

# 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

Gustavo Santos Paiva Laender Moura

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```
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.")
  }

  # 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"          "whoqol_timestamp"
[7] "whoqol_4_treatment" "whoqol_5_enjoyment"  "whoqol_6_meaning"
[13] "whoqol_10_energy"   "whoqol_11_appearance" "whoqol_12_finances"
[19] "whoqol_16_sleep"    "whoqol_17_activities" "whoqol_18_work"
[25] "whoqol_22_support"  "whoqol_23_housing"    "whoqol_24_health_service"
```

```
# 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
```

```
# 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_)
  }
}
```

```
# 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")

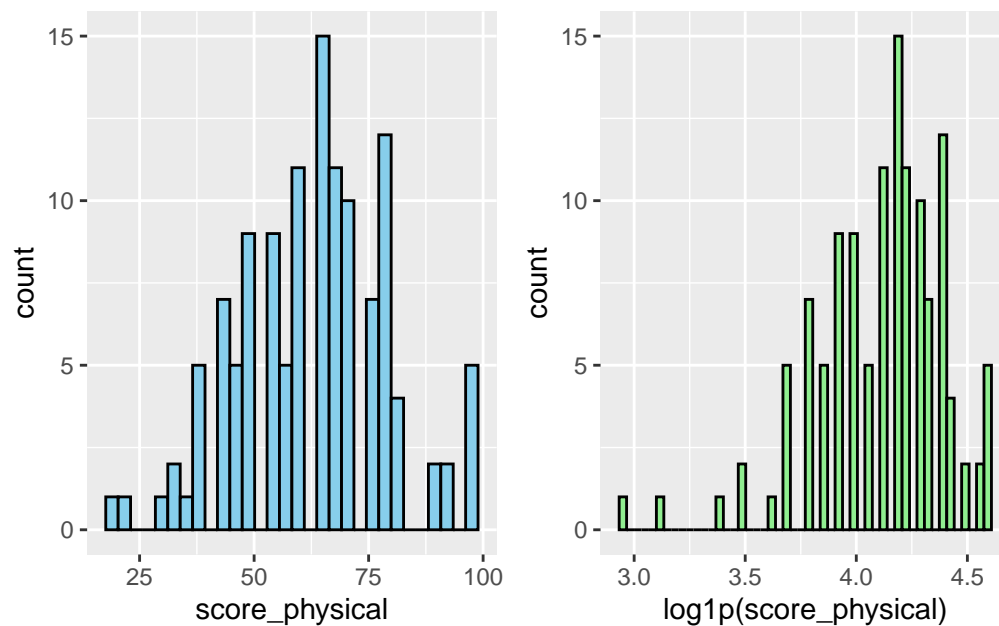
# Plot 2: Log-transformed data
score_physical_hist_2 <- data_model_V1V3 %>%
```

```

#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)

```



```

# 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	Tolerance 95% CI
------	-----	------------	--------------	-----------	------------------



allocation_group	1.23	[1.08, 1.66]	1.11	0.81	[0.60, 0.93]
visit	1.94	[1.57, 2.57]	1.39	0.51	[0.39, 0.64]
allocation_group:visit	2.16	[1.72, 2.86]	1.47	0.46	[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

```
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

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:visit2	-4.68	4.04	-1.16	2.52e- 1
6	Sensitivity	allocation_groupGrupo B:visit2	-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

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

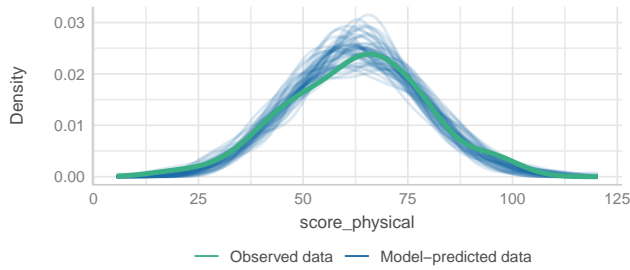
# Comparison of Model Performance Indices

Name	Model	AIC (weights)	AICc (weights)	BIC
score_physical_model	lmerModLmerTest	1029.2 (<.001)	1029.9 (<.001)	1046.2
score_physical_model_sens	lmerModLmerTest	920.5 (>.999)	921.3 (>.999)	937.1

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

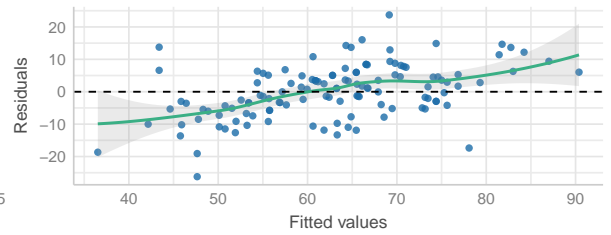
### Posterior Predictive Check

Model-predicted lines should resemble observed data line



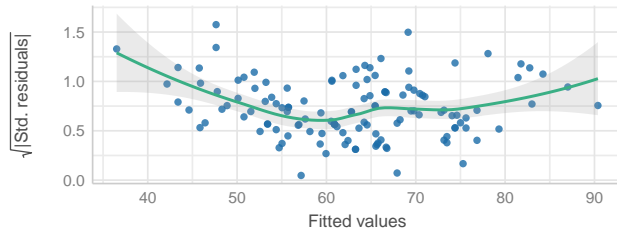
### Linearity

Reference line should be flat and horizontal



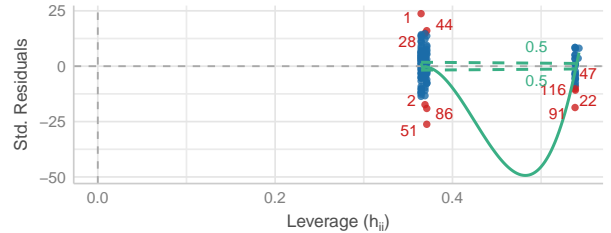
### Homogeneity of Variance

Reference line should be flat and horizontal



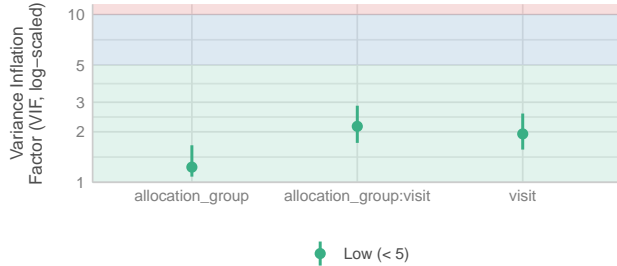
### Influential Observations

Points should be inside the contour lines



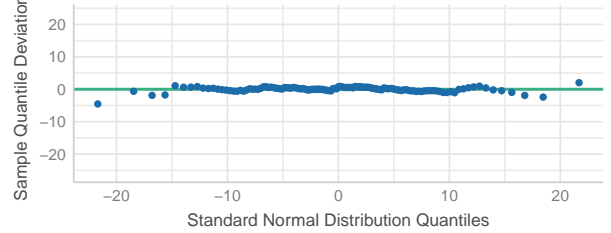
### Collinearity

High collinearity (VIF) may inflate parameter uncertainty



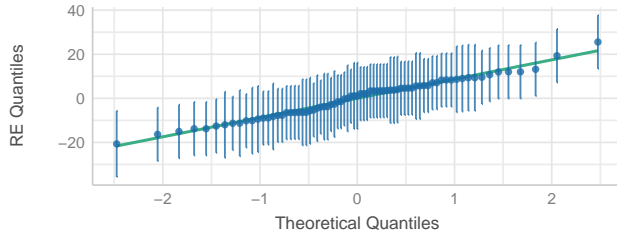
### Normality of Residuals

Dots should fall along the line



### Normality of Random Effects (record\_id)

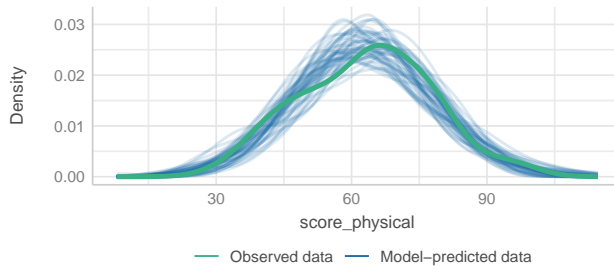
Dots should be plotted along the line



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

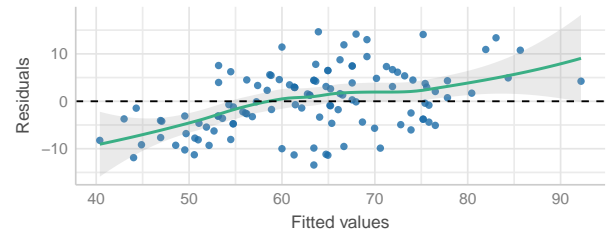
### Posterior Predictive Check

Model-predicted lines should resemble observed data line



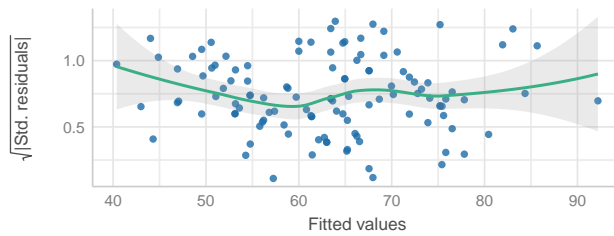
### Linearity

Reference line should be flat and horizontal



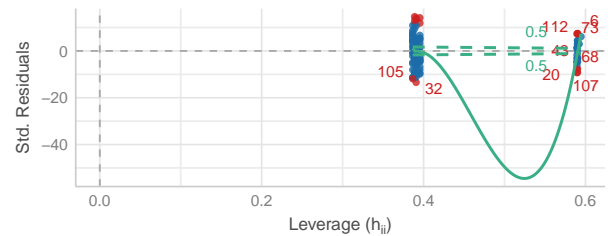
### Homogeneity of Variance

Reference line should be flat and horizontal



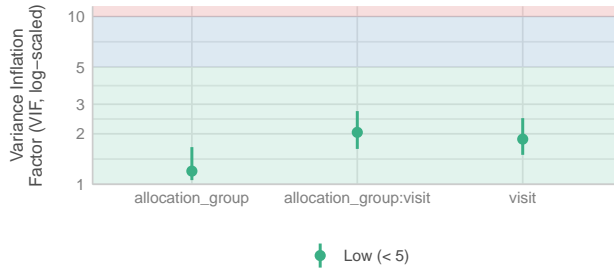
### Influential Observations

Points should be inside the contour lines



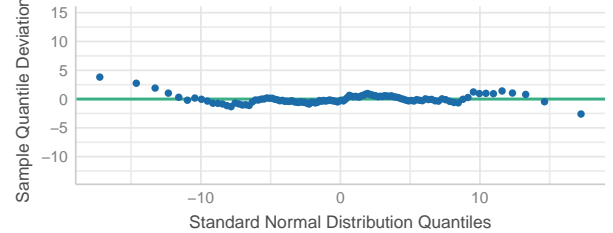
### Collinearity

High collinearity (VIF) may inflate parameter uncertainty



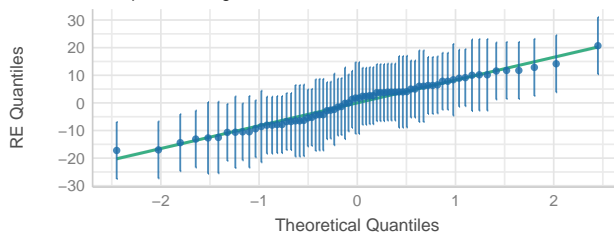
### Normality of Residuals

Dots should fall along the line



### Normality of Random Effects (record\_id)

Dots should be plotted along the line



## 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
```

```
)

score_physical_raw_emm <- regrid(score_physical_raw_emm)

# Table of marginal means
# score_physical_raw_emm

# Pairwise comparisons: Between groups at each visit
emmmeans::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

```
# Pairwise comparisons: Changes over time within each group
emmmeans::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:
```

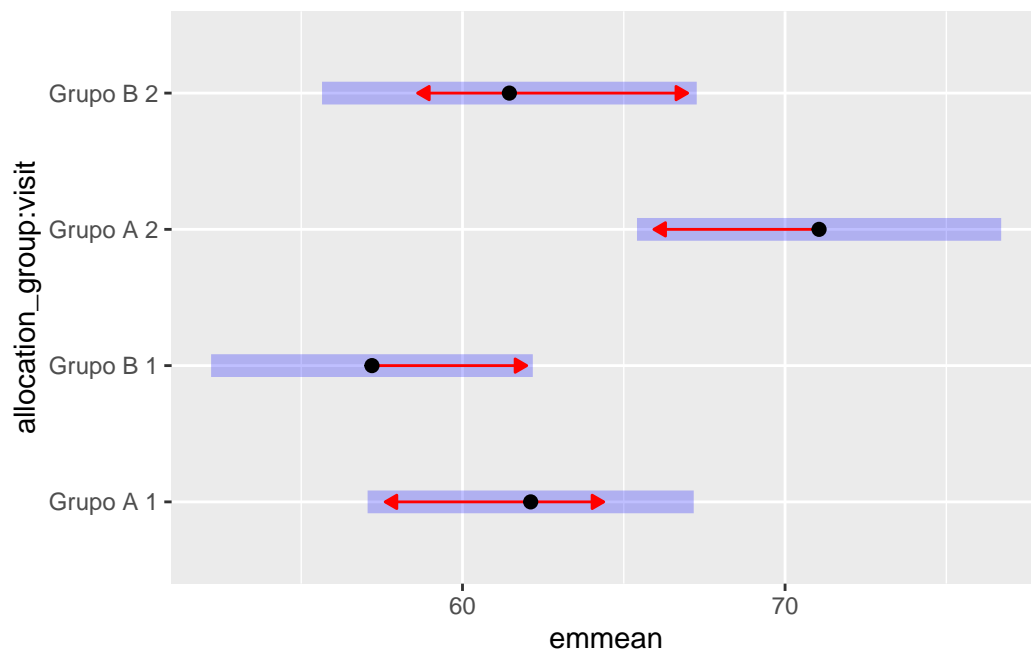
contrast	estimate	SE	df	lower.CL	upper.CL	t.ratio	p.value
visit1 - visit2	-4.26	2.91	102	-10.0	1.52	-1.463	0.1466

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

Confidence level used: 0.95

```
# 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
emmmeans::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
emmmeans::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:

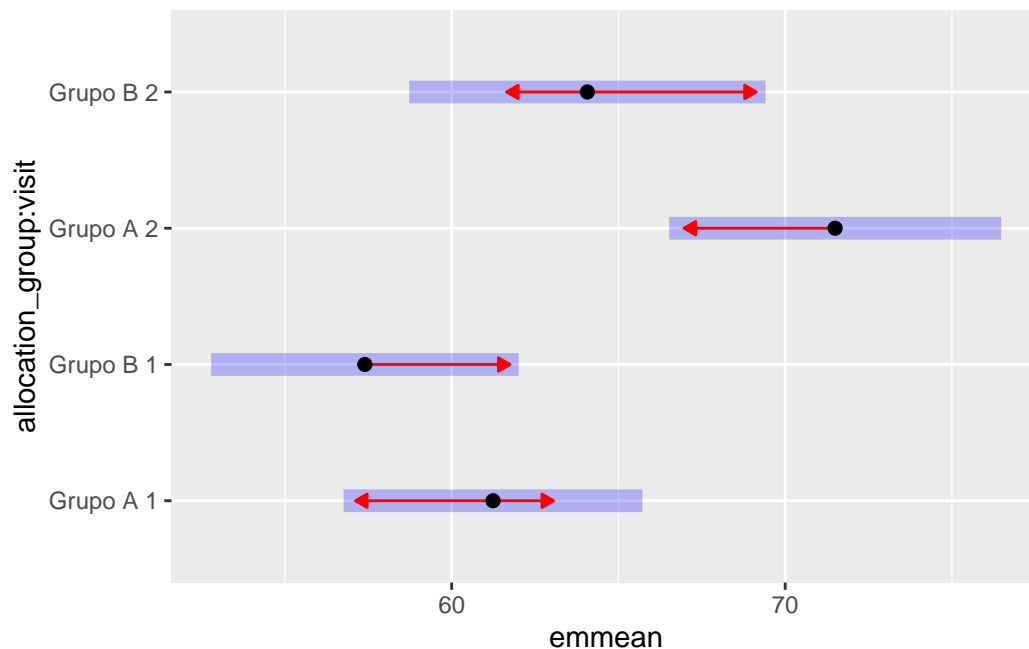
contrast	estimate	SE	df	lower.CL	upper.CL	t.ratio	p.value
visit1 - visit2	-6.67	2.58	91.7	-11.8	-1.56	-2.591	0.0111

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}

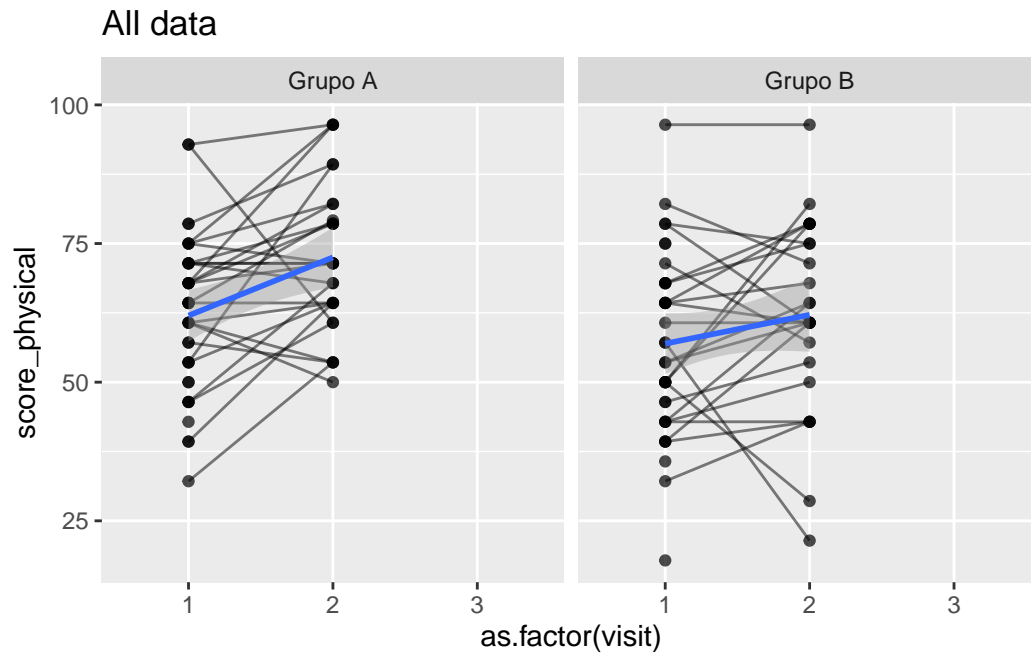
Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 1	4,92	[-2,18; 12,0]	0,172
Entre grupos	Visita 2	9,60	[1,50; 17,7]	0,021
Grupo Placebo	Visita 1 – Visita 2	-8,94	[-14,5; -3,34]	0,002
Grupo Eclipta	Visita 1 – Visita 2	-4,26	[-10,0; 1,52]	0,147

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

```
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)
```

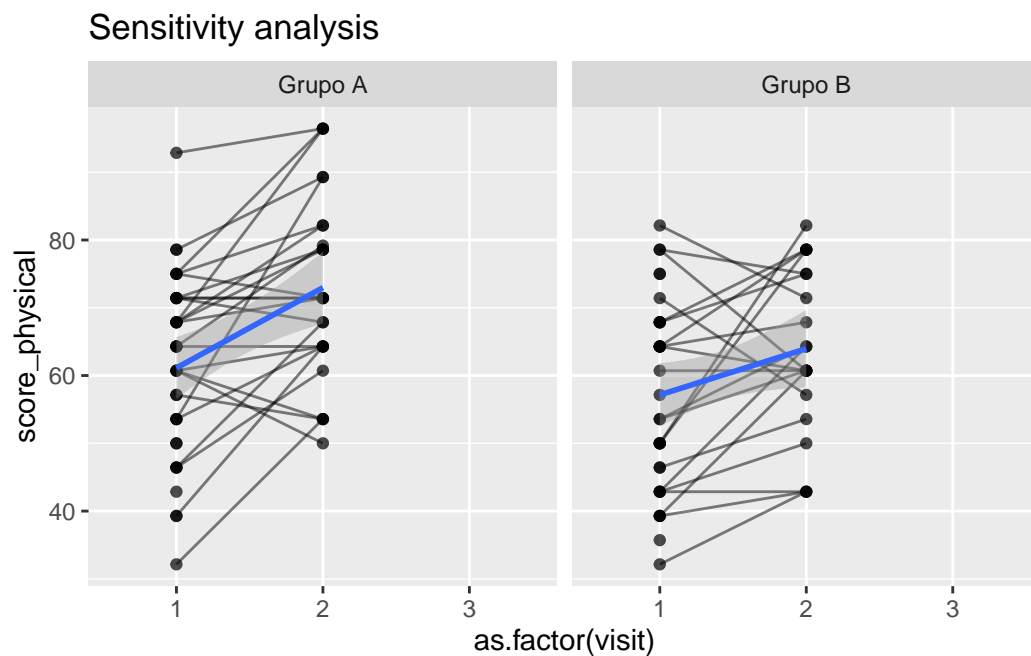


```
data_model_V1V3 %>%  
  filter(  
    !(record_id %in%  
      score_physical_model_check$influential_ids)  
  ) %>%  
  ggplot(  
    aes(  
      x = as.factor(visit),  
      y = score_physical,  
      group = record_id,  
    )  
  ) +  
  geom_line(alpha = 0.5) +  
  geom_point(alpha = 0.7) +
```

```

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

```



## 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)) +

```

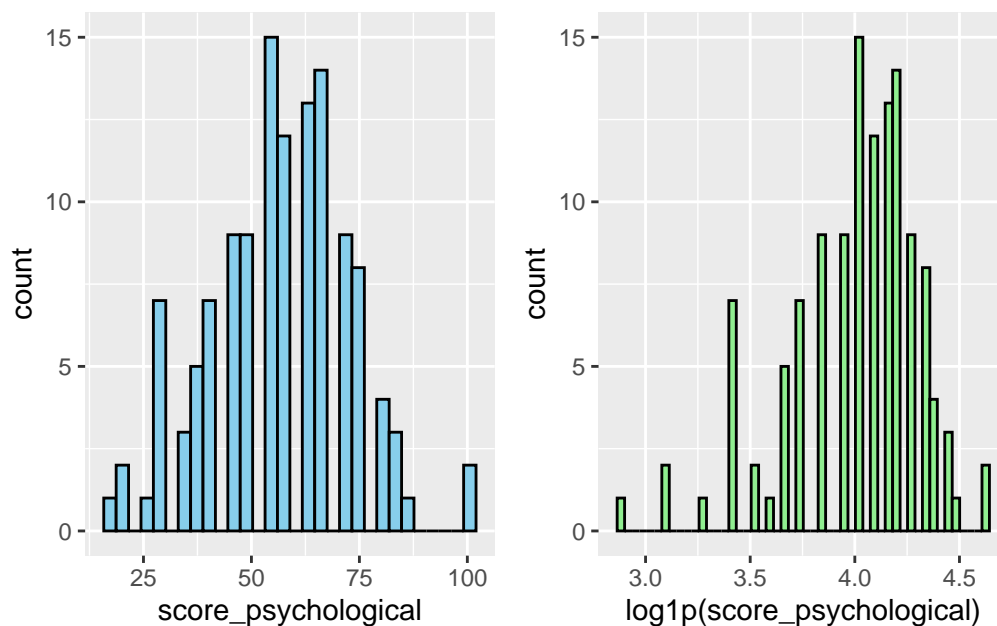
```

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)

```



```

# 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	Tolerance 95% CI
	allocation_group	1.17	[1.05, 1.63]	1.08	0.86	[0.61, 0.96]
	visit	1.94	[1.56, 2.56]	1.39	0.52	[0.39, 0.64]
	allocation_group:visit	2.09	[1.67, 2.77]	1.45	0.48	[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:visit2	-4.34	3.53	-1.23	2.25e- 1
6 Sensitivity	allocation_groupGrupo B:visit2	-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)
```

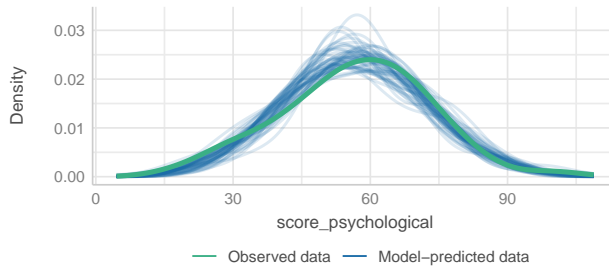
# Comparison of Model Performance Indices

Name	Model	AIC (weights)	AICc (weights)
score_psychological_model	lmerModLmerTest	1015.7 (<.001)	1016.4 (<.001)
score_psychological_model_sens	lmerModLmerTest	900.7 (>.999)	901.5 (>.999)

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

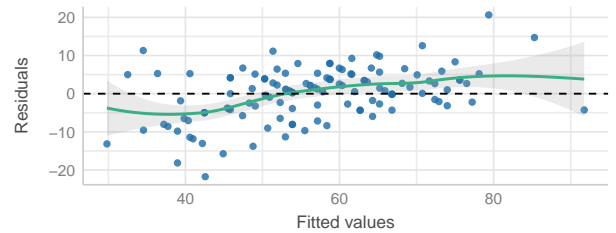
### Posterior Predictive Check

Model-predicted lines should resemble observed data line



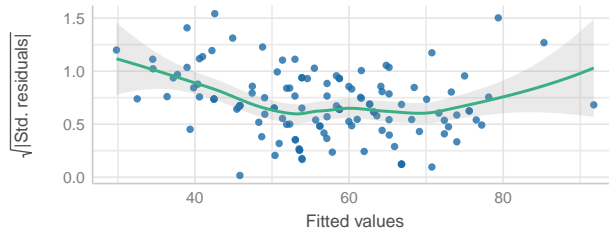
### Linearity

Reference line should be flat and horizontal



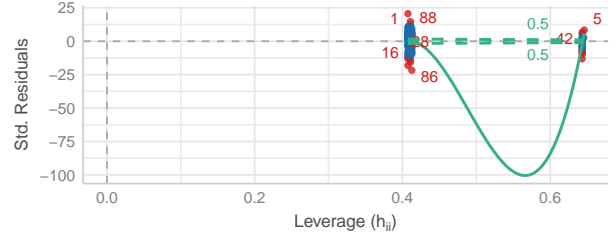
### Homogeneity of Variance

Reference line should be flat and horizontal



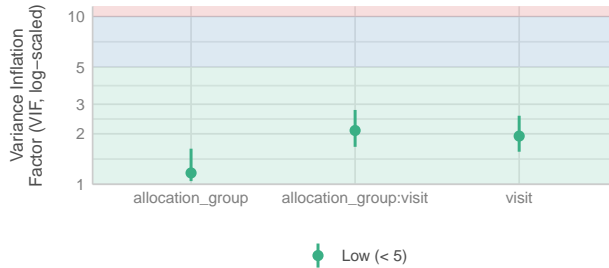
### Influential Observations

Points should be inside the contour lines



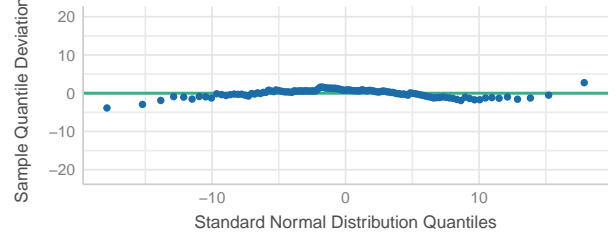
### Collinearity

High collinearity (VIF) may inflate parameter uncertainty



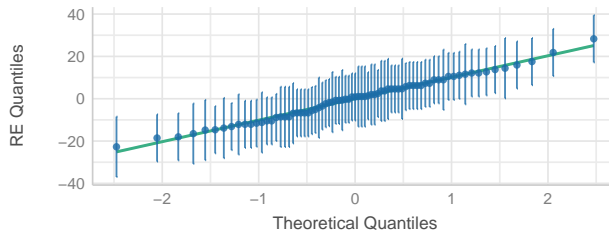
### Normality of Residuals

Dots should fall along the line



### Normality of Random Effects (record\_id)

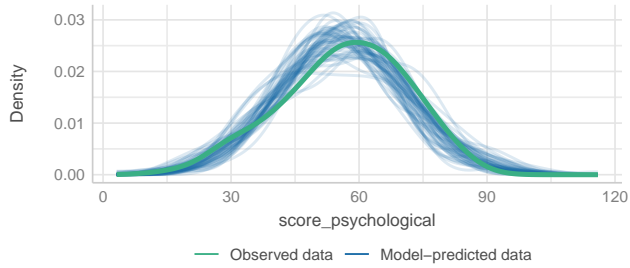
Dots should be plotted along the line



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

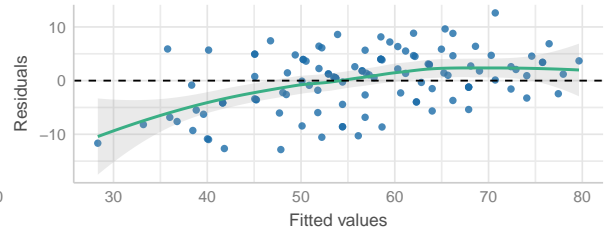
### Posterior Predictive Check

Model-predicted lines should resemble observed data line



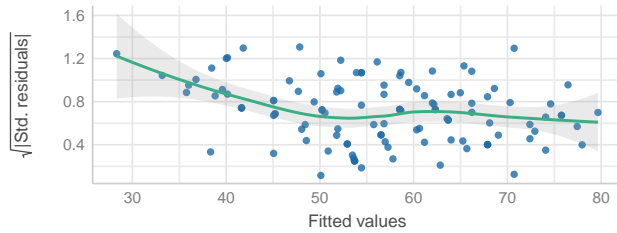
### Linearity

Reference line should be flat and horizontal



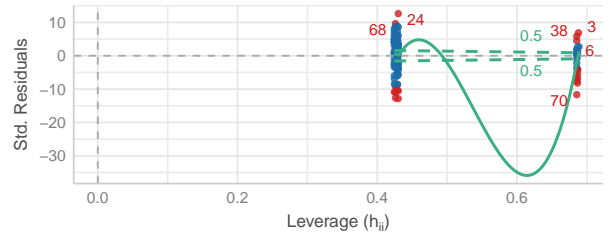
### Homogeneity of Variance

Reference line should be flat and horizontal



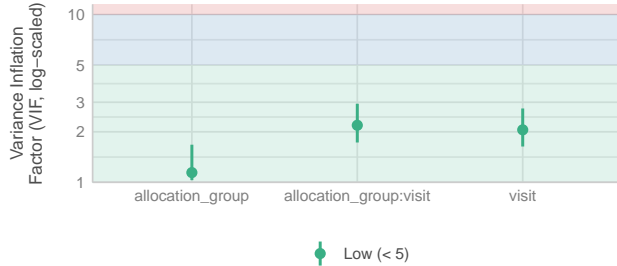
### Influential Observations

Points should be inside the contour lines



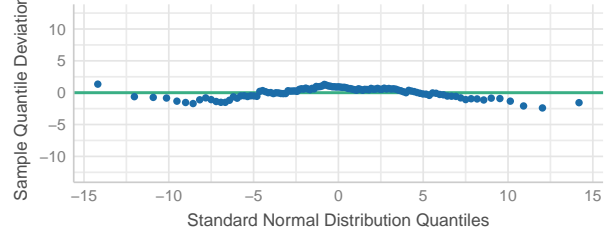
### Collinearity

High collinearity (VIF) may inflate parameter uncertainty



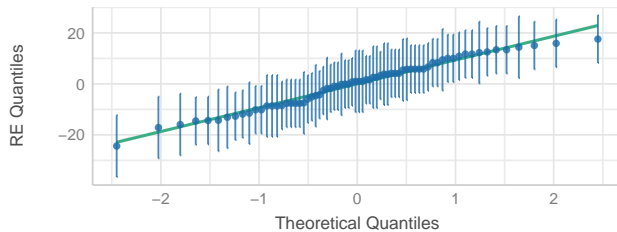
### Normality of Residuals

Dots should fall along the line



### Normality of Random Effects (record\_id)

Dots should be plotted along the line



## 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
```

```
)

score_psychological_raw_emm <- regrid(score_psychological_raw_emm)

# Table of marginal means
# score_psychological_raw_emm

# Pairwise comparisons: Between groups at each visit
emmmeans::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

# Pairwise comparisons: Changes over time within each group
emmmeans::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:
```

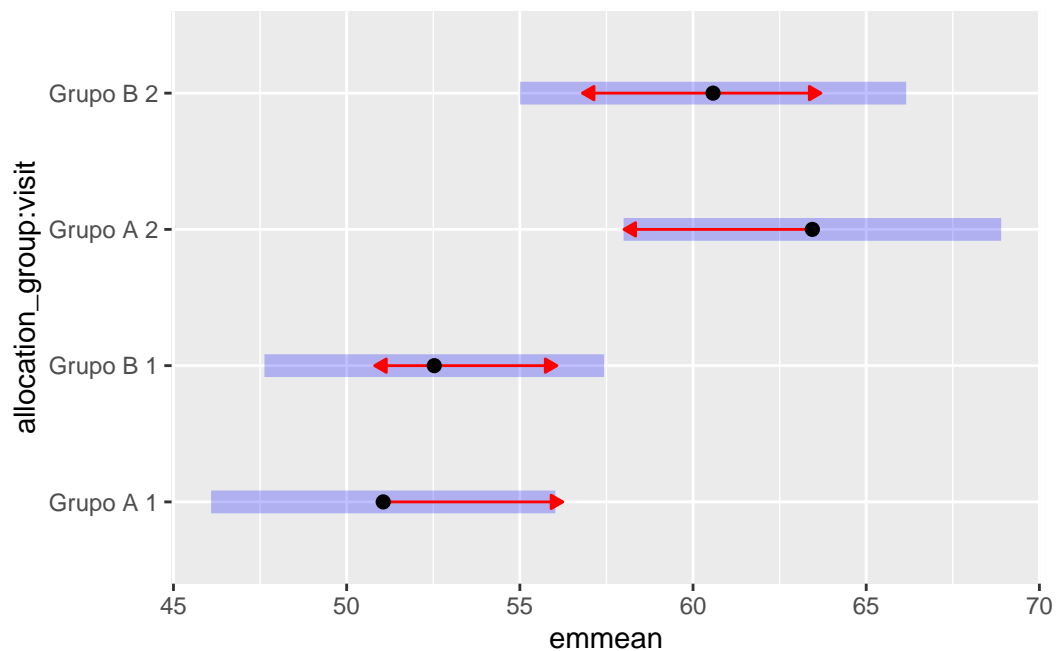
contrast	estimate	SE	df	lower.CL	upper.CL	t.ratio	p.value
visit1 - visit2	-8.05	2.55	95.2	-13.1	-2.99	-3.159	0.0021

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

Confidence level used: 0.95

```
# Plot of marginal means
```

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



#### 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
emmmeans::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
emmmeans::contrast(score_psychological_emm,
method = "pairwise", by = "allocation_group",
adjust = "bonferroni") %>% summary(infer = c(TRUE, TRUE))
```

allocation\_group = Grupo A:

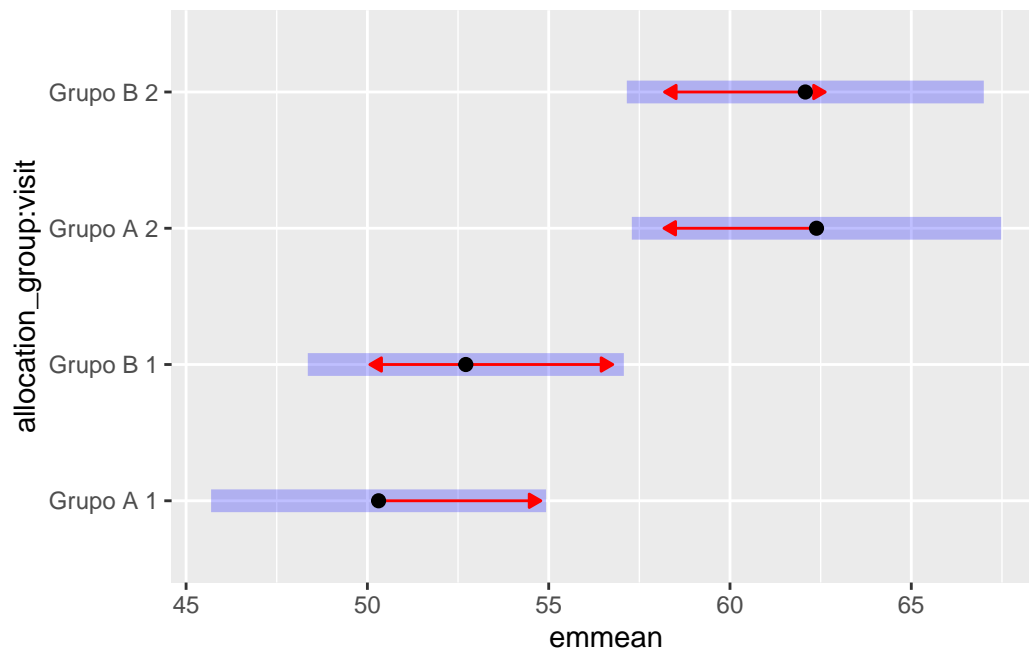
contrast	estimate	SE	df	lower.CL	upper.CL	t.ratio	p.value
visit1 - visit2	-12.08	2.21	85.7	-16.5	-7.69	-5.473	<.0001

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

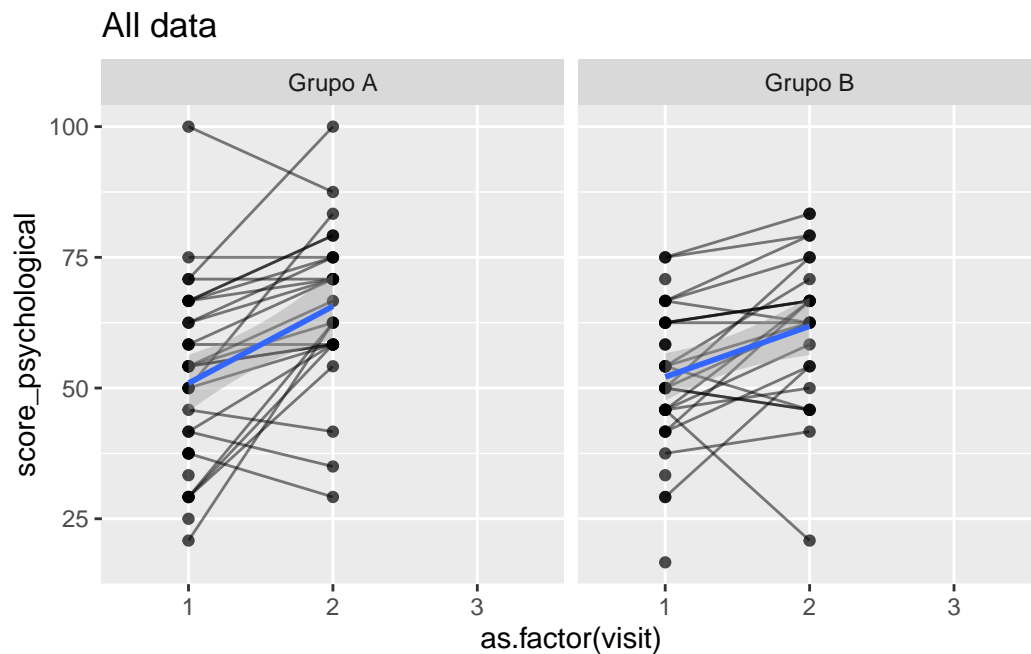
Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 1	-2,41	[-8,76; 3,94]	0,454
Entre grupos	Visita 2	0,31	[-6,78; 7,39]	0,931
Grupo Placebo	Visita 1 – Visita 2	-12,08	[-16,5; -7,69]	< 0,001
Grupo Eclipta	Visita 1 – Visita 2	-9,36	[-13,6; -5,09]	< 0,001

```
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)

```



```

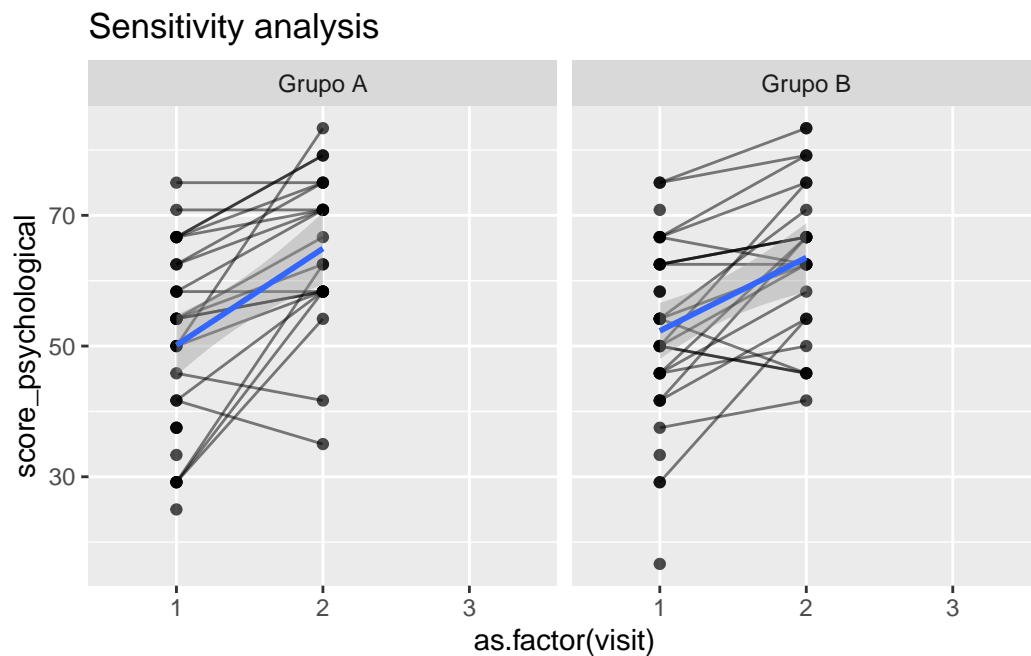
data_model_V1V3 %>%
  filter(
    !(record_id %in%
      score_psychological_model_check$influential_ids)
  ) %>%
  ggplot(
    aes(
      x = as.factor(visit),
      y = score_psychological,
      group = record_id,
    )
  ) +

```

```

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)

```



### 1.3 Domínio Social

Variável: score\_social

```

# Plot 1: Raw data
score_social_hist_1 <- data_model_V1V3 %>%
  #filter(
  #   score_social < 300

```

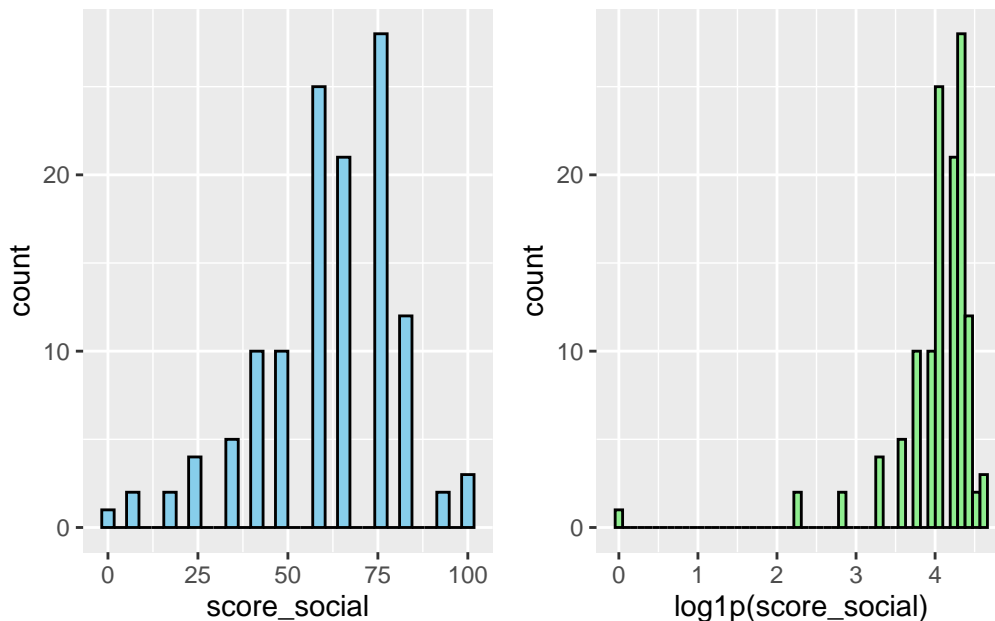
```

#) %>%
  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)

```



```

# 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	Tolerance 95% CI
allocation_group	1.17	[1.05, 1.63]	1.08	0.85	[0.61, 0.96]
visit	1.94	[1.56, 2.56]	1.39	0.52	[0.39, 0.64]
allocation_group:visit	2.10	[1.67, 2.78]	1.45	0.48	[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:visit2	-4.90	4.61	-1.06	2.93e- 1
6	Sensitivity	allocation_groupGrupo B:visit2	-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)
```

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

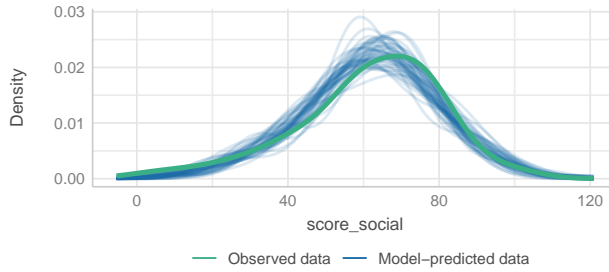
Name	Model	AIC (weights)	AICc (weights)	BIC (weights)
score_social_model	lmerModLmerTest	1081.5 (<.001)	1082.2 (<.001)	1098.5 (<.001)
score_social_model_sens	lmerModLmerTest	938.7 (>.999)	939.4 (>.999)	955.1 (>.999)

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



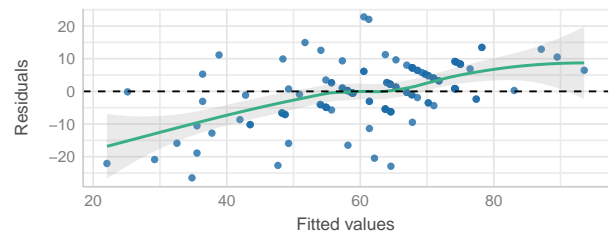
### Posterior Predictive Check

Model-predicted lines should resemble observed data line



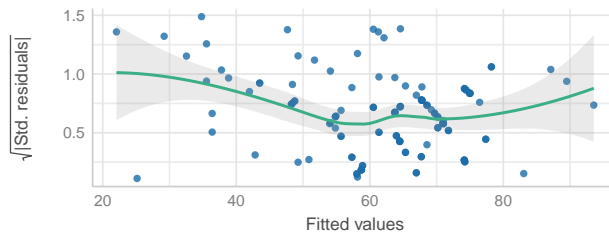
### Linearity

Reference line should be flat and horizontal



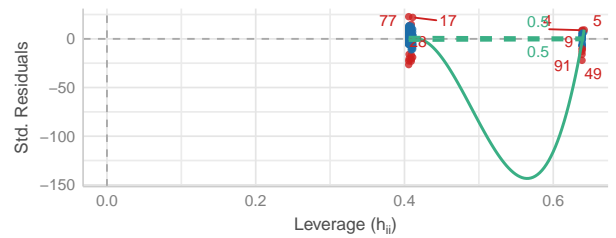
### Homogeneity of Variance

Reference line should be flat and horizontal



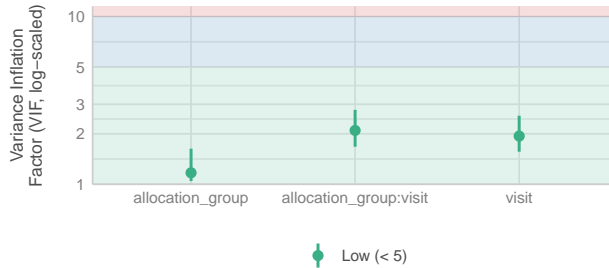
### Influential Observations

Points should be inside the contour lines



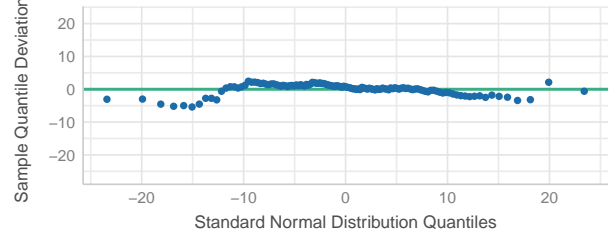
### Collinearity

High collinearity (VIF) may inflate parameter uncertainty



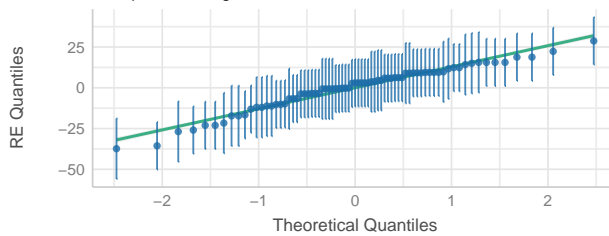
### Normality of Residuals

Dots should fall along the line



### Normality of Random Effects (record\_id)

Dots should be plotted along the line



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

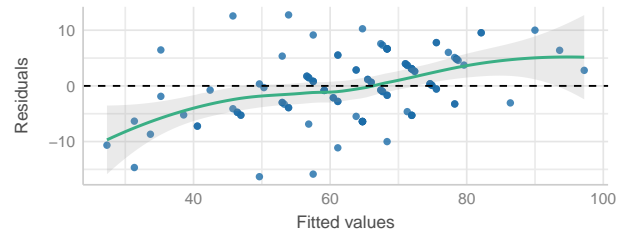
### Posterior Predictive Check

Model-predicted lines should resemble observed data line



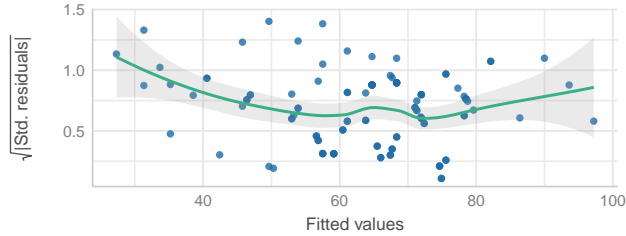
### Linearity

Reference line should be flat and horizontal



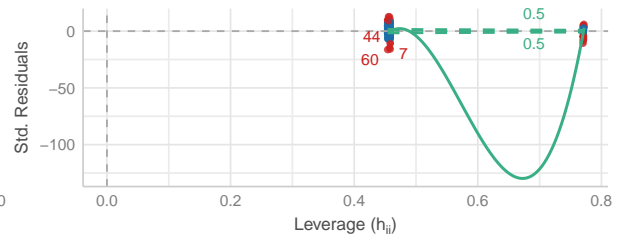
### Homogeneity of Variance

Reference line should be flat and horizontal



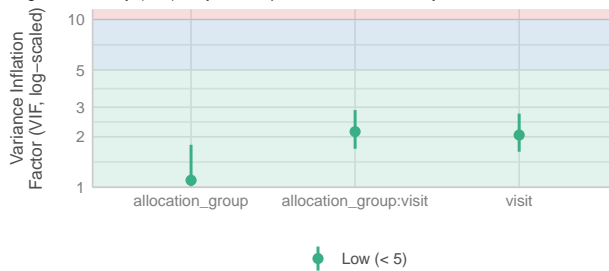
### Influential Observations

Points should be inside the contour lines



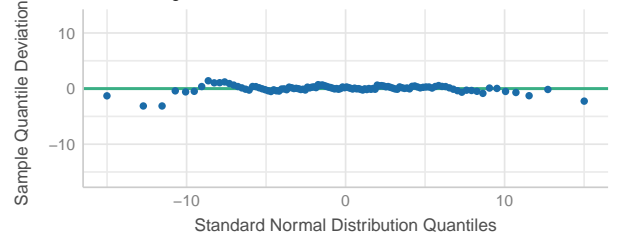
### Collinearity

High collinearity (VIF) may inflate parameter uncertainty



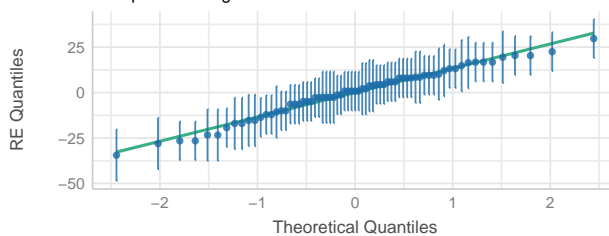
### Normality of Residuals

Dots should fall along the line



### Normality of Random Effects (record\_id)

Dots should be plotted along the line



## 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
```

```
)
```

```
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

```
# 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:
```

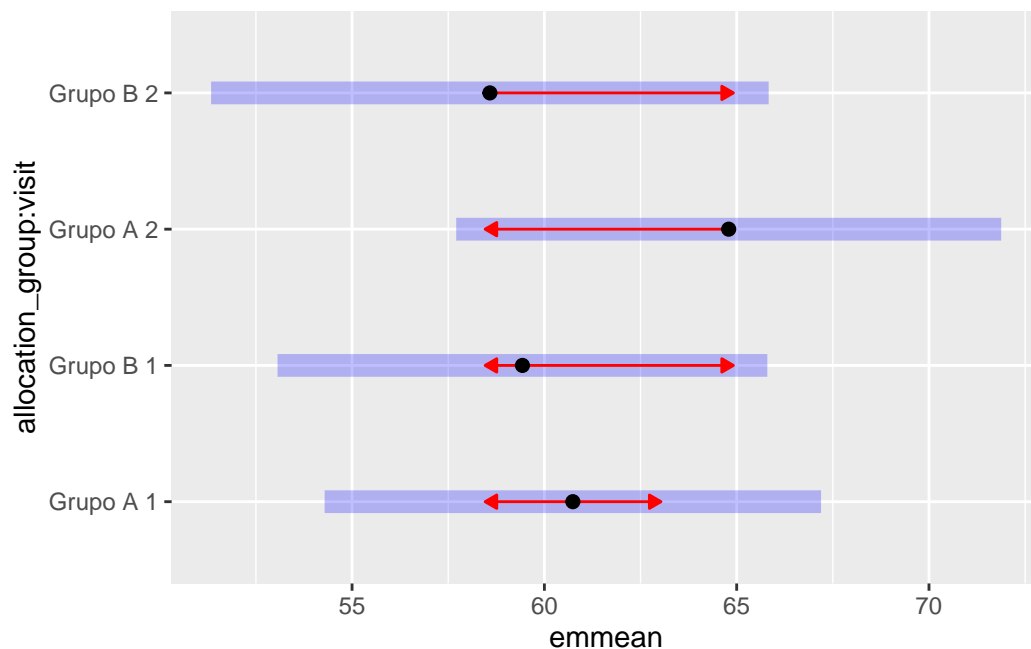
contrast	estimate	SE	df	lower.CL	upper.CL	t.ratio	p.value
visit1 - visit2	0.846	3.33	95.5	-5.76	7.45	0.254	0.7998

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

Confidence level used: 0.95

```
# 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:
```

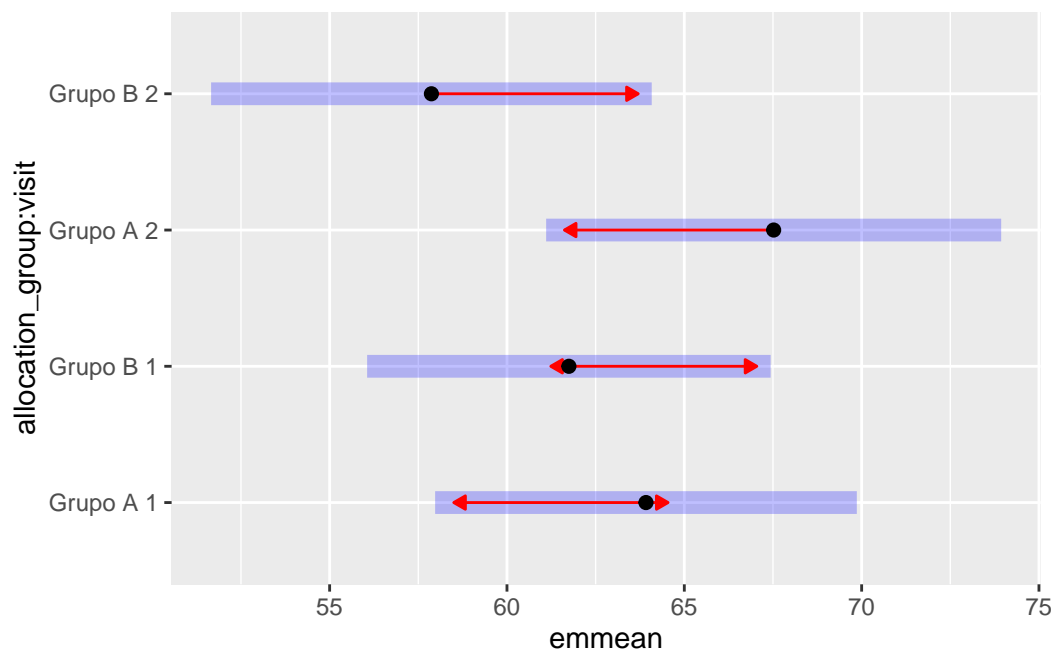
contrast	estimate	SE	df	lower.CL	upper.CL	t.ratio	p.value
visit1 - visit2	3.88	2.39	79.7	-0.882	8.64	1.621	0.1089

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

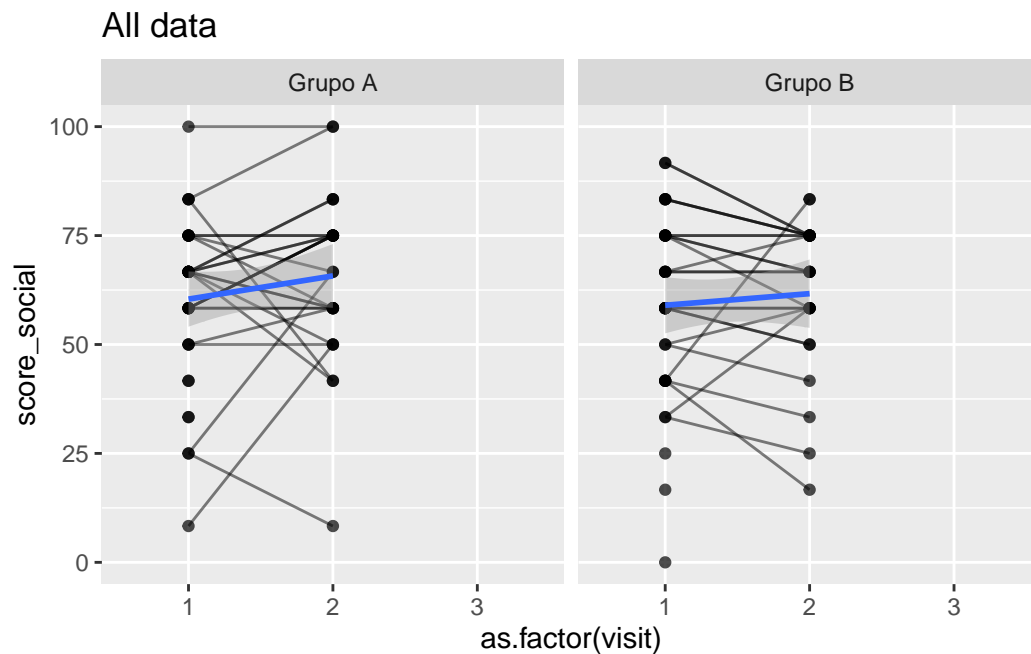
Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 1	2,17	[-6,06; 10,4]	0,601
Entre grupos	Visita 2	9,65	[0,72; 18,6]	0,035
Grupo Placebo	Visita 1 – Visita 2	-3,60	[-8,47; 1,27]	0,145
Grupo Eclipta	Visita 1 – Visita 2	3,88	[-0,88; 8,64]	0,109

```
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)

```



```

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,
    )
  ) +

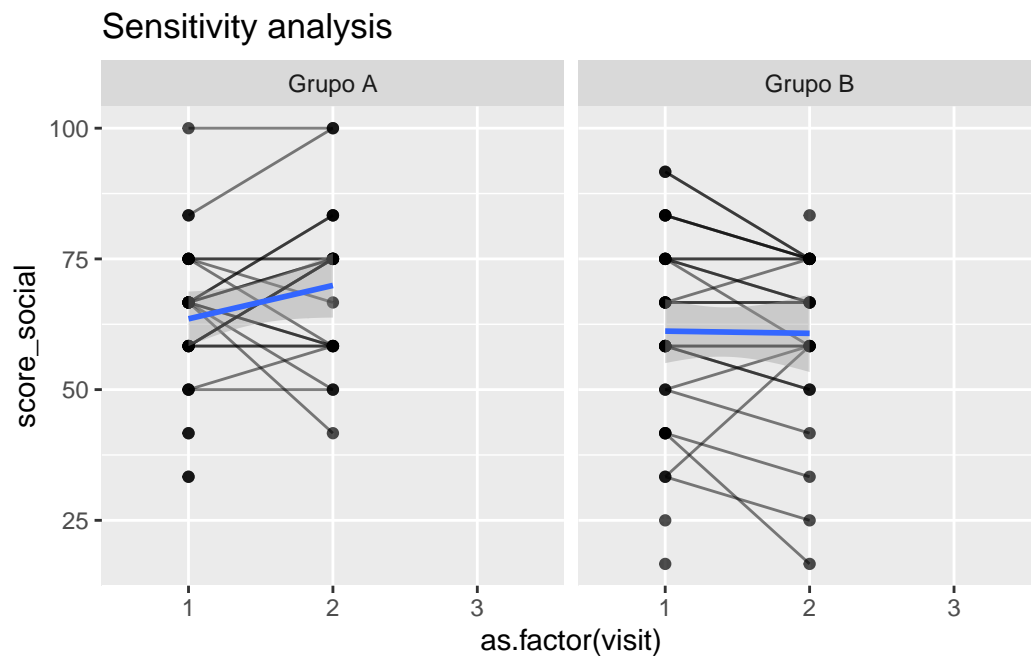
```



```

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)

```



## 1.4 Domínio Ambiental

Variável: score\_environment

```

# Plot 1: Raw data
score_environment_hist_1 <- data_model_V1V3 %>%
  #filter(
  #   score_environment < 300

```

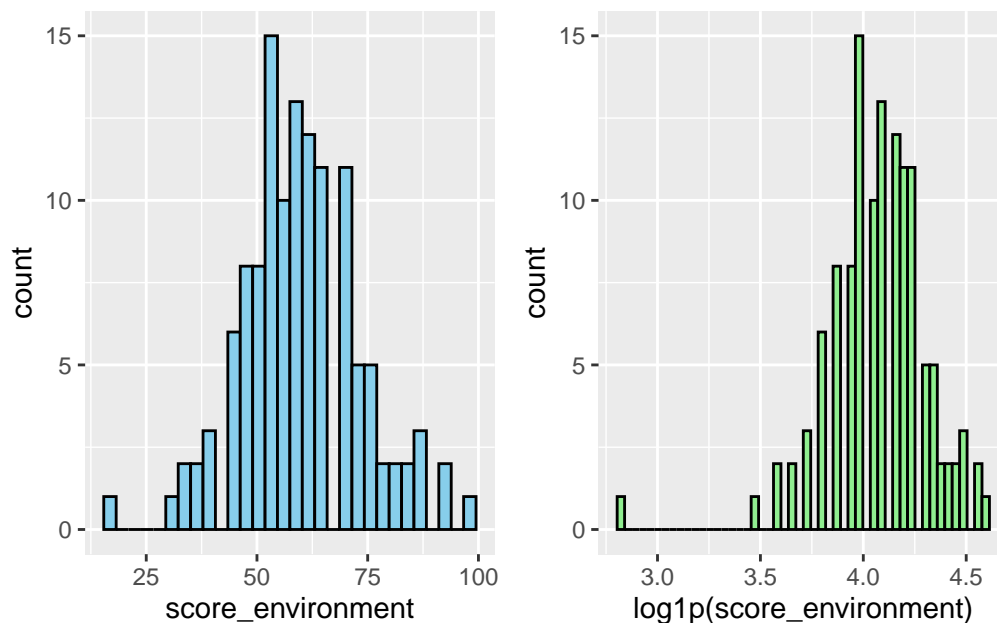
```

#) %>%
  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)

```



```

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

```
# 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

```
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:visit2	-1.15	2.63	-0.439	6.63e- 1
6	Sensitivity	allocation_groupGrupo B:visit2	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)
```

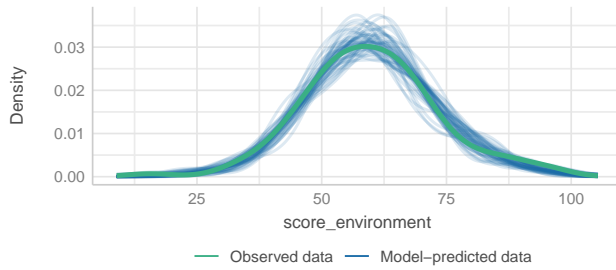
```
# Comparison of Model Performance Indices
```

Name	Model	AIC (weights)	AICc (weights)	BIC
score_environment_model	lmerModLmerTest	970.7 (<.001)	971.4 (<.001)	987.
score_environment_model_sens	lmerModLmerTest	852.9 (>.999)	853.7 (>.999)	869.

```
performance::check_model(score_environment_model)
```

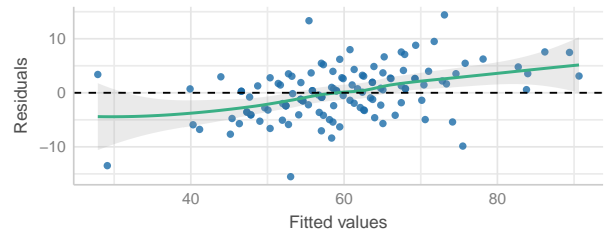
### Posterior Predictive Check

Model-predicted lines should resemble observed data line



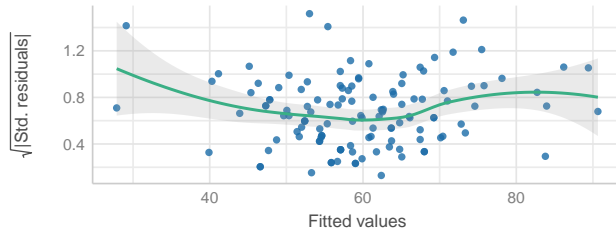
### Linearity

Reference line should be flat and horizontal



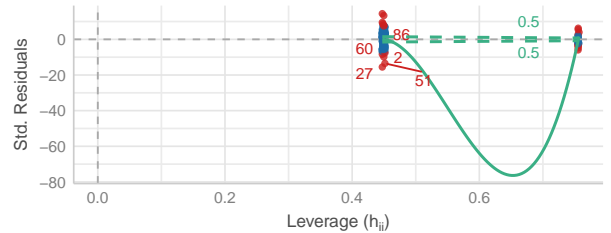
### Homogeneity of Variance

Reference line should be flat and horizontal



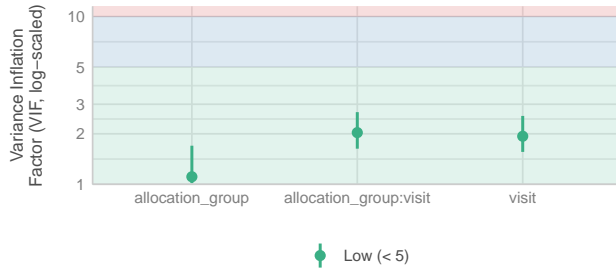
### Influential Observations

Points should be inside the contour lines



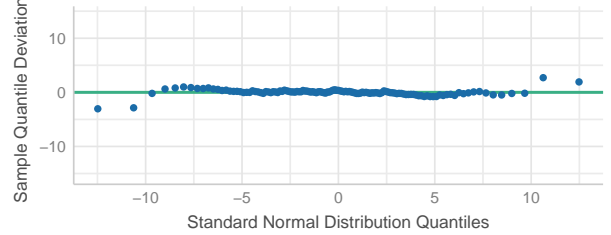
### Collinearity

High collinearity (VIF) may inflate parameter uncertainty



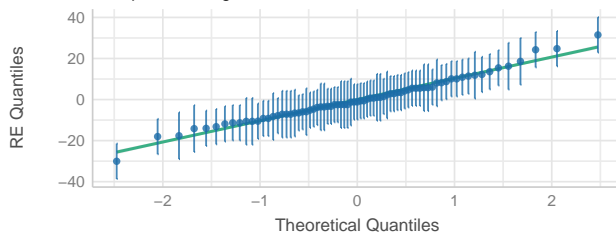
### Normality of Residuals

Dots should fall along the line



### Normality of Random Effects (record\_id)

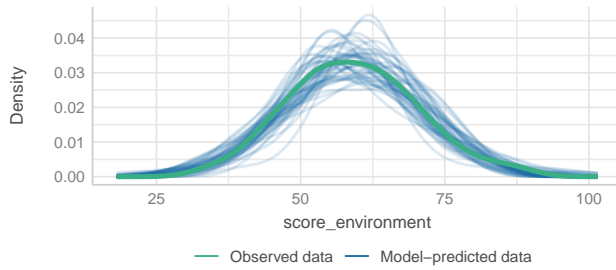
Dots should be plotted along the line



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

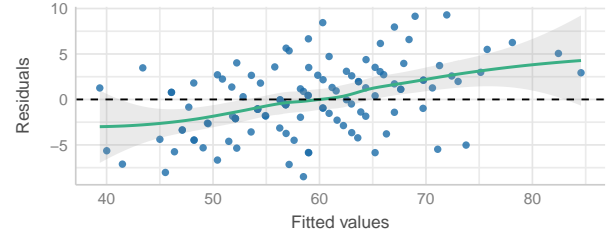
### Posterior Predictive Check

Model-predicted lines should resemble observed data line



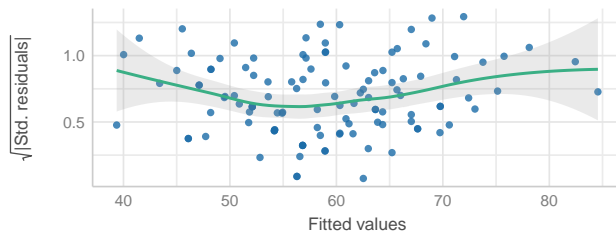
### Linearity

Reference line should be flat and horizontal



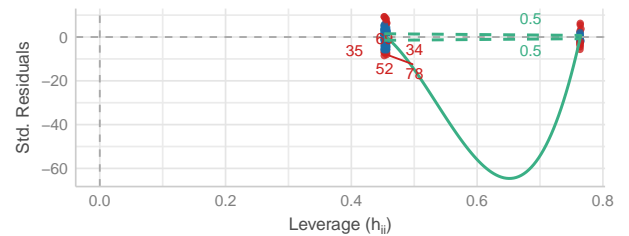
### Homogeneity of Variance

Reference line should be flat and horizontal



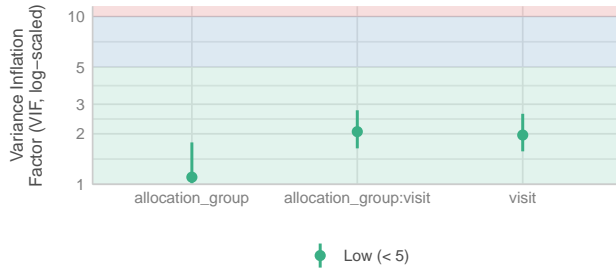
### Influential Observations

Points should be inside the contour lines



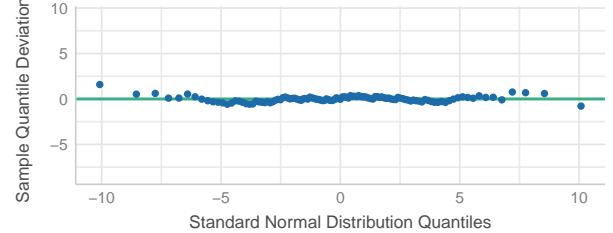
### Collinearity

High collinearity (VIF) may inflate parameter uncertainty



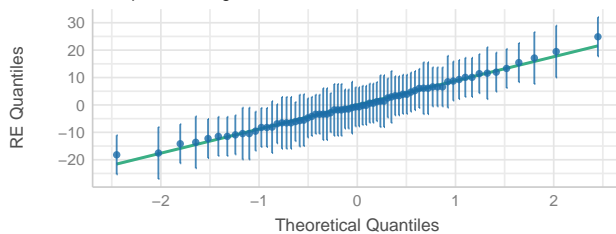
### Normality of Residuals

Dots should fall along the line



### Normality of Random Effects (record\_id)

Dots should be plotted along the line



## 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
```



```
)

score_environment_raw_emm <- regrid(score_environment_raw_emm)

# Table of marginal means
# score_environment_raw_emm

# Pairwise comparisons: Between groups at each visit
emmmeans::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

```
# Pairwise comparisons: Changes over time within each group
emmmeans::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:
```

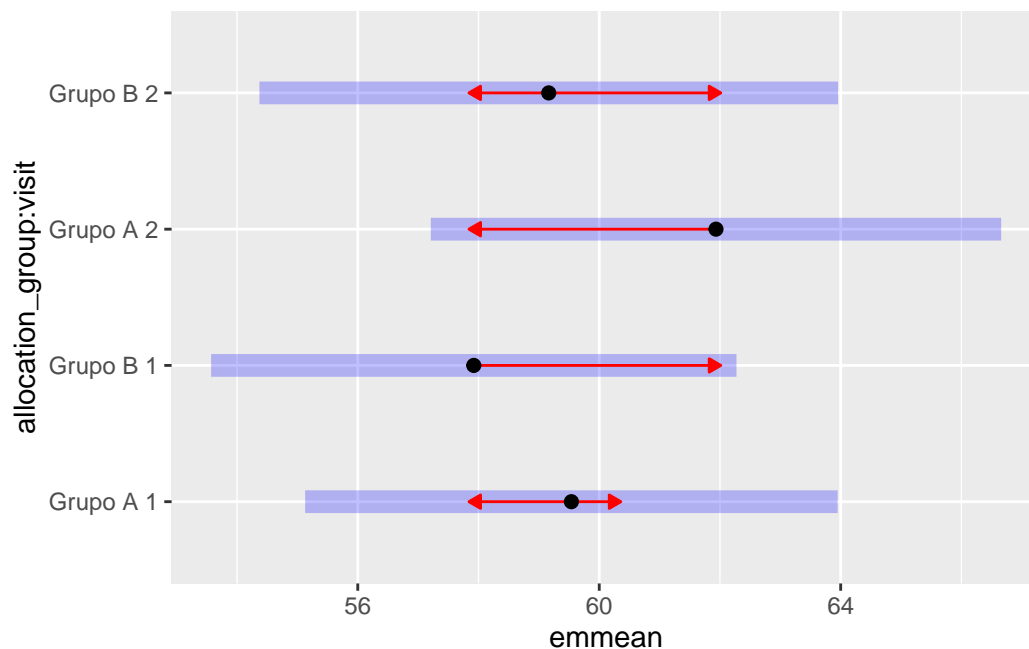
contrast	estimate	SE	df	lower.CL	upper.CL	t.ratio	p.value
visit1 - visit2	-1.24	1.90	88	-5.01	2.53	-0.655	0.5143

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

Confidence level used: 0.95

```
# 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
emmmeans::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
emmmeans::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:
```

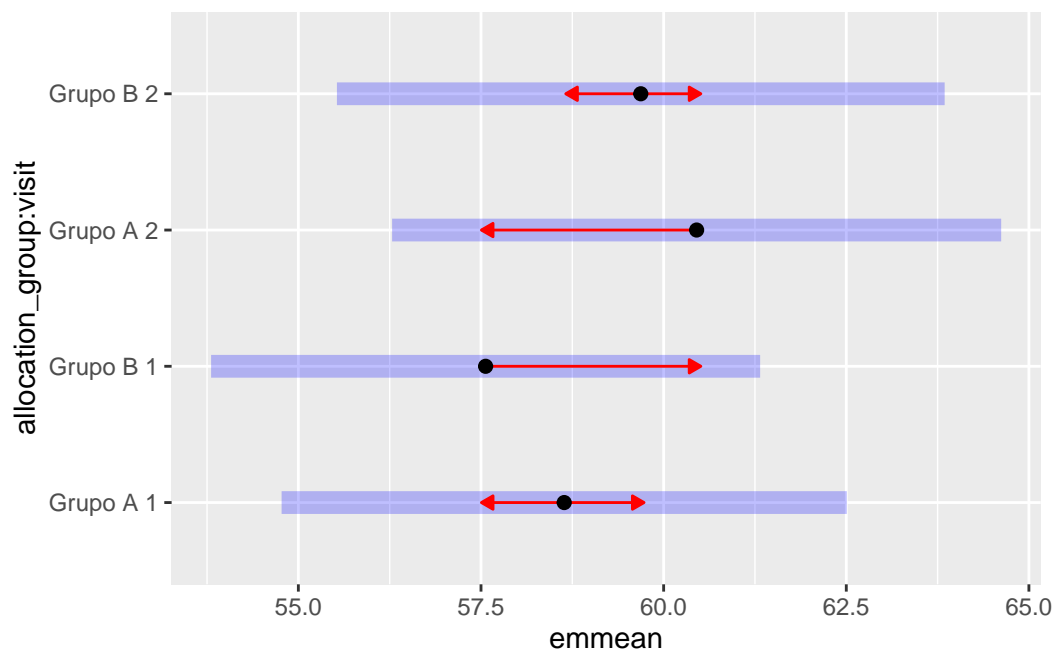
contrast	estimate	SE	df	lower.CL	upper.CL	t.ratio	p.value
visit1 - visit2	-2.12	1.63	81.1	-5.38	1.13	-1.300	0.1974

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

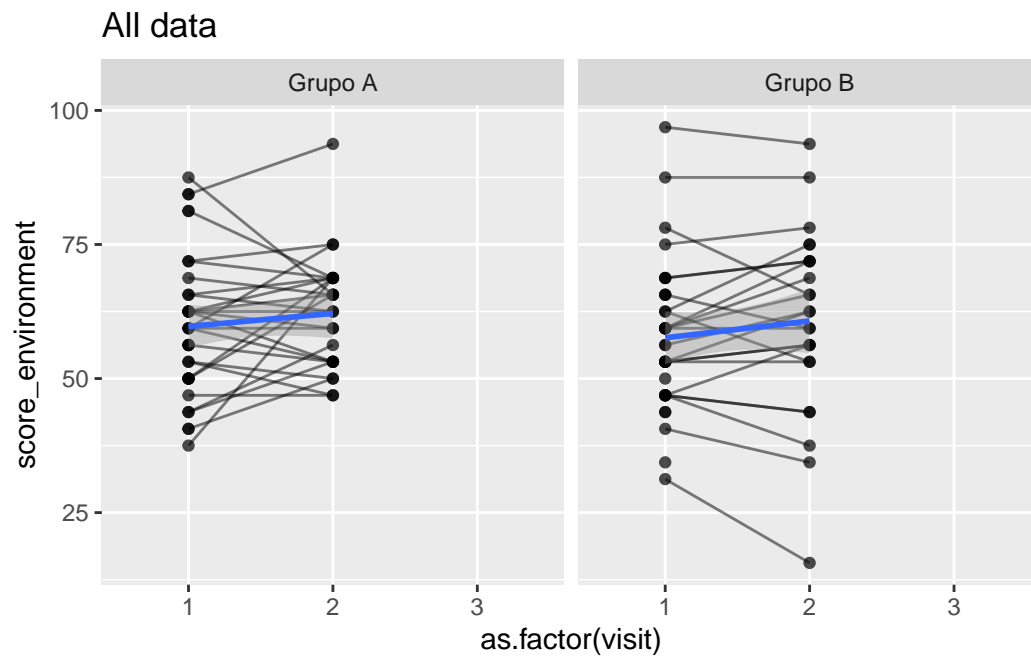
No modelo ajustado para o domínio ambiente do WHOQOL-BREF, não foram observadas diferenças significativas entre os grupos na visita 1 (estimativa = 1,62; IC 95%: -4,58 a 7,81) nem na visita 2 (estimativa = 2,77; IC 95%: -3,96 a 9,50). Também não houve alterações significativas ao longo do tempo dentro 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 de comparação	Comparação	Estimativa	IC 95%	p-valor
Grupo Eclipta	Visita 1 – Visita 2	-1,24	[-5,01; 2,53]	0,514

```
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)
```

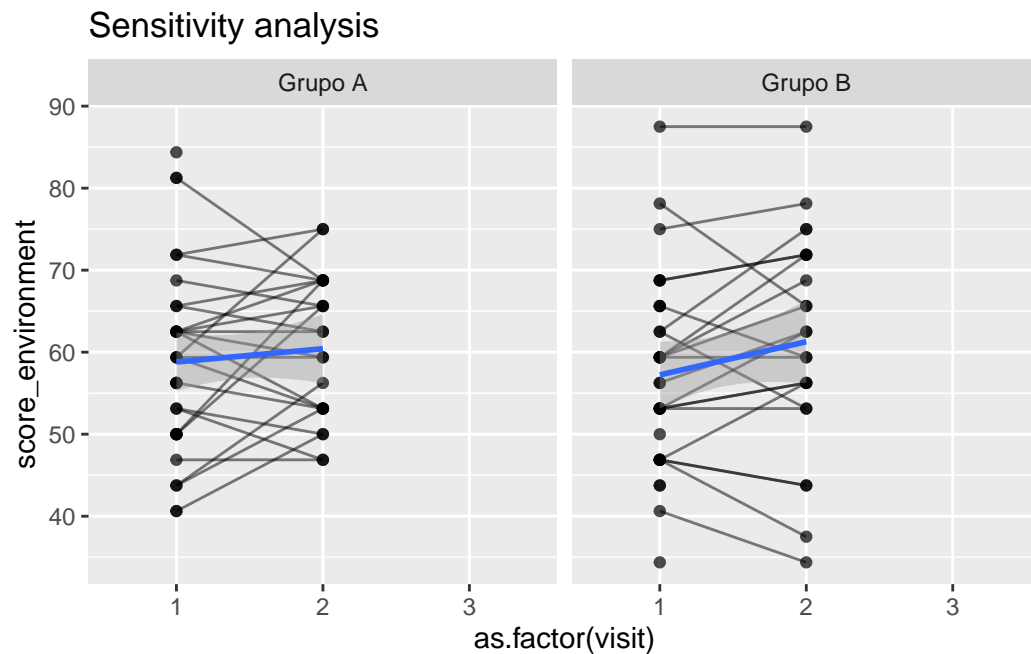


```
data_model_V1V3 %>%
  filter(
    !(record_id %in%
      score_environment_model_check$influential_ids)
  ) %>%
  ggplot(
    aes(
      x = as.factor(visit),
      y = score_environment,
      group = record_id,
    )
  ) +
  geom_line(alpha = 0.5) +
  geom_point(alpha = 0.7) +
  geom_smooth(
    aes(group = allocation_group),
    method = "lm",
```

```

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

```



## 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")

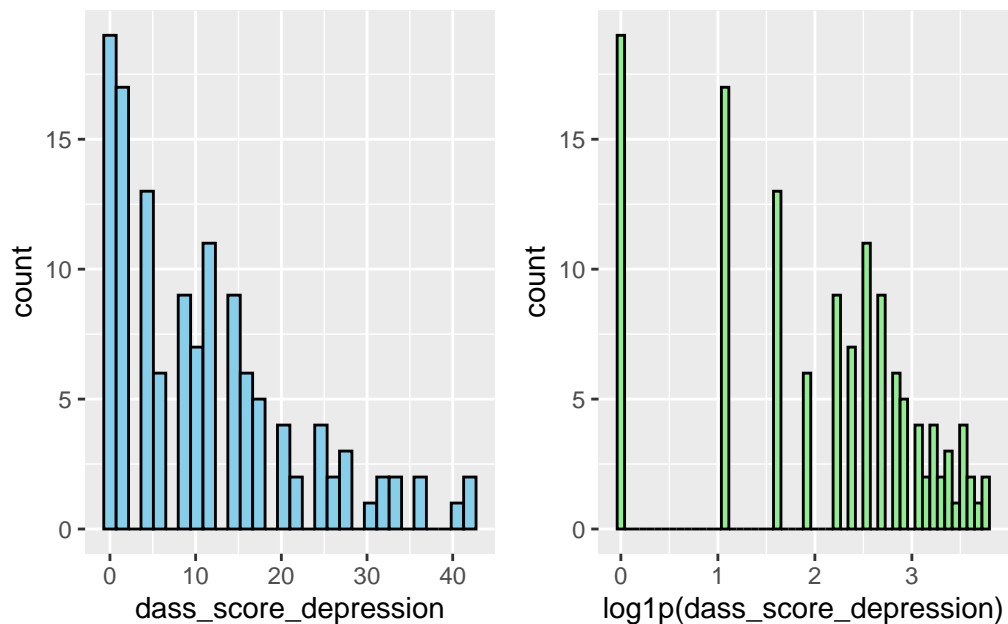
```

```

# 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)

```



```

# 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	Tolerance 95% CI
	allocation_group	1.22	[1.08, 1.65]	1.11	0.82	[0.61, 0.93]
	visit	1.94	[1.57, 2.55]	1.39	0.52	[0.39, 0.64]
	allocation_group:visit	2.13	[1.70, 2.81]	1.46	0.47	[0.36, 0.59]

```
# 3. Identify the 5 most "influential" clusters by magnitude of their random intercept
```

```
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

```
# Compare performance
```

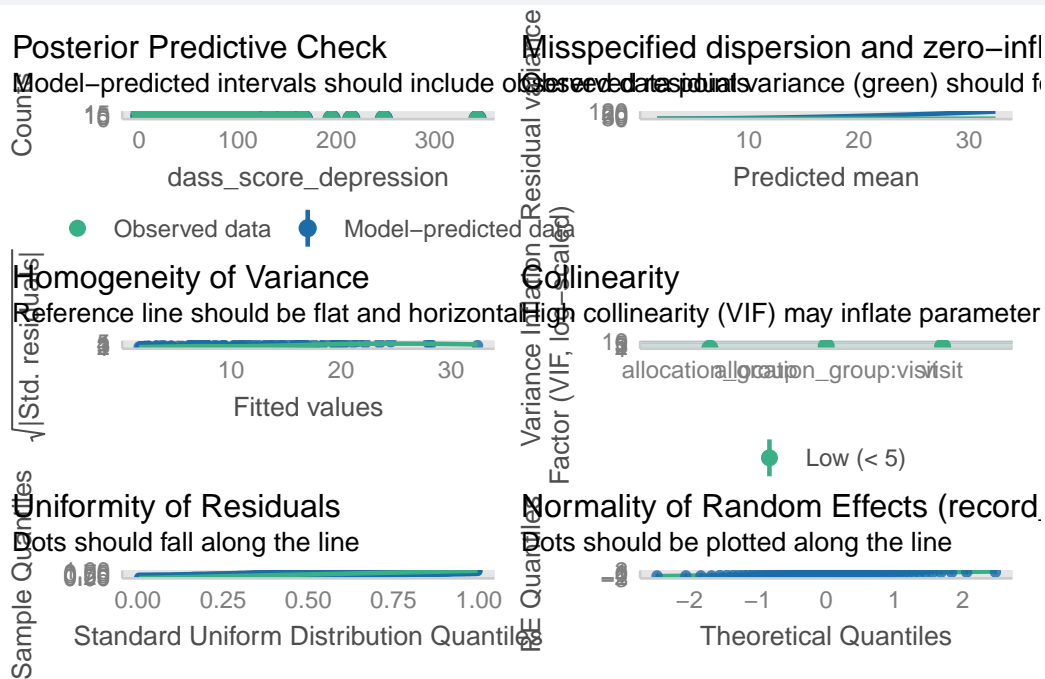
```
performance::compare_performance(  
  dass_score_depression_nb_model,
```

```
dass_score_depression_nb_model_sens
)
```

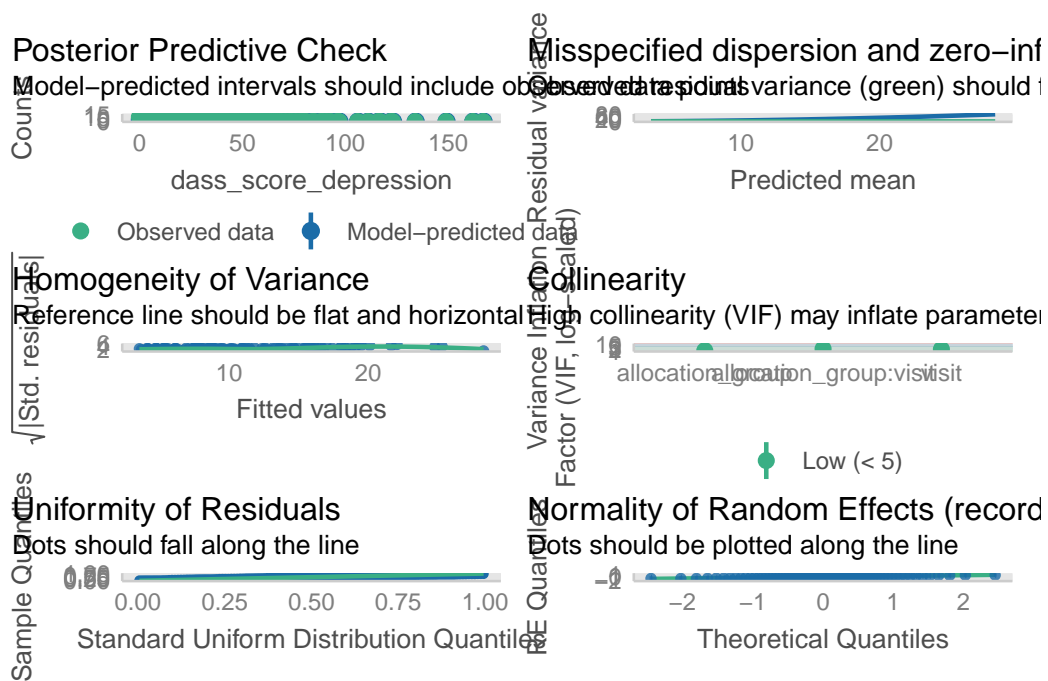
# Comparison of Model Performance Indices

Name	Model	AIC (weights)	AICc (weights)	BIC
dass_score_depression_nb_model	glmmTMB	882.6 (<.001)	883.3 (<.001)	899.6
dass_score_depression_nb_model_sens	glmmTMB	830.9 (>.999)	831.6 (>.999)	847.4

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



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



## 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	asyp.LCL	asyp.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	asyp.LCL	asyp.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
```

```
emmmeans::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	asyp.LCL	asyp.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	asyp.LCL	asyp.UCL	null	z.ratio	p.value
visit1 / visit3	1.5	0.345	Inf	0.959	2.36	1	1.777	0.0756

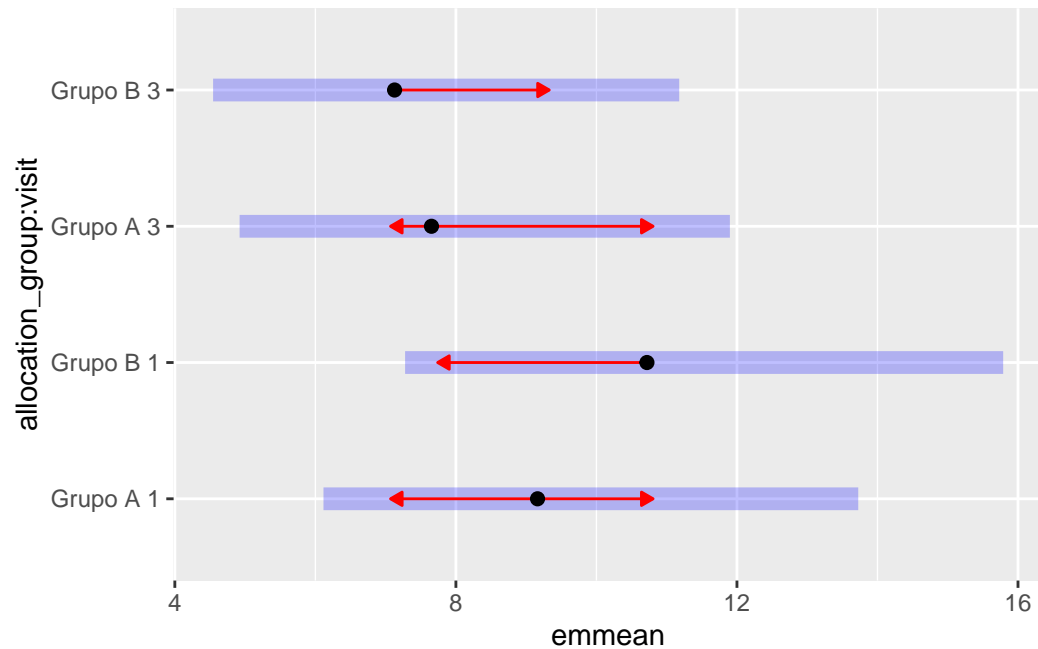
Confidence level used: 0.95

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	asympt.LCL	asympt.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	asympt.LCL	asympt.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

```
# 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	asympt.LCL	asympt.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	asympt.LCL	asympt.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

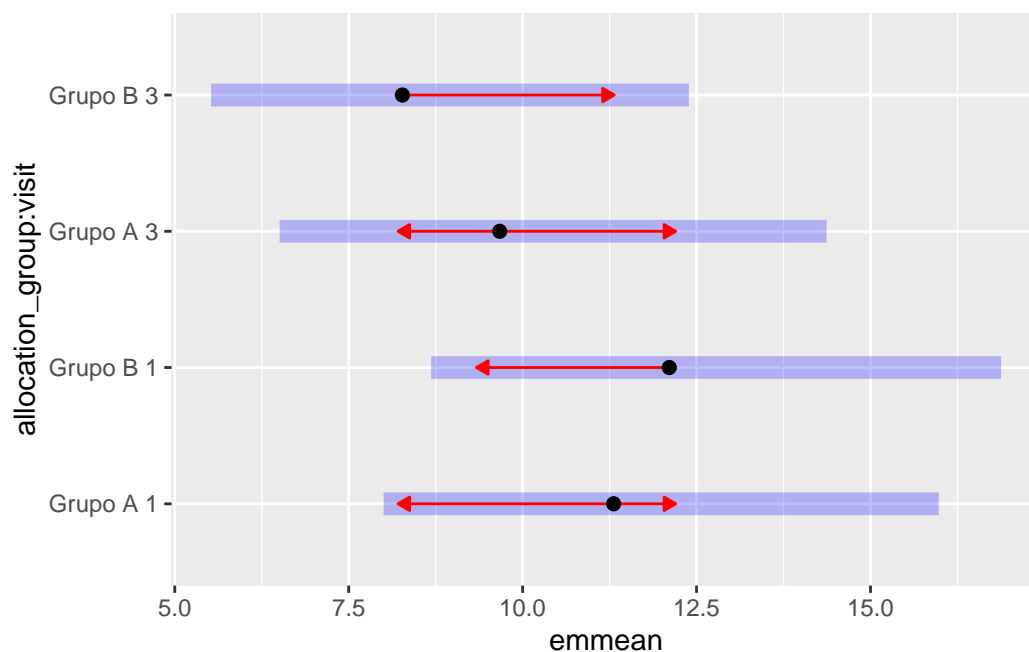
Intervals are back-transformed from the log scale

Tests are performed on the log scale



```
# Plot marginal means
```

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



### 2.1.0.3 Resultado

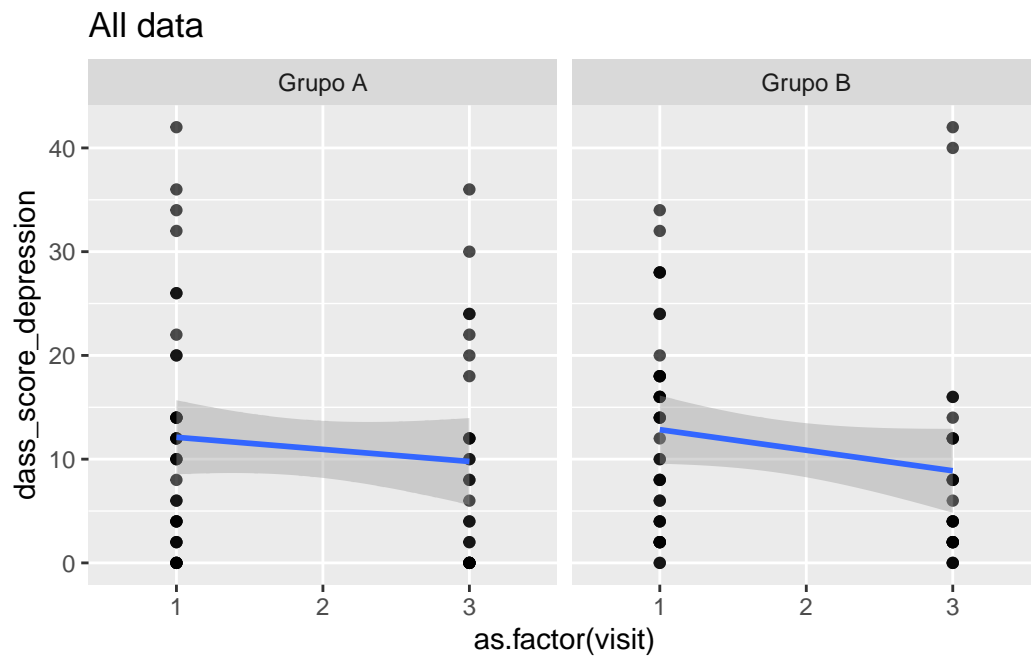
No modelo de regressão para o escore de depressão (DASS), não foram observadas diferenças significativas entre os grupos em nenhum dos momentos avaliados. Na visita 1, a razão dos escores do Grupo A em relação ao Grupo B foi de 0,855 (IC 95%: 0,502–1,46;  $p = 0,564$ ) e, na visita 3, 1,074 (IC 95%: 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 de comparação	Comparação	Razão	IC 95%	p-valor
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)
```

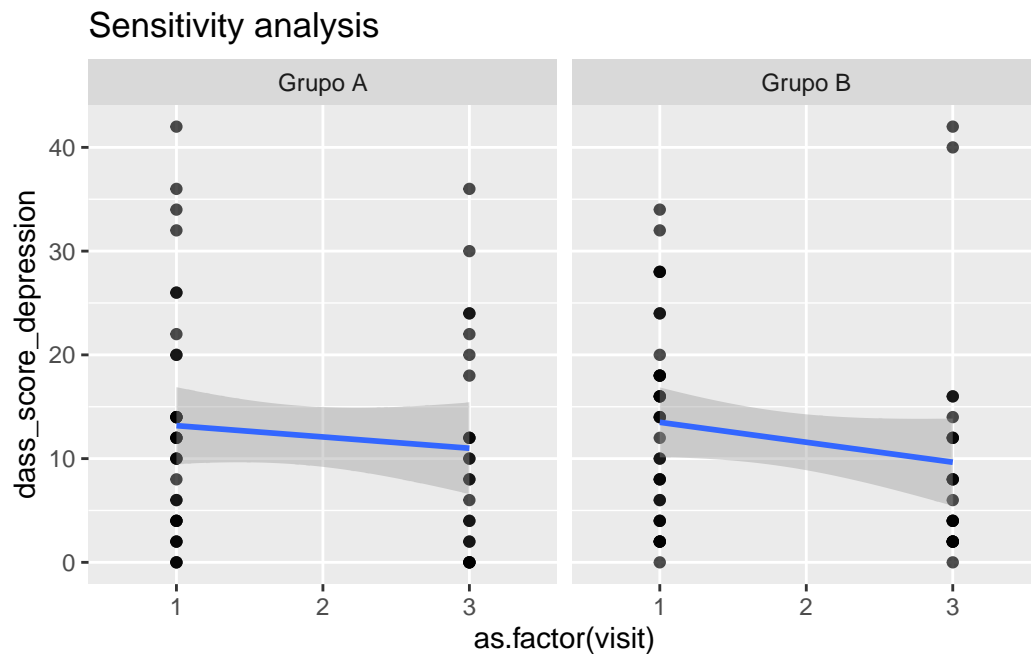


```
data_model_V1V3 %>%
  filter(
    !(record_id %in%
      influential_ids_nb)
  ) %>%
  ggplot(
    aes(
      x = as.factor(visit),
      y = dass_score_depression,
      group = record_id,
    )
  ) +
  geom_line(alpha = 0.5) +
  geom_point(alpha = 0.7) +
  geom_smooth(
    aes(group = allocation_group),
    method = "lm",
```

```

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

```



## 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

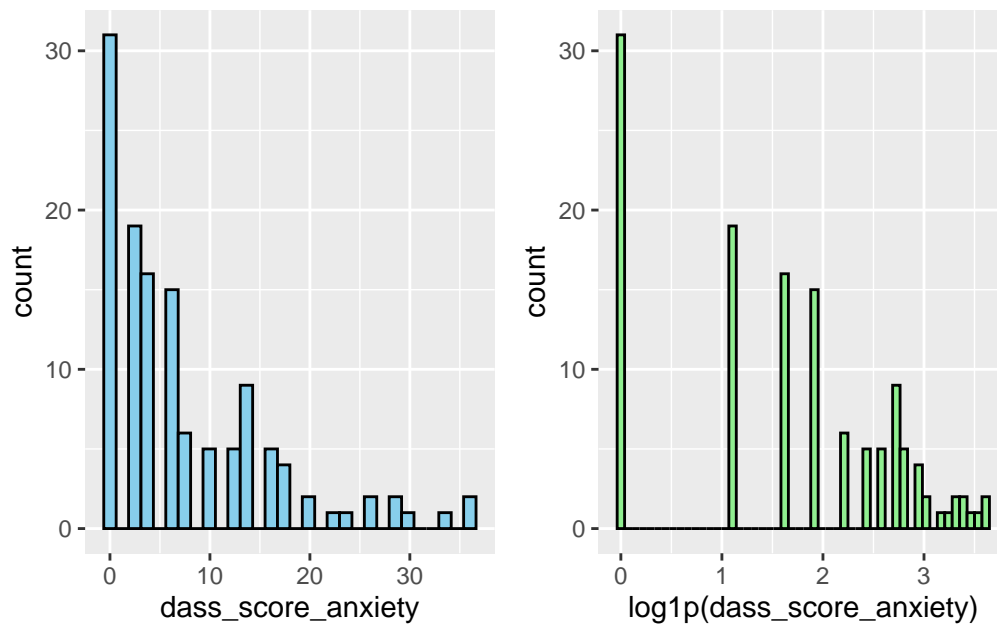
```

```

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)

```



```

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

```
# 3. Identify the 5 most "influential" clusters by magnitude of their random intercept
```

```
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
```

```
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

```
# Compare performance
```

```
performance::compare_performance(  
  dass_score_anxiety_nb_model,  
  dass_score_anxiety_nb_model_sens
```



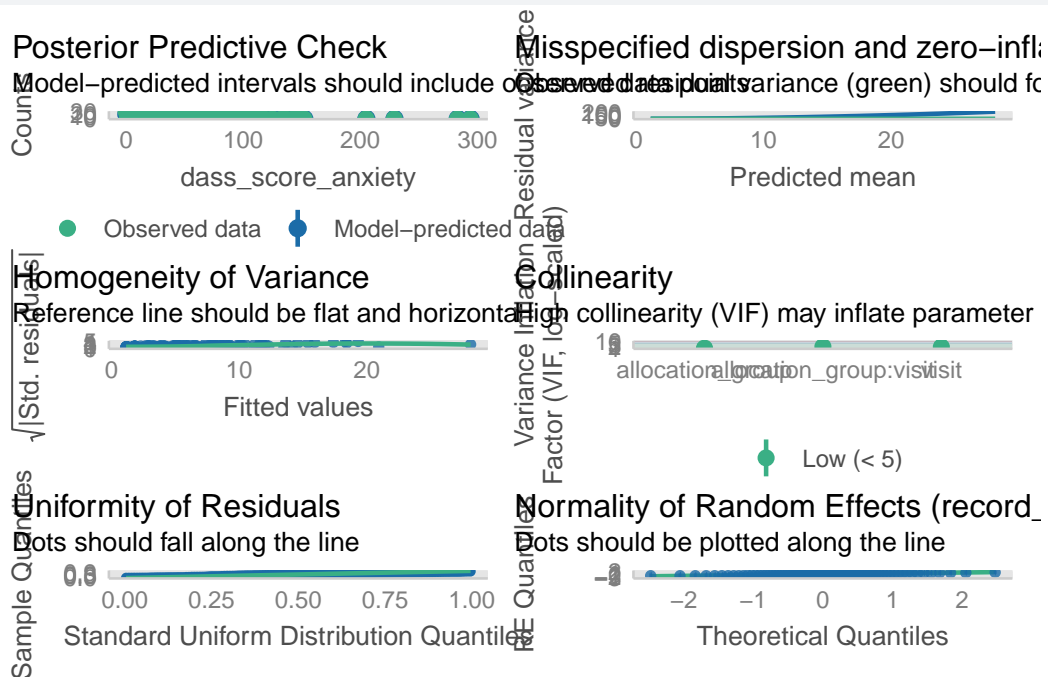
```
)
```

## # Comparison of Model Performance Indices

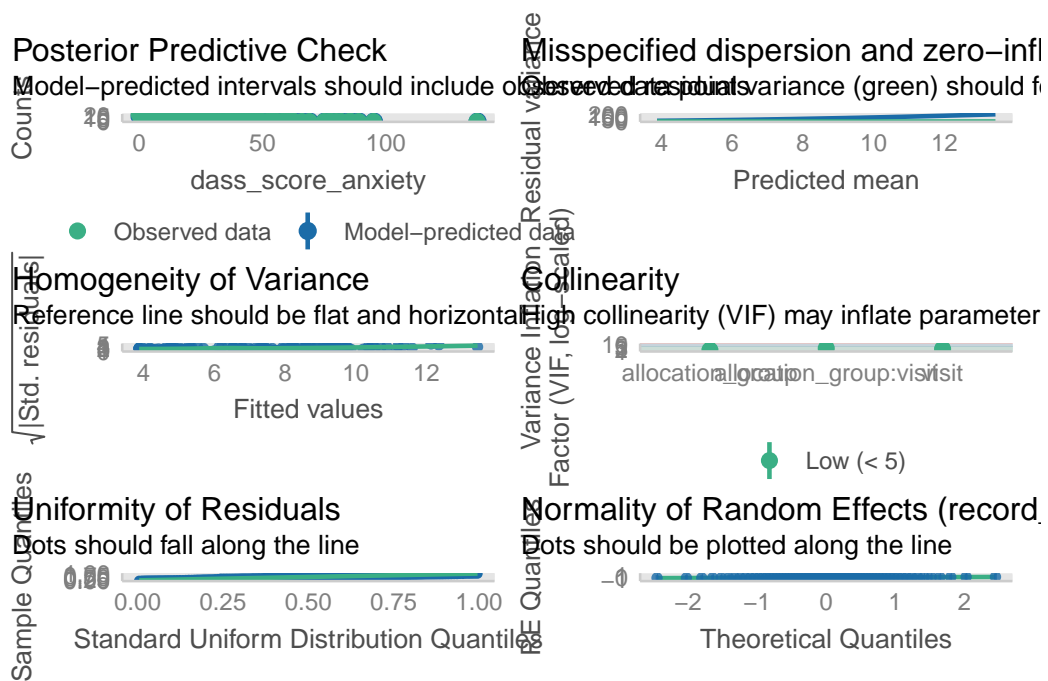
Name	Model	AIC (weights)	AICc (weights)	BIC (weights)
dass_score_anxiety_nb_model	glmmTMB	779.3 (<.001)	780.0 (<.001)	796.4 (<.001)
dass_score_anxiety_nb_model_sens	glmmTMB	725.7 (>.999)	726.5 (>.999)	742.3 (>.999)

## # Diagnostic checks

```
performance::check_model(dass_score_anxiety_nb_model)
```



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



## 2.2.0.2 Médias Marginais Estimadas

### 2.2.0.2.1 Todos os dados

```
# 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	asympt.LCL	asympt.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	asympt.LCL	asympt.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	asympt.LCL	asympt.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	asympt.LCL	asympt.UCL	null	z.ratio	p.value
visit1 / visit3	1.57	0.461	Inf	0.886	2.80	1	1.546	0.1222

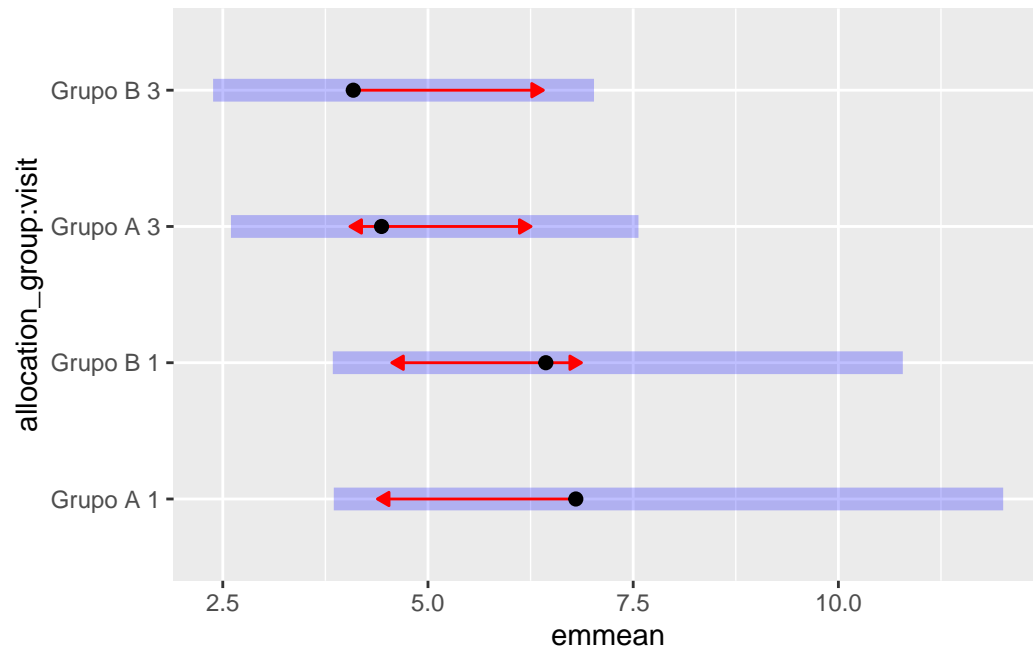
Confidence level used: 0.95

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	asyp.LCL	asyp.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	asyp.LCL	asyp.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
```

```
emmmeans::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	asyp.LCL	asyp.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	asyp.LCL	asyp.UCL	null	z.ratio	p.value
visit1 / visit3	1.69	0.488	Inf	0.956	2.97	1	1.804	0.0712

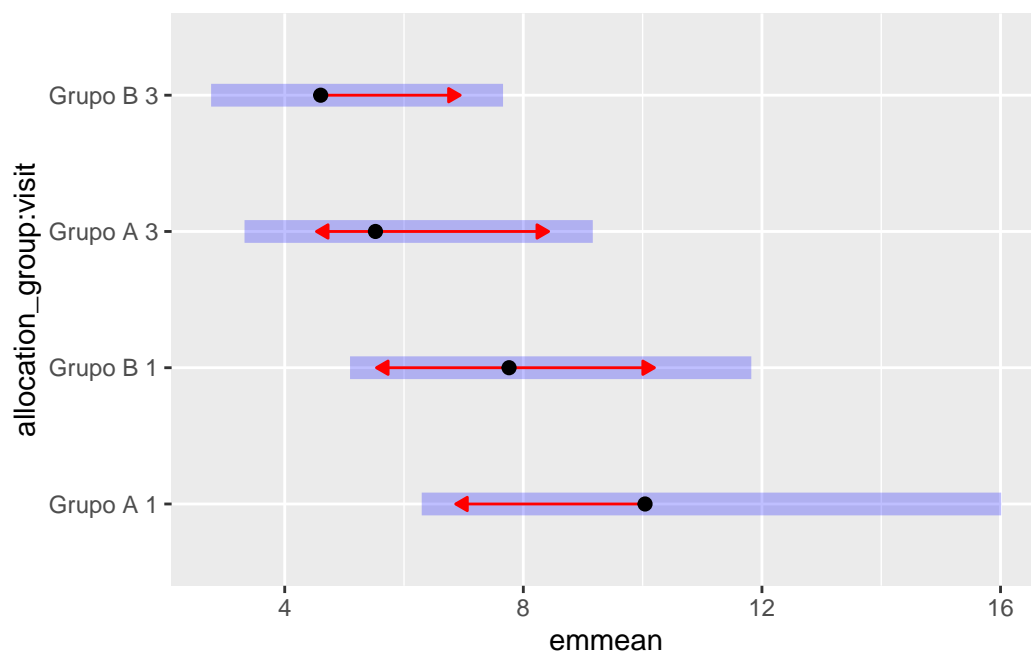
Confidence level used: 0.95

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.

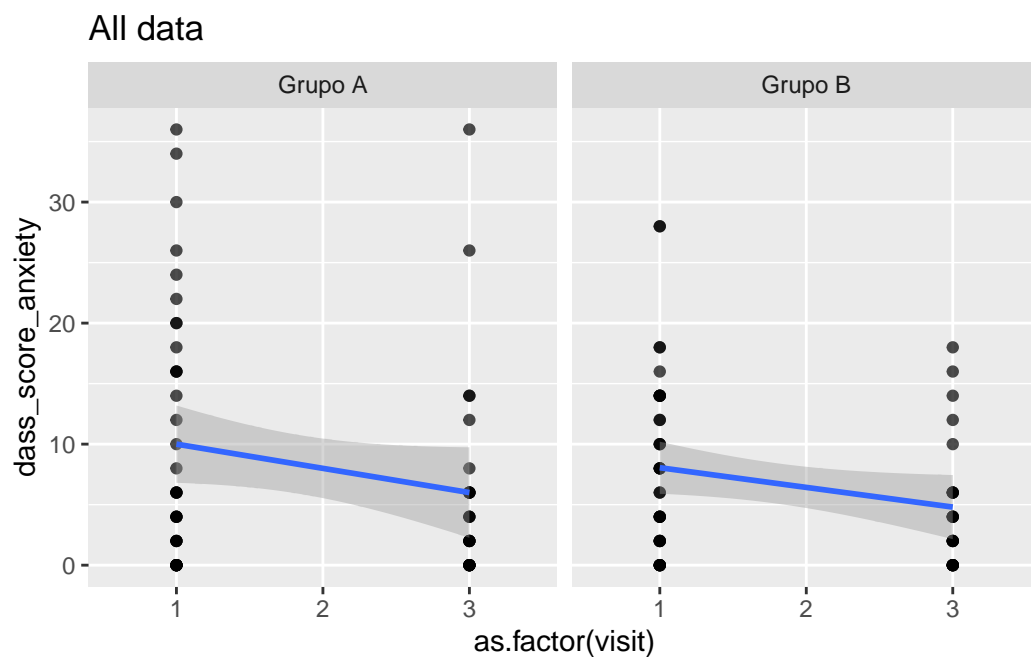
Tabela: Razões dos escores de ansiedade (DASS) entre grupos e ao longo do tempo – Todos os dados {#tbl-dass\_anxiety}

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)

```

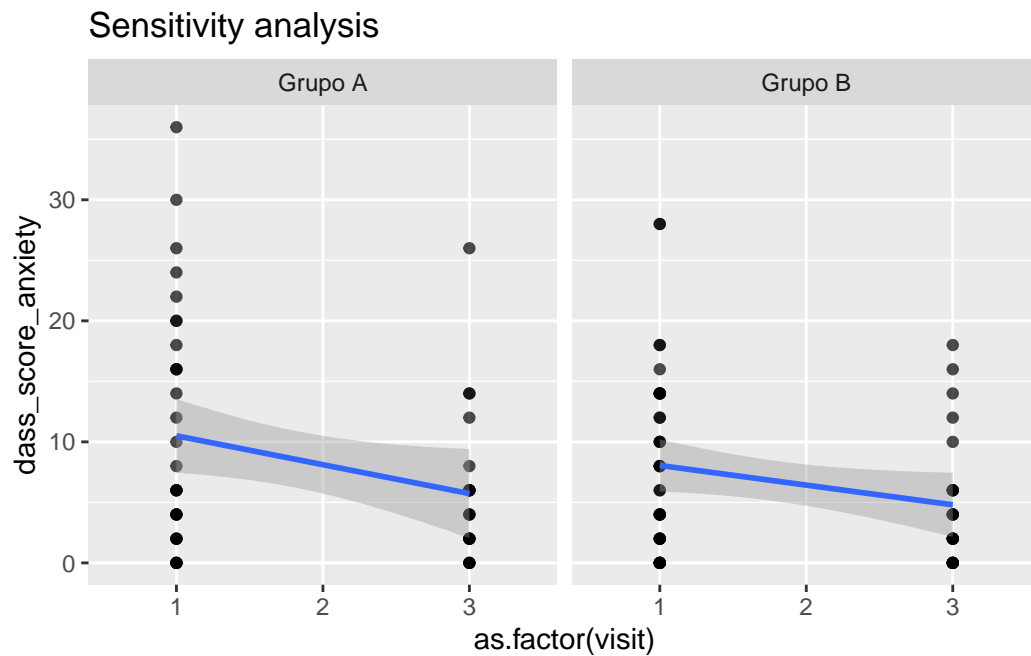


```

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)

```





## 2.3 Escore DASS - Estresse

Variável: `dass_score_stress`

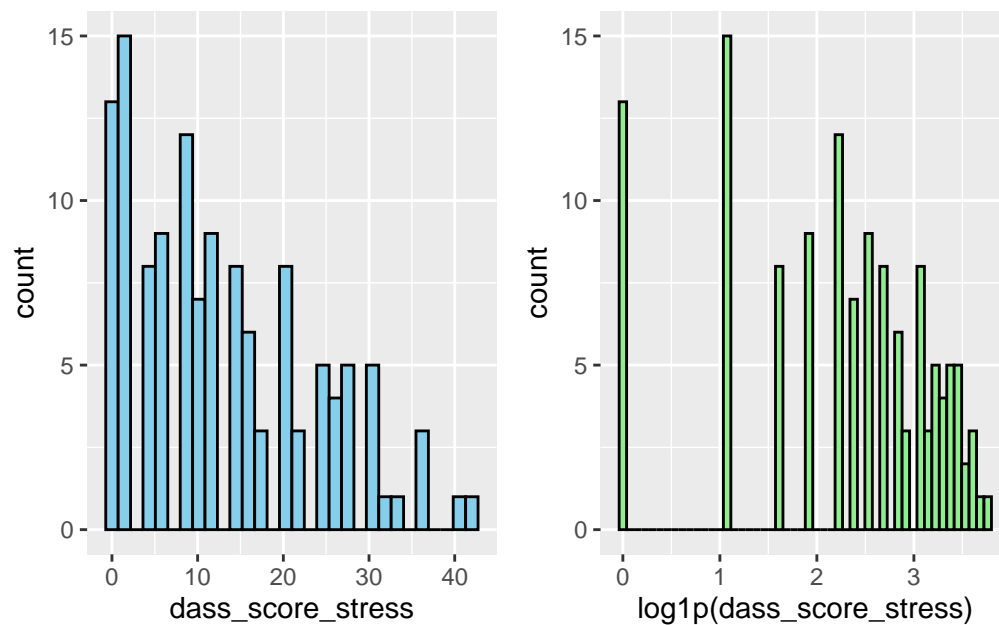
```
# Plot 1: Raw data
dass_score_stress_hist_1 <- data_model_V1V3 %>%
  #filter(
  #   dass_score_stress < 300
  #) %>%
  ggplot(aes(x = dass_score_stress)) +
  geom_histogram(bins = 30, fill = "skyblue", color = "black")

# 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)
```



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

# 3. Identify the 5 most "influential" clusters by magnitude of their random intercept

```
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

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

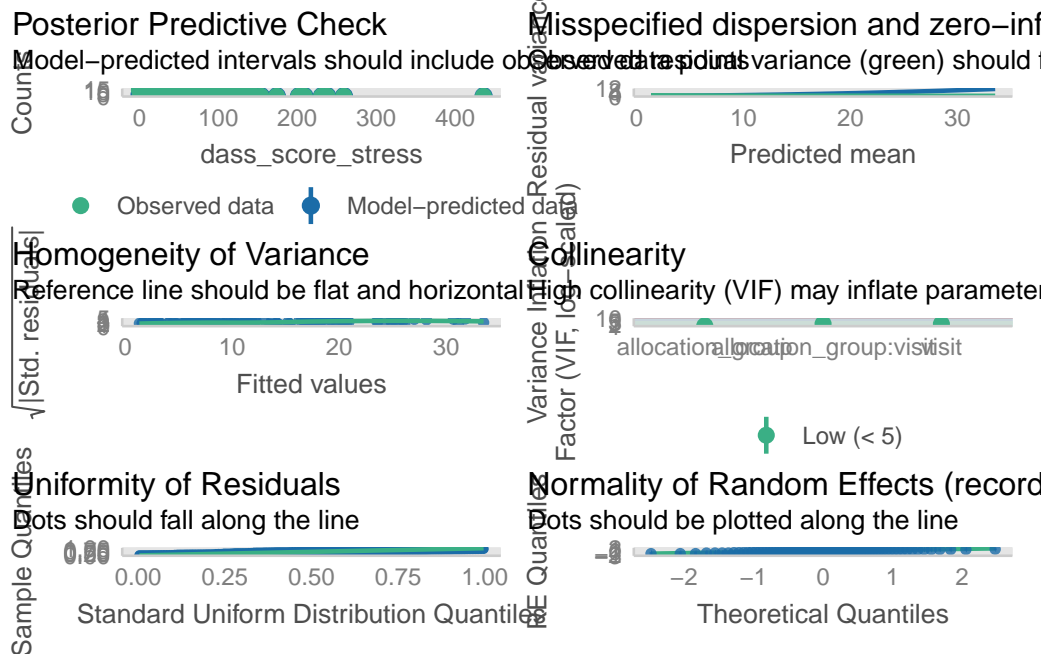
# Comparison of Model Performance Indices

Name	Model	AIC (weights)	AICc (weights)	BIC (weights)
dass_score_stress_nb_model	glmmTMB	908.9 (<.001)	909.6 (<.001)	926.0 (<.001)

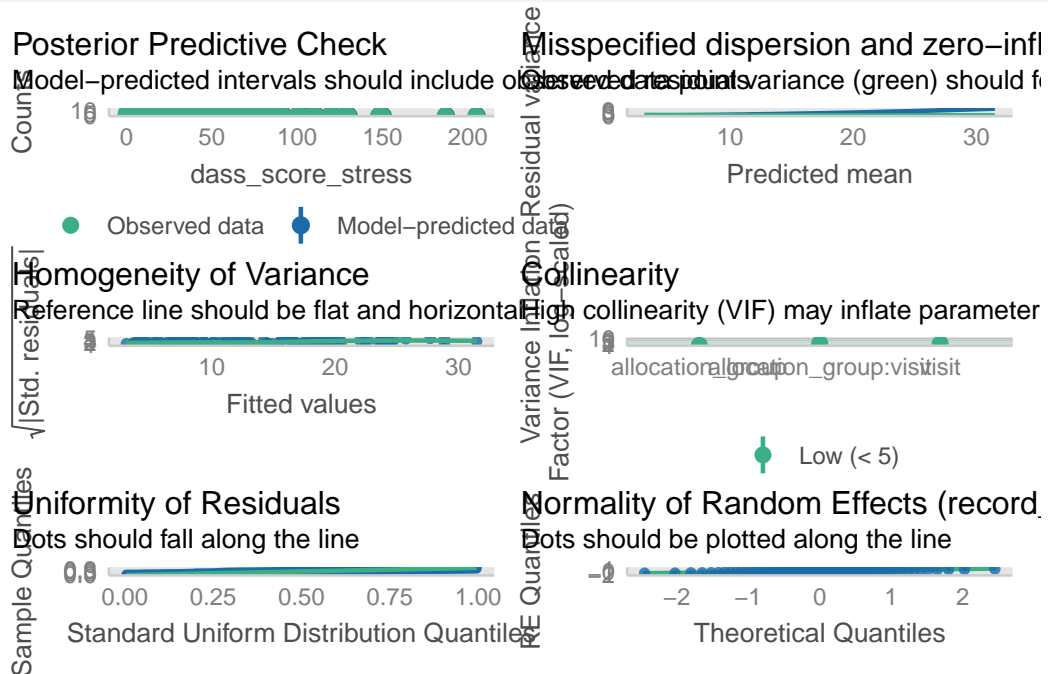
```
dass_score_stress_nb_model_sens | glmmTMB | 847.0 (>.999) | 847.8 (>.999) | 863.6 (>.
```

```
# Diagnostic checks
```

```
performance::check_model(dass_score_stress_nb_model)
```



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



### 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	asympt.LCL	asympt.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	asympt.LCL	asympt.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	asympt.LCL	asympt.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	asympt.LCL	asympt.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

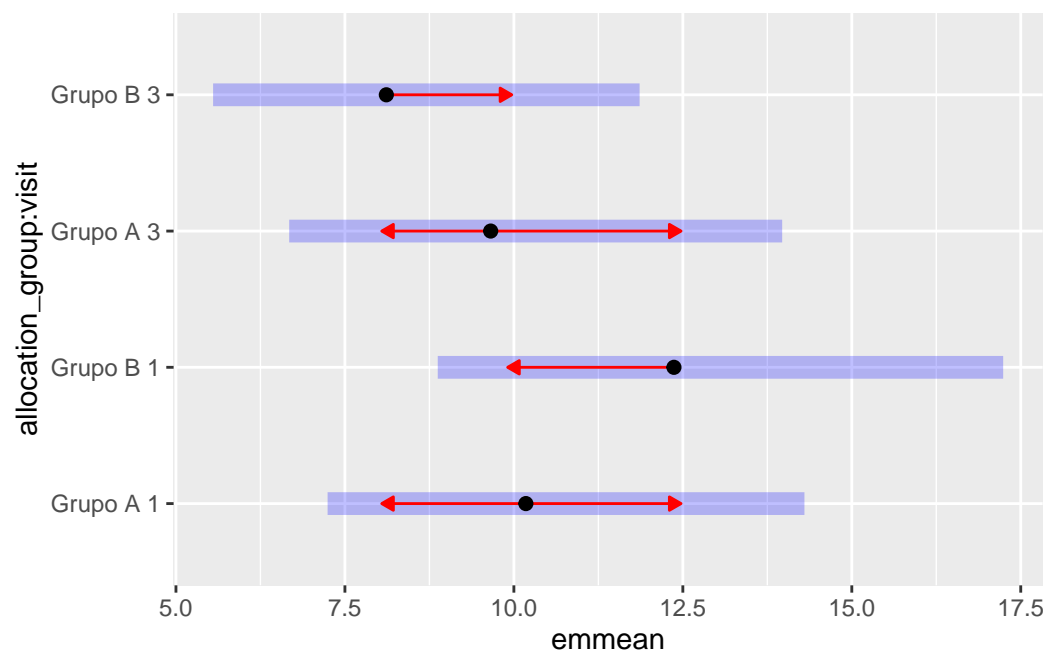
Intervals are back-transformed from the log scale

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	asympt.LCL	asympt.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	asympt.LCL	asympt.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

```
# 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	asympt.LCL	asympt.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	asympt.LCL	asympt.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

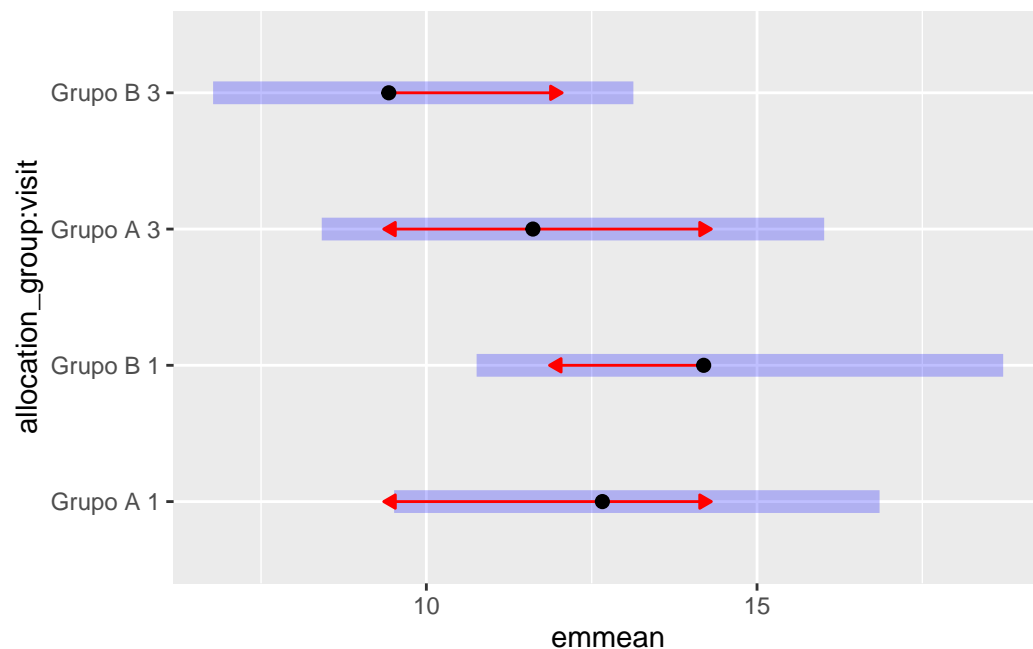
Intervals are back-transformed from the log scale

Tests are performed on the log scale

```

# 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}

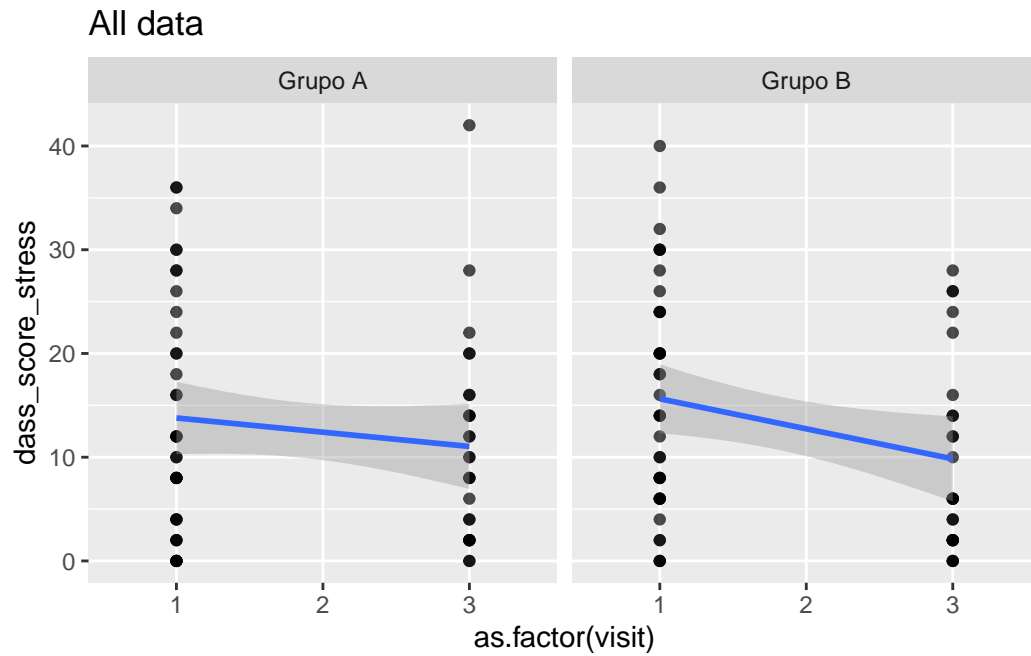
Grupo de comparação	Comparação	Razão	IC 95%	p-valor
Entre grupos	Visita 1	0,823	[0,515; 1,31]	0,414
Entre grupos	Visita 3	1,190	[0,701; 2,02]	0,519
Grupo Placebo	Visita 1 – Visita 3	1,05	[0,768; 1,45]	0,745
Grupo Eclipta	Visita 1 – Visita 3	1,52	[1,102; 2,11]	0,011

```
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)

```



```

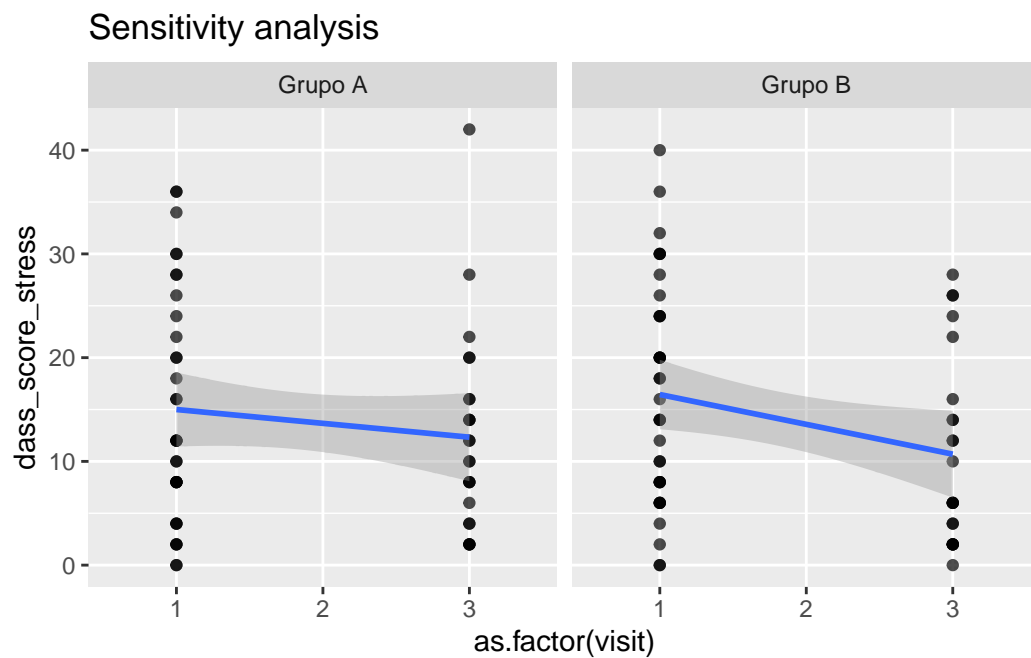
data_model_V1V3 %>%
  filter(
    !(record_id %in%
      influential_ids_nb)
  ) %>%
  ggplot(
    aes(
      x = as.factor(visit),
      y = dass_score_stress,
      group = record_id,
    )
  ) +
  geom_line(alpha = 0.5) +

```

```

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)

```



### 3 ECAP

Variável: ecap\_score

```

# Plot 1: Raw data
ecap_score_hist_1 <- data_model_V1V3 %>%
  #filter(
  #   ecap_score < 300
  #) %>%

```

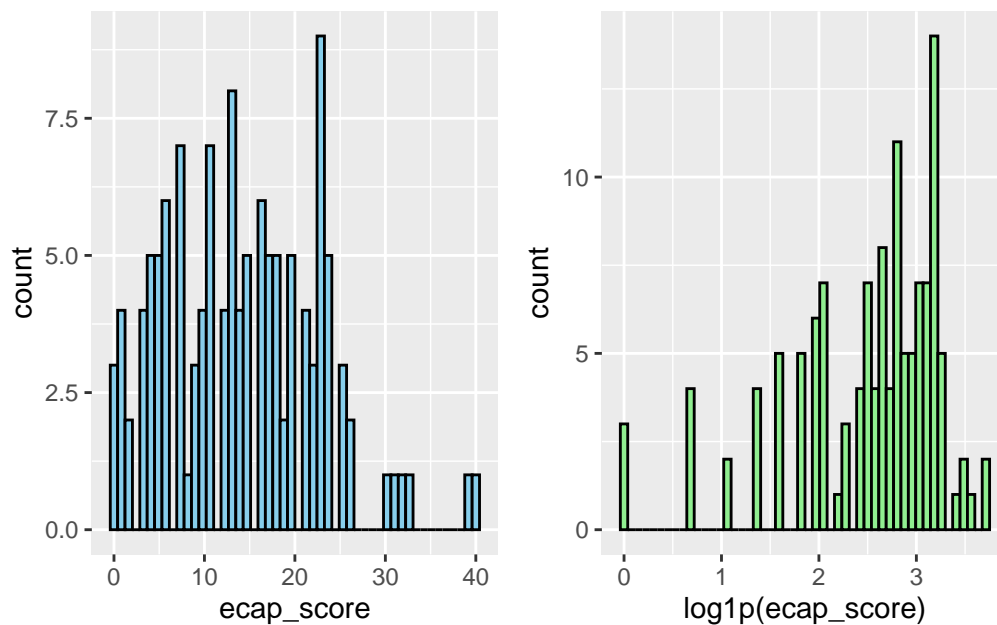
```

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)

```



```

# 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	Tolerance 95% CI
	allocation_group	1.10	[1.01, 1.74]	1.05	0.91	[0.58, 0.99]
	visit	1.93	[1.56, 2.55]	1.39	0.52	[0.39, 0.64]
	allocation_group:visit	2.02	[1.63, 2.67]	1.42	0.49	[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

```
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:visit3	1.52	1.55	0.978	3.32e- 1
6	Sensitivity	allocation_groupGrupo B:visit3	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)
```

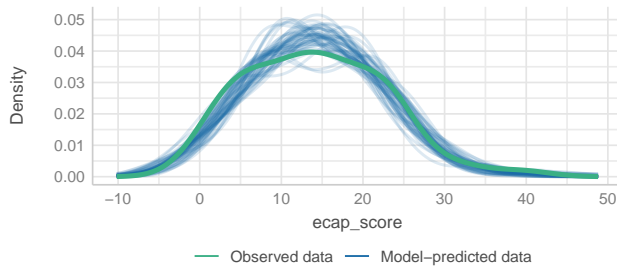
```
# Comparison of Model Performance Indices
```

Name	Model	AIC (weights)	AICc (weights)	BIC (weights)
ecap_score_model	lmerModLmerTest	856.3 (<.001)	857.0 (<.001)	873.4 (<.001)
ecap_score_model_sens	lmerModLmerTest	749.5 (>.999)	750.3 (>.999)	766.1 (>.999)

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

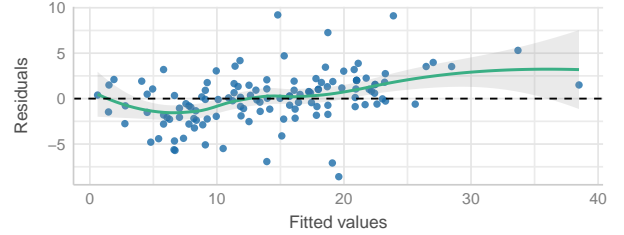
### Posterior Predictive Check

Model-predicted lines should resemble observed data line



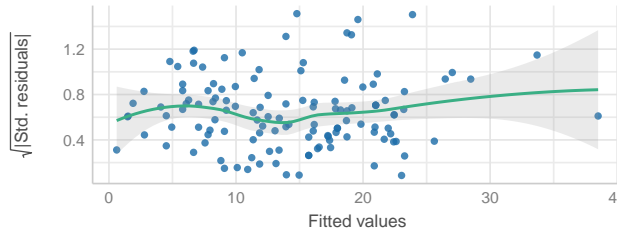
### Linearity

Reference line should be flat and horizontal



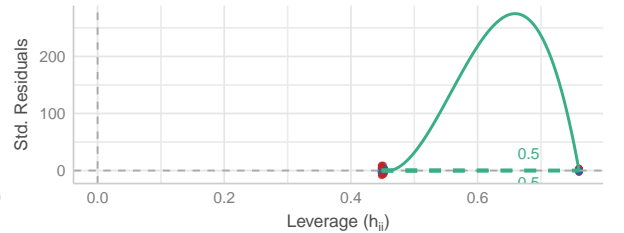
### Homogeneity of Variance

Reference line should be flat and horizontal



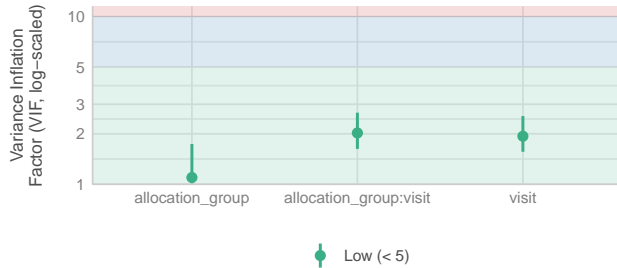
### Influential Observations

Points should be inside the contour lines



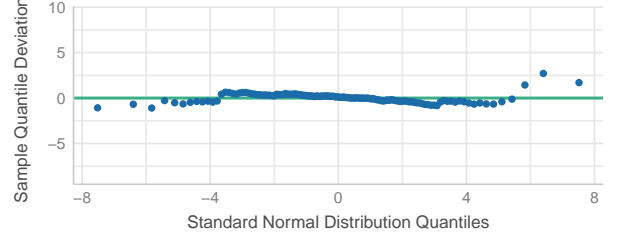
### Collinearity

High collinearity (VIF) may inflate parameter uncertainty



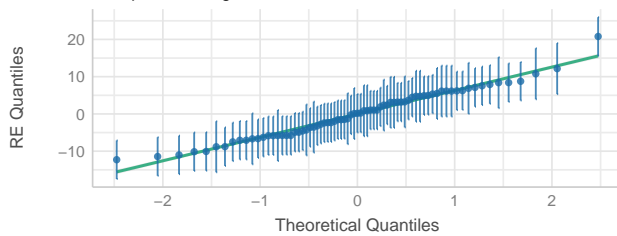
### Normality of Residuals

Dots should fall along the line



### Normality of Random Effects (record\_id)

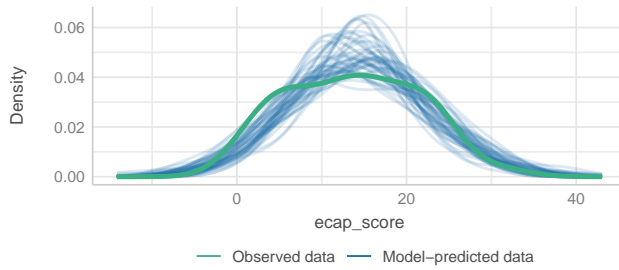
Dots should be plotted along the line



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

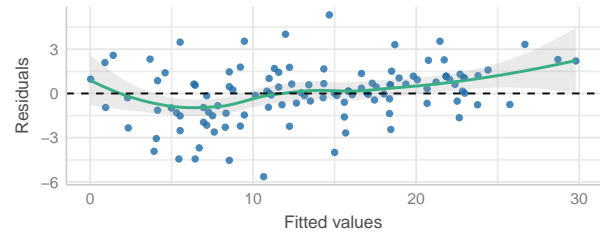
### Posterior Predictive Check

Model-predicted lines should resemble observed data line



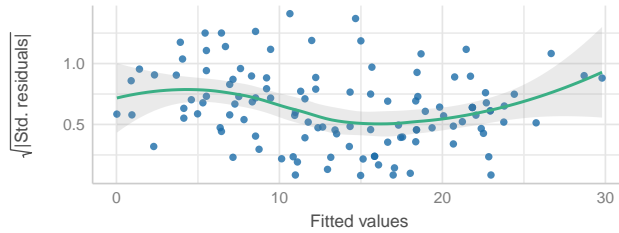
### Linearity

Reference line should be flat and horizontal



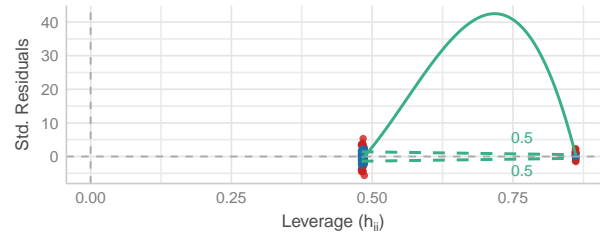
### Homogeneity of Variance

Reference line should be flat and horizontal



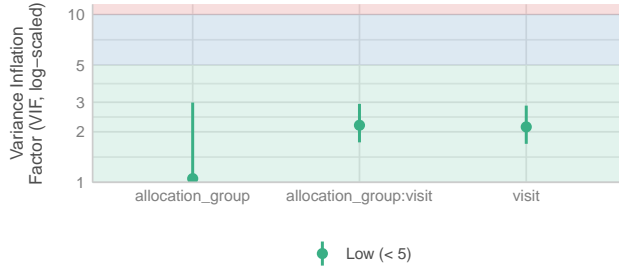
### Influential Observations

Points should be inside the contour lines



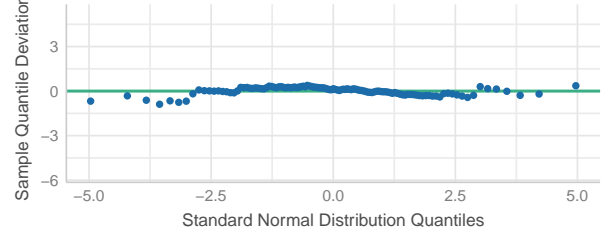
### Collinearity

High collinearity (VIF) may inflate parameter uncertainty



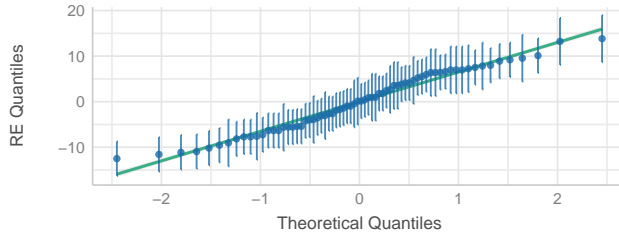
### Normality of Residuals

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

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

```
)
```

```
ecap_score_raw_emm <- regrid(ecap_score_raw_emm)
```

```
# Table of marginal means
```

```
# ecap_score_raw_emm
```

```
# Pairwise comparisons: Between groups at each visit
```

```
emmmeans::contrast(ecap_score_raw_emm,
```

```
method = "pairwise", by = "visit",
```

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

```
visit = 1:
```

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

```
visit = 3:
```

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

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

Confidence level used: 0.95

```
# Pairwise comparisons: Changes over time within each group
```

```
emmmeans::contrast(ecap_score_raw_emm,
```

```
method = "pairwise", by = "allocation_group",
```

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

```
allocation_group = Grupo A:
```

contrast	estimate	SE	df	lower.CL	upper.CL	t.ratio	p.value
visit1 - visit3	4.80	1.08	86.8	2.66	6.95	4.451	<.0001

```
allocation_group = Grupo B:
```

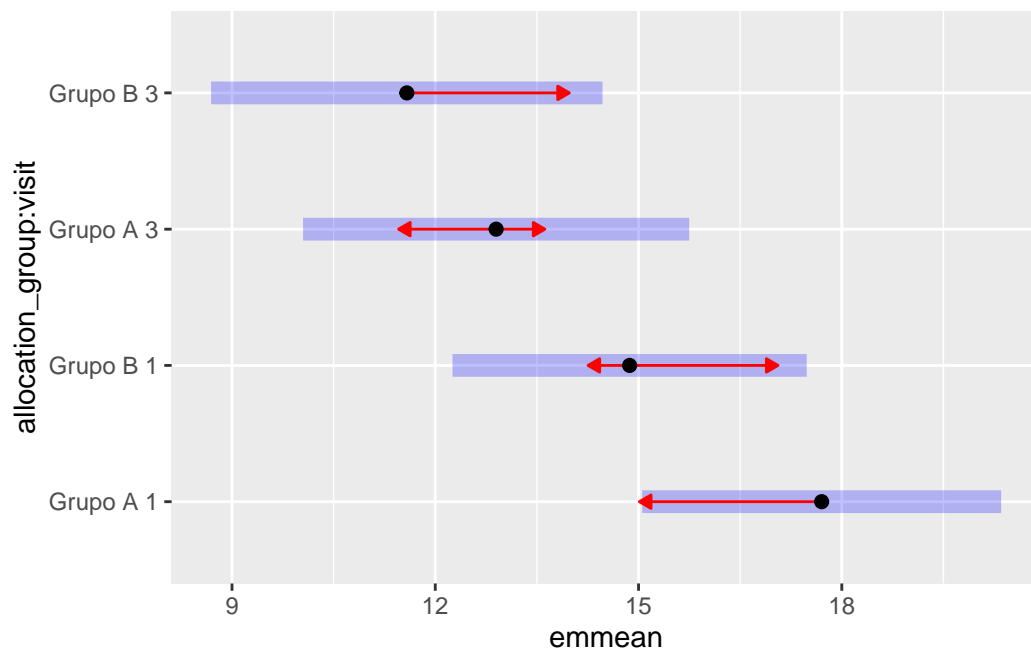
contrast	estimate	SE	df	lower.CL	upper.CL	t.ratio	p.value
visit1 - visit3	3.29	1.12	86.8	1.07	5.51	2.943	0.0042

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

Confidence level used: 0.95

```
# Plot of marginal means
```

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



### 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
emmmeans::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
emmmeans::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:
```

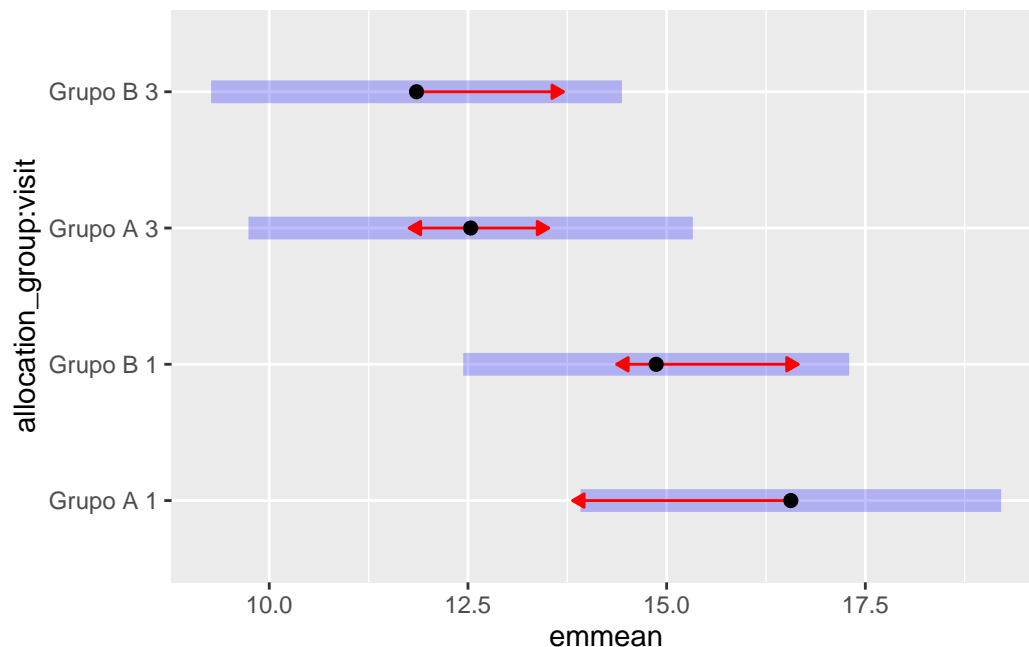
contrast	estimate	SE	df	lower.CL	upper.CL	t.ratio	p.value
visit1 - visit3	3.02	0.795	74.9	1.43	4.60	3.794	0.0003

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)
```



### 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.

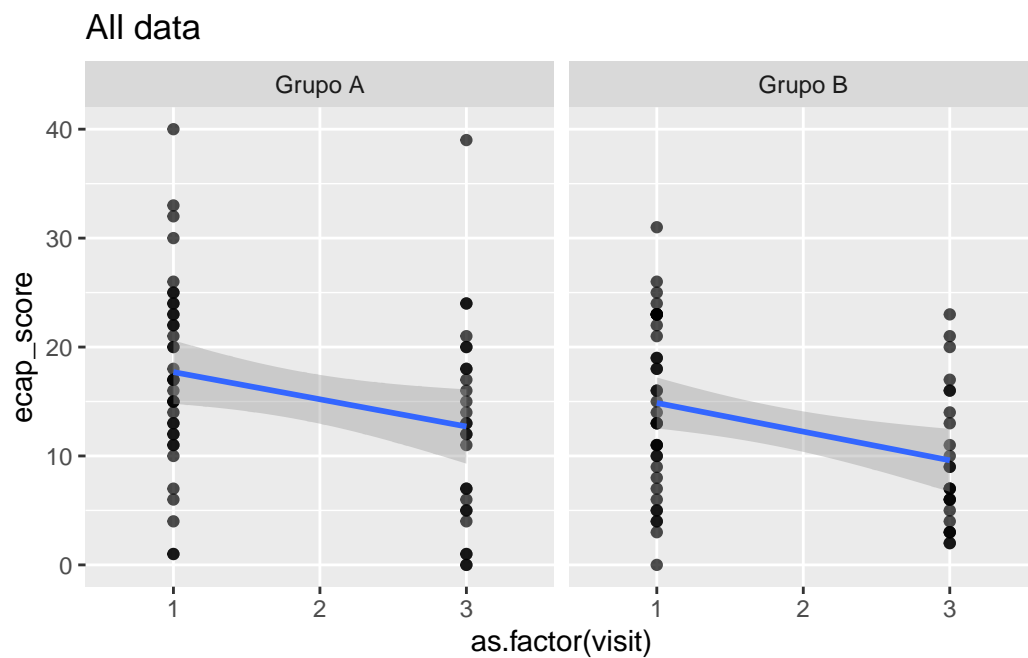
Tabela: Diferenças estimadas do escore de compulsão alimentar periódica (ECAP) entre grupos e ao longo do tempo – Todos os dados {#tbl-ecap\_score}

Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
Entre grupos	Visita 1	2,83	[-0,89; 6,56]	0,134



Grupo de comparação	Comparação	Estimativa	IC 95%	p-valor
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

```
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)
```

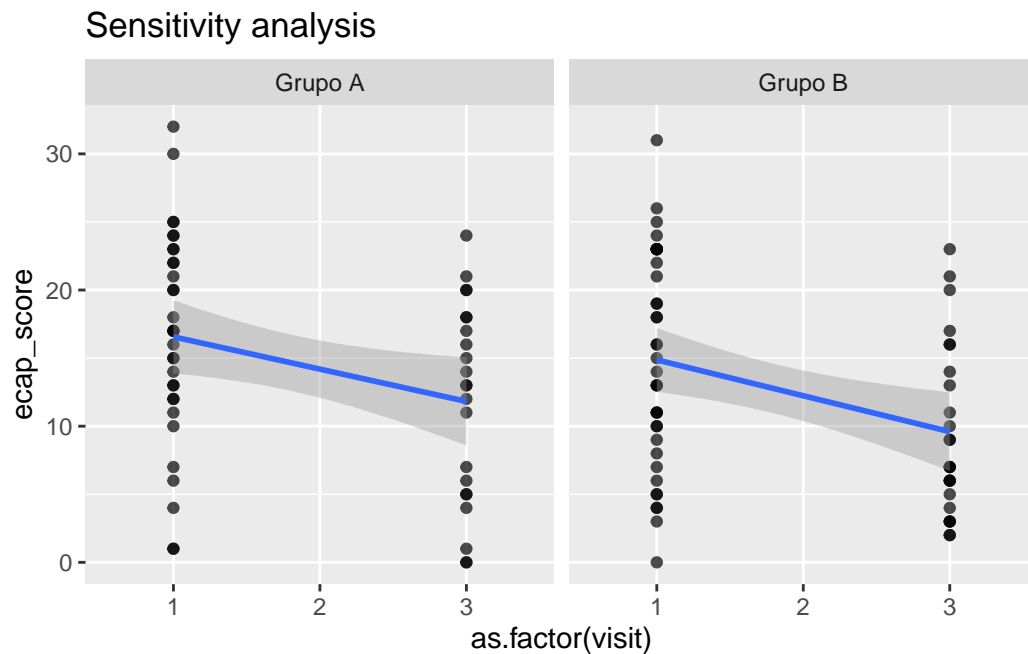


```
data_model_V1V3 %>%
  filter(
    !(record_id %in%
      ecap_score_model_check$influential_ids)
  ) %>%
  ggplot(
    aes(
      x = as.factor(visit),
      y = ecap_score,
      group = record_id,
    )
  ) +
  geom_line(alpha = 0.5) +
  geom_point(alpha = 0.7) +
  geom_smooth(
    aes(group = allocation_group),
    method = "lm",
```

```

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

```



## 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

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 knitr\_1.50  
[9] skimr\_2.1.5 lmerTest\_3.1-3 lme4\_1.1-37 Matrix\_1.7-0  
[17] dplyr\_1.1.4.9000 purrr\_1.0.4 readr\_2.1.5 tidyr\_1.3.1

loaded via a namespace (and not attached):

[1] tidyselect\_1.2.1 DHARMa\_0.4.7 viridisLite\_0.4.2 glmmTMB\_1.1.11  
[9] digest\_0.6.37 timechange\_0.3.0 estimability\_1.5.1 lifecycle\_1.0.4  
[17] tools\_4.4.1 utf8\_1.2.4 yaml\_2.3.10 labeling\_0.4.3  
[25] numDeriv\_2016.8-1.1 datawizard\_1.1.0 grid\_4.4.1 future\_1.34.0  
[33] MASS\_7.3-61 insight\_1.2.0 cli\_3.6.5 mvtnorm\_1.3-3  
[41] tzdb\_0.4.0 minqa\_1.2.8 splines\_4.4.1 parallel\_4.4.1  
[49] sandwich\_3.1-1 jsonlite\_2.0.0 hms\_1.1.3 pbkrtest\_0.5.4  
[57] parallelly\_1.44.0 glue\_1.8.0 nloptr\_2.2.1 codetools\_0.2-20  
[65] pillar\_1.10.2 htmltools\_0.5.8.1 TMB\_1.9.17 R6\_2.6.1  
[73] backports\_1.5.0 rbibutils\_2.3 broom\_1.0.7 Rcpp\_1.0.14  
[81] xfun\_0.52 zoo\_1.8-14 pkgconfig\_2.0.3