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: questionários

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2025-06-12

Índice

```
library(tidyverse)
library(readxl)
library(lubridate)
library(lme4)
library(lmerTest)
library(skimr)
library(performance)
library(gt)
library(patchwork)
library(emmeans)
library(knitr)
library(kableExtra)

data <- readRDS("local_files/Data_processed/data.rds")
data_model <- readRDS("local_files/Data_processed/data_model.rds") %>%
    mutate(
        visit = as.factor(visit),
        record_id = as.factor(record_id)
    )
data_model_V1V3 <- data_model %>%
    filter(!visit == "2")
```

```
sensitivity_check_lmer <- function(model, id_var = "record_id", top_n = 5) {
    require(influence.ME)
    require(dplyr)
    require(lme4)
    require(broom.mixed)

    # Compute influence measures
    infl <- influence(model, group = id_var)
    cooks <- cooks.distance(infl)

    # Extract IDs safely
    id_list <- rownames(as.data.frame(cooks))

    if (length(id_list) != length(cooks)) {
        stop("Mismatch between ID list and Cook's distances. Check grouping variable.")
    }
```

```r
# Build dataframe
cooks_df <- tibble::tibble(
    record_id = id_list,
    cooks_distance = as.numeric(cooks)
)

# Rule-based threshold (4/n rule)
influential_ids_rule <- cooks_df %>%
    filter(cooks_distance > (4 / nrow(cooks_df))) %>%
    pull(record_id)

# Top N most influential
top_ids <- cooks_df %>%
    arrange(desc(cooks_distance)) %>%
    slice_head(n = top_n) %>%
    pull(record_id)

# Combine unique IDs
influential_ids <- unique(c(influential_ids_rule, top_ids))

# Refit model excluding influential IDs
model_sens <- update(
    model,
    subset = !(get(id_var) %in% influential_ids)
)

# Compare fixed effects
comparison <- bind_rows(
    broom.mixed::tidy(model) %>% mutate(Model = "Original"),
    broom.mixed::tidy(model_sens) %>% mutate(Model = "Sensitivity")
) %>%
    select(Model, term, estimate, std.error, statistic, p.value) %>%
    arrange(term, Model)

# Output
list(
    cooks_table = cooks_df,
        influential_ids = influential_ids,
        model_original = model,
        model_sensitivity = model_sens,
        comparison_table = comparison
    )
}
```

1 WHOQOL

```
whoqol <- data %>%
    select(record_id, event_name,
           whoqol_timestamp:whoqol_26_negativity) %>%
    filter(
        !is.na(whoqol_timestamp)
    ) %>%
    mutate(
        visit = case_when(
            event_name == "1visit_arm_1" ~ 1L,
            event_name == "3visit_arm_1" ~ 2L,
            TRUE ~ NA_integer_
        ),
        visit = as.factor(visit),
        record_id = as.factor(record_id)
    )

names(whoqol)
```

```
 [1] "record_id"                 "event_name"
 [3] "whoqol_timestamp"          "whoqol_1_quality"
 [5] "whoqol_2_health"           "whoqol_3_pain"
 [7] "whoqol_4_treatment"        "whoqol_5_enjoyment"
 [9] "whoqol_6_meaning"          "whoqol_7_concentration"
[11] "whoqol_8_security"         "whoqol_9_environment"
[13] "whoqol_10_energy"          "whoqol_11_appearance"
[15] "whoqol_12_finances"        "whoqol_13_information"
[17] "whoqol_14_leisure"         "whoqol_15_mobility"
[19] "whoqol_16_sleep"           "whoqol_17_activities"
[21] "whoqol_18_work"            "whoqol_19_selfesteem"
```

```
[23] "whoqol_20_relationships"   "whoqol_21_sexual"
[25] "whoqol_22_support"         "whoqol_23_housing"
[27] "whoqol_24_health_services" "whoqol_25_transport"
[29] "whoqol_26_negativity"      "visit"
```

```r
# Reverse-score the 3 negatively phrased items: Q3, Q4, Q26
whoqol$whoqol_3_pain       <- 6 - whoqol$whoqol_3_pain       # Q3
whoqol$whoqol_4_treatment  <- 6 - whoqol$whoqol_4_treatment  # Q4
whoqol$whoqol_26_negativity <- 6 - whoqol$whoqol_26_negativity # Q26
```

```r
# Helper function: compute row mean only if at least N non-NA values
mean_if_enough <- function(x, min_valid) {
  if (sum(!is.na(x)) >= min_valid) {
    return(mean(x, na.rm = TRUE))
  } else {
    return(NA_real_)
  }
}
```

```r
# Physical domain: require at least 6 of 7
whoqol$score_physical <- apply(whoqol[, c(
  "whoqol_3_pain", "whoqol_4_treatment", "whoqol_10_energy",
  "whoqol_15_mobility", "whoqol_16_sleep", "whoqol_17_activities",
  "whoqol_18_work"
)], 1, mean_if_enough, min_valid = 6) * 4

# Psychological domain: require at least 5 of 6
whoqol$score_psychological <- apply(whoqol[, c(
  "whoqol_5_enjoyment", "whoqol_6_meaning", "whoqol_7_concentration",
  "whoqol_11_appearance", "whoqol_19_selfesteem", "whoqol_26_negativity"
)], 1, mean_if_enough, min_valid = 5) * 4

# Social domain: require at least 2 of 3
whoqol$score_social <- apply(whoqol[, c(
  "whoqol_20_relationships", "whoqol_21_sexual", "whoqol_22_support"
)], 1, mean_if_enough, min_valid = 2) * 4

# Environment domain: require at least 6 of 8
whoqol$score_environment <- apply(whoqol[, c(
  "whoqol_8_security", "whoqol_9_environment", "whoqol_12_finances",
  "whoqol_13_information", "whoqol_14_leisure", "whoqol_23_housing",
  "whoqol_24_health_services", "whoqol_25_transport"
)], 1, mean_if_enough, min_valid = 6) * 4
```

```
whoqol$score_physical      <- (whoqol$score_physical - 4) * (100 / 16)
whoqol$score_psychological <- (whoqol$score_psychological - 4) * (100 / 16)
whoqol$score_social        <- (whoqol$score_social - 4) * (100 / 16)
whoqol$score_environment   <- (whoqol$score_environment - 4) * (100 / 16)
```

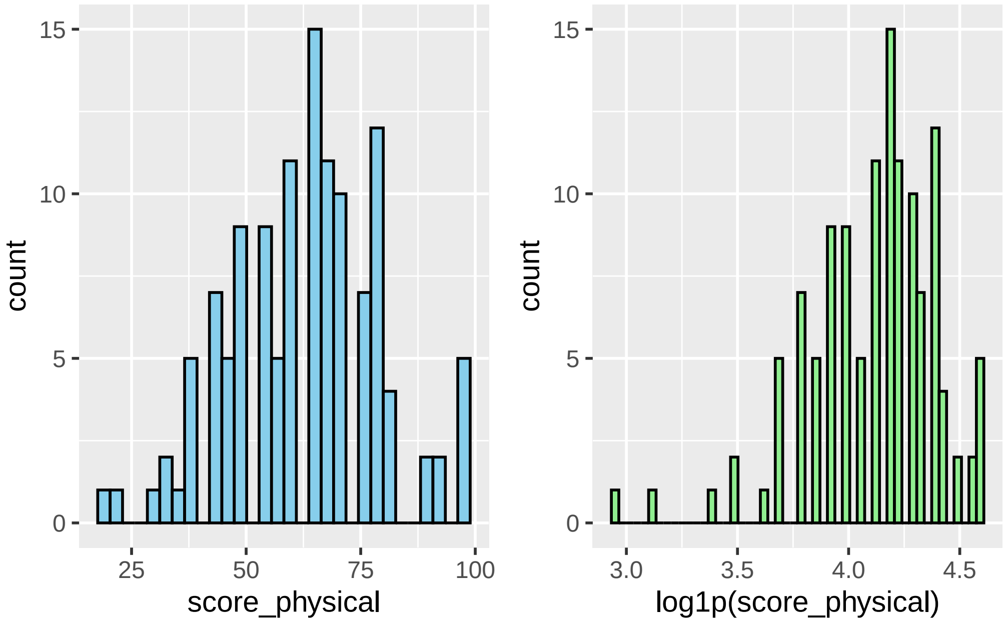
```
data_model_V1V3 <- data_model %>%
    left_join(
        whoqol %>%
            select(record_id, visit,
                   score_physical, score_psychological,
                   score_social, score_environment),
        by = c("record_id", "visit")
    )
```

1.1 Domínio Físico

Variável: `score_physical`

```
# Plot 1: Raw data
score_physical_hist_1 <- data_model_V1V3 %>%
    #filter(
    #    score_physical < 300
    #) %>%
    ggplot(aes(x = score_physical)) +
    geom_histogram(bins = 30, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
score_physical_hist_2 <- data_model_V1V3 %>%
    #filter(
    #    score_physical < 300
    #) %>%
    ggplot(aes(x = log1p(score_physical))) +
    geom_histogram(bins = 50, fill = "lightgreen", color = "black")

# Combine side by side
score_physical_hist_1 + score_physical_hist_2 # library(patchwork)
```

```
Warning: Removed 64 rows containing non-finite outside the scale range (`stat_bin()`).
Removed 64 rows containing non-finite outside the scale range (`stat_bin()`).
```



```
# LMM
score_physical_model <- lmer(score_physical ~ allocation_group * visit +
(1 | record_id), data = data_model_V1V3)
check_collinearity(score_physical_model)
```

```
# Check for Multicollinearity

Low Correlation

                   Term  VIF   VIF 95% CI Increased SE Tolerance
       allocation_group 1.23 [1.08, 1.66]         1.11      0.81
                  visit 1.94 [1.57, 2.57]         1.39      0.51
 allocation_group:visit 2.16 [1.72, 2.86]         1.47      0.46
 Tolerance 95% CI
     [0.60, 0.93]
     [0.39, 0.64]
     [0.35, 0.58]
```

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

```
# LMM Sensitivity
score_physical_model_sens <- update(object = score_physical_model,
                              subset = !(record_id %in%
        score_physical_model_check$influential_ids))
# Influential IDS
score_physical_model_check$influential_ids
```

```
[1] "1"  "15" "31" "52" "55"
```

1.1.0.1 Resumo dos modelos

```
summary(score_physical_model)
```

```
Linear mixed model fit by REML. t-tests use Satterthwaite's method [
lmerModLmerTest]
Formula: score_physical ~ allocation_group * visit + (1 | record_id)
   Data: data_model_V1V3

REML criterion at convergence: 1002.4

Scaled residuals:
     Min       1Q   Median       3Q      Max 
-2.48070 -0.49060  0.07219  0.49257  2.24373 

Random effects:
 Groups    Name        Variance Std.Dev.
 record_id (Intercept) 123.7    11.12   
 Residual              111.7    10.57   
Number of obs: 125, groups:  record_id, 75

Fixed effects:
                               Estimate Std. Error      df t value Pr(>|t|)    
(Intercept)                      62.114      2.548 101.808  24.379  < 2e-16 ***
allocation_groupGrupo B          -4.921      3.579 101.784  -1.375  0.17218    
visit2                            8.941      2.816  55.939   3.176  0.00243 ** 
allocation_groupGrupo B:visit2   -4.680      4.042  56.994  -1.158  0.25169    
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
Correlation of Fixed Effects:
            (Intr) all_GB visit2
allctn_grGB -0.712              
visit2      -0.442  0.315       
allctn_GB:2  0.308 -0.433 -0.697
```

```r
summary(score_physical_model_sens)
```

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

REML criterion at convergence: 894.7

Scaled residuals: 
     Min       1Q   Median       3Q      Max 
-1.54260 -0.53246 -0.03013  0.50900  1.68219 

Random effects:
 Groups    Name        Variance Std.Dev.
 record_id (Intercept) 103.69   10.183  
 Residual               75.85    8.709  
Number of obs: 116, groups:  record_id, 70

Fixed effects:
                               Estimate Std. Error     df t value Pr(>|t|)    
(Intercept)                      61.239      2.254 91.906  27.163  < 2e-16 ***
allocation_groupGrupo B          -3.843      3.236 91.954  -1.187    0.238    
visit2                           10.258      2.374 51.290   4.321 7.13e-05 ***
allocation_groupGrupo B:visit2   -3.586      3.493 52.314  -1.027    0.309    
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
            (Intr) all_GB visit2
allctn_grGB -0.697              
visit2      -0.415  0.289       
```

```
allctn_GB:2  0.282 -0.407 -0.680
```

```r
score_physical_model_check$comparison_table
```

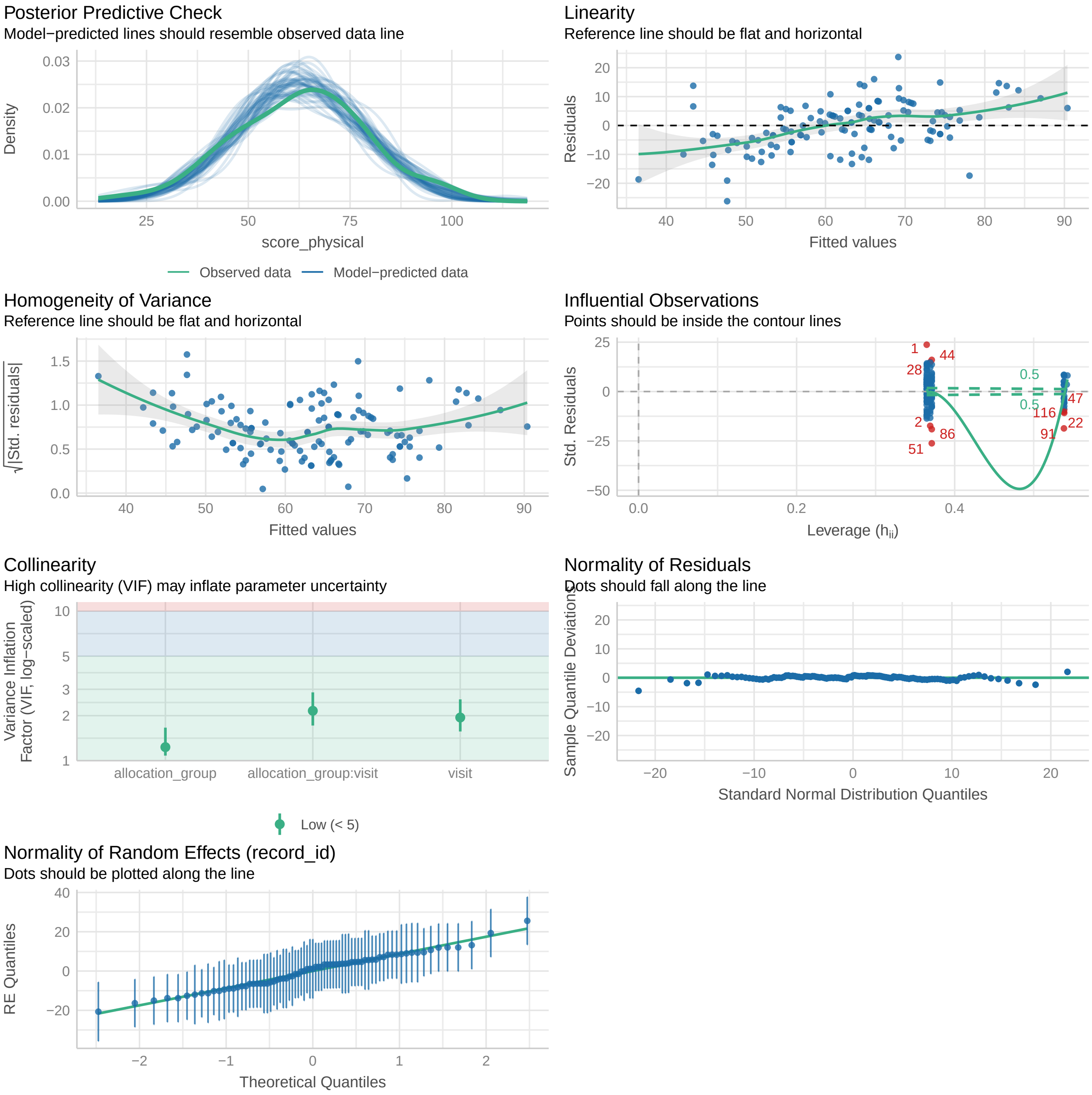
```
# A tibble: 12 x 6
   Model       term                        estimate std.error statistic   p.value
   <chr>       <chr>                          <dbl>     <dbl>     <dbl>     <dbl>
 1 Original    (Intercept)                    62.1       2.55     24.4   2.70e-44
 2 Sensitivity (Intercept)                    61.2       2.25     27.2   1.07e-45
 3 Original    allocation_groupGrupo B        -4.92      3.58     -1.37  1.72e- 1
 4 Sensitivity allocation_groupGrupo B        -3.84      3.24     -1.19  2.38e- 1
 5 Original    allocation_groupGrupo B:v~     -4.68      4.04     -1.16  2.52e- 1
 6 Sensitivity allocation_groupGrupo B:v~     -3.59      3.49     -1.03  3.09e- 1
 7 Original    sd__(Intercept)                11.1      NA        NA    NA
 8 Sensitivity sd__(Intercept)                10.2      NA        NA    NA
 9 Original    sd__Observation                10.6      NA        NA    NA
10 Sensitivity sd__Observation                 8.71     NA        NA    NA
11 Original    visit2                          8.94      2.82      3.18  2.43e- 3
12 Sensitivity visit2                         10.3       2.37      4.32  7.13e- 5
```

```r
performance::compare_performance(
    score_physical_model,
    score_physical_model_sens)
```

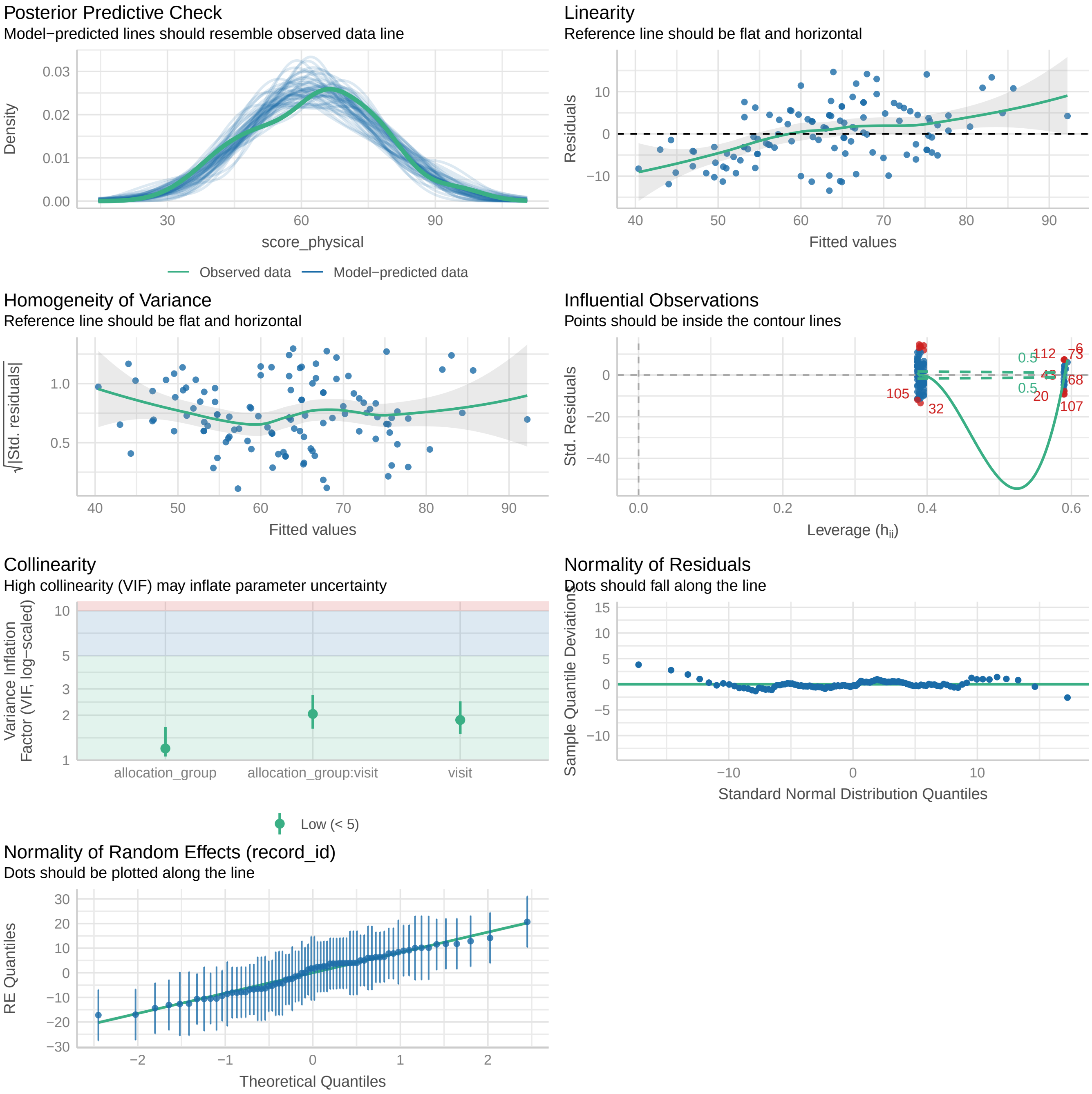
```
When comparing models, please note that probably not all models were fit
  from same data.
# Comparison of Model Performance Indices

Name                      |           Model |  AIC (weights) | AICc (weights)
-----------------------------------------------------------------------------
score_physical_model      | lmerModLmerTest | 1029.2 (<.001) | 1029.9 (<.001)
score_physical_model_sens | lmerModLmerTest |  920.5 (>.999) |  921.3 (>.999)

Name                      |  BIC (weights) | R2 (cond.) | R2 (marg.) |   ICC
----------------------------------------------------------------------------
score_physical_model      | 1046.2 (<.001) |      0.570 |      0.095 | 0.526
score_physical_model_sens |  937.1 (>.999) |      0.632 |      0.129 | 0.578

Name                      |  RMSE |  Sigma
------------------------------------------
score_physical_model      | 8.176 | 10.569
```

```
score_physical_model_sens | 6.566 |  8.709
```

```
performance::check_model(score_physical_model)
```



```
performance::check_model(score_physical_model_sens)
```



1.1.0.2 Médias Marginais Estimadas

1.1.0.2.1 Todos os dados

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

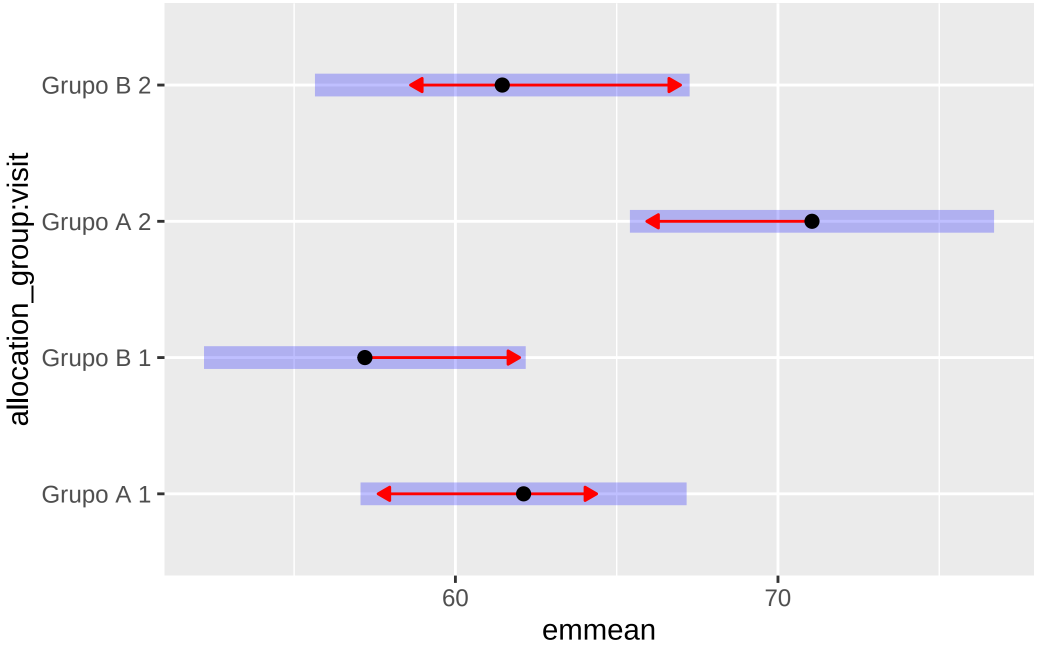
```r
score_physical_raw_emm <- regrid(score_physical_raw_emm)

# Table of marginal means
# score_physical_raw_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(score_physical_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     4.92 3.58 102    -2.18     12.0   1.375  0.1723

visit = 2:
 contrast          estimate   SE  df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B     9.60 4.09 116     1.50     17.7   2.348  0.0206

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

```r
# Pairwise comparisons: Changes over time within each group
emmeans::contrast(score_physical_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    -8.94 2.83 102    -14.5    -3.34  -3.164  0.0021

allocation_group = Grupo B:
 contrast        estimate   SE  df lower.CL upper.CL t.ratio p.value
 visit1 - visit2    -4.26 2.91 102    -10.0     1.52  -1.463  0.1466

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

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



1.1.0.2.2 Análise de sensibilidade

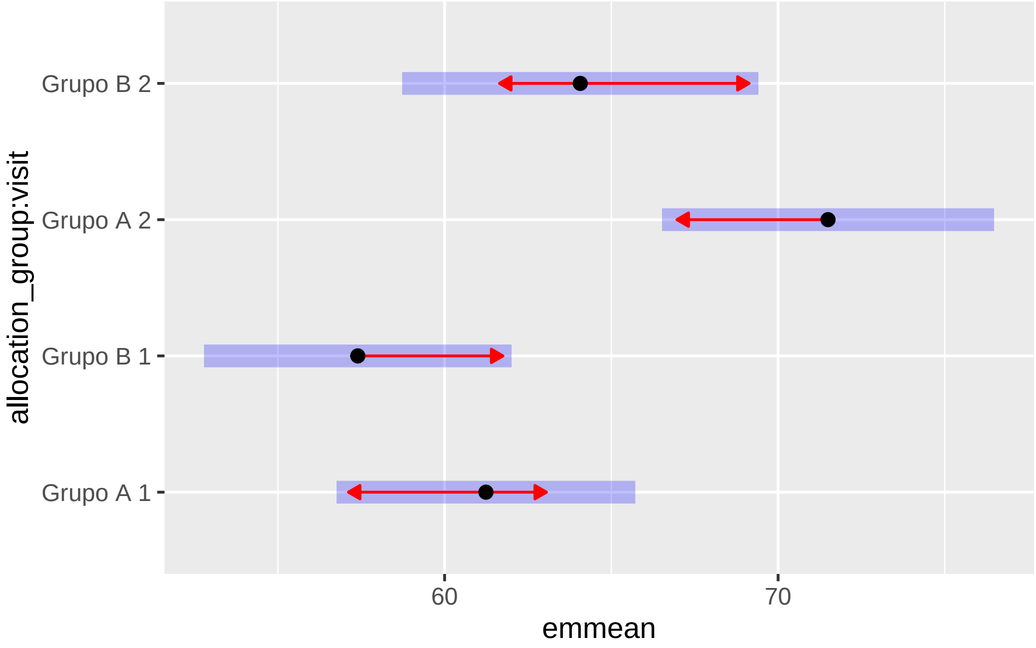
```
# Get EMMs for each group at each visit (Sensitivity Analysis)
score_physical_emm <- emmeans::emmeans(
    score_physical_model_sens,
    ~ allocation_group * visit
)

score_physical_emm <- regrid(score_physical_emm)

# Table of marginal means
# score_physical_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(score_physical_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      3.84 3.24 91.6   -2.586     10.3   1.187  0.2382

visit = 2:
 contrast           estimate   SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B     7.43 3.68 106.0    0.124     14.7   2.016  0.0463

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(score_physical_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   -10.26 2.38 91.6    -15.0    -5.53  -4.305  <.0001

allocation_group = Grupo B:
 contrast        estimate   SE   df lower.CL upper.CL t.ratio p.value
 visit1 - visit2    -6.67 2.58 91.7    -11.8    -1.56  -2.591  0.0111

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

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



1.1.0.3 Resultado

No modelo ajustado para o domínio físico do WHOQOL-BREF, não houve diferença significativa entre os grupos na visita 1 (estimativa = 4,92; IC 95%: –2,18 a 12,0). Na visita 2, o grupo placebo apresentou escores físicos em média 9,60 pontos superiores aos do grupo Eclipta (IC 95%: 1,50 a 17,7). Ao longo do tempo, o grupo placebo mostrou melhora significativa entre as visitas 1 e 2 (aumento médio de 8,94; IC 95%: 3,34 a 14,5), enquanto no grupo Eclipta essa mudança não foi significativa (aumento de 4,26; IC 95%: –1,52 a 10,0).

Em análise de sensibilidade, o achado entre grupos na visita 2 permaneceu (estimativa = 7,43; IC 95%: 0,12 a 14,7). Além disso, ambos os grupos exibiram melhora significativa ao longo do tempo: placebo (aumento médio de 10,26; IC 95%: 5,53 a 15,0) e Eclipta (aumento médio de 6,67; IC 95%: 1,56 a 11,8).

Tabela: Diferenças estimadas do escore físico do WHOQOL-BREF entre grupos (placebo vs Eclipta) e entre visitas dentro de cada grupo – Todos os dados {#tbl-score_physical}

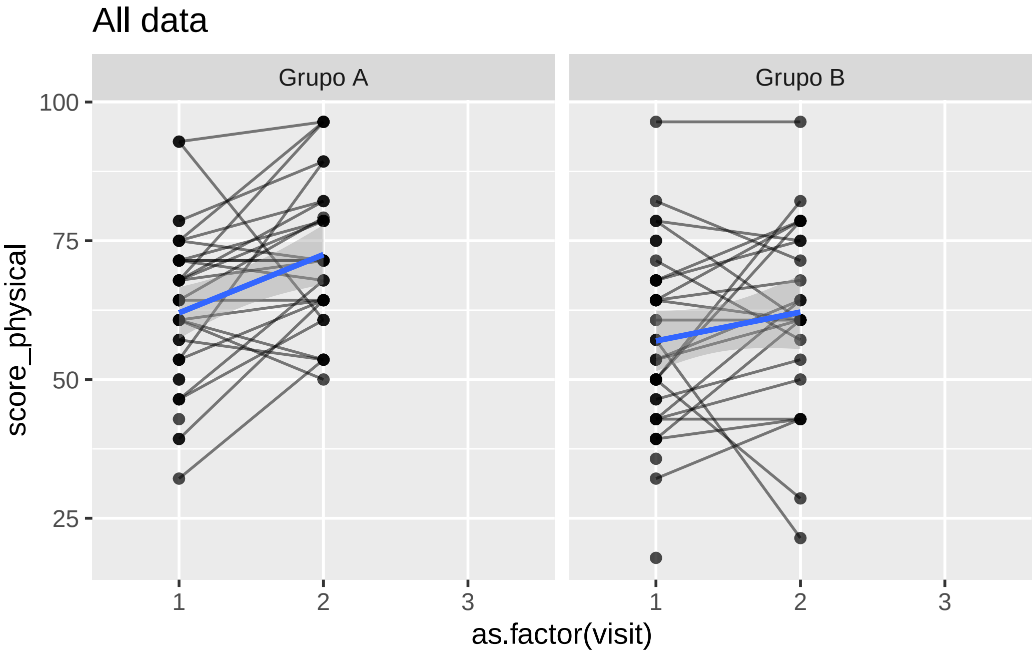
Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 1	4,92	[–2,18; 12,0]	0,172
Entre grupos	Visita 2	9,60	[1,50; 17,7]	0,021
Grupo Placebo	Visita 1 – Visita 2	–8,94	[–14,5; –3,34]	0,002
Grupo Eclipta	Visita 1 – Visita 2	–4,26	[–10,0; 1,52]	0,147

Tabela: Diferenças estimadas do escore físico do WHOQOL-BREF entre grupos (placebo vs Eclipta) e entre visitas dentro de cada grupo – Análise de sensibilidade {#tbl-score_phys_sens}

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 1	3,84	[–2,59; 10,3]	0,238
Entre grupos	Visita 2	7,43	[0,12; 14,7]	0,046
Grupo Placebo	Visita 1 – Visita 2	–10,26	[–15,0; –5,53]	< 0,001
Grupo Eclipta	Visita 1 – Visita 2	–6,67	[–11,8; –1,56]	0,011

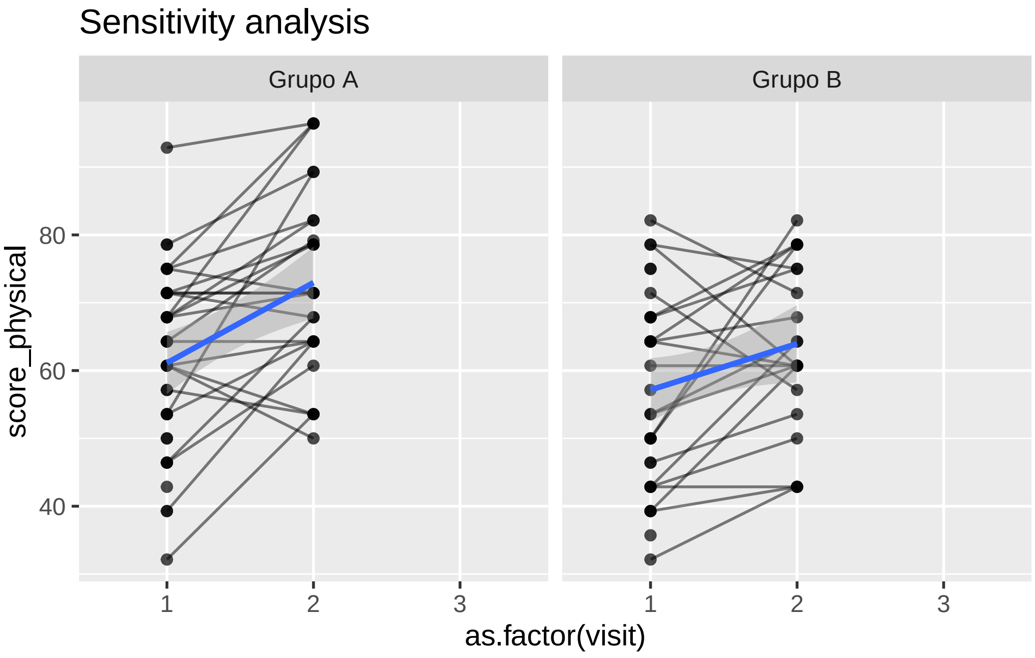
```r
ggplot(
    data = data_model_V1V3,
    aes(
        x = as.factor(visit),
        y = score_physical,
        group = record_id,
    )
) +
    geom_line(alpha = 0.5) +
    geom_point(alpha = 0.7) +
    geom_smooth(
        aes(group = allocation_group),
        method = "lm",
        se = TRUE,
        linewidth = 1
    ) +
    labs(title = "All data") +
    facet_wrap(~ allocation_group)
```

```
`geom_smooth()` using formula = 'y ~ x'
Warning: Removed 64 rows containing non-finite outside the scale range
(`stat_smooth()`).
Warning: Removed 64 rows containing missing values or values outside the scale range
(`geom_line()`).
Warning: Removed 64 rows containing missing values or values outside the scale range
(`geom_point()`).
```



```
data_model_V1V3 %>%
    filter(
        !(record_id %in%
        score_physical_model_check$influential_ids)
    ) %>%
    ggplot(
        aes(
            x = as.factor(visit),
            y = score_physical,
            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 60 rows containing non-finite outside the scale range
(`stat_smooth()`).
Warning: Removed 60 rows containing missing values or values outside the scale range
(`geom_line()`).
Warning: Removed 60 rows containing missing values or values outside the scale range
(`geom_point()`).
```

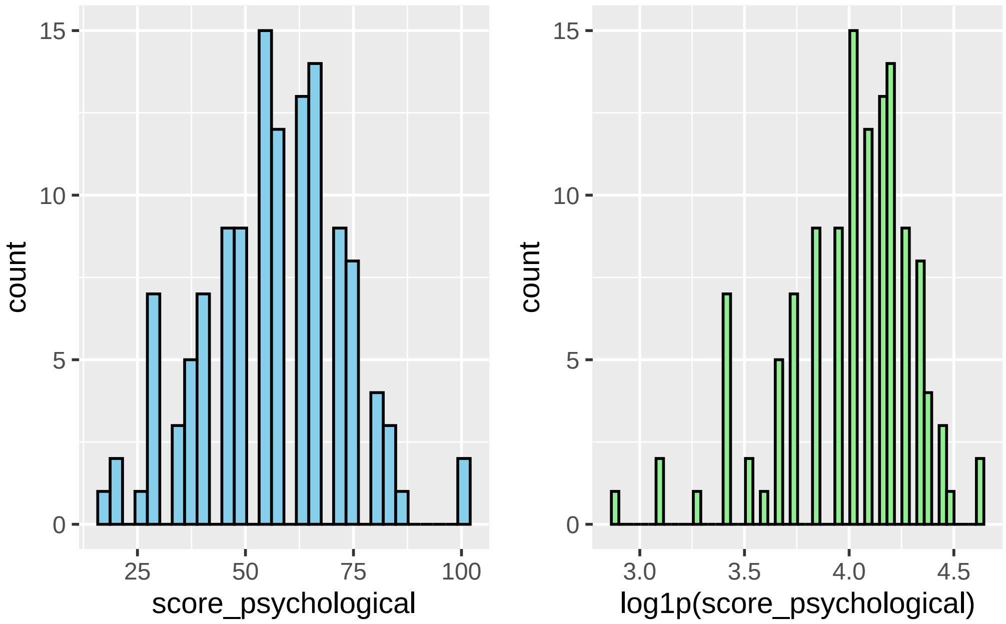


1.2 Domínio Psicológico

Variável: `score_psychological`

```
# Plot 1: Raw data
score_psychological_hist_1 <- data_model_V1V3 %>%
    #filter(
    #    score_psychological < 300
    #) %>%
    ggplot(aes(x = score_psychological)) +
    geom_histogram(bins = 30, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
score_psychological_hist_2 <- data_model_V1V3 %>%
    #filter(
    #    score_psychological < 300
    #) %>%
    ggplot(aes(x = log1p(score_psychological))) +
    geom_histogram(bins = 50, fill = "lightgreen", color = "black")

# Combine side by side
score_psychological_hist_1 + score_psychological_hist_2 # library(patchwork)
```

```
Warning: Removed 64 rows containing non-finite outside the scale range (`stat_bin()`).
Removed 64 rows containing non-finite outside the scale range (`stat_bin()`).
```



```
# LMM
score_psychological_model <- lmer(score_psychological ~ allocation_group * visit +
(1 | record_id), data = data_model_V1V3)
```

```
check_collinearity(score_psychological_model)
```

```
# Check for Multicollinearity

Low Correlation

                   Term  VIF   VIF 95% CI Increased SE Tolerance
       allocation_group 1.17 [1.05, 1.63]         1.08      0.86
                  visit 1.94 [1.56, 2.56]         1.39      0.52
 allocation_group:visit 2.09 [1.67, 2.77]         1.45      0.48
 Tolerance 95% CI
     [0.61, 0.96]
     [0.39, 0.64]
     [0.36, 0.60]
```

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

# LMM Sensitivity
score_psychological_model_sens <- update(object = score_psychological_model,
                              subset = !(record_id %in%
        score_psychological_model_check$influential_ids))
# Influential IDS
score_psychological_model_check$influential_ids
```

```
[1] "1"  "9"  "52" "69" "53"
```

1.2.0.1 Resumo dos modelos

```
summary(score_psychological_model)
```

```
Linear mixed model fit by REML. t-tests use Satterthwaite's method [
lmerModLmerTest]
Formula: score_psychological ~ allocation_group * visit + (1 | record_id)
   Data: data_model_V1V3

REML criterion at convergence: 989.4

Scaled residuals:
     Min       1Q   Median       3Q      Max
-2.37743 -0.45545  0.08376  0.45603  2.25720

Random effects:
 Groups    Name        Variance Std.Dev.
 record_id (Intercept) 144.42   12.017
 Residual               83.59    9.143
Number of obs: 125, groups:  record_id, 75

Fixed effects:
                               Estimate Std. Error     df t value Pr(>|t|)
(Intercept)                      51.056      2.503 94.733  20.397  < 2e-16 ***
allocation_groupGrupo B           1.473      3.516 94.709   0.419    0.676
visit2                           12.390      2.458 53.468   5.040 5.66e-06 ***
allocation_groupGrupo B:visit2   -4.341      3.533 54.284  -1.229    0.225
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
            (Intr) all_GB visit2
allctn_grGB -0.712
visit2      -0.388  0.276
allctn_GB:2  0.270 -0.380 -0.696
```

```
summary(score_psychological_model_sens)
```

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

REML criterion at convergence: 875.4

Scaled residuals:
    Min      1Q  Median      3Q     Max
-1.7072 -0.4831  0.1226  0.5263  1.6771

Random effects:
 Groups    Name        Variance Std.Dev.
 record_id (Intercept) 118.46   10.884
 Residual               56.61    7.524
Number of obs: 115, groups:  record_id, 70

Fixed effects:
                               Estimate Std. Error     df t value Pr(>|t|)
(Intercept)                      50.309      2.323 83.395  21.658  < 2e-16 ***
allocation_groupGrupo B           2.405      3.194 83.299   0.753    0.453
visit2                           12.076      2.198 45.501   5.493  1.7e-06 ***
allocation_groupGrupo B:visit2   -2.714      3.069 45.874  -0.884    0.381
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
            (Intr) all_GB visit2
allctn_grGB -0.727
visit2      -0.359  0.261
allctn_GB:2  0.257 -0.353 -0.716
```

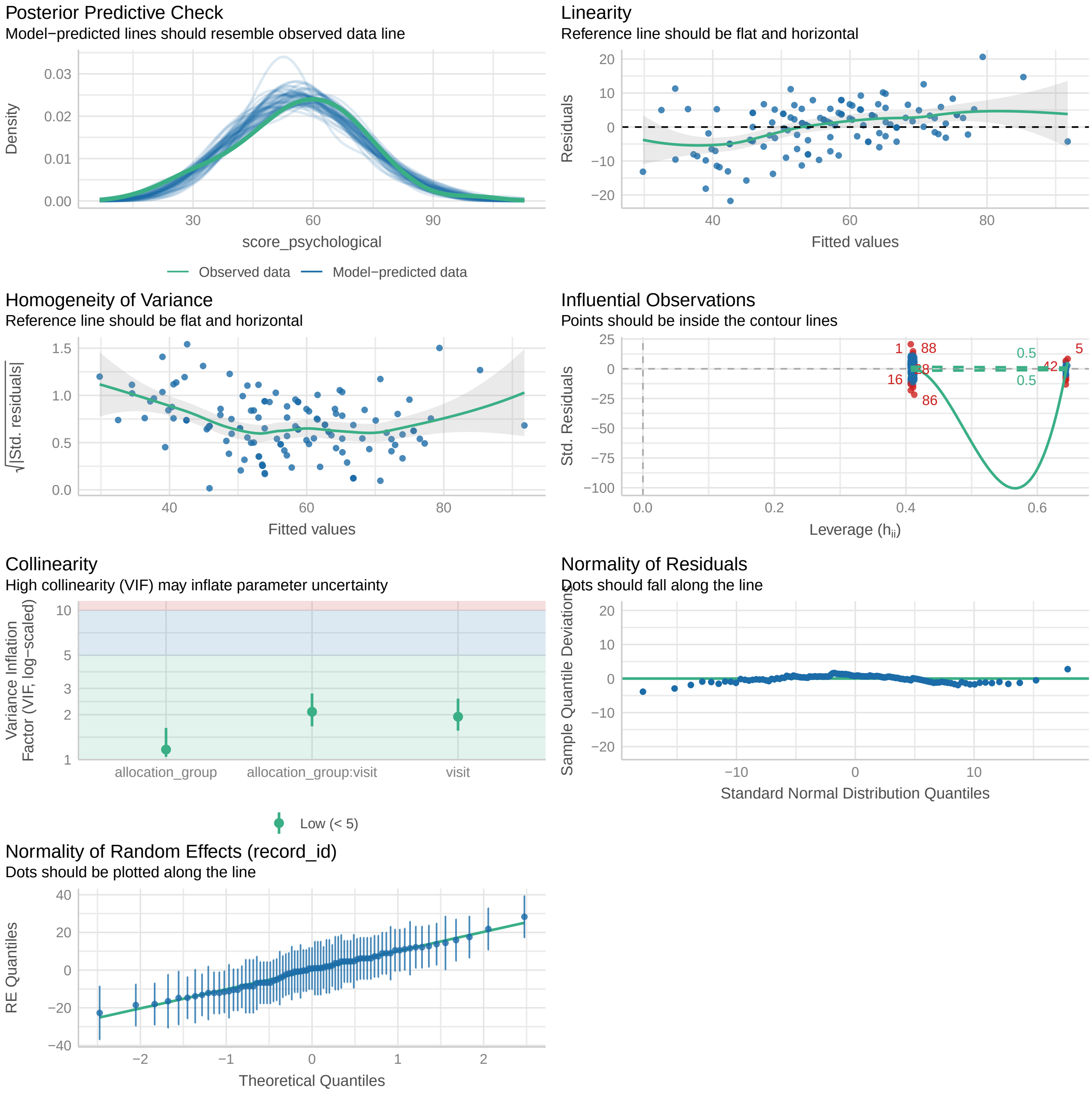
```
score_psychological_model_check$comparison_table
```

```
# A tibble: 12 x 6
   Model       term                         estimate std.error statistic   p.value
   <chr>       <chr>                           <dbl>     <dbl>     <dbl>     <dbl>
 1 Original    (Intercept)                     51.1       2.50    20.4    1.98e-36
 2 Sensitivity (Intercept)                     50.3       2.32    21.7    5.43e-36
 3 Original    allocation_groupGrupo B          1.47      3.52     0.419  6.76e- 1
 4 Sensitivity allocation_groupGrupo B          2.41      3.19     0.753  4.53e- 1
 5 Original    allocation_groupGrupo B:v~      -4.34      3.53    -1.23   2.25e- 1
 6 Sensitivity allocation_groupGrupo B:v~      -2.71      3.07    -0.884  3.81e- 1
 7 Original    sd__(Intercept)                 12.0      NA       NA     NA
 8 Sensitivity sd__(Intercept)                 10.9      NA       NA     NA
 9 Original    sd__Observation                  9.14     NA       NA     NA
10 Sensitivity sd__Observation                  7.52     NA       NA     NA
11 Original    visit2                          12.4       2.46     5.04   5.66e- 6
12 Sensitivity visit2                          12.1       2.20     5.49   1.70e- 6
```

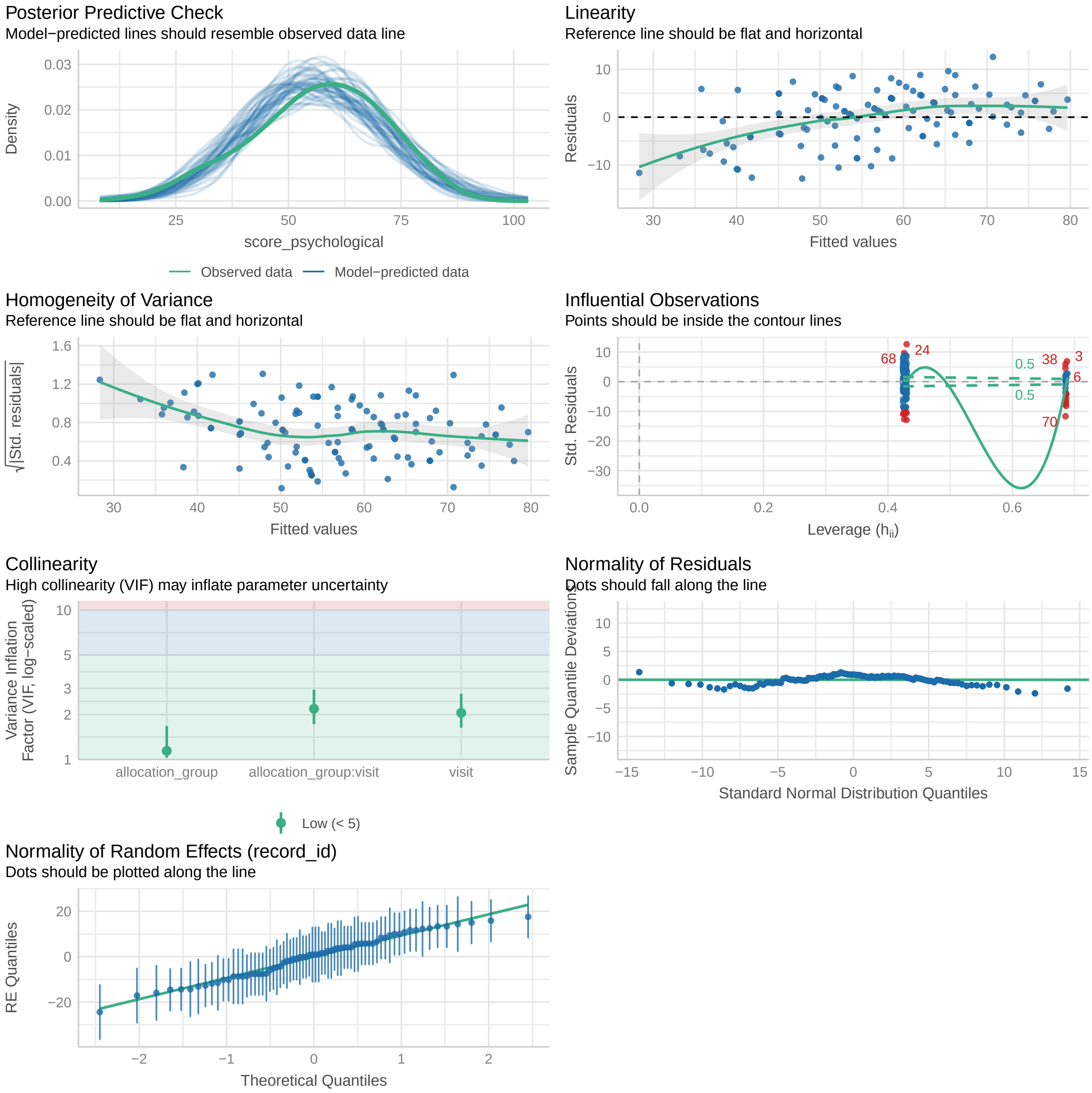
```
performance::compare_performance(
    score_psychological_model,
    score_psychological_model_sens)
```

```
When comparing models, please note that probably not all models were fit
  from same data.
# Comparison of Model Performance Indices

Name                           |           Model |  AIC (weights)
-----------------------------------------------------------------
score_psychological_model      | lmerModLmerTest | 1015.7 (<.001)
score_psychological_model_sens | lmerModLmerTest |  900.7 (>.999)

Name                           | AICc (weights) |  BIC (weights) | R2 (cond.)
------------------------------------------------------------------------------
score_psychological_model      | 1016.4 (<.001) | 1032.7 (<.001) |      0.672
score_psychological_model_sens |  901.5 (>.999) |  917.2 (>.999) |      0.722

Name                           | R2 (marg.) |   ICC |  RMSE | Sigma
-------------------------------------------------------------------
score_psychological_model      |      0.106 | 0.633 | 6.741 | 9.143
score_psychological_model_sens |      0.140 | 0.677 | 5.407 | 7.524
```

```
performance::check_model(score_psychological_model)
```



```r
performance::check_model(score_psychological_model_sens)
```



1.2.0.2 Médias Marginais Estimadas

1.2.0.2.1 Todos os dados

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

```r
score_psychological_raw_emm <- regrid(score_psychological_raw_emm)

# Table of marginal means
# score_psychological_raw_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(score_psychological_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    -1.47 3.52  95.2    -8.45     5.51  -0.419  0.6762

visit = 2:
 contrast          estimate   SE    df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B     2.87 3.94 111.3    -4.93    10.67   0.729  0.4678

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

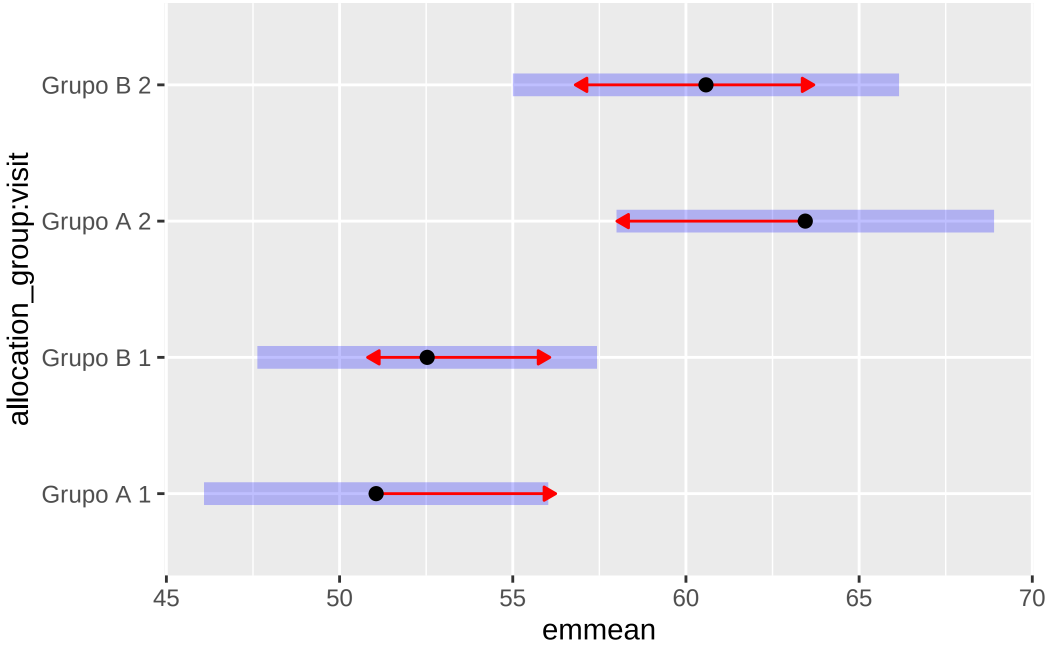
```r
# Pairwise comparisons: Changes over time within each group
emmeans::contrast(score_psychological_raw_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
allocation_group = Grupo A:
 contrast        estimate   SE   df lower.CL upper.CL t.ratio p.value
 visit1 - visit2   -12.39 2.47 95.2    -17.3    -7.49  -5.025  <.0001

allocation_group = Grupo B:
 contrast        estimate   SE   df lower.CL upper.CL t.ratio p.value
 visit1 - visit2    -8.05 2.55 95.2    -13.1    -2.99  -3.159  0.0021

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

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

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

```
Target overlap = 0.0334, overlap on graph = -0.0631
```



1.2.0.2.2 Análise de sensibilidade

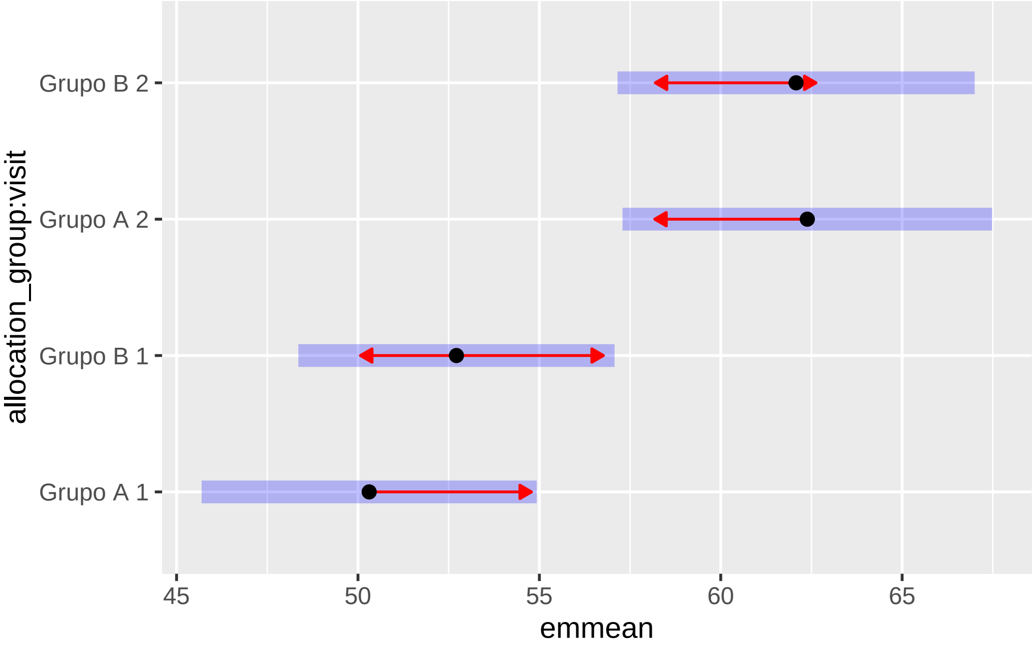
```
# Get EMMs for each group at each visit (Sensitivity Analysis)
score_psychological_emm <- emmeans::emmeans(
    score_psychological_model_sens,
    ~ allocation_group * visit
)

score_psychological_emm <- regrid(score_psychological_emm)

# Table of marginal means
# score_psychological_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(score_psychological_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    -2.405 3.19  85.5    -8.76     3.94  -0.753  0.4535


visit = 2:
 contrast          estimate   SE    df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    0.308 3.57 102.5    -6.78     7.39   0.086  0.9314

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(score_psychological_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   -12.08 2.21 85.7    -16.5    -7.69  -5.473  <.0001

allocation_group = Grupo B:
 contrast        estimate   SE   df lower.CL upper.CL t.ratio p.value
 visit1 - visit2    -9.36 2.15 85.5    -13.6    -5.09  -4.355  <.0001

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

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



1.2.0.3 Resultado

No modelo ajustado para o domínio psicológico do WHOQOL-BREF, não foram observadas diferenças estatisticamente significativas entre os grupos em nenhum dos momentos avaliados (visita 1: estimativa = –1,47; IC 95%: –8,45 a 5,51; visita 2: estimativa = 2,87; IC 95%: –4,93 a 10,67). Ao longo do tempo, ambos os grupos apresentaram melhora significativa do escore psicológico entre a visita 1 e a visita 2: placebo (aumento médio de 12,39; IC 95%: 7,49 a 17,3) e Eclipta (aumento médio de 8,05; IC 95%: 2,99 a 13,1).

Na análise de sensibilidade, os achados principais se mantiveram: não houve diferença entre grupos nas visitas 1 e 2, e as melhorias ao longo do tempo continuaram significativas para placebo (aumento de 12,08; IC 95%: 7,69 a 16,5) e Eclipta (aumento de 9,36; IC 95%: 5,09 a 13,6).

As estimativas, intervalos de confiança de 95% e p-valores estão apresentados nas Tabelas Tabela 3 e Tabela 4.

Tabela 3: Diferenças estimadas do escore psicológico do WHOQOL-BREF entre grupos (placebo vs Eclipta) e ao longo do tempo – Todos os dados

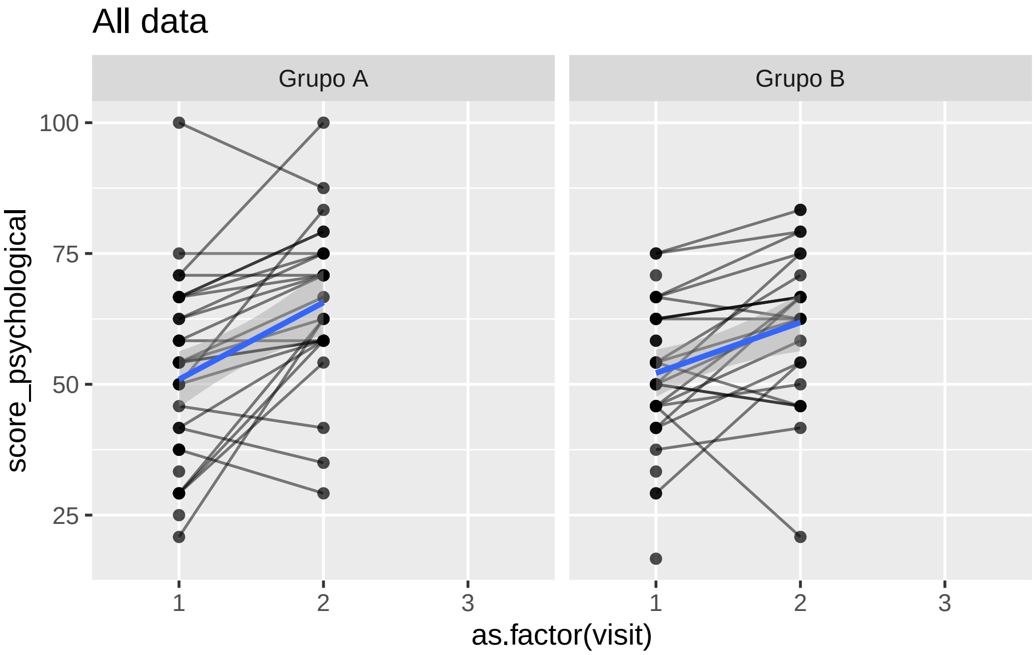
Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 1	–1,47	[–8,45; 5,51]	0,676
Entre grupos	Visita 2	2,87	[–4,93; 10,67]	0,468
Grupo Placebo	Visita 1 – Visita 2	–12,39	[–17,3; –7,49]	< 0,001
Grupo Eclipta	Visita 1 – Visita 2	–8,05	[–13,1; –2,99]	0,002

Tabela 4: Diferenças estimadas do escore psicológico do WHOQOL-BREF entre grupos (placebo vs Eclipta) e ao longo do tempo – Análise de sensibilidade

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 1	–2,41	[–8,76; 3,94]	0,454
Entre grupos	Visita 2	0,31	[–6,78; 7,39]	0,931
Grupo Placebo	Visita 1 – Visita 2	–12,08	[–16,5; –7,69]	< 0,001
Grupo Eclipta	Visita 1 – Visita 2	–9,36	[–13,6; –5,09]	< 0,001

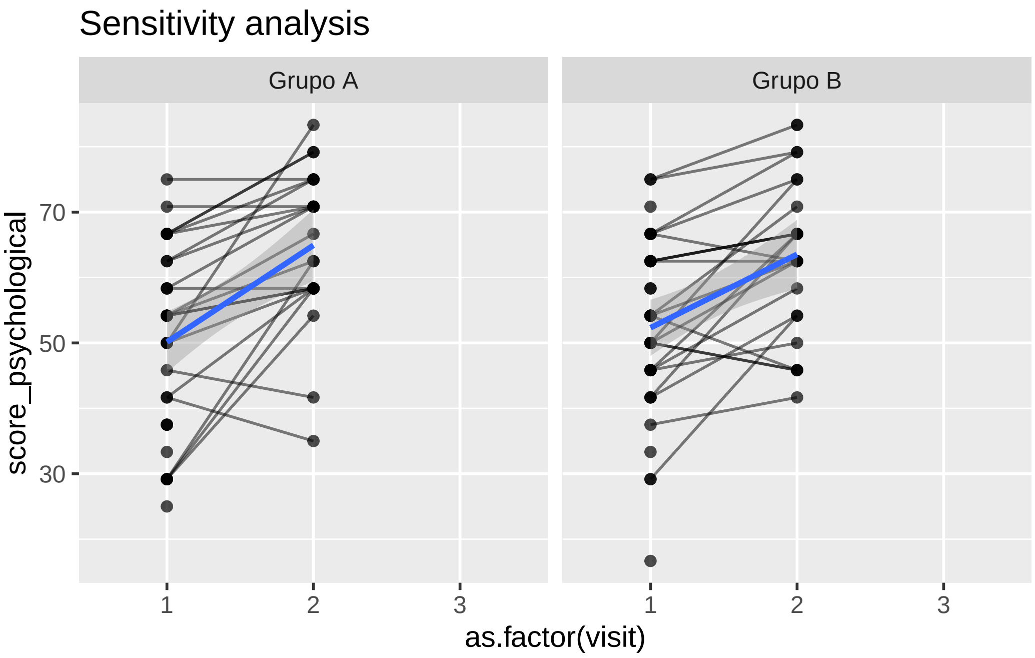
```r
ggplot(
    data = data_model_V1V3,
    aes(
        x = as.factor(visit),
        y = score_psychological,
        group = record_id,
    )
) +
    geom_line(alpha = 0.5) +
    geom_point(alpha = 0.7) +
    geom_smooth(
        aes(group = allocation_group),
        method = "lm",
        se = TRUE,
        linewidth = 1
    ) +
    labs(title = "All data") +
    facet_wrap(~ allocation_group)
```

```
`geom_smooth()` using formula = 'y ~ x'
Warning: Removed 64 rows containing non-finite outside the scale range
(`stat_smooth()`).
Warning: Removed 64 rows containing missing values or values outside the scale range
(`geom_line()`).
Warning: Removed 64 rows containing missing values or values outside the scale range
(`geom_point()`).
```



```
data_model_V1V3 %>%
    filter(
        !(record_id %in%
        score_psychological_model_check$influential_ids)
    ) %>%
    ggplot(
        aes(
            x = as.factor(visit),
            y = score_psychological,
            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 59 rows containing non-finite outside the scale range
(`stat_smooth()`).
Warning: Removed 59 rows containing missing values or values outside the scale range
(`geom_line()`).
Warning: Removed 59 rows containing missing values or values outside the scale range
(`geom_point()`).
```

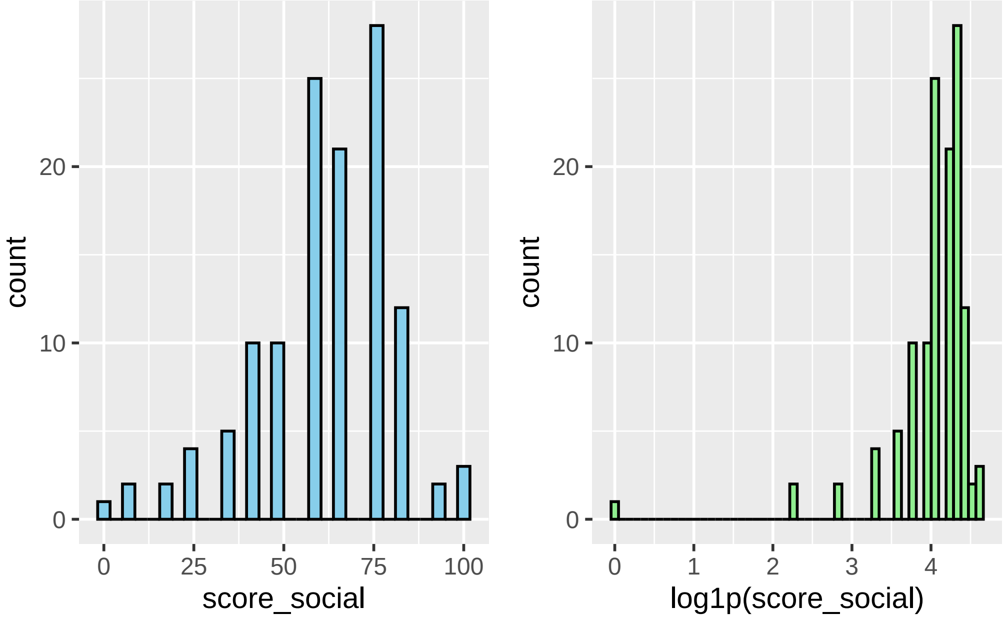


1.3 Domínio Social

Variável: `score_social`

```
# Plot 1: Raw data
score_social_hist_1 <- data_model_V1V3 %>%
    #filter(
    #    score_social < 300
    #) %>%
    ggplot(aes(x = score_social)) +
    geom_histogram(bins = 30, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
score_social_hist_2 <- data_model_V1V3 %>%
    #filter(
    #    score_social < 300
    #) %>%
    ggplot(aes(x = log1p(score_social))) +
    geom_histogram(bins = 50, fill = "lightgreen", color = "black")

# Combine side by side
score_social_hist_1 + score_social_hist_2 # library(patchwork)
```

```
Warning: Removed 64 rows containing non-finite outside the scale range (`stat_bin()`).
Removed 64 rows containing non-finite outside the scale range (`stat_bin()`).
```



```
# LMM
score_social_model <- lmer(score_social ~ allocation_group * visit +
(1 | record_id), data = data_model_V1V3)
```

```
check_collinearity(score_social_model)
```

```
# Check for Multicollinearity

Low Correlation

                  Term  VIF   VIF 95% CI Increased SE Tolerance
      allocation_group 1.17 [1.05, 1.63]         1.08      0.85
                 visit 1.94 [1.56, 2.56]         1.39      0.52
 allocation_group:visit 2.10 [1.67, 2.78]         1.45      0.48
 Tolerance 95% CI
     [0.61, 0.96]
     [0.39, 0.64]
     [0.36, 0.60]
```

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

# LMM Sensitivity
score_social_model_sens <- update(object = score_social_model,
                              subset = !(record_id %in%
        score_social_model_check$influential_ids))
# Influential IDS
score_social_model_check$influential_ids
```

```
[1] "9"  "11" "17" "30" "47" "50"
```

1.3.0.1 Resumo dos modelos

```
summary(score_social_model)
```

```
Linear mixed model fit by REML. t-tests use Satterthwaite's method [
lmerModLmerTest]
Formula: score_social ~ allocation_group * visit + (1 | record_id)
   Data: data_model_V1V3

REML criterion at convergence: 1053.1

Scaled residuals:
     Min       1Q   Median       3Q      Max 
-2.21519 -0.40567  0.06381  0.51324  1.90828 

Random effects:
 Groups    Name        Variance Std.Dev.
 record_id (Intercept) 241.8    15.55   
 Residual              142.7    11.95   
Number of obs: 125, groups:  record_id, 75

Fixed effects:
                              Estimate Std. Error     df t value Pr(>|t|)    
(Intercept)                     60.741      3.251 93.082  18.685   <2e-16 ***
allocation_groupGrupo B         -1.311      4.566 93.057  -0.287    0.775    
visit2                           4.051      3.211 50.794   1.262    0.213    
allocation_groupGrupo B:visit2  -4.898      4.615 51.610  -1.061    0.293    
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
            (Intr) all_GB visit2
allctn_grGB -0.712              
visit2      -0.390  0.278       
allctn_GB:2  0.272 -0.382 -0.696
```

```
summary(score_social_model_sens)
```

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

REML criterion at convergence: 911.8

Scaled residuals: 
     Min       1Q   Median       3Q      Max 
-1.96832 -0.47214  0.02736  0.47240  1.53891 

Random effects:
 Groups    Name        Variance Std.Dev.
 record_id (Intercept) 221.91   14.897
 Residual               68.67    8.287
Number of obs: 114, groups:  record_id, 69

Fixed effects:
                               Estimate Std. Error     df t value Pr(>|t|)
(Intercept)                      63.919      2.987 77.428  21.401   <2e-16 ***
allocation_groupGrupo B          -2.173      4.134 77.365  -0.526   0.6006
visit2                            3.600      2.442 44.251   1.474   0.1474
allocation_groupGrupo B:visit2   -7.477      3.412 44.412  -2.191   0.0337 *
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
            (Intr) all_GB visit2
allctn_grGB -0.723
visit2      -0.306  0.221
allctn_GB:2  0.219 -0.303 -0.716
```

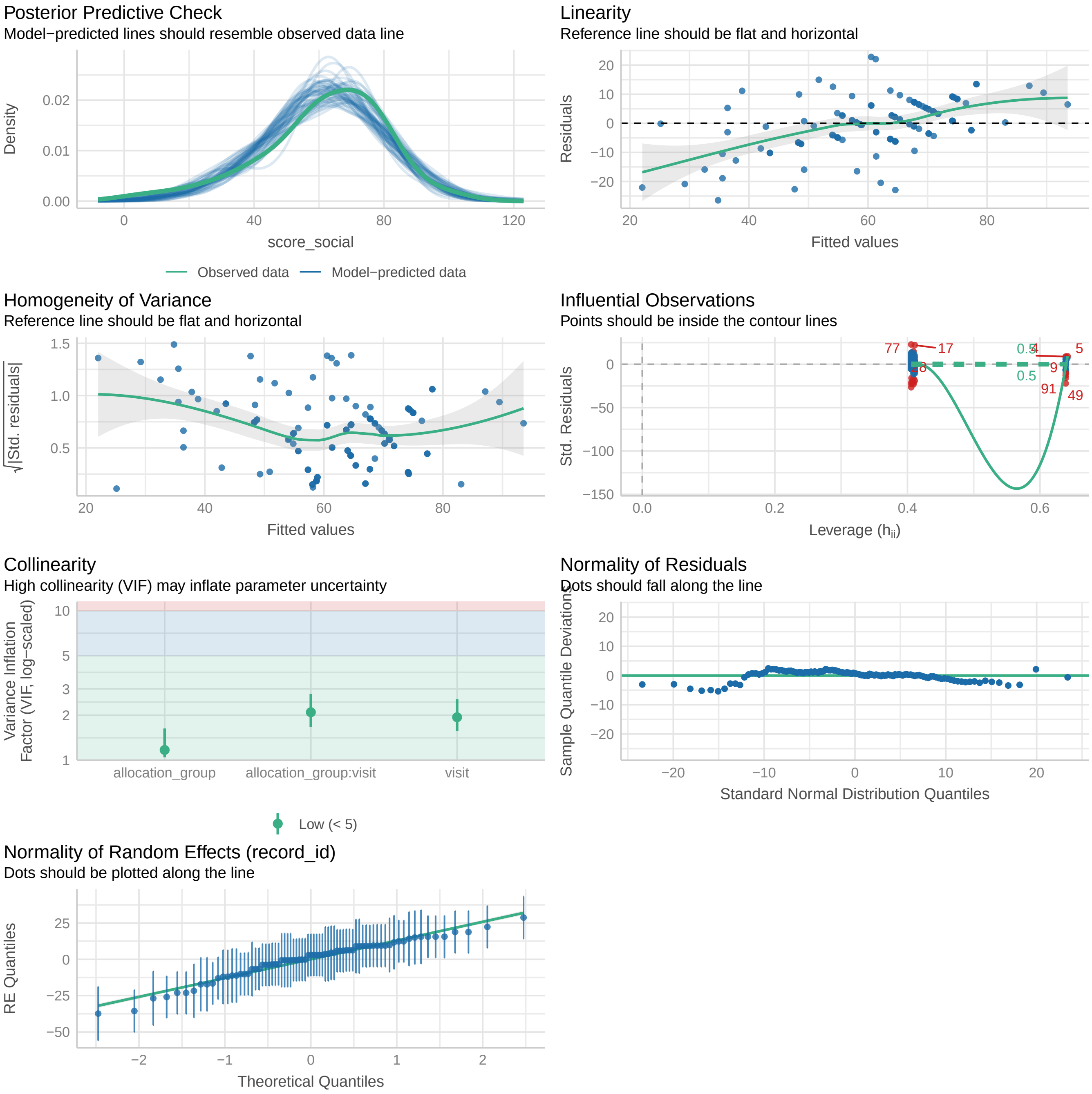
```
score_social_model_check$comparison_table
```

```
# A tibble: 12 x 6
   Model       term                         estimate std.error statistic   p.value
   <chr>       <chr>                           <dbl>     <dbl>     <dbl>     <dbl>
 1 Original    (Intercept)                     60.7       3.25    18.7    2.94e-33
 2 Sensitivity (Intercept)                     63.9       2.99    21.4    3.00e-34
 3 Original    allocation_groupGrupo B         -1.31      4.57    -0.287  7.75e- 1
 4 Sensitivity allocation_groupGrupo B         -2.17      4.13    -0.526  6.01e- 1
 5 Original    allocation_groupGrupo B:v~      -4.90      4.61    -1.06   2.93e- 1
 6 Sensitivity allocation_groupGrupo B:v~      -7.48      3.41    -2.19   3.37e- 2
 7 Original    sd__(Intercept)                 15.5      NA       NA     NA
 8 Sensitivity sd__(Intercept)                 14.9      NA       NA     NA
 9 Original    sd__Observation                 11.9      NA       NA     NA
10 Sensitivity sd__Observation                  8.29     NA       NA     NA
11 Original    visit2                           4.05      3.21     1.26   2.13e- 1
12 Sensitivity visit2                           3.60      2.44     1.47   1.47e- 1
```

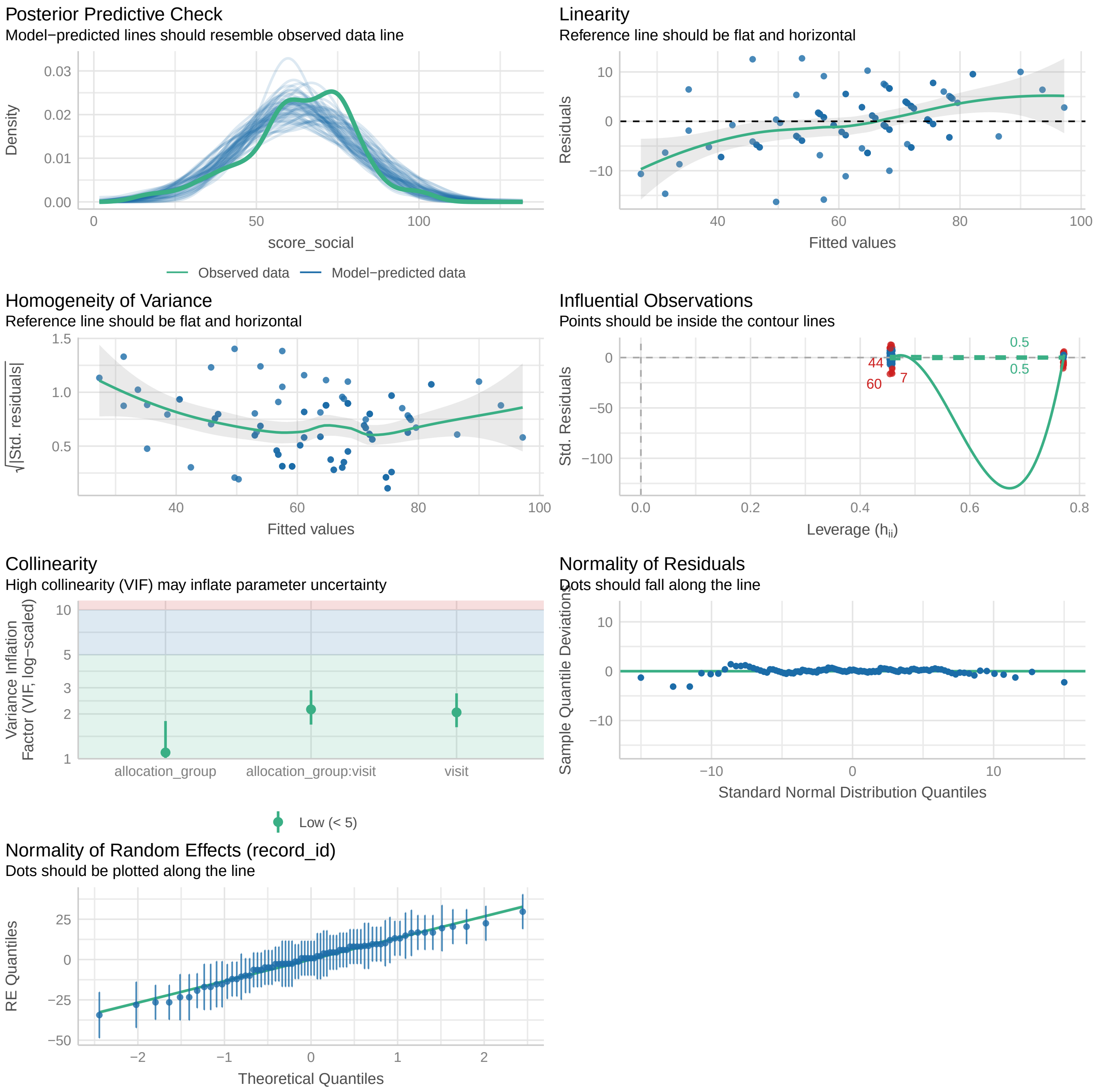
```
performance::compare_performance(
    score_social_model,
    score_social_model_sens)
```

```
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)
----------------------------------------------------------------------------
score_social_model      | lmerModLmerTest | 1081.5 (<.001) | 1082.2 (<.001)
score_social_model_sens | lmerModLmerTest |  938.7 (>.999) |  939.4 (>.999)

Name                    |  BIC (weights) | R2 (cond.) | R2 (marg.) |   ICC
---------------------------------------------------------------------------
score_social_model      | 1098.5 (<.001) |      0.634 |      0.013 | 0.629
score_social_model_sens |  955.1 (>.999) |      0.772 |      0.035 | 0.764

Name                    |  RMSE |  Sigma
----------------------------------------
score_social_model      | 8.826 | 11.947
score_social_model_sens | 5.726 |  8.287
```

```
performance::check_model(score_social_model)
```



```
performance::check_model(score_social_model_sens)
```



1.3.0.2 Médias Marginais Estimadas

1.3.0.2.1 Todos os dados

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

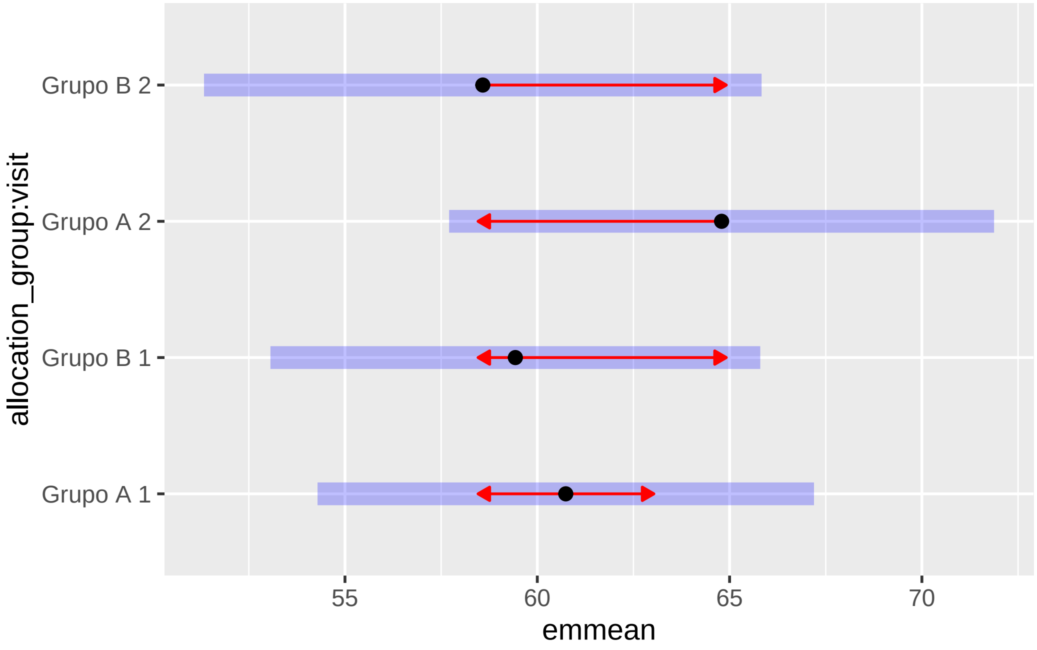
```r
score_social_raw_emm <- regrid(score_social_raw_emm)

# Table of marginal means
# score_social_raw_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(score_social_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     1.31 4.57  95.5    -7.76     10.4   0.287  0.7747

visit = 2:
 contrast          estimate   SE    df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B     6.21 5.12 111.5    -3.93     16.3   1.213  0.2275

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

```r
# Pairwise comparisons: Changes over time within each group
emmeans::contrast(score_social_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   -4.051 3.22 95.5   -10.45     2.34  -1.258  0.2115

allocation_group = Grupo B:
 contrast        estimate   SE   df lower.CL upper.CL t.ratio p.value
 visit1 - visit2    0.846 3.33 95.5    -5.76     7.45   0.254  0.7998

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

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



1.3.0.2.2 Análise de sensibilidade

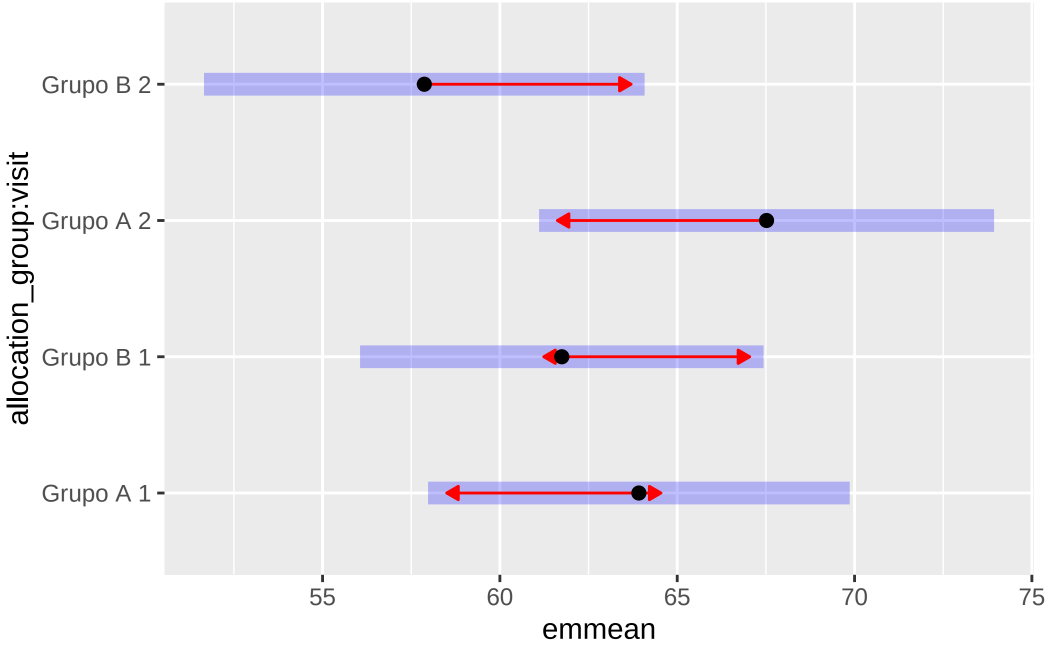
```
# Get EMMs for each group at each visit (Sensitivity Analysis)
score_social_emm <- emmeans::emmeans(
    score_social_model_sens,
    ~ allocation_group * visit
)

score_social_emm <- regrid(score_social_emm)

# Table of marginal means
# score_social_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(score_social_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     2.17 4.13 79.7   -6.055     10.4   0.526  0.6006

visit = 2:
 contrast          estimate   SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B     9.65 4.50 95.7    0.719     18.6   2.145  0.0345

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(score_social_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    -3.60 2.45 79.8   -8.474     1.27  -1.470  0.1454

allocation_group = Grupo B:
 contrast        estimate   SE   df lower.CL upper.CL t.ratio p.value
 visit1 - visit2     3.88 2.39 79.7   -0.882     8.64   1.621  0.1089

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

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



1.3.0.3 Resultado

No modelo ajustado para o domínio social do WHOQOL-BREF, não foram observadas diferenças significativas entre os grupos na visita 1 (estimativa = 1,31; IC 95%: –7,76 a 10,4) nem na visita 2 (estimativa = 6,21; IC 95%: –3,93 a 16,3). Também não houve mudanças significativas ao longo do tempo dentro de cada grupo (placebo: –4,05; IC 95%: –10,45 a 2,34; Eclipta: 0,85; IC 95%: –5,76 a 7,45).

Na análise de sensibilidade, surgiu diferença significativa entre os grupos na visita 2, com o grupo placebo apresentando escore social 9,65 pontos superior ao grupo Eclipta (IC 95%: 0,72 a 18,6). Não houve alterações significativas ao longo do tempo dentro de nenhum dos grupos na análise de sensibilidade.

As estimativas, intervalos de confiança de 95% e p-valores estão apresentados nas Tabelas Tabela 5 e Tabela 6.

Tabela 5: Diferenças estimadas do escore social do WHOQOL-BREF entre grupos e ao longo do tempo – Todos os dados

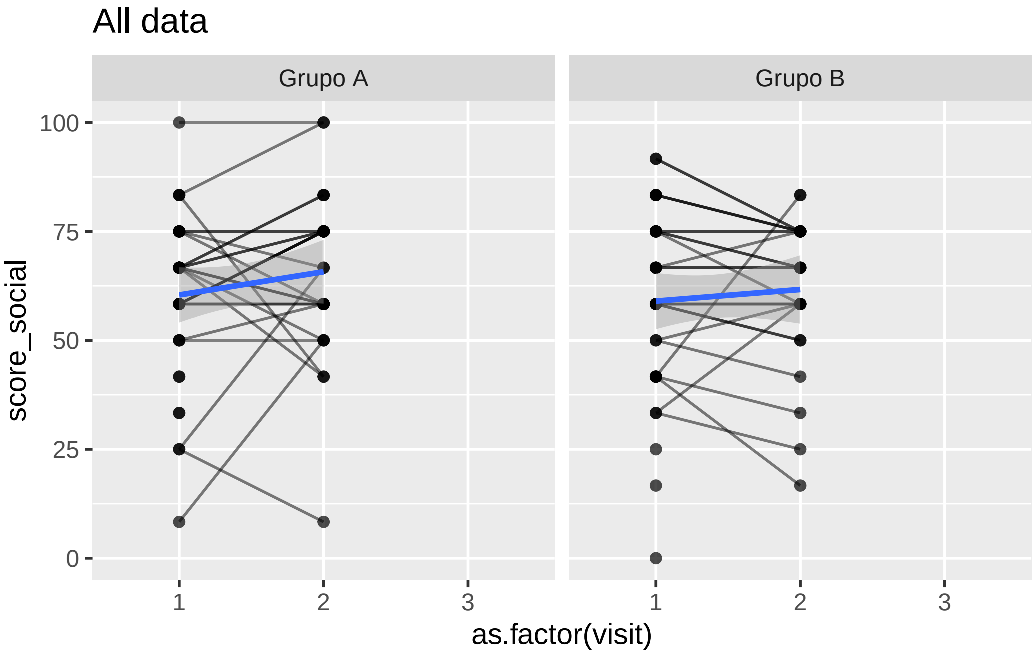
Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 1	1,31	[–7,76; 10,4]	0,775
Entre grupos	Visita 2	6,21	[–3,93; 16,3]	0,228
Grupo Placebo	Visita 1 – Visita 2	–4,05	[–10,45; 2,34]	0,212
Grupo Eclipta	Visita 1 – Visita 2	0,85	[–5,76; 7,45]	0,800

Tabela 6: Diferenças estimadas do escore social do WHOQOL-BREF entre grupos e ao longo do tempo – Análise de sensibilidade

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 1	2,17	[–6,06; 10,4]	0,601
Entre grupos	Visita 2	9,65	[0,72; 18,6]	0,035
Grupo Placebo	Visita 1 – Visita 2	–3,60	[–8,47; 1,27]	0,145
Grupo Eclipta	Visita 1 – Visita 2	3,88	[–0,88; 8,64]	0,109

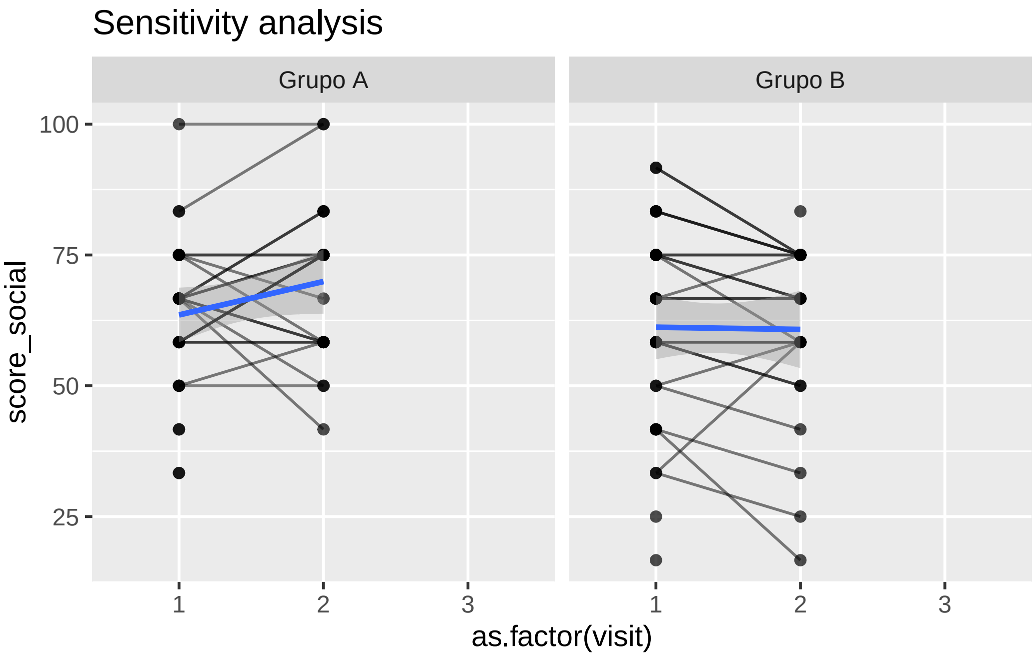
```r
ggplot(
    data = data_model_V1V3,
    aes(
        x = as.factor(visit),
        y = score_social,
        group = record_id,
    )
) +
    geom_line(alpha = 0.5) +
    geom_point(alpha = 0.7) +
    geom_smooth(
        aes(group = allocation_group),
        method = "lm",
        se = TRUE,
        linewidth = 1
    ) +
    labs(title = "All data") +
    facet_wrap(~ allocation_group)
```

```
`geom_smooth()` using formula = 'y ~ x'
Warning: Removed 64 rows containing non-finite outside the scale range
(`stat_smooth()`).
Warning: Removed 64 rows containing missing values or values outside the scale range
(`geom_line()`).
Warning: Removed 64 rows containing missing values or values outside the scale range
(`geom_point()`).
```



```
data_model_V1V3 %>%
    filter(
        !(record_id %in%
        score_social_model_check$influential_ids)
    ) %>%
    ggplot(
        aes(
            x = as.factor(visit),
            y = score_social,
            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 59 rows containing non-finite outside the scale range
(`stat_smooth()`).
Warning: Removed 59 rows containing missing values or values outside the scale range
(`geom_line()`).
Warning: Removed 59 rows containing missing values or values outside the scale range
(`geom_point()`).
```

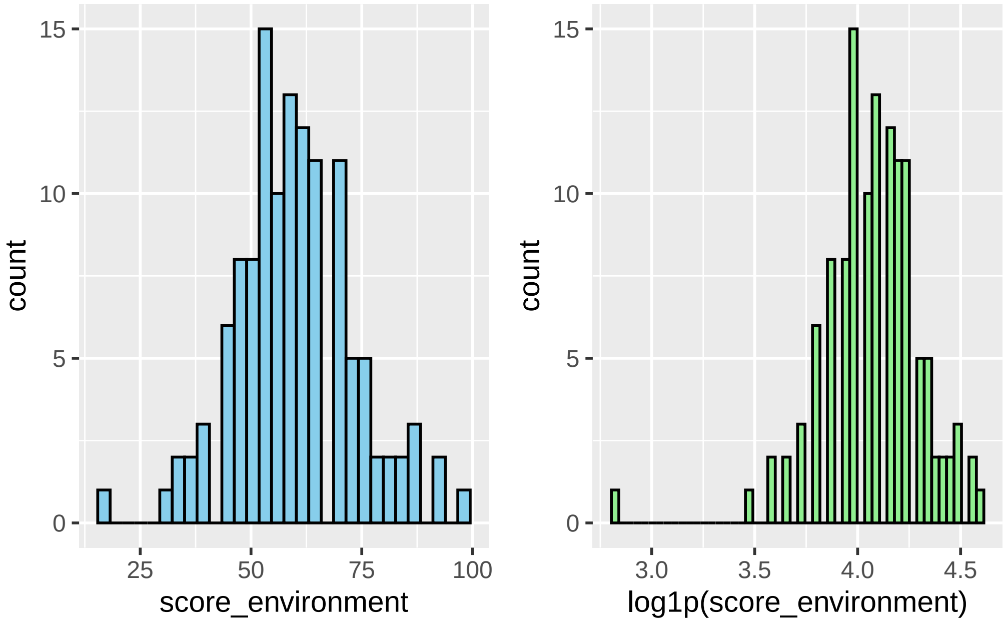


1.4 Domínio Ambiental

Variável: `score_environment`

```
# Plot 1: Raw data
score_environment_hist_1 <- data_model_V1V3 %>%
    #filter(
    #    score_environment < 300
    #) %>%
    ggplot(aes(x = score_environment)) +
    geom_histogram(bins = 30, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
score_environment_hist_2 <- data_model_V1V3 %>%
    #filter(
    #    score_environment < 300
    #) %>%
    ggplot(aes(x = log1p(score_environment))) +
    geom_histogram(bins = 50, fill = "lightgreen", color = "black")

# Combine side by side
score_environment_hist_1 + score_environment_hist_2 # library(patchwork)
```

```
Warning: Removed 64 rows containing non-finite outside the scale range (`stat_bin()`).
Removed 64 rows containing non-finite outside the scale range (`stat_bin()`).
```



```
# LMM
score_environment_model <- lmer(score_environment ~ allocation_group * visit +
(1 | record_id), data = data_model_V1V3)
check_collinearity(score_environment_model)
```

```
# Check for Multicollinearity
```

```
Low Correlation

                   Term  VIF   VIF 95% CI Increased SE Tolerance
       allocation_group 1.11 [1.02, 1.70]         1.05      0.90
                  visit 1.93 [1.56, 2.56]         1.39      0.52
 allocation_group:visit 2.03 [1.63, 2.69]         1.43      0.49
 Tolerance 95% CI
     [0.59, 0.98]
     [0.39, 0.64]
     [0.37, 0.61]
```

```r
# Sensitivity analysis
score_environment_model_check <- sensitivity_check_lmer(
    model = score_environment_model,
    id_var = "record_id",
    top_n = 5)

# LMM Sensitivity
score_environment_model_sens <- update(object = score_environment_model,
                              subset = !(record_id %in%
        score_environment_model_check$influential_ids))
# Influential IDS
score_environment_model_check$influential_ids
```

```
[1] "1"  "17" "31" "34" "53"
```

1.4.0.1 Resumo dos modelos

```r
summary(score_environment_model)
```

```
Linear mixed model fit by REML. t-tests use Satterthwaite's method [
lmerModLmerTest]
Formula: score_environment ~ allocation_group * visit + (1 | record_id)
   Data: data_model_V1V3

REML criterion at convergence: 946

Scaled residuals:
    Min      1Q  Median      3Q     Max
-2.3075 -0.4723  0.0543  0.4396  2.1422
```

```
Random effects:
 Groups    Name        Variance Std.Dev.
 record_id (Intercept) 134.76   11.609  
 Residual               45.25    6.727  
Number of obs: 125, groups:  record_id, 75

Fixed effects:
                               Estimate Std. Error     df t value Pr(>|t|)    
(Intercept)                      59.539      2.219 88.875  26.829   <2e-16 ***
allocation_groupGrupo B          -1.617      3.118 88.856  -0.519    0.605    
visit2                            2.395      1.826 53.295   1.311    0.195    
allocation_groupGrupo B:visit2   -1.153      2.628 53.856  -0.439    0.663    
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
            (Intr) all_GB visit2
allctn_grGB -0.712              
visit2      -0.321  0.228       
allctn_GB:2  0.223 -0.313 -0.695
```

```
summary(score_environment_model_sens)
```

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

REML criterion at convergence: 829.3

Scaled residuals:
     Min       1Q   Median       3Q      Max 
-1.52911 -0.47356 -0.00552  0.47242  1.67386 

Random effects:
 Groups    Name        Variance Std.Dev.
 record_id (Intercept) 95.97    9.797   
 Residual             30.84    5.554
Number of obs: 115, groups:  record_id, 70

Fixed effects:
                               Estimate Std. Error     df t value Pr(>|t|)
(Intercept)                      58.639      1.944 80.495  30.166   <2e-16 ***
allocation_groupGrupo B          -1.075      2.710 80.454  -0.397    0.693
visit2                            1.813      1.601 46.248   1.133    0.263
allocation_groupGrupo B:visit2    0.311      2.284 46.692   0.136    0.892
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
            (Intr) all_GB visit2
allctn_grGB -0.717
visit2      -0.312  0.224
allctn_GB:2  0.219 -0.305 -0.701
```

```
score_environment_model_check$comparison_table
```

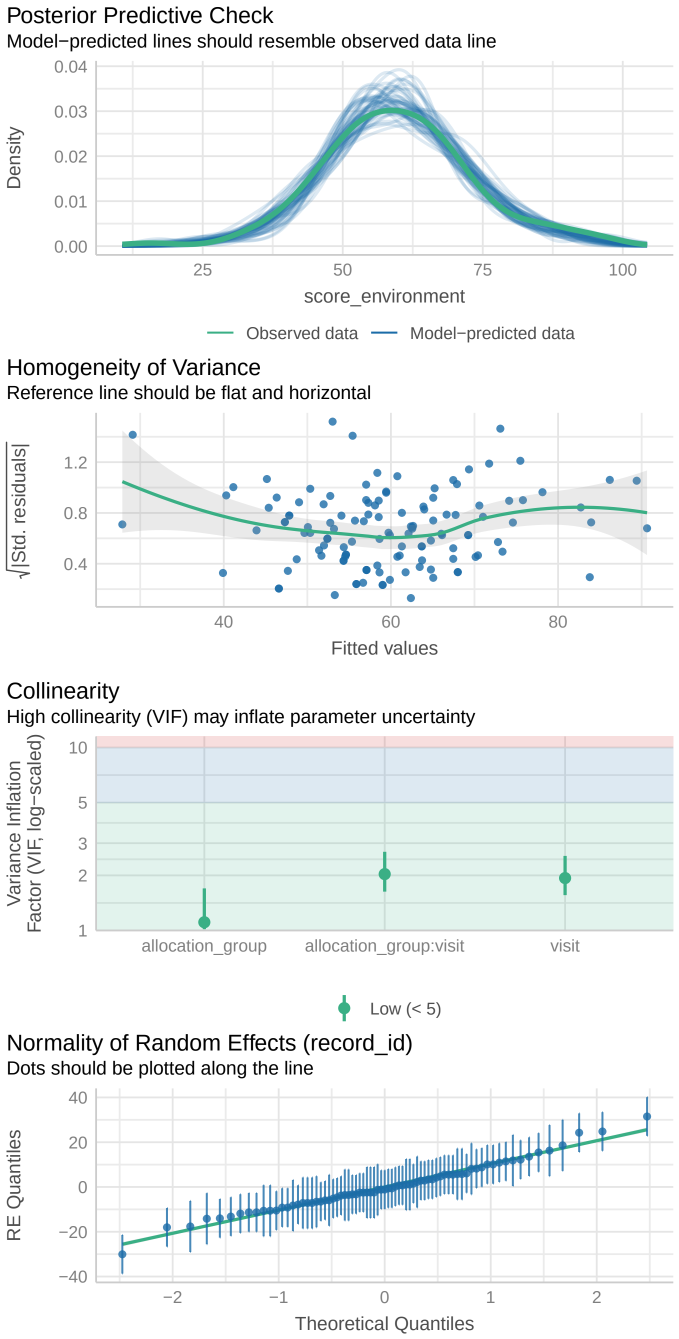
```
# A tibble: 12 x 6
   Model       term                        estimate std.error statistic  p.value
   <chr>       <chr>                          <dbl>     <dbl>     <dbl>    <dbl>
 1 Original    (Intercept)                   59.5        2.22    26.8    2.17e-44
 2 Sensitivity (Intercept)                   58.6        1.94    30.2    1.24e-45
 3 Original    allocation_groupGrupo B       -1.62       3.12    -0.519  6.05e- 1
 4 Sensitivity allocation_groupGrupo B       -1.08       2.71    -0.397  6.93e- 1
 5 Original    allocation_groupGrupo B:v~    -1.15       2.63    -0.439  6.63e- 1
 6 Sensitivity allocation_groupGrupo B:v~     0.311      2.28     0.136  8.92e- 1
 7 Original    sd__(Intercept)               11.6       NA       NA     NA
 8 Sensitivity sd__(Intercept)                9.80      NA       NA     NA
 9 Original    sd__Observation                6.73      NA       NA     NA
10 Sensitivity sd__Observation                5.55      NA       NA     NA
11 Original    visit2                         2.39       1.83     1.31   1.95e- 1
12 Sensitivity visit2                         1.81       1.60     1.13   2.63e- 1
```

```
performance::compare_performance(
    score_environment_model,
    score_environment_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)
------------------------------------------------------------------------------
score_environment_model       | lmerModLmerTest | 970.7 (<.001) |  971.4 (<.001)
score_environment_model_sens  | lmerModLmerTest | 852.9 (>.999) |  853.7 (>.999)

Name                          | BIC (weights) | R2 (cond.) | R2 (marg.) |   ICC
-----------------------------------------------------------------------------
score_environment_model       | 987.7 (<.001) |      0.751 |      0.011 | 0.749
score_environment_model_sens  | 869.4 (>.999) |      0.759 |      0.009 | 0.757

Name                          |  RMSE | Sigma
--------------------------------------------
score_environment_model       | 4.706 | 6.727
score_environment_model_sens  | 3.842 | 5.554
```

```
performance::check_model(score_environment_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

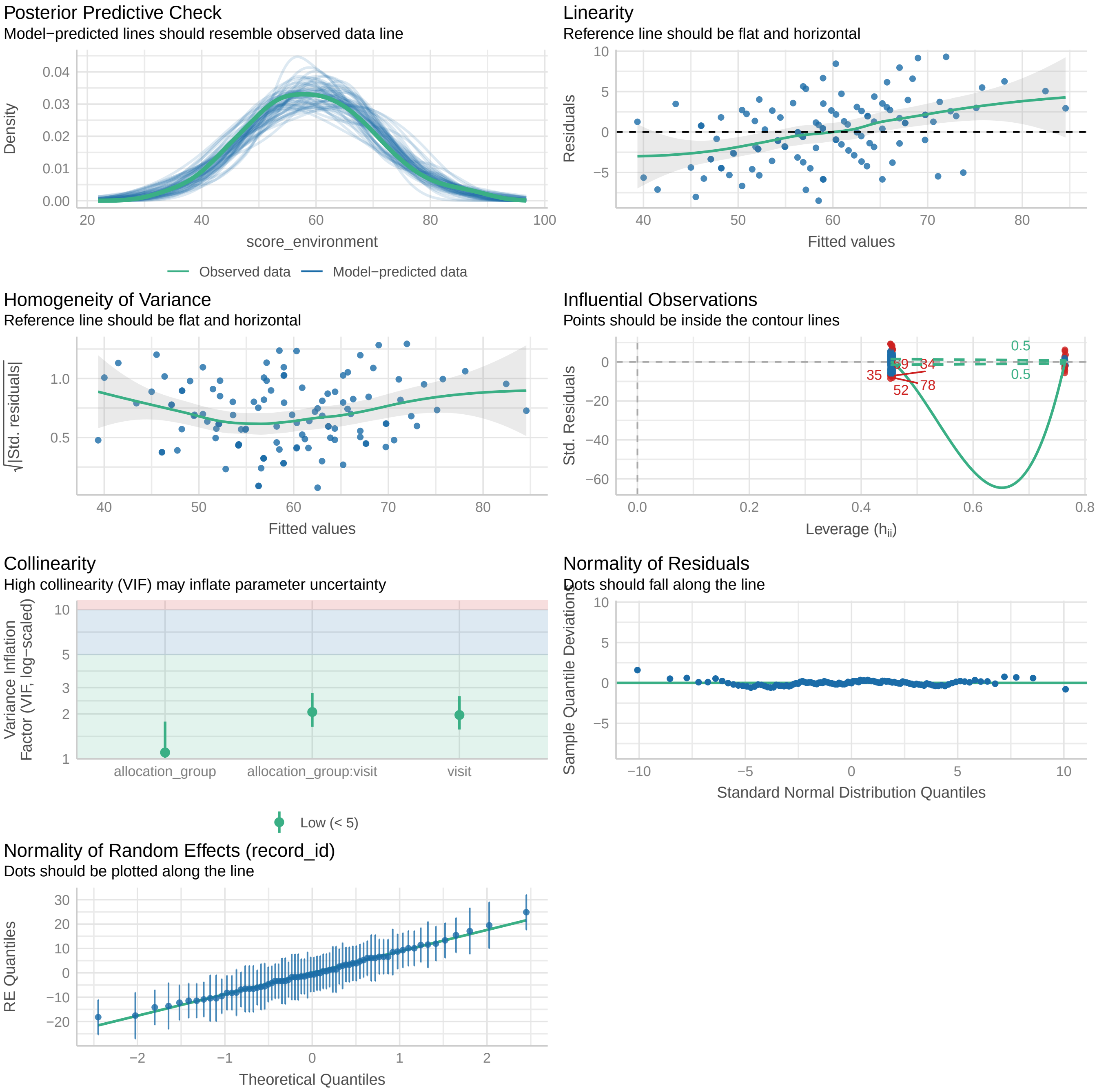
Normality of Residuals

Dots should fall along the line

Normality of Random Effects (record_id)

Dots should be plotted along the line

```r
performance::check_model(score_environment_model_sens)
```



1.4.0.2 Médias Marginais Estimadas

1.4.0.2.1 Todos os dados

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

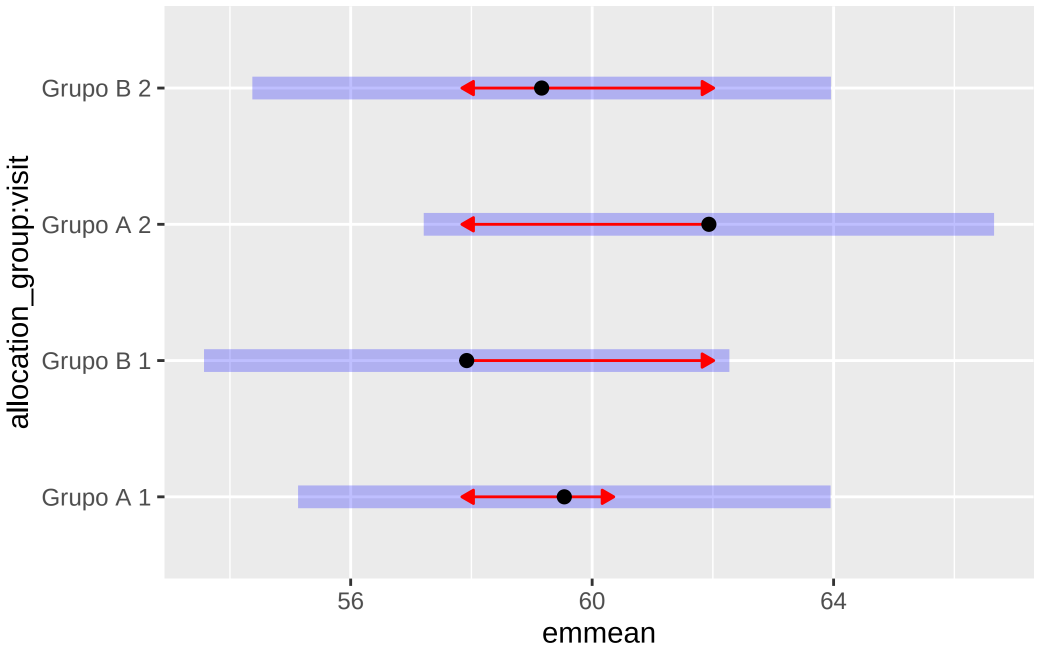
```r
score_environment_raw_emm <- regrid(score_environment_raw_emm)

# Table of marginal means
# score_environment_raw_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(score_environment_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     1.62 3.12  88    -4.58     7.81   0.519  0.6053

visit = 2:
 contrast          estimate   SE  df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B     2.77 3.39 104    -3.96     9.50   0.816  0.4162

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

```r
# Pairwise comparisons: Changes over time within each group
emmeans::contrast(score_environment_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    -2.39 1.83 88    -6.03     1.24  -1.308  0.1942

allocation_group = Grupo B:
 contrast        estimate   SE df lower.CL upper.CL t.ratio p.value
 visit1 - visit2    -1.24 1.90 88    -5.01     2.53  -0.655  0.5143

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

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



1.4.0.2.2 Análise de sensibilidade

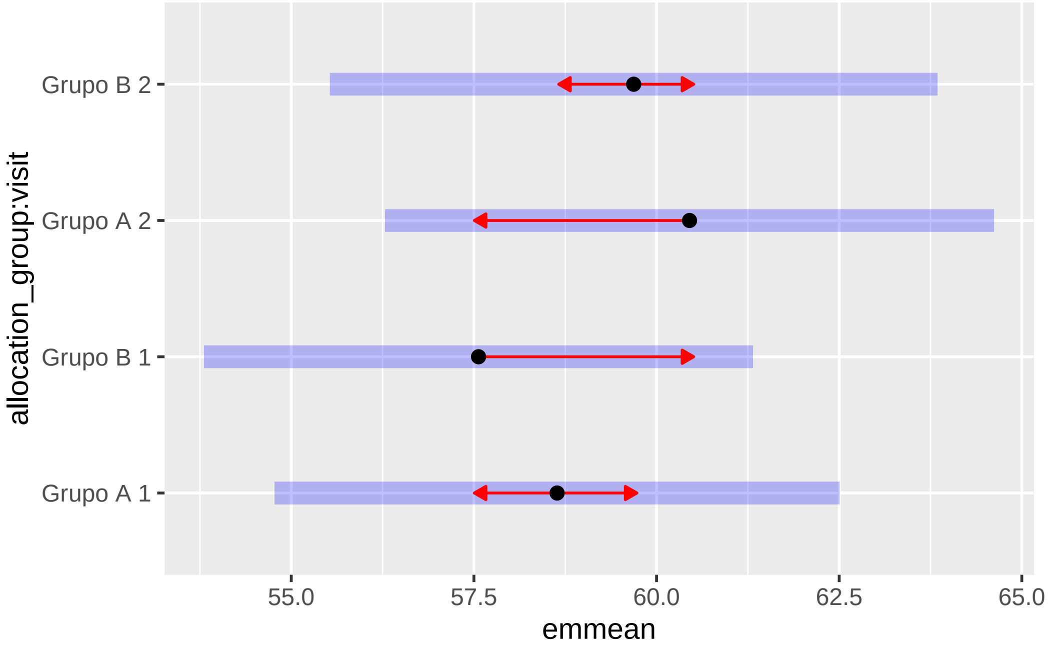
```
# Get EMMs for each group at each visit (Sensitivity Analysis)
score_environment_emm <- emmeans::emmeans(
    score_environment_model_sens,
    ~ allocation_group * visit
)

score_environment_emm <- regrid(score_environment_emm)

# Table of marginal means
# score_environment_emm

# Pairwise comparisons: Between groups at each visit
emmeans::contrast(score_environment_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    1.076 2.71 81.1    -4.32     6.47   0.397  0.6925

visit = 2:
 contrast          estimate   SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    0.765 2.97 96.8    -5.13     6.65   0.258  0.7972

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(score_environment_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    -1.81 1.61 81.2    -5.01     1.38  -1.129  0.2621

allocation_group = Grupo B:
 contrast        estimate   SE   df lower.CL upper.CL t.ratio p.value
 visit1 - visit2    -2.12 1.63 81.1    -5.38     1.13  -1.300  0.1974

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

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



1.4.0.3 Resultado

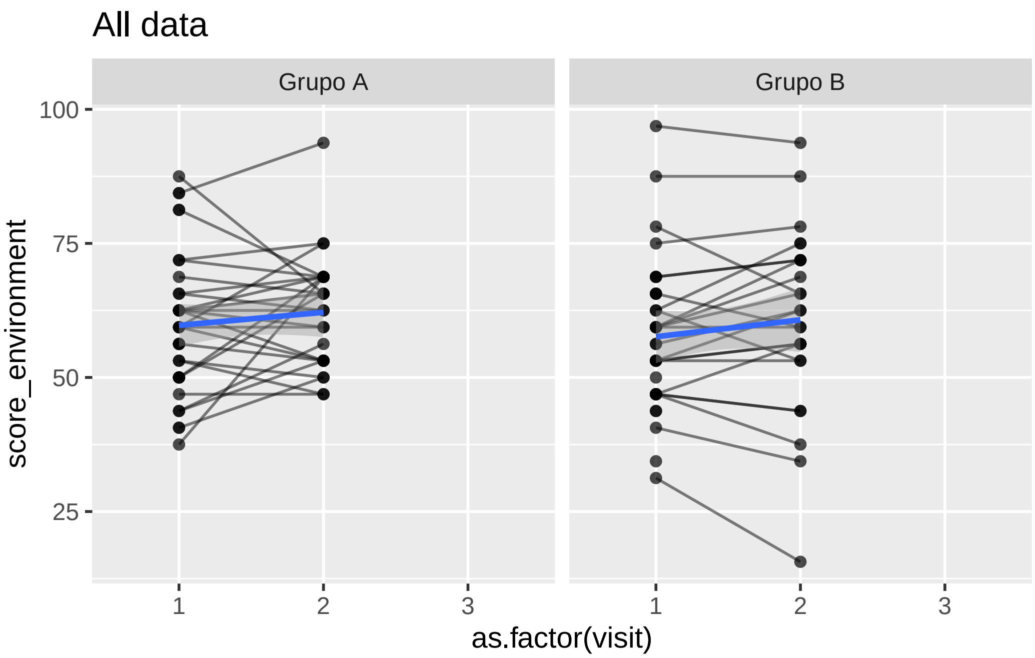
No modelo ajustado para o domínio ambiente do WHOQOL-BREF, não foram observadas diferenças significativas entre os grupos na visita 1 (estimativa = 1,62; IC 95%: –4,58 a 7,81) nem na visita 2 (estimativa = 2,77; IC 95%: –3,96 a 9,50). Também não houve alterações significativas ao longo do tempo dentro de cada grupo (placebo: –2,39; IC 95%: –6,03 a 1,24; Eclipta: –1,24; IC 95%: –5,01 a 2,53). A análise de sensibilidade manteve o mesmo padrão de resultados.

Tabela: Diferenças estimadas do escore ambiente do WHOQOL-BREF entre grupos (placebo vs Eclipta) e entre visitas dentro de cada grupo – Todos os dados {#tbl-score_environment}

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 1	1,62	[–4,58; 7,81]	0,605
Entre grupos	Visita 2	2,77	[–3,96; 9,50]	0,416
Grupo Placebo	Visita 1 – Visita 2	–2,39	[–6,03; 1,24]	0,194
Grupo Eclipta	Visita 1 – Visita 2	–1,24	[–5,01; 2,53]	0,514

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

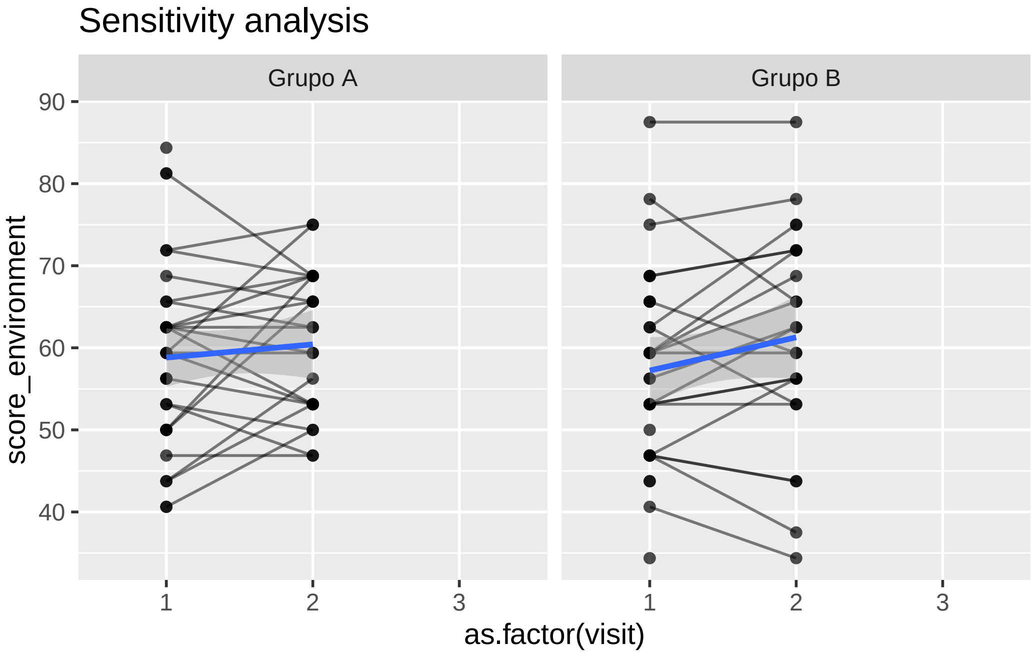
```
`geom_smooth()` using formula = 'y ~ x'
Warning: Removed 64 rows containing non-finite outside the scale range
(`stat_smooth()`).
Warning: Removed 64 rows containing missing values or values outside the scale range
(`geom_line()`).
Warning: Removed 64 rows containing missing values or values outside the scale range
(`geom_point()`).
```



```
data_model_V1V3 %>%
    filter(
        !(record_id %in%
        score_environment_model_check$influential_ids)
    ) %>%
    ggplot(
        aes(
            x = as.factor(visit),
            y = score_environment,
            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 59 rows containing non-finite outside the scale range
(`stat_smooth()`).
Warning: Removed 59 rows containing missing values or values outside the scale range
(`geom_line()`).
Warning: Removed 59 rows containing missing values or values outside the scale range
(`geom_point()`).
```



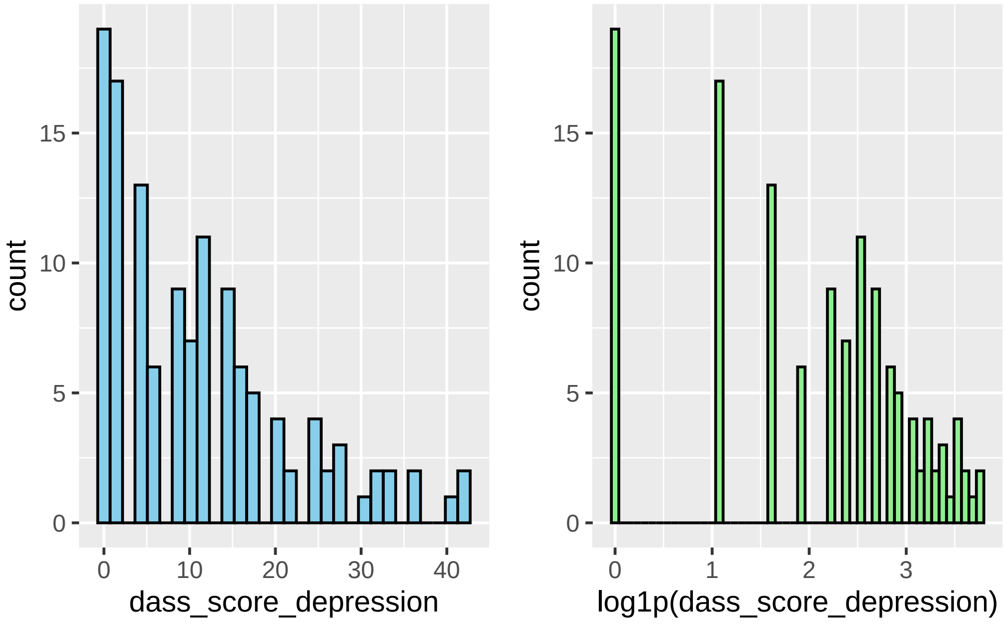
2 Escore DASS

2.1 Escore DASS - Depressão

Variável: `dass_score_depression`

```
# Plot 1: Raw data
dass_score_depression_hist_1 <- data_model_V1V3 %>%
    #filter(
    #    dass_score_depression < 300
    #) %>%
    ggplot(aes(x = dass_score_depression)) +
    geom_histogram(bins = 30, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
dass_score_depression_hist_2 <- data_model_V1V3 %>%
    #filter(
    #    dass_score_depression < 300
    #) %>%
    ggplot(aes(x = log1p(dass_score_depression))) +
    geom_histogram(bins = 50, fill = "lightgreen", color = "black")

# Combine side by side
dass_score_depression_hist_1 + dass_score_depression_hist_2 # library(patchwork)
```

```
Warning: Removed 62 rows containing non-finite outside the scale range (`stat_bin()`).
Removed 62 rows containing non-finite outside the scale range (`stat_bin()`).
```



```
# Fit a negative-binomial GLMM
dass_score_depression_nb_model <- glmmTMB::glmmTMB(
  formula = dass_score_depression ~ allocation_group * visit + (1 | record_id),
  family  = glmmTMB::nbinom2(),
  data    = data_model_V1V3
)

# Check collinearity
performance::check_collinearity(dass_score_depression_nb_model)
```

```
# Check for Multicollinearity

Low Correlation

                   Term  VIF   VIF 95% CI Increased SE Tolerance
       allocation_group 1.22 [1.08, 1.65]         1.11      0.82
```

```
                  visit 1.94 [1.57, 2.55]         1.39      0.52
 allocation_group:visit 2.13 [1.70, 2.81]         1.46      0.47
 Tolerance 95% CI
     [0.61, 0.93]
     [0.39, 0.64]
     [0.36, 0.59]
```

```
# 3. Identify the 5 most "influential" clusters by magnitude of their random intercepts
re_nb <- glmmTMB::ranef(dass_score_depression_nb_model)$cond$record_id
re_nb_df <- data.frame(
  record_id = rownames(re_nb),
  intercept = re_nb[, 1],
  stringsAsFactors = FALSE
)
influential_ids_nb <- re_nb_df %>%
  dplyr::arrange(dplyr::desc(abs(intercept))) %>%
  dplyr::slice_head(n = 5) %>%
  dplyr::pull(record_id)

# 4. Re-fit the model excluding those top-5 clusters
dass_score_depression_nb_model_sens <- update(
  dass_score_depression_nb_model,
  data = dplyr::filter(data_model_V1V3, !record_id %in% influential_ids_nb)
)

# 5. Inspect which record_ids were most extreme
influential_ids_nb
```

```
[1] "15" "13" "44" "61" "19"
```

2.1.0.1 Resumo dos modelos

```
# Model summaries
summary(dass_score_depression_nb_model)
```

```
 Family: nbinom2  ( log )
Formula:
dass_score_depression ~ allocation_group * visit + (1 | record_id)
Data: data_model_V1V3


      AIC       BIC    logLik -2*log(L)  df.resid
```

```
    882.6     899.6    -435.3     870.6       121

Random effects:

Conditional model:
 Groups    Name        Variance Std.Dev.
 record_id (Intercept) 0.7084   0.8417
Number of obs: 127, groups:  record_id, 75

Dispersion parameter for nbinom2 family (): 2.12

Conditional model:
                               Estimate Std. Error z value Pr(>|z|)
(Intercept)                      2.2151     0.2063  10.739   <2e-16 ***
allocation_groupGrupo B          0.1569     0.2717   0.578    0.563
visit3                          -0.1800     0.2271  -0.793    0.428
allocation_groupGrupo B:visit3  -0.2280     0.3194  -0.714    0.475
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
summary(dass_score_depression_nb_model_sens)
```

```
 Family: nbinom2  ( log )
Formula:
dass_score_depression ~ allocation_group * visit + (1 | record_id)
Data: dplyr::filter(data_model_V1V3, !record_id %in% influential_ids_nb)

      AIC       BIC    logLik -2*log(L)  df.resid
    830.9     847.4    -409.4     818.9       111

Random effects:

Conditional model:
 Groups    Name        Variance Std.Dev.
 record_id (Intercept) 0.3703   0.6085
Number of obs: 117, groups:  record_id, 70

Dispersion parameter for nbinom2 family (): 2.21
```

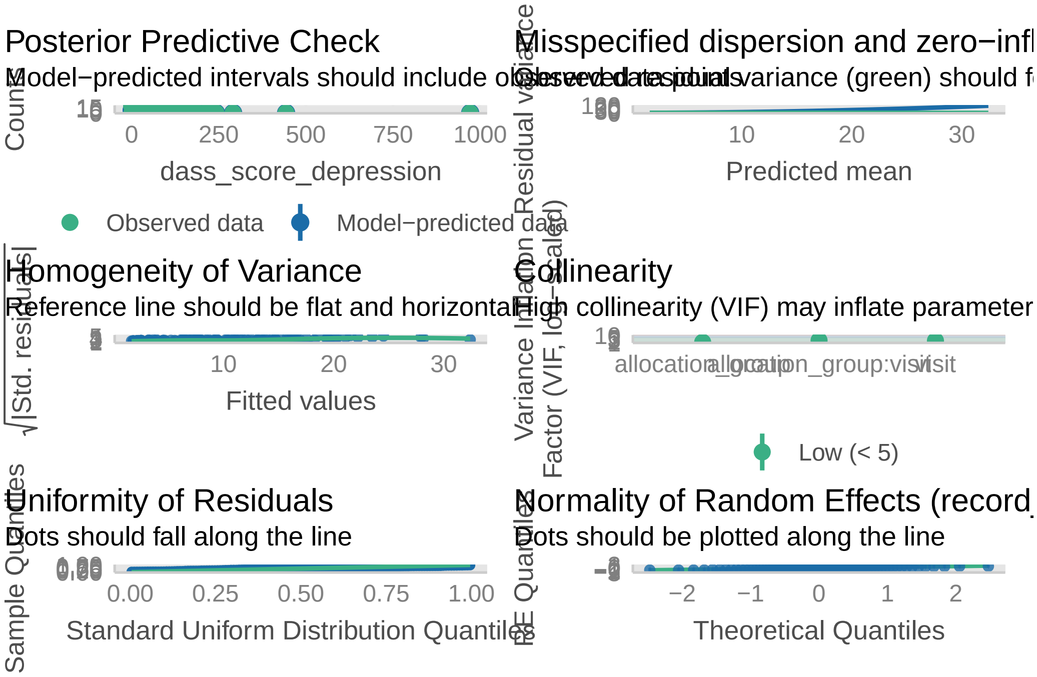
```
Conditional model:
                               Estimate Std. Error z value Pr(>|z|)    
(Intercept)                     2.42552    0.17649  13.743   <2e-16 ***
allocation_groupGrupo B         0.06835    0.23562   0.290    0.772    
visit3                         -0.15647    0.22055  -0.709    0.478    
allocation_groupGrupo B:visit3 -0.22457    0.31152  -0.721    0.471    
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```r
# Compare performance
performance::compare_performance(
  dass_score_depression_nb_model,
  dass_score_depression_nb_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)
------------------------------------------------------------------------------
dass_score_depression_nb_model      | glmmTMB | 882.6 (<.001) |  883.3 (<.001)
dass_score_depression_nb_model_sens | glmmTMB | 830.9 (>.999) |  831.6 (>.999)

Name                                | BIC (weights) | R2 (cond.) | R2 (marg.)
-----------------------------------------------------------------------------
dass_score_depression_nb_model      | 899.6 (<.001) |      0.626 |      0.022
dass_score_depression_nb_model_sens | 847.4 (>.999) |      0.479 |      0.025

Name                                |   ICC |  RMSE | Sigma | Score_log | Score_spherical
-----------------------------------------------------------------------------------------
dass_score_depression_nb_model      | 0.618 | 5.787 | 2.118 |    -2.975 |           0.064
dass_score_depression_nb_model_sens | 0.465 | 6.553 | 2.205 |    -3.171 |           0.076
```

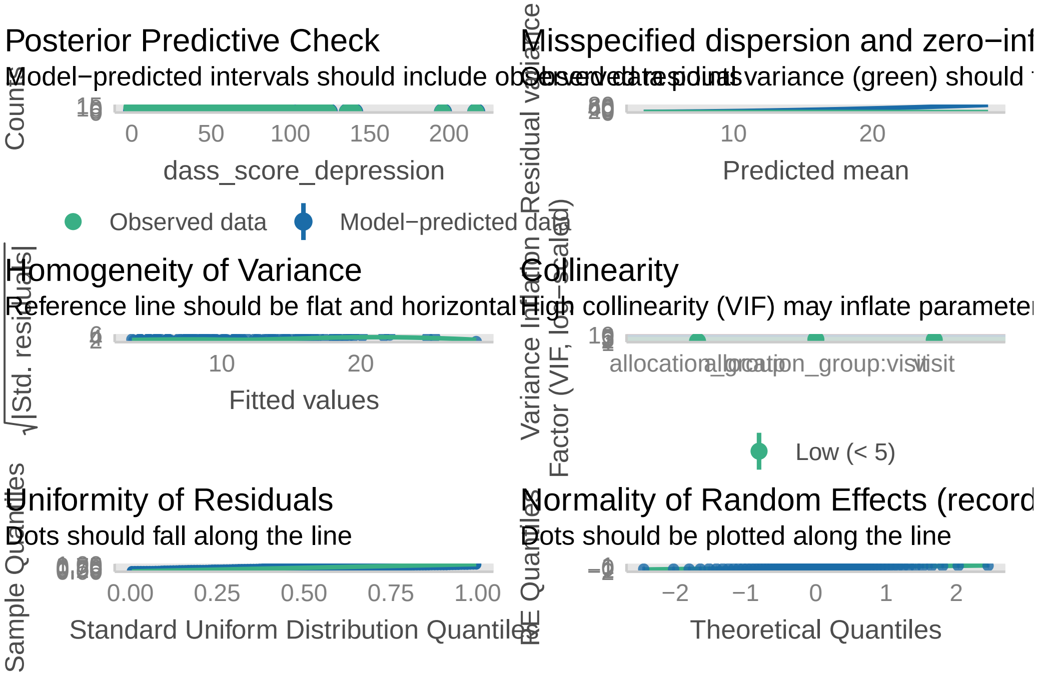
```r
# Diagnostic checks
performance::check_model(dass_score_depression_nb_model)
```

```
`check_outliers()` does not yet support models of class `glmmTMB`.
```



```
performance::check_model(dass_score_depression_nb_model_sens)
```

```
`check_outliers()` does not yet support models of class `glmmTMB`.
```



2.1.0.2 Médias Marginais Estimadas

2.1.0.2.1 Todos os dados

```
# Estimated marginal means on the response scale
dass_score_depression_nb_emm <- emmeans::emmeans(
  dass_score_depression_nb_model,
  ~ allocation_group * visit,
  type = "response"
)

# Pairwise contrasts by visit
emmeans::contrast(
  dass_score_depression_nb_emm,
  method = "pairwise",
  by     = "visit",
  adjust = "bonferroni"
) %>% summary(infer = c(TRUE, TRUE))
```

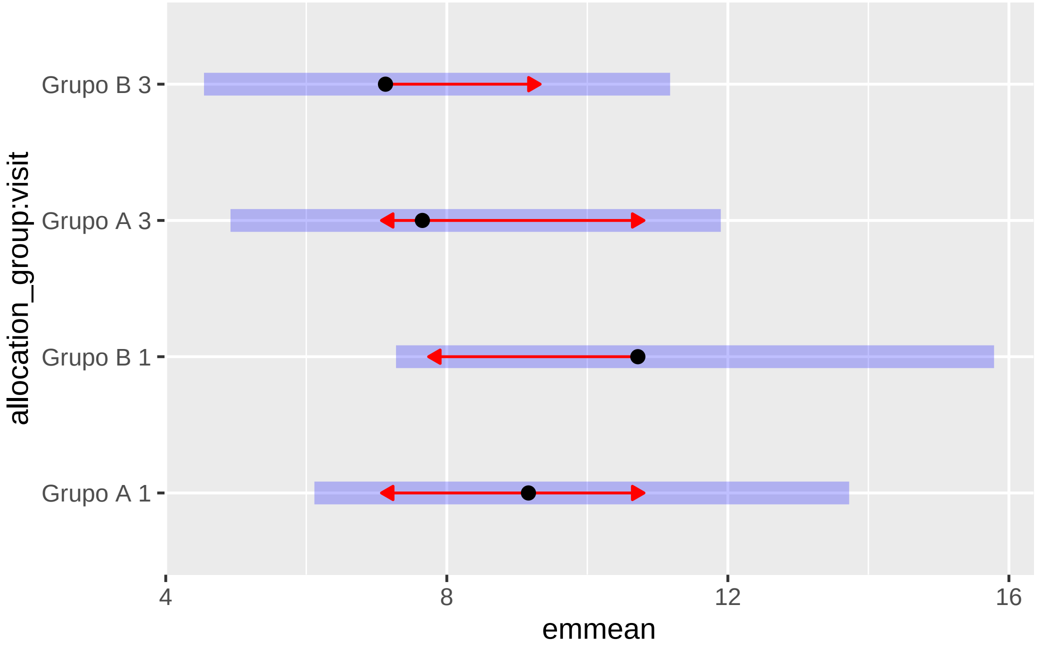
```
visit = 1:
 contrast          ratio    SE  df asymp.LCL asymp.UCL null z.ratio p.value
 Grupo A / Grupo B 0.855 0.232 Inf     0.502      1.46    1  -0.578  0.5635

visit = 3:
 contrast          ratio    SE  df asymp.LCL asymp.UCL null z.ratio p.value
 Grupo A / Grupo B 1.074 0.343 Inf     0.574      2.01    1   0.223  0.8237

Confidence level used: 0.95
Intervals are back-transformed from the log scale
Tests are performed on the log scale
```

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

```
allocation_group = Grupo A:
 contrast        ratio    SE  df asymp.LCL asymp.UCL null z.ratio p.value
 visit1 / visit3   1.2 0.272 Inf     0.767      1.87    1   0.793  0.4279

allocation_group = Grupo B:
 contrast        ratio    SE  df asymp.LCL asymp.UCL null z.ratio p.value
 visit1 / visit3   1.5 0.345 Inf     0.959      2.36    1   1.777  0.0756
```

```
Confidence level used: 0.95
Intervals are back-transformed from the log scale
Tests are performed on the log scale
```

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



2.1.0.2.2 Análise de sensibilidade

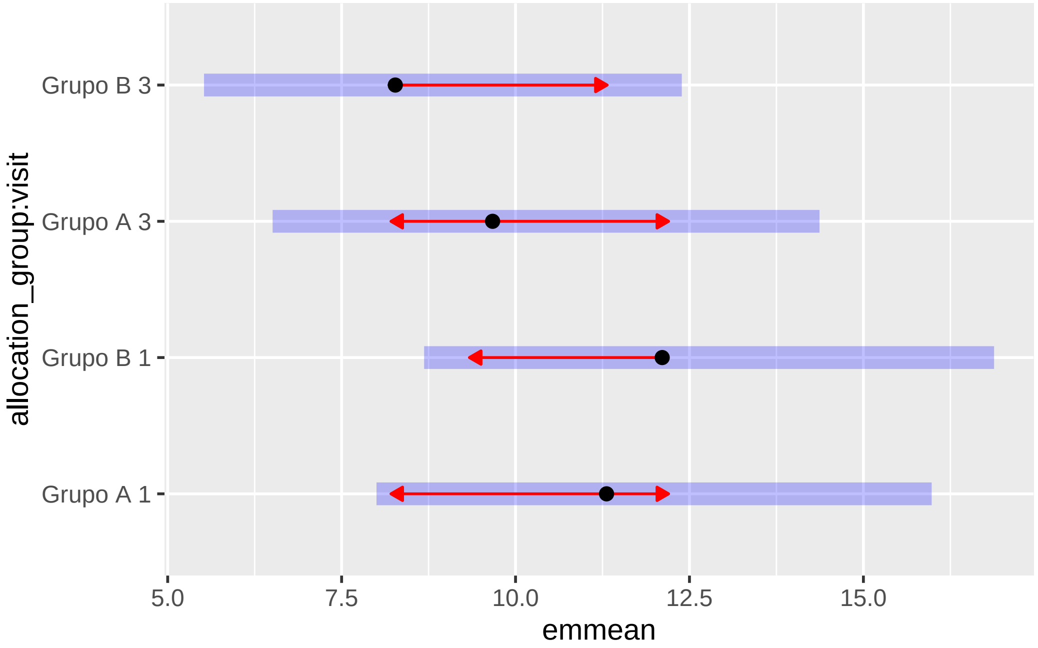
```
# Estimated marginal means on the response scale
dass_score_depression_nb_emm_sens <- emmeans::emmeans(
  dass_score_depression_nb_model_sens,
  ~ allocation_group * visit,
  type = "response"
)

# Pairwise contrasts by visit
emmeans::contrast(
  dass_score_depression_nb_emm_sens,
  method = "pairwise",
  by     = "visit",
  adjust = "bonferroni"
) %>% summary(infer = c(TRUE, TRUE))
```

```
visit = 1:
 contrast          ratio    SE  df asymp.LCL asymp.UCL null z.ratio p.value
 Grupo A / Grupo B 0.934 0.220 Inf     0.589      1.48    1  -0.290  0.7718

visit = 3:
 contrast          ratio    SE  df asymp.LCL asymp.UCL null z.ratio p.value
 Grupo A / Grupo B 1.169 0.335 Inf     0.667      2.05    1   0.546  0.5853

Confidence level used: 0.95
Intervals are back-transformed from the log scale
Tests are performed on the log scale
```

```r
# Pairwise contrasts over time within each group
emmeans::contrast(
  dass_score_depression_nb_emm_sens,
  method = "pairwise",
  by     = "allocation_group",
  adjust = "bonferroni"
) %>% summary(infer = c(TRUE, TRUE))
```

```
allocation_group = Grupo A:
 contrast        ratio    SE  df asymp.LCL asymp.UCL null z.ratio p.value
 visit1 / visit3  1.17 0.258 Inf     0.759      1.80    1   0.709  0.4780

allocation_group = Grupo B:
 contrast        ratio    SE  df asymp.LCL asymp.UCL null z.ratio p.value
 visit1 / visit3  1.46 0.325 Inf     0.948      2.26    1   1.717  0.0860

Confidence level used: 0.95
Intervals are back-transformed from the log scale
Tests are performed on the log scale
```

```r
# Plot marginal means
plot(dass_score_depression_nb_emm_sens, comparisons = TRUE)
```



2.1.0.3 Resultado

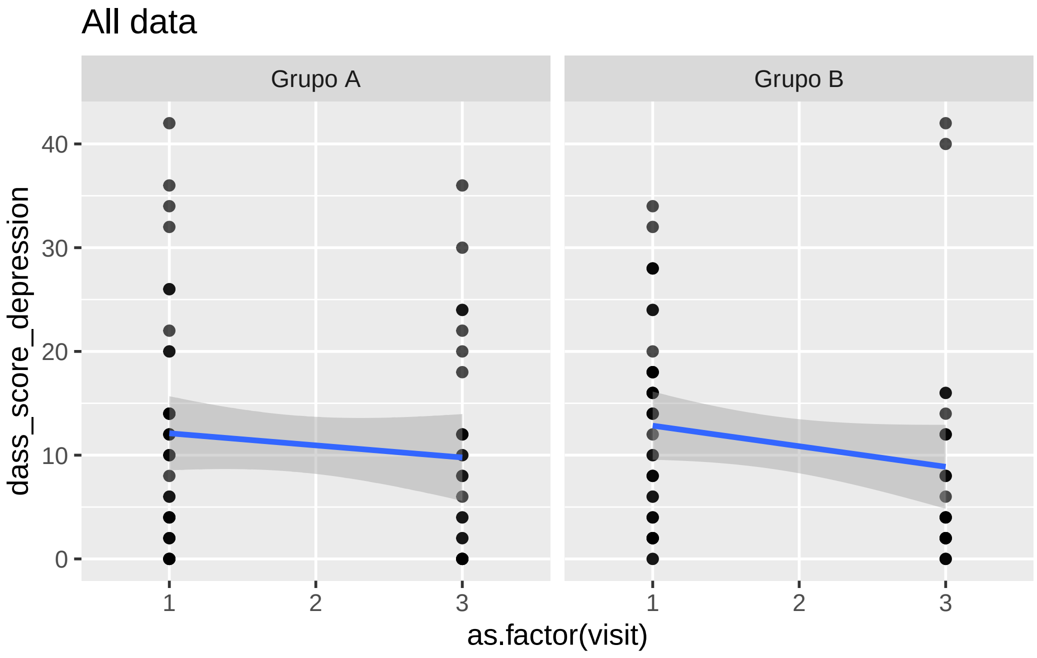
No modelo de regressão para o escore de depressão (DASS), não foram observadas diferenças significativas entre os grupos em nenhum dos momentos avaliados. Na visita 1, a razão dos escores do Grupo A em relação ao Grupo B foi de 0,855 (IC 95%: 0,502–1,46; p = 0,564) e, na visita 3, 1,074 (IC 95%: 0,574–2,01; p = 0,824). Ao longo do tempo, também não houve mudança significativa dentro de cada grupo: Grupo Placebo (visita 1 vs visita 3, razão = 1,20; IC 95%: 0,767–1,87; p = 0,428) e Grupo Eclipta (visita 1 vs visita 3, razão = 1,50; IC 95%: 0,959–2,36; p = 0,076). A análise de sensibilidade apresentou padrão consistente, sem alterações relevantes nas conclusões.

Tabela: Razões dos escores de depressão (DASS) entre grupos e ao longo do tempo – Todos os dados {#tbl-dass_depression}

Grupo de comparação	Comparação	Razão	IC 95%	p-valor
Entre grupos	Visita 1	0,855	[0,502; 1,46]	0,564
Entre grupos	Visita 3	1,074	[0,574; 2,01]	0,824
Grupo Placebo	Visita 1 – Visita 3	1,20	[0,767; 1,87]	0,428
Grupo Eclipta	Visita 1 – Visita 3	1,50	[0,959; 2,36]	0,076

```
ggplot(
    data = data_model_V1V3,
    aes(
        x = as.factor(visit),
        y = dass_score_depression,
        group = record_id,
    )
) +
    geom_line(alpha = 0.5) +
    geom_point(alpha = 0.7) +
    geom_smooth(
        aes(group = allocation_group),
        method = "lm",
        se = TRUE,
        linewidth = 1
    ) +
    labs(title = "All data") +
    facet_wrap(~ allocation_group)
```

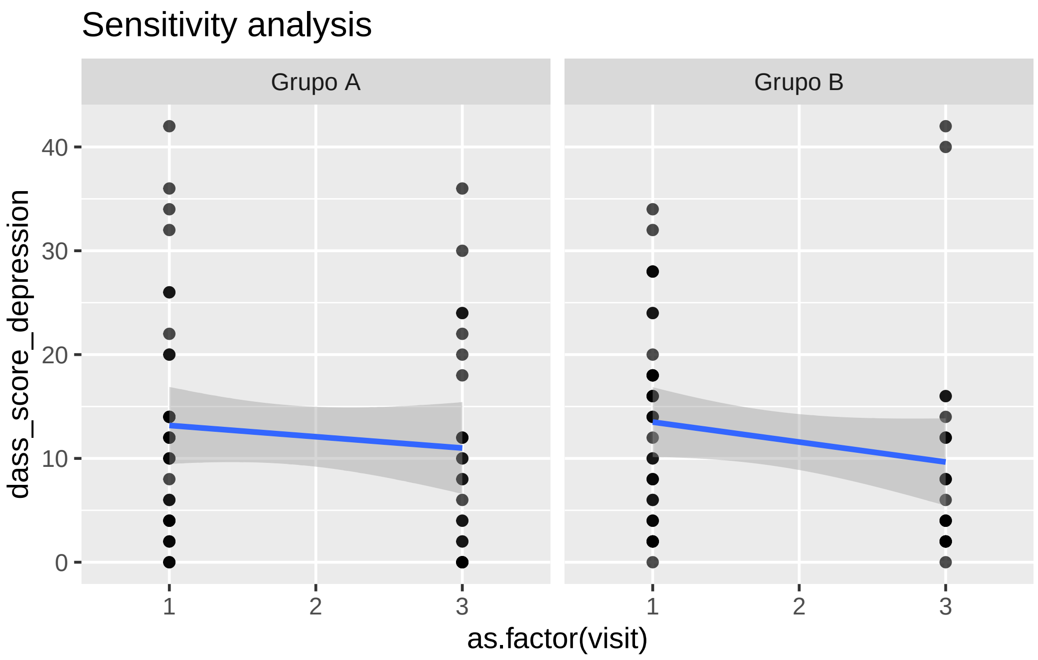
```
`geom_smooth()` using formula = 'y ~ x'
Warning: Removed 62 rows containing non-finite outside the scale range
(`stat_smooth()`).
Warning: Removed 10 rows containing missing values or values outside the scale range
(`geom_line()`).
Warning: Removed 62 rows containing missing values or values outside the scale range
(`geom_point()`).
```



```
data_model_V1V3 %>%
    filter(
        !(record_id %in%
        influential_ids_nb)
```

```r
    ) %>%
    ggplot(
        aes(
            x = as.factor(visit),
            y = dass_score_depression,
            group = record_id,
        )
    ) +
    geom_line(alpha = 0.5) +
    geom_point(alpha = 0.7) +
    geom_smooth(
        aes(group = allocation_group),
        method = "lm",
        se = TRUE,
        linewidth = 1
    ) +
    labs(title = "Sensitivity analysis") +
    facet_wrap(~ allocation_group)
```

```
`geom_smooth()` using formula = 'y ~ x'
Warning: Removed 57 rows containing non-finite outside the scale range
(`stat_smooth()`).
Warning: Removed 10 rows containing missing values or values outside the scale range
(`geom_line()`).
Warning: Removed 57 rows containing missing values or values outside the scale range
(`geom_point()`).
```

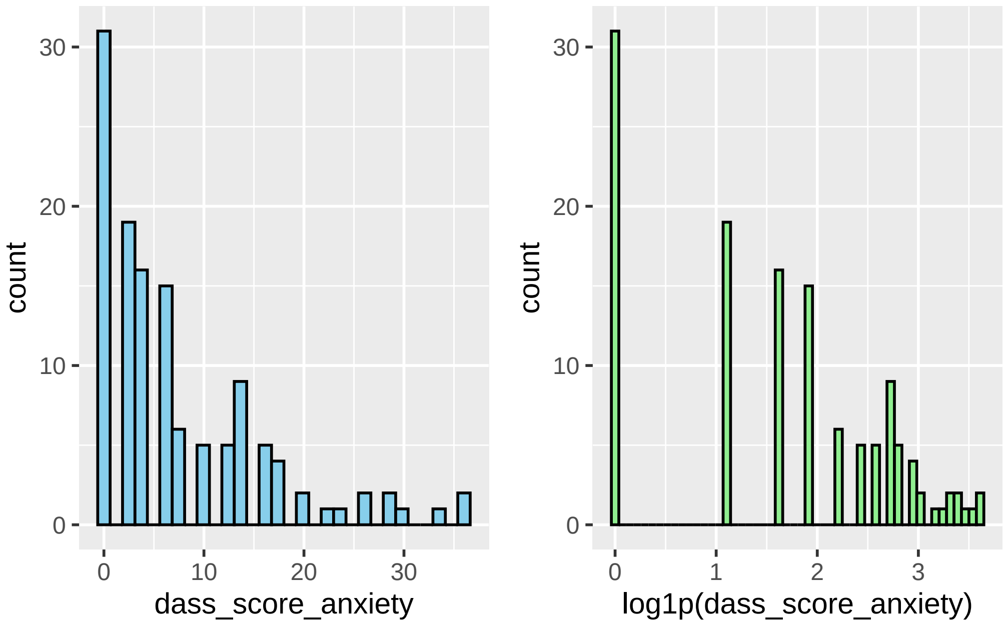


2.2 Escore DASS - Ansiedade

Variável: dass_score_anxiety

```
# Plot 1: Raw data
dass_score_anxiety_hist_1 <- data_model_V1V3 %>%
    #filter(
    #    dass_score_anxiety < 300
    #) %>%
    ggplot(aes(x = dass_score_anxiety)) +
    geom_histogram(bins = 30, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
dass_score_anxiety_hist_2 <- data_model_V1V3 %>%
    #filter(
    #    dass_score_anxiety < 300
    #) %>%
    ggplot(aes(x = log1p(dass_score_anxiety))) +
    geom_histogram(bins = 50, fill = "lightgreen", color = "black")

# Combine side by side
dass_score_anxiety_hist_1 + dass_score_anxiety_hist_2 # library(patchwork)
```

```
Warning: Removed 62 rows containing non-finite outside the scale range (`stat_bin()`).
Removed 62 rows containing non-finite outside the scale range (`stat_bin()`).
```



```r
# Fit a negative-binomial GLMM
dass_score_anxiety_nb_model <- glmmTMB::glmmTMB(
  formula = dass_score_anxiety ~ allocation_group * visit + (1 | record_id),
  family  = glmmTMB::nbinom2(),
  data    = data_model_V1V3
)

# Check collinearity
performance::check_collinearity(dass_score_anxiety_nb_model)
```

```
# Check for Multicollinearity

Low Correlation

                   Term  VIF   VIF 95% CI Increased SE Tolerance
       allocation_group 1.26 [1.10, 1.67]         1.12      0.80
                  visit 1.78 [1.46, 2.33]         1.33      0.56
 allocation_group:visit 1.96 [1.58, 2.58]         1.40      0.51
 Tolerance 95% CI
     [0.60, 0.91]
     [0.43, 0.69]
     [0.39, 0.63]
```

```
# 3. Identify the 5 most "influential" clusters by magnitude of their random intercepts
re_nb <- glmmTMB::ranef(dass_score_anxiety_nb_model)$cond$record_id
re_nb_df <- data.frame(
  record_id = rownames(re_nb),
  intercept = re_nb[, 1],
  stringsAsFactors = FALSE
)
influential_ids_nb <- re_nb_df %>%
  dplyr::arrange(dplyr::desc(abs(intercept))) %>%
  dplyr::slice_head(n = 5) %>%
  dplyr::pull(record_id)

# 4. Re-fit the model excluding those top-5 clusters
dass_score_anxiety_nb_model_sens <- update(
  dass_score_anxiety_nb_model,
  data = dplyr::filter(data_model_V1V3, !record_id %in% influential_ids_nb)
)

# 5. Inspect which record_ids were most extreme
influential_ids_nb
```

```
[1] "5"  "27" "44" "46" "61"
```

2.2.0.1 Resumo dos modelos

```
# Model summaries
summary(dass_score_anxiety_nb_model)
```

```
 Family: nbinom2  ( log )
Formula:
dass_score_anxiety ~ allocation_group * visit + (1 | record_id)
Data: data_model_V1V3

      AIC       BIC    logLik -2*log(L)  df.resid
    779.3     796.4    -383.7     767.3       121

Random effects:

Conditional model:
 Groups    Name        Variance Std.Dev.
 record_id (Intercept) 0.8548   0.9245
Number of obs: 127, groups:  record_id, 75

Dispersion parameter for nbinom2 family (): 1.53

Conditional model:
                               Estimate Std. Error z value Pr(>|z|)
(Intercept)                     1.91708    0.29004   6.610 3.85e-11 ***
allocation_groupGrupo B        -0.05521    0.31626  -0.175    0.861
visit3                         -0.42772    0.28697  -1.490    0.136
allocation_groupGrupo B:visit3 -0.02559    0.38784  -0.066    0.947
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```r
summary(dass_score_anxiety_nb_model_sens)
```

```
 Family: nbinom2  ( log )
Formula:
dass_score_anxiety ~ allocation_group * visit + (1 | record_id)
Data: dplyr::filter(data_model_V1V3, !record_id %in% influential_ids_nb)

      AIC       BIC    logLik -2*log(L)  df.resid
    725.7     742.3    -356.8     713.7       111

Random effects:

Conditional model:
 Groups    Name        Variance Std.Dev.
 record_id (Intercept) 0.1036   0.3219
Number of obs: 117, groups:  record_id, 70

Dispersion parameter for nbinom2 family ():    1

Conditional model:
                               Estimate Std. Error z value Pr(>|z|)
(Intercept)                     2.30662    0.23808   9.689   <2e-16 ***
allocation_groupGrupo B        -0.25752    0.27156  -0.948   0.3430
visit3                         -0.59810    0.31116  -1.922   0.0546 .
allocation_groupGrupo B:visit3  0.07566    0.42503   0.178   0.8587
```

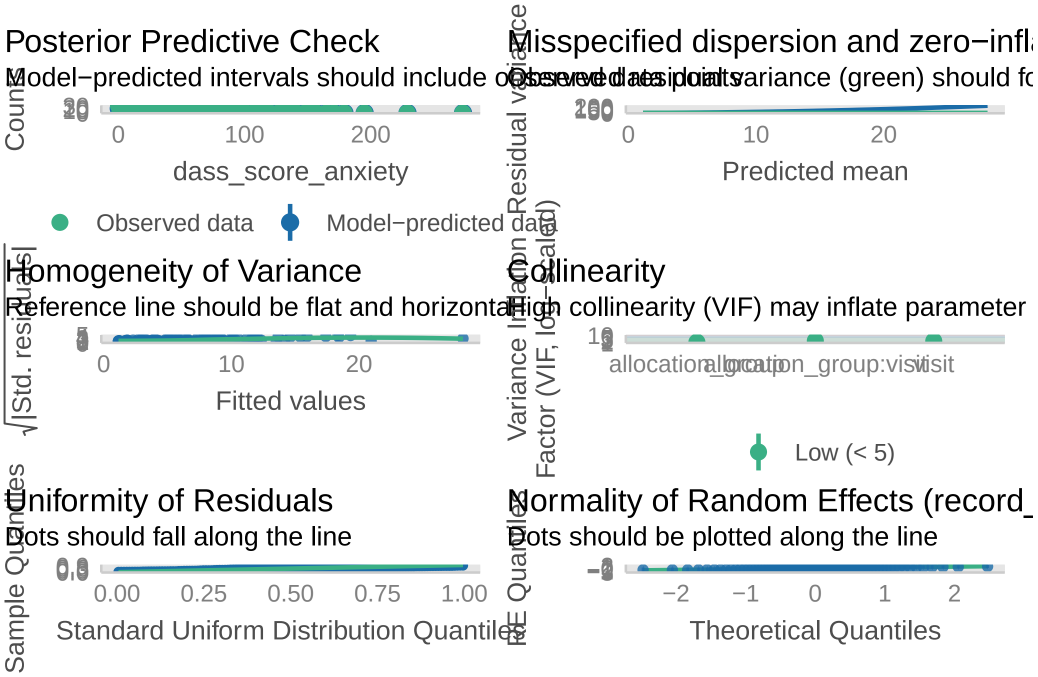
```
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```r
# Compare performance
performance::compare_performance(
  dass_score_anxiety_nb_model,
  dass_score_anxiety_nb_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)
---------------------------------------------------------------------------
dass_score_anxiety_nb_model      | glmmTMB | 779.3 (<.001) |  780.0 (<.001)
dass_score_anxiety_nb_model_sens | glmmTMB | 725.7 (>.999) |  726.5 (>.999)

Name                             | BIC (weights) | R2 (cond.) | R2 (marg.)
--------------------------------------------------------------------------
dass_score_anxiety_nb_model      | 796.4 (<.001) |      0.614 |      0.033
dass_score_anxiety_nb_model_sens | 742.3 (>.999) |      0.203 |      0.093

Name                             |   ICC |  RMSE | Sigma | Score_log | Score_spherical
------------------------------------------------------------------------------------
dass_score_anxiety_nb_model      | 0.601 | 4.631 | 1.530 |    -2.568 |           0.064
dass_score_anxiety_nb_model_sens | 0.121 | 6.709 | 1.003 |    -3.016 |           0.080
```

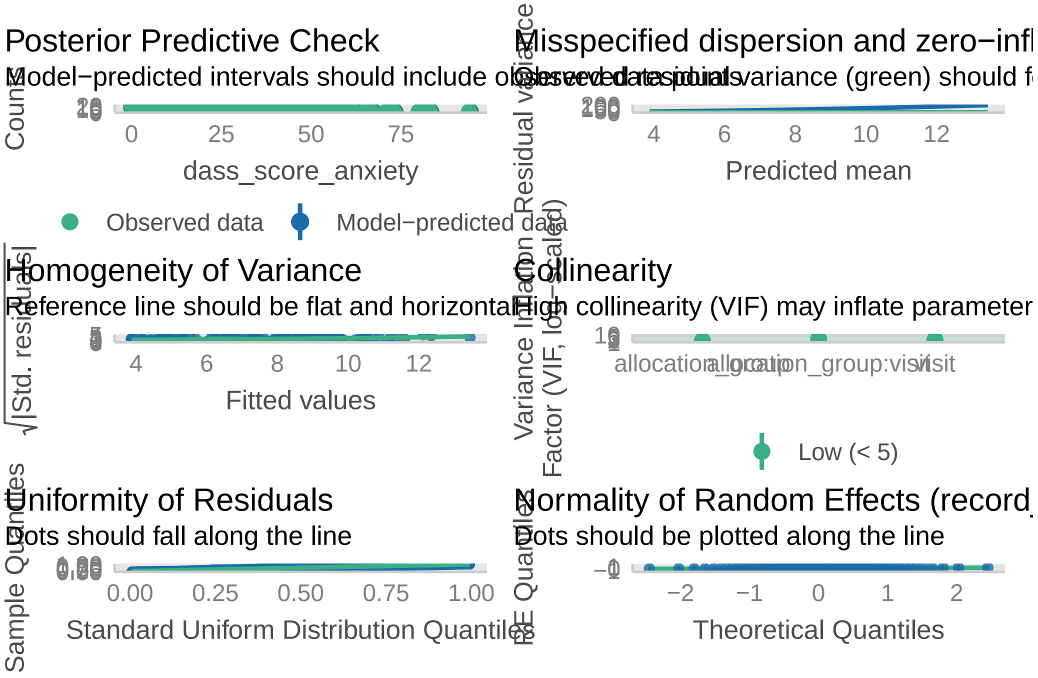
```r
# Diagnostic checks
performance::check_model(dass_score_anxiety_nb_model)
```

```
`check_outliers()` does not yet support models of class `glmmTMB`.
```



```r
performance::check_model(dass_score_anxiety_nb_model_sens)
```

```
`check_outliers()` does not yet support models of class `glmmTMB`.
```



2.2.0.2 Médias Marginais Estimadas

2.2.0.2.1 Todos os dados

```r
# Estimated marginal means on the response scale
dass_score_anxiety_nb_emm <- emmeans::emmeans(
  dass_score_anxiety_nb_model,
  ~ allocation_group * visit,
  type = "response"
)

# Pairwise contrasts by visit
emmeans::contrast(
  dass_score_anxiety_nb_emm,
  method = "pairwise",
  by     = "visit",
  adjust = "bonferroni"
) %>% summary(infer = c(TRUE, TRUE))
```

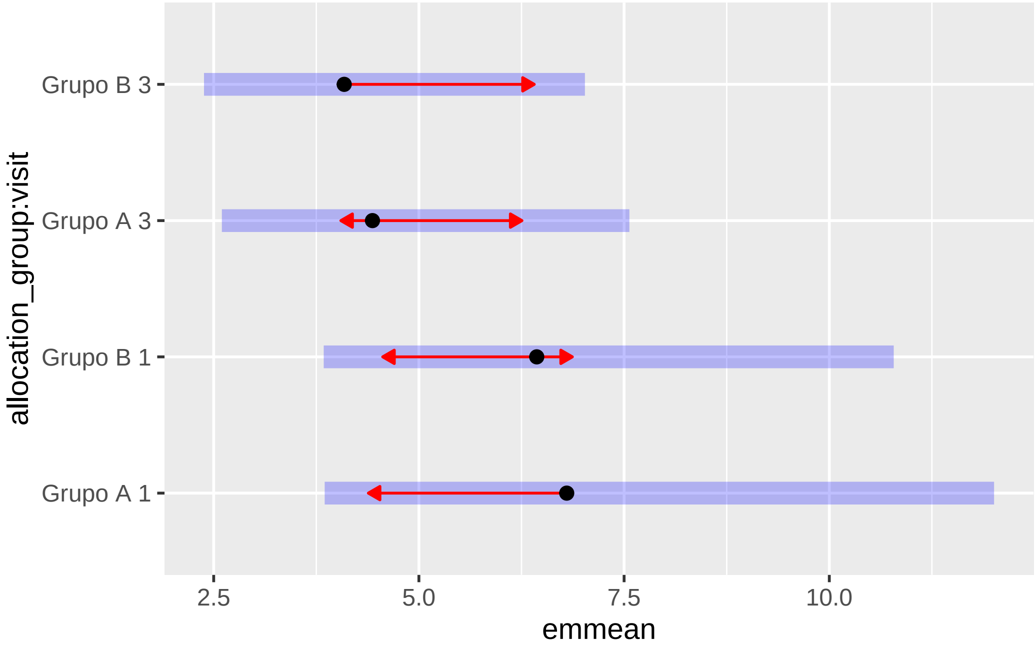
```
visit = 1:
 contrast          ratio    SE  df asymp.LCL asymp.UCL null z.ratio p.value
 Grupo A / Grupo B  1.06 0.334 Inf     0.569      1.96    1   0.175  0.8614

visit = 3:
 contrast          ratio    SE  df asymp.LCL asymp.UCL null z.ratio p.value
 Grupo A / Grupo B  1.08 0.407 Inf     0.519      2.26    1   0.215  0.8296

Confidence level used: 0.95
Intervals are back-transformed from the log scale
Tests are performed on the log scale
```

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

```
allocation_group = Grupo A:
 contrast        ratio    SE  df asymp.LCL asymp.UCL null z.ratio p.value
 visit1 / visit3  1.53 0.440 Inf     0.874      2.69    1   1.490  0.1361

allocation_group = Grupo B:
 contrast        ratio    SE  df asymp.LCL asymp.UCL null z.ratio p.value
 visit1 / visit3  1.57 0.461 Inf     0.886      2.80    1   1.546  0.1222
```

```
Confidence level used: 0.95
Intervals are back-transformed from the log scale
Tests are performed on the log scale
```

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



2.2.0.2.2 Análise de sensibilidade

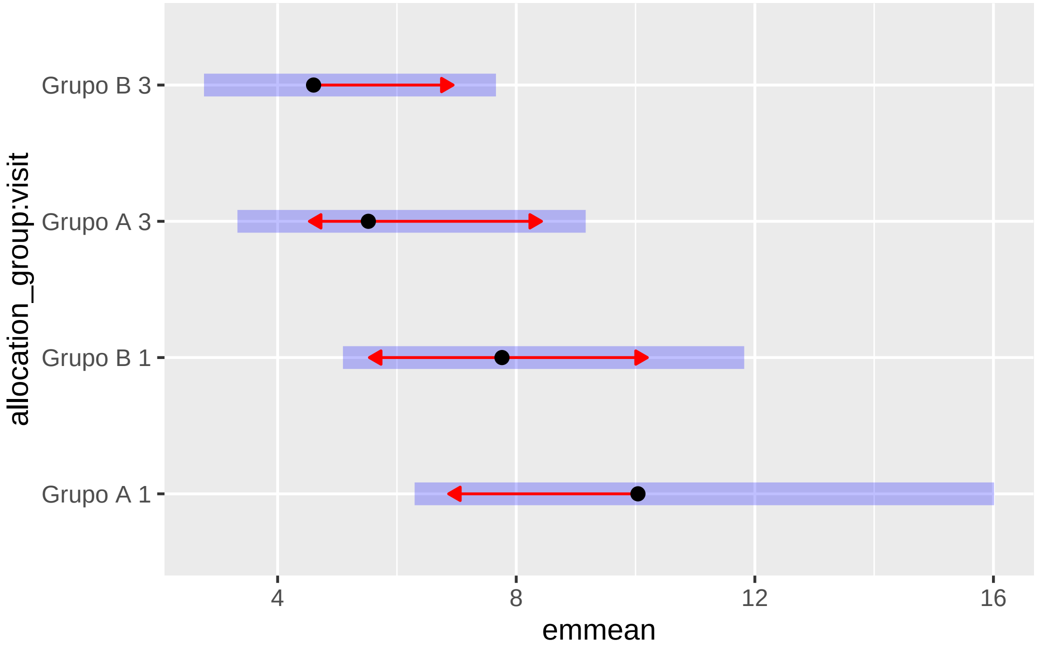
```
# Estimated marginal means on the response scale
dass_score_anxiety_nb_emm_sens <- emmeans::emmeans(
  dass_score_anxiety_nb_model_sens,
  ~ allocation_group * visit,
  type = "response"
)

# Pairwise contrasts by visit
emmeans::contrast(
  dass_score_anxiety_nb_emm_sens,
  method = "pairwise",
  by     = "visit",
  adjust = "bonferroni"
) %>% summary(infer = c(TRUE, TRUE))
```

```
visit = 1:
 contrast          ratio    SE  df asymp.LCL asymp.UCL null z.ratio p.value
 Grupo A / Grupo B  1.29 0.351 Inf     0.760      2.20    1   0.948  0.3430

visit = 3:
 contrast          ratio    SE  df asymp.LCL asymp.UCL null z.ratio p.value
 Grupo A / Grupo B  1.20 0.411 Inf     0.613      2.35    1   0.531  0.5955

Confidence level used: 0.95
Intervals are back-transformed from the log scale
Tests are performed on the log scale
```

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

```
allocation_group = Grupo A:
 contrast        ratio    SE  df asymp.LCL asymp.UCL null z.ratio p.value
 visit1 / visit3  1.82 0.566 Inf     0.988      3.35    1   1.922  0.0546

allocation_group = Grupo B:
 contrast        ratio    SE  df asymp.LCL asymp.UCL null z.ratio p.value
 visit1 / visit3  1.69 0.488 Inf     0.956      2.97    1   1.804  0.0712

Confidence level used: 0.95
Intervals are back-transformed from the log scale
Tests are performed on the log scale
```

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



2.2.0.3 Resultado

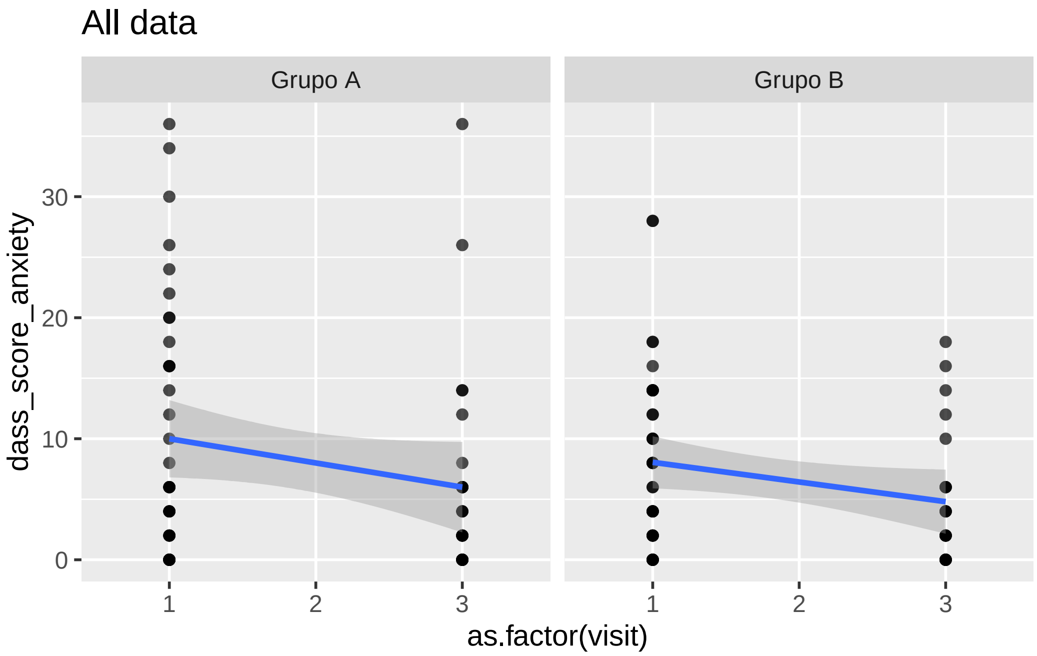
No modelo ajustado para o escore de ansiedade (DASS), não houve diferenças significativas entre os grupos em nenhum dos momentos avaliados (visita 1: razão = 1,06; IC 95%: 0,57–1,96; p = 0,861; visita 3: razão = 1,08; IC 95%: 0,52–2,26; p = 0,830). Também não houve alteração significativa ao longo do tempo dentro de cada grupo (placebo: visita 1 vs visita 3, razão = 1,53; IC 95%: 0,87–2,69; p = 0,136; Eclipta: razão = 1,57; IC 95%: 0,89–2,80; p = 0,122). A análise de sensibilidade manteve o mesmo padrão de resultados.

Tabela: Razões dos escores de ansiedade (DASS) entre grupos e ao longo do tempo – Todos os dados {#tbl-dass_anxiety}

Grupo de comparação	Comparação	Razão	IC 95%	p-valor
Entre grupos	Visita 1	1,06	[0,57; 1,96]	0,861
Entre grupos	Visita 3	1,08	[0,52; 2,26]	0,830
Grupo Placebo	Visita 1 – Visita 3	1,53	[0,87; 2,69]	0,136
Grupo Eclipta	Visita 1 – Visita 3	1,57	[0,89; 2,80]	0,122

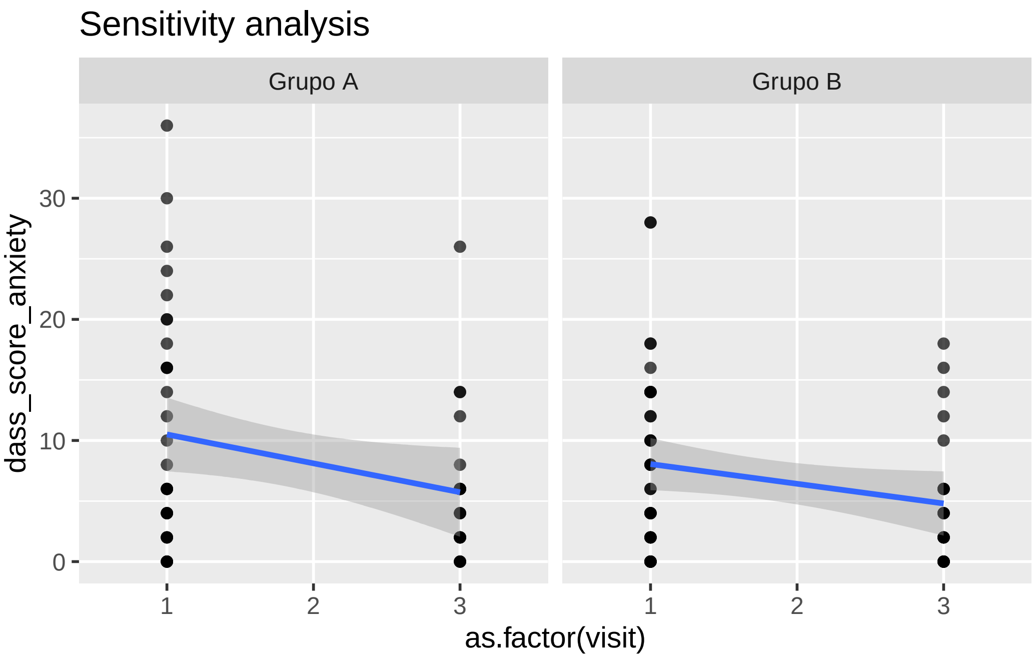
```
ggplot(
    data = data_model_V1V3,
    aes(
        x = as.factor(visit),
        y = dass_score_anxiety,
        group = record_id,
    )
) +
    geom_line(alpha = 0.5) +
    geom_point(alpha = 0.7) +
    geom_smooth(
        aes(group = allocation_group),
        method = "lm",
        se = TRUE,
        linewidth = 1
    ) +
    labs(title = "All data") +
    facet_wrap(~ allocation_group)
```

```
`geom_smooth()` using formula = 'y ~ x'
Warning: Removed 62 rows containing non-finite outside the scale range
(`stat_smooth()`).
Warning: Removed 10 rows containing missing values or values outside the scale range
(`geom_line()`).
Warning: Removed 62 rows containing missing values or values outside the scale range
(`geom_point()`).
```



```
data_model_V1V3 %>%
    filter(
        !(record_id %in%
        influential_ids_nb)
    ) %>%
    ggplot(
        aes(
            x = as.factor(visit),
            y = dass_score_anxiety,
            group = record_id,
        )
    ) +
    geom_line(alpha = 0.5) +
    geom_point(alpha = 0.7) +
    geom_smooth(
        aes(group = allocation_group),
        method = "lm",
        se = TRUE,
        linewidth = 1
    ) +
    labs(title = "Sensitivity analysis") +
    facet_wrap(~ allocation_group)
```

```
`geom_smooth()` using formula = 'y ~ x'
Warning: Removed 57 rows containing non-finite outside the scale range
(`stat_smooth()`).
Warning: Removed 10 rows containing missing values or values outside the scale range
(`geom_line()`).
Warning: Removed 57 rows containing missing values or values outside the scale range
(`geom_point()`).
```

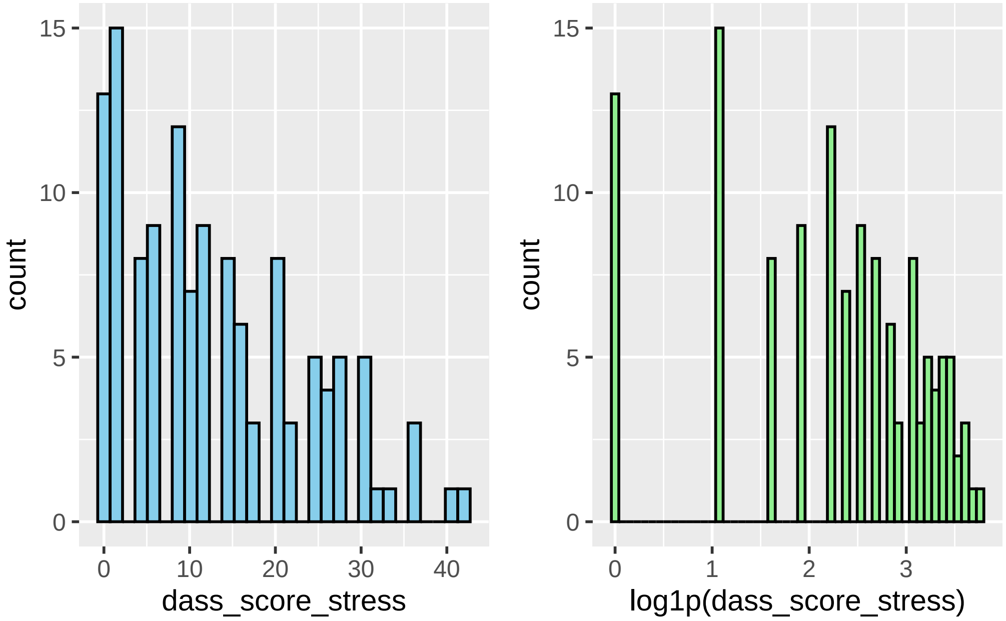


2.3 Escore DASS - Estresse

Variável: `dass_score_stress`

```
# Plot 1: Raw data
dass_score_stress_hist_1 <- data_model_V1V3 %>%
    #filter(
    #    dass_score_stress < 300
    #) %>%
    ggplot(aes(x = dass_score_stress)) +
    geom_histogram(bins = 30, fill = "skyblue", color = "black")

# Plot 2: Log-transformed data
dass_score_stress_hist_2 <- data_model_V1V3 %>%
    #filter(
    #    dass_score_stress < 300
    #) %>%
    ggplot(aes(x = log1p(dass_score_stress))) +
    geom_histogram(bins = 50, fill = "lightgreen", color = "black")

# Combine side by side
dass_score_stress_hist_1 + dass_score_stress_hist_2 # library(patchwork)
```

```
Warning: Removed 62 rows containing non-finite outside the scale range (`stat_bin()`).
Removed 62 rows containing non-finite outside the scale range (`stat_bin()`).
```



```r
# Fit a negative-binomial GLMM
dass_score_stress_nb_model <- glmmTMB::glmmTMB(
  formula = dass_score_stress ~ allocation_group * visit + (1 | record_id),
  family  = glmmTMB::nbinom2(),
  data    = data_model_V1V3
)

# Check collinearity
performance::check_collinearity(dass_score_stress_nb_model)
```

```
# Check for Multicollinearity

Low Correlation

                   Term  VIF   VIF 95% CI Increased SE Tolerance
       allocation_group 1.13 [1.03, 1.64]         1.06      0.89
                  visit 1.92 [1.55, 2.52]         1.39      0.52
 allocation_group:visit 2.03 [1.63, 2.67]         1.42      0.49
 Tolerance 95% CI
     [0.61, 0.97]
     [0.40, 0.64]
     [0.37, 0.61]
```

```r
# 3. Identify the 5 most "influential" clusters by magnitude of their random intercepts
re_nb <- glmmTMB::ranef(dass_score_stress_nb_model)$cond$record_id
re_nb_df <- data.frame(
  record_id = rownames(re_nb),
  intercept = re_nb[, 1],
  stringsAsFactors = FALSE
)
influential_ids_nb <- re_nb_df %>%
  dplyr::arrange(dplyr::desc(abs(intercept))) %>%
  dplyr::slice_head(n = 5) %>%
  dplyr::pull(record_id)

# 4. Re-fit the model excluding those top-5 clusters
dass_score_stress_nb_model_sens <- update(
  dass_score_stress_nb_model,
  data = dplyr::filter(data_model_V1V3, !record_id %in% influential_ids_nb)
)


# 5. Inspect which record_ids were most extreme
influential_ids_nb
```

```
[1] "15" "44" "53" "74" "13"
```

2.3.0.1 Resumo dos modelos

```
# Model summaries
summary(dass_score_stress_nb_model)
```

```
 Family: nbinom2  ( log )
Formula:
dass_score_stress ~ allocation_group * visit + (1 | record_id)
Data: data_model_V1V3

      AIC       BIC    logLik -2*log(L)  df.resid
    908.9     926.0    -448.5     896.9       121

Random effects:

Conditional model:
 Groups    Name        Variance Std.Dev.
 record_id (Intercept) 0.7258   0.852
Number of obs: 127, groups:  record_id, 75

Dispersion parameter for nbinom2 family (): 4.77

Conditional model:
                               Estimate Std. Error z value Pr(>|z|)
(Intercept)                     2.32017    0.17349  13.373   <2e-16 ***
allocation_groupGrupo B         0.19497    0.23866   0.817    0.414
visit3                         -0.05252    0.16119  -0.326    0.745
allocation_groupGrupo B:visit3 -0.36916    0.22956  -1.608    0.108
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
summary(dass_score_stress_nb_model_sens)
```

```
 Family: nbinom2  ( log )
Formula:
```

```
dass_score_stress ~ allocation_group * visit + (1 | record_id)
Data: dplyr::filter(data_model_V1V3, !record_id %in% influential_ids_nb)

      AIC       BIC    logLik -2*log(L)  df.resid
    847.0     863.6    -417.5     835.0       111

Random effects:

Conditional model:
 Groups    Name        Variance Std.Dev.
 record_id (Intercept) 0.3768   0.6138
Number of obs: 117, groups:  record_id, 70

Dispersion parameter for nbinom2 family (): 4.68

Conditional model:
                               Estimate Std. Error z value Pr(>|z|)
(Intercept)                     2.53856    0.14591  17.398   <2e-16 ***
allocation_groupGrupo B         0.11420    0.19884   0.574    0.566
visit3                         -0.08659    0.16281  -0.532    0.595
allocation_groupGrupo B:visit3 -0.32208    0.22939  -1.404    0.160
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

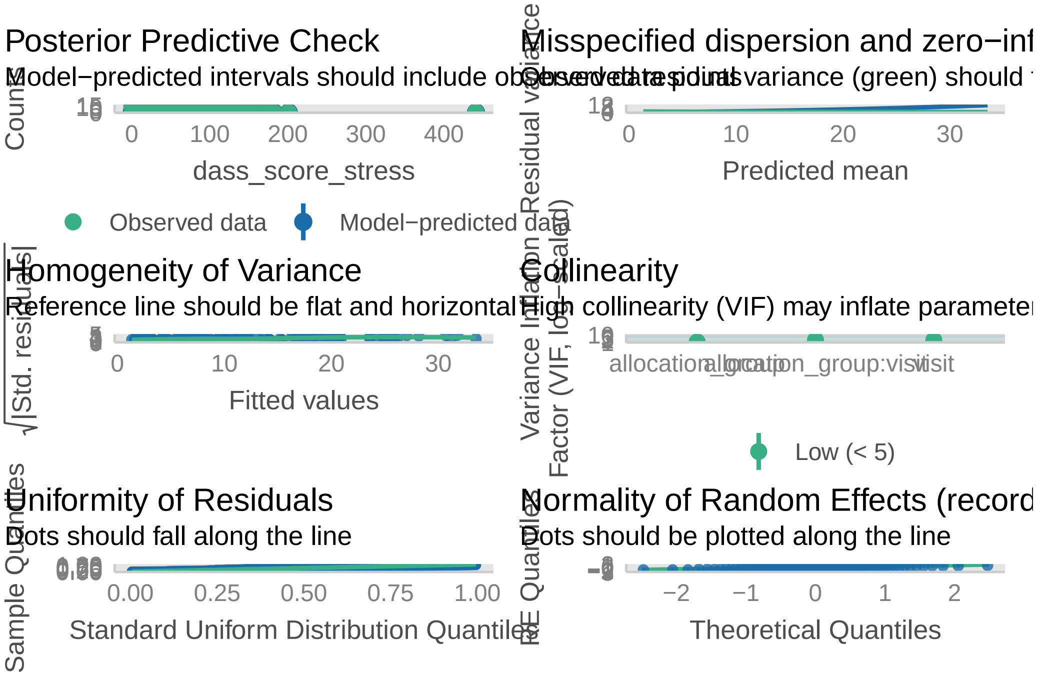
```r
# Compare performance
performance::compare_performance(
  dass_score_stress_nb_model,
  dass_score_stress_nb_model_sens
)
```

```
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)
--------------------------------------------------------------------------
dass_score_stress_nb_model      | glmmTMB | 908.9 (<.001) |  909.6 (<.001)
dass_score_stress_nb_model_sens | glmmTMB | 847.0 (>.999) |  847.8 (>.999)
```

```
Name                            | BIC (weights) | R2 (cond.) | R2 (marg.)
--------------------------------------------------------------------------
dass_score_stress_nb_model      | 926.0 (<.001) |      0.754 |      0.022
dass_score_stress_nb_model_sens | 863.6 (>.999) |      0.617 |      0.033

Name                            |   ICC |  RMSE | Sigma | Score_log | Score_spherical
------------------------------------------------------------------------------------
dass_score_stress_nb_model      | 0.749 | 4.356 | 4.774 |    -3.082 |           0.061
dass_score_stress_nb_model_sens | 0.604 | 5.033 | 4.682 |    -3.263 |           0.075
```

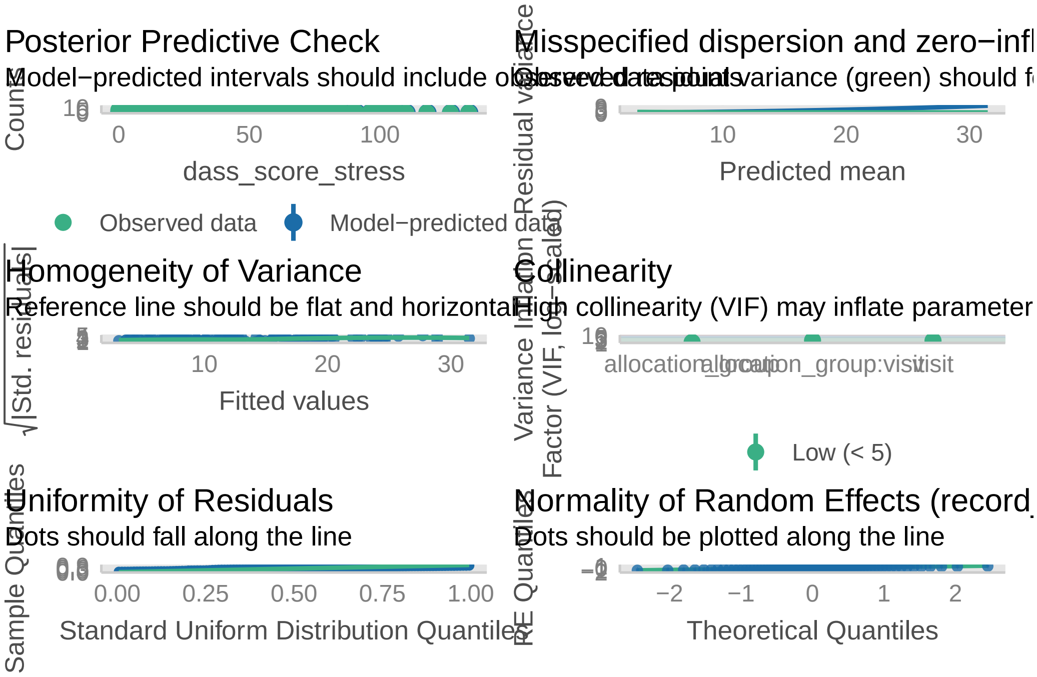
```r
# Diagnostic checks
performance::check_model(dass_score_stress_nb_model)
```

```
`check_outliers()` does not yet support models of class `glmmTMB`.
```



```r
performance::check_model(dass_score_stress_nb_model_sens)
```

```
`check_outliers()` does not yet support models of class `glmmTMB`.
```



2.3.0.2 Médias Marginais Estimadas

2.3.0.2.1 Todos os dados

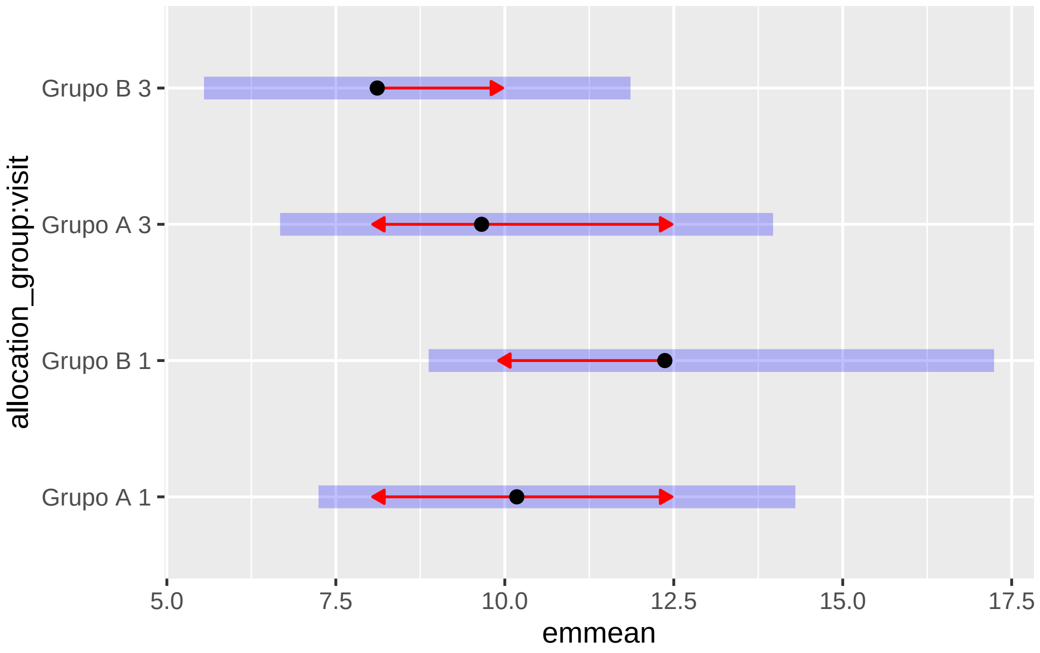
```
# Estimated marginal means on the response scale
dass_score_stress_nb_emm <- emmeans::emmeans(
  dass_score_stress_nb_model,
  ~ allocation_group * visit,
  type = "response"
)

# Pairwise contrasts by visit
emmeans::contrast(
  dass_score_stress_nb_emm,
  method = "pairwise",
  by     = "visit",
  adjust = "bonferroni"
) %>% summary(infer = c(TRUE, TRUE))
```

```
visit = 1:
 contrast          ratio    SE  df asymp.LCL asymp.UCL null z.ratio p.value
 Grupo A / Grupo B 0.823 0.196 Inf     0.515      1.31    1  -0.817  0.4140


visit = 3:
 contrast          ratio    SE  df asymp.LCL asymp.UCL null z.ratio p.value
 Grupo A / Grupo B 1.190 0.321 Inf     0.701      2.02    1   0.645  0.5187

Confidence level used: 0.95
Intervals are back-transformed from the log scale
Tests are performed on the log scale
```

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

```
allocation_group = Grupo A:
 contrast        ratio    SE  df asymp.LCL asymp.UCL null z.ratio p.value
 visit1 / visit3  1.05 0.170 Inf     0.768      1.45    1   0.326  0.7445

allocation_group = Grupo B:
 contrast        ratio    SE  df asymp.LCL asymp.UCL null z.ratio p.value
 visit1 / visit3  1.52 0.253 Inf     1.102      2.11    1   2.544  0.0110

Confidence level used: 0.95
Intervals are back-transformed from the log scale
Tests are performed on the log scale
```

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



2.3.0.2.2 Análise de sensibilidade

```
# Estimated marginal means on the response scale
dass_score_stress_nb_emm_sens <- emmeans::emmeans(
  dass_score_stress_nb_model_sens,
  ~ allocation_group * visit,
  type = "response"
)

# Pairwise contrasts by visit
emmeans::contrast(
  dass_score_stress_nb_emm_sens,
  method = "pairwise",
  by     = "visit",
  adjust = "bonferroni"
) %>% summary(infer = c(TRUE, TRUE))
```

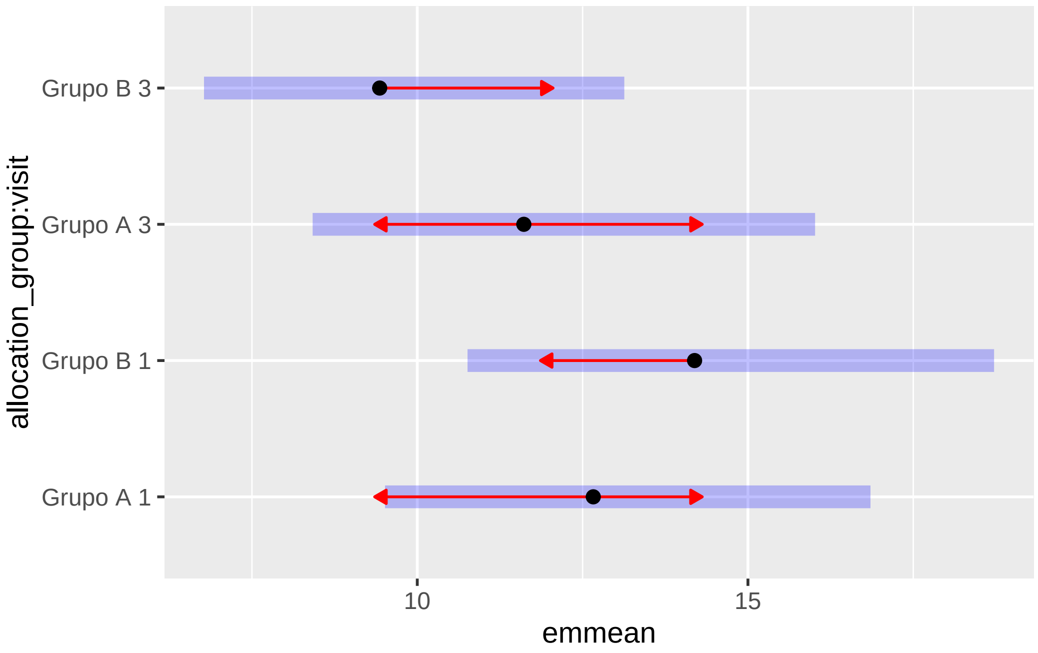
```
visit = 1:
 contrast          ratio    SE  df asymp.LCL asymp.UCL null z.ratio p.value
 Grupo A / Grupo B 0.892 0.177 Inf     0.604      1.32    1  -0.574  0.5658

visit = 3:
 contrast          ratio    SE  df asymp.LCL asymp.UCL null z.ratio p.value
 Grupo A / Grupo B 1.231 0.290 Inf     0.776      1.95    1   0.883  0.3771
```

```
Confidence level used: 0.95
Intervals are back-transformed from the log scale
Tests are performed on the log scale
```

```r
# Pairwise contrasts over time within each group
emmeans::contrast(
  dass_score_stress_nb_emm_sens,
  method = "pairwise",
  by     = "allocation_group",
  adjust = "bonferroni"
) %>% summary(infer = c(TRUE, TRUE))
```

```
allocation_group = Grupo A:
 contrast        ratio    SE  df asymp.LCL asymp.UCL null z.ratio p.value
 visit1 / visit3  1.09 0.178 Inf     0.793      1.50    1   0.532  0.5948

allocation_group = Grupo B:
 contrast        ratio    SE  df asymp.LCL asymp.UCL null z.ratio p.value
 visit1 / visit3  1.50 0.248 Inf     1.090      2.08    1   2.481  0.0131

Confidence level used: 0.95
Intervals are back-transformed from the log scale
Tests are performed on the log scale
```

```r
# Plot marginal means
plot(dass_score_stress_nb_emm_sens, comparisons = TRUE)
```



2.3.0.3 Resultado

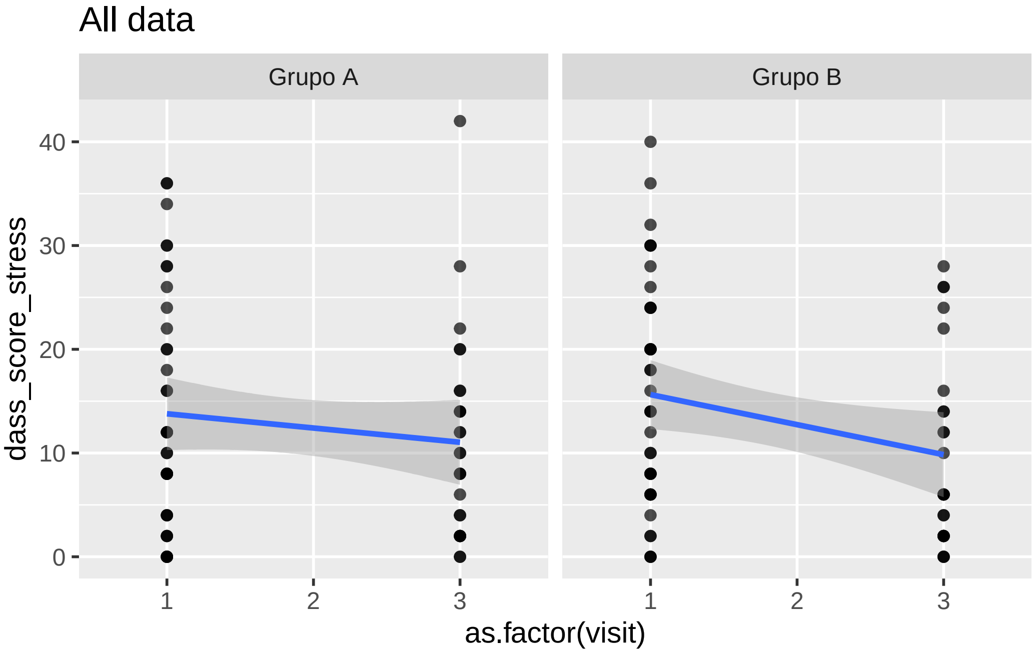
No modelo ajustado para o escore de estresse (DASS), não houve diferenças significativas entre os grupos em nenhum dos momentos avaliados (visita 1: razão = 0,823; IC 95%: 0,515–1,31; p = 0,414; visita 3: razão = 1,190; IC 95%: 0,701–2,02; p = 0,519). Ao longo do tempo, o grupo Eclipta apresentou redução significativa do escore de estresse entre visita 1 e visita 3 (razão = 1,52; IC 95%: 1,102–2,11; p = 0,011), enquanto o grupo placebo não mostrou mudança significativa (razão = 1,05; IC 95%: 0,768–1,45; p = 0,745).

Tabela: Razões dos escores de estresse (DASS) entre grupos e ao longo do tempo – Todos os dados {#tbl-dass_stress}

Grupo de comparação	Comparação	Razão	IC 95%	p-valor
Entre grupos	Visita 1	0,823	[0,515; 1,31]	0,414
Entre grupos	Visita 3	1,190	[0,701; 2,02]	0,519
Grupo Placebo	Visita 1 – Visita 3	1,05	[0,768; 1,45]	0,745
Grupo Eclipta	Visita 1 – Visita 3	1,52	[1,102; 2,11]	0,011

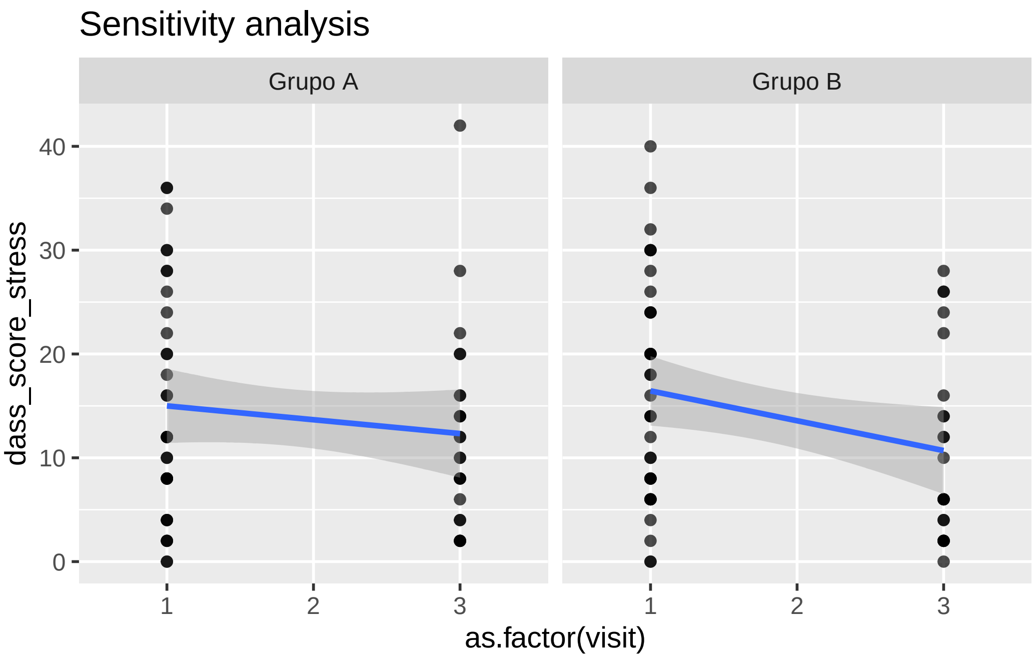
```r
ggplot(
    data = data_model_V1V3,
    aes(
        x = as.factor(visit),
        y = dass_score_stress,
        group = record_id,
    )
) +
    geom_line(alpha = 0.5) +
    geom_point(alpha = 0.7) +
    geom_smooth(
        aes(group = allocation_group),
        method = "lm",
        se = TRUE,
        linewidth = 1
    ) +
    labs(title = "All data") +
    facet_wrap(~ allocation_group)
```

```
`geom_smooth()` using formula = 'y ~ x'
Warning: Removed 62 rows containing non-finite outside the scale range
(`stat_smooth()`).
Warning: Removed 10 rows containing missing values or values outside the scale range
(`geom_line()`).
Warning: Removed 62 rows containing missing values or values outside the scale range
(`geom_point()`).
```



```
data_model_V1V3 %>%
    filter(
        !(record_id %in%
        influential_ids_nb)
    ) %>%
    ggplot(
        aes(
            x = as.factor(visit),
            y = dass_score_stress,
            group = record_id,
        )
    ) +
    geom_line(alpha = 0.5) +
    geom_point(alpha = 0.7) +
    geom_smooth(
        aes(group = allocation_group),
        method = "lm",
        se = TRUE,
        linewidth = 1
    ) +
    labs(title = "Sensitivity analysis") +
    facet_wrap(~ allocation_group)
```

```
`geom_smooth()` using formula = 'y ~ x'
Warning: Removed 57 rows containing non-finite outside the scale range
(`stat_smooth()`).
Warning: Removed 10 rows containing missing values or values outside the scale range
(`geom_line()`).
Warning: Removed 57 rows containing missing values or values outside the scale range
(`geom_point()`).
```

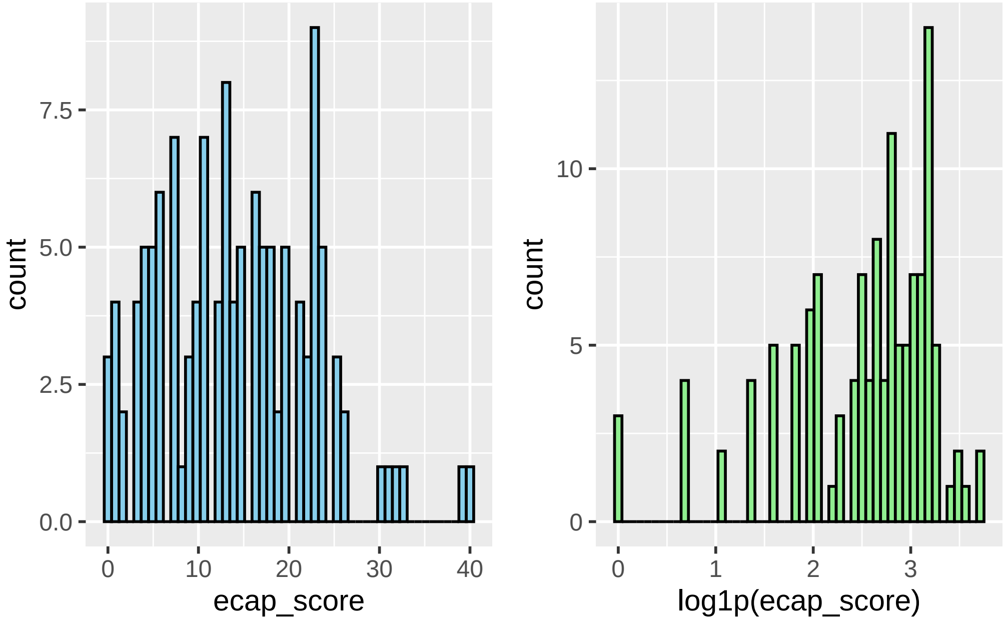


3 ECAP

Variável: ecap_score

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

# Plot 2: Log-transformed data
ecap_score_hist_2 <- data_model_V1V3 %>%
    #filter(
    #    ecap_score < 300
    #) %>%
    ggplot(aes(x = log1p(ecap_score))) +
    geom_histogram(bins = 50, fill = "lightgreen", color = "black")

# Combine side by side
ecap_score_hist_1 + ecap_score_hist_2 # library(patchwork)
```

```
Warning: Removed 62 rows containing non-finite outside the scale range (`stat_bin()`).
Removed 62 rows containing non-finite outside the scale range (`stat_bin()`).
```



```
# LMM
ecap_score_model <- lmer(ecap_score ~ allocation_group * visit +
(1 | record_id), data = data_model_V1V3)
check_collinearity(ecap_score_model)
```

```
# Check for Multicollinearity

Low Correlation

                   Term  VIF   VIF 95% CI Increased SE Tolerance
       allocation_group 1.10 [1.01, 1.74]         1.05      0.91
                  visit 1.93 [1.56, 2.55]         1.39      0.52
 allocation_group:visit 2.02 [1.63, 2.67]         1.42      0.49
 Tolerance 95% CI
     [0.58, 0.99]
     [0.39, 0.64]
     [0.37, 0.62]
```

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

# LMM Sensitivity
ecap_score_model_sens <- update(object = ecap_score_model,
                               subset = !(record_id %in%
        ecap_score_model_check$influential_ids))
# Influential IDS
ecap_score_model_check$influential_ids
```

```
[1] "5"  "17" "27" "75" "32"
```

3.0.0.1 Resumo dos modelos

```
# Model comparison
summary(ecap_score_model)
```

```
Linear mixed model fit by REML. t-tests use Satterthwaite's method [
lmerModLmerTest]
Formula: ecap_score ~ allocation_group * visit + (1 | record_id)
   Data: data_model_V1V3
```

```
REML criterion at convergence: 835.7

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

Random effects:
 Groups    Name        Variance Std.Dev.
 record_id (Intercept) 49.51    7.037   
 Residual              16.21    4.026   
Number of obs: 127, groups:  record_id, 75

Fixed effects:
                               Estimate Std. Error     df t value Pr(>|t|)    
(Intercept)                      17.703      1.333 86.599  13.283  < 2e-16 ***
allocation_groupGrupo B          -2.834      1.872 86.599  -1.514    0.134    
visit3                           -4.804      1.077 53.296  -4.460 4.27e-05 ***
allocation_groupGrupo B:visit3    1.516      1.550 53.783   0.978    0.332    
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
            (Intr) all_GB visit3
allctn_grGB -0.712              
visit3      -0.305  0.217       
allctn_GB:3  0.212 -0.298 -0.695
```

```r
summary(ecap_score_model_sens)
```

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

REML criterion at convergence: 730.2

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

Random effects:
 Groups    Name        Variance Std.Dev.
 record_id (Intercept) 48.405   6.957   
 Residual               8.068   2.840   
Number of obs: 117, groups:  record_id, 70

Fixed effects:
                              Estimate Std. Error      df t value Pr(>|t|)    
(Intercept)                    16.5625     1.3284 74.1376  12.468  < 2e-16 ***
allocation_groupGrupo B        -1.6941     1.8030 74.1376  -0.940    0.350    
visit3                         -4.0284     0.8468 46.2841  -4.757 1.95e-05 ***
allocation_groupGrupo B:visit3   1.0129     1.1605 46.3772   0.873    0.387    
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
            (Intr) all_GB visit3
allctn_grGB -0.737              
visit3      -0.224  0.165       
allctn_GB:3  0.164 -0.222 -0.730
```

```
ecap_score_model_check$comparison_table
```

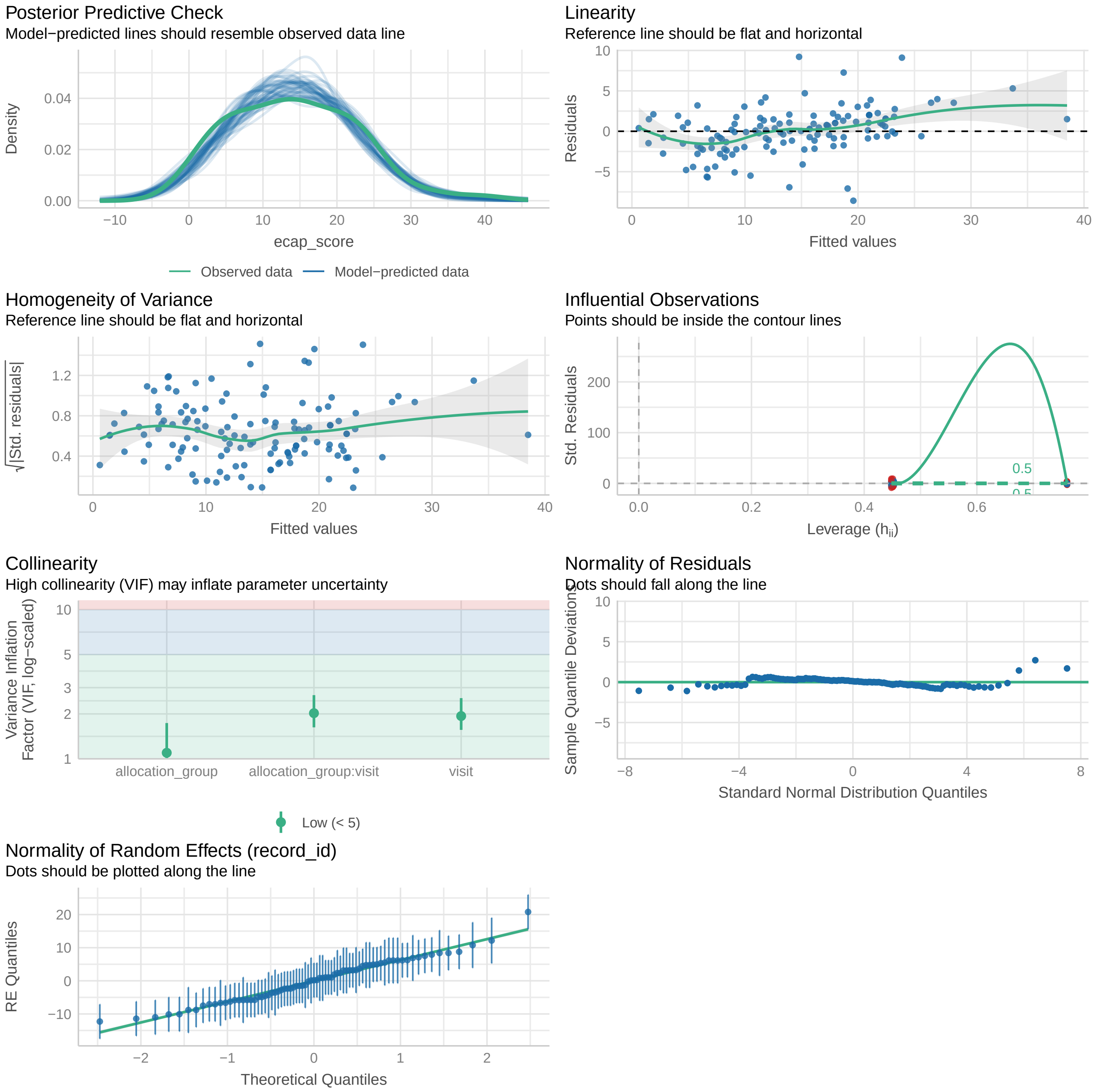
```
# A tibble: 12 x 6
   Model       term                       estimate std.error statistic   p.value
   <chr>       <chr>                         <dbl>     <dbl>     <dbl>     <dbl>
 1 Original    (Intercept)                   17.7       1.33    13.3    1.33e-22
 2 Sensitivity (Intercept)        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

```
11 Original    visit3                          -4.80     1.08     -4.46   4.27e- 5
12 Sensitivity visit3                          -4.03     0.847    -4.76   1.95e- 5
```

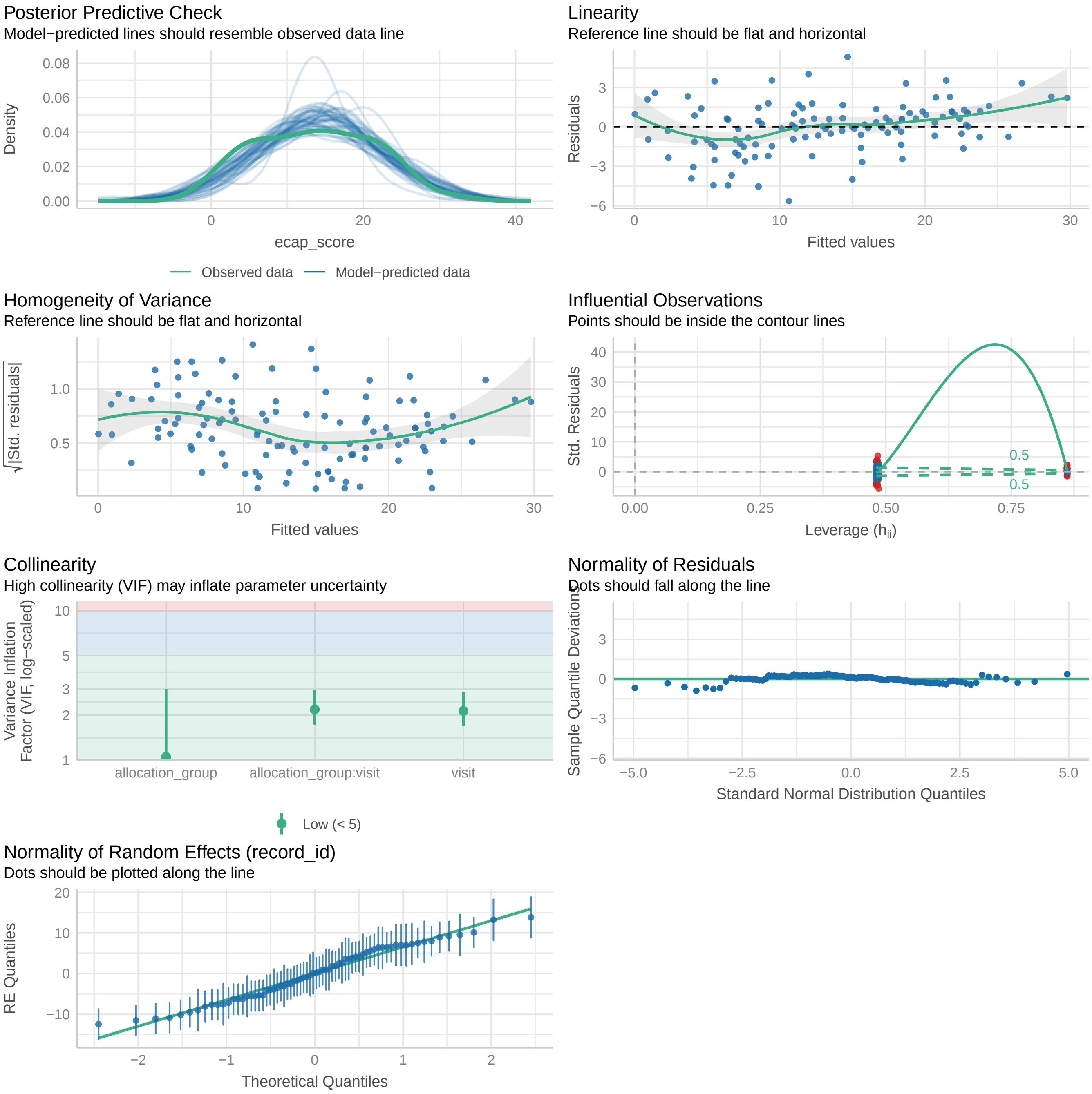
```
performance::compare_performance(
    ecap_score_model,
    ecap_score_model_sens)
```

```
When comparing models, please note that probably not all models were fit
  from same data.
# Comparison of Model Performance Indices

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

Name                  | BIC (weights) | R2 (cond.) | R2 (marg.) |   ICC |  RMSE | Sigma
----------------------------------------------------------------------------------------
ecap_score_model      | 873.4 (<.001) |      0.772 |      0.074 | 0.753 | 2.829 | 4.026
ecap_score_model_sens | 766.1 (>.999) |      0.865 |      0.057 | 0.857 | 1.889 | 2.840
```

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



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



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

3.0.0.2 Médias Marginais Estimadas

3.0.0.2.1 Todos os dados

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

```r
ecap_score_raw_emm <- regrid(ecap_score_raw_emm)

# Table of marginal means
# ecap_score_raw_emm

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

```
visit = 1:
 contrast          estimate   SE    df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B     2.83 1.87  86.8   -0.887     6.56   1.514  0.1337

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

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

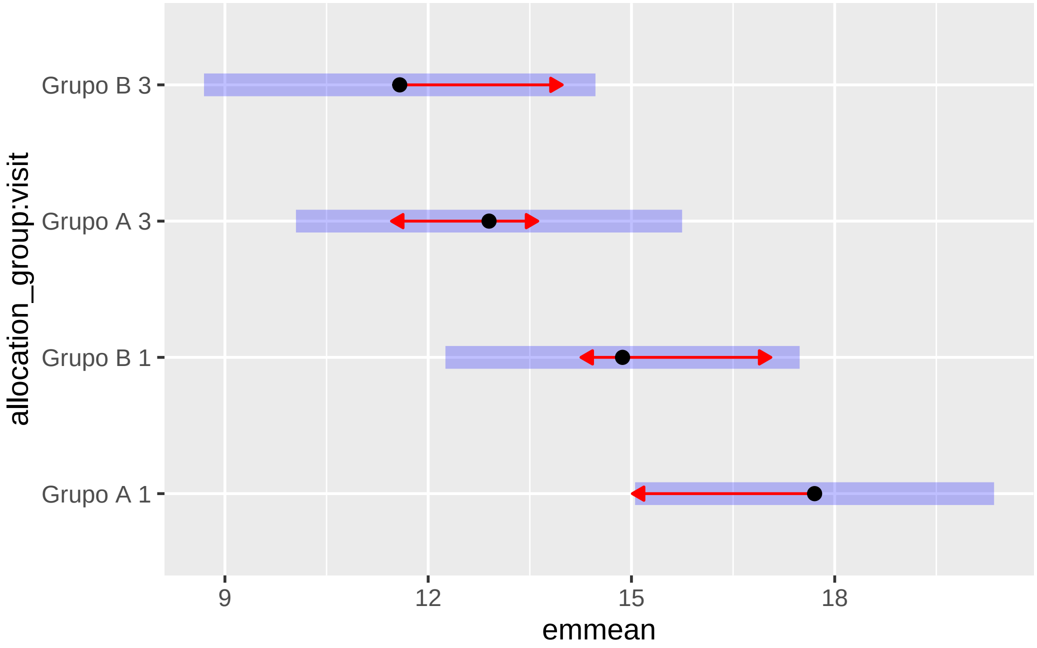
```r
# Pairwise comparisons: Changes over time within each group
emmeans::contrast(ecap_score_raw_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

```
allocation_group = Grupo A:
 contrast        estimate   SE   df lower.CL upper.CL t.ratio p.value
 visit1 - visit3     4.80 1.08 86.8     2.66     6.95   4.451  <.0001

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

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

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

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

```
Target overlap = 0.6139, overlap on graph = -0.4769
```



3.0.0.2.2 Análise de sensibilidade

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

ecap_score_emm <- regrid(ecap_score_emm)

# Table of marginal means
# ecap_score_emm

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

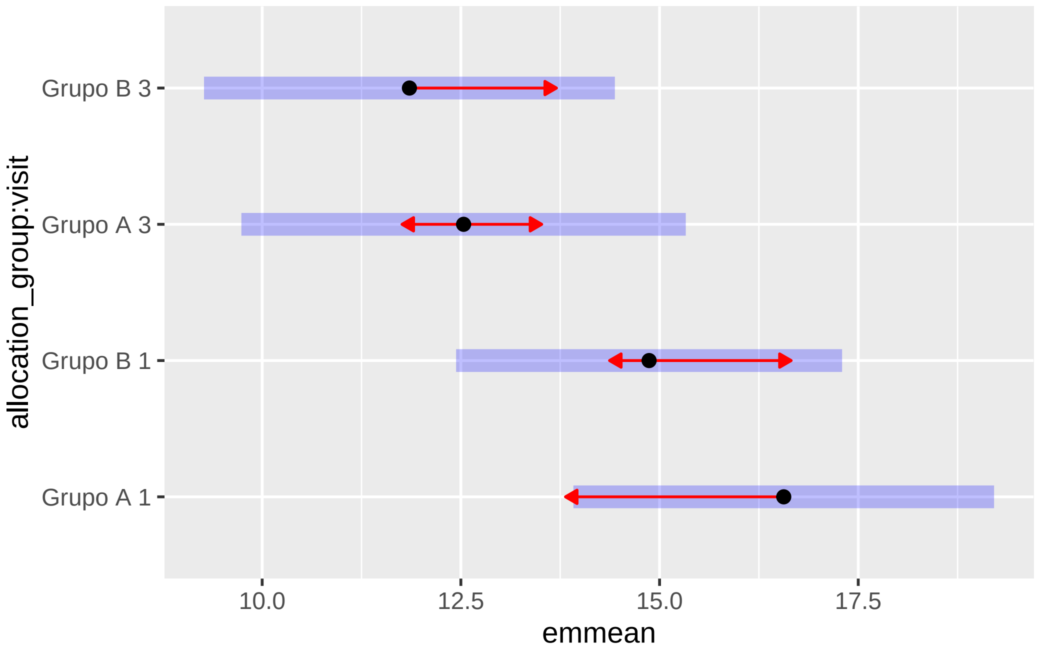
```
visit = 1:
 contrast          estimate   SE   df lower.CL upper.CL t.ratio p.value
 Grupo A - Grupo B    1.694 1.80 74.9    -1.90     5.29   0.940  0.3505


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

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

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

```
allocation_group = Grupo A:
 contrast        estimate    SE   df lower.CL upper.CL t.ratio p.value
 visit1 - visit3     4.03 0.848 74.9     2.34     5.72   4.750  <.0001

allocation_group = Grupo B:
 contrast        estimate    SE   df lower.CL upper.CL t.ratio p.value
 visit1 - visit3     3.02 0.795 74.9     1.43     4.60   3.794  0.0003

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

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

```
Warning: Comparison discrepancy in group "1", Grupo A visit1 - Grupo B visit3:
    Target overlap = 0.0362, overlap on graph = -0.0243
Warning: Comparison discrepancy in group "1", Grupo B visit1 - Grupo A visit3:
    Target overlap = 0.5228, overlap on graph = -0.5748
```



3.0.0.3 Resultado

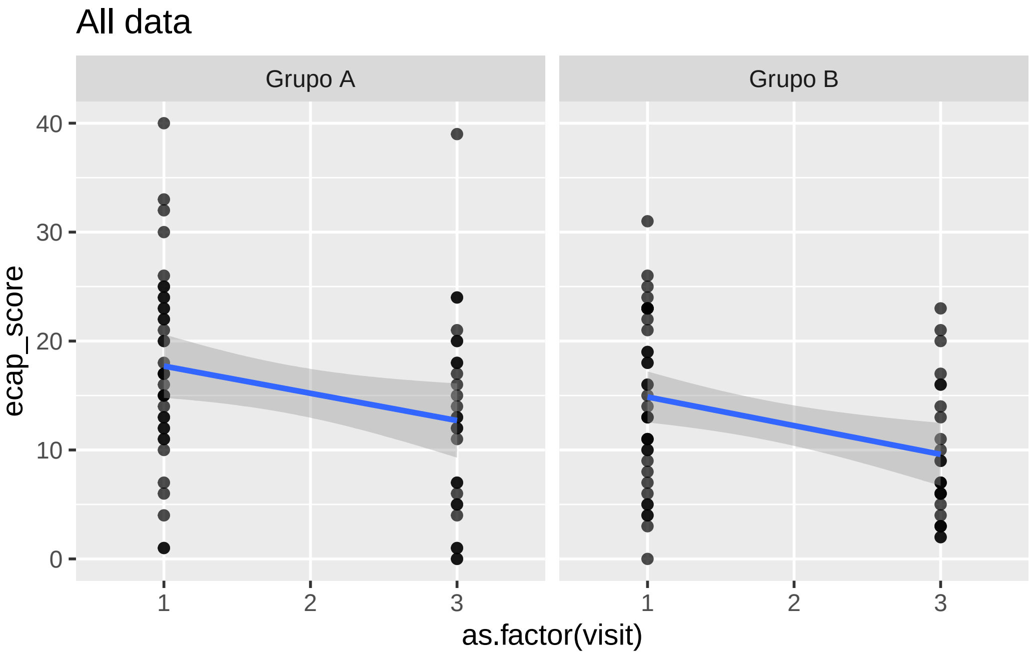
No modelo ajustado para o escore de compulsão alimentar periódica (ECAP), não foram observadas diferenças significativas entre os grupos em nenhuma das visitas (visita 1: estimativa = 2,83; IC 95%: [–0,89; 6,56]; p = 0,134; visita 3: estimativa = 1,32; IC 95%: [–2,74; 5,38]; p = 0,521). Ao longo do tempo, ambos os grupos apresentaram redução significativa do escore de compulsão alimentar entre a visita 1 e a visita 3: Grupo Placebo (aumento médio de 4,80; IC 95%: [2,66; 6,95]; p < 0,001) e Grupo Eclipta (aumento médio de 3,29; IC 95%: [1,07; 5,51]; p = 0,004). A análise de sensibilidade confirmou esses achados sem alterações relevantes.

Tabela: Diferenças estimadas do escore de compulsão alimentar periódica (ECAP) entre grupos e ao longo do tempo – Todos os dados {#tbl-ecap_score}

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 1	2,83	[–0,89; 6,56]	0,134
Entre grupos	Visita 3	1,32	[–2,74; 5,38]	0,521
Grupo Placebo	Visita 1 – Visita 3	4,80	[2,66; 6,95]	< 0,001
Grupo Eclipta	Visita 1 – Visita 3	3,29	[1,07; 5,51]	0,004

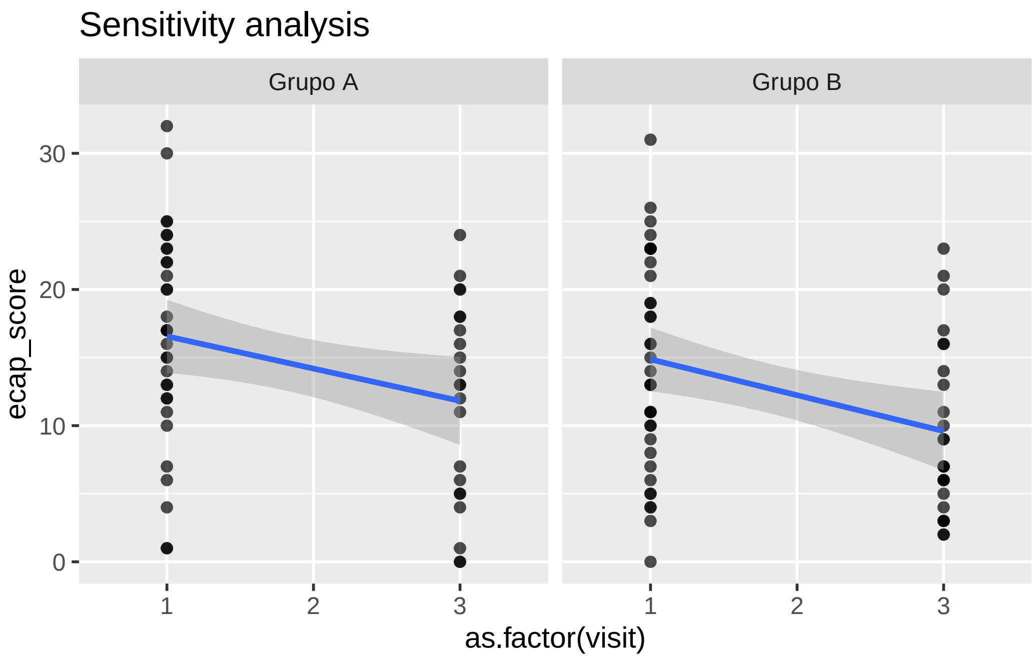
```r
ggplot(
    data = data_model_V1V3,
    aes(
        x = as.factor(visit),
        y = ecap_score,
        group = record_id,
    )
) +
    geom_line(alpha = 0.5) +
    geom_point(alpha = 0.7) +
    geom_smooth(
        aes(group = allocation_group),
        method = "lm",
        se = TRUE,
        linewidth = 1
    ) +
    labs(title = "All data") +
    facet_wrap(~ allocation_group)
```

```
`geom_smooth()` using formula = 'y ~ x'
Warning: Removed 62 rows containing non-finite outside the scale range
(`stat_smooth()`).
Warning: Removed 10 rows containing missing values or values outside the scale range
(`geom_line()`).
Warning: Removed 62 rows containing missing values or values outside the scale range
(`geom_point()`).
```



```
data_model_V1V3 %>%
    filter(
        !(record_id %in%
        ecap_score_model_check$influential_ids)
    ) %>%
    ggplot(
        aes(
            x = as.factor(visit),
            y = ecap_score,
            group = record_id,
        )
    ) +
    geom_line(alpha = 0.5) +
    geom_point(alpha = 0.7) +
    geom_smooth(
        aes(group = allocation_group),
        method = "lm",
        se = TRUE,
        linewidth = 1
    ) +
    labs(title = "Sensitivity analysis") +
    facet_wrap(~ allocation_group)
```

```
`geom_smooth()` using formula = 'y ~ x'
Warning: Removed 57 rows containing non-finite outside the scale range
(`stat_smooth()`).
Warning: Removed 10 rows containing missing values or values outside the scale range
(`geom_line()`).
Warning: Removed 57 rows containing missing values or values outside the scale range
(`geom_point()`).
```



4 Informações da Sessão

```
sessionInfo()
```

```
R version 4.4.1 (2024-06-14)
Platform: aarch64-apple-darwin20
Running under: macOS 15.5

Matrix products: default
BLAS:   /Library/Frameworks/R.framework/Versions/4.4-arm64/Resources/lib/libRblas.0.dylib
LAPACK: /Library/Frameworks/R.framework/Versions/4.4-arm64/Resources/lib/libRlapack.dylib;  LAPACK version

locale:
[1] en_US.UTF-8/en_US.UTF-8/en_US.UTF-8/C/en_US.UTF-8/en_US.UTF-8

time zone: America/Sao_Paulo
tzcode source: internal

attached base packages:
[1] stats     graphics  grDevices utils     datasets  methods   base

other attached packages:
 [1] broom.mixed_0.2.9.6 influence.ME_0.9-9  kableExtra_1.4.0.12
 [4] knitr_1.50          emmeans_1.11.1      patchwork_1.3.0
 [7] gt_1.0.0            performance_0.13.0  skimr_2.1.5
[10] lmerTest_3.1-3      lme4_1.1-37         Matrix_1.7-0
[13] readxl_1.4.3        lubridate_1.9.4     forcats_1.0.0
[16] stringr_1.5.1       dplyr_1.1.4.9000    purrr_1.0.4
[19] readr_2.1.5         tidyr_1.3.1         tibble_3.2.1
[22] ggplot2_3.5.1       tidyverse_2.0.0

loaded via a namespace (and not attached):
 [1] tidyselect_1.2.1    DHARMa_0.4.7        viridisLite_0.4.2
 [4] glmmTMB_1.1.11      farver_2.1.2        fastmap_1.2.0
 [7] TH.data_1.1-3       bayestestR_0.15.3   digest_0.6.37
[10] estimability_1.5.1  timechange_0.3.0    lifecycle_1.0.4
[13] survival_3.7-0      magrittr_2.0.3      compiler_4.4.1
[16] rlang_1.1.6         tools_4.4.1         utf8_1.2.4
[19] yaml_2.3.10         labeling_0.4.3      xml2_1.3.8
[22] repr_1.1.7          multcomp_1.4-28     withr_3.0.2
[25] numDeriv_2016.8-1.1 datawizard_1.1.0    grid_4.4.1
[28] future_1.34.0       xtable_1.8-4        colorspace_2.1-1
[31] globals_0.16.3      scales_1.3.0        MASS_7.3-61
[34] insight_1.2.0       cli_3.6.5           mvtnorm_1.3-3
[37] rmarkdown_2.29      reformulas_0.4.1    generics_0.1.3
[40] rstudioapi_0.17.1   tzdb_0.4.0          minqa_1.2.8
[43] splines_4.4.1       parallel_4.4.1      cellranger_1.1.0
[46] base64enc_0.1-3     vctrs_0.6.5         boot_1.3-31
[49] sandwich_3.1-1      jsonlite_2.0.0      hms_1.1.3
[52] pbkrtest_0.5.4      ggrepel_0.9.6       listenv_0.9.1
[55] systemfonts_1.2.3   see_0.11.0          parallelly_1.44.0
[58] glue_1.8.0          nloptr_2.2.1        codetools_0.2-20
[61] stringi_1.8.7       gtable_0.3.6        munsell_0.5.1
[64] furrr_0.3.1         pillar_1.10.2       htmltools_0.5.8.1
[67] TMB_1.9.17          R6_2.6.1            textshaping_0.4.0
[70] Rdpack_2.6.4        evaluate_1.0.3      lattice_0.22-6
[73] backports_1.5.0     rbibutils_2.3       broom_1.0.7
[76] Rcpp_1.0.14         svglite_2.2.1       coda_0.19-4.1
[79] nlme_3.1-166        mgcv_1.9-1          xfun_0.52
[82] zoo_1.8-14          pkgconfig_2.0.3
```