

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

3.1 Aspartato Aminotransferase

Variável: labs_ast

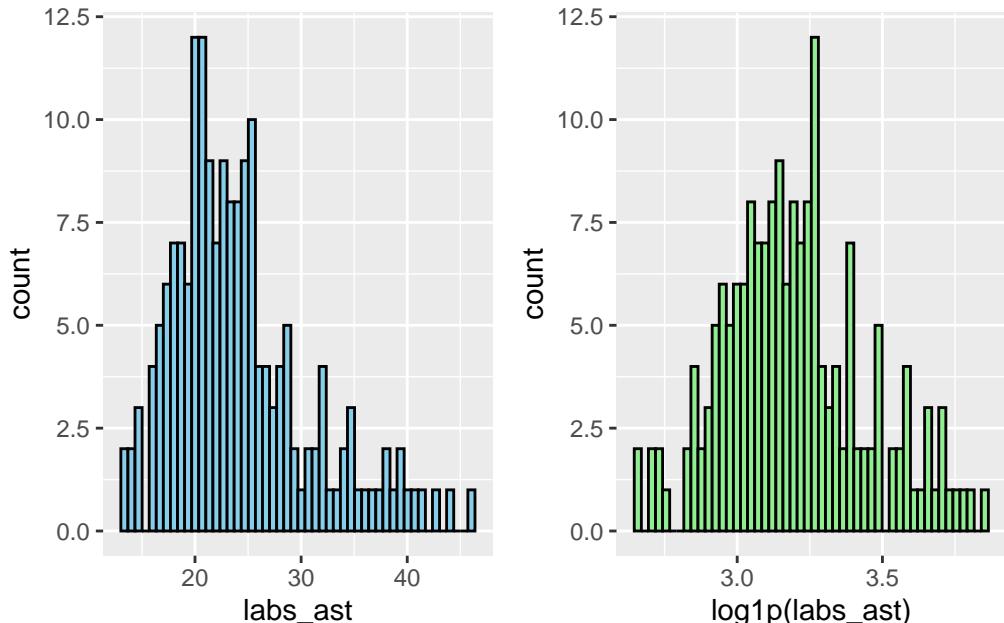
```
# Plot 1: Raw data
labs_ast_hist_1 <- data_model %>%
  filter(
    labs_ast < 300
  ) %>%
  ggplot(aes(x = labs_ast)) +
  geom_histogram(bins = 50, fill = "skyblue", color = "black")
```

```
# Plot 2: Log-transformed data
```

```
labs_ast_hist_2 <- data_model %>%
  filter(
    labs_ast < 300
  ) %>%
  ggplot(aes(x = log1p(labs_ast))) +
  geom_histogram(bins = 50, fill = "lightgreen", color = "black")
```

```
# Combine side by side
```

```
labs_ast_hist_1 + labs_ast_hist_2 # library(patchwork)
```



```
# LMM
```

```
labs_ast_model <- lmer(log1p(labs_ast) ~ allocation_group * visit +
```

```
(1 | record_id), data = data_model)
check_collinearity(labs_ast_model)

# Check for Multicollinearity
```

Low Correlation

| Term | VIF | VIF 95% CI | Increased SE | Tolerance |
|------------------------|------|--------------|--------------|-----------|
| allocation_group | 1.39 | [1.21, 1.74] | 1.18 | 0.72 |
| visit | 3.53 | [2.81, 4.54] | 1.88 | 0.28 |
| allocation_group:visit | 4.18 | [3.30, 5.39] | 2.04 | 0.24 |

Tolerance 95% CI

- [0.57, 0.83]
- [0.22, 0.36]
- [0.19, 0.30]

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

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

# Influential IDS
labs_ast_model_check$influential_ids
```

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

3.1.1 Resumo dos modelos

```
# Model comparison
summary(labs_ast_model)

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

REML criterion at convergence: 5.8

Scaled residuals:

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

Random effects:

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

Number of obs: 179, groups: record_id, 75

Fixed effects:

| | Estimate | Std. Error | df | t value |
|--------------------------------|------------|------------|------------|---------|
| (Intercept) | 3.211717 | 0.041563 | 126.794430 | 77.273 |
| allocation_groupGrupo B | -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_groupGrupo B:visit2 | -0.015833 | 0.066802 | 109.278386 | -0.237 |
| allocation_groupGrupo B:visit3 | 0.025422 | 0.071565 | 111.735957 | 0.355 |
| | Pr(> t) | | | |
| (Intercept) | <2e-16 *** | | | |
| allocation_groupGrupo B | 0.724 | | | |
| visit2 | 0.854 | | | |
| visit3 | 0.851 | | | |
| allocation_groupGrupo B:visit2 | 0.813 | | | |
| allocation_groupGrupo B:visit3 | 0.723 | | | |
| --- | | | | |

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

Correlation of Fixed Effects:

| (Intr) | all_GB | visit2 | visit3 | a_GB:2 |
|-------------|--------|--------|--------|--------|
| allctn_grGB | -0.712 | | | |
| visit2 | -0.481 | 0.343 | | |
| visit3 | -0.446 | 0.317 | 0.442 | |
| allctn_GB:2 | 0.330 | -0.463 | -0.684 | -0.303 |
| allctn_GB:3 | 0.308 | -0.432 | -0.305 | -0.690 |
| | | | | 0.424 |

```
summary(labs_ast_model_sens)
```

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

REML criterion at convergence: -33.2

Scaled residuals:

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

Random effects:

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

Number of obs: 166, groups: record_id, 70

Fixed effects:

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

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

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

```

Correlation of Fixed Effects:

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

```

```

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

```

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

```

labs_ast_3performance

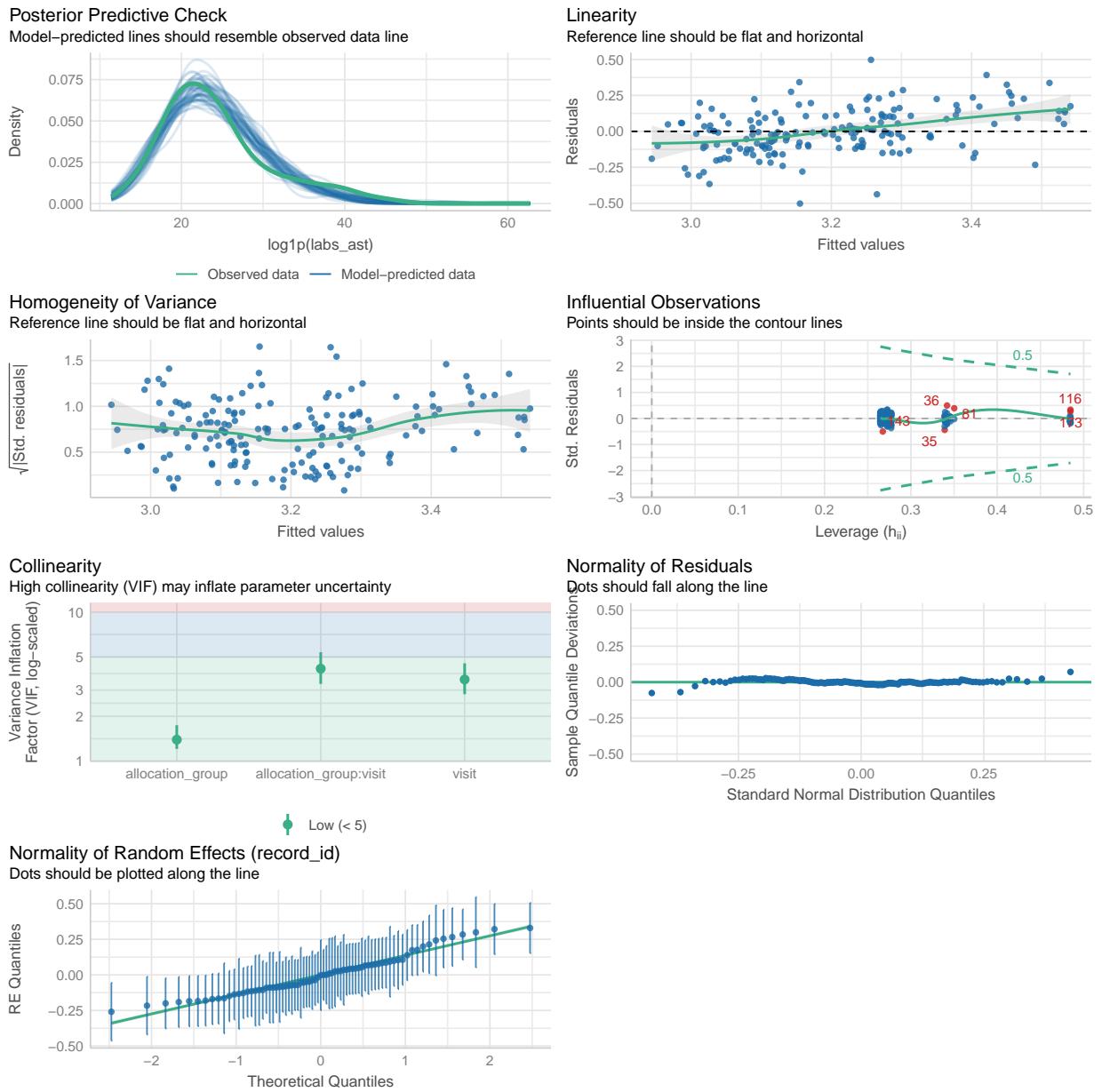
# Comparison of Model Performance Indices

```

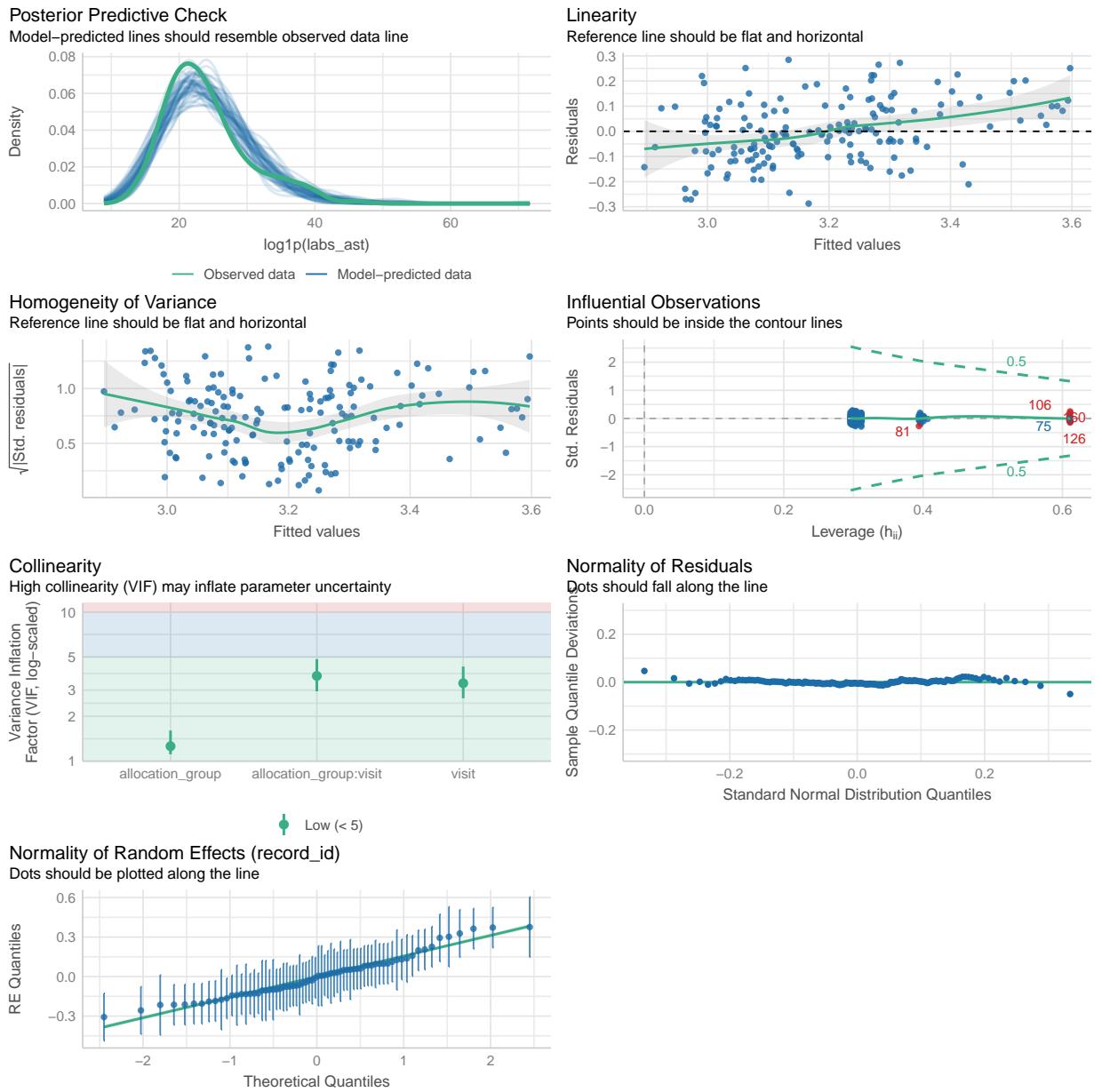
| Name | Model | AIC (weights) | AICc (weights) |
|---------------------|-----------------|----------------|----------------|
| labs_ast_model | lmerModLmerTest | 1139.5 (<.001) | 1140.3 (<.001) |
| labs_ast_model_sens | lmerModLmerTest | 1014.1 (>.999) | 1015.0 (>.999) |

| Name | BIC (weights) | R2 (cond.) | R2 (marg.) | ICC | RMSE | Sigma |
|---------------------|----------------|------------|------------|-------|-------|-------|
| labs_ast_model | 1165.0 (<.001) | 0.472 | 0.003 | 0.470 | 0.154 | 0.184 |
| labs_ast_model_sens | 1039.0 (>.999) | 0.605 | 0.013 | 0.600 | 0.122 | 0.150 |

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



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



3.1.2 Médias Marginais Estimadas

3.1.2.1 Todos os dados

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

labs_ast_raw_emm <- regrid(labs_ast_raw_emm)
```

```

# Table of marginal means
# labs_ast_raw_emm

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

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

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

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

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

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

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

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

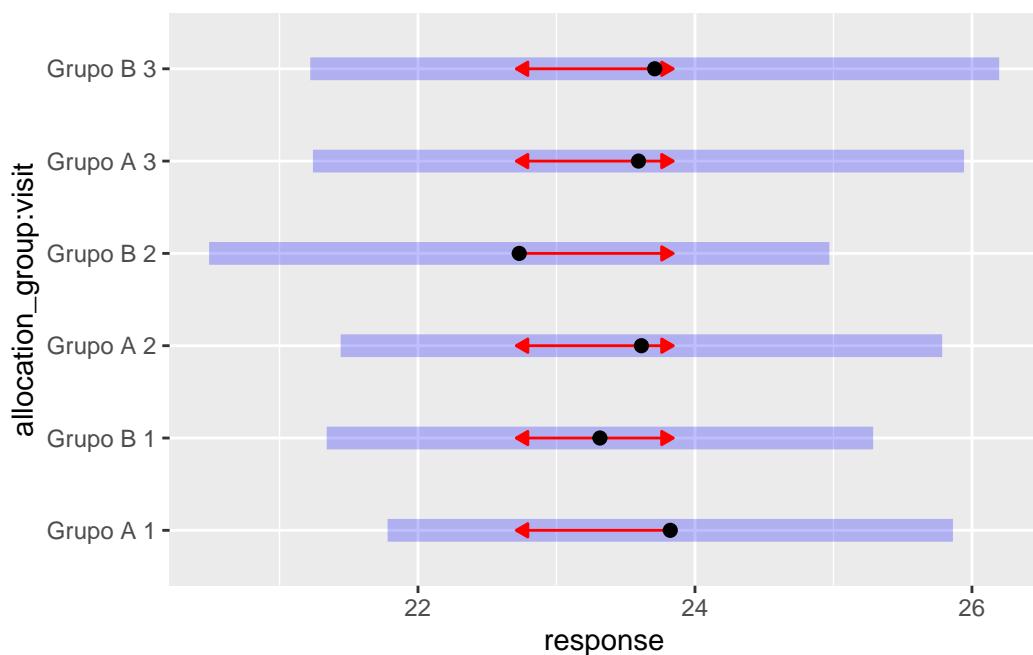
```

```

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests

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

```



3.1.2.2 Análise de sensibilidade

```

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

labs_ast_emm <- regrid(labs_ast_emm)

# Table of marginal means
# labs_ast_emm

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

```

```

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

```

```

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

```

```

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

```

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

```

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

```

```

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

```

```

allocation_group = Grupo B:
  contrast      estimate    SE  df lower.CL upper.CL t.ratio p.value
visit1 - visit2     0.920 0.983 104     -1.47      3.31   0.936  1.0000
visit1 - visit3    -0.807 1.130 104     -3.55      1.93  -0.716  1.0000
visit2 - visit3    -1.727 1.150 131     -4.51      1.06  -1.505  0.4043

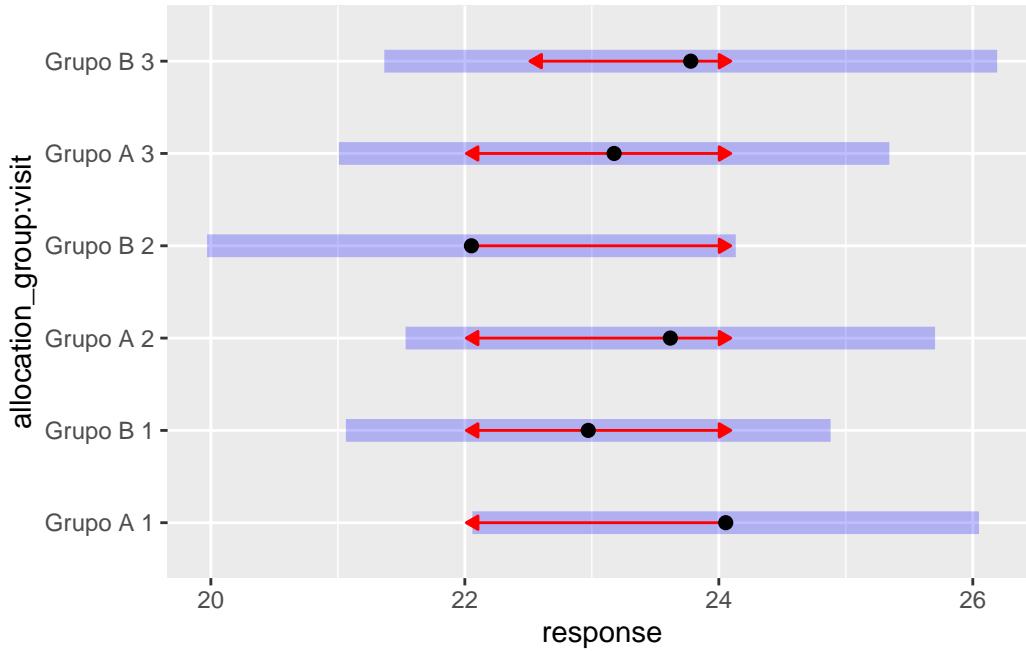
```

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
 Confidence level used: 0.95
 Conf-level adjustment: bonferroni method for 3 estimates
 P value adjustment: bonferroni method for 3 tests

```

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

```



3.1.3 Resultado

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

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

| Grupo de comparação | Comparação | Estimativa | IC 95% | p-valor |
|---------------------|---------------------|------------|----------------|---------|
| Entre grupos | Visita 1 | 0,51 | [-2,33 ; 3,35] | 0,724 |
| Entre grupos | Visita 2 | 0,88 | [-2,24 ; 4,00] | 0,577 |
| Entre grupos | Visita 3 | -0,12 | [-3,54 ; 3,31] | 0,946 |
| Grupo Placebo | Visita 1 - Visita 2 | 0,21 | [-2,53 ; 2,95] | 1,000 |
| Grupo Placebo | Visita 1 - Visita 3 | 0,23 | [-2,73 ; 3,19] | 1,000 |
| Grupo Placebo | Visita 2 - Visita 3 | 0,02 | [-2,98 ; 3,02] | 1,000 |
| Grupo Eclipta | Visita 1 - Visita 2 | 0,58 | [-2,25 ; 3,42] | 1,000 |
| Grupo Eclipta | Visita 1 - Visita 3 | -0,40 | [-3,49 ; 2,70] | 1,000 |
| Grupo Eclipta | Visita 2 - Visita 3 | -0,98 | [-4,20 ; 2,24] | 1,000 |

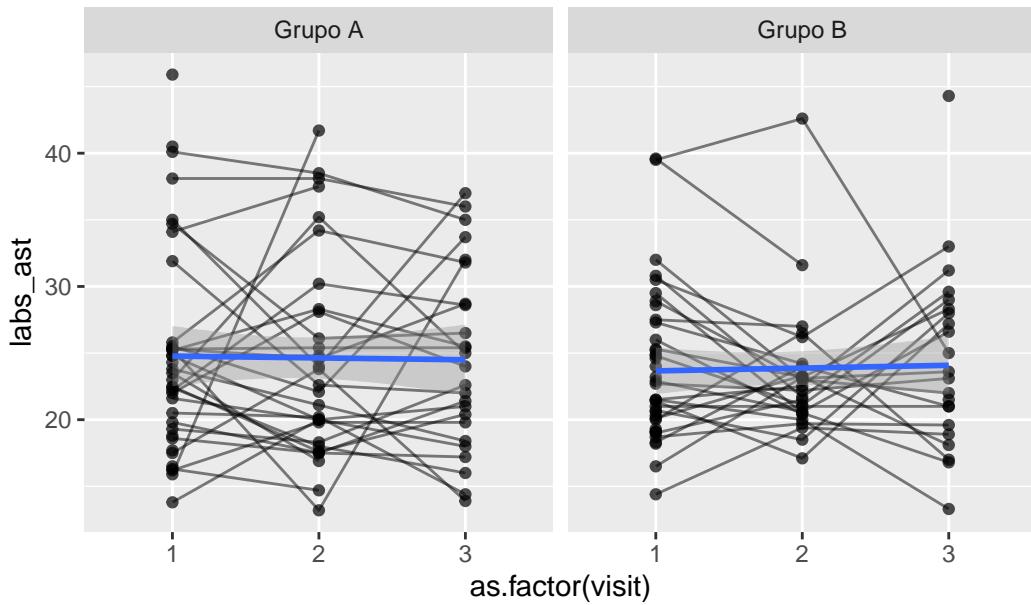
```

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

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

```

All data



```

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

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

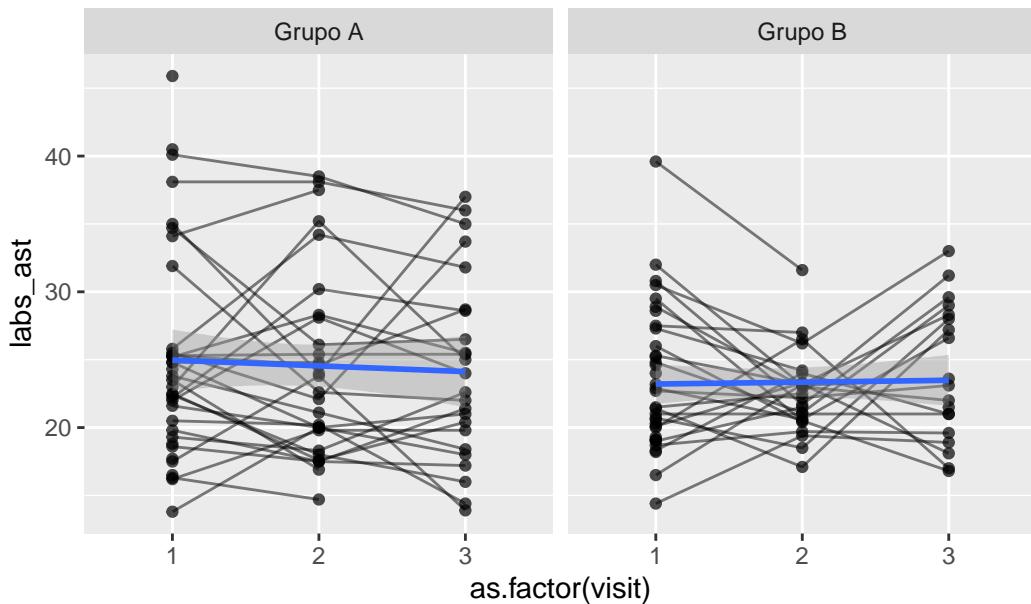
```

```

Warning: Removed 9 rows containing non-finite outside the scale range
(`stat_smooth()`).
Warning: Removed 8 rows containing missing values or values outside the scale range
(`geom_line()`).
Warning: Removed 9 rows containing missing values or values outside the scale range
(`geom_point()`).

```

Sensitivity analysis



3.2 Alanina Aminotransferase

```

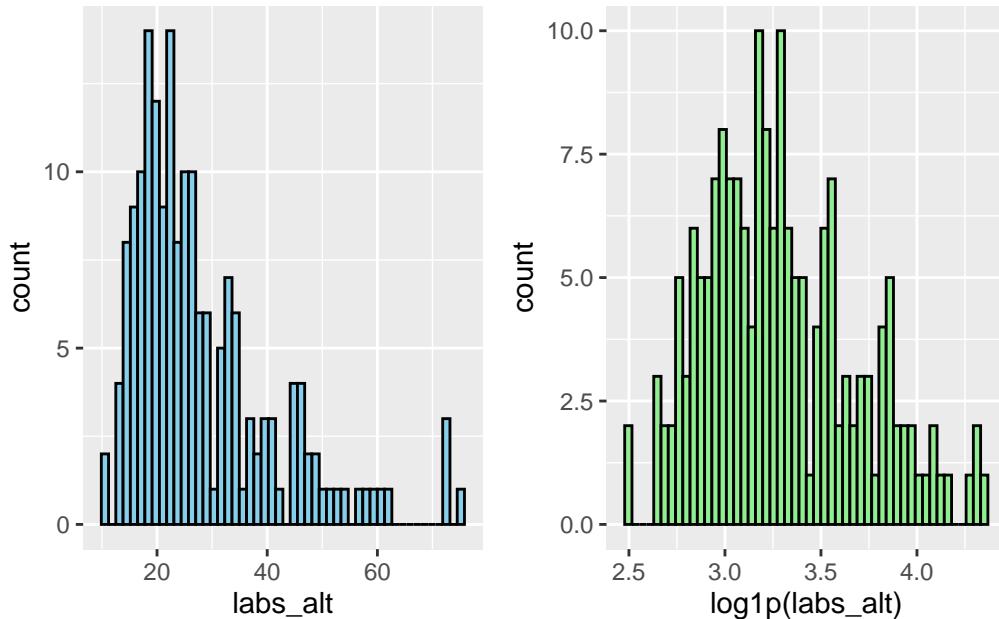
# Plot 1: Raw data
labs_alt_hist_1 <- data_model %>%
  #filter(
  #  labs_alt < 300
  #) %>%
  ggplot(aes(x = labs_alt)) +
  geom_histogram(bins = 50, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
labs_alt_hist_2 <- data_model %>%
  #filter(
  #  labs_alt < 300
  #) %>%
  ggplot(aes(x = log1p(labs_alt))) +
  geom_histogram(bins = 50, fill = "lightgreen", color = "black")

```

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

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



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

# Check for Multicollinearity
```

Low Correlation

| Term | VIF | VIF 95% CI | Increased SE | Tolerance |
|------------------------|--------------|--------------|--------------|-----------|
| allocation_group | 1.21 | [1.08, 1.54] | 1.10 | 0.83 |
| visit | 3.50 | [2.79, 4.49] | 1.87 | 0.29 |
| allocation_group:visit | 3.84 | [3.04, 4.94] | 1.96 | 0.26 |
| Tolerance 95% CI | | | | |
| | [0.65, 0.92] | | | |
| | [0.22, 0.36] | | | |
| | [0.20, 0.33] | | | |

```

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

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

# Influential IDS
labs_alt_model_check$influential_ids

[1] "33" "75" "5"  "58" "63"

```

3.2.1 Resumo dos modelos

```

# Model comparison
summary(labs_alt_model)

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

```

REML criterion at convergence: 132.2

Scaled residuals:

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

Random effects:

| Groups | Name | Variance | Std.Dev. |
|-----------|-------------|----------|----------|
| record_id | (Intercept) | 0.10863 | 0.3296 |
| | Residual | 0.05485 | 0.2342 |

Number of obs: 179, groups: record_id, 75

Fixed effects:

| | Estimate | Std. Error | df | t value | Pr(> t) |
|-------------|----------|------------|-----------|---------|----------|
| (Intercept) | 3.34045 | 0.06647 | 102.44387 | 50.254 | <2e-16 |

```

allocation_groupGrupo B      -0.10187   0.09338 102.44387 -1.091   0.278
visit2                      -0.07956   0.05867 103.85033 -1.356   0.178
visit3                      -0.03364   0.06353 105.34376 -0.529   0.598
allocation_groupGrupo B:visit2 0.06143   0.08602 105.75034  0.714   0.477
allocation_groupGrupo B:visit3 0.07920   0.09237 106.88087  0.857   0.393

```

```

(Intercept) ***

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

```

Correlation of Fixed Effects:

```

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

```

```
summary(labs_alt_model_sens)
```

```

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

```

REML criterion at convergence: 88.4

Scaled residuals:

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

Random effects:

| Groups | Name | Variance | Std.Dev. |
|--------|------|----------|----------|
|--------|------|----------|----------|

```

record_id (Intercept) 0.09385  0.3063
Residual                 0.04238  0.2059
Number of obs: 165, groups: record_id, 70

Fixed effects:

Estimate Std. Error      df t value Pr(>|t|)
(Intercept)          3.249918  0.064250 90.966334 50.582 <2e-16
allocation_group Grupo B -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 Grupo B:visit2 -0.009275  0.078377 94.689442 -0.118  0.906
allocation_group Grupo B:visit3  0.043535  0.085567 95.767451  0.509  0.612

```

```

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

```

Correlation of Fixed Effects:

```

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

```

```

performance::compare_performance(
  labs_alt_model,
  labs_alt_model_sens)

```

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

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

| Name | | Model | | AIC (weights) | | AICc (weights) |
|------|--|-------|--|---------------|--|----------------|
|------|--|-------|--|---------------|--|----------------|

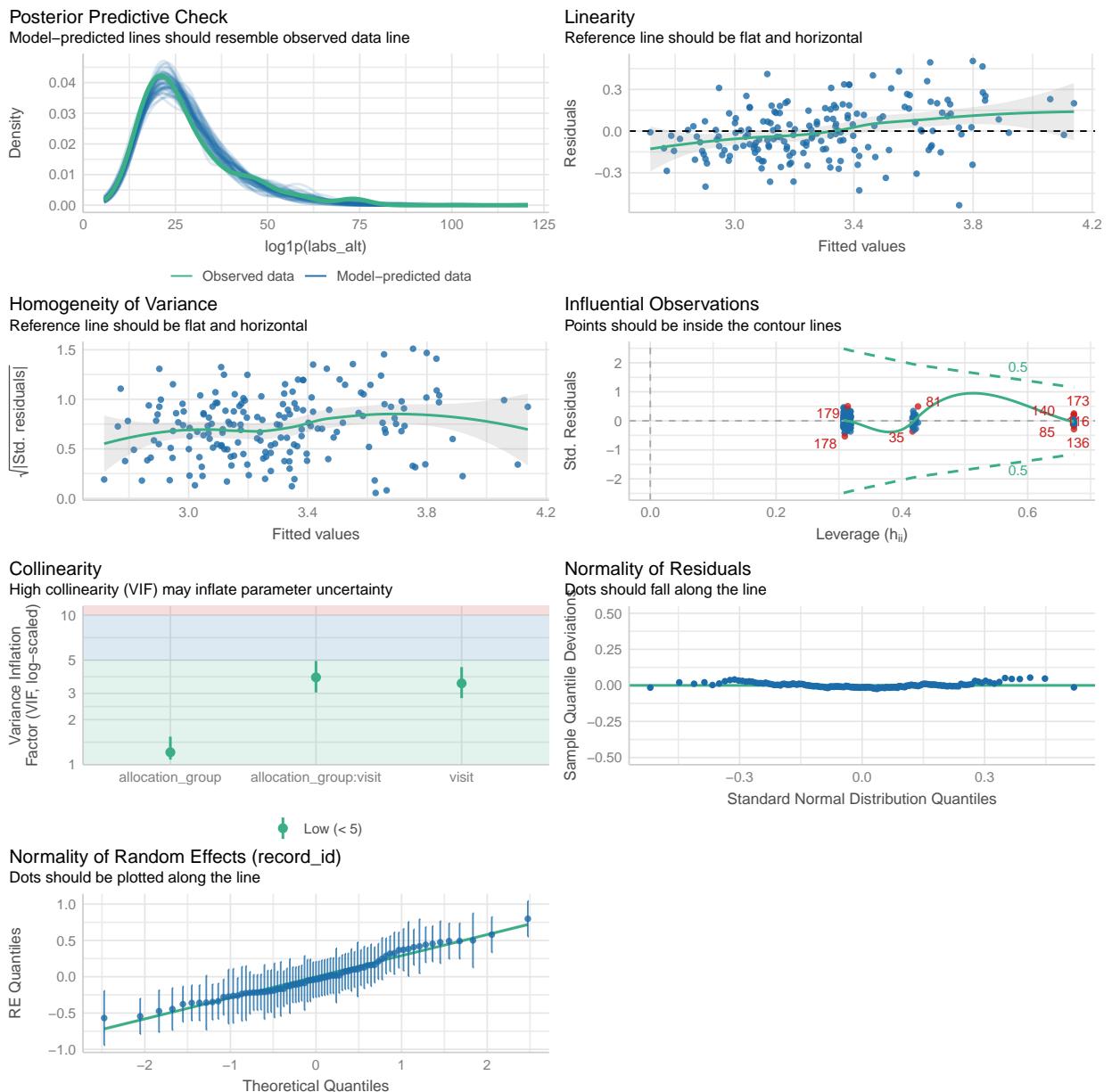
```

labs_alt_model      | lmerModLmerTest | 1302.9 (<.001) | 1303.8 (<.001)
labs_alt_model_sens | lmerModLmerTest | 1150.5 (>.999) | 1151.4 (>.999)

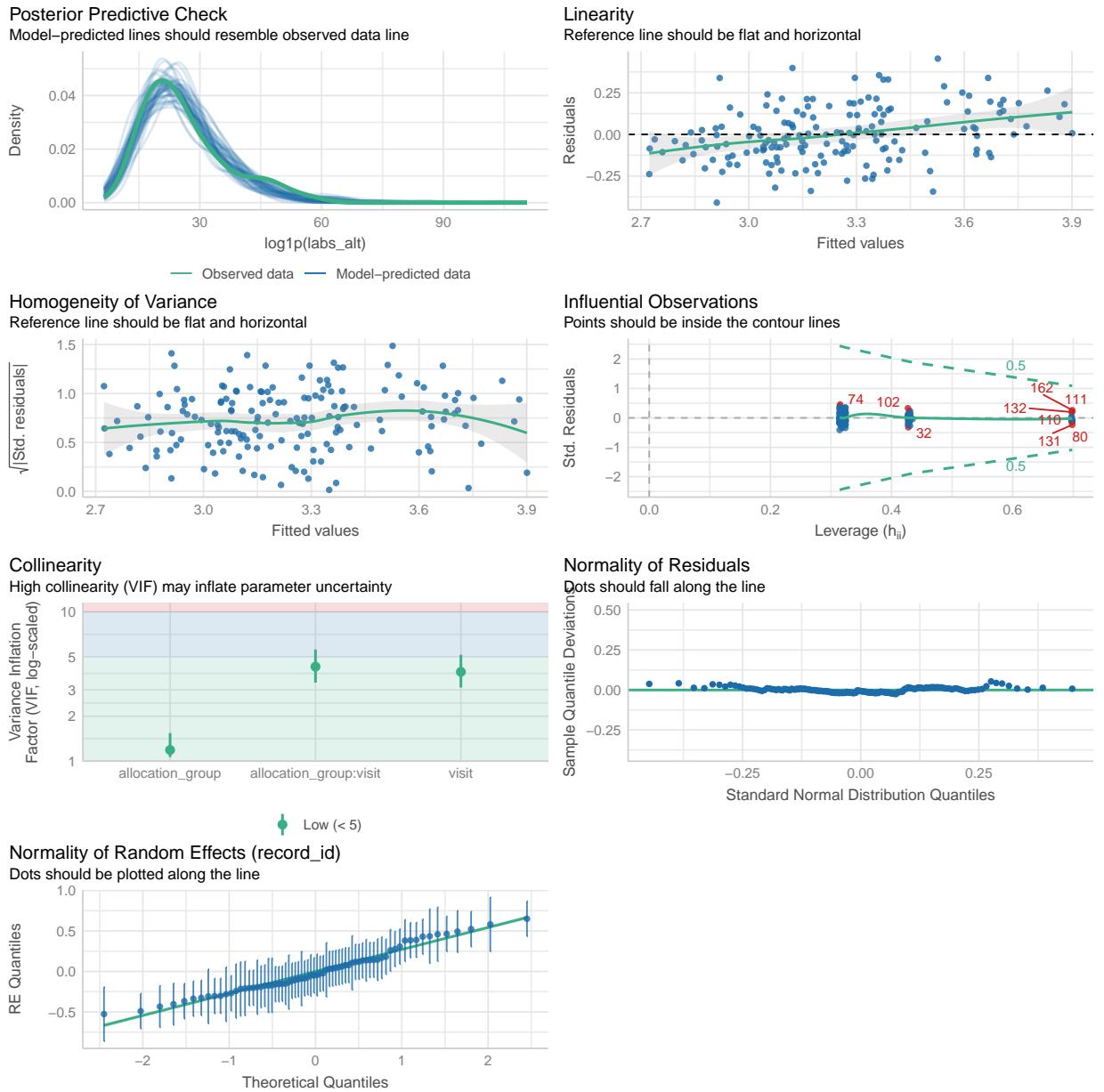
```

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

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



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



3.2.2 Médias Marginais Estimadas

3.2.2.1 Todos os dados

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

labs_alt_raw_emm <- regrid(labs_alt_raw_emm)
```

```

# Table of marginal means
# labs_alt_raw_emm

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

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

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

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

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

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

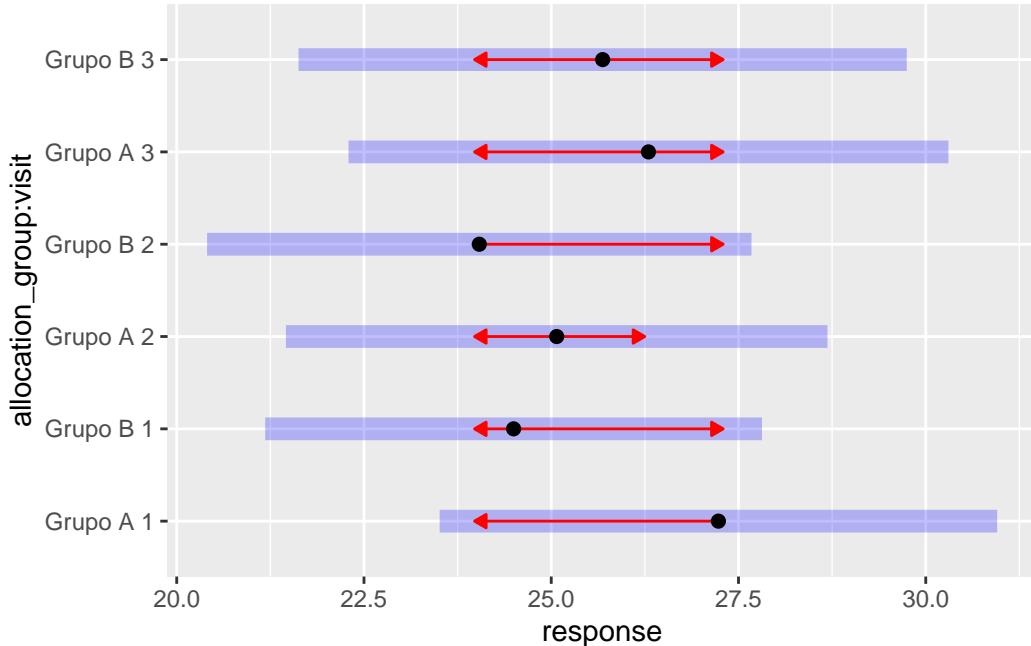
allocation_group = Grupo A:
  contrast      estimate   SE  df lower.CL upper.CL t.ratio p.value
  visit1 - visit2    2.159 1.59 104     -1.71     6.03    1.357  0.5332
  visit1 - visit3    0.934 1.76 104     -3.35     5.21    0.531  1.0000
  visit2 - visit3   -1.225 1.72 118     -5.41     2.96   -0.711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

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

```

```
Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests
```

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



3.2.2.2 Análise de sensibilidade

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

labs_alt_emm <- regrid(labs_alt_emm)

# Table of marginal means
# labs_alt_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(labs_alt_emm,
  method = "pairwise", by = "visit",
```

```

adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

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

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

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

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

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

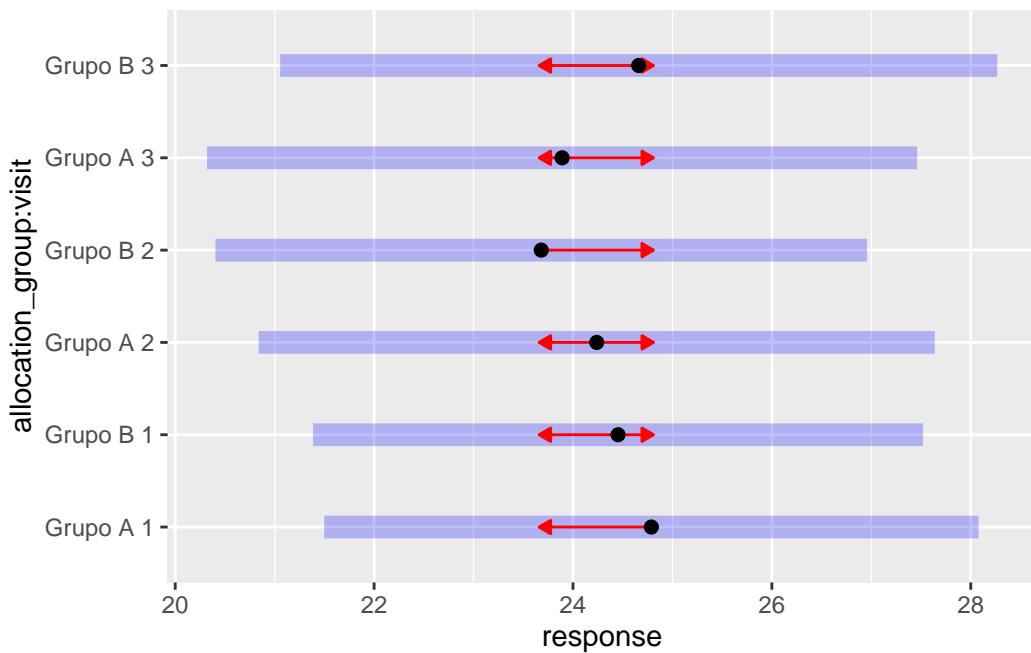
allocation_group = Grupo A:
contrast      estimate    SE    df lower.CL upper.CL t.ratio p.value
visit1 - visit2    0.549 1.41  93.7     -2.88      3.98   0.390  1.0000
visit1 - visit3    0.897 1.53  93.7     -2.84      4.63   0.586  1.0000
visit2 - visit3    0.348 1.54 107.7     -3.39      4.09   0.226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



3.2.3 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 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 de comparação | Comparação | Estimativa | IC 95% | p-valor |
|---------------------|---------------------|------------|----------------|---------|
| Grupo Eclipta | Visita 2 - Visita 3 | -1,65 | [-6,07 ; 2,78] | 1,000 |

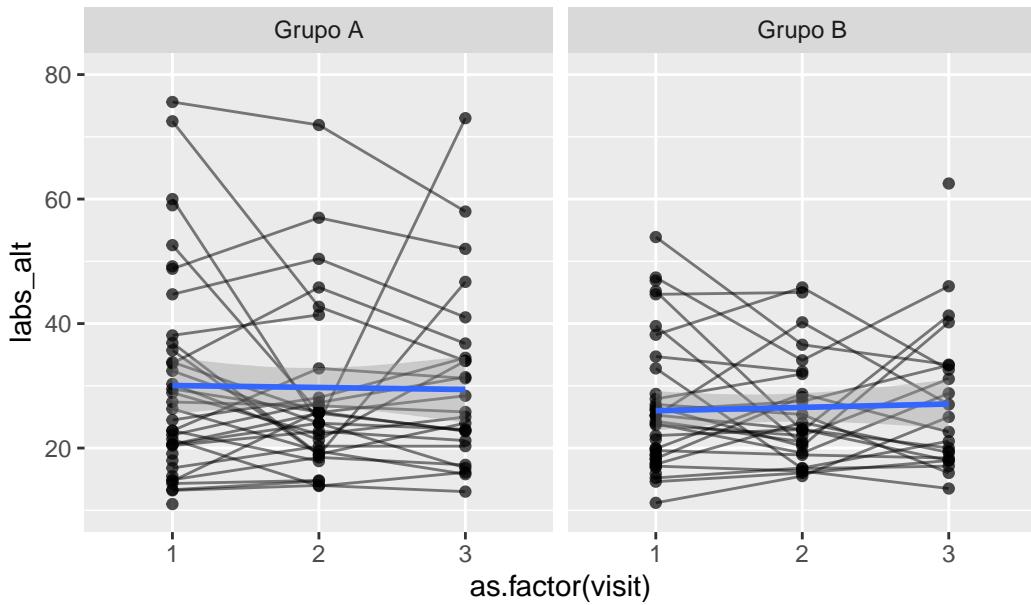
```

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

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

```

All data



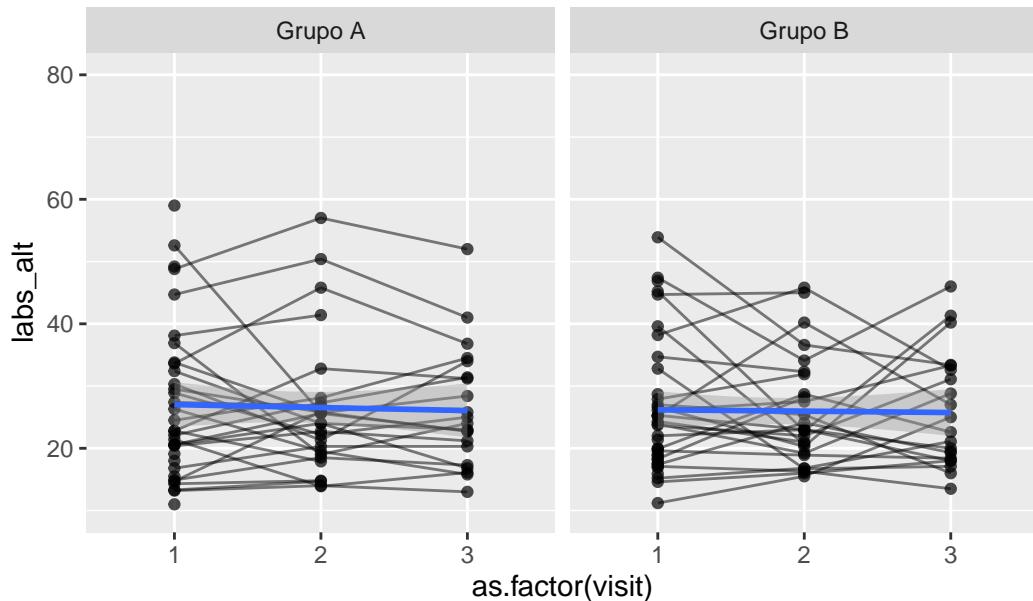
```
data_model %>%
  filter(
    !(record_id %in%
      labs_alt_model_check$influential_ids)
  ) %>%
  ggplot(
    aes(
      x = as.factor(visit),
      y = labs_alt,
      group = record_id,
    )
  ) +
  geom_line(alpha = 0.5) +
  geom_point(alpha = 0.7) +
  geom_smooth(
    aes(group = allocation_group),
    method = "lm",
    se = TRUE,
    linewidth = 1
  ) +
  labs(title = "Sensitivity analysis") +
  facet_wrap(~ allocation_group) +
  coord_cartesian(ylim = c(10, 80))
```

```

`geom_smooth()` using formula = 'y ~ x'
Warning: Removed 9 rows containing non-finite outside the scale range
(`stat_smooth()`).
Warning: Removed 8 rows containing missing values or values outside the scale range
(`geom_line()`).
Warning: Removed 9 rows containing missing values or values outside the scale range
(`geom_point()`).

```

Sensitivity analysis



3.3 Gama Glutamil-transferase

Variável: labs_ggt

```

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

# Plot 2: Log-transformed data
labs_ggt_hist_2 <- data_model %>%
  filter(
    labs_ggt < 300
  ) %>%

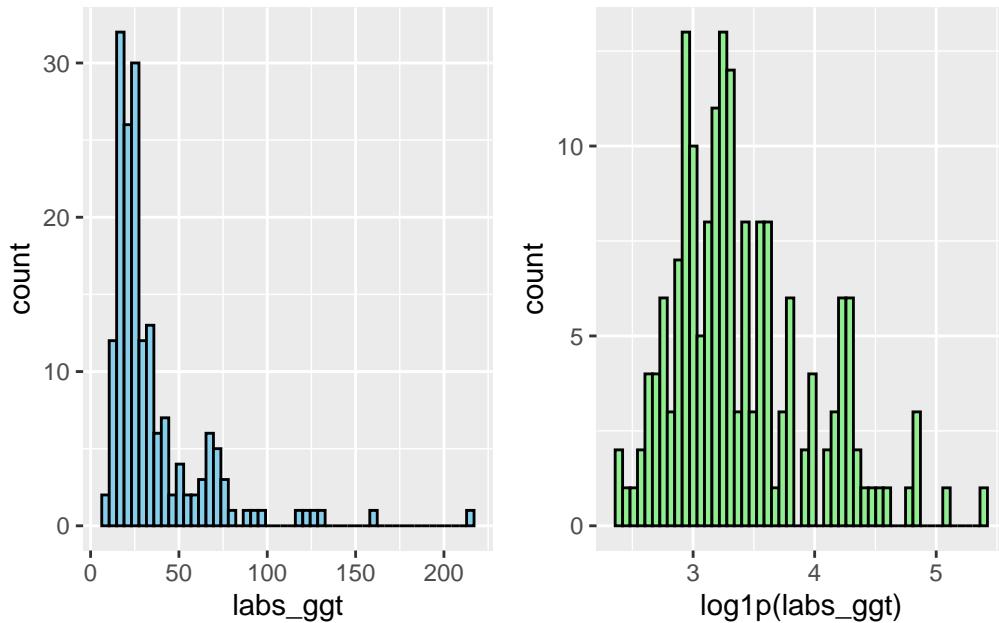
```

```

ggplot(aes(x = log1p(labs_ggt))) +
  geom_histogram(bins = 50, fill = "lightgreen", color = "black")

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

```



```

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

# Check for Multicollinearity

```

Low Correlation

| Term | VIF | VIF 95% CI | Increased SE | Tolerance |
|------------------------|--------------|--------------|--------------|-----------|
| allocation_group | 1.08 | [1.01, 1.64] | 1.04 | 0.93 |
| visit | 3.40 | [2.71, 4.36] | 1.84 | 0.29 |
| allocation_group:visit | 3.51 | [2.79, 4.51] | 1.87 | 0.28 |
| Tolerance 95% CI | | | | |
| | [0.61, 0.99] | | | |
| | [0.23, 0.37] | | | |
| | [0.22, 0.36] | | | |

```

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

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

# Influential IDS
labs_ggt_model_check$influential_ids

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

```

3.3.1 Resumo dos modelos

```

# Model comparison
summary(labs_ggt_model)

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

REML criterion at convergence: 214.3

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

Random effects:
Groups      Name        Variance Std.Dev.
record_id (Intercept) 0.35840  0.5987
Residual            0.05825  0.2413
Number of obs: 178, groups: record_id, 75

Fixed effects:
Estimate Std. Error      df t value Pr(>|t|) 
(Intercept)  3.36365   0.10612 81.55575 31.697 <2e-16

```

| | | | | | | |
|------------------|----------------|----------|---------|----------|--------|-------|
| allocation_group | Grupo B | 0.05279 | 0.14908 | 81.55575 | 0.354 | 0.724 |
| visit2 | | -0.02673 | 0.06095 | 98.79849 | -0.439 | 0.662 |
| visit3 | | 0.01219 | 0.06614 | 99.26017 | 0.184 | 0.854 |
| allocation_group | Grupo B:visit2 | 0.04689 | 0.08964 | 99.59537 | 0.523 | 0.602 |
| allocation_group | Grupo B:visit3 | 0.02698 | 0.09736 | 99.95801 | 0.277 | 0.782 |

(Intercept) ***
 allocation_group
 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 | -0.243 | 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_groupGrupo B 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_groupGrupo B:visit2 0.06129 0.07498 89.97944 0.817 0.416
allocation_groupGrupo B: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

```

```

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) |
|------|--|-------|---------------|----------------|
|------|--|-------|---------------|----------------|

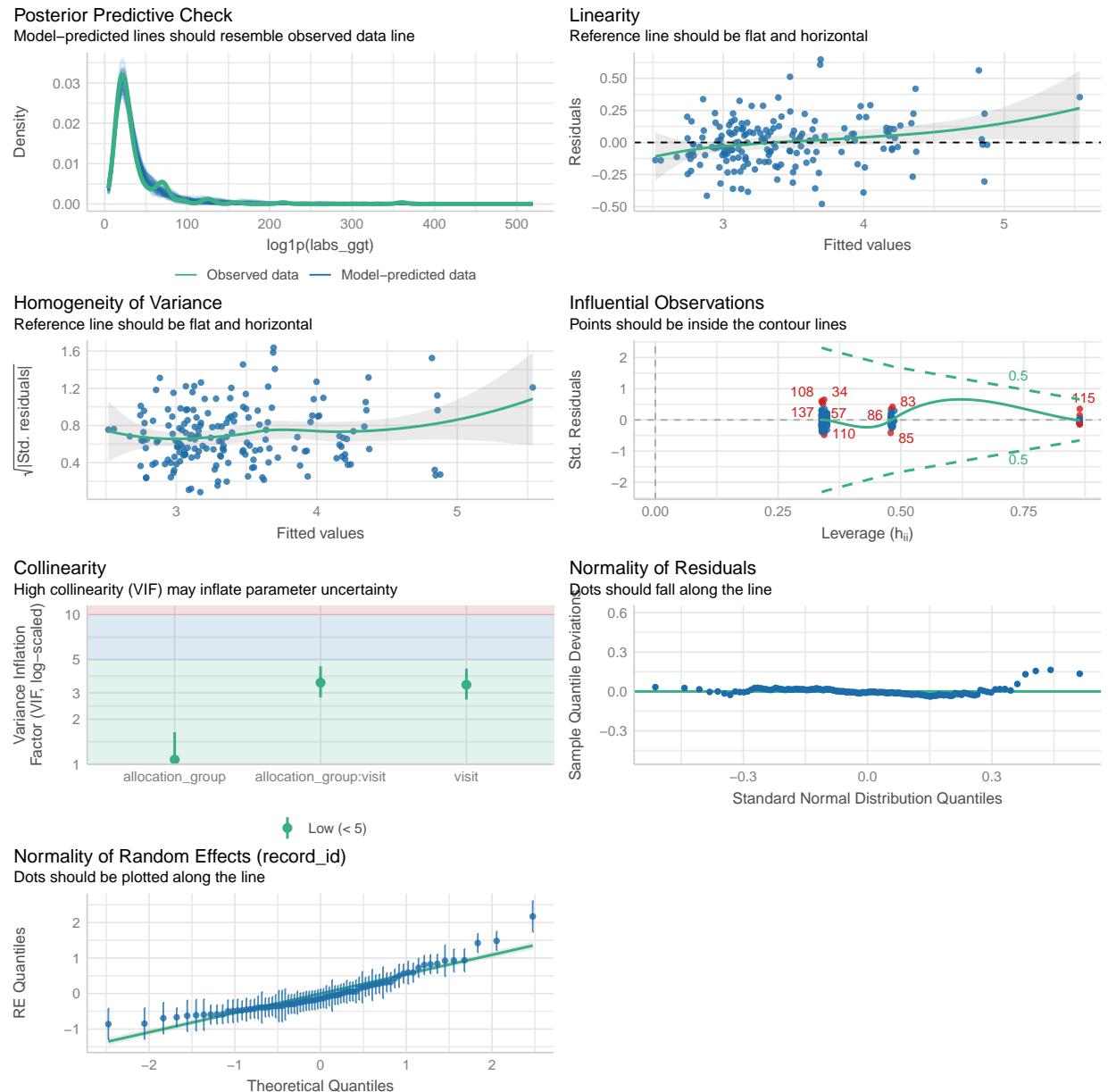
```

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

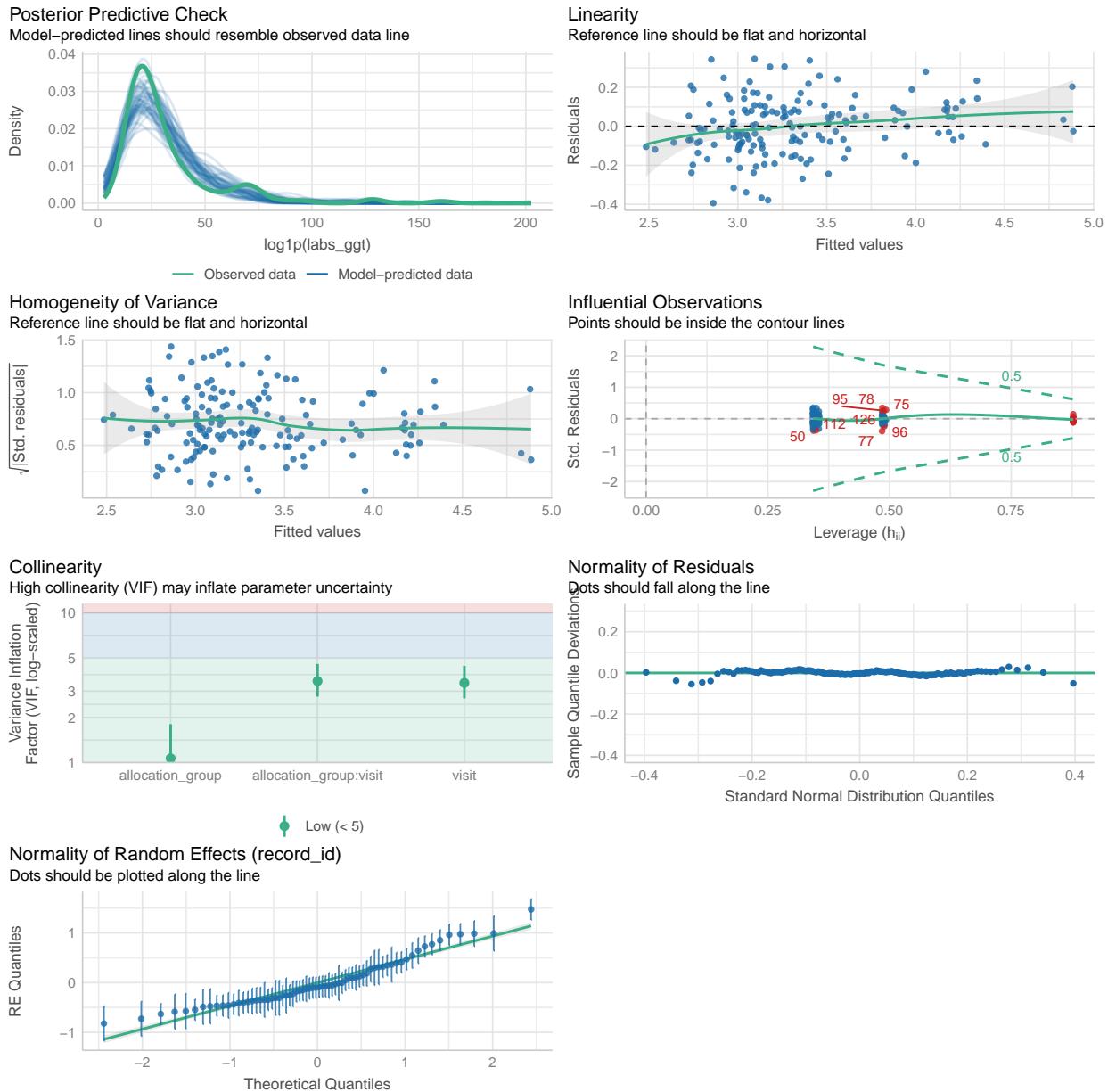
```

| 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)
```



3.3.2 Médias Marginais Estimadas

3.3.2.1 Todos os dados

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

labs_ggt_raw_emm <- regrid(labs_ggt_raw_emm)
```

```

# Table of marginal means
# labs_ggt_raw_emm

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

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

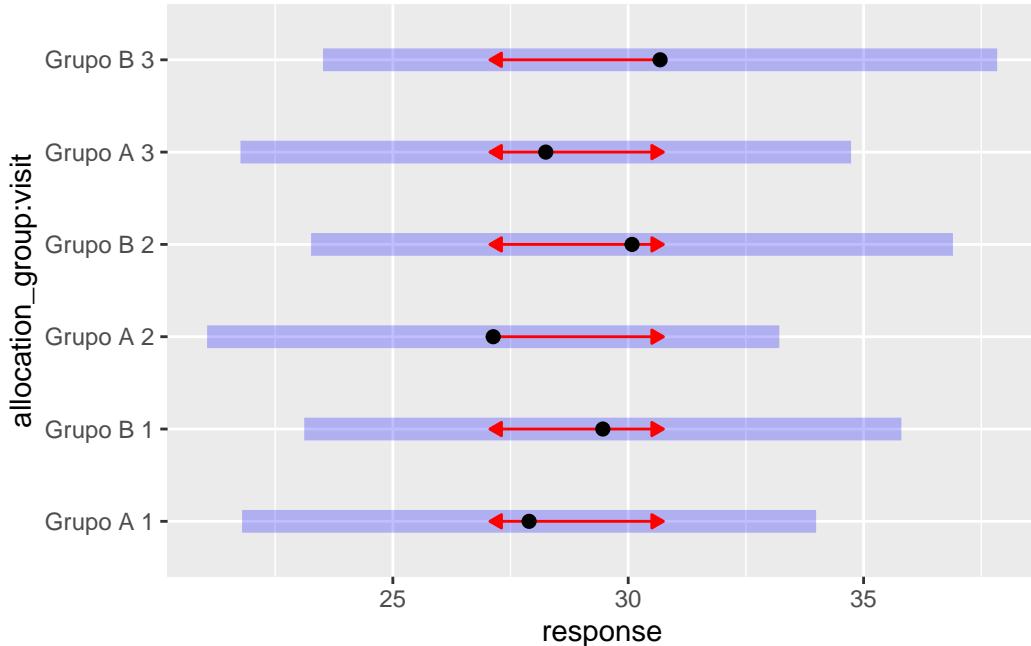
allocation_group = Grupo B:
  contrast      estimate    SE    df lower.CL upper.CL t.ratio p.value
  visit1 - visit2  -0.620 2.03  84.1    -5.58     4.34  -0.305  1.0000
  visit1 - visit3  -1.217 2.24  84.1    -6.69     4.26  -0.543  1.0000
  visit2 - visit3  -0.596 2.33 100.6    -6.27     5.08  -0.256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

```

```
Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests
```

```
# Plot of marginal means
```

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



3.3.2.2 Análise de sensibilidade

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

labs_ggt_emm <- regrid(labs_ggt_emm)

# Table of marginal means
# labs_ggt_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(labs_ggt_emm,
  method = "pairwise", by = "visit",
```

```

adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

visit = 1:
contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
Grupo A - Grupo B    -3.87 3.49 74.8     -10.8      3.08  -1.110  0.2705

visit = 2:
contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
Grupo A - Grupo B    -5.63 3.73 80.4     -13.0      1.79  -1.510  0.1351

visit = 3:
contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
Grupo A - Grupo B    -4.54 3.92 88.4     -12.3      3.25  -1.158  0.2501

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

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

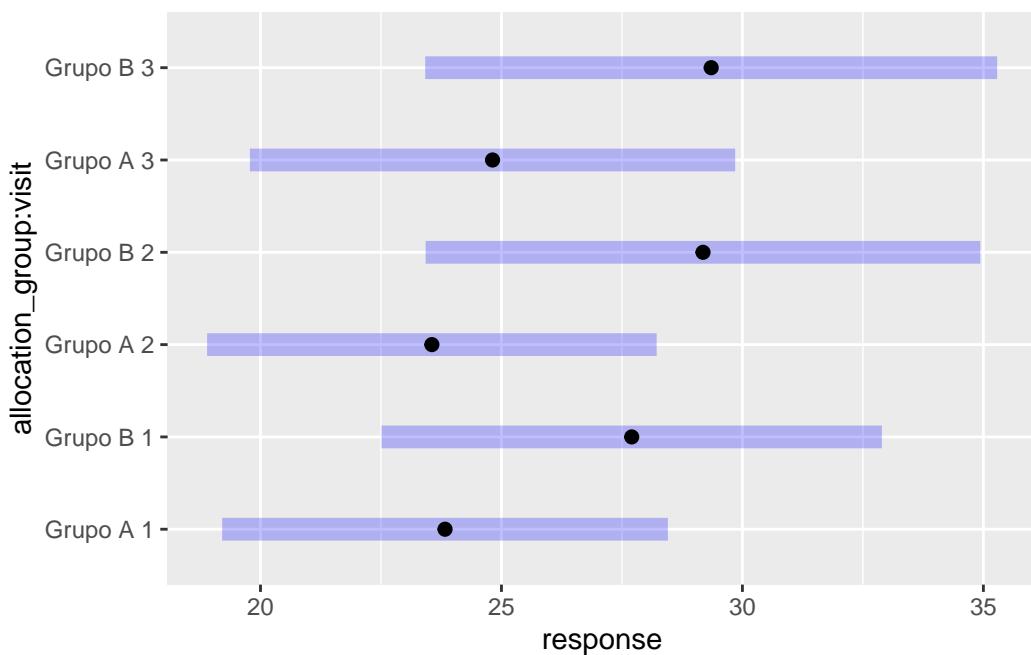
allocation_group = Grupo A:
contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit2    0.273 1.25 74.8     -2.80      3.34  0.218  1.0000
visit1 - visit3   -0.986 1.42 74.8     -4.46      2.49  -0.694  1.0000
visit2 - visit3   -1.259 1.42 80.4     -4.73      2.21  -0.888  1.0000

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)
```



3.3.3 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 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 de comparação | Comparação | Estimativa | IC 95% | p-valor |
|---------------------|---------------------|------------|----------------|---------|
| Grupo Eclipta | Visita 2 - Visita 3 | -0,60 | [-6,27 ; 5,08] | 1,000 |

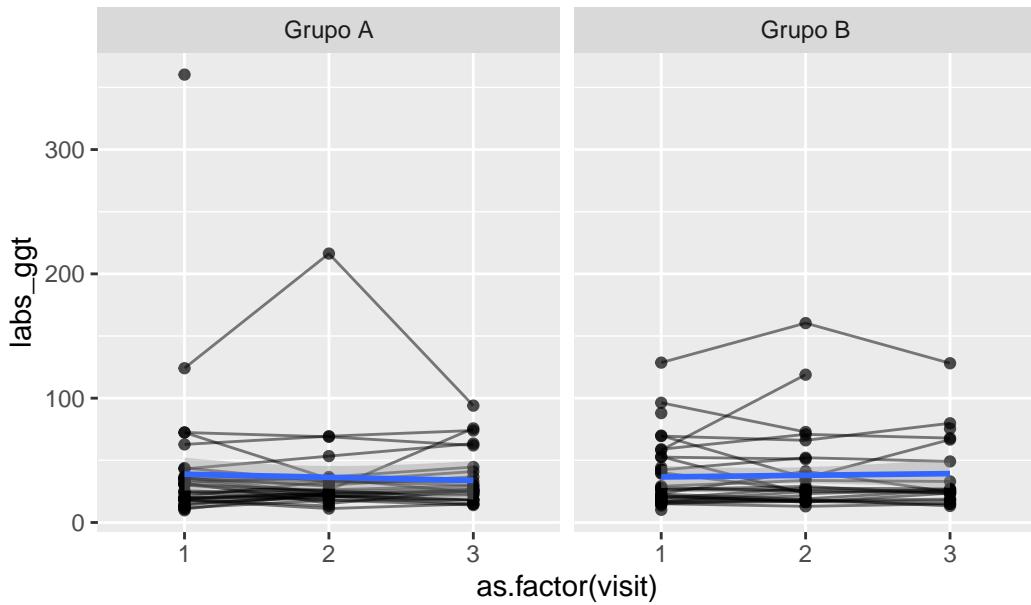
```

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

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

```

All data



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

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

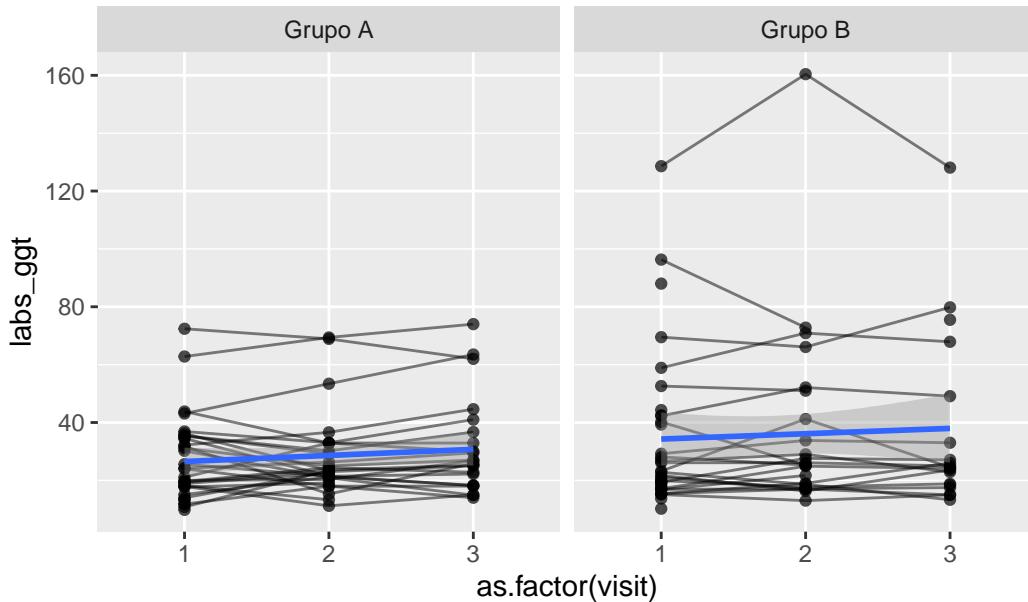
```

facet_wrap(~ allocation_group)

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

```

Sensitivity analysis



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

3.4 Fosfatase Alcalina

Variável: labs_alkp

```

# Plot 1: Raw data
labs_alkp_hist_1 <- data_model %>%
  #filter(
  #  labs_alkp < 300
  #) %>%
  ggplot(aes(x = labs_alkp)) +
  geom_histogram(bins = 50, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
labs_alkp_hist_2 <- data_model %>%

```

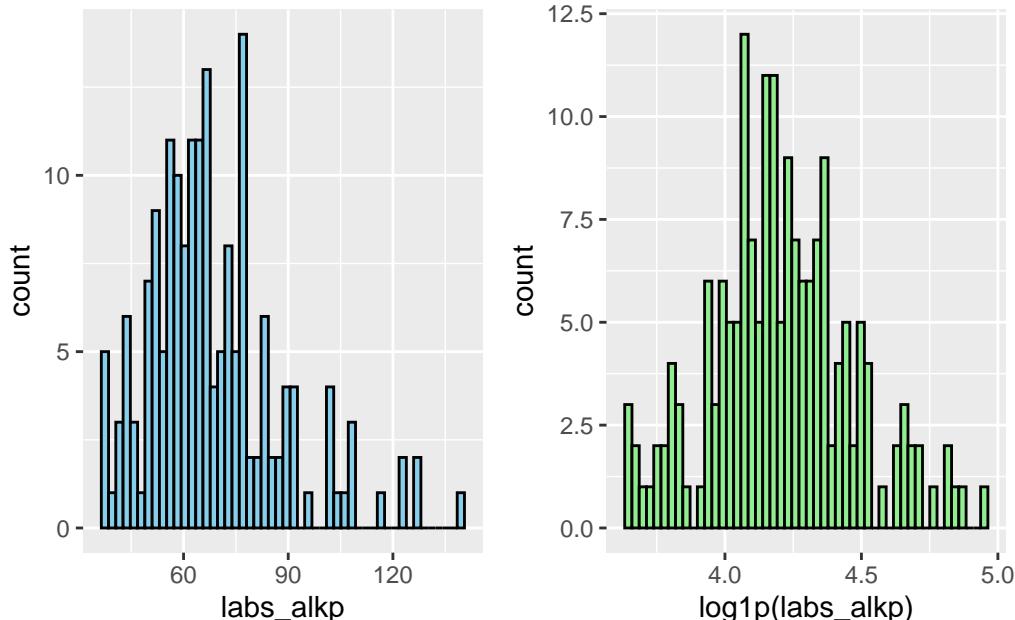
```

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

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

```

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



```

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

# Check for Multicollinearity

```

Low Correlation

| | Term | VIF | VIF 95% CI | Increased SE | Tolerance |
|--|------------------------|------|--------------|--------------|-----------|
| | allocation_group | 1.08 | [1.01, 1.62] | 1.04 | 0.93 |
| | visit | 3.40 | [2.71, 4.36] | 1.84 | 0.29 |
| | allocation_group:visit | 3.52 | [2.80, 4.52] | 1.88 | 0.28 |
| | Tolerance 95% CI | | | | |

```

[0.62, 0.99]
[0.23, 0.37]
[0.22, 0.36]

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

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

# Influential IDS
labs_alkp_model_check$influential_ids

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

```

3.4.1 Resumo dos modelos

```

# Model comparison
summary(labs_alkp_model)

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

REML criterion at convergence: -87.9

Scaled residuals:
    Min      1Q  Median      3Q     Max 
-2.02732 -0.46612  0.01043  0.43200  2.62132

Random effects:
Groups      Name        Variance Std.Dev.
record_id (Intercept) 0.06041  0.2458
Residual            0.01021  0.1010
Number of obs: 178, groups: record_id, 75

```

Fixed effects:

| | Estimate | Std. Error | df | t value |
|--------------------------------|--|------------|------------|---------|
| (Intercept) | 4.210088 | 0.043688 | 84.150015 | 96.367 |
| allocation_groupGrupo B | 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_groupGrupo B:visit2 | 0.018421 | 0.037511 | 101.816342 | 0.491 |
| allocation_groupGrupo B:visit3 | 0.004182 | 0.040741 | 102.191761 | 0.103 |
| | Pr(> t) | | | |
| (Intercept) | <2e-16 *** | | | |
| allocation_groupGrupo B | 0.5904 | | | |
| visit2 | 0.0692 . | | | |
| visit3 | 0.2770 | | | |
| allocation_groupGrupo B:visit2 | 0.6244 | | | |
| allocation_groupGrupo B:visit3 | 0.9184 | | | |
| --- | | | | |
| Signif. codes: | 0 *** 0.001 ** 0.01 * 0.05 . 0.1 ' ' 1 | | | |

Correlation of Fixed Effects:

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

```
summary(labs_alkp_model_sens)
```

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

REML criterion at convergence: -118.6

Scaled residuals:

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

Random effects:

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

Number of obs: 167, groups: record_id, 71

Fixed effects:

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

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

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

Correlation of Fixed Effects:

| (Intr) | all_GB | visit2 | visit3 | a_GB:2 |
|-------------|--------|--------|--------|--------|
| allctn_grGB | -0.712 | | | |
| visit2 | -0.200 | 0.143 | | |
| visit3 | -0.183 | 0.131 | 0.454 | |
| allctn_GB:2 | 0.136 | -0.191 | -0.677 | -0.307 |
| allctn_GB:3 | 0.125 | -0.176 | -0.310 | -0.684 |
| | | | | 0.438 |

```
performance::compare_performance(  
  labs_alkp_model,  
  labs_alkp_model_sens)
```

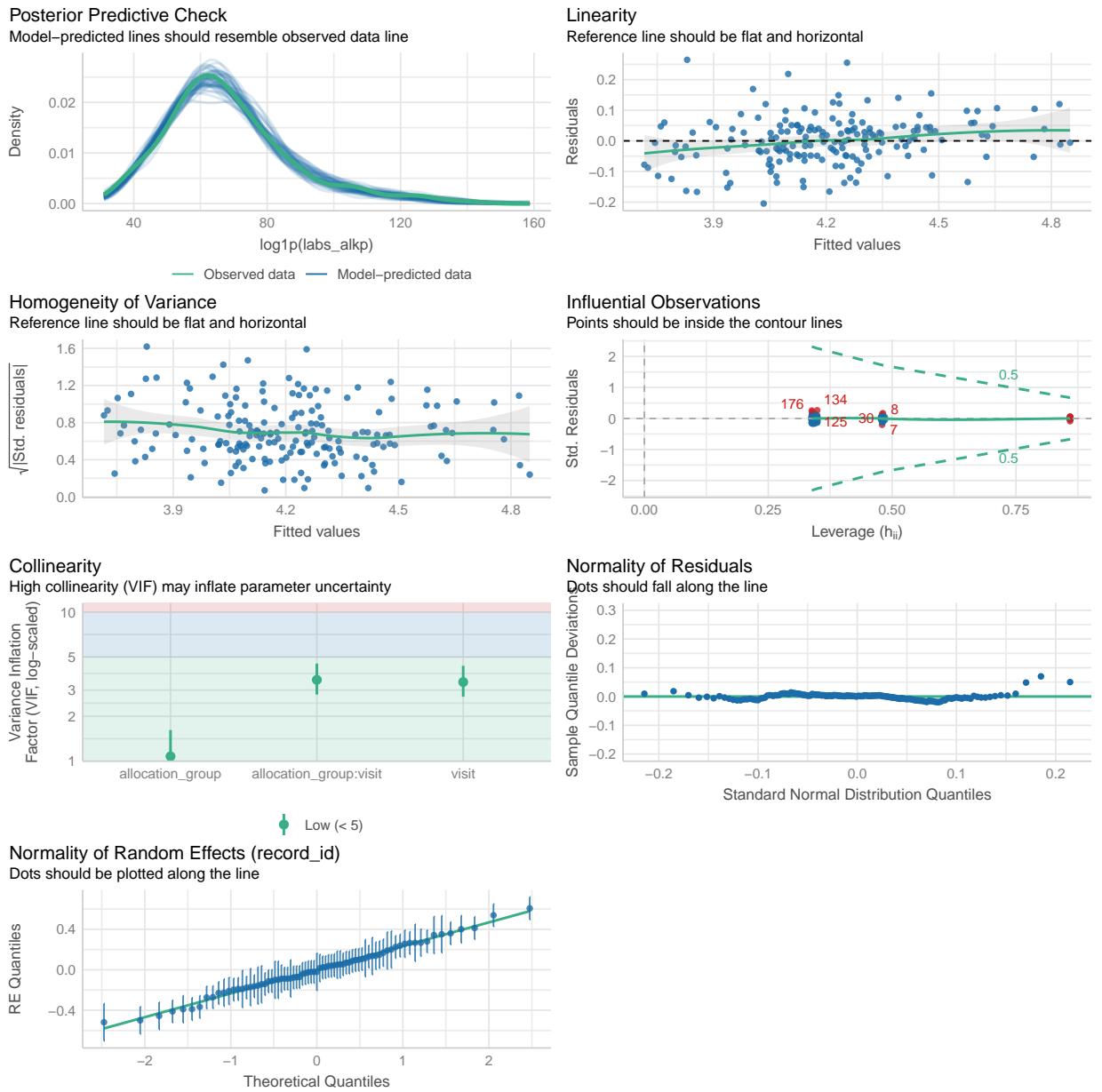
When comparing models, please note that probably not all models were fit from same data.

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

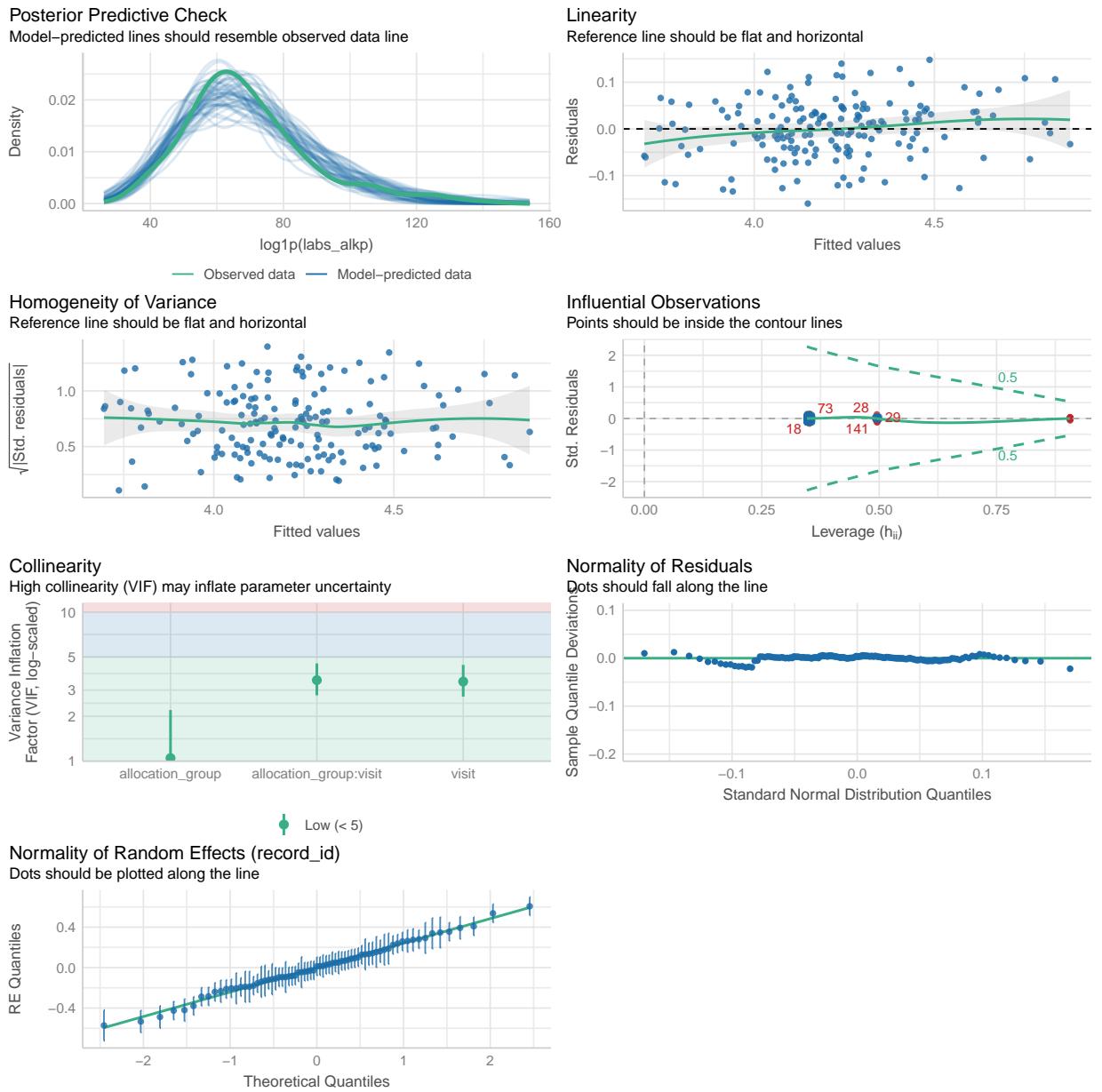
| Name | Model | AIC (weights) | AICc (weights) |
|----------------------|-----------------|----------------|----------------|
| <hr/> | | | |
| labs_alkp_model | lmerModLmerTest | 1394.9 (<.001) | 1395.7 (<.001) |
| labs_alkp_model_sens | lmerModLmerTest | 1274.2 (>.999) | 1275.1 (>.999) |

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


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



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



3.4.2 Médias Marginais Estimadas

3.4.2.1 Todos os dados

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

labs_alkp_raw_emm <- regrid(labs_alkp_raw_emm)
```

```

# Table of marginal means
# labs_alkp_raw_emm

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

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

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

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

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

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

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

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

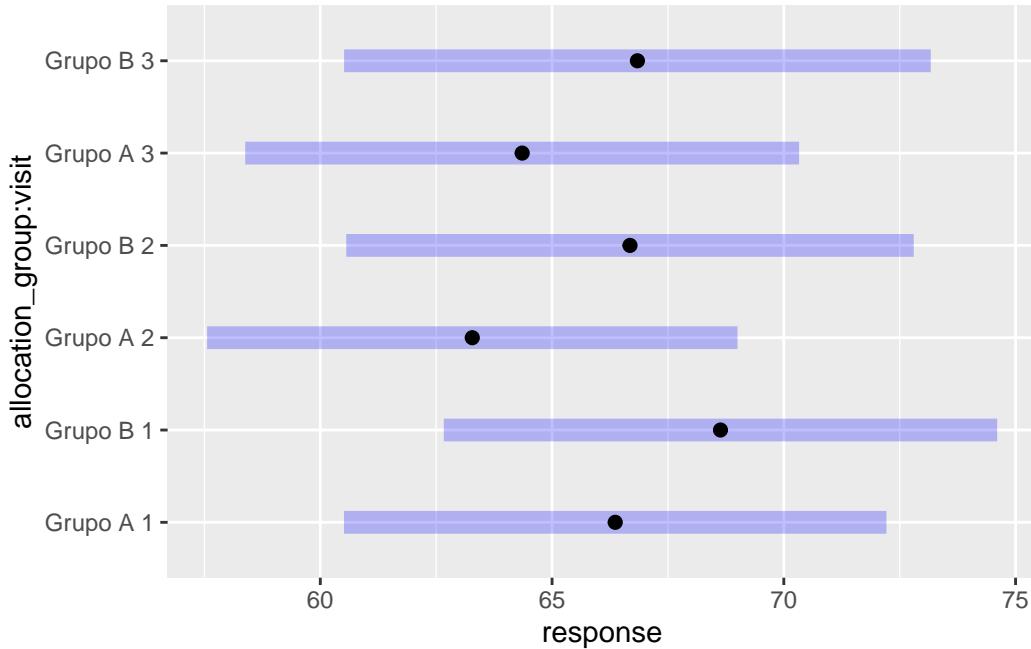
```

```

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests

# Plot of marginal means
plot(labs_alkp_raw_emm)

```



3.4.2.2 Análise de sensibilidade

```

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

# Table of marginal means
# labs_alkp_emm

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

visit = 1:
  contrast      estimate       SE     df lower.CL upper.CL t.ratio p.value

```

```
Grupo A - Grupo B -0.0717 0.0626 75.8 -0.196 0.0530 -1.146 0.2554
```

```
visit = 2:
```

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

```
visit = 3:
```

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

Note: contrasts are still on the log1p scale. Consider using

regrid() if you want contrasts of back-transformed estimates.

Degrees-of-freedom method: kenward-roger

Confidence level used: 0.95

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

allocation_group = Grupo A:

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

allocation_group = Grupo B:

| contrast | estimate | SE | df | lower.CL | upper.CL | t.ratio | p.value |
|-----------------|----------|--------|------|----------|----------|---------|---------|
| visit1 - visit2 | 0.04144 | 0.0232 | 94.5 | -0.01521 | 0.0981 | 1.783 | 0.2333 |
| visit1 - visit3 | 0.05555 | 0.0250 | 94.6 | -0.00529 | 0.1164 | 2.225 | 0.0853 |
| visit2 - visit3 | 0.01410 | 0.0259 | 92.9 | -0.04902 | 0.0772 | 0.545 | 1.0000 |

Note: contrasts are still on the log1p scale. Consider using

regrid() if you want contrasts of back-transformed estimates.

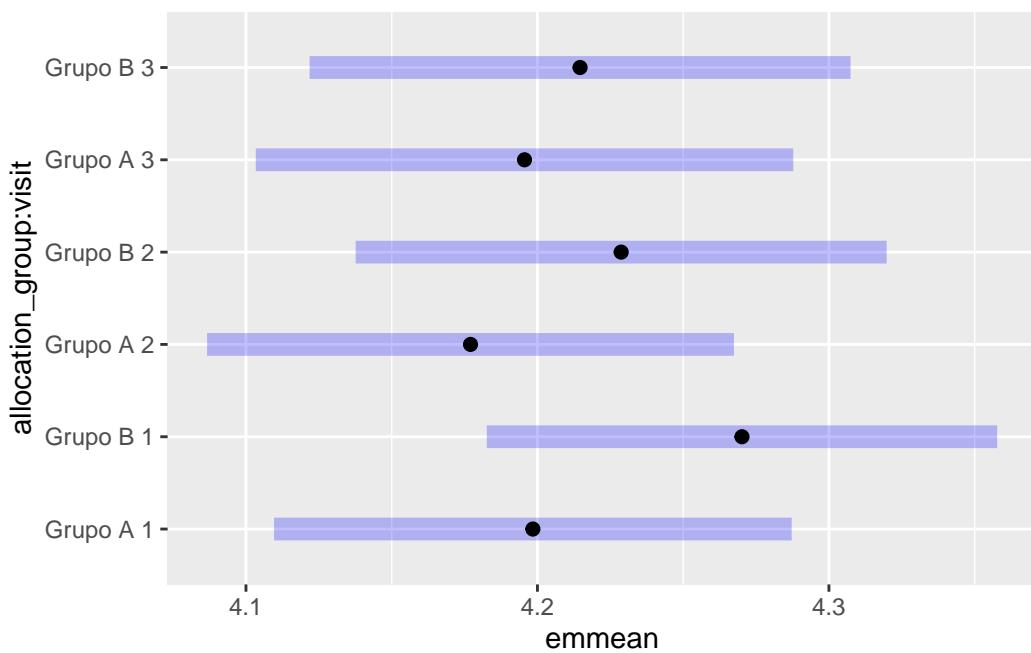
Degrees-of-freedom method: kenward-roger

Confidence level used: 0.95

Conf-level adjustment: bonferroni method for 3 estimates

P value adjustment: bonferroni method for 3 tests

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



3.4.3 Resultado

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

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

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

| Grupo de comparação | Comparação | Estimativa | IC 95% | p-valor |
|---------------------|---------------------|------------|----------------|---------|
| Grupo Eclipta | Visita 2 - Visita 3 | -0,16 | [-5,28 ; 4,96] | 1,000 |

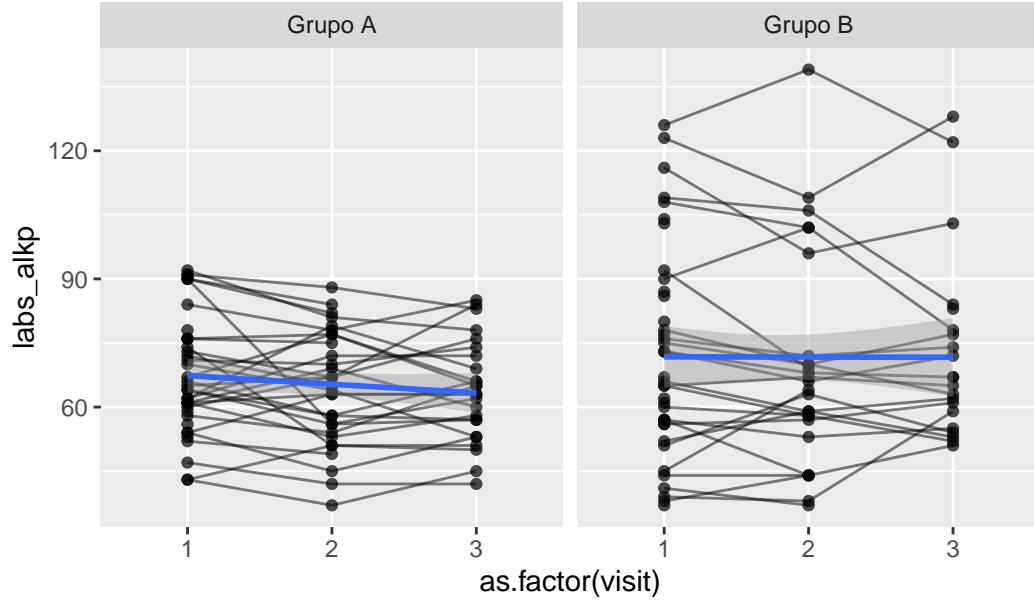
```

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

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

```

All data



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

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

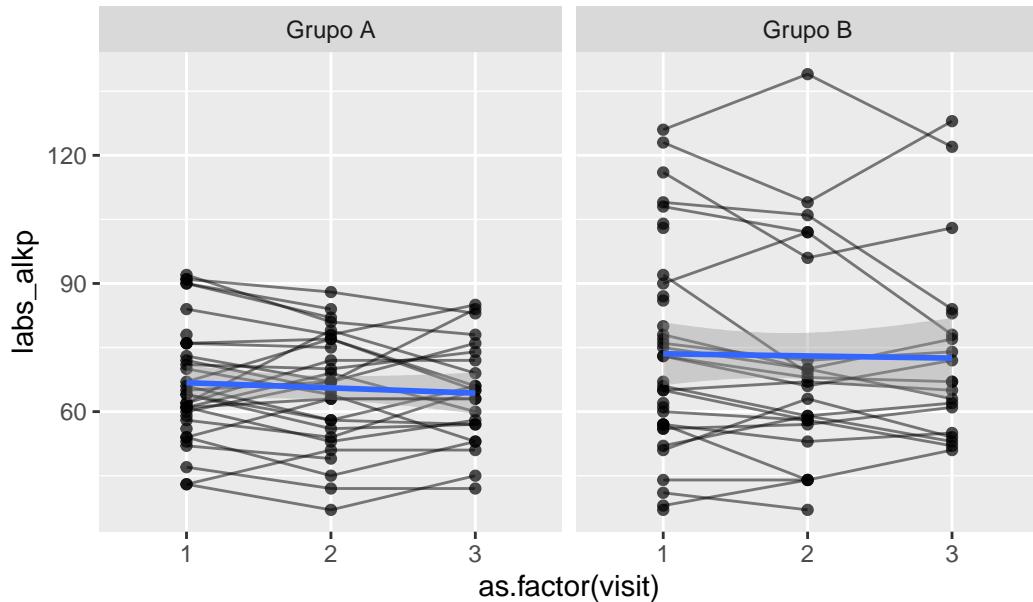
```

  facet_wrap(~ allocation_group)

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

```

Sensitivity analysis



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

3.5 Colesterol Total

Variável: labs_cholesterol

```

# Plot 1: Raw data
labs_cholesterol_hist_1 <- data_model %>%
  #filter(
  #  labs_cholesterol < 300
  #) %>%
  ggplot(aes(x = labs_cholesterol)) +
  geom_histogram(bins = 50, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
labs_cholesterol_hist_2 <- data_model %>%

```

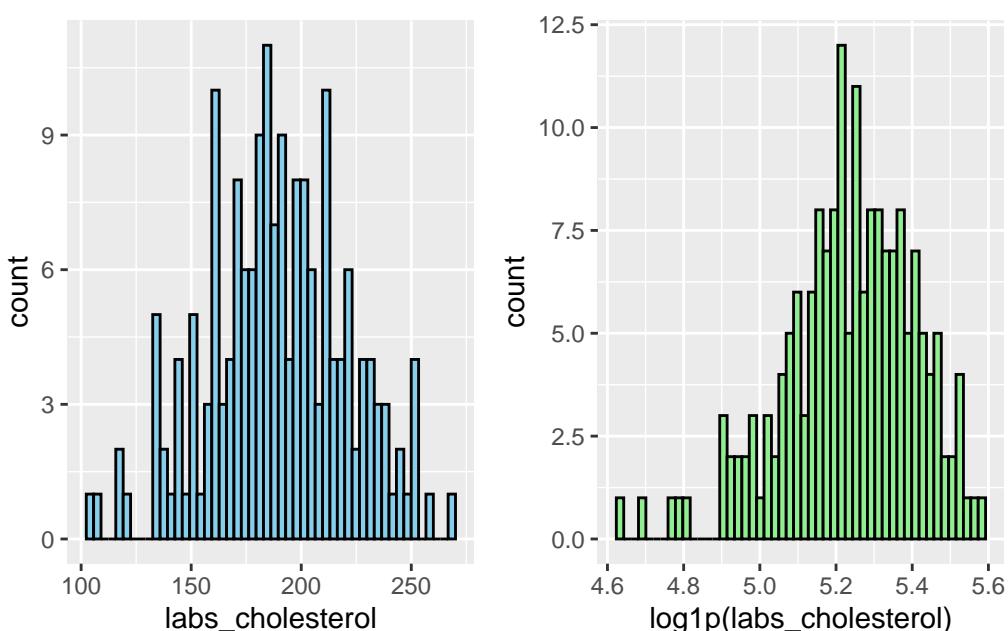
```

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

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

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

```



```

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

# Check for Multicollinearity

```

Low Correlation

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

```

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

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

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

# Influential IDs
labs_cholesterol_model_check$influential_ids

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

```

3.5.1 Resumo dos modelos

```

# Model comparison
summary(labs_cholesterol_model)

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

REML criterion at convergence: 1617.3

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

Random effects:
Groups      Name        Variance Std.Dev.
record_id (Intercept) 743.1     27.26
Residual            257.0     16.03
Number of obs: 179, groups: record_id, 75

```

Fixed effects:

| | Estimate | Std. Error | df | t value | Pr(> t) |
|--------------------------------|----------|------------|----------|---------|----------|
| (Intercept) | 191.2270 | 5.1990 | 96.6933 | 36.782 | <2e-16 |
| allocation_groupGrupo B | -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_groupGrupo B:visit2 | -0.1153 | 5.9143 | 106.8530 | -0.019 | 0.984 |
| allocation_groupGrupo B:visit3 | -7.7590 | 6.3553 | 107.5905 | -1.221 | 0.225 |

(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 -0.332 0.236
visit3 -0.306 0.218 0.451
allctn_GB:2 0.226 -0.317 -0.681 -0.308
allctn_GB:3 0.210 -0.295 -0.310 -0.687 0.436

summary(labs_cholesterol_model_sens)

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

REML criterion at convergence: 1418.7

Scaled residuals:

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

Random effects:

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

Number of obs: 164, groups: record_id, 70

Fixed effects:

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

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

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

Correlation of Fixed Effects:

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

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

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

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

| Name | Model | AIC (weights) | AICc (weights) |
|------|-------|---------------|----------------|
|------|-------|---------------|----------------|

| | | | |
|------------------------|-----------------|----------------|----------------|
| labs_cholesterol_model | lmerModLmerTest | 1661.8 (<.001) | 1662.7 (<.001) |
|------------------------|-----------------|----------------|----------------|

| | | | |
|-----------------------------|-----------------|----------------|----------------|
| labs_cholesterol_model_sens | lmerModLmerTest | 1461.2 (>.999) | 1462.1 (>.999) |
|-----------------------------|-----------------|----------------|----------------|

| Name | BIC (weights) | R2 (cond.) | R2 (marg.) | ICC |
|------|---------------|------------|------------|-----|
|------|---------------|------------|------------|-----|

| | | | | |
|------------------------|----------------|-------|-------|-------|
| labs_cholesterol_model | 1687.3 (<.001) | 0.746 | 0.011 | 0.743 |
|------------------------|----------------|-------|-------|-------|

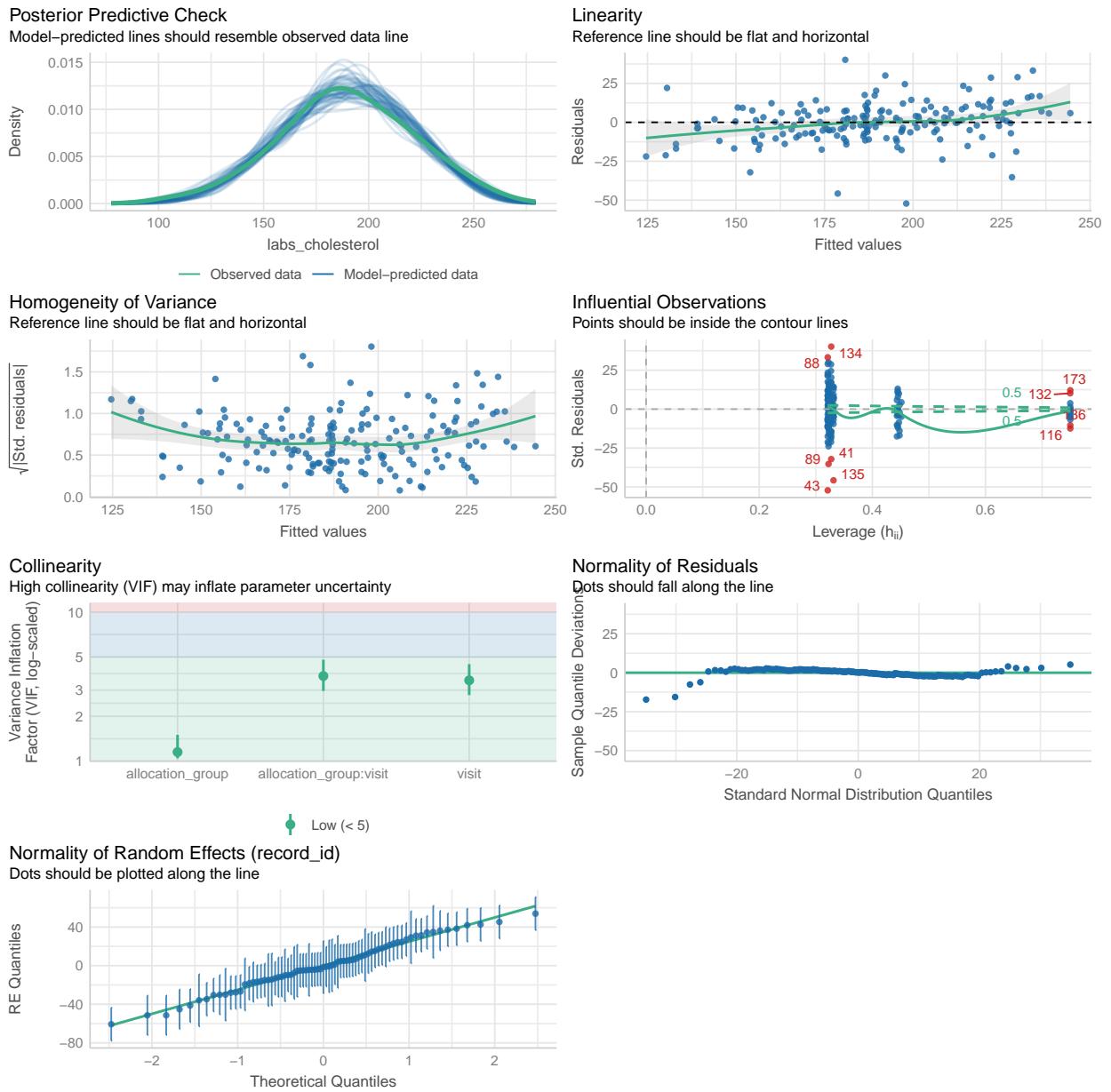
| | | | | |
|-----------------------------|----------------|-------|-------|-------|
| labs_cholesterol_model_sens | 1486.0 (>.999) | 0.841 | 0.011 | 0.839 |
|-----------------------------|----------------|-------|-------|-------|

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

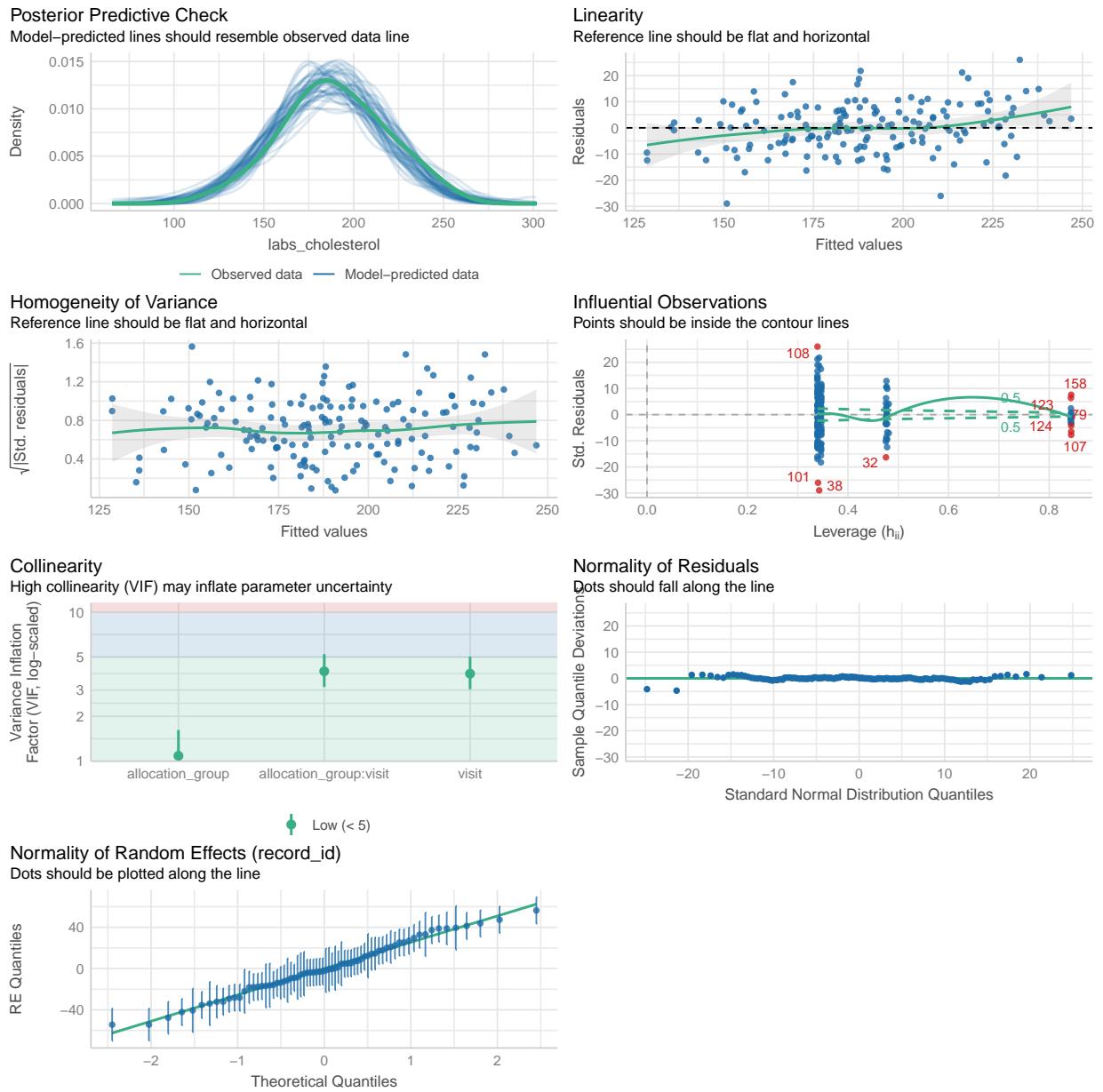
| | | |
|------------------------|--------|--------|
| labs_cholesterol_model | 12.602 | 16.030 |
|------------------------|--------|--------|

| | | |
|-----------------------------|-------|--------|
| labs_cholesterol_model_sens | 9.049 | 11.822 |
|-----------------------------|-------|--------|

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



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



3.5.2 Médias Marginais Estimadas

3.5.2.1 Todos os dados

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

labs_cholesterol_raw_emm <- regrid(labs_cholesterol_raw_emm)
```

```

# Table of marginal means
# labs_cholesterol_raw_emm

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

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

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

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

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

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

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

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

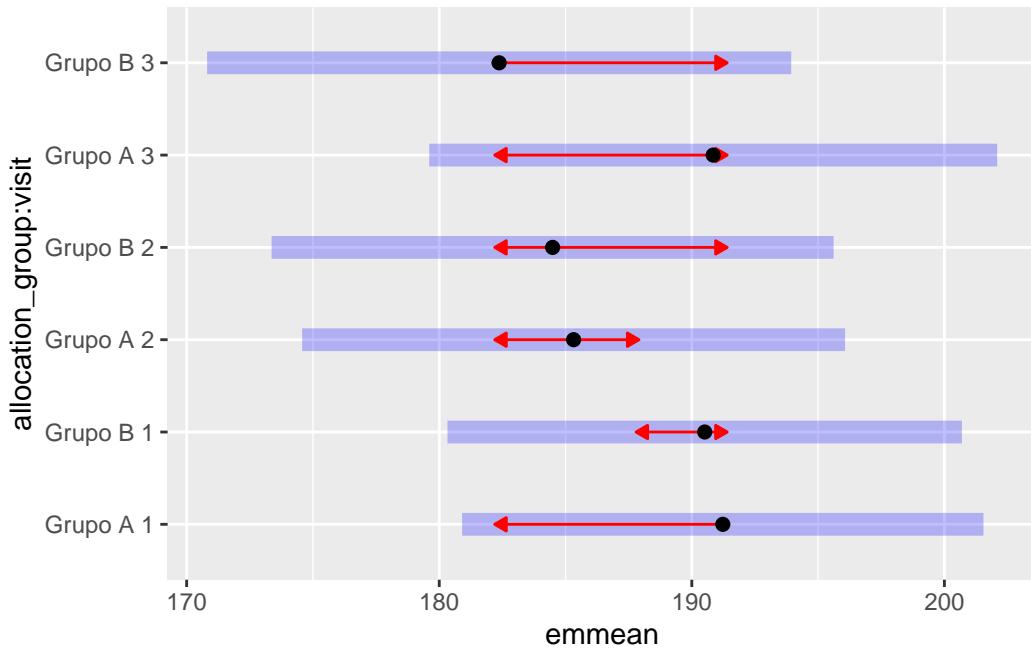
```

```

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests

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

```



3.5.2.2 Análise de sensibilidade

```

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

labs_cholesterol_emm <- regrid(labs_cholesterol_emm)

# Table of marginal means
# labs_cholesterol_emm

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

```

```

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

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

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

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

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

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

allocation_group = Grupo B:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit2     7.54 3.28 79.8     -0.478     15.56    2.300  0.0723
visit1 - visit3     6.07 3.51 79.8     -2.516     14.65    1.729  0.2632
visit2 - visit3    -1.47 3.65 97.7    -10.355      7.41   -0.404  1.0000

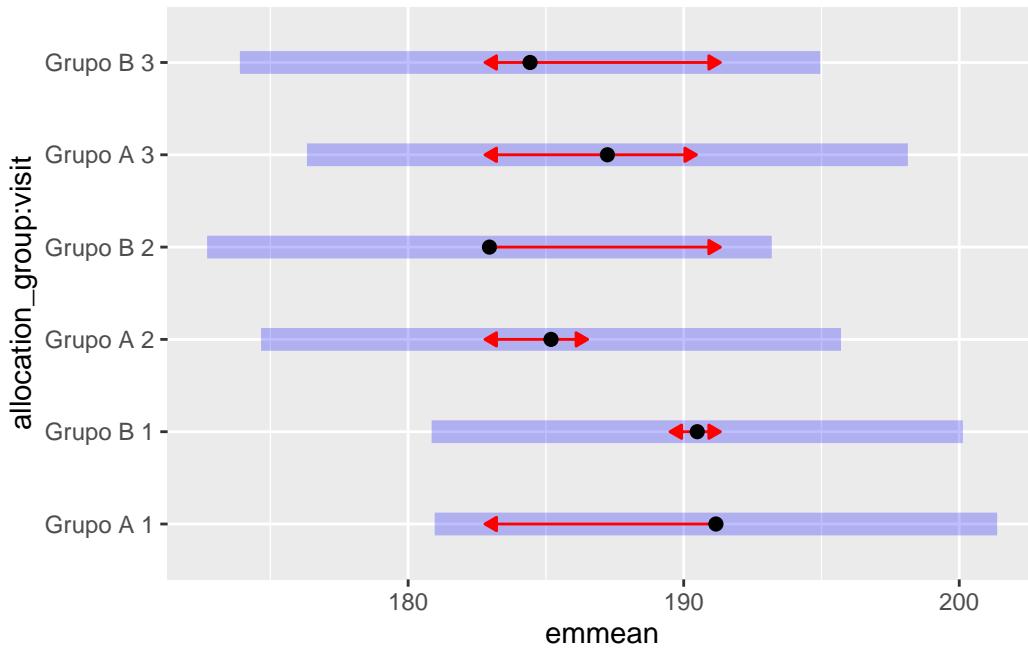
Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests

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

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

```

Target overlap = 0.7468, overlap on graph = -1.2872



3.5.3 Resultado

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

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

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

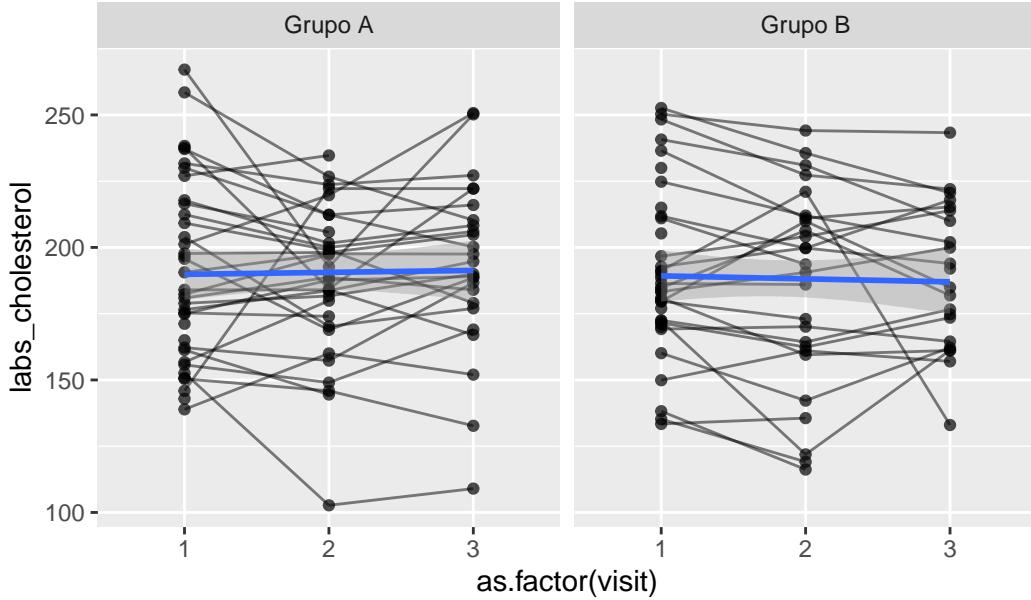
```

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

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

```

All data



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

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

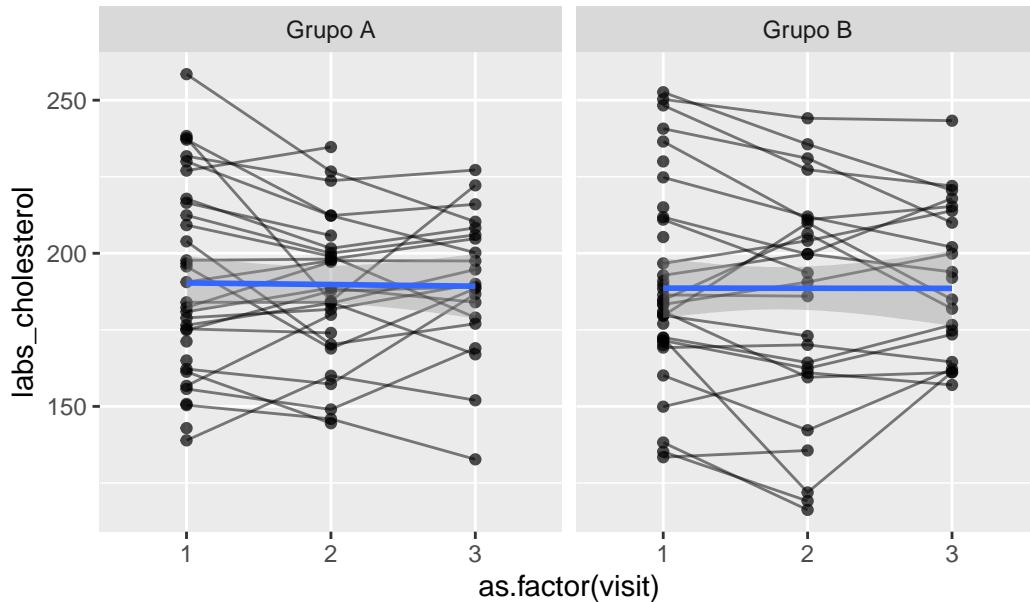
```

facet_wrap(~ allocation_group)

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

```

Sensitivity analysis



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

3.6 LDL Colesterol

Variável: labs_ldl

```

# Plot 1: Raw data
labs_ldl_hist_1 <- data_model %>%
  #filter(
  #  labs_ldl < 300
  #) %>%
  ggplot(aes(x = labs_ldl)) +
  geom_histogram(bins = 50, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
labs_ldl_hist_2 <- data_model %>%

```

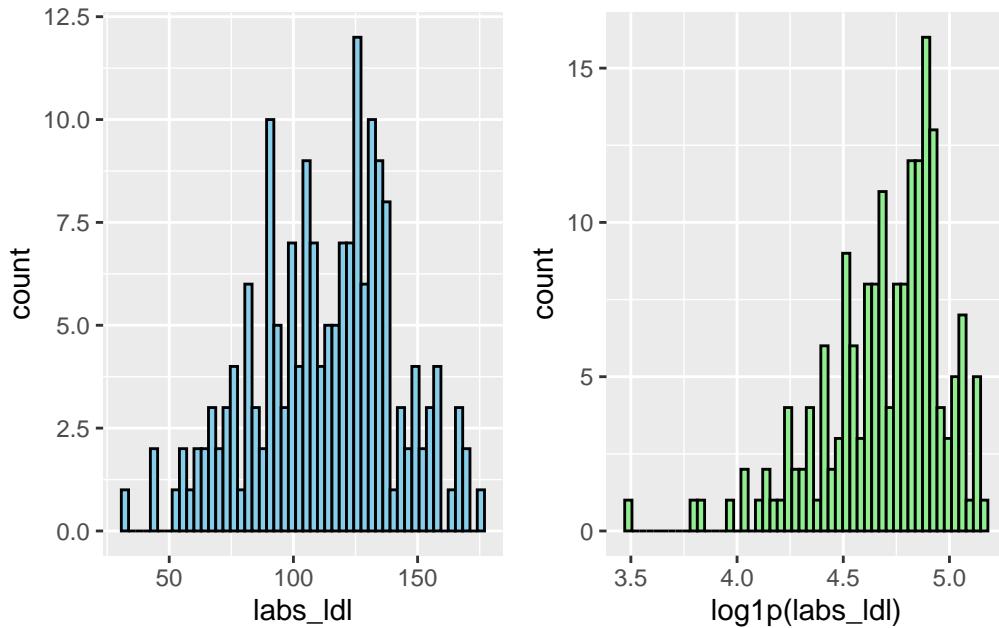
```

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

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

```

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



```

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

# Check for Multicollinearity

```

Low Correlation

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

```

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

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

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

# Influential IDS
labs_ldl_model_check$influential_ids

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

```

3.6.1 Resumo dos modelos

```

# Model comparison
summary(labs_ldl_model)

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

```

REML criterion at convergence: 1601.5

Scaled residuals:

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

Random effects:

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

Number of obs: 179, groups: record_id, 75

Fixed effects:

| | Estimate | Std. Error | df | t value | Pr(> t) |
|--------------------------------|----------|------------|----------|---------|----------|
| (Intercept) | 115.4919 | 4.8081 | 98.3445 | 24.020 | <2e-16 |
| allocation_groupGrupo 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_groupGrupo B:visit2 | 1.9191 | 5.8182 | 105.6037 | 0.330 | 0.742 |
| allocation_groupGrupo B:visit3 | -5.9060 | 6.2502 | 106.5086 | -0.945 | 0.347 |

(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 -0.354 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 | Grupo B | -3.8299 | 6.7068 | 75.3685 | -0.571 | 0.5697 |
| visit2 | | -5.1922 | 2.9125 | 87.5739 | -1.783 | 0.0781 |
| visit3 | | 0.6698 | 3.2198 | 88.0305 | 0.208 | 0.8357 |
| allocation_group | Grupo B:visit2 | 1.8681 | 4.1755 | 88.1990 | 0.447 | 0.6557 |
| allocation_group | Grupo B:visit3 | -5.5726 | 4.5483 | 88.5080 | -1.225 | 0.2237 |

(Intercept) ***

allocation_group

visit2 .

visit3

allocation_group

Grupo B:visit2

allocation_group

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

Correlation of Fixed Effects:

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

performance::compare_performance(

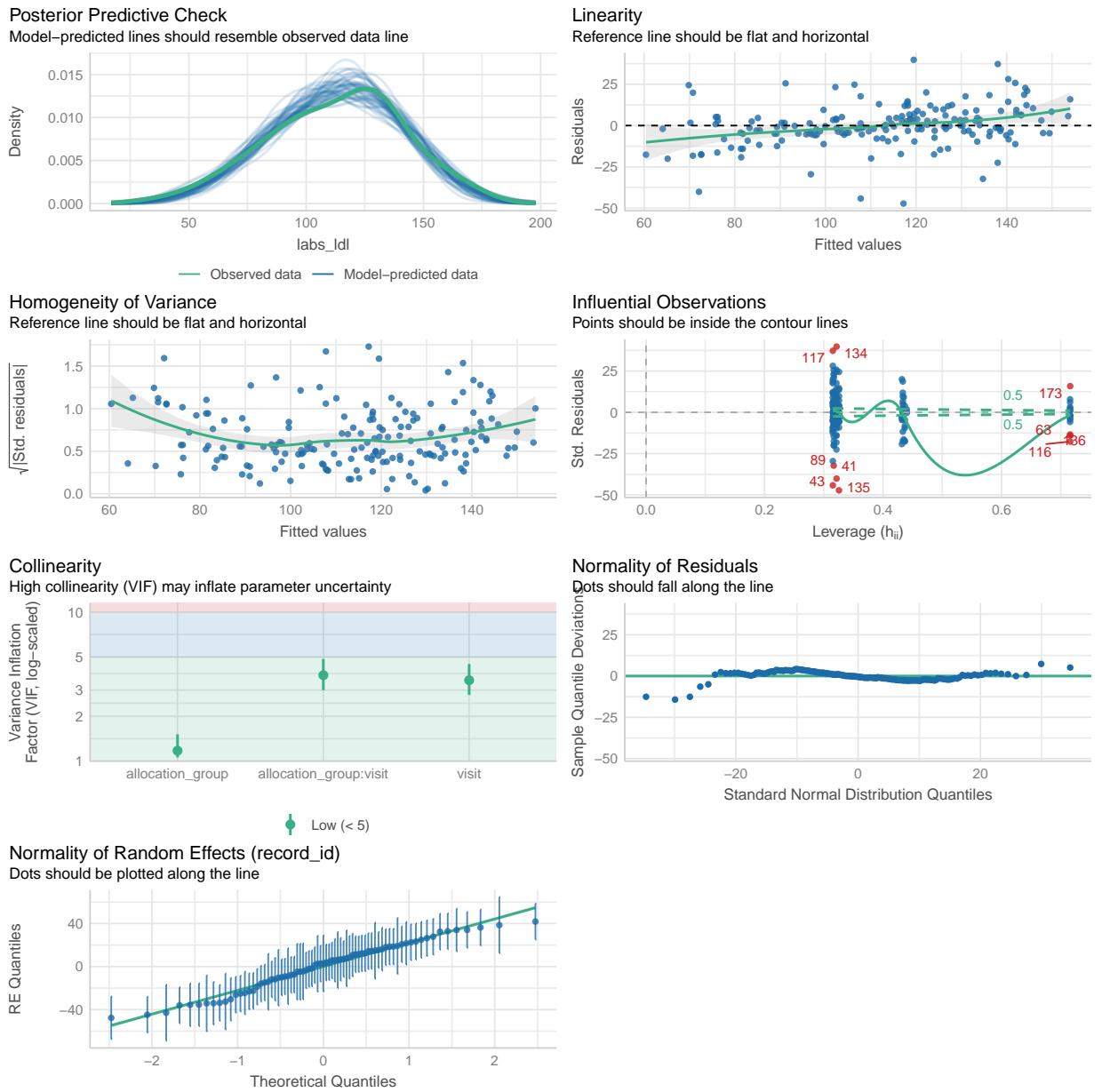
 labs_ldl_model,

 labs_ldl_model_sens)

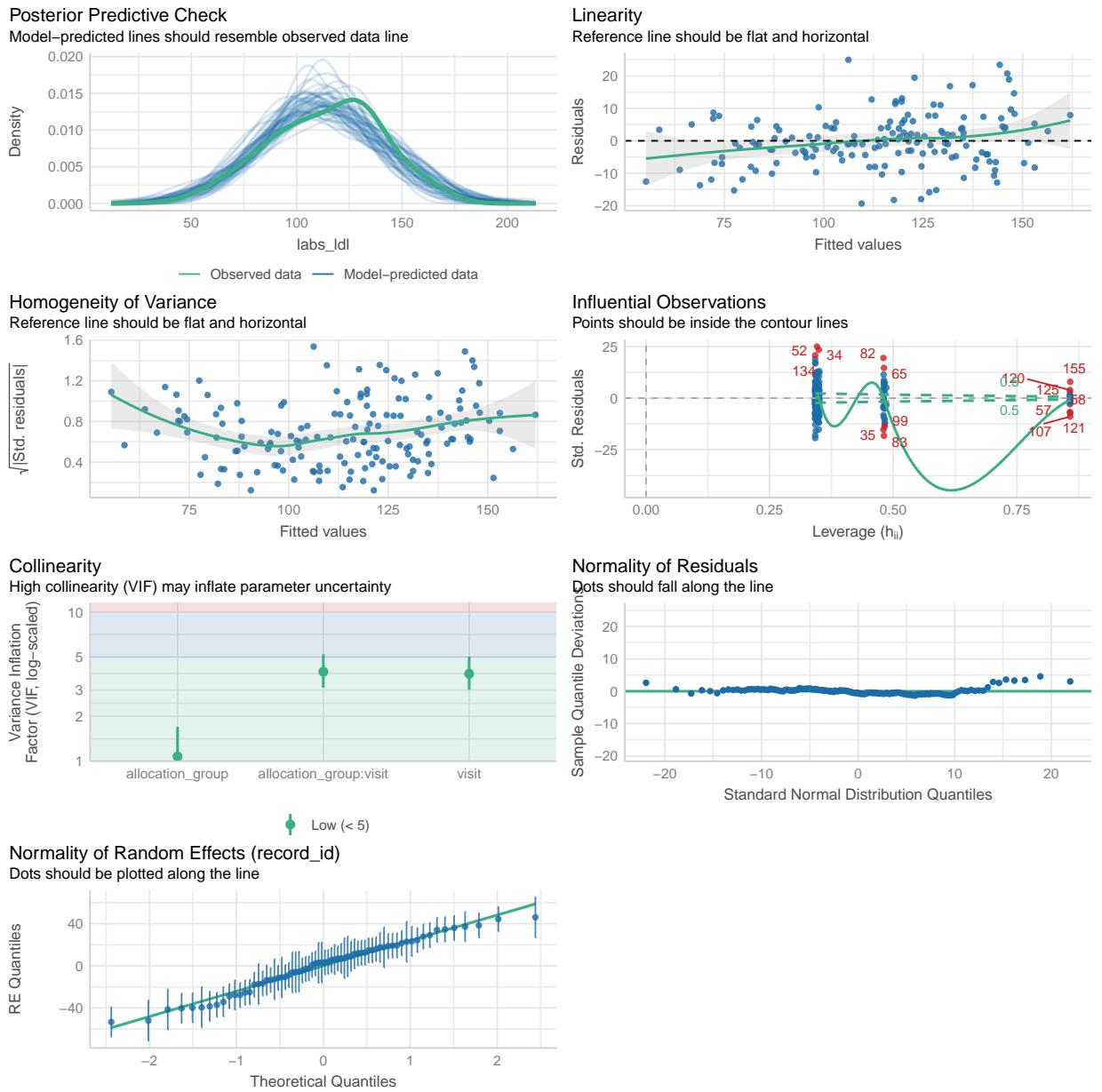
When comparing models, please note that probably not all models were fit
from same data.

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

| Name | Model | AIC (weights) | AICc (weights) | | | |
|--|-----------------|----------------|----------------|-------|--------|--------|
| <hr/> | | | | | | |
| labs_ldl_model | lmerModLmerTest | 1645.5 (<.001) | 1646.4 (<.001) | | | |
| labs_ldl_model_sens | lmerModLmerTest | 1380.5 (>.999) | 1381.5 (>.999) | | | |
| Name | BIC (weights) | R2 (cond.) | R2 (marg.) | ICC | RMSE | Sigma |
| labs_ldl_model | 1671.0 (<.001) | 0.712 | 0.014 | 0.708 | 12.514 | 15.802 |
| labs_ldl_model_sens | 1405.0 (>.999) | 0.855 | 0.014 | 0.853 | 8.043 | 10.574 |
| performance::check_model(labs_ldl_model) | | | | | | |



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



3.6.2 Médias Marginais Estimadas

3.6.2.1 Todos os dados

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

labs_ldl_raw_emm <- regrid(labs_ldl_raw_emm)
```

```

# Table of marginal means
# labs_ldl_raw_emm

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

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

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

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

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

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

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

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

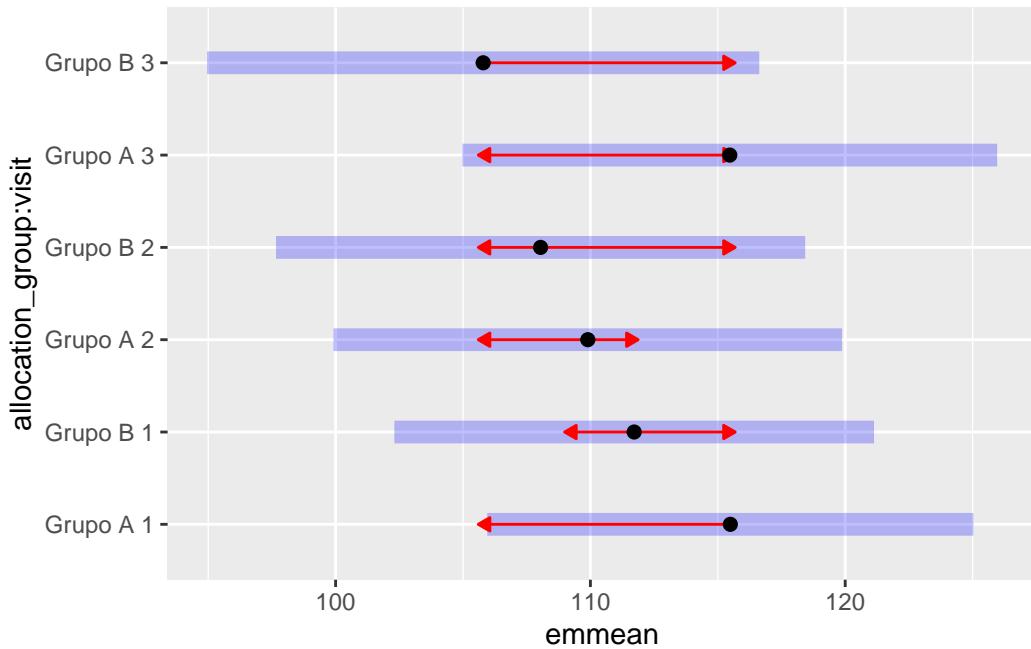
```

```

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests

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

```



3.6.2.2 Análise de sensibilidade

```

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

labs_ldl_emm <- regrid(labs_ldl_emm)

# Table of marginal means
# labs_ldl_emm

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

```

```

visit = 1:
  contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
  Grupo A - Grupo B     3.83 6.71 76.2    -9.53     17.2    0.571  0.5697

visit = 2:
  contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
  Grupo A - Grupo B     1.96 7.02 84.3   -11.99     15.9    0.280  0.7805

visit = 3:
  contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
  Grupo A - Grupo B     9.40 7.25 94.8    -4.98     23.8    1.298  0.1976

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

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

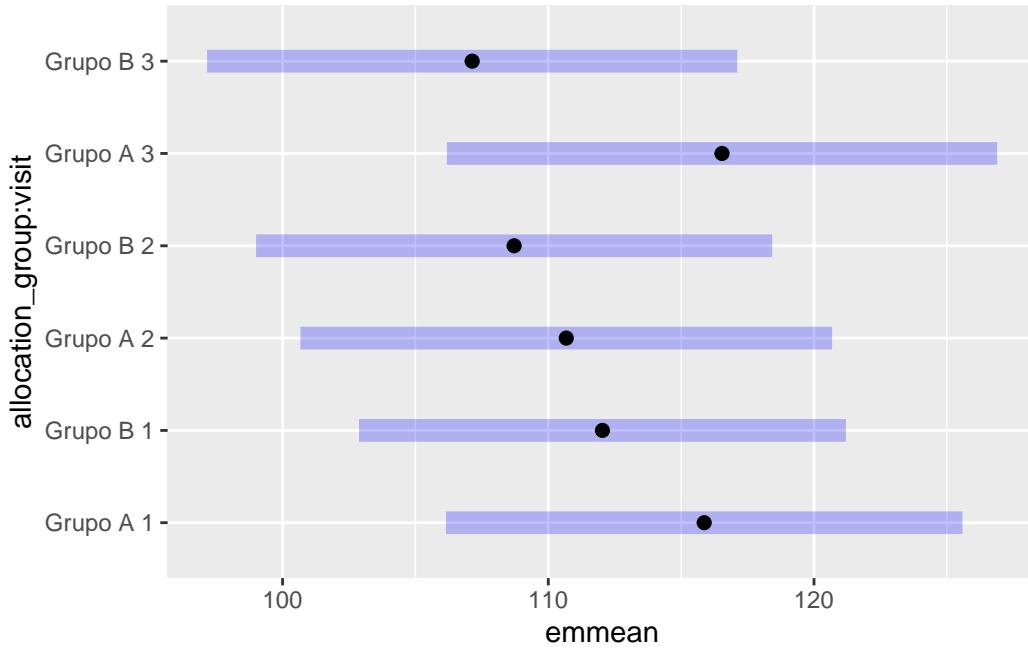
allocation_group = Grupo A:
  contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
  visit1 - visit2     5.19 2.91 76.2    -1.94     12.33    1.782  0.2364
  visit1 - visit3    -0.67 3.22 76.2    -8.56      7.22   -0.208  1.0000
  visit2 - visit3    -5.86 3.24 84.3   -13.77      2.05  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

```



3.6.3 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 Placebo | Visita 2 - Visita 3 | -5,57 | [-16,13 ; 4,98] | 0,606 |
| Grupo Eclipta | Visita 1 - Visita 2 | 3,67 | [-6,71 ; 14,06] | 1,000 |
| Grupo Eclipta | Visita 1 - Visita 3 | 5,93 | [-5,15 ; 17,00] | 0,586 |
| Grupo Eclipta | Visita 2 - Visita 3 | 2,25 | [-9,26 ; 13,76] | 1,000 |

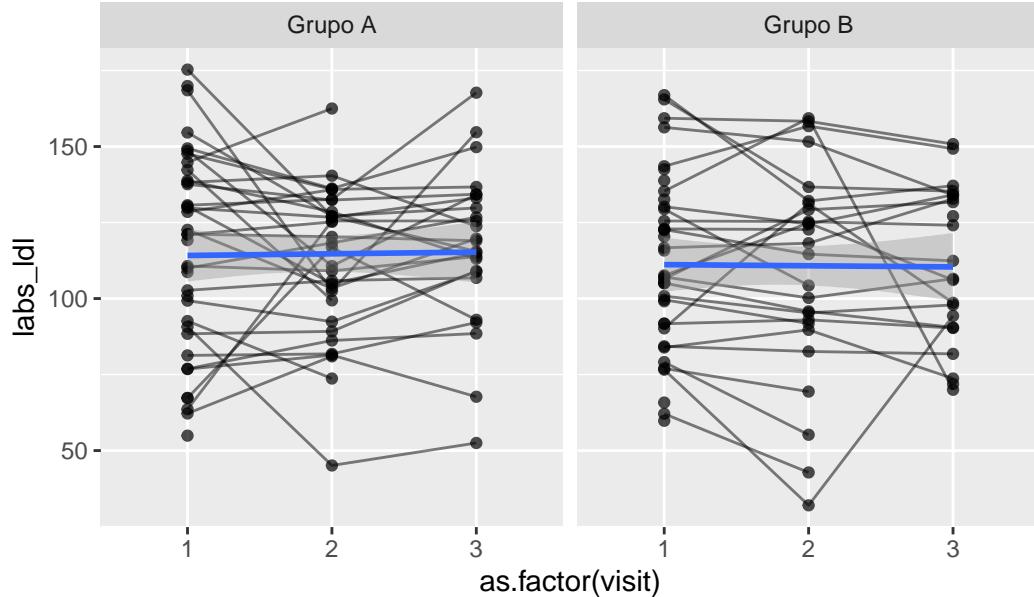
```

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

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

```

All data



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

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

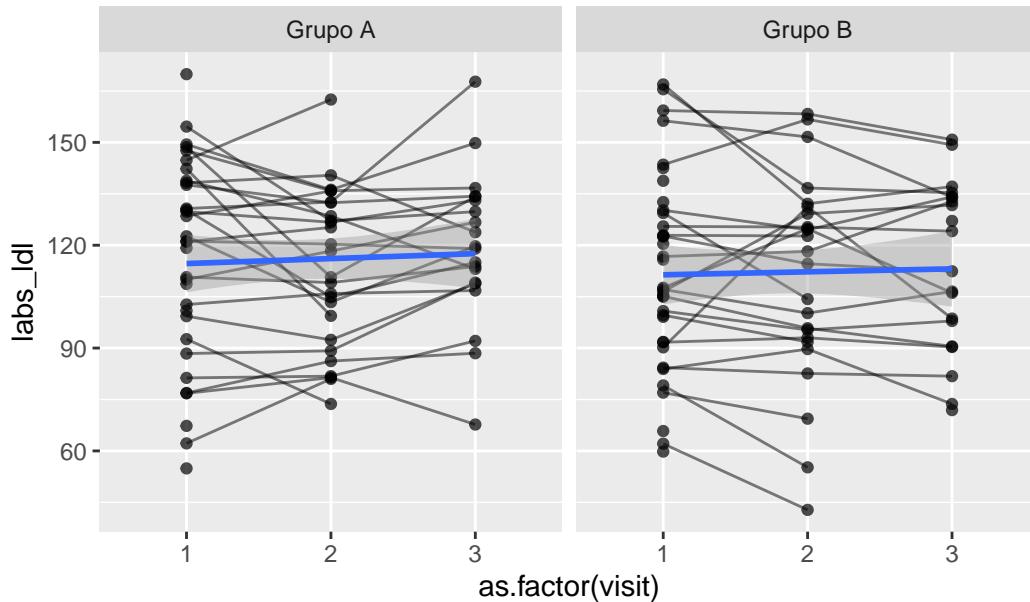
```

facet_wrap(~ allocation_group)

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

```

Sensitivity analysis



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

3.7 HDL Colesterol

Variável: labs_hdl

```

# Plot 1: Raw data
labs_hdl_hist_1 <- data_model %>%
  #filter(
  #  labs_hdl < 300
  #) %>%
  ggplot(aes(x = labs_hdl)) +
  geom_histogram(bins = 50, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
labs_hdl_hist_2 <- data_model %>%

```

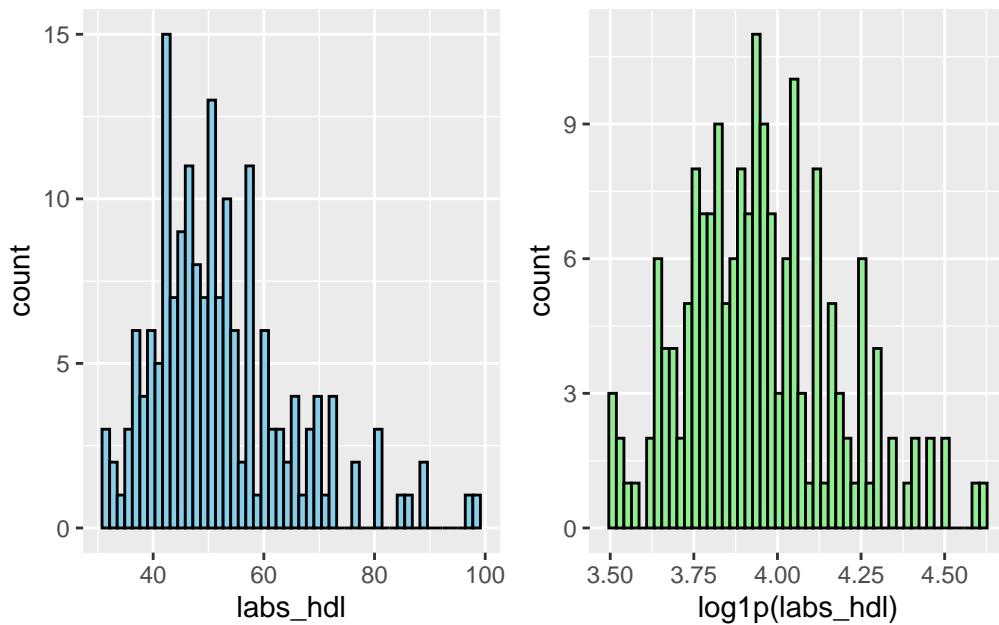
```

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

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

```

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



```

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

# Check for Multicollinearity

```

Low Correlation

| | Term | VIF | VIF 95% CI | Increased SE | Tolerance |
|--|------------------------|------|--------------|--------------|-----------|
| | allocation_group | 1.16 | [1.05, 1.51] | 1.08 | 0.86 |
| | visit | 3.49 | [2.78, 4.48] | 1.87 | 0.29 |
| | allocation_group:visit | 3.74 | [2.97, 4.81] | 1.93 | 0.27 |
| | Tolerance 95% CI | | | | |

```

[0.66, 0.95]
[0.22, 0.36]
[0.21, 0.34]

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

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

# Influential IDs
labs_hdl_model_check$influential_ids

[1] "16" "75" "38" "42" "26"

```

3.7.1 Resumo dos modelos

```

# Model comparison
summary(labs_hdl_model)

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

```

REML criterion at convergence: -79.8

Scaled residuals:

| Min | 1Q | Median | 3Q | Max |
|---------|---------|---------|--------|--------|
| -2.4161 | -0.4907 | -0.0289 | 0.4389 | 3.0395 |

Random effects:

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

Number of obs: 179, groups: record_id, 75

Fixed effects:

| | Estimate | Std. Error | df | t value | Pr(> t) |
|--------------------------------|----------|------------|-----------|---------|----------|
| (Intercept) | 3.94481 | 0.03815 | 94.81644 | 103.399 | <2e-16 |
| allocation_groupGrupo B | 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_groupGrupo B:visit2 | -0.02214 | 0.04420 | 104.26672 | -0.501 | 0.618 |
| allocation_groupGrupo B:visit3 | -0.03185 | 0.04749 | 105.05887 | -0.671 | 0.504 |

(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 -0.338 0.241
visit3 -0.312 0.222 0.451
allctn_GB:2 0.230 -0.324 -0.681 -0.307
allctn_GB:3 0.214 -0.301 -0.310 -0.687 0.435

summary(labs_hdl_model_sens)

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

REML criterion at convergence: -109.5

Scaled residuals:

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

Random effects:

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

Number of obs: 166, groups: record_id, 70

Fixed effects:

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

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

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

Correlation of Fixed Effects:

| | (Intr) | all_GB | visit2 | visit3 | a_GB:2 |
|-------------|--------|--------|--------|--------|--------|
| allctn_grGB | -0.707 | | | | |
| visit2 | -0.295 | 0.209 | | | |
| visit3 | -0.275 | 0.194 | 0.457 | | |
| allctn_GB:2 | 0.200 | -0.283 | -0.677 | -0.310 | |
| allctn_GB:3 | 0.184 | -0.260 | -0.306 | -0.670 | 0.440 |

```
performance::compare_performance(  
  labs_hdl_model,  
  labs_hdl_model_sens)
```

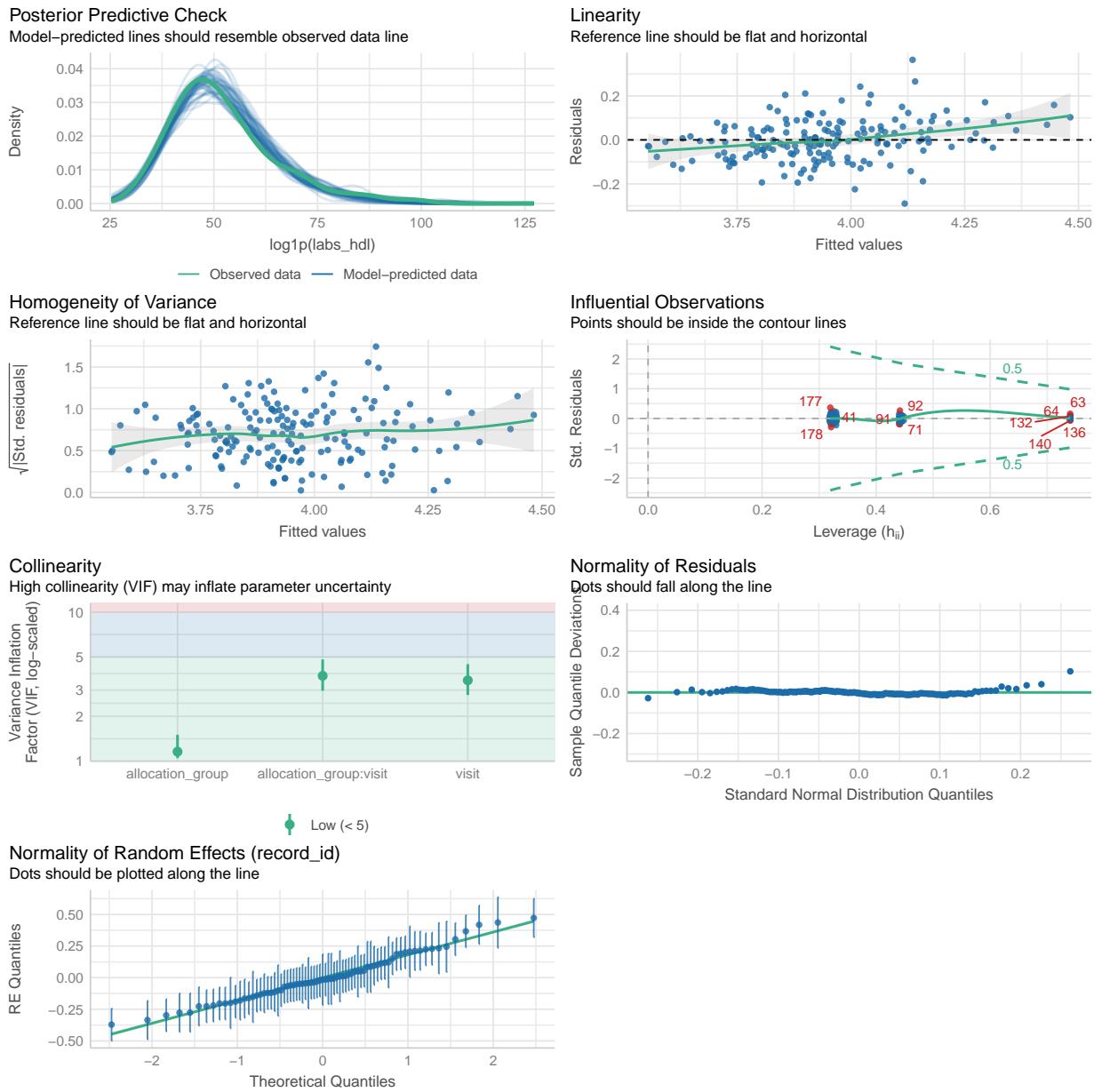
When comparing models, please note that probably not all models were fit
from same data.

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

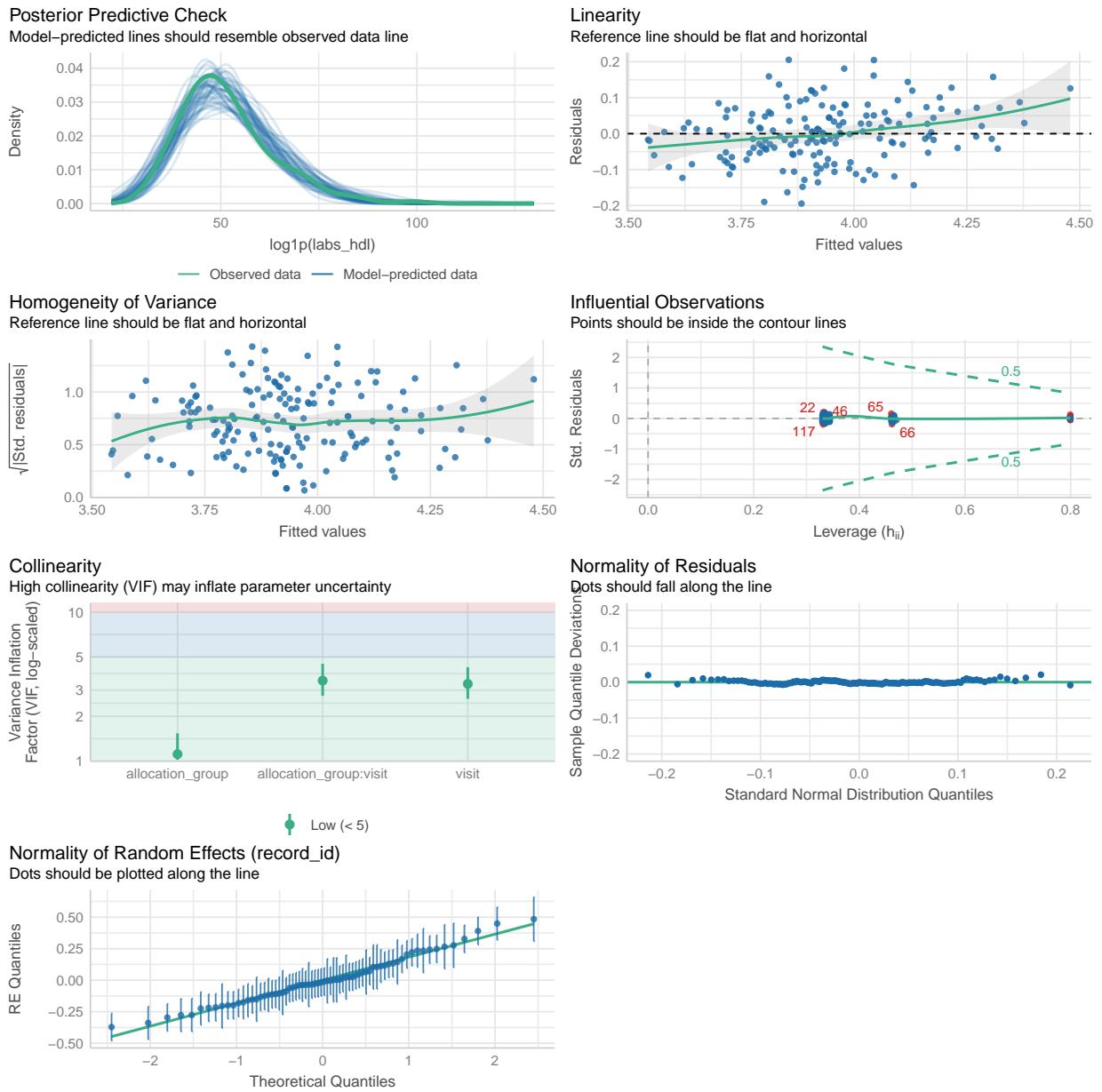
| Name | Model | AIC (weights) | AICc (weights) |
|---------------------|-----------------|----------------|----------------|
| <hr/> | | | |
| labs_hdl_model | lmerModLmerTest | 1319.8 (<.001) | 1320.7 (<.001) |
| labs_hdl_model_sens | lmerModLmerTest | 1181.6 (>.999) | 1182.5 (>.999) |

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


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



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



3.7.2 Médias Marginais Estimadas

3.7.2.1 Todos os dados

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

labs_hdl_raw_emm <- regrid(labs_hdl_raw_emm)
```

```

# Table of marginal means
# labs_hdl_raw_emm

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

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

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

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

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

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

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

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

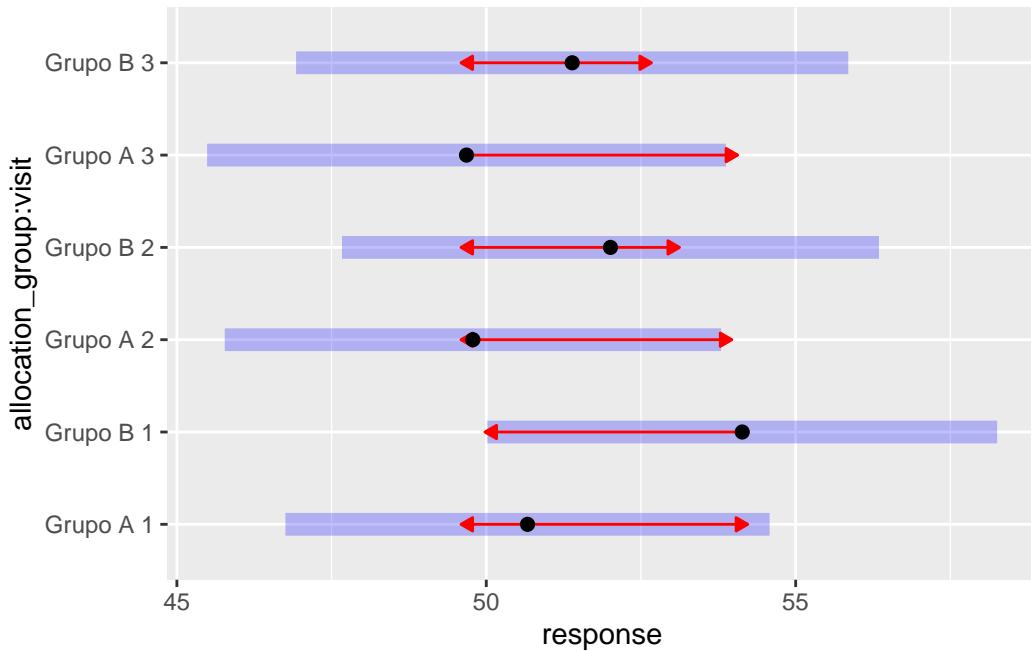
```

```

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests

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

```



3.7.2.2 Análise de sensibilidade

```

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

labs_hdl_emm <- regrid(labs_hdl_emm)

# Table of marginal means
# labs_hdl_emm

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

```

```

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

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

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

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

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

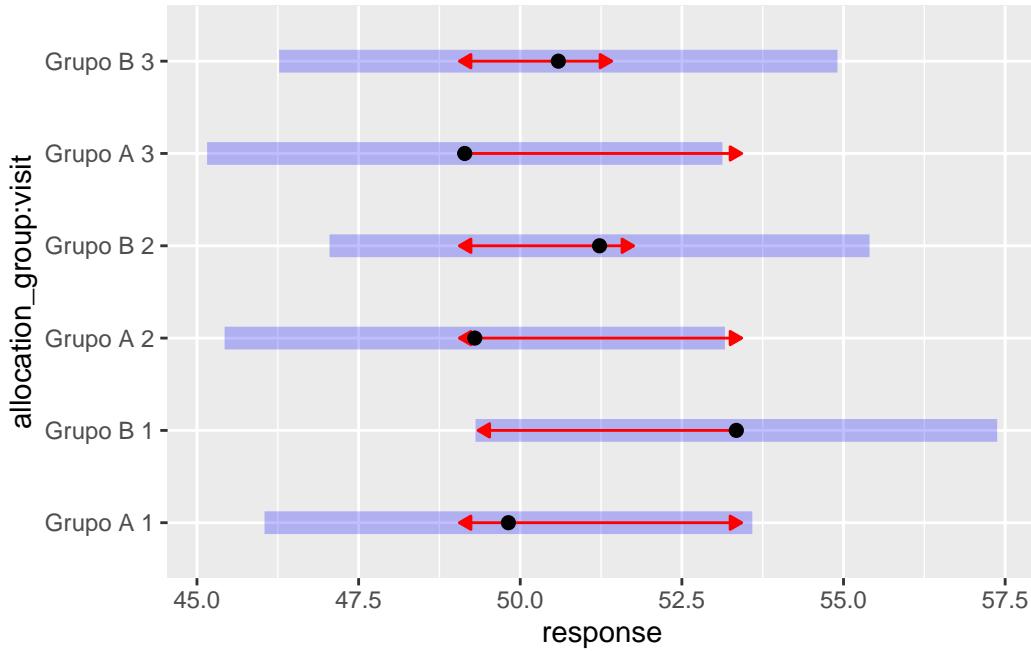
allocation_group = Grupo A:
  contrast      estimate    SE    df lower.CL upper.CL t.ratio p.value
visit1 - visit2     0.520 1.32  83.9     -2.71      3.75   0.394  1.0000
visit1 - visit3     0.675 1.41  83.9     -2.78      4.13   0.477  1.0000
visit2 - visit3     0.155 1.42  93.9     -3.31      3.62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

allocation_group = Grupo B:
  contrast      estimate    SE    df lower.CL upper.CL t.ratio p.value
visit1 - visit2     2.116 1.51  83.9     -1.57      5.80   1.403  0.4931
visit1 - visit3     2.753 1.63  83.9     -1.24      6.75   1.684  0.2874
visit2 - visit3     0.637 1.66 105.0     -3.40      4.67   0.384  1.0000

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests

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

```



3.7.3 Resultado

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

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

| Grupo de comparação | Comparação | Estimativa | IC 95% | p-valor |
|---------------------|---------------------|------------|----------------|---------|
| Entre grupos | Visita 1 | -3,47 | [-9,15 ; 2,21] | 0,228 |
| Entre grupos | Visita 2 | -2,22 | [-8,14 ; 3,69] | 0,458 |
| Entre grupos | Visita 3 | -1,71 | [-7,83 ; 4,42] | 0,582 |
| Grupo Placebo | Visita 1 - Visita 2 | 0,88 | [-2,87 ; 4,64] | 1,000 |
| Grupo Placebo | Visita 1 - Visita 3 | 0,99 | [-3,08 ; 5,05] | 1,000 |
| Grupo Placebo | Visita 2 - Visita 3 | 0,10 | [-3,96 ; 4,17] | 1,000 |
| Grupo Eclipta | Visita 1 - Visita 2 | 2,13 | [-2,12 ; 6,38] | 0,675 |
| Grupo Eclipta | Visita 1 - Visita 3 | 2,75 | [-1,74 ; 7,24] | 0,418 |
| Grupo Eclipta | Visita 2 - Visita 3 | 0,62 | [-3,99 ; 5,22] | 1,000 |

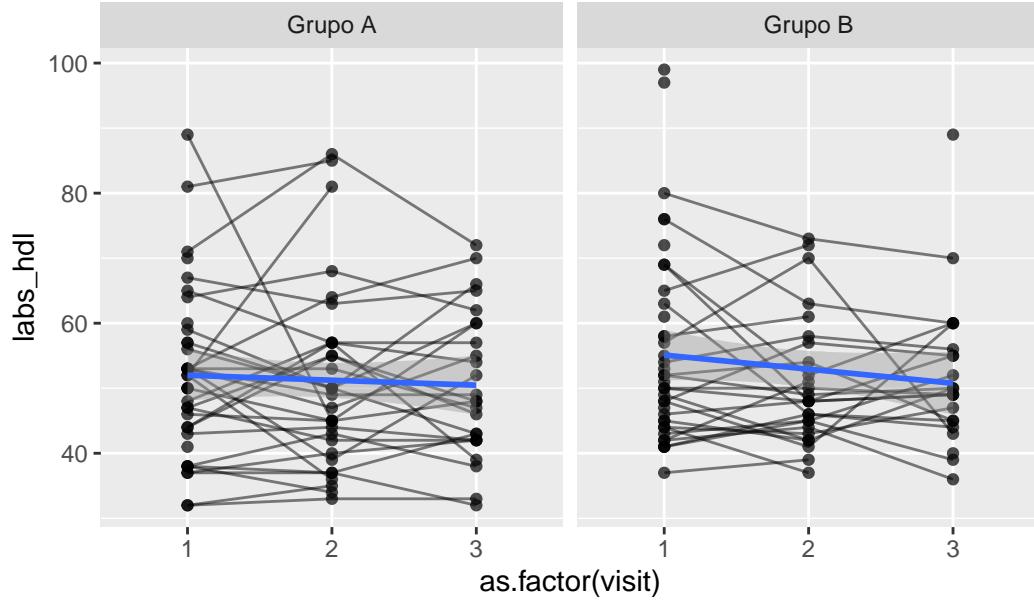
```

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

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

```

All data



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

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

```

facet_wrap(~ allocation_group)

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

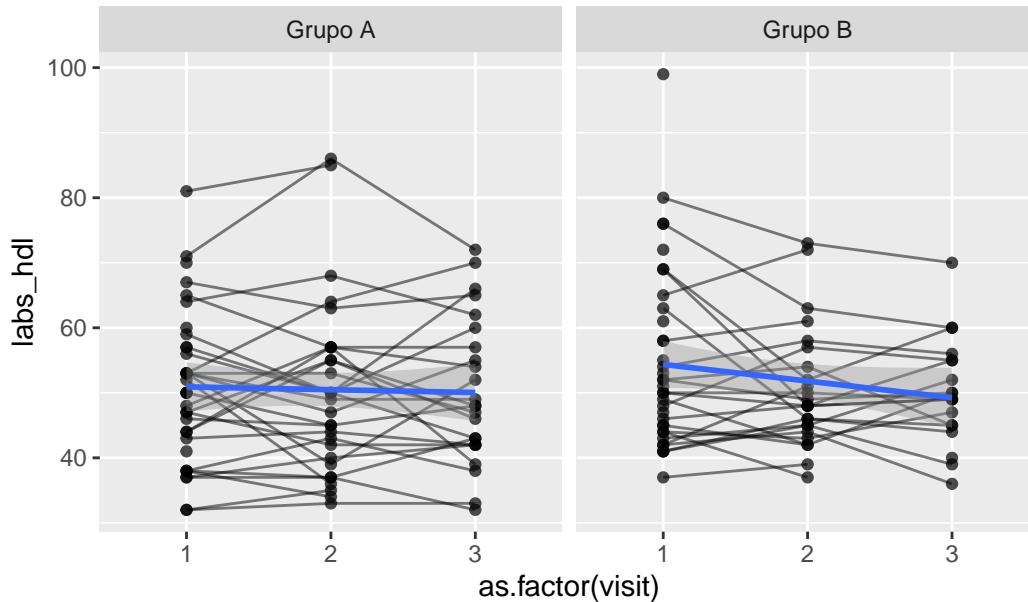
Warning: Removed 8 rows containing non-finite outside the scale range
(`stat_smooth()`).

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

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

```

Sensitivity analysis



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

3.8 Triglicerídeos

Variável: labs_triglycerides

```

# Plot 1: Raw data
labs_triglycerides_hist_1 <- data_model %>%
  #filter(
  #  labs_triglycerides < 300
  #) %>%
  ggplot(aes(x = labs_triglycerides)) +
  geom_histogram(bins = 50, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
labs_triglycerides_hist_2 <- data_model %>%

```

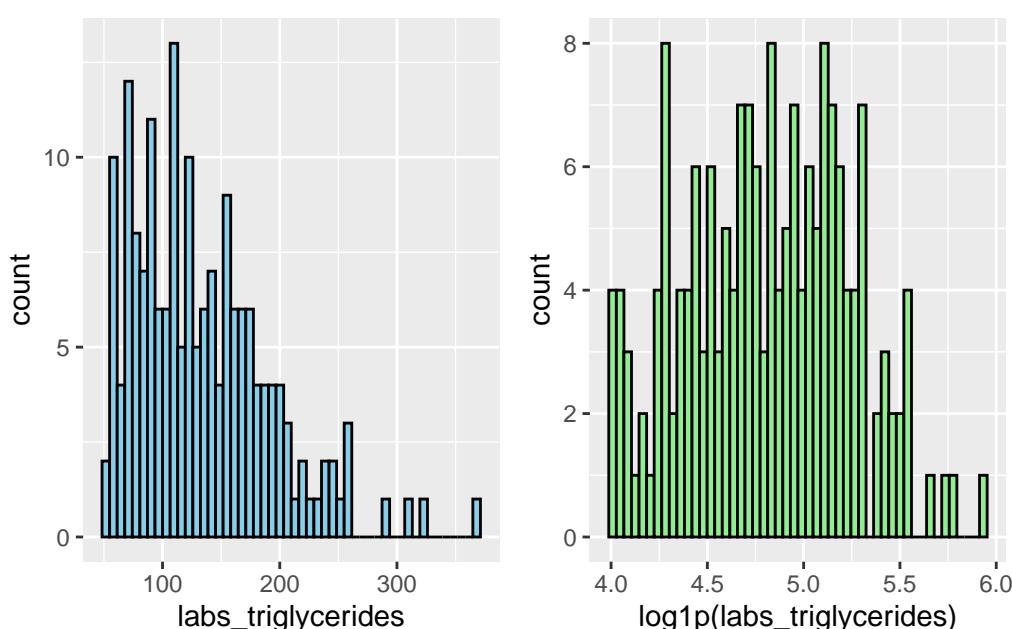
```

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

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

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

```



```

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

# Check for Multicollinearity

```

Low Correlation

| | Term | VIF | VIF 95% CI | Increased SE | Tolerance |
|--|------------------------|------|--------------|--------------|-----------|
| | allocation_group | 1.20 | [1.08, 1.53] | 1.10 | 0.83 |
| | visit | 3.50 | [2.79, 4.49] | 1.87 | 0.29 |
| | allocation_group:visit | 3.82 | [3.03, 4.92] | 1.95 | 0.26 |
| | Tolerance 95% CI | | | | |

```

[0.65, 0.93]
[0.22, 0.36]
[0.20, 0.33]

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

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

# Influential IDs
labs_triglycerides_model_check$influential_ids

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

```

3.8.1 Resumo dos modelos

```

# Model comparison
summary(labs_triglycerides_model)

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

REML criterion at convergence: 156.5

Scaled residuals:
    Min      1Q  Median      3Q     Max 
-2.48575 -0.55624 -0.06875  0.50582  2.77617 

Random effects:
Groups      Name        Variance Std.Dev.
record_id (Intercept) 0.12894  0.3591
Residual            0.06212  0.2492
Number of obs: 179, groups: record_id, 75

```

Fixed effects:

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

(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      -0.374  0.266
visit3      -0.345  0.246  0.449
allctn_GB:2  0.255 -0.358 -0.682 -0.306
allctn_GB:3  0.238 -0.334 -0.309 -0.688  0.433
```

```
summary(labs_triglycerides_model_sens)
```

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

REML criterion at convergence: 110.8

Scaled residuals:

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

Random effects:

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

Number of obs: 164, groups: record_id, 70

Fixed effects:

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

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

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

Correlation of Fixed Effects:

| | (Intr) | all_GB | visit2 | visit3 | a_GB:2 | |
|-------------|--------|--------|--------|--------|--------|-------|
| allctn_gr | GB | -0.727 | | | | |
| visit2 | | -0.333 | 0.242 | | | |
| visit3 | | -0.303 | 0.220 | 0.444 | | |
| allctn_GB:2 | | 0.232 | -0.320 | -0.699 | -0.310 | |
| allctn_GB:3 | | 0.214 | -0.295 | -0.314 | -0.709 | 0.431 |

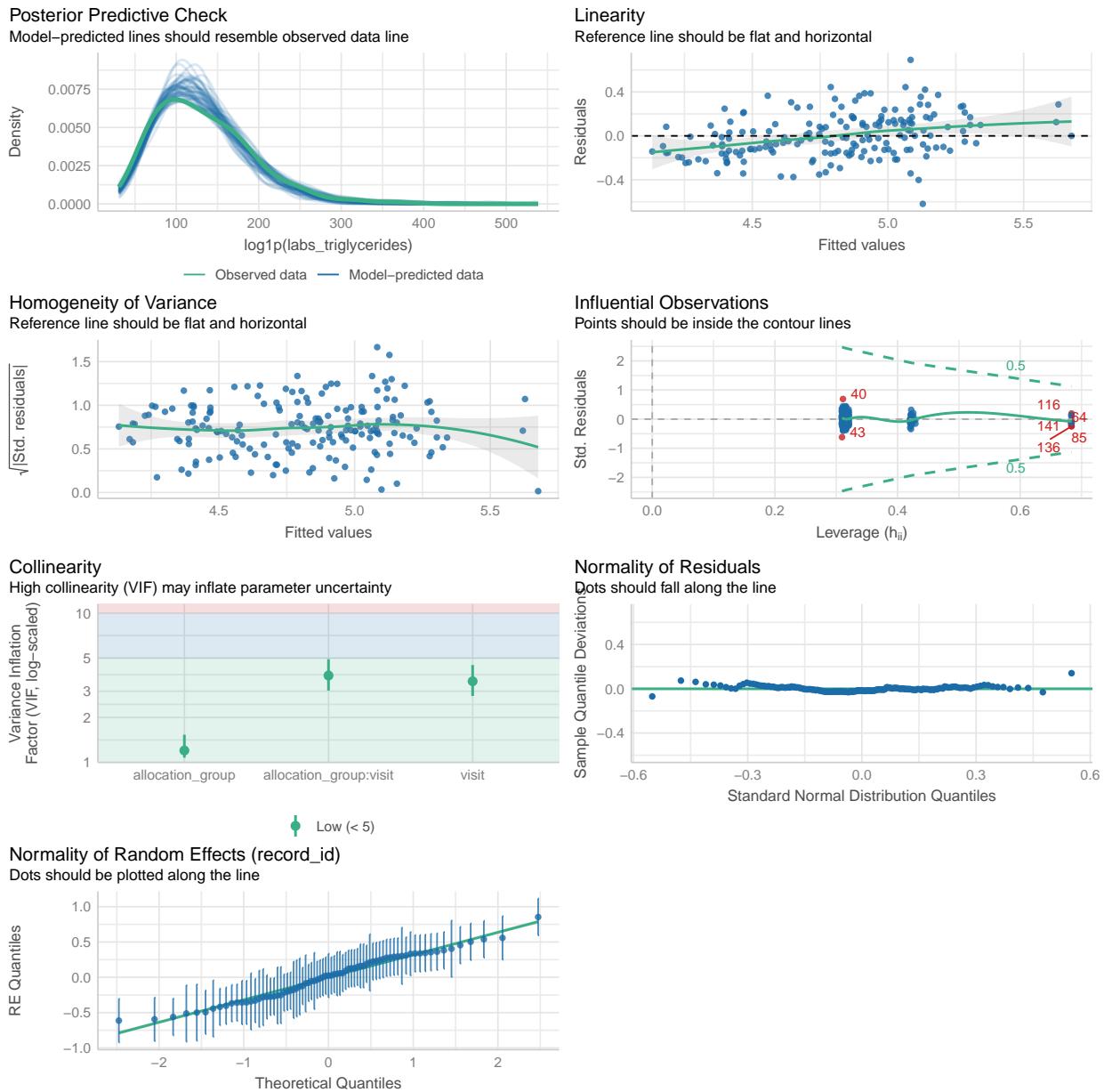
```
performance::compare_performance(  
  labs_triglycerides_model,  
  labs_triglycerides_model_sens)
```

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

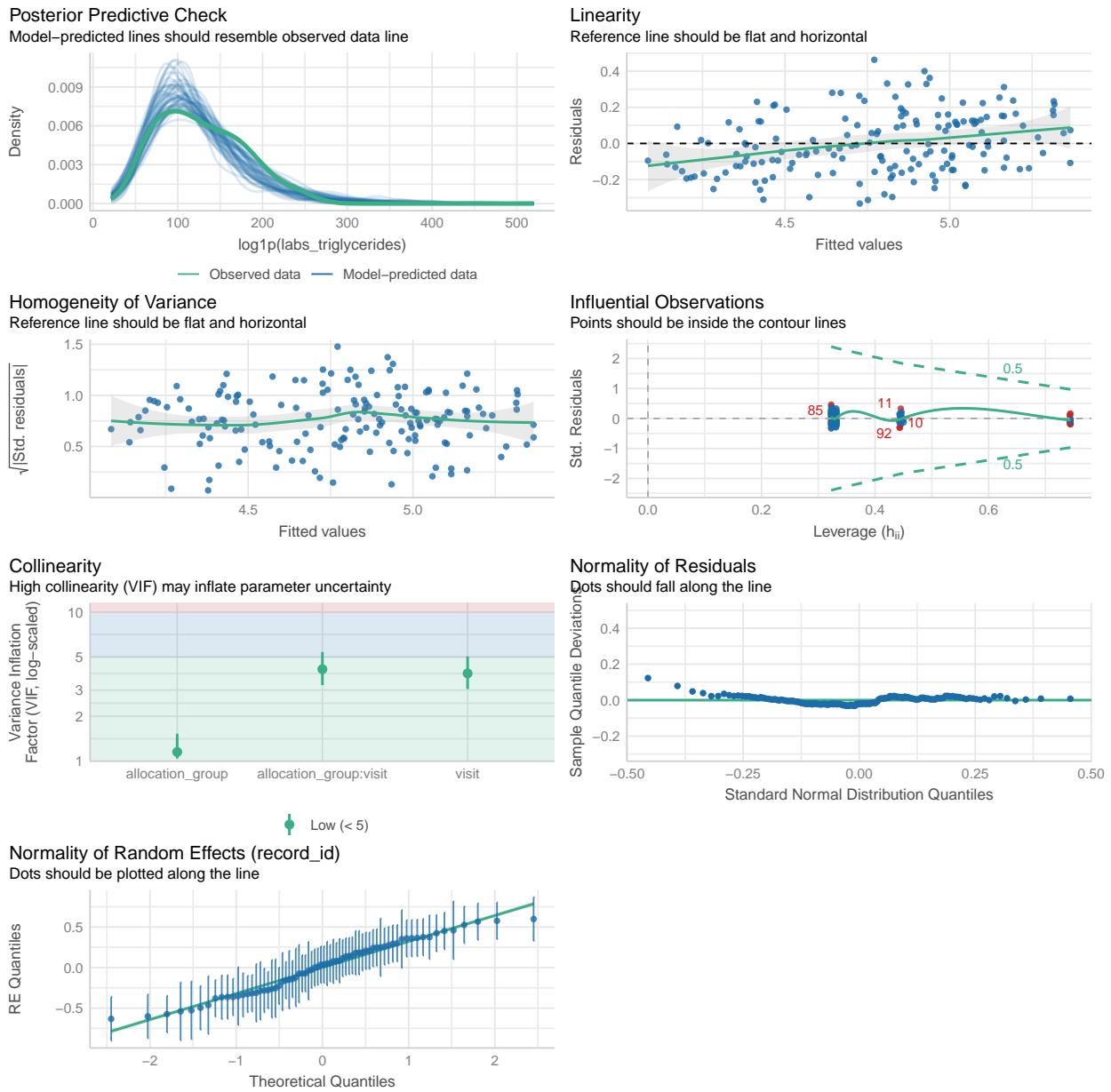
```
# Comparison of Model Performance Indices
```

| Name | Model | AIC (weights) | | |
|-------------------------------|-----------------|----------------|------------|-------|
| <hr/> | | | | |
| labs_triglycerides_model | lmerModLmerTest | 1873.1 (<.001) | | |
| labs_triglycerides_model_sens | lmerModLmerTest | 1671.7 (>.999) | | |
| Name | AICC (weights) | BIC (weights) | R2 (cond.) | |
| labs_triglycerides_model | 1873.9 (<.001) | 1898.6 (<.001) | 0.676 | |
| labs_triglycerides_model_sens | 1672.6 (>.999) | 1696.5 (>.999) | 0.739 | |
| Name | R2 (marg.) | ICC | RMSE | Sigma |
| labs_triglycerides_model | 0.004 | 0.675 | 0.199 | 0.249 |
| labs_triglycerides_model_sens | 0.012 | 0.736 | 0.166 | 0.212 |

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



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



3.8.2 Médias Marginais Estimadas

3.8.2.1 Todos os dados

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

labs_triglycerides_raw_emm <- regrid(labs_triglycerides_raw_emm)
```

```

# Table of marginal means
# labs_triglycerides_raw_emm

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

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

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

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

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

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

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

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

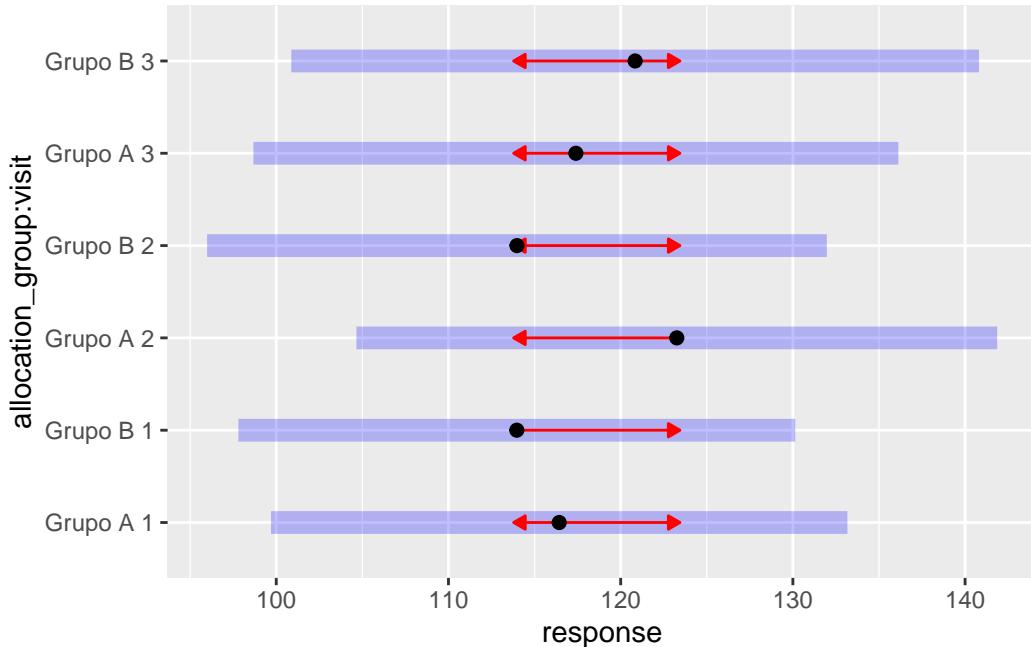
```

```

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests

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

```



3.8.2.2 Análise de sensibilidade

```

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

labs_triglycerides_emm <- regrid(labs_triglycerides_emm)

# Table of marginal means
# labs_triglycerides_emm

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

```

```

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

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

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

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

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

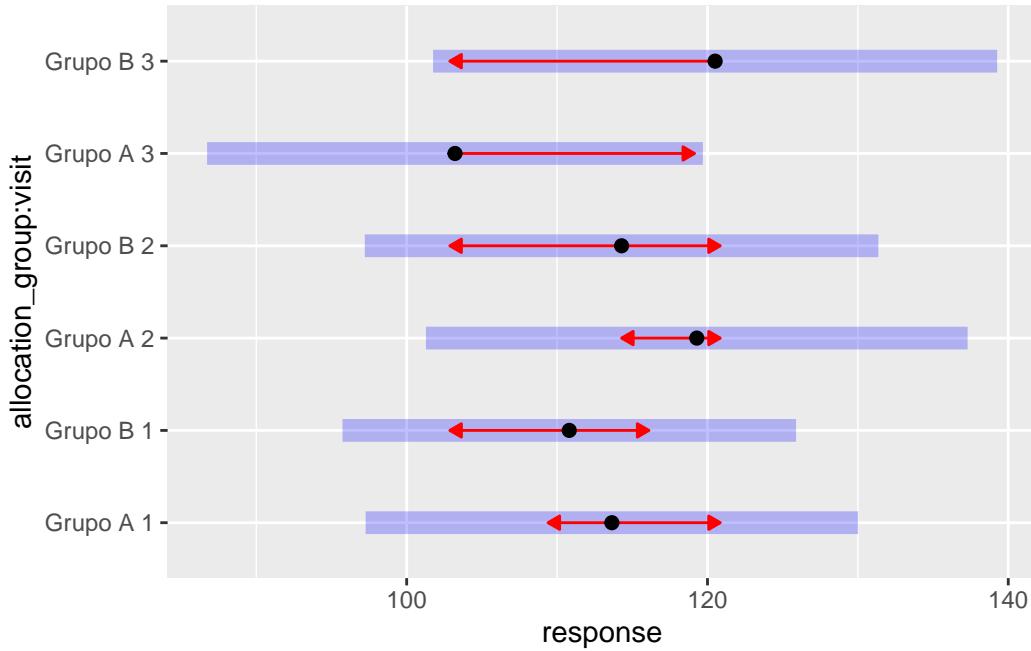
allocation_group = Grupo A:
  contrast      estimate    SE    df lower.CL upper.CL t.ratio p.value
visit1 - visit2     -5.65 6.74   88.9     -22.10    10.81  -0.837  1.0000
visit1 - visit3    10.43 6.81   88.9     -6.17     27.04   1.533  0.3866
visit2 - visit3    16.08 7.12  101.6     -1.25     33.40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

allocation_group = Grupo B:
  contrast      estimate    SE    df lower.CL upper.CL t.ratio p.value
visit1 - visit2     -3.48 6.67   88.9     -19.75    12.79  -0.522  1.0000
visit1 - visit3    -9.70 7.43   88.9     -27.83     8.44  -1.305  0.5861
visit2 - visit3    -6.22 7.76  114.3     -25.07    12.63  -0.802  1.0000

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests

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

```



3.8.3 Resultado

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

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

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

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

| Grupo de comparação | Comparação | Estimativa | IC 95% | p-valor |
|---------------------|---------------------|------------|----------------|---------|
| Grupo Eclipta | Visita 1 - Visita 2 | -0,01 | [-18,8 ; 18,8] | 1,000 |
| Grupo Eclipta | Visita 1 - Visita 3 | -6,87 | [-27,7 ; 14,0] | 1,000 |
| Grupo Eclipta | Visita 2 - Visita 3 | -6,86 | [-28,4 ; 14,7] | 1,000 |

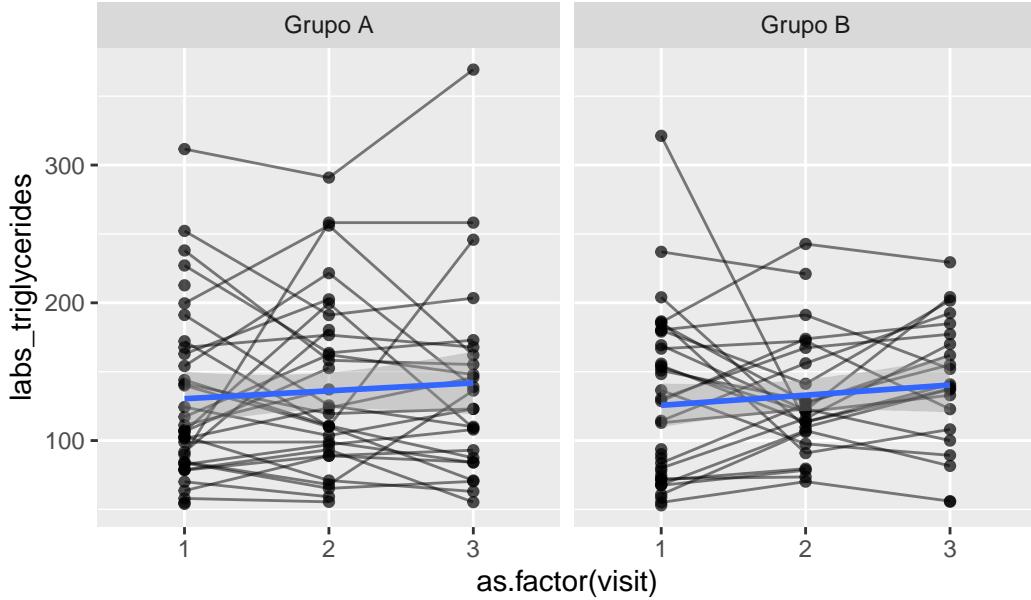
```

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

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

```

All data



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

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

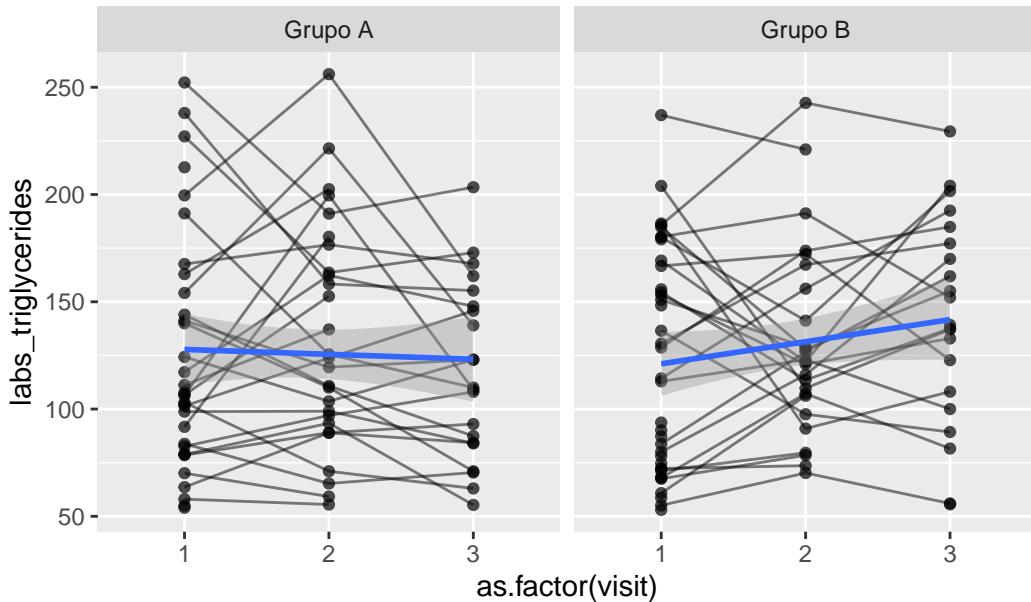
```

facet_wrap(~ allocation_group)

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

```

Sensitivity analysis



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

3.9 Glicemia de jejum

Variável: labs_glucose

```

# Plot 1: Raw data
labs_glucose_hist_1 <- data_model %>%
  #filter(
  #  labs_glucose < 140
  #) %>%
  ggplot(aes(x = labs_glucose)) +
  geom_histogram(bins = 50, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
labs_glucose_hist_2 <- data_model %>%

```

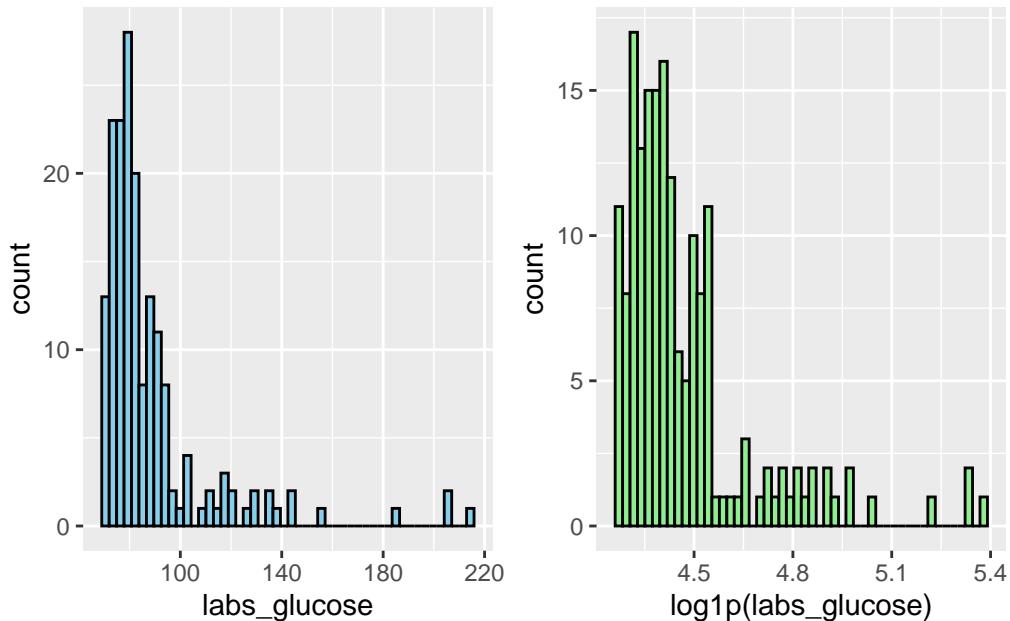
```

#filter(
  #  labs_glucose < 140
  #) %>%
  ggplot(aes(x = log1p(labs_glucose))) +
  geom_histogram(bins = 50, fill = "lightgreen", color = "black")

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

```

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



```

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

# Check for Multicollinearity

```

Low Correlation

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

```

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

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

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

# Influential IDs
labs_glucose_model_check$influential_ids

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

```

3.9.1 Resumo dos modelos

```

# Model comparison
summary(labs_glucose_model)

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

REML criterion at convergence: -153

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

Random effects:
Groups      Name        Variance Std.Dev.
record_id (Intercept) 0.030440 0.17447
Residual            0.008319 0.09121
Number of obs: 176, groups: record_id, 74

```

Fixed effects:

| | Estimate | Std. Error | df | t value |
|--------------------------------|------------|------------|------------|---------|
| (Intercept) | 4.445812 | 0.032366 | 92.773372 | 137.362 |
| allocation_groupGrupo B | 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_groupGrupo B:visit2 | -0.019077 | 0.034014 | 105.360265 | -0.561 |
| allocation_groupGrupo B:visit3 | -0.007509 | 0.036617 | 106.709642 | -0.205 |
| | Pr(> t) | | | |
| (Intercept) | <2e-16 *** | | | |
| allocation_groupGrupo B | 0.949 | | | |
| visit2 | 0.695 | | | |
| visit3 | 0.154 | | | |
| allocation_groupGrupo B:visit2 | 0.576 | | | |
| allocation_groupGrupo B:visit3 | 0.838 | | | |
| --- | | | | |
| Signif. codes: | 0 *** | 0.001 ** | 0.01 * | 0.05 . |
| | 1 | | | |

Correlation of Fixed Effects:

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

```
summary(labs_glucose_model_sens)
```

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

REML criterion at convergence: -224.4

Scaled residuals:

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

Random effects:

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

Number of obs: 161, groups: record_id, 69

Fixed effects:

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

Pr(>|t|)

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

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

Correlation of Fixed Effects:

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

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

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

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

| Name | Model | AIC (weights) | AICc (weights) |
|------|-------|---------------|----------------|
|------|-------|---------------|----------------|

| | | | |
|--------------------|-----------------|----------------|----------------|
| labs_glucose_model | lmerModLmerTest | 1404.0 (<.001) | 1404.9 (<.001) |
|--------------------|-----------------|----------------|----------------|

| | | | |
|-------------------------|-----------------|----------------|----------------|
| labs_glucose_model_sens | lmerModLmerTest | 1183.8 (>.999) | 1184.7 (>.999) |
|-------------------------|-----------------|----------------|----------------|

| Name | BIC (weights) | R2 (cond.) | R2 (marg.) | ICC |
|------|---------------|------------|------------|-----|
|------|---------------|------------|------------|-----|

| | | | | |
|--------------------|----------------|-------|-------|-------|
| labs_glucose_model | 1429.4 (<.001) | 0.787 | 0.006 | 0.785 |
|--------------------|----------------|-------|-------|-------|

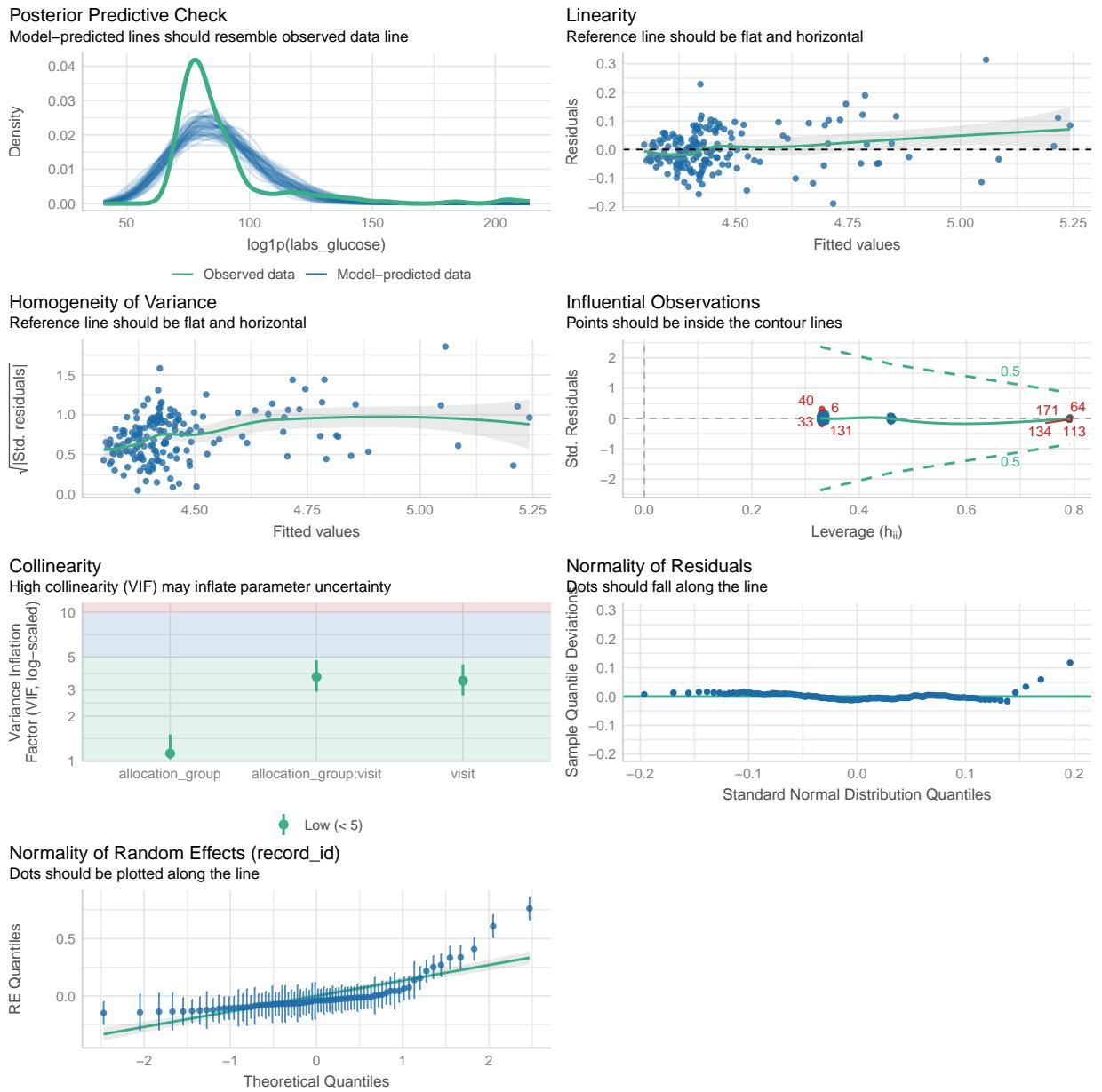
| | | | | |
|-------------------------|----------------|-------|-------|-------|
| labs_glucose_model_sens | 1208.4 (>.999) | 0.675 | 0.007 | 0.672 |
|-------------------------|----------------|-------|-------|-------|

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

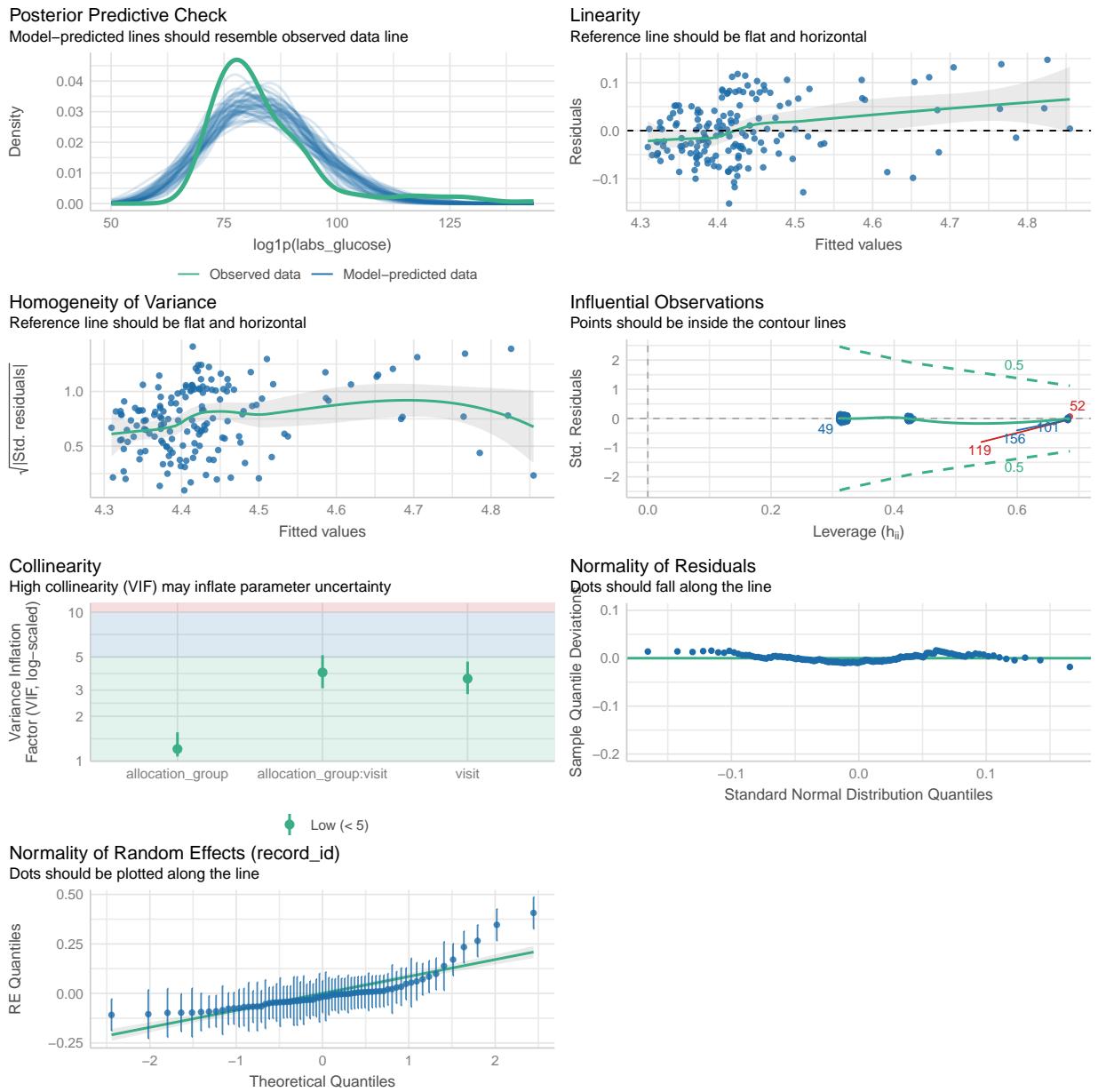
| | | |
|--------------------|-------|-------|
| labs_glucose_model | 0.071 | 0.091 |
|--------------------|-------|-------|

| | | |
|-------------------------|-------|-------|
| labs_glucose_model_sens | 0.061 | 0.076 |
|-------------------------|-------|-------|

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



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



3.9.2 Médias Marginais Estimadas

3.9.2.1 Todos os dados

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

labs_glucose_raw_emm <- regrid(labs_glucose_raw_emm)
```

```

# Table of marginal means
# labs_glucose_raw_emm

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

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

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

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

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

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

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

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

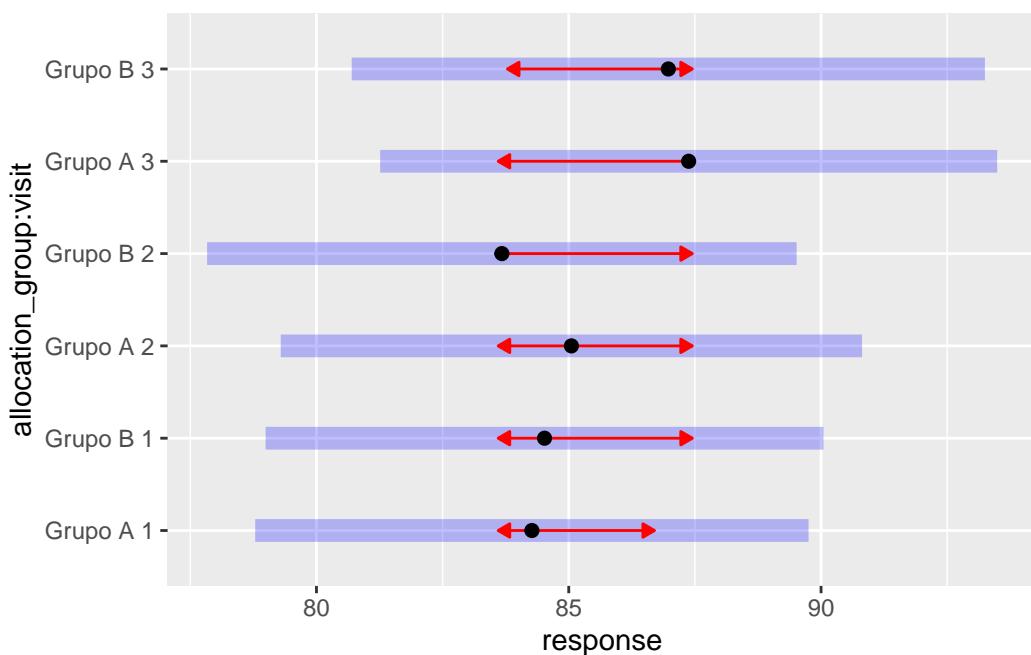
```

```

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests

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

```



3.9.2.2 Análise de sensibilidade

```

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

labs_glucose_emm <- regrid(labs_glucose_emm)

# Table of marginal means
# labs_glucose_emm

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

```

```

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

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

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

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

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

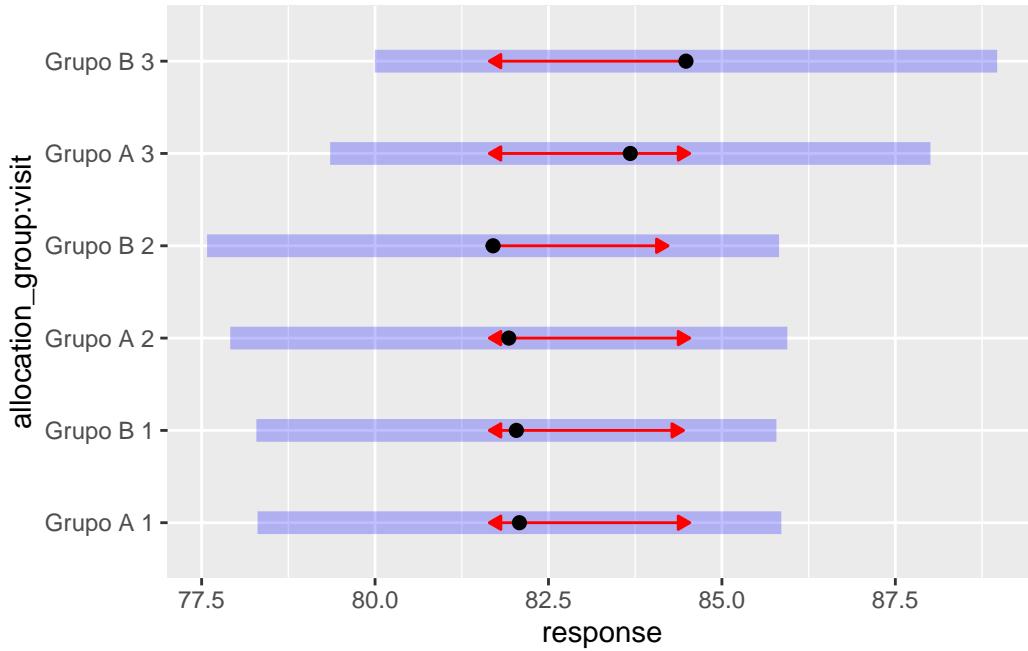
allocation_group = Grupo A:
  contrast      estimate    SE    df lower.CL upper.CL t.ratio p.value
visit1 - visit2   0.153 1.69  93.6    -3.97     4.28   0.091  1.0000
visit1 - visit3  -1.598 1.85  93.6    -6.12     2.92  -0.862  1.0000
visit2 - visit3  -1.752 1.90 109.6    -6.36     2.86  -0.924  1.0000

allocation_group = Grupo B:
  contrast      estimate    SE    df lower.CL upper.CL t.ratio p.value
visit1 - visit2   0.336 1.78  95.5    -4.00     4.67   0.189  1.0000
visit1 - visit3  -2.445 1.98  95.5    -7.26     2.37  -1.237  0.6578
visit2 - visit3  -2.781 2.03 120.0    -7.72     2.16  -1.367  0.5226

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests

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

```



3.9.3 Resultado

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

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

| Grupo de comparação | Comparação | Estimativa | IC 95% | p-valor |
|---------------------|---------------------|------------|----------------|---------|
| Entre grupos | Visita 1 | -0,25 | [-8,04 ; 7,54] | 0,949 |
| Entre grupos | Visita 2 | 1,38 | [-6,83 ; 9,59] | 0,740 |
| Entre grupos | Visita 3 | 0,40 | [-8,36 ; 9,17] | 0,928 |
| Grupo Placebo | Visita 1 - Visita 2 | -0,78 | [-5,65 ; 4,08] | 1,000 |
| Grupo Placebo | Visita 1 - Visita 3 | -3,11 | [-8,42 ; 2,20] | 0,471 |
| Grupo Placebo | Visita 2 - Visita 3 | -2,32 | [-7,73 ; 3,08] | 0,894 |
| Grupo Eclipta | Visita 1 - Visita 2 | 0,85 | [-4,31 ; 6,00] | 1,000 |
| Grupo Eclipta | Visita 1 - Visita 3 | -2,45 | [-8,17 ; 3,26] | 0,894 |
| Grupo Eclipta | Visita 2 - Visita 3 | -3,30 | [-9,10 ; 2,51] | 0,510 |

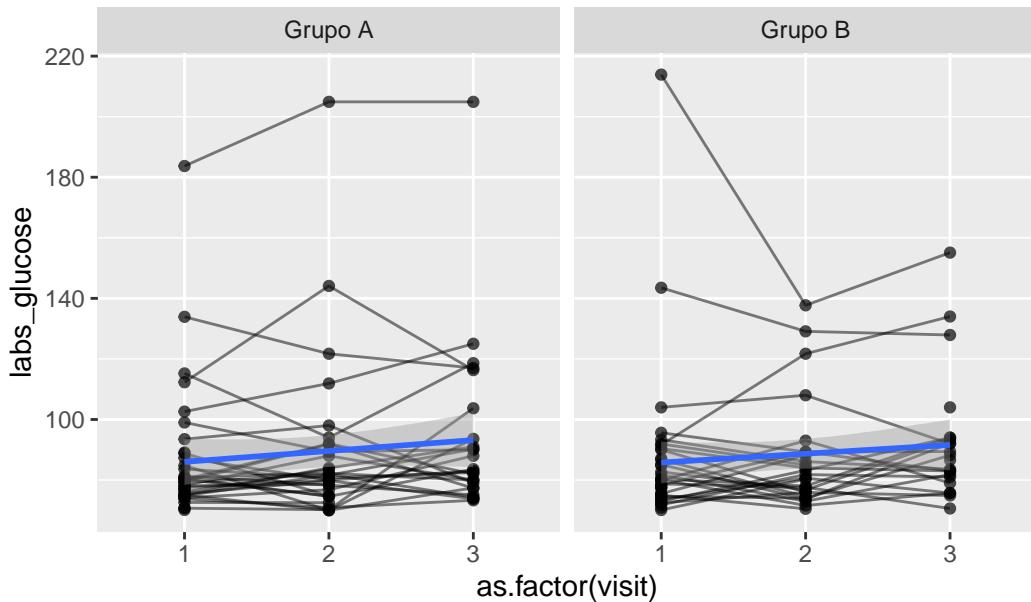
```

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

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

```

All data



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

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

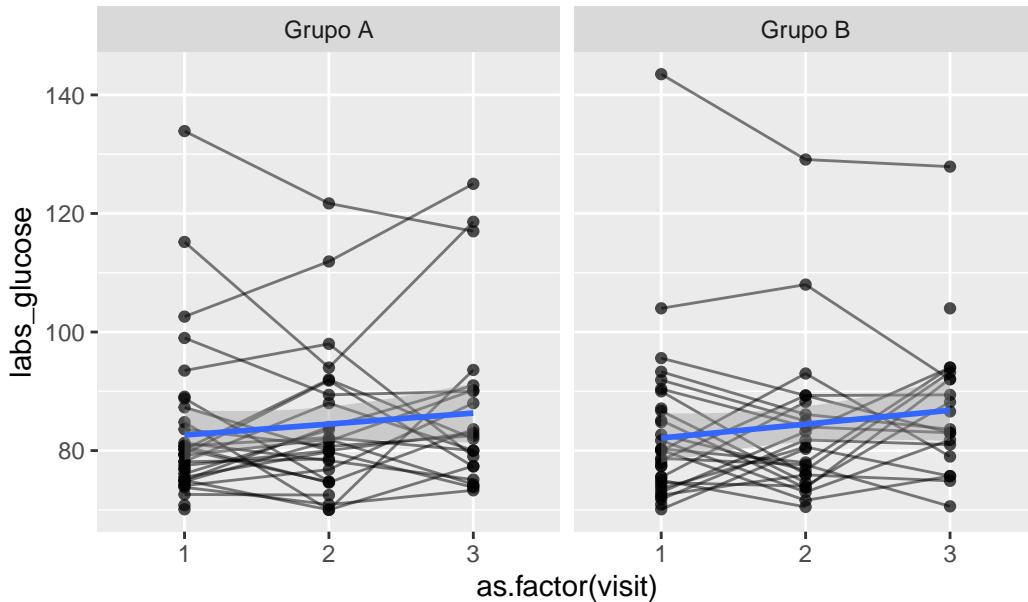
```

facet_wrap(~ allocation_group)

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

```

Sensitivity analysis



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

3.10 Hemoglobina Glicosilada

Variável: labs_hba1c

```

# Plot 1: Raw data
labs_hba1c_hist_1 <- data_model %>%
  #filter(
  #  labs_hba1c < 300
  #) %>%
  ggplot(aes(x = labs_hba1c)) +
  geom_histogram(bins = 50, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
labs_hba1c_hist_2 <- data_model %>%

```

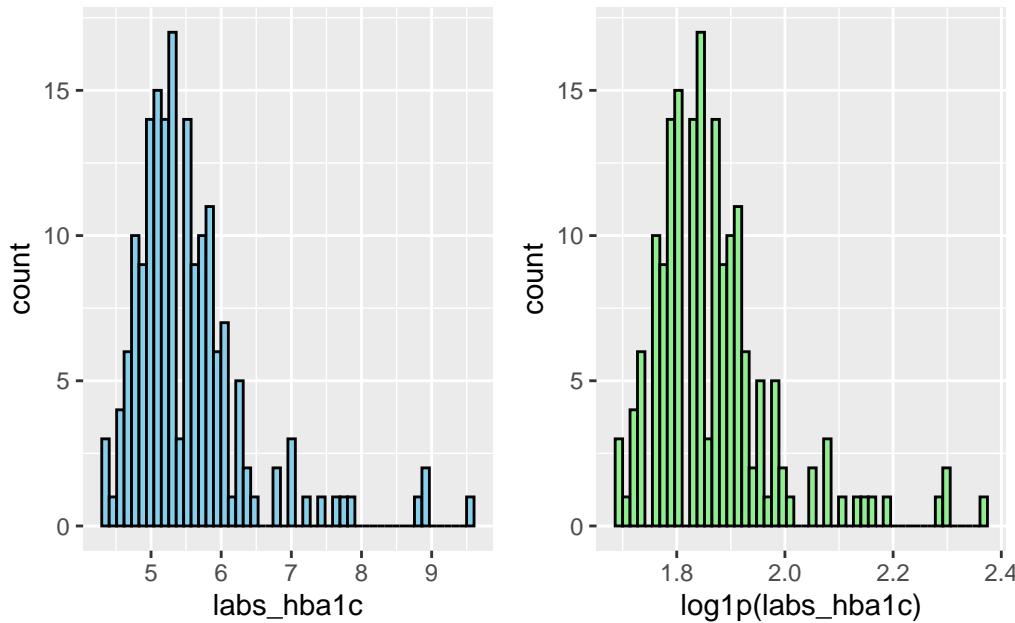
```

#filter(
  #  labs_hba1c < 300
  #) %>%
  ggplot(aes(x = log1p(labs_hba1c))) +
  geom_histogram(bins = 50, fill = "lightgreen", color = "black")

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

```

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



```

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

# Check for Multicollinearity

```

Low Correlation

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

```

[0.52, 1.00]
[0.21, 0.35]
[0.21, 0.34]

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

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

# Influential IDS
labs_hba1c_model_check$influential_ids

[1] "16" "17" "34" "56" "52"

```

3.10.1 Resumo dos modelos

```

# Model comparison
summary(labs_hba1c_model)

Linear mixed model fit by REML. t-tests use Satterthwaite's method [
lmerModLmerTest]
Formula: log1p(labs_hba1c) ~ allocation_group * visit + (1 | record_id)
Data: data_model

REML criterion at convergence: -411.1

Scaled residuals:
    Min      1Q  Median      3Q     Max 
-3.3899 -0.3924 -0.0647  0.3801  3.3624 

Random effects:
Groups      Name        Variance Std.Dev. 
record_id (Intercept) 0.011000 0.10488 
Residual            0.001301 0.03607 
Number of obs: 176, groups: record_id, 75

```

Fixed effects:

| | Estimate | Std. Error | df | t value |
|--------------------------------|------------|------------|-----------|---------|
| (Intercept) | 1.869e+00 | 1.823e-02 | 8.210e+01 | 102.481 |
| allocation_groupGrupo B | -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_groupGrupo B:visit2 | -4.818e-03 | 1.358e-02 | 1.003e+02 | -0.355 |
| allocation_groupGrupo B:visit3 | -2.942e-03 | 1.455e-02 | 1.005e+02 | -0.202 |
| | Pr(> t) | | | |
| (Intercept) | <2e-16 *** | | | |
| allocation_groupGrupo B | 0.449 | | | |
| visit2 | 0.961 | | | |
| visit3 | 0.170 | | | |
| allocation_groupGrupo B:visit2 | 0.724 | | | |
| allocation_groupGrupo B:visit3 | 0.840 | | | |
| --- | | | | |
| Signif. codes: | 0 *** | 0.001 ** | 0.01 * | 0.05 . |
| | ' | ' | ' | ' |
| | ' | ' | ' | ' |

Correlation of Fixed Effects:

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

```
summary(labs_hba1c_model_sens)
```

```
Linear mixed model fit by REML. t-tests use Satterthwaite's method [
lmerModLmerTest]
Formula: log1p(labs_hba1c) ~ allocation_group * visit + (1 | record_id)
Data: data_model
Subset: !(record_id %in% labs_hba1c_model_check$influential_ids)
```

REML criterion at convergence: -468.7

Scaled residuals:

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

Random effects:

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

Number of obs: 161, groups: record_id, 70

Fixed effects:

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

Pr(>|t|)

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

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

Correlation of Fixed Effects:

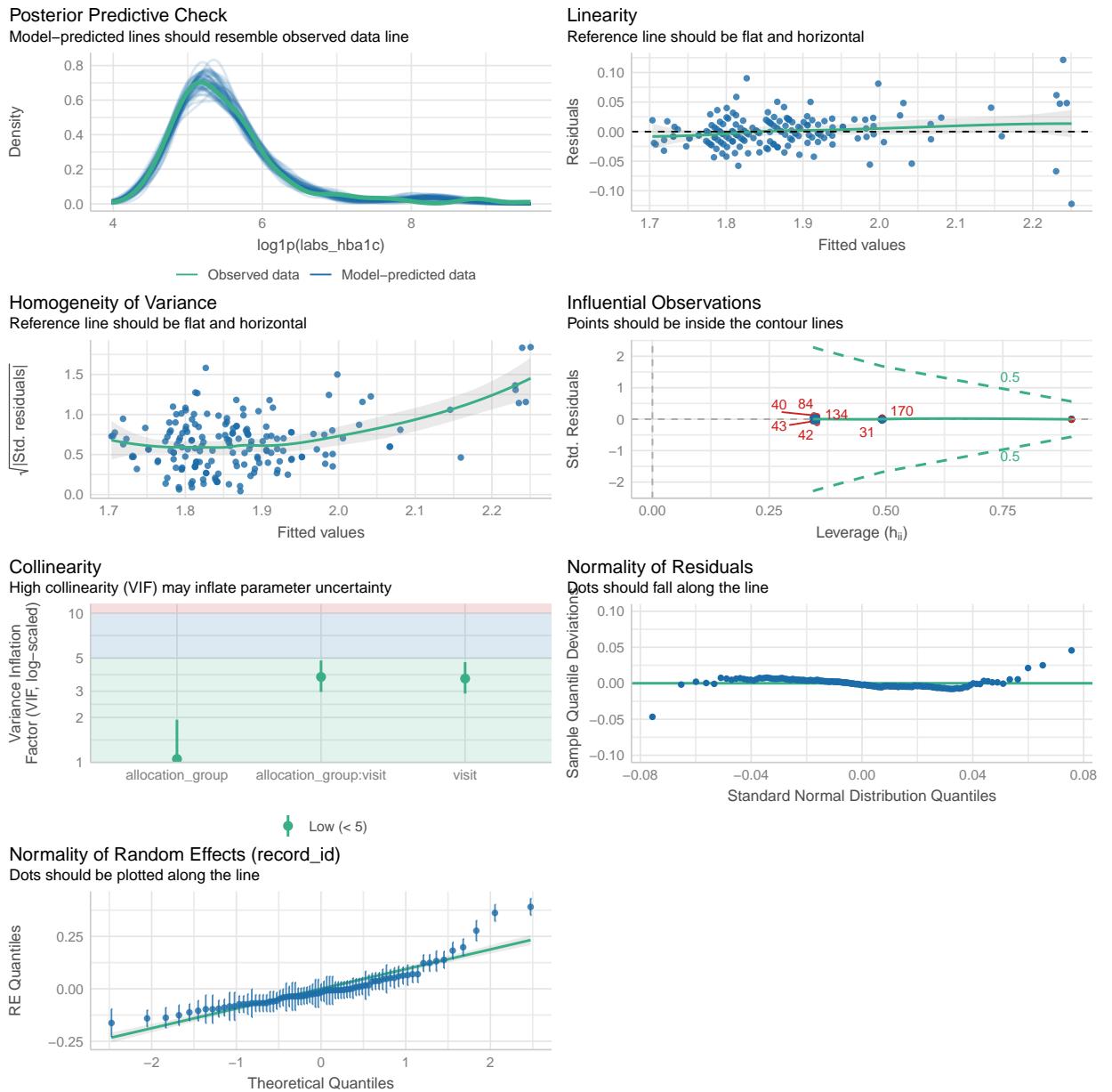
| | (Intr) | all_GB | visit2 | visit3 | a_GB:2 |
|-------------|--------|--------|--------|--------|--------|
| allctn_grGB | -0.697 | | | | |
| visit2 | -0.192 | 0.134 | | | |
| visit3 | -0.178 | 0.124 | 0.430 | | |
| allctn_GB:2 | 0.128 | -0.183 | -0.665 | -0.286 | |
| allctn_GB:3 | 0.118 | -0.170 | -0.285 | -0.664 | 0.423 |

```
performance::compare_performance(  
  labs_hba1c_model,  
  labs_hba1c_model_sens)
```

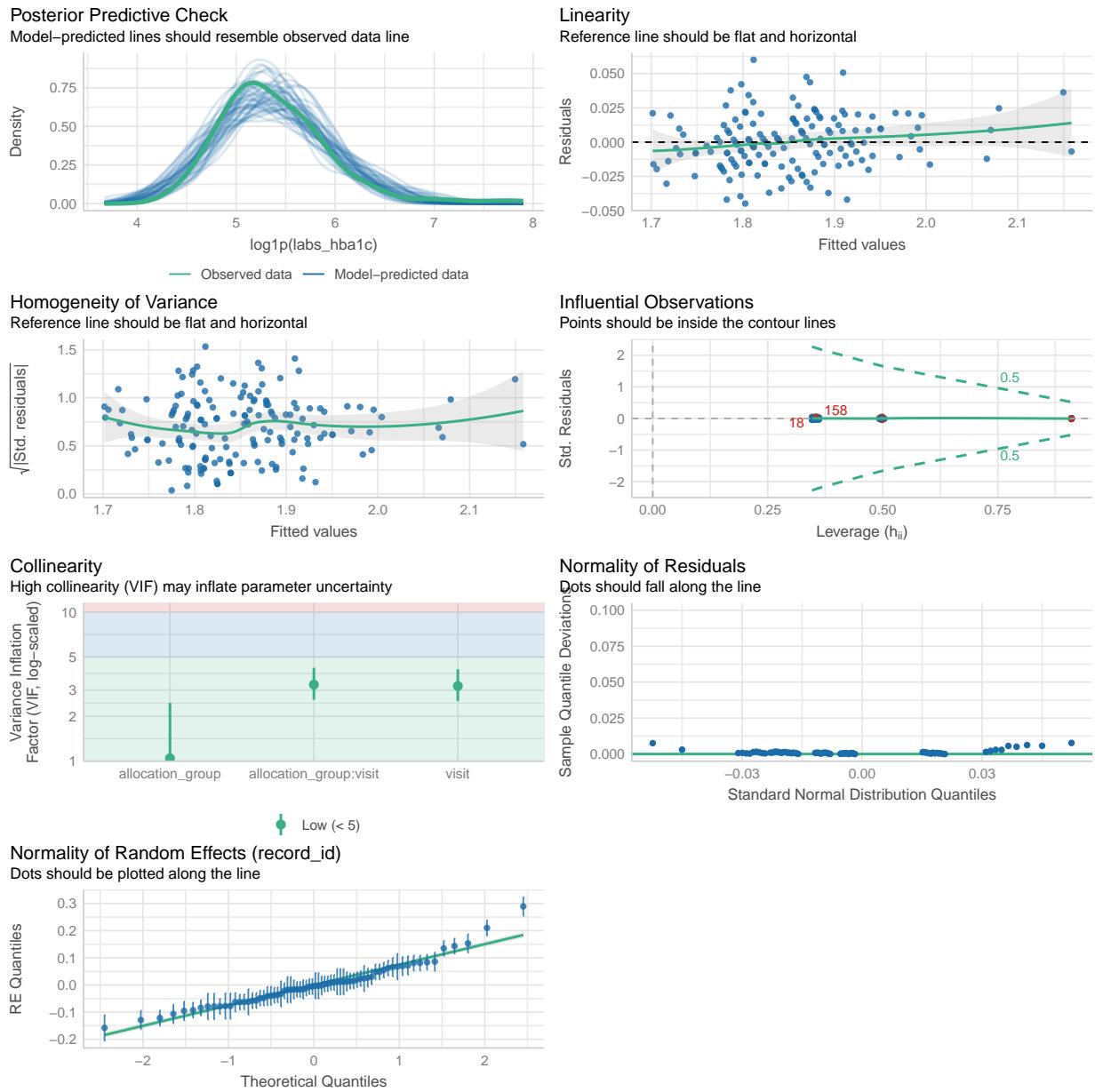
When comparing models, please note that probably not all models were fit
from same data.

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

| Name | Model | AIC (weights) | AICc (weights) | | | |
|--|-----------------|---------------|----------------|-------|-------|-------|
| <hr/> | | | | | | |
| labs_hba1c_model | lmerModLmerTest | 220.5 (<.001) | 221.4 (<.001) | | | |
| labs_hba1c_model_sens | lmerModLmerTest | 97.5 (>.999) | 98.5 (>.999) | | | |
| Name | BIC (weights) | R2 (cond.) | R2 (marg.) | ICC | RMSE | Sigma |
| <hr/> | | | | | | |
| labs_hba1c_model | 245.9 (<.001) | 0.896 | 0.013 | 0.894 | 0.027 | 0.036 |
| labs_hba1c_model_sens | 122.2 (>.999) | 0.911 | 0.040 | 0.907 | 0.019 | 0.026 |
| performance::check_model(labs_hba1c_model) | | | | | | |



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



3.10.2 Médias Marginais Estimadas

3.10.2.1 Todos os dados

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

labs_hba1c_raw_emm <- regrid(labs_hba1c_raw_emm)
```

```

# Table of marginal means
# labs_hba1c_raw_emm

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

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

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

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

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

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

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

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

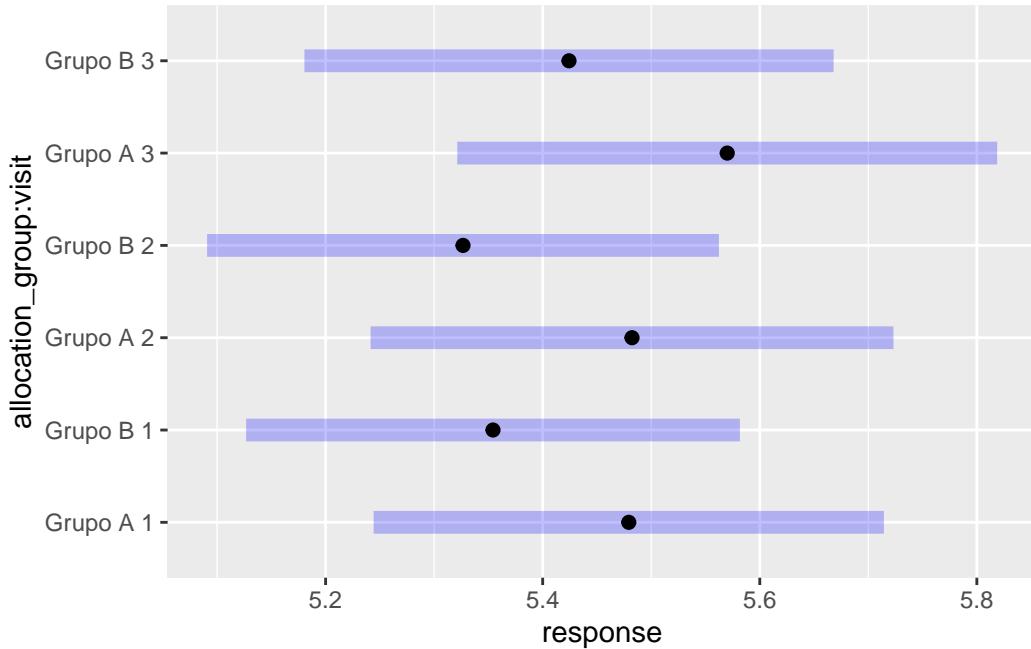
```

```

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests

# Plot of marginal means
plot(labs_hba1c_raw_emm)

```



3.10.2.2 Análise de sensibilidade

```

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

# Table of marginal means
# labs_hba1c_emm

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

visit = 1:
  contrast      estimate       SE     df lower.CL upper.CL t.ratio p.value

```

```
Grupo A - Grupo B  0.0329 0.0201 74.3 -0.00710  0.0728  1.639  0.1055
```

visit = 2:

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

visit = 3:

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

Note: contrasts are still on the log1p scale. Consider using

regrid() if you want contrasts of back-transformed estimates.

Degrees-of-freedom method: kenward-roger

Confidence level used: 0.95

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

allocation_group = Grupo A:

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

allocation_group = Grupo B:

| contrast | estimate | SE | df | lower.CL | upper.CL | t.ratio | p.value |
|-----------------|----------|---------|------|----------|----------|---------|---------|
| visit1 - visit2 | 0.00435 | 0.00757 | 89.4 | -0.0141 | 0.02282 | 0.574 | 1.0000 |
| visit1 - visit3 | -0.01258 | 0.00819 | 89.5 | -0.0326 | 0.00741 | -1.536 | 0.3845 |
| visit2 - visit3 | -0.01693 | 0.00852 | 87.9 | -0.0377 | 0.00387 | -1.986 | 0.1504 |

Note: contrasts are still on the log1p scale. Consider using

regrid() if you want contrasts of back-transformed estimates.

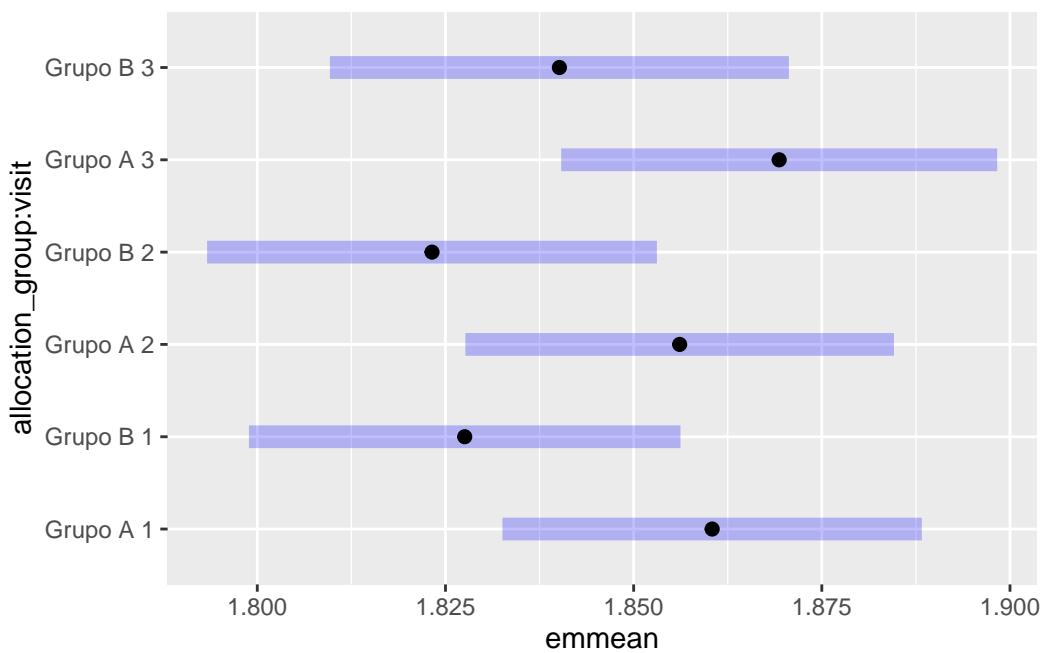
Degrees-of-freedom method: kenward-roger

Confidence level used: 0.95

Conf-level adjustment: bonferroni method for 3 estimates

P value adjustment: bonferroni method for 3 tests

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



3.10.3 Resultado

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

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

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

| Grupo de comparação | Comparação | Estimativa | IC 95% | p-valor |
|---------------------|---------------------|------------|----------------|---------|
| Grupo Eclipta | Visita 2 - Visita 3 | -0,10 | [-0,27 ; 0,07] | 0,489 |

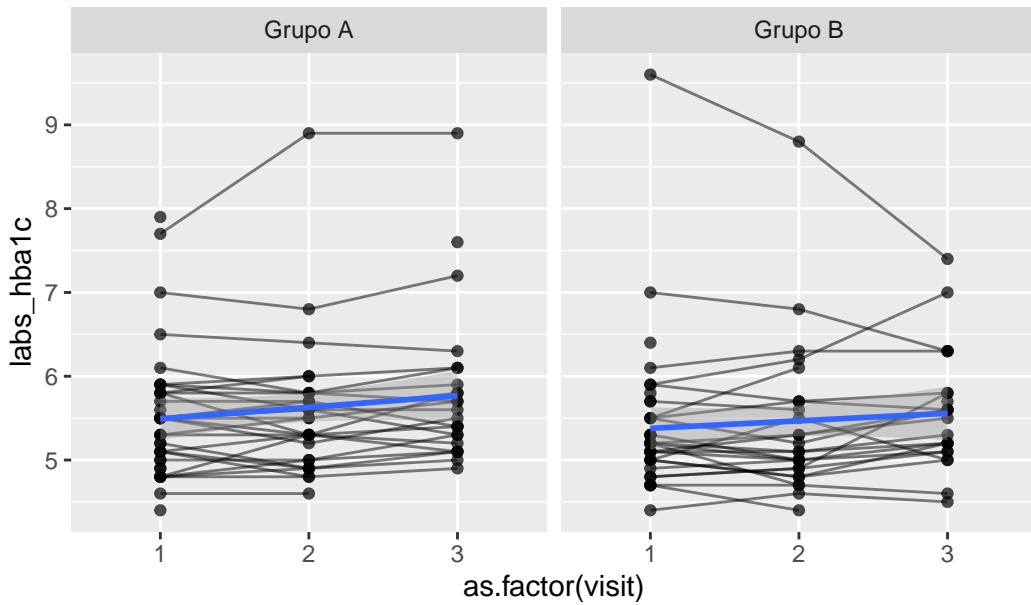
```

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") +
```

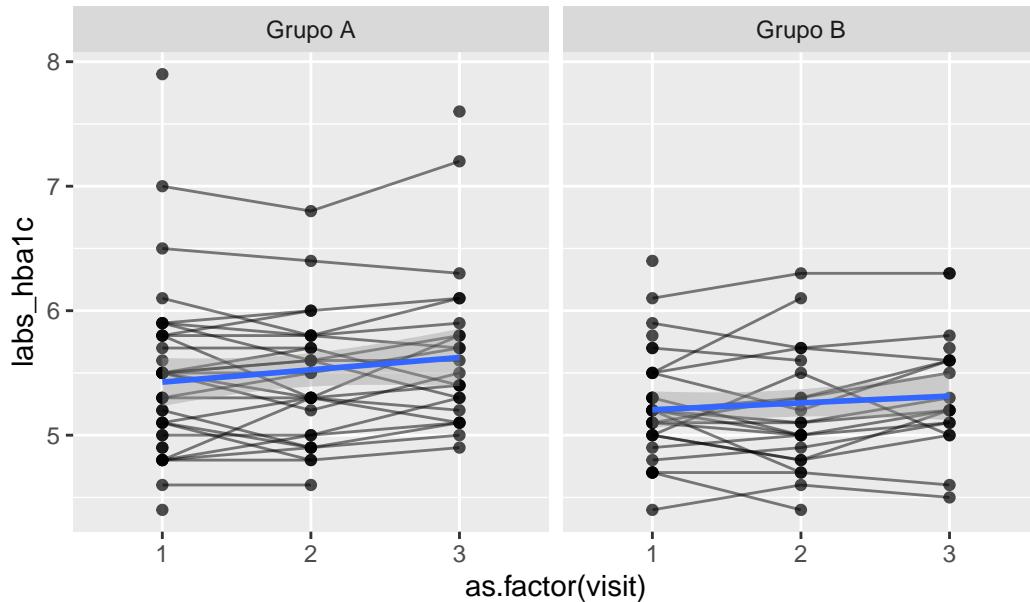
```

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))
```

3.11 Insulina

Variável: labs_insulin

```

# Plot 1: Raw data
labs_insulin_hist_1 <- data_model %>%
  #filter(
  #  labs_insulin < 300
  #) %>%
  ggplot(aes(x = labs_insulin)) +
  geom_histogram(bins = 50, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
labs_insulin_hist_2 <- data_model %>%

```

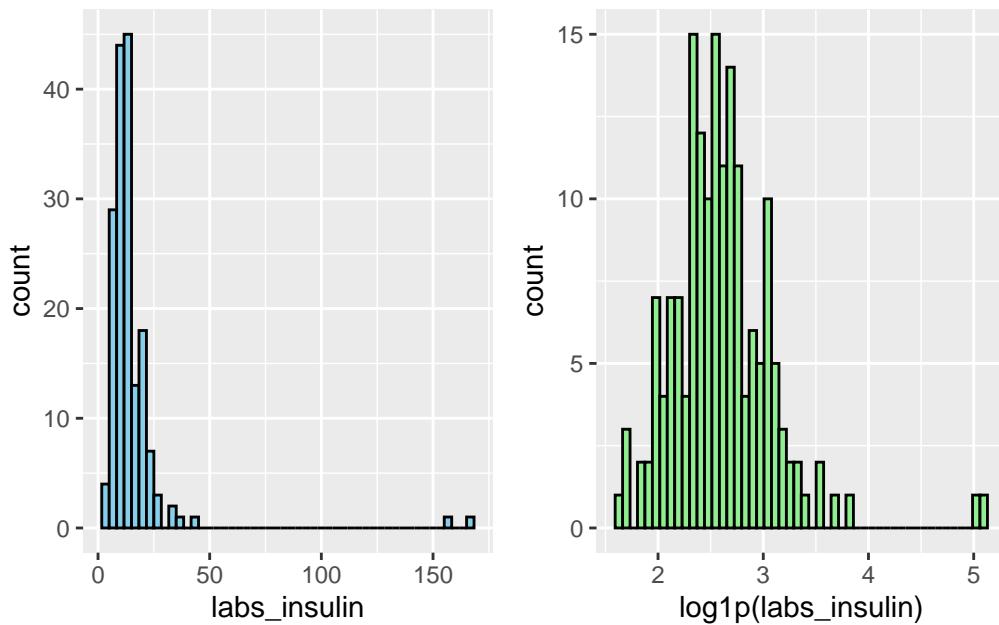
```

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

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

```

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



```

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

# Check for Multicollinearity

```

Low Correlation

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

```

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

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

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

# Influential IDS
labs_insulin_model_check$influential_ids

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

```

3.11.1 Resumo dos modelos

```

# Model comparison
summary(labs_insulin_model)

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

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

```

REML criterion at convergence: 187.4

Scaled residuals:

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

Random effects:

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

Number of obs: 169, groups: record_id, 74

Fixed effects:

| | Estimate | Std. Error | df | t value | Pr(> t) |
|--------------------------------|----------|------------|-----------|---------|----------|
| (Intercept) | 2.64624 | 0.07855 | 107.03898 | 33.689 | <2e-16 |
| allocation_groupGrupo B | -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_groupGrupo B:visit2 | 0.08449 | 0.10664 | 101.86854 | 0.792 | 0.4300 |
| allocation_groupGrupo B:visit3 | 0.06963 | 0.11919 | 103.64642 | 0.584 | 0.5603 |

(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 -0.378 0.267
visit3 -0.351 0.248 0.409
allctn_GB:2 0.263 -0.372 -0.695 -0.284
allctn_GB:3 0.235 -0.332 -0.274 -0.670 0.394

summary(labs_insulin_model_sens)

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

REML criterion at convergence: 115.2

Scaled residuals:

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

Random effects:

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

Number of obs: 154, groups: record_id, 69

Fixed effects:

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

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

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

Correlation of Fixed Effects:

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

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

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

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

| Name | Model | AIC (weights) | AICc (weights) |
|------|-------|---------------|----------------|
|------|-------|---------------|----------------|

| | | | |
|--------------------|-----------------|----------------|----------------|
| labs_insulin_model | lmerModLmerTest | 1062.1 (<.001) | 1063.0 (<.001) |
|--------------------|-----------------|----------------|----------------|

| | | | |
|-------------------------|-----------------|---------------|---------------|
| labs_insulin_model_sens | lmerModLmerTest | 900.0 (>.999) | 901.0 (>.999) |
|-------------------------|-----------------|---------------|---------------|

| Name | BIC (weights) | R2 (cond.) | R2 (marg.) | ICC |
|------|---------------|------------|------------|-----|
|------|---------------|------------|------------|-----|

| | | | | |
|--------------------|----------------|-------|-------|-------|
| labs_insulin_model | 1087.2 (<.001) | 0.649 | 0.016 | 0.643 |
|--------------------|----------------|-------|-------|-------|

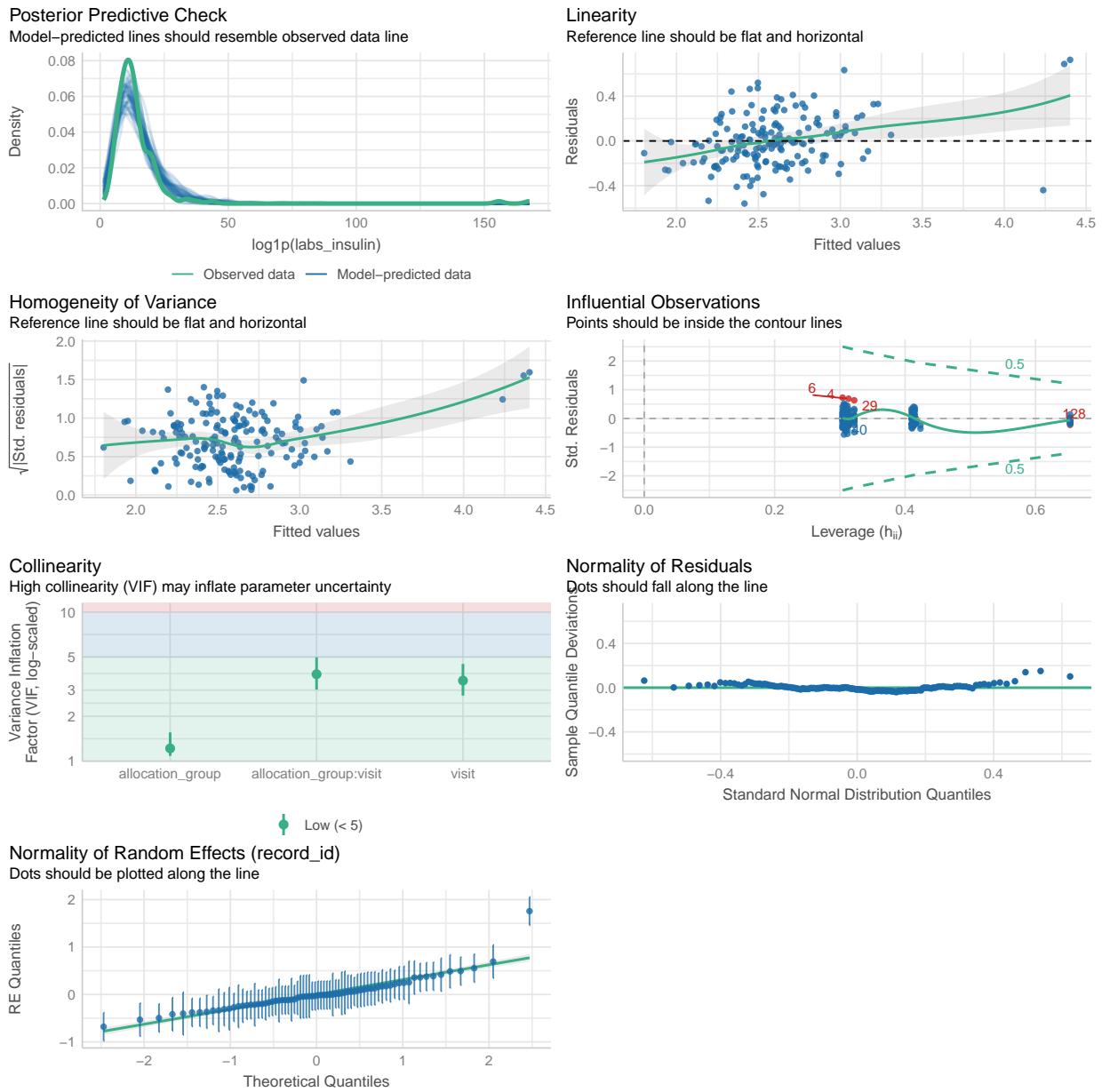
| | | | | |
|-------------------------|---------------|-------|-------|-------|
| labs_insulin_model_sens | 924.3 (>.999) | 0.605 | 0.025 | 0.595 |
|-------------------------|---------------|-------|-------|-------|

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

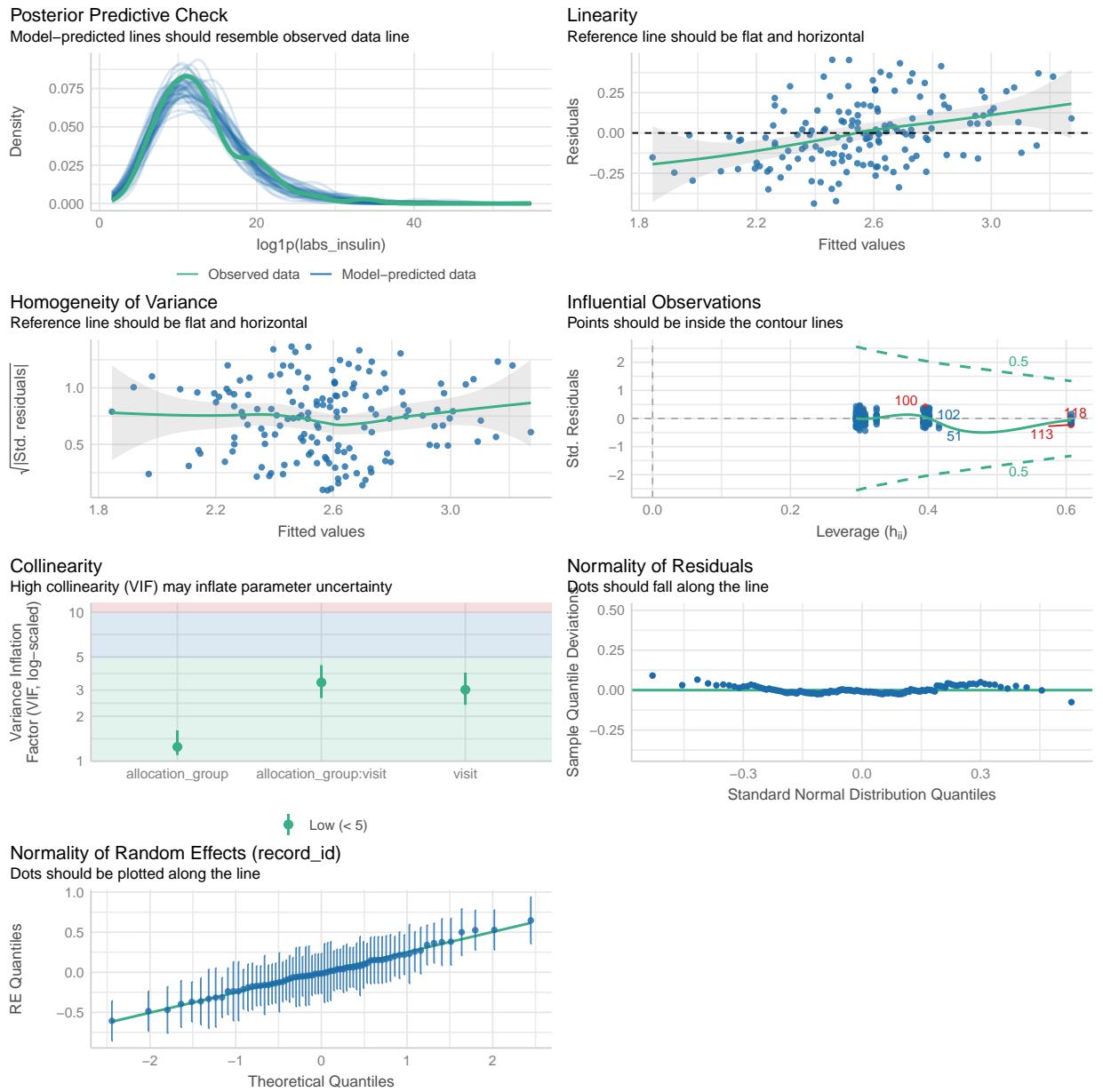
| | | |
|--------------------|-------|-------|
| labs_insulin_model | 0.227 | 0.285 |
|--------------------|-------|-------|

| | | |
|-------------------------|-------|-------|
| labs_insulin_model_sens | 0.195 | 0.244 |
|-------------------------|-------|-------|

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



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



3.11.2 Médias Marginais Estimadas

3.11.2.1 Todos os dados

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

labs_insulin_raw_emm <- regrid(labs_insulin_raw_emm)
```

```

# Table of marginal means
# labs_insulin_raw_emm

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

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

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

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

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

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

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

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

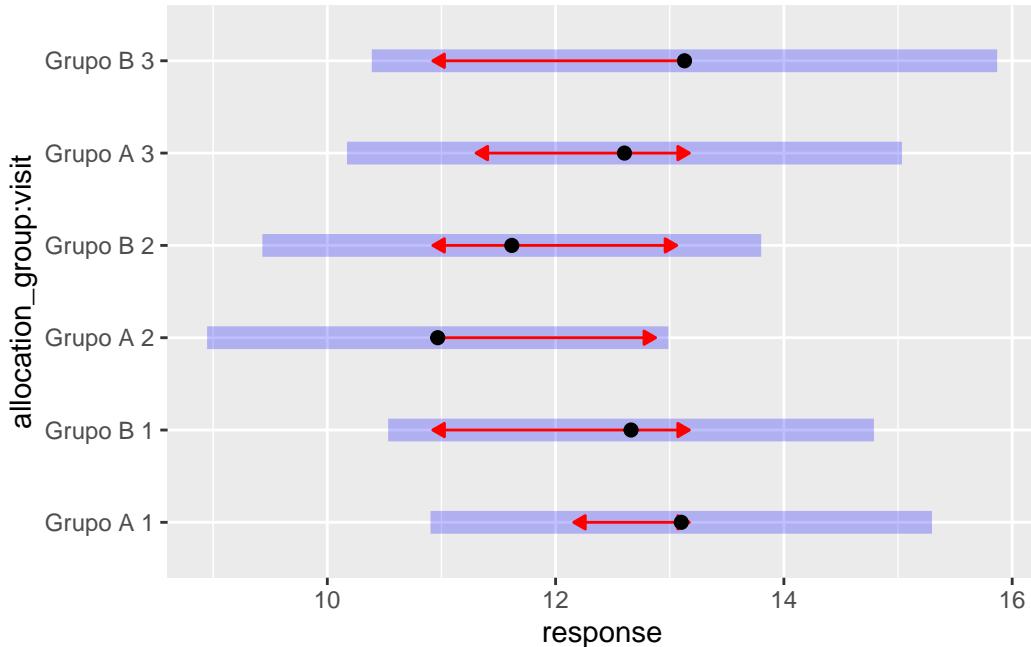
```

```

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests

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

```



3.11.2.2 Análise de sensibilidade

```

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

labs_insulin_emm <- regrid(labs_insulin_emm)

# Table of marginal means
# labs_insulin_emm

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

```

```

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

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

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

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

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

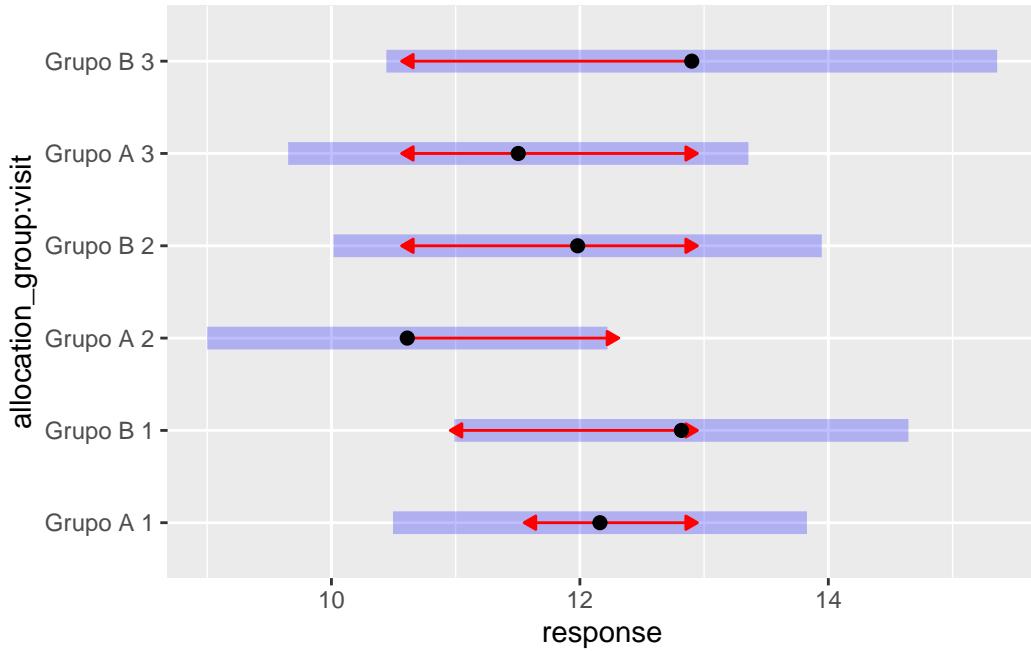
allocation_group = Grupo A:
  contrast      estimate    SE    df lower.CL upper.CL t.ratio p.value
visit1 - visit2    1.551 0.792  99.9    -0.377     3.48   1.959  0.1586
visit1 - visit3    0.658 0.886  99.9    -1.499     2.81   0.743  1.0000
visit2 - visit3   -0.893 0.888 120.3    -3.049     1.26  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

allocation_group = Grupo B:
  contrast      estimate    SE    df lower.CL upper.CL t.ratio p.value
visit1 - visit2    0.835 0.941  99.9    -1.456     3.13   0.888  1.0000
visit1 - visit3   -0.083 1.170  99.9    -2.943     2.78   -0.071  1.0000
visit2 - visit3   -0.919 1.210 127.6    -3.848     2.01   -0.761  1.0000

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests

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

```



3.11.3 Resultado

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

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

| Grupo de comparação | Comparação | Estimativa | IC 95% | p-valor |
|---------------------|---------------------|------------|----------------|---------|
| Entre grupos | Visita 1 | 0,44 | [-2,62 ; 3,50] | 0,776 |
| Entre grupos | Visita 2 | -0,65 | [-3,63 ; 2,33] | 0,667 |
| Entre grupos | Visita 3 | -0,53 | [-4,19 ; 3,14] | 0,777 |
| Grupo Placebo | Visita 1 - Visita 2 | 2,13 | [-0,21 ; 4,48] | 0,087 |
| Grupo Placebo | Visita 1 - Visita 3 | 0,50 | [-2,19 ; 3,18] | 1,000 |
| Grupo Placebo | Visita 2 - Visita 3 | -1,64 | [-4,28 ; 1,01] | 0,407 |
| Grupo Eclipta | Visita 1 - Visita 2 | 1,05 | [-1,39 ; 3,48] | 0,898 |
| Grupo Eclipta | Visita 1 - Visita 3 | -0,47 | [-3,49 ; 2,55] | 1,000 |
| Grupo Eclipta | Visita 2 - Visita 3 | -1,51 | [-4,57 ; 1,54] | 0,695 |

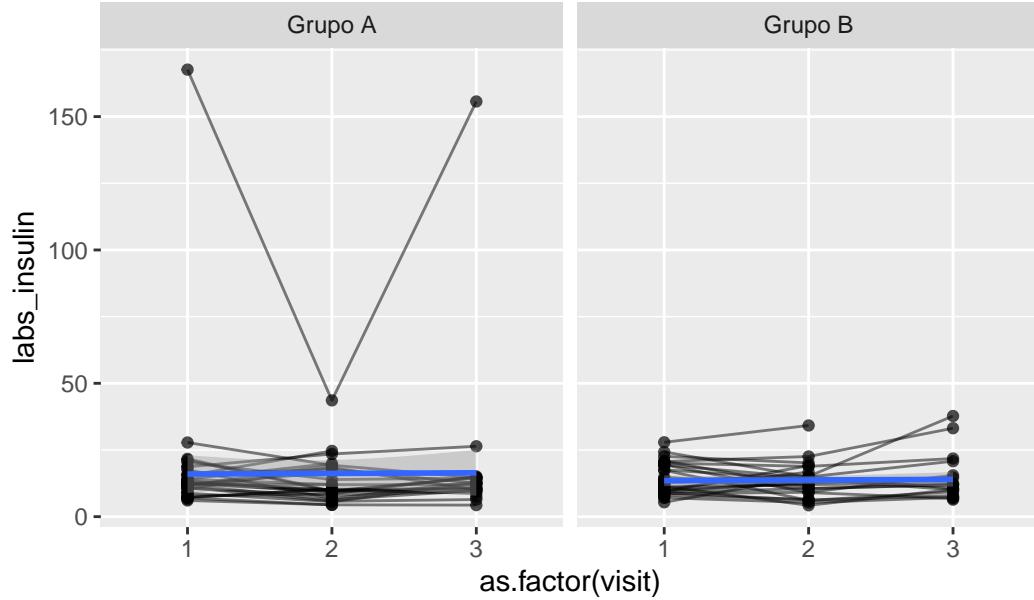
```

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

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

```

All data



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

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

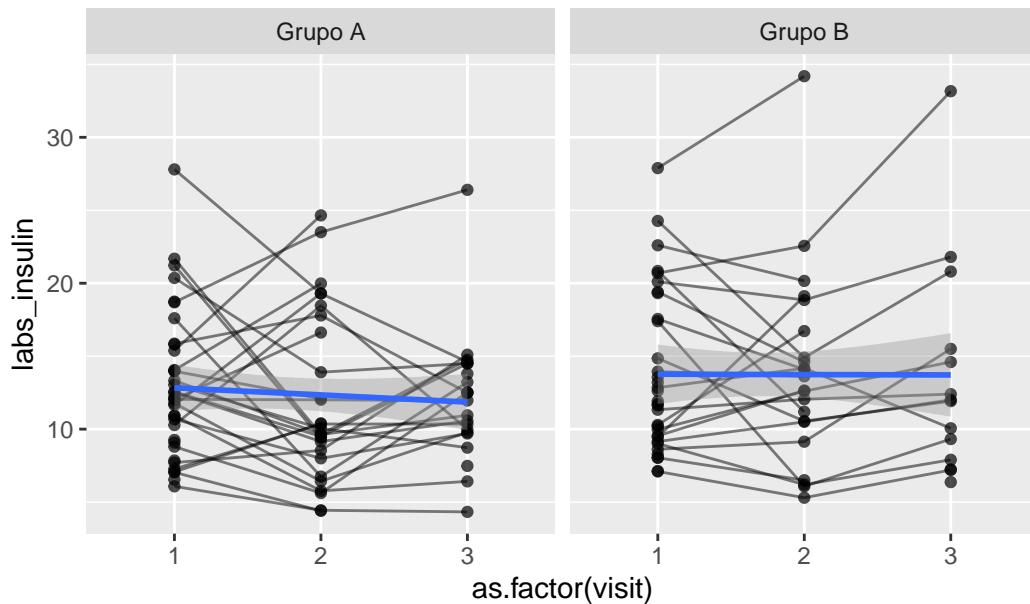
```

facet_wrap(~ allocation_group)

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

```

Sensitivity analysis



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

3.12 HOMA-IR

Variável: labs_homa_ir

```

# Plot 1: Raw data
labs_homa_ir_hist_1 <- data_model %>%
  #filter(
  #  labs_homa_ir < 300
  #) %>%
  ggplot(aes(x = labs_homa_ir)) +
  geom_histogram(bins = 50, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
labs_homa_ir_hist_2 <- data_model %>%

```

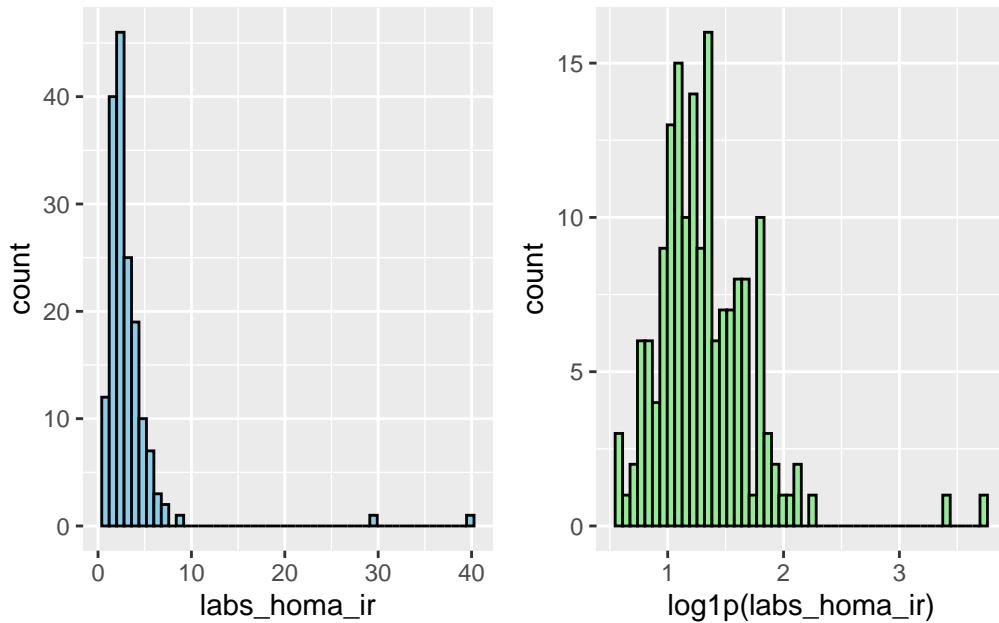
```

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

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

```

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



```

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

# Check for Multicollinearity

```

Low Correlation

| | Term | VIF | VIF 95% CI | Increased SE | Tolerance |
|--|------------------------|------|--------------|--------------|-----------|
| | allocation_group | 1.24 | [1.10, 1.58] | 1.11 | 0.81 |
| | visit | 3.42 | [2.71, 4.42] | 1.85 | 0.29 |
| | allocation_group:visit | 3.83 | [3.02, 4.97] | 1.96 | 0.26 |
| | Tolerance 95% CI | | | | |

```

[0.63, 0.91]
[0.23, 0.37]
[0.20, 0.33]

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

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

# Influential IDS
labs_homa_ir_model_check$influential_ids

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

```

3.12.1 Resumo dos modelos

```

# Model comparison
summary(labs_homa_ir_model)

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

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

```

REML criterion at convergence: 144.6

Scaled residuals:

| Min | 1Q | Median | 3Q | Max |
|---------|---------|---------|--------|--------|
| -2.2411 | -0.5509 | -0.0823 | 0.4113 | 3.4196 |

Random effects:

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

Number of obs: 167, groups: record_id, 73

Fixed effects:

| | Estimate | Std. Error | df | t value |
|--------------------------------|--|------------|------------|---------|
| (Intercept) | 1.336898 | 0.068660 | 106.824873 | 19.471 |
| allocation_groupGrupo 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_groupGrupo B:visit2 | 0.062435 | 0.095196 | 100.497655 | 0.656 |
| allocation_groupGrupo B:visit3 | 0.056616 | 0.107100 | 103.972738 | 0.529 |
| | Pr(> t) | | | |
| (Intercept) | <2e-16 *** | | | |
| allocation_groupGrupo B | 0.6752 | | | |
| visit2 | 0.0851 . | | | |
| visit3 | 0.8898 | | | |
| allocation_groupGrupo B:visit2 | 0.5134 | | | |
| allocation_groupGrupo 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_grGB -0.699
visit2     -0.385  0.269
visit3     -0.358  0.250  0.409
allctn_GB:2  0.267 -0.385 -0.693 -0.283
allctn_GB:3  0.237 -0.349 -0.271 -0.664  0.399
```

```
summary(labs_homa_ir_model_sens)
```

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

REML criterion at convergence: 73

Scaled residuals:

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

Random effects:

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

Number of obs: 152, groups: record_id, 68

Fixed effects:

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

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

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

Correlation of Fixed Effects:

| (Intr) | all_GB | visit2 | visit3 | a_GB:2 |
|-------------|--------|--------|--------|--------|
| allctn_grGB | -0.693 | | | |
| visit2 | -0.388 | 0.269 | | |
| visit3 | -0.357 | 0.248 | 0.401 | |
| allctn_GB:2 | 0.265 | -0.386 | -0.685 | -0.275 |
| allctn_GB:3 | 0.231 | -0.345 | -0.260 | -0.647 |
| | | | | 0.386 |

```
performance::compare_performance(  
  labs_homa_ir_model,  
  labs_homa_ir_model_sens)
```

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

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

| Name | Model | AIC (weights) | AICc (weights) |
|------|-------|---------------|----------------|
|------|-------|---------------|----------------|

| | | | |
|--------------------|-----------------|---------------|---------------|
| labs_homa_ir_model | lmerModLmerTest | 579.2 (<.001) | 580.1 (<.001) |
|--------------------|-----------------|---------------|---------------|

| | | | |
|-------------------------|-----------------|---------------|---------------|
| labs_homa_ir_model_sens | lmerModLmerTest | 454.2 (>.999) | 455.2 (>.999) |
|-------------------------|-----------------|---------------|---------------|

| Name | BIC (weights) | R2 (cond.) | R2 (marg.) | ICC |
|------|---------------|------------|------------|-----|
|------|---------------|------------|------------|-----|

| | | | | |
|--------------------|---------------|-------|-------|-------|
| labs_homa_ir_model | 604.1 (<.001) | 0.635 | 0.014 | 0.630 |
|--------------------|---------------|-------|-------|-------|

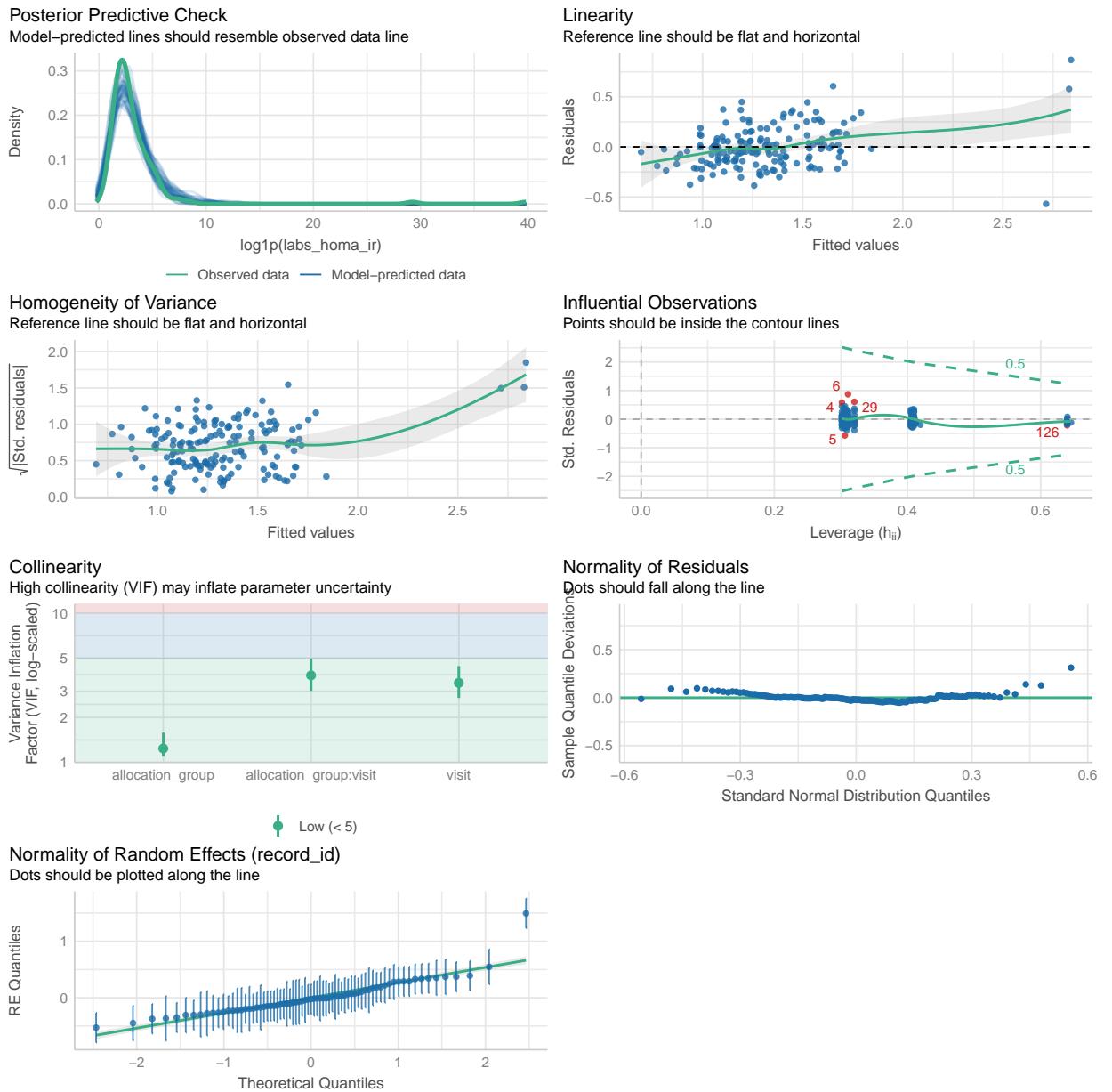
| | | | | |
|-------------------------|---------------|-------|-------|-------|
| labs_homa_ir_model_sens | 478.4 (>.999) | 0.625 | 0.014 | 0.620 |
|-------------------------|---------------|-------|-------|-------|

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

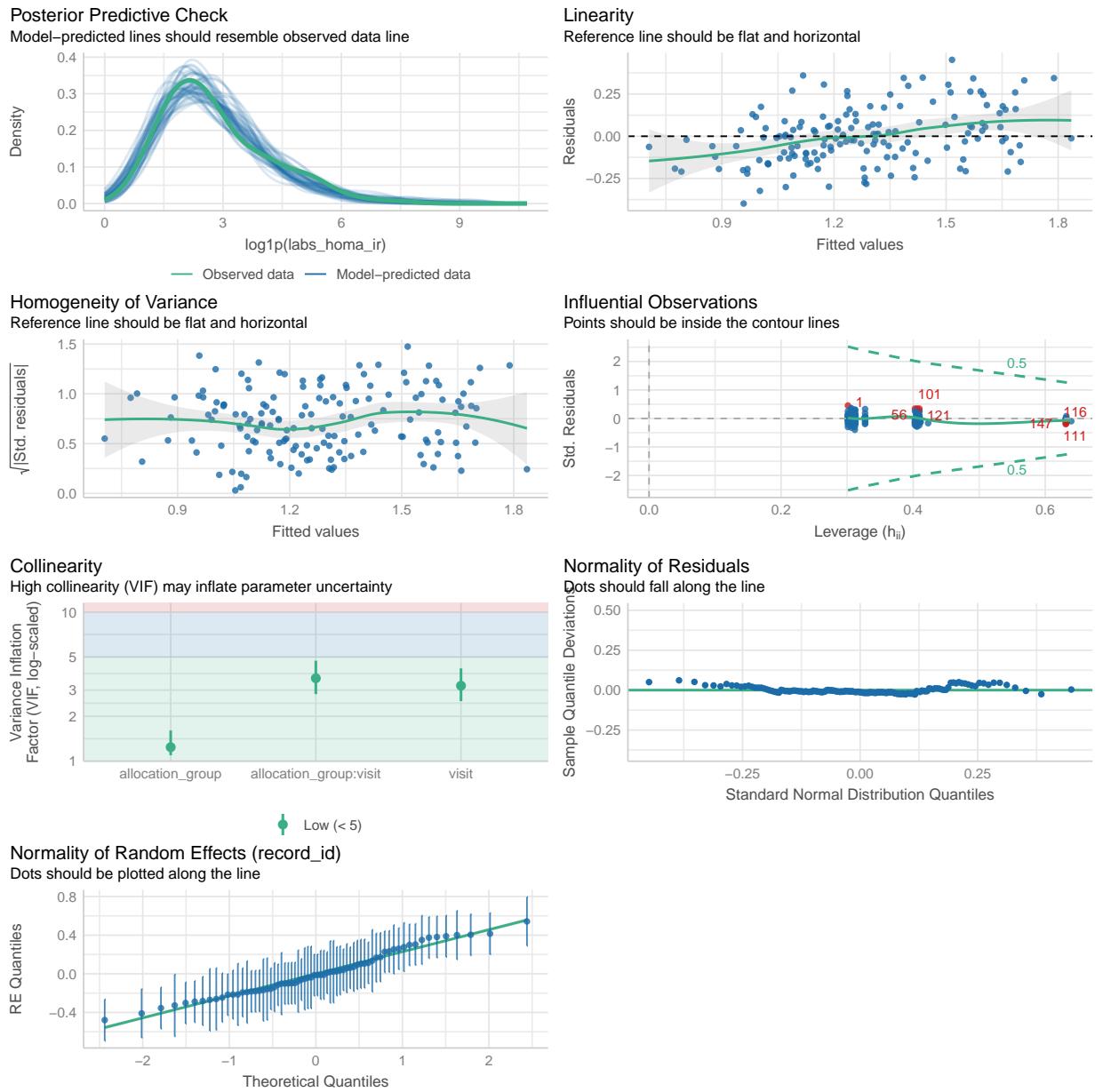
| | | |
|--------------------|-------|-------|
| labs_homa_ir_model | 0.203 | 0.254 |
|--------------------|-------|-------|

| | | |
|-------------------------|-------|-------|
| labs_homa_ir_model_sens | 0.165 | 0.208 |
|-------------------------|-------|-------|

```
performance::check_model(labs_homa_ir_model)
```



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



3.12.2 Médias Marginais Estimadas

3.12.2.1 Todos os dados

```
# Get EMMs for each group at each visit
labs_homa_ir_raw_emm <- emmeans::emmeans(
  labs_homa_ir_model,
  ~ allocation_group * visit
)

labs_homa_ir_raw_emm <- regrid(labs_homa_ir_raw_emm)
```

```

# Table of marginal means
# labs_homa_ir_raw_emm

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

visit = 1:
  contrast      estimate    SE  df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B   0.1539 0.366 103   -0.572    0.880   0.420  0.6752

visit = 2:
  contrast      estimate    SE  df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B  -0.0726 0.369 125   -0.802    0.657  -0.197  0.8441

visit = 3:
  contrast      estimate    SE  df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B  -0.0595 0.456 139   -0.961    0.842  -0.131  0.8963

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

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

allocation_group = Grupo A:
  contrast      estimate    SE  df lower.CL upper.CL t.ratio p.value
visit1 - visit2   0.4127 0.237 103   -0.163    0.988   1.744  0.2522
visit1 - visit3  -0.0378 0.273 103   -0.702    0.626  -0.138  1.0000
visit2 - visit3  -0.4505 0.274 125   -1.116    0.215  -1.642  0.3093

allocation_group = Grupo B:
  contrast      estimate    SE  df lower.CL upper.CL t.ratio p.value
visit1 - visit2   0.1862 0.244 106   -0.406    0.779   0.764  1.0000
visit1 - visit3  -0.2512 0.308 106   -1.001    0.498  -0.815  1.0000
visit2 - visit3  -0.4374 0.311 128   -1.191    0.316  -1.408  0.4849

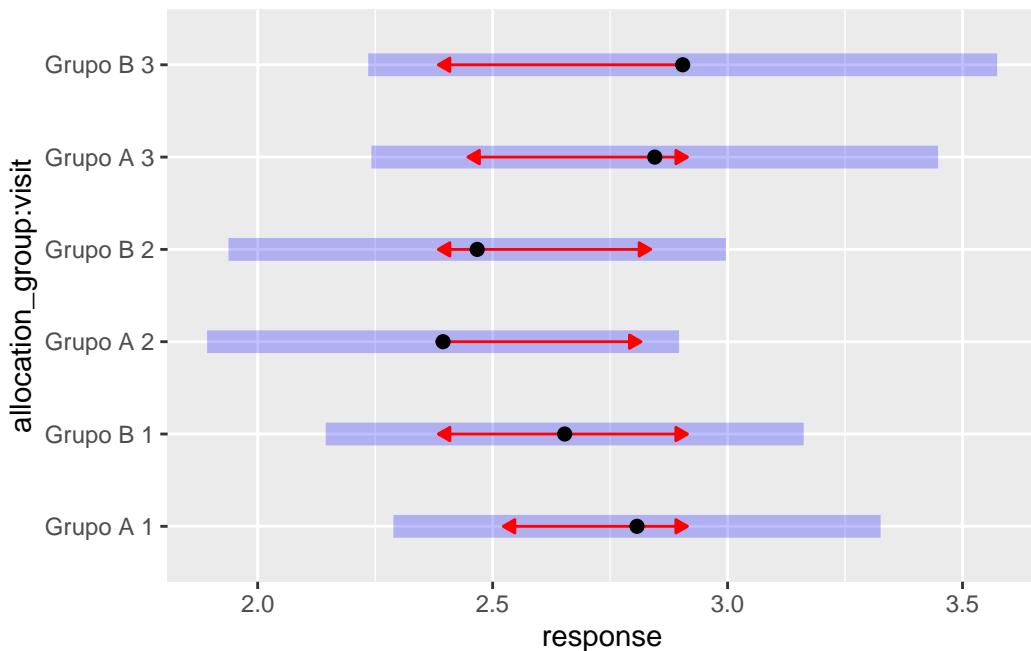
```

```

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests

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

```



3.12.2.2 Análise de sensibilidade

```

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

labs_homa_ir_emm <- regrid(labs_homa_ir_emm)

# Table of marginal means
# labs_homa_ir_emm

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

```

```
visit = 1:  
  contrast      estimate      SE   df lower.CL upper.CL t.ratio p.value  
 Grupo A - Grupo B -0.0319 0.299 96   -0.625    0.561  -0.107  0.9153
```

```
visit = 2:  
  contrast      estimate      SE   df lower.CL upper.CL t.ratio p.value  
 Grupo A - Grupo B -0.2111 0.308 117   -0.821    0.398  -0.686  0.4942
```

```
visit = 3:  
  contrast      estimate      SE   df lower.CL upper.CL t.ratio p.value  
 Grupo A - Grupo B -0.1258 0.369 130   -0.855    0.603  -0.341  0.7334
```

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

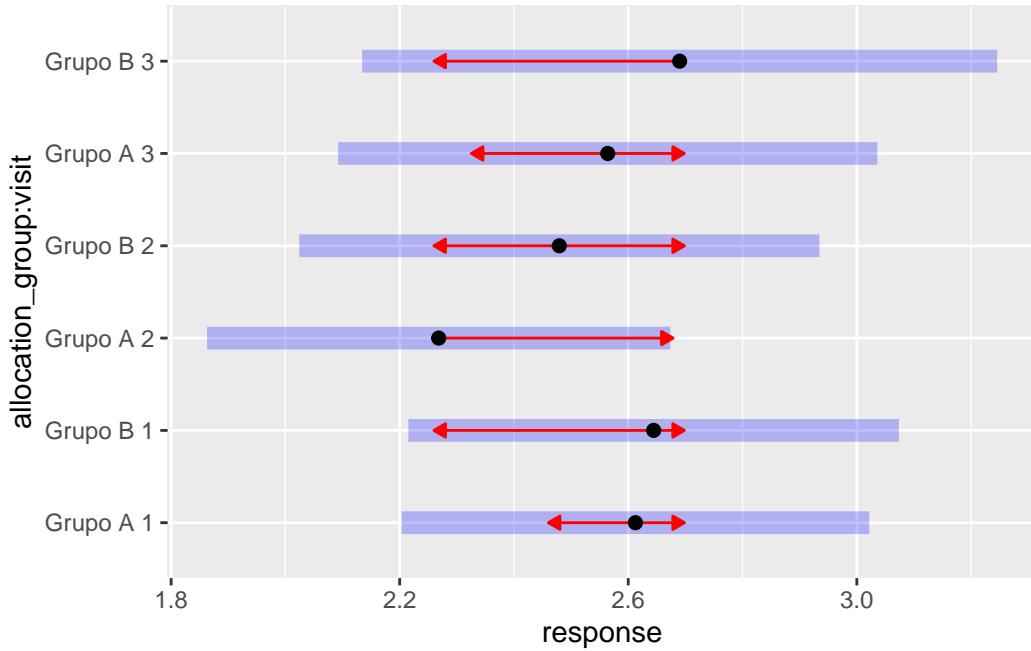
```
# Pairwise comparisons: Changes over time within each group  
emmmeans::contrast(labs_homa_ir_emm,  
method = "pairwise", by = "allocation_group",  
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
allocation_group = Grupo A:  
  contrast      estimate      SE   df lower.CL upper.CL t.ratio p.value  
 visit1 - visit2  0.3443 0.192  96.0   -0.122    0.811   1.798  0.2261  
 visit1 - visit3  0.0485 0.218  96.0   -0.482    0.579   0.223  1.0000  
 visit2 - visit3 -0.2958 0.221 116.6   -0.832    0.240   -1.341  0.5479
```

```
allocation_group = Grupo B:  
  contrast      estimate      SE   df lower.CL upper.CL t.ratio p.value  
 visit1 - visit2  0.1651 0.211  98.1   -0.350    0.680   0.781  1.0000  
 visit1 - visit3 -0.0455 0.264  98.1   -0.687    0.596   -0.173  1.0000  
 visit2 - visit3 -0.2106 0.268 120.7   -0.861    0.440   -0.786  1.0000
```

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests

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



3.12.3 Resultado

No modelo ajustado para os níveis de HOMA-IR, não foram observadas diferenças estatisticamente significativas entre os grupos em nenhum dos três momentos avaliados. Além disso, as comparações dentro de cada grupo ao longo do tempo não revelaram mudanças significativas. A análise de sensibilidade, realizada com a exclusão de observações influentes, confirmou a robustez dos achados, com estimativas semelhantes e ausência de diferenças significativas entre os grupos ou ao longo das visitas. As estimativas, intervalos de confiança de 95% e valores de p estão apresentados na Tabela 12.

Tabela 12: Diferenças estimadas dos níveis de HOMA-IR entre os grupos de alocação (placebo vs Eclipta) e entre visitas dentro de cada grupo

| Grupo de comparação | Comparação | Estimativa | IC 95% | p-valor |
|---------------------|---------------------|------------|----------------|---------|
| Entre grupos | Visita 1 | 0,15 | [-0,57 ; 0,88] | 0,675 |
| Entre grupos | Visita 2 | -0,07 | [-0,80 ; 0,66] | 0,844 |
| Entre grupos | Visita 3 | -0,06 | [-0,96 ; 0,84] | 0,896 |
| Grupo Placebo | Visita 1 - Visita 2 | 0,41 | [-0,16 ; 0,99] | 0,252 |
| Grupo Placebo | Visita 1 - Visita 3 | -0,04 | [-0,70 ; 0,63] | 1,000 |
| Grupo Placebo | Visita 2 - Visita 3 | -0,45 | [-1,12 ; 0,22] | 0,309 |
| Grupo Eclipta | Visita 1 - Visita 2 | 0,19 | [-0,41 ; 0,78] | 1,000 |
| Grupo Eclipta | Visita 1 - Visita 3 | -0,25 | [-1,00 ; 0,50] | 1,000 |
| Grupo Eclipta | Visita 2 - Visita 3 | -0,44 | [-1,19 ; 0,32] | 0,485 |

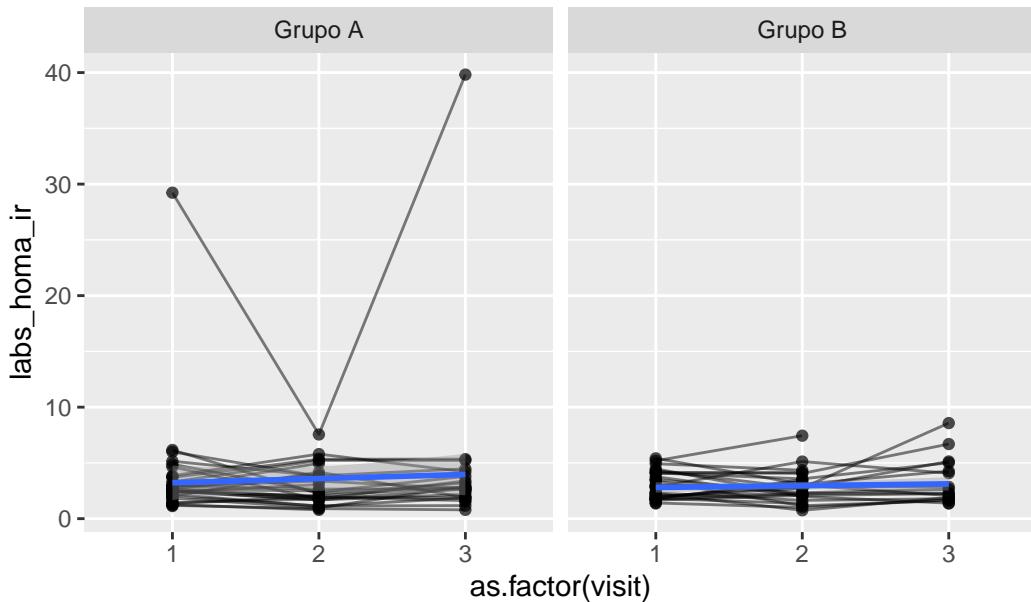
```

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

`geom_smooth()` using formula = 'y ~ x'
Warning: Removed 22 rows containing non-finite outside the scale range
(`stat_smooth()`).
Warning: Removed 18 rows containing missing values or values outside the scale range
(`geom_line()`).
Warning: Removed 22 rows containing missing values or values outside the scale range
(`geom_point()`).

```

All data



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

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

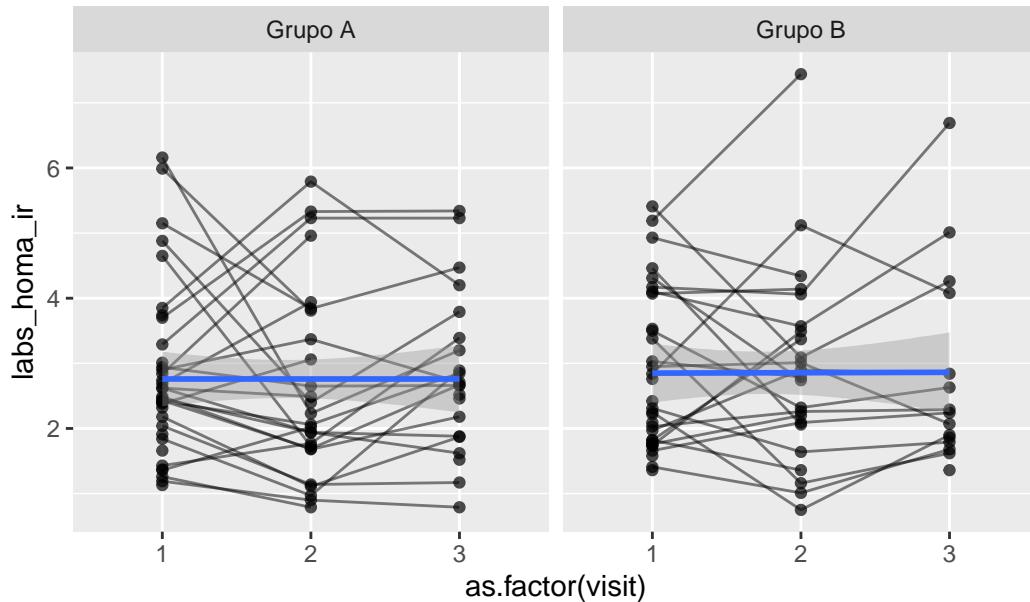
```

facet_wrap(~ allocation_group)

`geom_smooth()` using formula = 'y ~ x'
Warning: Removed 22 rows containing non-finite outside the scale range
(`stat_smooth()`).
Warning: Removed 18 rows containing missing values or values outside the scale range
(`geom_line()`).
Warning: Removed 22 rows containing missing values or values outside the scale range
(`geom_point()`).

```

Sensitivity analysis



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

3.13 Índice QUICK

Variável: labs_quick_index

```

# Plot 1: Raw data
labs_quick_index_hist_1 <- data_model %>%
  #filter(
  #  labs_quick_index < 300
  #) %>%
  ggplot(aes(x = labs_quick_index)) +
  geom_histogram(bins = 50, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
labs_quick_index_hist_2 <- data_model %>%

```

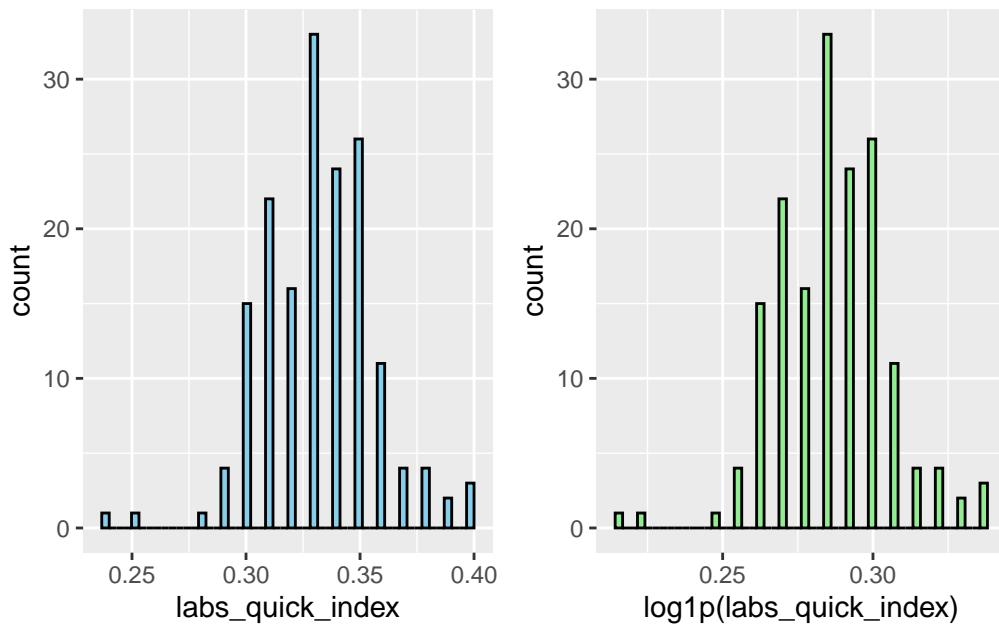
```

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

# Combine side by side
labs_quick_index_hist_1 + labs_quick_index_hist_2 # library(patchwork)

```

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



```

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

# Check for Multicollinearity

```

Low Correlation

| Term | VIF | VIF 95% CI | Increased SE | Tolerance |
|------------------------|------|--------------|--------------|-----------|
| allocation_group | 1.25 | [1.11, 1.60] | 1.12 | 0.80 |
| visit | 3.42 | [2.71, 4.42] | 1.85 | 0.29 |
| allocation_group:visit | 3.85 | [3.03, 5.00] | 1.96 | 0.26 |
| Tolerance 95% CI | | | | |

```

[0.63, 0.90]
[0.23, 0.37]
[0.20, 0.33]

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

# LMM Sensitivity
labs_quick_index_model_sens <- update(object = labs_quick_index_model,
                                         subset = !(record_id %in%
                                         labs_quick_index_model_check$influential_ids))

# Influential IDs
labs_quick_index_model_check$influential_ids

[1] "2"  "4"  "11" "19" "8"

```

3.13.1 Resumo dos modelos

```

# Model comparison
summary(labs_quick_index_model)

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

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

REML criterion at convergence: -754.1

Scaled residuals:
    Min      1Q  Median      3Q     Max 
-2.0927 -0.4844  0.0304  0.5467  2.4024 

Random effects:
Groups      Name        Variance Std.Dev. 
record_id (Intercept) 0.0003959 0.01990 
Residual            0.0002488 0.01577 
Number of obs: 167, groups: record_id, 73

```

Fixed effects:

| | Estimate | Std. Error | df | t value |
|--------------------------------|------------|------------|------------|---------|
| (Intercept) | 0.330541 | 0.004174 | 107.176150 | 79.186 |
| allocation_groupGrupo B | 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_groupGrupo B:visit2 | -0.003691 | 0.005903 | 99.395689 | -0.625 |
| allocation_groupGrupo B:visit3 | -0.005408 | 0.006638 | 103.075477 | -0.815 |
| | Pr(> t) | | | |
| (Intercept) | <2e-16 *** | | | |
| allocation_groupGrupo B | 0.8331 | | | |
| visit2 | 0.0436 * | | | |
| visit3 | 0.5994 | | | |
| allocation_groupGrupo B:visit2 | 0.5332 | | | |
| allocation_groupGrupo B:visit3 | 0.4171 | | | |
| --- | | | | |
| Signif. codes: | 0 *** | 0.001 ** | 0.01 * | 0.05 . |
| | 1 | | | |

Correlation of Fixed Effects:

```
(Intr) all_GB visit2 visit3 a_GB:2
allctn_grGB -0.699
visit2     -0.394  0.275
visit3     -0.366  0.256  0.408
allctn_GB:2  0.273 -0.393 -0.693 -0.283
allctn_GB:3  0.243 -0.357 -0.271 -0.664  0.399
```

```
summary(labs_quick_index_model_sens)
```

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

REML criterion at convergence: -714.5

Scaled residuals:

| Min | 1Q | Median | 3Q | Max |
|---------|---------|--------|--------|--------|
| -1.8870 | -0.4995 | 0.0244 | 0.5783 | 2.3369 |

Random effects:

| Groups | Name | Variance | Std.Dev. |
|-----------|-------------|-----------|----------|
| record_id | (Intercept) | 0.0002799 | 0.01673 |
| | Residual | 0.0002110 | 0.01452 |

Number of obs: 152, groups: record_id, 68

Fixed effects:

| | Estimate | Std. Error | df | t value |
|-------------------------|------------|------------|-----------|---------|
| (Intercept) | 3.317e-01 | 3.745e-03 | 1.010e+02 | 88.573 |
| allocation_group | 5.364e-04 | 5.405e-03 | 1.021e+02 | 0.099 |
| visit2 | 6.683e-03 | 3.894e-03 | 8.696e+01 | 1.716 |
| visit3 | 1.888e-03 | 4.221e-03 | 8.872e+01 | 0.447 |
| allocation_group:visit2 | -5.420e-03 | 5.685e-03 | 8.792e+01 | -0.953 |
| allocation_group:visit3 | -5.218e-03 | 6.509e-03 | 9.243e+01 | -0.802 |

| | Pr(> t) |
|-------------------------|------------|
| (Intercept) | <2e-16 *** |
| allocation_group | 0.9212 |
| visit2 | 0.0897 . |
| visit3 | 0.6558 |
| allocation_group:visit2 | 0.3430 |
| allocation_group:visit3 | 0.4248 |

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

Correlation of Fixed Effects:

| | (Intr) | all_GB | visit2 | visit3 | a_GB:2 |
|-------------|--------|--------|--------|--------|--------|
| allctn_grGB | -0.693 | | | | |
| visit2 | -0.413 | 0.286 | | | |
| visit3 | -0.381 | 0.264 | 0.400 | | |
| allctn_GB:2 | 0.283 | -0.411 | -0.685 | -0.274 | |
| allctn_GB:3 | 0.247 | -0.368 | -0.260 | -0.648 | 0.385 |

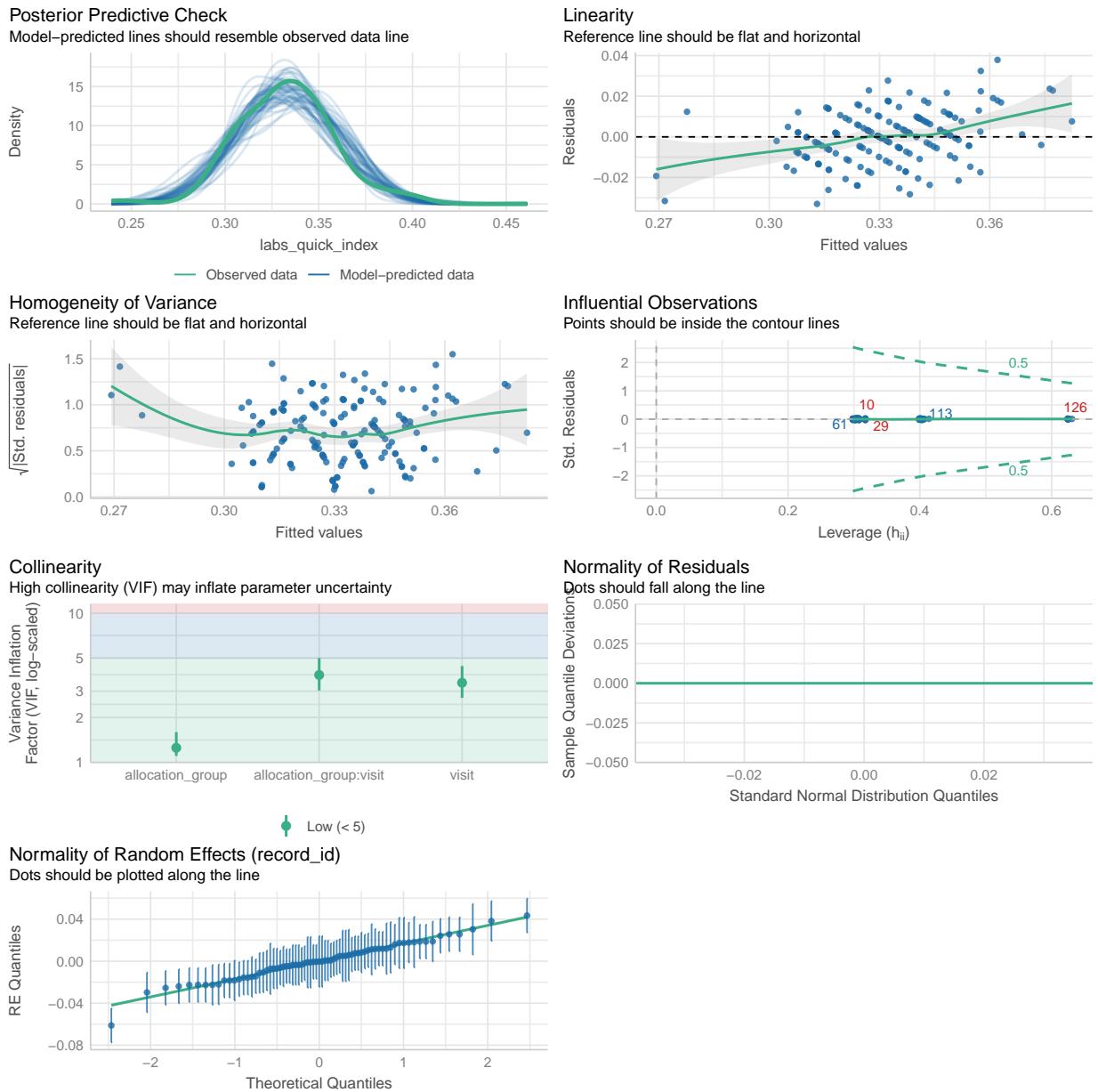
```
performance::compare_performance(  
  labs_quick_index_model,  
  labs_quick_index_model_sens)
```

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

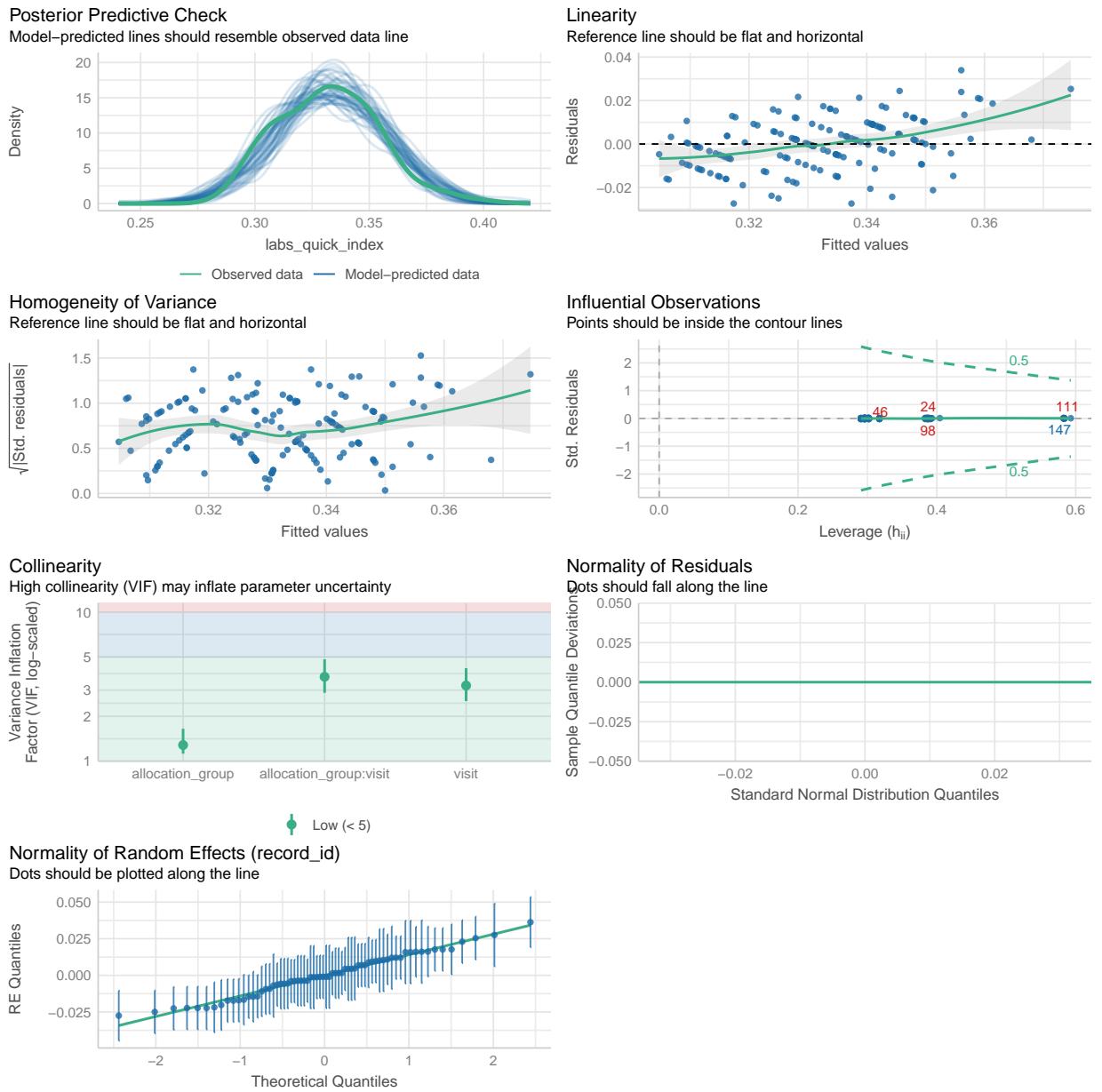
```
# Comparison of Model Performance Indices
```

| Name | Model | AIC (weights) | AICc (weights) | |
|-----------------------------|-----------------|----------------|----------------|-------|
| <hr/> | | | | |
| labs_quick_index_model | lmerModLmerTest | -793.2 (>.999) | -792.3 (>.999) | |
| labs_quick_index_model_sens | lmerModLmerTest | -754.3 (<.001) | -753.3 (<.001) | |
| Name | BIC (weights) | R2 (cond.) | R2 (marg.) | ICC |
| labs_quick_index_model | -768.3 (>.999) | 0.621 | 0.017 | 0.614 |
| labs_quick_index_model_sens | -730.1 (<.001) | 0.576 | 0.014 | 0.570 |
| Name | RMSE | Sigma | | |
| labs_quick_index_model | 0.013 | 0.016 | | |
| labs_quick_index_model_sens | 0.012 | 0.015 | | |

```
performance::check_model(labs_quick_index_model)
```



```
performance::check_model(labs_quick_index_model_sens)
```



3.13.2 Médias Marginais Estimadas

3.13.2.1 Todos os dados

```
# Get EMMs for each group at each visit
labs_quick_index_raw_emm <- emmeans::emmeans(
  labs_quick_index_model,
  ~ allocation_group * visit
)

labs_quick_index_raw_emm <- regrid(labs_quick_index_raw_emm)
```

```

# Table of marginal means
# labs_quick_index_raw_emm

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

visit = 1:
  contrast      estimate      SE  df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B -0.00126 0.00597 105  -0.0131   0.0106  -0.211  0.8331

visit = 2:
  contrast      estimate      SE  df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B  0.00243 0.00655 126  -0.0105   0.0154   0.371  0.7113

visit = 3:
  contrast      estimate      SE  df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B  0.00415 0.00719 140  -0.0101   0.0184   0.577  0.5648

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

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

allocation_group = Grupo A:
  contrast      estimate      SE  df lower.CL upper.CL t.ratio p.value
visit1 - visit2 -0.00836 0.00410 105  -0.01833  0.00160  -2.041  0.1312
visit1 - visit3 -0.00232 0.00441 105  -0.01306  0.00842  -0.526  1.0000
visit2 - visit3  0.00604 0.00464 126  -0.00521  0.01729   1.303  0.5848

allocation_group = Grupo B:
  contrast      estimate      SE  df lower.CL upper.CL t.ratio p.value
visit1 - visit2 -0.00467 0.00426 107  -0.01504  0.00569  -1.096  0.8263
visit1 - visit3  0.00309 0.00498 107  -0.00902  0.01519   0.620  1.0000
visit2 - visit3  0.00776 0.00513 130  -0.00469  0.02020   1.512  0.3989

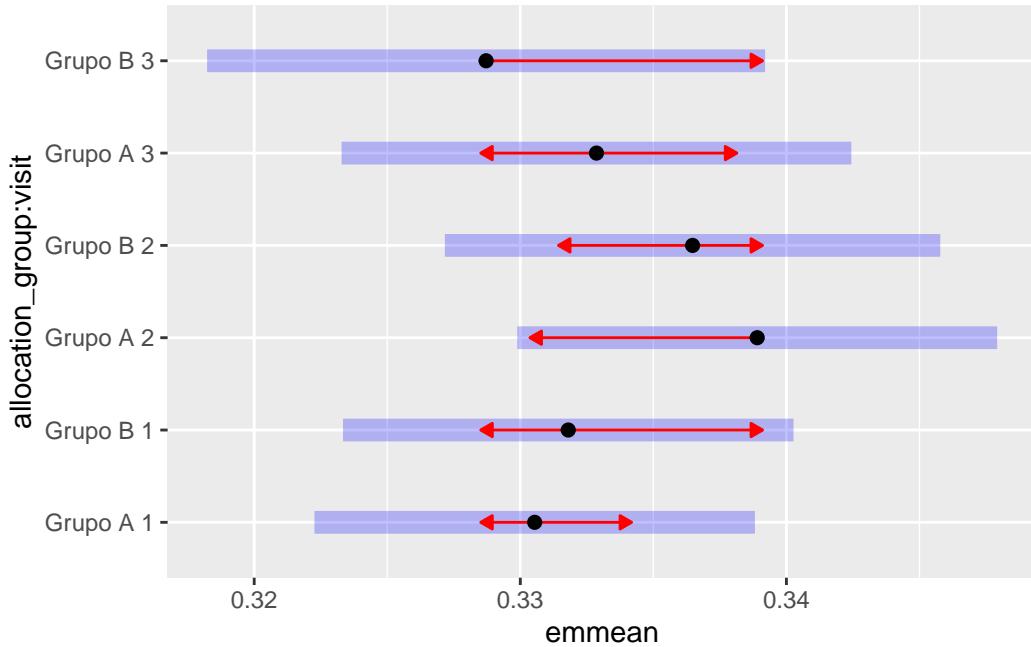
```

```

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests

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

```



3.13.2.2 Análise de sensibilidade

```

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

labs_quick_index_emm <- regrid(labs_quick_index_emm)

# Table of marginal means
# labs_quick_index_emm

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

```

```

visit = 1:
  contrast      estimate      SE  df lower.CL upper.CL t.ratio p.value
Grupo A - Grupo B -0.000536  0.00541 101 -0.01126   0.0102  -0.099  0.9212

visit = 2:
  contrast      estimate      SE  df lower.CL upper.CL t.ratio p.value
Grupo A - Grupo B  0.004884  0.00603 122 -0.00706   0.0168   0.810  0.4197

visit = 3:
  contrast      estimate      SE  df lower.CL upper.CL t.ratio p.value
Grupo A - Grupo B  0.004682  0.00678 134 -0.00873   0.0181   0.691  0.4910

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

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

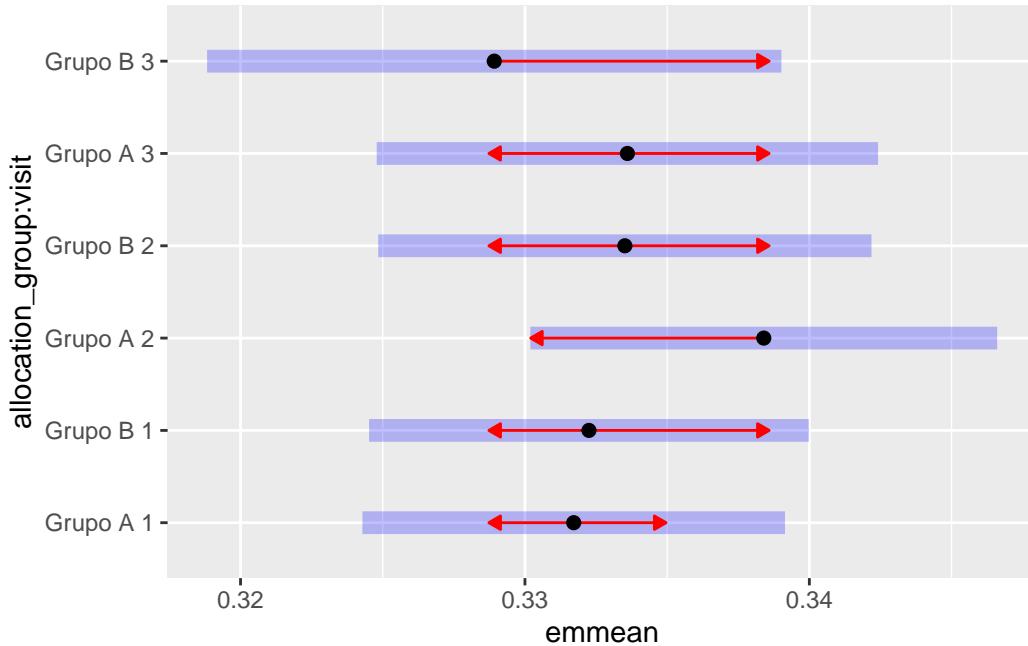
allocation_group = Grupo A:
  contrast      estimate      SE  df lower.CL upper.CL t.ratio p.value
visit1 - visit2 -0.00668  0.00390 101 -0.01618  0.00281  -1.713  0.2691
visit1 - visit3 -0.00189  0.00423 101 -0.01219  0.00841  -0.446  1.0000
visit2 - visit3  0.00480  0.00446 122 -0.00603  0.01562   1.075  0.8531

allocation_group = Grupo B:
  contrast      estimate      SE  df lower.CL upper.CL t.ratio p.value
visit1 - visit2 -0.00126  0.00415 103 -0.01136  0.00884  -0.304  1.0000
visit1 - visit3  0.00333  0.00497 103 -0.00878  0.01544   0.670  1.0000
visit2 - visit3  0.00459  0.00515 125 -0.00790  0.01709   0.892  1.0000

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests

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

```



3.13.3 Resultado

No modelo ajustado para o índice de sensibilidade à insulina (Quick Index), não foram observadas diferenças estatisticamente significativas entre os grupos em nenhum dos três momentos avaliados. Da mesma forma, as comparações ao longo do tempo dentro de cada grupo também não mostraram variações significativas. A análise de sensibilidade, realizada com a exclusão das observações influentes, confirmou os achados da análise principal. As estimativas permaneceram consistentes, sem diferenças estatisticamente significativas entre os grupos ou ao longo do tempo. As estimativas, intervalos de confiança de 95% e valores de p estão apresentados na Tabela 13.

Tabela 13: Diferenças estimadas do índice Quick entre os grupos de alocação (placebo vs Eclipta) e entre visitas dentro de cada grupo

| Grupo de comparação | Comparação | Estimativa | IC 95% | p-valor |
|---------------------|---------------------|------------|------------------|---------|
| Entre grupos | Visita 1 | -0,001 | [-0,013 ; 0,011] | 0,833 |
| Entre grupos | Visita 2 | 0,002 | [-0,011 ; 0,015] | 0,711 |
| Entre grupos | Visita 3 | 0,004 | [-0,010 ; 0,018] | 0,565 |
| Grupo Placebo | Visita 1 - Visita 2 | -0,008 | [-0,018 ; 0,002] | 0,131 |
| Grupo Placebo | Visita 1 - Visita 3 | -0,002 | [-0,013 ; 0,008] | 1,000 |
| Grupo Placebo | Visita 2 - Visita 3 | 0,006 | [-0,005 ; 0,017] | 0,585 |
| Grupo Eclipta | Visita 1 - Visita 2 | -0,005 | [-0,015 ; 0,006] | 0,826 |
| Grupo Eclipta | Visita 1 - Visita 3 | 0,003 | [-0,009 ; 0,015] | 1,000 |
| Grupo Eclipta | Visita 2 - Visita 3 | 0,008 | [-0,005 ; 0,020] | 0,399 |

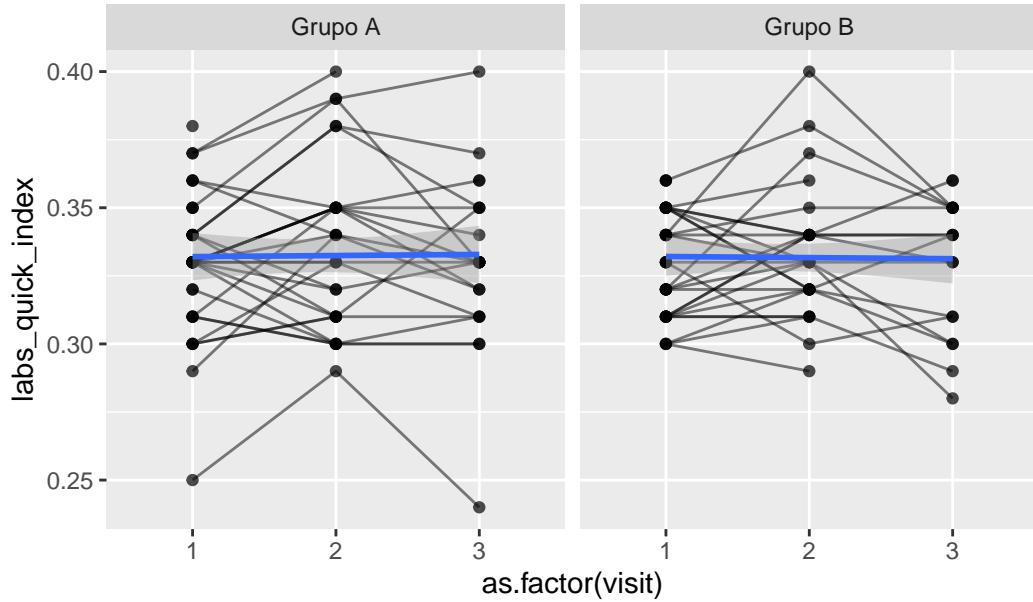
```

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

`geom_smooth()` using formula = 'y ~ x'
Warning: Removed 22 rows containing non-finite outside the scale range
(`stat_smooth()`).
Warning: Removed 18 rows containing missing values or values outside the scale range
(`geom_line()`).
Warning: Removed 22 rows containing missing values or values outside the scale range
(`geom_point()`).

```

All data



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

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

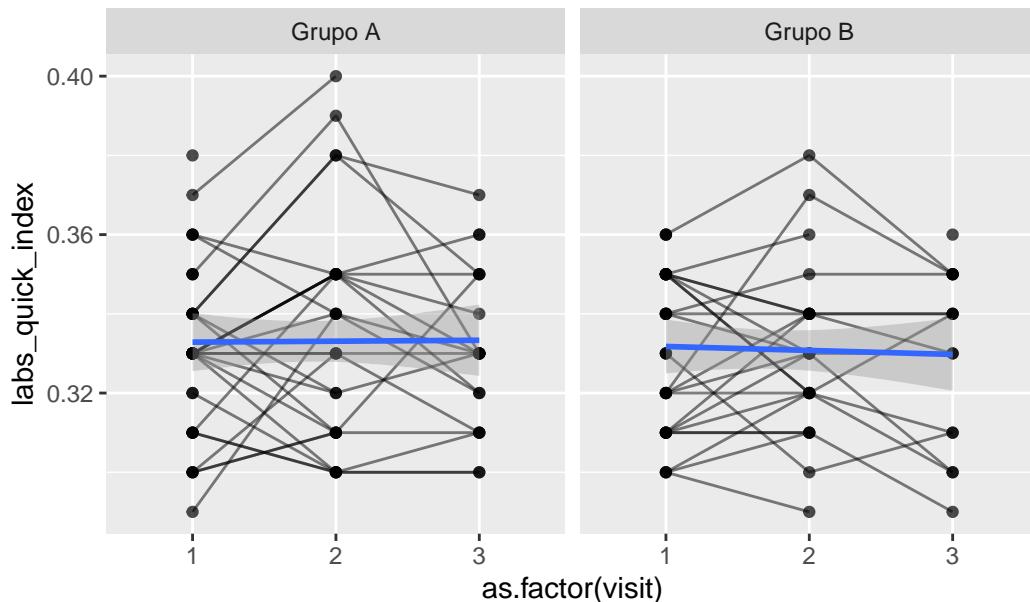
```

facet_wrap(~ allocation_group)

`geom_smooth()` using formula = 'y ~ x'
Warning: Removed 22 rows containing non-finite outside the scale range
(`stat_smooth()`).
Warning: Removed 18 rows containing missing values or values outside the scale range
(`geom_line()`).
Warning: Removed 22 rows containing missing values or values outside the scale range
(`geom_point()`).

```

Sensitivity analysis



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

3.14 Circunferência abdominal

Variável: abdomen

```

# Plot 1: Raw data
abdomen_hist_1 <- data_model %>%
  #filter(
  #  abdomen < 300
  #) %>%
  ggplot(aes(x = abdomen)) +
  geom_histogram(bins = 50, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
abdomen_hist_2 <- data_model %>%

```

```

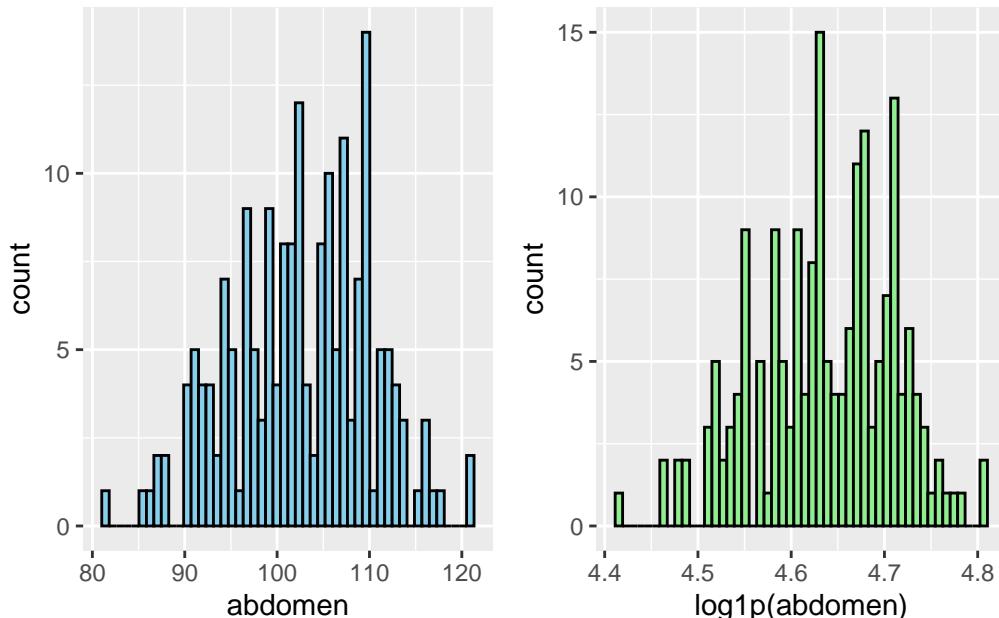
#filter(
  #    abdomen < 300
  #) %>%
  ggplot(aes(x = log1p(abdomen))) +
  geom_histogram(bins = 50, fill = "lightgreen", color = "black")

# Combine side by side
abdomen_hist_1 + abdomen_hist_2 # library(patchwork)

```

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

Removed 2 rows containing non-finite outside the scale range (`stat_bin()`).



```

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

# Check for Multicollinearity

```

Low Correlation

| | Term | VIF | VIF 95% CI | Increased SE | Tolerance |
|--|------------------------|------|--------------|--------------|-----------|
| | allocation_group | 1.08 | [1.01, 1.60] | 1.04 | 0.93 |
| | visit | 3.74 | [2.98, 4.79] | 1.93 | 0.27 |
| | allocation_group:visit | 3.87 | [3.08, 4.96] | 1.97 | 0.26 |
| | Tolerance 95% CI | | | | |

```

[0.62, 0.99]
[0.21, 0.34]
[0.20, 0.32]

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

# LMM Sensitivity
abdomen_model_sens <- update(object = abdomen_model,
                                subset = !(record_id %in%
                                abdomen_model_check$influential_ids))

# Influential IDs
abdomen_model_check$influential_ids

[1] "8"  "42" "47" "53" "63"

```

3.14.1 Resumo dos modelos

```

# Model comparison
summary(abdomen_model)

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

```

REML criterion at convergence: -568.7

Scaled residuals:

| Min | 1Q | Median | 3Q | Max |
|----------|----------|---------|---------|---------|
| -2.23622 | -0.44732 | 0.00364 | 0.48062 | 2.42979 |

Random effects:

| Groups | Name | Variance | Std.Dev. |
|-----------|-------------|-----------|----------|
| record_id | (Intercept) | 0.0047493 | 0.06892 |
| | Residual | 0.0007424 | 0.02725 |

Number of obs: 187, groups: record_id, 75

Fixed effects:

| | Estimate | Std. Error | df | t value |
|--------------------------------|--|------------|------------|---------|
| (Intercept) | 4.646300 | 0.012183 | 84.898832 | 381.378 |
| allocation_groupGrupo B | -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_groupGrupo B:visit2 | 0.006622 | 0.009887 | 111.494381 | 0.670 |
| allocation_groupGrupo B:visit3 | 0.022973 | 0.010437 | 111.762586 | 2.201 |
| | Pr(> t) | | | |
| (Intercept) | <2e-16 *** | | | |
| allocation_groupGrupo B | 0.3812 | | | |
| visit2 | 0.2067 | | | |
| visit3 | 0.0292 * | | | |
| allocation_groupGrupo B:visit2 | 0.5044 | | | |
| allocation_groupGrupo B:visit3 | 0.0298 * | | | |
| --- | | | | |
| Signif. codes: | 0 *** 0.001 ** 0.01 * 0.05 . 0.1 ' ' 1 | | | |

Correlation of Fixed Effects:

```
(Intr) all_GB visit2 visit3 a_GB:2
allctn_grGB -0.712
visit2     -0.239  0.170
visit3     -0.227  0.162  0.469
allctn_GB:2  0.167 -0.234 -0.696 -0.327
allctn_GB:3  0.158 -0.222 -0.326 -0.695  0.467
```

```
summary(abdomen_model_sens)
```

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

REML criterion at convergence: -552.6

Scaled residuals:

| Min | 1Q | Median | 3Q | Max |
|----------|----------|---------|---------|---------|
| -2.17405 | -0.44945 | 0.00727 | 0.51473 | 1.83706 |

Random effects:

| Groups | Name | Variance | Std.Dev. |
|-----------|-------------|----------|----------|
| record_id | (Intercept) | 0.004706 | 0.06860 |
| Residual | | 0.000536 | 0.02315 |

Number of obs: 172, groups: record_id, 70

Fixed effects:

| | Estimate | Std. Error | df | t value |
|-------------------------|-----------|------------|------------|---------|
| (Intercept) | 4.646664 | 0.012604 | 75.952119 | 368.673 |
| allocation_group | -0.016907 | 0.017336 | 75.952119 | -0.975 |
| visit2 | -0.001980 | 0.006272 | 100.199396 | -0.316 |
| visit3 | -0.009382 | 0.006665 | 100.412373 | -1.408 |
| allocation_group:visit2 | 0.001495 | 0.008783 | 100.495350 | 0.170 |
| allocation_group:visit3 | 0.020633 | 0.009324 | 100.671803 | 2.213 |

| | Pr(> t) |
|-------------------------|------------|
| (Intercept) | <2e-16 *** |
| allocation_group | 0.3325 |
| visit2 | 0.7529 |
| visit3 | 0.1623 |
| allocation_group:visit2 | 0.8652 |
| allocation_group:visit3 | 0.0292 * |

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

Correlation of Fixed Effects:

| | (Intr) | all_GB | visit2 | visit3 | a_GB:2 |
|-------------|--------|--------|--------|--------|--------|
| allctn_gr | GB | -0.727 | | | |
| visit2 | | -0.205 | 0.149 | | |
| visit3 | | -0.193 | 0.141 | 0.466 | |
| allctn_GB:2 | | 0.147 | -0.202 | -0.714 | -0.333 |
| allctn_GB:3 | | 0.138 | -0.190 | -0.333 | -0.715 |
| | | | | | 0.466 |

```
performance::compare_performance(  
  abdomen_model,  
  abdomen_model_sens)
```

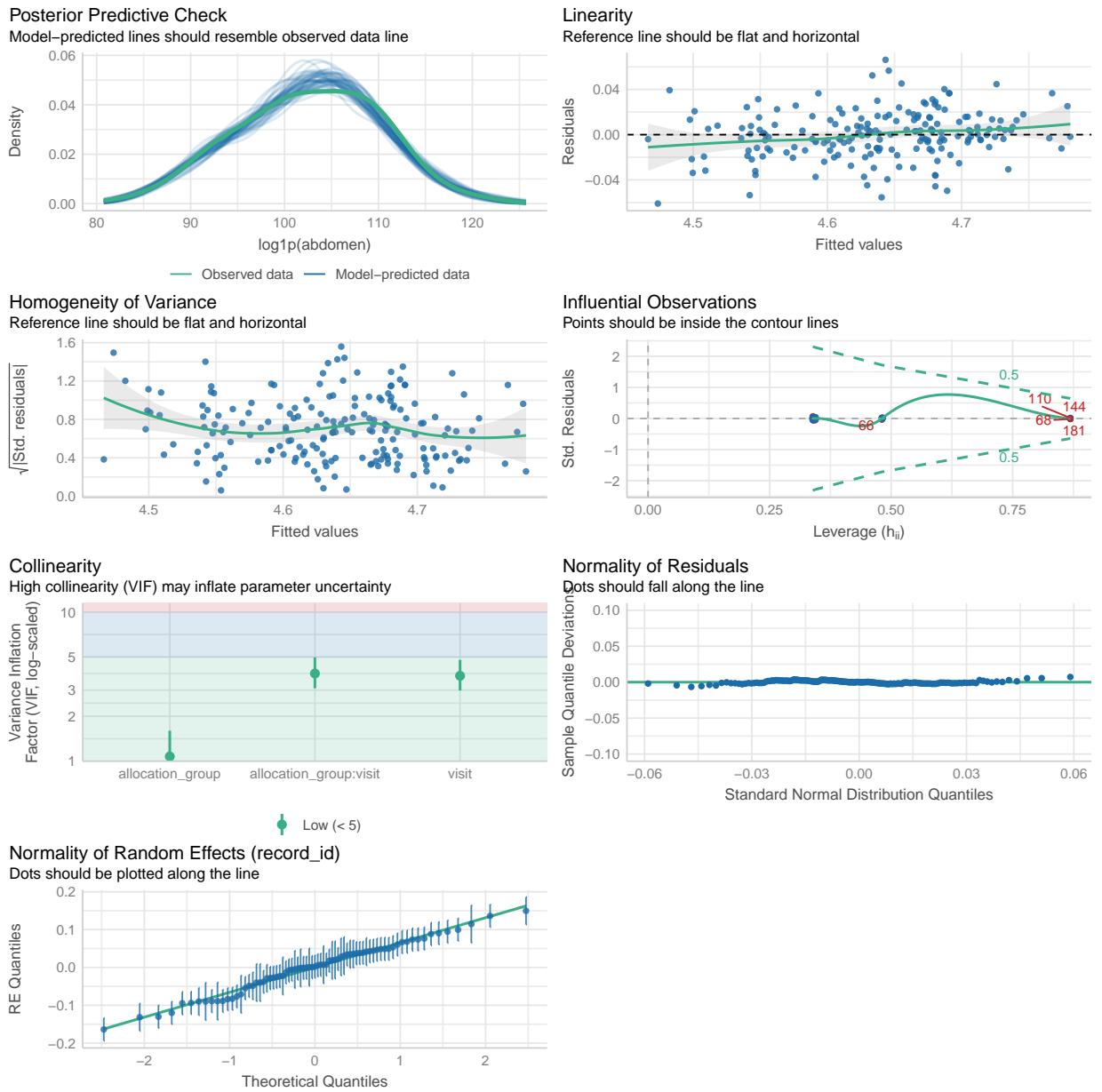
When comparing models, please note that probably not all models were fit
from same data.

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

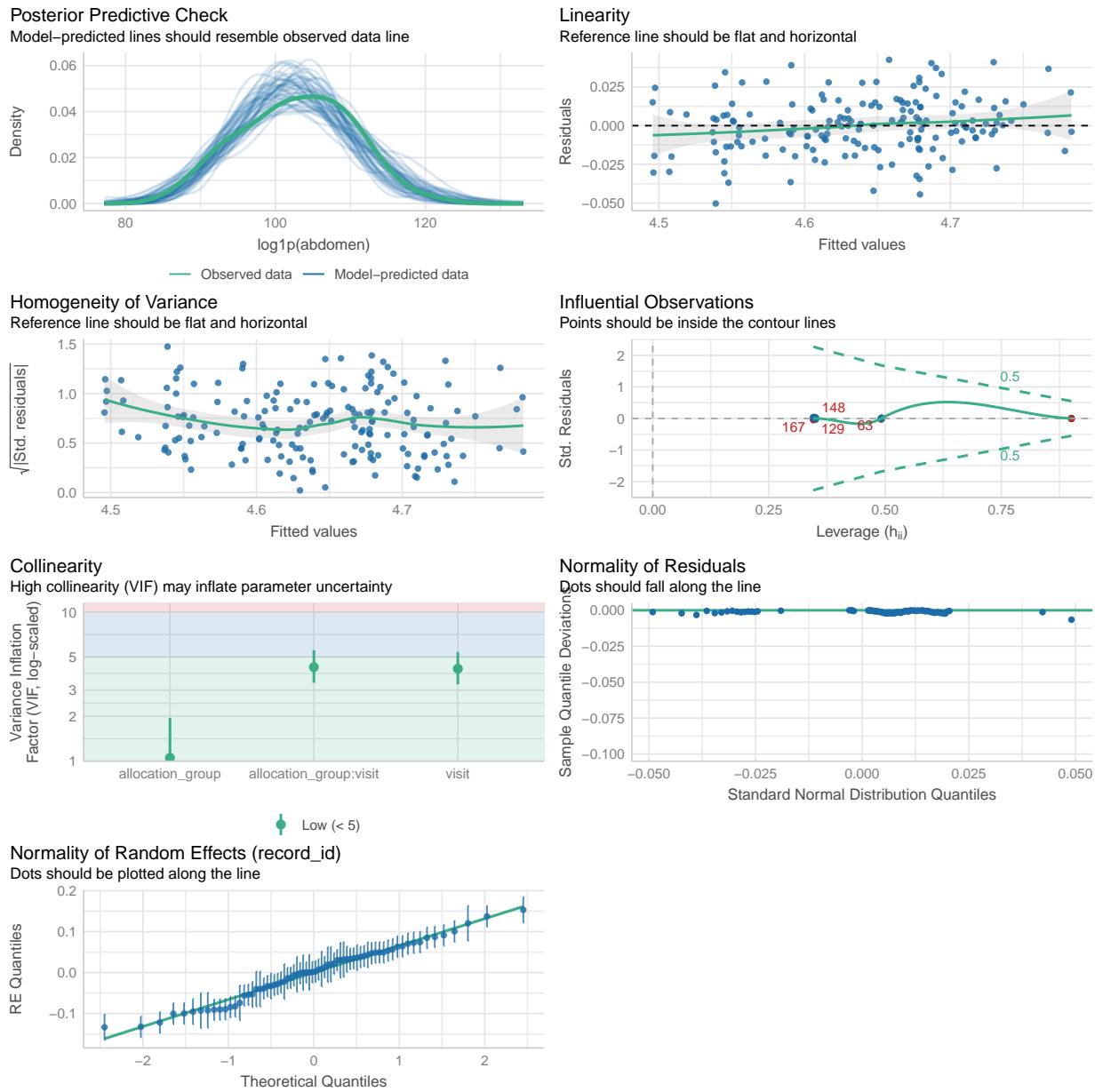
| Name | Model | AIC (weights) | AICc (weights) |
|--------------------|-----------------|----------------|----------------|
| <hr/> | | | |
| abdomen_model | lmerModLmerTest | 1134.8 (<.001) | 1135.6 (<.001) |
| abdomen_model_sens | lmerModLmerTest | 1011.7 (>.999) | 1012.6 (>.999) |

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



3.14.2 Médias Marginais Estimadas

3.14.2.1 Todos os dados

```
# Get EMMs for each group at each visit
abdomen_raw_emm <- emmeans::emmeans(
  abdomen_model,
  ~ allocation_group * visit
)
```

```
abdomen_raw_emm <- regrid(abdomen_raw_emm)
```

```

# Table of marginal means
# abdomen_raw_emm

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

visit = 1:
  contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
  Grupo A - Grupo B    1.558 1.77 84.3     -1.96      5.08   0.880  0.3813

visit = 2:
  contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
  Grupo A - Grupo B    0.869 1.82 91.4     -2.74      4.47   0.478  0.6335

visit = 3:
  contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
  Grupo A - Grupo B   -0.814 1.85 96.8     -4.49      2.86  -0.440  0.6609

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

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

allocation_group = Grupo A:
  contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
  visit1 - visit2    0.907 0.714 84.3    -0.837     2.651   1.270  0.6225
  visit1 - visit3    1.656 0.749 84.3    -0.173     3.484   2.212  0.0891
  visit2 - visit3    0.749 0.750 91.4    -1.080     2.577   0.999  0.9617

allocation_group = Grupo B:
  contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
  visit1 - visit2    0.217 0.728 84.3    -1.561     1.996   0.298  1.0000
  visit1 - visit3   -0.716 0.775 84.3    -2.609     1.176  -0.925  1.0000
  visit2 - visit3   -0.934 0.779 95.7    -2.831     0.964  -1.199  0.7002

```

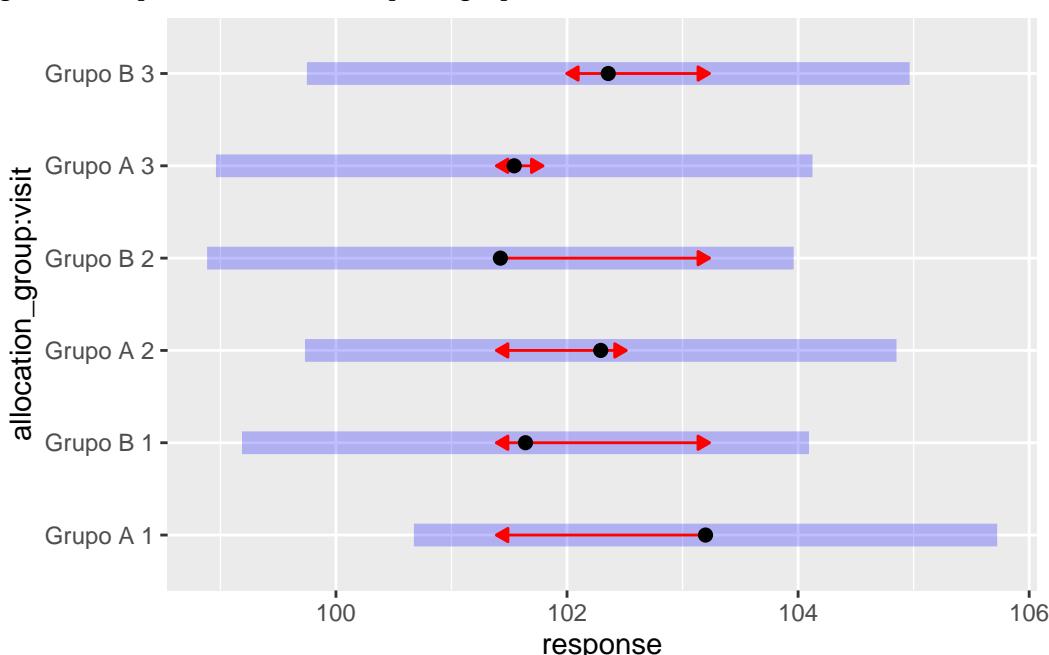
```

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests

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

Warning: Comparison discrepancy in group "1", Grupo A visit3 - Grupo B visit3:
Target overlap = 0.8487, overlap on graph = -0.3329

```



3.14.2.2 Análise de sensibilidade

```

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

abdomen_emm <- regrid(abdomen_emm)

# Table of marginal means
# abdomen_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(abdomen_emm,

```

```

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

visit = 1:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B     1.747 1.79 75.5     -1.82      5.32    0.975  0.3328

visit = 2:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B     1.591 1.84 81.5     -2.06      5.25    0.866  0.3889

visit = 3:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    -0.386 1.87 86.0     -4.10      3.33   -0.206  0.8370

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

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

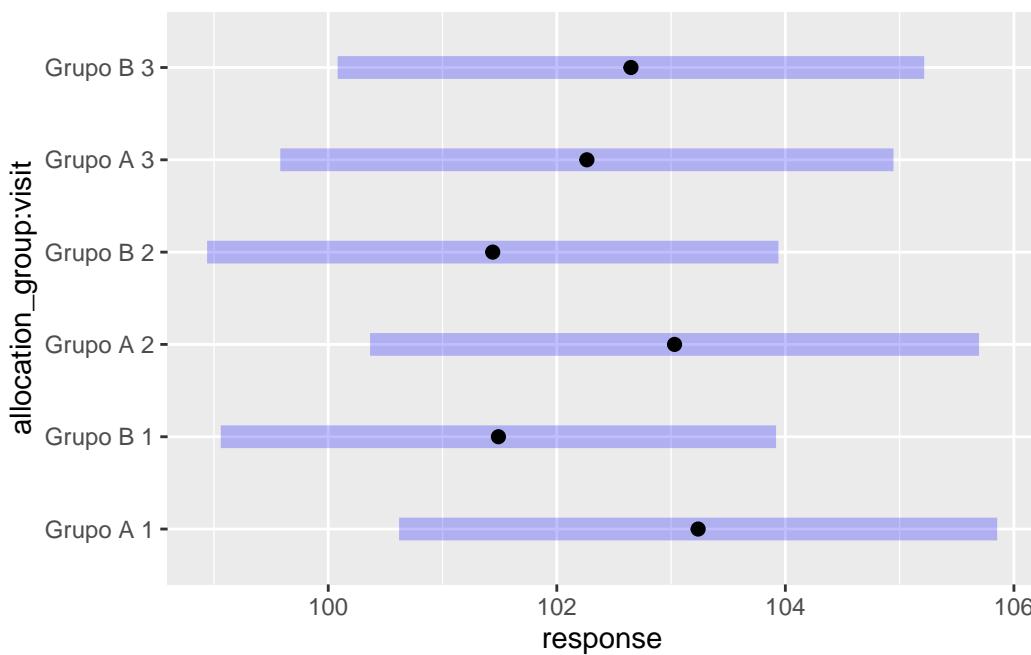
allocation_group = Grupo A:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit2    0.2062 0.653 75.5     -1.393     1.806    0.316  1.0000
visit1 - visit3    0.9734 0.691 75.5     -0.719     2.665    1.409  0.4892
visit2 - visit3    0.7672 0.693 81.5     -0.928     2.462    1.106  0.8156

allocation_group = Grupo B:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit2    0.0497 0.630 75.5     -1.494     1.593    0.079  1.0000
visit1 - visit3   -1.1596 0.674 75.5     -2.809     0.490   -1.721  0.2679
visit2 - visit3   -1.2094 0.676 84.1     -2.861     0.443   -1.788  0.2319

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests

```

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



3.14.3 Resultado

No modelo ajustado para a circunferência abdominal, não foram observadas diferenças estatisticamente significativas entre os grupos em nenhum dos três momentos avaliados. As comparações dentro dos grupos ao longo do tempo também não revelaram mudanças significativas. Embora a diferença entre as visitas 1 e 3 no grupo placebo tenha se aproximado da significância ($p = 0,089$), essa tendência não foi confirmada na análise de sensibilidade. Após a exclusão das observações influentes, os resultados permaneceram estáveis, sem diferenças estatisticamente significativas entre os grupos ou ao longo do tempo. As estimativas, intervalos de confiança de 95% e valores de p estão apresentados na Tabela 14.

Tabela 14: Diferenças estimadas da circunferência abdominal entre os grupos de alocação (placebo vs Eclipta) e entre visitas dentro de cada grupo

| Grupo de comparação | Comparação | Estimativa | IC 95% | p-valor |
|---------------------|---------------------|------------|----------------|---------|
| Entre grupos | Visita 1 | 1,56 | [-1,96 ; 5,08] | 0,381 |
| Entre grupos | Visita 2 | 0,87 | [-2,74 ; 4,47] | 0,634 |
| Entre grupos | Visita 3 | -0,81 | [-4,49 ; 2,86] | 0,661 |
| Grupo Placebo | Visita 1 - Visita 2 | 0,91 | [-0,84 ; 2,65] | 0,623 |
| Grupo Placebo | Visita 1 - Visita 3 | 1,66 | [-0,17 ; 3,48] | 0,089 |
| Grupo Placebo | Visita 2 - Visita 3 | 0,75 | [-1,08 ; 2,58] | 0,962 |
| Grupo Eclipta | Visita 1 - Visita 2 | 0,22 | [-1,56 ; 2,00] | 1,000 |

| Grupo de comparação | Comparação | Estimativa | IC 95% | p-valor |
|---------------------|---------------------|------------|----------------|---------|
| 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 |

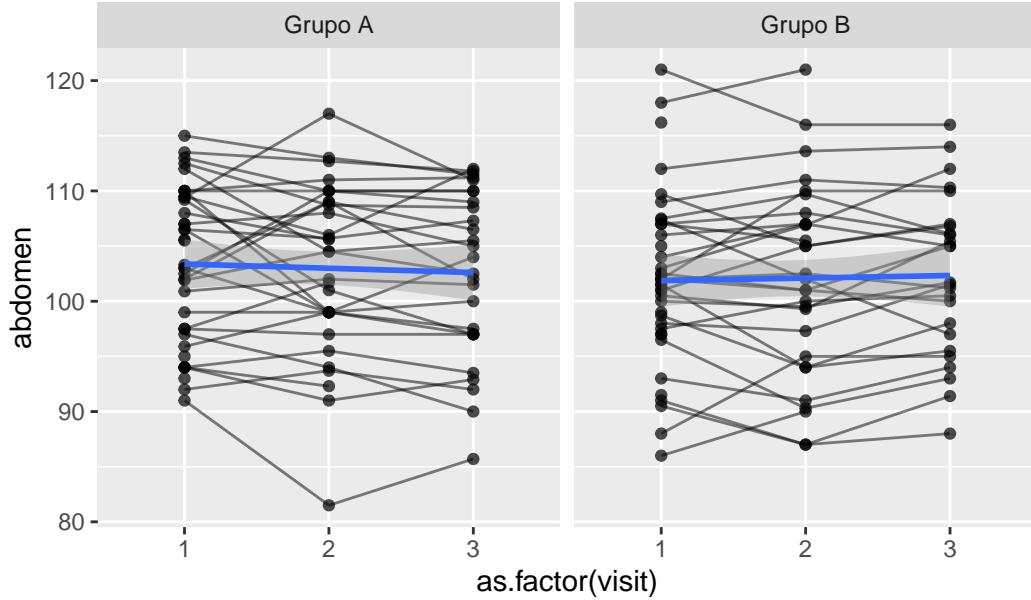
```

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") +
```

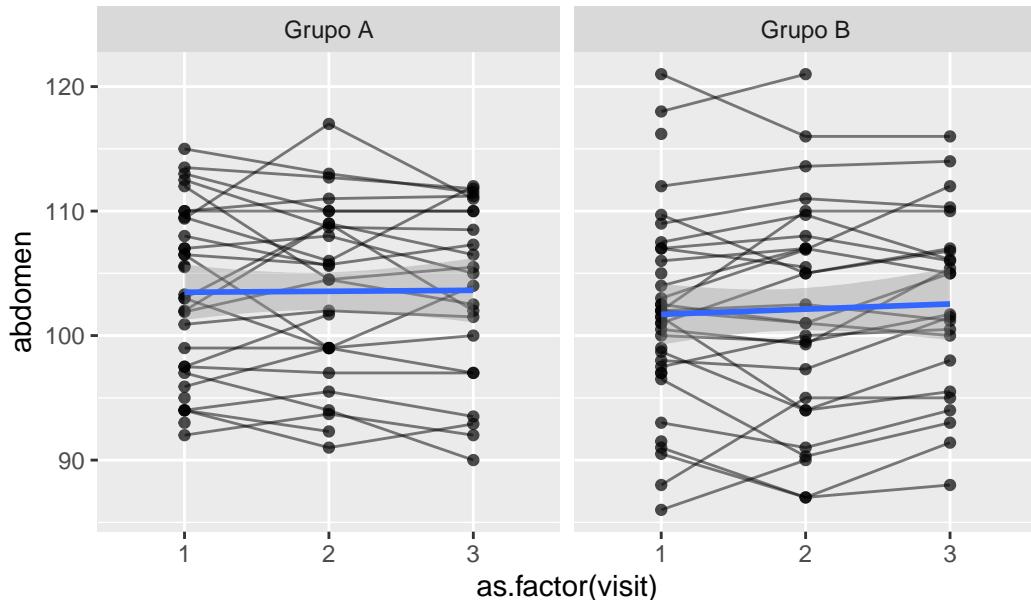
```

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))
```

3.15 Índice de Massa Corporal

Variável: bmi

```

# Plot 1: Raw data
bmi_hist_1 <- data_model %>%
  #filter(
  #  bmi < 300
  #) %>%
  ggplot(aes(x = bmi)) +
  geom_histogram(bins = 50, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
bmi_hist_2 <- data_model %>%

```

```

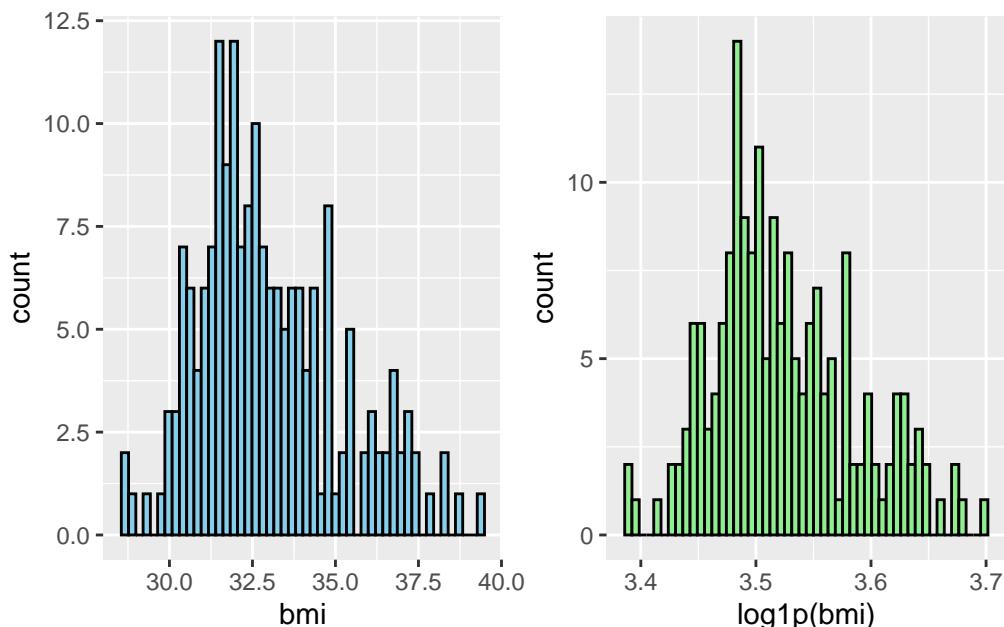
#filter(
  #   bmi < 300
#) %>%
ggplot(aes(x = log1p(bmi))) +
  geom_histogram(bins = 50, fill = "lightgreen", color = "black")

# Combine side by side
bmi_hist_1 + bmi_hist_2 # library(patchwork)

```

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

Removed 2 rows containing non-finite outside the scale range (`stat_bin()`).



```

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

# Check for Multicollinearity

```

Low Correlation

| Term | VIF | VIF 95% CI | Increased SE | Tolerance |
|------------------------|------|--------------|--------------|-----------|
| allocation_group | 1.05 | [1.00, 1.88] | 1.03 | 0.95 |
| visit | 3.74 | [2.98, 4.78] | 1.93 | 0.27 |
| allocation_group:visit | 3.83 | [3.05, 4.91] | 1.96 | 0.26 |
| Tolerance 95% CI | | | | |

```

[0.53, 1.00]
[0.21, 0.34]
[0.20, 0.33]

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

# LMM Sensitivity
bmi_model_sens <- update(object = bmi_model,
                           subset = !(record_id %in%
                                         bmi_model_check$influential_ids))

# Influential IDs
bmi_model_check$influential_ids

[1] "8"  "50" "53" "74" "32"

```

3.15.1 Resumo dos modelos

```

# Model comparison
summary(bmi_model)

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

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

Data: data_model

```

REML criterion at convergence: 615.9

Scaled residuals:

| Min | 1Q | Median | 3Q | Max |
|---------|---------|---------|--------|--------|
| -3.4029 | -0.4671 | -0.0177 | 0.4841 | 3.3103 |

Random effects:

| Groups | Name | Variance | Std.Dev. |
|-----------|-------------|----------|----------|
| record_id | (Intercept) | 4.1025 | 2.0255 |
| | Residual | 0.4525 | 0.6727 |

Number of obs: 187, groups: record_id, 75

Fixed effects:

| | Estimate | Std. Error | df | t value | Pr(> t) |
|--------------------------------|----------|------------|----------|---------|----------|
| (Intercept) | 32.9678 | 0.3509 | 81.3398 | 93.961 | < 2e-16 |
| allocation_groupGrupo B | 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_groupGrupo B:visit2 | 0.3364 | 0.2445 | 110.4215 | 1.375 | 0.17179 |
| allocation_groupGrupo B:visit3 | 0.5709 | 0.2582 | 110.6050 | 2.211 | 0.02910 |

(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 -0.205 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_groupGrupo B | 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
```

```
performance::compare_performance(
  bmi_model,
  bmi_model_sens)
```

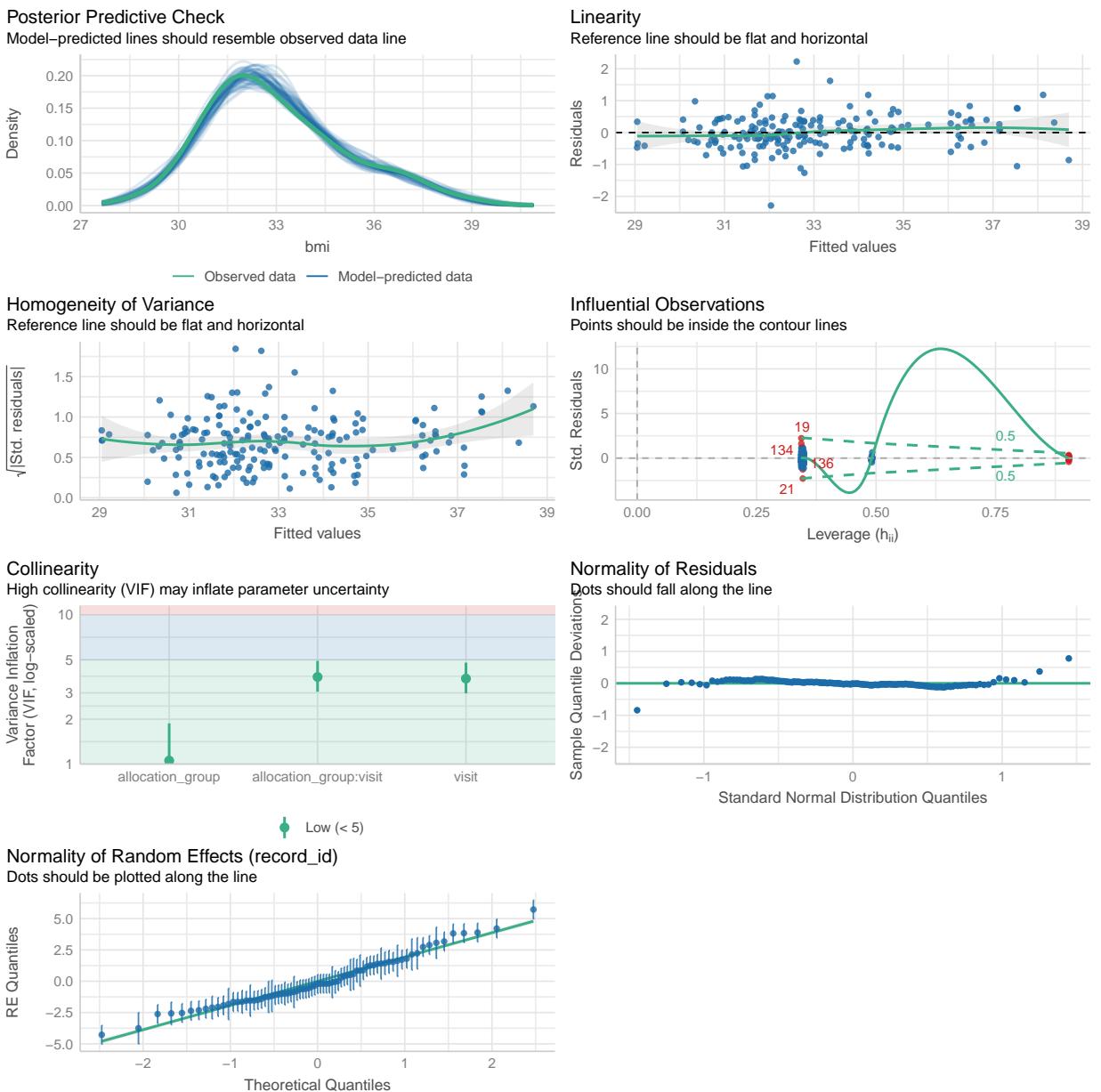
When comparing models, please note that probably not all models were fit
from same data.

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

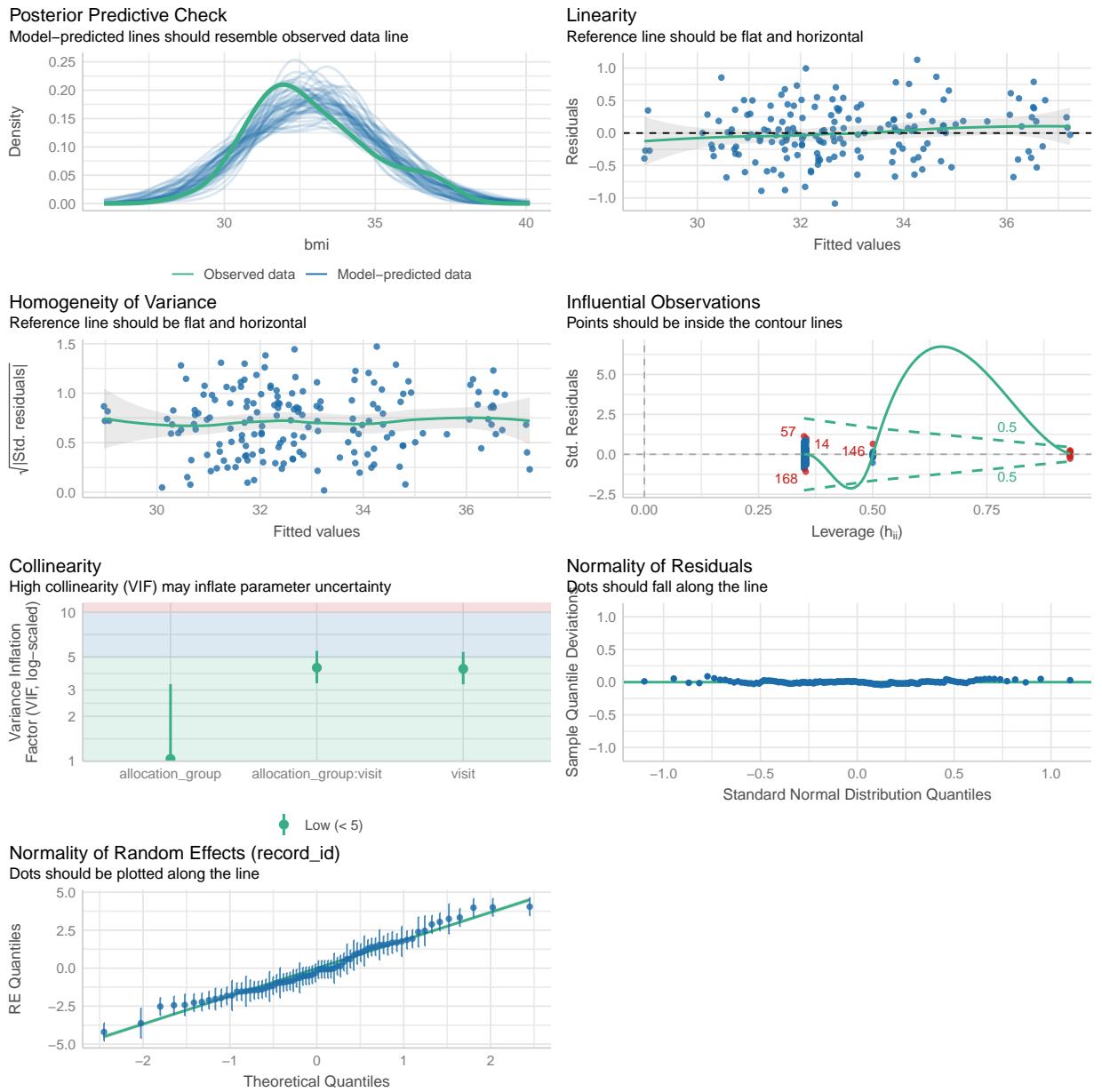
| Name | | Model | AIC (weights) | AICc (weights) |
|----------------|-----------------|---------------|---------------|----------------|
| bmi_model | lmerModLmerTest | 624.2 (<.001) | 625.0 (<.001) | |
| bmi_model_sens | lmerModLmerTest | 515.0 (>.999) | 515.9 (>.999) | |

| 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)
```



3.15.2 Médias Marginais Estimadas

3.15.2.1 Todos os dados

```
# Get EMMs for each group at each visit
bmi_raw_emm <- emmeans::emmeans(
  bmi_model,
  ~ allocation_group * visit
)
```

```
bmi_raw_emm <- regrid(bmi_raw_emm)
```

```

# Table of marginal means
# bmi_raw_emm

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

visit = 1:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
  Grupo A - Grupo B   -0.360 0.493 81.0    -1.34    0.6210  -0.730  0.4675

visit = 2:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
  Grupo A - Grupo B   -0.696 0.505 86.4    -1.70    0.3068  -1.380  0.1712

visit = 3:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
  Grupo A - Grupo B   -0.931 0.511 90.4    -1.95    0.0851  -1.820  0.0720

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

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

allocation_group = Grupo A:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
  visit1 - visit2  0.32626 0.170 81.0   -0.0899    0.742   1.916  0.1765
  visit1 - visit3  0.57397 0.179 81.0    0.1355    1.012   3.200  0.0059
  visit2 - visit3  0.24771 0.180 86.4   -0.1917    0.687   1.376  0.5167

allocation_group = Grupo B:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
  visit1 - visit2 -0.01010 0.176 81.0   -0.4396    0.419   -0.057  1.0000
  visit1 - visit3  0.00309 0.186 81.0   -0.4514    0.458   0.017  1.0000
  visit2 - visit3  0.01319 0.187 89.7   -0.4426    0.469   0.071  1.0000

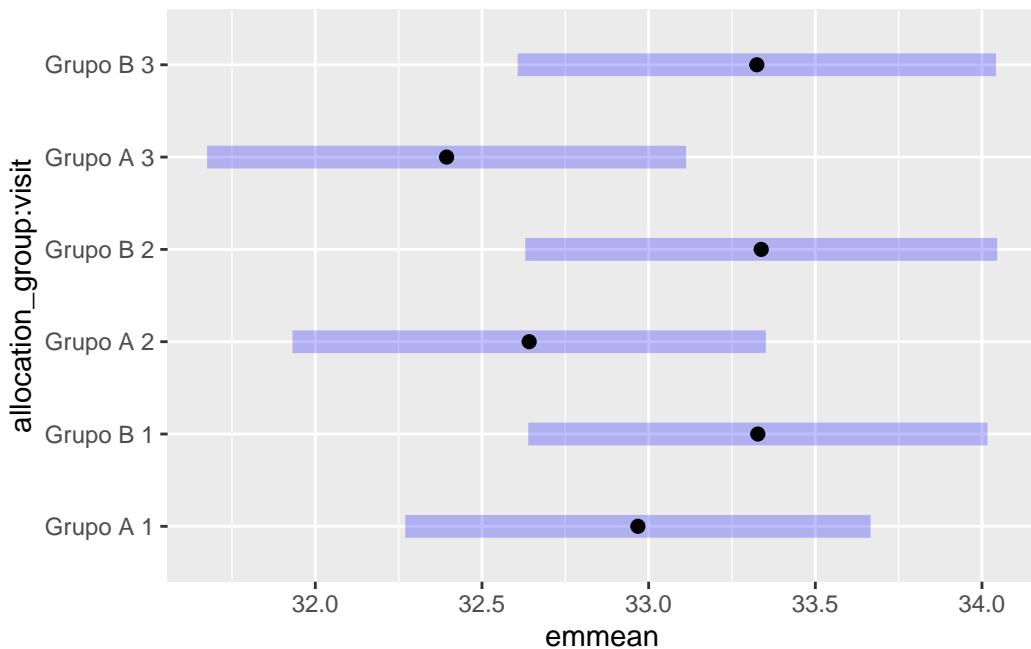
```

```

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests

# Plot of marginal means
plot(bmi_raw_emm)

```



3.15.2.2 Análise de sensibilidade

```

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

bmi_emm <- regrid(bmi_emm)

# Table of marginal means
# bmi_emm

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

```

```

visit = 1:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B   -0.547 0.473 73.0     -1.49     0.395 -1.158  0.2508

visit = 2:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B   -0.669 0.481 77.1     -1.63     0.289 -1.391  0.1682

visit = 3:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B   -0.750 0.486 80.2     -1.72     0.218 -1.541  0.1271

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

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

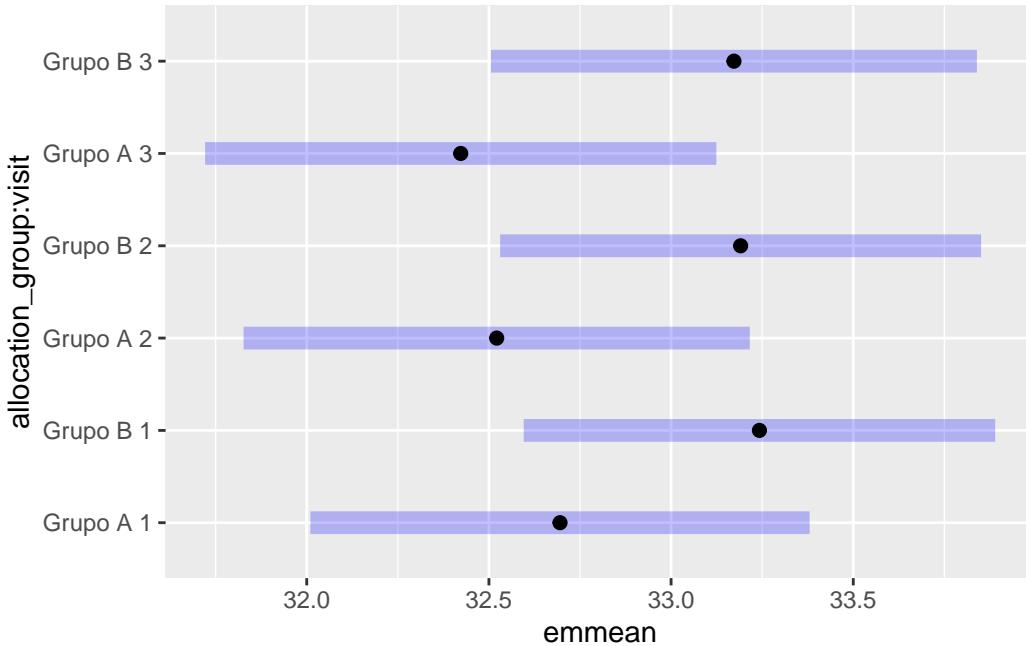
allocation_group = Grupo A:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit2   0.1738 0.141 73.0    -0.173     0.520  1.228  0.6699
visit1 - visit3   0.2725 0.150 73.0    -0.096     0.641  1.812  0.2222
visit2 - visit3   0.0987 0.151 77.1    -0.270     0.468  0.655  1.0000

allocation_group = Grupo B:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit2   0.0516 0.139 73.0    -0.288     0.392  0.372  1.0000
visit1 - visit3   0.0699 0.147 73.0    -0.291     0.431  0.475  1.0000
visit2 - visit3   0.0184 0.148 78.9    -0.343     0.380  0.124  1.0000

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests

# Plot of marginal means
plot(bmi_emm)

```



3.15.3 Resultado

No modelo ajustado para o índice de massa corporal (IMC), não foram observadas diferenças estatisticamente significativas entre os grupos em nenhum dos três momentos avaliados. No entanto, dentro do grupo placebo, observou-se uma redução estatisticamente significativa entre as visitas 1 e 3 ($p = 0,0059$). Para investigar a robustez desse achado, foi realizada uma análise de sensibilidade com exclusão das cinco observações mais influentes (IDs: 8, 50, 53, 74 e 32). Após a exclusão, a diferença intra grupo placebo deixou de ser significativa ($p = 0,222$), sugerindo que o resultado original foi influenciado por outliers.

As figuras de diagnóstico do modelo indicaram leve heterocedasticidade e presença de observações influentes, justificando a realização da análise de sensibilidade. A comparação entre os modelos mostrou melhora nos índices de ajuste após a exclusão dos dados influentes (AIC e BIC consideravelmente menores e RMSE reduzido), além de maior normalidade dos resíduos e aleatoriedade nos efeitos aleatórios.

As estimativas, intervalos de confiança de 95% e valores de p estão apresentados na Tabela 15. As estimativas, intervalos de confiança de 95% e valores de p da análise de sensibilidade estão apresentadas na Tabela 16.

Tabela 15: Diferenças estimadas do índice de massa corporal (IMC) entre os grupos de alocação (placebo vs Eclipta) e entre visitas dentro de cada grupo

| Grupo de comparação | Comparação | Estimativa | IC 95% | p-valor |
|---------------------|---------------------|------------|----------------|---------|
| Entre grupos | Visita 1 | -0,36 | [-1,34 ; 0,62] | 0,468 |
| Entre grupos | Visita 2 | -0,70 | [-1,70 ; 0,31] | 0,171 |
| Entre grupos | Visita 3 | -0,93 | [-1,95 ; 0,09] | 0,072 |
| Grupo Placebo | Visita 1 - Visita 2 | 0,33 | [-0,09 ; 0,74] | 0,177 |

| Grupo de comparação | Comparação | Estimativa | IC 95% | p-valor |
|---------------------|---------------------|------------|----------------|---------|
| 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)

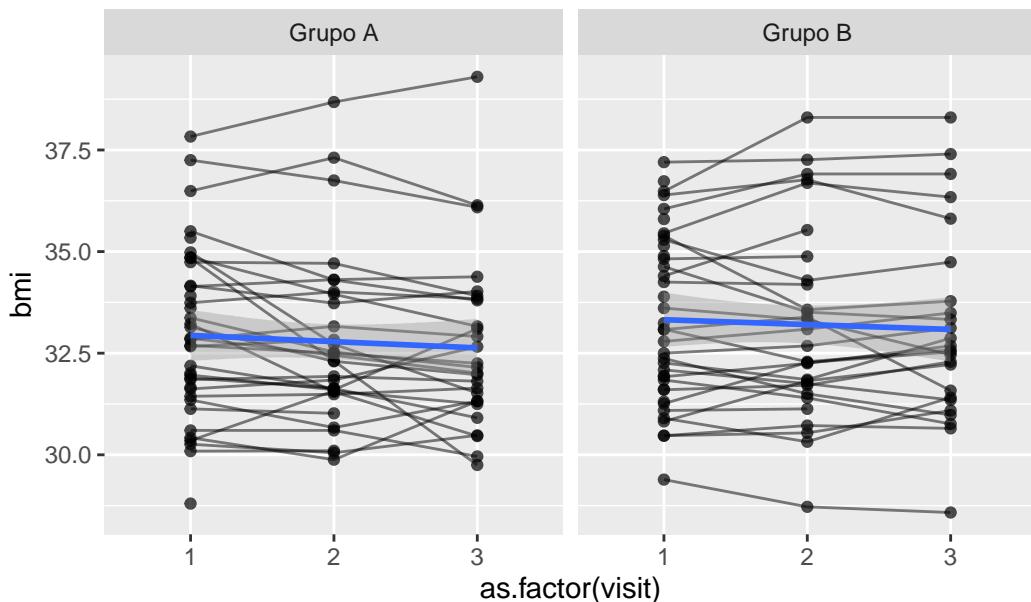
`geom_smooth()` using formula = 'y ~ x'
Warning: Removed 2 rows containing non-finite outside the scale range
(`stat_smooth()`).

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'

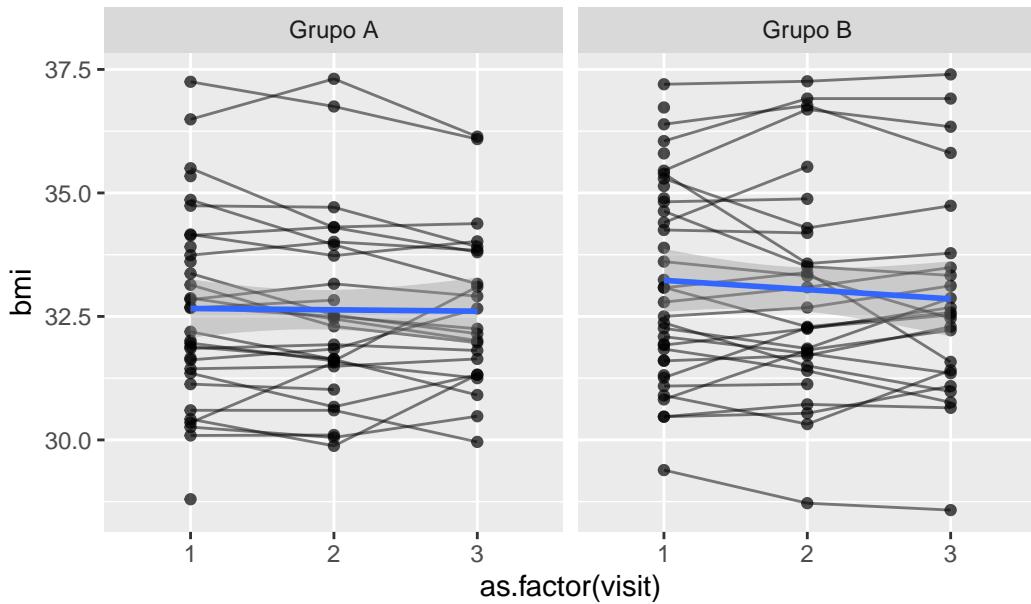
Warning: Removed 2 rows containing non-finite outside the scale range
(`stat_smooth()`).

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))
```

3.16 Pressão Arterial Média

Variável: mean_bp_mean

```

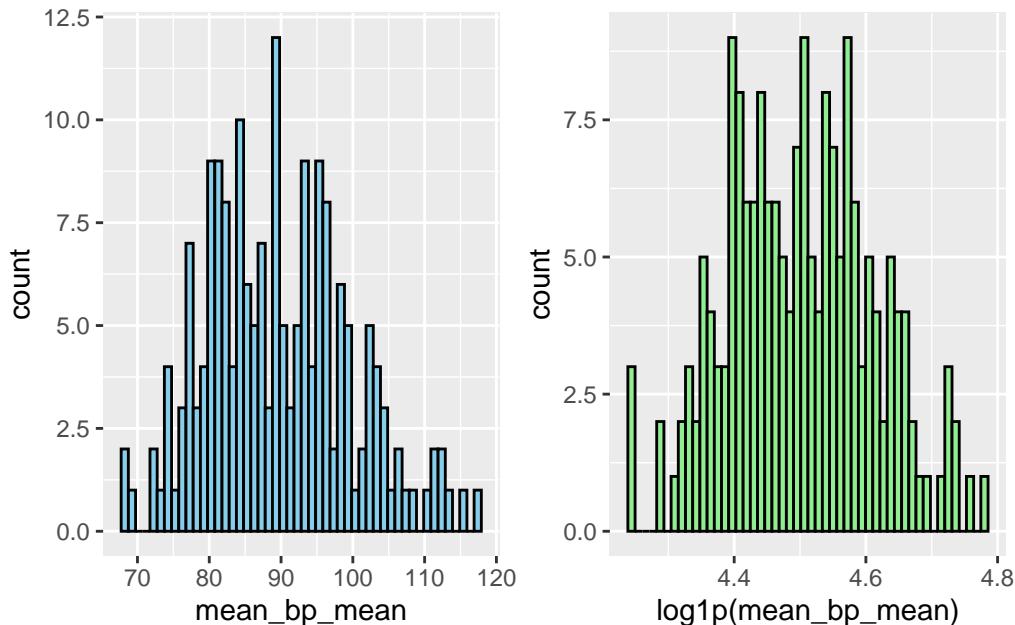
# Plot 1: Raw data
mean_bp_mean_hist_1 <- data_model %>%
  #filter(
  #  mean_bp_mean < 300
  #) %>%
  ggplot(aes(x = mean_bp_mean)) +
  geom_histogram(bins = 50, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
mean_bp_mean_hist_2 <- data_model %>%
  #filter(
  #  mean_bp_mean < 300
  #) %>%
  ggplot(aes(x = log1p(mean_bp_mean))) +
  geom_histogram(bins = 50, fill = "lightgreen", color = "black")

# Combine side by side
mean_bp_mean_hist_1 + mean_bp_mean_hist_2 # library(patchwork)

Warning: Removed 4 rows containing non-finite outside the scale range (`stat_bin()`).
Removed 4 rows containing non-finite outside the scale range (`stat_bin()`).

```



```

# LMM
mean_bp_mean_model <- lmer(mean_bp_mean ~ allocation_group * visit +
  (1 | record_id), data = data_model)

```

```

check_collinearity(mean_bp_mean_model)

# Check for Multicollinearity

Low Correlation

      Term   VIF   VIF 95% CI Increased SE Tolerance
allocation_group 1.22 [1.09, 1.54]          1.10      0.82
           visit 3.88 [3.09, 4.98]          1.97      0.26
allocation_group:visit 4.29 [3.39, 5.51]      2.07      0.23
Tolerance 95% CI
[0.65, 0.92]
[0.20, 0.32]
[0.18, 0.29]

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

# LMM Sensitivity
mean_bp_mean_model_sens <- update(object = mean_bp_mean_model,
                                     subset = !(record_id %in%
                                                 mean_bp_mean_model_check$influential_ids))

# Influential IDS
mean_bp_mean_model_check$influential_ids

[1] "46" "17" "45" "27" "50"

```

3.16.1 Resumo dos modelos

```

# Model comparison
summary(mean_bp_mean_model)

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

REML criterion at convergence: 1286.9

```

Scaled residuals:

| Min | 1Q | Median | 3Q | Max |
|----------|----------|----------|---------|---------|
| -2.62758 | -0.53598 | -0.01067 | 0.48135 | 3.02975 |

Random effects:

| Groups | Name | Variance | Std.Dev. |
|-----------|-------------|----------|----------|
| record_id | (Intercept) | 67.94 | 8.243 |
| Residual | | 34.36 | 5.862 |

Number of obs: 185, groups: record_id, 75

Fixed effects:

| | Estimate | Std. Error | df | t value | Pr(> t) |
|-------------------------|----------|------------|---------|---------|------------|
| (Intercept) | 89.595 | 1.663 | 104.881 | 53.882 | <2e-16 *** |
| allocation_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 ' ' |
| | | | | | 1 |

Correlation of Fixed Effects:

| | (Intr) | all_GB | visit2 | visit3 | a_GB:2 |
|-------------|--------|--------|--------|--------|--------|
| allctn_grGB | -0.712 | | | | |
| visit2 | -0.371 | 0.264 | | | |
| visit3 | -0.362 | 0.257 | 0.448 | | |
| allctn_GB:2 | 0.262 | -0.368 | -0.706 | -0.317 | |
| allctn_GB:3 | 0.252 | -0.353 | -0.312 | -0.696 | 0.451 |

`summary(mean_bp_mean_model_sens)`

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

REML criterion at convergence: 1154

Scaled residuals:

| Min | 1Q | Median | 3Q | Max |
|----------|----------|----------|---------|---------|
| -1.93844 | -0.57618 | -0.01579 | 0.55161 | 1.94113 |

Random effects:

| Groups | Name | Variance | Std.Dev. |
|-----------|-------------|----------|----------|
| record_id | (Intercept) | 66.38 | 8.147 |
| Residual | | 25.49 | 5.049 |

Number of obs: 171, groups: record_id, 70

Fixed effects:

| | Estimate | Std. Error | df | t value | Pr(> t) |
|--------------------------------|--|------------|---------|---------|-------------|
| (Intercept) | 88.940 | 1.668 | 90.996 | 53.307 | < 2e-16 *** |
| allocation_groupGrupo B | 3.765 | 2.295 | 90.996 | 1.641 | 0.10434 |
| visit2 | -2.137 | 1.375 | 101.567 | -1.554 | 0.12337 |
| visit3 | -4.528 | 1.440 | 102.162 | -3.144 | 0.00218 ** |
| allocation_groupGrupo B:visit2 | -2.666 | 1.911 | 102.226 | -1.395 | 0.16591 |
| allocation_groupGrupo B:visit3 | 1.794 | 2.012 | 102.825 | 0.892 | 0.37455 |
| --- | | | | | |
| Signif. codes: | 0 *** 0.001 ** 0.01 * 0.05 . 0.1 ' ' 1 | | | | |

Correlation of Fixed Effects:

| | (Intr) | all_GB | visit2 | visit3 | a_GB:2 |
|-------------|--------|--------|--------|--------|--------|
| allctn_grGB | -0.727 | | | | |
| visit2 | -0.337 | 0.245 | | | |
| visit3 | -0.321 | 0.234 | 0.451 | | |
| allctn_GB:2 | 0.242 | -0.333 | -0.720 | -0.324 | |
| allctn_GB:3 | 0.230 | -0.316 | -0.323 | -0.716 | 0.453 |

```
performance::compare_performance(  
  mean_bp_mean_model,  
  mean_bp_mean_model_sens)
```

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

Comparison of Model Performance Indices

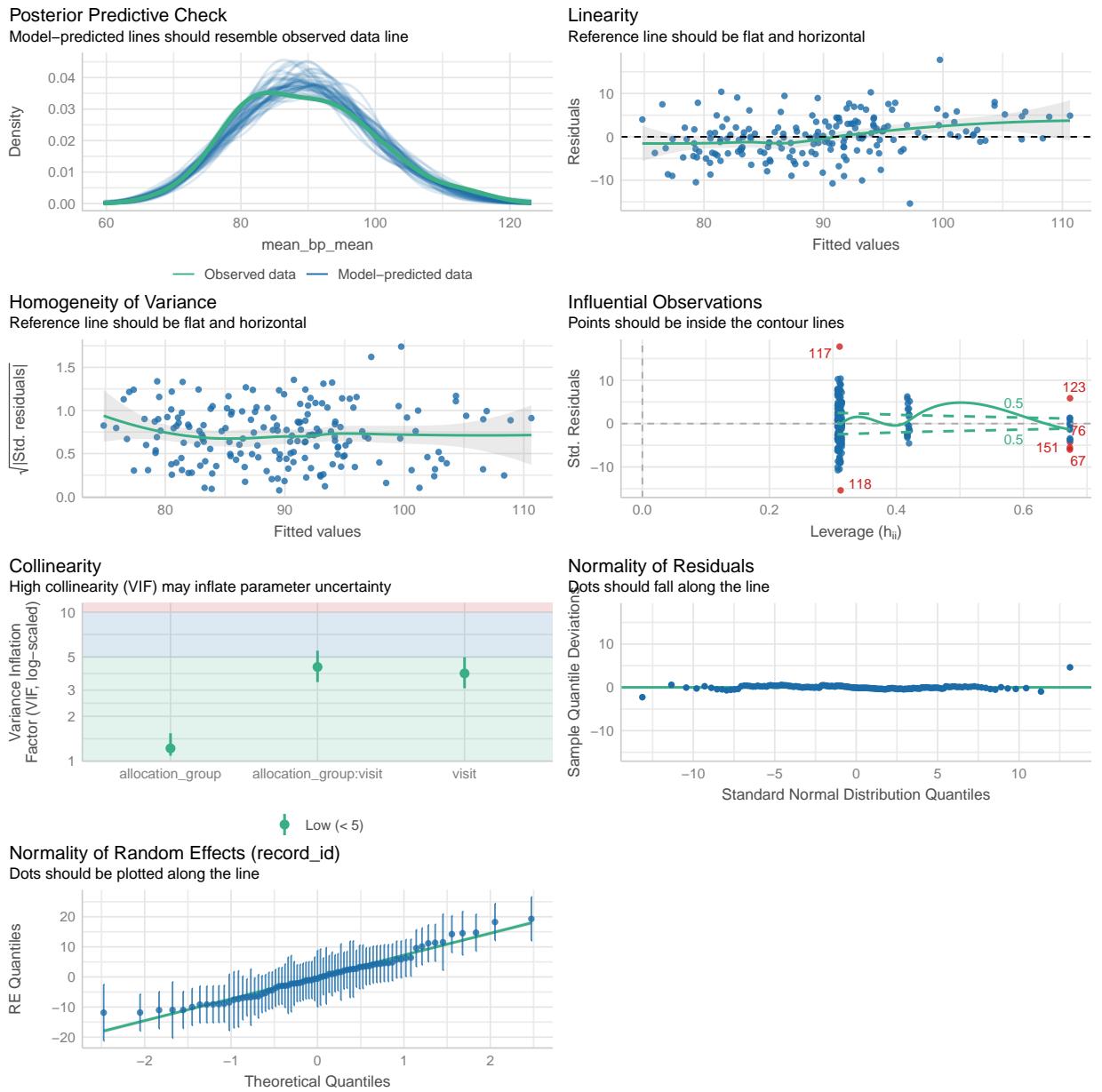
| Name | | Model | AIC (weights) | AICc (weights) |
|------|--|-------|---------------|----------------|
|------|--|-------|---------------|----------------|

```
-----  
mean_bp_mean_model | lmerModLmerTest | 1318.4 (<.001) | 1319.2 (<.001)  
mean_bp_mean_model_sens | lmerModLmerTest | 1184.7 (>.999) | 1185.6 (>.999)
```

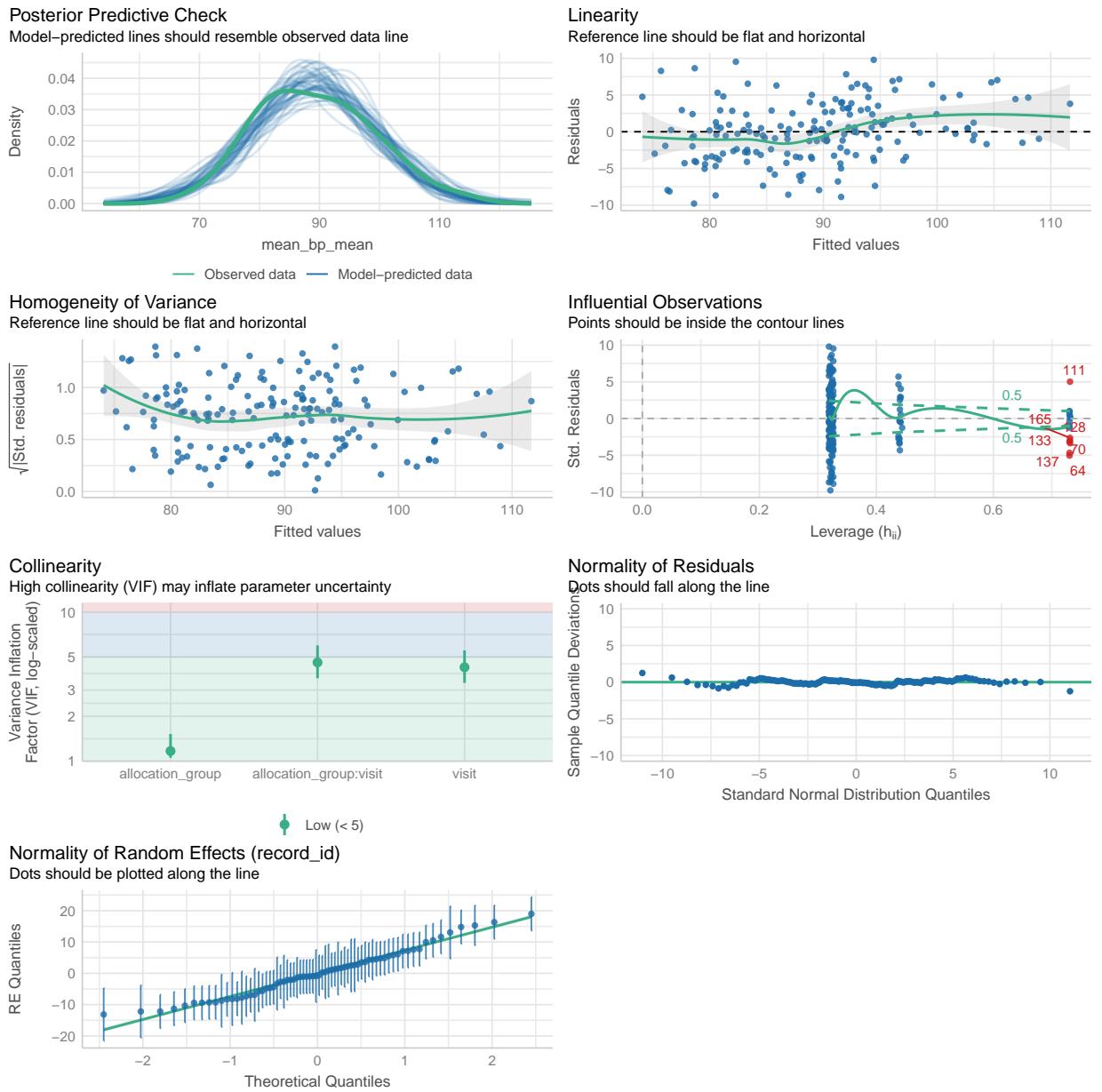
| Name | BIC (weights) | R2 (cond.) | R2 (marg.) | ICC |
|-------------------------|----------------|------------|------------|-------|
| mean_bp_mean_model | 1344.2 (<.001) | 0.677 | 0.038 | 0.664 |
| mean_bp_mean_model_sens | 1209.8 (>.999) | 0.742 | 0.070 | 0.723 |

| Name | RMSE | Sigma |
|-------------------------|-------|-------|
| mean_bp_mean_model | 4.720 | 5.862 |
| mean_bp_mean_model_sens | 4.005 | 5.049 |

```
performance::check_model(mean_bp_mean_model)
```



```
performance::check_model(mean_bp_mean_model_sens)
```



3.16.2 Médias Marginais Estimadas

3.16.2.1 Todos os dados

```
# Get EMMs for each group at each visit
mean_bp_mean_raw_emm <- emmeans::emmeans(
  mean_bp_mean_model,
  ~ allocation_group * visit
)

mean_bp_mean_raw_emm <- regrid(mean_bp_mean_raw_emm)
```

```

# Table of marginal means
# mean_bp_mean_raw_emm

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

visit = 1:
  contrast      estimate   SE  df lower.CL upper.CL t.ratio p.value
  Grupo A - Grupo B -2.7754 2.34 105    -7.41     1.856  -1.188  0.2375

visit = 2:
  contrast      estimate   SE  df lower.CL upper.CL t.ratio p.value
  Grupo A - Grupo B  0.0381 2.52 125    -4.95     5.022   0.015  0.9880

visit = 3:
  contrast      estimate   SE  df lower.CL upper.CL t.ratio p.value
  Grupo A - Grupo B -4.2106 2.59 131    -9.34     0.922  -1.623  0.1070

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

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

allocation_group = Grupo A:
  contrast      estimate   SE  df lower.CL upper.CL t.ratio p.value
  visit1 - visit2  1.21 1.51 105  -2.4559     4.87   0.802  1.0000
  visit1 - visit3  3.71 1.55 105  -0.0494     7.48   2.401  0.0543
  visit2 - visit3  2.51 1.60 125  -1.3844     6.39   1.563  0.3618

allocation_group = Grupo B:
  contrast      estimate   SE  df lower.CL upper.CL t.ratio p.value
  visit1 - visit2  4.02 1.51 105   0.3469     7.70   2.662  0.0269
  visit1 - visit3  2.28 1.60 105  -1.6056     6.16   1.427  0.4697
  visit2 - visit3 -1.74 1.62 127  -5.6828     2.20  -1.074  0.8549

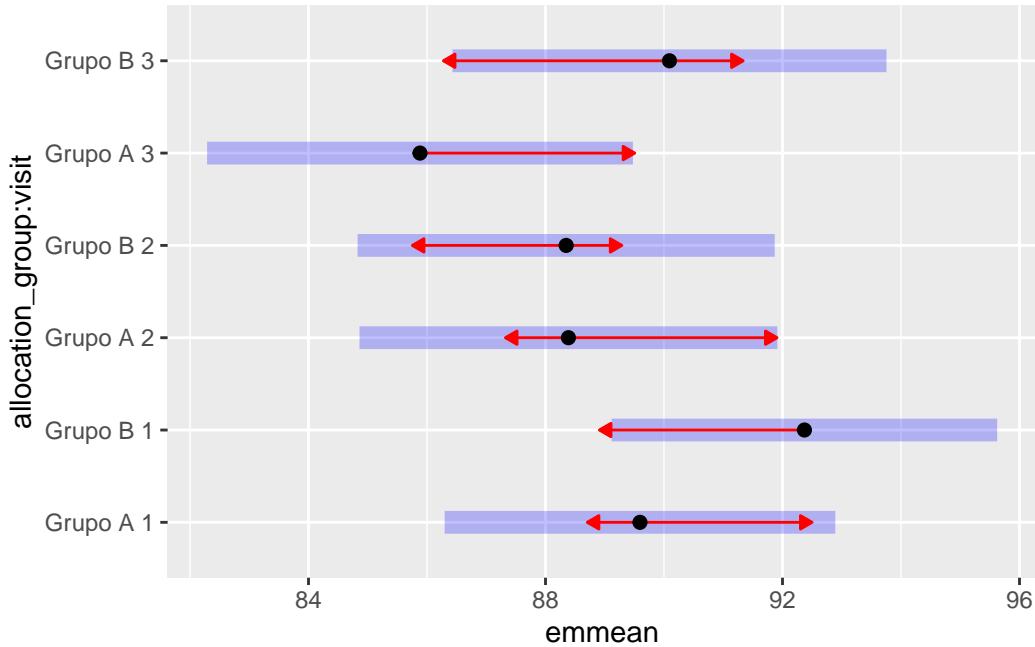
```

```

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests

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

```



3.16.2.2 Análise de sensibilidade

```

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

mean_bp_mean_emm <- regrid(mean_bp_mean_emm)

# Table of marginal means
# mean_bp_mean_emm

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

```

```

visit = 1:
  contrast      estimate    SE    df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B     -3.76 2.29  91.4     -8.32     0.793 -1.641  0.1043

visit = 2:
  contrast      estimate    SE    df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B     -1.10 2.45 107.3     -5.96     3.758 -0.448  0.6548

visit = 3:
  contrast      estimate    SE    df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B     -5.56 2.53 115.6    -10.57    -0.548 -2.197  0.0300

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

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

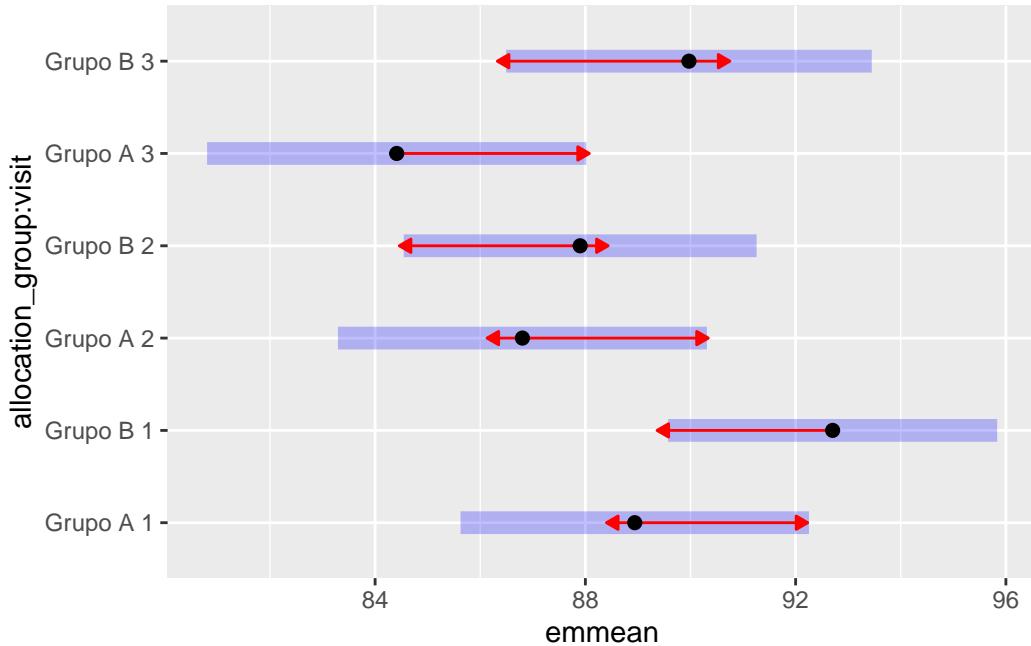
allocation_group = Grupo A:
  contrast      estimate    SE    df lower.CL upper.CL t.ratio p.value
visit1 - visit2     2.14 1.38  91.4    -1.221     5.49   1.552  0.3722
visit1 - visit3     4.53 1.44  91.4     1.012     8.04   3.141  0.0068
visit2 - visit3     2.39 1.48 107.3    -1.202     5.98   1.619  0.3254

allocation_group = Grupo B:
  contrast      estimate    SE    df lower.CL upper.CL t.ratio p.value
visit1 - visit2     4.80 1.33  91.4     1.565     8.04   3.617  0.0015
visit1 - visit3     2.73 1.41  91.4    -0.698     6.17   1.943  0.1654
visit2 - visit3    -2.07 1.43 110.3    -5.540     1.40   -1.450  0.4495

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests

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

```



3.16.3 Resultado

No modelo ajustado para a média da pressão arterial, não foram observadas diferenças estatisticamente significativas entre os grupos em nenhum dos três momentos avaliados. No entanto, observou-se uma redução da pressão arterial entre as visitas 1 e 2 no grupo Eclipta (diferença média de 4,02 mmHg; IC 95%: 0,35 a 7,70), e uma tendência à redução entre as visitas 1 e 3 no grupo placebo (diferença média de 3,71 mmHg; IC 95%: -0,05 a 7,48).

Na análise de sensibilidade, realizada com exclusão das observações mais influentes, foi identificada uma diferença significativa entre os grupos na visita 3, com o grupo Eclipta apresentando pressão arterial média 5,56 mmHg inferior ao grupo placebo (IC 95%: -10,57 a -0,55). A redução entre as visitas 1 e 3 no grupo placebo tornou-se significativa e mais pronunciada, com diferença de 4,53 mmHg (IC 95%: 1,01 a 8,04), e a diferença entre as visitas 1 e 2 no grupo Eclipta foi mantida (diferença de 4,80 mmHg; IC 95%: 1,57 a 8,04). Essas mudanças foram acompanhadas por melhora nos indicadores de ajuste do modelo. As melhorias nos indicadores de ajuste (AIC, BIC, RMSE e R²) reforçam a adequação do modelo sensível.

As estimativas, intervalos de confiança de 95% e valores de p estão apresentadas nas Tabelas [Tabela 19](#) e [Tabela 20](#).

Tabela 17: Diferenças estimadas da pressão arterial média entre os grupos de alocação (placebo vs Eclipta) e entre visitas dentro de cada grupo – Todos os dados

| Grupo de comparação | Comparação | Estimativa | IC 95% | p-valor |
|---------------------|------------|------------|----------------|---------|
| Entre grupos | Visita 1 | -2,78 | [-7,41 ; 1,86] | 0,238 |
| Entre grupos | Visita 2 | 0,04 | [-4,95 ; 5,02] | 0,988 |
| Entre grupos | Visita 3 | -4,21 | [-9,34 ; 0,92] | 0,107 |

| Grupo de comparação | Comparação | Estimativa | IC 95% | p-valor |
|------------------------|---------------------|------------|------------------|---------|
| Grupo Placebo | Visita 1 - Visita 2 | 1,21 | [-2,46 ; 4,87] | 1,000 |
| Grupo Placebo | Visita 1 - Visita 3 | 3,71 | [-0,05 ; 7,48] | 0,054 |
| Grupo Placebo | Visita 2 - Visita 3 | 2,51 | [-1,38 ; 6,39] | 0,362 |
| Grupo Eclipta | Visita 1 - Visita 2 | 4,02 | [0,35 ; 7,70] | 0,027 |
| Grupo Eclipta | Visita 1 - Visita 3 | 2,28 | [-1,61 ; 6,16] | 0,470 |
| Grupo Eclipta | Visita 2 - Visita 3 | -1,74 | [-5,68 ; 2,20] | 0,855 |

Tabela 18: Diferenças estimadas da pressão arterial média entre os grupos de alocação (placebo vs Eclipta) e entre visitas dentro de cada grupo – Análise de sensibilidade

| Grupo de comparação | Comparação | Estimativa | IC 95% | p-valor |
|------------------------|---------------------|------------|--------------------|---------|
| Entre grupos | Visita 1 | -3,76 | [-8,32 ; 0,79] | 0,104 |
| Entre grupos | Visita 2 | -1,10 | [-5,96 ; 3,76] | 0,655 |
| Entre grupos | Visita 3 | -5,56 | [-10,57 ; -0,55] | 0,030 |
| Grupo Placebo | Visita 1 - Visita 2 | 2,14 | [-1,22 ; 5,49] | 0,372 |
| Grupo Placebo | Visita 1 - Visita 3 | 4,53 | [1,01 ; 8,04] | 0,007 |
| Grupo Placebo | Visita 2 - Visita 3 | 2,39 | [-1,20 ; 5,98] | 0,325 |
| Grupo Eclipta | Visita 1 - Visita 2 | 4,80 | [1,57 ; 8,04] | 0,002 |
| Grupo Eclipta | Visita 1 - Visita 3 | 2,73 | [-0,70 ; 6,17] | 0,165 |
| Grupo Eclipta | Visita 2 - Visita 3 | -2,07 | [-5,54 ; 1,40] | 0,450 |

```
ggplot(
  data = data_model,
  aes(
    x = as.factor(visit),
    y = mean_bp_mean,
    group = record_id,
  )
) +
  geom_line(alpha = 0.5) +
  geom_point(alpha = 0.7) +
  geom_smooth(
    aes(group = allocation_group),
    method = "lm",
    se = TRUE,
```

```

    linewidth = 1
) +
  labs(title = "All data") +
  facet_wrap(~ allocation_group)

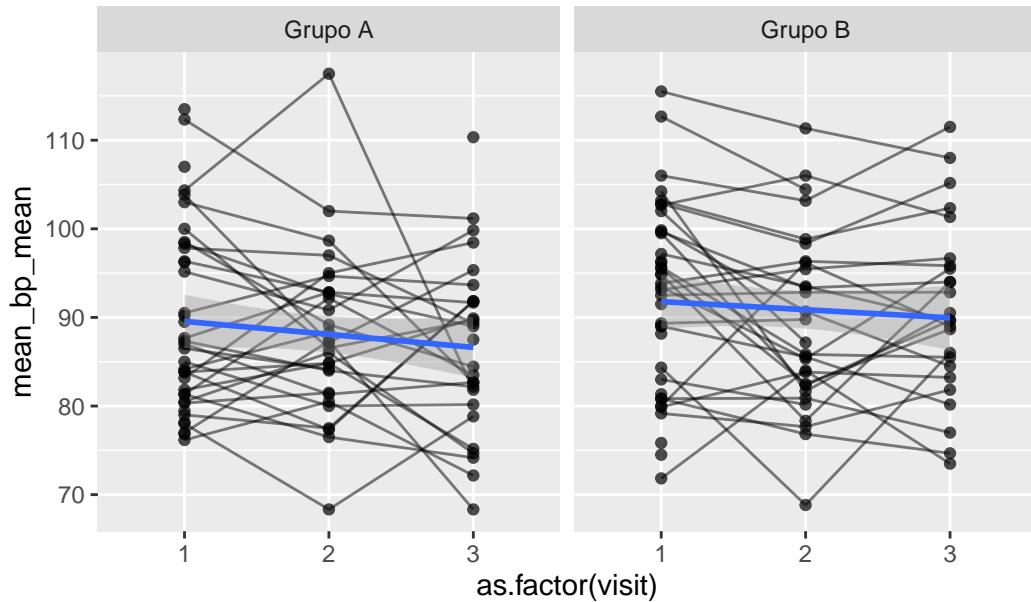
`geom_smooth()` using formula = 'y ~ x'
Warning: Removed 4 rows containing non-finite outside the scale range
(`stat_smooth()`).

Warning: Removed 2 rows containing missing values or values outside the scale range
(`geom_line()`).

Warning: Removed 4 rows containing missing values or values outside the scale range
(`geom_point()`).

```

All data



```

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

data_model %>%
  filter(
    !(record_id %in%
      mean_bp_mean_model_check$influential_ids)
  ) %>%
  ggplot(
    aes(
      x = as.factor(visit),
      y = mean_bp_mean,
      group = record_id,

```

```

)
) +
geom_line(alpha = 0.5) +
geom_point(alpha = 0.7) +
geom_smooth(
  aes(group = allocation_group),
  method = "lm",
  se = TRUE,
  linewidth = 1
) +
labs(title = "Sensitivity analysis") +
facet_wrap(~ allocation_group)

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

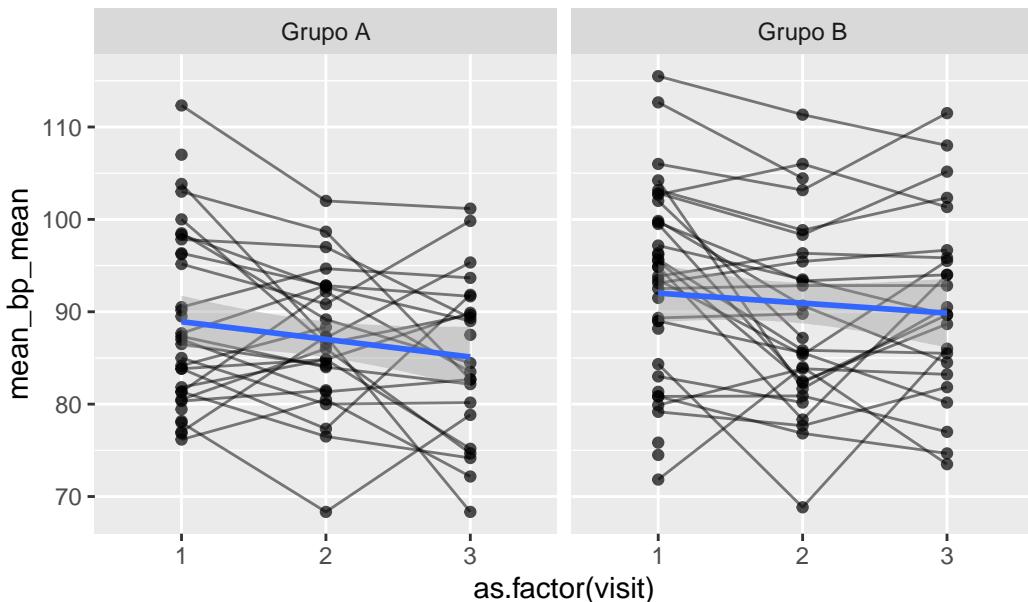
Warning: Removed 3 rows containing non-finite outside the scale range
(`stat_smooth()`).

Warning: Removed 2 rows containing missing values or values outside the scale range
(`geom_line()`).

Warning: Removed 3 rows containing missing values or values outside the scale range
(`geom_point()`).

```

Sensitivity analysis



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

3.17 PRESSÃO ARTERIAL

Importante destacar que, ao invés de resumir cada visita em um único valor, incorporamos ao modelo todas as leituras realizadas em cada participante em cada ponto de avaliação (2 a 3 medidas por visita). Essa estratégia aumentou o número total de observações disponíveis para os modelos lineares mistos. O intercepto aleatório por participante continuou a controlar a correlação entre medidas repetidas do mesmo indivíduo, permitindo capturar tanto a variabilidade intraindividual (entre as 2–3 leituras de cada visita) quanto a variabilidade interindividual, sem prejuízo à robustez dos resultados.

```
data_bp_long <- readRDS('local_files/Data_processed/data_bp_long.rds') %>%
  mutate(
    visit = as.factor(visit)
  )
```

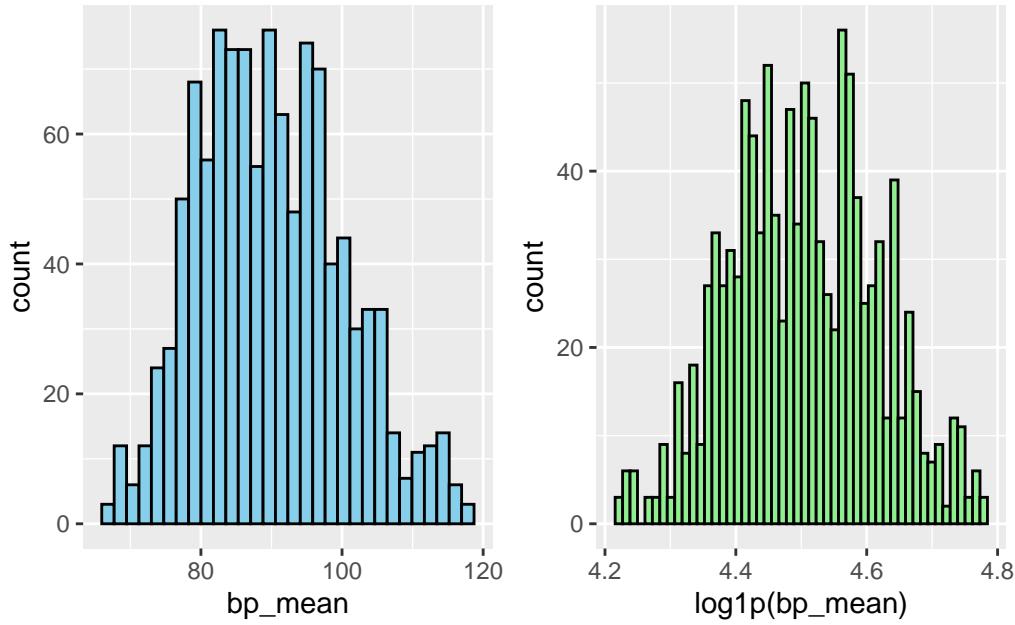
3.17.1 Pressão Arterial Média

Variável: `bp_mean`

```
# Plot 1: Raw data
bp_mean_hist_1 <- data_bp_long %>%
  #filter(
  #  bp_mean < 300
  #) %>%
  ggplot(aes(x = bp_mean)) +
  geom_histogram(bins = 30, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
bp_mean_hist_2 <- data_bp_long %>%
  #filter(
  #  bp_mean < 300
  #) %>%
  ggplot(aes(x = log1p(bp_mean))) +
  geom_histogram(bins = 50, fill = "lightgreen", color = "black")

# Combine side by side
bp_mean_hist_1 + bp_mean_hist_2 # library(patchwork)
```



```
# LMM
bp_mean_model <- lmer(bp_mean ~ allocation_group * visit +
(1 | record_id), data = data_bp_long)
check_collinearity(bp_mean_model)

# Check for Multicollinearity
```

Low Correlation

| Term | VIF | VIF 95% CI | Increased SE | Tolerance |
|------------------------|--------------|--------------|--------------|-----------|
| allocation_group | 1.03 | [1.00, 1.28] | 1.01 | 0.98 |
| visit | 3.83 | [3.47, 4.24] | 1.96 | 0.26 |
| allocation_group:visit | 3.87 | [3.51, 4.30] | 1.97 | 0.26 |
| Tolerance 95% CI | | | | |
| | [0.78, 1.00] | | | |
| | [0.24, 0.29] | | | |
| | [0.23, 0.29] | | | |

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

Warning in checkConv(attr(opt, "derivs"), opt\$par, ctrl = control\$checkConv, :

```

Model failed to converge with max|grad| = 0.00564557 (tol = 0.002, component 1)

# LMM Sensitivity
bp_mean_model_sens <- update(object = bp_mean_model,
                                subset = !(record_id %in%
                                bp_mean_model_check$influential_ids))

# Influential IDS
bp_mean_model_check$influential_ids

[1] "1"  "4"  "10" "13" "17" "18" "19" "22" "23" "26" "27" "31" "32" "34" "37"
[16] "38" "39" "45" "46" "47" "51" "52" "53" "54" "58" "63" "64" "69" "71"

```

3.17.1.1 Resumo dos modelos

```
summary(bp_mean_model)
```

```

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

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

Data: data_bp_long

```

REML criterion at convergence: 7010.5

Scaled residuals:

| Min | 1Q | Median | 3Q | Max |
|---------|---------|---------|--------|--------|
| -3.4686 | -0.5899 | -0.0157 | 0.5536 | 3.3685 |

Random effects:

| Groups | Name | Variance | Std.Dev. |
|-----------|-------------|----------|----------|
| record_id | (Intercept) | 81.26 | 9.014 |
| | Residual | 25.19 | 5.019 |

Number of obs: 1113, groups: record_id, 75

Fixed effects:

| | Estimate | Std. Error | df | t value | Pr(> t) |
|--------------------------------|----------|------------|-----------|---------|----------|
| (Intercept) | 89.8090 | 1.5300 | 76.2999 | 58.700 | < 2e-16 |
| allocation_groupGrupo B | 2.7084 | 2.1518 | 76.6090 | 1.259 | 0.211973 |
| visit2 | -1.6710 | 0.5224 | 1041.0211 | -3.199 | 0.001422 |
| visit3 | -4.0199 | 0.5299 | 1042.2597 | -7.586 | 7.28e-14 |
| allocation_groupGrupo B:visit2 | -2.8069 | 0.7391 | 1042.5621 | -3.798 | 0.000154 |
| allocation_groupGrupo B:visit3 | 1.3575 | 0.7631 | 1043.1895 | 1.779 | 0.075531 |

```

(Intercept) ***  

allocation_groupGrupo B  

visit2 **  

visit3 ***  

allocation_groupGrupo B:visit2 ***  

allocation_groupGrupo B:visit3 .  

---  

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

```

Correlation of Fixed Effects:

| | (Intr) | all_GB | visit2 | visit3 | a_GB:2 |
|-------------|--------|--------|--------|--------|--------|
| allctn_grGB | -0.711 | | | | |
| visit2 | -0.142 | 0.101 | | | |
| visit3 | -0.137 | 0.097 | 0.479 | | |
| allctn_GB:2 | 0.100 | -0.139 | -0.707 | -0.338 | |
| allctn_GB:3 | 0.095 | -0.131 | -0.332 | -0.694 | 0.472 |

```
summary(bp_mean_model_sens)
```

```

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

lmerModLmerTest]  

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

Data: data_bp_long  

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

```

REML criterion at convergence: 2871.8

Scaled residuals:

| Min | 1Q | Median | 3Q | Max |
|----------|----------|----------|---------|---------|
| -2.17909 | -0.65916 | -0.03621 | 0.63690 | 2.49223 |

Random effects:

| Groups | Name | Variance | Std.Dev. |
|-----------|-------------|----------|----------|
| record_id | (Intercept) | 94.529 | 9.723 |
| | Residual | 7.816 | 2.796 |

Number of obs: 546, groups: record_id, 46

Fixed effects:

| | Estimate | Std. Error | df | t value | Pr(> t) |
|--------------------------------|----------|------------|----------|---------|----------|
| (Intercept) | 88.9393 | 2.0946 | 44.4582 | 42.462 | < 2e-16 |
| allocation_groupGrupo B | 3.1831 | 2.9015 | 44.5612 | 1.097 | 0.278508 |
| visit2 | -1.5490 | 0.4163 | 497.8714 | -3.721 | 0.000221 |
| visit3 | -5.1020 | 0.4403 | 497.9669 | -11.588 | < 2e-16 |
| allocation_groupGrupo B:visit2 | -2.3391 | 0.5917 | 498.3073 | -3.953 | 8.82e-05 |
| allocation_groupGrupo B:visit3 | 1.6228 | 0.6284 | 498.2316 | 2.582 | 0.010097 |

```

(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 -0.722
visit2     -0.071  0.051
visit3     -0.063  0.046  0.450
allctn_GB:2  0.050 -0.069 -0.704 -0.317
allctn_GB:3  0.044 -0.062 -0.315 -0.701  0.459

```

```

performance::compare_performance(
  bp_mean_model,
  bp_mean_model_sens)

```

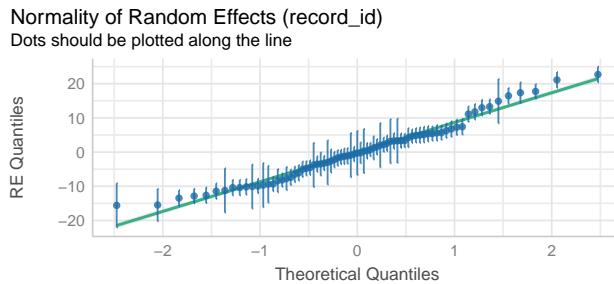
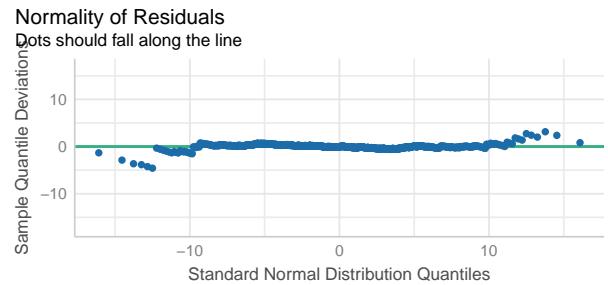
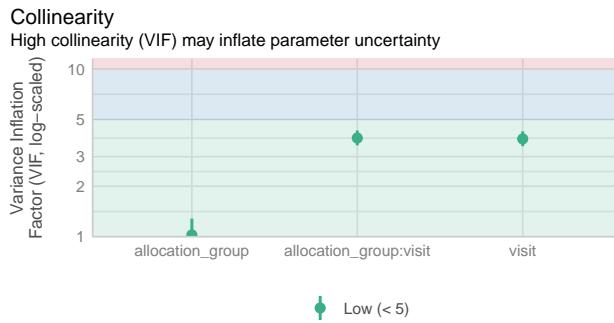
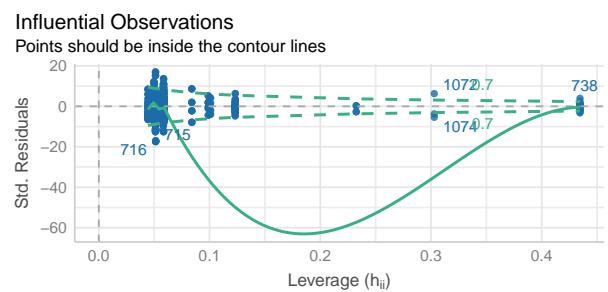
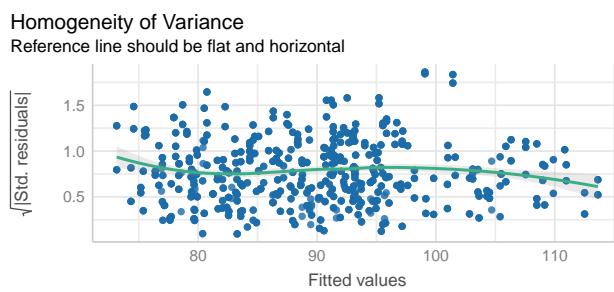
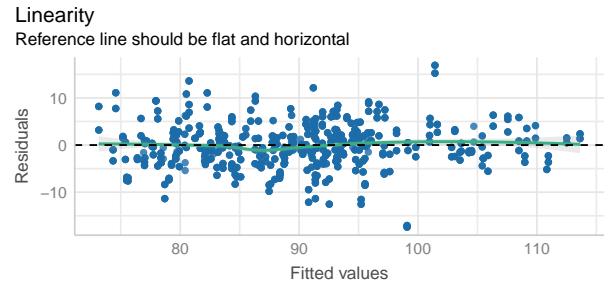
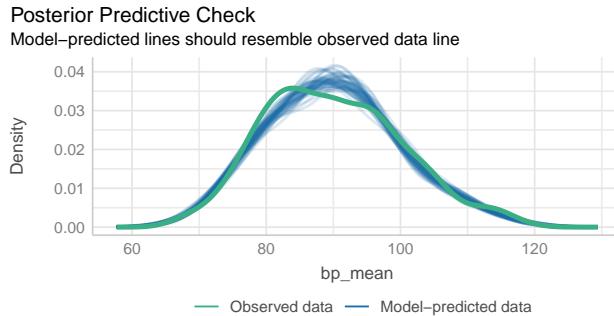
When comparing models, please note that probably not all models were fit from same data.

Comparison of Model Performance Indices

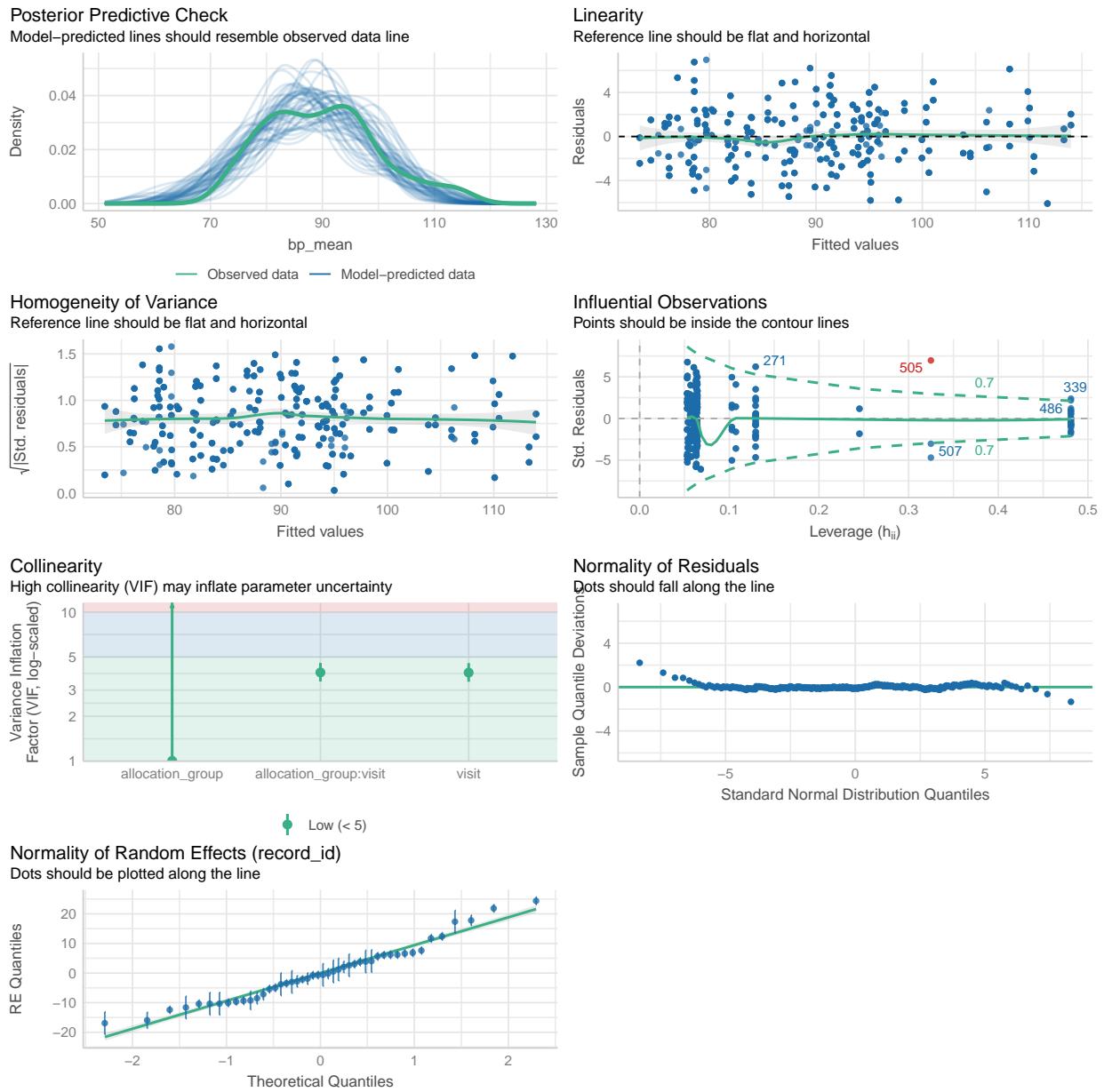
| Name | | Model | AIC (weights) | AICc (weights) | | | |
|--------------------|-----------------|----------------|----------------|----------------|-----|------|-------|
| bp_mean_model | lmerModLmerTest | 7033.6 (<.001) | 7033.7 (<.001) | | | | |
| bp_mean_model_sens | lmerModLmerTest | 2894.5 (>.999) | 2894.8 (>.999) | | | | |
| Name | | BIC (weights) | R2 (cond.) | R2 (marg.) | ICC | RMSE | Sigma |

| | | | |
|--------------------|----------------|-------|-------------------------------|
| bp_mean_model | 7073.7 (<.001) | 0.773 | 0.040 0.763 4.845 5.019 |
| bp_mean_model_sens | 2928.9 (>.999) | 0.928 | 0.055 0.924 2.667 2.796 |

```
performance::check_model(bp_mean_model)
```



```
performance::check_model(bp_mean_model_sens)
```



3.17.1.2 Médias Marginais Estimadas

3.17.1.2.1 Todos os dados

```
# Get EMMS for each group at each visit
bp_mean_raw_emm <- emmeans::emmeans(
  bp_mean_model,
  ~ allocation_group * visit
)

bp_mean_raw_emm <- regrid(bp_mean_raw_emm)
```

```

# Table of marginal means
# bp_mean_raw_emm

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

visit = 1:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
  Grupo A - Grupo B -2.7084 2.15 76.4     -6.99     1.577  -1.259  0.2120

visit = 2:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
  Grupo A - Grupo B  0.0985 2.18 79.1     -4.23     4.430   0.045  0.9640

visit = 3:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
  Grupo A - Grupo B -4.0659 2.19 80.0     -8.42     0.286  -1.859  0.0667

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

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

allocation_group = Grupo A:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
  visit1 - visit2  1.67 0.522 76.4     0.392    2.950   3.198  0.0060
  visit1 - visit3  4.02 0.530 76.4     2.723    5.317   7.585 <.0001
  visit2 - visit3  2.35 0.537 79.1     1.035    3.663   4.372  0.0001

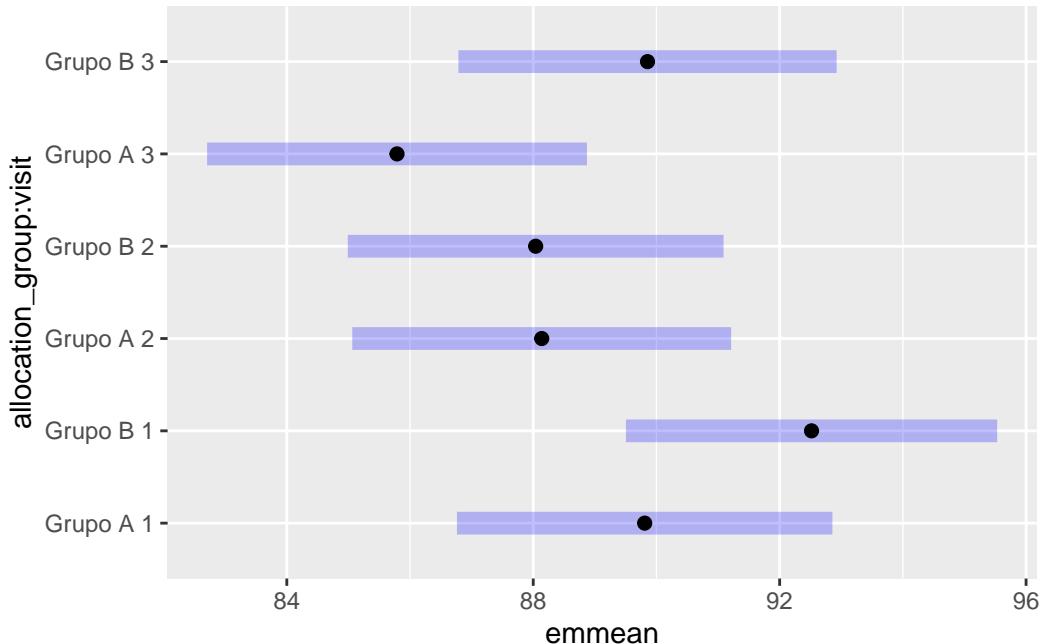
allocation_group = Grupo B:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
  visit1 - visit2  4.48 0.523 77.0     3.198    5.758   8.563 <.0001
  visit1 - visit3  2.66 0.549 77.0     1.318    4.006   4.848 <.0001
  visit2 - visit3 -1.82 0.555 80.7    -3.172   -0.459  -3.272  0.0047

```

```
Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests
```

```
# Plot of marginal means
```

```
plot(bp_mean_raw_emm)
```



3.17.1.2.2 Análise de sensibilidade

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

bp_mean_emm <- regrid(bp_mean_emm)

# Table of marginal means
# bp_mean_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(bp_mean_emm,
  method = "pairwise", by = "visit",
```

```

adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

visit = 1:
contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
Grupo A - Grupo B   -3.183 2.90 44.4     -9.03      2.66  -1.097  0.2785

visit = 2:
contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
Grupo A - Grupo B   -0.844 2.92 45.4     -6.73      5.04  -0.289  0.7739

visit = 3:
contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
Grupo A - Grupo B   -4.806 2.93 45.9     -10.70     1.09  -1.640  0.1078

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

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

allocation_group = Grupo A:
contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit2   1.549 0.416 44.4     0.513     2.585   3.721  0.0017
visit1 - visit3   5.102 0.440 44.4     4.006     6.198  11.587 <.0001
visit2 - visit3   3.553 0.450 45.4     2.435     4.671   7.901 <.0001

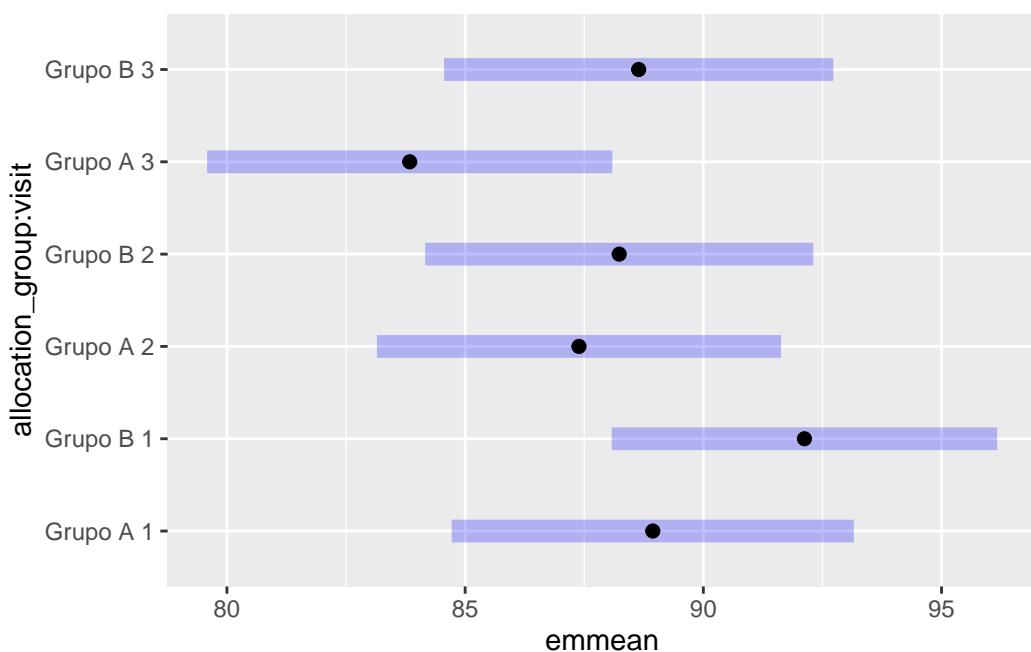
allocation_group = Grupo B:
contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit2   3.888 0.421 44.6     2.842     4.934   9.245 <.0001
visit1 - visit3   3.479 0.448 44.6     2.364     4.595   7.759 <.0001
visit2 - visit3  -0.409 0.449 46.0    -1.524     0.706  -0.911  1.0000

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests

```

```
# Plot of marginal means
```

```
plot(bp_mean_emm)
```



3.17.1.3 Resultado

No modelo ajustado para a pressão arterial média não foram observadas diferenças estatisticamente significativas entre os grupos em nenhum dos três momentos avaliados (visita 1: estimativa = -2,71 mmHg; IC 95%: -6,99 a 1,58; p = 0,212; visita 2: estimativa = 0,10 mmHg; IC 95%: -4,23 a 4,43; p = 0,964; visita 3: estimativa = -4,07 mmHg; IC 95%: -8,42 a 0,29; p = 0,067).

Ambos os grupos apresentaram redução significativa da pressão arterial entre as visitas 1 e 2 (placebo: -1,67 mmHg; IC 95%: -2,95 a -0,39; p = 0,006; eclipta: -4,48 mmHg; IC 95%: -5,76 a -3,20; p < 0,001) e entre as visitas 1 e 3 (placebo: -4,02 mmHg; IC 95%: -5,32 a -2,72; p < 0,001; eclipta: -2,66 mmHg; IC 95%: -4,01 a -1,32; p < 0,001). No grupo placebo houve ainda redução entre as visitas 2 e 3 (-2,35 mmHg; IC 95%: -3,66 a -1,04; p = 0,0001), enquanto no grupo eclipta essa redução entre a visita 2 e a 3 foi significativa apenas no modelo completo.

Na análise de sensibilidade, as reduções entre as visitas 1 e 2 e entre as visitas 1 e 3 mantiveram-se significativas em ambos os grupos. Porém, a redução entre as visitas 2 e 3 no grupo eclipta deixou de ser significativa (-0,41 mmHg; IC 95%: -1,52 a 0,71; p = 1,000).

Tabelas com estimativas, IC 95% e p-valores:

Tabela 19: Diferenças estimadas da pressão arterial média entre grupos (placebo vs eclipta) e entre visitas – Todos os dados

| Grupo de comparação | Comparação | Estimativa (mmHg) | IC 95% | p-valor |
|---------------------|------------|-------------------|---------------|---------|
| Entre grupos | Visita 1 | -2,71 | [-6,99; 1,58] | 0,212 |
| Entre grupos | Visita 2 | 0,10 | [-4,23; 4,43] | 0,964 |

| Grupo de comparação | Comparação | Estimativa (mmHg) | IC 95% | p-valor |
|---------------------|---------------------|-------------------|----------------|---------|
| Entre grupos | Visita 3 | -4,07 | [-8,42; 0,29] | 0,067 |
| Grupo Placebo | Visita 1 – Visita 2 | -1,67 | [-2,95; -0,39] | 0,006 |
| Grupo Placebo | Visita 1 – Visita 3 | -4,02 | [-5,32; -2,72] | < 0,001 |
| Grupo Placebo | Visita 2 – Visita 3 | -2,35 | [-3,66; -1,04] | 0,0001 |
| Grupo Eclipta | Visita 1 – Visita 2 | -4,48 | [-5,76; -3,20] | < 0,001 |
| Grupo Eclipta | Visita 1 – Visita 3 | -2,66 | [-4,01; -1,32] | < 0,001 |
| Grupo Eclipta | Visita 2 – Visita 3 | 1,82 | [0,46; 3,17] | 0,005 |

Tabela 20: Diferenças estimadas da pressão arterial média – Análise de sensibilidade

| Grupo de comparação | Comparação | Estimativa (mmHg) | IC 95% | p-valor |
|---------------------|---------------------|-------------------|----------------|---------|
| Entre grupos | Visita 1 | -3,18 | [-9,03; 2,66] | 0,279 |
| Entre grupos | Visita 2 | -0,84 | [-6,73; 5,04] | 0,774 |
| Entre grupos | Visita 3 | -4,81 | [-10,70; 1,09] | 0,108 |
| Grupo Placebo | Visita 1 – Visita 2 | -1,55 | [-2,59; -0,51] | 0,002 |
| Grupo Placebo | Visita 1 – Visita 3 | -5,10 | [-6,20; -4,01] | < 0,001 |
| Grupo Placebo | Visita 2 – Visita 3 | -3,55 | [-4,67; -2,44] | < 0,001 |
| Grupo Eclipta | Visita 1 – Visita 2 | -3,89 | [-4,93; -2,84] | < 0,001 |
| Grupo Eclipta | Visita 1 – Visita 3 | -3,48 | [-4,60; -2,36] | < 0,001 |
| Grupo Eclipta | Visita 2 – Visita 3 | 0,41 | [-1,52; 0,71] | 1,000 |

```
ggplot(
  data = data_bp_long,
  aes(
    x = as.factor(visit),
    y = bp_mean,
    group = record_id,
  )
) +
  geom_line(alpha = 0.5) +
  geom_point(alpha = 0.7) +
  geom_smooth(
    aes(group = allocation_group),
    method = "lm",
    se = TRUE,
    linewidth = 1
```

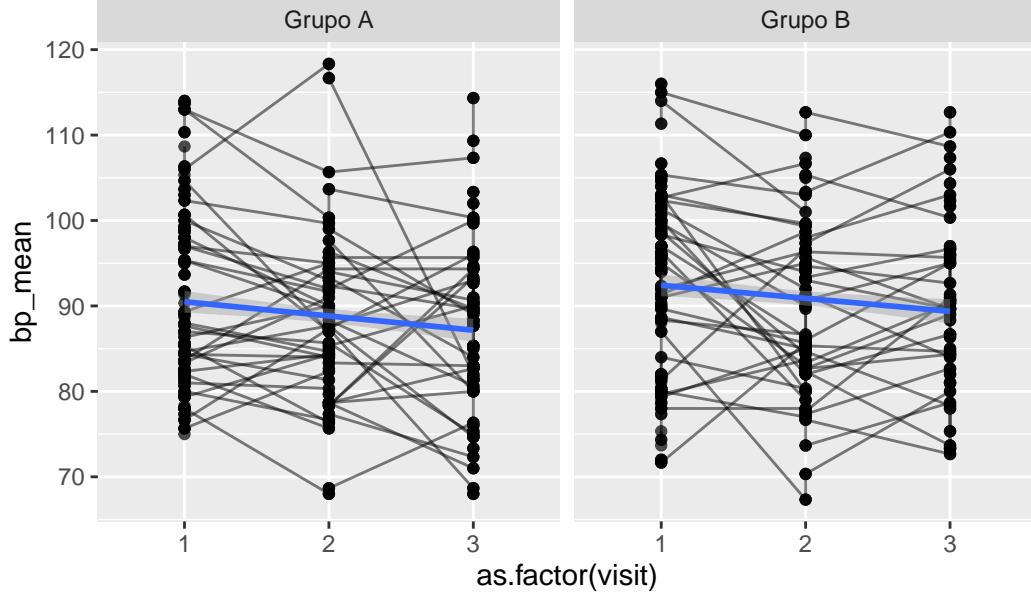
```

) +
  labs(title = "All data") +
  facet_wrap(~ allocation_group)

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

```

All data



```

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

```

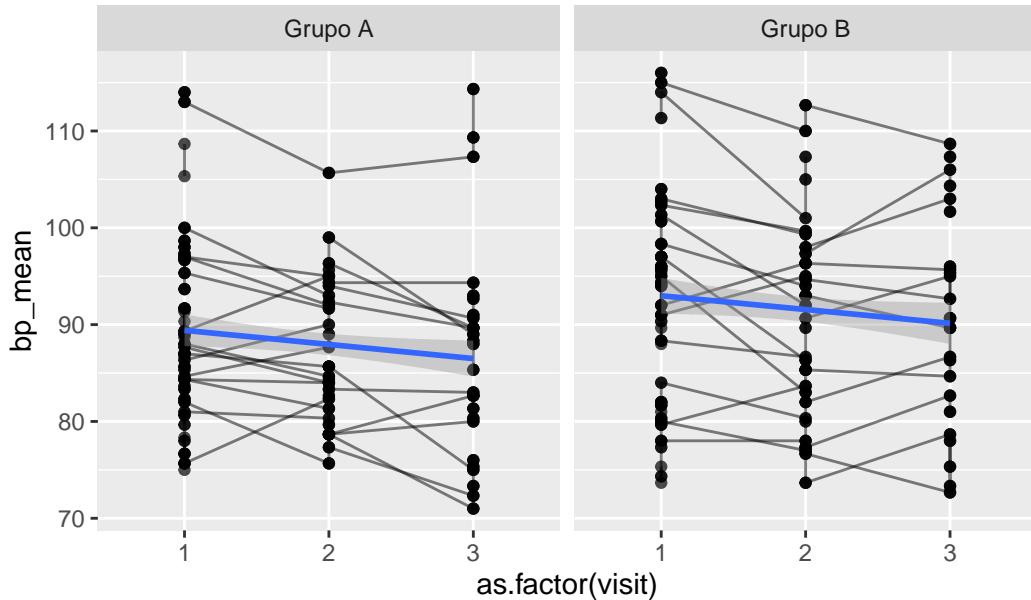
```

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

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

```

Sensitivity analysis



3.17.2 Pressão Arterial Sistólica

Variável: systolic

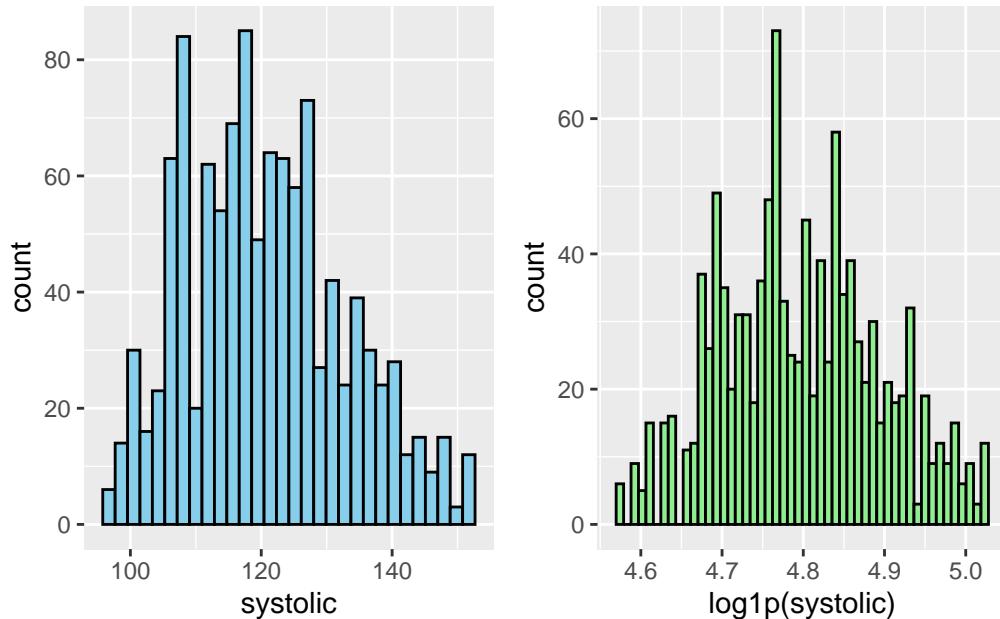
```

# Plot 1: Raw data
systolic_hist_1 <- data_bp_long %>%
  #filter(
  #  systolic < 300
  #) %>%
  ggplot(aes(x = systolic)) +
  geom_histogram(bins = 30, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
systolic_hist_2 <- data_bp_long %>%
  #filter(
  #  systolic < 300
  #) %>%
  ggplot(aes(x = log1p(systolic))) +
  geom_histogram(bins = 50, fill = "lightgreen", color = "black")

```

```
# Combine side by side
systolic_hist_1 + systolic_hist_2 # library(patchwork)
```



```
# LMM
systolic_model <- lmer(log1p(systolic) ~ allocation_group * visit +
(1 | record_id), data = data_bp_long)
check_collinearity(systolic_model)

# Check for Multicollinearity
```

Low Correlation

| Term | VIF | VIF 95% CI | Increased SE | Tolerance |
|------------------------|--------------|--------------|--------------|-----------|
| allocation_group | 1.03 | [1.00, 1.22] | 1.02 | 0.97 |
| visit | 3.83 | [3.47, 4.25] | 1.96 | 0.26 |
| allocation_group:visit | 3.89 | [3.52, 4.31] | 1.97 | 0.26 |
| Tolerance 95% CI | | | | |
| | [0.82, 1.00] | | | |
| | [0.24, 0.29] | | | |
| | [0.23, 0.28] | | | |

```
# Sensitivity analysis
systolic_model_check <- sensitivity_check_lmer(
  model = systolic_model,
  id_var = "record_id",
```

```

top_n = 5)

# LMM Sensitivity
systolic_model_sens <- update(object = systolic_model,
                                subset = !(record_id %in%
                                systolic_model_check$influential_ids))

# Influential IDS
systolic_model_check$influential_ids

[1] "1"  "4"  "10" "12" "13" "16" "17" "18" "19" "22" "23" "26" "27" "31" "32"
[16] "34" "37" "38" "39" "41" "45" "46" "47" "52" "53" "54" "58" "61" "63" "65"
[31] "69" "71" "72" "74"

```

3.17.2.1 Resumo dos modelos

```

summary(systolic_model)

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

```

REML criterion at convergence: -3077.1

Scaled residuals:

| Min | 1Q | Median | 3Q | Max |
|----------|----------|----------|---------|---------|
| -3.06595 | -0.61196 | -0.01167 | 0.62427 | 2.83791 |

Random effects:

| Groups | Name | Variance | Std.Dev. |
|-----------|-------------|----------|----------|
| record_id | (Intercept) | 0.007252 | 0.08516 |
| | Residual | 0.002818 | 0.05308 |

Number of obs: 1113, groups: record_id, 75

Fixed effects:

| | Estimate | Std. Error | df | t value |
|------------------|------------|------------|-----------|---------|
| (Intercept) | 4.792e+00 | 1.456e-02 | 7.756e+01 | 329.002 |
| allocation_group | 2.609e-02 | 2.049e-02 | 7.792e+01 | 1.273 |
| visit2 | -1.520e-02 | 5.523e-03 | 1.043e+03 | -2.753 |
| visit3 | -4.020e-02 | 5.601e-03 | 1.044e+03 | -7.178 |

```

allocation_groupGrupo B:visit2 -2.193e-02  7.813e-03  1.045e+03  -2.807
allocation_groupGrupo B:visit3   1.666e-02  8.066e-03  1.045e+03   2.066
                                         Pr(>|t|)

(Intercept) < 2e-16 ***
allocation_groupGrupo B      0.20664
visit2        0.00601 **
visit3        1.34e-12 ***
allocation_groupGrupo B:visit2  0.00510 **
allocation_groupGrupo B:visit3  0.03911 *
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```

Correlation of Fixed Effects:

```

          (Intr) all_GB visit2 visit3 a_GB:2
allctn_grGB -0.711
visit2       -0.158  0.113
visit3       -0.153  0.109  0.478
allctn_GB:2  0.112 -0.155 -0.707 -0.338
allctn_GB:3  0.106 -0.146 -0.332 -0.694  0.471

```

```
summary(systolic_model_sens)
```

```

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

```

REML criterion at convergence: -1653.2

Scaled residuals:

| Min | 1Q | Median | 3Q | Max |
|----------|----------|----------|---------|---------|
| -2.42310 | -0.70717 | -0.04306 | 0.62788 | 2.21616 |

Random effects:

| Groups | Name | Variance | Std.Dev. |
|-----------|-------------|-----------|----------|
| record_id | (Intercept) | 0.0080365 | 0.08965 |
| | Residual | 0.0008443 | 0.02906 |

Number of obs: 441, groups: record_id, 41

Fixed effects:

| | Estimate | Std. Error | df | t value |
|--------------------------------|--|------------|------------|---------|
| (Intercept) | 4.771322 | 0.019826 | 39.496588 | 240.654 |
| allocation_groupGrupo B | 0.041052 | 0.028424 | 39.701164 | 1.444 |
| visit2 | -0.010491 | 0.004477 | 398.072789 | -2.343 |
| visit3 | -0.036465 | 0.004803 | 398.110452 | -7.592 |
| allocation_groupGrupo B:visit2 | -0.022957 | 0.006840 | 398.846655 | -3.356 |
| allocation_groupGrupo B:visit3 | 0.018660 | 0.007688 | 398.549816 | 2.427 |
| | Pr(> t) | | | |
| (Intercept) | < 2e-16 *** | | | |
| allocation_groupGrupo B | 0.156511 | | | |
| visit2 | 0.019601 * | | | |
| visit3 | 2.27e-13 *** | | | |
| allocation_groupGrupo B:visit2 | 0.000866 *** | | | |
| allocation_groupGrupo B:visit3 | 0.015665 * | | | |
| --- | | | | |
| Signif. codes: | 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1 | | | |

Correlation of Fixed Effects:

```
(Intr) all_GB visit2 visit3 a_GB:2  
allctn_grGB -0.698  
visit2     -0.079  0.055  
visit3     -0.070  0.048  0.441  
allctn_GB:2  0.052 -0.075 -0.655 -0.289  
allctn_GB:3  0.043 -0.063 -0.275 -0.625  0.426
```

```
performance::compare_performance(  
    systolic_model,  
    systolic_model_sens)
```

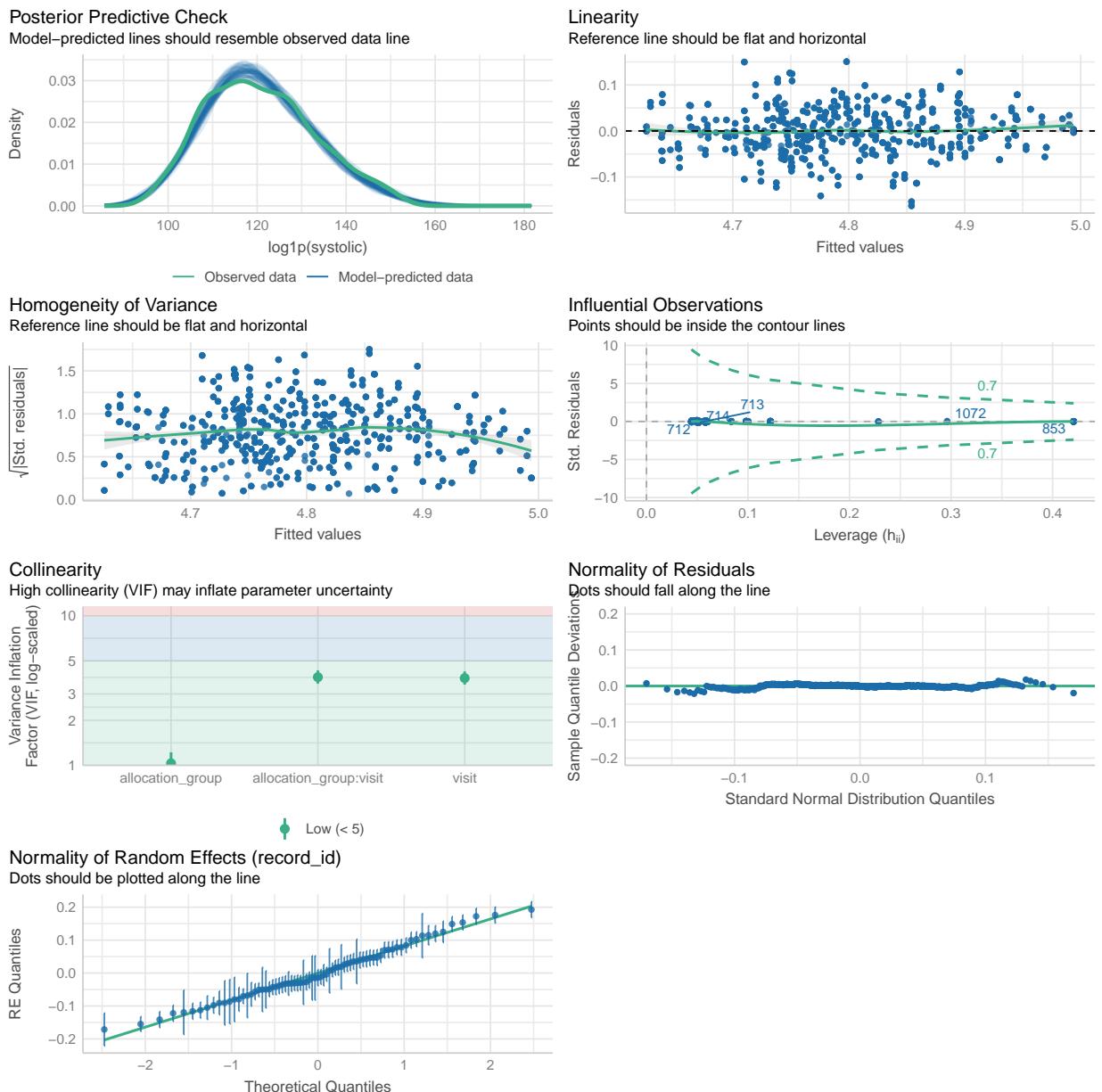
When comparing models, please note that probably not all models were fit from same data.

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

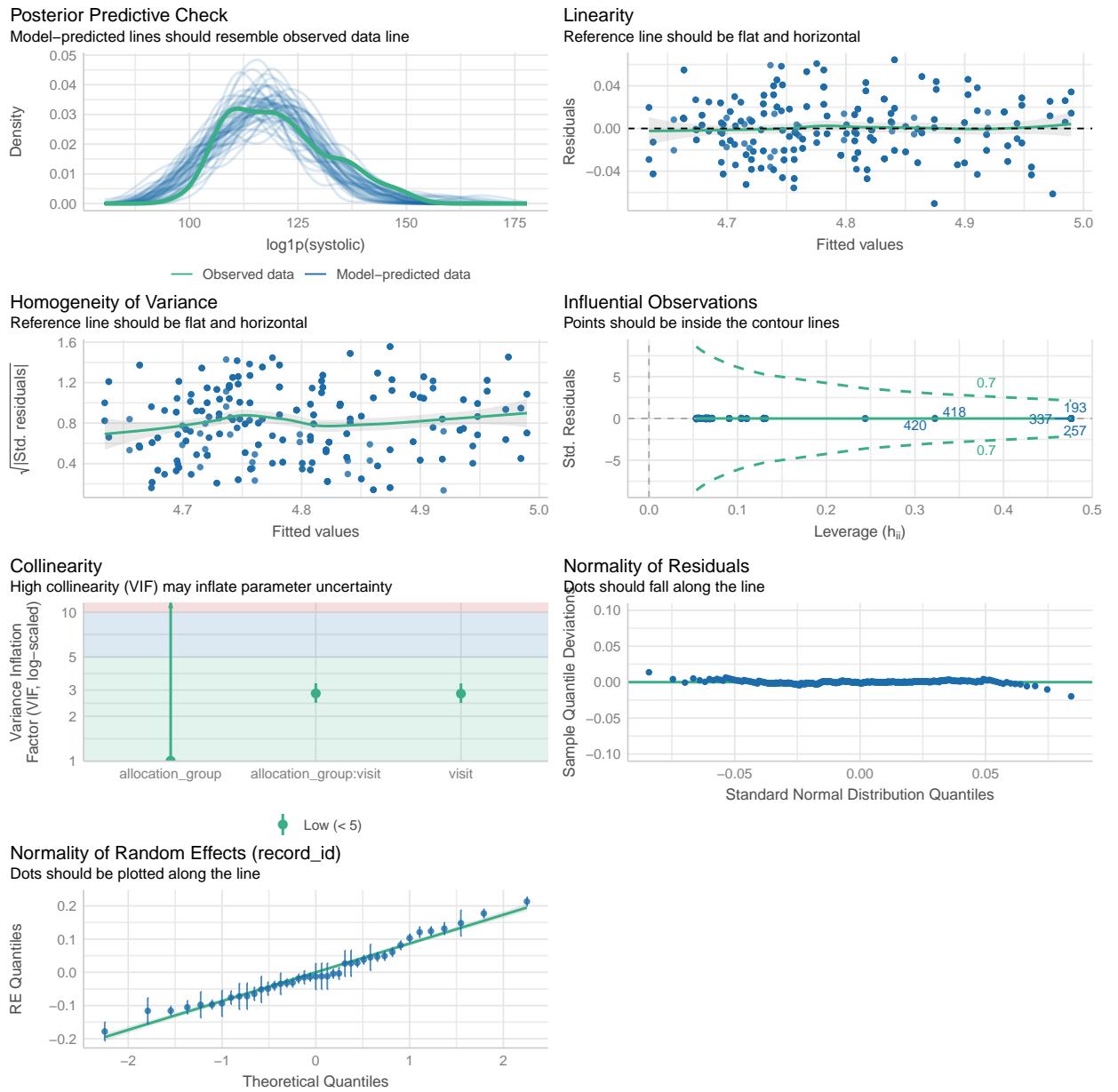
| Name | | Model | AIC (weights) | AICc (weights) |
|---------------------|-----------------|----------------|----------------|----------------|
| systolic_model | lmerModLmerTest | 7568.9 (<.001) | 7569.0 (<.001) | |
| systolic_model_sens | lmerModLmerTest | 2545.4 (>.999) | 2545.7 (>.999) | |

| Name | BIC (weights) | R2 (cond.) | R2 (marg.) | ICC | RMSE | Sigma |
|---------------------|----------------|------------|------------|-------|-------|-------|
| systolic_model | 7609.0 (<.001) | 0.731 | 0.040 | 0.720 | 0.051 | 0.053 |
| systolic_model_sens | 2578.1 (>.999) | 0.911 | 0.063 | 0.905 | 0.028 | 0.029 |

```
performance::check_model(systolic_model)
```



```
performance::check_model(systolic_model_sens)
```



3.17.2.2 Médias Marginais Estimadas

3.17.2.2.1 Todos os dados

```
# Get EMMS for each group at each visit
systolic_raw_emm <- emmeans::emmeans(
  systolic_model,
  ~ allocation_group * visit
)

systolic_raw_emm <- regrid(systolic_raw_emm)
```

```

# Table of marginal means
# systolic_raw_emm

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

visit = 1:
  contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
  Grupo A - Grupo B    -3.185 2.50 77.3     -8.16     1.795  -1.273  0.2067

visit = 2:
  contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
  Grupo A - Grupo B    -0.495 2.47 80.6     -5.41     4.420  -0.200  0.8417

visit = 3:
  contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
  Grupo A - Grupo B    -5.055 2.47 81.6     -9.97    -0.138  -2.045  0.0440

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

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

allocation_group = Grupo A:
  contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
  visit1 - visit2     1.82 0.660 77.3     0.202    3.4332   2.754  0.0220
  visit1 - visit3     4.75 0.662 77.3     3.127    6.3691   7.167 <.0001
  visit2 - visit3     2.93 0.667 80.6     1.300    4.5607   4.394  0.0001

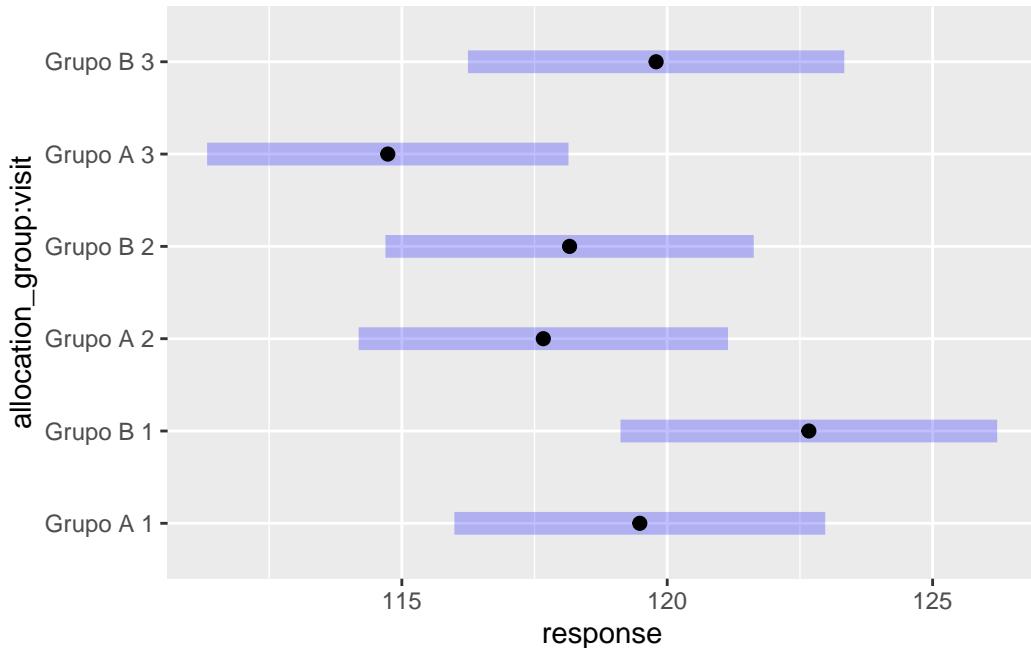
allocation_group = Grupo B:
  contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
  visit1 - visit2     4.51 0.672 78.0     2.865    6.1507   6.713 <.0001
  visit1 - visit3     2.88 0.708 78.0     1.145    4.6103   4.064  0.0003
  visit2 - visit3    -1.63 0.705 82.4    -3.353    0.0925  -2.313  0.0697

```

```
Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests
```

```
# Plot of marginal means
```

```
plot(systolic_raw_emm)
```



3.17.2.2.2 Análise de sensibilidade

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

systolic_emm <- regrid(systolic_emm)

# Table of marginal means
# systolic_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(systolic_emm,
  method = "pairwise", by = "visit",
```

```

adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

visit = 1:
contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
Grupo A - Grupo B     -4.95 3.43 39.3    -11.88     1.986  -1.443  0.1570

visit = 2:
contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
Grupo A - Grupo B     -2.13 3.39 40.5     -8.98     4.713  -0.630  0.5325

visit = 3:
contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
Grupo A - Grupo B     -7.01 3.41 41.3    -13.88    -0.128  -2.057  0.0461

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

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

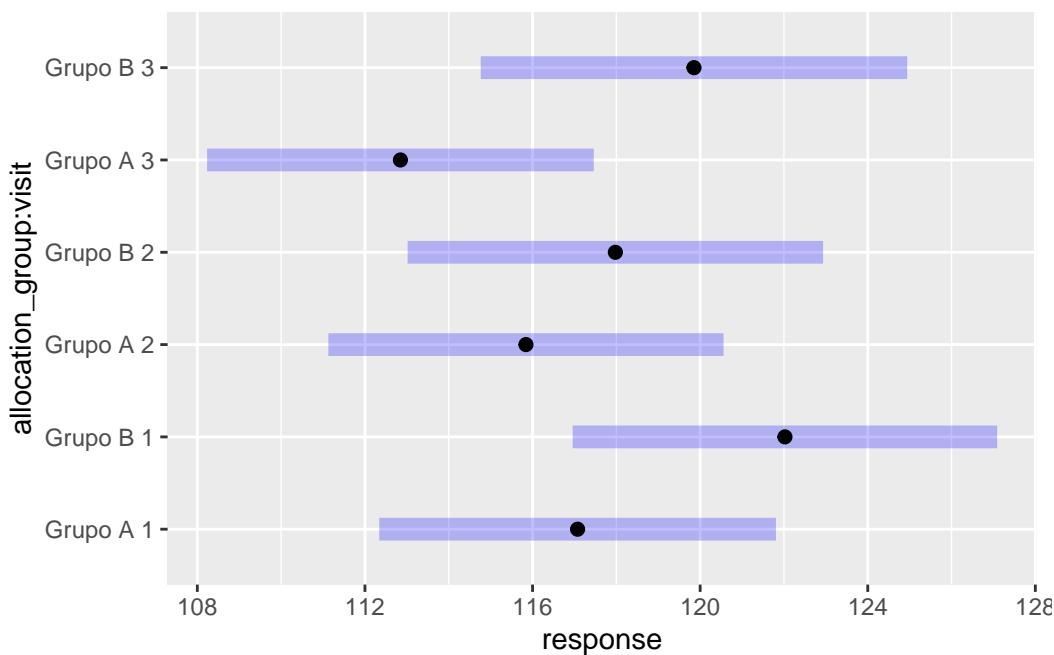
allocation_group = Grupo A:
contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit2     1.23 0.526 39.3   -0.0822    2.5468   2.344  0.0726
visit1 - visit3     4.23 0.559 39.3    2.8301    5.6260   7.563 <.0001
visit2 - visit3     3.00 0.569 40.5    1.5750    4.4166   5.266 <.0001

allocation_group = Grupo B:
contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit2     4.05 0.627 39.7    2.4801    5.6135   6.456 <.0001
visit1 - visit3     2.17 0.730 39.7    0.3474    3.9946   2.976  0.0149
visit2 - visit3    -1.88 0.731 41.9   -3.7000   -0.0516   -2.564  0.0420

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests

```

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



3.17.2.3 Resultado

No modelo ajustado para pressão arterial sistólica, não houve diferença significativa entre os grupos nas visitas 1 (estimativa = -3,19 mmHg; IC 95%: -8,16 a 1,80; p = 0,207) e 2 (estimativa = -0,50 mmHg; IC 95%: -5,41 a 4,42; p = 0,842). Na visita 3, a pressão sistólica no grupo placebo foi em média 5,06 mmHg inferior ao grupo Eclipta (estimativa = -5,06 mmHg; IC 95%: -9,97 a -0,14; p = 0,044).

Ao longo do tempo, ambos os grupos exibiram redução significativa da pressão sistólica: - **Grupo Placebo**: redução de 1,82 mmHg entre visita 1 e 2 (IC 95%: 0,20 a 3,43; p = 0,022), de 4,75 mmHg entre visita 1 e 3 (IC 95%: 3,13 a 6,37; p < 0,001) e de 2,93 mmHg entre visita 2 e 3 (IC 95%: 1,30 a 4,56; p < 0,001). - **Grupo Eclipta**: redução de 4,51 mmHg entre visita 1 e 2 (IC 95%: 2,87 a 6,15; p < 0,001) e de 2,88 mmHg entre visita 1 e 3 (IC 95%: 1,15 a 4,61; p = 0,0003); não houve redução significativa entre visita 2 e 3 (-1,63 mmHg; IC 95%: -3,35 a 0,09; p = 0,070).

Na análise de sensibilidade, o contraste entre grupos na visita 3 permaneceu significativo (estimativa = -7,01 mmHg; IC 95%: -13,88 a -0,13; p = 0,046). As reduções dentro de cada grupo entre visita 1 e 3 mantiveram-se (placebo: -5,10 mmHg; IC 95%: -6,20 a -4,01; p < 0,001; eclipta: -3,48 mmHg; IC 95%: -4,60 a -2,36; p < 0,001), e a redução entre visita 2 e 3 no grupo eclipta continuou significativa (-1,88 mmHg; IC 95%: -3,70 a -0,05; p = 0,042), enquanto a redução entre visita 1 e 2 no placebo deixou de ser significativa (-1,55 mmHg; IC 95%: -2,59 a -0,51; p = 0,073).

Tabela 21: Diferenças estimadas da pressão arterial sistólica entre grupos e entre visitas – Todos os dados

| Grupo de comparação | Comparação | Estimativa (mmHg) | IC 95% | p-valor |
|---------------------|------------|-------------------|---------------|---------|
| Entre grupos | Visita 1 | -3,19 | [-8,16; 1,80] | 0,207 |

| Grupo de comparação | Comparação | Estimativa (mmHg) | IC 95% | p-valor |
|---------------------|-------------------|-------------------|----------------|---------|
| Entre grupos | Visita 2 | -0,50 | [-5,41; 4,42] | 0,842 |
| Entre grupos | Visita 3 | -5,06 | [-9,97; -0,14] | 0,044 |
| Grupo Placebo | Visita 1–Visita 2 | -1,82 | [0,20; 3,43] | 0,022 |
| Grupo Placebo | Visita 1–Visita 3 | -4,75 | [3,13; 6,37] | < 0,001 |
| Grupo Placebo | Visita 2–Visita 3 | -2,93 | [1,30; 4,56] | < 0,001 |
| Grupo Eclipta | Visita 1–Visita 2 | -4,51 | [2,87; 6,15] | < 0,001 |
| Grupo Eclipta | Visita 1–Visita 3 | -2,88 | [1,15; 4,61] | 0,0003 |
| Grupo Eclipta | Visita 2–Visita 3 | -1,63 | [-3,35; 0,09] | 0,070 |

Tabela 22: Diferenças estimadas da pressão arterial sistólica – Análise de sensibilidade

| Grupo de comparação | Comparação | Estimativa (mmHg) | IC 95% | p-valor |
|---------------------|-------------------|-------------------|-----------------|---------|
| Entre grupos | Visita 1 | -4,95 | [-11,88; 1,99] | 0,157 |
| Entre grupos | Visita 2 | -2,13 | [-8,98; 4,71] | 0,533 |
| Entre grupos | Visita 3 | -7,01 | [-13,88; -0,13] | 0,046 |
| Grupo Placebo | Visita 1–Visita 2 | -1,55 | [-2,59; -0,51] | 0,073 |
| Grupo Placebo | Visita 1–Visita 3 | -5,10 | [-6,20; -4,01] | < 0,001 |
| Grupo Placebo | Visita 2–Visita 3 | -3,55 | [-4,67; -2,44] | < 0,001 |
| Grupo Eclipta | Visita 1–Visita 2 | -3,89 | [-4,93; -2,84] | < 0,001 |
| Grupo Eclipta | Visita 1–Visita 3 | -3,48 | [-4,60; -2,36] | < 0,001 |
| Grupo Eclipta | Visita 2–Visita 3 | -1,88 | [-3,70; -0,05] | 0,042 |

```
ggplot(
  data = data_bp_long,
  aes(
    x = as.factor(visit),
    y = systolic,
    group = record_id,
  )
) +
  geom_line(alpha = 0.5) +
  geom_point(alpha = 0.7) +
  geom_smooth(
    aes(group = allocation_group),
    method = "lm",
    se = TRUE,
```

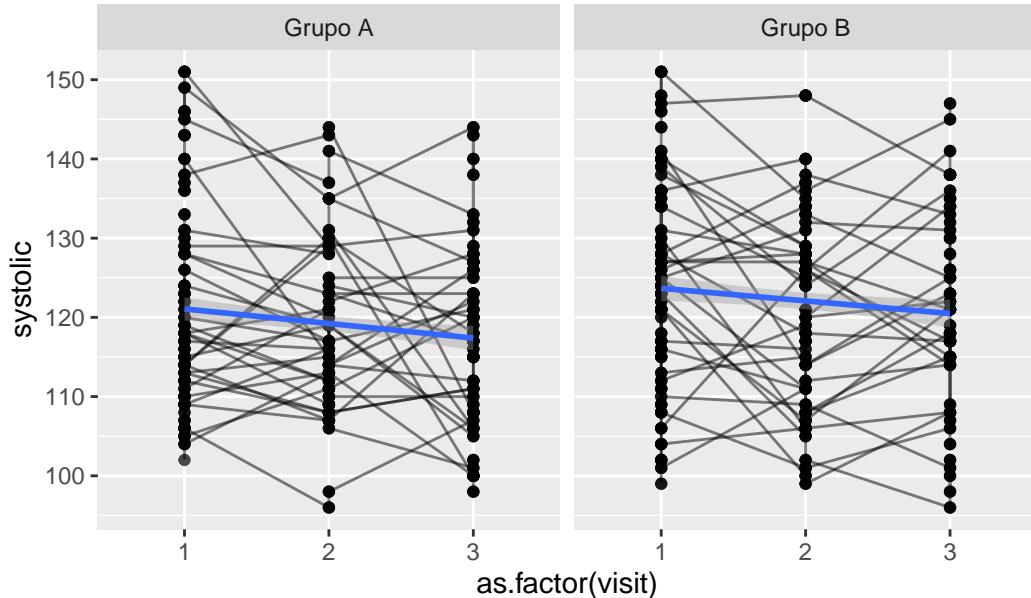
```

        linewidth = 1
    ) +
  labs(title = "All data") +
  facet_wrap(~ allocation_group)

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

```

All data



```

data_bp_long %>%
  filter(
    !(record_id %in%
      systolic_model_check$influential_ids)
  ) %>%
  ggplot(
    aes(
      x = as.factor(visit),
      y = systolic,
      group = record_id,
    )
  ) +
  geom_line(alpha = 0.5) +
  geom_point(alpha = 0.7) +
  geom_smooth(
    aes(group = allocation_group),
    method = "lm",
    se = TRUE,
  )

```

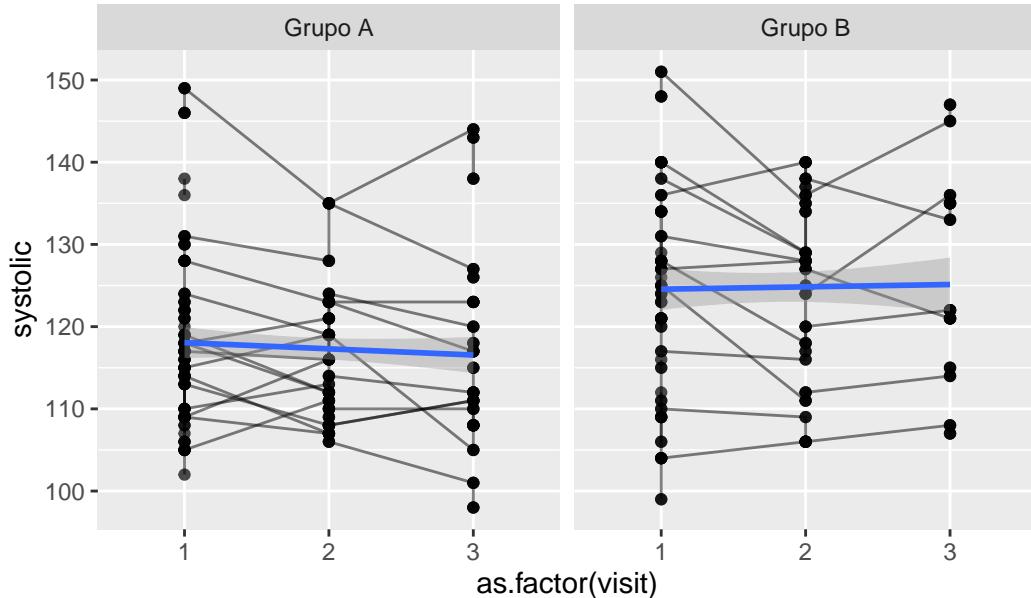
```

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

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

```

Sensitivity analysis



3.17.3 Pressão Arterial Diastólica

Variável: diastolic

```

# Plot 1: Raw data
diastolic_hist_1 <- data_bp_long %>%
  #filter(
  #  diastolic < 300
  #) %>%
  ggplot(aes(x = diastolic)) +
  geom_histogram(bins = 30, fill = "skyblue", color = "black")

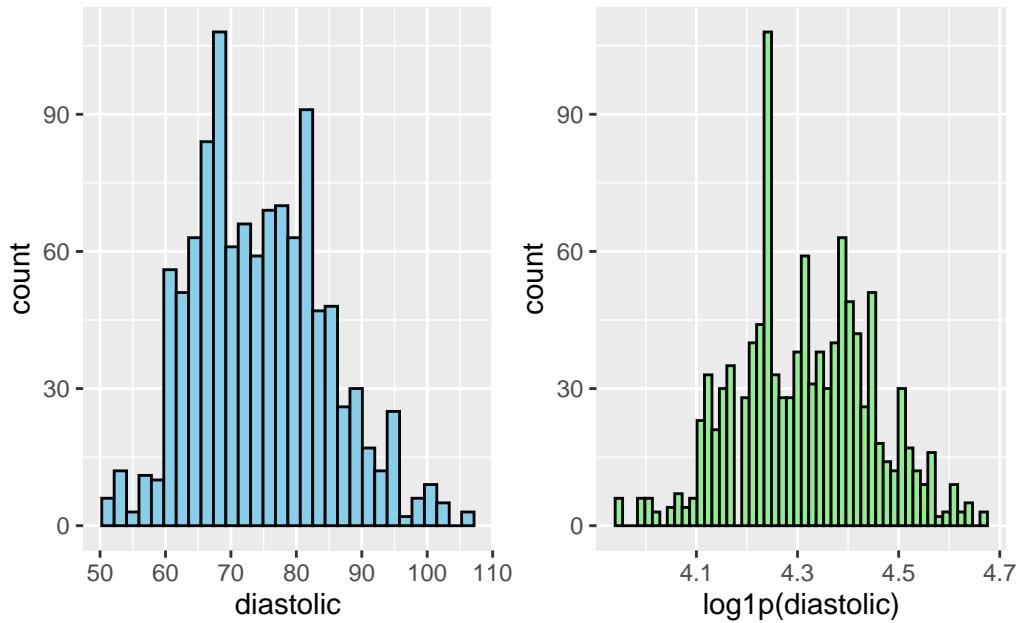
```

```

# Plot 2: Log-transformed data
diastolic_hist_2 <- data_bp_long %>%
  #filter(
  #  diastolic < 300
  #) %>%
  ggplot(aes(x = log1p(diastolic))) +
  geom_histogram(bins = 50, fill = "lightgreen", color = "black")

```

```
# Combine side by side
diastolic_hist_1 + diastolic_hist_2 # library(patchwork)
```



```
# LMM
diastolic_model <- lmer(log1p(diastolic) ~ allocation_group * visit +
(1 | record_id), data = data_bp_long)
check_collinearity(diastolic_model)
```

```
# Check for Multicollinearity
```

Low Correlation

| Term | VIF | VIF 95% CI | Increased SE | Tolerance |
|------------------------|------|--------------|--------------|-----------|
| allocation_group | 1.02 | [1.00, 1.29] | 1.01 | 0.98 |
| visit | 3.83 | [3.47, 4.24] | 1.96 | 0.26 |
| allocation_group:visit | 3.87 | [3.51, 4.29] | 1.97 | 0.26 |

Tolerance 95% CI

- [0.77, 1.00]
- [0.24, 0.29]
- [0.23, 0.29]

```
# Sensitivity analysis
diastolic_model_check <- sensitivity_check_lmer(
  model = diastolic_model,
  id_var = "record_id",
```

```

top_n = 5

# LMM Sensitivity
diastolic_model_sens <- update(object = diastolic_model,
                                 subset = !(record_id %in%
                                             diastolic_model_check$influential_ids))

# Influential IDS
diastolic_model_check$influential_ids

[1] "1"  "4"  "9"  "10" "13" "17" "18" "19" "20" "21" "22" "23" "26" "27" "32"
[16] "34" "37" "38" "39" "45" "46" "47" "52" "54" "56" "58" "63" "64" "69" "71"
[31] "75"

```

3.17.3.1 Resumo dos modelos

```

summary(diastolic_model)

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

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

Data: data_bp_long

```

REML criterion at convergence: -2610.1

Scaled residuals:

| Min | 1Q | Median | 3Q | Max |
|---------|---------|--------|--------|--------|
| -3.0300 | -0.5971 | 0.0085 | 0.5673 | 3.2997 |

Random effects:

| Groups | Name | Variance | Std.Dev. |
|-----------|-------------|----------|----------|
| record_id | (Intercept) | 0.013982 | 0.11825 |
| | Residual | 0.004229 | 0.06503 |

Number of obs: 1113, groups: record_id, 75

Fixed effects:

| | Estimate | Std. Error | df | t value |
|------------------|------------|------------|-----------|---------|
| (Intercept) | 4.317e+00 | 2.005e-02 | 7.593e+01 | 215.282 |
| allocation_group | 3.222e-02 | 2.821e-02 | 7.623e+01 | 1.142 |
| visit2 | -2.013e-02 | 6.769e-03 | 1.041e+03 | -2.973 |
| visit3 | -4.721e-02 | 6.866e-03 | 1.042e+03 | -6.876 |

```

allocation_groupGrupo B:visit2 -3.683e-02 9.577e-03 1.042e+03 -3.846
allocation_groupGrupo B:visit3  1.627e-02 9.887e-03 1.043e+03  1.645
Pr(>|t|)

(Intercept) < 2e-16 ***
allocation_groupGrupo B 0.256880
visit2 0.003013 **
visit3 1.06e-11 ***
allocation_groupGrupo B:visit2 0.000127 ***
allocation_groupGrupo B:visit3 0.100214
---
Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```

Correlation of Fixed Effects:

| | (Intr) | all_GB | visit2 | visit3 | a_GB:2 |
|-------------|--------|--------|--------|--------|--------|
| allctn_grGB | -0.711 | | | | |
| visit2 | -0.140 | 0.100 | | | |
| visit3 | -0.135 | 0.096 | 0.479 | | |
| allctn_GB:2 | 0.099 | -0.137 | -0.707 | -0.338 | |
| allctn_GB:3 | 0.094 | -0.130 | -0.332 | -0.694 | 0.472 |

```
summary(diastolic_model_sens)
```

```

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

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

Data: data_bp_long
Subset: !(record_id %in% diastolic_model_check$influential_ids)

```

REML criterion at convergence: -1677.8

Scaled residuals:

| Min | 1Q | Median | 3Q | Max |
|----------|----------|----------|---------|---------|
| -2.71801 | -0.66604 | -0.03126 | 0.65483 | 2.92478 |

Random effects:

| Groups | Name | Variance | Std.Dev. |
|-----------|-------------|----------|----------|
| record_id | (Intercept) | 0.017286 | 0.13148 |
| Residual | | 0.001356 | 0.03682 |

Number of obs: 510, groups: record_id, 44

Fixed effects:

| | Estimate | Std. Error | df | t value |
|--------------------------------|--|------------|------------|---------|
| (Intercept) | 4.331558 | 0.030479 | 42.381568 | 142.116 |
| allocation_groupGrupo B | 0.018610 | 0.040443 | 42.413113 | 0.460 |
| visit2 | -0.018719 | 0.006188 | 463.802406 | -3.025 |
| visit3 | -0.056333 | 0.006591 | 463.886716 | -8.547 |
| allocation_groupGrupo B:visit2 | -0.025477 | 0.008163 | 464.002361 | -3.121 |
| allocation_groupGrupo B:visit3 | 0.016096 | 0.008706 | 463.957521 | 1.849 |
| | Pr(> t) | | | |
| (Intercept) | < 2e-16 *** | | | |
| allocation_groupGrupo B | 0.64775 | | | |
| visit2 | 0.00262 ** | | | |
| visit3 | < 2e-16 *** | | | |
| allocation_groupGrupo B:visit2 | 0.00191 ** | | | |
| allocation_groupGrupo B:visit3 | 0.06513 . | | | |
| --- | | | | |
| Signif. codes: | 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1 | | | |

Correlation of Fixed Effects:

```
(Intr) all_GB visit2 visit3 a_GB:2  
allctn_grGB -0.754  
visit2     -0.066  0.050  
visit3     -0.058  0.044  0.429  
allctn_GB:2  0.050 -0.067 -0.758 -0.325  
allctn_GB:3  0.044 -0.059 -0.325 -0.757  0.448
```

```
performance::compare_performance(  
  diastolic_model,  
  diastolic_model_sens)
```

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

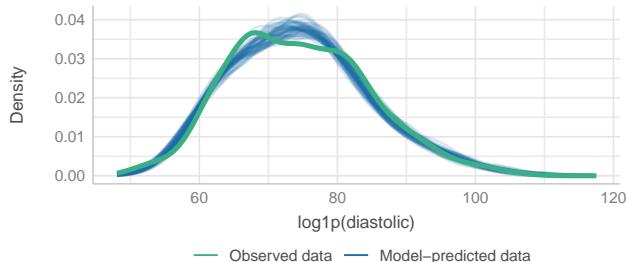
```
# Comparison of Model Performance Indices
```

| Name | | Model | AIC (weights) | AICc (weights) |
|----------------------|-----------------|----------------|----------------|----------------|
| diastolic_model | lmerModLmerTest | 6968.0 (<.001) | 6968.2 (<.001) | |
| diastolic_model_sens | lmerModLmerTest | 2718.9 (>.999) | 2719.1 (>.999) | |

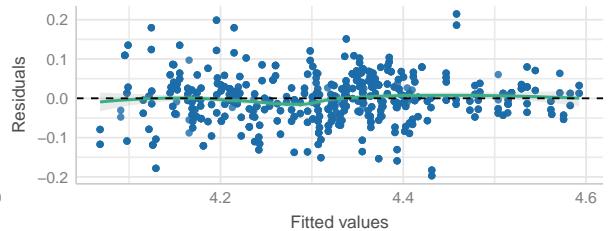
| Name | BIC (weights) | R2 (cond.) | R2 (marg.) | ICC | RMSE | Sigma |
|----------------------|----------------|------------|------------|-------|-------|-------|
| diastolic_model | 7008.1 (<.001) | 0.776 | 0.034 | 0.768 | 0.063 | 0.065 |
| diastolic_model_sens | 2752.7 (>.999) | 0.929 | 0.027 | 0.927 | 0.035 | 0.037 |

```
performance::check_model(diastolic_model)
```

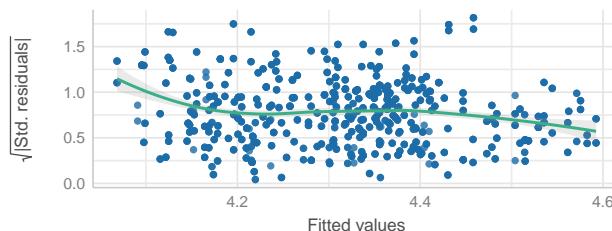
Posterior Predictive Check
Model-predicted lines should resemble observed data line



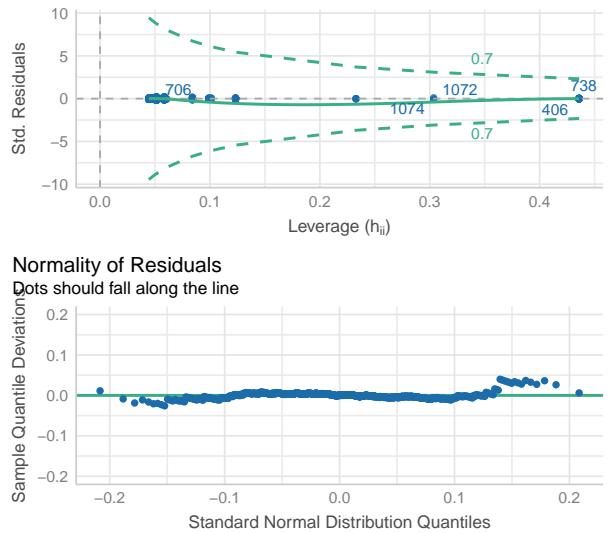
Linearity
Reference line should be flat and horizontal



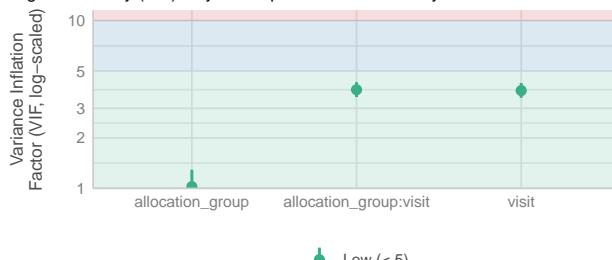
Homogeneity of Variance
Reference line should be flat and horizontal



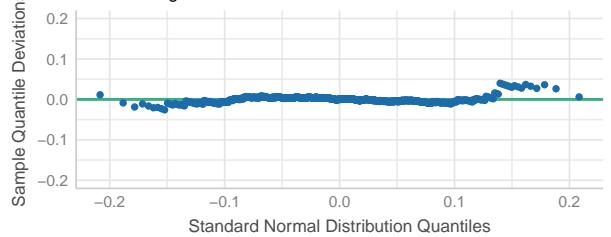
Influential Observations
Points should be inside the contour lines



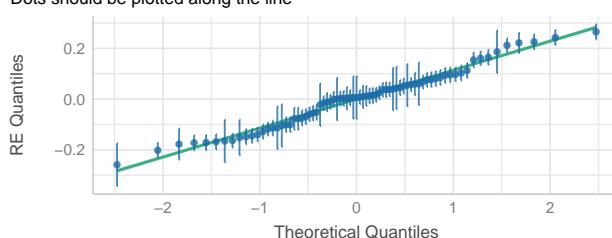
Collinearity
High collinearity (VIF) may inflate parameter uncertainty



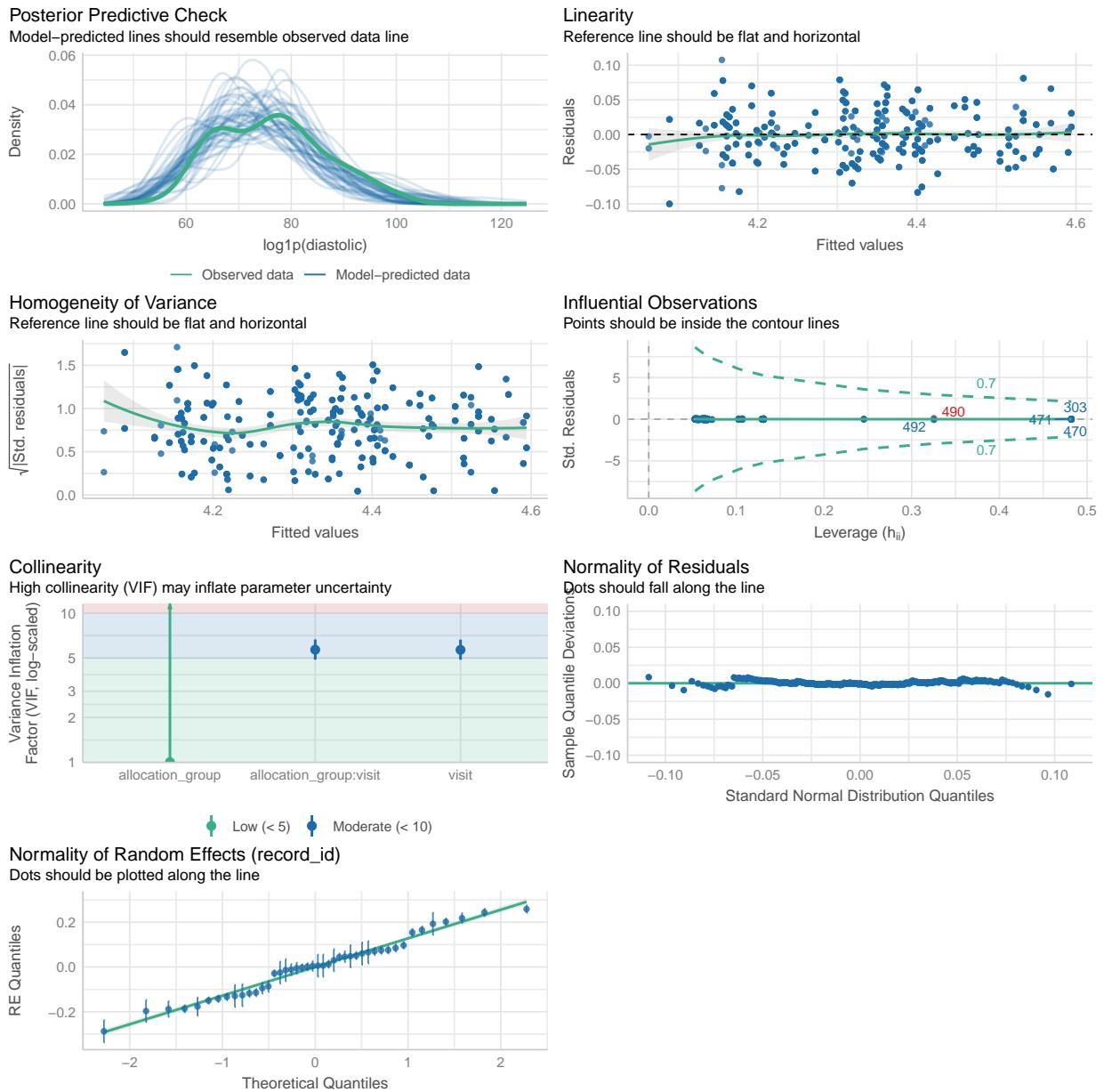
Normality of Residuals
Dots should fall along the line



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



```
performance::check_model(diastolic_model_sens)
```



3.17.3.2 Médias Marginais Estimadas

3.17.3.2.1 Todos os dados

```
# Get EMMS for each group at each visit
diastolic_raw_emm <- emmeans::emmeans(
  diastolic_model,
  ~ allocation_group * visit
)

diastolic_raw_emm <- regrid(diastolic_raw_emm)
```

```

# Table of marginal means
# diastolic_raw_emm

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

visit = 1:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
  Grupo A - Grupo B   -2.456 2.15 76.3     -6.74    1.826  -1.142  0.2569

visit = 2:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
  Grupo A - Grupo B    0.338 2.09 79.0     -3.82    4.501   0.162  0.8719

visit = 3:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
  Grupo A - Grupo B   -3.554 2.10 79.8     -7.74    0.628  -1.691  0.0947

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

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

allocation_group = Grupo A:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
  visit1 - visit2    1.49 0.503 76.3     0.264     2.72    2.973  0.0118
  visit1 - visit3    3.46 0.505 76.3     2.221     4.69    6.844 <.0001
  visit2 - visit3    1.96 0.506 79.0     0.726     3.20    3.881  0.0006

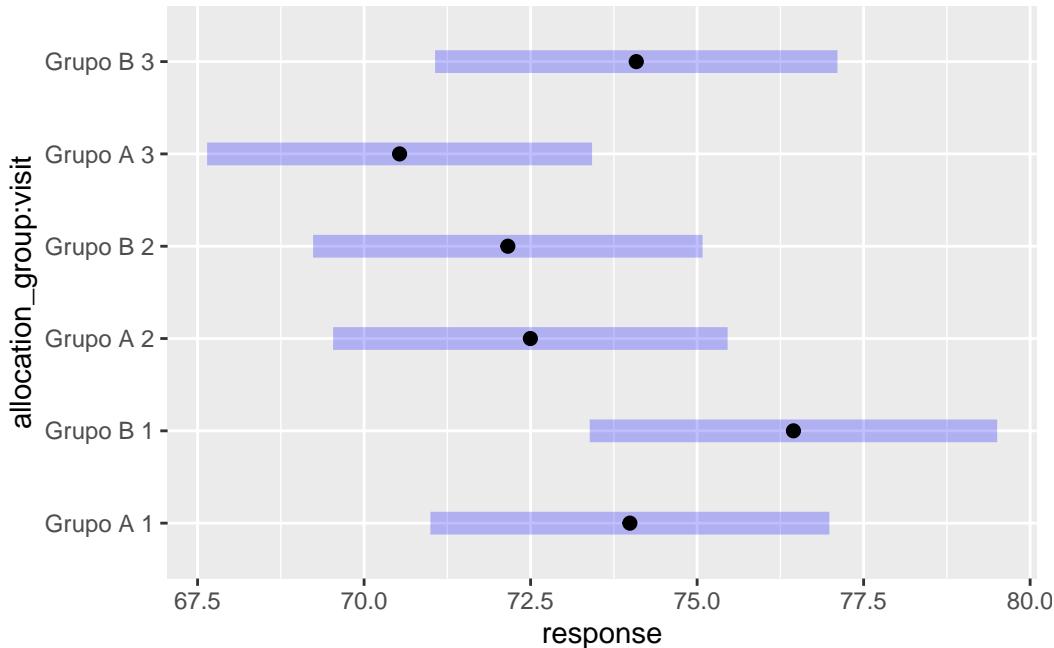
allocation_group = Grupo B:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
  visit1 - visit2    4.29 0.514 76.9     3.030     5.55    8.343 <.0001
  visit1 - visit3    2.36 0.542 76.9     1.033     3.69    4.353  0.0001
  visit2 - visit3   -1.93 0.535 80.5    -3.237    -0.62   -3.605  0.0016

```

```
Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests
```

```
# Plot of marginal means
```

```
plot(diastolic_raw_emm)
```



3.17.3.2.2 Análise de sensibilidade

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

diastolic_emm <- regrid(diastolic_emm)

# Table of marginal means
# diastolic_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(diastolic_emm,
  method = "pairwise", by = "visit",
```

```

adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

visit = 1:
contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
Grupo A - Grupo B    -1.429 3.10 42.4     -7.69      4.83  -0.461  0.6474

visit = 2:
contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
Grupo A - Grupo B     0.511 3.03 43.6     -5.60      6.62   0.169  0.8669

visit = 3:
contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
Grupo A - Grupo B    -2.539 2.98 44.2     -8.55      3.47  -0.851  0.3993

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

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

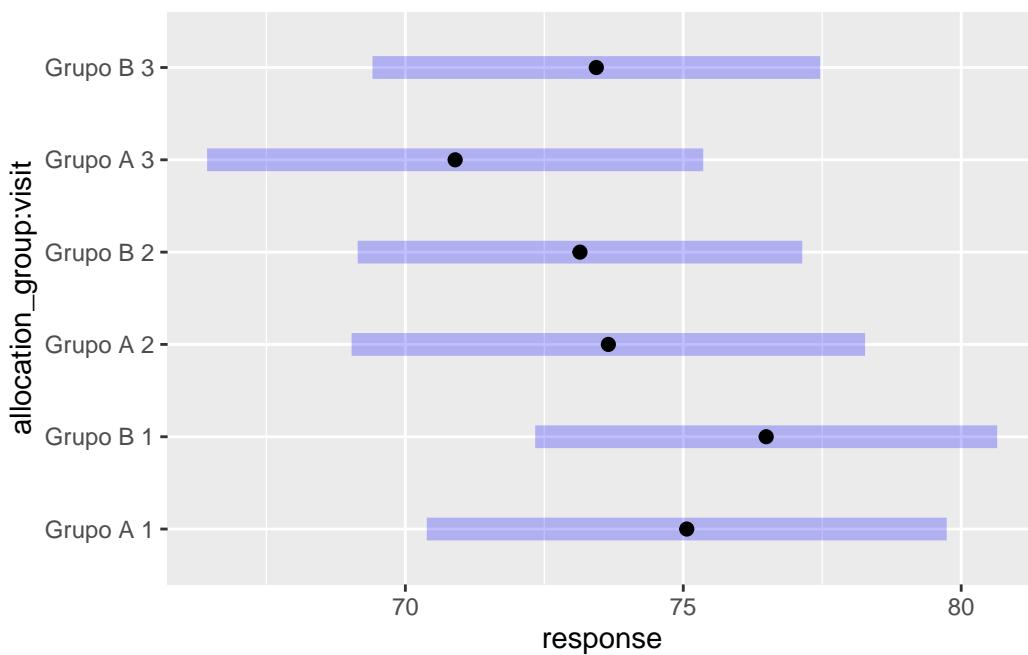
allocation_group = Grupo A:
contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit2     1.411 0.467 42.4     0.247     2.574    3.022  0.0127
visit1 - visit3     4.166 0.498 42.4     2.926     5.407    8.371 <.0001
visit2 - visit3     2.756 0.507 43.6     1.495     4.017    5.440 <.0001

allocation_group = Grupo B:
contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit2     3.350 0.410 42.5     2.327     4.373    8.162 <.0001
visit1 - visit3     3.056 0.436 42.5     1.969     4.143    7.009 <.0001
visit2 - visit3    -0.294 0.420 43.6    -1.341     0.752   -0.700  1.0000

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests

```

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



3.17.3.3 Resultado

No modelo ajustado para a pressão arterial diastólica, não houve diferenças estatisticamente significativas entre os grupos em nenhum dos três momentos avaliados (visita 1: estimativa = -2,46 mmHg; IC 95%: -6,74 a 1,83; p = 0,257; visita 2: estimativa = 0,34 mmHg; IC 95%: -3,82 a 4,50; p = 0,872; visita 3: estimativa = -3,55 mmHg; IC 95%: -7,74 a 0,63; p = 0,095).

Contudo, ambos os grupos apresentaram redução significativa da pressão diastólica ao longo do tempo: -

Grupo Placebo: redução média de 1,49 mmHg entre visita 1 e 2 (IC 95%: 0,26 a 2,72; p = 0,012), de 3,46 mmHg entre visita 1 e 3 (IC 95%: 2,22 a 4,69; p < 0,001) e de 1,96 mmHg entre visita 2 e 3 (IC 95%: 0,73 a 3,20; p = 0,001).

- **Grupo Eclipta:** redução média de 4,29 mmHg entre visita 1 e 2 (IC 95%: 3,03 a 5,55; p < 0,001), de 2,36 mmHg entre visita 1 e 3 (IC 95%: 1,03 a 3,69; p < 0,001) e de 1,93 mmHg entre visita 2 e 3 (IC 95%: 1,24 a 3,23; p = 0,002).

Na análise de sensibilidade, as reduções entre visita 1 e 2 e entre visita 1 e 3 mantiveram-se significativas em ambos os grupos. Já a redução entre visita 2 e 3 no grupo Eclipta deixou de ser significativa (-0,29 mmHg; IC 95%: -1,34 a 0,75; p = 1,000).

Tabela 23: Diferenças estimadas da pressão diastólica entre grupos e ao longo do tempo – Modelo completo

| Grupo de comparação | Comparação | Estimativa (mmHg) | IC 95% | p-valor |
|---------------------|---------------------|-------------------|---------------|---------|
| Entre grupos | Visita 1 | -2,46 | [-6,74; 1,83] | 0,257 |
| Entre grupos | Visita 2 | 0,34 | [-3,82; 4,50] | 0,872 |
| Entre grupos | Visita 3 | -3,55 | [-7,74; 0,63] | 0,095 |
| Grupo Placebo | Visita 1 – Visita 2 | -1,49 | [0,26; 2,72] | 0,012 |

| Grupo de comparação | Comparação | Estimativa (mmHg) | IC 95% | p-valor |
|---------------------|---------------------|-------------------|--------------|---------|
| Grupo Placebo | Visita 1 – Visita 3 | -3,46 | [2,22; 4,69] | < 0,001 |
| Grupo Placebo | Visita 2 – Visita 3 | -1,96 | [0,73; 3,20] | 0,001 |
| Grupo Eclipta | Visita 1 – Visita 2 | -4,29 | [3,03; 5,55] | < 0,001 |
| Grupo Eclipta | Visita 1 – Visita 3 | -2,36 | [1,03; 3,69] | < 0,001 |
| Grupo Eclipta | Visita 2 – Visita 3 | -1,93 | [1,24; 3,23] | 0,002 |

Tabela 24: Diferenças estimadas da pressão diastólica – Análise de sensibilidade

| Grupo de comparação | Comparação | Estimativa (mmHg) | IC 95% | p-valor |
|---------------------|---------------------|-------------------|---------------|---------|
| Entre grupos | Visita 1 | -1,43 | [-7,69; 4,83] | 0,647 |
| Entre grupos | Visita 2 | 0,51 | [-5,60; 6,62] | 0,867 |
| Entre grupos | Visita 3 | -2,54 | [-8,55; 3,47] | 0,399 |
| Grupo Placebo | Visita 1 – Visita 2 | -1,41 | [0,25; 2,57] | 0,013 |
| Grupo Placebo | Visita 1 – Visita 3 | -4,17 | [2,93; 5,41] | < 0,001 |
| Grupo Placebo | Visita 2 – Visita 3 | -2,76 | [1,50; 4,02] | < 0,001 |
| Grupo Eclipta | Visita 1 – Visita 2 | -3,35 | [2,33; 4,37] | < 0,001 |
| Grupo Eclipta | Visita 1 – Visita 3 | -3,06 | [1,97; 4,14] | < 0,001 |
| Grupo Eclipta | Visita 2 – Visita 3 | -0,29 | [-1,34; 0,75] | 1,000 |

```
ggplot(
  data = data_bp_long,
  aes(
    x = as.factor(visit),
    y = diastolic,
    group = record_id,
  )
) +
  geom_line(alpha = 0.5) +
  geom_point(alpha = 0.7) +
  geom_smooth(
    aes(group = allocation_group),
    method = "lm",
    se = TRUE,
    linewidth = 1
) +
```

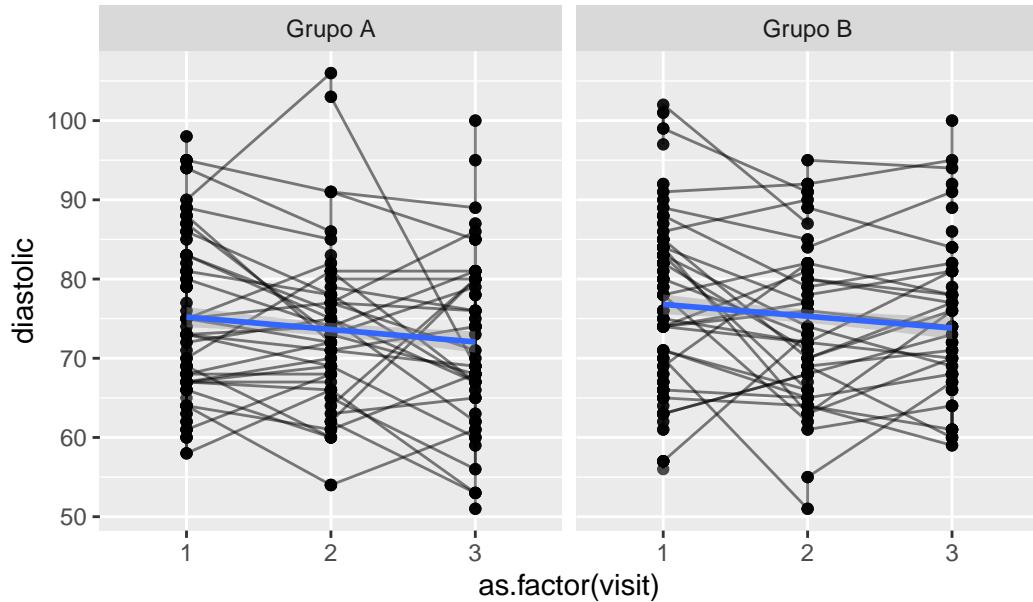
```

  labs(title = "All data") +
  facet_wrap(~ allocation_group)

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

```

All data



```

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

```

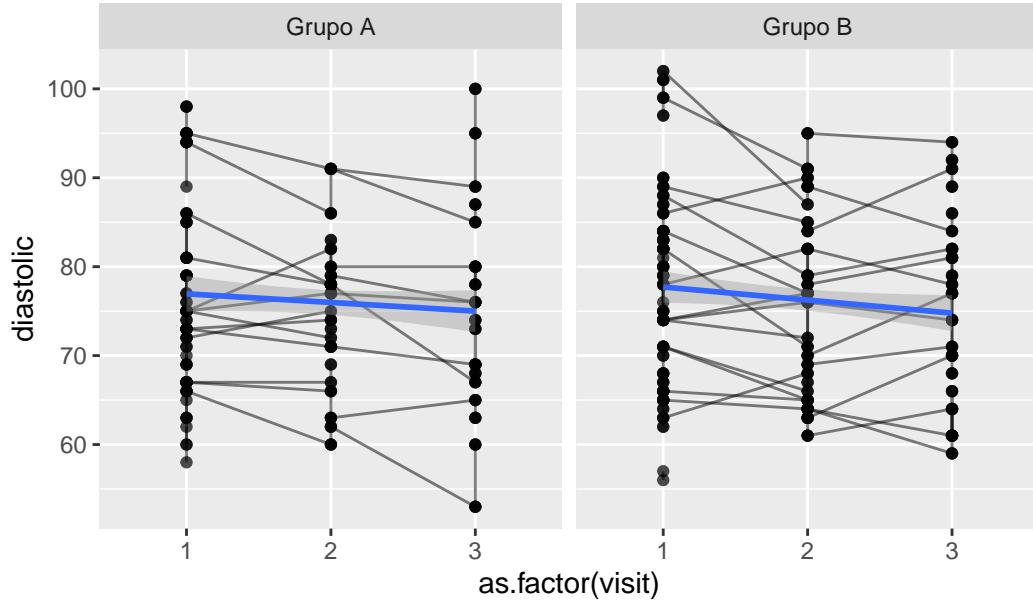
```

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

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

```

Sensitivity analysis



3.18 Escore EVS

Variável: evs_score

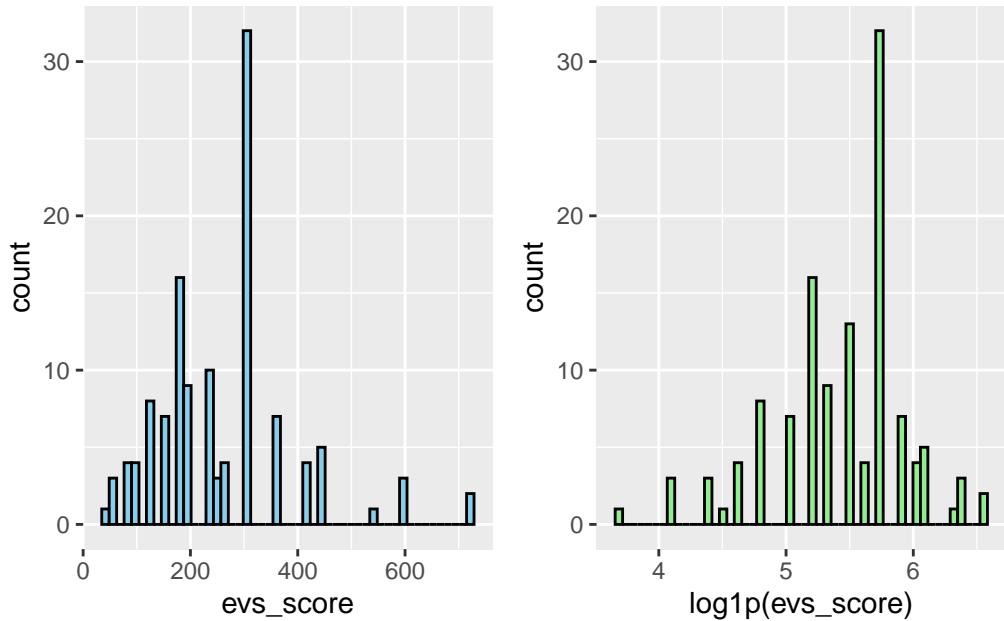
```

# Plot 1: Raw data
evs_score_hist_1 <- data_model %>%
  filter(
    evs_score >0
  ) %>%
  ggplot(aes(x = evs_score)) +
  geom_histogram(bins = 50, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
evs_score_hist_2 <- data_model %>%
  filter(
    evs_score >0
  ) %>%
  ggplot(aes(x = log1p(evs_score))) +
  geom_histogram(bins = 50, fill = "lightgreen", color = "black")

```

```
# Combine side by side
evs_score_hist_1 + evs_score_hist_2 # library(patchwork)
```



```
# LMM

data_model_evs <- data_model %>%
  filter(evs_score > 0)

evs_score_model <- lmer(log1p(evs_score) ~ allocation_group * visit +
(1 | record_id), data = data_model_evs)
check_collinearity(evs_score_model)

# Check for Multicollinearity
```

Low Correlation

| | Term | VIF | VIF 95% CI | Increased SE | Tolerance | Tolerance 95% CI |
|--|------------------|------|--------------|--------------|-----------|------------------|
| | allocation_group | 2.02 | [1.62, 2.66] | 1.42 | 0.50 | [0.38, 0.62] |
| | visit | 3.96 | [3.02, 5.35] | 1.99 | 0.25 | [0.19, 0.33] |

Moderate Correlation

| | Term | VIF | VIF 95% CI | Increased SE | Tolerance |
|--|------------------------|------|--------------|--------------|-----------|
| | allocation_group:visit | 5.59 | [4.18, 7.61] | 2.36 | 0.18 |
| | Tolerance 95% CI | | | | |

```
[0.13, 0.24]
```

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

# LMM Sensitivity
evs_score_model_sens <- update(object = evs_score_model,
                                  subset = !(record_id %in%
                                  evs_score_model_check$influential_ids))
# Influential IDS
evs_score_model_check$influential_ids
```

[1] "18" "44" "68" "50" "12"

3.18.1 Resumo dos modelos

```
# Model comparison
summary(evs_score_model)

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

REML criterion at convergence: 196.5

Scaled residuals:
    Min      1Q  Median      3Q     Max 
-2.5002 -0.4282  0.1341  0.4983  1.9054 

Random effects:
Groups      Name        Variance Std.Dev. 
record_id (Intercept) 0.1002   0.3166  
Residual           0.1919   0.4380  
Number of obs: 123, groups: record_id, 56

Fixed effects:
```

| Estimate | Std. Error | df | t value | Pr(> t) |
|----------|------------|----|---------|----------|
|----------|------------|----|---------|----------|

```

(Intercept)           5.45023   0.12407 113.97017  43.927 <2e-16
allocation_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_groupGrupo B | -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

```

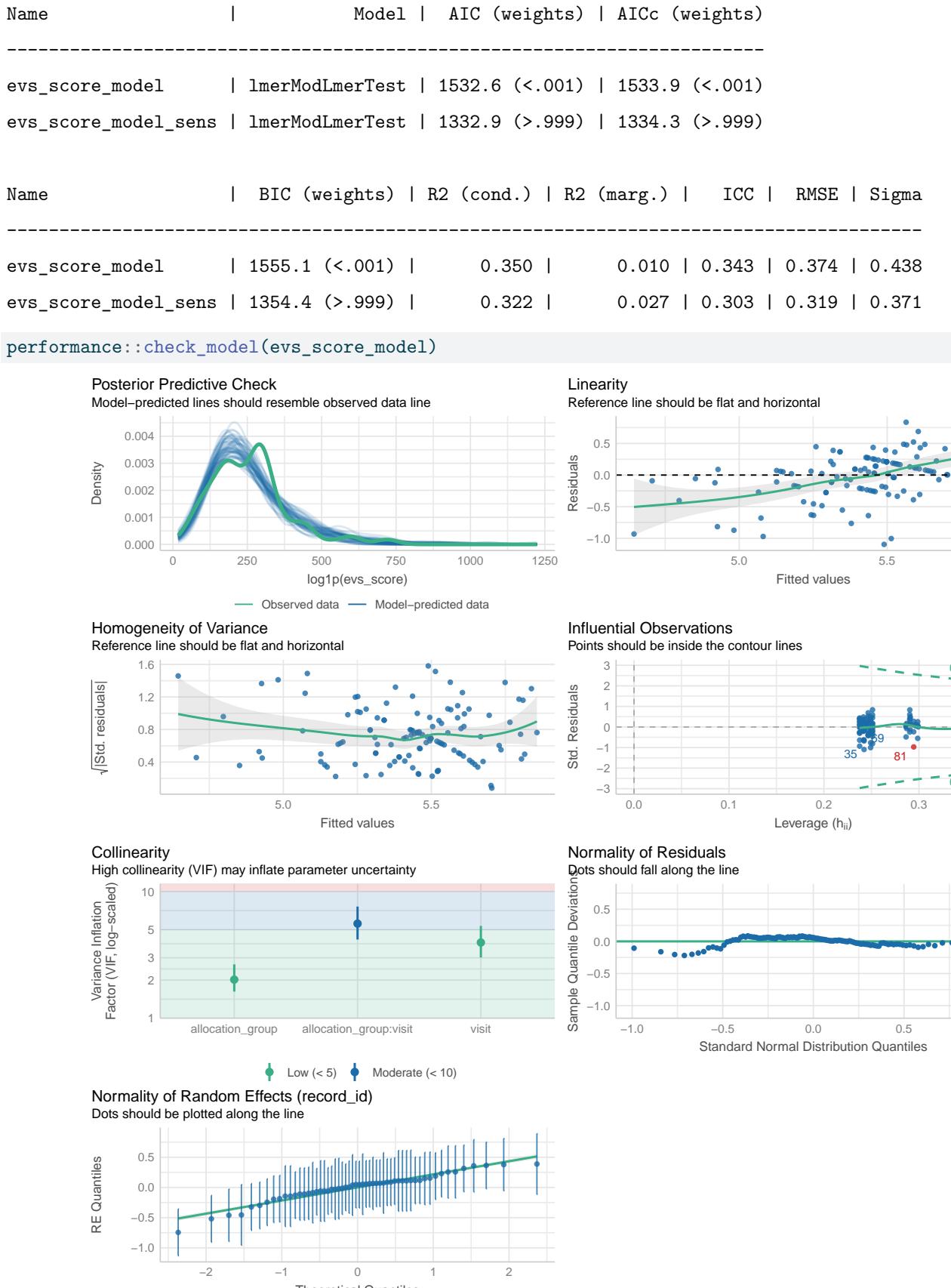
```

performance::compare_performance(
  evs_score_model,
  evs_score_model_sens)

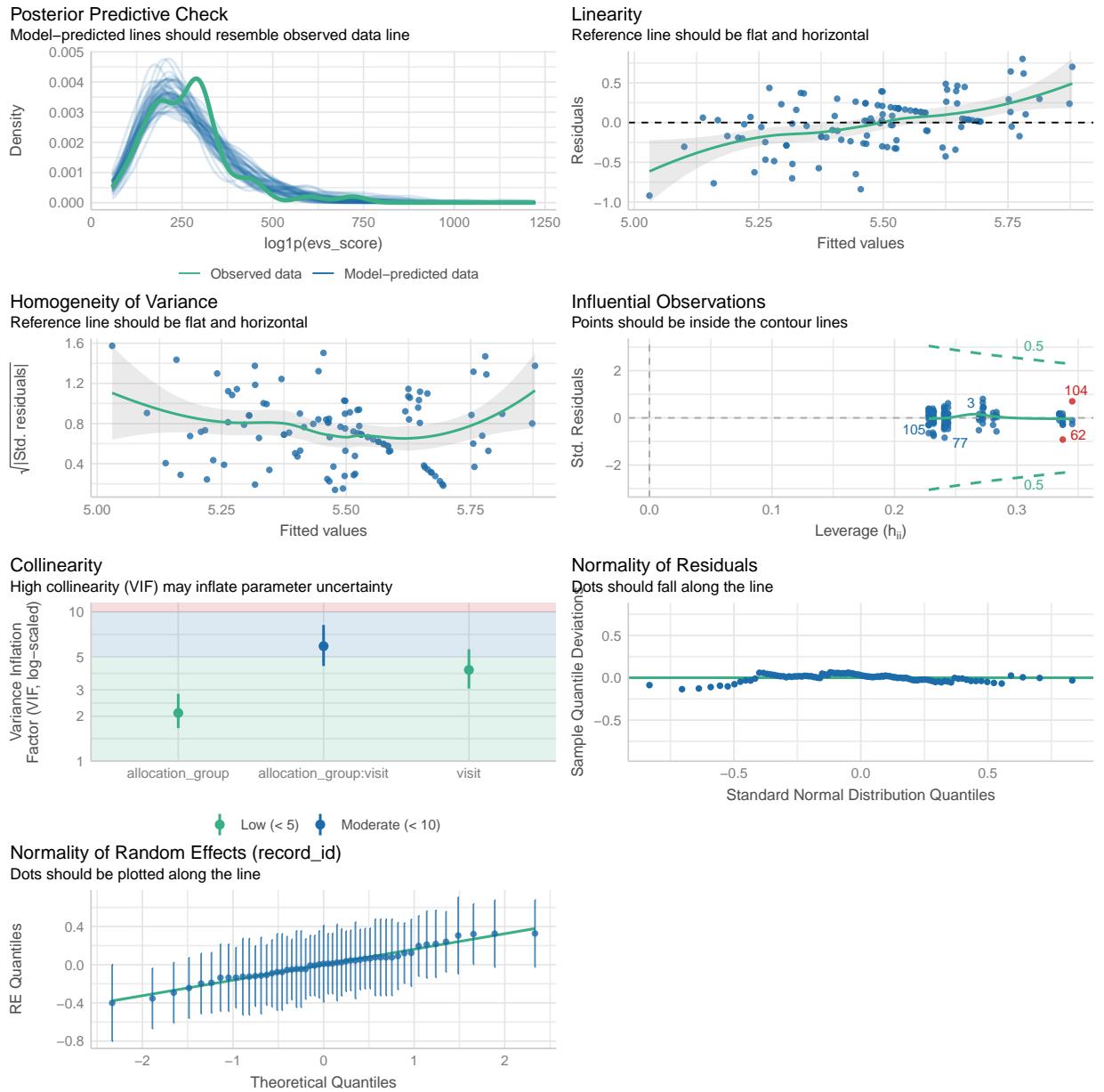
```

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

Comparison of Model Performance Indices



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



3.18.2 Médias Marginais Estimadas

3.18.2.1 Todos os dados

```
# Get EMMs for each group at each visit
evs_score_raw_emm <- emmeans::emmeans(
  evs_score_model,
  ~ allocation_group * visit
)

evs_score_raw_emm <- regrid(evs_score_raw_emm)
```

```

# Table of marginal means
# evs_score_raw_emm

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

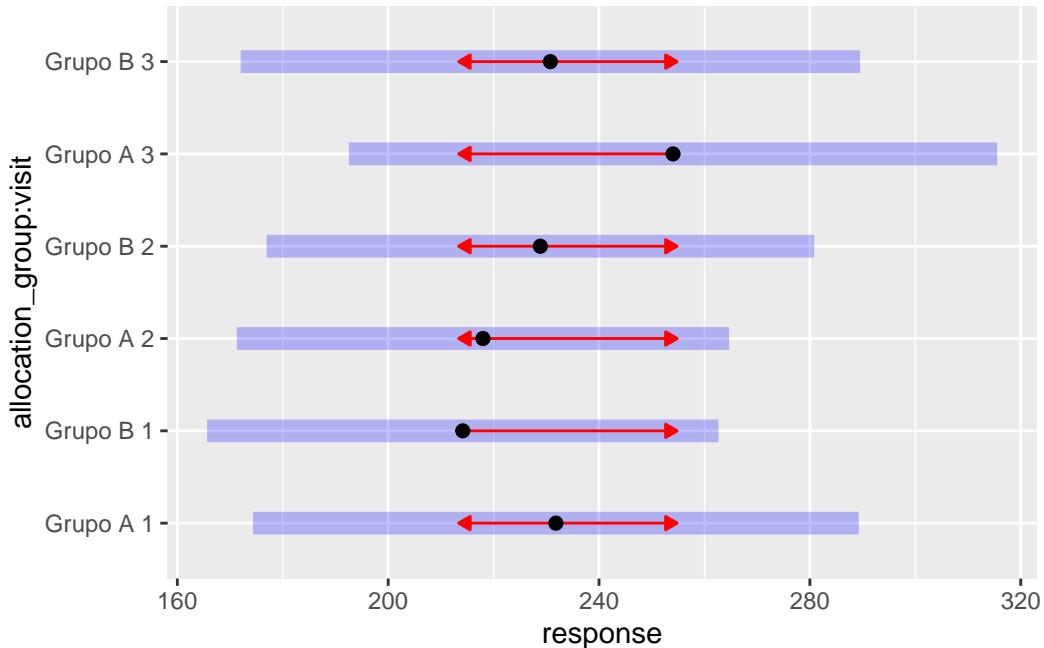
allocation_group = Grupo A:
  contrast      estimate   SE  df lower.CL upper.CL t.ratio p.value
  visit1 - visit2    13.8 32.2 104     -64.5     92.2   0.430  1.0000
  visit1 - visit3   -22.2 36.6 113    -111.1     66.7  -0.607  1.0000
  visit2 - visit3   -36.1 33.2 104    -116.9     44.7  -1.086  0.8402

allocation_group = Grupo B:
  contrast      estimate   SE  df lower.CL upper.CL t.ratio p.value
  visit1 - visit2   -14.7 30.9 108     -89.9     60.4  -0.476  1.0000
  visit1 - visit3   -16.6 33.4 109    -97.7     64.5  -0.498  1.0000
  visit2 - visit3    -1.9 33.6 108    -83.7     79.9  -0.057  1.0000

```

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests

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



3.18.2.2 Análise de sensibilidade

```

# Get EMMs for each group at each visit (Sensitivity Analysis)

evs_score_emm <- emmeans::emmeans(
  evs_score_model_sens,
  ~ allocation_group * visit
)

evs_score_emm <- regrid(evs_score_emm)

# Table of marginal means

# evs_score_emm

# Pairwise comparisons: Between groups at each visit

emmeans::contrast(evs_score_emm,
  method = "pairwise", by = "visit",

```

```

adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

visit = 1:
contrast      estimate    SE    df lower.CL upper.CL t.ratio p.value
Grupo A - Grupo B     30.11 36.9   98.3     -43.1     103.3    0.816  0.4163

visit = 2:
contrast      estimate    SE    df lower.CL upper.CL t.ratio p.value
Grupo A - Grupo B     5.24 31.5   94.7     -57.4      67.8    0.166  0.8684

visit = 3:
contrast      estimate    SE    df lower.CL upper.CL t.ratio p.value
Grupo A - Grupo B    44.49 40.5  101.1     -35.9     124.9    1.098  0.2750

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

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

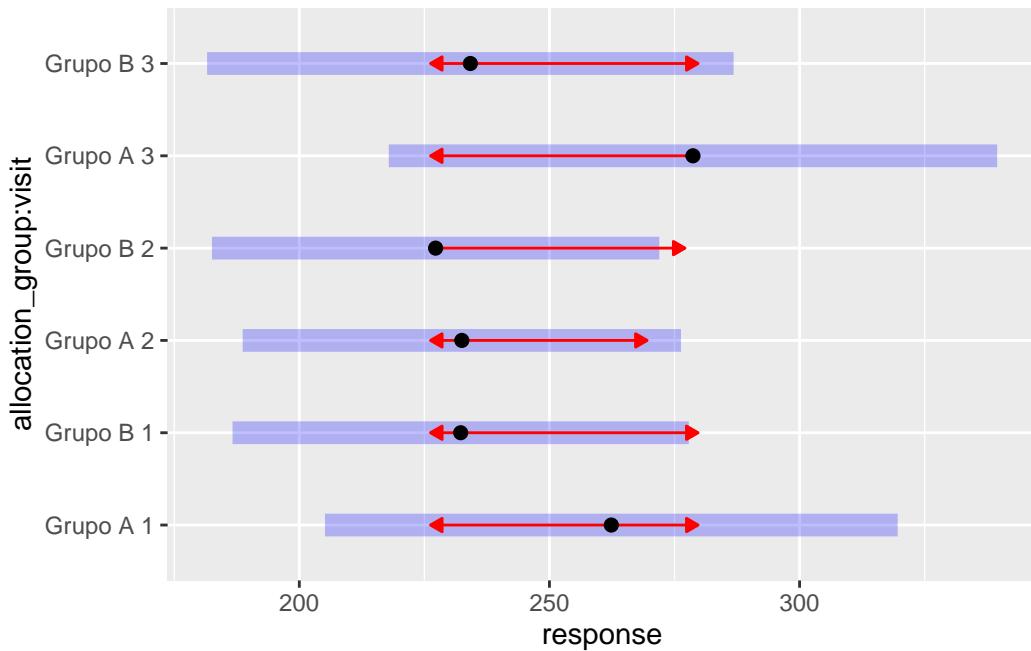
allocation_group = Grupo A:
contrast      estimate    SE    df lower.CL upper.CL t.ratio p.value
visit1 - visit2    29.88 32.1   94.7     -48.3     108.0    0.932  1.0000
visit1 - visit3   -16.32 37.1  101.1     -106.6     73.9   -0.440  1.0000
visit2 - visit3   -46.20 33.1   94.7     -127.0     34.6   -1.394  0.5001

allocation_group = Grupo B:
contrast      estimate    SE    df lower.CL upper.CL t.ratio p.value
visit1 - visit2     5.01 28.5   97.7     -64.4      74.4    0.176  1.0000
visit1 - visit3   -1.93 31.2   98.3     -77.9      74.0   -0.062  1.0000
visit2 - visit3   -6.95 30.4   97.7     -80.9      67.0   -0.229  1.0000

Degrees-of-freedom method: inherited from kenward-roger when re-gridding
Confidence level used: 0.95
Conf-level adjustment: bonferroni method for 3 estimates
P value adjustment: bonferroni method for 3 tests

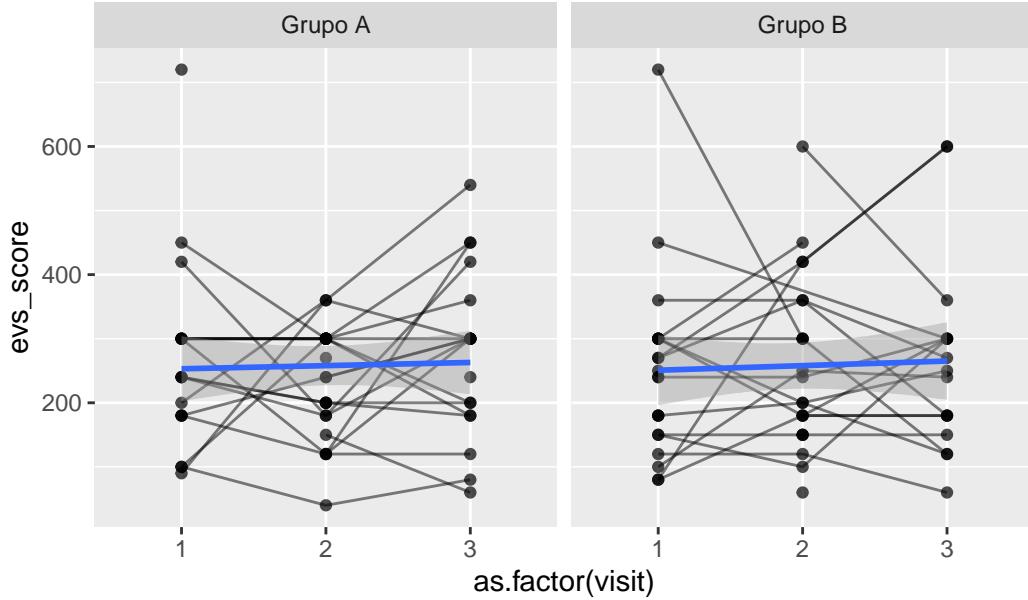
```

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



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

All data



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

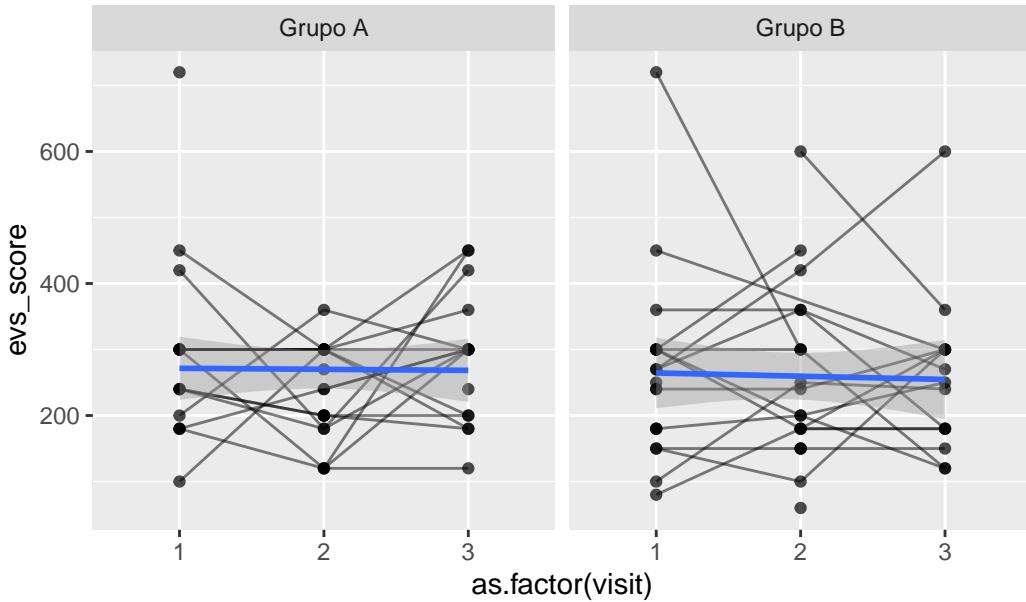
data_model_evs %>%
  filter(
    !(record_id %in%
      evs_score_model_check$influential_ids)
  ) %>%
  ggplot(
    aes(
      x = as.factor(visit),
      y = evs_score,
      group = record_id,
    )
  ) +
  geom_line(alpha = 0.5) +
  geom_point(alpha = 0.7) +
  geom_smooth(
    aes(group = allocation_group),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

```

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

```

Sensitivity analysis



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

3.18.3 EVS - modelo em 2 partes

```

data_model_evs <- data_model %>%
  mutate(
    exercised = if_else(evs_score > 0, 1, 0)
  )

model_part1 <- glmer(
  exercised ~ allocation_group * visit + (1 | record_id),
  data = data_model_evs,
  family = binomial
)

summary(model_part1)

```

What factors are associated with whether someone exercises at all during the week? Generalized linear
 What factors are associated with whether someone exercises at all during the week? Approximation)
 What factors are associated with whether someone exercises at all during the week? Family: binomial
 What factors are associated with whether someone exercises at all during the week? Formula: exercised
 What factors are associated with whether someone exercises at all during the week? Data: data_mode

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

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

What factors are associated with whether someone exercises at all during the week? 209.4 232.

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

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

What factors are associated with whether someone exercises at all during the week? Min 1Q Median

What factors are associated with whether someone exercises at all during the week? -2.3438 -0.3319 0.0000

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

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

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

What factors are associated with whether someone exercises at all during the week? record_id (Intercept)

What factors are associated with whether someone exercises at all during the week? Number of obs: 187

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

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

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

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

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

What factors are associated with whether someone exercises at all during the week? visit2

What factors are associated with whether someone exercises at all during the week? visit3

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

What factors are associated with whether someone exercises at all during the week? visit2

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

What factors are associated with whether someone exercises at all during the week? Signif. codes: 0 ***

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

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

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

What factors are associated with whether someone exercises at all during the week? allctn_grGB -0.675

What factors are associated with whether someone exercises at all during the week? visit2 -0.331

What factors are associated with whether someone exercises at all during the week? visit3 -0.379

What factors are associated with whether someone exercises at all during the week? allctn_GB:2 0.282

What factors are associated with whether someone exercises at all during the week? allctn_GB:3 0.284

```

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 (log-transformed)

Among those who do exercise, what factors are associated with how much they exercise (log-transformed)

Among those who do exercise, what factors are associated with how much they exercise (log-transformed)

Among those who do exercise, what factors are associated with how much they exercise (log-transformed)

Among those who do exercise, what factors are associated with how much they exercise (log-transformed)

Among those who do exercise, what factors are associated with how much they exercise (log-transformed)

Among those who do exercise, what factors are associated with how much they exercise (log-transformed)

Among those who do exercise, what factors are associated with how much they exercise (log-transformed)

Among those who do exercise, what factors are associated with how much they exercise (log-transformed)

3.18.3.1 Resultado

Para analisar o escore de atividade física semanal (evs_score), que representa o produto entre os dias por semana e os minutos por dia de exercício relatados por cada participante, foi adotado um modelo em dois estágios. Esta abordagem se mostrou mais adequada devido à presença de 33.9% de valores iguais a zero (pacientes inativos) e à distribuição assimétrica dos valores positivos (pacientes ativos).

No primeiro estágio, foi ajustado um modelo de regressão logística mista com intercepto aleatório por participante para estimar a probabilidade de o participante relatar qualquer atividade física ($\text{evs_score} > 0$). Observou-se que, independentemente do grupo, a chance de relatar exercício aumentou significativamente na visita 2 ($\text{OR} \approx 24$, $p = 0,002$) 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 $\text{evs_score} > 0$, utilizando a transformação logarítmica dos minutos semanais de exercício como variável dependente. Neste modelo, nenhuma diferença significativa foi observada entre os grupos ou ao longo do tempo em relação à quantidade de exercício realizada entre os participantes ativos. Ou seja, embora mais participantes tenham relatado prática de atividade física nas visitas seguintes, a duração total semanal entre aqueles que se exercitavam permaneceu estável.

Esses resultados sugerem que o efeito observado ao longo do tempo se concentrou em uma maior adesão à prática de atividade física, mas não em um aumento da quantidade entre os que já praticavam.

4 Variáveis coletadas na primeira e terceira visitas

4.1 Ângulo de Fase

Variável: phase_angle

```
# Plot 1: Raw data
phase_angle_hist_1 <- data_model_V1V3 %>%
  filter(
```

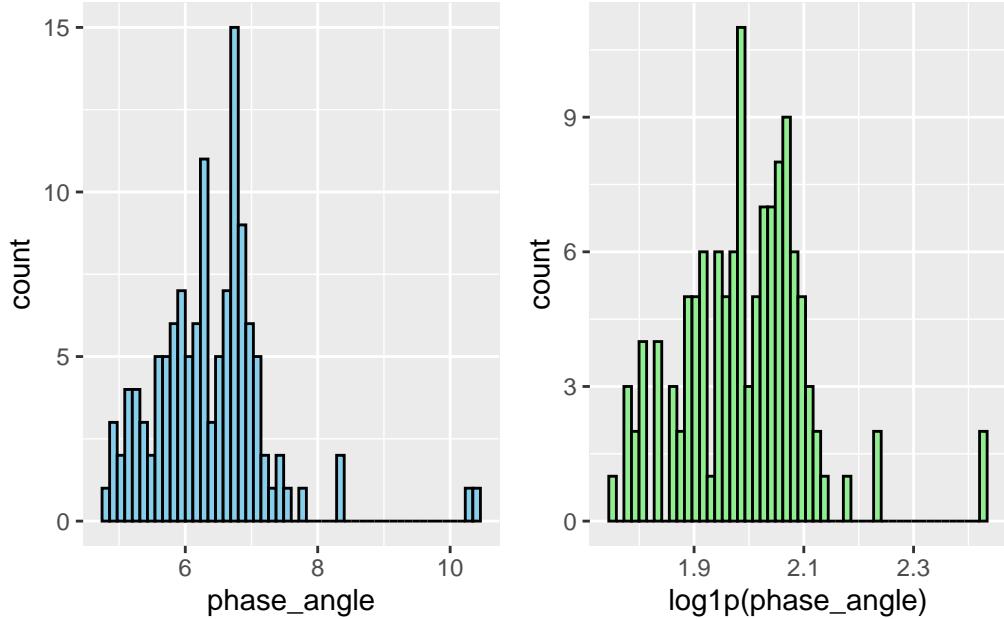
```

    phase_angle < 300
) %>%
ggplot(aes(x = phase_angle)) +
geom_histogram(bins = 50, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
phase_angle_hist_2 <- data_model_V1V3 %>%
filter(
  phase_angle < 300
) %>%
ggplot(aes(x = log1p(phase_angle))) +
geom_histogram(bins = 50, fill = "lightgreen", color = "black")

# Combine side by side
phase_angle_hist_1 + phase_angle_hist_2 # library(patchwork)

```



```

# LMM
phase_angle_model <- lmer(log1p(phase_angle) ~ allocation_group * visit +
(1 | record_id), data = data_model_V1V3
check_collinearity(phase_angle_model)

# Check for Multicollinearity

```

Low Correlation

| Term | VIF | VIF 95% CI | Increased SE | Tolerance |
|------------------------|--------------|--------------|--------------|-----------|
| allocation_group | 1.07 | [1.01, 1.97] | 1.04 | 0.93 |
| visit | 1.86 | [1.51, 2.46] | 1.37 | 0.54 |
| allocation_group:visit | 1.93 | [1.55, 2.54] | 1.39 | 0.52 |
| Tolerance 95% CI | | | | |
| | [0.51, 0.99] | | | |
| | [0.41, 0.66] | | | |
| | [0.39, 0.64] | | | |

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

# LMM Sensitivity
phase_angle_model_sens <- update(object = phase_angle_model,
  subset = !(record_id %in%
  phase_angle_model_check$influential_ids))

# Influential IDS
phase_angle_model_check$influential_ids
```

[1] "38" "46" "50" "74" "58"

4.1.1 Resumo dos modelos

```
# Model comparison
summary(phase_angle_model)

Linear mixed model fit by REML. t-tests use Satterthwaite's method [
lmerModLmerTest]
Formula: log1p(phase_angle) ~ allocation_group * visit + (1 | record_id)
Data: data_model_V1V3
```

REML criterion at convergence: -221.5

Scaled residuals:

| Min | 1Q | Median | 3Q | Max |
|---------|---------|--------|--------|--------|
| -2.3340 | -0.3586 | 0.0353 | 0.3389 | 3.5151 |

Random effects:

```

Groups      Name          Variance Std.Dev.
record_id (Intercept) 0.010030 0.10015
Residual           0.002521 0.05021
Number of obs: 125, groups: record_id, 75

```

Fixed effects:

| | Estimate | Std. Error | df | t value | Pr(> t) |
|-------------------------|--|------------|-----------|---------|----------|
| (Intercept) | 2.021165 | 0.018418 | 82.634225 | 109.738 | <2e-16 |
| allocation_group | -0.045637 | 0.025875 | 82.634225 | -1.764 | 0.0815 |
| visit3 | -0.011701 | 0.013479 | 49.678850 | -0.868 | 0.3895 |
| allocation_group:visit3 | 0.007182 | 0.019804 | 50.362921 | 0.363 | 0.7184 |
| (Intercept) | *** | | | | |
| allocation_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_gr | -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

```
performance::compare_performance(  
  phase_angle_model,  
  phase_angle_model_sens)
```

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

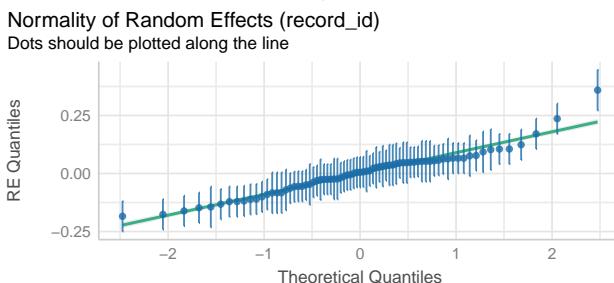
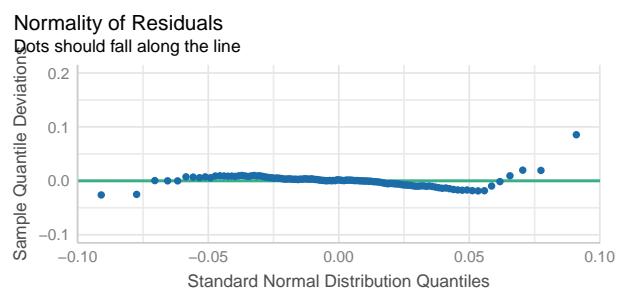
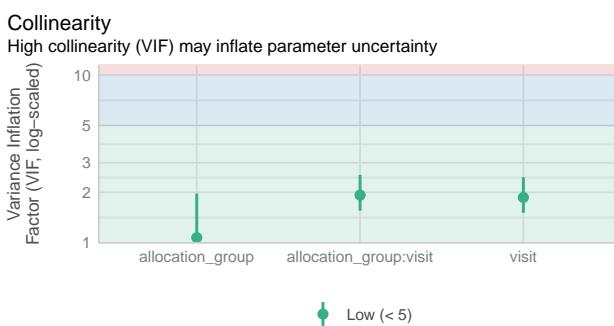
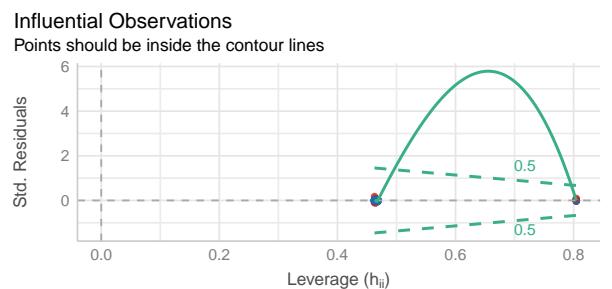
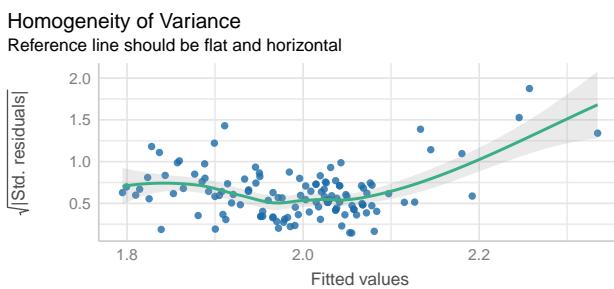
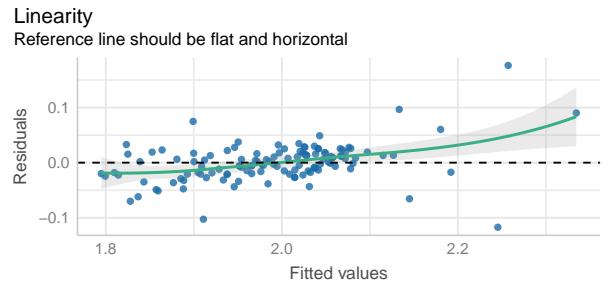
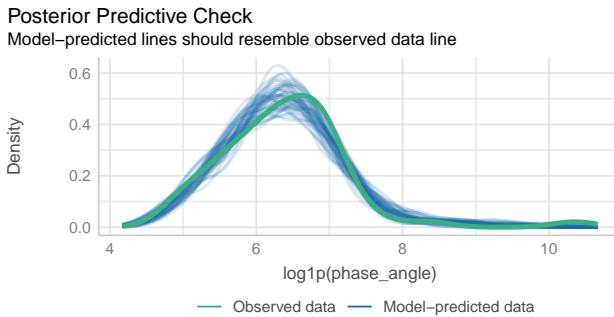
Comparison of Model Performance Indices

| Name | | Model | AIC (weights) | AICc (weights) |
|------------------------|-----------------|---------------|---------------|----------------|
| phase_angle_model | lmerModLmerTest | 262.3 (<.001) | 263.0 (<.001) | |
| phase_angle_model_sens | lmerModLmerTest | 168.0 (>.999) | 168.8 (>.999) | |

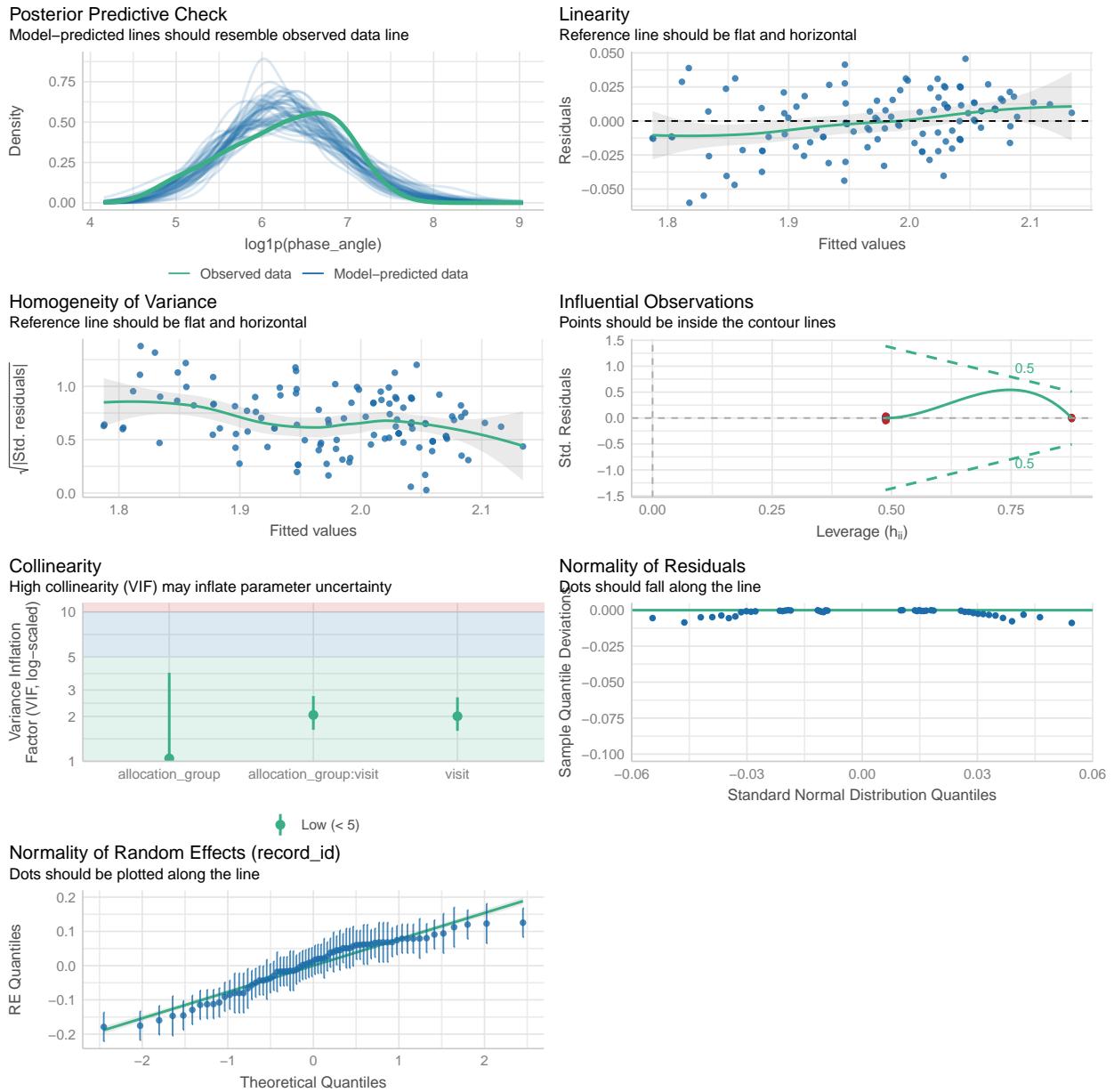
| Name | BIC (weights) | R2 (cond.) | R2 (marg.) | ICC |
|------------------------|---------------|------------|------------|-------|
| phase_angle_model | 279.3 (<.001) | 0.806 | 0.036 | 0.799 |
| phase_angle_model_sens | 184.5 (>.999) | 0.879 | 0.049 | 0.873 |

| Name | RMSE | Sigma |
|------------------------|-------|-------|
| phase_angle_model | 0.034 | 0.050 |
| phase_angle_model_sens | 0.021 | 0.032 |

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



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



4.1.2 Médias Marginais Estimadas

4.1.2.1 Todos os dados

```
# Get EMMs for each group at each visit
phase_angle_raw_emm <- emmeans::emmeans(
  phase_angle_model,
  ~ allocation_group * visit
)

phase_angle_raw_emm <- regrid(phase_angle_raw_emm)
```

```

# Table of marginal means
# phase_angle_raw_emm

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

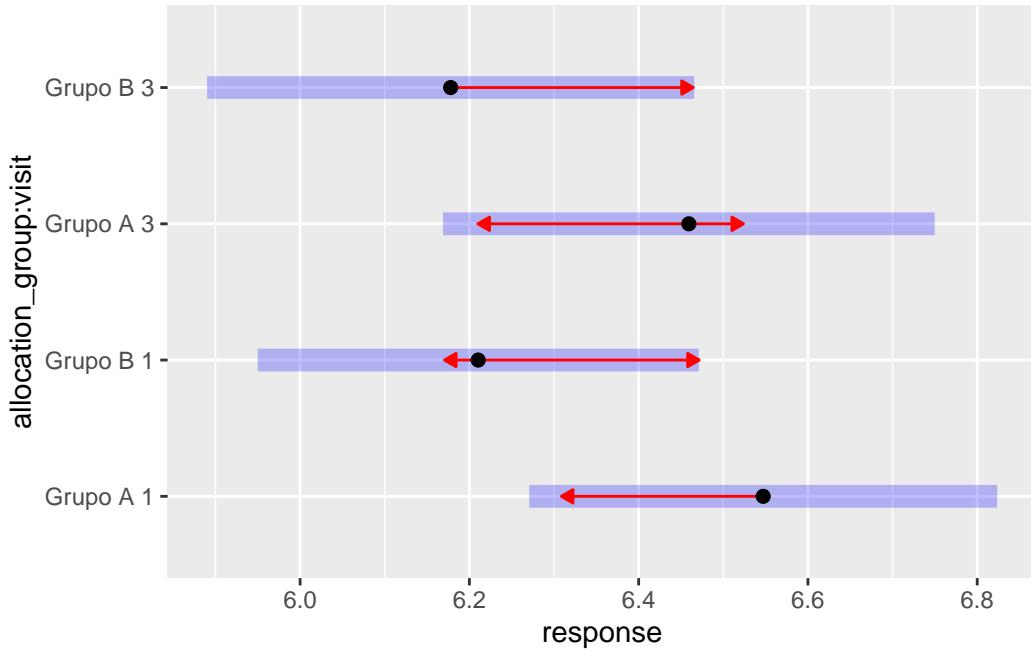
allocation_group = Grupo A:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
 visit1 - visit3   0.0878 0.101 83.6   -0.113     0.289   0.868  0.3880

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

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

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

```



4.1.2.2 Análise de sensibilidade

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

phase_angle_emm <- regrid(phase_angle_emm)

# Table of marginal means
# phase_angle_emm

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

visit = 1:
  contrast      estimate      SE   df lower.CL upper.CL t.ratio p.value
  Grupo A - Grupo B    0.330 0.155 73.9    0.0211    0.639    2.129  0.0366

visit = 3:
  contrast      estimate      SE   df lower.CL upper.CL t.ratio p.value
```

```
Grupo A - Grupo B      0.201 0.163 86.3  -0.1229      0.524    1.233  0.2210
```

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

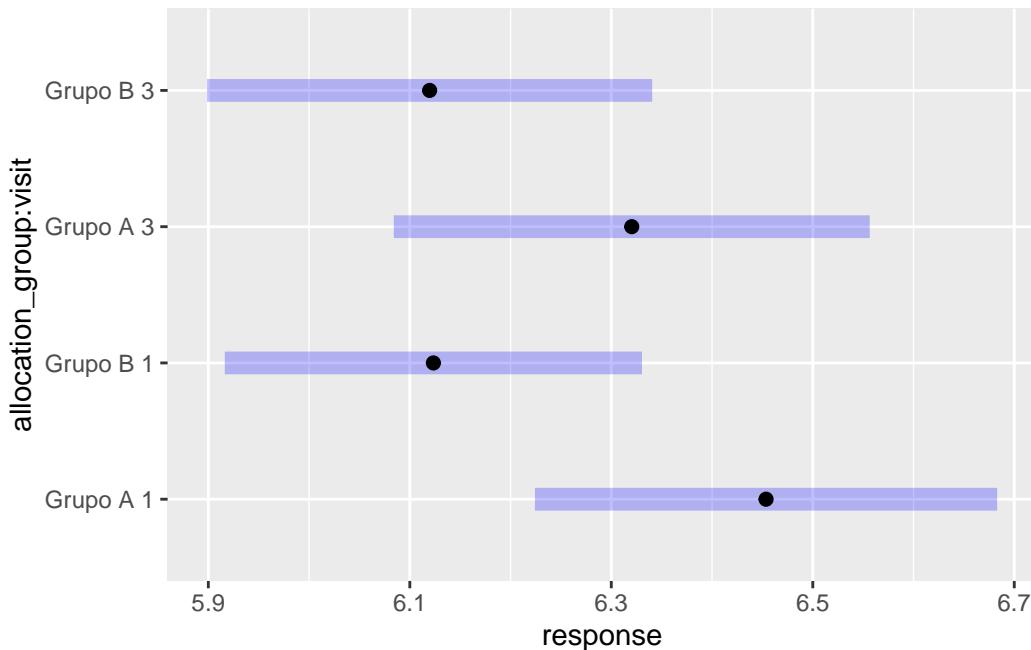
```
# Pairwise comparisons: Changes over time within each group
emmmeans::contrast(phase_angle_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

allocation_group = Grupo A:
contrast      estimate      SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit3  0.13331 0.0682 73.9 -0.00255     0.269    1.955  0.0543

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

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

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



4.1.3 Resultado

No modelo ajustado para o desfecho primário do estudo, o ângulo de fase, observou-se uma tendência à diferença entre os grupos na visita 1 (estimativa = 0,34; IC 95% [-0,04 ; 0,72]), embora sem significância estatística. Na visita 3, as médias estimadas também foram semelhantes entre os grupos (estimativa = 0,28; IC 95% [-0,13 ; 0,69]). Dentro de cada grupo, não foram detectadas mudanças significativas ao longo do tempo.

A análise de sensibilidade, com exclusão de observações influentes, revelou um aumento da magnitude do efeito entre os grupos na visita 1, com significância estatística (estimativa = 0,33; IC 95% [0,02 ; 0,64]), sugerindo que o grupo placebo apresentou valores de ângulo de fase ligeiramente superiores no início do estudo. As demais comparações permaneceram não significativas, e as estimativas dentro dos grupos ao longo do tempo se mantiveram estáveis.

As estimativas, intervalos de confiança de 95% e valores de p estão apresentados na Tabela 25 e Tabela 26

Tabela 25: Diferenças estimadas do ângulo de fase entre os grupos de alocação (placebo vs Eclipta) e entre visitas dentro de cada grupo (todos os dados)

| Grupo de comparação | Comparação | Estimativa | IC 95% | p-valor |
|---------------------|---------------------|------------|----------------|---------|
| Entre grupos | Visita 1 | 0,34 | [-0,04 ; 0,72] | 0,082 |
| Entre grupos | Visita 3 | 0,28 | [-0,13 ; 0,69] | 0,175 |
| Grupo Placebo | Visita 1 - Visita 3 | 0,09 | [-0,11 ; 0,29] | 0,388 |
| Grupo Eclipta | Visita 1 - Visita 3 | 0,03 | [-0,18 ; 0,24] | 0,757 |

Tabela 26: Diferenças estimadas do ângulo de fase entre os grupos de alocação (placebo vs Eclipta) e entre visitas dentro de cada grupo (Análise de sensibilidade)

| Grupo de comparação | Comparação | Estimativa | IC 95% | p-valor |
|---------------------|---------------------|------------|----------------|---------|
| Entre grupos | Visita 1 | 0,33 | [0,02 ; 0,64] | 0,037 |
| Entre grupos | Visita 3 | 0,20 | [-0,12 ; 0,52] | 0,221 |
| Grupo Placebo | Visita 1 - Visita 3 | 0,13 | [-0,00 ; 0,27] | 0,054 |
| Grupo Eclipta | Visita 1 - Visita 3 | 0,00 | [-0,13 ; 0,14] | 0,955 |

```
ggplot(
  data = data_model_V1V3,
  aes(
    x = as.factor(visit),
    y = phase_angle,
    group = record_id,
  )
```

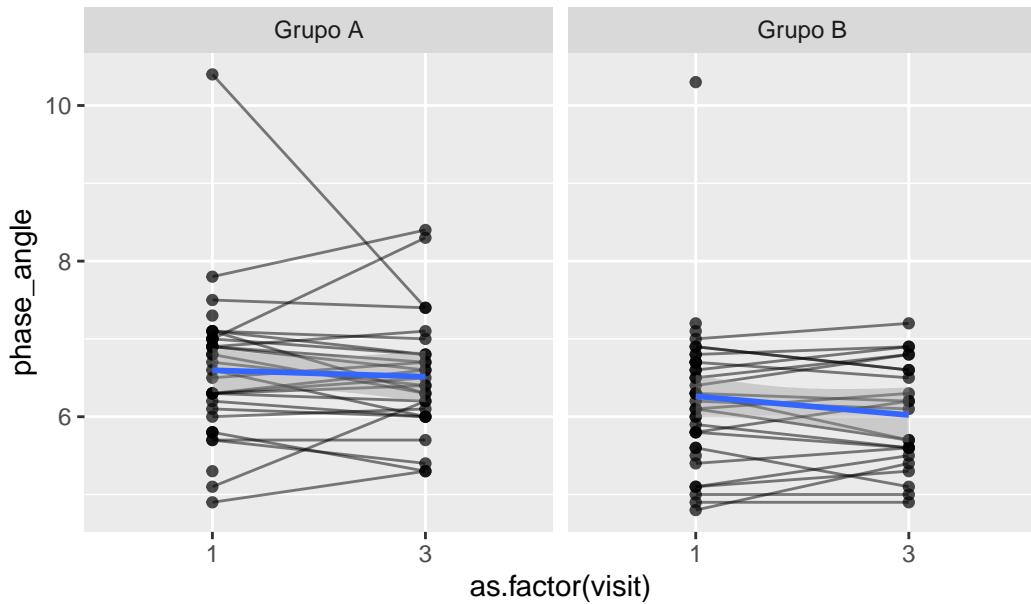
```

) +
  geom_line(alpha = 0.5) +
  geom_point(alpha = 0.7) +
  geom_smooth(
    aes(group = allocation_group),
    method = "lm",
    se = TRUE,
    linewidth = 1
  ) +
  labs(title = "All data") +
  facet_wrap(~ allocation_group)

`geom_smooth()` using formula = 'y ~ x'
Warning: Removed 3 rows containing non-finite outside the scale range
(`stat_smooth()`).
Warning: Removed 3 rows containing missing values or values outside the scale range
(`geom_line()`).
Warning: Removed 3 rows containing missing values or values outside the scale range
(`geom_point()`).

```

All data



```

data_model_V1V3 %>%
  filter(
    !(record_id %in%
      phase_angle_model_check$influential_ids)
  ) %>%

```

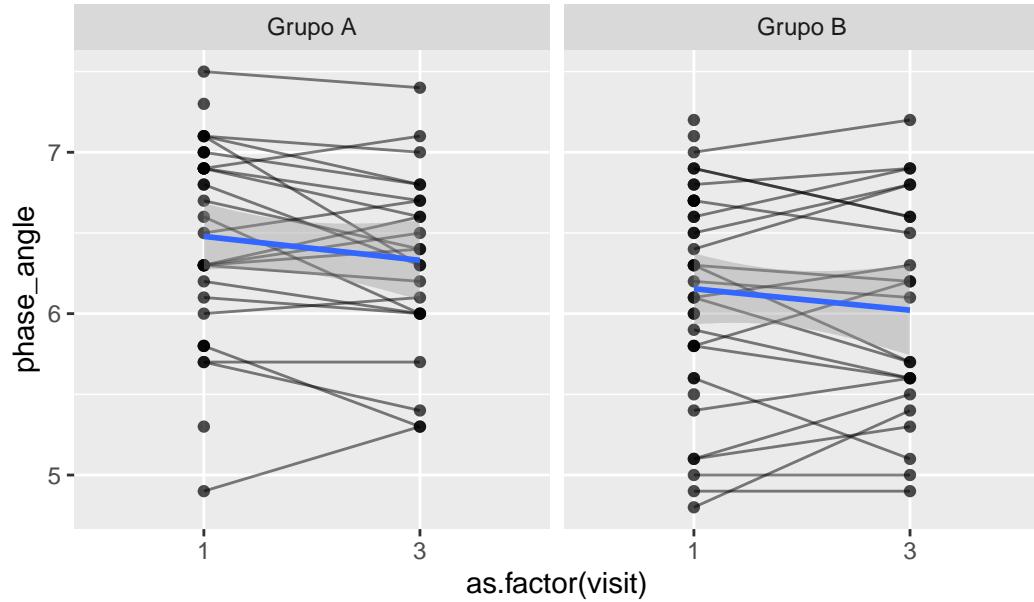
```

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

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

```

Sensitivity analysis



4.2 Reatância

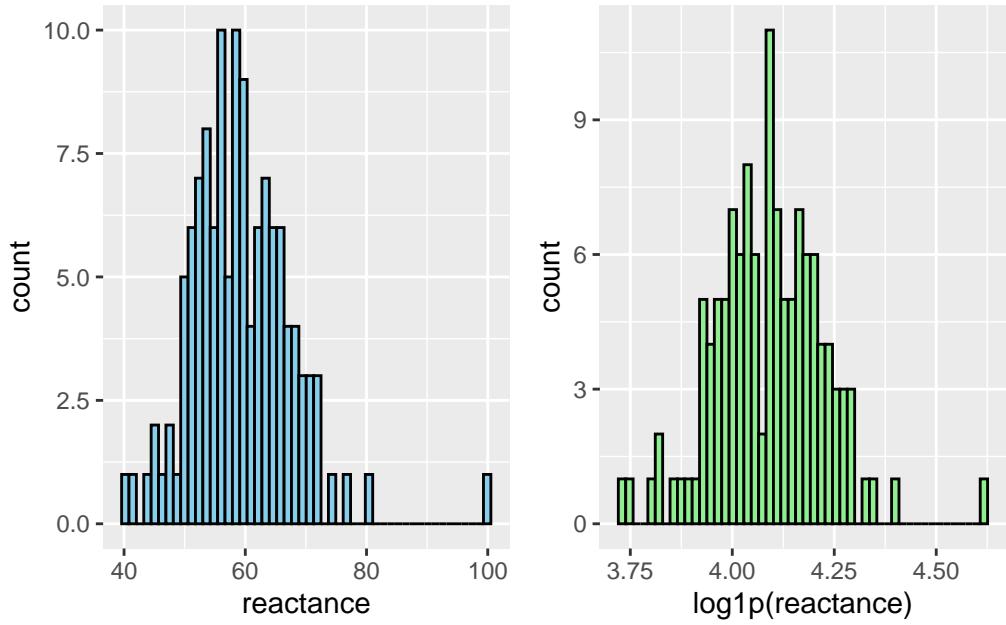
Variável: reactance

```
# Plot 1: Raw data
reactance_hist_1 <- data_model_V1V3 %>%
  #filter(
  #  reactance < 300
  #) %>%
  ggplot(aes(x = reactance)) +
  geom_histogram(bins = 50, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
reactance_hist_2 <- data_model_V1V3 %>%
  #filter(
  #  reactance < 300
  #) %>%
  ggplot(aes(x = log1p(reactance))) +
  geom_histogram(bins = 50, fill = "lightgreen", color = "black")

# Combine side by side
reactance_hist_1 + reactance_hist_2 # library(patchwork)
```

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



```
# LMM
reactance_model <- lmer(log1p(reactance) ~ allocation_group * visit +
(1 | record_id), data = data_model_V1V3)
check_collinearity(reactance_model)

# Check for Multicollinearity
```

Low Correlation

| Term | VIF | VIF 95% CI | Increased SE | Tolerance |
|------------------------|--------------|--------------|--------------|-----------|
| allocation_group | 1.12 | [1.02, 1.68] | 1.06 | 0.90 |
| visit | 1.87 | [1.52, 2.47] | 1.37 | 0.53 |
| allocation_group:visit | 1.97 | [1.58, 2.60] | 1.40 | 0.51 |
| Tolerance 95% CI | | | | |
| | [0.60, 0.98] | | | |
| | [0.41, 0.66] | | | |
| | [0.38, 0.63] | | | |

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

```

# LMM Sensitivity
reactance_model_sens <- update(object = reactance_model,
                                 subset = !(record_id %in%
                                 reactance_model_check$influential_ids))

# Influential IDS
reactance_model_check$influential_ids

[1] "22" "50" "74" "1" "31"

```

4.2.1 Resumo dos modelos

```

# Model comparison
summary(reactance_model)

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

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

Data: data_model_V1V3

```

REML criterion at convergence: -154.5

Scaled residuals:

| Min | 1Q | Median | 3Q | Max |
|----------|----------|---------|---------|---------|
| -2.01721 | -0.46574 | 0.01052 | 0.54712 | 2.07167 |

Random effects:

| Groups | Name | Variance | Std.Dev. |
|-----------|-------------|----------|----------|
| record_id | (Intercept) | 0.013481 | 0.11611 |
| | Residual | 0.005657 | 0.07522 |

Number of obs: 125, groups: record_id, 75

Fixed effects:

| | Estimate | Std. Error | df | t value | Pr(> t) |
|--------------------------------|----------|------------|----------|---------|----------|
| (Intercept) | 4.10499 | 0.02274 | 86.69858 | 180.493 | <2e-16 |
| allocation_groupGrupo B | -0.01206 | 0.03195 | 86.69858 | -0.377 | 0.707 |
| visit3 | -0.01119 | 0.02006 | 49.12966 | -0.558 | 0.579 |
| allocation_groupGrupo B:visit3 | 0.01600 | 0.02942 | 50.14982 | 0.544 | 0.589 |

(Intercept) ***
allocation_groupGrupo B

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

Correlation of Fixed Effects:

| | (Intr) | all_GB | visit3 |
|-------------|--------|--------|--------|
| allctn_grGB | -0.712 | | |
| visit3 | -0.335 | 0.239 | |
| allctn_GB:3 | 0.229 | -0.321 | -0.682 |

```
summary(reactance_model_sens)
```

```
Linear mixed model fit by REML. t-tests use Satterthwaite's method [  
lmerModLmerTest]  
Formula: log1p(reactance) ~ allocation_group * visit + (1 | record_id)  
Data: data_model_V1V3  
Subset: !(record_id %in% reactance_model_check$influential_ids)
```

REML criterion at convergence: -179.8

Scaled residuals:

| Min | 1Q | Median | 3Q | Max |
|----------|----------|---------|---------|---------|
| -1.59721 | -0.57888 | 0.01363 | 0.51723 | 1.65081 |

Random effects:

| Groups | Name | Variance | Std.Dev. |
|-----------|-------------|----------|----------|
| record_id | (Intercept) | 0.008423 | 0.09177 |
| | Residual | 0.004527 | 0.06728 |

Number of obs: 116, groups: record_id, 70

Fixed effects:

| | Estimate | Std. Error | df | t value | Pr(> t) |
|--------------------------------|----------|------------|----------|---------|----------|
| (Intercept) | 4.12073 | 0.01924 | 85.06056 | 214.231 | <2e-16 |
| allocation_groupGrupo B | -0.02913 | 0.02720 | 85.06056 | -1.071 | 0.287 |
| visit3 | -0.01607 | 0.01855 | 47.78854 | -0.866 | 0.391 |
| allocation_groupGrupo B:visit3 | 0.02453 | 0.02730 | 48.84683 | 0.899 | 0.373 |

(Intercept) ***

```

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

```

Correlation of Fixed Effects:

| | (Intr) | all_GB | visit3 |
|-------------|--------|--------|--------|
| allctn_grGB | -0.707 | | |
| visit3 | -0.363 | 0.256 | |
| allctn_GB:3 | 0.246 | -0.348 | -0.680 |

```

performance::compare_performance(
  reactance_model,
  reactance_model_sens)

```

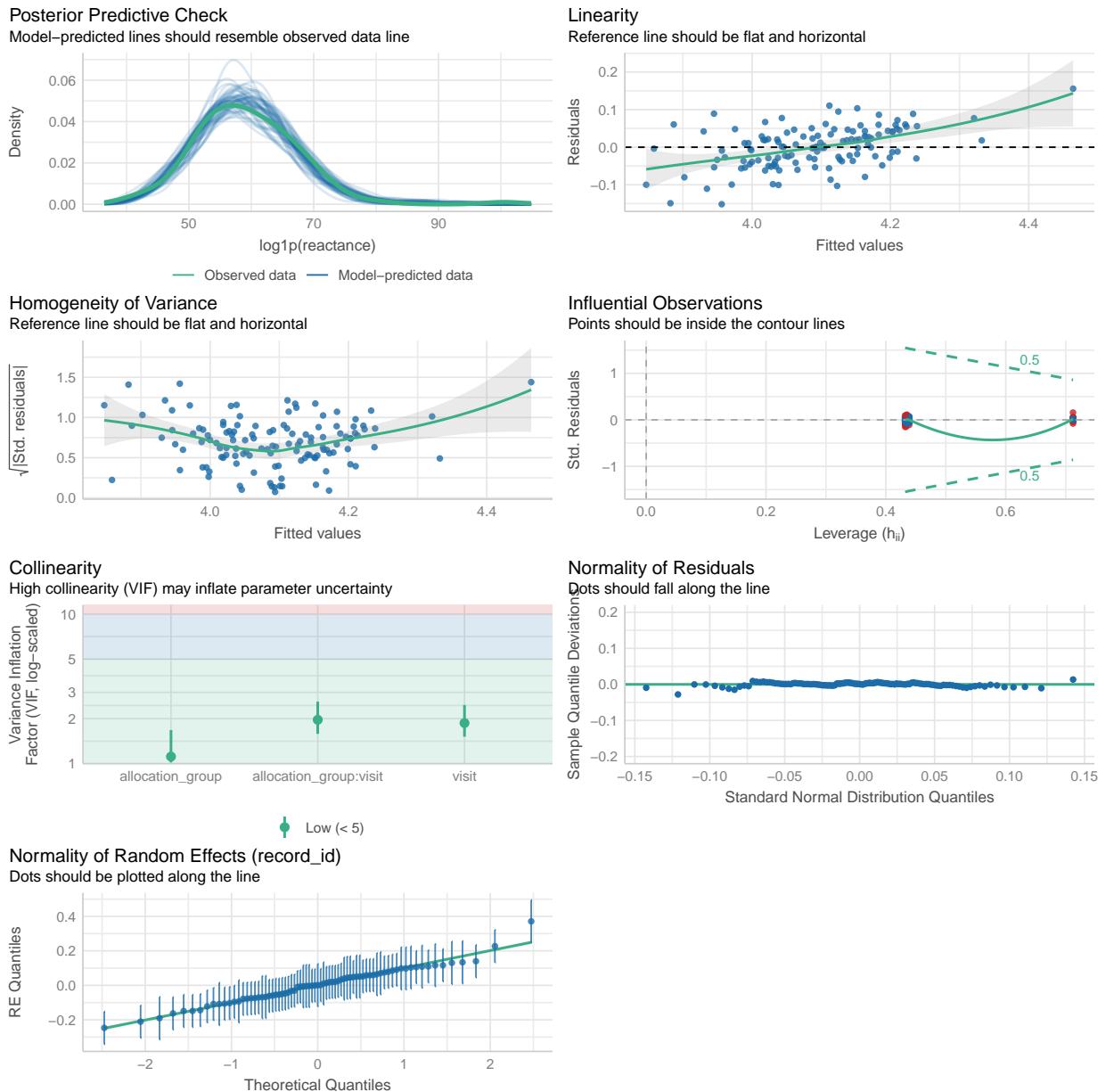
When comparing models, please note that probably not all models were fit from same data.

Comparison of Model Performance Indices

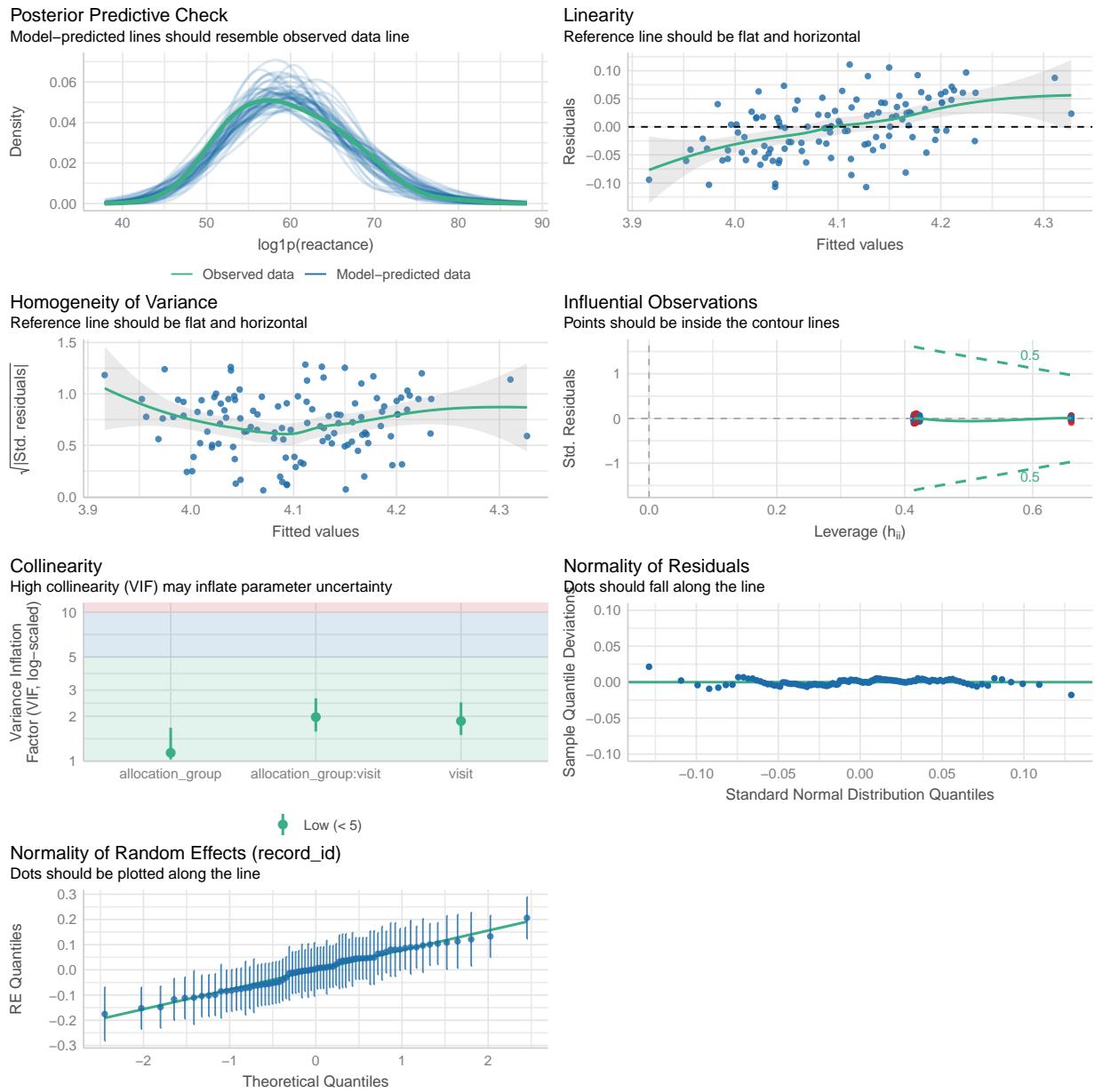
| Name | Model | AIC (weights) | AICc (weights) |
|----------------------|-----------------|---------------|----------------|
| reactance_model | lmerModLmerTest | 856.3 (<.001) | 857.0 (<.001) |
| reactance_model_sens | lmerModLmerTest | 758.9 (>.999) | 759.7 (>.999) |

| Name | BIC (weights) | R2 (cond.) | R2 (marg.) | ICC | RMSE | Sigma |
|----------------------|---------------|------------|------------|-------|-------|-------|
| reactance_model | 873.3 (<.001) | 0.705 | 0.001 | 0.704 | 0.054 | 0.075 |
| reactance_model_sens | 775.5 (>.999) | 0.654 | 0.010 | 0.650 | 0.049 | 0.067 |

```
performance::check_model(reactance_model)
```



```
performance::check_model(reactance_model_sens)
```



4.2.2 Médias Marginais Estimadas

4.2.2.1 Todos os dados

```
# Get EMMs for each group at each visit
reactance_raw_emm <- emmeans::emmeans(
  reactance_model,
  ~ allocation_group * visit
)

reactance_raw_emm <- regrid(reactance_raw_emm)
```

```

# Table of marginal means
# reactance_raw_emm

# Pairwise comparisons: Between groups at each visit
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))

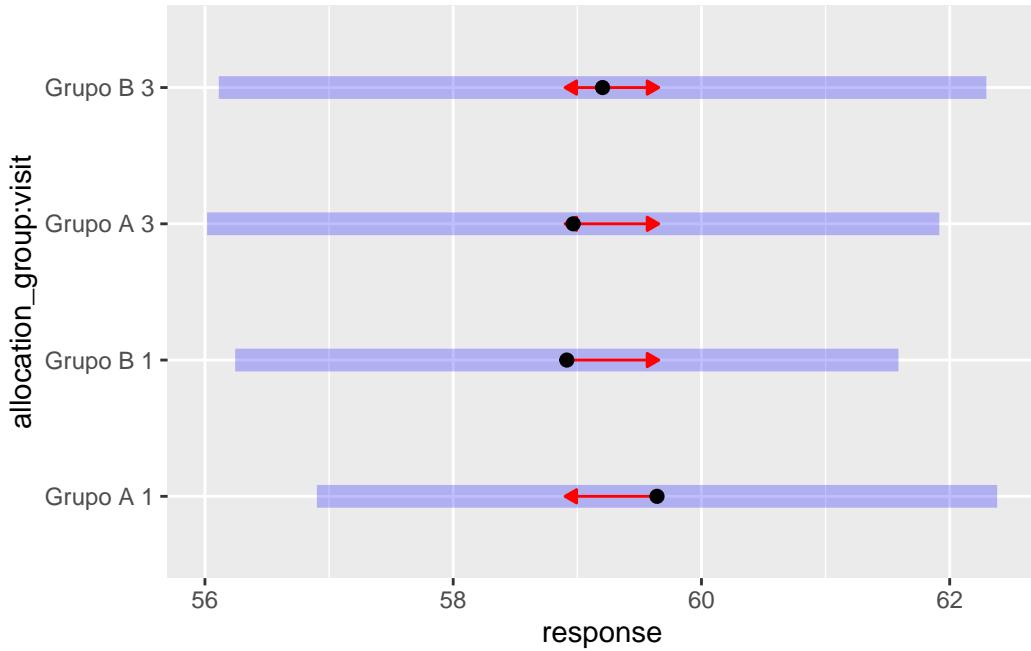
allocation_group = Grupo A:
  contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
 visit1 - visit3    0.675 1.21 89.2     -1.73      3.08   0.558  0.5785

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)

```



4.2.2.2 Análise de sensibilidade

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

reactance_emm <- regrid(reactance_emm)

# Table of marginal means
# reactance_emm

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

visit = 1:
  contrast      estimate    SE    df lower.CL upper.CL t.ratio p.value
  Grupo A - Grupo B   1.769 1.65  85.8    -1.52     5.05   1.071  0.2874

visit = 3:
  contrast      estimate    SE    df lower.CL upper.CL t.ratio p.value
```

```
Grupo A - Grupo B      0.278 1.89 103.4     -3.46      4.02    0.147  0.8830
```

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

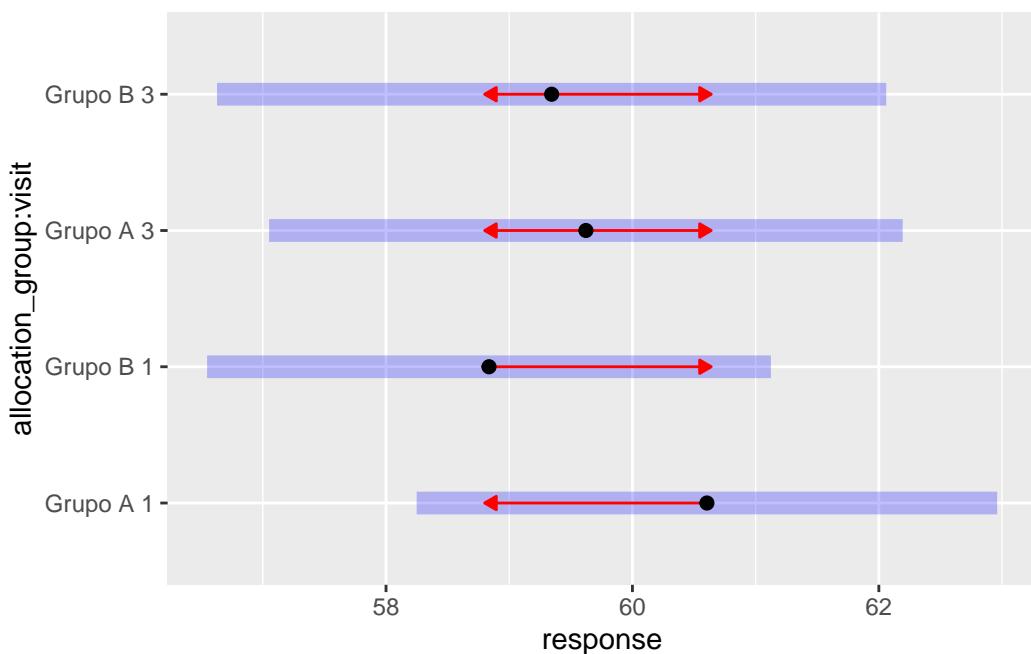
```
# Pairwise comparisons: Changes over time within each group
emmeans::contrast(reactance_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

allocation_group = Grupo A:
contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit3  0.982 1.13 85.8     -1.27      3.24    0.865  0.3892

allocation_group = Grupo B:
contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit3 -0.508 1.21 85.8     -2.91      1.90   -0.420  0.6756
```

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

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



4.2.3 Resultado

No modelo ajustado para os valores de reatância, não foram observadas diferenças estatisticamente significativas entre os grupos em nenhum dos momentos avaliados. As estimativas de diferença entre os grupos na visita 1 (estimativa = 0,73; IC 95% [-3,10 ; 4,55]) e na visita 3 (estimativa = -0,24; IC 95% [-4,51 ; 4,04]) apresentaram ampla sobreposição dos intervalos de confiança com zero. Da mesma forma, não foram identificadas mudanças significativas ao longo do tempo dentro de cada grupo.

A análise de sensibilidade não alterou substancialmente os resultados. Embora tenha havido um leve aumento da estimativa de diferença entre os grupos na visita 1 (estimativa = 1,77; IC 95% [-1,52 ; 5,05]), essa diferença continuou não significativa. As demais comparações permaneceram estáveis, sem alterações relevantes nas conclusões.

As estimativas, intervalos de confiança de 95% e valores de p estão apresentados na Tabela 27.

Tabela 27: Diferenças estimadas da reatância entre os grupos de alocação (placebo vs Eclipta) e entre visitas dentro de cada grupo

| Grupo de comparação | Comparação | Estimativa | IC 95% | p-valor |
|---------------------|---------------------|------------|----------------|---------|
| Entre grupos | Visita 1 | 0,73 | [-3,10 ; 4,55] | 0,707 |
| Entre grupos | Visita 3 | -0,24 | [-4,51 ; 4,04] | 0,913 |
| Grupo Placebo | Visita 1 - Visita 3 | 0,68 | [-1,73 ; 3,08] | 0,579 |
| Grupo Eclipta | Visita 1 - Visita 3 | -0,29 | [-2,87 ; 2,29] | 0,825 |

```
ggplot(
  data = data_model_V1V3,
  aes(
    x = as.factor(visit),
    y = reactance,
    group = record_id,
  )
) +
  geom_line(alpha = 0.5) +
  geom_point(alpha = 0.7) +
  geom_smooth(
    aes(group = allocation_group),
    method = "lm",
    se = TRUE,
    linewidth = 1
) +
  labs(title = "All data") +
```

```

facet_wrap(~ allocation_group)

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

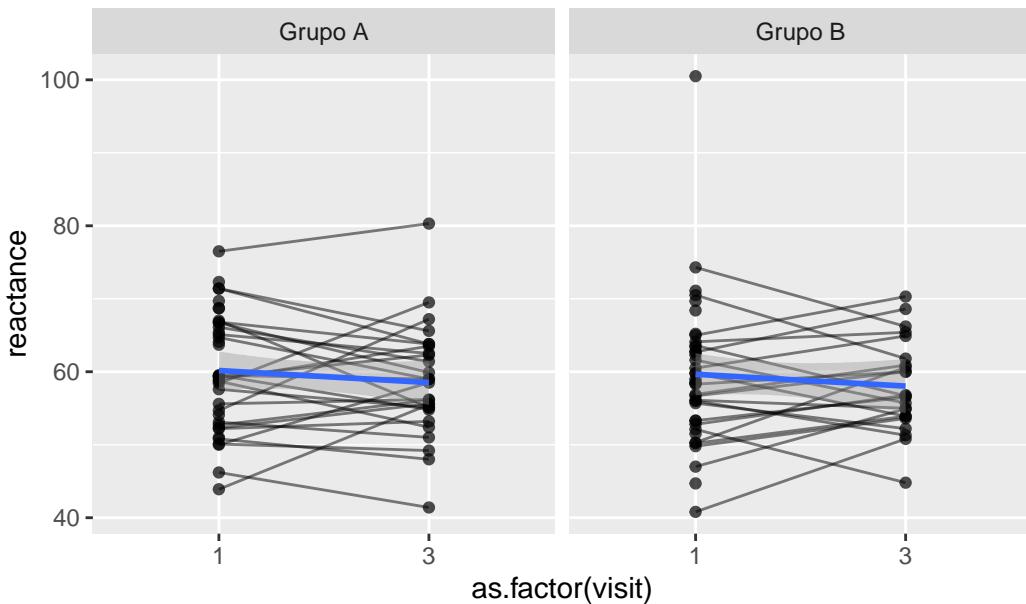
Warning: Removed 3 rows containing non-finite outside the scale range
(`stat_smooth()`).

Warning: Removed 3 rows containing missing values or values outside the scale range
(`geom_line()`).

Warning: Removed 3 rows containing missing values or values outside the scale range
(`geom_point()`).

```

All data



```

data_model_V1V3 %>%
  filter(
    !(record_id %in%
      reactance_model_check$influential_ids)
  ) %>%
  ggplot(
    aes(
      x = as.factor(visit),
      y = reactance,
      group = record_id,
    )
  ) +
  geom_line(alpha = 0.5) +
  geom_point(alpha = 0.7) +
  geom_smooth(

```

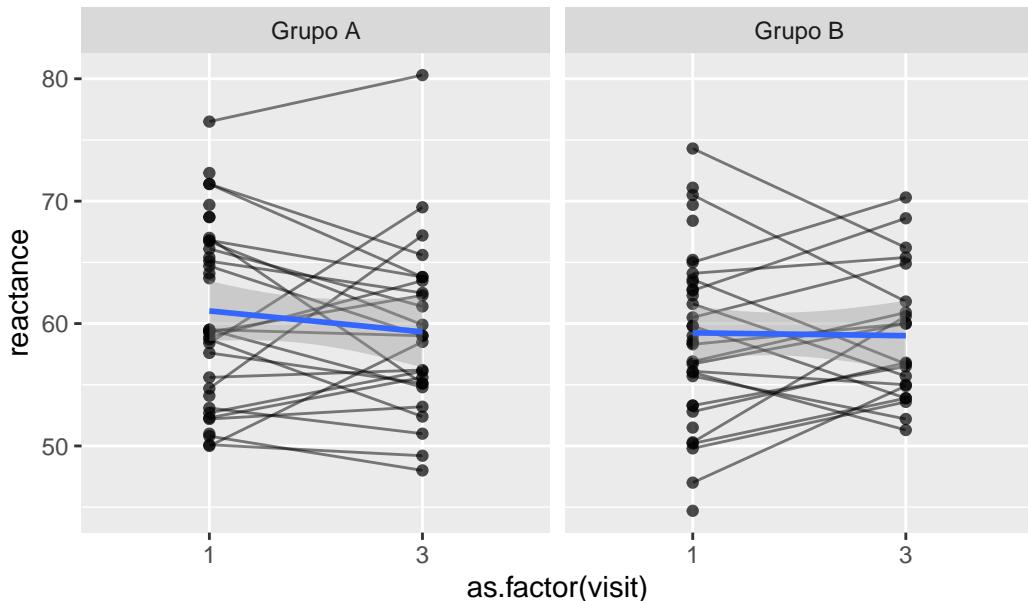
```

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

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

```

Sensitivity analysis



4.3 Resistência

Variável: `resistance`

```

# Plot 1: Raw data
resistance_hist_1 <- data_model_V1V3 %>%
  #filter(
  #  resistance < 300
  #) %>%

```

```

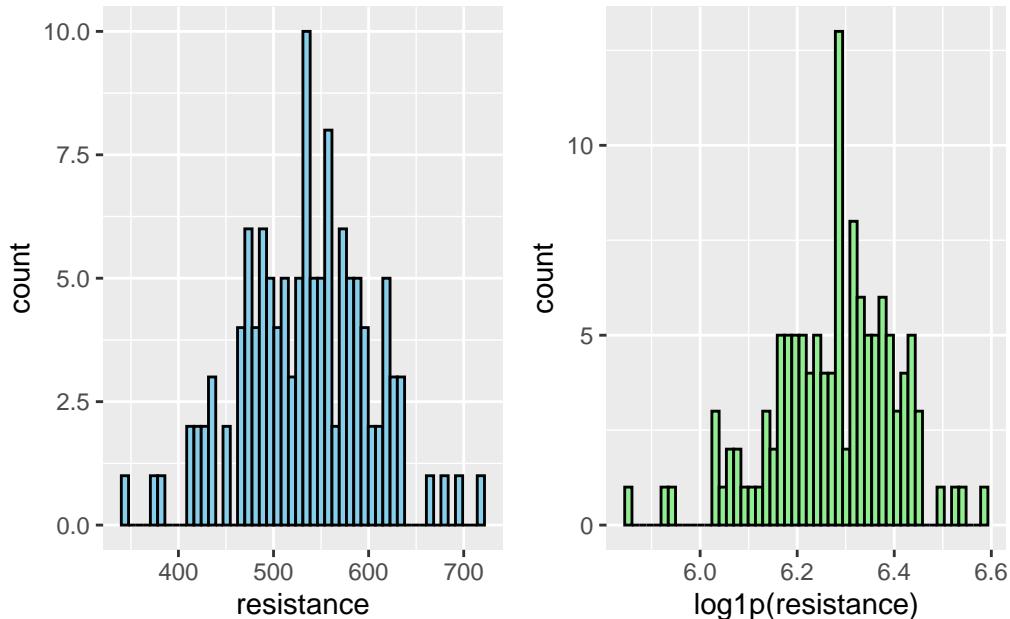
ggplot(aes(x = resistance)) +
  geom_histogram(bins = 50, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
resistance_hist_2 <- data_model_V1V3 %>%
  #filter(
  #  resistance < 300
  #) %>%
  ggplot(aes(x = log1p(resistance))) +
  geom_histogram(bins = 50, fill = "lightgreen", color = "black")

# Combine side by side
resistance_hist_1 + resistance_hist_2 # library(patchwork)

```

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



```

# LMM
resistance_model <- lmer(resistance ~ allocation_group * visit +
(1 | record_id), data = data_model_V1V3)
check_collinearity(resistance_model)

# Check for Multicollinearity

```

Low Correlation

| Term | VIF | VIF 95% CI | Increased SE | Tolerance |
|------------------------|--------------|--------------|--------------|-----------|
| allocation_group | 1.09 | [1.01, 1.82] | 1.04 | 0.92 |
| visit | 1.87 | [1.51, 2.46] | 1.37 | 0.54 |
| allocation_group:visit | 1.94 | [1.56, 2.56] | 1.39 | 0.52 |
| Tolerance 95% CI | | | | |
| | [0.55, 0.99] | | | |
| | [0.41, 0.66] | | | |
| | [0.39, 0.64] | | | |

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

# LMM Sensitivity
resistance_model_sens <- update(object = resistance_model,
  subset = !(record_id %in%
  resistance_model_check$influential_ids))

# Influential IDS
resistance_model_check$influential_ids
```

[1] "1" "34" "46" "64" "4"

4.3.1 Resumo dos modelos

```
# Model comparison
summary(resistance_model)

Linear mixed model fit by REML. t-tests use Satterthwaite's method [
lmerModLmerTest]
Formula: resistance ~ allocation_group * visit + (1 | record_id)
Data: data_model_V1V3
```

REML criterion at convergence: 1326.5

Scaled residuals:

| Min | 1Q | Median | 3Q | Max |
|----------|----------|---------|---------|---------|
| -3.15014 | -0.38120 | 0.03119 | 0.40613 | 3.07461 |

Random effects:

```

Groups      Name          Variance Std.Dev.
record_id (Intercept) 3316.7   57.59
Residual           992.1   31.50
Number of obs: 125, groups: record_id, 75

```

Fixed effects:

| | Estimate | Std. Error | df | t value | Pr(> t) |
|-------------------------|--|------------|--------|---------|------------|
| (Intercept) | 524.476 | 10.791 | 85.554 | 48.601 | <2e-16 *** |
| allocation_group | 20.506 | 15.161 | 85.554 | 1.353 | 0.180 |
| visit3 | 2.234 | 8.438 | 51.500 | 0.265 | 0.792 |
| allocation_group:visit3 | 4.651 | 12.392 | 52.296 | 0.375 | 0.709 |
| --- | | | | | |
| Signif. codes: | 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1 | | | | |

Correlation of Fixed Effects:

| (Intr) | all_GB | visit3 |
|-------------|--------|--------|
| allctn_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_groupGrupo B | 9.586 | 13.228 | 77.137 | 0.725 | 0.471 |
| visit3 | -3.225 | 6.679 | 46.655 | -0.483 | 0.631 |
| allocation_groupGrupo B:visit3 | 10.852 | 9.855 | 47.200 | 1.101 | 0.276 |
| --- | | | | | |

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

Correlation of Fixed Effects:

```
(Intr) all_GB visit3
allctn_grGB -0.707
visit3      -0.262  0.185
allctn_GB:3  0.178 -0.251 -0.678
```

```
performance::compare_performance(
  resistance_model,
  resistance_model_sens)
```

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

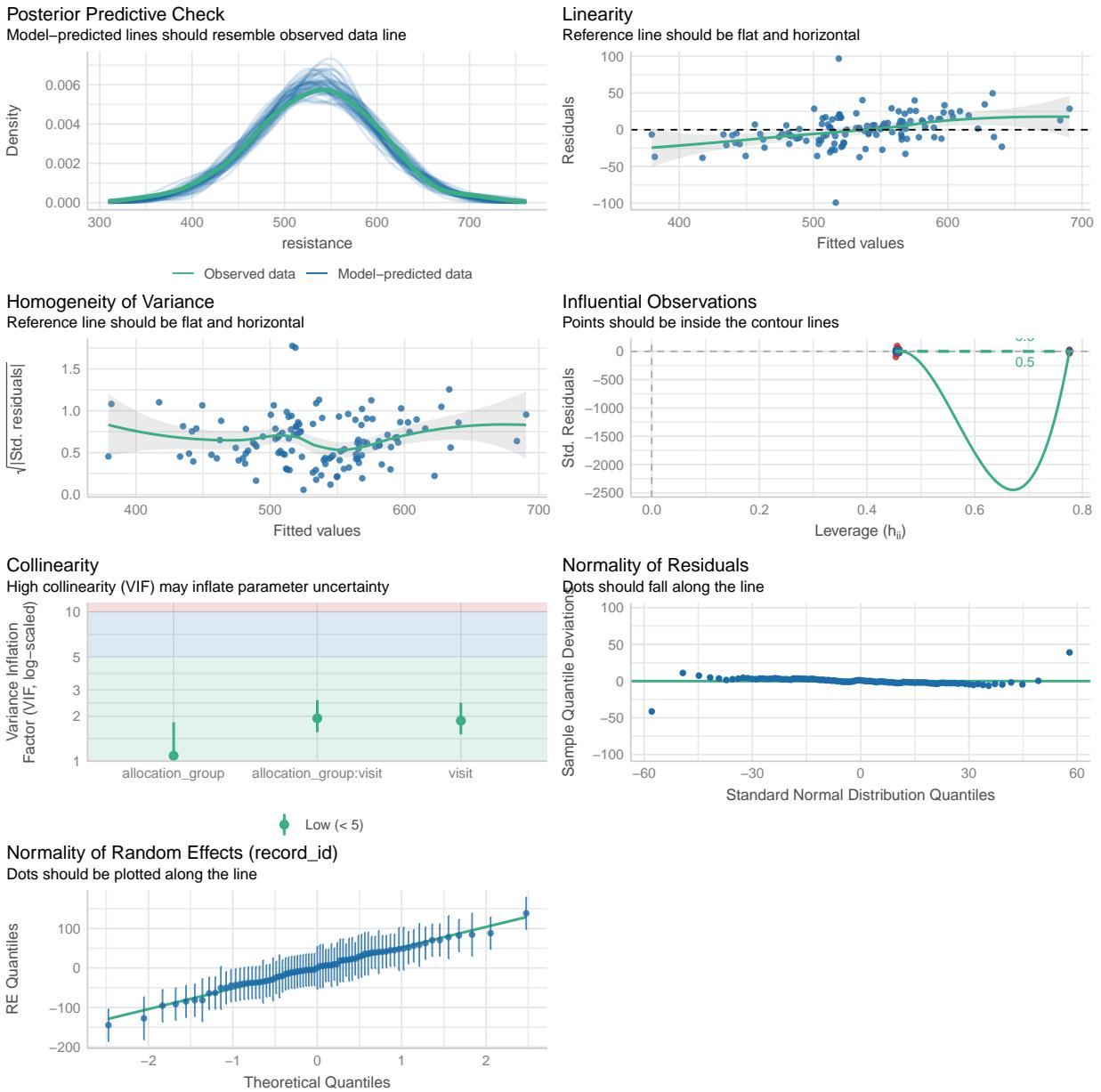
Comparison of Model Performance Indices

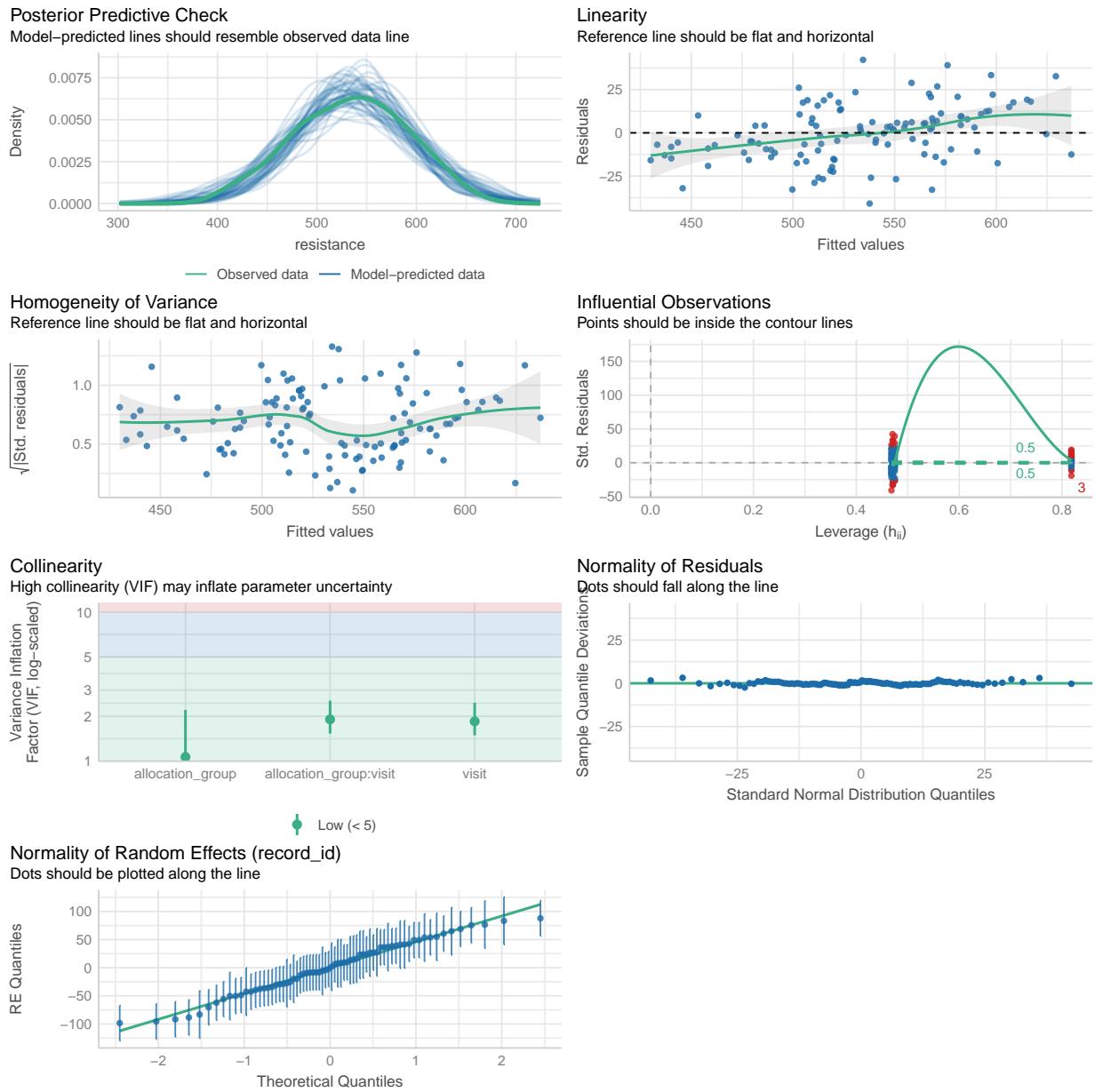
| Name | | Model | AIC (weights) | AICc (weights) |
|-----------------------|-----------------|----------------|----------------|----------------|
| ----- | | | | |
| resistance_model | lmerModLmerTest | 1363.8 (<.001) | 1364.5 (<.001) | |
| resistance_model_sens | lmerModLmerTest | 1218.5 (>.999) | 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)
```





4.3.2 Médias Marginais Estimadas

4.3.2.1 Todos os dados

```
# Get EMMs for each group at each visit
resistance_raw_emm <- emmeans::emmeans(
  resistance_model,
  ~ allocation_group * visit
)

resistance_raw_emm <- regrid(resistance_raw_emm)
```

```

# Table of marginal means
# resistance_raw_emm

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

visit = 1:
  contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    -20.5 15.2 85.3     -50.6      9.64  -1.353  0.1798

visit = 3:
  contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    -25.2 16.7 101.9     -58.2      7.93  -1.508  0.1346

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

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

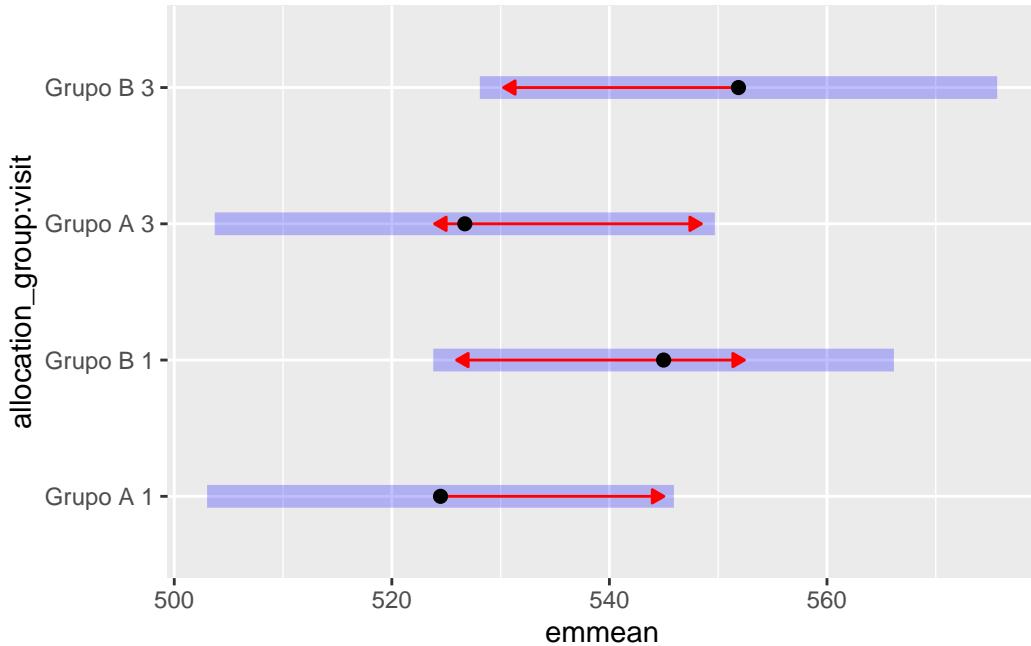
allocation_group = Grupo A:
  contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit3    -2.23 8.45 85.3      -19      14.6  -0.264  0.7922

allocation_group = Grupo B:
  contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit3    -6.88 9.10 85.3      -25      11.2  -0.757  0.4514

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

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

```



4.3.2.2 Análise de sensibilidade

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

resistance_emm <- regrid(resistance_emm)

# Table of marginal means
# resistance_emm

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

visit = 1:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
  Grupo A - Grupo B     -9.59 13.2 77.0     -35.9     16.76  -0.725  0.4709

visit = 3:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
```

```
Grupo A - Grupo B    -20.44 14.4 91.8     -49.0      8.14  -1.420  0.1589
```

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

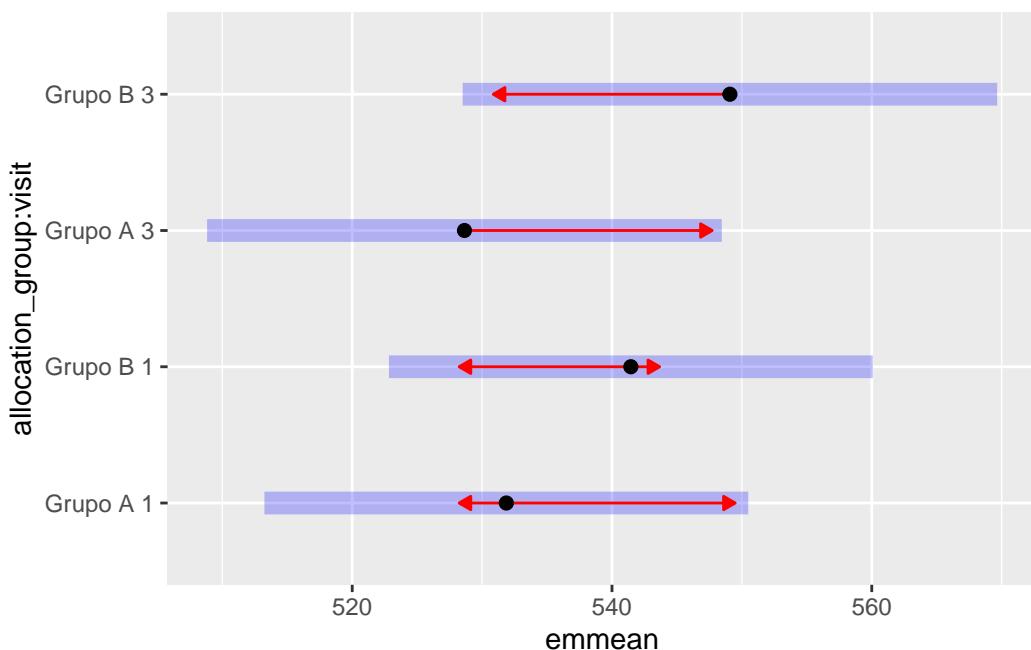
```
# Pairwise comparisons: Changes over time within each group
emmeans::contrast(resistance_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

allocation_group = Grupo A:
contrast      estimate   SE df lower.CL upper.CL t.ratio p.value
visit1 - visit3    3.22 6.69 77    -10.1     16.55   0.482  0.6312

allocation_group = Grupo B:
contrast      estimate   SE df lower.CL upper.CL t.ratio p.value
visit1 - visit3   -7.63 7.27 77    -22.1      6.84  -1.050  0.2970
```

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

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



4.3.3 Resultado

No modelo ajustado para os valores de resistência bioelétrica corporal, não foram observadas diferenças estatisticamente significativas entre os grupos em nenhum dos momentos avaliados. As estimativas de diferença entre os grupos foram de -20,5 ohms (IC 95%: -50,6 a 9,6) na visita 1 e -25,2 ohms (IC 95%: -58,2 a 7,9) na visita 3. Tampouco foram observadas mudanças significativas ao longo do tempo dentro de cada grupo.

A análise de sensibilidade, com exclusão das observações mais influentes, não alterou substancialmente os resultados. As estimativas permaneceram similares, com diferença entre os grupos de -9,6 ohms (IC 95%: -35,9 a 16,8) na visita 1 e -20,4 ohms (IC 95%: -49,0 a 8,1) na visita 3, também sem significância estatística. Da mesma forma, não houve mudanças significativas entre as visitas dentro de cada grupo. As estimativas e intervalos de confiança de 95% estão apresentados na Tabela Tabela 28.

Tabela 28: Diferenças estimadas nos valores de resistência elétrica entre os grupos de alocação (placebo vs Eclipta) e entre visitas dentro de cada grupo – Todos os dados

| Grupo de comparação | Comparação | Estimativa | IC 95% | p-valor |
|---------------------|---------------------|------------|----------------|---------|
| Entre grupos | Visita 1 | -20,5 | [-50,6 ; 9,6] | 0,180 |
| Entre grupos | Visita 3 | -25,2 | [-58,2 ; 7,9] | 0,135 |
| Grupo Placebo | Visita 1 - Visita 3 | -2,23 | [-19,0 ; 14,6] | 0,792 |
| Grupo Eclipta | Visita 1 - Visita 3 | -6,88 | [-25,0 ; 11,2] | 0,451 |

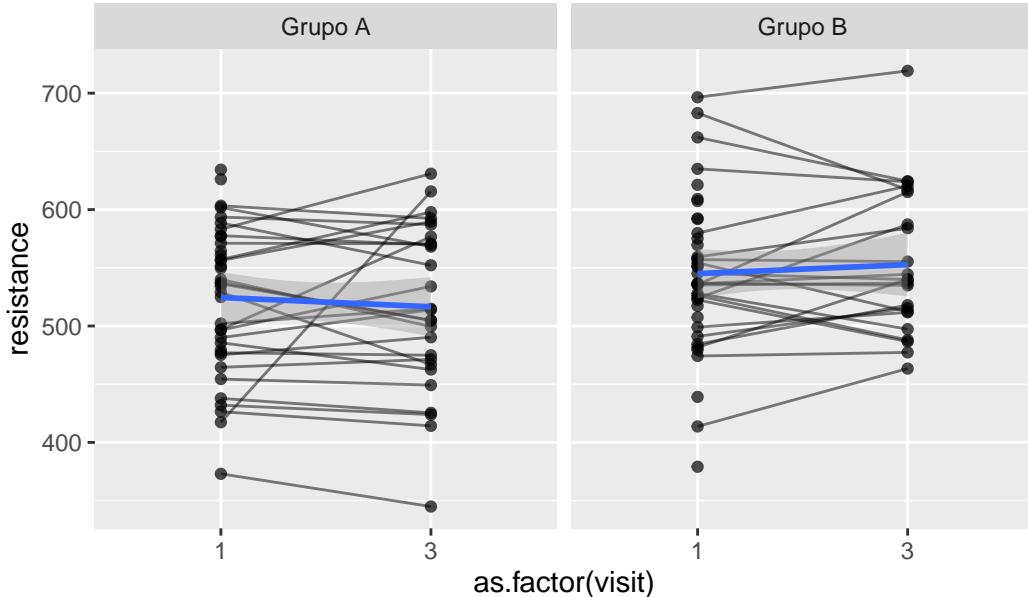
```
ggplot(
  data = data_model_V1V3,
  aes(
    x = as.factor(visit),
    y = resistance,
    group = record_id,
  )
) +
  geom_line(alpha = 0.5) +
  geom_point(alpha = 0.7) +
  geom_smooth(
    aes(group = allocation_group),
    method = "lm",
    se = TRUE,
    linewidth = 1
) +
  labs(title = "All data") +
  facet_wrap(~ allocation_group)
```

```

`geom_smooth()` using formula = 'y ~ x'
Warning: Removed 3 rows containing non-finite outside the scale range
(`stat_smooth()`).
Warning: Removed 3 rows containing missing values or values outside the scale range
(`geom_line()`).
Warning: Removed 3 rows containing missing values or values outside the scale range
(`geom_point()`).

```

All data



```

data_model_V1V3 %>%
  filter(
    !(record_id %in%
      resistance_model_check$influential_ids)
  ) %>%
  ggplot(
    aes(
      x = as.factor(visit),
      y = resistance,
      group = record_id,
    )
  ) +
  geom_line(alpha = 0.5) +
  geom_point(alpha = 0.7) +
  geom_smooth(
    aes(group = allocation_group),

```

```

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

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

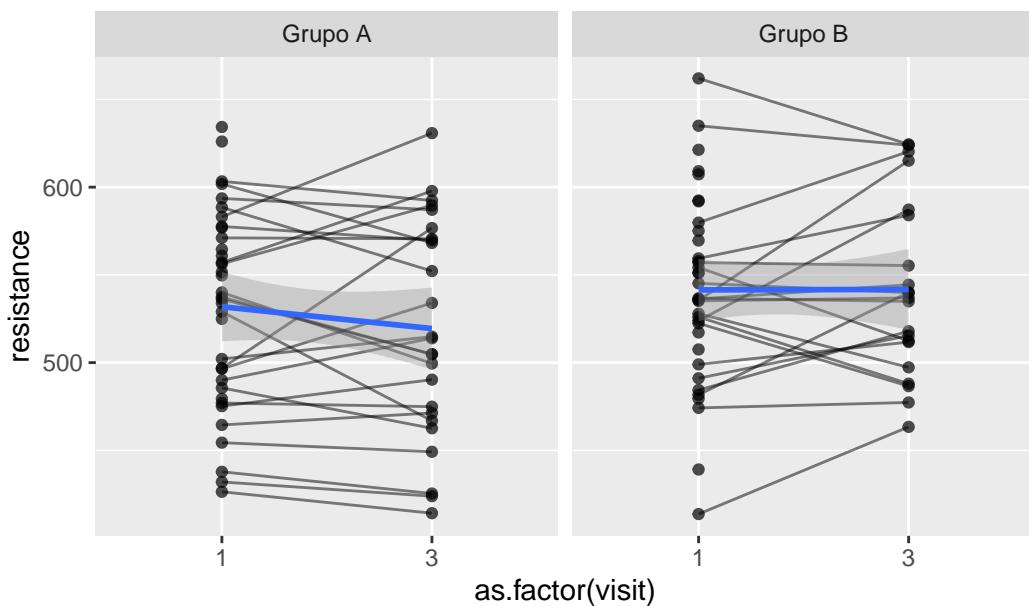
Warning: Removed 2 rows containing non-finite outside the scale range
(`stat_smooth()`).

Warning: Removed 2 rows containing missing values or values outside the scale range
(`geom_line()`).

Warning: Removed 2 rows containing missing values or values outside the scale range
(`geom_point()`).

```

Sensitivity analysis



4.4 Força de Prensão Palmar

Variável: handgrip

```

# Plot 1: Raw data
handgrip_hist_1 <- data_model_V1V3 %>%
  #filter(
  #  handgrip < 300
  #) %>%
  ggplot(aes(x = handgrip)) +

```

```

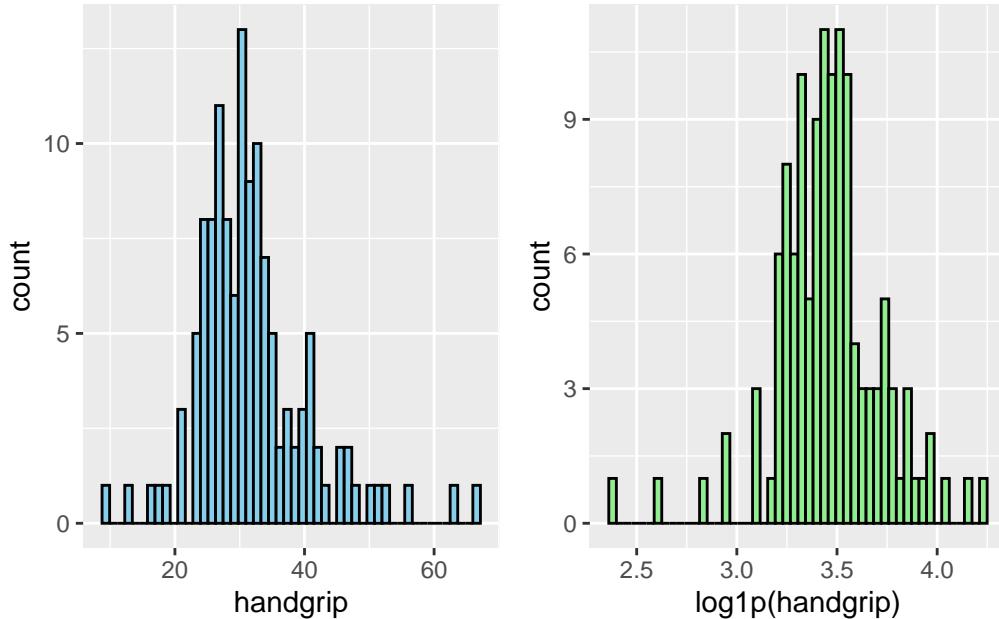
geom_histogram(bins = 50, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
handgrip_hist_2 <- data_model_V1V3 %>%
  #filter(
  #  handgrip < 300
  #) %>%
  ggplot(aes(x = log1p(handgrip))) +
  geom_histogram(bins = 50, fill = "lightgreen", color = "black")

# Combine side by side
handgrip_hist_1 + handgrip_hist_2 # library(patchwork)

```

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



```

# LMM
handgrip_model <- lmer(log1p(handgrip) ~ allocation_group * visit +
(1 | record_id), data = data_model_V1V3)
check_collinearity(handgrip_model)

# Check for Multicollinearity

```

Low Correlation

| Term | VIF | VIF 95% | CI Increased SE | Tolerance |
|------|-----|---------|-----------------|-----------|
|------|-----|---------|-----------------|-----------|

```

    allocation_group 1.06 [1.00, 2.22]      1.03      0.94
                visit 1.93 [1.56, 2.55]      1.39      0.52
allocation_group:visit 1.99 [1.60, 2.62]      1.41      0.50

Tolerance 95% CI
[0.45, 1.00]
[0.39, 0.64]
[0.38, 0.62]

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

# LMM Sensitivity
handgrip_model_sens <- update(object = handgrip_model,
                                 subset = !(record_id %in%
handgrip_model_check$influential_ids))

# Influential IDs
handgrip_model_check$influential_ids

[1] "16" "23" "31" "72" "56"

```

4.4.1 Resumo dos modelos

```

# Model comparison
summary(handgrip_model)

Linear mixed model fit by REML. t-tests use Satterthwaite's method [
lmerModLmerTest]
Formula: log1p(handgrip) ~ allocation_group * visit + (1 | record_id)
Data: data_model_V1V3

REML criterion at convergence: -36.3

```

Scaled residuals:

| Min | 1Q | Median | 3Q | Max |
|---------|---------|--------|--------|--------|
| -3.2121 | -0.2737 | 0.0096 | 0.3023 | 2.3599 |

Random effects:

| Groups | Name | Variance | Std.Dev. |
|--------|------|----------|----------|
|--------|------|----------|----------|

```
record_id (Intercept) 0.05291  0.2300  
Residual              0.01046  0.1023  
Number of obs: 127, groups: record_id, 75
```

Fixed effects:

| | Estimate | Std. Error | df | t value | Pr(> t) |
|--------------------------------|----------|------------|----------|---------|----------|
| (Intercept) | 3.51478 | 0.04138 | 81.97737 | 84.934 | <2e-16 |
| allocation_groupGrupo B | -0.09908 | 0.05814 | 81.97737 | -1.704 | 0.0921 |
| visit3 | 0.02794 | 0.02752 | 52.37961 | 1.015 | 0.3146 |
| allocation_groupGrupo B:visit3 | -0.07741 | 0.03962 | 52.70060 | -1.954 | 0.0561 |

(Intercept) ***
allocation_groupGrupo B .
visit3
allocation_groupGrupo B:visit3 .

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

Correlation of Fixed Effects:

| | (Intr) | all_GB | visit3 |
|-------------|--------|--------|--------|
| allctn_grGB | -0.712 | | |
| visit3 | -0.248 | 0.177 | |
| allctn_GB:3 | 0.172 | -0.242 | -0.694 |

```
summary(handgrip_model_sens)
```

```
Linear mixed model fit by REML. t-tests use Satterthwaite's method [  
lmerModLmerTest]  
Formula: log1p(handgrip) ~ allocation_group * visit + (1 | record_id)  
Data: data_model_V1V3  
Subset: !(record_id %in% handgrip_model_check$influential_ids)
```

REML criterion at convergence: -112.4

Scaled residuals:

| Min | 1Q | Median | 3Q | Max |
|----------|----------|---------|---------|---------|
| -2.07607 | -0.35838 | 0.02018 | 0.31173 | 2.01345 |

Random effects:

```

Groups      Name          Variance Std.Dev.
record_id (Intercept) 0.037729 0.19424
Residual           0.003193 0.05651
Number of obs: 117, groups: record_id, 70

Fixed effects:
              Estimate Std. Error      df t value Pr(>|t|)
(Intercept)      3.49708   0.03372 70.87133 103.723 <2e-16
allocation_group Grupo B -0.06327   0.04838 70.87133 -1.308  0.195
visit3            0.02342   0.01559 45.19417  1.503  0.140
allocation_group Grupo B:visit3 -0.01675   0.02329 45.40129 -0.719  0.476

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

Correlation of Fixed Effects:
              (Intr) all_GB visit3
allctn_grGB -0.697
visit3       -0.169  0.118
allctn_GB:3  0.113 -0.162 -0.669

performance::compare_performance(
  handgrip_model,
  handgrip_model_sens)

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

# Comparison of Model Performance Indices

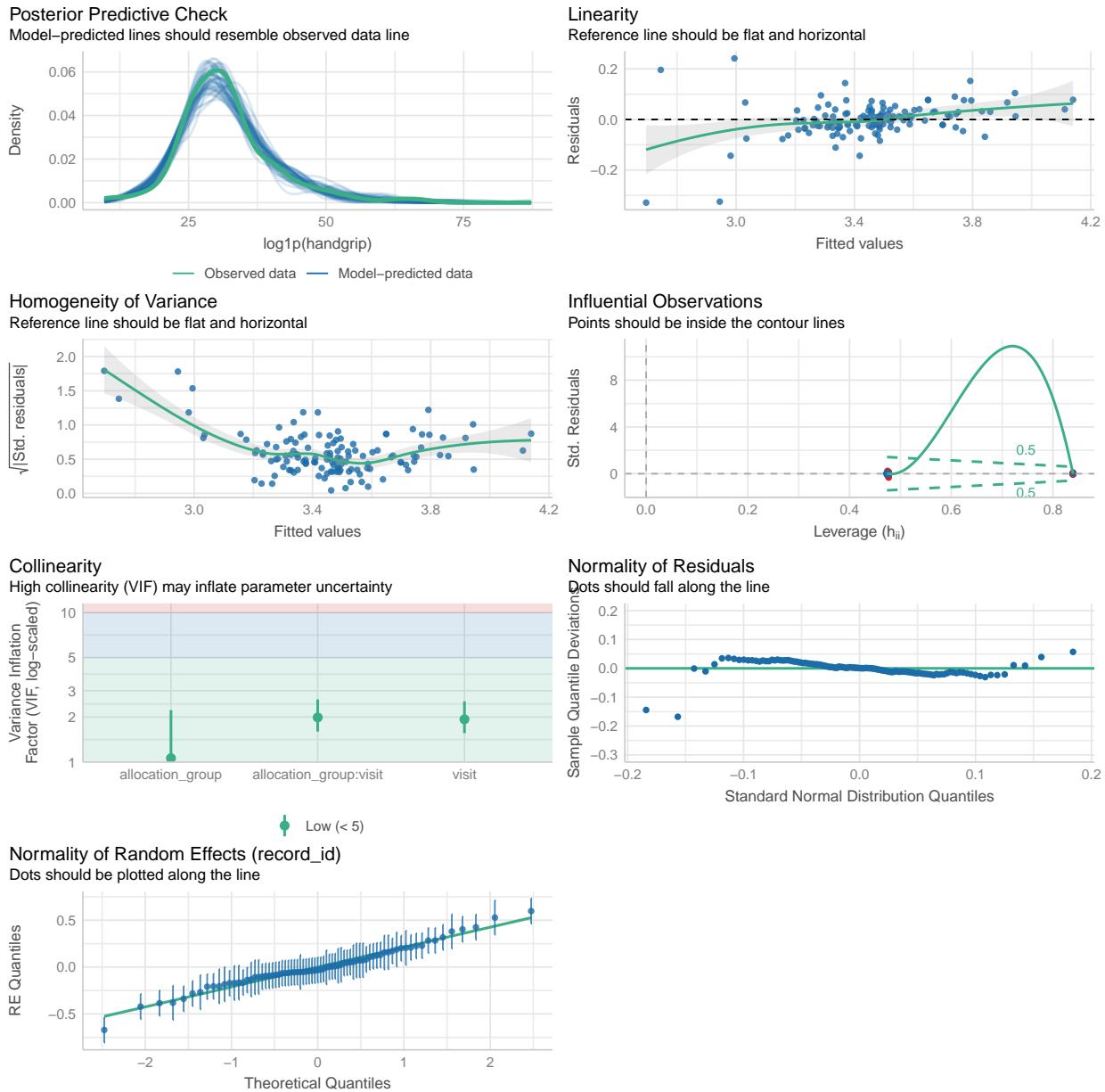
Name          | Model | AIC (weights) | AICc (weights)
-----
handgrip_model | lmerModLmerTest | 834.9 (<.001) | 835.6 (<.001)
handgrip_model_sens | lmerModLmerTest | 689.5 (>.999) | 690.3 (>.999)

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

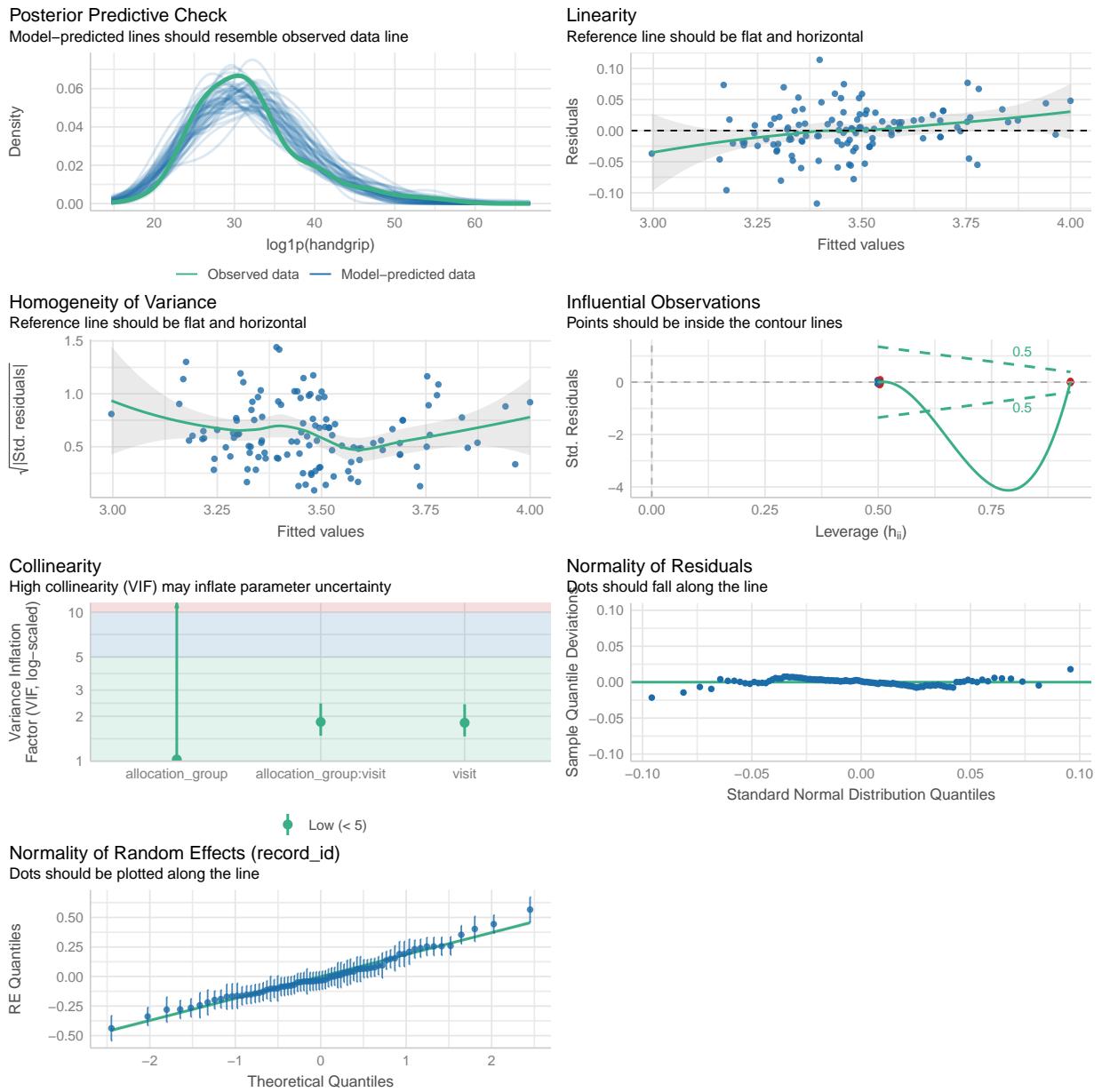
```

| | | | |
|---------------------|---------------|-------|-------------------------------|
| handgrip_model | 851.9 (<.001) | 0.846 | 0.069 0.835 0.069 0.102 |
| handgrip_model_sens | 706.1 (>.999) | 0.924 | 0.031 0.922 0.036 0.057 |

```
performance::check_model(handgrip_model)
```



```
performance::check_model(handgrip_model_sens)
```



4.4.2 Médias Marginais Estimadas

4.4.2.1 Todos os dados

```
# Get EMMs for each group at each visit
handgrip_raw_emm <- emmeans::emmeans(
  handgrip_model,
  ~ allocation_group * visit
)

handgrip_raw_emm <- regrid(handgrip_raw_emm)
```

```

# Table of marginal means
# handgrip_raw_emm

# Pairwise comparisons: Between groups at each visit
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))

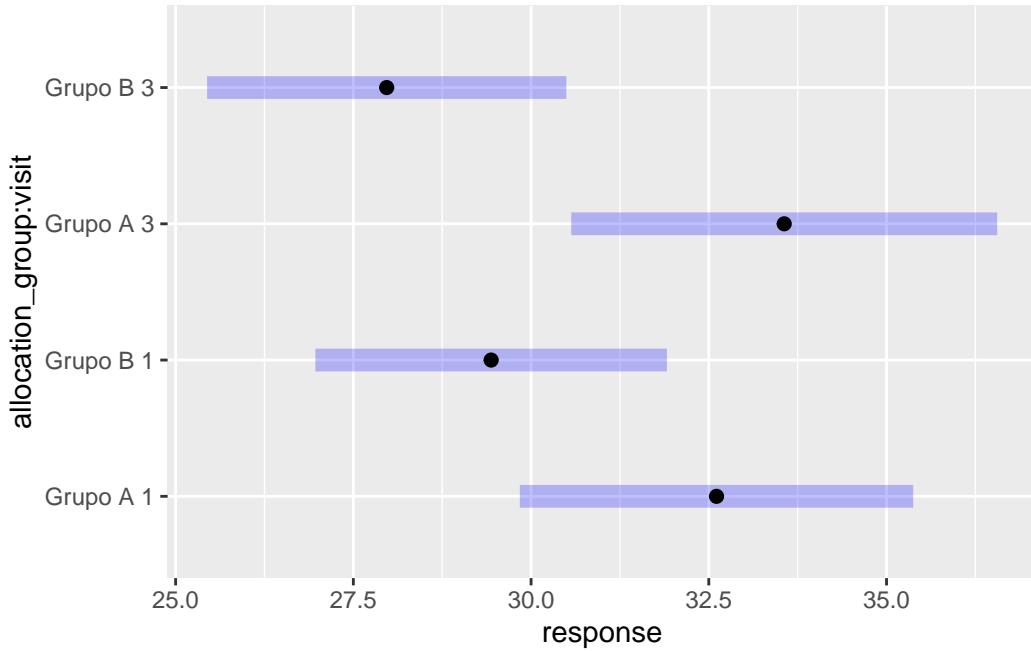
allocation_group = Grupo A:
contrast      estimate   SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit3   -0.952 0.943 81.9    -2.829     0.924   -1.009  0.3157

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)

```



4.4.2.2 Análise de sensibilidade

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

handgrip_emm <- regrid(handgrip_emm)

# Table of marginal means
# handgrip_emm

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

visit = 1:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
  Grupo A - Grupo B     2.02 1.55 71.7    -1.061     5.11   1.308  0.1951

visit = 3:
  contrast      estimate    SE   df lower.CL upper.CL t.ratio p.value
```

```
Grupo A - Grupo B      2.60 1.63 79.0   -0.644      5.84    1.595  0.1147
```

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

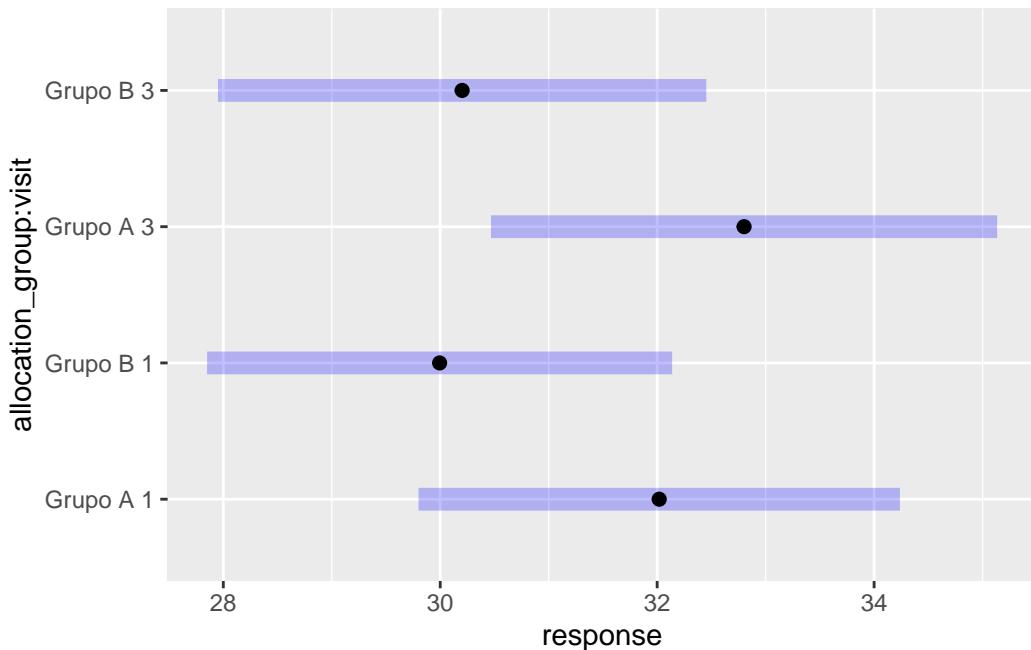
```
# Pairwise comparisons: Changes over time within each group
emmeans::contrast(handgrip_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))

allocation_group = Grupo A:
contrast      estimate     SE   df lower.CL upper.CL t.ratio p.value
visit1 - visit3 -0.782 0.523 71.7    -1.83    0.261 -1.495  0.1394

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

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

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



4.4.3 Resultado

No modelo ajustado para a força de preensão manual, observou-se uma diferença estatisticamente significativa entre os grupos na visita 3, com o grupo placebo apresentando força média 5,59 kgf superior ao grupo Eclipta (IC 95%: 1,67 a 9,51). Na visita 1, a diferença entre os grupos foi de 3,17 kgf (IC 95%: -0,54 a 6,88), sem alcançar significância estatística. Dentro de cada grupo, não foram observadas mudanças significativas ao longo do tempo.

Na análise de sensibilidade, os efeitos observados foram atenuados e perderam significância estatística. A diferença entre os grupos na visita 3 reduziu-se para 2,60 kgf (IC 95%: -0,64 a 5,84), e na visita 1 para 2,02 kgf (IC 95%: -1,06 a 5,11). Também não houve mudanças significativas entre as visitas dentro de cada grupo. Esses achados sugerem que os resultados observados no modelo completo podem ter sido influenciados por observações com alto impacto.

As estimativas, intervalos de confiança de 95% e valores de p estão apresentadas nas Tabelas [Tabela 29](#) e [Tabela 30](#).

Tabela 29: Diferenças estimadas da força de preensão manual entre os grupos de alocação (placebo vs Eclipta) e entre visitas dentro de cada grupo – Todos os dados

| Grupo de comparação | Comparação | Estimativa | IC 95% | p-valor |
|---------------------|---------------------|------------|----------------|---------|
| Entre grupos | Visita 1 | 3,17 | [-0,54 ; 6,88] | 0,093 |
| Entre grupos | Visita 3 | 5,59 | [1,67 ; 9,51] | 0,006 |
| Grupo Placebo | Visita 1 - Visita 3 | -0,95 | [-2,83 ; 0,92] | 0,316 |
| Grupo Eclipta | Visita 1 - Visita 3 | 1,47 | [-0,21 ; 3,15] | 0,085 |

Tabela 30: Diferenças estimadas da força de preensão manual entre os grupos de alocação (placebo vs Eclipta) e entre visitas dentro de cada grupo – Análise de sensibilidade

| Grupo de comparação | Comparação | Estimativa | IC 95% | p-valor |
|---------------------|---------------------|------------|----------------|---------|
| Entre grupos | Visita 1 | 2,02 | [-1,06 ; 5,11] | 0,195 |
| Entre grupos | Visita 3 | 2,60 | [-0,64 ; 5,84] | 0,115 |
| Grupo Placebo | Visita 1 - Visita 3 | -0,78 | [-1,83 ; 0,26] | 0,139 |
| Grupo Eclipta | Visita 1 - Visita 3 | -0,21 | [-1,28 ; 0,87] | 0,702 |

```
ggplot(
  data = data_model_V1V3,
  aes(
    x = as.factor(visit),
    y = handgrip,
    group = record_id,
  )
```

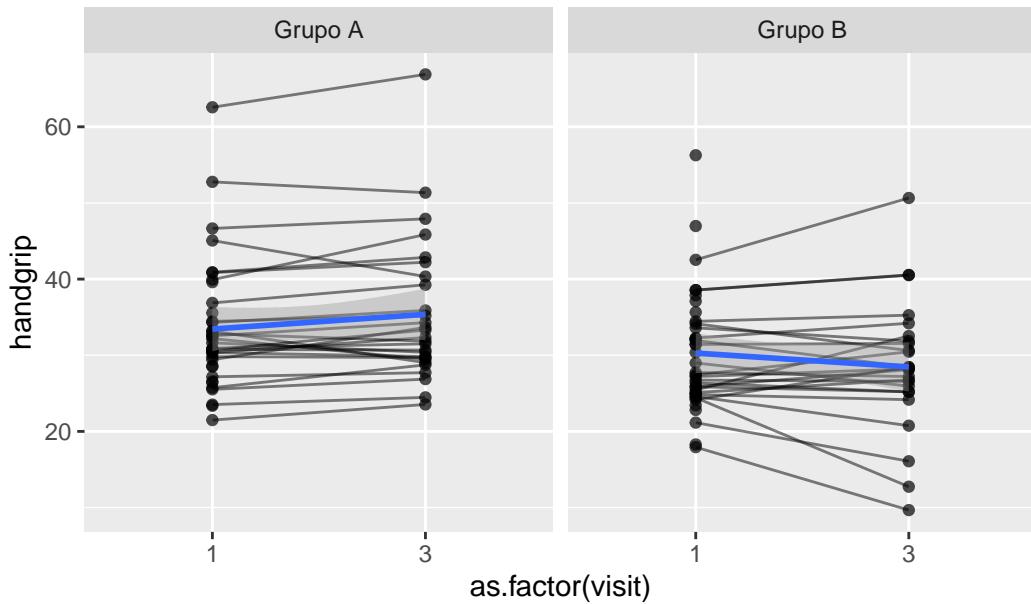
```

) +
  geom_line(alpha = 0.5) +
  geom_point(alpha = 0.7) +
  geom_smooth(
    aes(group = allocation_group),
    method = "lm",
    se = TRUE,
    linewidth = 1
  ) +
  labs(title = "All data") +
  facet_wrap(~ allocation_group)

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

```

All data



```

data_model_V1V3 %>%
  filter(
    !(record_id %in%
      handgrip_model_check$influential_ids)
  ) %>%

```

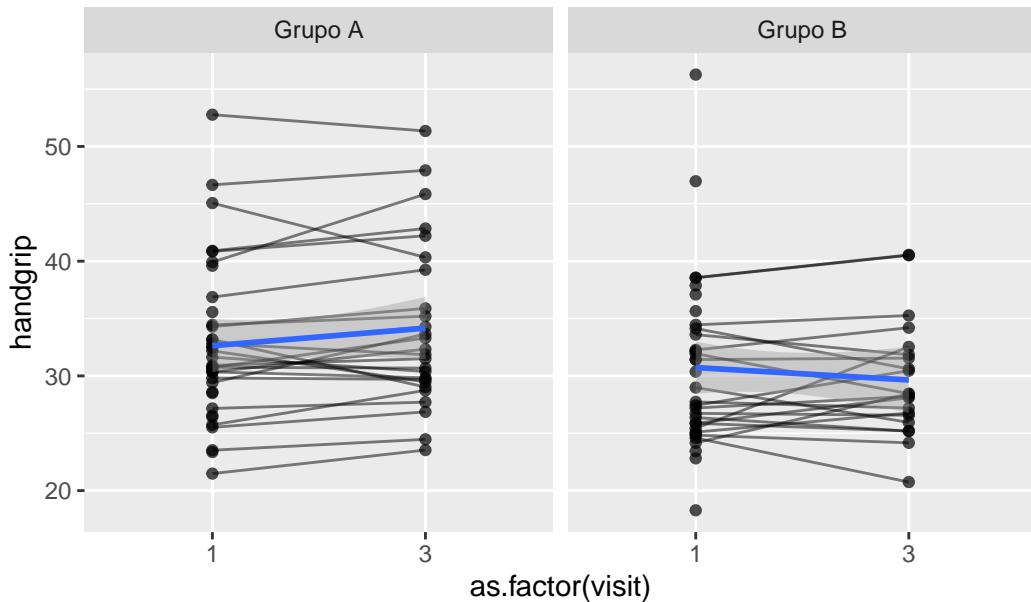
```

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

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

```

Sensitivity analysis



5 Informações da Sessão

```
sessionInfo()
```

```
R version 4.4.1 (2024-06-14)
Platform: aarch64-apple-darwin20
Running under: macOS 15.5

Matrix products: default
BLAS:      /Library/Frameworks/R.framework/Versions/4.4-arm64/Resources/lib/libRblas.0.dylib
LAPACK:    /Library/Frameworks/R.framework/Versions/4.4-arm64/Resources/lib/libRlapack.dylib;  LAPACK ve

locale:
[1] en_US.UTF-8/en_US.UTF-8/en_US.UTF-8/C/en_US.UTF-8/en_US.UTF-8

time zone: America/Sao_Paulo
tzcode source: internal

attached base packages:
[1] stats      graphics   grDevices  utils      datasets   methods    base

other attached packages:
[1] broom.mixed_0.2.9.6 influence.ME_0.9-9  kableExtra_1.4.0.12
```

```

[4] knitr_1.50           emmeans_1.11.1      patchwork_1.3.0
[7] gt_1.0.0             performance_0.13.0  skimr_2.1.5
[10] lmerTest_3.1-3     lme4_1.1-37       Matrix_1.7-0
[13] here_1.0.1          readxl_1.4.3       lubridate_1.9.4
[16]forcats_1.0.0       stringr_1.5.1      dplyr_1.1.4.9000
[19] purrr_1.0.4         readr_2.1.5       tidyverse_2.0.0
[22] tibble_3.2.1        ggplot2_3.5.1      tidyverse_2.0.0

```

loaded via a namespace (and not attached):

```

[1] tidyselect_1.2.1    viridisLite_0.4.2   farver_2.1.2
[4] fastmap_1.2.0      TH.data_1.1-3       bayestestR_0.15.3
[7] digest_0.6.37      timechange_0.3.0   estimability_1.5.1
[10] lifecycle_1.0.4    survival_3.7-0    magrittr_2.0.3
[13] compiler_4.4.1     rlang_1.1.6       tools_4.4.1
[16] yaml_2.3.10       labeling_0.4.3   xml2_1.3.8
[19] repr_1.1.7         multcomp_1.4-28  withr_3.0.2
[22] numDeriv_2016.8-1.1 datawizard_1.1.0  grid_4.4.1
[25] future_1.34.0      xtable_1.8-4     colorspace_2.1-1
[28] globals_0.16.3     scales_1.3.0     MASS_7.3-61
[31] insight_1.2.0      cli_3.6.5       mvtnorm_1.3-3
[34] rmarkdown_2.29      reformulas_0.4.1  generics_0.1.3
[37] rstudioapi_0.17.1  tzdb_0.4.0      minqa_1.2.8
[40] splines_4.4.1      parallel_4.4.1   cellranger_1.1.0
[43] base64enc_0.1-3    vctrs_0.6.5     boot_1.3-31
[46] sandwich_3.1-1     jsonlite_2.0.0   hms_1.1.3
[49] pbkrtest_0.5.4     ggrepel_0.9.6   listenv_0.9.1
[52] systemfonts_1.2.3  see_0.11.0     parallely_1.44.0
[55] glue_1.8.0          nloptr_2.2.1   codetools_0.2-20
[58] stringi_1.8.7      gtable_0.3.6   munsell_0.5.1
[61] furrr_0.3.1        pillar_1.10.2  htmltools_0.5.8.1
[64] R6_2.6.1            textshaping_0.4.0 Rdpack_2.6.4
[67] rprojroot_2.0.4    evaluate_1.0.3   lattice_0.22-6
[70] backports_1.5.0    rbibutils_2.3   broom_1.0.7
[73] Rcpp_1.0.14          svglite_2.2.1  coda_0.19-4.1
[76] nlme_3.1-166        mgcv_1.9-1     xfun_0.52
[79] zoo_1.8-14          pkgconfig_2.0.3

```