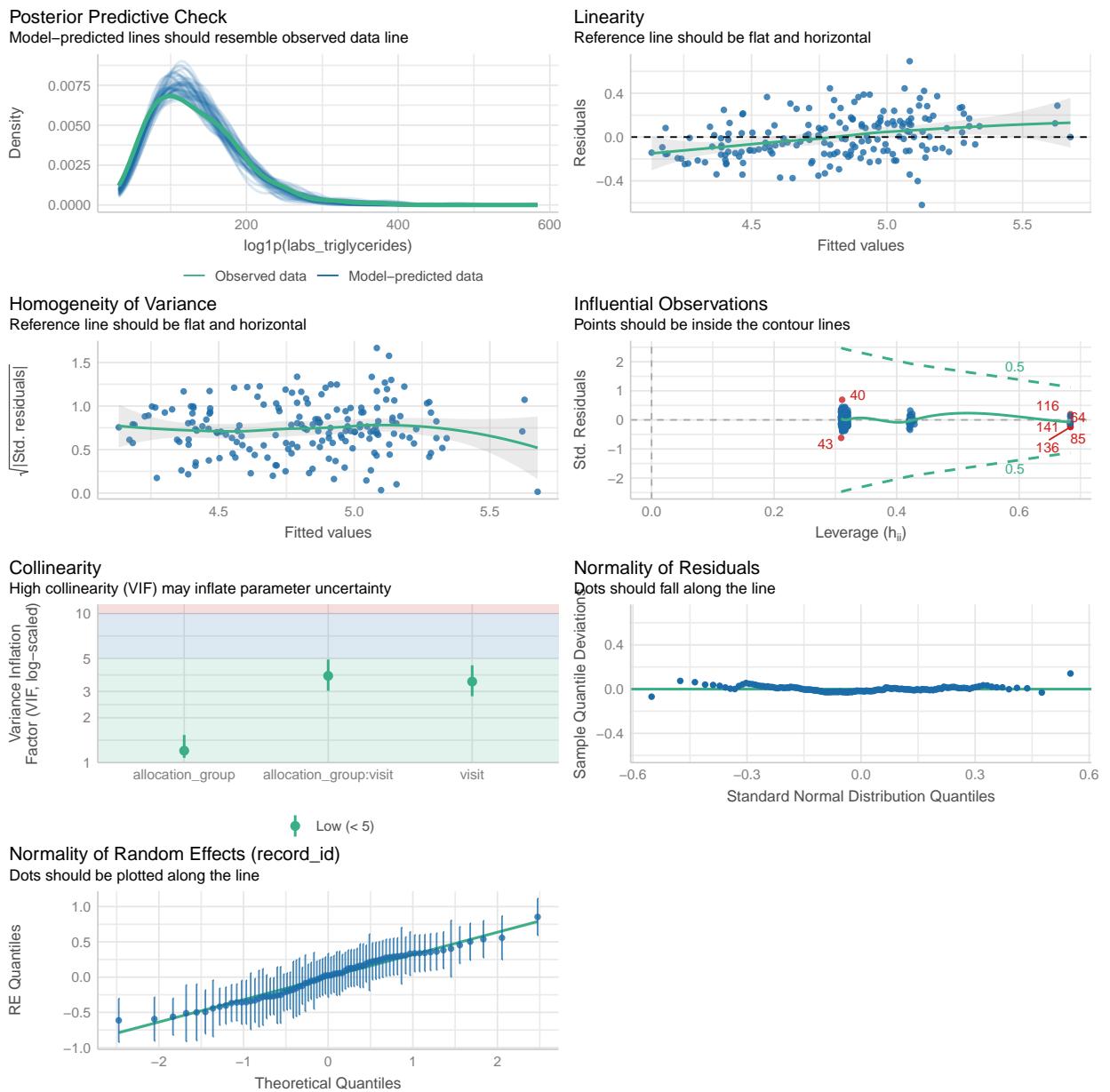
```
# Comparison of Model Performance Indices
```

Name		Model	AIC (weights)
<hr/>			
labs_triglycerides_model		lmerModLmerTest	1873.1 (<.001)
labs_triglycerides_model_sens		lmerModLmerTest	1671.7 (>.999)

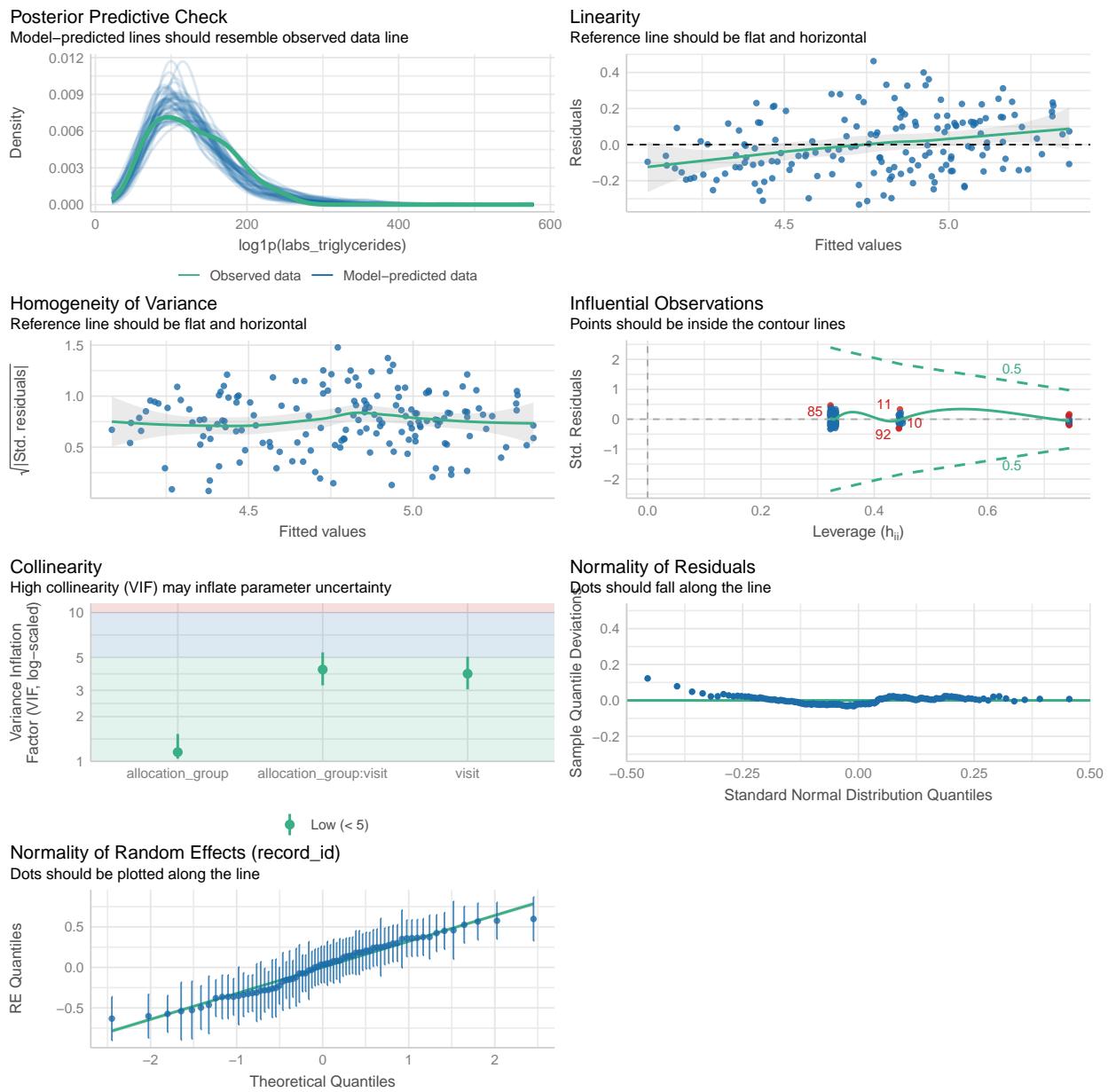
Name		AICC (weights)	BIC (weights)	R2 (cond.)
<hr/>				
labs_triglycerides_model		1873.9 (<.001)	1898.6 (<.001)	0.676
labs_triglycerides_model_sens		1672.6 (>.999)	1696.5 (>.999)	0.739

Name		R2 (marg.)	ICC	RMSE	Sigma
<hr/>					
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)
```



3.0.8.2 Médias Marginais Estimadas

3.0.8.2.1 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

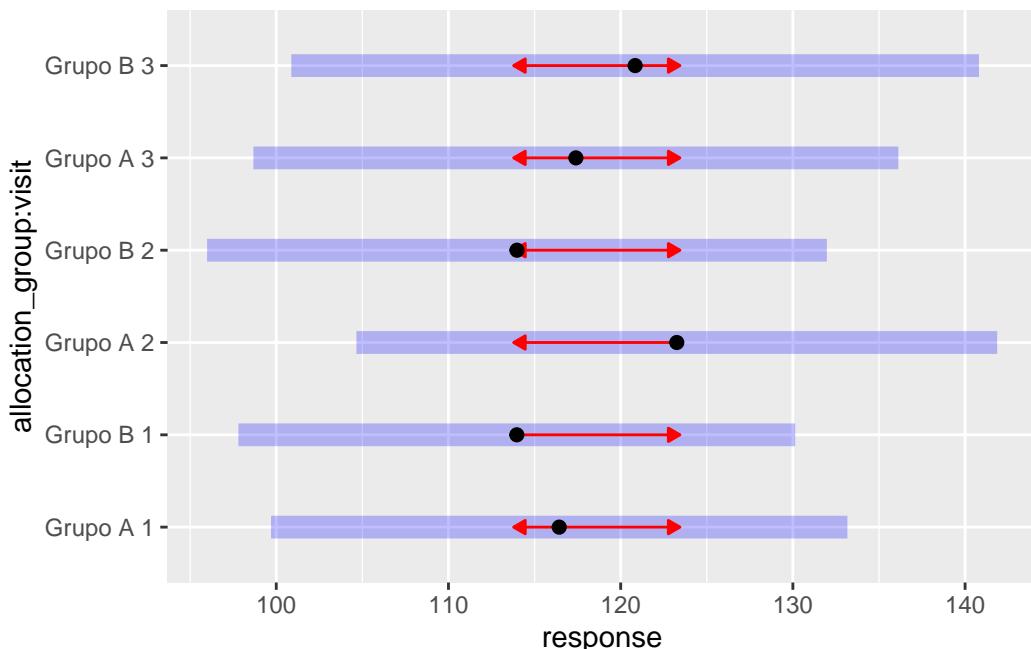
Conf-level adjustment: bonferroni method for 3 estimates

P value adjustment: bonferroni method for 3 tests

```

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

```



3.0.8.2.2 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

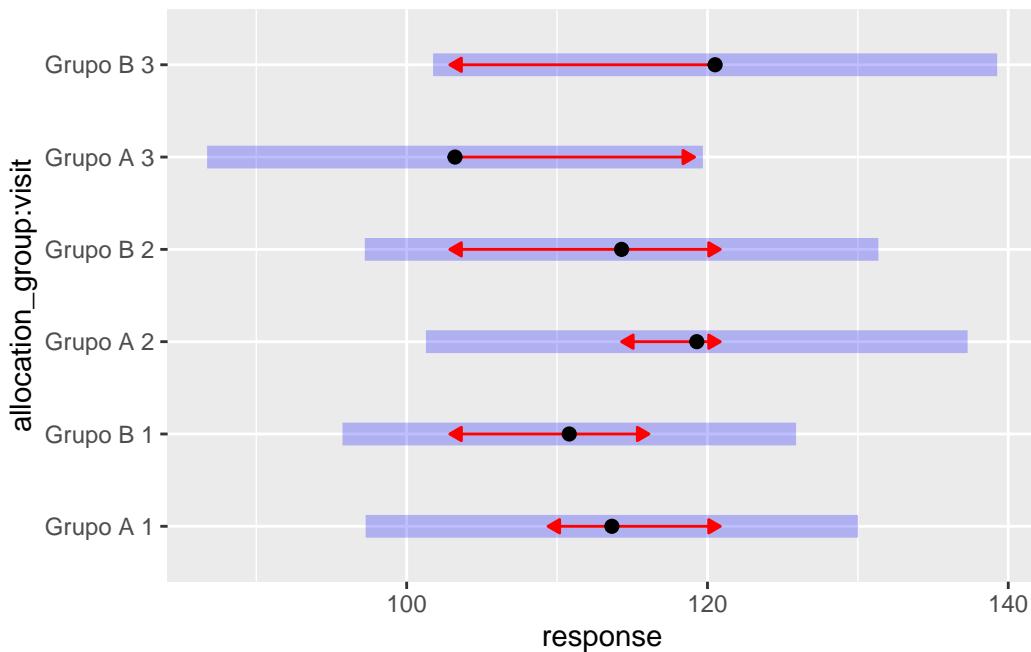
Degrees-of-freedom method: inherited from kenward-roger when re-gridding

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)
```



3.0.8.3 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
)

```

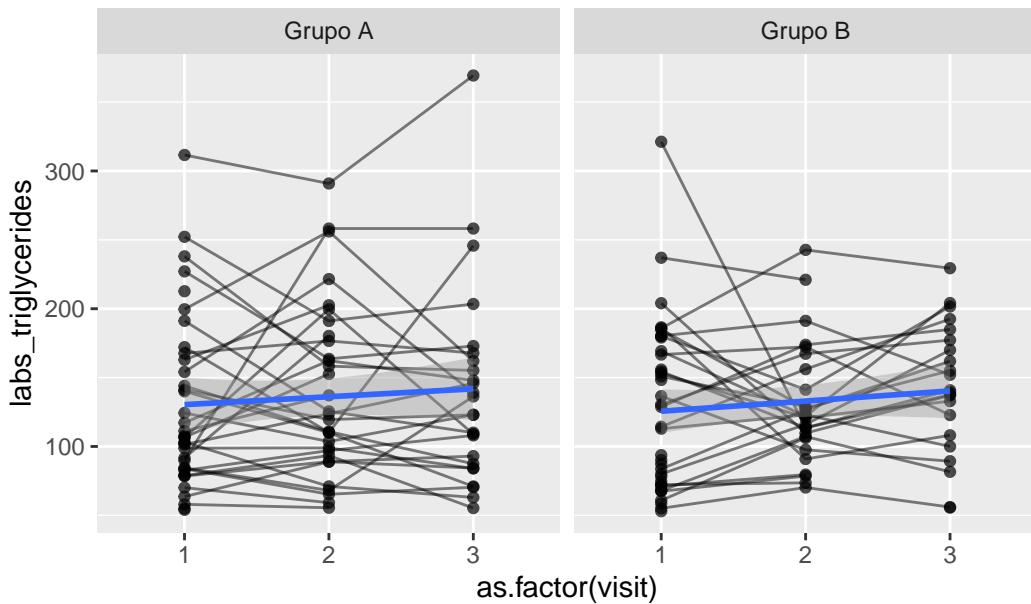
```

) +
  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)
  ) %>%

```

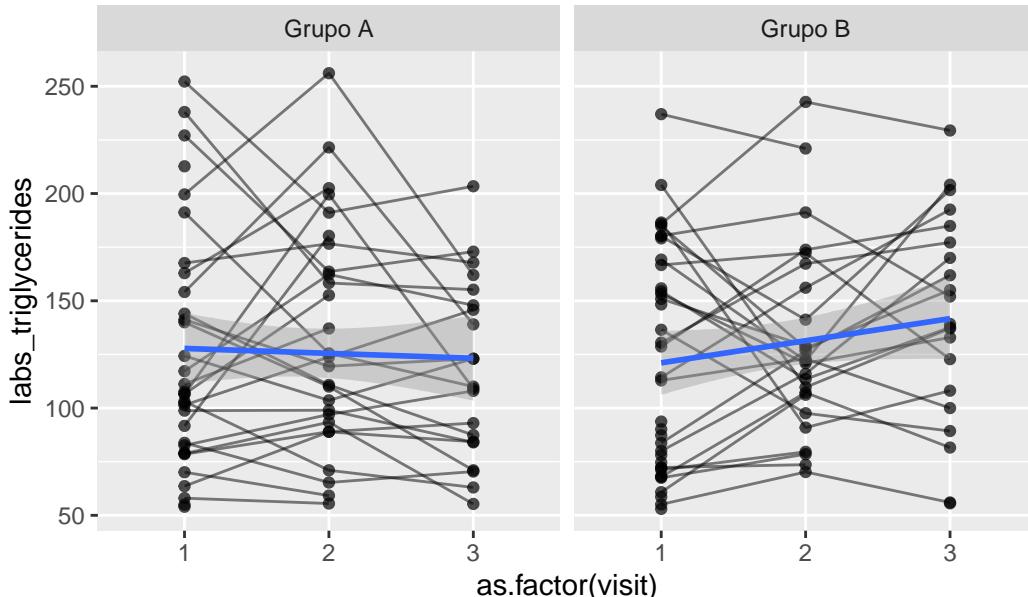
```

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))
```

3.0.9 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
  #) %>%
```

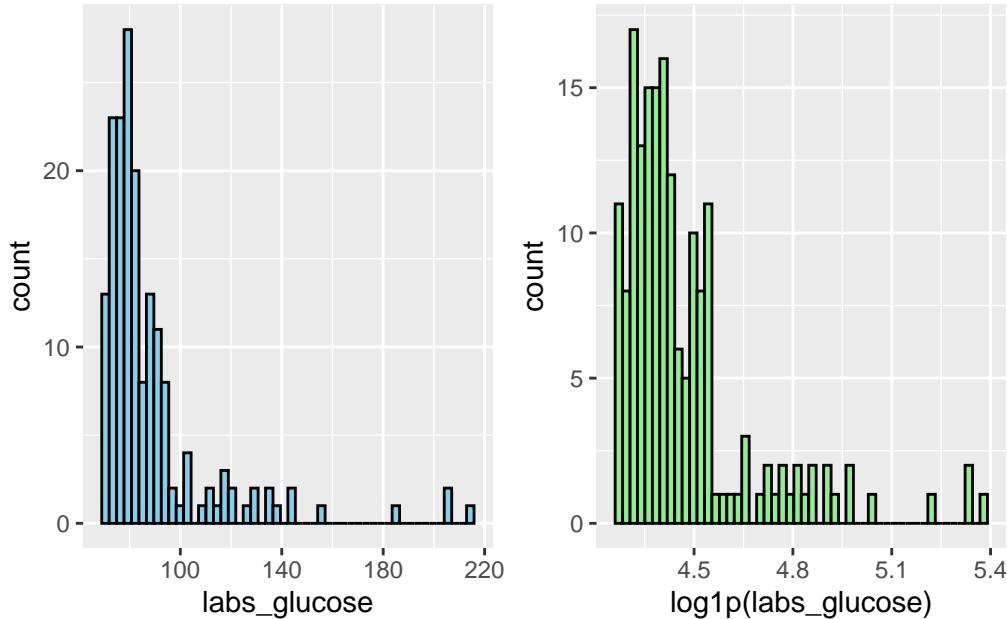
```

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"

```

3.0.9.1 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	Grupo B	-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_groupGrupo B:visit2 -0.0022058  0.0295835 97.2662772 -0.075
allocation_groupGrupo B:visit3  0.0099619  0.0320363 99.3466017  0.311

Pr(>|t|)

(Intercept)           <2e-16 ***

allocation_groupGrupo B      0.987
visit2                   0.928
visit3                   0.389
allocation_groupGrupo B:visit2 0.941
allocation_groupGrupo B: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

```
labs_glucose_model_check$comparison_table
```

```
# A tibble: 16 x 6
```

Model	term	estimate	std.error	statistic	p.value
<chr>	<chr>	<dbl>	<dbl>	<dbl>	<dbl>
1 Original	(Intercept)	4.45e+0	0.0324	137.	5.55e-109
2 Sensitivity	(Intercept)	4.42e+0	0.0229	193.	1.57e-126
3 Original	allocation_groupGrupo B	2.94e-3	0.0459	0.0640	9.49e- 1
4 Sensitivity	allocation_groupGrupo B	-5.28e-4	0.0323	-0.0164	9.87e- 1

```

5 Original allocation_groupGrupo B:~ -1.91e-2 0.0340 -0.561 5.76e- 1
6 Sensitivity allocation_groupGrupo B:~ -2.21e-3 0.0296 -0.0746 9.41e- 1
7 Original allocation_groupGrupo B:~ -7.51e-3 0.0366 -0.205 8.38e- 1
8 Sensitivity allocation_groupGrupo B:~ 9.96e-3 0.0320 0.311 7.56e- 1
9 Original sd__(Intercept) 1.74e-1 NA NA NA
10 Sensitivity sd__(Intercept) 1.09e-1 NA NA NA
11 Original sd__Observation 9.12e-2 NA NA NA
12 Sensitivity sd__Observation 7.64e-2 NA NA NA
13 Original visit2 9.14e-3 0.0232 0.393 6.95e- 1
14 Sensitivity visit2 -1.85e-3 0.0204 -0.0906 9.28e- 1
15 Original visit3 3.58e-2 0.0249 1.44 1.54e- 1
16 Sensitivity visit3 1.91e-2 0.0220 0.866 3.89e- 1

```

```

  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.

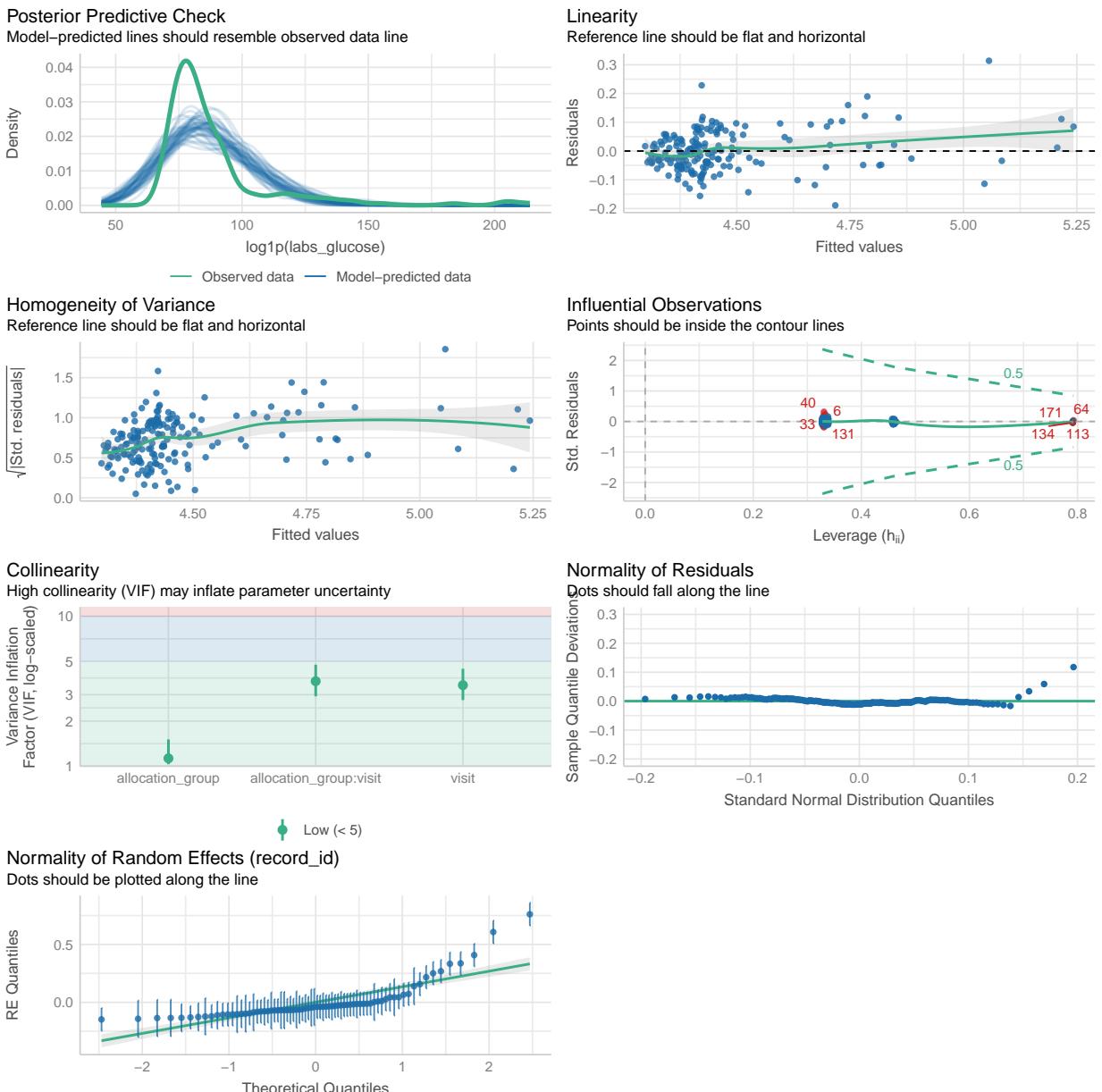
```
# Comparison of Model Performance Indices
```

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

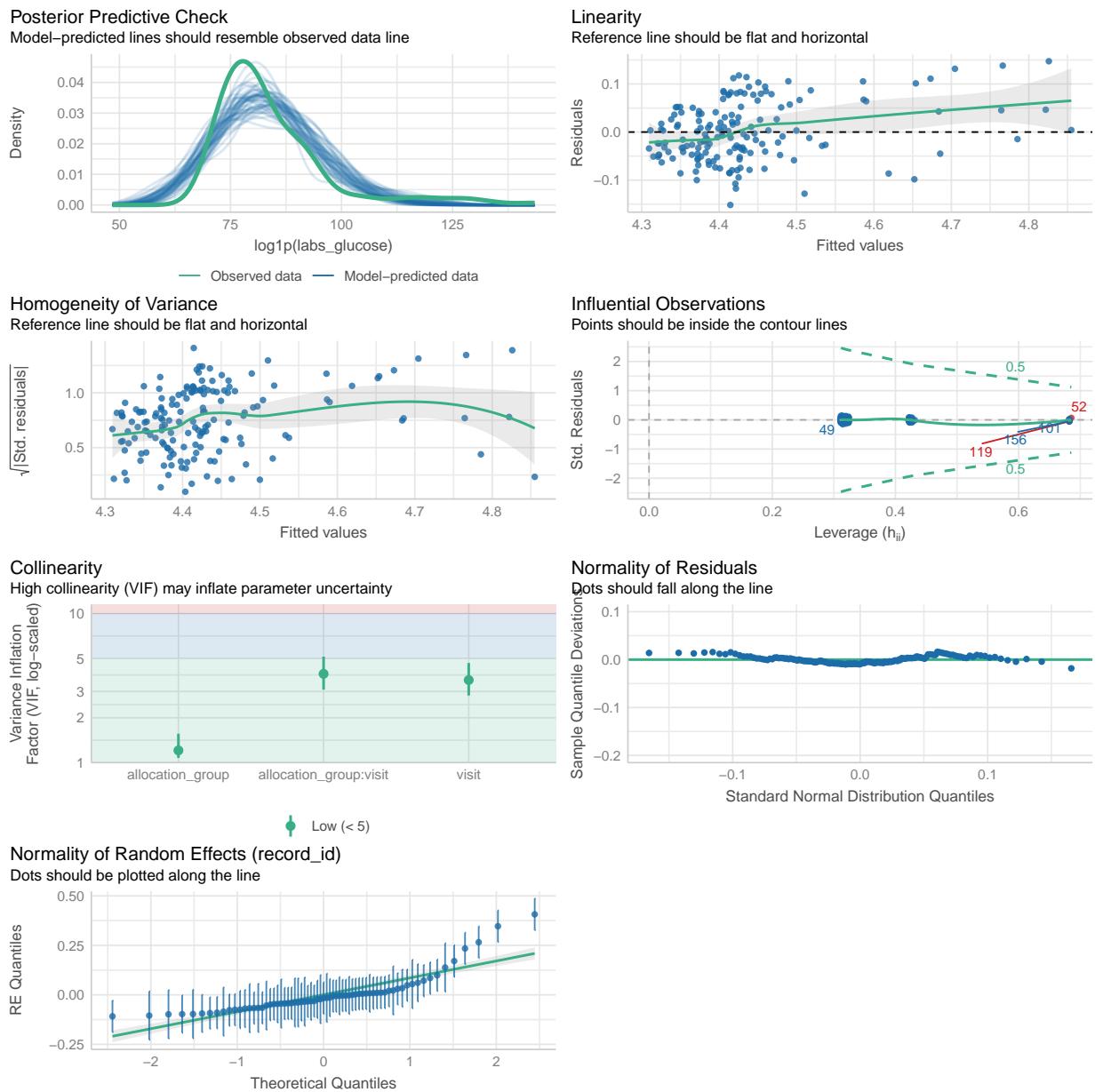
Name		BIC (weights)	R2 (cond.)	R2 (marg.)	ICC
<hr/>					
labs_glucose_model		1429.4 (<.001)	0.787	0.006	0.785
labs_glucose_model_sens		1208.4 (>.999)	0.675	0.007	0.672

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)
```



3.0.9.2 Médias Marginais Estimadas

3.0.9.2.1 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

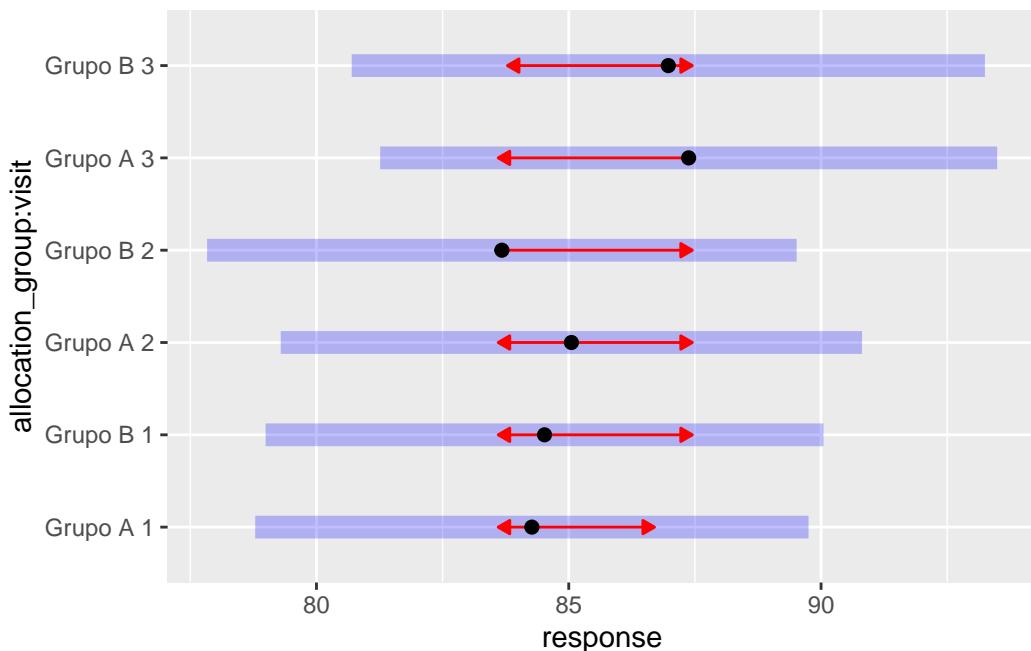
Confidence level used: 0.95

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)
```



3.0.9.2.2 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

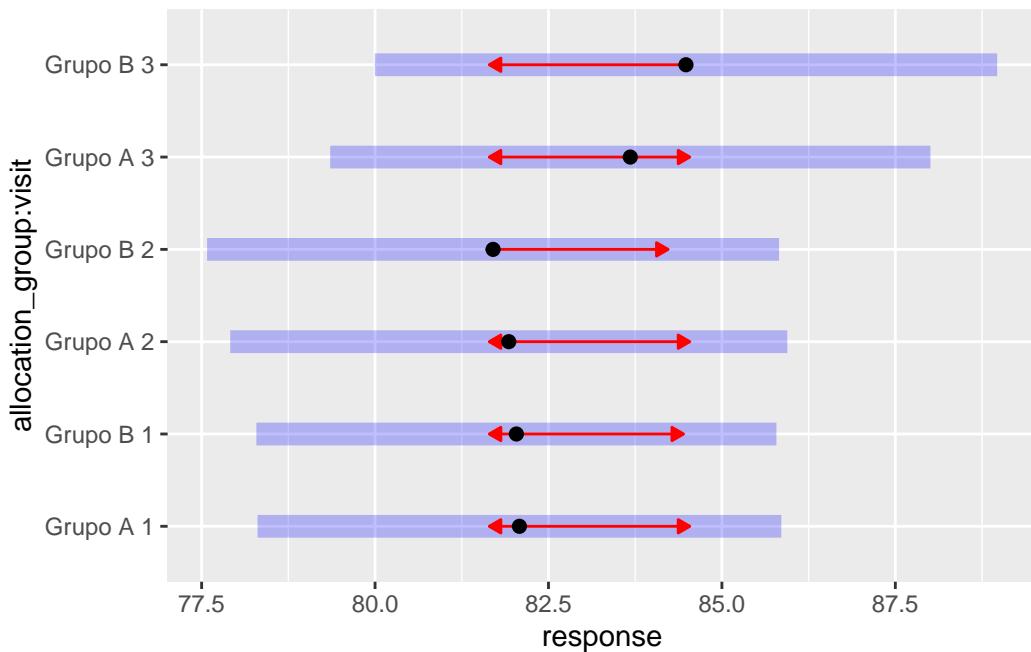
Degrees-of-freedom method: inherited from kenward-roger when re-gridding

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)
```



3.0.9.3 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
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 de comparação	Comparação	Estimativa	IC 95%	p-valor
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)

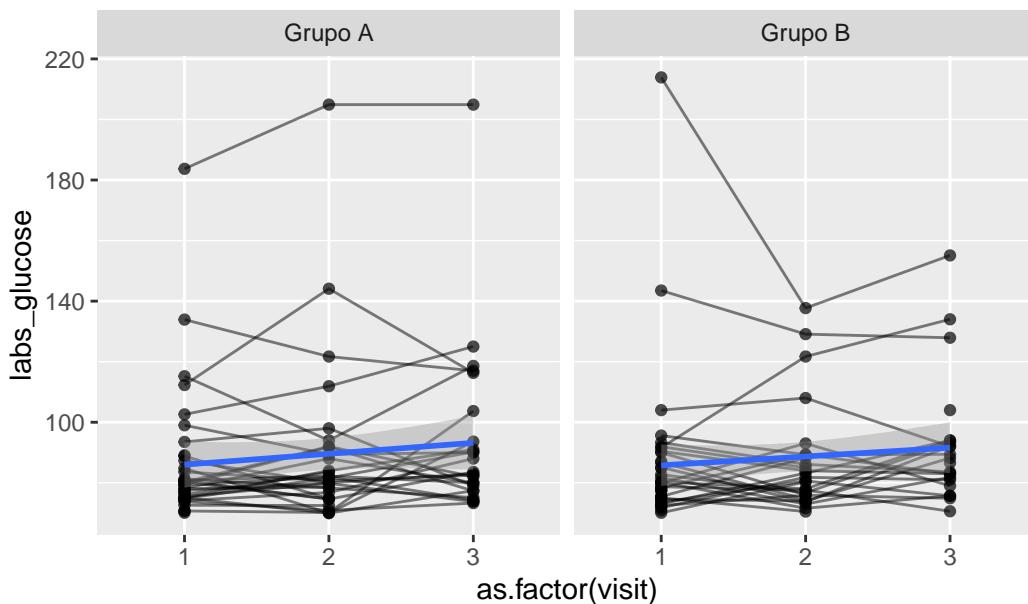
`geom_smooth()` using formula = 'y ~ x'
Warning: Removed 13 rows containing non-finite outside the scale range
(`stat_smooth()`).

```

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)

```

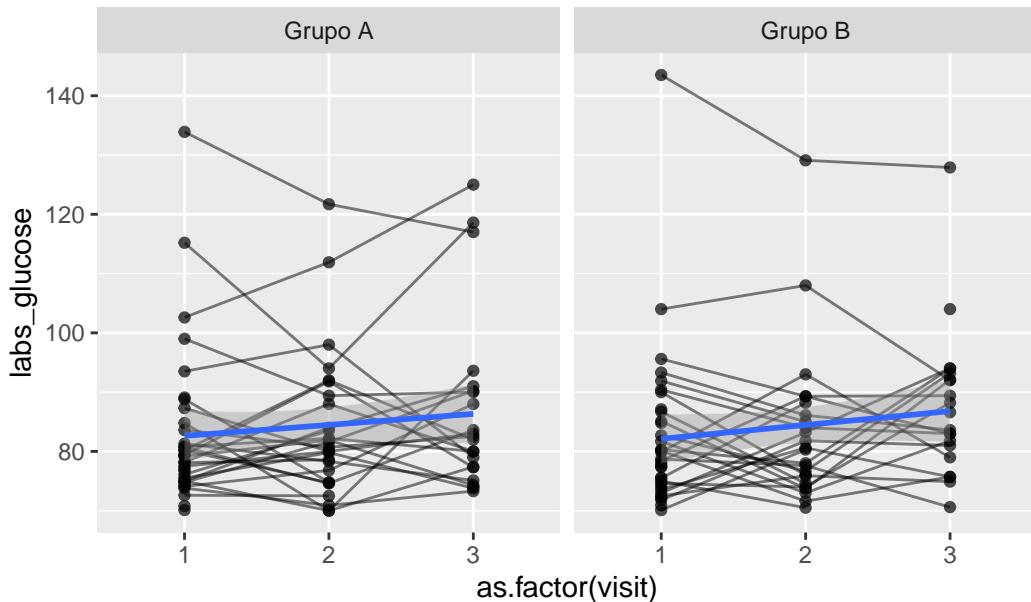
`geom_smooth()` using formula = 'y ~ x'

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))
```

3.0.10 Hemoglobina Glicosilada

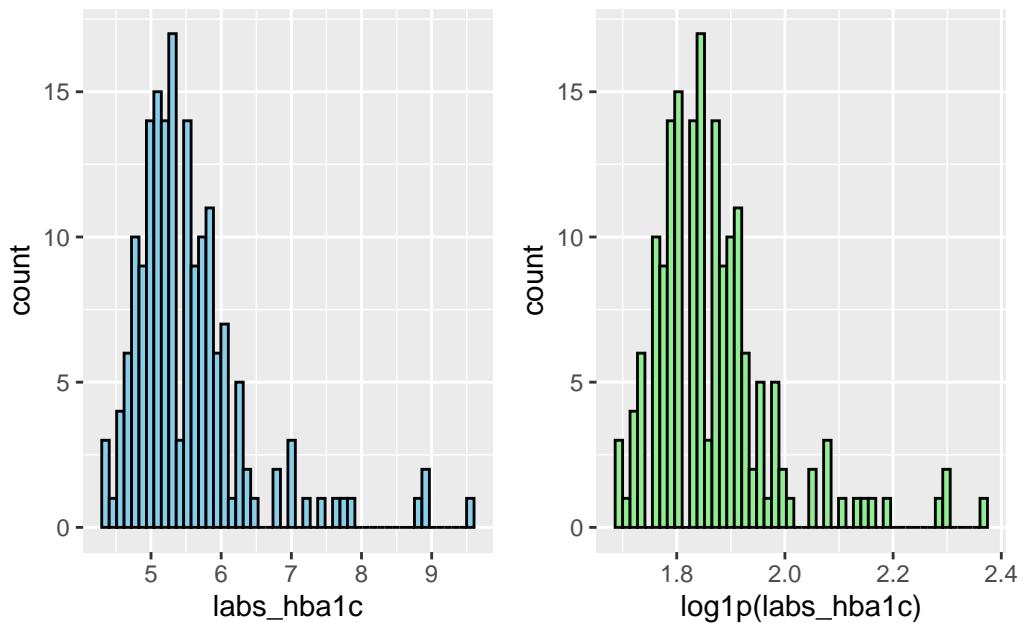
Variável: labs_hba1c

```
# 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"

```

3.0.10.1 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_gr	-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_groupGrupo B          0.106
visit2                           0.524
visit3                           0.224
allocation_groupGrupo B:visit2   0.997
allocation_groupGrupo B: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

```
labs_hba1c_model_check$comparison_table
```

A tibble: 16 x 6

Model	term	estimate	std.error	statistic	p.value
<chr>	<chr>	<dbl>	<dbl>	<dbl>	<dbl>
1 Original	(Intercept)	1.87e+0	0.0182	102.	2.07e-88
2 Sensitivity	(Intercept)	1.86e+0	0.0140	133.	2.86e-90
3 Original	allocation_groupGrupo B	-1.95e-2	0.0256	-0.761	4.49e- 1
4 Sensitivity	allocation_groupGrupo B	-3.29e-2	0.0201	-1.64	1.06e- 1
5 Original	allocation_groupGrupo B:v~	-4.82e-3	0.0136	-0.355	7.24e- 1
6 Sensitivity	allocation_groupGrupo B:v~	-3.27e-5	0.0101	-0.00323	9.97e- 1
7 Original	allocation_groupGrupo B:v~	-2.94e-3	0.0146	-0.202	8.40e- 1
8 Sensitivity	allocation_groupGrupo B:v~	3.68e-3	0.0110	0.336	7.38e- 1
9 Original	sd__(Intercept)	1.05e-1	NA	NA	NA
10 Sensitivity	sd__(Intercept)	7.99e-2	NA	NA	NA

```

11 Original      sd__Observation          3.61e-2  NA        NA        NA
12 Sensitivity  sd__Observation          2.55e-2  NA        NA        NA
13 Original      visit2                  4.59e-4  0.00936   0.0491   9.61e- 1
14 Sensitivity  visit2                  -4.31e-3 0.00674   -0.640    5.24e- 1
15 Original      visit3                  1.39e-2  0.0101    1.38     1.70e- 1
16 Sensitivity  visit3                  8.90e-3  0.00727   1.22     2.24e- 1

performance::compare_performance(
  labs_hba1c_model,
  labs_hba1c_model_sens)

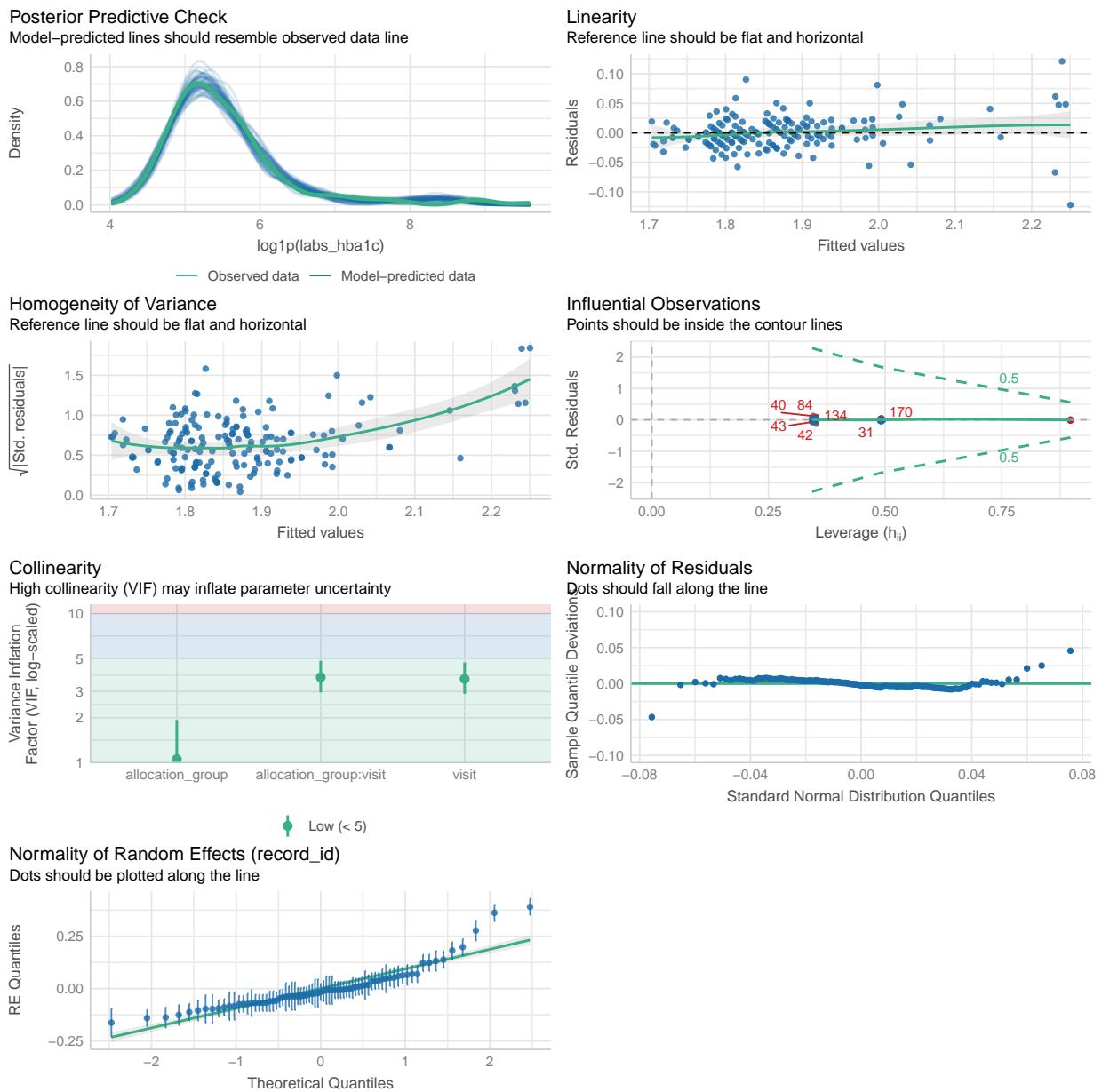
```

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

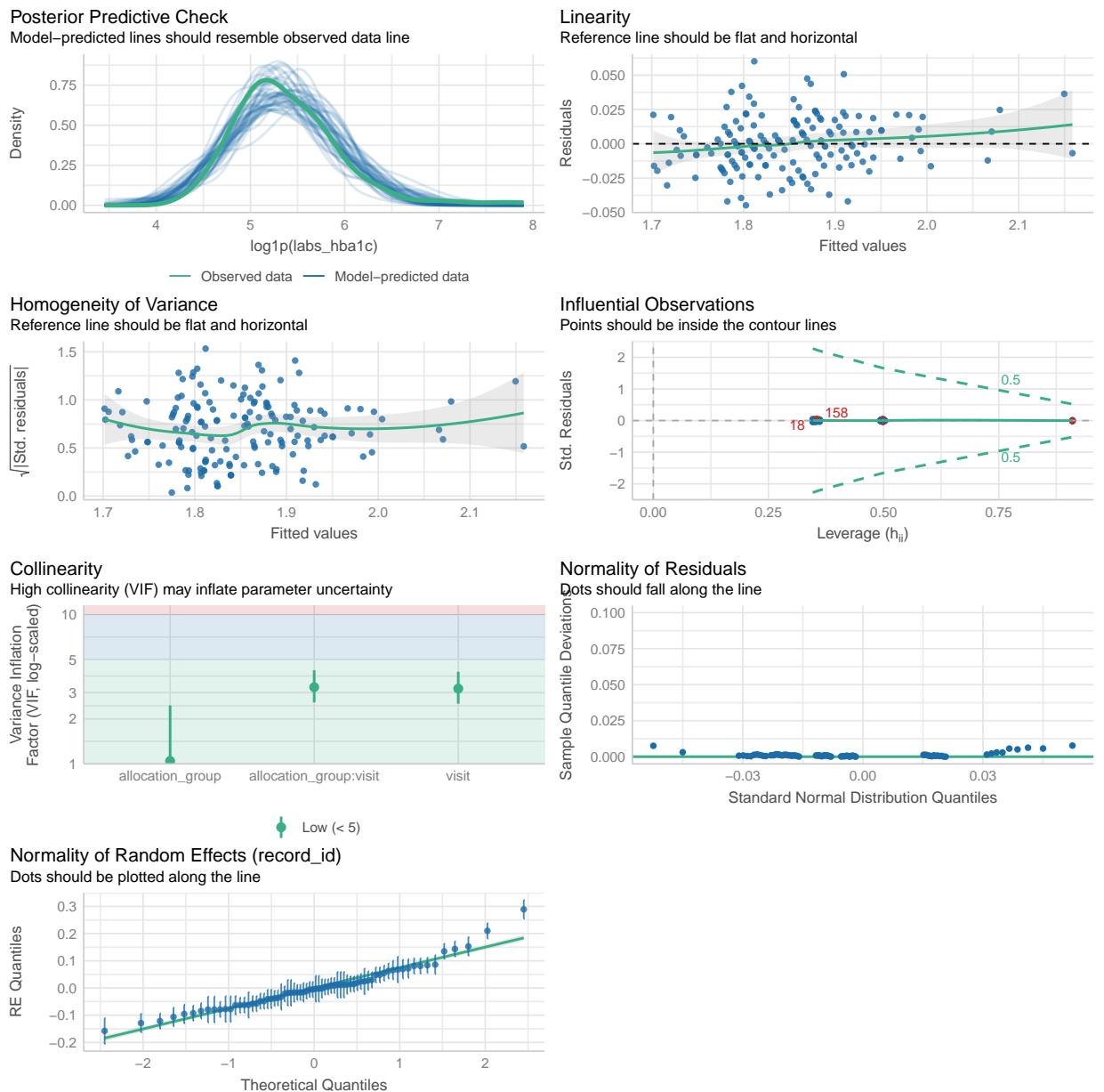
```
# Comparison of Model Performance Indices
```

Name		Model	AIC (weights)	AICc (weights)			
<hr/>							
labs_hba1c_model		lmerModLmerTest	220.5 (<.001)	221.4 (<.001)			
labs_hba1c_model_sens		lmerModLmerTest	97.5 (>.999)	98.5 (>.999)			
<hr/>							
Name		BIC (weights)	R2 (cond.)	R2 (marg.)	ICC	RMSE	Sigm
<hr/>							
labs_hba1c_model		245.9 (<.001)	0.896	0.013	0.894	0.027	0.03
labs_hba1c_model_sens		122.2 (>.999)	0.911	0.040	0.907	0.019	0.02

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



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



3.0.10.2 Médias Marginais Estimadas

3.0.10.2.1 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

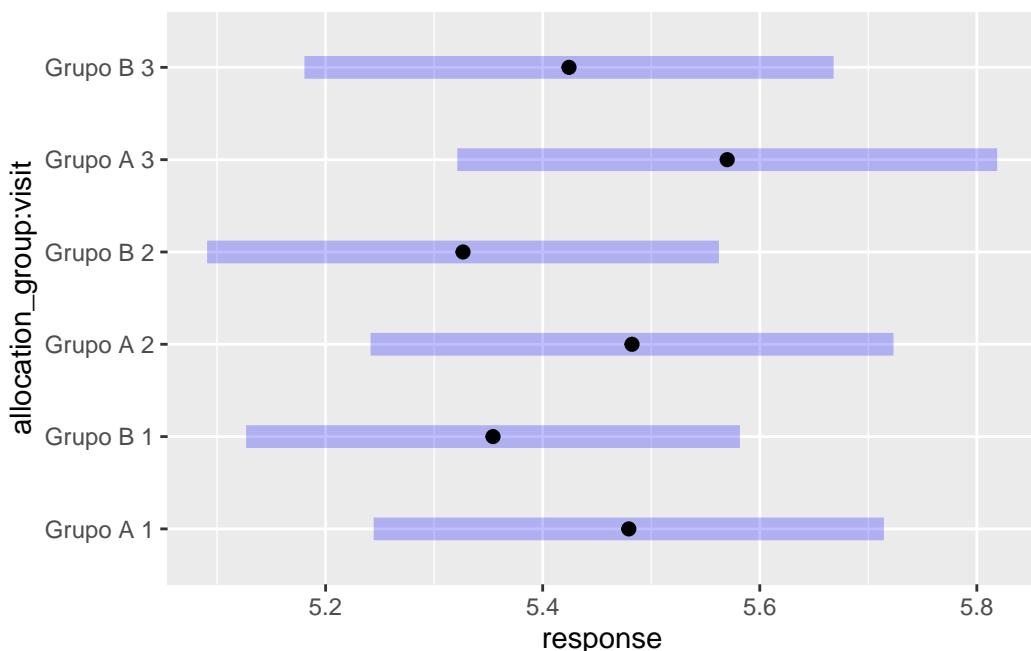
Conf-level adjustment: bonferroni method for 3 estimates

P value adjustment: bonferroni method for 3 tests

```

# Plot of marginal means
plot(labs_hb1c_raw_emm)

```



3.0.10.2.2 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.

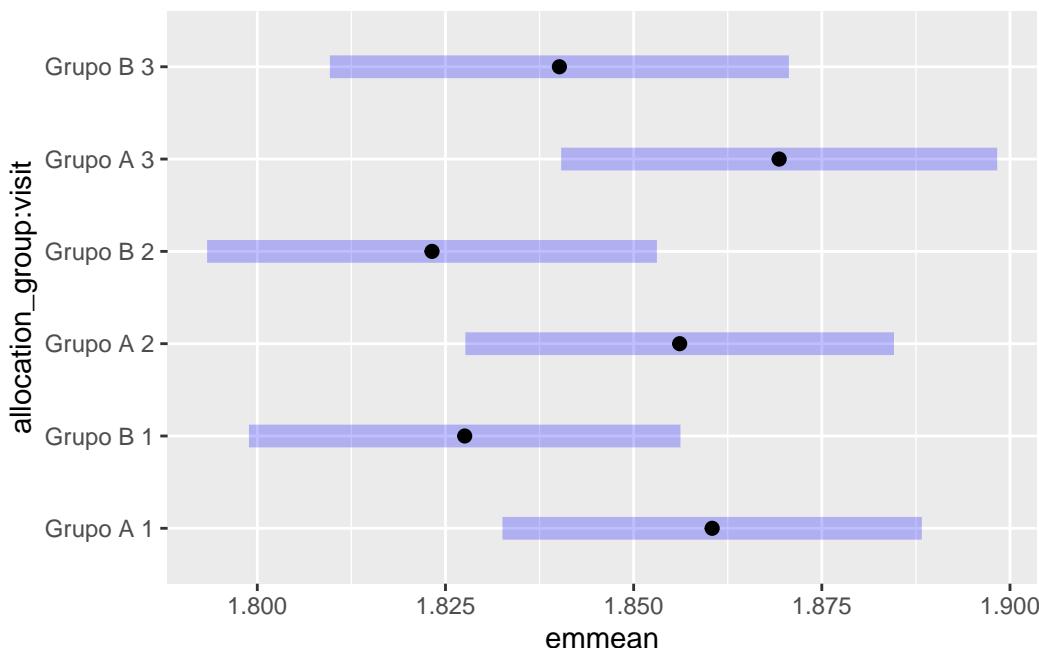
Degrees-of-freedom method: kenward-roger

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)
```



3.0.10.3 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 de comparação	Comparação	Estimativa	IC 95%	p-valor
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_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 = "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()`).

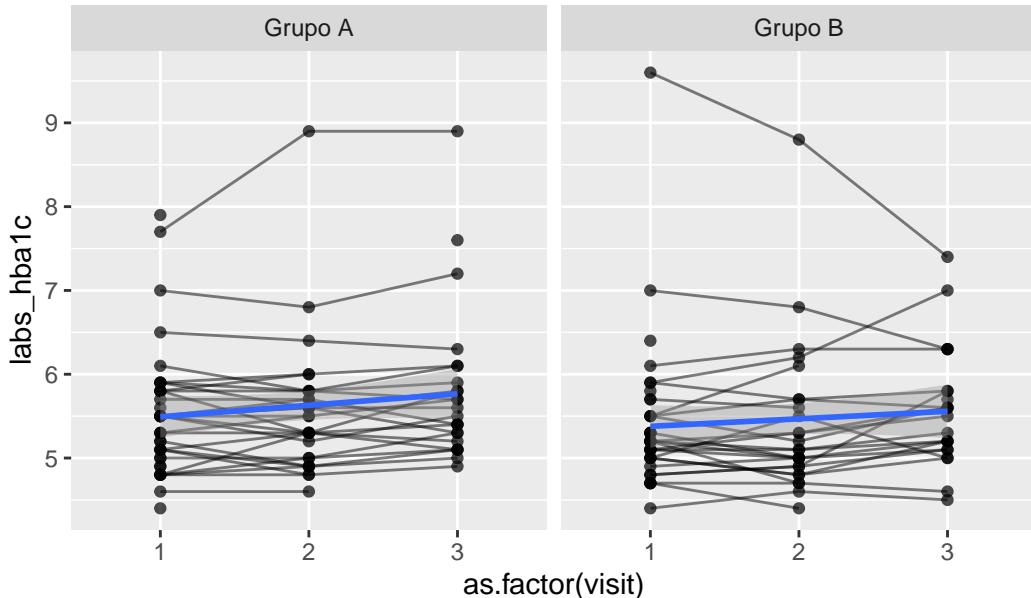
Warning: Removed 9 rows containing missing values or values outside the scale range

```

```
(`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)

```

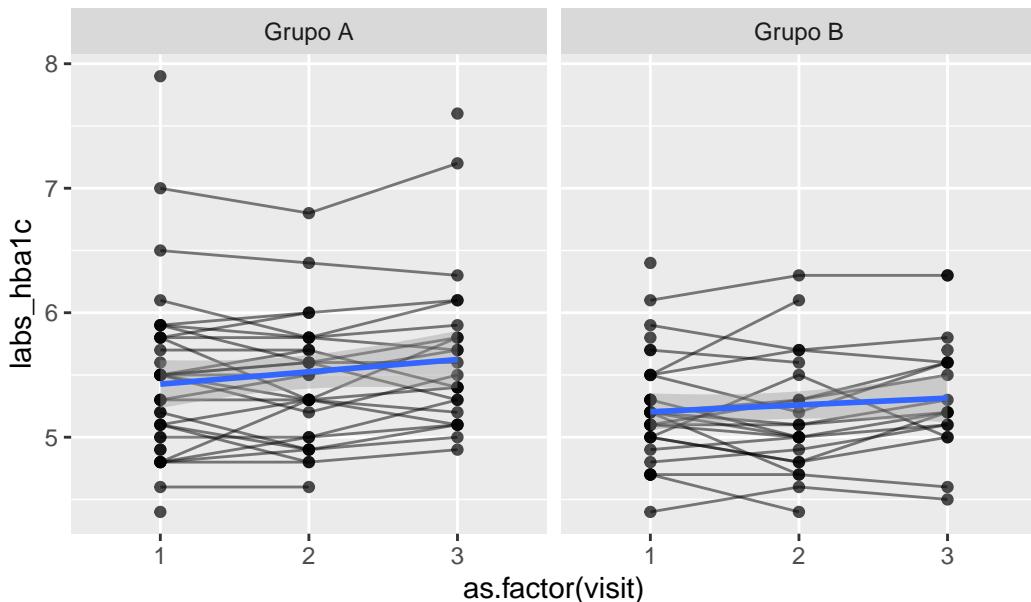
`geom_smooth()` using formula = 'y ~ x'

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))
```

3.0.11 Insulina

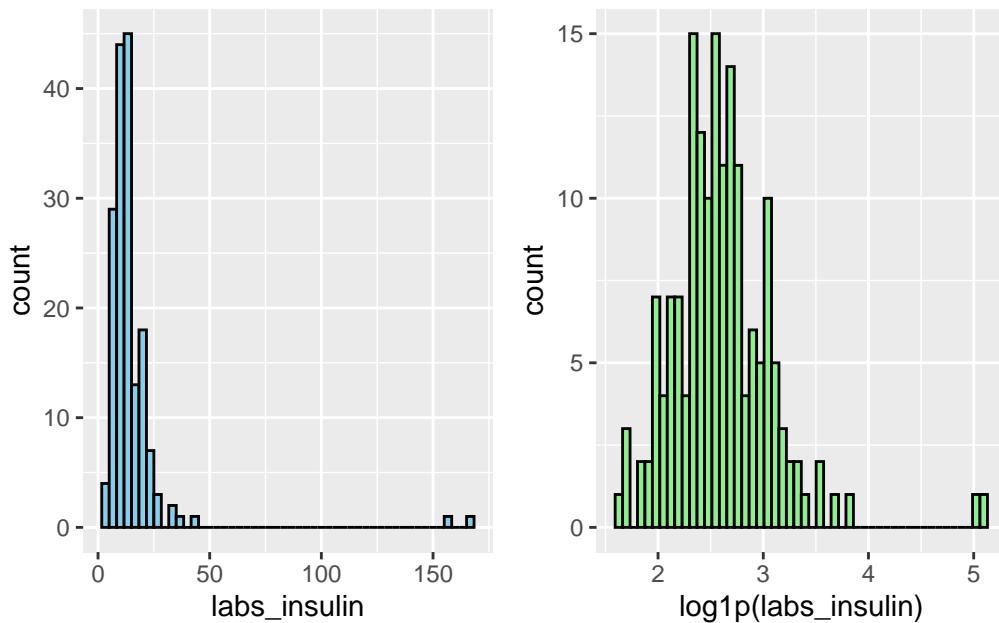
Variável: labs_insulin

```
# 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"

```

3.0.11.1 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_gr	GB	-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_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	-0.692				
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

```
 labs_insulin_model_check$comparison_table
```

A tibble: 16 x 6

Model	term	estimate	std.error	statistic	p.value
<chr>	<chr>	<dbl>	<dbl>	<dbl>	<dbl>
1 Original	(Intercept)	2.65	0.0785	33.7	8.51e-59
2 Sensitivity	(Intercept)	2.58	0.0638	40.4	3.13e-64
3 Original	allocation_groupGrupo B	-0.0317	0.111	-0.285	7.76e- 1
4 Sensitivity	allocation_groupGrupo B	0.0486	0.0923	0.527	5.99e- 1
5 Original	allocation_groupGrupo B:v~	0.0845	0.107	0.792	4.30e- 1
6 Sensitivity	allocation_groupGrupo B:v~	0.0630	0.0954	0.660	5.11e- 1
7 Original	allocation_groupGrupo B:v~	0.0696	0.119	0.584	5.60e- 1
8 Sensitivity	allocation_groupGrupo B:v~	0.0573	0.109	0.524	6.01e- 1
9 Original	sd__(Intercept)	0.383	NA	NA	NA
10 Sensitivity	sd__(Intercept)	0.295	NA	NA	NA

```

11 Original    sd__Observation          0.285   NA      NA      NA
12 Sensitivity sd__Observation          0.244   NA      NA      NA
13 Original    visit2                  -0.164   0.0741 -2.21   2.91e- 2
14 Sensitivity visit2                  -0.125   0.0642 -1.95   5.40e- 2
15 Original    visit3                  -0.0359  0.0799 -0.450  6.54e- 1
16 Sensitivity visit3                  -0.0513  0.0694 -0.739  4.62e- 1

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.

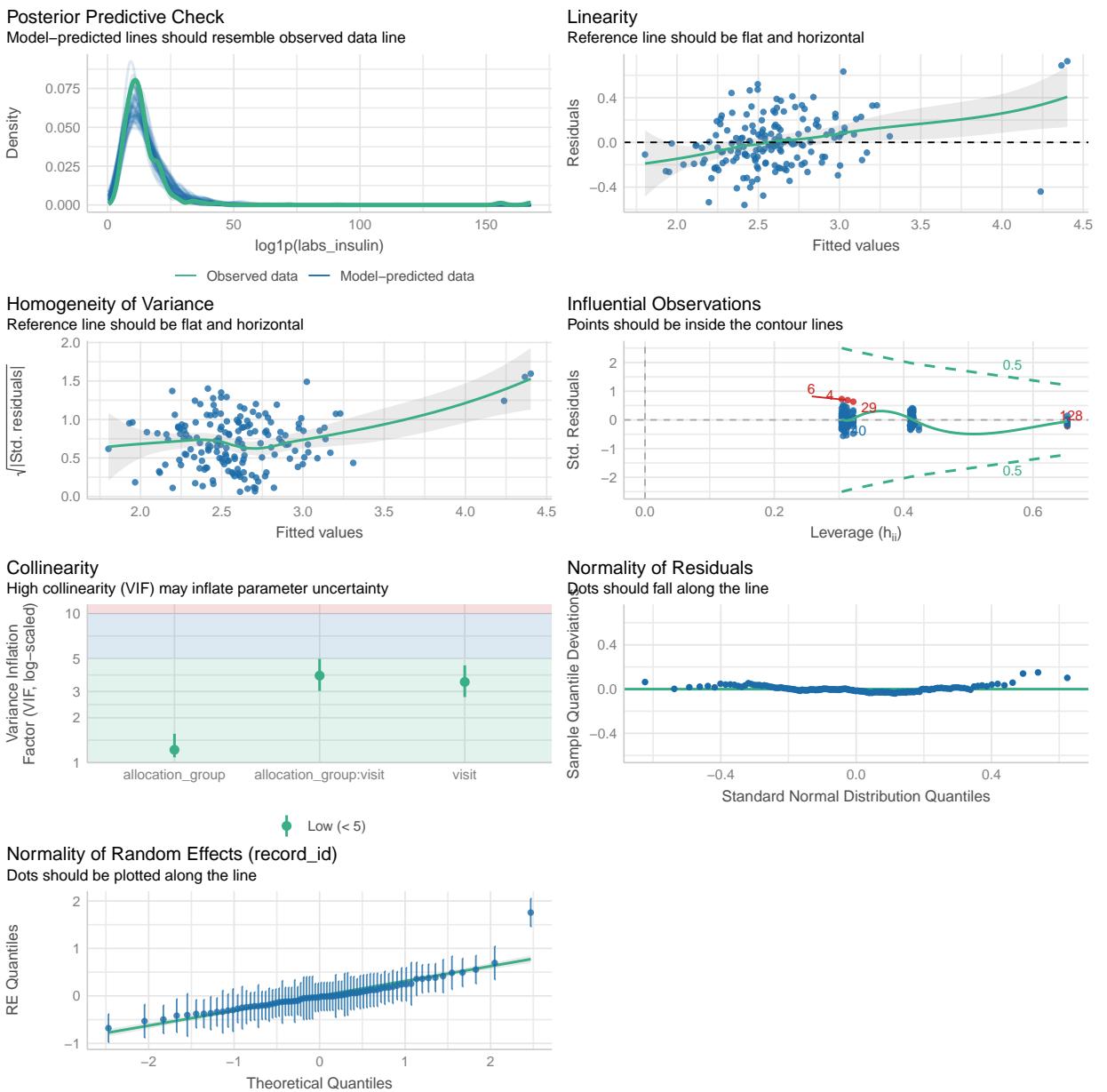
```
# Comparison of Model Performance Indices
```

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)
```



3.0.11.2 Médias Marginais Estimadas

3.0.11.2.1 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

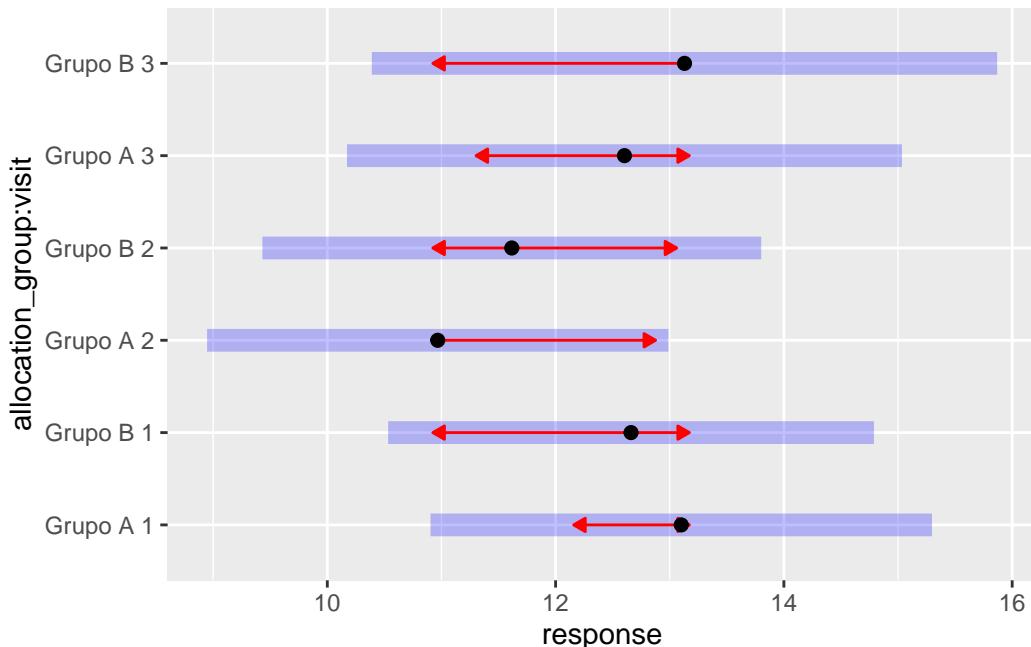
Confidence level used: 0.95

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)
```



3.0.11.2.2 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

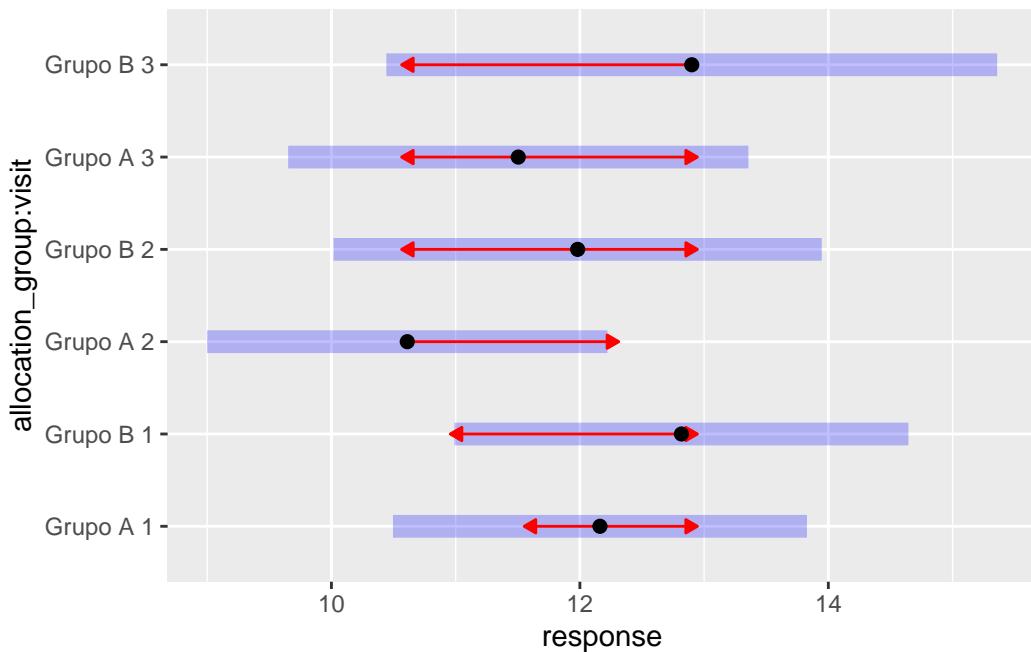
Degrees-of-freedom method: inherited from kenward-roger when re-gridding

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)
```



3.0.11.3 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
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 de comparação	Comparação	Estimativa	IC 95%	p-valor
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'

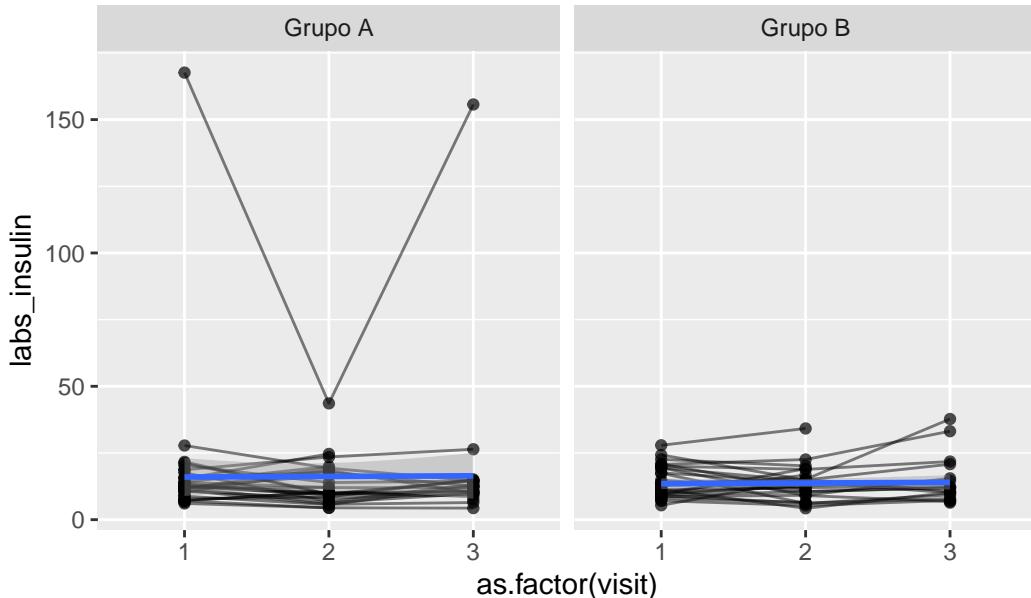
Warning: Removed 20 rows containing non-finite outside the scale range
(`stat_smooth()`).

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)

```

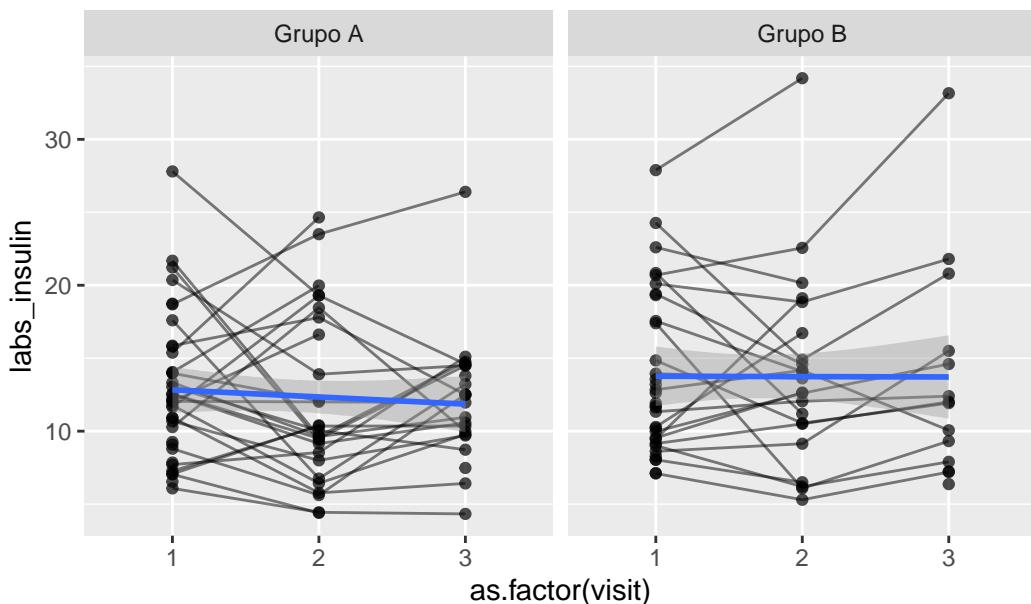
`geom_smooth()` using formula = 'y ~ x'

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))
```

3.0.12 HOMA-IR

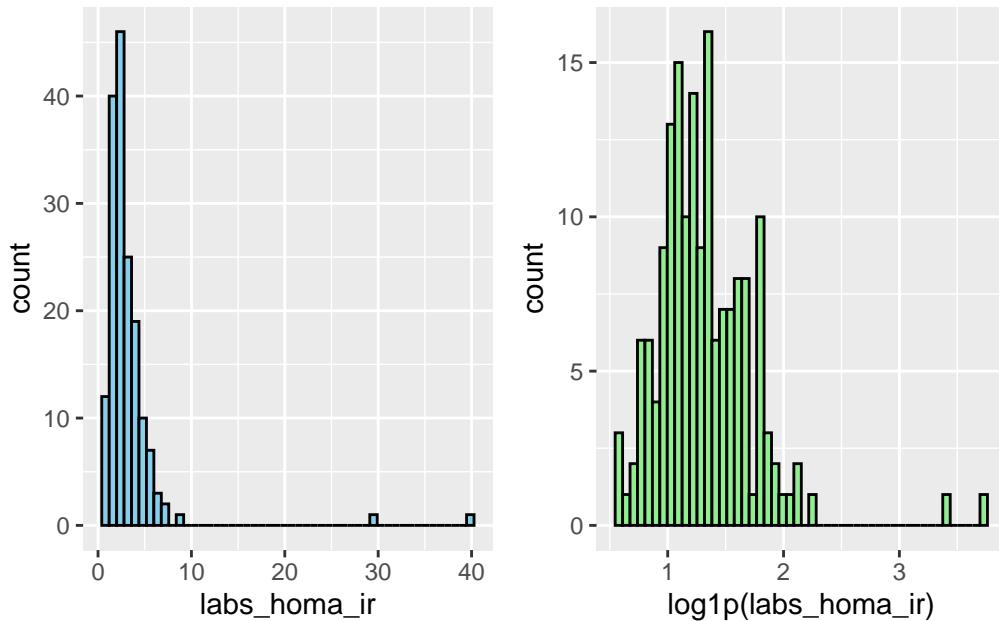
Variável: labs_homa_ir

```
# 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"

```

3.0.12.1 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	Grupo B	-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	Grupo B:visit2	0.062435	0.095196	100.497655	0.656
allocation_group	Grupo B:visit3	0.056616	0.107100	103.972738	0.529
	Pr(> t)				
(Intercept)		<2e-16	***		
allocation_group	Grupo B	0.6752			
visit2		0.0851	.		
visit3		0.8898			
allocation_group	Grupo B:visit2	0.5134			
allocation_group	Grupo B: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	GB	-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	0.053800	0.081686	88.465703	0.659	0.5119
allocation_group	0.025914	0.093706	92.342897	0.277	0.7827

(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	-0.693				
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

```
 labs_homa_ir_model_check$comparison_table
```

A tibble: 16 x 6

Model	term	estimate	std.error	statistic	p.value
<chr>	<chr>	<dbl>	<dbl>	<dbl>	<dbl>
1 Original	(Intercept)	1.34	0.0687	19.5	6.28e-37
2 Sensitivity	(Intercept)	1.28	0.0571	22.5	2.24e-40
3 Original	allocation_groupGrupo B	-0.0413	0.0982	-0.420	6.75e- 1
4 Sensitivity	allocation_groupGrupo B	0.00878	0.0823	0.107	9.15e- 1
5 Original	allocation_groupGrupo B:v~	0.0624	0.0952	0.656	5.13e- 1
6 Sensitivity	allocation_groupGrupo B:v~	0.0538	0.0817	0.659	5.12e- 1
7 Original	allocation_groupGrupo B:v~	0.0566	0.107	0.529	5.98e- 1
8 Sensitivity	allocation_groupGrupo B:v~	0.0259	0.0937	0.277	7.83e- 1
9 Original	sd__(Intercept)	0.331	NA	NA	NA
10 Sensitivity	sd__(Intercept)	0.266	NA	NA	NA

```

11 Original    sd__Observation      0.254     NA      NA      NA
12 Sensitivity sd__Observation      0.208     NA      NA      NA
13 Original    visit2              -0.115     0.0660   -1.74   8.51e- 2
14 Sensitivity visit2              -0.100     0.0559   -1.79   7.68e- 2
15 Original    visit3              0.00987    0.0711   0.139   8.90e- 1
16 Sensitivity visit3             -0.0135    0.0607   -0.223   8.24e- 1

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.

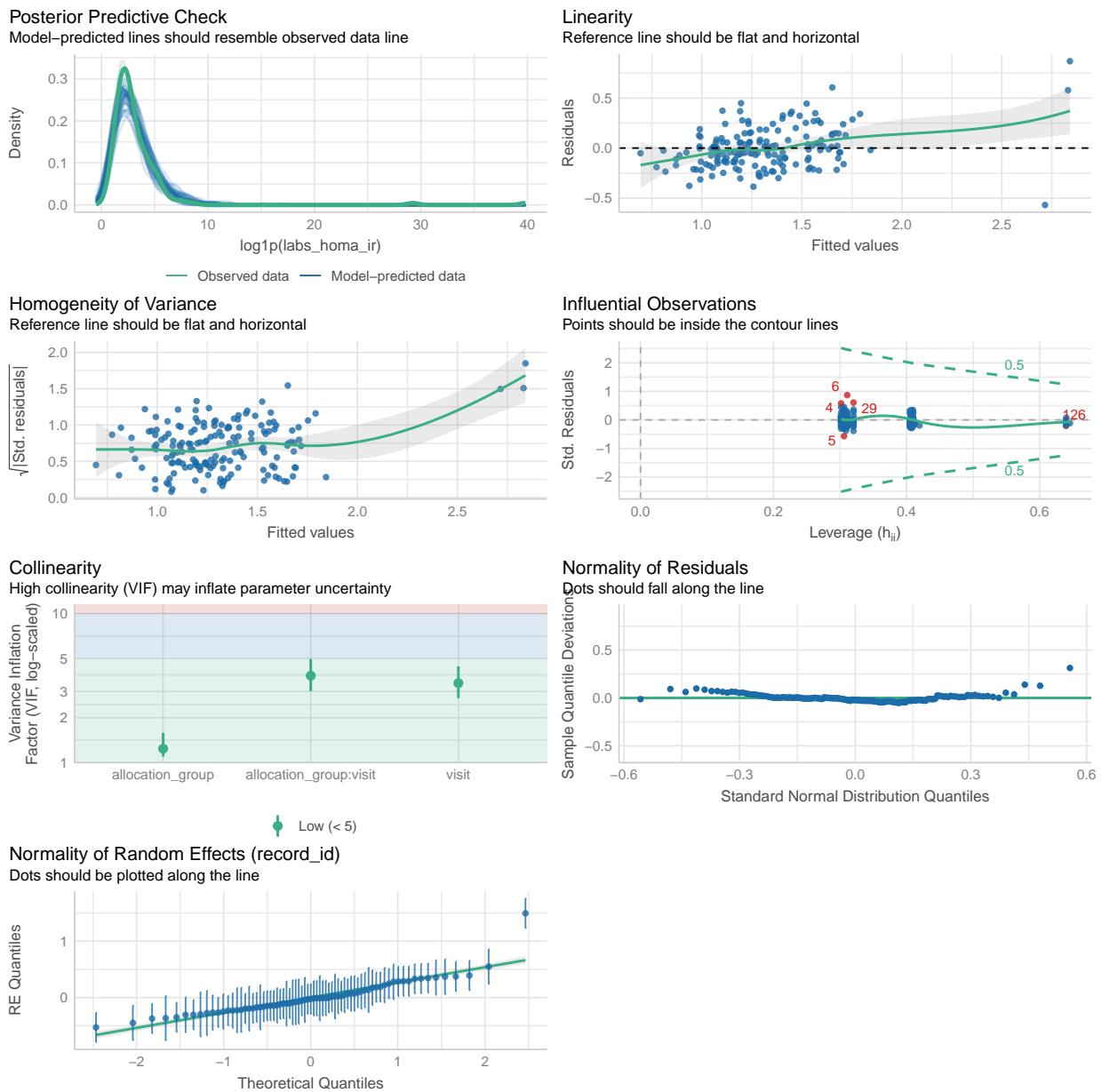
```
# Comparison of Model Performance Indices
```

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)

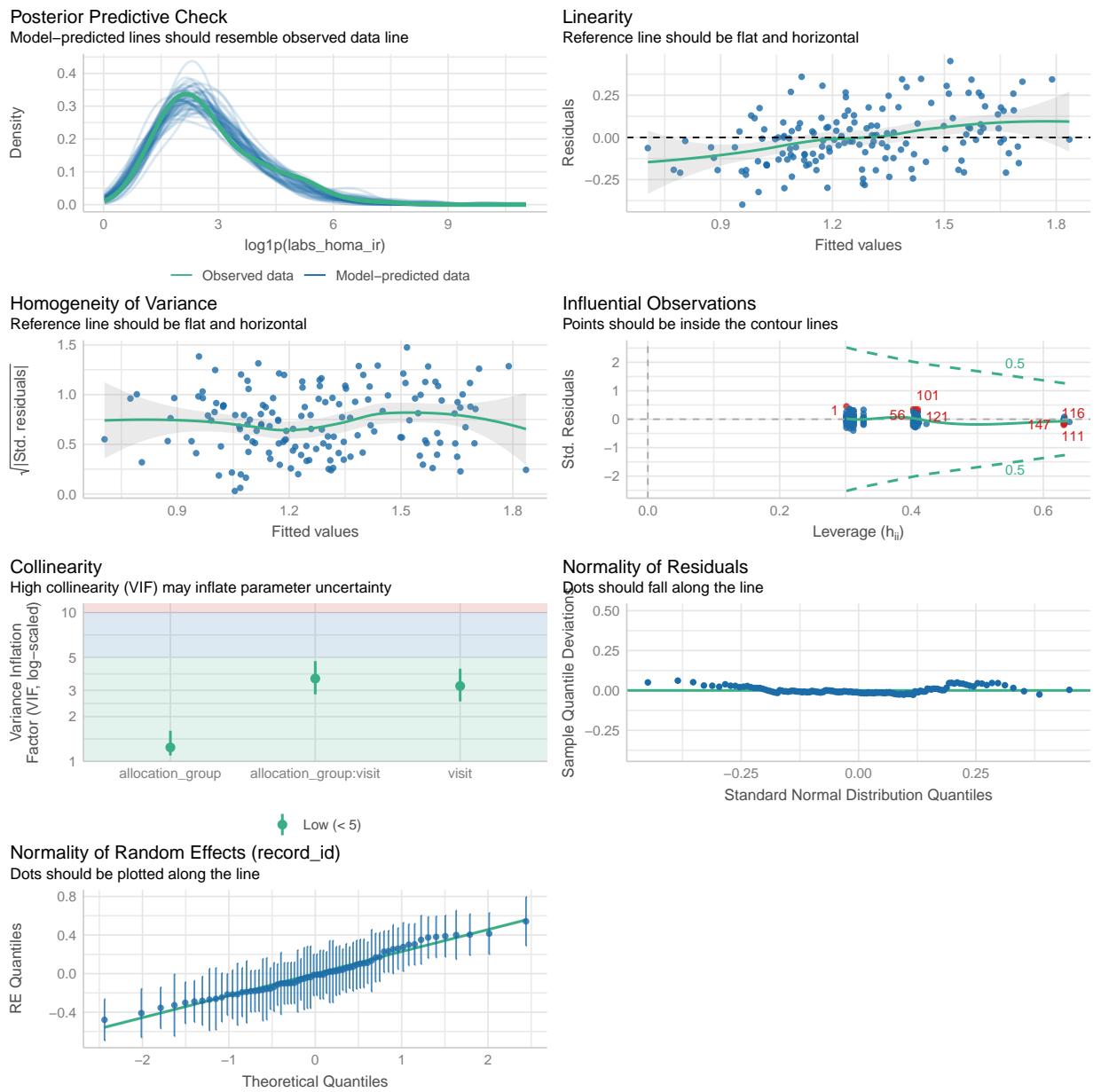
Name	BIC (weights)	R2 (cond.)	R2 (marg.)	ICC
labs_homa_ir_model	604.1 (<.001)	0.635	0.014	0.630
labs_homa_ir_model_sens	478.4 (>.999)	0.625	0.014	0.620

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)
```



```
performance::check_model(labs_homa_ir_model_sens)
```



3.0.12.2 Médias Marginais Estimadas

3.0.12.2.1 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

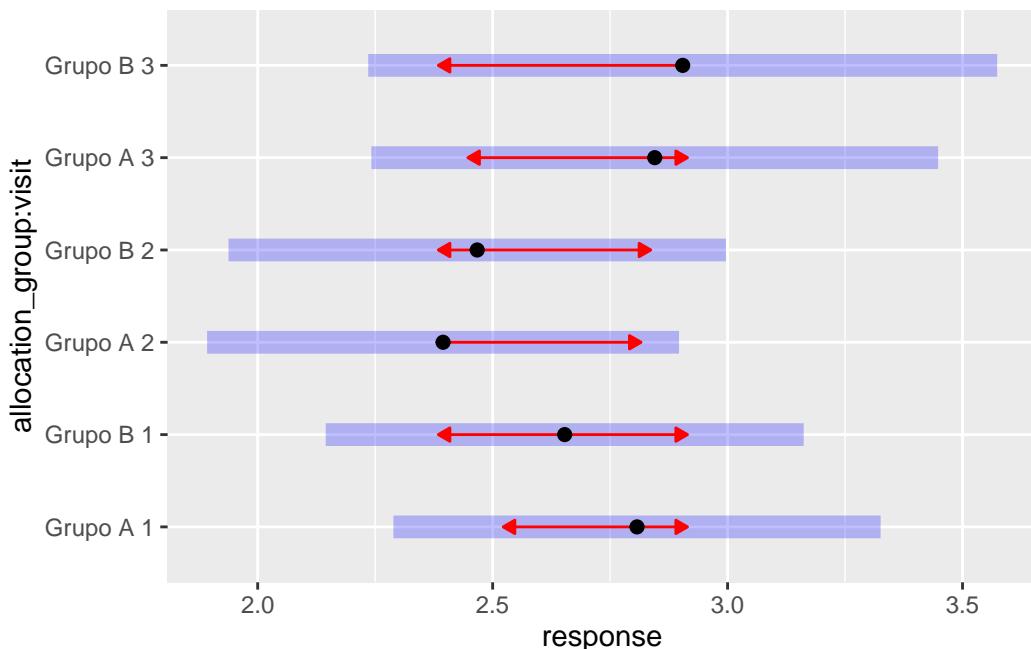
Confidence level used: 0.95

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)
```



3.0.12.2.2 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

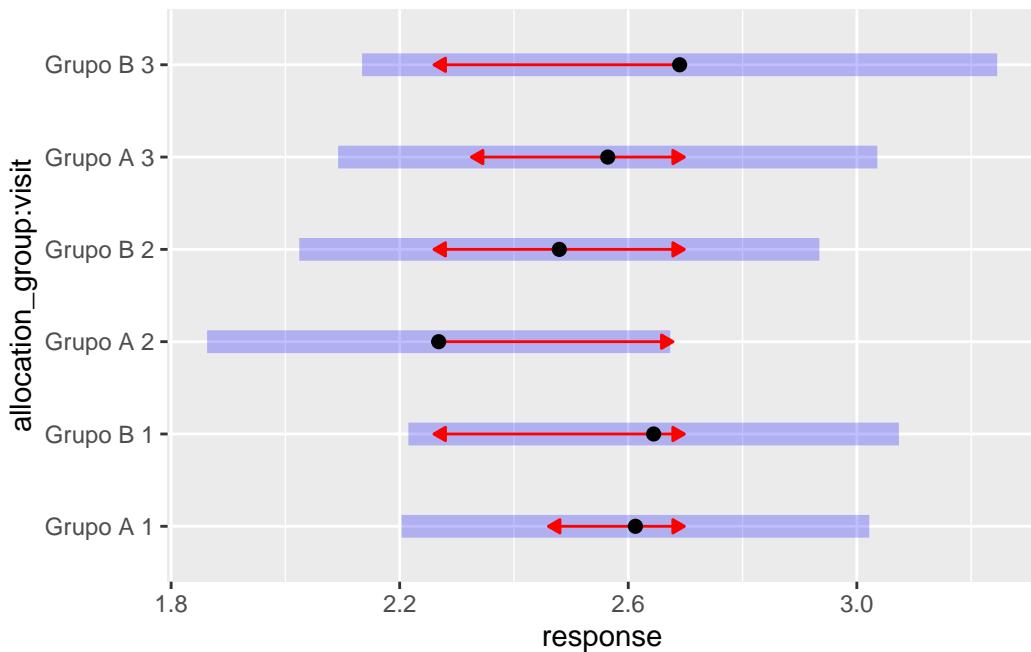
Degrees-of-freedom method: inherited from kenward-roger when re-gridding

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)
```



3.0.12.3 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
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 de comparação	Comparação	Estimativa	IC 95%	p-valor
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()`).

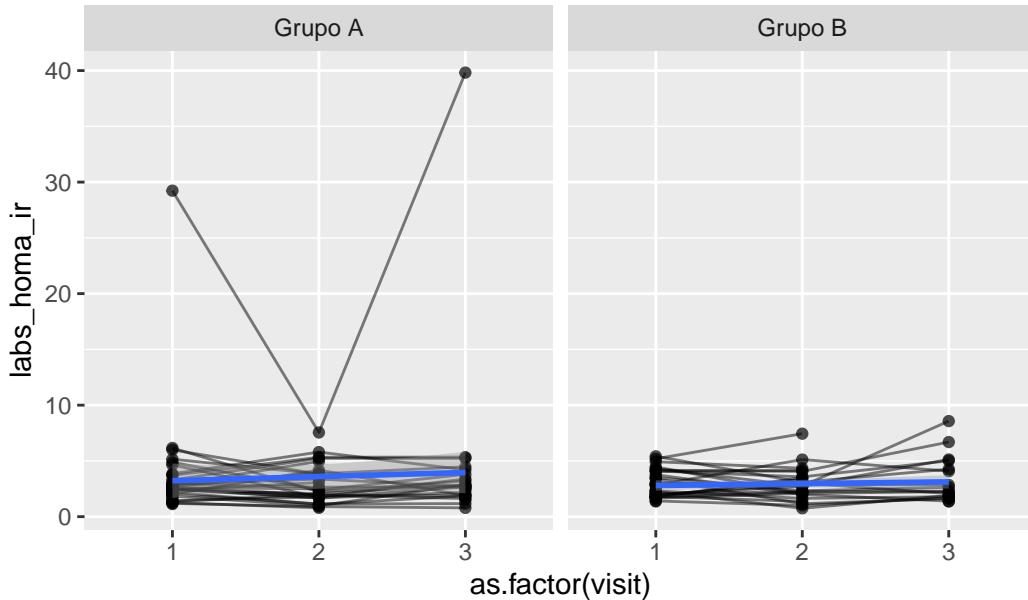
Warning: Removed 18 rows containing missing values or values outside the scale range

```
(`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)

```

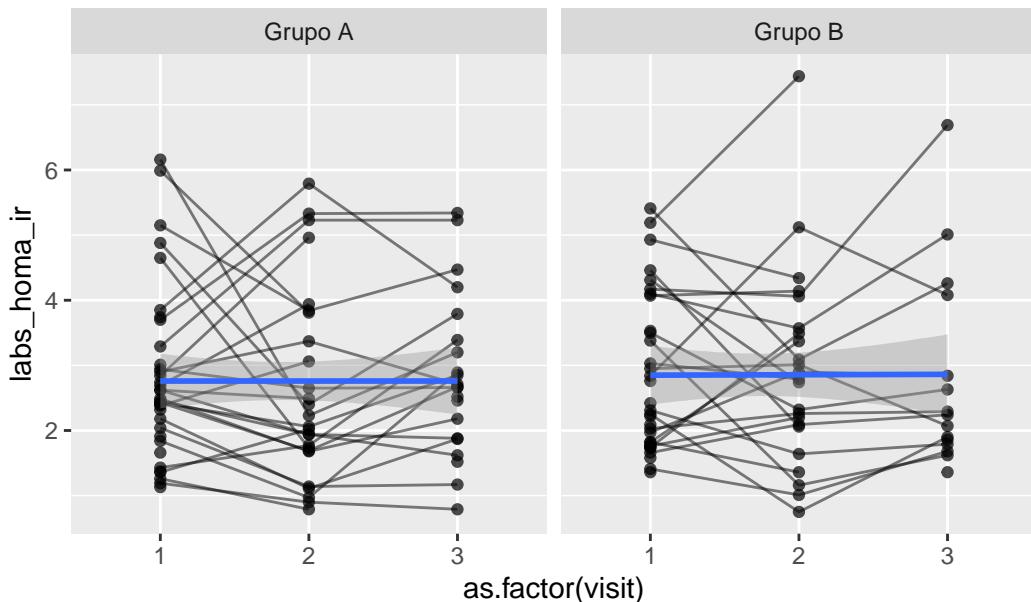
`geom_smooth()` using formula = 'y ~ x'

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))
```

3.0.13 Índice QUICK

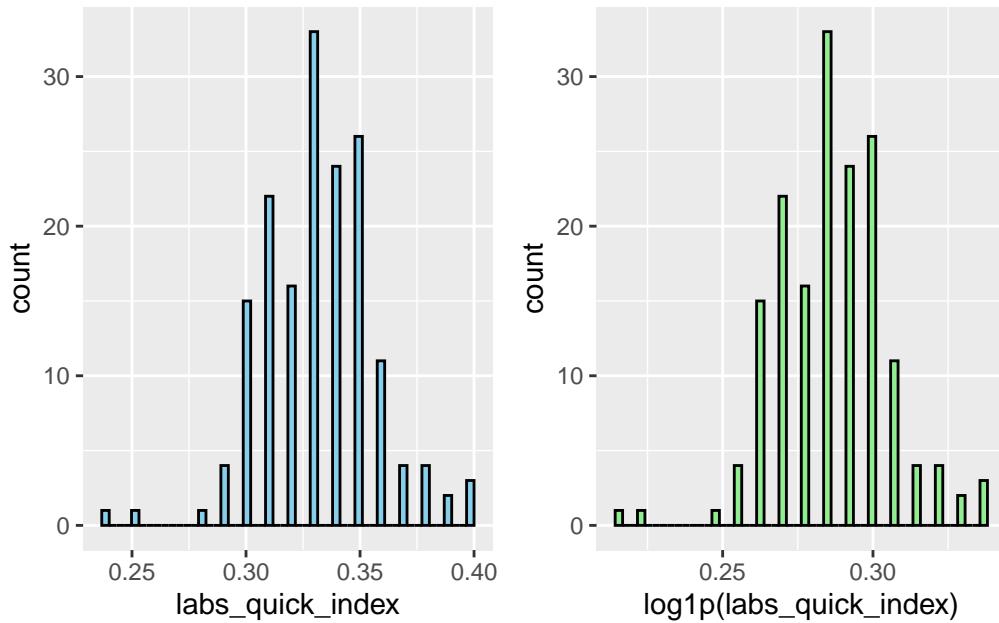
Variável: labs_quick_index

```
# 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"

```

3.0.13.1 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										
<hr/>											
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	-0.394	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_groupGrupo B             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_groupGrupo B:visit2     -5.420e-03  5.685e-03 8.792e+01  -0.953
allocation_groupGrupo B:visit3     -5.218e-03  6.509e-03 9.243e+01  -0.802
                                         Pr(>|t|)    
(Intercept)                         <2e-16 *** 

```

```

allocation_groupGrupo B      0.9212
visit2                      0.0897 .
visit3                      0.6558
allocation_groupGrupo B:visit2 0.3430
allocation_groupGrupo B: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

```
labs_quick_index_model_check$comparison_table
```

```
# A tibble: 16 x 6
```

Model	term	estimate	std.error	statistic	p.value
<chr>	<chr>	<dbl>	<dbl>	<dbl>	<dbl>
1 Original	(Intercept)	3.31e-1	0.00417	79.2	6.23e-97
2 Sensitivity	(Intercept)	3.32e-1	0.00375	88.6	1.42e-97
3 Original	allocation_groupGrupo B	1.26e-3	0.00597	0.211	8.33e- 1
4 Sensitivity	allocation_groupGrupo B	5.36e-4	0.00541	0.0992	9.21e- 1
5 Original	allocation_groupGrupo B:v~	-3.69e-3	0.00590	-0.625	5.33e- 1
6 Sensitivity	allocation_groupGrupo B:v~	-5.42e-3	0.00569	-0.953	3.43e- 1
7 Original	allocation_groupGrupo B:v~	-5.41e-3	0.00664	-0.815	4.17e- 1
8 Sensitivity	allocation_groupGrupo B:v~	-5.22e-3	0.00651	-0.802	4.25e- 1
9 Original	sd__(Intercept)	1.99e-2	NA	NA	NA
10 Sensitivity	sd__(Intercept)	1.67e-2	NA	NA	NA

```

11 Original    sd__Observation      1.58e-2  NA       NA       NA
12 Sensitivity sd__Observation      1.45e-2  NA       NA       NA
13 Original    visit2              8.36e-3  0.00409  2.04    4.36e- 2
14 Sensitivity visit2              6.68e-3  0.00389  1.72    8.97e- 2
15 Original    visit3              2.32e-3  0.00441  0.527   5.99e- 1
16 Sensitivity visit3              1.89e-3  0.00422  0.447   6.56e- 1

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.

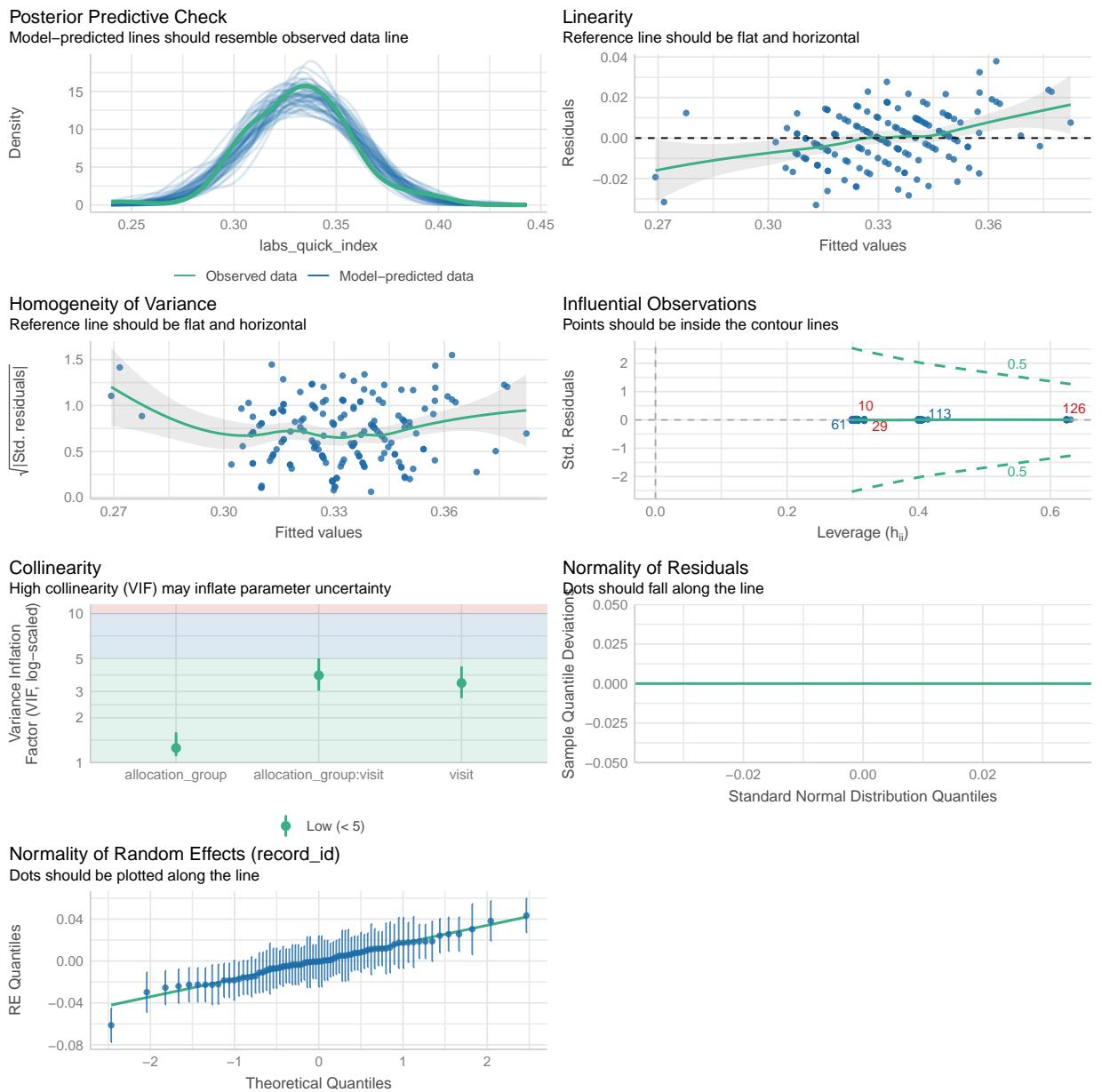
```
# Comparison of Model Performance Indices
```

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)

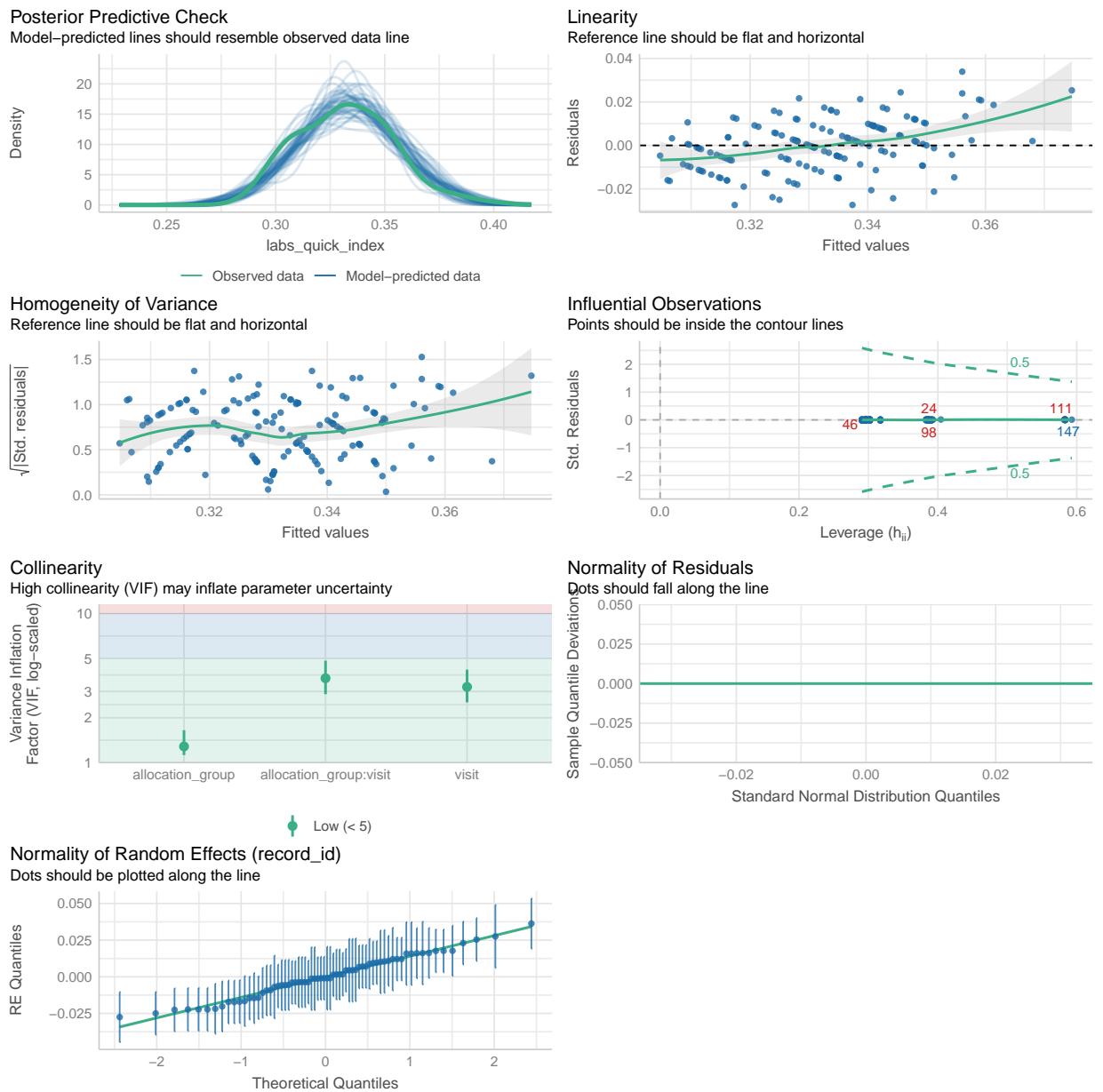
Name	BIC (weights)	R2 (cond.)	R2 (marg.)	ICC
labs_quick_index_model	-768.3 (>.999)	0.621	0.017	0.614
labs_quick_index_model_sens	-730.1 (<.001)	0.576	0.014	0.570

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)
```



3.0.13.2 Médias Marginais Estimadas

3.0.13.2.1 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

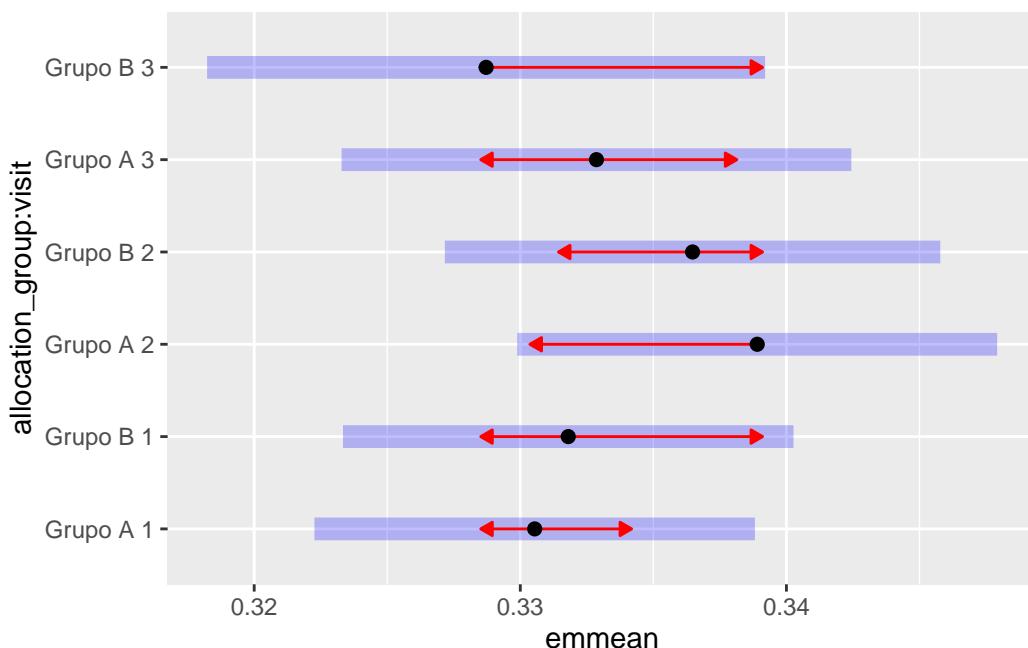
Conf-level adjustment: bonferroni method for 3 estimates

P value adjustment: bonferroni method for 3 tests

```

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

```



3.0.13.2.2 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

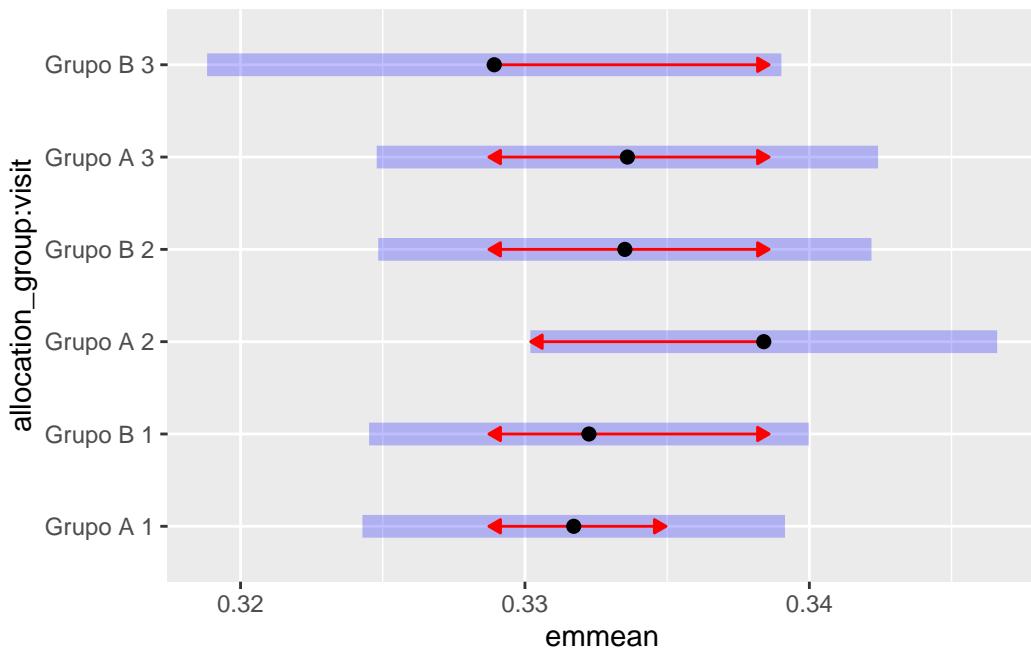
Confidence level used: 0.95

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)
```



3.0.13.3 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
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 de comparação	Comparação	Estimativa	IC 95%	p-valor
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)

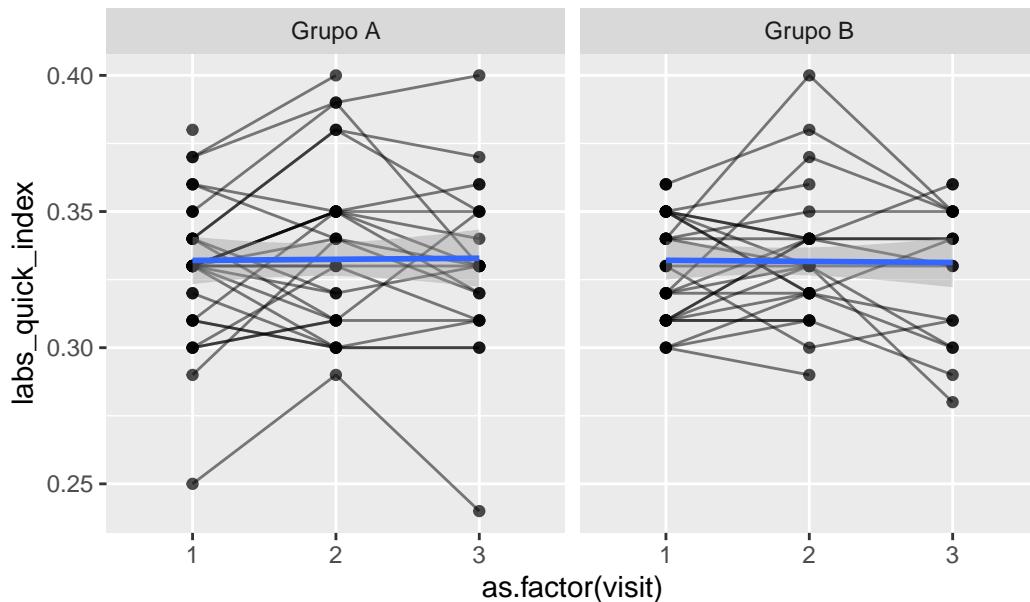
`geom_smooth()` using formula = 'y ~ x'
Warning: Removed 22 rows containing non-finite outside the scale range
(`stat_smooth()`).

```

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)

```

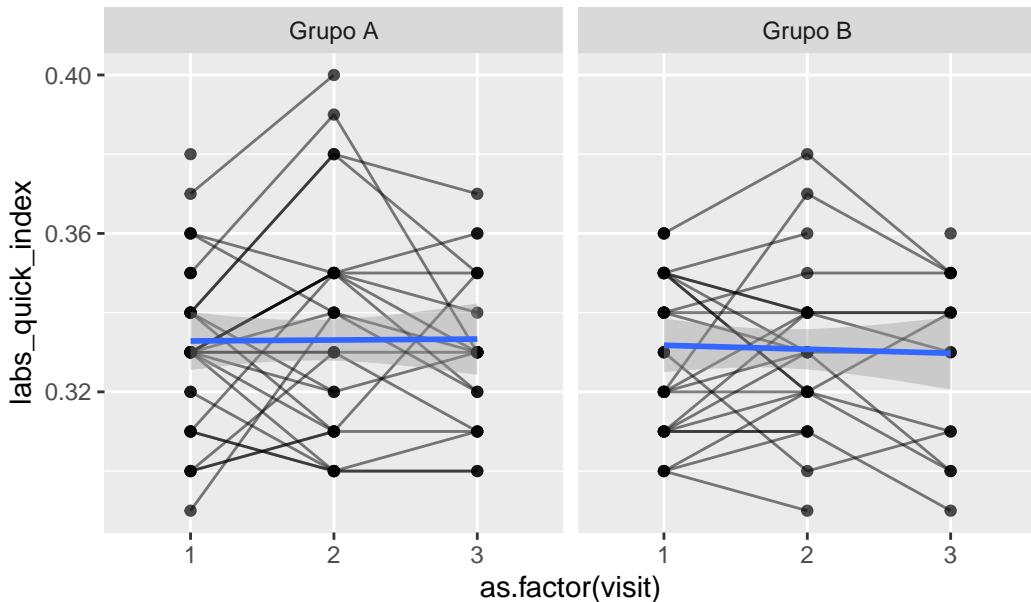
`geom_smooth()` using formula = 'y ~ x'

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))
```

3.0.14 Circunferência abdominal

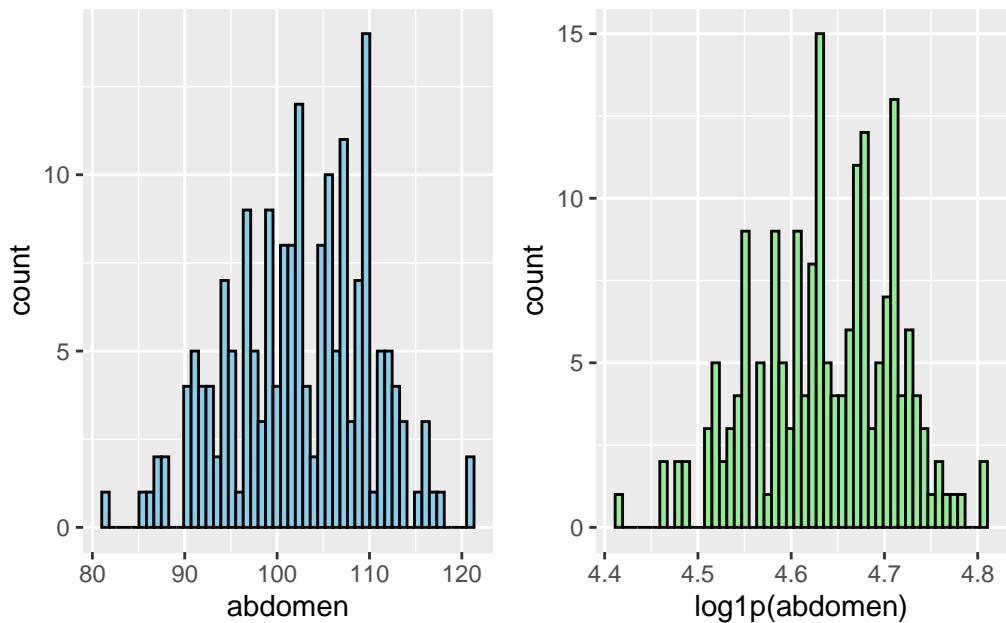
Variável: abdomen

```
# 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"

```

3.0.14.1 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 *										
<hr/>											
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	-0.239	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_groupGrupo B      0.3325
visit2                      0.7529
visit3                      0.1623
allocation_groupGrupo B:visit2 0.8652
allocation_groupGrupo B: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

`abdomen_model_check$comparison_table`

A tibble: 16 x 6

Model	term	estimate	std.error	statistic	p.value
<chr>	<chr>	<dbl>	<dbl>	<dbl>	<dbl>
1 Original	(Intercept)	4.65	0.0122	381.	4.49e-139
2 Sensitivity	(Intercept)	4.65	0.0126	369.	2.66e-125
3 Original	allocation_groupGrupo B	-0.0151	0.0171	-0.880	3.81e- 1
4 Sensitivity	allocation_groupGrupo B	-0.0169	0.0173	-0.975	3.33e- 1
5 Original	allocation_groupGrupo B:~	0.00662	0.00989	0.670	5.04e- 1
6 Sensitivity	allocation_groupGrupo B:~	0.00149	0.00878	0.170	8.65e- 1
7 Original	allocation_groupGrupo B:~	0.0230	0.0104	2.20	2.98e- 2
8 Sensitivity	allocation_groupGrupo B:~	0.0206	0.00932	2.21	2.92e- 2
9 Original	sd__(Intercept)	0.0689	NA	NA	NA
10 Sensitivity	sd__(Intercept)	0.0686	NA	NA	NA

```

11 Original    sd__Observation      0.0272   NA       NA       NA
12 Sensitivity sd__Observation      0.0232   NA       NA       NA
13 Original    visit2              -0.00874  0.00688 -1.27    2.07e- 1
14 Sensitivity visit2              -0.00198  0.00627 -0.316   7.53e- 1
15 Original    visit3              -0.0160   0.00725 -2.21    2.92e- 2
16 Sensitivity visit3              -0.00938  0.00666 -1.41    1.62e- 1

performance::compare_performance(
  abdomen_model,
  abdomen_model_sens)

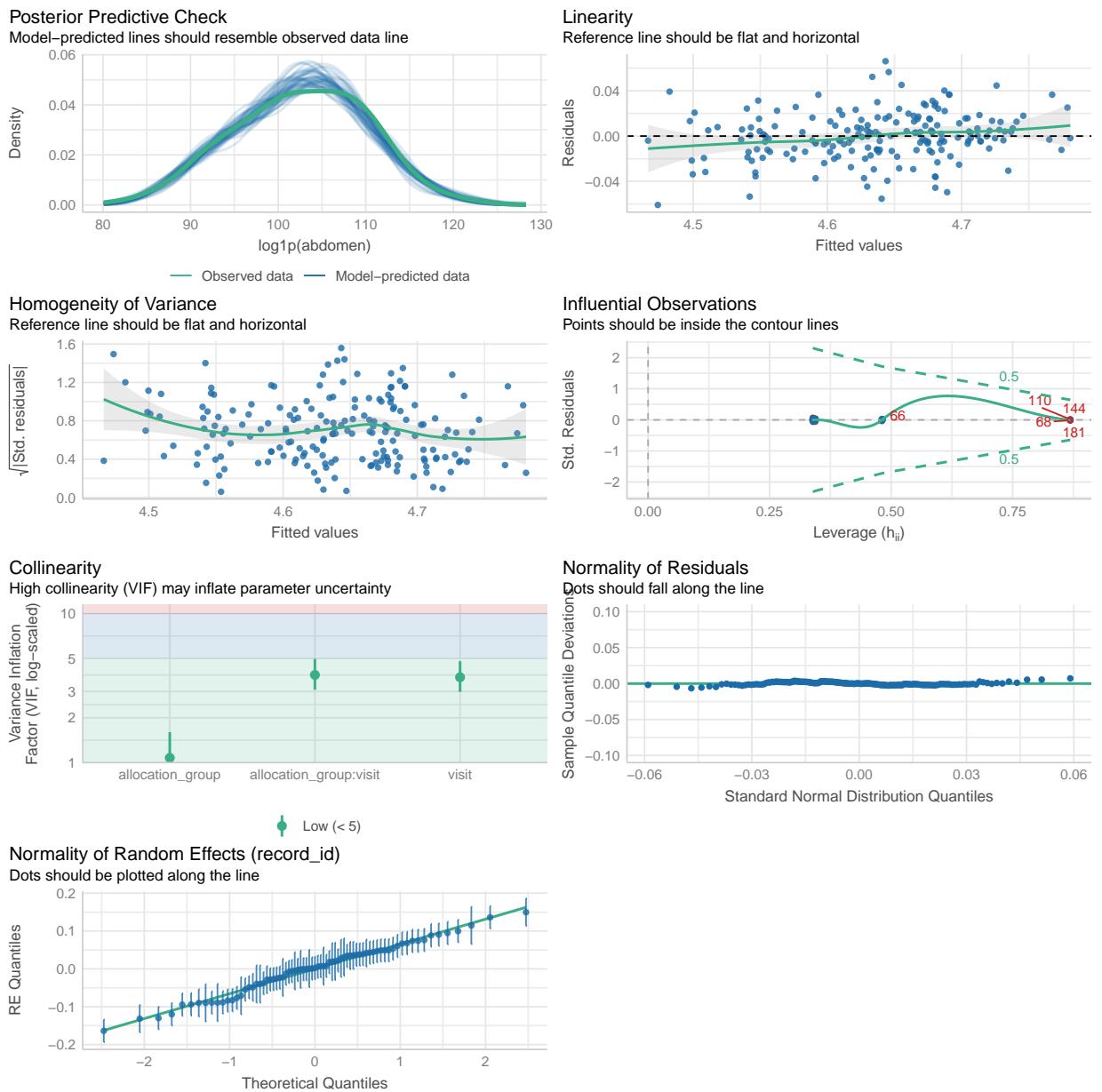
```

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

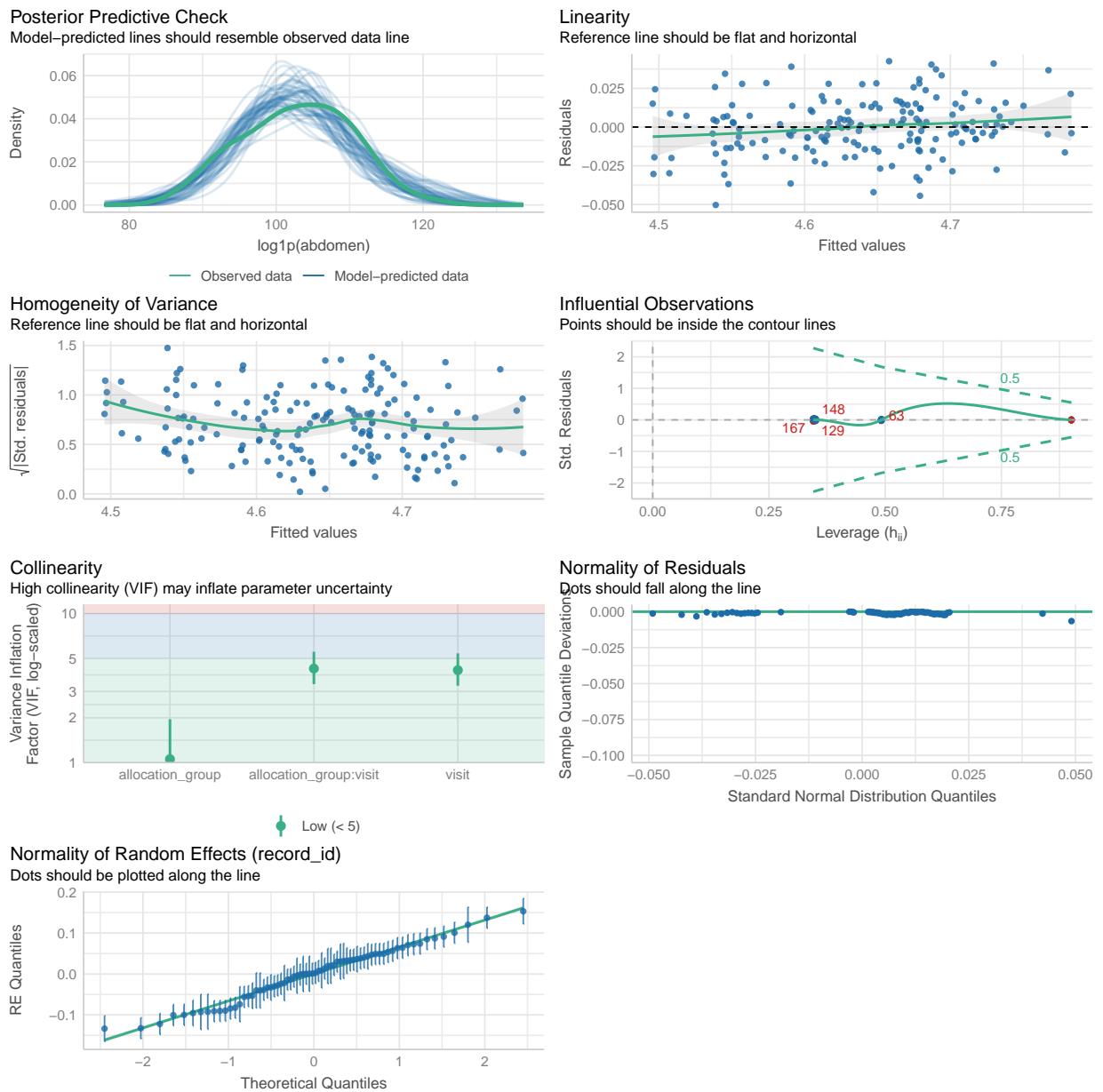
```
# Comparison of Model Performance Indices
```

Name		Model	AIC (weights)	AICc (weights)
<hr/>				
abdomen_model	lmerModLmerTest	1134.8 (<.001)	1135.6 (<.001)	
abdomen_model_sens	lmerModLmerTest	1011.7 (>.999)	1012.6 (>.999)	
<hr/>				
Name		BIC (weights)	R2 (cond.)	R2 (marg.) ICC RMSE Sigma
<hr/>				
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)
```



3.0.14.2 Médias Marginais Estimadas

3.0.14.2.1 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

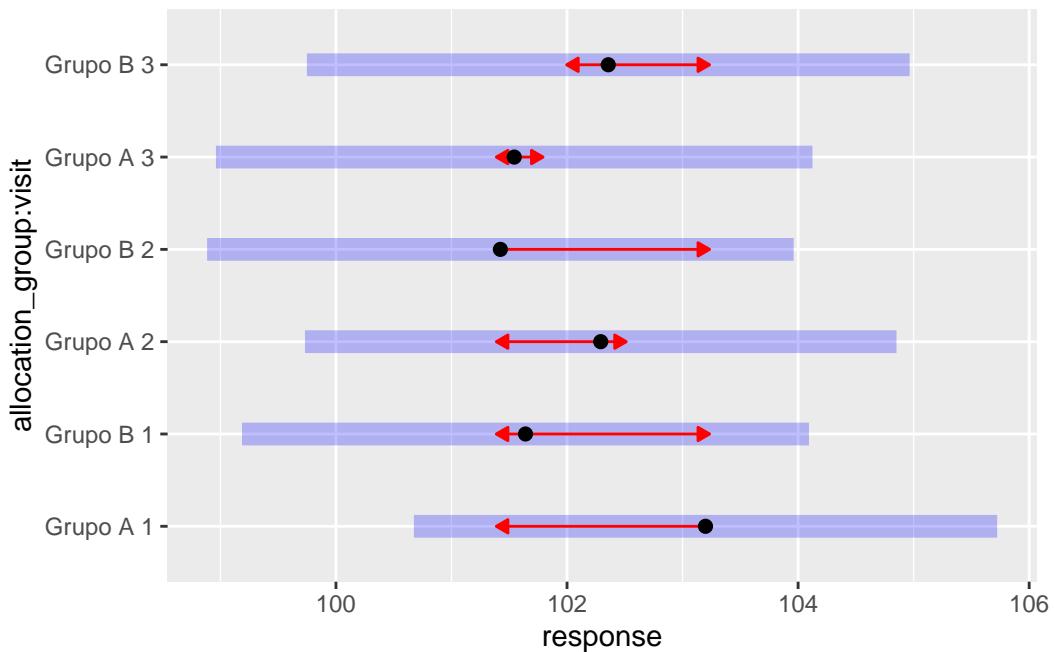
```

# 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



3.0.14.2.2 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	visit1 - visit2	0.2062	0.653	75.5	-1.393	1.806	0.316	1.0000
visit1 - visit3	visit1 - visit3	0.9734	0.691	75.5	-0.719	2.665	1.409	0.4892
visit2 - visit3	visit2 - visit3	0.7672	0.693	81.5	-0.928	2.462	1.106	0.8156

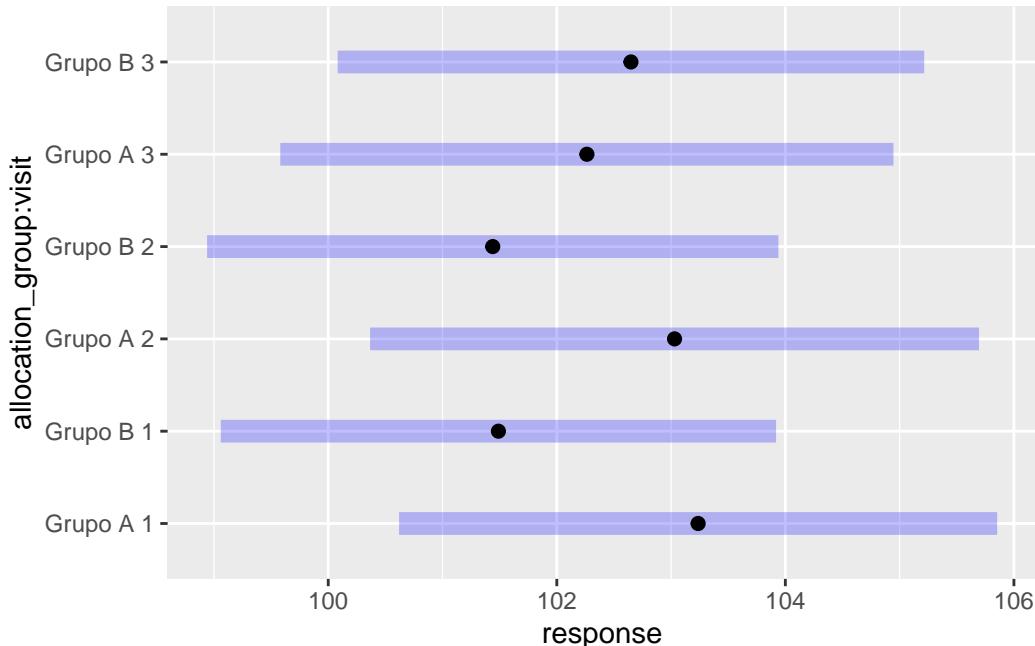
allocation_group = Grupo B:

	contrast	estimate	SE	df	lower.CL	upper.CL	t.ratio	p.value
visit1 - visit2	visit1 - visit2	0.0497	0.630	75.5	-1.494	1.593	0.079	1.0000
visit1 - visit3	visit1 - visit3	-1.1596	0.674	75.5	-2.809	0.490	-1.721	0.2679
visit2 - visit3	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)
```



3.0.14.3 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
)

```

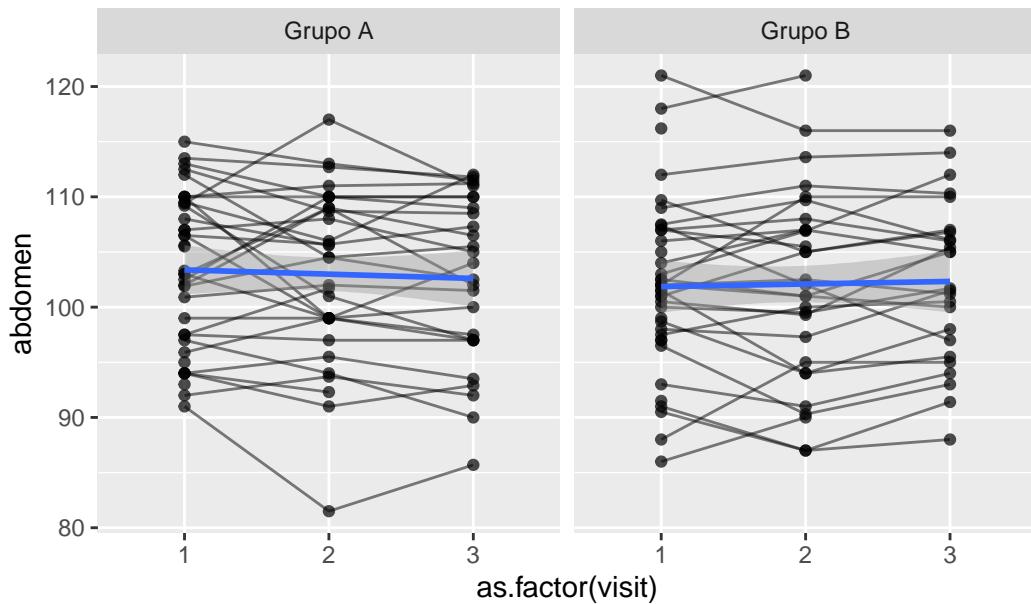
```

) +
  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)
  ) %>%

```

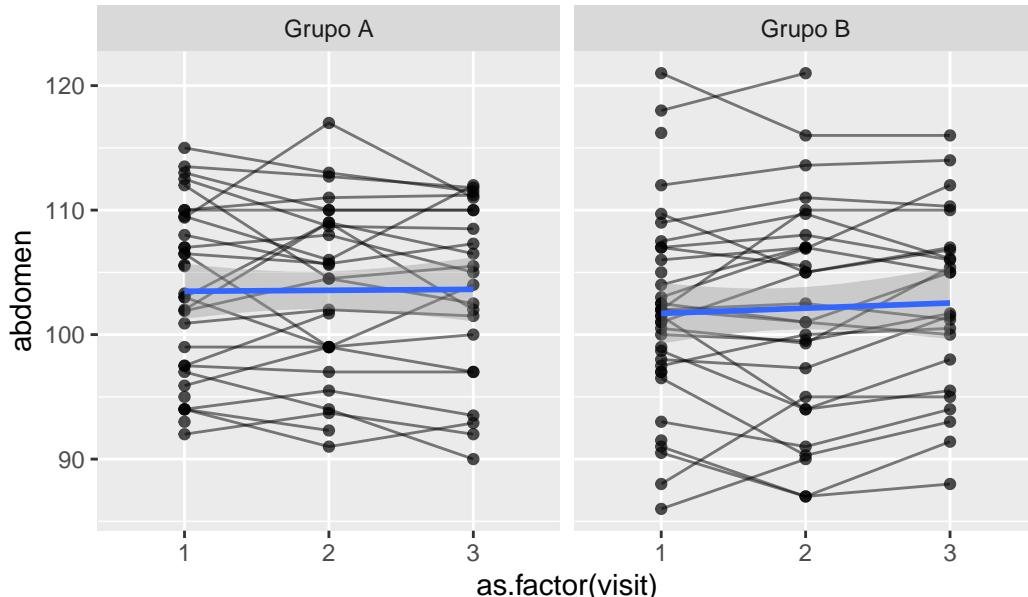
```

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



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

3.0.15 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
  #) %>%
```

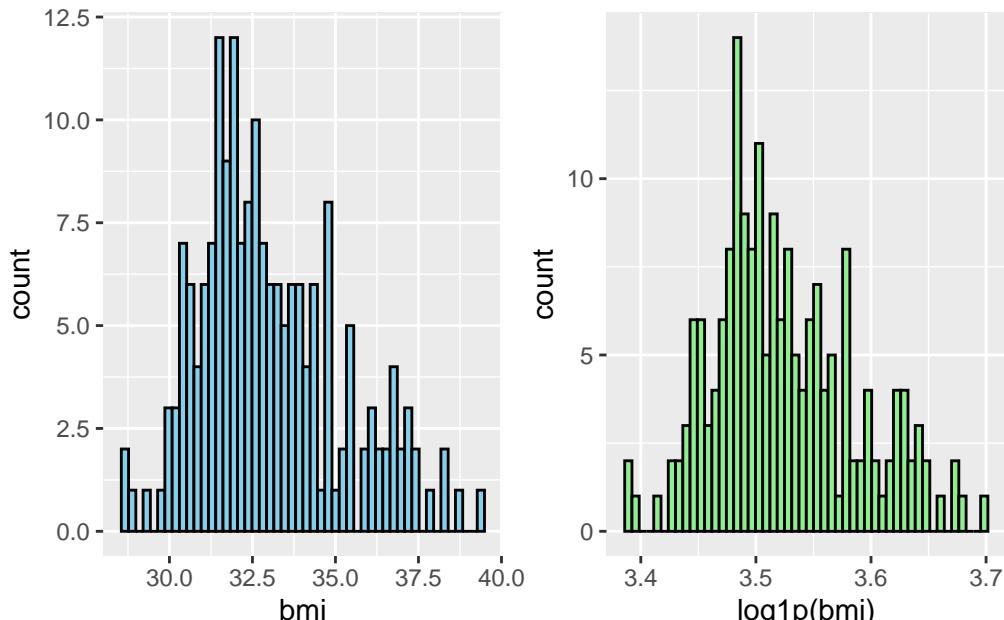
```

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"

```

3.0.15.1 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_groupGrupo B:visit2  0.1222      0.1981 99.4346  0.617   0.5388
allocation_groupGrupo B: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_grGB	-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

```
bmi_model_check$comparison_table
```

A tibble: 16 x 6

Model	term	estimate	std.error	statistic	p.value
<chr>	<chr>	<dbl>	<dbl>	<dbl>	<dbl>
1 Original	(Intercept)	33.0	0.351	94.0	9.96e-85
2 Sensitivity	(Intercept)	32.7	0.344	95.1	2.73e-78
3 Original	allocation_groupGrupo B	0.360	0.493	0.730	4.68e- 1
4 Sensitivity	allocation_groupGrupo B	0.547	0.473	1.16	2.51e- 1
5 Original	allocation_groupGrupo B:v~	0.336	0.245	1.38	1.72e- 1
6 Sensitivity	allocation_groupGrupo B:v~	0.122	0.198	0.617	5.39e- 1
7 Original	allocation_groupGrupo B:v~	0.571	0.258	2.21	2.91e- 2
8 Sensitivity	allocation_groupGrupo B:v~	0.203	0.210	0.963	3.38e- 1
9 Original	sd__(Intercept)	2.03	NA	NA	NA
10 Sensitivity	sd__(Intercept)	1.90	NA	NA	NA
11 Original	sd__Observation	0.673	NA	NA	NA

```

12 Sensitivity sd__Observation          0.521    NA      NA      NA
13 Original    visit2                  -0.326    0.170   -1.92   5.78e- 2
14 Sensitivity visit2                 -0.174    0.141   -1.23   2.22e- 1
15 Original    visit3                  -0.574    0.179   -3.20   1.79e- 3
16 Sensitivity visit3                 -0.272    0.150   -1.81   7.29e- 2

```

```

  performance::compare_performance(
    bmi_model,
    bmi_model_sens)

```

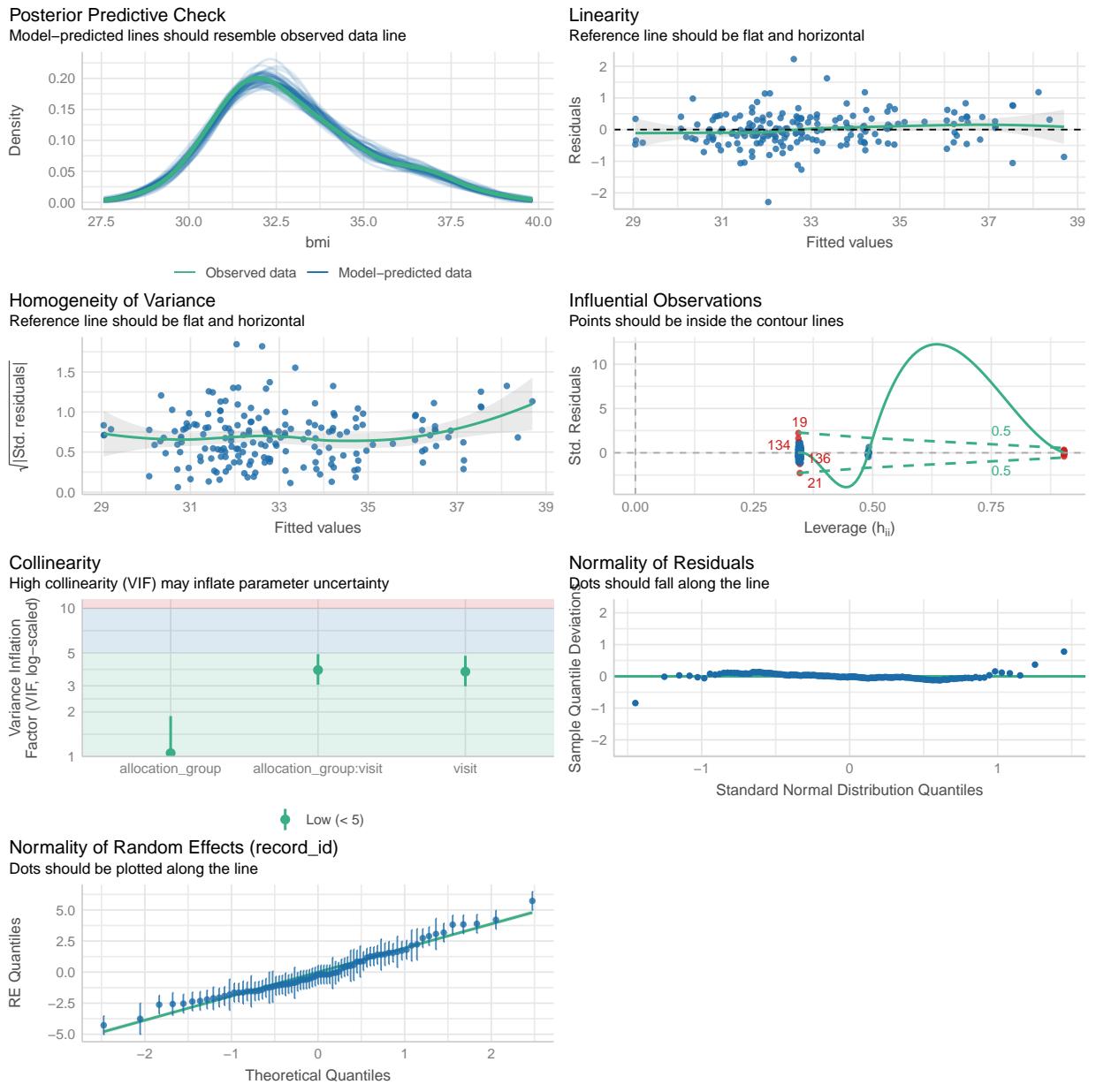
When comparing models, please note that probably not all models were fit from same data.

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

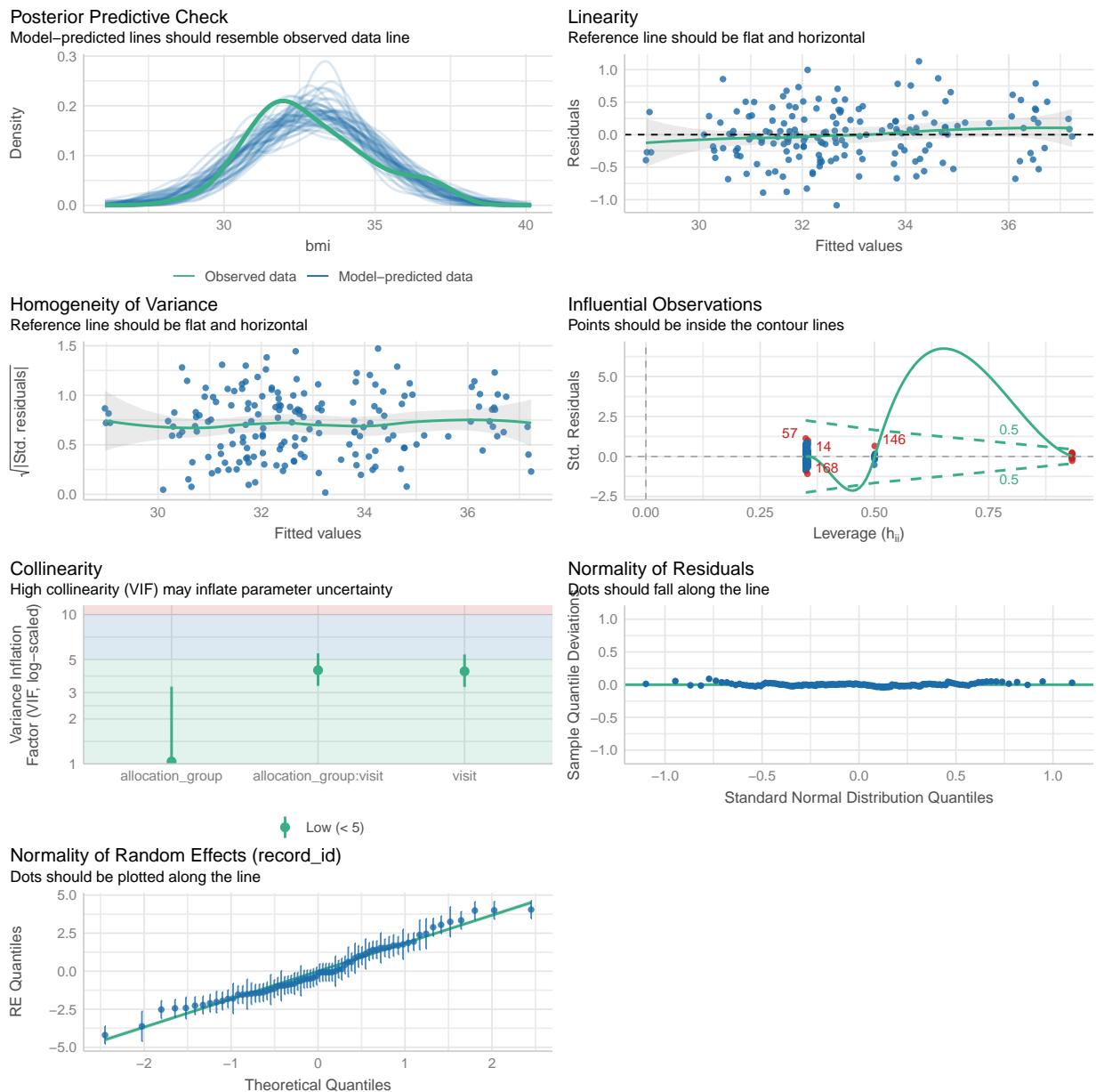
Name	Model	AIC (weights)	AICc (weights)
bmi_model	lmerModLmerTest	624.2 (<.001)	625.0 (<.001)
bmi_model_sens	lmerModLmerTest	515.0 (>.999)	515.9 (>.999)

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)
```



```
performance::check_model(bmi_model_sens)
```



3.0.15.2 Médias Marginais Estimadas

3.0.15.2.1 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

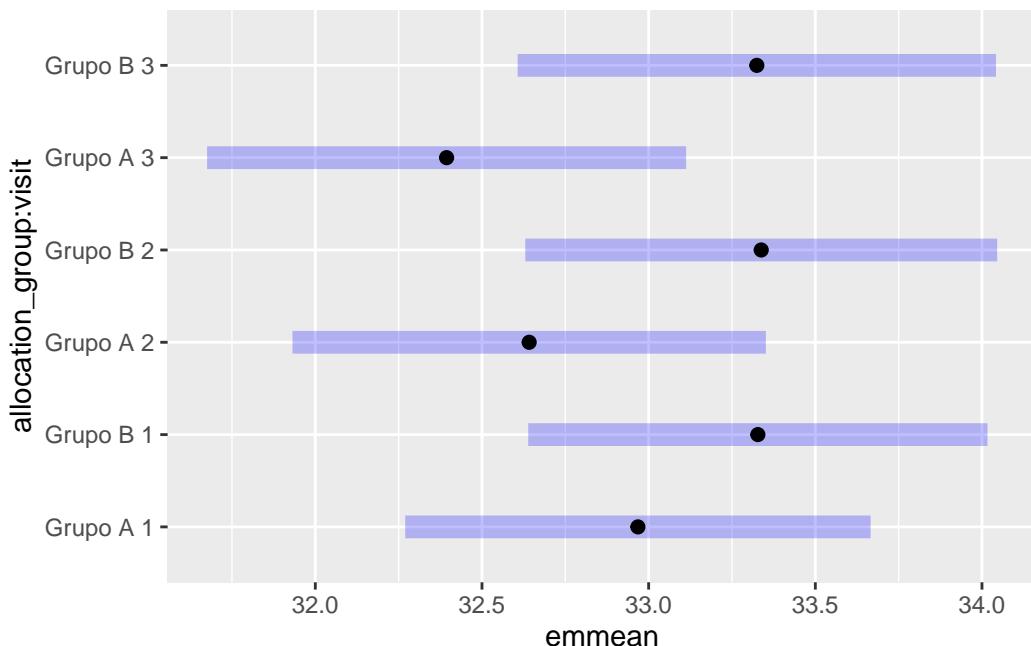
Conf-level adjustment: bonferroni method for 3 estimates

P value adjustment: bonferroni method for 3 tests

```

# Plot of marginal means
plot(bmi_raw_emm)

```



3.0.15.2.2 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

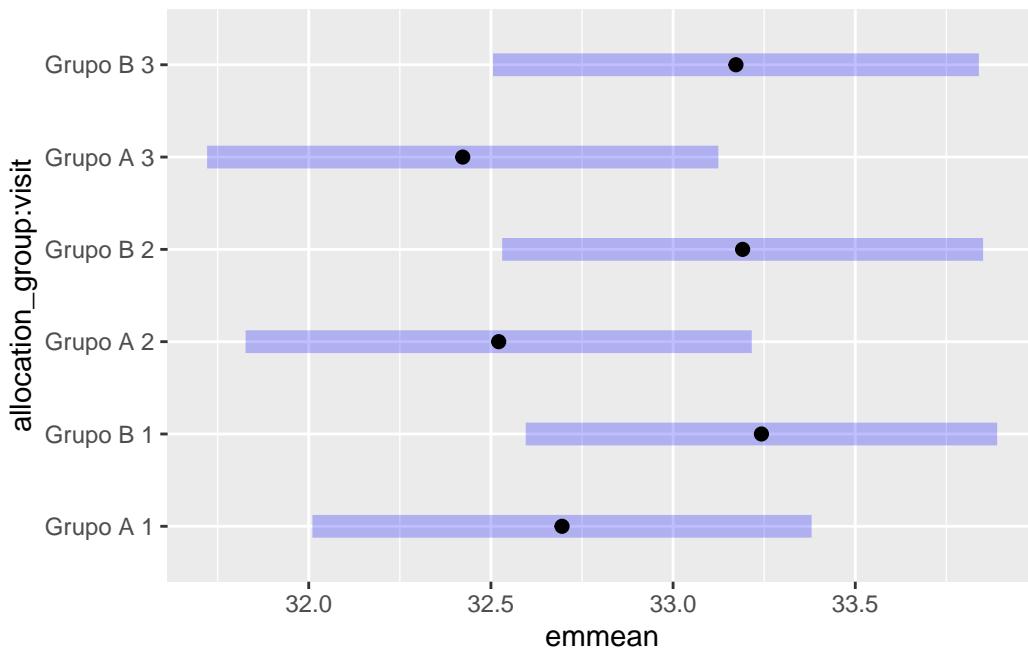
Degrees-of-freedom method: inherited from kenward-roger when re-gridding

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)
```



3.0.15.3 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

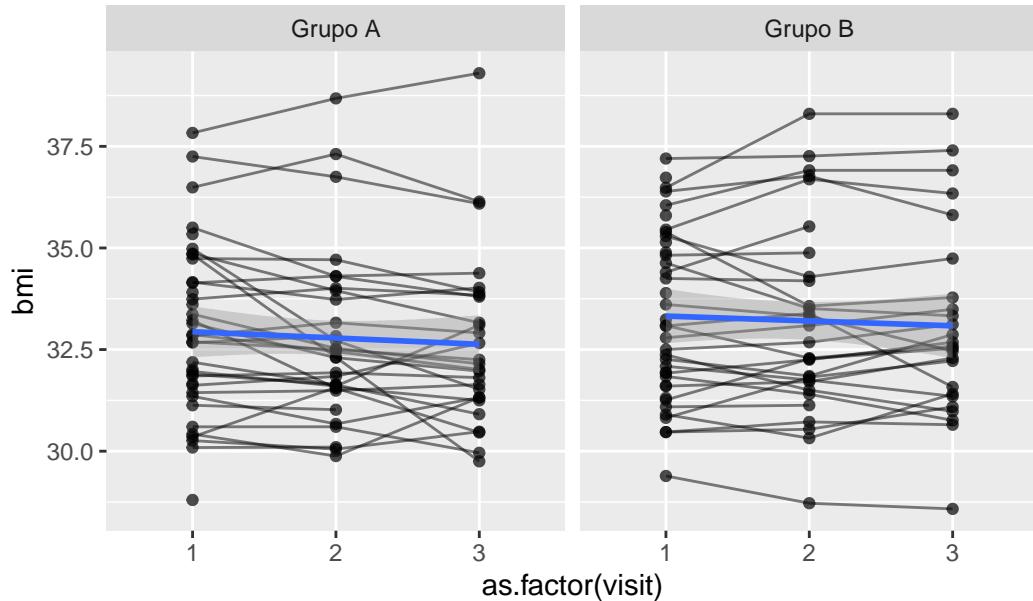
```

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(
    !(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'

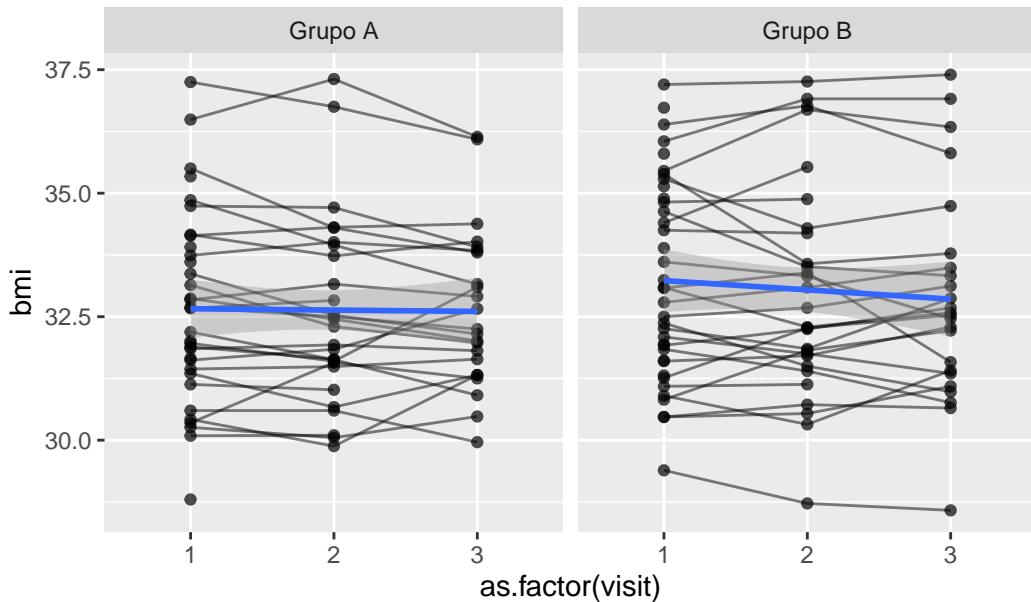
Warning: Removed 2 rows containing non-finite outside the scale range
(`stat_smooth()`).

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))
```

3.0.16 Pressão Arterial Média

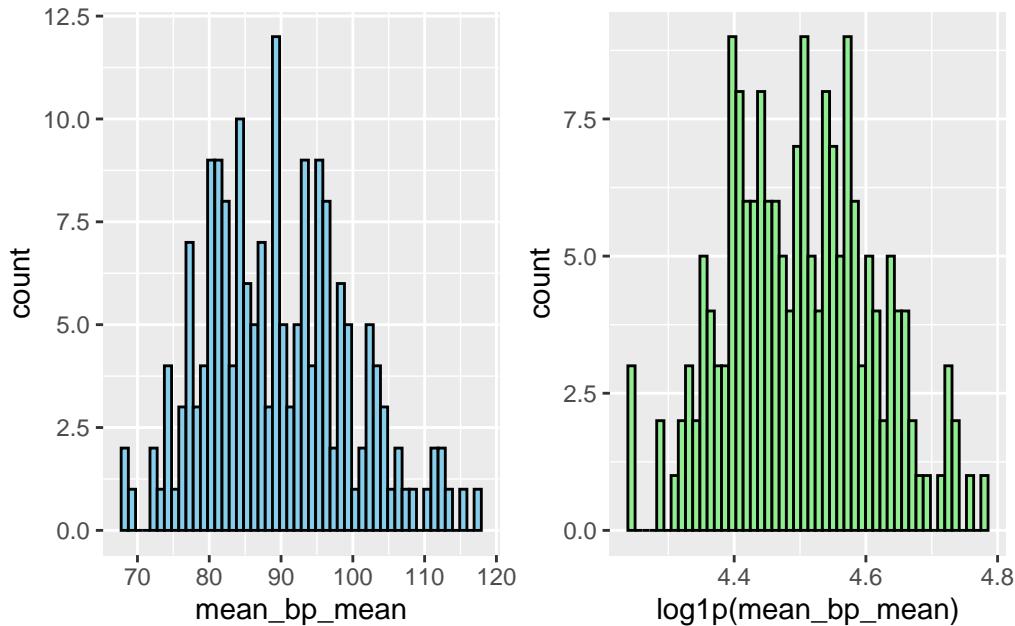
Variável: mean_bp_mean

```
# 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"

```

3.0.16.1 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_group	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_group:visit2	-2.813	2.130	112.538	-1.321	0.1893
allocation_group:visit3	1.435	2.220	113.267	0.647	0.5192

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

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_group	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_group:visit2	-2.666	1.911	102.226	-1.395	0.16591
allocation_group:visit3	1.794	2.012	102.825	0.892	0.37455

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

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
```

```
mean_bp_mean_model_check$comparison_table
```

```
# A tibble: 16 x 6
```

Model	term	estimate	std.error	statistic	p.value
<chr>	<chr>	<dbl>	<dbl>	<dbl>	<dbl>
1 Original	(Intercept)	89.6	1.66	53.9	2.88e-78
2 Sensitivity	(Intercept)	88.9	1.67	53.3	2.03e-70
3 Original	allocation_groupGrupo B	2.78	2.34	1.19	2.37e- 1
4 Sensitivity	allocation_groupGrupo B	3.76	2.29	1.64	1.04e- 1
5 Original	allocation_groupGrupo B:v~	-2.81	2.13	-1.32	1.89e- 1
6 Sensitivity	allocation_groupGrupo B:v~	-2.67	1.91	-1.40	1.66e- 1
7 Original	allocation_groupGrupo B:v~	1.44	2.22	0.647	5.19e- 1
8 Sensitivity	allocation_groupGrupo B:v~	1.79	2.01	0.892	3.75e- 1
9 Original	sd__(Intercept)	8.24	NA	NA	NA
10 Sensitivity	sd__(Intercept)	8.15	NA	NA	NA
11 Original	sd__Observation	5.86	NA	NA	NA
12 Sensitivity	sd__Observation	5.05	NA	NA	NA
13 Original	visit2	-1.21	1.50	-0.803	4.24e- 1
14 Sensitivity	visit2	-2.14	1.38	-1.55	1.23e- 1
15 Original	visit3	-3.71	1.54	-2.40	1.79e- 2
16 Sensitivity	visit3	-4.53	1.44	-3.14	2.18e- 3

```
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
------	---------------	------------	------------	-----

```
-----
```

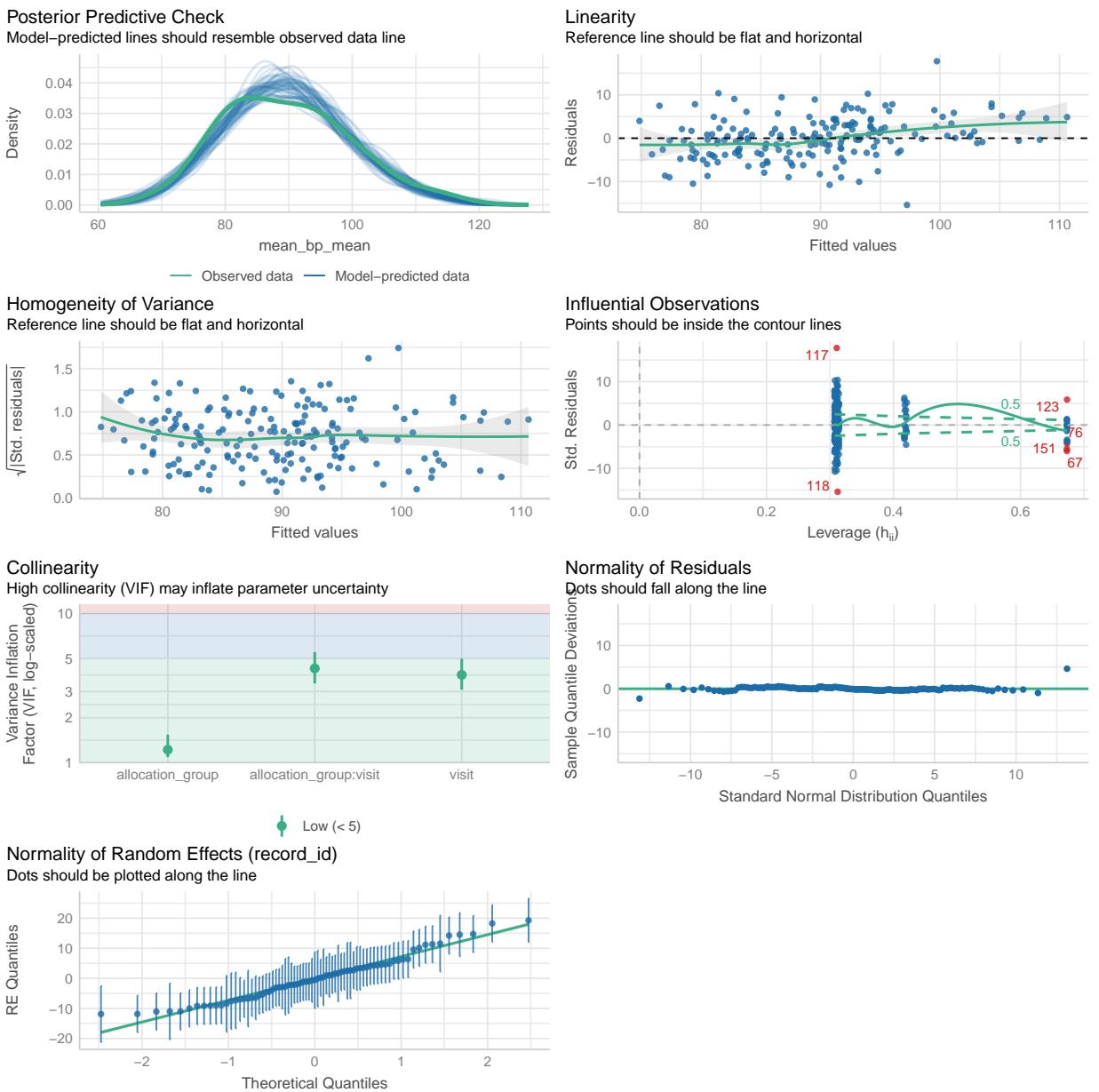
mean_bp_mean_model	1344.2 (<.001)	0.677	0.038	0.664
mean_bp_mean_model_sens	1209.8 (>.999)	0.742	0.070	0.723

Name	RMSE	Sigma
------	------	-------

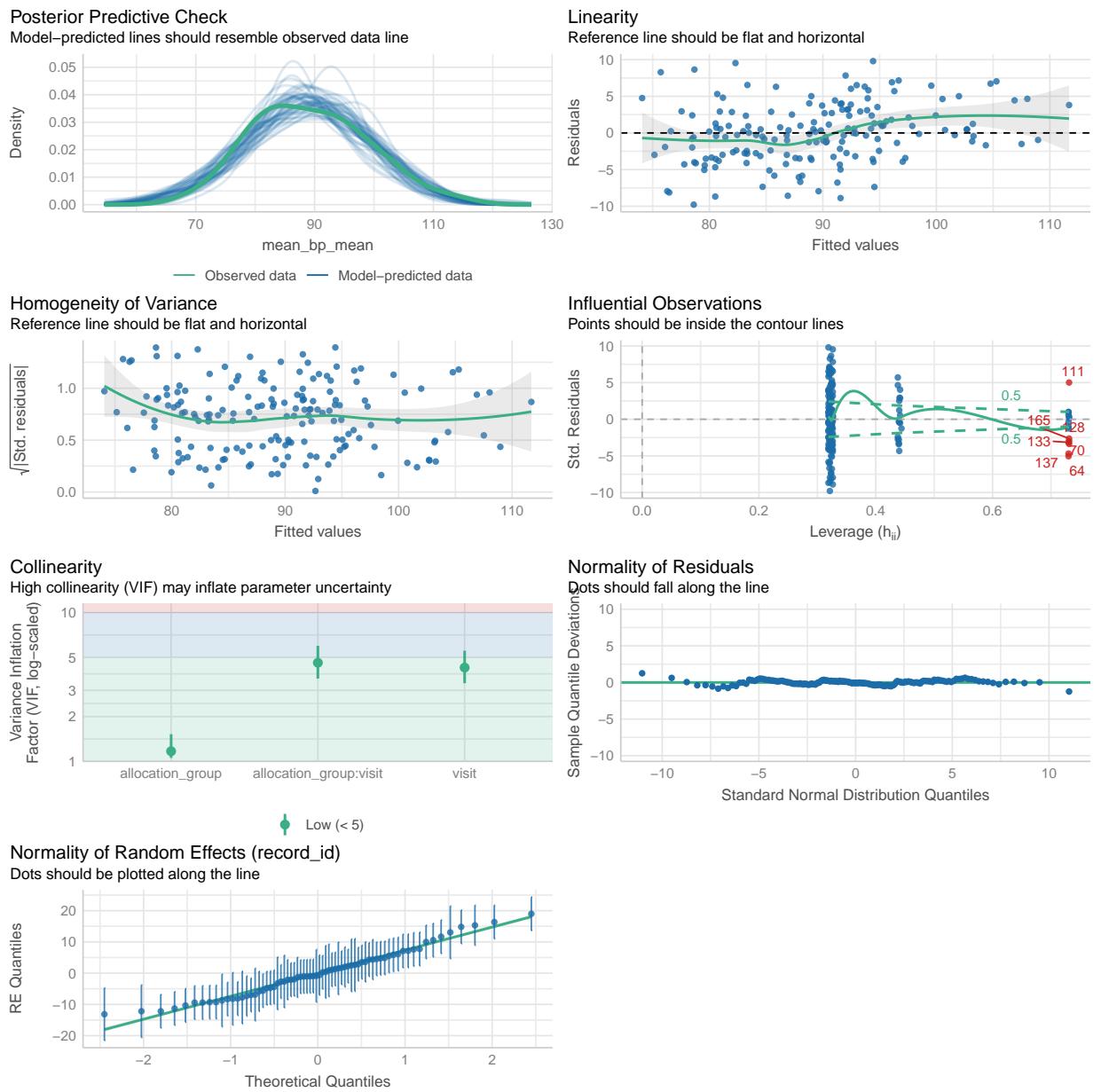
```
-----
```

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)
```



3.0.16.2 Médias Marginais Estimadas

3.0.16.2.1 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

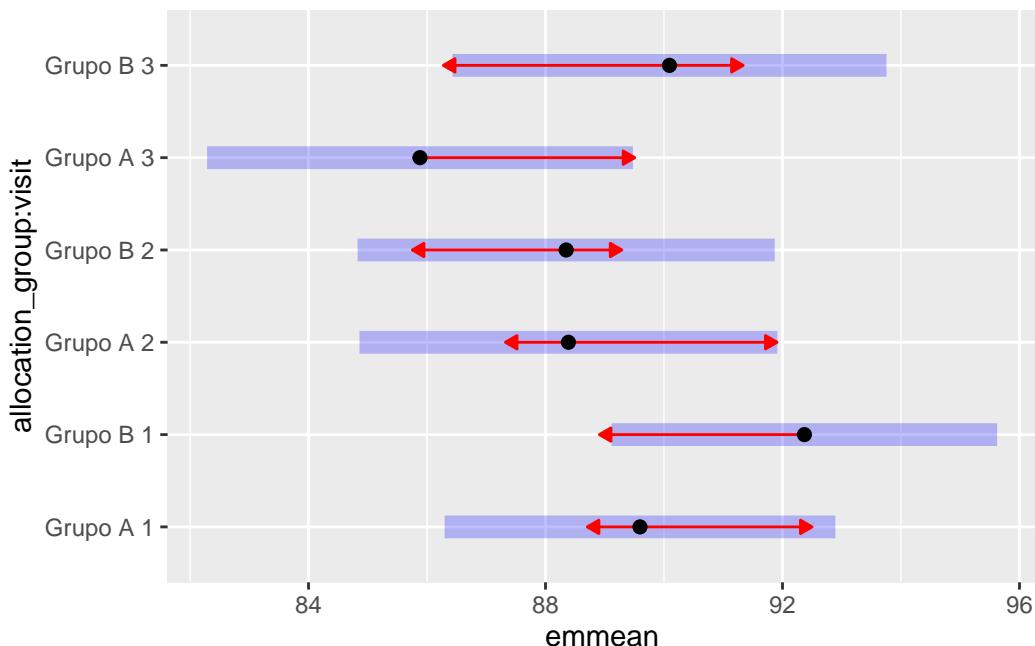
Conf-level adjustment: bonferroni method for 3 estimates

P value adjustment: bonferroni method for 3 tests

```

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

```



3.0.16.2.2 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

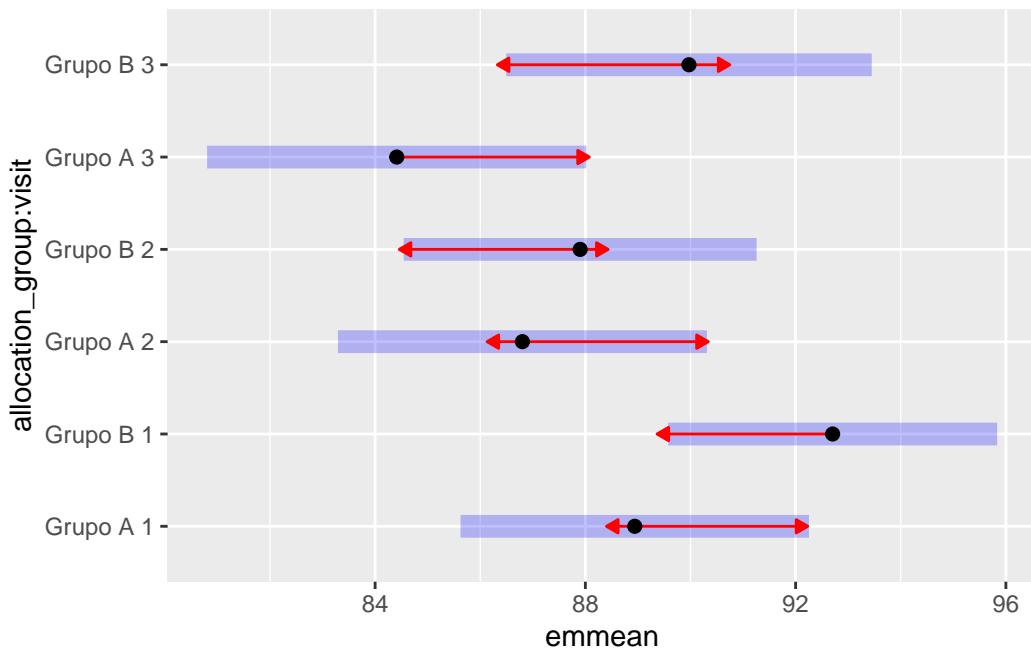
Degrees-of-freedom method: inherited from kenward-roger when re-gridding

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)
```



3.0.16.3 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 17 e Tabela 18.

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

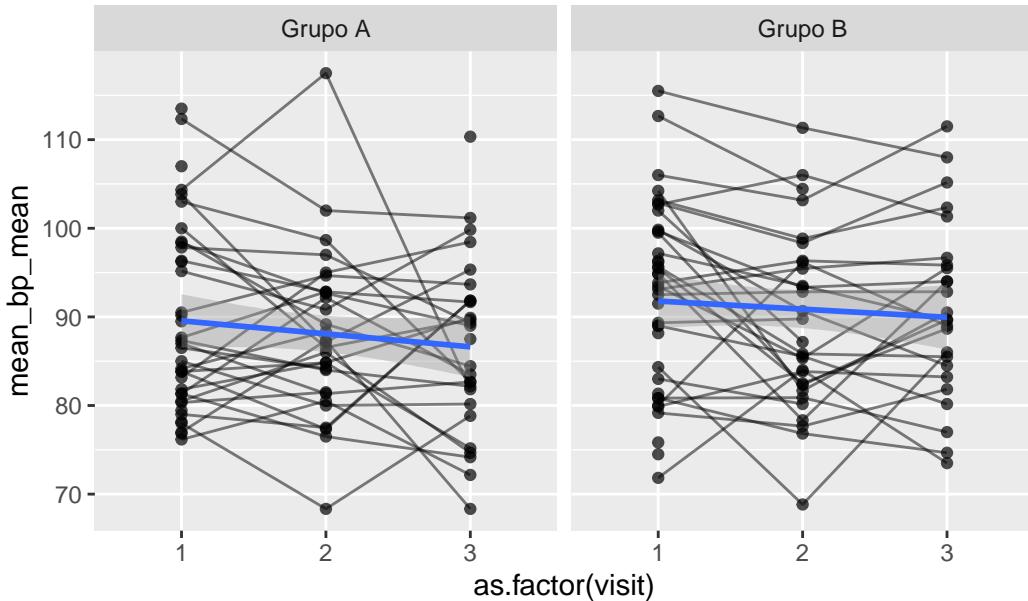
```

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'

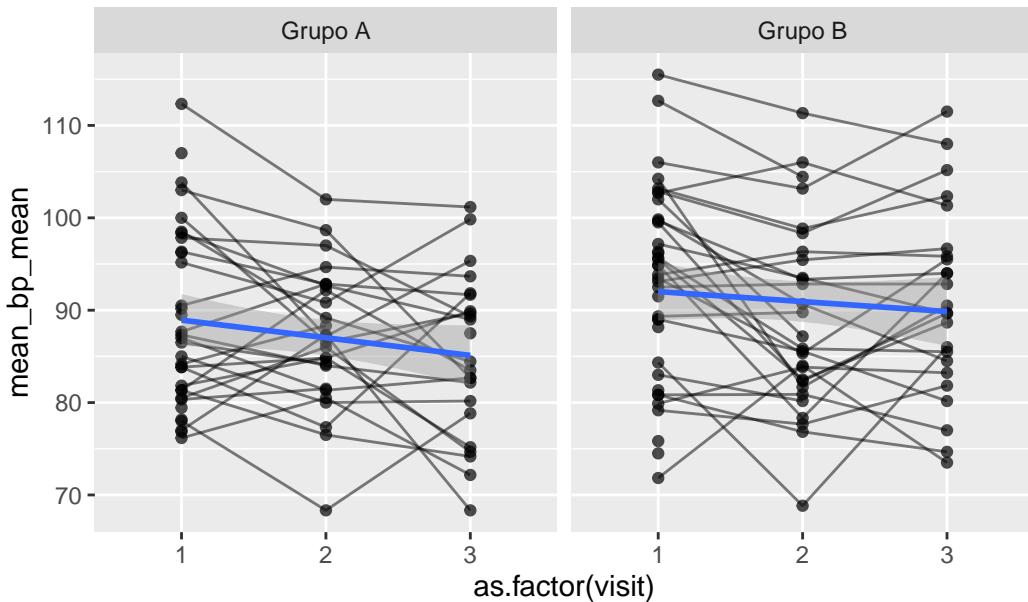
Warning: Removed 3 rows containing non-finite outside the scale range
(`stat_smooth()`).

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))
```

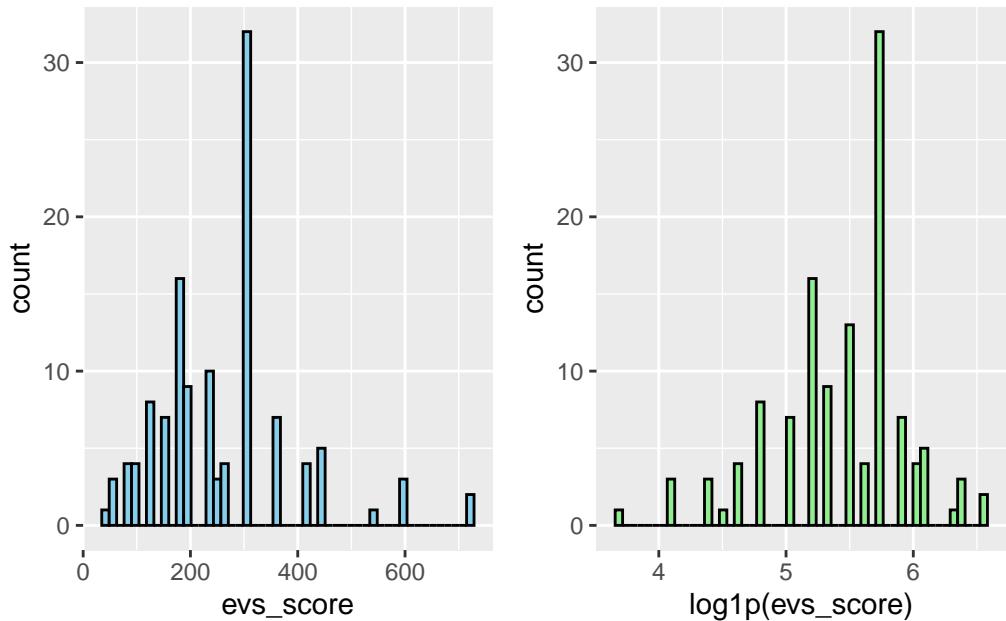
3.0.17 Escore EVS

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"

```

3.0.17.1 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_groupGrupo B	-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_groupGrupo B:visit2	0.12742	0.19735	80.22191	0.646	0.520
allocation_groupGrupo B:visit3	-0.01678	0.20995	78.03049	-0.080	0.937

(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 -0.738
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_groupGrupo B:visit2 0.09871   0.17636  68.03387   0.560   0.578
allocation_groupGrupo B:visit3 -0.05185   0.18957  65.91159  -0.274   0.785

(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	-0.743				
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

```
evs_score_model_check$comparison_table
```

```
# A tibble: 16 x 6
```

Model	term	estimate	std.error	statistic	p.value
<chr>	<chr>	<dbl>	<dbl>	<dbl>	<dbl>
1 Original	(Intercept)	5.45	0.124	43.9	2.81e-73
2 Sensitivity	(Intercept)	5.57	0.109	51.1	5.58e-74
3 Original	allocation_groupGrupo B	-0.0789	0.168	-0.469	6.40e- 1
4 Sensitivity	allocation_groupGrupo B	-0.121	0.147	-0.828	4.10e- 1
5 Original	allocation_groupGrupo B:v~	0.127	0.197	0.646	5.20e- 1

```

6 Sensitivity allocation_groupGrupo B:v~ 0.0987 0.176 0.560 5.78e- 1
7 Original allocation_groupGrupo B:v~ -0.0168 0.210 -0.0799 9.37e- 1
8 Sensitivity allocation_groupGrupo B:v~ -0.0519 0.190 -0.274 7.85e- 1
9 Original sd__(Intercept) 0.317 NA NA NA
10 Sensitivity sd__(Intercept) 0.245 NA NA NA
11 Original sd__Observation 0.438 NA NA NA
12 Sensitivity sd__Observation 0.371 NA NA NA
13 Original visit2 -0.0613 0.141 -0.435 6.65e- 1
14 Sensitivity visit2 -0.120 0.127 -0.951 3.45e- 1
15 Original visit3 0.0912 0.149 0.610 5.43e- 1
16 Sensitivity visit3 0.0601 0.136 0.443 6.59e- 1

```

```

  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
```

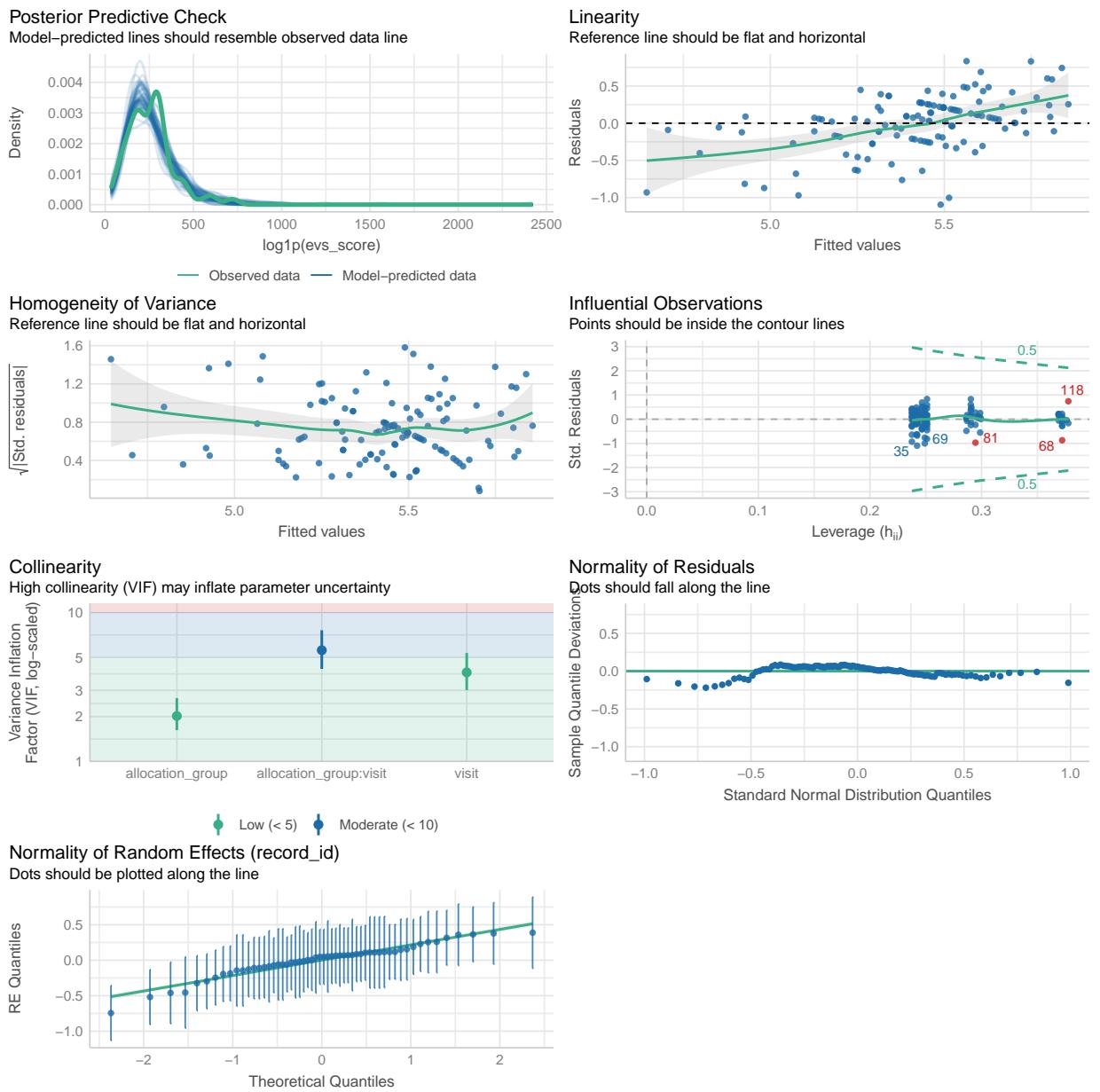
Name	Model	AIC (weights)	AICc (weights)
evs_score_model	lmerModLmerTest	1532.6 (<.001)	1533.9 (<.001)
evs_score_model_sens	lmerModLmerTest	1332.9 (>.999)	1334.3 (>.999)

Name	BIC (weights)	R2 (cond.)	R2 (marg.)	ICC	RMSE	Sig
evs_score_model	1555.1 (<.001)	0.350	0.010	0.343	0.374	0.43
evs_score_model_sens	1354.4 (>.999)	0.322	0.027	0.303	0.319	0.37

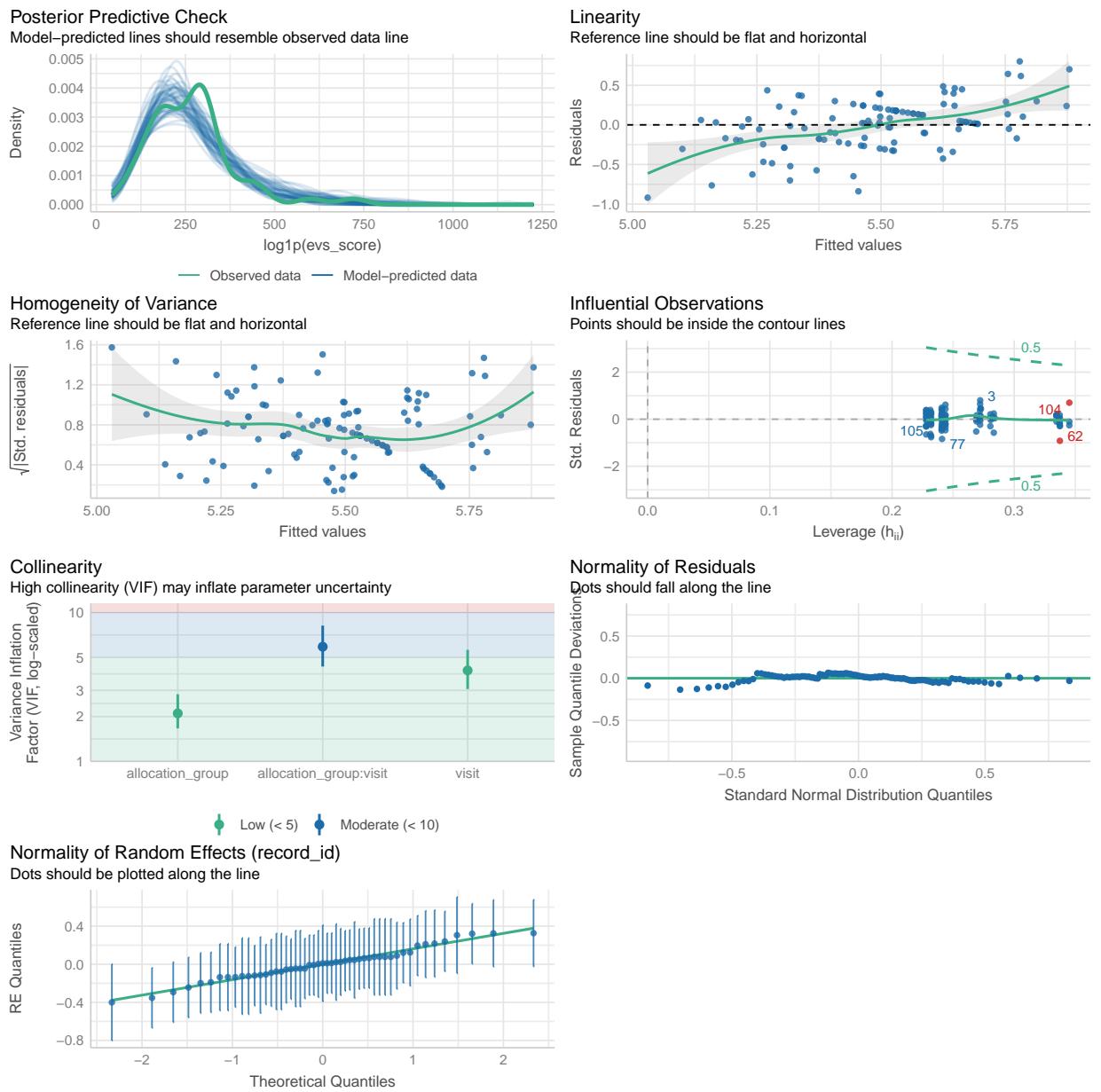
```

  performance::check_model(evs_score_model)

```



```
performance::check_model(evs_score_model_sens)
```



3.0.17.2 Médias Marginais Estimadas

3.0.17.2.1 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

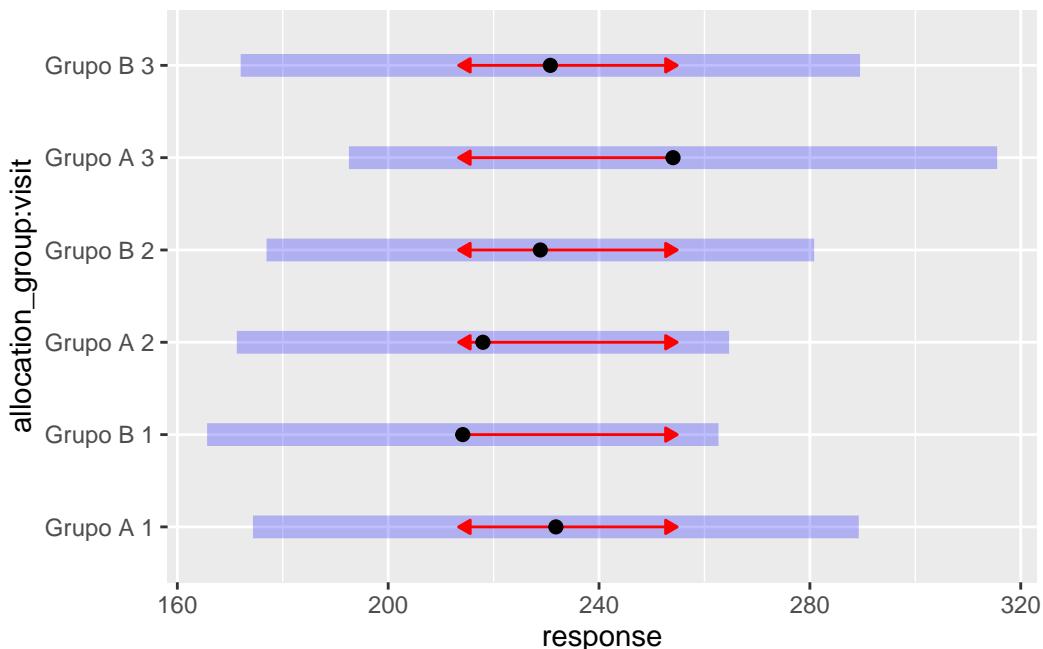
Conf-level adjustment: bonferroni method for 3 estimates

P value adjustment: bonferroni method for 3 tests

```

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

```



3.0.17.2.2 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

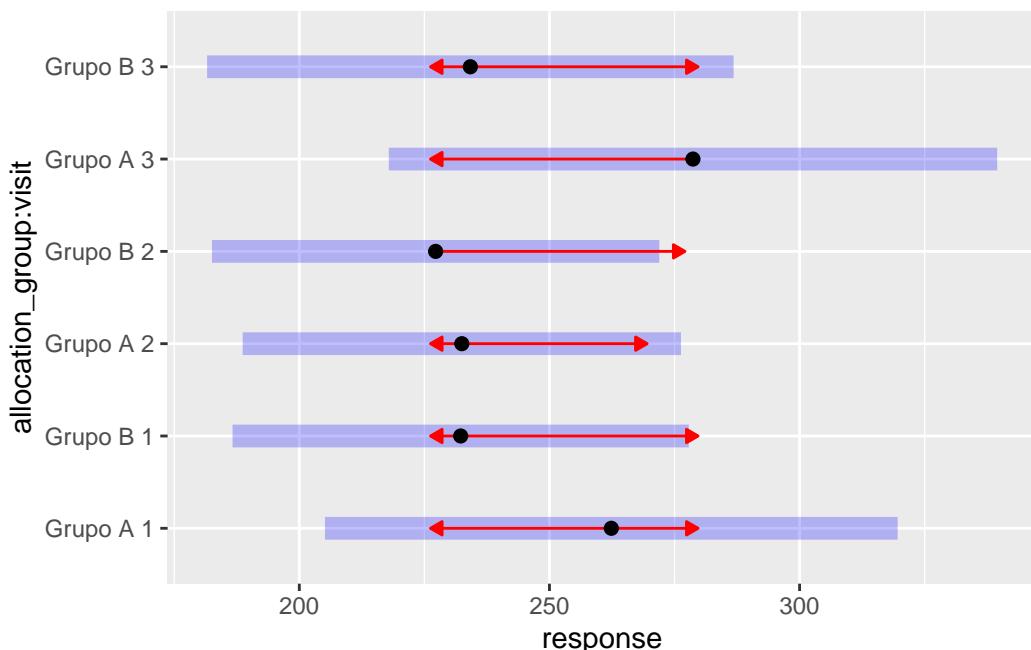
Degrees-of-freedom method: inherited from kenward-roger when re-gridding

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") +

```

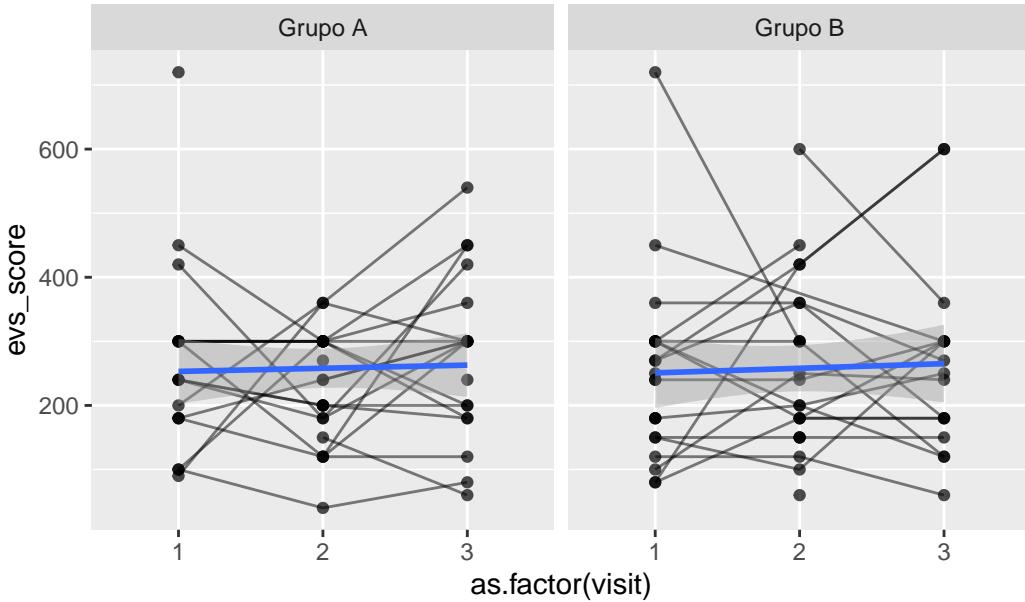
```

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) +

```

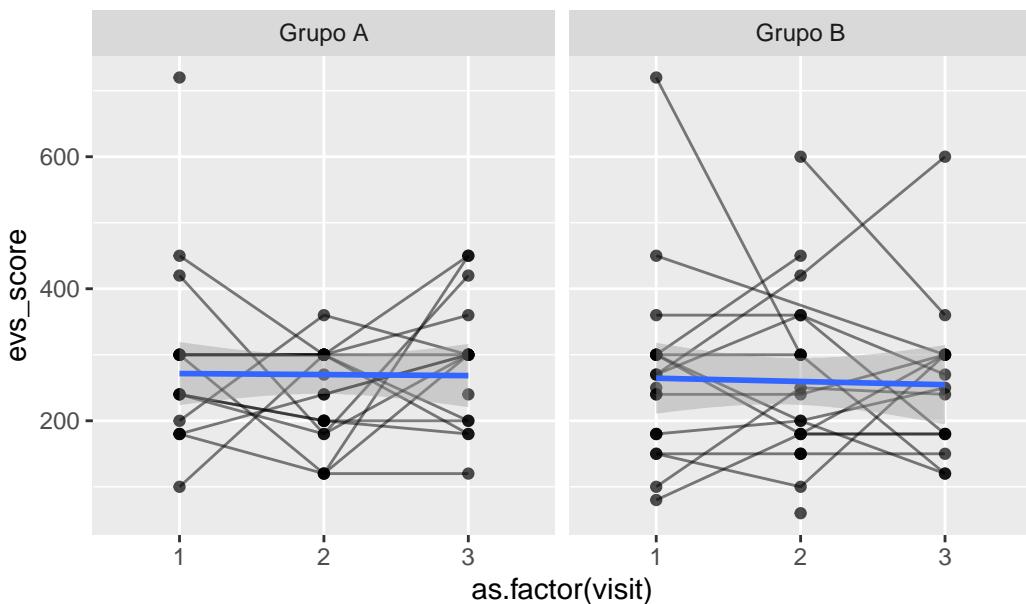
```

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))
```

3.0.17.3 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? Gen

What factors are associated with whether someone exercises at all during the week? A

What factors are associated with whether someone exercises at all during the week? Fa

What factors are associated with whether someone exercises at all during the week? For

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?

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?

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?

What factors are associated with whether someone exercises at all during the week? Sc

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? -2.

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? Ran

What factors are associated with whether someone exercises at all during the week? Gr

What factors are associated with whether someone exercises at all during the week? re

What factors are associated with whether someone exercises at all during the week? Num

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? Fix

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? (In

What factors are associated with whether someone exercises at all during the week? all

What factors are associated with whether someone exercises at all during the week? vis
What factors are associated with whether someone exercises at all during the week? vis
What factors are associated with whether someone exercises at all during the week? all
What factors are associated with whether someone exercises at all during the week? all
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? Sig
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? Cor
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? all
What factors are associated with whether someone exercises at all during the week? vis
What factors are associated with whether someone exercises at all during the week? vis
What factors are associated with whether someone exercises at all during the week? all
What factors are associated with whether someone exercises at all during the week? all

```
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)
```

Among those who do exercise, what factors are associated with how much they exercise (1
Among those who do exercise, what factors are associated with how much they exercise (1
Among those who do exercise, what factors are associated with how much they exercise (1
Among those who do exercise, what factors are associated with how much they exercise (1
Among those who do exercise, what factors are associated with how much they exercise (1
Among those who do exercise, what factors are associated with how much they exercise (1

Among those who do exercise, what factors are associated with how much they exercise (

Among those who do exercise, what factors are associated with how much they exercise (

Among those who do exercise, what factors are associated with how much they exercise (

Among those who do exercise, what factors are associated with how much they exercise (

Among those who do exercise, what factors are associated with how much they exercise (

Among those who do exercise, what factors are associated with how much they exercise (

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

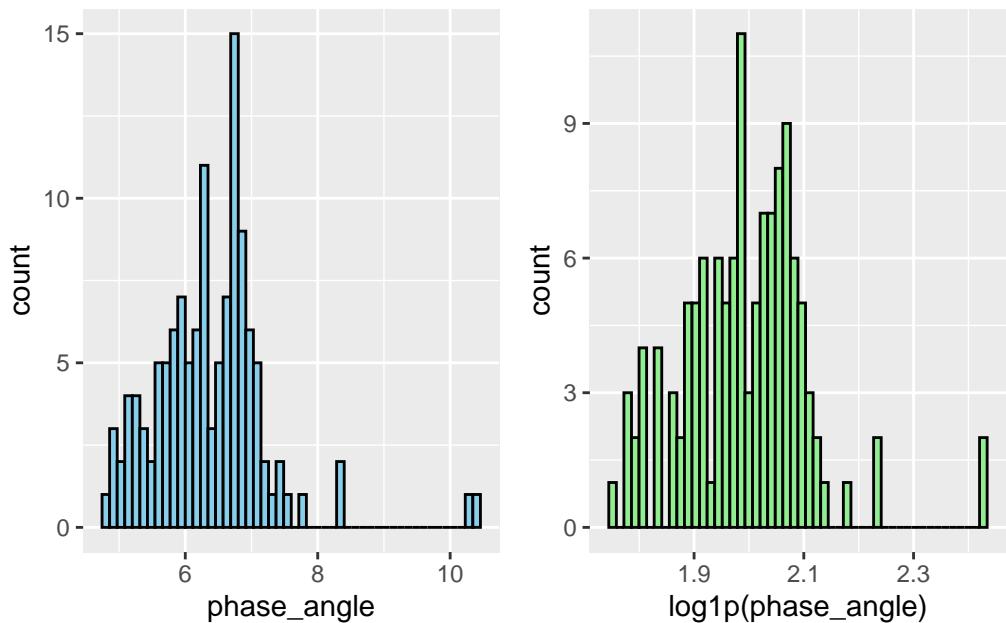
4.0.1 Ângulo de Fase

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"

```

4.0.1.1 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_groupGrupo B	-0.045637	0.025875	82.634225	-1.764	0.0815
visit3	-0.011701	0.013479	49.678850	-0.868	0.3895
allocation_groupGrupo B: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 ' '

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_group	-0.045312	0.021248	74.173320	-2.133	0.0363
visit3	-0.018047	0.009238	46.006589	-1.954	0.0569
allocation_group:visit3	0.017523	0.013049	46.227426	1.343	0.1859
(Intercept)	***				
allocation_group	*				
visit3	.				
allocation_group: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

```

```
phase_angle_model_check$comparison_table
```

```
# A tibble: 12 x 6
```

Model	term	estimate	std.error	statistic	p.value
<chr>	<chr>	<dbl>	<dbl>	<dbl>	<dbl>
1 Original	(Intercept)	2.02	0.0184	110.	2.68e-91
2 Sensitivity	(Intercept)	2.01	0.0154	130.	2.82e-89
3 Original	allocation_groupGrupo B	-0.0456	0.0259	-1.76	8.15e- 2
4 Sensitivity	allocation_groupGrupo B	-0.0453	0.0212	-2.13	3.63e- 2
5 Original	allocation_groupGrupo B:v~	0.00718	0.0198	0.363	7.18e- 1
6 Sensitivity	allocation_groupGrupo B:v~	0.0175	0.0130	1.34	1.86e- 1
7 Original	sd__(Intercept)	0.100	NA	NA	NA
8 Sensitivity	sd__(Intercept)	0.0829	NA	NA	NA
9 Original	sd__Observation	0.0502	NA	NA	NA
10 Sensitivity	sd__Observation	0.0316	NA	NA	NA
11 Original	visit3	-0.0117	0.0135	-0.868	3.90e- 1
12 Sensitivity	visit3	-0.0180	0.00924	-1.95	5.69e- 2

```
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
```

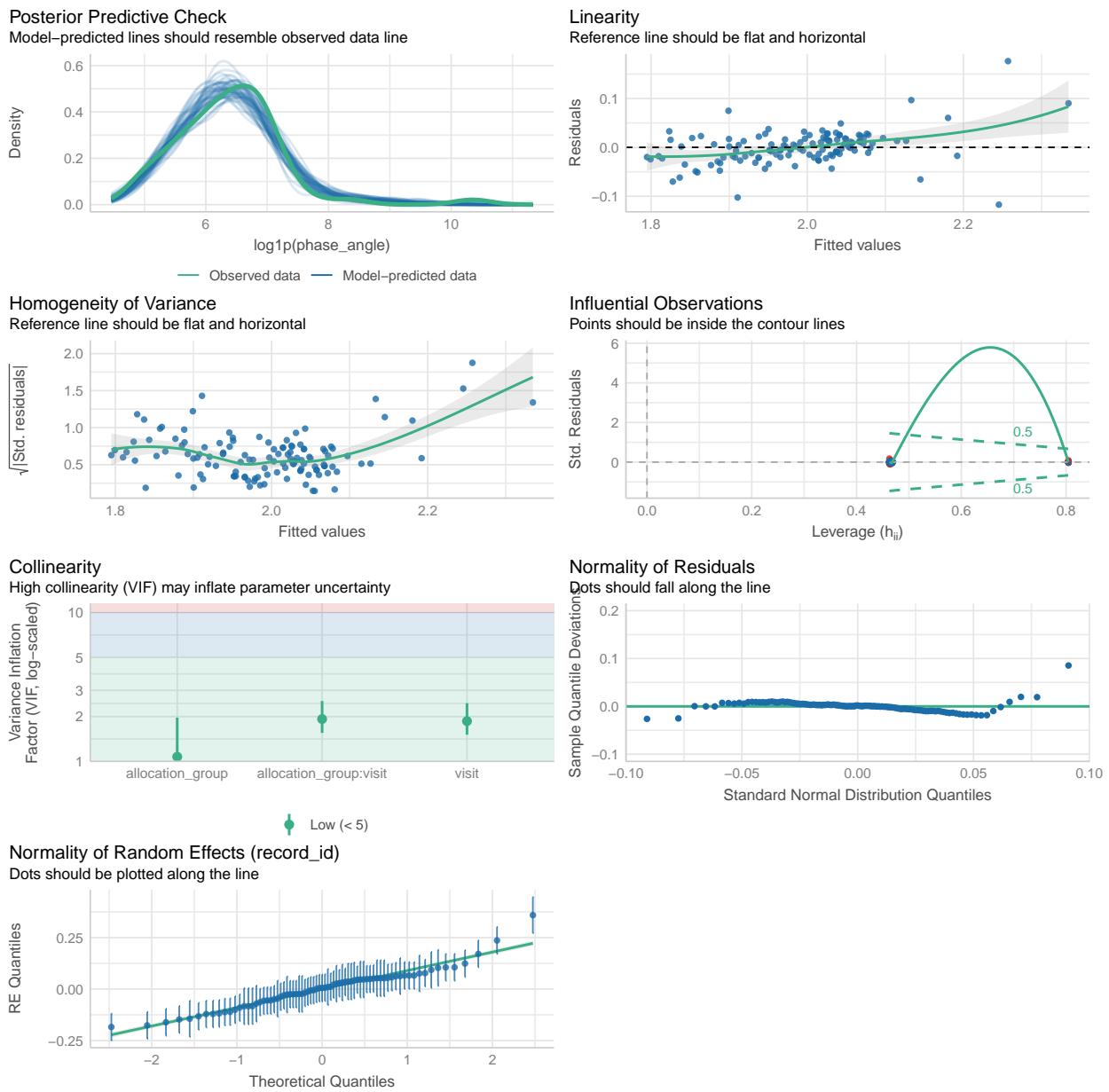
Name		Model	AIC (weights)	AICc (weights)
<hr/>				
phase_angle_model		lmerModLmerTest	262.3 (<.001)	263.0 (<.001)

```
phase_angle_model_sens | lmerModLmerTest | 168.0 (>.999) | 168.8 (>.999)
```

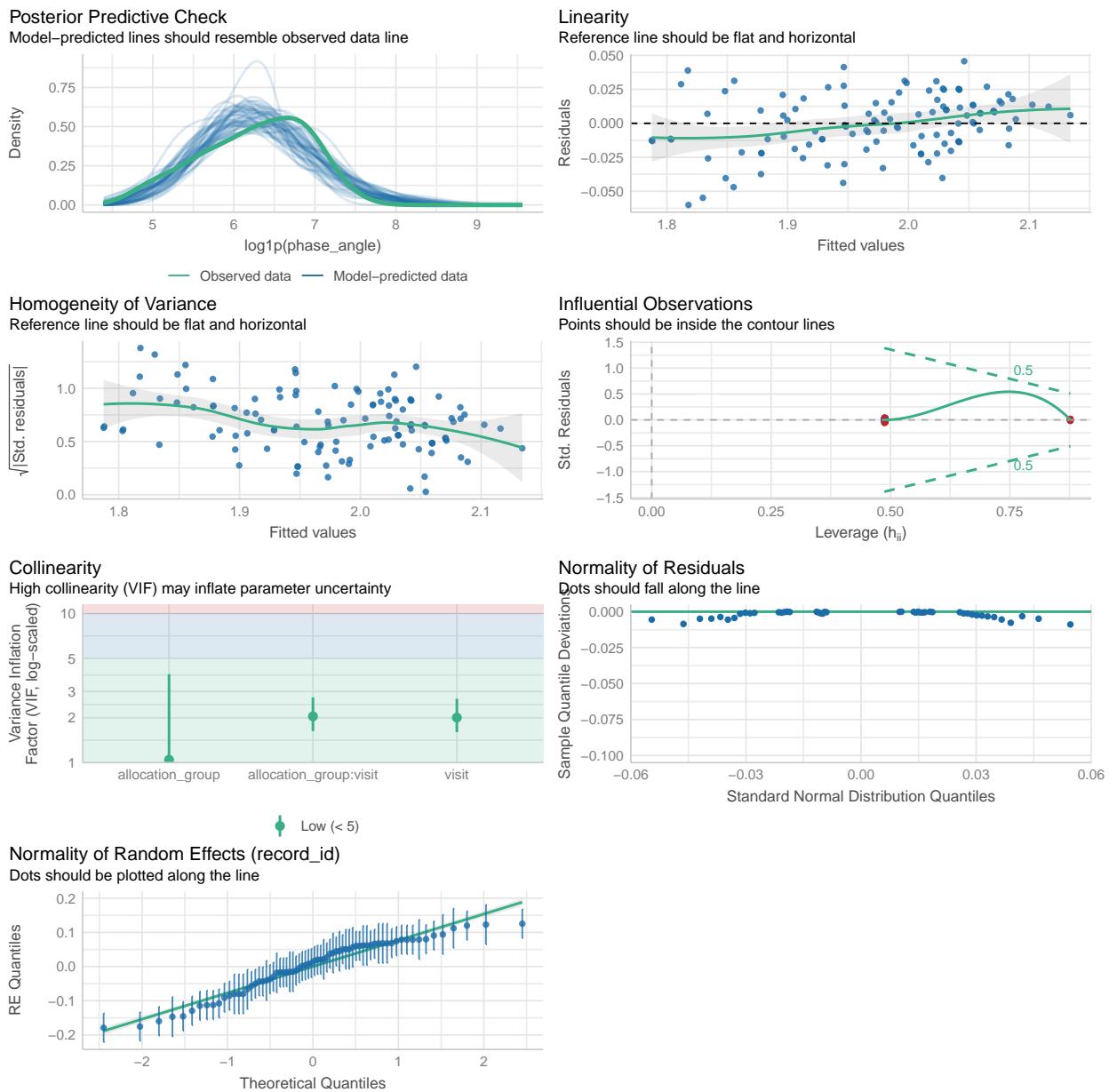
Name	BIC (weights)	R2 (cond.)	R2 (marg.)	ICC
<hr/>				
phase_angle_model	279.3 (<.001)	0.806	0.036	0.799
phase_angle_model_sens	184.5 (>.999)	0.879	0.049	0.873

Name	RMSE	Sigma
<hr/>		
phase_angle_model	0.034	0.050
phase_angle_model_sens	0.021	0.032

```
performance::check_model(phase_angle_model)
```



```
performance::check_model(phase_angle_model_sens)
```



4.0.1.2 Médias Marginais Estimadas

4.0.1.2.1 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

```

```

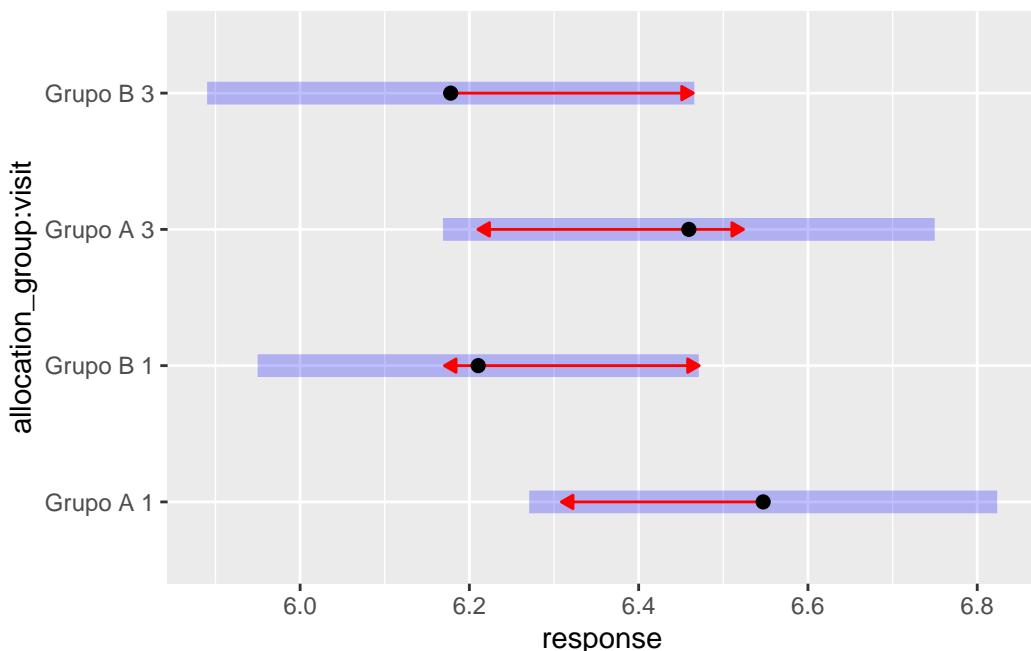
allocation_group = Grupo B:
contrast      estimate     SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit3  0.0325 0.105 83.6   -0.175    0.240    0.311  0.7566

```

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)
```



4.0.1.2.2 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

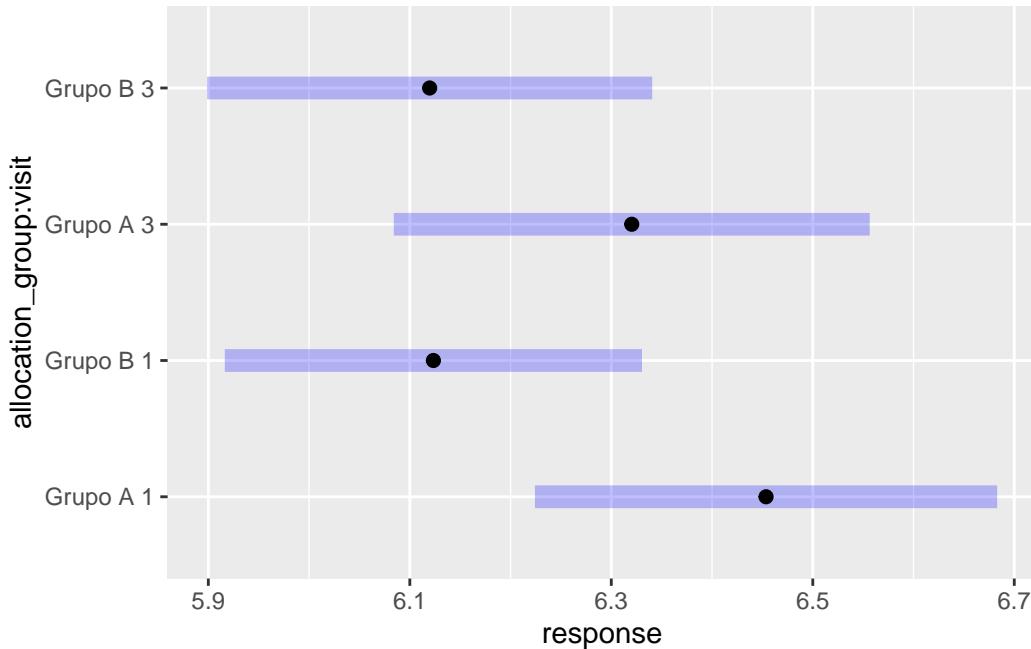
allocation_group = Grupo B:
  contrast estimate SE df lower.CL upper.CL t.ratio p.value
  visit1 - visit3 0.00373 0.0657 73.9 -0.12725 0.135 0.057 0.9549

```

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

```
# Plot of marginal means
```

```
plot(phase_angle_emm)
```



```
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",
```

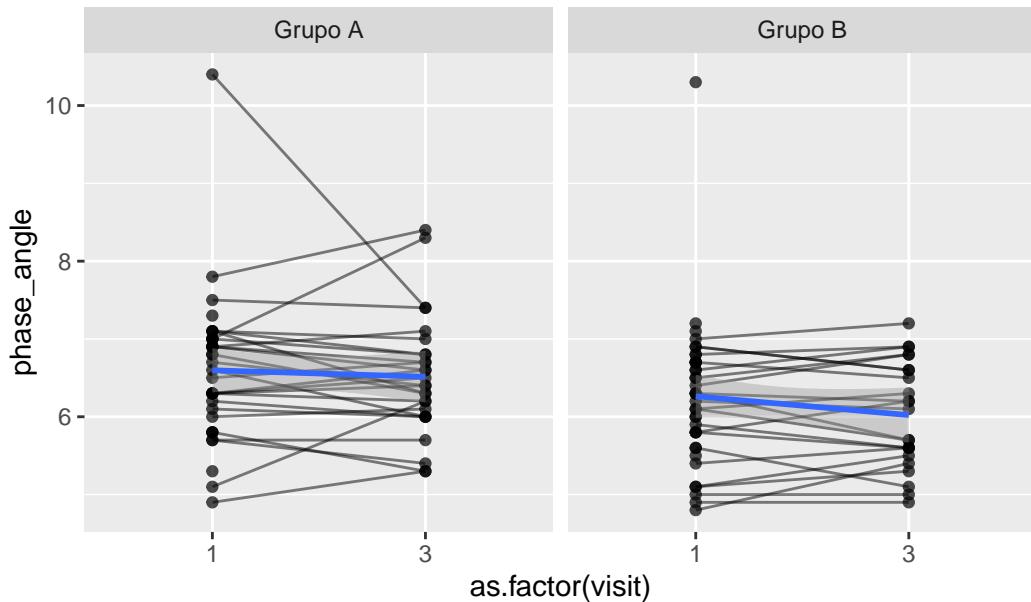
```

    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)
  ) %>%

```

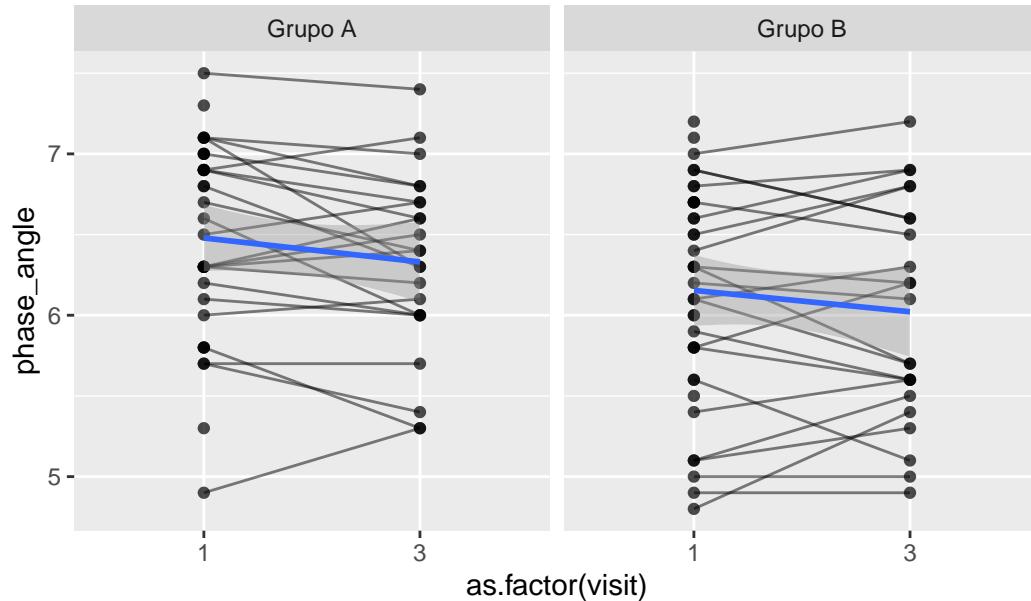
```

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



4.0.2 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))) +
```

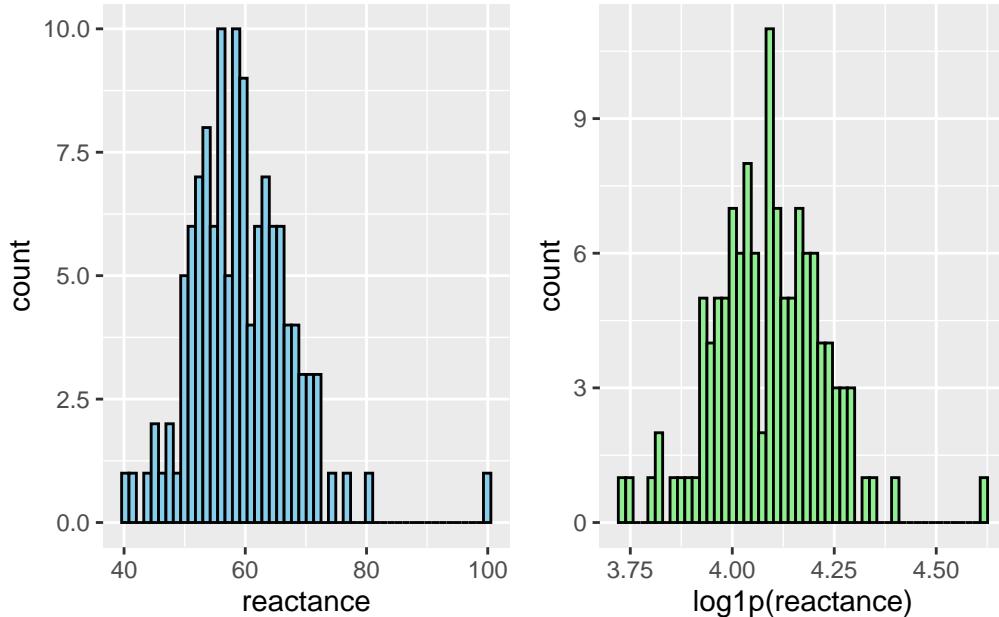
```

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"

```

4.0.2.1 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_group	-0.01206	0.03195	86.69858	-0.377	0.707
visit3	-0.01119	0.02006	49.12966	-0.558	0.579
allocation_group:visit3	0.01600	0.02942	50.14982	0.544	0.589

(Intercept) ***

allocation_group

visit3

allocation_group: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_group	-0.02913	0.02720	85.06056	-1.071	0.287
visit3	-0.01607	0.01855	47.78854	-0.866	0.391
allocation_group:visit3	0.02453	0.02730	48.84683	0.899	0.373

(Intercept) ***
allocation_group
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	-0.707		
visit3	-0.363	0.256	
allctn_GB:3	0.246	-0.348	-0.680

```
reactance_model_check$comparison_table
```

A tibble: 12 x 6

Model	term	estimate	std.error	statistic	p.value
<chr>	<chr>	<dbl>	<dbl>	<dbl>	<dbl>
1 Original	(Intercept)	4.10	0.0227	180.	1.83e-113
2 Sensitivity	(Intercept)	4.12	0.0192	214.	5.10e-118
3 Original	allocation_groupGrupo B	-0.0121	0.0320	-0.377	7.07e- 1
4 Sensitivity	allocation_groupGrupo B	-0.0291	0.0272	-1.07	2.87e- 1
5 Original	allocation_groupGrupo B:~	0.0160	0.0294	0.544	5.89e- 1
6 Sensitivity	allocation_groupGrupo B:~	0.0245	0.0273	0.899	3.73e- 1
7 Original	sd__(Intercept)	0.116	NA	NA	NA
8 Sensitivity	sd__(Intercept)	0.0918	NA	NA	NA
9 Original	sd__Observation	0.0752	NA	NA	NA
10 Sensitivity	sd__Observation	0.0673	NA	NA	NA
11 Original	visit3	-0.0112	0.0201	-0.558	5.79e- 1
12 Sensitivity	visit3	-0.0161	0.0185	-0.866	3.91e- 1

```
performance::compare_performance(
  reactance_model,
  reactance_model_sens)
```

When comparing models, please note that probably not all models were fit

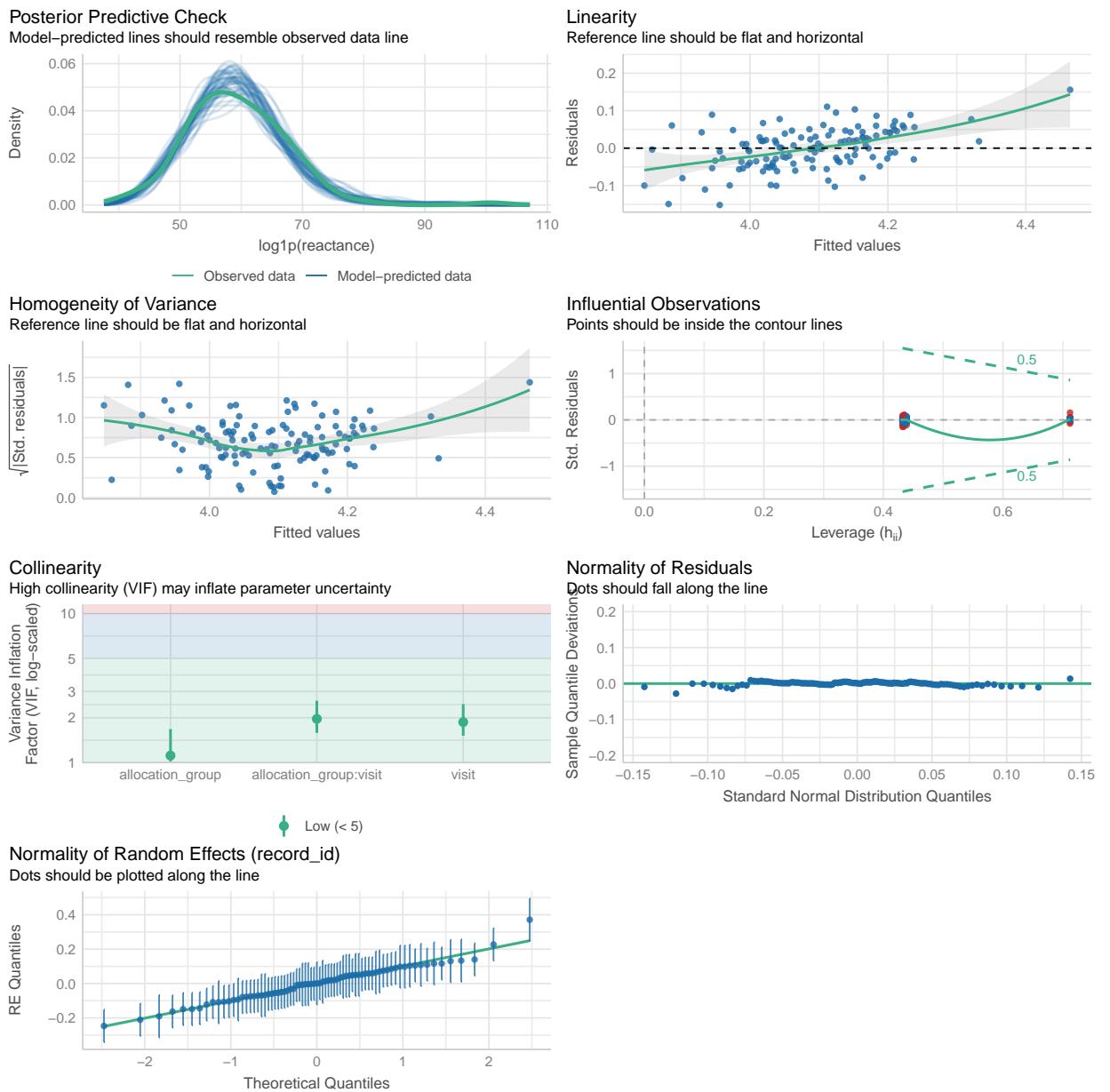
from same data.

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

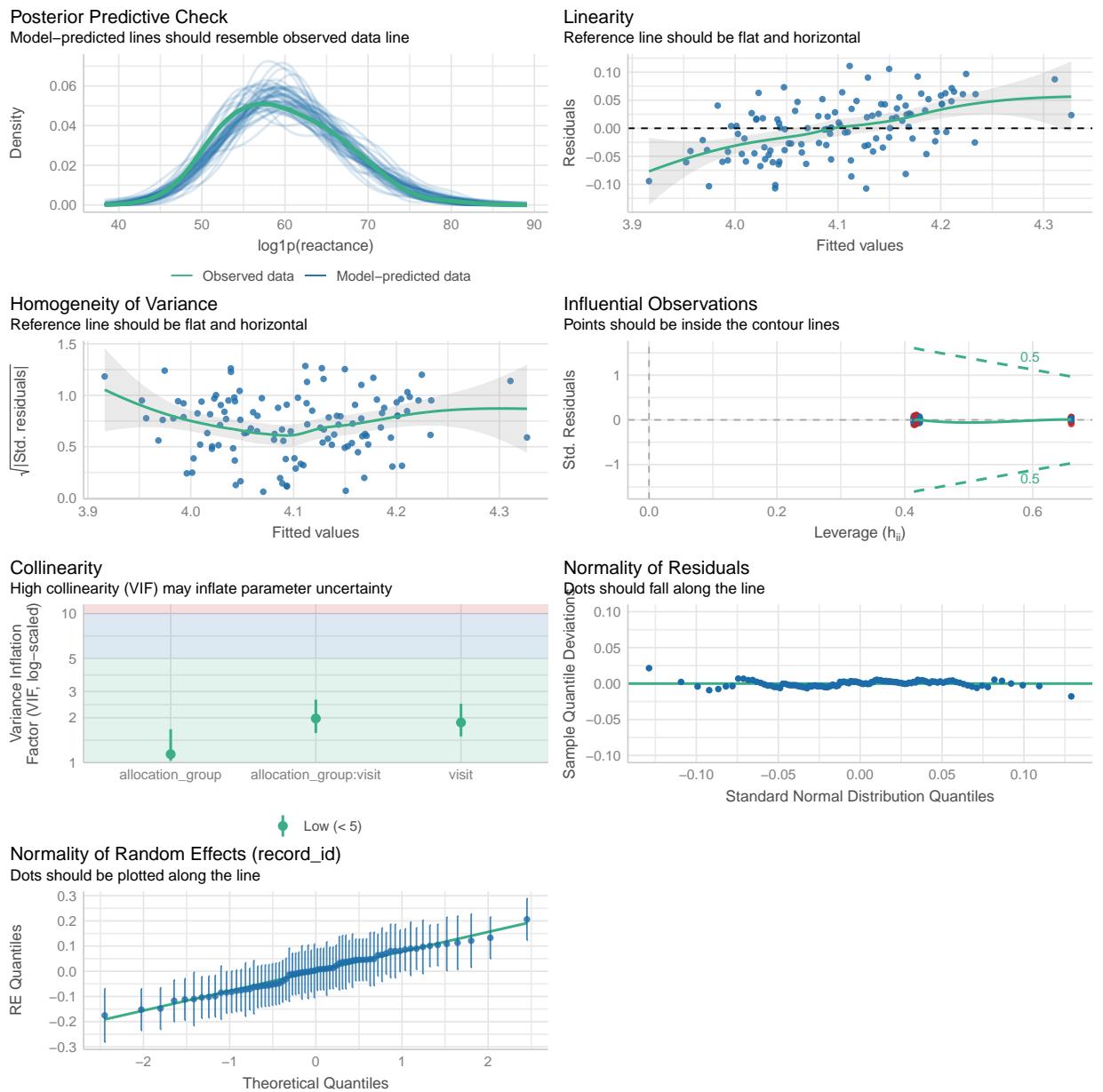
Name	Model	AIC (weights)	AICc (weights)
reactance_model	lmerModLmerTest	856.3 (<.001)	857.0 (<.001)
reactance_model_sens	lmerModLmerTest	758.9 (>.999)	759.7 (>.999)

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)
```



4.0.2.2 Médias Marginais Estimadas ##### 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
emmeans::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
emmeans::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

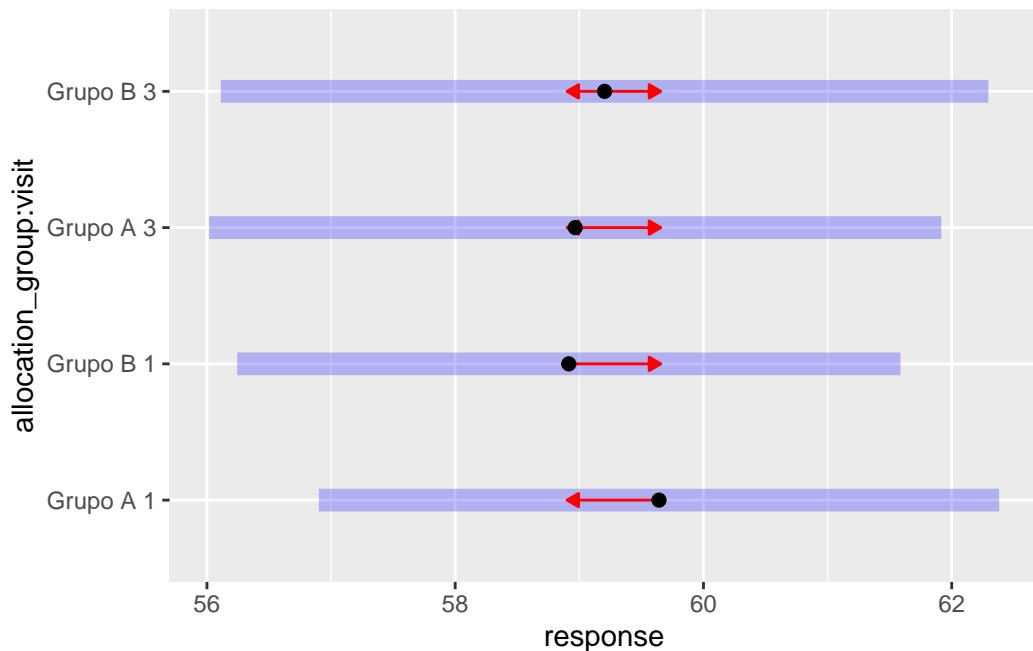
allocation_group = Grupo B:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
```

```
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)
```



4.0.2.2.1 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

```

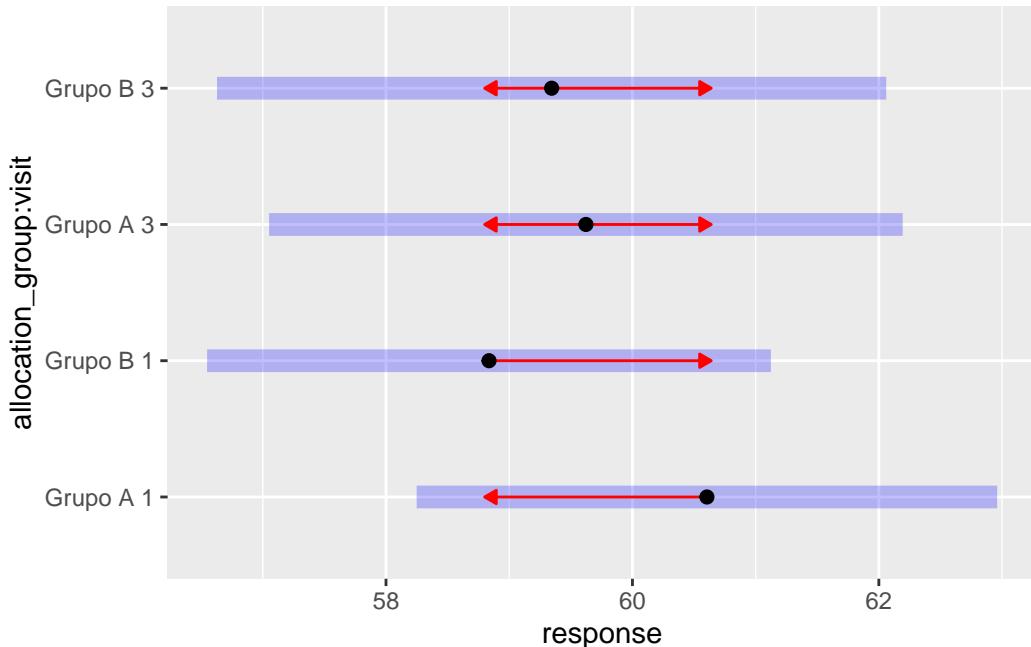
```

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)
```



```
ggplot(
  data = data_model_V1V3,
  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
```

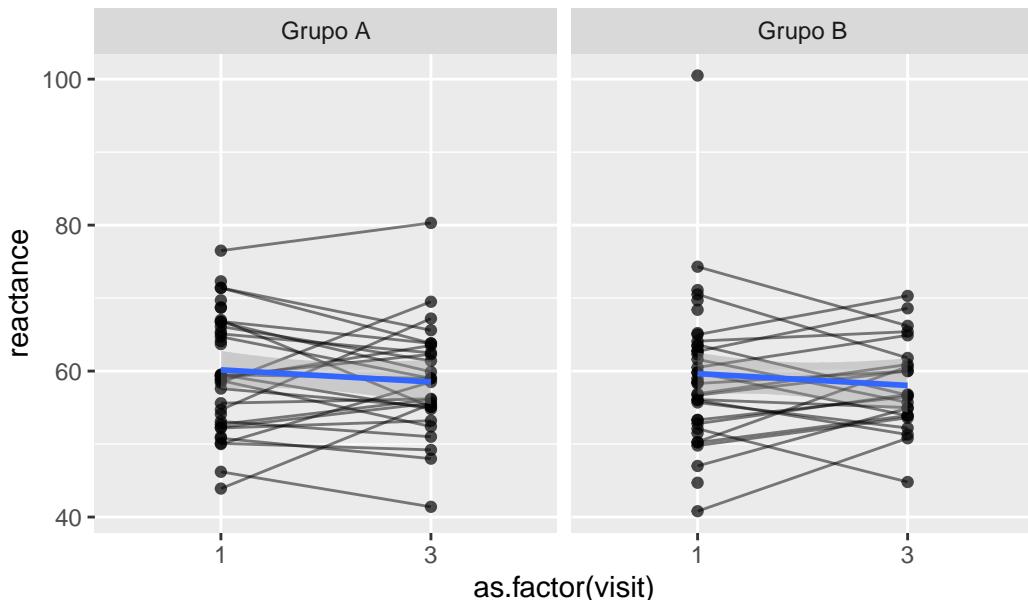
```

) +
  labs(title = "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)

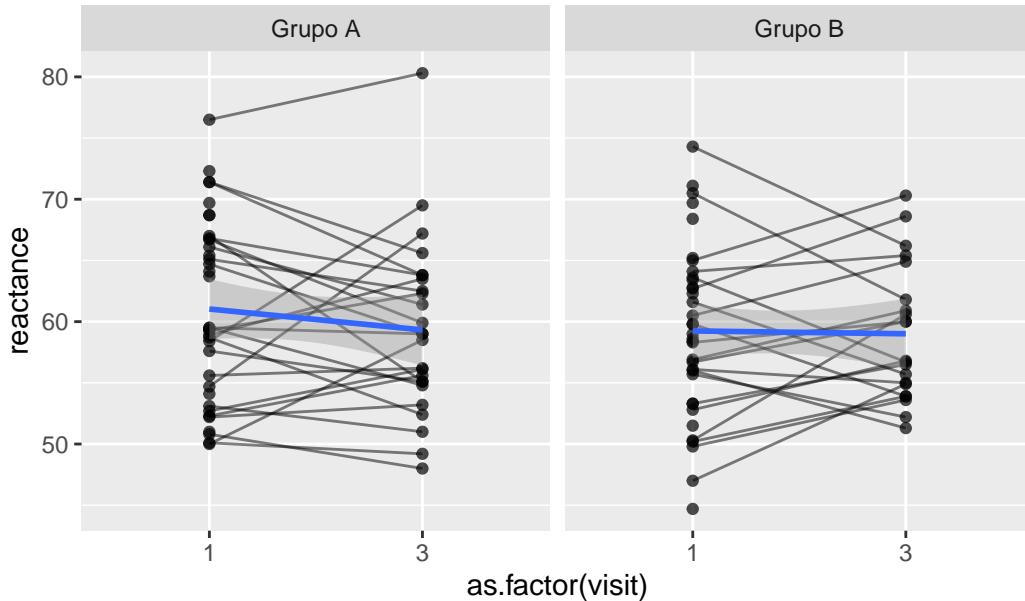
`geom_smooth()` using formula = 'y ~ x'
Warning: Removed 2 rows containing non-finite outside the scale range
(`stat_smooth()`).

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



4.0.3 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))) +
```

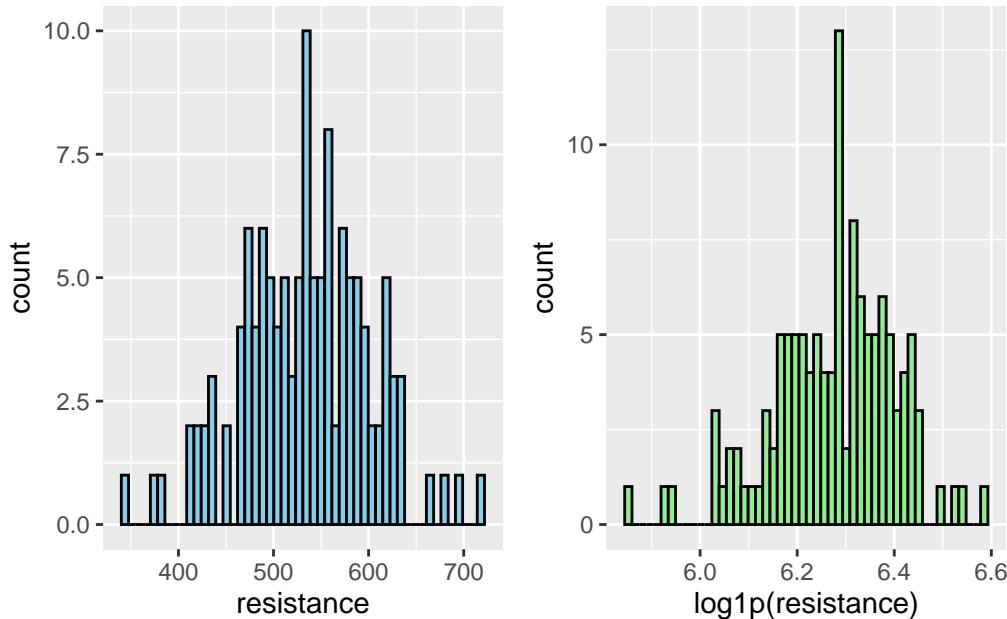
```

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"

```

4.0.3.1 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_grGB	-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_group	9.586	13.228	77.137	0.725	0.471
visit3	-3.225	6.679	46.655	-0.483	0.631
allocation_group: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_gr	GB -0.707	
visit3	-0.262 0.185	
allctn_GB:3	0.178 -0.251 -0.678	

```

resistance_model_check$comparison_table

# A tibble: 12 x 6
  Model      term        estimate std.error statistic p.value
  <chr>     <chr>       <dbl>     <dbl>     <dbl>    <dbl>
1 Original (Intercept)   524.      10.8      48.6    4.33e-64
2 Sensitivity (Intercept) 532.      9.35      56.9    9.89e-65
3 Original allocation_groupGrupo B  20.5      15.2      1.35    1.80e- 1
4 Sensitivity allocation_groupGrupo B  9.59      13.2      0.725   4.71e- 1
5 Original allocation_groupGrupo B:v~  4.65      12.4      0.375   7.09e- 1
6 Sensitivity allocation_groupGrupo B:v~ 10.9      9.85      1.10    2.76e- 1
7 Original sd__(Intercept)  57.6      NA        NA       NA
8 Sensitivity sd__(Intercept) 49.9      NA        NA       NA
9 Original sd__Observation  31.5      NA        NA       NA
10 Sensitivity sd__Observation 23.9      NA        NA       NA
11 Original visit3          2.23      8.44      0.265   7.92e- 1
12 Sensitivity visit3      -3.22      6.68      -0.483   6.31e- 1

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
```

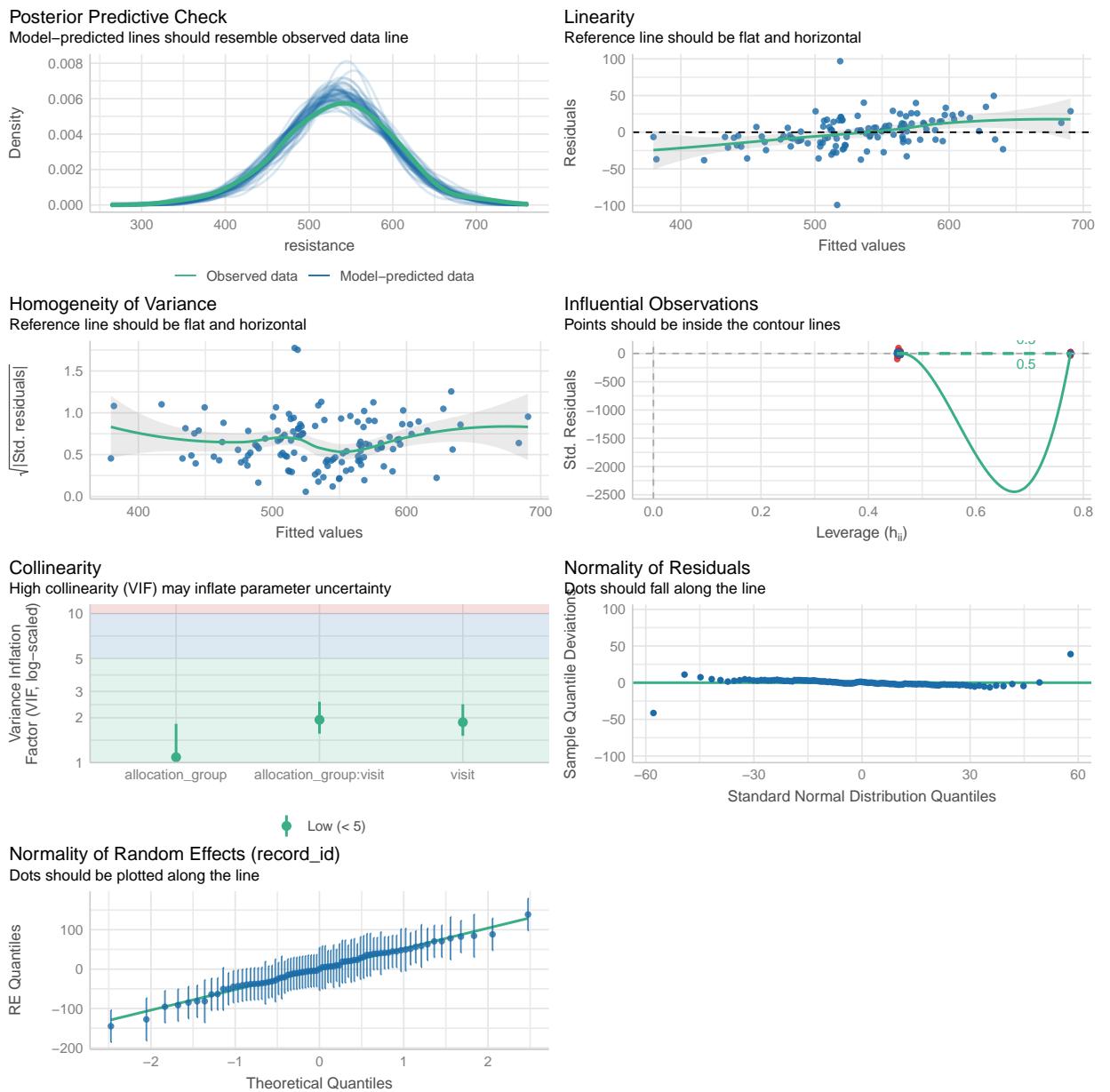
Name		Model	AIC (weights)	AICc (weights)
<hr/>				
resistance_model		lmerModLmerTest	1363.8 (<.001)	1364.5 (<.001)
resistance_model_sens		lmerModLmerTest	1218.5 (>.999)	1219.3 (>.999)
Name		BIC (weights)	R2 (cond.)	R2 (marg.) ICC

```
-----  
resistance_model | 1380.8 (<.001) | 0.776 | 0.029 | 0.770  
resistance_model_sens | 1235.0 (>.999) | 0.816 | 0.018 | 0.813
```

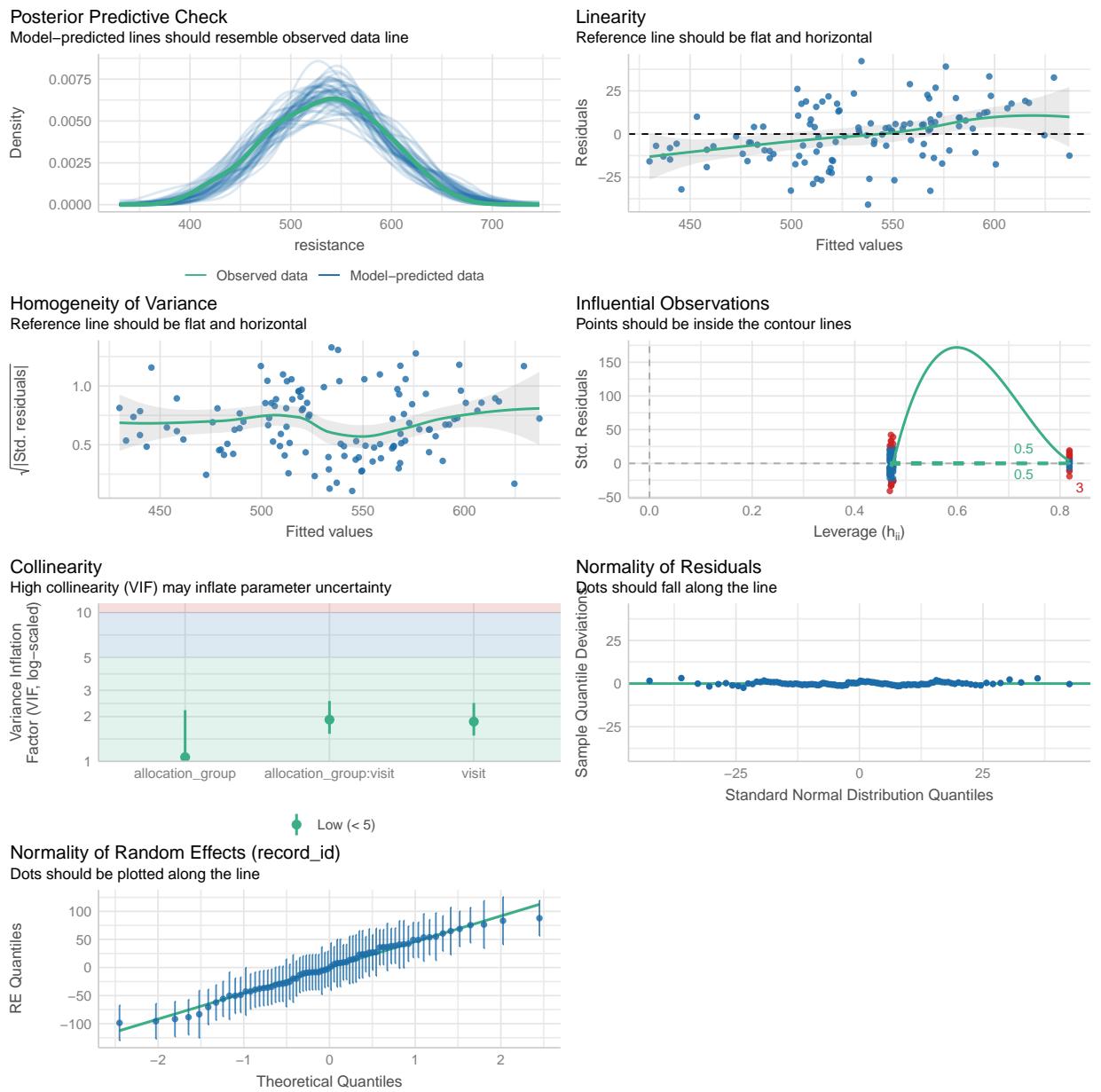
```
Name | RMSE | Sigma
```

```
-----  
resistance_model | 21.823 | 31.498  
resistance_model_sens | 16.183 | 23.934
```

```
performance::check_model(resistance_model)
```



```
performance::check_model(resistance_model_sens)
```



4.0.3.2 Médias Marginais Estimadas

4.0.3.2.1 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

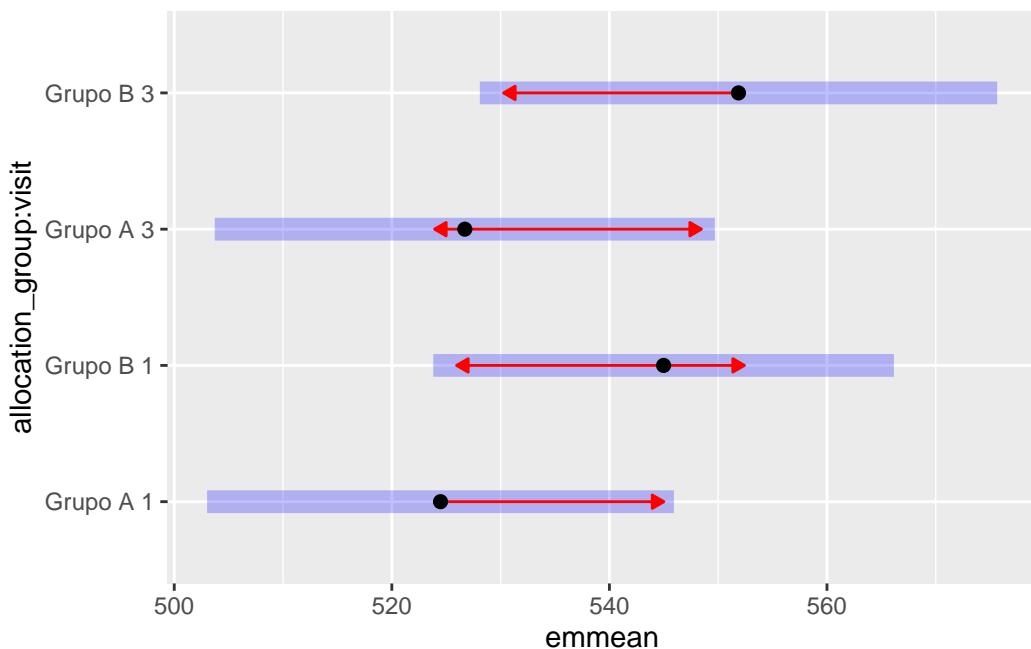
Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95

```

```

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

```



4.0.3.2.2 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

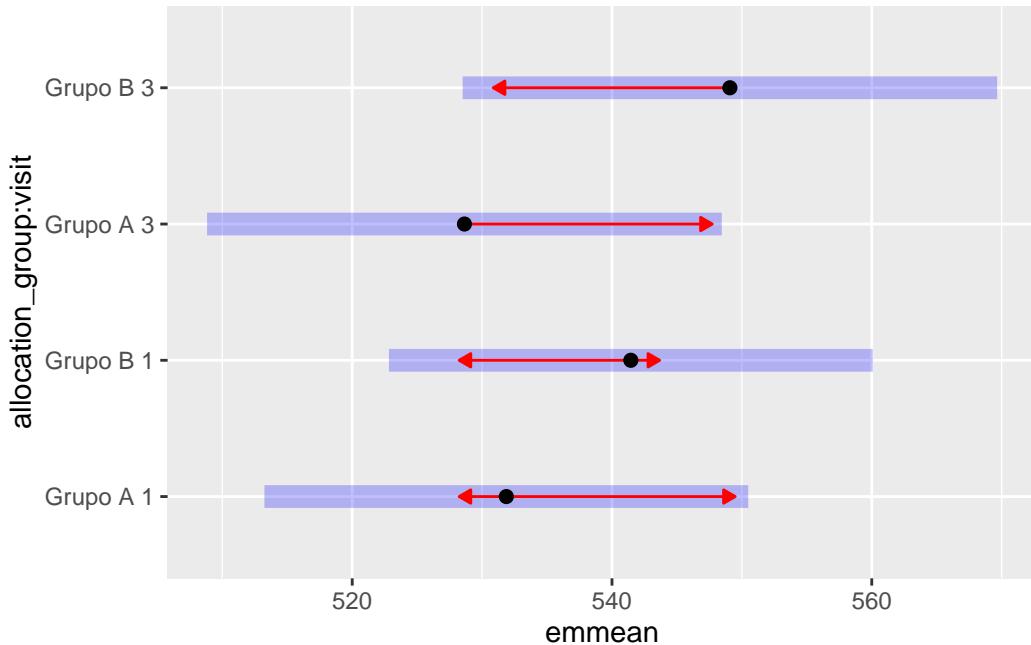

allocation_group = Grupo B:

  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)
```



```
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)

```

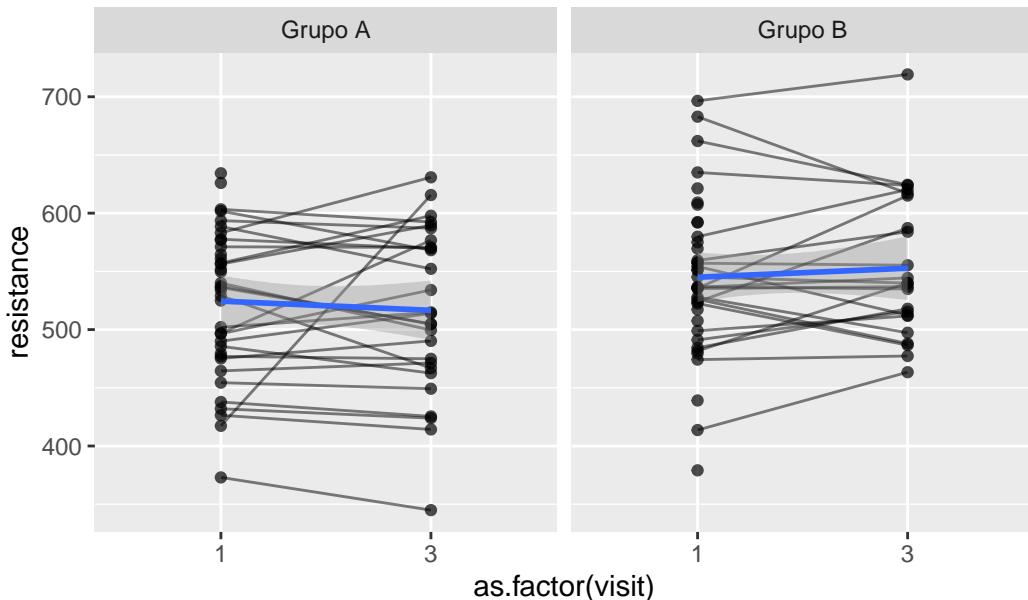
`geom_smooth()` using formula = 'y ~ x'

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)
  ) %>%

```

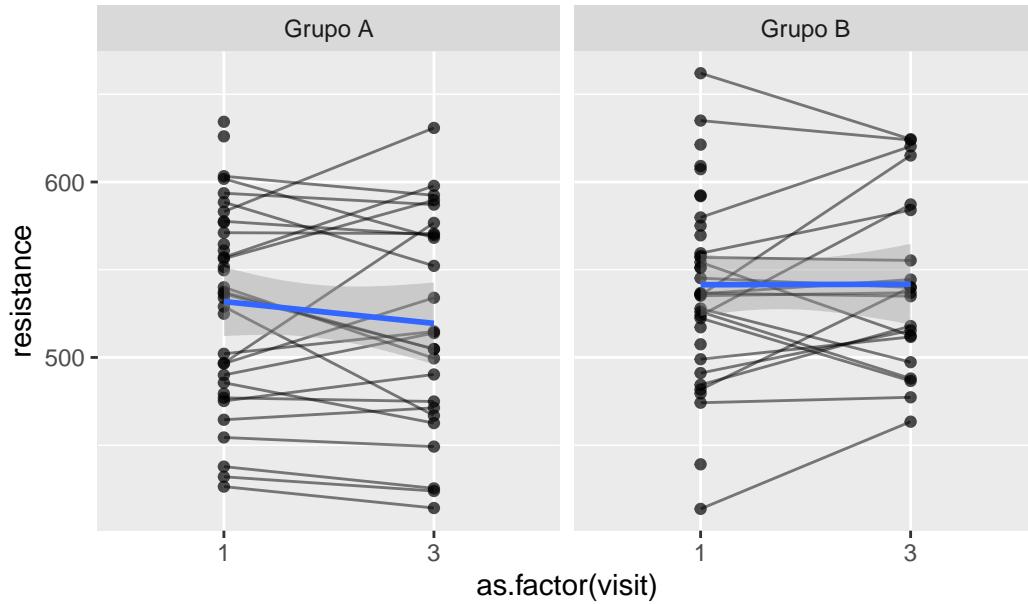
```

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



4.0.4 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))) +
```

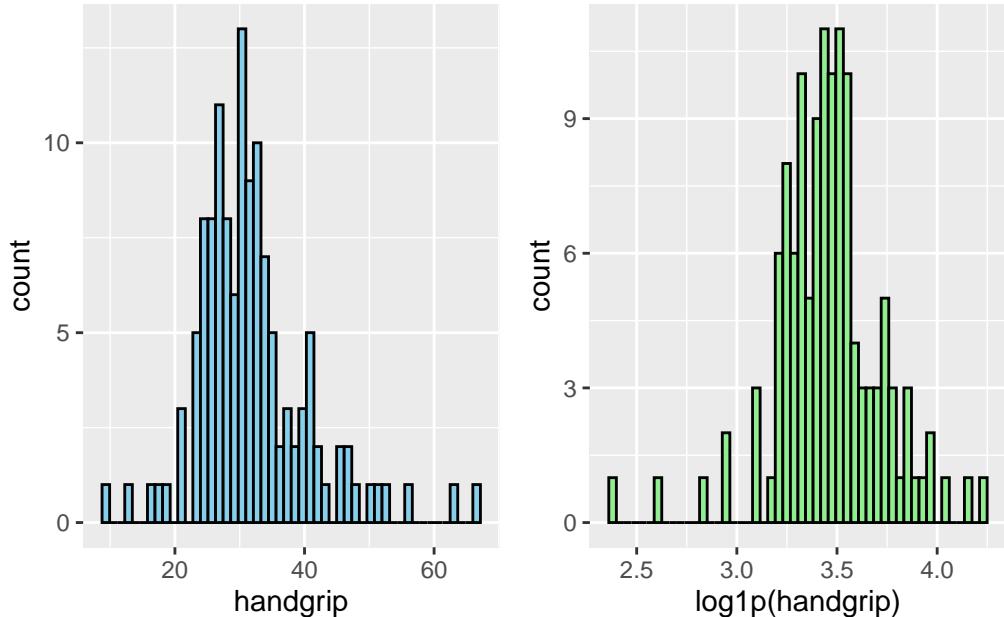
```

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"

```

4.0.4.1 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_group	-0.09908	0.05814	81.97737	-1.704	0.0921
visit3	0.02794	0.02752	52.37961	1.015	0.3146
allocation_group:visit3	-0.07741	0.03962	52.70060	-1.954	0.0561

(Intercept) ***
allocation_group

visit3
allocation_group: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_group	-0.06327	0.04838	70.87133	-1.308	0.195
visit3	0.02342	0.01559	45.19417	1.503	0.140
allocation_group:visit3	-0.01675	0.02329	45.40129	-0.719	0.476

(Intercept) ***
allocation_group
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

```
handgrip_model_check$comparison_table
```

A tibble: 12 x 6

Model	term	estimate	std.error	statistic	p.value
<chr>	<chr>	<dbl>	<dbl>	<dbl>	<dbl>
1 Original	(Intercept)	3.51	0.0414	84.9	1.11e-81
2 Sensitivity	(Intercept)	3.50	0.0337	104.	3.80e-79
3 Original	allocation_groupGrupo B	-0.0991	0.0581	-1.70	9.21e- 2
4 Sensitivity	allocation_groupGrupo B	-0.0633	0.0484	-1.31	1.95e- 1
5 Original	allocation_groupGrupo B:v~	-0.0774	0.0396	-1.95	5.61e- 2
6 Sensitivity	allocation_groupGrupo B:v~	-0.0167	0.0233	-0.719	4.76e- 1
7 Original	sd__(Intercept)	0.230	NA	NA	NA
8 Sensitivity	sd__(Intercept)	0.194	NA	NA	NA
9 Original	sd__Observation	0.102	NA	NA	NA
10 Sensitivity	sd__Observation	0.0565	NA	NA	NA
11 Original	visit3	0.0279	0.0275	1.02	3.15e- 1
12 Sensitivity	visit3	0.0234	0.0156	1.50	1.40e- 1

```
performance::compare_performance(
  handgrip_model,
  handgrip_model_sens)
```

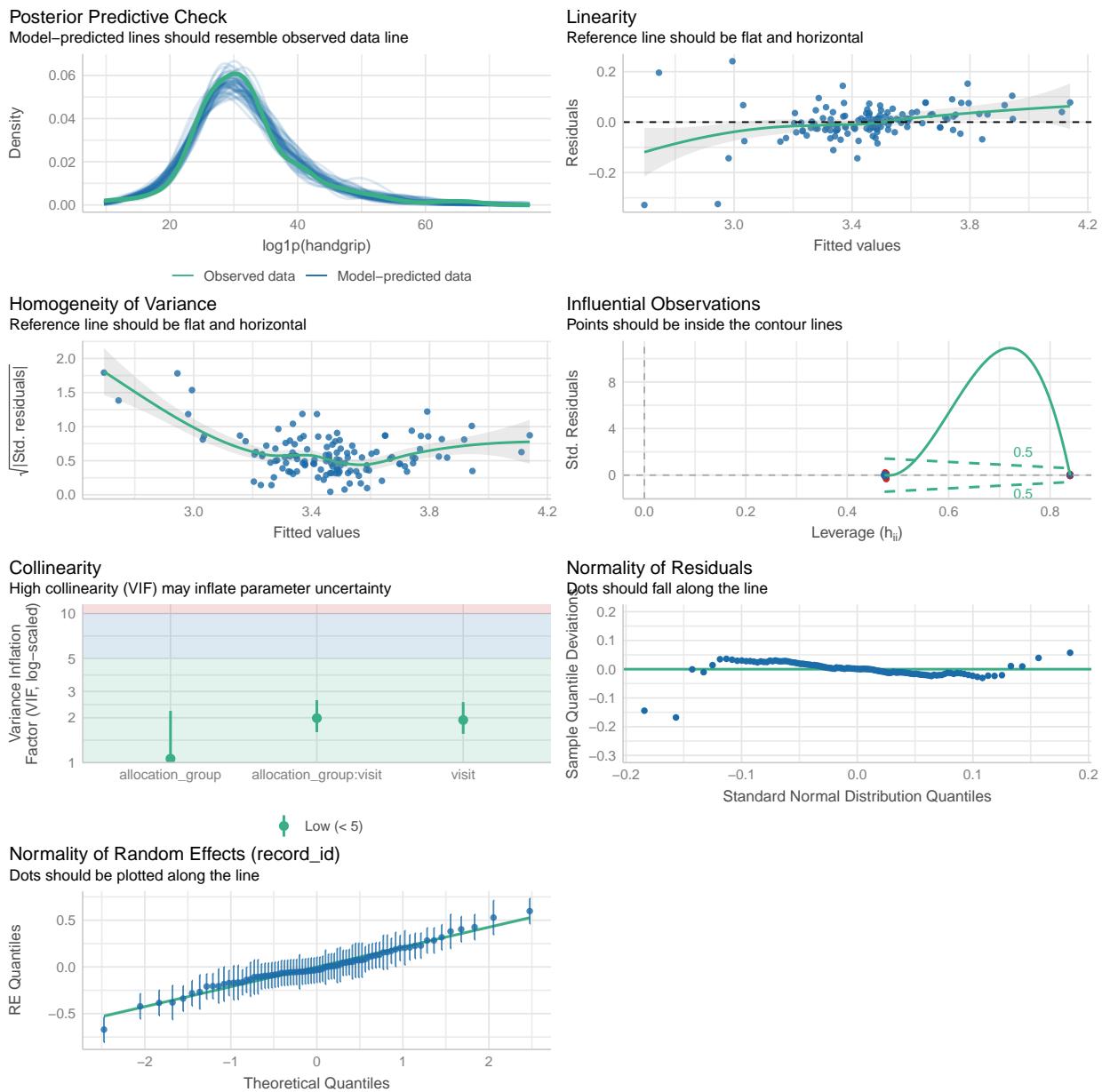
When comparing models, please note that probably not all models were fit

from same data.

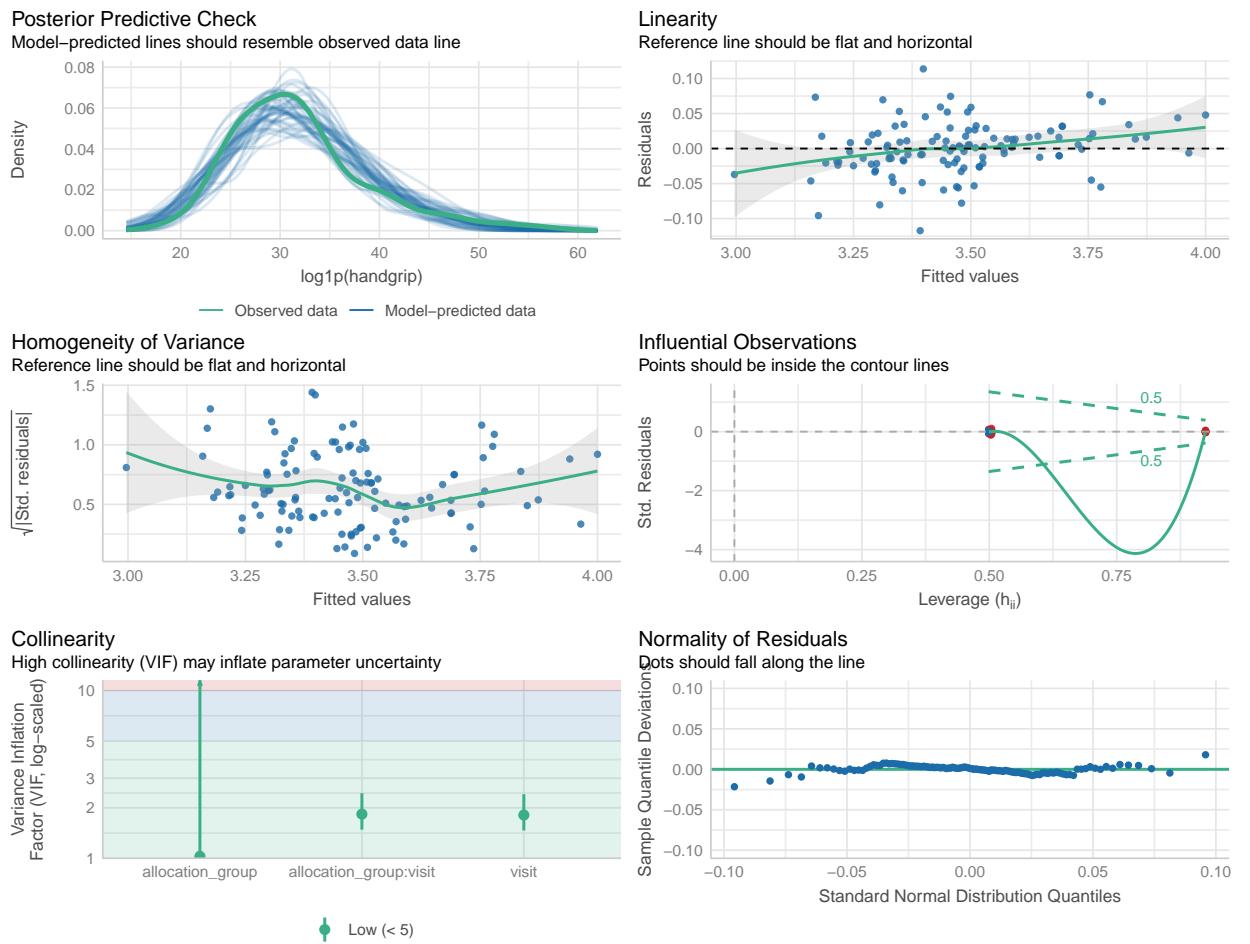
```
# Comparison of Model Performance Indices
```

Name	Model	AIC (weights)	AICc (weights)			
<hr/>						
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)
```



4.0.4.2 Médias Marginais Estimadas

4.0.4.2.1 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
emmeans::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
emmeans::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

```

```

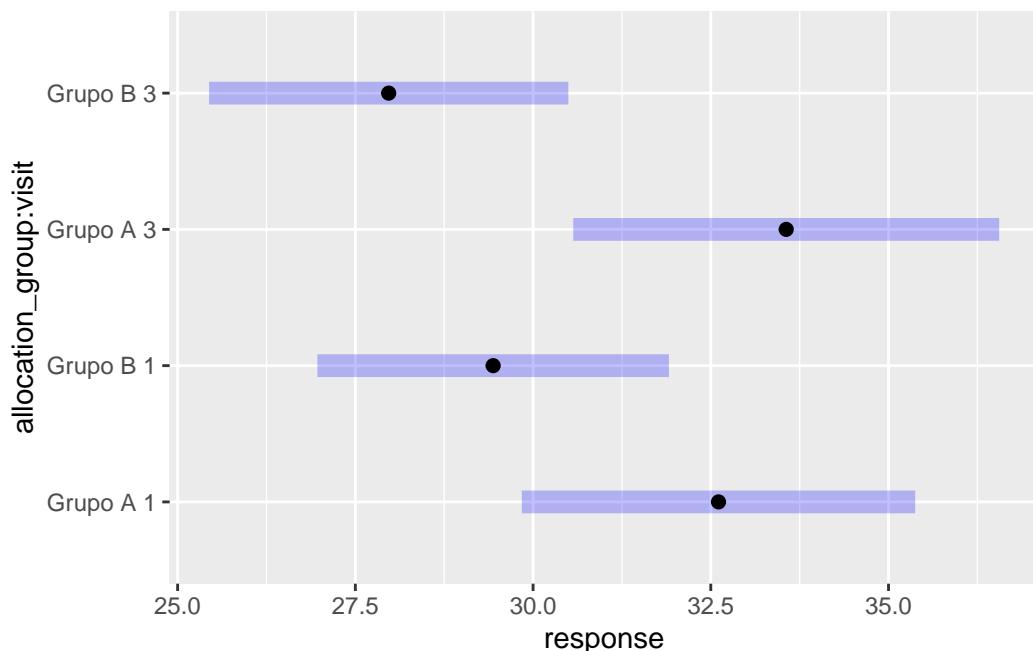
allocation_group = Grupo B:
contrast      estimate     SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit3    1.469 0.844 81.9    -0.209     3.147    1.742  0.0853

```

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

```
# Plot of marginal means
```

```
plot(handgrip_raw_emm)
```



4.0.4.2.2 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

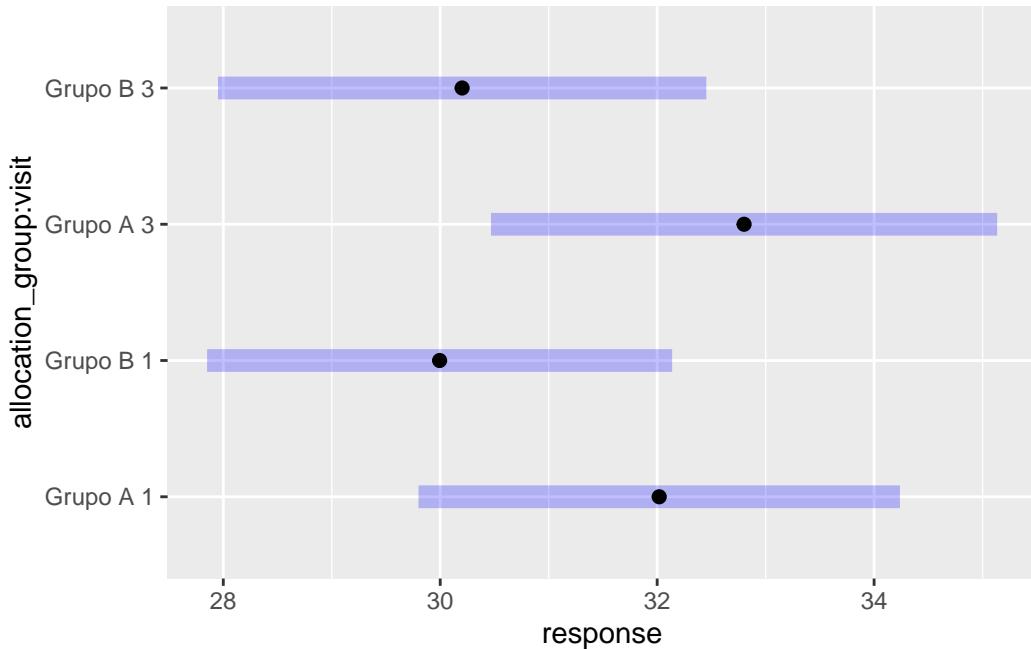
allocation_group = Grupo B:
  contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
  visit1 - visit3   -0.208 0.540 71.7     -1.28     0.868   -0.385  0.7017

```

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

```
# Plot of marginal means
```

```
plot(handgrip_emm)
```



```
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)

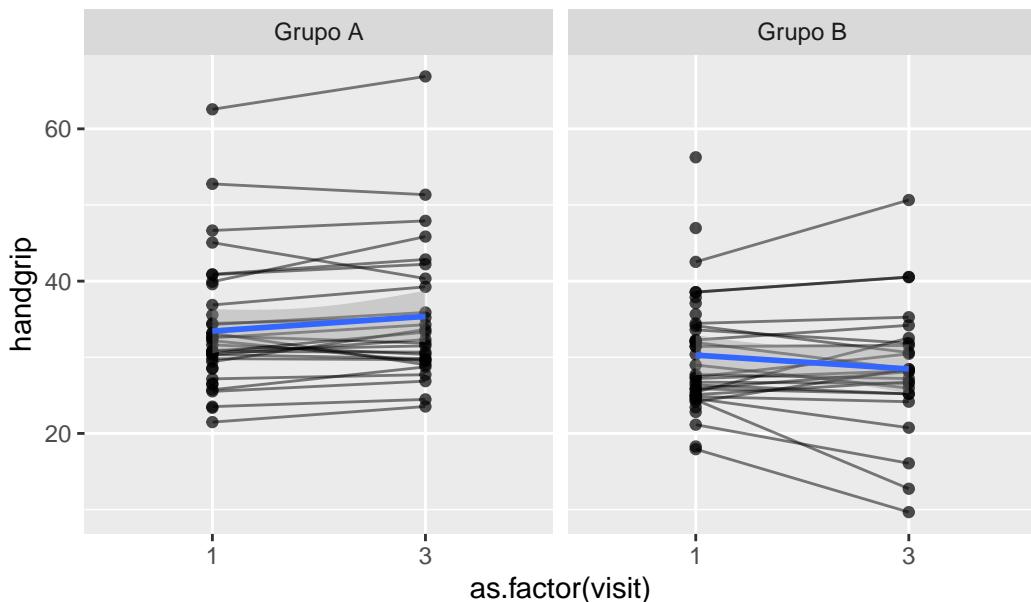
`geom_smooth()` using formula = 'y ~ x'
Warning: Removed 1 row containing non-finite outside the scale range
(`stat_smooth()`).

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)
  ) %>%

```

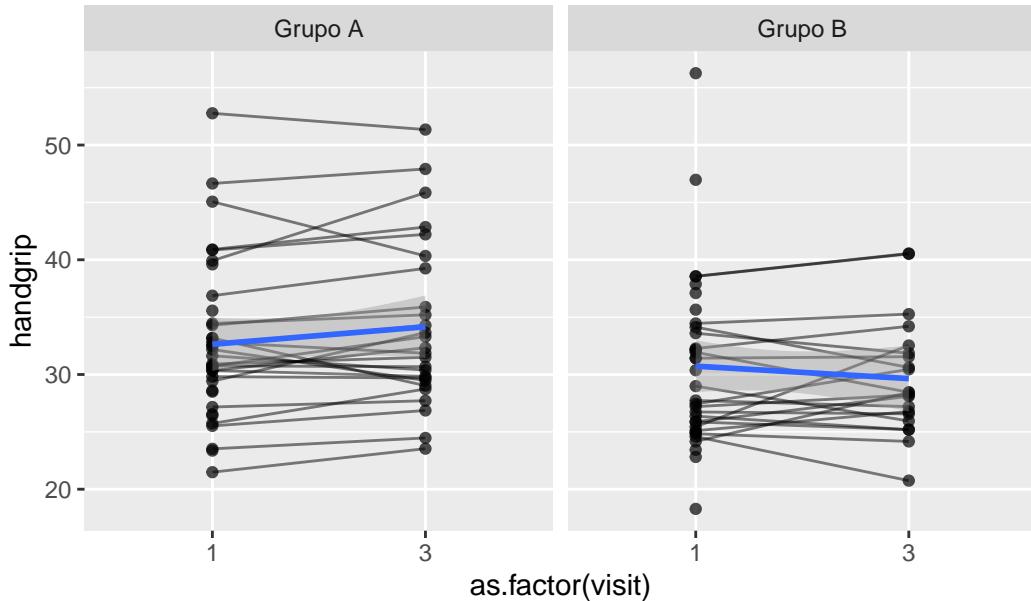
```

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



4.0.5 WHOQOL-Bref

Variável: `whoqol_score_overall`

```
# Plot 1: Raw data
whoqol_score_overall_hist_1 <- data_model_V1V3 %>%
  #filter(
  #  whoqol_score_overall < 300
  #) %>%
  ggplot(aes(x = whoqol_score_overall)) +
  geom_histogram(bins = 30, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
whoqol_score_overall_hist_2 <- data_model_V1V3 %>%
  #filter(
  #  whoqol_score_overall < 300
  #) %>%
  ggplot(aes(x = log1p(whoqol_score_overall))) +
```

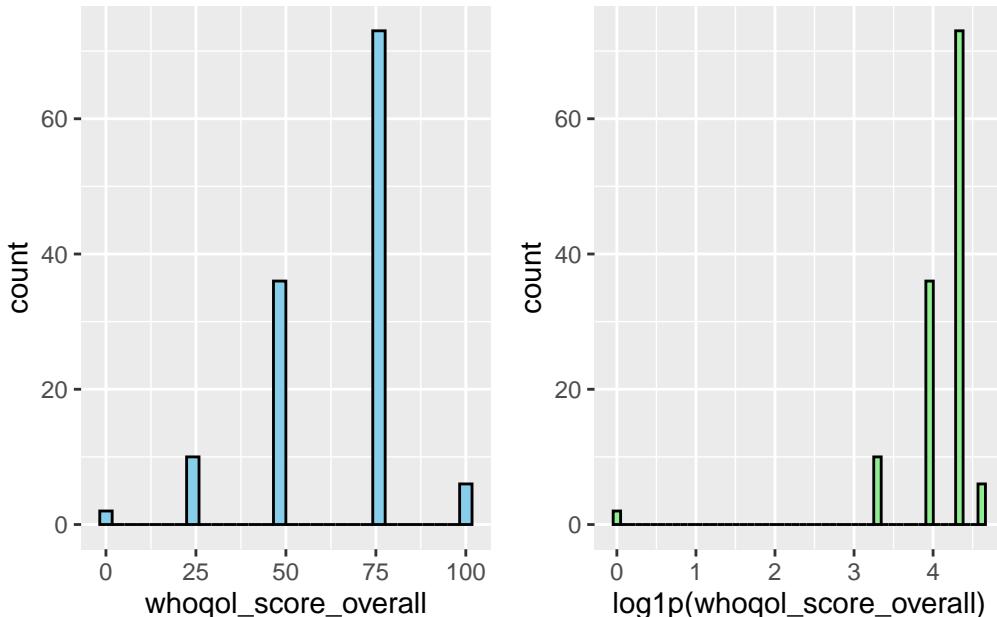
```

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

# Combine side by side
whoqol_score_overall_hist_1 + whoqol_score_overall_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
whoqol_score_overall_model <- lmer(whoqol_score_overall ~ allocation_group * visit +
(1 | record_id), data = data_model_V1V3)
check_collinearity(whoqol_score_overall_model)

# Check for Multicollinearity

```

Low Correlation

Term	VIF	VIF 95% CI	Increased SE	Tolerance
allocation_group	1.48	[1.24, 1.94]	1.22	0.68
visit	1.96	[1.58, 2.58]	1.40	0.51

```

allocation_group:visit 2.40 [1.90, 3.20]           1.55      0.42
Tolerance 95% CI
[0.52, 0.80]
[0.39, 0.63]
[0.31, 0.53]

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

# LMM Sensitivity
whoqol_score_overall_model_sens <- update(object = whoqol_score_overall_model,
                                             subset = !(record_id %in%
                                             whoqol_score_overall_model_check$influential_ids))

# Influential IDS
whoqol_score_overall_model_check$influential_ids
[1] "40" "59" "58" "13" "1"

```

4.0.5.1 Resumo dos modelos

```

# Model comparison
summary(whoqol_score_overall_model)

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

Formula: whoqol_score_overall ~ allocation_group * visit + (1 | record_id)
Data: data_model_V1V3

REML criterion at convergence: 1076.8

```

Scaled residuals:

Min	1Q	Median	3Q	Max
-2.88516	-0.42143	0.01301	0.80806	2.10468

Random effects:

Groups	Name	Variance	Std.Dev.
record_id	(Intercept)	61.58	7.847
Residual		274.92	16.581

Number of obs: 127, groups: record_id, 75

Fixed effects:

	Estimate	Std. Error	df	t value	Pr(> t)
(Intercept)	58.1081	3.0157	118.5952	19.269	< 2e-16
allocation_group	0.4445	4.2367	118.5952	0.105	0.91661
visit3	13.5646	4.2563	52.9849	3.187	0.00241
allocation_group:visit3	-0.3821	6.0857	54.5865	-0.063	0.95017

(Intercept) ***

allocation_group

visit3 **

allocation_group: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	-0.579	0.412
allctn_GB:3	0.405	-0.569
		-0.699

```
summary(whoqol_score_overall_model_sens)
```

Linear mixed model fit by REML. t-tests use Satterthwaite's method [
lmerModLmerTest]
Formula: whoqol_score_overall ~ allocation_group * visit + (1 | record_id)
Data: data_model_V1V3
Subset: !(record_id %in% whoqol_score_overall_model_check\$influential_ids)

REML criterion at convergence: 973.6

Scaled residuals:

Min	1Q	Median	3Q	Max
-2.2180	-0.6142	0.1795	0.9336	2.5120

Random effects:

Groups	Name	Variance	Std.Dev.
record_id	(Intercept)	4.396	2.097
	Residual	242.981	15.588

Number of obs: 119, groups: record_id, 70

Fixed effects:

	Estimate	Std. Error	df	t value	Pr(> t)
(Intercept)	58.333	2.738	114.970	21.306	<2e-16 ***
allocation_group	1.802	3.766	114.970	0.478	0.633
visit3	13.523	4.188	60.836	3.229	0.002 **
allocation_group:visit3	-1.656	5.821	62.004	-0.284	0.777

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

Correlation of Fixed Effects:

```

    (Intr) all_GB visit3
allctn_grGB -0.727
visit3      -0.642  0.467
allctn_GB:3  0.462 -0.636 -0.719

```

```
whoqol_score_overall_model_check$comparison_table
```

```
# A tibble: 12 x 6
```

Model	term	estimate	std.error	statistic	p.value
<chr>	<chr>	<dbl>	<dbl>	<dbl>	<dbl>
1 Original	(Intercept)	58.1	3.02	19.3	2.48e-38
2 Sensitivity	(Intercept)	58.3	2.74	21.3	9.96e-42
3 Original	allocation_groupGrupo B	0.445	4.24	0.105	9.17e- 1
4 Sensitivity	allocation_groupGrupo B	1.80	3.77	0.478	6.33e- 1
5 Original	allocation_groupGrupo B:v~	-0.382	6.09	-0.0628	9.50e- 1
6 Sensitivity	allocation_groupGrupo B:v~	-1.66	5.82	-0.284	7.77e- 1
7 Original	sd__(Intercept)	7.85	NA	NA	NA
8 Sensitivity	sd__(Intercept)	2.10	NA	NA	NA
9 Original	sd__Observation	16.6	NA	NA	NA
10 Sensitivity	sd__Observation	15.6	NA	NA	NA
11 Original	visit3	13.6	4.26	3.19	2.41e- 3
12 Sensitivity	visit3	13.5	4.19	3.23	2.00e- 3

```
performance::compare_performance(
  whoqol_score_overall_model,
  whoqol_score_overall_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)
------	--	-------	--	---------------

```

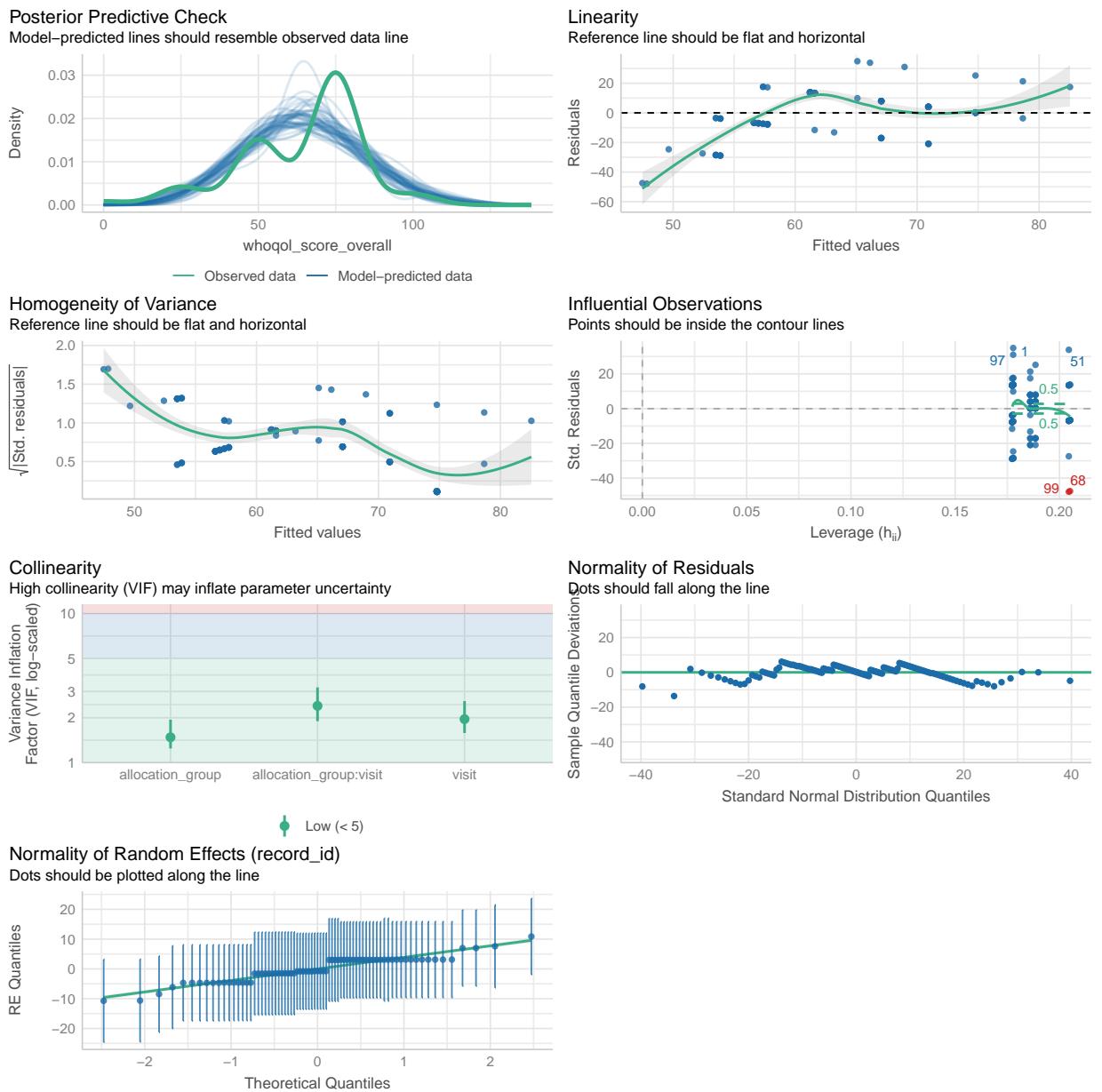
whoqol_score_overall_model      | lmerModLmerTest | 1105.5 (<.001)
whoqol_score_overall_model_sens | lmerModLmerTest | 1001.4 (>.999)

Name                         | AICc (weights) | BIC (weights) | R2 (cond.)
-----
whoqol_score_overall_model     | 1106.2 (<.001) | 1122.6 (<.001) | 0.277
whoqol_score_overall_model_sens | 1002.2 (>.999) | 1018.1 (>.999) | 0.153

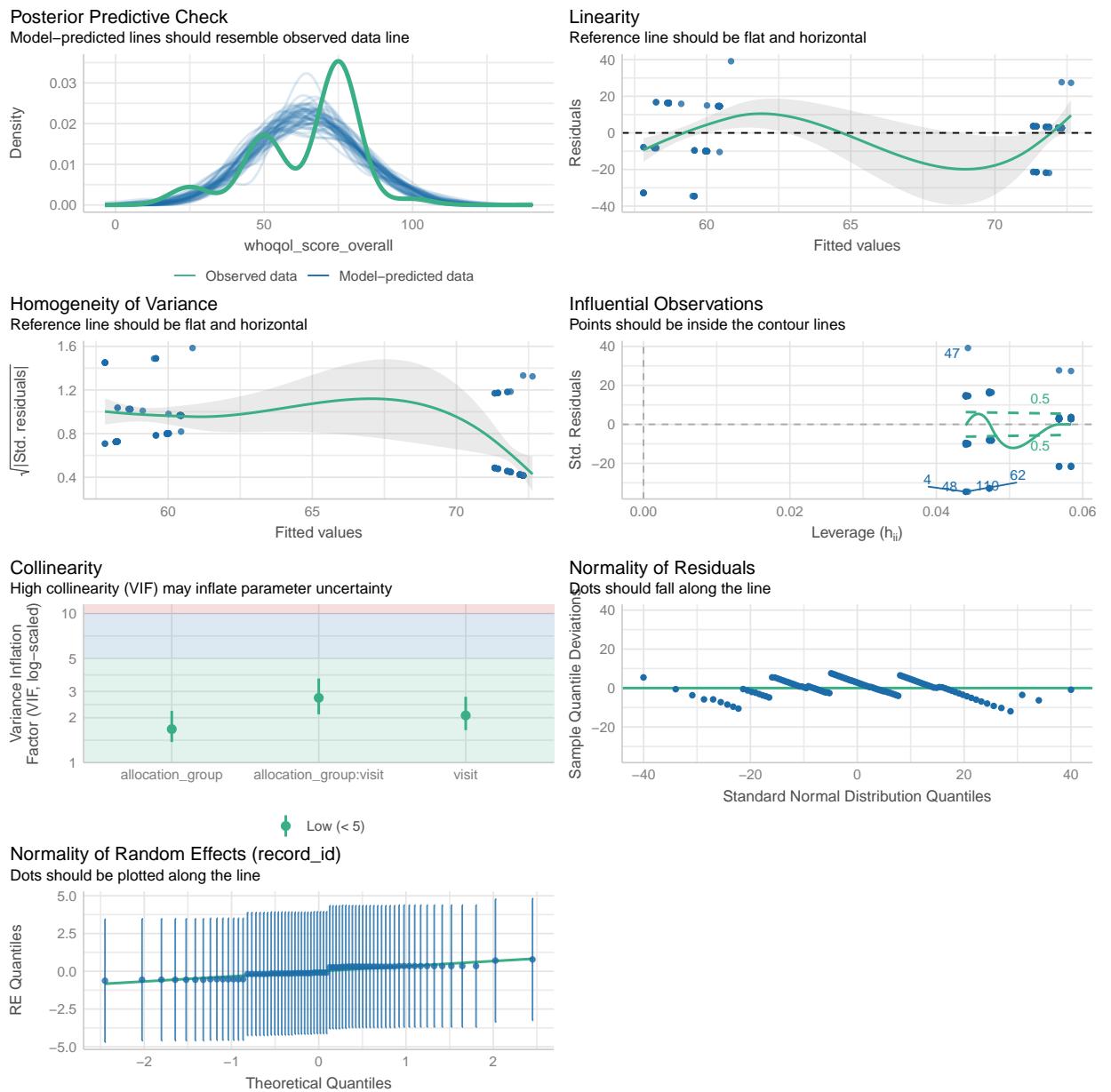
Name                         | R2 (marg.) | ICC | RMSE | Sigma
-----
whoqol_score_overall_model     | 0.115 | 0.183 | 14.955 | 16.581
whoqol_score_overall_model_sens | 0.138 | 0.018 | 15.189 | 15.588

performance::check_model(whoqol_score_overall_model)

```



```
performance::check_model(whoqol_score_overall_model_sens)
```



4.0.5.2 Médias Marginais Estimadas

4.0.5.2.1 Todos os dados

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

```

)

whoqol_score_overall_raw_emm <- regrid(whoqol_score_overall_raw_emm)

# Table of marginal means
# whoqol_score_overall_raw_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(whoqol_score_overall_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 -0.4445 4.24 120     -8.83     7.94 -0.105  0.9166

visit = 3:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
  Grupo A - Grupo B -0.0624 5.09 123    -10.15    10.02 -0.012  0.9902

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(whoqol_score_overall_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 -13.6 4.27 120    -22.0    -5.11  -3.176  0.0019

```

```

allocation_group = Grupo B:
contrast      estimate   SE  df lower.CL upper.CL t.ratio p.value
visit1 - visit3     -13.2 4.37 120     -21.8     -4.53   -3.017  0.0031

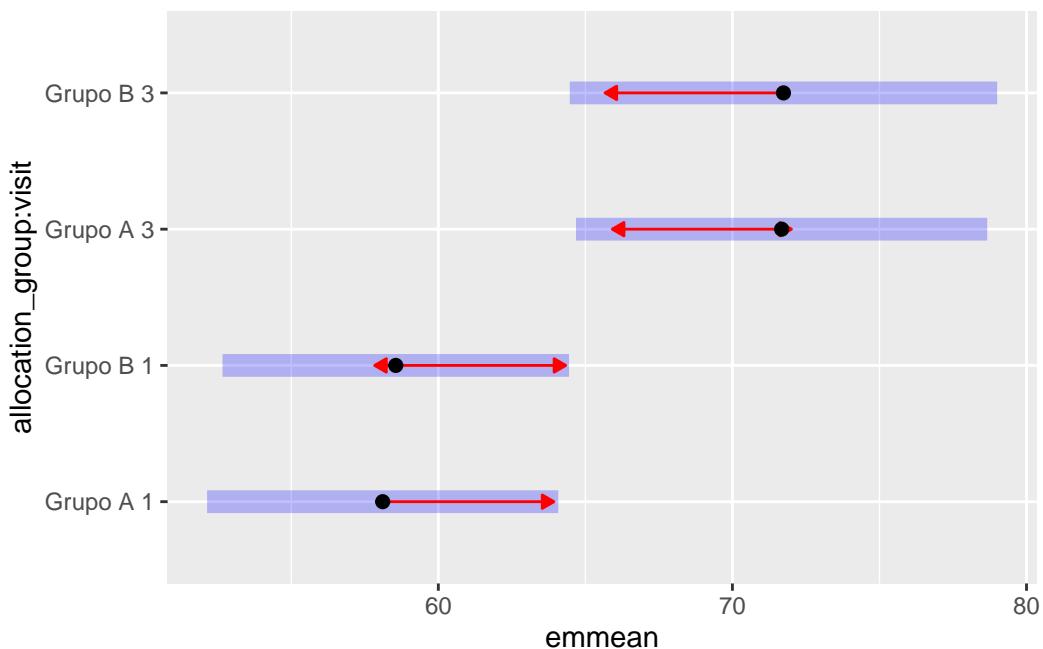
```

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

Confidence level used: 0.95

```
# Plot of marginal means
```

```
plot(whoqol_score_overall_raw_emm, comparisons = TRUE)
```



4.0.5.2.2 Análise de sensibilidade

```

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

whoqol_score_overall_emm <- regrid(whoqol_score_overall_emm)

```

```

# Table of marginal means

# whoqol_score_overall_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(whoqol_score_overall_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    -1.802 3.77 115     -9.26      5.66  -0.478  0.6332

visit = 3:
  contrast      estimate   SE  df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    -0.146 4.52 115     -9.10      8.81  -0.032  0.9743

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(whoqol_score_overall_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     -13.5 4.20 115     -21.8     -5.20  -3.218  0.0017

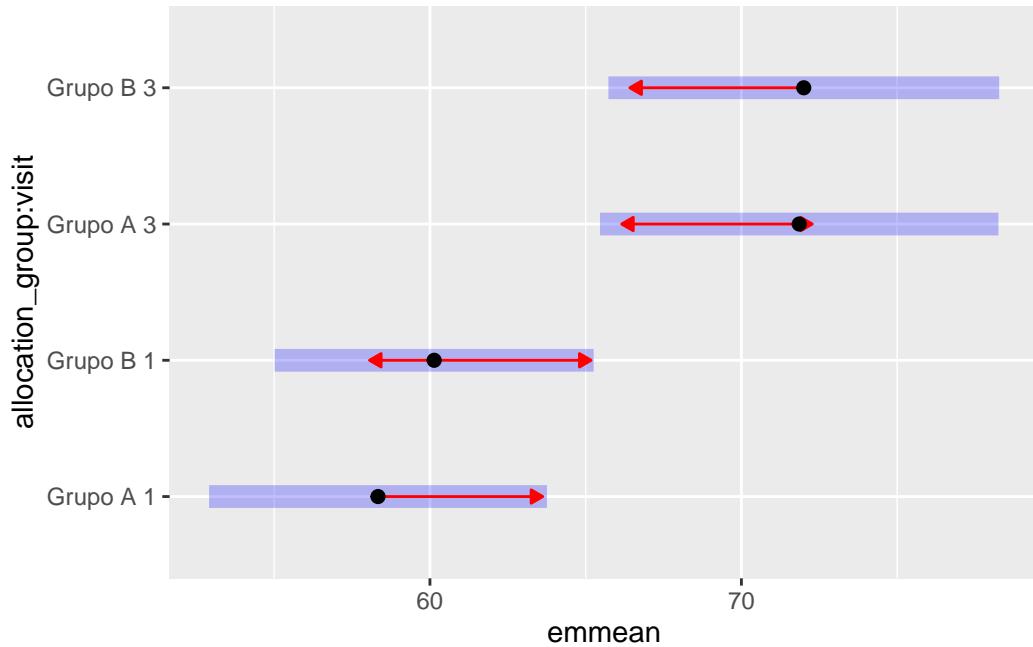
allocation_group = Grupo B:
  contrast      estimate   SE  df lower.CL upper.CL t.ratio p.value
visit1 - visit3     -11.9 4.06 115     -19.9     -3.83  -2.923  0.0042

```

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

```
# Plot of marginal means
```

```
plot(whoqol_score_overall_emm, comparisons = TRUE)
```



```
ggplot(  
  data = data_model_V1V3,  
  aes(  
    x = as.factor(visit),  
    y = whoqol_score_overall,  
    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)

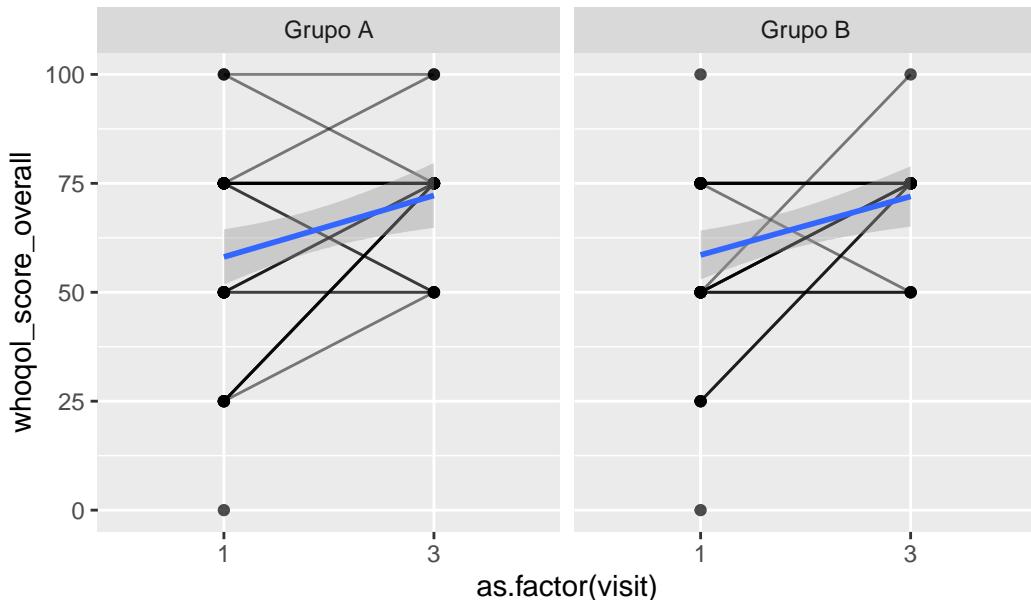
`geom_smooth()` using formula = 'y ~ x'
Warning: Removed 1 row containing non-finite outside the scale range
(`stat_smooth()`).

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%
      whoqol_score_overall_model_check$influential_ids)
  ) %>%

```

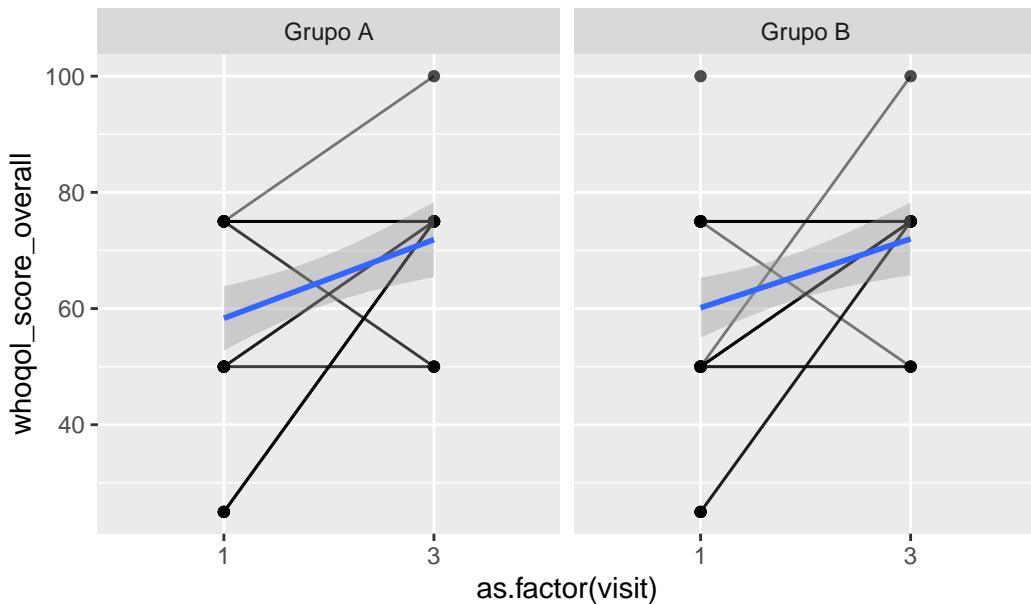
```

ggplot(
  aes(
    x = as.factor(visit),
    y = whoqol_score_overall,
    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



4.0.6 Escore DASS Depressão

Variável: `dass_score_depression`

```
# Plot 1: Raw data
dass_score_depression_hist_1 <- data_model_V1V3 %>%
  #filter(
  #  dass_score_depression < 300
  #) %>%
  ggplot(aes(x = dass_score_depression)) +
  geom_histogram(bins = 50, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
dass_score_depression_hist_2 <- data_model_V1V3 %>%
  #filter(
  #  dass_score_depression < 300
  #) %>%
  ggplot(aes(x = log1p(dass_score_depression))) +
```

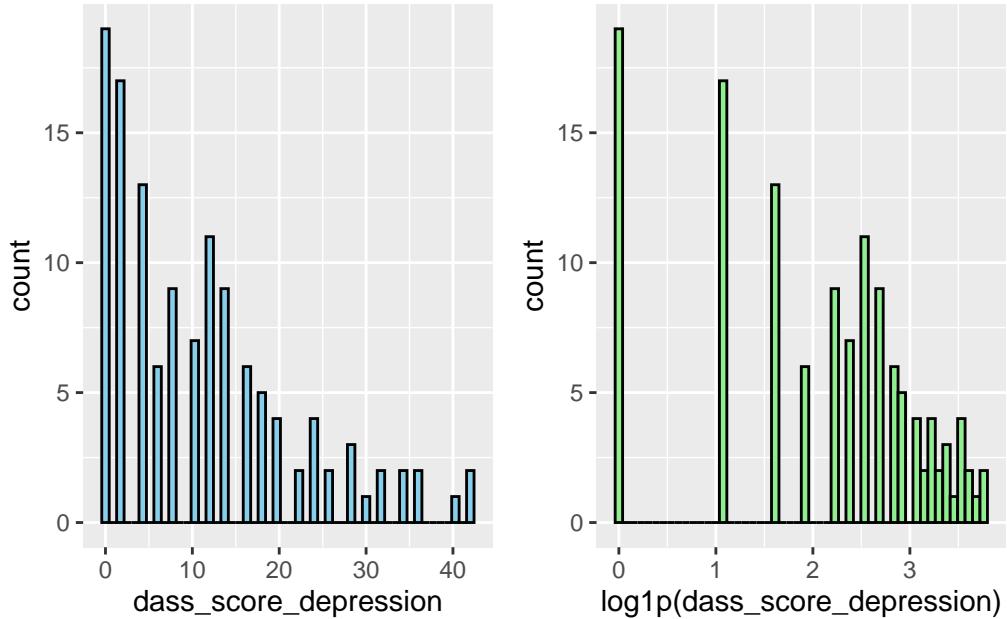
```

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

# Combine side by side
dass_score_depression_hist_1 + dass_score_depression_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
dass_score_depression_model <- lmer(dass_score_depression ~ allocation_group * visit +
(1 | record_id), data = data_model_V1V3)
check_collinearity(dass_score_depression_model)

# Check for Multicollinearity

```

Low Correlation

	Term	VIF	VIF 95% CI	Increased SE	Tolerance
	allocation_group	1.16	[1.04, 1.63]	1.08	0.86
	visit	1.94	[1.57, 2.56]	1.39	0.52

```

allocation_group:visit 2.08 [1.67, 2.76]           1.44      0.48
Tolerance 95% CI
[0.62, 0.96]
[0.39, 0.64]
[0.36, 0.60]

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

# LMM Sensitivity
dass_score_depression_model_sens <- update(object = dass_score_depression_model,
                                              subset = !(record_id %in%
                                              dass_score_depression_model_check$influential_ids))

# Influential IDS
dass_score_depression_model_check$influential_ids
[1] "5"  "33" "40" "52" "72"

```

4.0.6.1 Resumo dos modelos

```

# Model comparison
summary(dass_score_depression_model)

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

Formula: dass_score_depression ~ allocation_group * visit + (1 | record_id)
Data: data_model_V1V3

REML criterion at convergence: 919.3

```

Scaled residuals:

Min	1Q	Median	3Q	Max
-1.7301	-0.4783	-0.1322	0.4659	2.6332

Random effects:

Groups	Name	Variance	Std.Dev.
record_id	(Intercept)	71.2	8.438
	Residual	42.0	6.481

Number of obs: 127, groups: record_id, 75

Fixed effects:

	Estimate	Std. Error	df	t value	Pr(> t)
(Intercept)	12.1081	1.7491	92.6628	6.922	5.69e-10 ***
allocation_group	0.7340	2.4573	92.6628	0.299	0.766
visit3	-0.5851	1.7191	52.7321	-0.340	0.735
allocation_group:visit3	-2.0423	2.4702	53.4729	-0.827	0.412

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	-0.378	0.269
allctn_GB:3	0.263	-0.369
		-0.696

```
summary(dass_score_depression_model_sens)
```

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

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

Data: data_model_V1V3

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

REML criterion at convergence: 809.9

Scaled residuals:

Min	1Q	Median	3Q	Max
-1.34183	-0.54206	-0.06214	0.52856	2.01888

Random effects:

Groups	Name	Variance	Std.Dev.
record_id	(Intercept)	49.5	7.036
	Residual	28.5	5.339

Number of obs: 118, groups: record_id, 70

Fixed effects:

	Estimate	Std. Error	df	t value	Pr(> t)
(Intercept)	10.5714	1.4929	83.3854	7.081	4.16e-10 ***
allocation_group	Grupo B	1.2000	2.1112	83.3854	0.568
visit3		-0.3657	1.4455	45.2450	-0.253
allocation_group	Grupo B:visit3	-3.2922	2.1225	46.3392	-1.551

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

Correlation of Fixed Effects:

(Intr)	all_GB	visit3
allctn_gr	GB -0.707	
visit3	-0.377	0.267
allctn_GB:3	0.257	-0.363
		-0.681

```
dass_score_depression_model_check$comparison_table

# A tibble: 12 x 6
  Model      term        estimate std.error statistic p.value
  <chr>     <chr>       <dbl>     <dbl>     <dbl>    <dbl>
1 Original  (Intercept)   12.1      1.75      6.92  5.69e-10
2 Sensitivity (Intercept) 10.6      1.49      7.08  4.16e-10
3 Original  allocation_group Grupo B  0.734     2.46      0.299 7.66e- 1
4 Sensitivity allocation_group Grupo B  1.20      2.11      0.568 5.71e- 1
5 Original  allocation_group Grupo B:v~ -2.04      2.47     -0.827 4.12e- 1
6 Sensitivity allocation_group Grupo B:v~ -3.29      2.12     -1.55  1.28e- 1
7 Original  sd__(Intercept)  8.44      NA        NA      NA
8 Sensitivity sd__(Intercept)  7.04      NA        NA      NA
9 Original  sd__Observation  6.48      NA        NA      NA
10 Sensitivity sd__Observation  5.34      NA        NA      NA
11 Original  visit3        -0.585     1.72     -0.340 7.35e- 1
12 Sensitivity visit3        -0.366     1.45     -0.253 8.01e- 1

performance::compare_performance(
  dass_score_depression_model,
  dass_score_depression_model_sens)
```

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

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

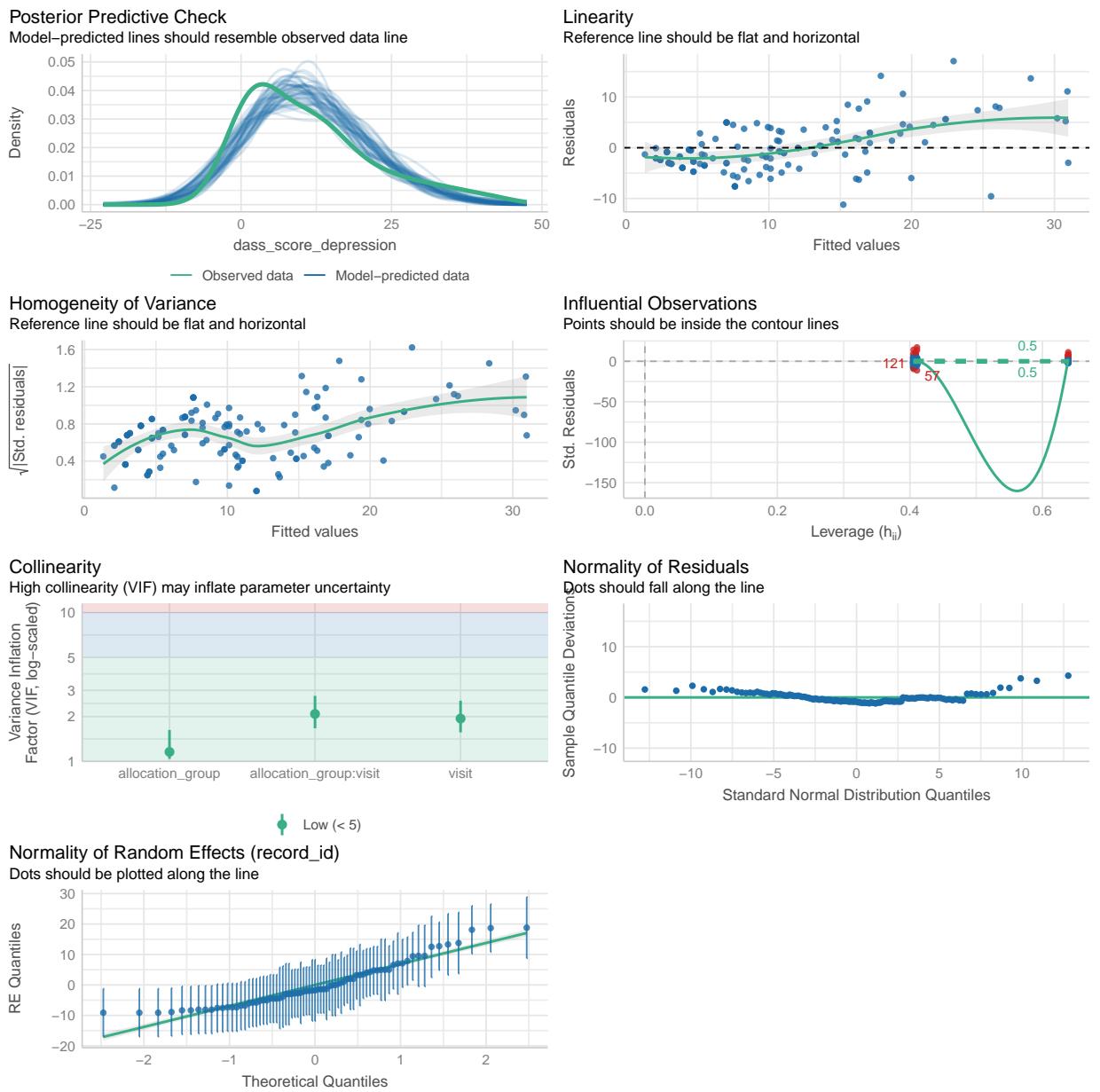
Name		Model		AIC (weights)
<hr/>				
dass_score_depression_model		lmerModLmerTest		942.8 (<.001)
dass_score_depression_model_sens		lmerModLmerTest		832.2 (>.999)
Name		AICc (weights)		BIC (weights)
		R2 (cond.)		

```
-----  
dass_score_depression_model | 943.5 (<.001) | 959.8 (<.001) | 0.632  
dass_score_depression_model_sens | 832.9 (>.999) | 848.8 (>.999) | 0.642
```

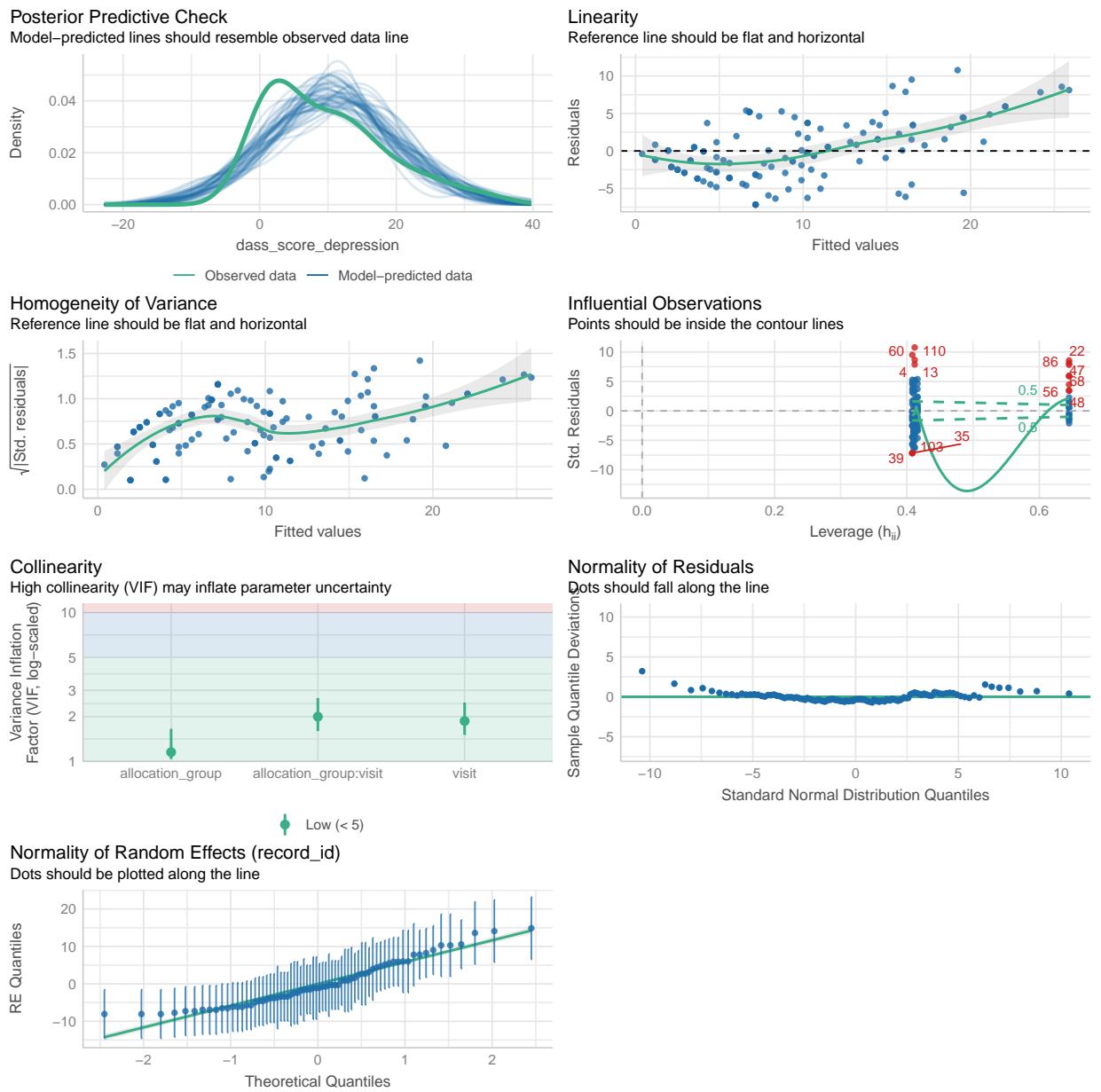
Name	R2 (marg.)	ICC	RMSE	Sigma
------	------------	-----	------	-------

dass_score_depression_model	0.008	0.629	4.809	6.481
dass_score_depression_model_sens	0.020	0.635	3.942	5.339

```
performance::check_model(dass_score_depression_model)
```



```
performance::check_model(dass_score_depression_model_sens)
```



4.0.6.2 Médias Marginais Estimadas

4.0.6.2.1 Todos os dados

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

```

)

dass_score_depression_raw_emm <- regrid(dass_score_depression_raw_emm)

# Table of marginal means
# dass_score_depression_raw_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(dass_score_depression_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   -0.734 2.46  94.7    -5.61     4.14  -0.299  0.7658

visit = 3:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
  Grupo A - Grupo B    1.308 2.77 112.8    -4.19     6.80   0.472  0.6381

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(dass_score_depression_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   0.585 1.72  94.7   -2.837     4.01   0.339  0.7350

```

```

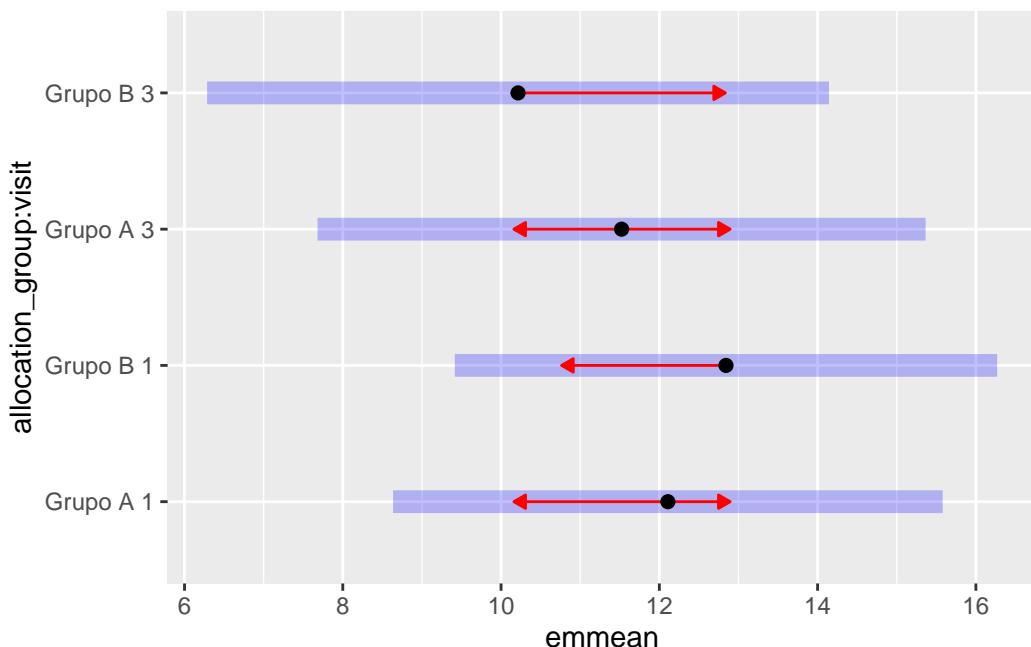
allocation_group = Grupo B:
contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit3    2.627 1.78 94.7   -0.906     6.16   1.476  0.1432

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

```

```
# Plot of marginal means
```

```
plot(dass_score_depression_raw_emm, comparisons = TRUE)
```



4.0.6.2.2 Análise de sensibilidade

```

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

dass_score_depression_emm <- regrid(dass_score_depression_emm)

```

```

# Table of marginal means

# dass_score_depression_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(dass_score_depression_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     -1.20 2.11  87.6     -5.40     3.00  -0.568  0.5712

visit = 3:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B      2.09 2.39 103.7     -2.66     6.84   0.874  0.3843

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(dass_score_depression_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     0.366 1.45  87.6     -2.515     3.25   0.252  0.8014

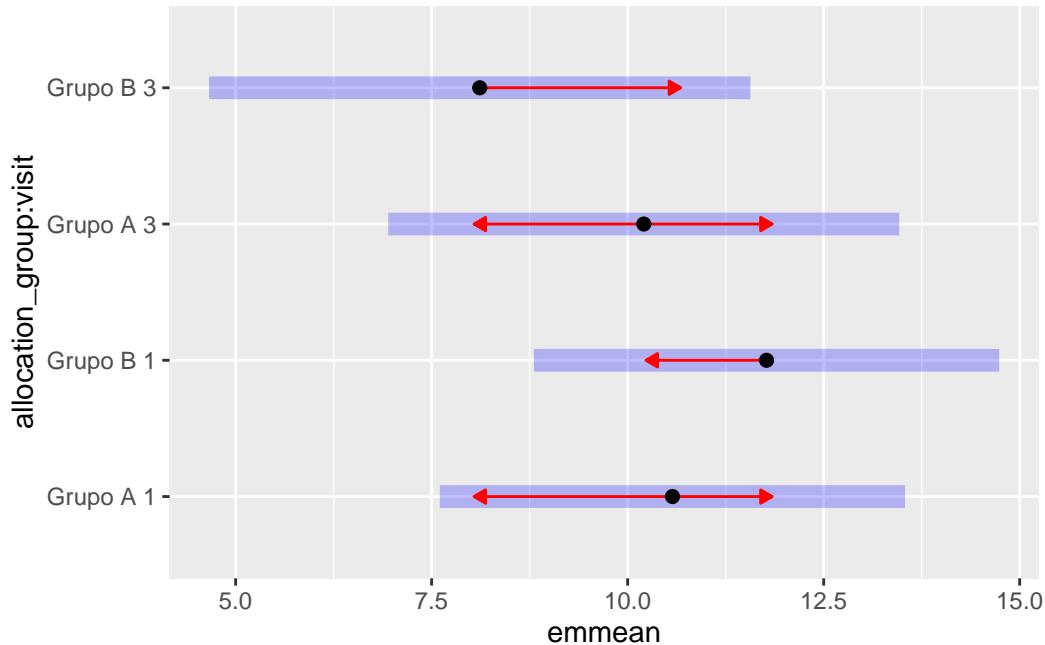
allocation_group = Grupo B:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit3     3.658 1.56  87.6      0.557     6.76   2.344  0.0213

```

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

```
# Plot of marginal means
```

```
plot(dass_score_depression_emm, comparisons = TRUE)
```



```
ggplot(  
  data = data_model_V1V3,  
  aes(  
    x = as.factor(visit),  
    y = dass_score_depression,  
    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)

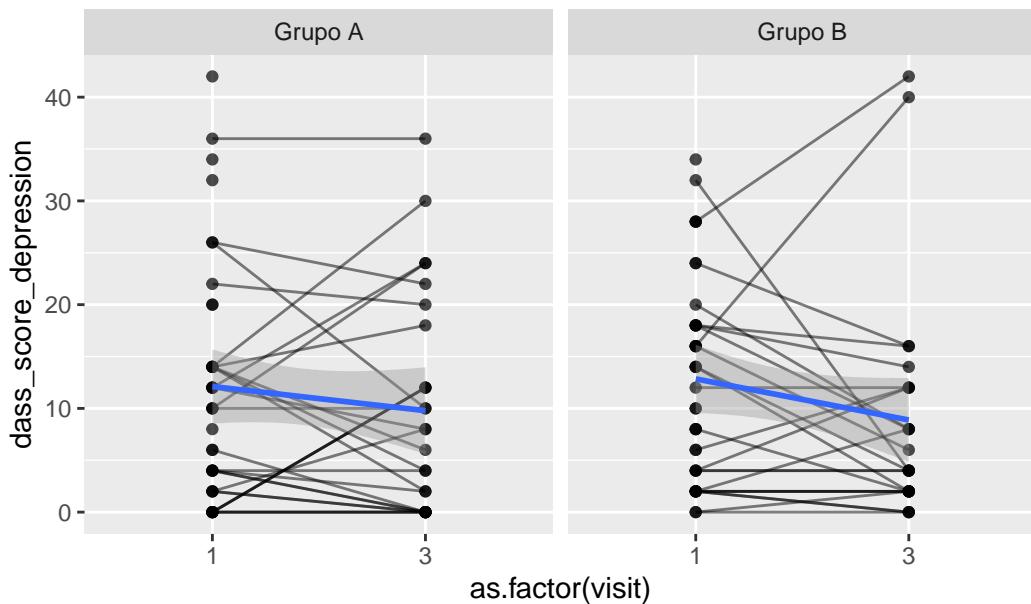
`geom_smooth()` using formula = 'y ~ x'
Warning: Removed 1 row containing non-finite outside the scale range
(`stat_smooth()`).

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%
      dass_score_depression_model_check$influential_ids)
  ) %>%

```

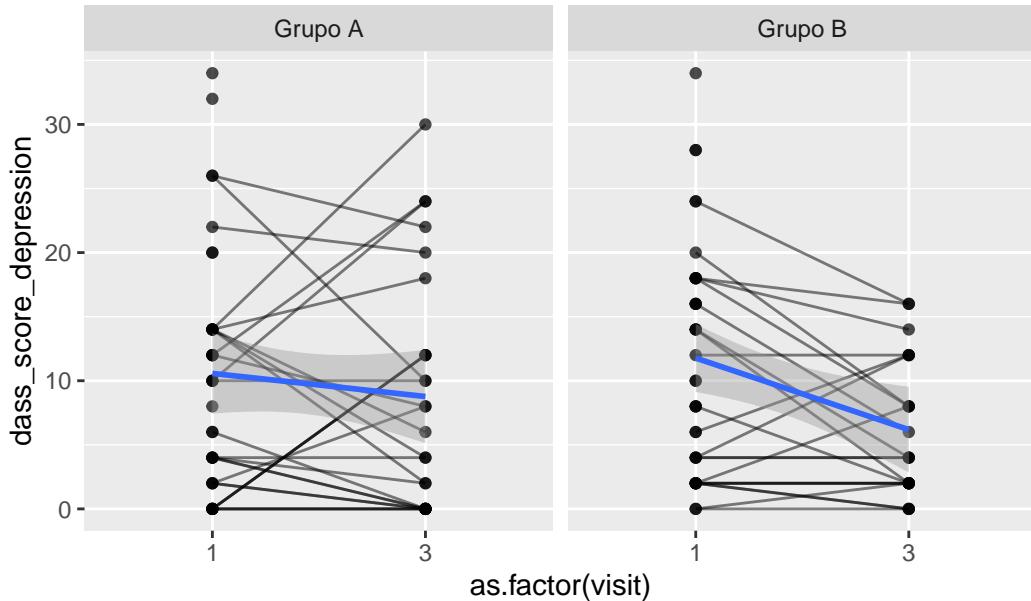
```

ggplot(
  aes(
    x = as.factor(visit),
    y = dass_score_depression,
    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



4.0.7 Escore DASS Ansiedade

Variável: `dass_score_anxiety`

```
# Plot 1: Raw data
dass_score_anxiety_hist_1 <- data_model_V1V3 %>%
  #filter(
  #  dass_score_anxiety < 300
  #) %>%
  ggplot(aes(x = dass_score_anxiety)) +
  geom_histogram(bins = 50, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
dass_score_anxiety_hist_2 <- data_model_V1V3 %>%
  #filter(
  #  dass_score_anxiety < 300
  #) %>%
  ggplot(aes(x = log1p(dass_score_anxiety))) +
```

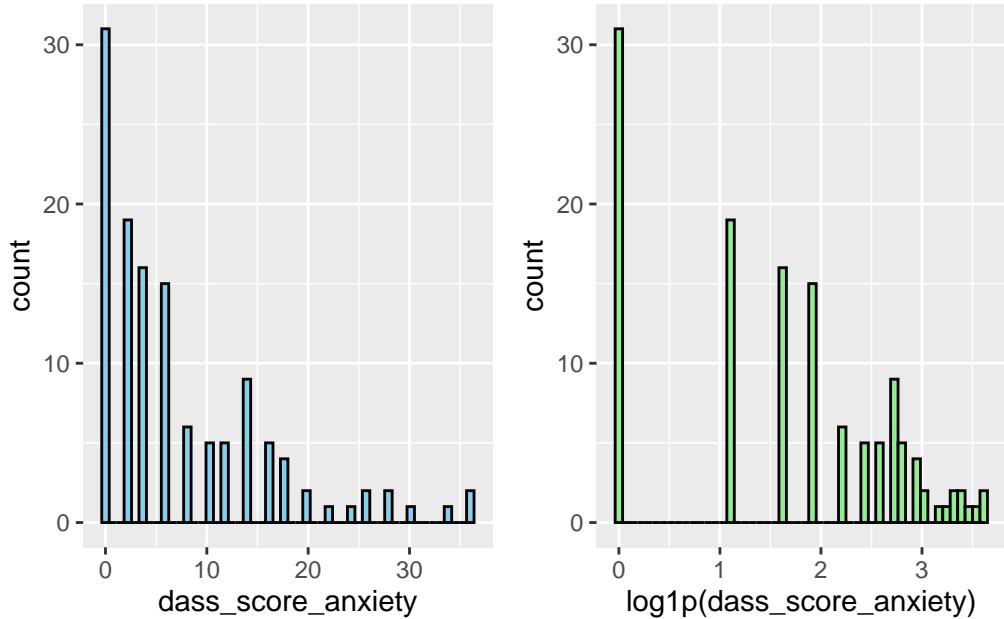
```

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

# Combine side by side
dass_score_anxiety_hist_1 + dass_score_anxiety_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
dass_score_anxiety_model <- lmer(dass_score_anxiety ~ allocation_group * visit +
(1 | record_id), data = data_model_V1V3)
check_collinearity(dass_score_anxiety_model)

# Check for Multicollinearity

```

Low Correlation

	Term	VIF	VIF 95% CI	Increased SE	Tolerance
	allocation_group	1.13	[1.03, 1.64]	1.06	0.88
	visit	1.94	[1.57, 2.56]	1.39	0.52

```

allocation_group:visit 2.06 [1.65, 2.72]           1.43      0.49
Tolerance 95% CI
[0.61, 0.97]
[0.39, 0.64]
[0.37, 0.61]

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

# LMM Sensitivity
dass_score_anxiety_model_sens <- update(object = dass_score_anxiety_model,
                                         subset = !(record_id %in%
                                         dass_score_anxiety_model_check$influential_ids))

# Influential IDS
dass_score_anxiety_model_check$influential_ids
[1] "5"  "17" "34" "40" "75"

```

4.0.7.1 Resumo dos modelos

```

# Model comparison
summary(dass_score_anxiety_model)

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

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

Data: data_model_V1V3

REML criterion at convergence: 858.1

```

Scaled residuals:

Min	1Q	Median	3Q	Max
-1.7457	-0.4812	-0.0894	0.3203	2.0986

Random effects:

Groups	Name	Variance	Std.Dev.
record_id	(Intercept)	48.89	6.992
	Residual	23.16	4.812

Number of obs: 127, groups: record_id, 75

Fixed effects:

	Estimate	Std. Error	df	t value	Pr(> t)
(Intercept)	10.000	1.395	88.971	7.166	2.15e-10 ***
allocation_group	-1.947	1.960	88.971	-0.993	0.3232
visit3	-2.492	1.281	51.525	-1.945	0.0572 .
allocation_group:visit3	0.578	1.842	52.160	0.314	0.7549

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	-0.350	0.249
allctn_GB:3	0.244	-0.342
		-0.696

```
summary(dass_score_anxiety_model_sens)
```

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

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

Data: data_model_V1V3

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

REML criterion at convergence: 753.9

Scaled residuals:

Min	1Q	Median	3Q	Max
-1.81435	-0.48518	-0.07783	0.32482	1.91373

Random effects:

Groups	Name	Variance	Std.Dev.
record_id	(Intercept)	34.86	5.904
Residual		15.55	3.943

Number of obs: 118, groups: record_id, 70

Fixed effects:

	Estimate	Std. Error	df	t value	Pr(> t)
(Intercept)	7.5758	1.2359	80.2104	6.130	3.12e-08 ***
allocation_group	0.6405	1.6999	80.2104	0.377	0.707
visit3	-1.3006	1.1140	45.2880	-1.168	0.249
allocation_group:visit3	-1.3058	1.5705	45.8720	-0.831	0.410

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

Correlation of Fixed Effects:

(Intr)	all_GB	visit3
allctn_gr	GB -0.727	
visit3	-0.342	0.249
allctn_GB:3	0.243	-0.334
		-0.709

```
dass_score_anxiety_model_check$comparison_table

# A tibble: 12 x 6
  Model      term        estimate std.error statistic p.value
  <chr>     <chr>       <dbl>     <dbl>     <dbl>    <dbl>
1 Original (Intercept)   10.0      1.40      7.17  2.15e-10
2 Sensitivity (Intercept) 7.58      1.24      6.13  3.12e- 8
3 Original allocation_groupGrupo B -1.95      1.96     -0.993 3.23e- 1
4 Sensitivity allocation_groupGrupo B  0.640     1.70      0.377 7.07e- 1
5 Original allocation_groupGrupo B:v~  0.578      1.84      0.314 7.55e- 1
6 Sensitivity allocation_groupGrupo B:v~ -1.31      1.57     -0.831 4.10e- 1
7 Original sd__(Intercept)  6.99      NA        NA      NA
8 Sensitivity sd__(Intercept) 5.90      NA        NA      NA
9 Original sd__Observation  4.81      NA        NA      NA
10 Sensitivity sd__Observation 3.94      NA        NA      NA
11 Original visit3          -2.49      1.28     -1.95  5.72e- 2
12 Sensitivity visit3       -1.30      1.11     -1.17  2.49e- 1

performance::compare_performance(
  dass_score_anxiety_model,
  dass_score_anxiety_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)
<hr/>			
dass_score_anxiety_model		lmerModLmerTest	879.5 (<.001)
dass_score_anxiety_model_sens		lmerModLmerTest	774.1 (>.999)

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

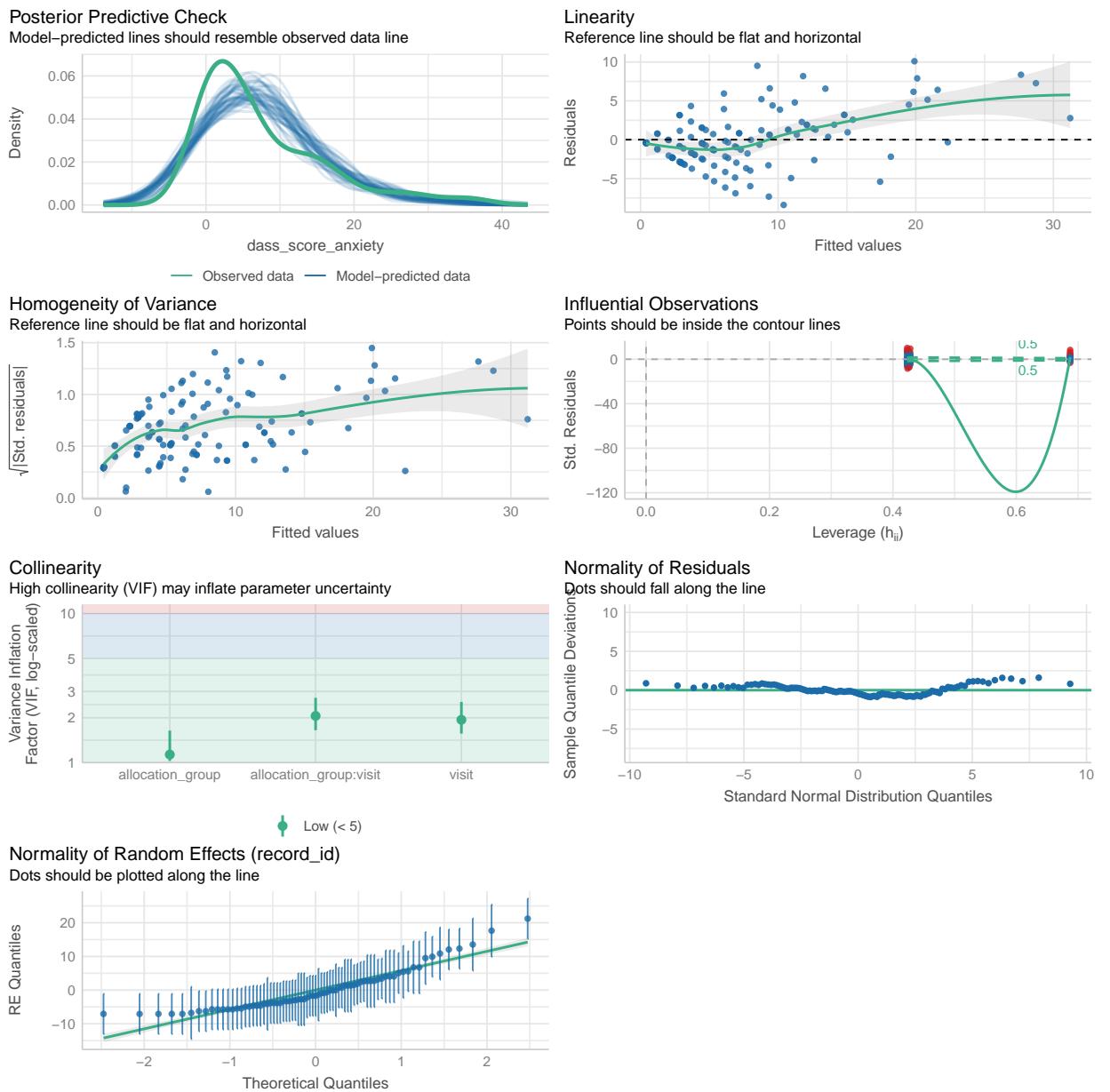
```
-----  
dass_score_anxiety_model | 880.2 (<.001) | 896.5 (<.001) | 0.687  
dass_score_anxiety_model_sens | 774.9 (>.999) | 790.8 (>.999) | 0.698
```

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

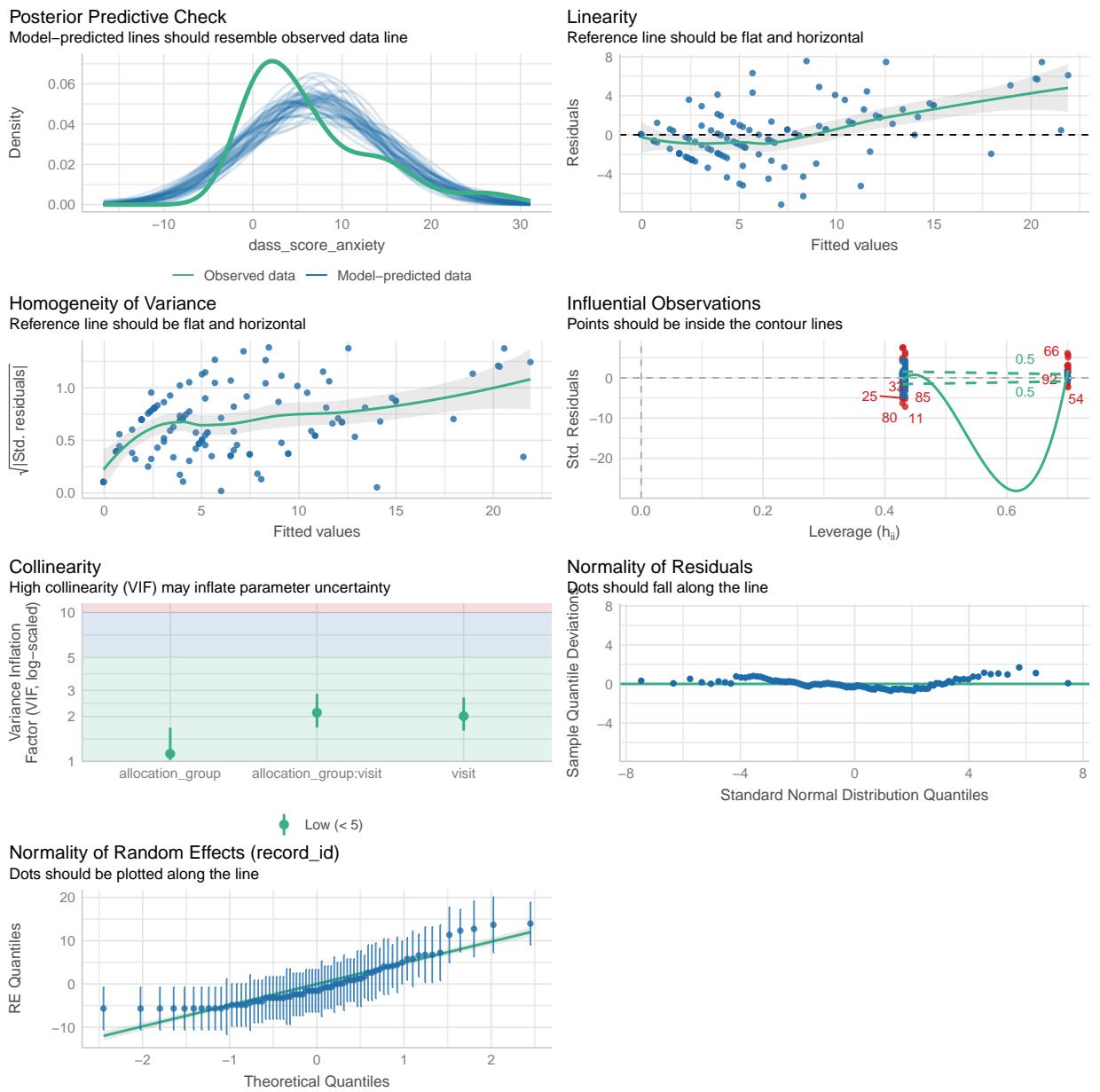
```
-----
```

dass_score_anxiety_model	0.026	0.679	3.494	4.812
dass_score_anxiety_model_sens	0.020	0.692	2.839	3.943

```
performance::check_model(dass_score_anxiety_model)
```



```
performance::check_model(dass_score_anxiety_model_sens)
```



4.0.7.2 Médias Marginais Estimadas

4.0.7.2.1 Todos os dados

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

```

)

dass_score_anxiety_raw_emm <- regrid(dass_score_anxiety_raw_emm)

# Table of marginal means
# dass_score_anxiety_raw_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(dass_score_anxiety_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     1.95 1.96  91.5     -1.95     5.84   0.993  0.3232

visit = 3:
  contrast      estimate    SE    df lower.CL upper.CL t.ratio p.value
  Grupo A - Grupo B     1.37 2.19 109.8     -2.96     5.70   0.626  0.5325

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(dass_score_anxiety_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    2.49 1.28  91.5    -0.0582     5.04   1.941  0.0554

```

```

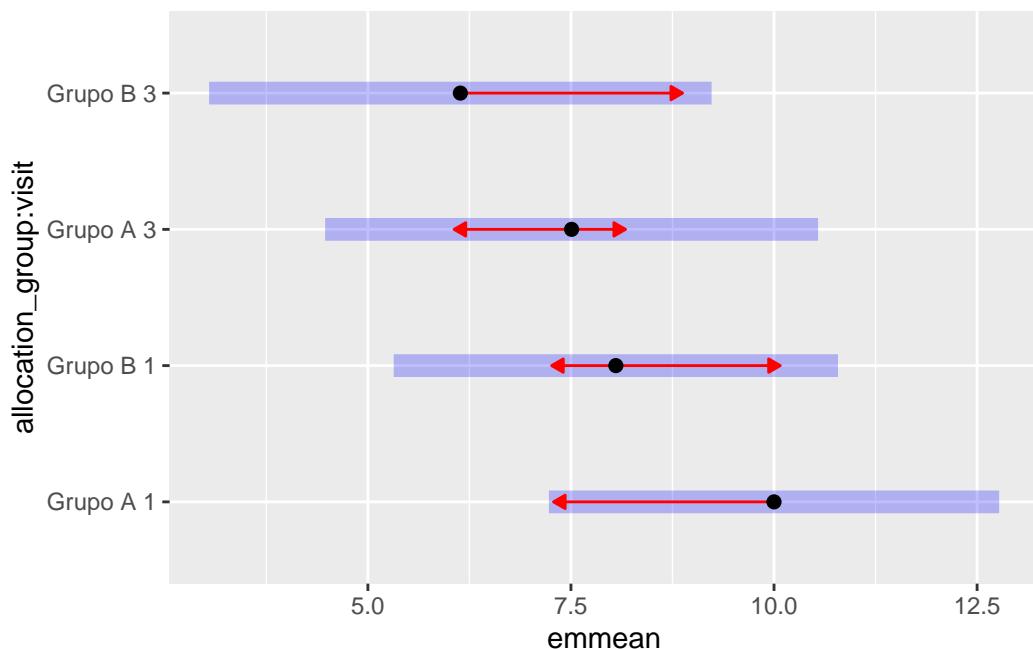
allocation_group = Grupo B:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit3     1.91 1.33 91.5  -0.7220      4.55    1.442  0.1527

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

```

```
# Plot of marginal means
```

```
plot(dass_score_anxiety_raw_emm, comparisons = TRUE)
```



4.0.7.2.2 Análise de sensibilidade

```

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

#dass_score_anxiety_emm <- regrid(dass_score_anxiety_emm)

```

```

# Table of marginal means

# dass_score_anxiety_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(dass_score_anxiety_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   -0.640 1.70  84.2    -4.02     2.74  -0.377  0.7073

visit = 3:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    0.665 1.89 103.8    -3.09     4.42   0.351  0.7261

Degrees-of-freedom method: kenward-roger
Confidence level used: 0.95

# Pairwise comparisons: Changes over time within each group
emmeans::contrast(dass_score_anxiety_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     1.30 1.12 50.2   -0.942     3.54   1.165  0.2497

allocation_group = Grupo B:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit3     2.61 1.11 51.4    0.377     4.84   2.347  0.0228

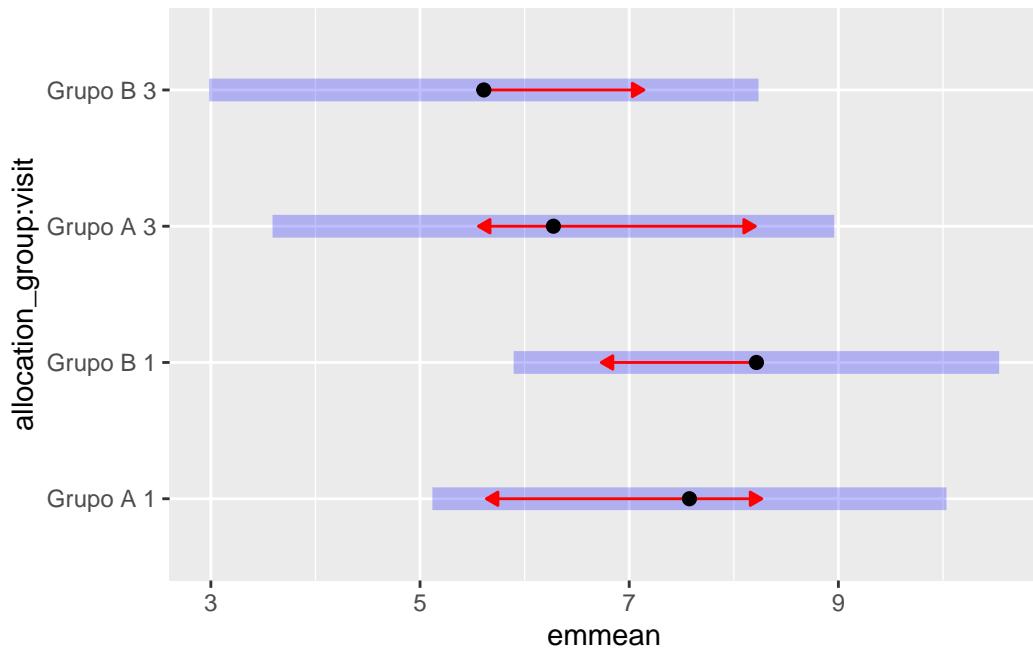
```

Degrees-of-freedom method: kenward-roger

Confidence level used: 0.95

```
# Plot of marginal means
```

```
plot(dass_score_anxiety_emm, comparisons = TRUE)
```



```
ggplot(  
  data = data_model_V1V3,  
  aes(  
    x = as.factor(visit),  
    y = dass_score_anxiety,  
    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)

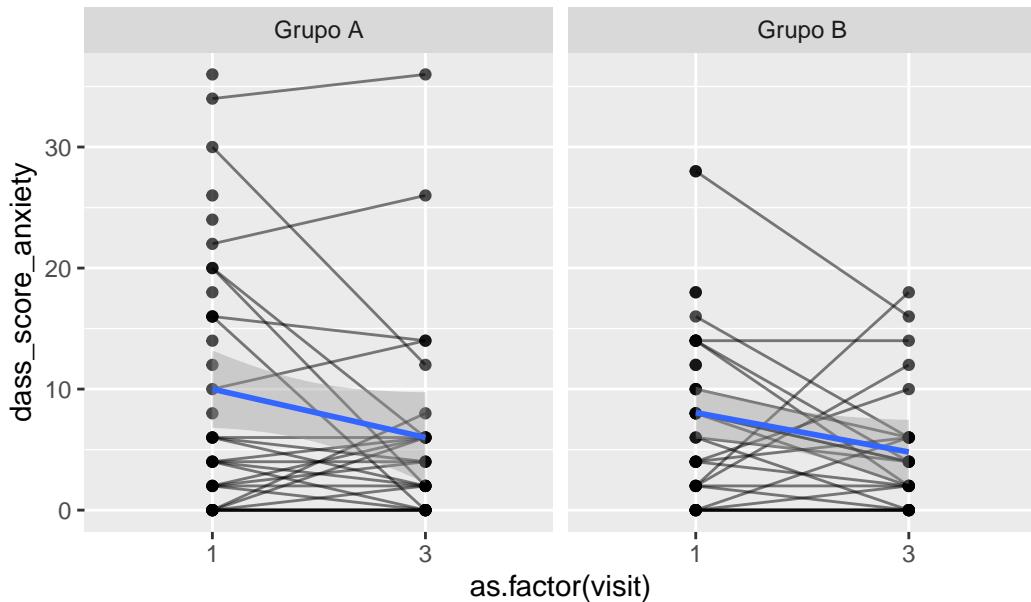
`geom_smooth()` using formula = 'y ~ x'
Warning: Removed 1 row containing non-finite outside the scale range
(`stat_smooth()`).

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%
      dass_score_anxiety_model_check$influential_ids)
  ) %>%

```

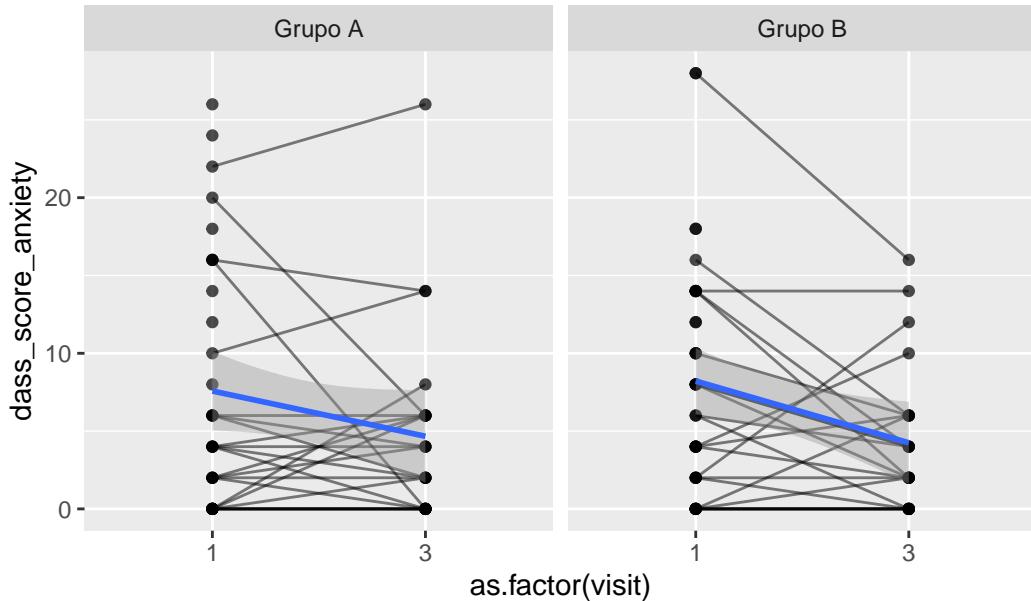
```

ggplot(
  aes(
    x = as.factor(visit),
    y = dass_score_anxiety,
    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



4.0.8 Escore DASS Estresse

Variável: `dass_score_stress`

```
# Plot 1: Raw data
dass_score_stress_hist_1 <- data_model_V1V3 %>%
  #filter(
  #  dass_score_stress < 300
  #) %>%
  ggplot(aes(x = dass_score_stress)) +
  geom_histogram(bins = 50, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
dass_score_stress_hist_2 <- data_model_V1V3 %>%
  #filter(
  #  dass_score_stress < 300
  #) %>%
  ggplot(aes(x = log1p(dass_score_stress))) +
```

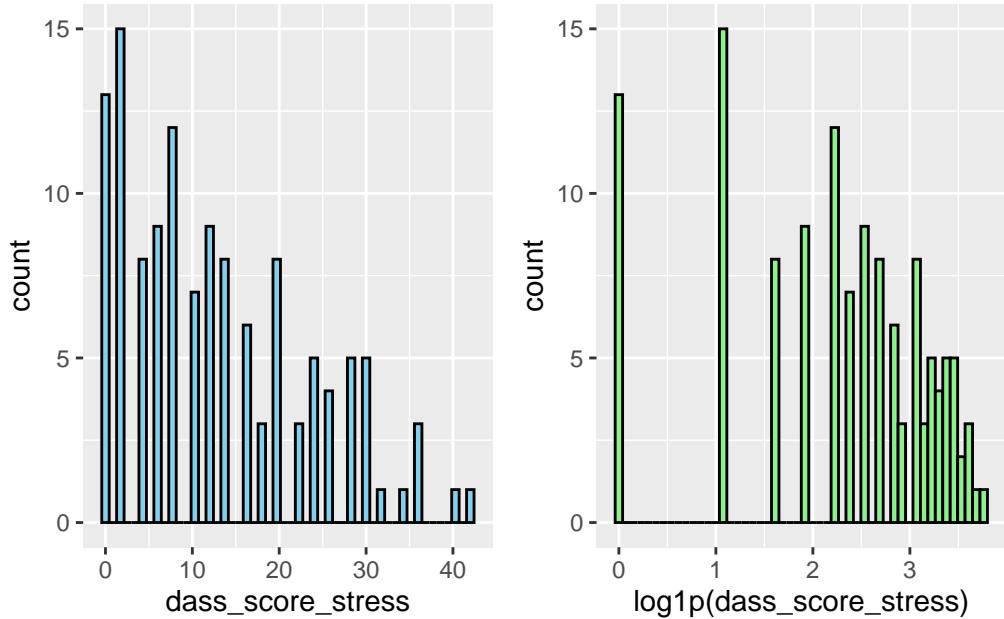
```

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

# Combine side by side
dass_score_stress_hist_1 + dass_score_stress_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
dass_score_stress_model <- lmer(dass_score_stress ~ allocation_group * visit +
(1 | record_id), data = data_model_V1V3)
check_collinearity(dass_score_stress_model)

# Check for Multicollinearity

```

Low Correlation

	Term	VIF	VIF 95% CI	Increased SE	Tolerance
	allocation_group	1.11	[1.02, 1.67]	1.06	0.90
	visit	1.94	[1.56, 2.55]	1.39	0.52

```

allocation_group:visit 2.04 [1.64, 2.70]           1.43      0.49
Tolerance 95% CI
[0.60, 0.98]
[0.39, 0.64]
[0.37, 0.61]

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

# LMM Sensitivity
dass_score_stress_model_sens <- update(object = dass_score_stress_model,
                                         subset = !(record_id %in%
                                         dass_score_stress_model_check$influential_ids))

# Influential IDS
dass_score_stress_model_check$influential_ids
[1] "5"   "33"  "17"  "9"   "75"

```

4.0.8.1 Resumo dos modelos

```

# Model comparison
summary(dass_score_stress_model)

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

Formula: dass_score_stress ~ allocation_group * visit + (1 | record_id)
Data: data_model_V1V3

REML criterion at convergence: 907

```

Scaled residuals:

Min	1Q	Median	3Q	Max
-1.64513	-0.49228	-0.07173	0.41647	1.90199

Random effects:

Groups	Name	Variance	Std.Dev.
record_id	(Intercept)	80.36	8.964
Residual		31.64	5.625

Number of obs: 127, groups: record_id, 75

Fixed effects:

	Estimate	Std. Error	df	t value	Pr(> t)
(Intercept)	13.784	1.740	87.597	7.922	6.85e-12 ***
allocation_group	1.848	2.444	87.597	0.756	0.452
visit3	-1.201	1.501	52.347	-0.800	0.427
allocation_group:visit3	-2.846	2.159	52.905	-1.318	0.193

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	-0.327	0.233
allctn_GB:3	0.228	-0.320
		-0.695

```
summary(dass_score_stress_model_sens)
```

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

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

Data: data_model_V1V3

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

REML criterion at convergence: 813.8

Scaled residuals:

Min	1Q	Median	3Q	Max
-1.49217	-0.55892	-0.02159	0.43419	1.69021

Random effects:

Groups	Name	Variance	Std.Dev.
record_id	(Intercept)	82.42	9.079
	Residual	21.34	4.620

Number of obs: 117, groups: record_id, 70

Fixed effects:

	Estimate	Std. Error	df	t value	Pr(> t)
(Intercept)	12.4848	1.7732	75.9658	7.041	7.37e-10 ***
allocation_group	2.7584	2.4390	75.9658	1.131	0.262
visit3	-0.8971	1.3409	45.4828	-0.669	0.507
allocation_group:visit3	-2.1671	1.8740	45.7129	-1.156	0.254

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

Correlation of Fixed Effects:

(Intr)	all_GB	visit3
allctn_gr	GB -0.727	
visit3	-0.272	0.198
allctn_GB:3	0.195	-0.268
		-0.715

```
dass_score_stress_model_check$comparison_table

# A tibble: 12 x 6
  Model      term        estimate std.error statistic p.value
  <chr>     <chr>       <dbl>     <dbl>     <dbl>    <dbl>
1 Original (Intercept)   13.8      1.74      7.92  6.85e-12
2 Sensitivity (Intercept) 12.5      1.77      7.04  7.37e-10
3 Original allocation_groupGrupo B  1.85      2.44      0.756 4.52e- 1
4 Sensitivity allocation_groupGrupo B  2.76      2.44      1.13  2.62e- 1
5 Original allocation_groupGrupo B:v~ -2.85      2.16     -1.32  1.93e- 1
6 Sensitivity allocation_groupGrupo B:v~ -2.17      1.87     -1.16  2.54e- 1
7 Original sd__(Intercept)  8.96      NA        NA      NA
8 Sensitivity sd__(Intercept)  9.08      NA        NA      NA
9 Original sd__Observation  5.63      NA        NA      NA
10 Sensitivity sd__Observation  4.62      NA        NA      NA
11 Original visit3          -1.20      1.50     -0.800 4.27e- 1
12 Sensitivity visit3       -0.897     1.34     -0.669 5.07e- 1

performance::compare_performance(
  dass_score_stress_model,
  dass_score_stress_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/>				
dass_score_stress_model	lmerModLmerTest	930.0 (<.001)	930.7 (<.001)	
dass_score_stress_model_sens	lmerModLmerTest	836.2 (>.999)	837.0 (>.999)	

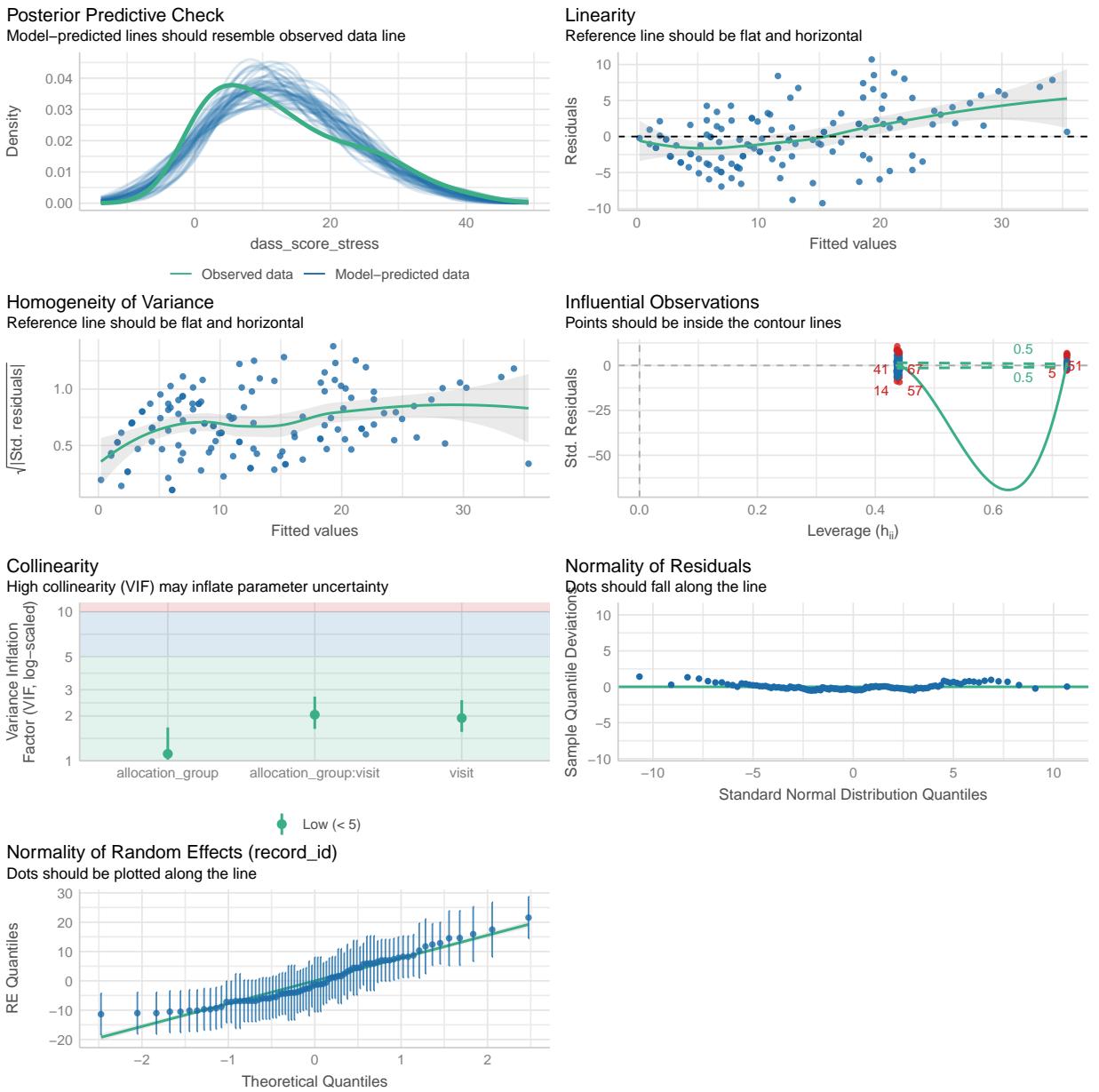
Name		BIC (weights)	R2 (cond.)	R2 (marg.)	ICC
<hr/>					

```
-----  
dass_score_stress_model | 947.1 (<.001) | 0.723 | 0.020 | 0.717  
dass_score_stress_model_sens | 852.8 (>.999) | 0.799 | 0.021 | 0.794
```

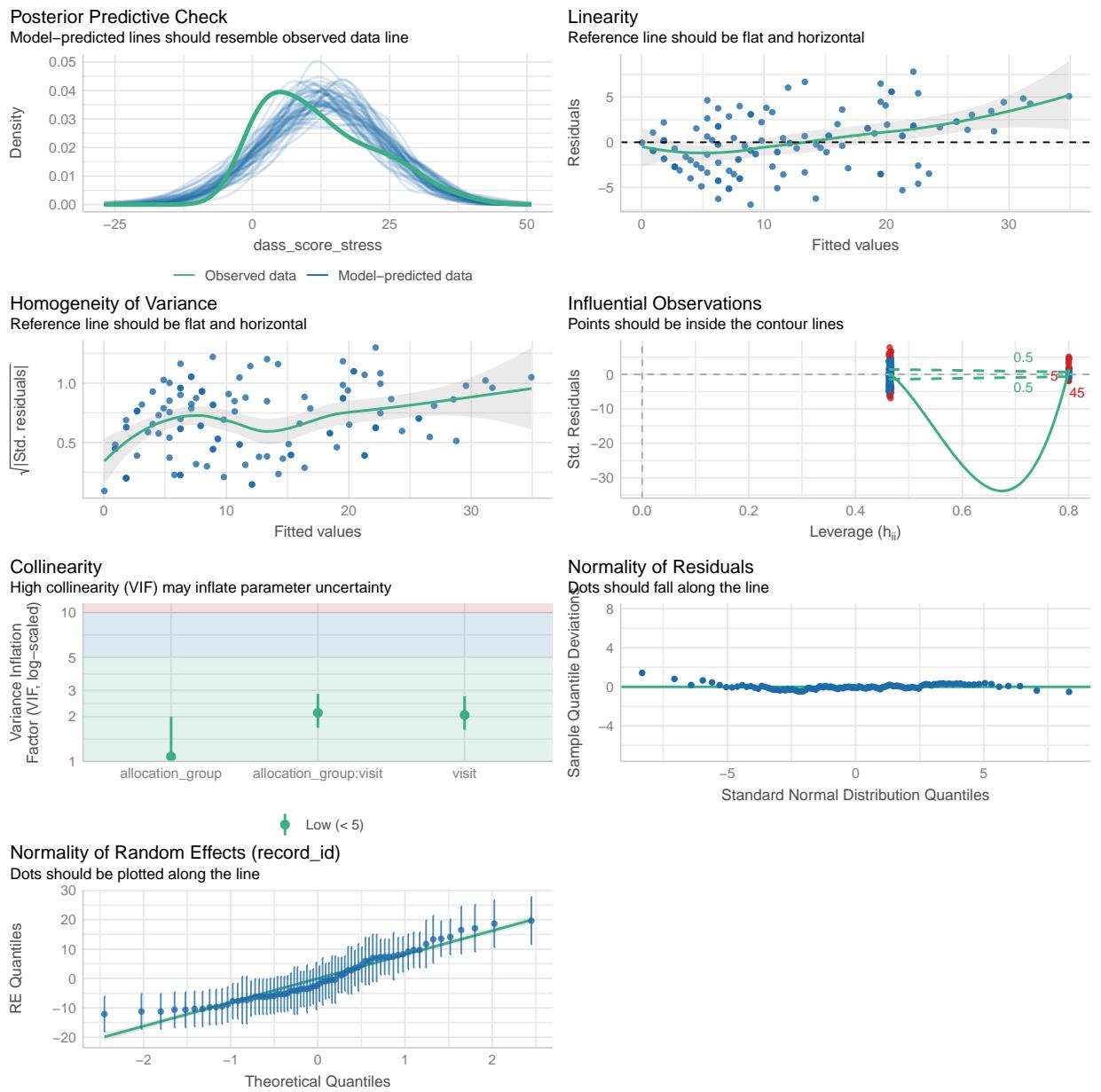
Name	RMSE	Sigma
------	------	-------

dass_score_stress_model	4.016	5.625
dass_score_stress_model_sens	3.164	4.620

```
performance::check_model(dass_score_stress_model)
```



```
performance::check_model(dass_score_stress_model_sens)
```



4.0.8.2 Médias Marginais Estimadas

4.0.8.2.1 Todos os dados

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

```

)

dass_score_stress_raw_emm <- regrid(dass_score_stress_raw_emm)

# Table of marginal means
# dass_score_stress_raw_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(dass_score_stress_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    -1.848 2.44  89     -6.70      3.01  -0.756  0.4517

visit = 3:
  contrast      estimate   SE  df lower.CL upper.CL t.ratio p.value
  Grupo A - Grupo B     0.998 2.70 107     -4.35      6.35   0.370  0.7123

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(dass_score_stress_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     1.20 1.50 89     -1.789      4.19   0.798  0.4268

```

```

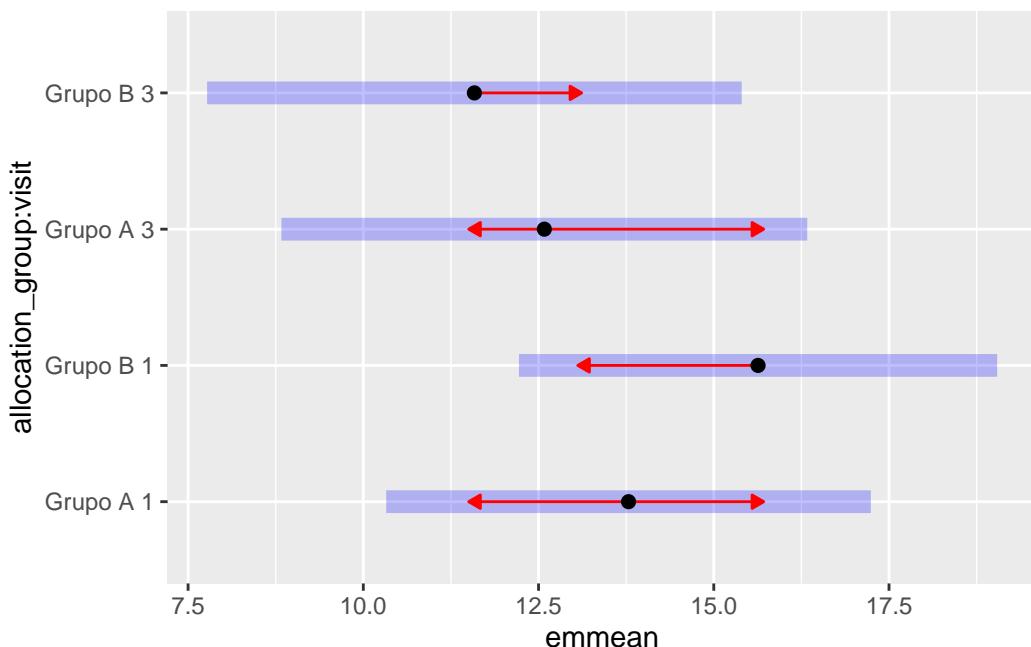
allocation_group = Grupo B:
contrast      estimate   SE df lower.CL upper.CL t.ratio p.value
visit1 - visit3     4.05 1.56 89      0.955      7.14    2.600  0.0109

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

```

```
# Plot of marginal means
```

```
plot(dass_score_stress_raw_emm, comparisons = TRUE)
```



4.0.8.2.2 Análise de sensibilidade

```

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

dass_score_stress_emm <- regrid(dass_score_stress_emm)

```

```

# Table of marginal means

# dass_score_stress_emm


# Pairwise comparisons: Between groups at each visit

emmeans::contrast(dass_score_stress_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   -2.758 2.44 78.2     -7.61      2.10  -1.131  0.2615


visit = 3:

  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B   -0.591 2.65 95.0     -5.85      4.67  -0.223  0.8240


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(dass_score_stress_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    0.897 1.34 78.2    -1.778      3.57    0.668  0.5063


allocation_group = Grupo B:

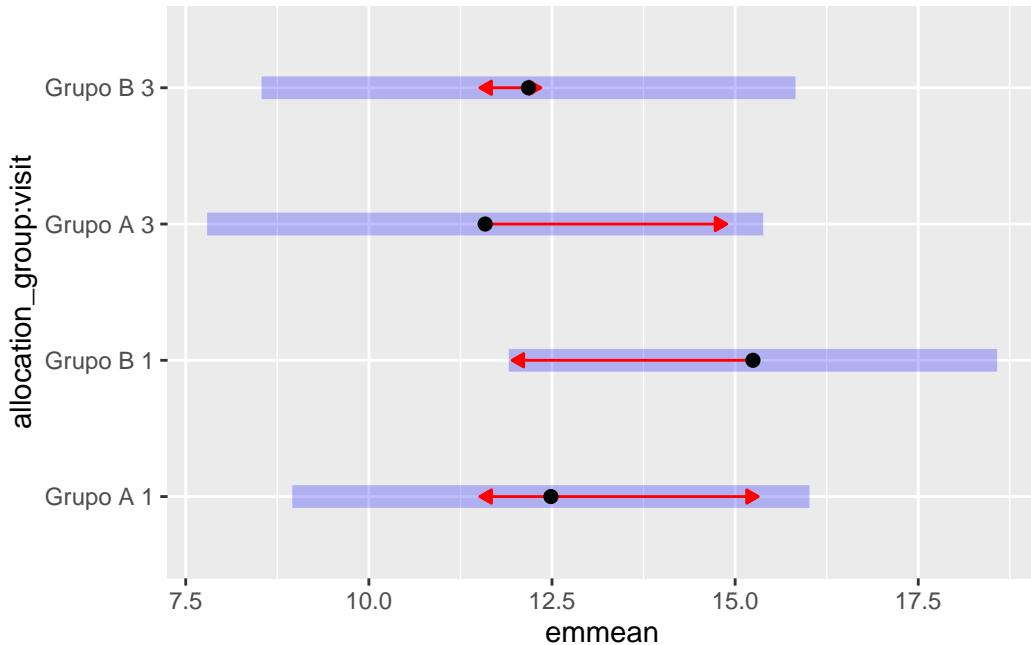
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
 visit1 - visit3    3.064 1.31 78.2     0.452      5.68    2.335  0.0221

```

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

```
# Plot of marginal means
```

```
plot(dass_score_stress_emm, comparisons = TRUE)
```



```
ggplot(  
  data = data_model_V1V3,  
  aes(  
    x = as.factor(visit),  
    y = dass_score_stress,  
    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)

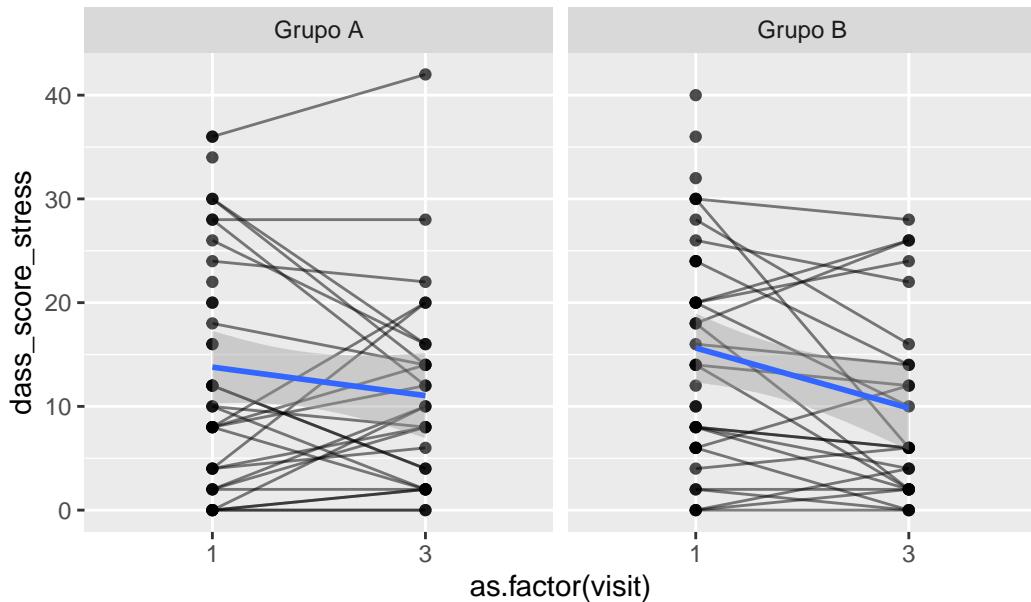
`geom_smooth()` using formula = 'y ~ x'
Warning: Removed 1 row containing non-finite outside the scale range
(`stat_smooth()`).

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%
      dass_score_stress_model_check$influential_ids)
  ) %>%

```

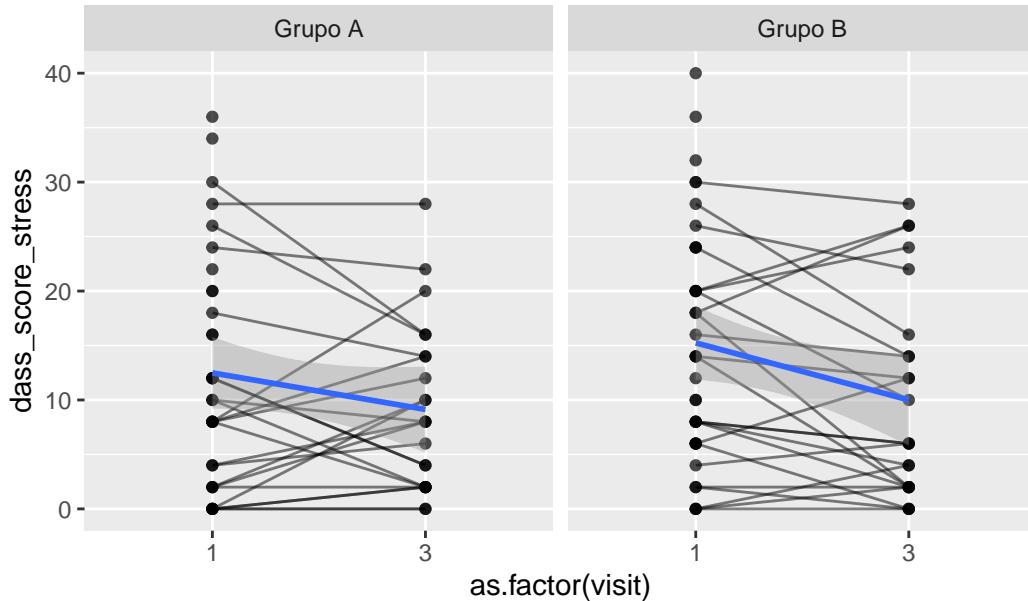
```

ggplot(
  aes(
    x = as.factor(visit),
    y = dass_score_stress,
    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



4.0.9 ECAP

Variável: `ecap_score`

```
# Plot 1: Raw data
ecap_score_hist_1 <- data_model_V1V3 %>%
  #filter(
  #  ecap_score < 300
  #) %>%
  ggplot(aes(x = ecap_score)) +
  geom_histogram(bins = 50, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
ecap_score_hist_2 <- data_model_V1V3 %>%
  #filter(
  #  ecap_score < 300
  #) %>%
  ggplot(aes(x = log1p(ecap_score))) +
```

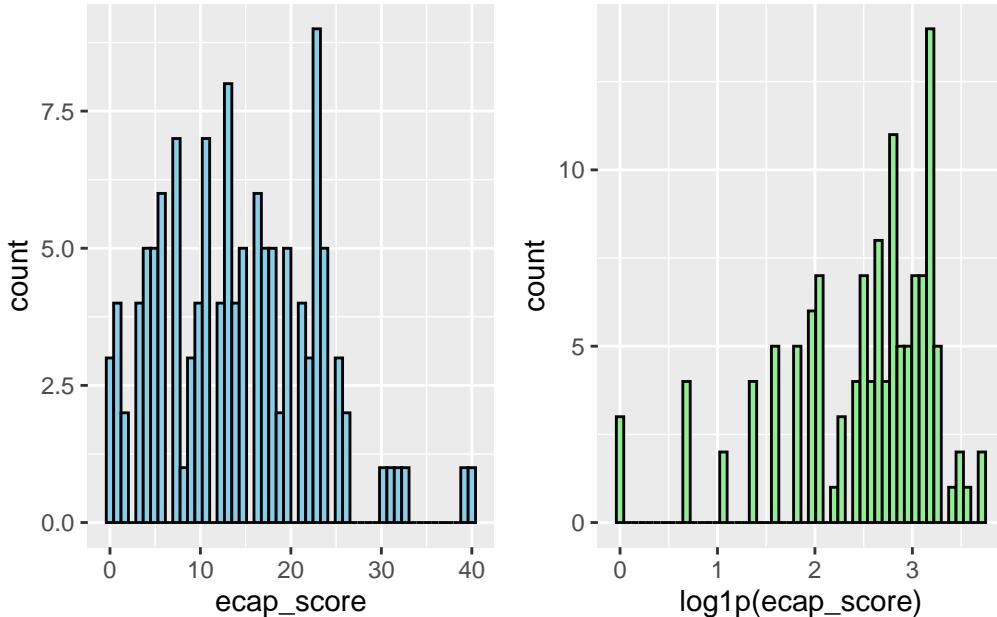
```

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

# Combine side by side
ecap_score_hist_1 + ecap_score_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
ecap_score_model <- lmer(ecap_score ~ allocation_group * visit +
(1 | record_id), data = data_model_V1V3)
check_collinearity(ecap_score_model)

# Check for Multicollinearity

```

Low Correlation

	Term	VIF	VIF 95% CI	Increased SE	Tolerance
	allocation_group	1.10	[1.01, 1.74]	1.05	0.91
	visit	1.93	[1.56, 2.55]	1.39	0.52

```

allocation_group:visit 2.02 [1.63, 2.67]           1.42      0.49
Tolerance 95% CI
[0.58, 0.99]
[0.39, 0.64]
[0.37, 0.62]

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

# LMM Sensitivity
ecap_score_model_sens <- update(object = ecap_score_model,
                                    subset = !(record_id %in%
                                               ecap_score_model_check$influential_ids))
# Influential IDS
ecap_score_model_check$influential_ids
[1] "5"  "17" "27" "75" "32"

```

4.0.9.1 Resumo dos modelos

```

# Model comparison
summary(ecap_score_model)

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

Formula: ecap_score ~ allocation_group * visit + (1 | record_id)
Data: data_model_V1V3

REML criterion at convergence: 835.7

```

Scaled residuals:

Min	1Q	Median	3Q	Max
-2.13439	-0.37025	0.02934	0.38576	2.28808

Random effects:

Groups	Name	Variance	Std.Dev.
record_id	(Intercept)	49.51	7.037
	Residual	16.21	4.026

Number of obs: 127, groups: record_id, 75

Fixed effects:

	Estimate	Std. Error	df	t value	Pr(> t)
(Intercept)	17.703	1.333	86.599	13.283	< 2e-16 ***
allocation_group	-2.834	1.872	86.599	-1.514	0.134
visit3	-4.804	1.077	53.296	-4.460	4.27e-05 ***
allocation_group:visit3	1.516	1.550	53.783	0.978	0.332

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	-0.305	0.217
allctn_GB:3	0.212	-0.298
		-0.695

```
summary(ecap_score_model_sens)
```

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

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

Data: data_model_V1V3

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

REML criterion at convergence: 730.2

Scaled residuals:

Min	1Q	Median	3Q	Max
-1.98686	-0.33484	0.05521	0.40898	1.87592

Random effects:

Groups	Name	Variance	Std.Dev.
record_id	(Intercept)	48.405	6.957
	Residual	8.068	2.840

Number of obs: 117, groups: record_id, 70

Fixed effects:

	Estimate	Std. Error	df	t value	Pr(> t)	
(Intercept)	16.5625	1.3284	74.1376	12.468	< 2e-16 ***	
allocation_group	Grupo B	-1.6941	1.8030	74.1376	-0.940	0.350
visit3		-4.0284	0.8468	46.2841	-4.757	1.95e-05 ***
allocation_group	Grupo B:visit3	1.0129	1.1605	46.3772	0.873	0.387

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

Correlation of Fixed Effects:

(Intr)	all_GB	visit3
allctn_gr	GB	-0.737
visit3		-0.224 0.165
allctn_GB:3		0.164 -0.222 -0.730

```
ecap_score_model_check$comparison_table
```

```
# A tibble: 12 x 6
```

Model	term	estimate	std.error	statistic	p.value
<chr>	<chr>	<dbl>	<dbl>	<dbl>	<dbl>
1 Original	(Intercept)	17.7	1.33	13.3	1.33e-22
2 Sensitivity	(Intercept)	16.6	1.33	12.5	7.09e-20
3 Original	allocation_groupGrupo B	-2.83	1.87	-1.51	1.34e- 1
4 Sensitivity	allocation_groupGrupo B	-1.69	1.80	-0.940	3.50e- 1
5 Original	allocation_groupGrupo B:v~	1.52	1.55	0.978	3.32e- 1
6 Sensitivity	allocation_groupGrupo B:v~	1.01	1.16	0.873	3.87e- 1
7 Original	sd__(Intercept)	7.04	NA	NA	NA
8 Sensitivity	sd__(Intercept)	6.96	NA	NA	NA
9 Original	sd__Observation	4.03	NA	NA	NA
10 Sensitivity	sd__Observation	2.84	NA	NA	NA
11 Original	visit3	-4.80	1.08	-4.46	4.27e- 5
12 Sensitivity	visit3	-4.03	0.847	-4.76	1.95e- 5

```
performance::compare_performance(  
  ecap_score_model,  
  ecap_score_model_sens)
```

When comparing models, please note that probably not all models were fit

from same data.

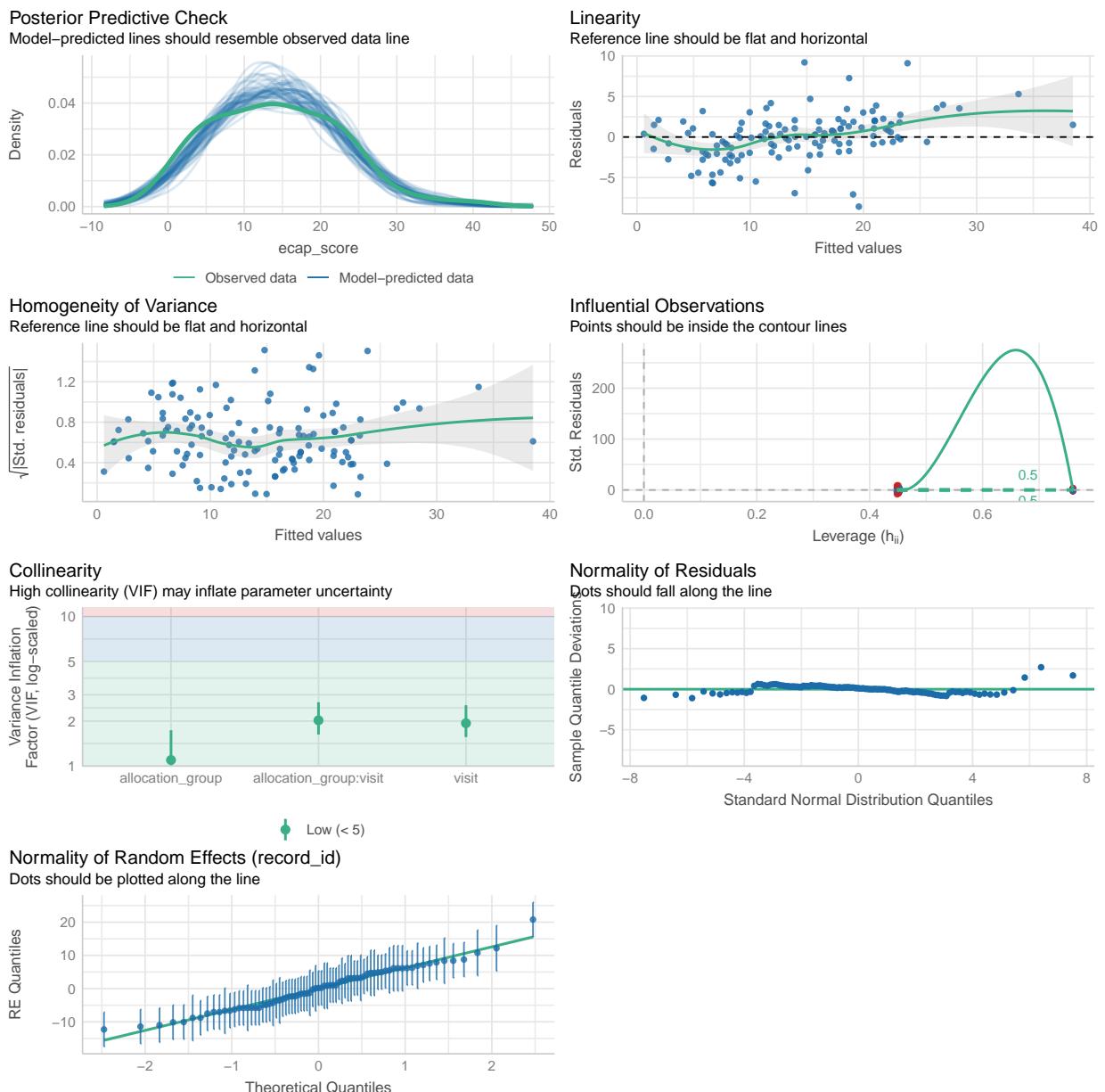
```
# Comparison of Model Performance Indices
```

Name		Model	AIC (weights)	AICc (weights)
<hr/>				
ecap_score_model		lmerModLmerTest	856.3 (<.001)	857.0 (<.001)
ecap_score_model_sens		lmerModLmerTest	749.5 (>.999)	750.3 (>.999)

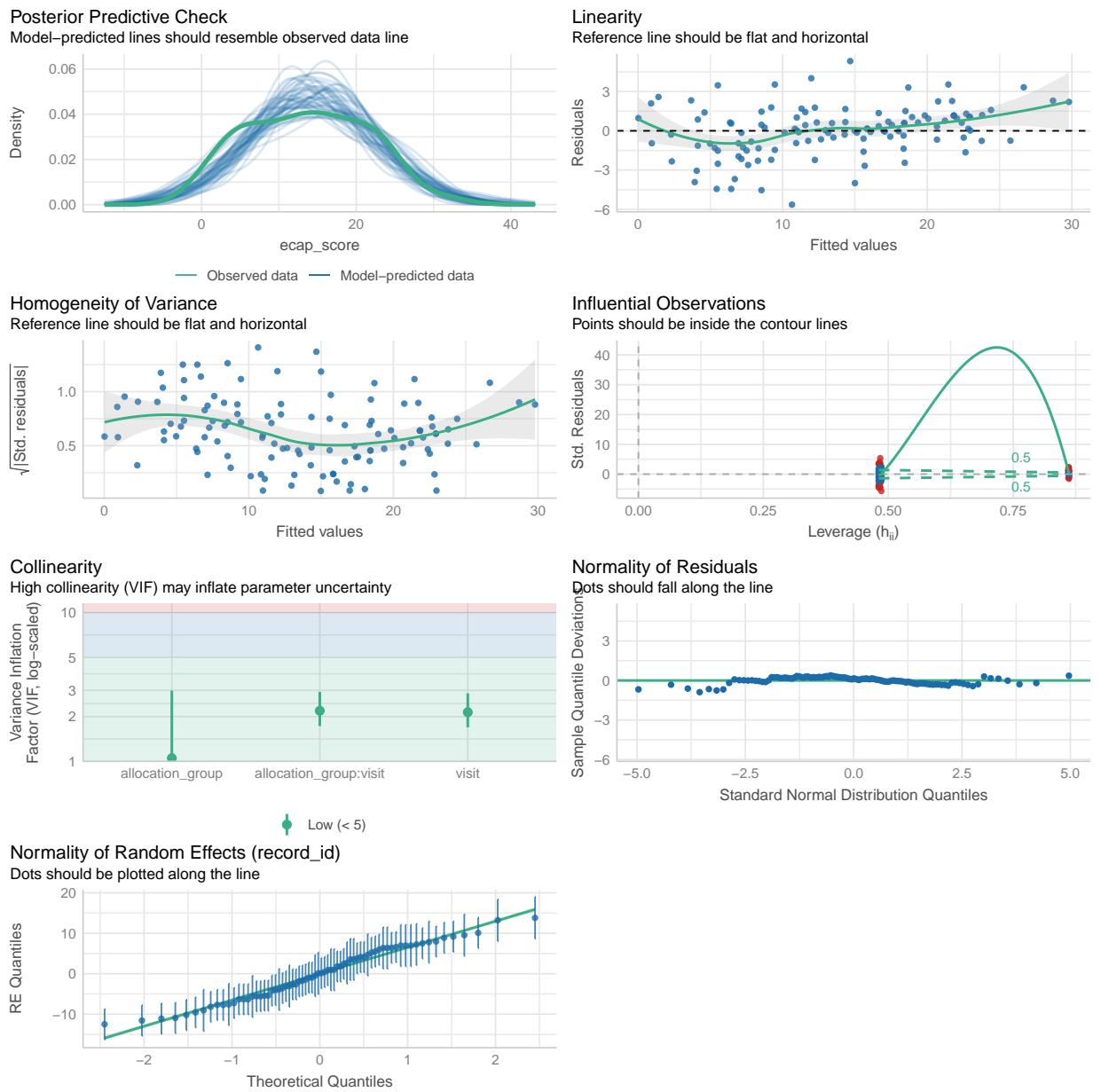
Name	BIC (weights)	R2 (cond.)	R2 (marg.)	ICC	RMSE	Sigma
------	---------------	------------	------------	-----	------	-------

ecap_score_model	873.4 (<.001)	0.772	0.074 0.753 2.829 4.02
ecap_score_model_sens	766.1 (>.999)	0.865	0.057 0.857 1.889 2.84

```
performance::check_model(ecap_score_model)
```



```
performance::check_model(ecap_score_model_sens)
```



4.0.9.2 Médias Marginais Estimadas

4.0.9.2.1 Todos os dados

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

```

)

ecap_score_raw_emm <- regrid(ecap_score_raw_emm)

# Table of marginal means
# ecap_score_raw_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(ecap_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     2.83 1.87  86.8   -0.887     6.56    1.514  0.1337

visit = 3:
  contrast      estimate    SE    df lower.CL upper.CL t.ratio p.value
  Grupo A - Grupo B     1.32 2.05 104.1   -2.741     5.38    0.644  0.5210

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(ecap_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 - visit3     4.80 1.08  86.8      2.66     6.95    4.451  <.0001

```

```

allocation_group = Grupo B:

contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit3     3.29 1.12 86.8      1.07      5.51    2.943  0.0042

```

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

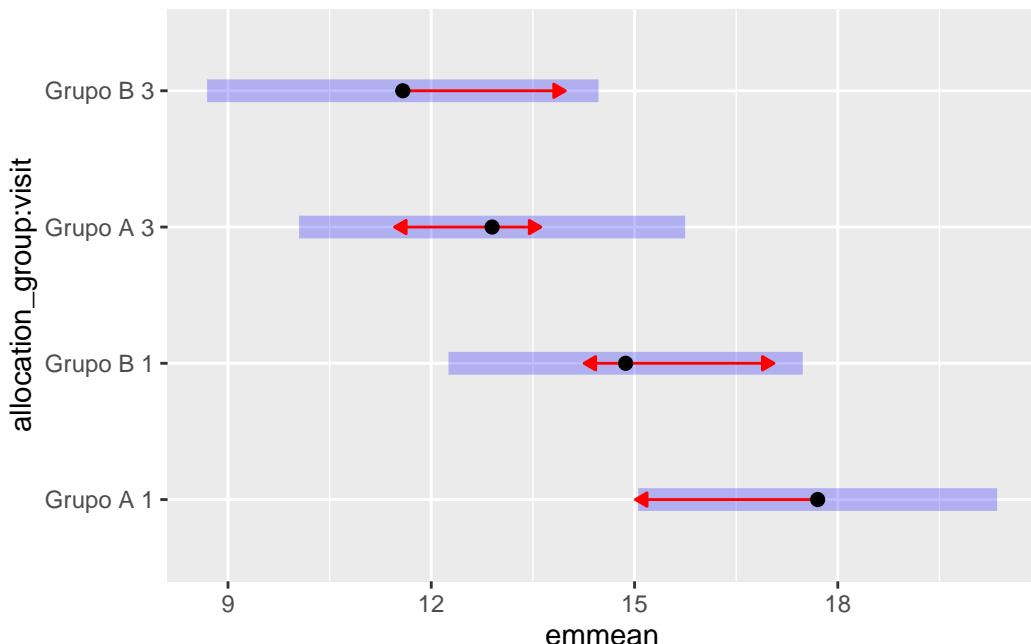
Confidence level used: 0.95

```
# Plot of marginal means
```

```
plot(ecap_score_raw_emm, comparisons = TRUE)
```

Warning: Comparison discrepancy in group "1", Grupo B visit1 - Grupo A visit3:

Target overlap = 0.6139, overlap on graph = -0.4769



4.0.9.2.2 Análise de sensibilidade

```

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

```

```

ecap_score_emm <- regrid(ecap_score_emm)

# Table of marginal means
# ecap_score_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(ecap_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     1.694 1.80 74.9     -1.90      5.29    0.940  0.3505

visit = 3:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
  Grupo A - Grupo B     0.681 1.92 88.9     -3.13      4.49    0.355  0.7231

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(ecap_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 - visit3     4.03 0.848 74.9      2.34      5.72    4.750  <.0001

allocation_group = Grupo B:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value

```

```
visit1 - visit3      3.02 0.795 74.9      1.43      4.60    3.794  0.0003
```

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

Confidence level used: 0.95

```
# Plot of marginal means
```

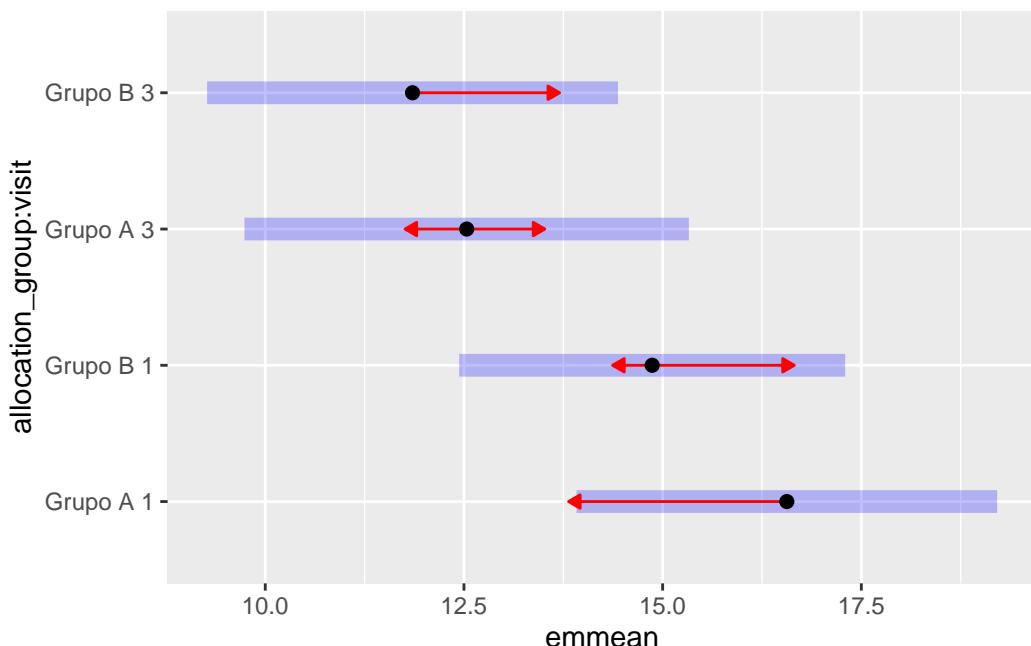
```
plot(ecap_score_emm, comparisons = TRUE)
```

Warning: Comparison discrepancy in group "1", Grupo A visit1 - Grupo B visit3:

Target overlap = 0.0362, overlap on graph = -0.0243

Warning: Comparison discrepancy in group "1", Grupo B visit1 - Grupo A visit3:

Target overlap = 0.5228, overlap on graph = -0.5748



```
ggplot(  
  data = data_model_V1V3,  
  aes(  
    x = as.factor(visit),  
    y = ecap_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'

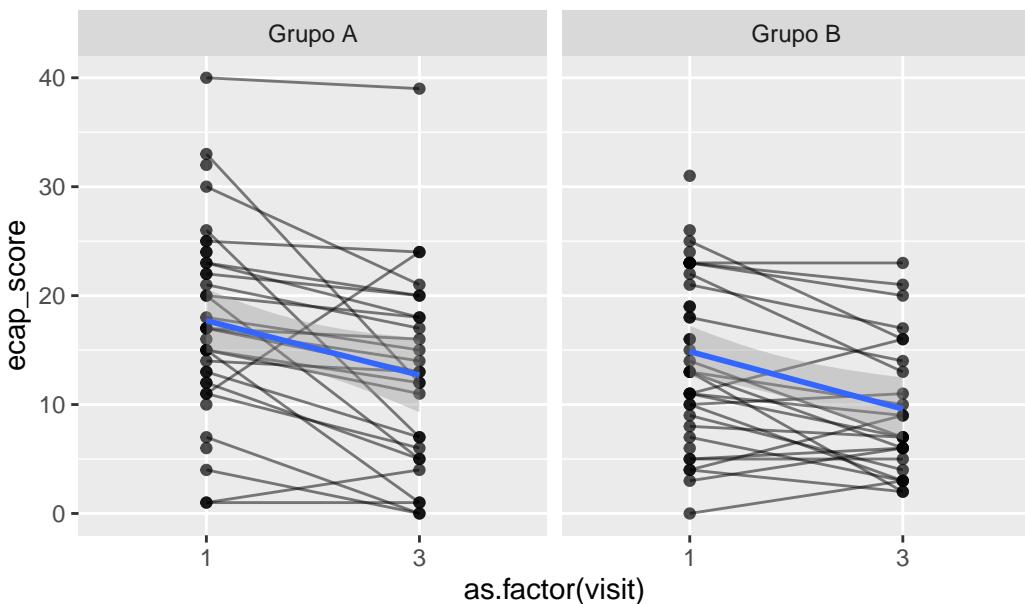
Warning: Removed 1 row containing non-finite outside the scale range
(`stat_smooth()`).

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%
      ecap_score_model_check$influential_ids)
  ) %>%
  ggplot(
    aes(
      x = as.factor(visit),
      y = ecap_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)

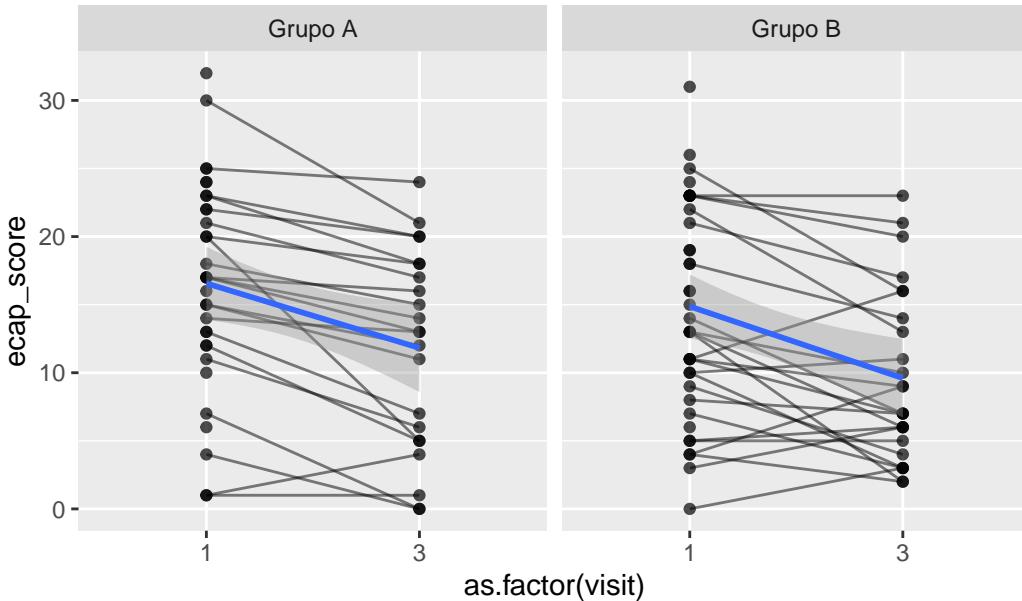
`geom_smooth()` using formula = 'y ~ x'
Warning: Removed 1 row containing non-finite outside the scale range
(`stat_smooth()`).

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

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  emmeans_1.11.1
[4] patchwork_1.3.0      gt_1.0.0          performance_0.13.0
[7] skimr_2.1.5         lmerTest_3.1-3    lme4_1.1-37
[10] Matrix_1.7-0       here_1.0.1        readxl_1.4.3
[13] lubridate_1.9.4    forcats_1.0.0      stringr_1.5.1
[16] dplyr_1.1.4.9000   purrr_1.0.4       readr_2.1.5
[19] tidyverse_1.3.1     tibble_3.2.1      ggplot2_3.5.1
[22] tidyverse_2.0.0
```

loaded via a namespace (and not attached):

```
[1] tidyselect_1.2.1    farver_2.1.2      fastmap_1.2.0
[4] TH.data_1.1-3      bayestestR_0.15.3   digest_0.6.37
[7] timechange_0.3.0   estimability_1.5.1  lifecycle_1.0.4
[10] survival_3.7-0    magrittr_2.0.3     compiler_4.4.1
[13] rlang_1.1.6       tools_4.4.1       utf8_1.2.4
[16] yaml_2.3.10       knitr_1.50       labeling_0.4.3
[19] xml2_1.3.8        repr_1.1.7       multcomp_1.4-28
[22] withr_3.0.2       numDeriv_2016.8-1.1 datawizard_1.1.0
[25] grid_4.4.1         xtable_1.8-4      colorspace_2.1-1
[28] future_1.34.0     globals_0.16.3    scales_1.3.0
[31] MASS_7.3-61        insight_1.2.0    cli_3.6.5
[34] mvtnorm_1.3-3     rmarkdown_2.29    reformulas_0.4.1
[37] generics_0.1.3     rstudioapi_0.17.1  tzdb_0.4.0
[40] minqa_1.2.8       splines_4.4.1     parallel_4.4.1
[43] cellranger_1.1.0   base64enc_0.1-3   vctrs_0.6.5
[46] boot_1.3-31       sandwich_3.1-1   jsonlite_2.0.0
```

```
[49] hms_1.1.3           pbkrtest_0.5.4      ggrepel_0.9.6
[52] listenv_0.9.1       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] pillar_1.10.2       furrr_0.3.1       htmltools_0.5.8.1
[64] R6_2.6.1            Rdpack_2.6.4      rprojroot_2.0.4
[67] evaluate_1.0.3       lattice_0.22-6    rbibutils_2.3
[70] backports_1.5.0     broom_1.0.7       Rcpp_1.0.14
[73] coda_0.19-4.1       nlme_3.1-166     mgcv_1.9-1
[76] xfun_0.52           zoo_1.8-14       pkgconfig_2.0.3
```