Code

* Show All Code
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# Exposure to placental insufficiency alters postnatal growth trajectory in extremely low birth weight infants

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## 0. Packages and functions

packages <- c("tidyverse",

"lme4",

"lmerTest",

"psych",

"vcd",

"ggpubr",

"optimx",

"effsize",

"PropCIs")

for (i in packages) {

if (!(i %in% installed.packages())) {

install.packages(i)

}

}

for (i in packages) {

lapply(i, library, character.only = TRUE)

}

## Registered S3 methods overwritten by 'ggplot2':

## method from

## [.quosures rlang

## c.quosures rlang

## print.quosures rlang

## Registered S3 method overwritten by 'rvest':

## method from

## read\_xml.response xml2

## ── Attaching packages ─────────────────────────────────────────────────────────────────────────────────────────────────────────────────────── tidyverse 1.2.1 ──

## ✔ ggplot2 3.1.1 ✔ purrr 0.3.2

## ✔ tibble 2.1.1 ✔ dplyr 0.8.0.1

## ✔ tidyr 0.8.3 ✔ stringr 1.4.0

## ✔ readr 1.3.1 ✔ forcats 0.4.0

## ── Conflicts ────────────────────────────────────────────────────────────────────────────────────────────────────────────────────────── tidyverse\_conflicts() ──

## ✖ dplyr::filter() masks stats::filter()

## ✖ dplyr::lag() masks stats::lag()

## Loading required package: Matrix

##

## Attaching package: 'Matrix'

## The following object is masked from 'package:tidyr':

##

## expand

##

## Attaching package: 'lmerTest'

## The following object is masked from 'package:lme4':

##

## lmer

## The following object is masked from 'package:stats':

##

## step

##

## Attaching package: 'psych'

## The following objects are masked from 'package:ggplot2':

##

## %+%, alpha

## Loading required package: grid

## Loading required package: magrittr

##

## Attaching package: 'magrittr'

## The following object is masked from 'package:purrr':

##

## set\_names

## The following object is masked from 'package:tidyr':

##

## extract

##

## Attaching package: 'effsize'

## The following object is masked from 'package:psych':

##

## cohen.d

require(ggplot2)

# check and create folder

folder.check <- function(folder.name = NULL, current.dir) {

setwd(current.dir)

if (file.exists(folder.name)) {

return(setwd(file.path(current.dir, folder.name)))

} else {

dir.create(file.path(current.dir, folder.name))

return(setwd(file.path(current.dir, folder.name)))

}

}

cat.cont.graph <- function(cat.table, cont.table, cat.name, cont.name) {

temp.df <- data.frame(cat.name = cat.table[cat.name], cont.name = cont.table[cont.name])

temp.df <- na.omit(temp.df)

formula <- as.formula(paste0(cont.name, " ~ ", cat.name))

m <- aggregate(formula, temp.df, mean)

colnames(m)[colnames(m) %in% cont.name] = "mean"

sd <- aggregate(temp.df[cont.name], temp.df[cat.name], sd)

colnames(sd)[colnames(sd) %in% cont.name] = "sd"

table <- merge(m, sd)

if (nrow(table) == 2) {

ttest <- t.test(cont.table[,cont.name]~cat.table[,cat.name])

pval <- round(ttest$p.value, 4)

stat <- round(ttest$statistic, 2)

df <- round(ttest$parameter, 2)

} else {

pval <- ""

stat <- ""

df <- ""

}

k <- ggplot2::ggplot(table, aes\_(as.name(cat.name), as.name("mean"), fill = as.name(cat.name))) +

geom\_bar(stat = "identity") +

geom\_errorbar(aes(ymin = mean-sd, ymax = mean+sd), width = 0.2) +

labs(x = cat.name, y = cont.name,

title = paste0(cont.name, " ~ ", cat.name),

subtitle = paste0("t[df=",df,"] = ", stat, ", p-value = ", pval)) +

theme\_bw(base\_size = 16) +

theme(axis.text=element\_text(size=14),

axis.title=element\_text(size=16, face="bold"),

plot.margin = margin(5,5,5,5, "mm"))

return(k)

}

## 1. Data upload to R

require(readr)

continuous.df <- data.frame(readr::read\_csv("continuous\_variables.csv"))

## Parsed with column specification:

## cols(

## id = col\_double(),

## calories\_7d = col\_double(),

## aminoAcid\_7d = col\_double(),

## protein\_fullEF = col\_double(),

## calories\_fullEF = col\_double(),

## Abx\_days = col\_double(),

## birth\_wt = col\_double()

## )

categorical.df <- data.frame(readr::read\_csv("categorical\_variables.csv", col\_types = cols(

id = col\_double(),

pla\_insuff = col\_factor(levels = c("No", "Yes")),

Gender = col\_factor(levels = c("male", "female")),

BPD = col\_factor(levels = c("No", "Yes")),

IVH = col\_factor(levels = c("No", "Yes")),

Sepsis = col\_factor(levels = c("No", "Yes")),

ROP = col\_factor(levels = c("No", "Yes")),

sga = col\_factor(levels = c("No", "Yes"))

)))

## Warning: The following named parsers don't match the column names: sga

weight <- data.frame(readr::read\_csv("weight.csv"))

## Parsed with column specification:

## cols(

## id = col\_double(),

## time\_week = col\_double(),

## wt\_z\_score = col\_double()

## )

maternal\_demographics.df <- data.frame(readr::read\_csv("maternal\_characteristics.csv"))

## Parsed with column specification:

## cols(

## id = col\_double(),

## maternal\_age = col\_double(),

## maternal\_race = col\_character(),

## antenatal\_steroid = col\_double(),

## delivery\_method = col\_double(),

## maternal\_obesity = col\_double(),

## maternal\_smoking = col\_double()

## )

neonatal\_demographics.df <- data.frame(readr::read\_csv("neonatal\_characteristics.csv"))

## Parsed with column specification:

## cols(

## id = col\_double(),

## gender = col\_character(),

## apgar\_1min = col\_double(),

## apgar\_5min = col\_double(),

## ga\_birth = col\_double(),

## birth\_weight = col\_double(),

## small\_for\_ga = col\_double()

## )

#data summary

summary(continuous.df)

## id calories\_7d aminoAcid\_7d protein\_fullEF

## Min. : 1.00 Min. :25.43 Min. :1.540 Min. :1.360

## 1st Qu.: 27.50 1st Qu.:46.43 1st Qu.:2.950 1st Qu.:3.385

## Median : 50.00 Median :53.29 Median :3.100 Median :3.580

## Mean : 50.65 Mean :53.47 Mean :3.056 Mean :3.479

## 3rd Qu.: 75.50 3rd Qu.:61.07 3rd Qu.:3.245 3rd Qu.:3.735

## Max. :100.00 Max. :77.00 Max. :3.650 Max. :4.330

## calories\_fullEF Abx\_days birth\_wt

## Min. : 72.4 Min. : 0.00 Min. :-2.3500

## 1st Qu.:100.8 1st Qu.: 4.00 1st Qu.:-0.9950

## Median :104.3 Median : 9.00 Median :-0.3300

## Mean :104.6 Mean :11.63 Mean :-0.4263

## 3rd Qu.:109.8 3rd Qu.:17.00 3rd Qu.: 0.1350

## Max. :120.6 Max. :57.00 Max. : 1.7800

summary(categorical.df)

## id pla\_insuff Gender BPD IVH Sepsis

## Min. : 1.00 No :57 male :40 No :30 No :83 No :73

## 1st Qu.: 27.50 Yes:34 female:51 Yes:61 Yes: 8 Yes:18

## Median : 50.00

## Mean : 50.65

## 3rd Qu.: 75.50

## Max. :100.00

## ROP SGA

## No :71 Length:91

## Yes:20 Class :character

## Mode :character

##

##

##

summary(maternal\_demographics.df)

## id maternal\_age maternal\_race antenatal\_steroid

## Min. : 1.00 Min. :15.00 Length:91 Min. :0.000

## 1st Qu.: 27.50 1st Qu.:23.00 Class :character 1st Qu.:1.000

## Median : 50.00 Median :27.00 Mode :character Median :1.000

## Mean : 50.65 Mean :27.93 Mean :0.978

## 3rd Qu.: 75.50 3rd Qu.:32.00 3rd Qu.:1.000

## Max. :100.00 Max. :43.00 Max. :1.000

## delivery\_method maternal\_obesity maternal\_smoking

## Min. :0.0000 Min. :0.0000 Min. :0.0000

## 1st Qu.:1.0000 1st Qu.:0.0000 1st Qu.:0.0000

## Median :1.0000 Median :0.0000 Median :0.0000

## Mean :0.7802 Mean :0.0989 Mean :0.3297

## 3rd Qu.:1.0000 3rd Qu.:0.0000 3rd Qu.:1.0000

## Max. :1.0000 Max. :1.0000 Max. :1.0000

summary(neonatal\_demographics.df)

## id gender apgar\_1min apgar\_5min

## Min. : 1.00 Length:91 Min. :1.000 Min. :2.000

## 1st Qu.: 27.50 Class :character 1st Qu.:3.000 1st Qu.:6.000

## Median : 50.00 Mode :character Median :5.000 Median :7.000

## Mean : 50.65 Mean :4.725 Mean :6.857

## 3rd Qu.: 75.50 3rd Qu.:6.000 3rd Qu.:8.000

## Max. :100.00 Max. :9.000 Max. :9.000

## ga\_birth birth\_weight small\_for\_ga

## Min. :23.14 Min. :-2.3500 Min. :0.0000

## 1st Qu.:25.14 1st Qu.:-0.9950 1st Qu.:0.0000

## Median :26.29 Median :-0.3250 Median :0.0000

## Mean :26.37 Mean :-0.4261 Mean :0.1868

## 3rd Qu.:27.50 3rd Qu.: 0.1345 3rd Qu.:0.0000

## Max. :31.57 Max. : 1.7780 Max. :1.0000

summary(weight)

## id time\_week wt\_z\_score

## Min. : 1.00 Min. :24.00 Min. :-4.530

## 1st Qu.: 28.00 1st Qu.:30.86 1st Qu.:-2.060

## Median : 51.00 Median :35.00 Median :-1.420

## Mean : 50.73 Mean :35.50 Mean :-1.544

## 3rd Qu.: 74.00 3rd Qu.:39.43 3rd Qu.:-0.900

## Max. :100.00 Max. :50.00 Max. : 1.430

## 2. Correlation analysis

require(psych)

require(vcd)

# set up folder for graph storage

folder.check(folder.name = "Results", getwd())

folder.check(folder.name = "correlations", getwd())

# continuous variables

pdf(file = paste0(getwd(), "/continuous\_correlation.pdf"), width = 24, height = 24)

psych::pairs.panels(continuous.df[-1], method = "spearman", bg = "yellow", pch = 21, stars = F)

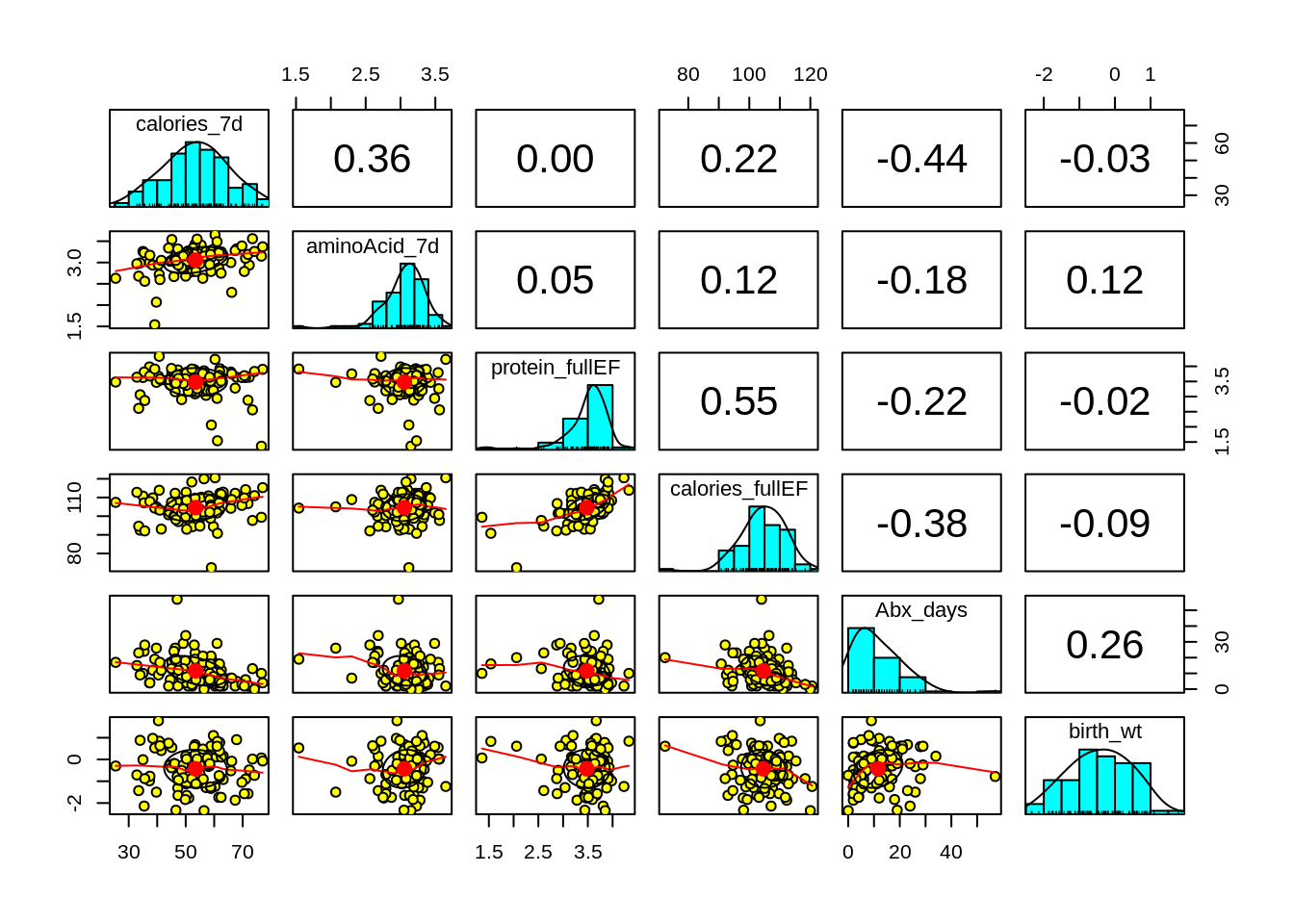
dev.off()

## png

## 2

#for html markdown

psych::pairs.panels(continuous.df[-1], method = "spearman", bg = "yellow", pch = 21, stars = F)



# categorical variables

pdf(file = paste0(getwd(), "/categorical\_correlation.pdf"), width = 10, height = 7, onefile = TRUE)

categorical.df.temp <- categorical.df[-1]

for (i in 1:(ncol(categorical.df.temp)-1)) {

for (j in (i+1):ncol(categorical.df.temp)) {

d <- c(colnames(categorical.df.temp)[i], colnames(categorical.df.temp[j]))

temp.df <- categorical.df.temp[, d]

temp.df <- temp.df[complete.cases(temp.df),]

temp.df.table <- table(temp.df)

if(min(matrix(temp.df.table)) < 5) {

fishert <- fisher.test(temp.df.table)

}

mosaic.plot <- vcd::mosaic(temp.df.table,

main = paste0(colnames(categorical.df.temp)[i], " vs ", colnames(categorical.df.temp)[j]),

sub = paste0("Fisher exact test p-value: ",ifelse(exists("fishert"), round(fishert$p.value, digits = 3),"")),

border = "black",

gp = shading\_hsv,

gp\_args = list(interpolate = 1:4),

legend=TRUE

)

}

}

dev.off()

## png

## 2

#for html markdown

categorical.df.temp <- categorical.df[-1]

for (i in 1:(ncol(categorical.df.temp)-1)) {

for (j in (i+1):ncol(categorical.df.temp)) {

d <- c(colnames(categorical.df.temp)[i], colnames(categorical.df.temp[j]))

temp.df <- categorical.df.temp[, d]

temp.df <- temp.df[complete.cases(temp.df),]

temp.df.table <- table(temp.df)

if(min(matrix(temp.df.table)) < 5) {

fishert <- fisher.test(temp.df.table)

}

mosaic.plot <- vcd::mosaic(temp.df.table,

main = paste0(colnames(categorical.df.temp)[i], " vs ", colnames(categorical.df.temp)[j]),

sub = paste0("Fisher exact test p-value: ",ifelse(exists("fishert"), round(fishert$p.value, digits = 3),"")),

border = "black",

gp = shading\_hsv,

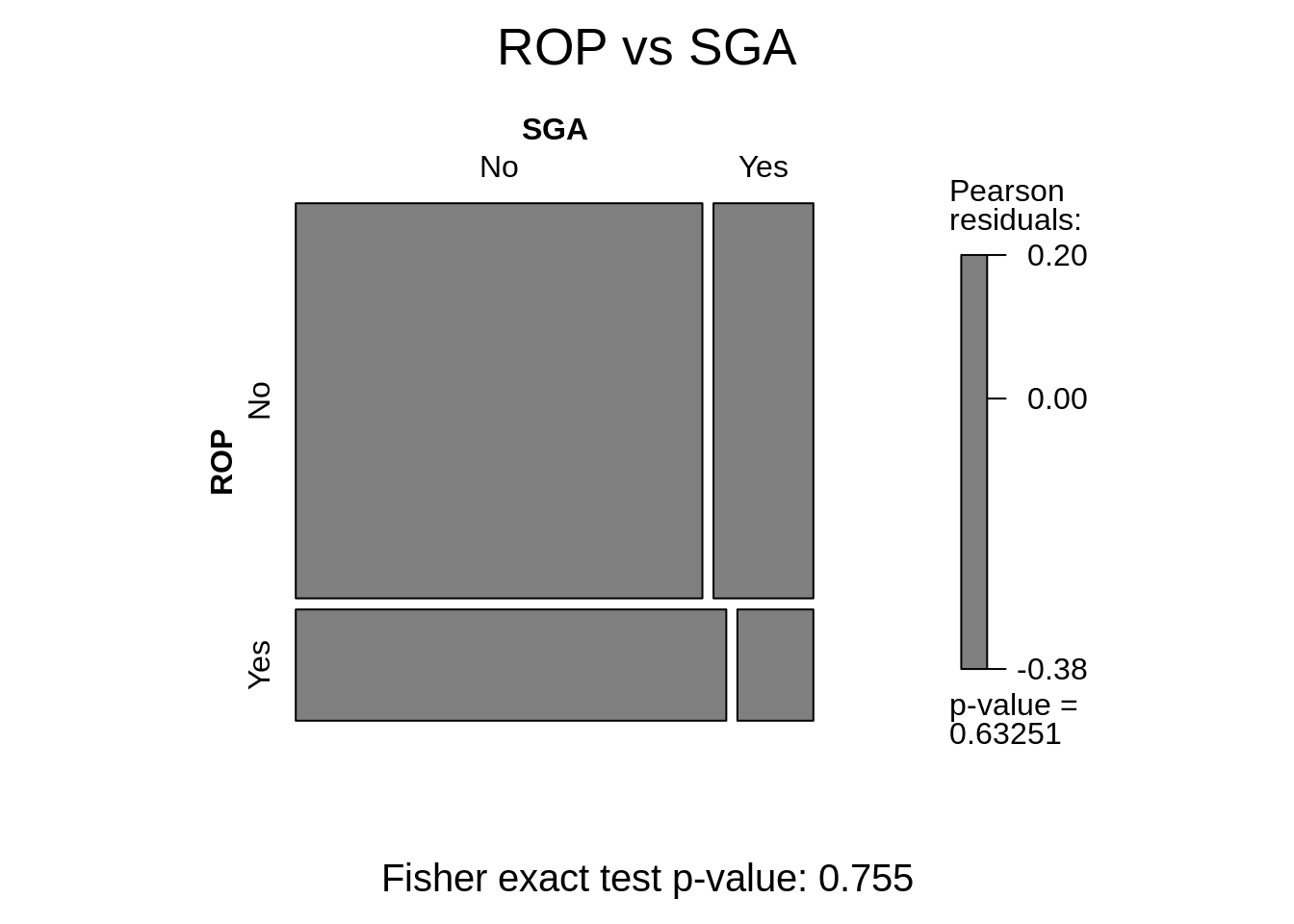
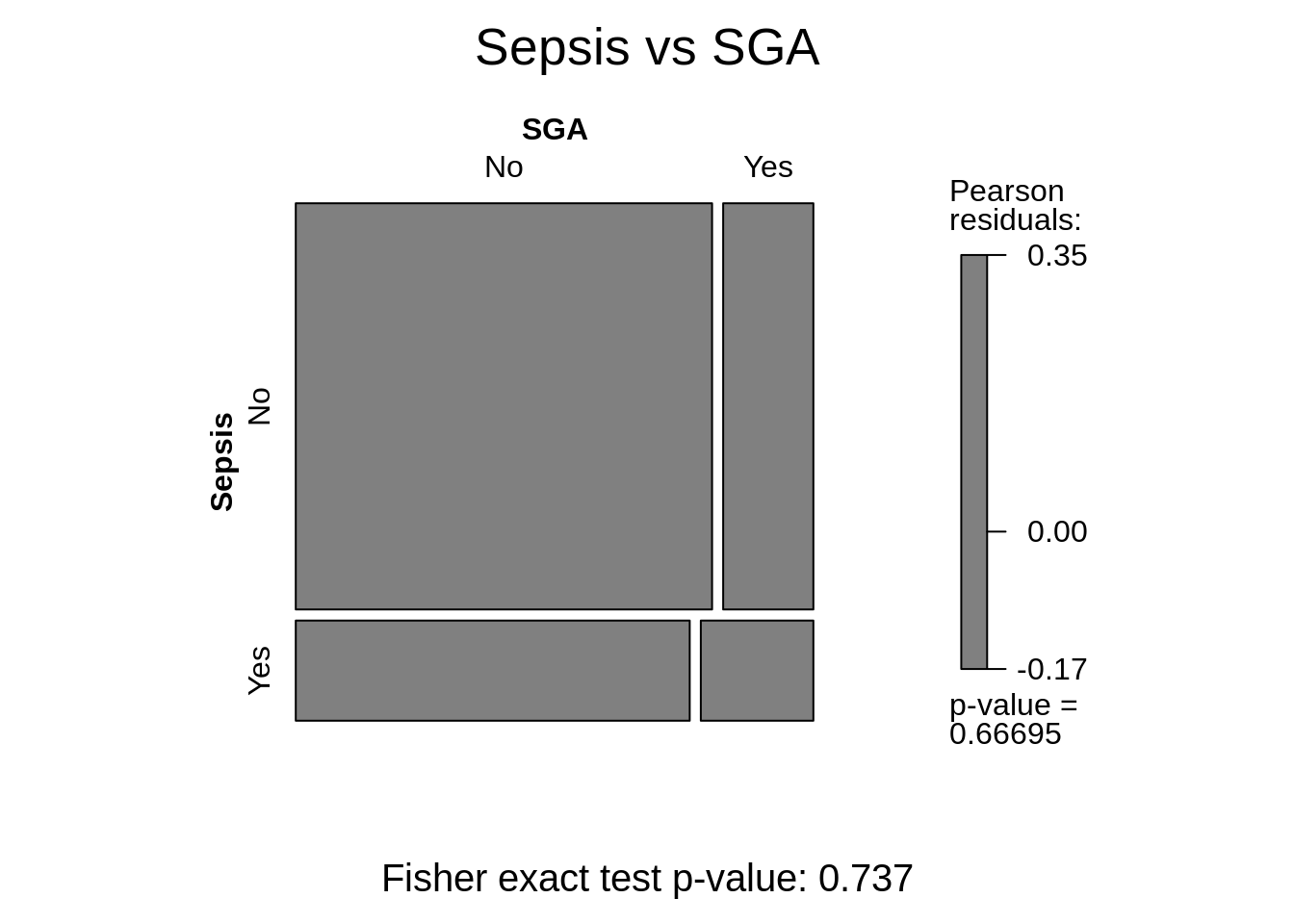
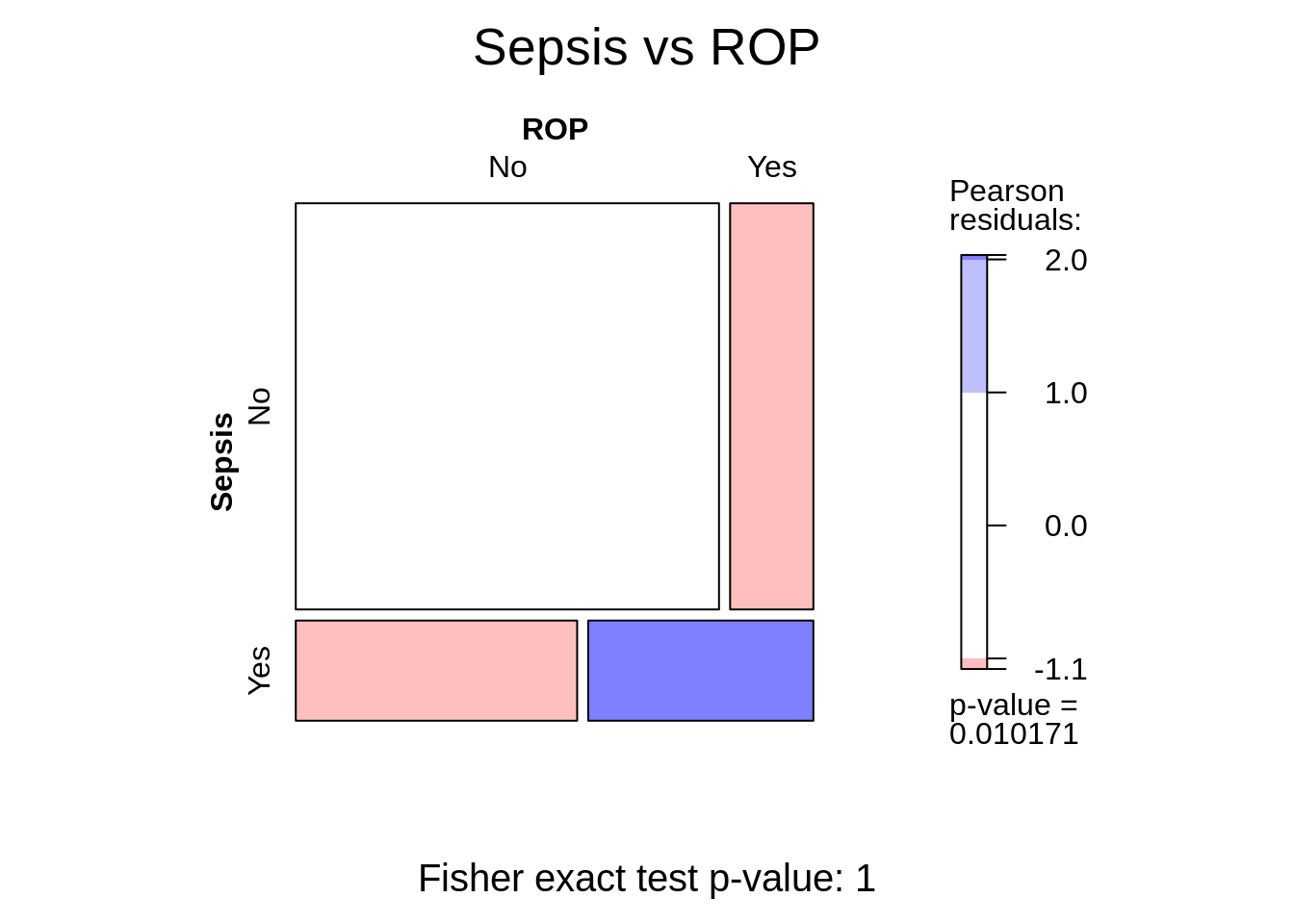
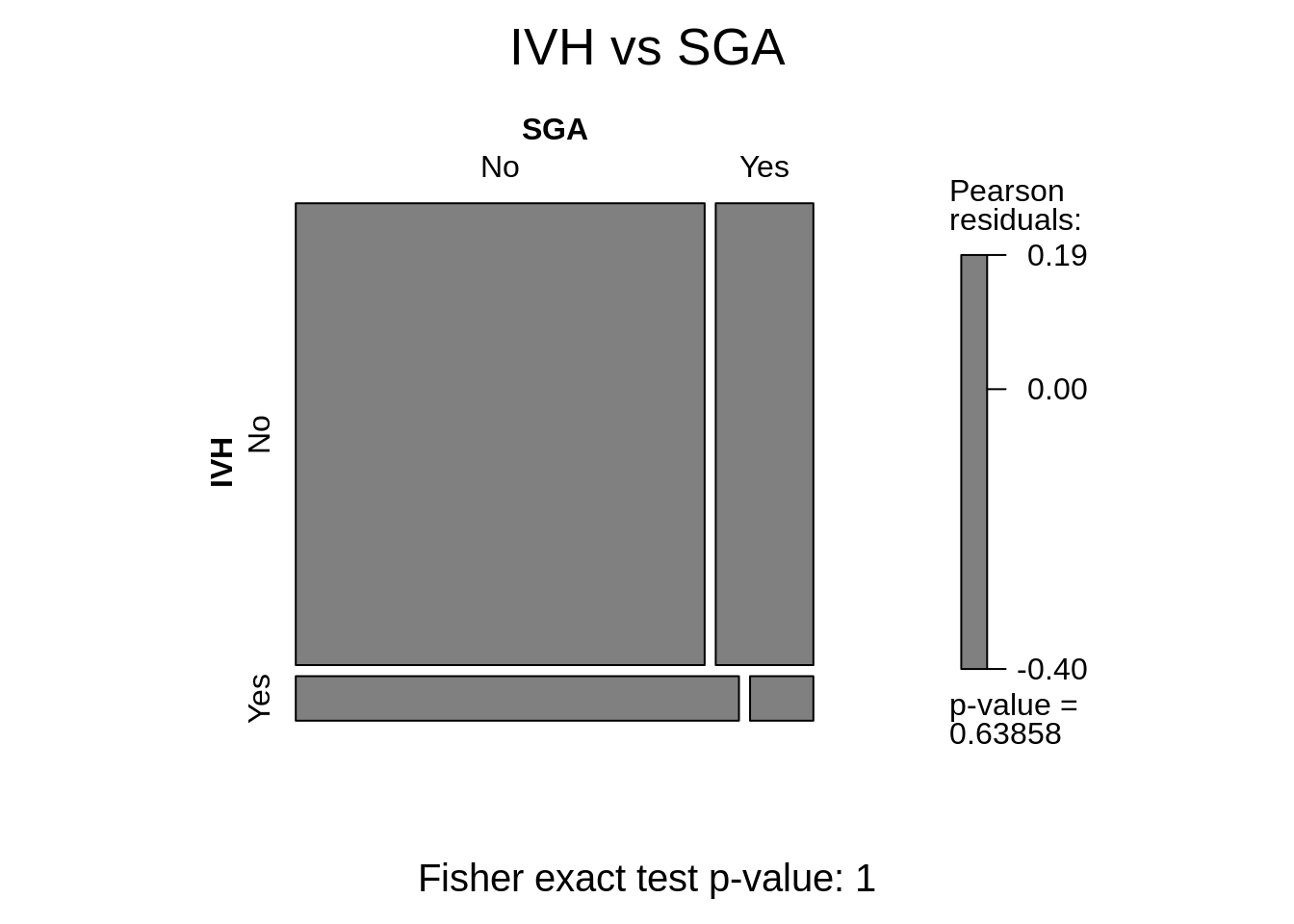
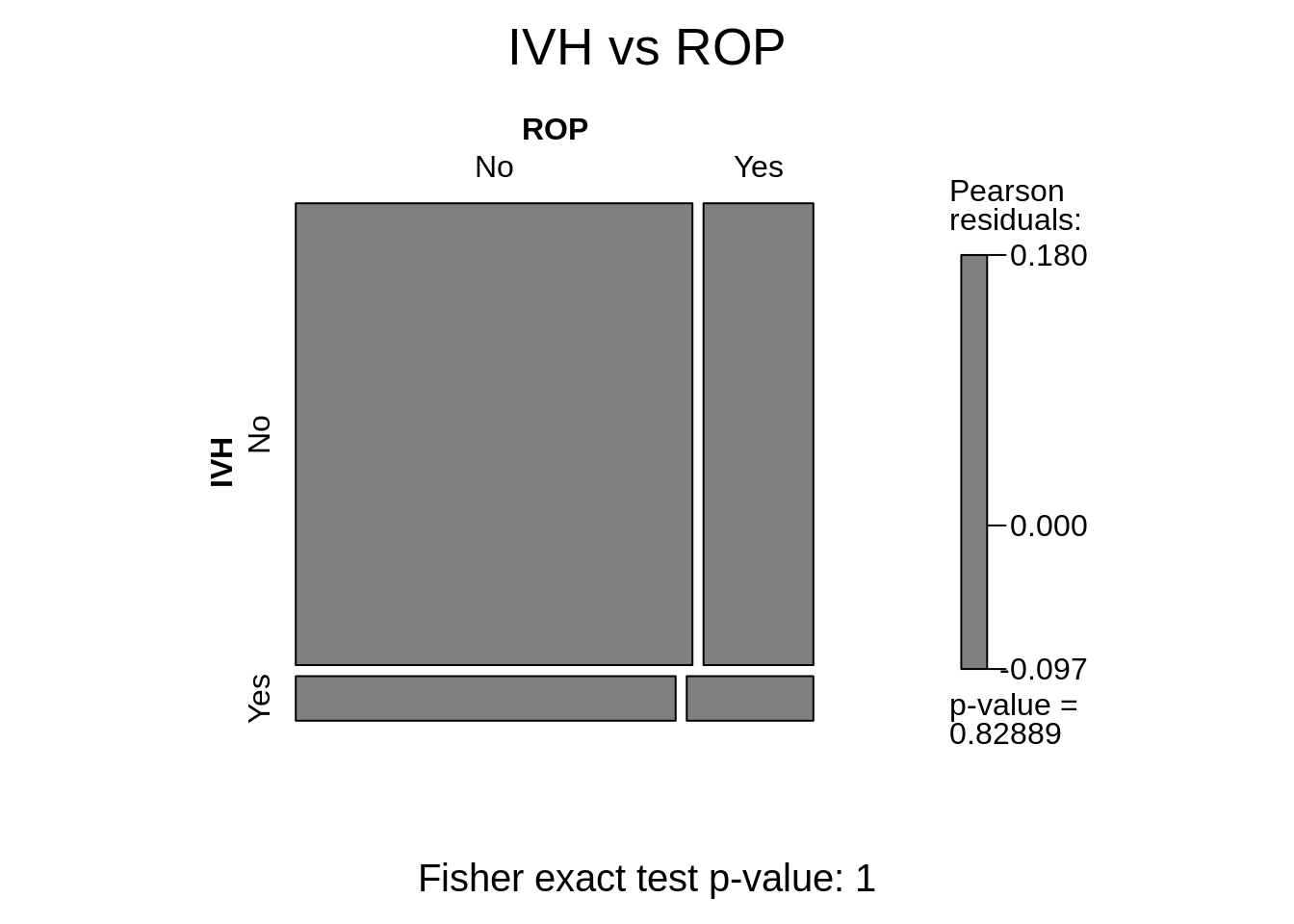
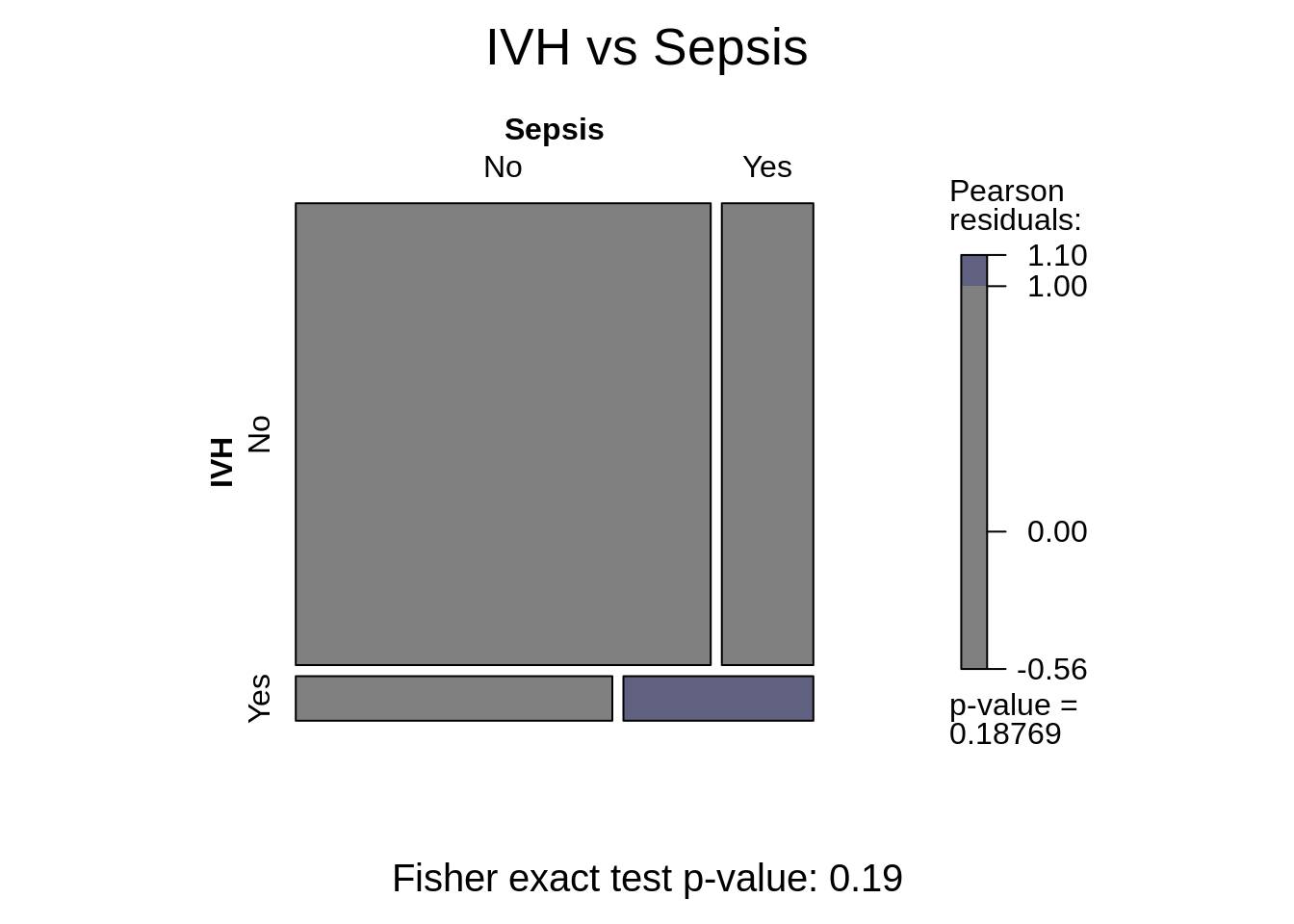
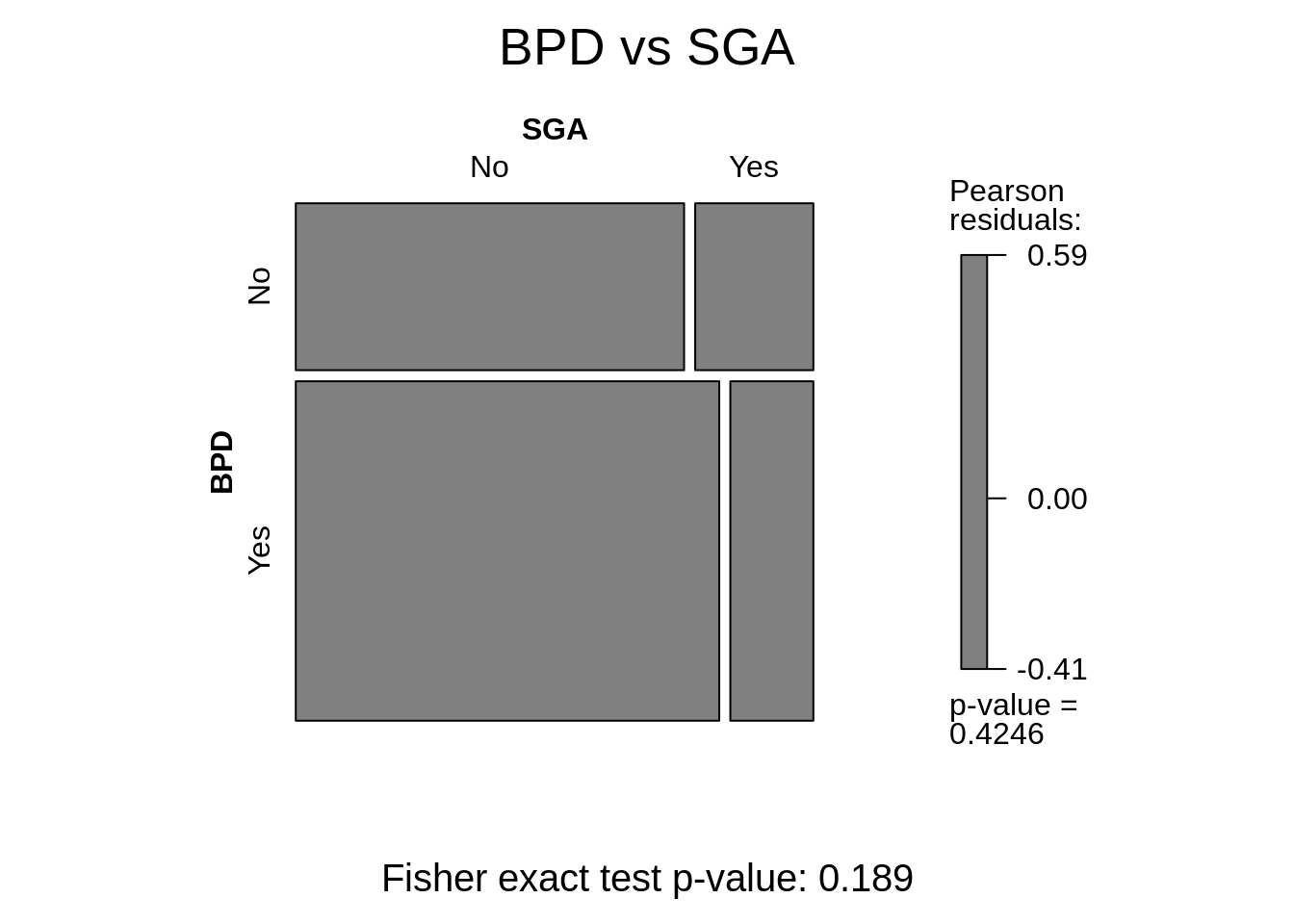
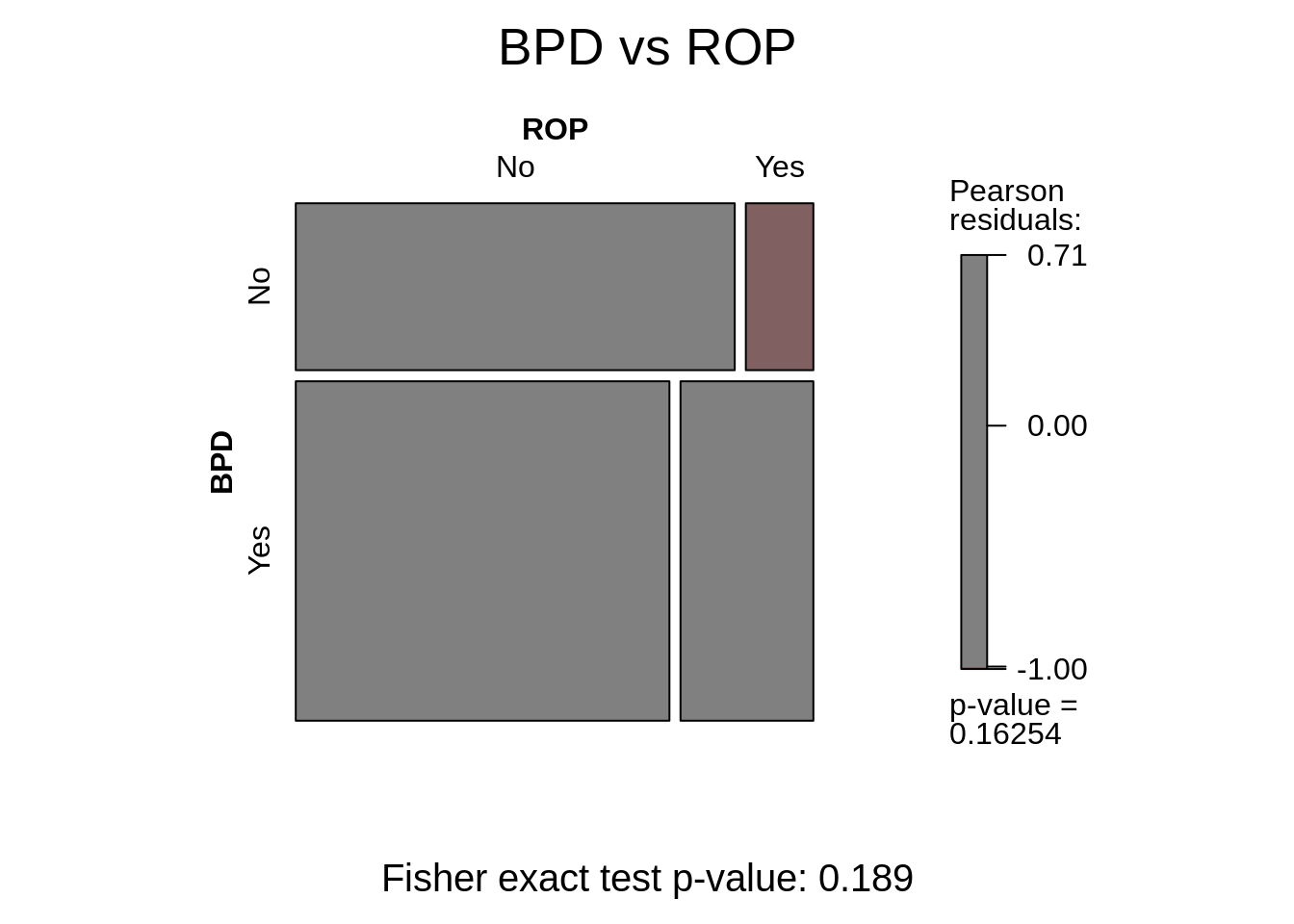
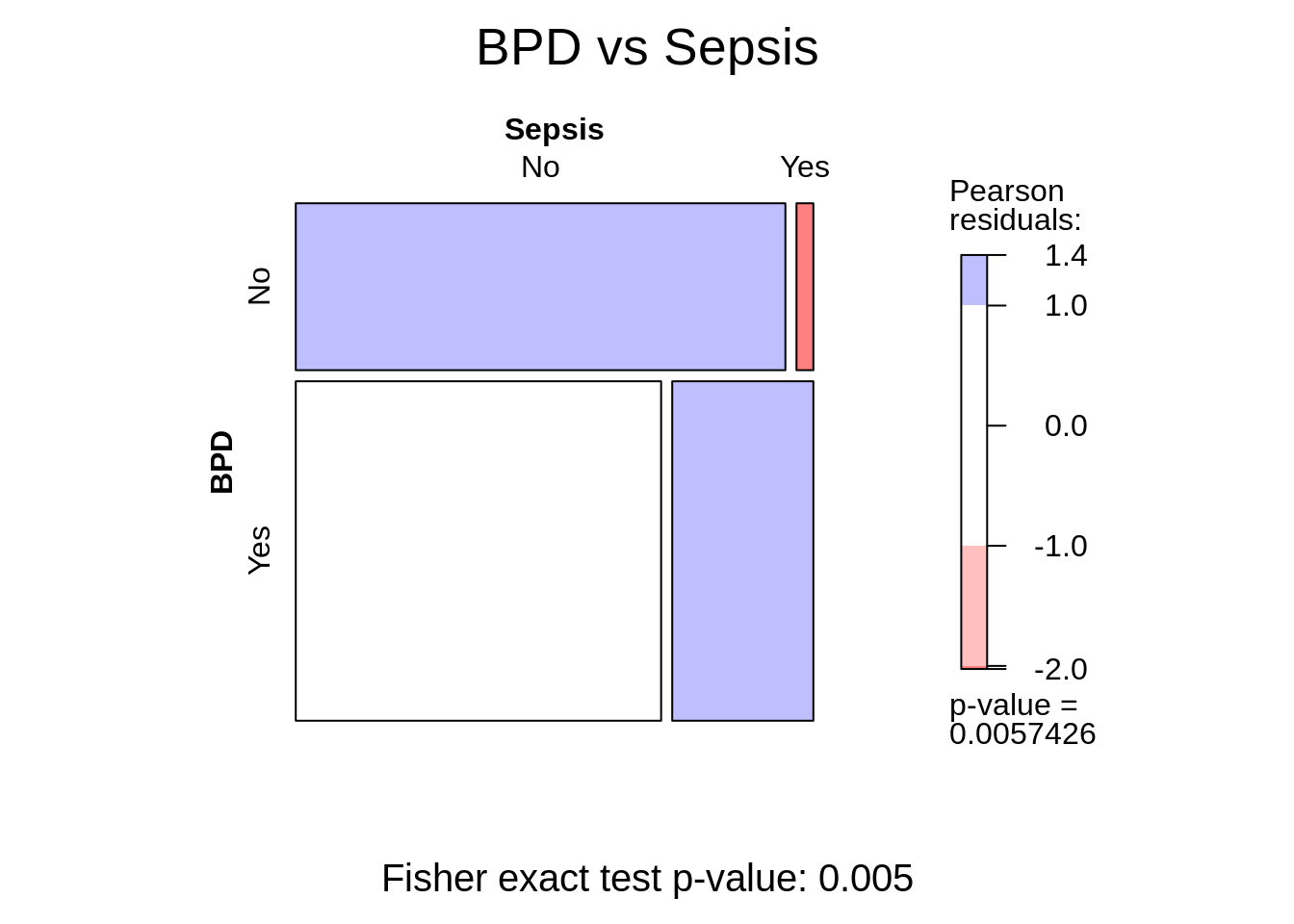
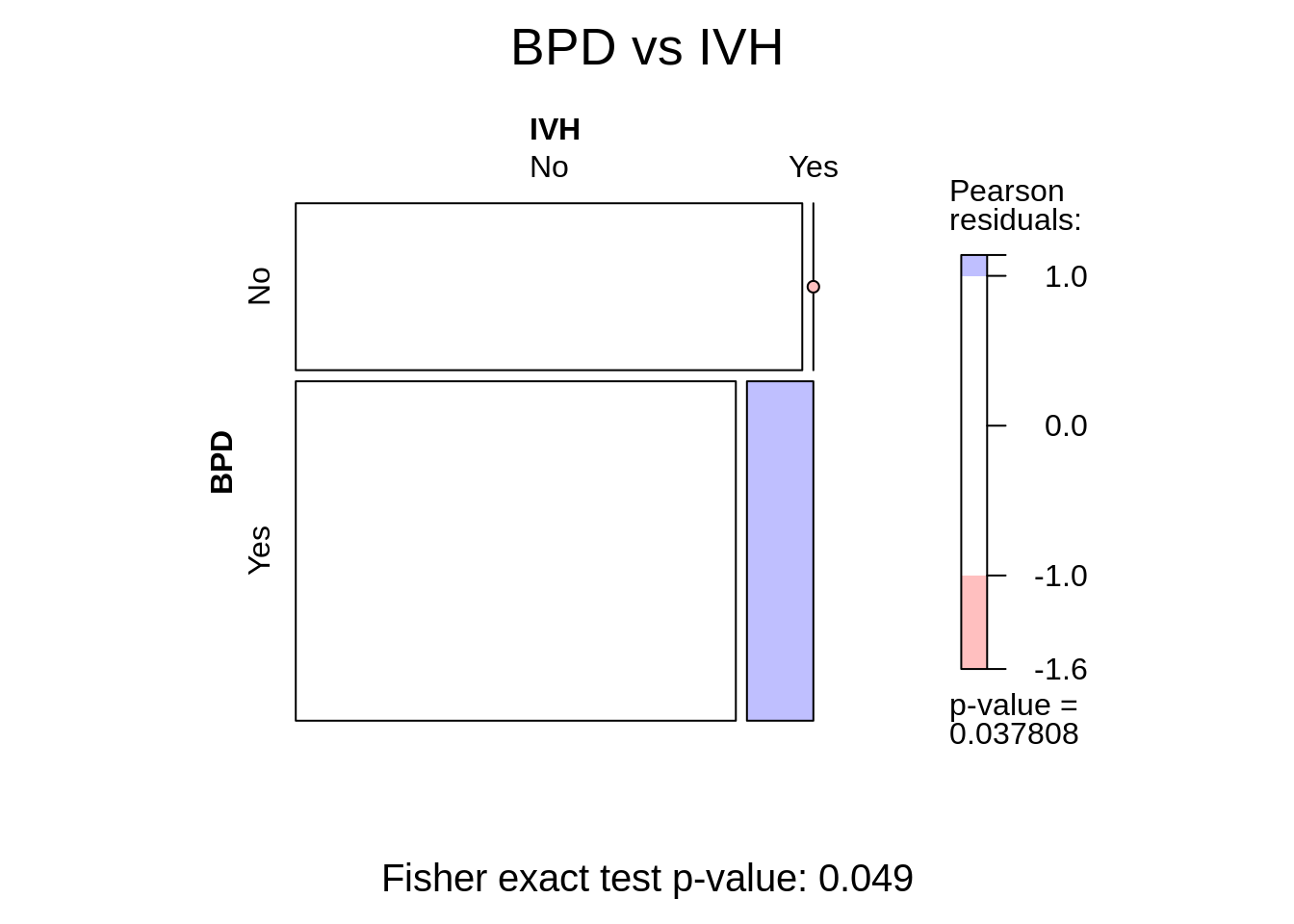
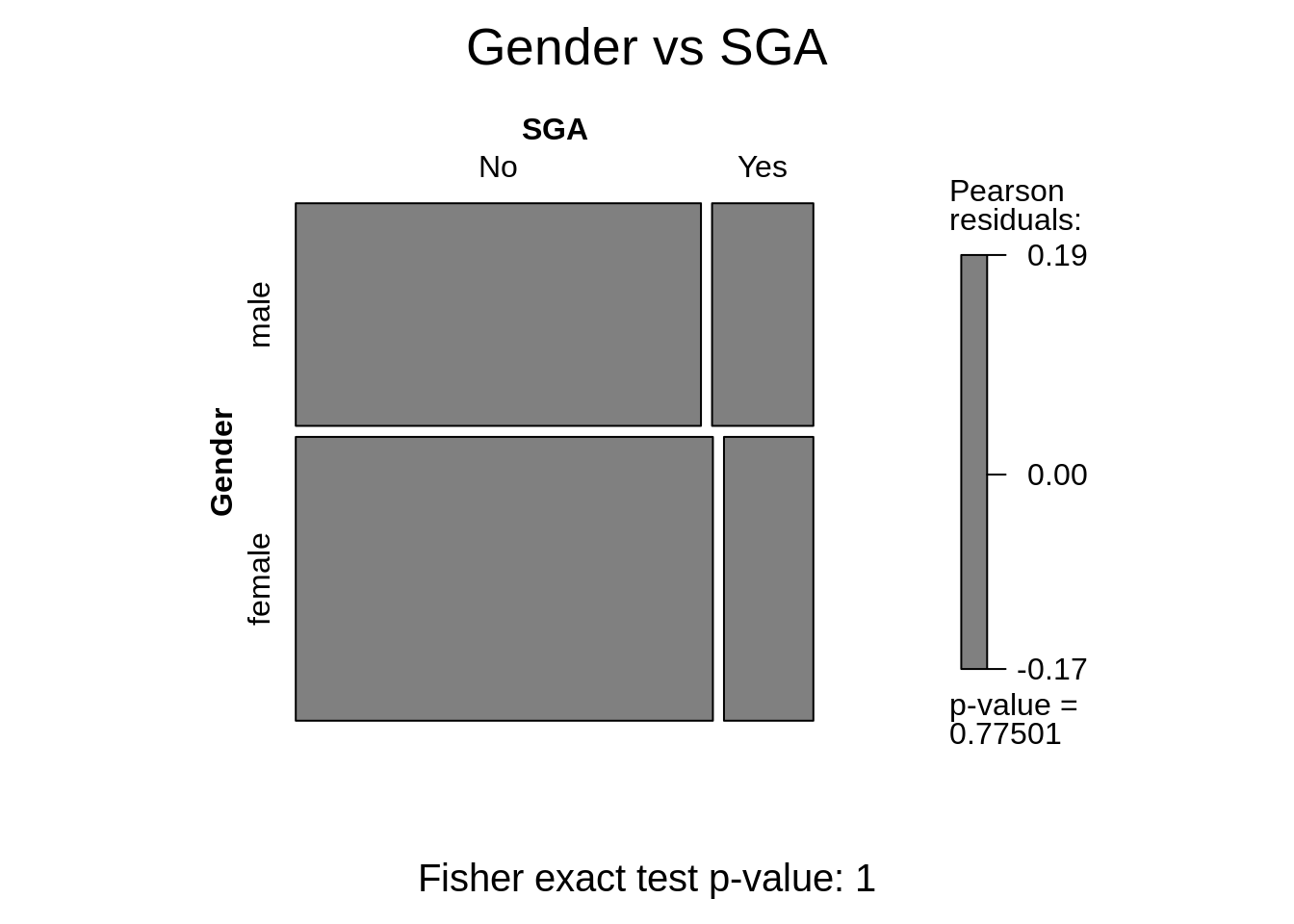
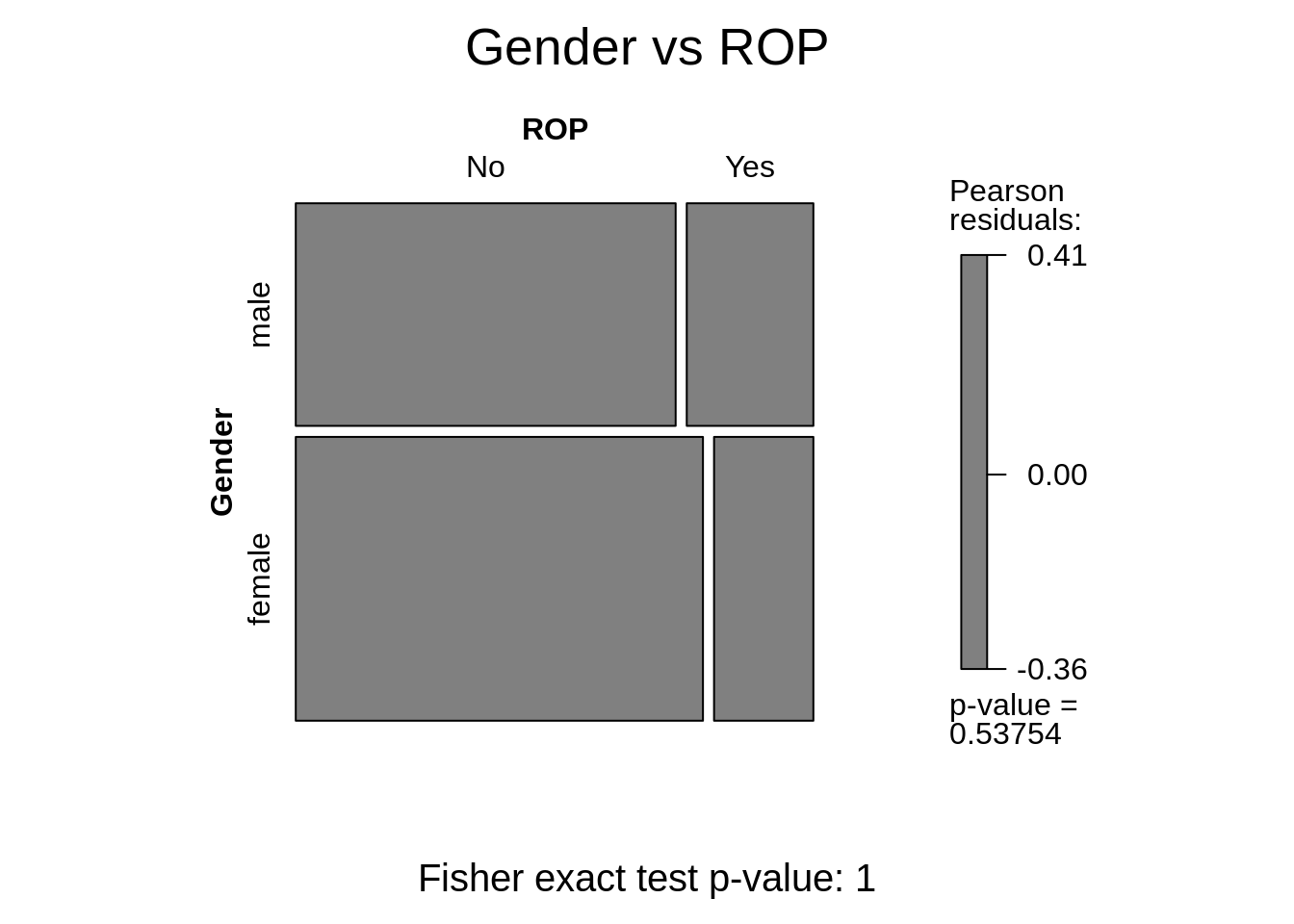
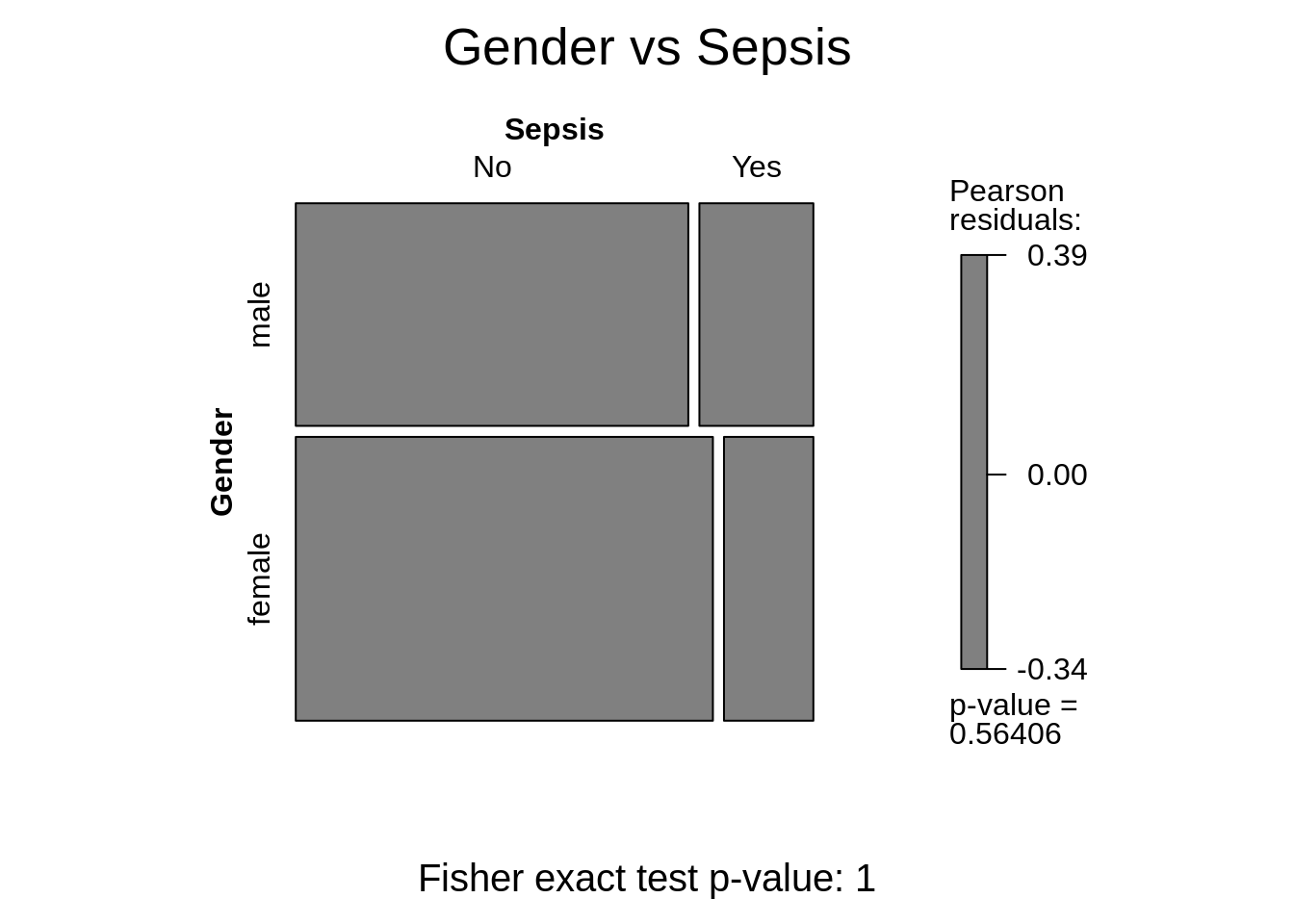
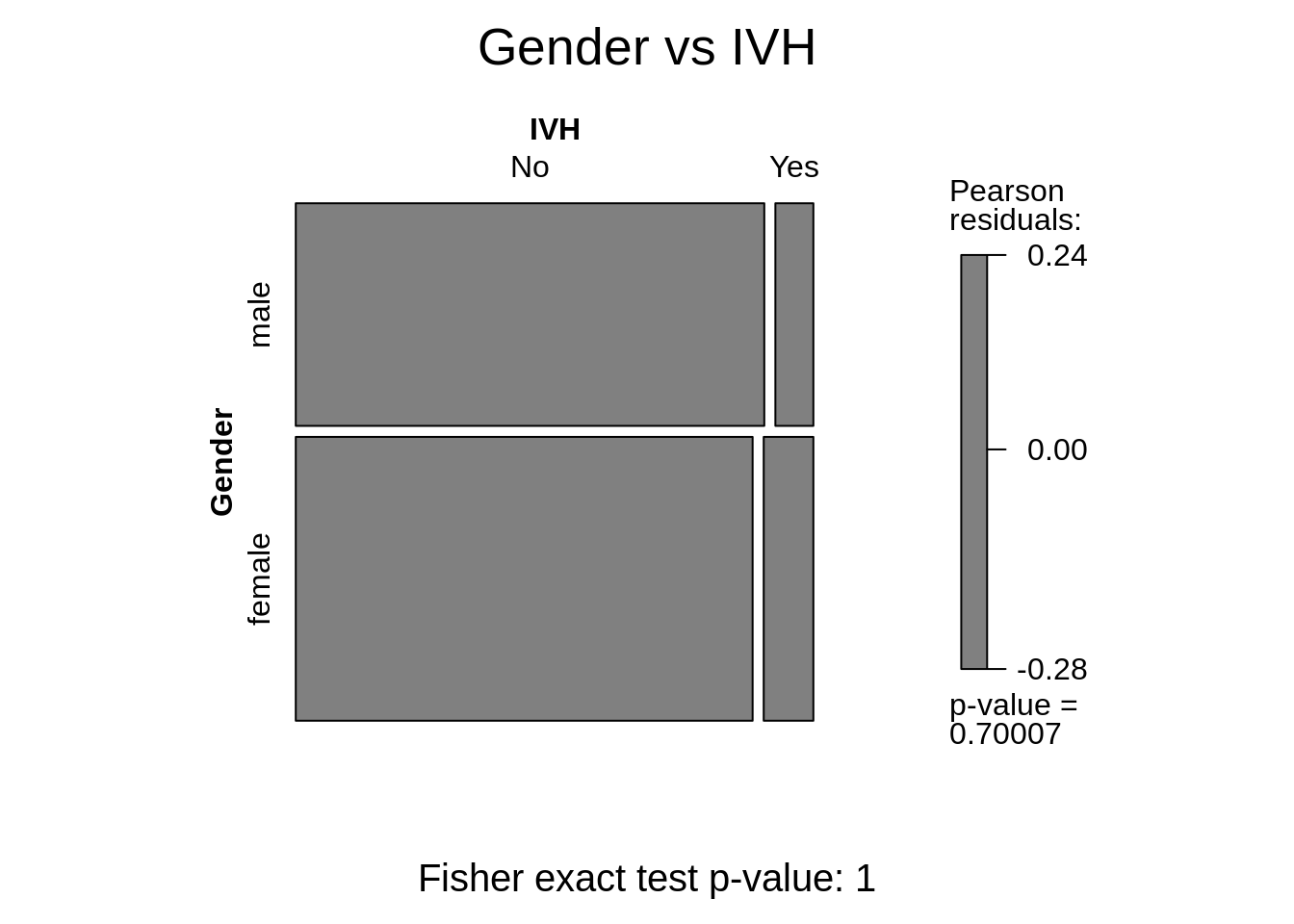
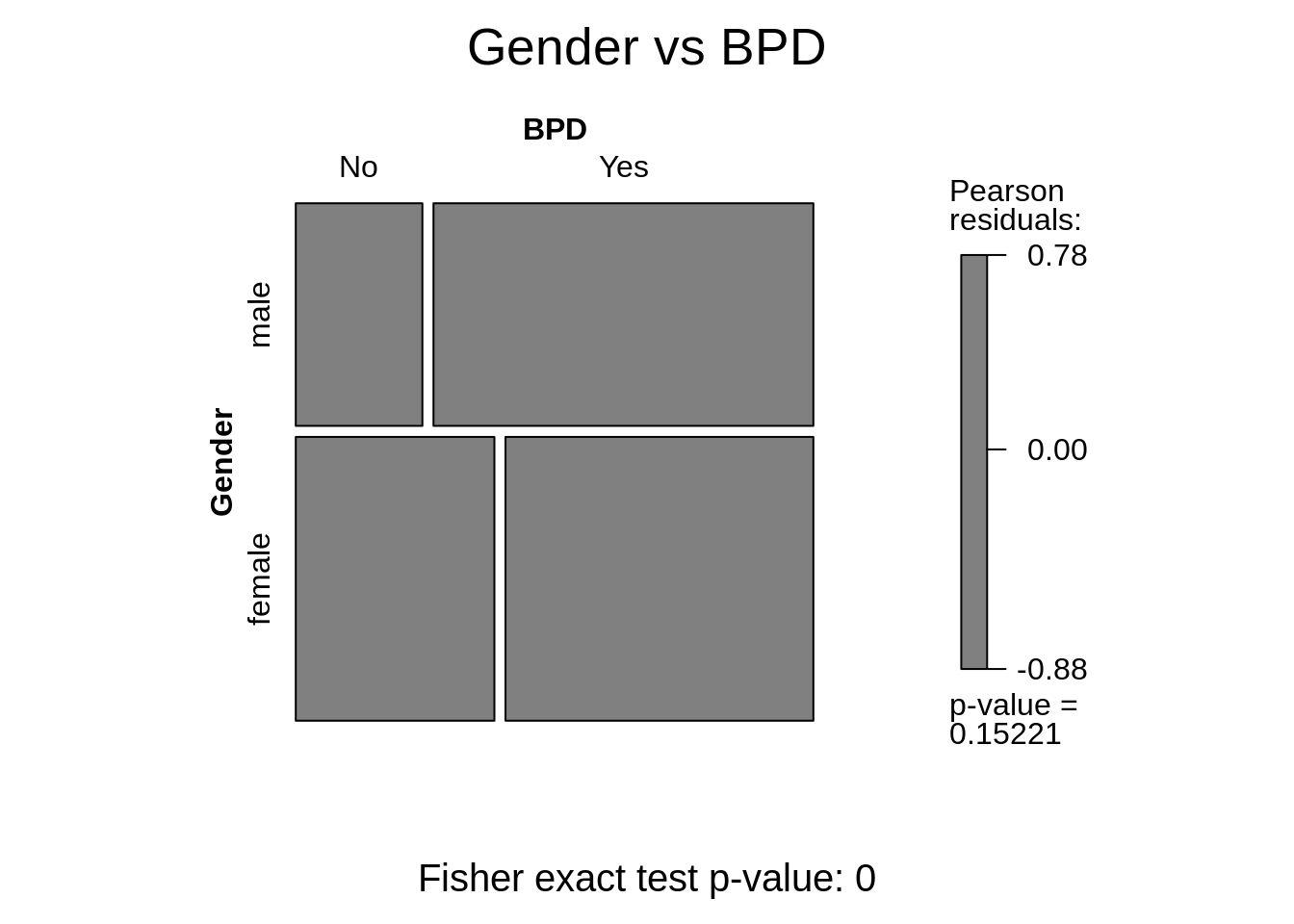
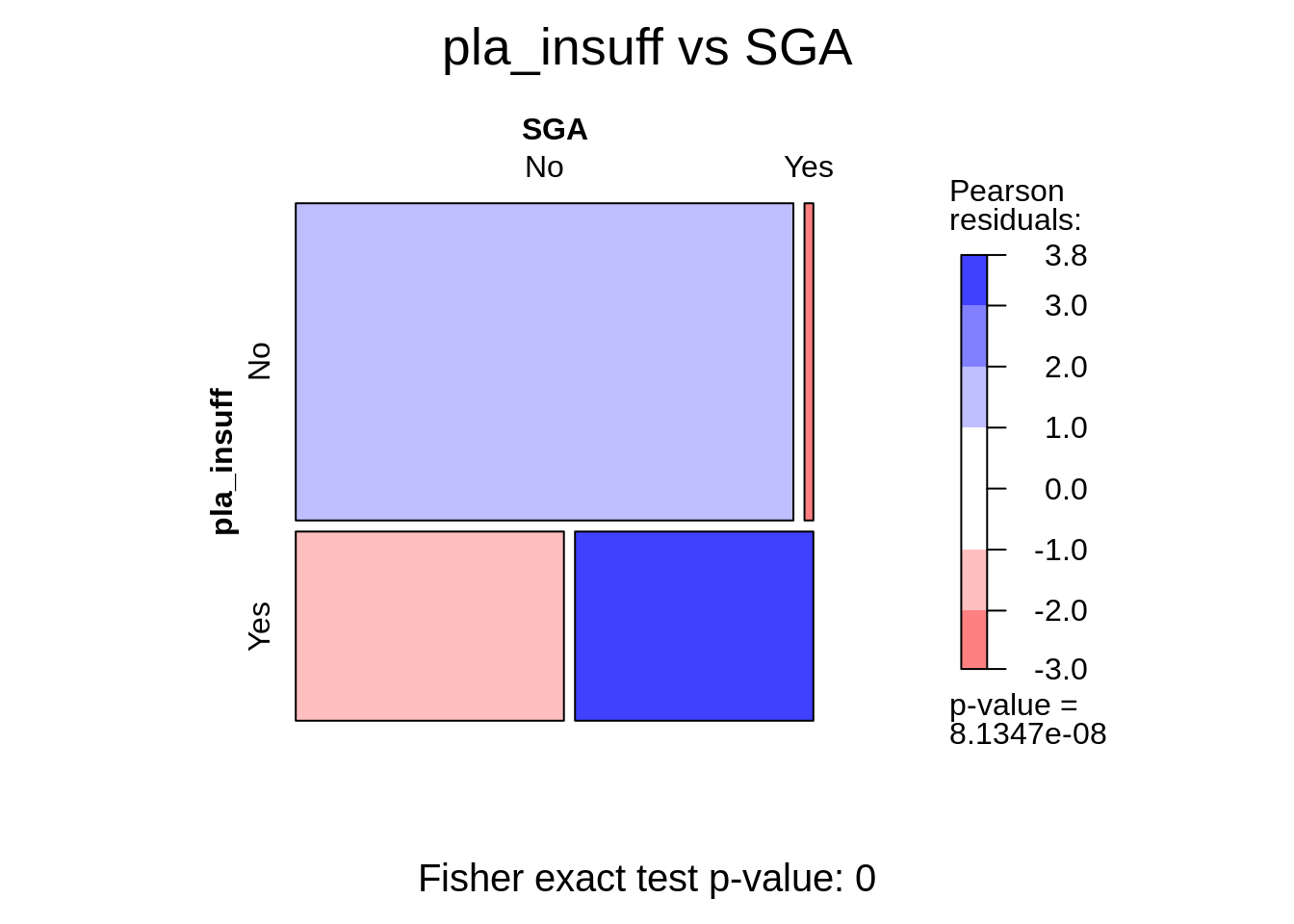
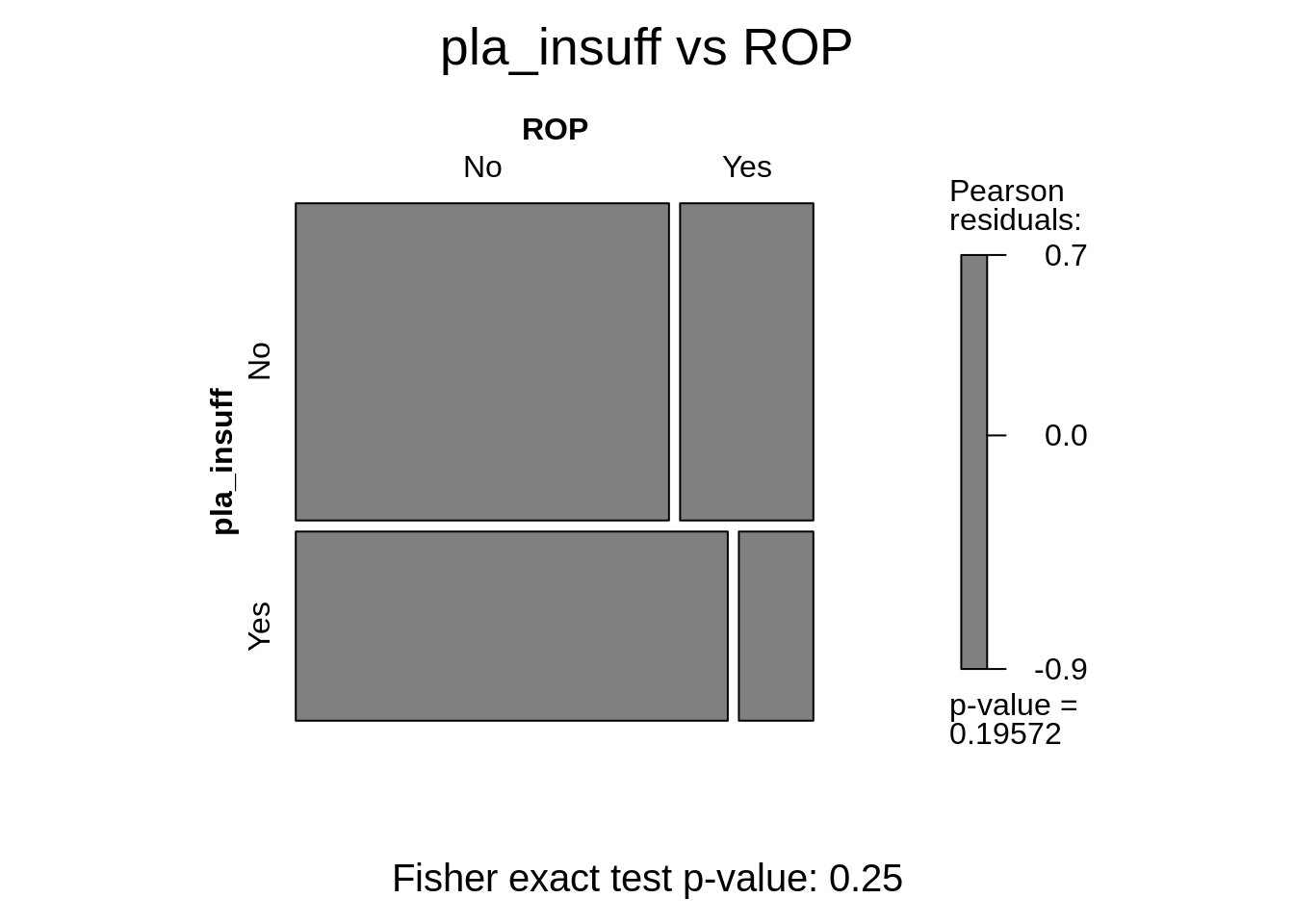
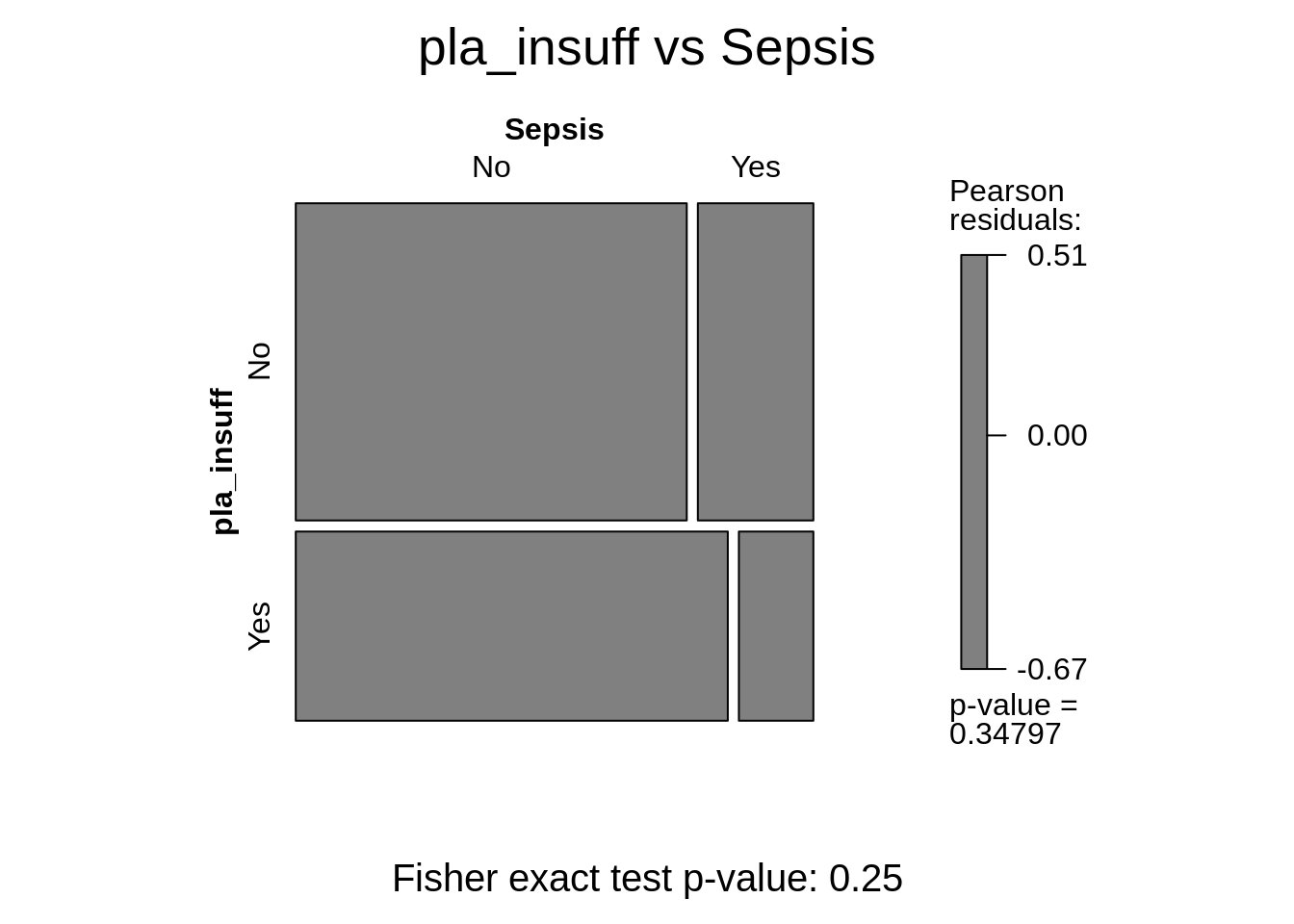
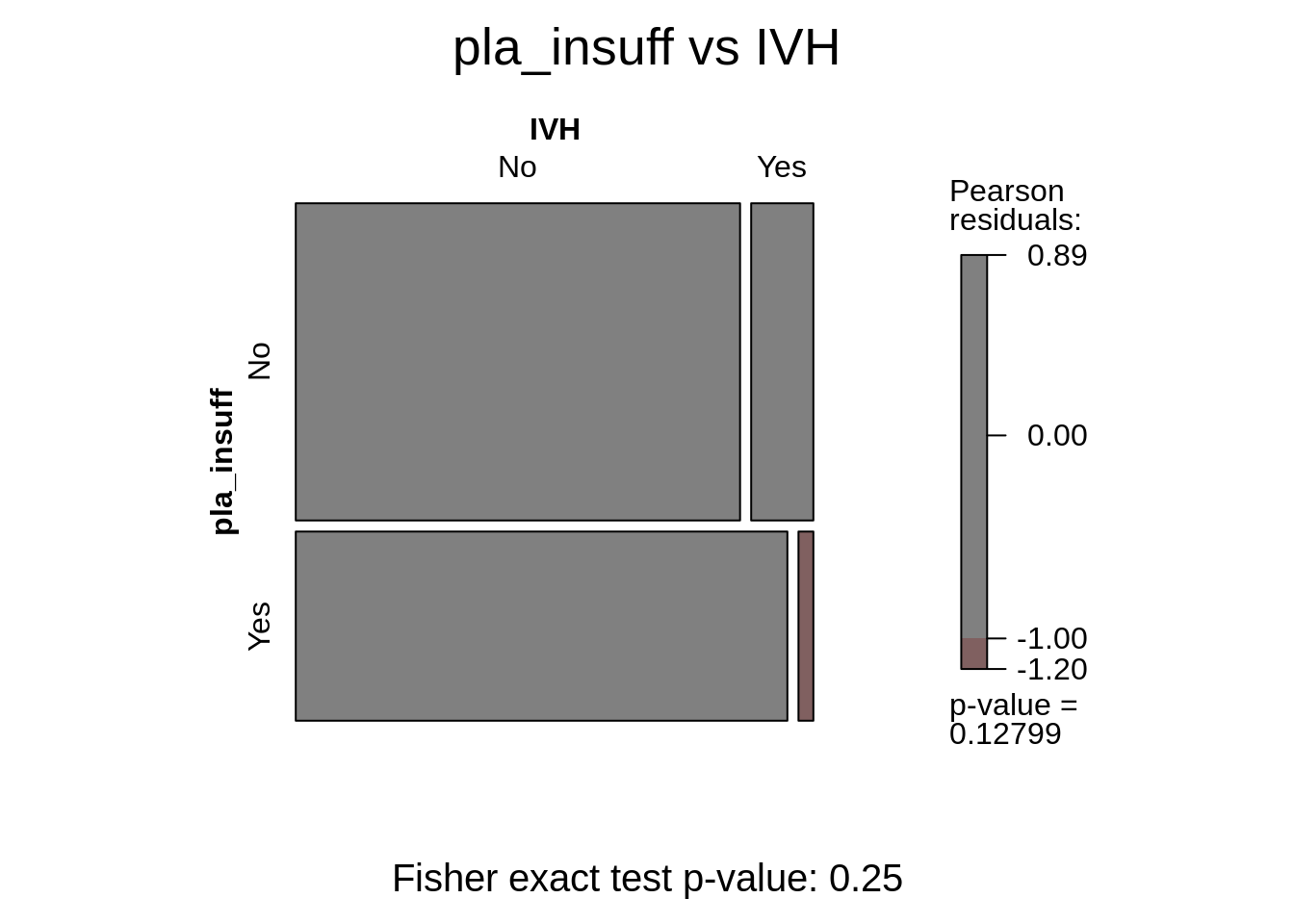
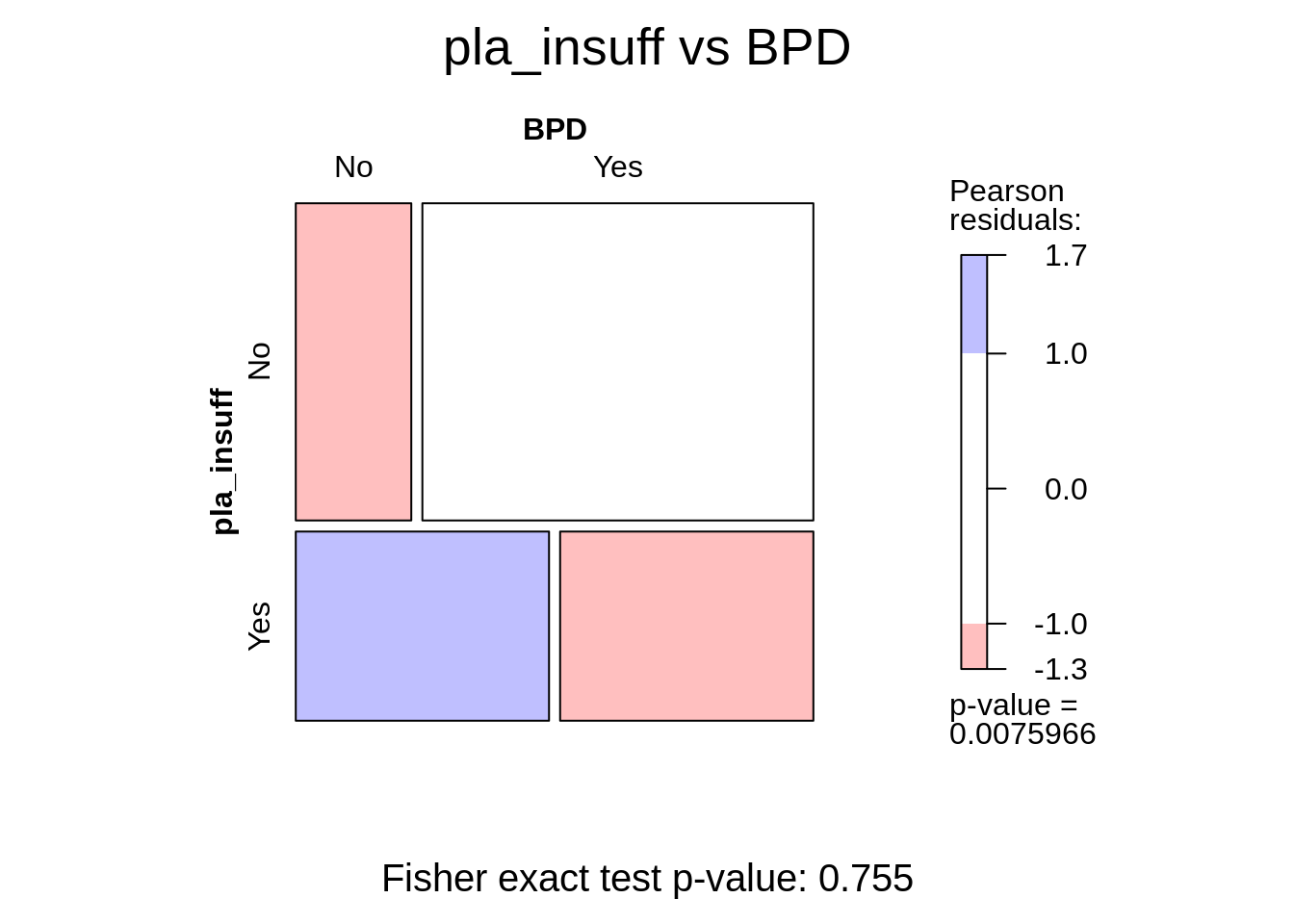
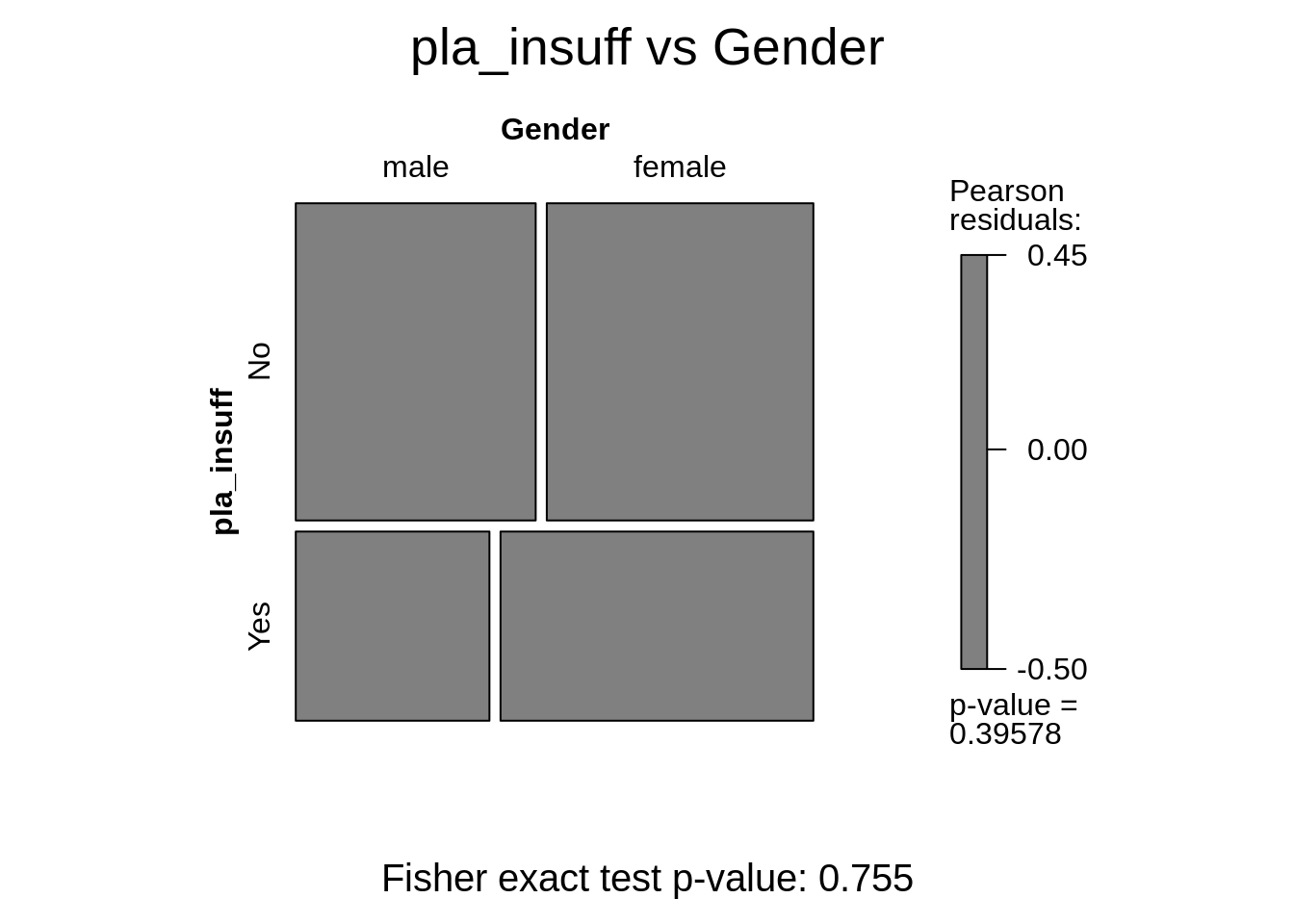
gp\_args = list(interpolate = 1:4),

legend=TRUE

)

}

}



#categorical vs. continuous variables

categorical.df.temp <- categorical.df[-1]

continuous.df.temp <- continuous.df[-1]

cat.col <- colnames(categorical.df.temp)

cont.col <- colnames(continuous.df.temp)

pdf(file = paste0(getwd(), "/continuous\_categorical\_correlation.pdf"), width = 18, height = 10, onefile = TRUE)

for (i in cat.col) {

p <- list()

for (j in cont.col) {

p[[j]] <- cat.cont.graph(categorical.df.temp, continuous.df.temp, i, j)

}

plot <- ggpubr::ggarrange(plotlist = p, ncol = 3, nrow = 2)

plot <- ggpubr::annotate\_figure(plot,

top = text\_grob(paste("Categorical variable:", i), color = "maroon", size = 32)

)

print(plot)

}

dev.off()

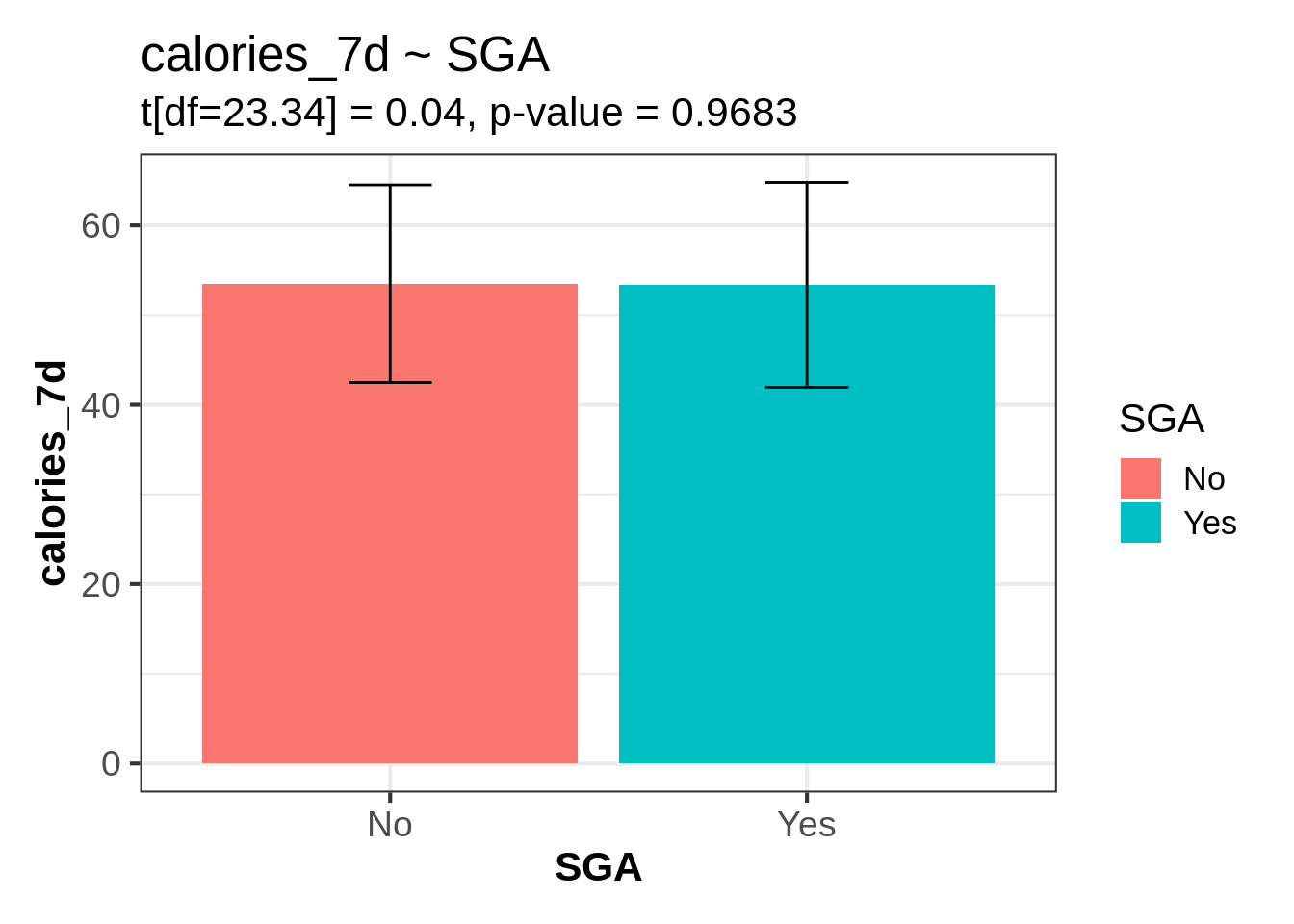
## png

## 2

#for html markdown

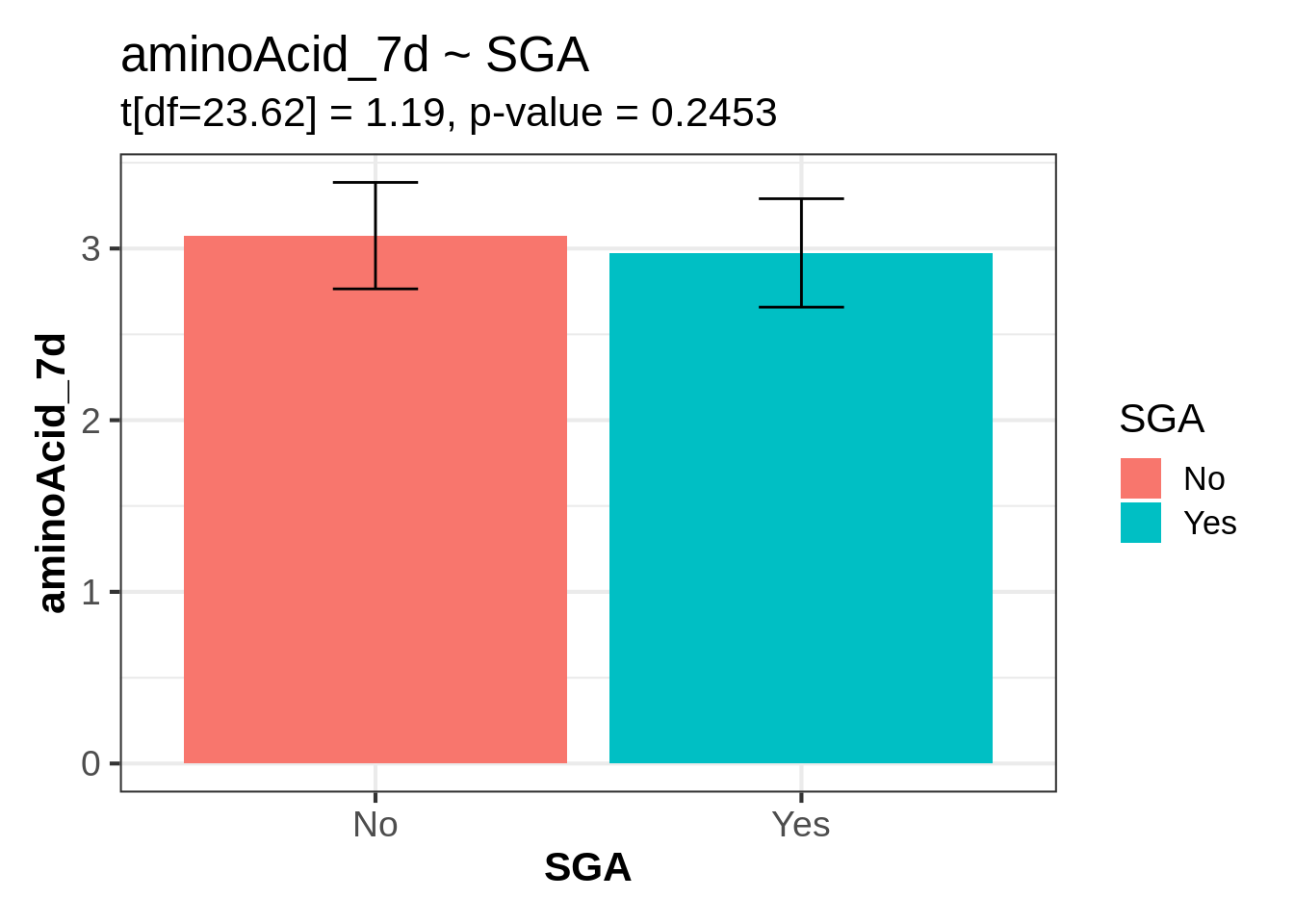
print(p)

## $calories\_7d



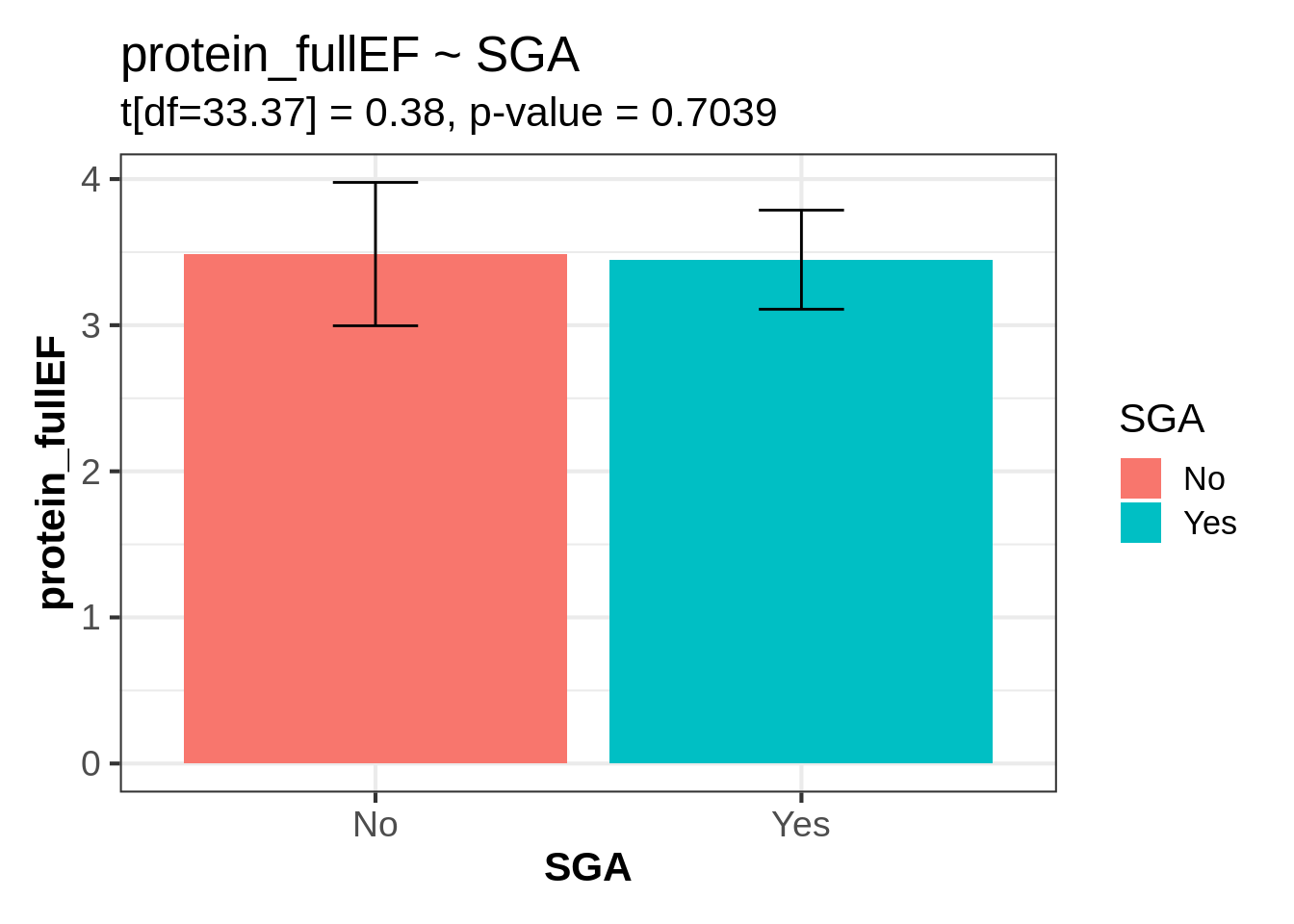
##

## $aminoAcid\_7d



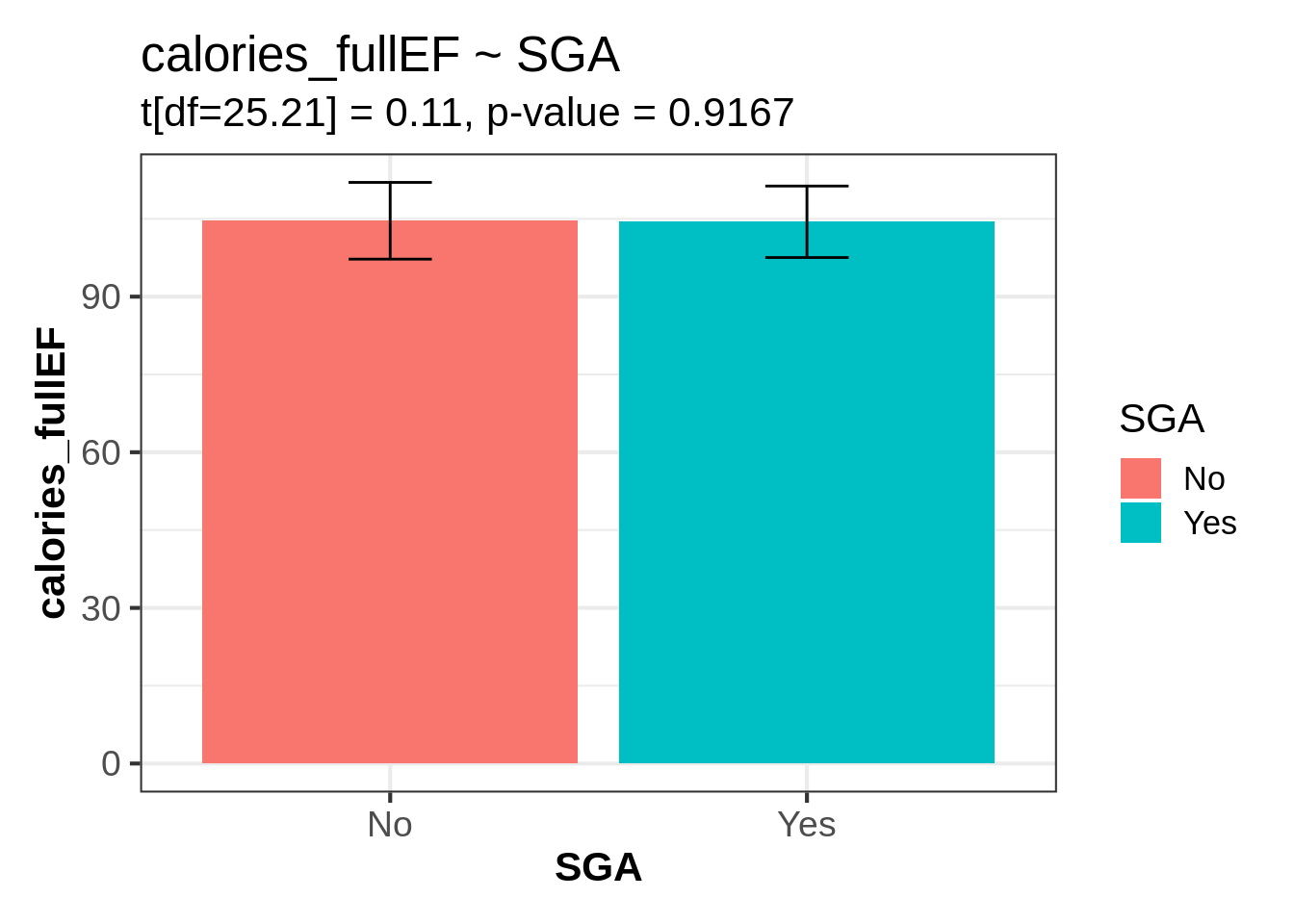
##

## $protein\_fullEF



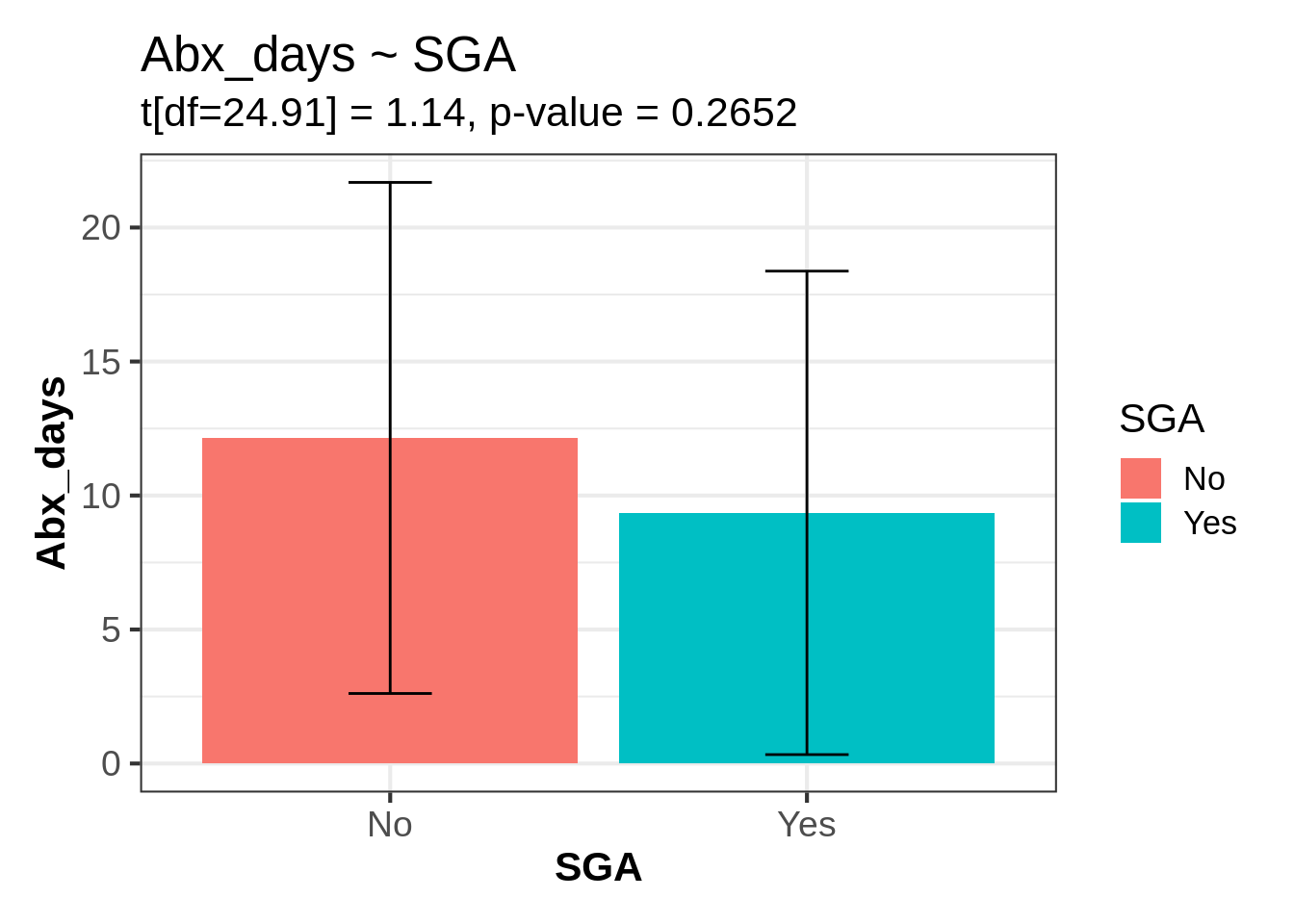
##

## $calories\_fullEF



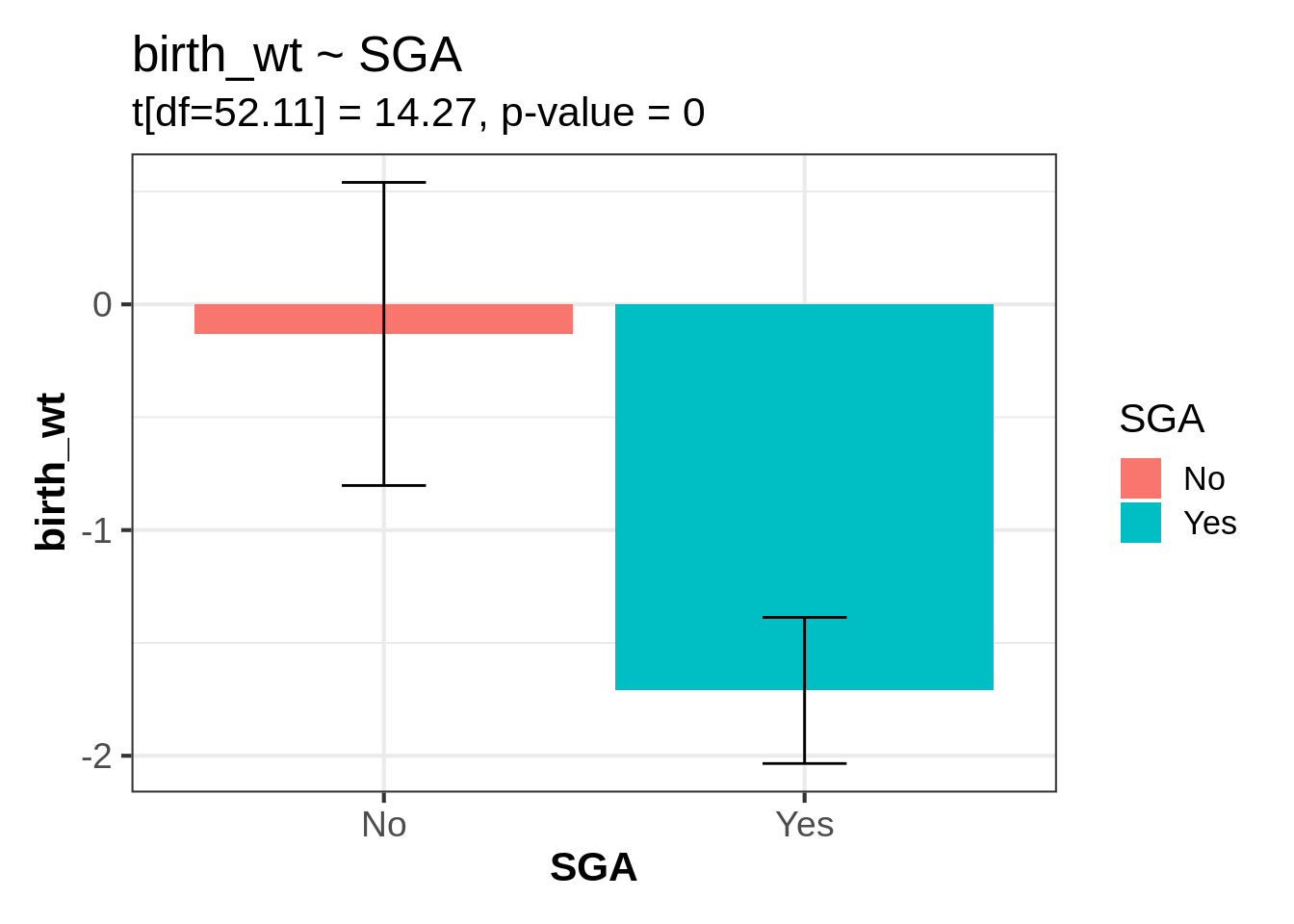
##

## $Abx\_days



##

## $birth\_wt



## 3. Spaghetti plot

require(tidyverse)

require(ggpubr)

# retrieve fixed-effects variable names

categorical.fixed.variables <- colnames(categorical.df)[-1]

long.df <- data.frame()

long.df <- inner\_join(weight, categorical.df, by = "id")

long.df <- inner\_join(long.df, continuous.df, by = "id")

long.df <- inner\_join(long.df, maternal\_demographics.df, by = "id")

long.df <- inner\_join(long.df, neonatal\_demographics.df, by = "id")

long.df[["id"]] <- as.factor(long.df[["id"]])

# set up folder for plot storage

folder.check(folder.name = "Results", getwd())

folder.check(folder.name = "spaghetti\_plot", getwd())

pdf(file = paste0(getwd(), "/spaghetti plots.pdf"), width = 18, height = 18, onefile = TRUE)

p <- list()

for (i in categorical.fixed.variables) {

p[[i]] <- ggplot2::ggplot(long.df, aes(x = time\_week, y = wt\_z\_score, group = id)) +

geom\_line(aes\_(color = as.name(i))) +

theme\_bw() +

theme(legend.position = "bottom",

legend.title = element\_text(size=12),

legend.text = element\_text(size=12),

axis.text=element\_text(size=12),

axis.title=element\_text(size=14, face="bold", margin = margin(10,10,10,10,"mm")),

plot.margin = margin(5,5,5,5, "mm")) +

labs(x = "week", y = "weight z-score",

title = "Trend of weight z-score",

subtitle = paste0("Color-coded by ", i))

}

plot <- ggpubr::ggarrange(plotlist = p, ncol = 3, nrow =3)

plot <- ggpubr::annotate\_figure(plot,

top = text\_grob("Spaghetti Plots", color = "maroon", size = 32))

print(plot)

dev.off()

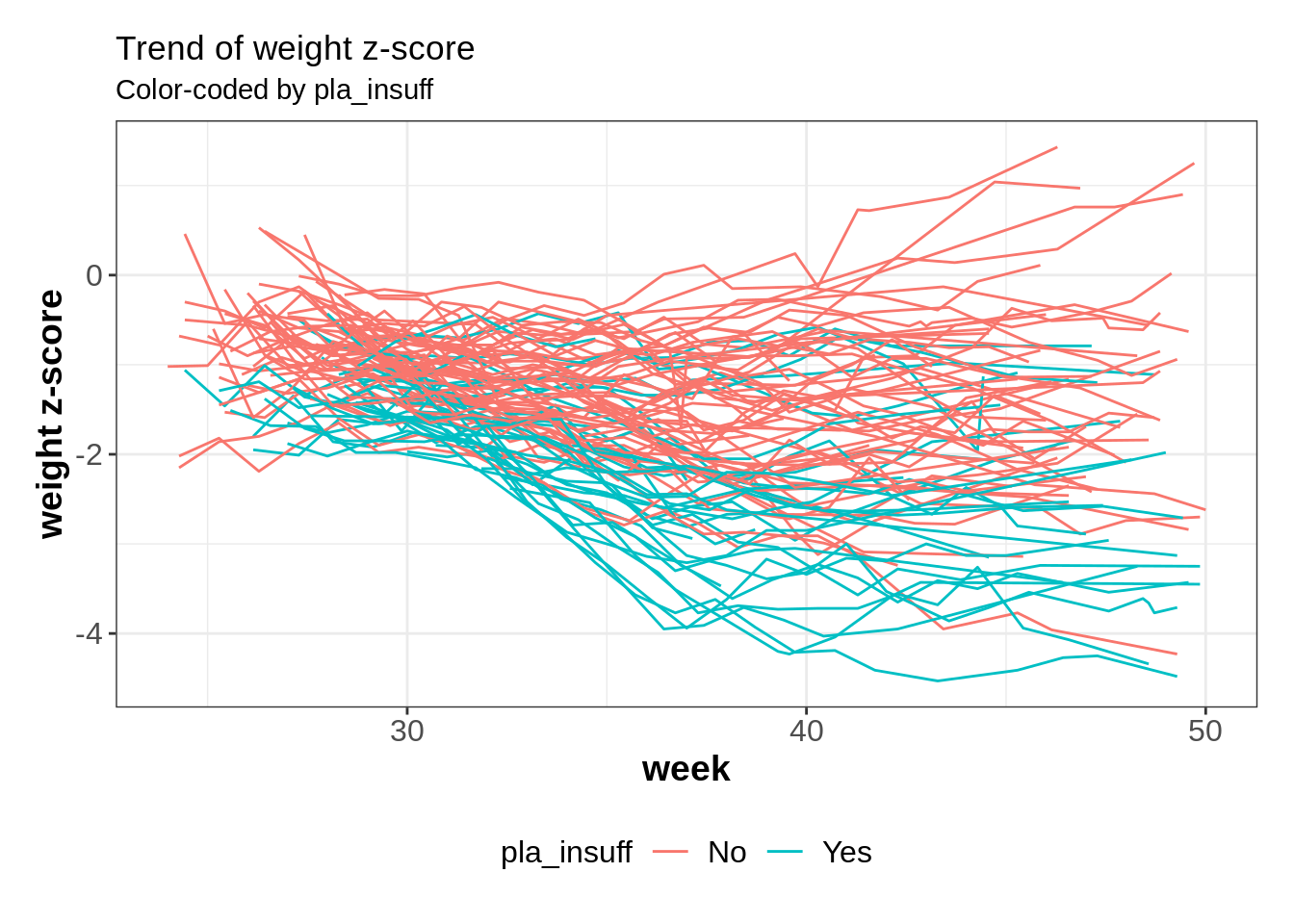
## png

## 2

#for html markdown

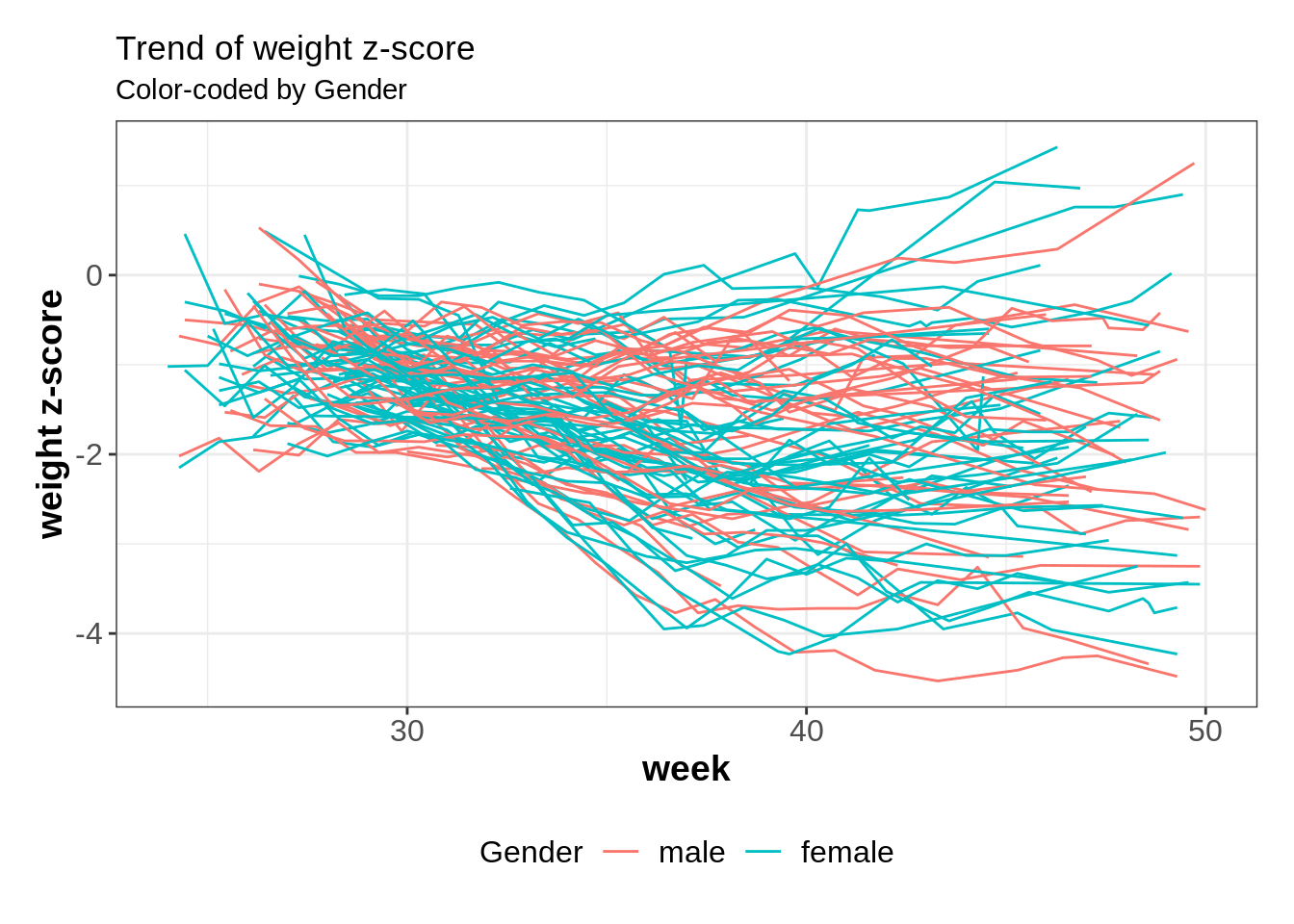
print(p)

## $pla\_insuff



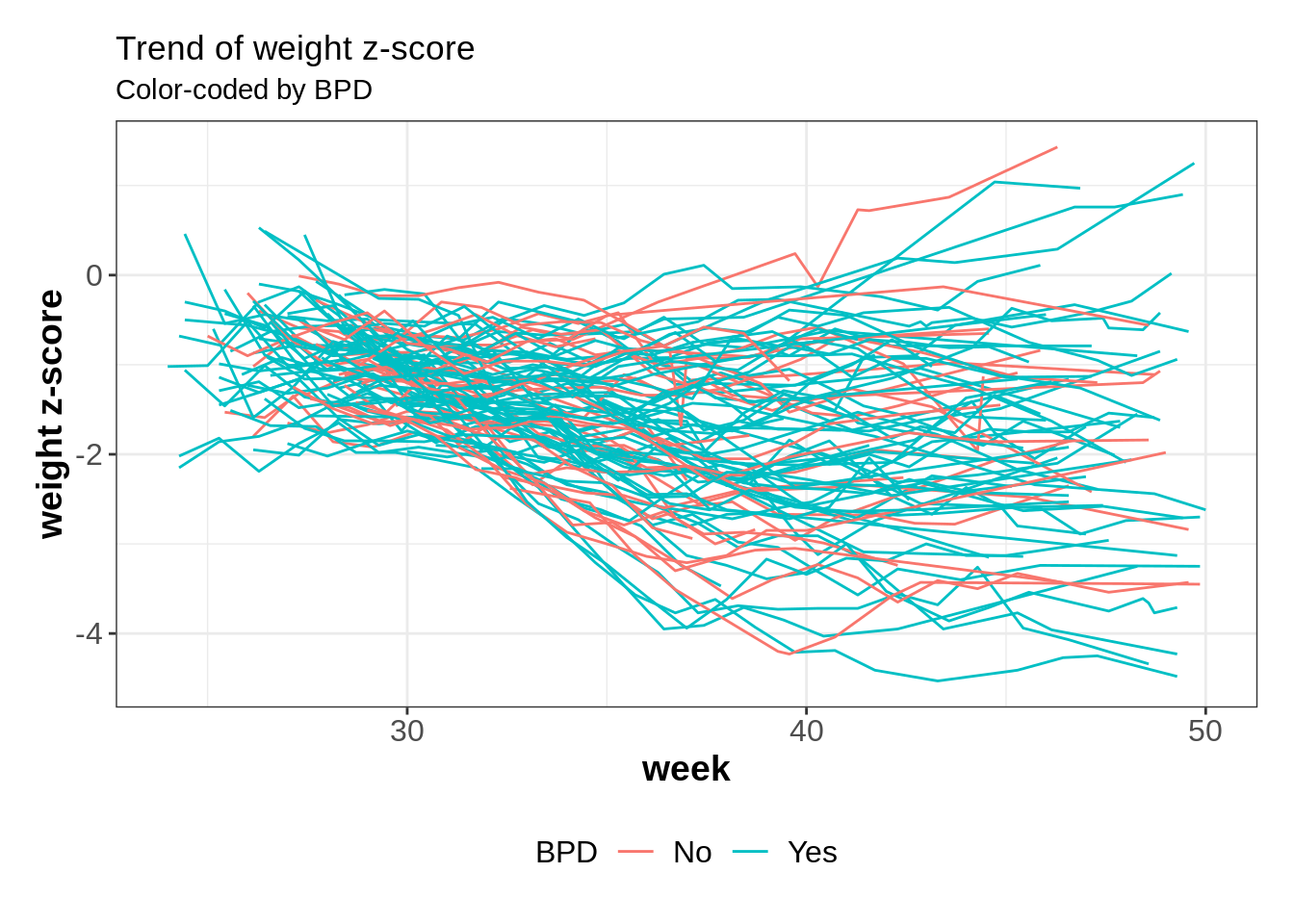
##

## $Gender



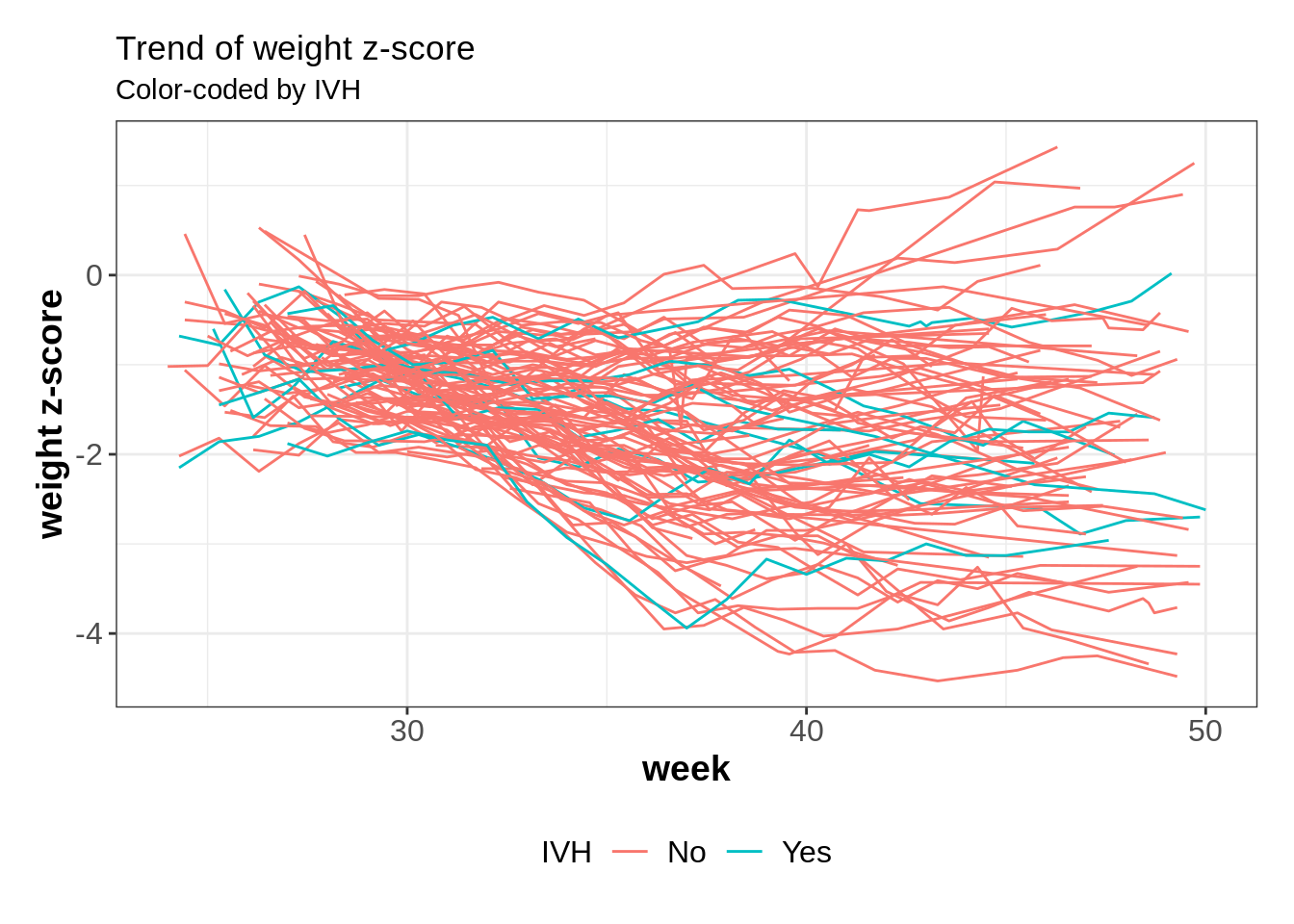
##

## $BPD



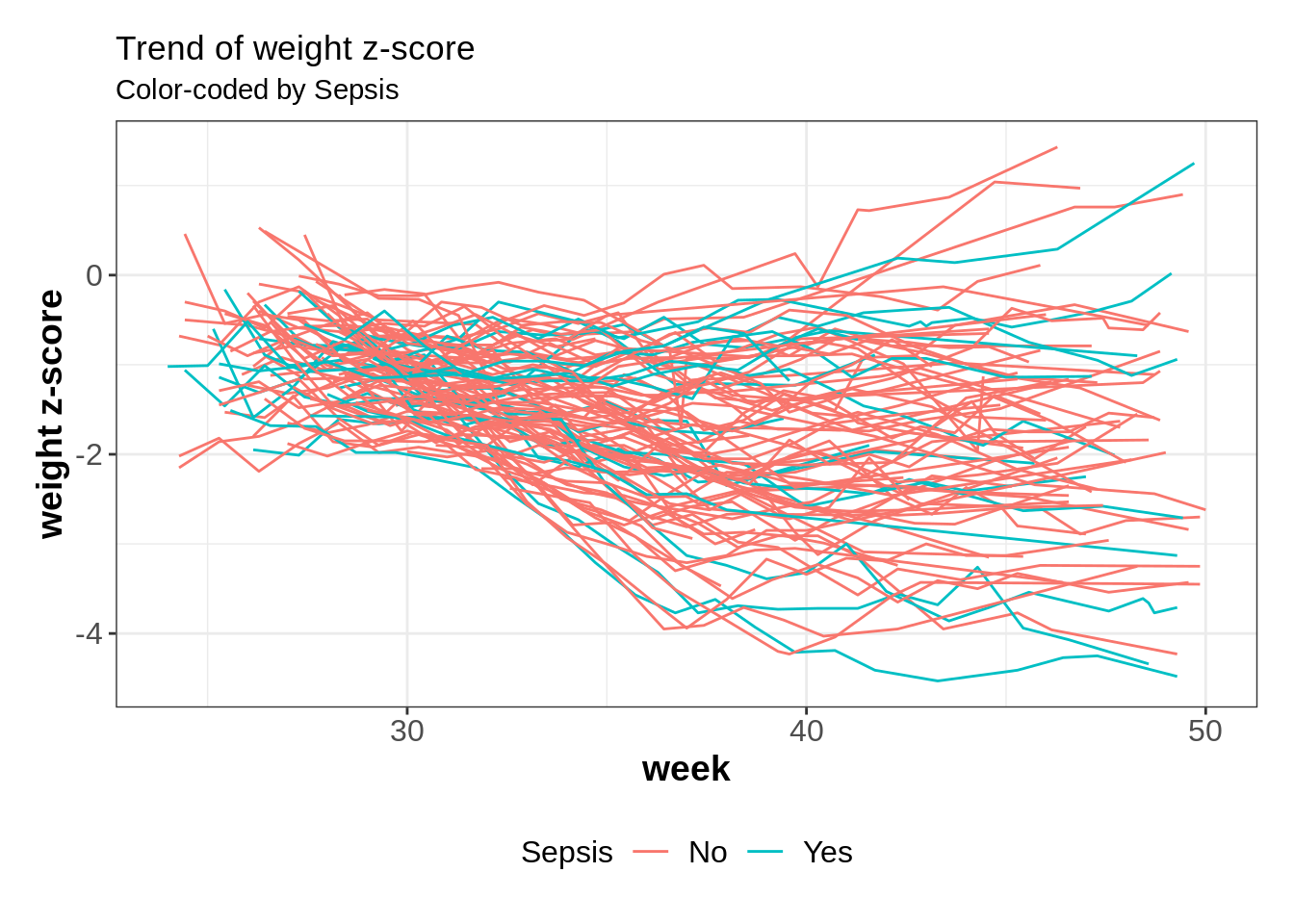
##

## $IVH



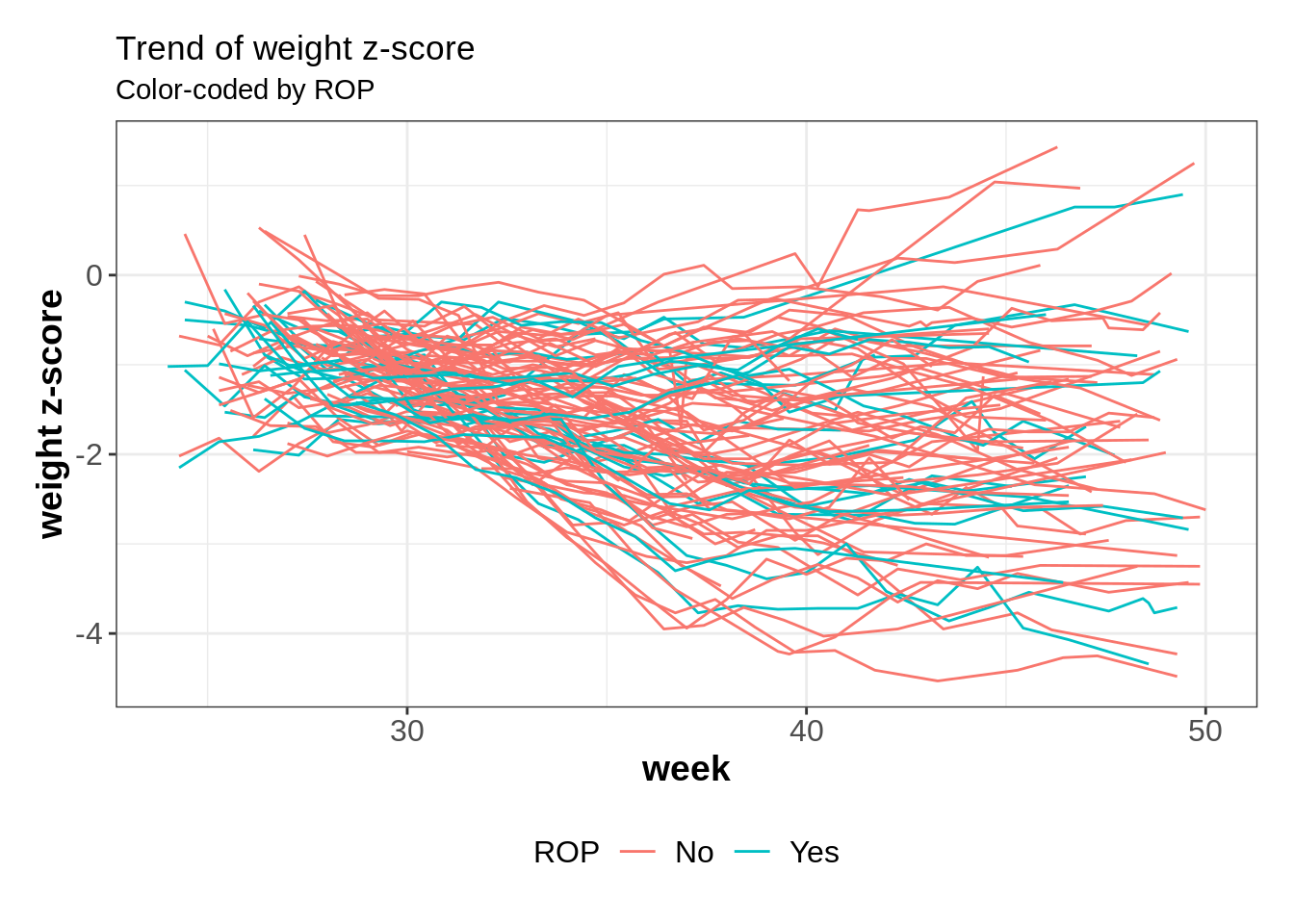
##

## $Sepsis



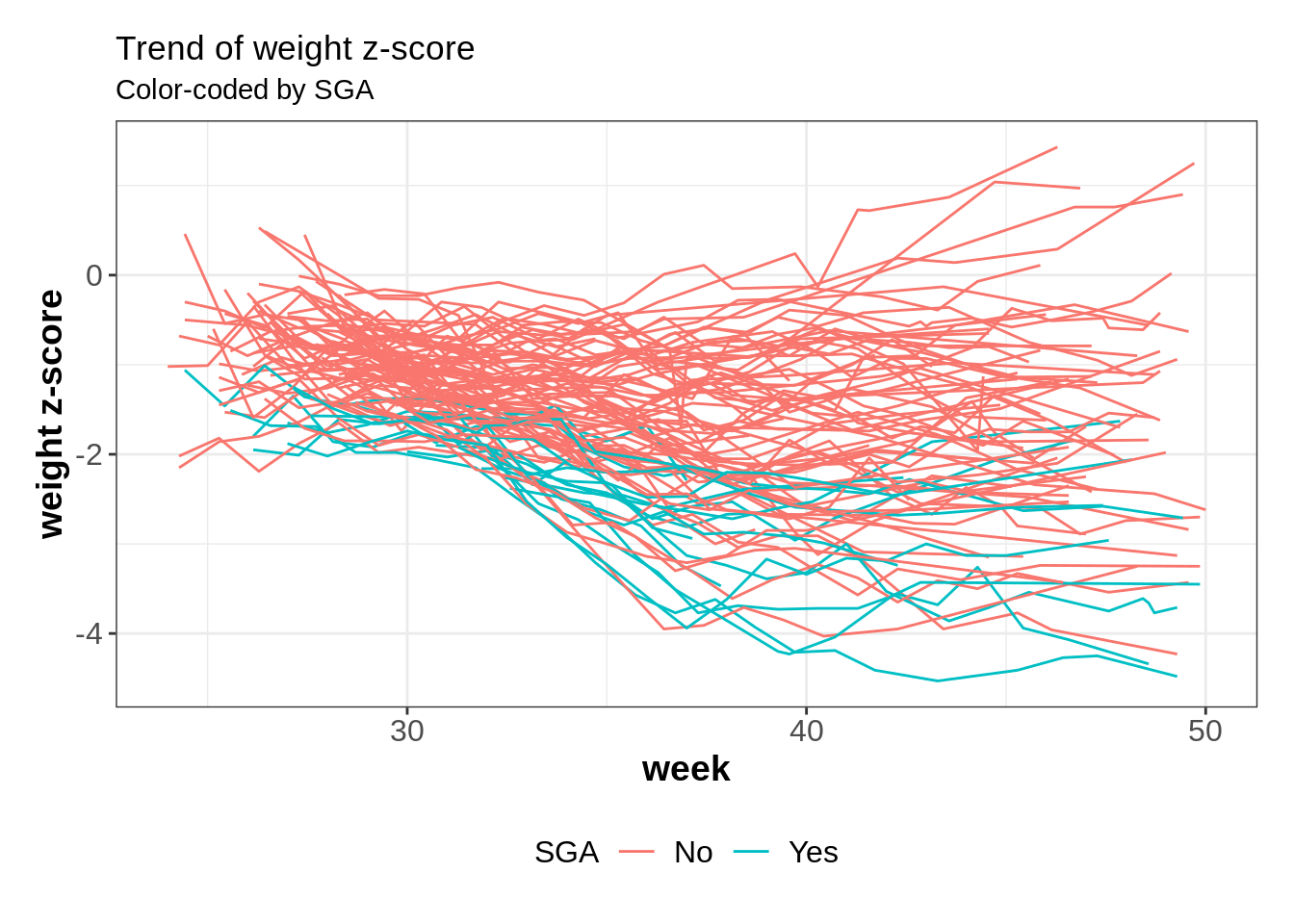
##

## $ROP



##

## $SGA



## 4. Grid search for time\_week shift constant

GA <- unique(weight$time\_week)

c.grid <- seq(min(GA), max(GA), 0.1)

cor.terms <- rep(NA, length(c.grid))

for (i in 1:length(c.grid)) {

cor.terms[i] <- cor((GA-c.grid[i]), (GA-c.grid[i])^2)

}

shift.constant <- c.grid[which.min(abs(cor.terms))]

cat("Shift time\_week by", shift.constant, "will minimize correlation between (time\_week) and (time\_week)^2")

## Shift time\_week by 37.3 will minimize correlation between (time\_week) and (time\_week)^2

cat("\nPearson r before shift:", cor(GA, GA^2))

##

## Pearson r before shift: 0.9960433

cat("\nPearson r after shift:", cor((GA-shift.constant), (GA-shift.constant)^2))

##

## Pearson r after shift: 0.009998993

## 5. Mixed-effects modeling with lme4 without considering covariates

require(lme4)

require(lmerTest)

require(optimx)

require(kableExtra)

## Loading required package: kableExtra

##

## Attaching package: 'kableExtra'

## The following object is masked from 'package:dplyr':

##

## group\_rows

long.df.scale <- long.df

long.df.scale[,"time\_week"] <- as.numeric(long.df.scale[,"time\_week"])

long.df.scale[,"time\_week"] <- long.df.scale[,"time\_week"] - shift.constant

formula\_list <- list()

formula\_list[[1]] <- "wt\_z\_score ~ 1 + time\_week + (time\_week | id)"

formula\_list[[2]] <- "wt\_z\_score ~ 1 + time\_week + I(time\_week^2) + (time\_week + I(time\_week^2) | id)"

formula\_list[[3]] <- "wt\_z\_score ~ pla\_insuff + time\_week + I(time\_week^2) + (time\_week + I(time\_week^2) | id)"

formula\_list[[4]] <- "wt\_z\_score ~ pla\_insuff + pla\_insuff:time\_week + time\_week + I(time\_week^2) + (time\_week + I(time\_week^2) | id)"

formula\_list[[5]] <- "wt\_z\_score ~ pla\_insuff + pla\_insuff:I(time\_week^2) + time\_week + I(time\_week^2) + (time\_week + I(time\_week^2) | id)"

formula\_list[[6]] <- "wt\_z\_score ~ pla\_insuff + pla\_insuff:time\_week + pla\_insuff:I(time\_week^2) + time\_week + I(time\_week^2) + (time\_week + I(time\_week^2) | id)"

formula\_list[[7]] <- "wt\_z\_score ~ birth\_weight + time\_week + I(time\_week^2) + (time\_week + I(time\_week^2) | id)"

formula\_list[[8]] <- "wt\_z\_score ~ birth\_weight + birth\_weight:time\_week + time\_week + I(time\_week^2) + (time\_week + I(time\_week^2) | id)"

formula\_list[[9]] <- "wt\_z\_score ~ birth\_weight + birth\_weight:I(time\_week^2) + time\_week + I(time\_week^2) + (time\_week + I(time\_week^2) | id)"

formula\_list[[10]] <- "wt\_z\_score ~ birth\_weight + birth\_weight:time\_week + birth\_weight:I(time\_week^2) + time\_week + I(time\_week^2) + (time\_week + I(time\_week^2) | id)"

formula\_list[[11]] <- "wt\_z\_score ~ SGA + time\_week + I(time\_week^2) + (time\_week + I(time\_week^2) | id)"

formula\_list[[12]] <- "wt\_z\_score ~ SGA + SGA:time\_week + time\_week + I(time\_week^2) + (time\_week + I(time\_week^2) | id)"

formula\_list[[13]] <- "wt\_z\_score ~ SGA + SGA:I(time\_week^2) + time\_week + I(time\_week^2) + (time\_week + I(time\_week^2) | id)"

formula\_list[[14]] <- "wt\_z\_score ~ SGA + SGA:time\_week + SGA:I(time\_week^2) + time\_week + I(time\_week^2) + (time\_week + I(time\_week^2) | id)"

summary <- list()

basic\_analysis <- list()

for (i in seq\_along(formula\_list)) {

formula <- as.formula(formula\_list[[i]])

lmer.analysis <- lmerTest::lmer(formula,

data = long.df.scale,

REML = FALSE,

control = lme4::lmerControl(optimizer = "optimx",

calc.derivs = FALSE,

optCtrl = list(method = "nlminb"))

)

summary[[i]] <- list(as.character(formula(lmer.analysis)),

as.numeric(summary(lmer.analysis)$AICtab["AIC"]),

as.numeric(summary(lmer.analysis)$AICtab["BIC"]),

as.numeric(summary(lmer.analysis)$AICtab["logLik"]),

as.numeric(summary(lmer.analysis)$AICtab["deviance"]),

as.numeric(summary(lmer.analysis)$AICtab["df.resid"]))

basic\_analysis[[i]] <- lmer.analysis

}

basic\_AIC <- data.frame()

for (i in seq\_along(1:length(formula\_list))) {

summary[[i]][[1]] <- as.character(summary[[i]][[1]])

summary[[i]][[1]] <- paste(summary[[i]][[1]][2], summary[[i]][[1]][1], summary[[i]][[1]][3])

for (j in seq\_along(1:length(summary[[i]]))) {

basic\_AIC[i,j] <- summary[[i]][[j]]

}

}

colnames(basic\_AIC) <- c("formula", "AIC", "BIC", "logLik", "deviance", "df\_resid")

folder.check(folder.name = "Results", getwd())

folder.check(folder.name = "mixed\_effects\_modeling", getwd())

write\_csv(basic\_AIC, "basic\_analysis.csv")

#for html markdown

kable(basic\_AIC[c(1,2,3,4,5,6),c(1:3)], row.names = FALSE) %>%

add\_header\_above(c("Placental insufficiency" = 3)) %>%

kable\_styling(bootstrap\_options = "striped", full\_width = T)

| **Placental insufficiency** | | |
| --- | --- | --- |
| **formula** | **AIC** | **BIC** |
| wt\_z\_score ~ 1 + time\_week + (time\_week | id) | 1330.3420 | 1361.9471 |
| wt\_z\_score ~ 1 + time\_week + I(time\_week^2) + (time\_week + I(time\_week^2) | id) | 713.6808 | 766.3561 |
| wt\_z\_score ~ pla\_insuff + time\_week + I(time\_week^2) + (time\_week + I(time\_week^2) | id) | 689.4996 | 747.4423 |
| wt\_z\_score ~ pla\_insuff + pla\_insuff:time\_week + time\_week + I(time\_week^2) + (time\_week + I(time\_week^2) | id) | 679.4182 | 742.6285 |
| wt\_z\_score ~ pla\_insuff + pla\_insuff:I(time\_week^2) + time\_week + I(time\_week^2) + (time\_week + I(time\_week^2) | id) | 690.8984 | 754.1087 |
| wt\_z\_score ~ pla\_insuff + pla\_insuff:time\_week + pla\_insuff:I(time\_week^2) + time\_week + I(time\_week^2) + (time\_week + I(time\_week^2) | id) | 681.0658 | 749.5437 |

kable(basic\_AIC[c(1,2,7:10),c(1:3)], row.names = FALSE) %>%

add\_header\_above(c("Birth weight" = 3)) %>%

kable\_styling(bootstrap\_options = "striped", full\_width = T)

| **Birth weight** | | |
| --- | --- | --- |
| **formula** | **AIC** | **BIC** |
| wt\_z\_score ~ 1 + time\_week + (time\_week | id) | 1330.3420 | 1361.9471 |
| wt\_z\_score ~ 1 + time\_week + I(time\_week^2) + (time\_week + I(time\_week^2) | id) | 713.6808 | 766.3561 |
| wt\_z\_score ~ birth\_weight + time\_week + I(time\_week^2) + (time\_week + I(time\_week^2) | id) | 645.5346 | 703.4774 |
| wt\_z\_score ~ birth\_weight + birth\_weight:time\_week + time\_week + I(time\_week^2) + (time\_week + I(time\_week^2) | id) | 637.6573 | 700.8676 |
| wt\_z\_score ~ birth\_weight + birth\_weight:I(time\_week^2) + time\_week + I(time\_week^2) + (time\_week + I(time\_week^2) | id) | 646.5258 | 709.7361 |
| wt\_z\_score ~ birth\_weight + birth\_weight:time\_week + birth\_weight:I(time\_week^2) + time\_week + I(time\_week^2) + (time\_week + I(time\_week^2) | id) | 638.9894 | 707.4673 |

kable(basic\_AIC[c(1,2,11:14),c(1:3)], row.names = FALSE) %>%

add\_header\_above(c("Small-for-gestataional age" = 3)) %>%

kable\_styling(bootstrap\_options = "striped", full\_width = T)

| **Small-for-gestataional age** | | |
| --- | --- | --- |
| **formula** | **AIC** | **BIC** |
| wt\_z\_score ~ 1 + time\_week + (time\_week | id) | 1330.3420 | 1361.9471 |
| wt\_z\_score ~ 1 + time\_week + I(time\_week^2) + (time\_week + I(time\_week^2) | id) | 713.6808 | 766.3561 |
| wt\_z\_score ~ SGA + time\_week + I(time\_week^2) + (time\_week + I(time\_week^2) | id) | 680.7296 | 738.6724 |
| wt\_z\_score ~ SGA + SGA:time\_week + time\_week + I(time\_week^2) + (time\_week + I(time\_week^2) | id) | 675.9549 | 739.1652 |
| wt\_z\_score ~ SGA + SGA:I(time\_week^2) + time\_week + I(time\_week^2) + (time\_week + I(time\_week^2) | id) | 680.1556 | 743.3659 |
| wt\_z\_score ~ SGA + SGA:time\_week + SGA:I(time\_week^2) + time\_week + I(time\_week^2) + (time\_week + I(time\_week^2) | id) | 676.1992 | 744.6770 |

## 6. Mixed-effects modeling with lme4 considering covariates

# packages

require(foreach)

## Loading required package: foreach

##

## Attaching package: 'foreach'

## The following objects are masked from 'package:purrr':

##

## accumulate, when

require(doParallel)

## Loading required package: doParallel

## Loading required package: iterators

## Loading required package: parallel

require(optimx)

require(parallel)

require(kableExtra)

basic\_variables\_pla <- c("id", "time\_week", "wt\_z\_score", "pla\_insuff")

basic\_variables\_bw <- c("time\_week", "wt\_z\_score", "birth\_wt")

nutrition\_variables <- c("calories\_7d", "aminoAcid\_7d", "protein\_fullEF", "calories\_fullEF")

comorbidity\_variables <- c("BPD", "IVH", "Sepsis", "ROP", "Abx\_days")

demographics\_variables <- c("Gender", "maternal\_obesity", "maternal\_smoking", "maternal\_race")

long.df.scale\_nutrition <- long.df.scale[,c(basic\_variables\_pla, nutrition\_variables)]

long.df.scale\_comorbidity <- long.df.scale[,c(basic\_variables\_pla, comorbidity\_variables)]

long.df.scale\_demographics <- long.df.scale[,c(basic\_variables\_pla, demographics\_variables)]

fm <- formula\_list[[4]]

## construct all possible combinations of covariates

var\_list\_demographics <- data.frame()

var\_list\_comorbidity <- data.frame()

var\_list\_nutrition <- data.frame()

fit <- function(variables, data) {

var\_list <- data.frame()

for (i in seq\_along(1:length(variables))) {

v <- list()

v <- combn(variables, i, simplify = TRUE)

v <- t(v)

v <- as.data.frame(v)

v <- unite(v, variables, sep = " + ")

var\_list <- rbind(var\_list, v)

}

for (i in seq\_along(1:length(var\_list$variables))) {

formula <- str\_replace(fm, "pla\_insuff \\+ pla\_insuff\\:time\_week \\+ ", paste0(var\_list$variables[i], " + pla\_insuff \\+ pla\_insuff\\:time\_week \\+ "))

var\_list$formula[i] <- formula

}

var\_list <- rbind(c("", fm), var\_list)

cl <- makePSOCKcluster(detectCores())

registerDoParallel(cl)

fit.all <- list()

fit.all <- foreach (i = seq\_along(1:nrow(var\_list)),

.combine = rbind,

.packages = c("lmerTest", "lme4", "optimx")) %dopar% {

formula <- var\_list$formula[i]

formula.formula <- as.formula(formula)

fit <- lmerTest::lmer(formula.formula,

data=data,

REML=F,

control = lmerControl(optimizer = "optimx", calc.derivs = FALSE,

optCtrl = list(method = "nlminb")))

return(list(formula(fit),

as.numeric(summary(fit)$AICtab["AIC"]),

as.numeric(summary(fit)$AICtab["BIC"]),

as.numeric(summary(fit)$AICtab["logLik"]),

as.numeric(summary(fit)$AICtab["deviance"]),

as.numeric(summary(fit)$AICtab["df.resid"]),

summary(fit)$coefficient,

fit))

}

for (i in seq\_along(1:nrow(var\_list))) {

fit.all[[i]] <- as.character(fit.all[[i]])

fit.all[[i]] <- paste(fit.all[[i]][2], fit.all[[i]][1],fit.all[[i]][3])

}

fit.all <- as.data.frame(fit.all)

colnames(fit.all) <- c("formula", "AIC", "BIC", "logLik", "deviance", "df\_resid", "coefficient", "results")

fit.all.results <- fit.all$results

fit.all$results <- NULL

fit.all$formula <- as.character(fit.all$formula)

var\_list <- left\_join(var\_list, fit.all, by = c("formula" = "formula"))

var\_list$AIC <- unlist(var\_list$AIC)

var\_list$BIC <- unlist(var\_list$BIC)

var\_list$logLik <- unlist(var\_list$logLik)

var\_list$deviance <- unlist(var\_list$deviance)

var\_list$df\_resid <- unlist(var\_list$df\_resid)

stopCluster(cl)

var\_list <- rownames\_to\_column(var\_list, var = "id")

var\_list$id <- as.numeric(var\_list$id)

return(list(var\_list, fit.all.results))

}

fit\_nutrition <- fit(nutrition\_variables, long.df.scale\_nutrition)

fit\_comorbidity <- fit(comorbidity\_variables, long.df.scale\_comorbidity)

fit\_demographics <- fit(demographics\_variables, long.df.scale\_demographics)

nutrition\_AIC <- fit\_nutrition[[1]]

comorbidity\_AIC <- fit\_comorbidity[[1]]

demographics\_AIC <- fit\_demographics[[1]]

nutrition\_results <- fit\_nutrition[[2]]

comorbidity\_results <- fit\_comorbidity[[2]]

demographics\_restuls <- fit\_demographics[[2]]

rm(fit\_nutrition)

rm(fit\_comorbidity)

rm(fit\_demographics)

folder.check(folder.name = "Results", getwd())

folder.check(folder.name = "mixed\_effects\_modeling", getwd())

write\_csv(nutrition\_AIC[,c(1:8)], "nutrition\_covariates.csv")

write\_csv(comorbidity\_AIC[,c(1:8)], "comorbidity\_covariates.csv")

write\_csv(demographics\_AIC[,c(1:8)], "demographics\_covariates.csv")

### 6.1 Nutrition covariates

#for html Markdown

kableExtra::kable(nutrition\_AIC[order(nutrition\_AIC$AIC),c(2,4,5)]) %>%

add\_header\_above(c("Variable combination - order by increasing AIC" = 4)) %>%

kable\_styling(bootstrap\_options = "striped", full\_width = T) %>%

scroll\_box(width = "100%", height = "300px")

| **Variable combination - order by increasing AIC** | | | |
| --- | --- | --- | --- |
|  | **variables** | **AIC** | **BIC** |
| 2 | calories\_7d | 665.7006 | 734.1784 |
| 7 | calories\_7d + protein\_fullEF | 667.2470 | 740.9923 |
| 6 | calories\_7d + aminoAcid\_7d | 667.3022 | 741.0476 |
| 8 | calories\_7d + calories\_fullEF | 667.5225 | 741.2679 |
| 14 | calories\_7d + protein\_fullEF + calories\_fullEF | 668.0562 | 747.0691 |
| 12 | calories\_7d + aminoAcid\_7d + protein\_fullEF | 668.8561 | 747.8690 |
| 13 | calories\_7d + aminoAcid\_7d + calories\_fullEF | 669.0935 | 748.1063 |
| 16 | calories\_7d + aminoAcid\_7d + protein\_fullEF + calories\_fullEF | 669.5730 | 753.8534 |
| 3 | aminoAcid\_7d | 677.9651 | 746.4429 |
| 1 |  | 679.4182 | 742.6285 |
| 9 | aminoAcid\_7d + protein\_fullEF | 679.9314 | 753.6768 |
| 10 | aminoAcid\_7d + calories\_fullEF | 679.9600 | 753.7053 |
| 5 | calories\_fullEF | 681.3447 | 749.8225 |
| 4 | protein\_fullEF | 681.4040 | 749.8819 |
| 15 | aminoAcid\_7d + protein\_fullEF + calories\_fullEF | 681.9292 | 760.9421 |
| 11 | protein\_fullEF + calories\_fullEF | 683.3421 | 757.0875 |

kableExtra::kable(nutrition\_AIC[order(nutrition\_AIC$BIC),c(2,4,5)]) %>%

add\_header\_above(c("Variable combination - order by increasing BIC" = 4)) %>%

kable\_styling(bootstrap\_options = "striped", full\_width = T) %>%

scroll\_box(width = "100%", height = "300px")

| **Variable combination - order by increasing BIC** | | | |
| --- | --- | --- | --- |
|  | **variables** | **AIC** | **BIC** |
| 2 | calories\_7d | 665.7006 | 734.1784 |
| 7 | calories\_7d + protein\_fullEF | 667.2470 | 740.9923 |
| 6 | calories\_7d + aminoAcid\_7d | 667.3022 | 741.0476 |
| 8 | calories\_7d + calories\_fullEF | 667.5225 | 741.2679 |
| 1 |  | 679.4182 | 742.6285 |
| 3 | aminoAcid\_7d | 677.9651 | 746.4429 |
| 14 | calories\_7d + protein\_fullEF + calories\_fullEF | 668.0562 | 747.0691 |
| 12 | calories\_7d + aminoAcid\_7d + protein\_fullEF | 668.8561 | 747.8690 |
| 13 | calories\_7d + aminoAcid\_7d + calories\_fullEF | 669.0935 | 748.1063 |
| 5 | calories\_fullEF | 681.3447 | 749.8225 |
| 4 | protein\_fullEF | 681.4040 | 749.8819 |
| 9 | aminoAcid\_7d + protein\_fullEF | 679.9314 | 753.6768 |
| 10 | aminoAcid\_7d + calories\_fullEF | 679.9600 | 753.7053 |
| 16 | calories\_7d + aminoAcid\_7d + protein\_fullEF + calories\_fullEF | 669.5730 | 753.8534 |
| 11 | protein\_fullEF + calories\_fullEF | 683.3421 | 757.0875 |
| 15 | aminoAcid\_7d + protein\_fullEF + calories\_fullEF | 681.9292 | 760.9421 |

### 6.2 Comorbidity covariates

kableExtra::kable(comorbidity\_AIC[order(comorbidity\_AIC$AIC),c(2,4,5)]) %>%

add\_header\_above(c("Variable combination - order by increasing AIC" = 4)) %>%

kable\_styling(bootstrap\_options = "striped", full\_width = T) %>%

scroll\_box(width = "100%", height = "300px")

| **Variable combination - order by increasing AIC** | | | |
| --- | --- | --- | --- |
|  | **variables** | **AIC** | **BIC** |
| 6 | Abx\_days | 674.0393 | 742.5172 |
| 16 | ROP + Abx\_days | 674.2833 | 748.0286 |
| 25 | IVH + ROP + Abx\_days | 674.5296 | 753.5425 |
| 13 | IVH + Abx\_days | 674.6278 | 748.3732 |
| 10 | BPD + Abx\_days | 675.8047 | 749.5500 |
| 15 | Sepsis + Abx\_days | 675.8470 | 749.5923 |
| 12 | IVH + ROP | 676.0726 | 749.8179 |
| 22 | BPD + ROP + Abx\_days | 676.0940 | 755.1069 |
| 26 | Sepsis + ROP + Abx\_days | 676.2406 | 755.2535 |
| 29 | BPD + IVH + ROP + Abx\_days | 676.4174 | 760.6978 |
| 24 | IVH + Sepsis + Abx\_days | 676.4195 | 755.4324 |
| 19 | BPD + IVH + Abx\_days | 676.4678 | 755.4807 |
| 31 | IVH + Sepsis + ROP + Abx\_days | 676.4883 | 760.7688 |
| 18 | BPD + IVH + ROP | 677.2554 | 756.2683 |
| 23 | IVH + Sepsis + ROP | 677.4665 | 756.4794 |
| 21 | BPD + Sepsis + Abx\_days | 677.6771 | 756.6899 |
| 3 | IVH | 677.6808 | 746.1587 |
| 5 | ROP | 678.0476 | 746.5254 |
| 30 | BPD + Sepsis + ROP + Abx\_days | 678.0766 | 762.3570 |
| 11 | IVH + Sepsis | 678.2206 | 751.9660 |
| 28 | BPD + IVH + Sepsis + Abx\_days | 678.3155 | 762.5959 |
| 32 | BPD + IVH + Sepsis + ROP + Abx\_days | 678.3960 | 767.9440 |
| 7 | BPD + IVH | 678.4479 | 752.1933 |
| 9 | BPD + ROP | 678.5204 | 752.2658 |
| 27 | BPD + IVH + Sepsis + ROP | 678.9356 | 763.2160 |
| 14 | Sepsis + ROP | 679.0908 | 752.8362 |
| 2 | BPD | 679.3993 | 747.8771 |
| 1 |  | 679.4182 | 742.6285 |
| 4 | Sepsis | 679.5089 | 747.9867 |
| 17 | BPD + IVH + Sepsis | 679.5640 | 758.5769 |
| 20 | BPD + Sepsis + ROP | 680.0704 | 759.0833 |
| 8 | BPD + Sepsis | 680.3587 | 754.1041 |

kableExtra::kable(comorbidity\_AIC[order(comorbidity\_AIC$BIC),c(2,4,5)]) %>%

add\_header\_above(c("Variable combination - order by increasing BIC" = 4)) %>%

kable\_styling(bootstrap\_options = "striped", full\_width = T) %>%

scroll\_box(width = "100%", height = "300px")

| **Variable combination - order by increasing BIC** | | | |
| --- | --- | --- | --- |
|  | **variables** | **AIC** | **BIC** |
| 6 | Abx\_days | 674.0393 | 742.5172 |
| 1 |  | 679.4182 | 742.6285 |
| 3 | IVH | 677.6808 | 746.1587 |
| 5 | ROP | 678.0476 | 746.5254 |
| 2 | BPD | 679.3993 | 747.8771 |
| 4 | Sepsis | 679.5089 | 747.9867 |
| 16 | ROP + Abx\_days | 674.2833 | 748.0286 |
| 13 | IVH + Abx\_days | 674.6278 | 748.3732 |
| 10 | BPD + Abx\_days | 675.8047 | 749.5500 |
| 15 | Sepsis + Abx\_days | 675.8470 | 749.5923 |
| 12 | IVH + ROP | 676.0726 | 749.8179 |
| 11 | IVH + Sepsis | 678.2206 | 751.9660 |
| 7 | BPD + IVH | 678.4479 | 752.1933 |
| 9 | BPD + ROP | 678.5204 | 752.2658 |
| 14 | Sepsis + ROP | 679.0908 | 752.8362 |
| 25 | IVH + ROP + Abx\_days | 674.5296 | 753.5425 |
| 8 | BPD + Sepsis | 680.3587 | 754.1041 |
| 22 | BPD + ROP + Abx\_days | 676.0940 | 755.1069 |
| 26 | Sepsis + ROP + Abx\_days | 676.2406 | 755.2535 |
| 24 | IVH + Sepsis + Abx\_days | 676.4195 | 755.4324 |
| 19 | BPD + IVH + Abx\_days | 676.4678 | 755.4807 |
| 18 | BPD + IVH + ROP | 677.2554 | 756.2683 |
| 23 | IVH + Sepsis + ROP | 677.4665 | 756.4794 |
| 21 | BPD + Sepsis + Abx\_days | 677.6771 | 756.6899 |
| 17 | BPD + IVH + Sepsis | 679.5640 | 758.5769 |
| 20 | BPD + Sepsis + ROP | 680.0704 | 759.0833 |
| 29 | BPD + IVH + ROP + Abx\_days | 676.4174 | 760.6978 |
| 31 | IVH + Sepsis + ROP + Abx\_days | 676.4883 | 760.7688 |
| 30 | BPD + Sepsis + ROP + Abx\_days | 678.0766 | 762.3570 |
| 28 | BPD + IVH + Sepsis + Abx\_days | 678.3155 | 762.5959 |
| 27 | BPD + IVH + Sepsis + ROP | 678.9356 | 763.2160 |
| 32 | BPD + IVH + Sepsis + ROP + Abx\_days | 678.3960 | 767.9440 |

### 6.3 Demographics covariates

kableExtra::kable(demographics\_AIC[order(demographics\_AIC$AIC),c(2,4,5)]) %>%

add\_header\_above(c("Variable combination - order by increasing AIC" = 4)) %>%

kable\_styling(bootstrap\_options = "striped", full\_width = T) %>%

scroll\_box(width = "100%", height = "300px")

| **Variable combination - order by increasing AIC** | | | |
| --- | --- | --- | --- |
|  | **variables** | **AIC** | **BIC** |
| 1 |  | 679.4182 | 742.6285 |
| 3 | maternal\_obesity | 681.0933 | 749.5711 |
| 2 | Gender | 681.4096 | 749.8874 |
| 4 | maternal\_smoking | 681.4112 | 749.8890 |
| 6 | Gender + maternal\_obesity | 683.0926 | 756.8380 |
| 9 | maternal\_obesity + maternal\_smoking | 683.0929 | 756.8383 |
| 7 | Gender + maternal\_smoking | 683.4044 | 757.1498 |
| 12 | Gender + maternal\_obesity + maternal\_smoking | 685.0923 | 764.1052 |
| 5 | maternal\_race | 688.1525 | 777.7005 |
| 10 | maternal\_obesity + maternal\_race | 689.8743 | 784.6897 |
| 11 | maternal\_smoking + maternal\_race | 690.1393 | 784.9548 |
| 8 | Gender + maternal\_race | 690.1398 | 784.9553 |
| 13 | Gender + maternal\_obesity + maternal\_race | 691.8738 | 791.9568 |
| 15 | maternal\_obesity + maternal\_smoking + maternal\_race | 691.8740 | 791.9569 |
| 14 | Gender + maternal\_smoking + maternal\_race | 692.1299 | 792.2129 |
| 16 | Gender + maternal\_obesity + maternal\_smoking + maternal\_race | 693.8736 | 799.2241 |

kableExtra::kable(demographics\_AIC[order(demographics\_AIC$BIC),c(2,4,5)]) %>%

add\_header\_above(c("Variable combination - order by increasing BIC" = 4)) %>%

kable\_styling(bootstrap\_options = "striped", full\_width = T) %>%

scroll\_box(width = "100%", height = "300px")

| **Variable combination - order by increasing BIC** | | | |
| --- | --- | --- | --- |
|  | **variables** | **AIC** | **BIC** |
| 1 |  | 679.4182 | 742.6285 |
| 3 | maternal\_obesity | 681.0933 | 749.5711 |
| 2 | Gender | 681.4096 | 749.8874 |
| 4 | maternal\_smoking | 681.4112 | 749.8890 |
| 6 | Gender + maternal\_obesity | 683.0926 | 756.8380 |
| 9 | maternal\_obesity + maternal\_smoking | 683.0929 | 756.8383 |
| 7 | Gender + maternal\_smoking | 683.4044 | 757.1498 |
| 12 | Gender + maternal\_obesity + maternal\_smoking | 685.0923 | 764.1052 |
| 5 | maternal\_race | 688.1525 | 777.7005 |
| 10 | maternal\_obesity + maternal\_race | 689.8743 | 784.6897 |
| 11 | maternal\_smoking + maternal\_race | 690.1393 | 784.9548 |
| 8 | Gender + maternal\_race | 690.1398 | 784.9553 |
| 13 | Gender + maternal\_obesity + maternal\_race | 691.8738 | 791.9568 |
| 15 | maternal\_obesity + maternal\_smoking + maternal\_race | 691.8740 | 791.9569 |
| 14 | Gender + maternal\_smoking + maternal\_race | 692.1299 | 792.2129 |
| 16 | Gender + maternal\_obesity + maternal\_smoking + maternal\_race | 693.8736 | 799.2241 |

## 7. Assessing interaction term between covariates and time\_week

formula\_cov <- list()

formula\_cov[[1]] <- "wt\_z\_score ~ calories\_7d + Abx\_days + pla\_insuff + time\_week + I(time\_week^2) + pla\_insuff:time\_week + (time\_week + I(time\_week^2) | id)"

formula\_cov[[2]] <- "wt\_z\_score ~ calories\_7d + calories\_7d:time\_week + Abx\_days + pla\_insuff + time\_week + I(time\_week^2) + pla\_insuff:time\_week + (time\_week + I(time\_week^2) | id)"

formula\_cov[[3]] <- "wt\_z\_score ~ calories\_7d + Abx\_days + Abx\_days:time\_week + pla\_insuff + time\_week + I(time\_week^2) + pla\_insuff:time\_week + (time\_week + I(time\_week^2) | id)"

summary\_cov <- list()

cov\_interaction\_analysis <- list()

for (i in seq\_along(formula\_cov)) {

formula <- as.formula(formula\_cov[[i]])

lmer.analysis <- lmerTest::lmer(formula,

data = long.df.scale,

REML = FALSE,

control = lme4::lmerControl(optimizer = "optimx",

calc.derivs = FALSE,

optCtrl = list(method = "nlminb"))

)

summary\_cov[[i]] <- list(as.character(formula(lmer.analysis)),

as.numeric(summary(lmer.analysis)$AICtab["AIC"]),

as.numeric(summary(lmer.analysis)$AICtab["BIC"]),

as.numeric(summary(lmer.analysis)$AICtab["logLik"]),

as.numeric(summary(lmer.analysis)$AICtab["deviance"]),

as.numeric(summary(lmer.analysis)$AICtab["df.resid"]))

cov\_interaction\_analysis[[i]] <- lmer.analysis

}

cov\_AIC <- data.frame()

for (i in seq\_along(1:length(formula\_cov))) {

summary\_cov[[i]][[1]] <- as.character(summary\_cov[[i]][[1]])

summary\_cov[[i]][[1]] <- paste(summary\_cov[[i]][[1]][2], summary\_cov[[i]][[1]][1], summary\_cov[[i]][[1]][3])

for (j in seq\_along(1:length(summary\_cov[[i]]))) {

cov\_AIC[i,j] <- summary\_cov[[i]][[j]]

}

}

colnames(cov\_AIC) <- c("formula", "AIC", "BIC", "logLik", "deviance", "df\_resid")

folder.check(folder.name = "Results", getwd())

folder.check(folder.name = "mixed\_effects\_modeling", getwd())

write\_csv(cov\_AIC, "covariate\_interaction\_analysis.csv")

kableExtra::kable(cov\_AIC[order(cov\_AIC$AIC),c(1:3)]) %>%

add\_header\_above(c("Various combination of covariate-by-time interaction - order by increasing AIC" = 4)) %>%

kable\_styling(bootstrap\_options = "striped", full\_width = T)

| **Various combination of covariate-by-time interaction - order by increasing AIC** | | | |
| --- | --- | --- | --- |
|  | **formula** | **AIC** | **BIC** |
| 1 | wt\_z\_score ~ calories\_7d + Abx\_days + pla\_insuff + time\_week + I(time\_week^2) + pla\_insuff:time\_week + (time\_week + I(time\_week^2) | id) | 665.4144 | 739.1597 |
| 3 | wt\_z\_score ~ calories\_7d + Abx\_days + Abx\_days:time\_week + pla\_insuff + time\_week + I(time\_week^2) + pla\_insuff:time\_week + (time\_week + I(time\_week^2) | id) | 666.5000 | 745.5129 |
| 2 | wt\_z\_score ~ calories\_7d + calories\_7d:time\_week + Abx\_days + pla\_insuff + time\_week + I(time\_week^2) + pla\_insuff:time\_week + (time\_week + I(time\_week^2) | id) | 667.3888 | 746.4017 |

kableExtra::kable(cov\_AIC[order(cov\_AIC$BIC),c(1:3)]) %>%

add\_header\_above(c("Various combination of covariate-by-time interaction - order by increasing BIC" = 4)) %>%

kable\_styling(bootstrap\_options = "striped", full\_width = T)

| **Various combination of covariate-by-time interaction - order by increasing BIC** | | | |
| --- | --- | --- | --- |
|  | **formula** | **AIC** | **BIC** |
| 1 | wt\_z\_score ~ calories\_7d + Abx\_days + pla\_insuff + time\_week + I(time\_week^2) + pla\_insuff:time\_week + (time\_week + I(time\_week^2) | id) | 665.4144 | 739.1597 |
| 3 | wt\_z\_score ~ calories\_7d + Abx\_days + Abx\_days:time\_week + pla\_insuff + time\_week + I(time\_week^2) + pla\_insuff:time\_week + (time\_week + I(time\_week^2) | id) | 666.5000 | 745.5129 |
| 2 | wt\_z\_score ~ calories\_7d + calories\_7d:time\_week + Abx\_days + pla\_insuff + time\_week + I(time\_week^2) + pla\_insuff:time\_week + (time\_week + I(time\_week^2) | id) | 667.3888 | 746.4017 |

## 8. Table and plot

require(sjPlot)

## Loading required package: sjPlot

## Learn more about sjPlot with 'browseVignettes("sjPlot")'.

folder.check(folder.name = "Results", getwd())

folder.check(folder.name = "Tables and plots", getwd())

fit.plot.pla <- basic\_analysis[[4]]

fit.plot.bw <- basic\_analysis[[8]]

# Plotting placental insufficiency-by-time interaction

pdf(file = "plot\_pla.pdf", onefile = TRUE, width = 8, height = 6)

k <- plot\_model(fit.plot.pla, show.values = TRUE,

title = "Mixed-effects modeling - coefficient plot",

auto.label = FALSE,

value.offset = 0.3,

axis.title = c("estimates", "variable"),

vline.color = "darkorchid",

order.terms = c(1,4,2,3),

digits = 3)

l <- plot\_model(fit.plot.pla, type = "pred",

terms = c("time\_week", "pla\_insuff"),

title = "Predicted values of wt z score by time")

## Model contains polynomial or cubic / quadratic terms. Consider using `terms="time\_week [all]"` to get smooth plots. See also package-vignette 'Marginal Effects at Specific Values'.

print(k + theme\_bw())

print(l + theme\_bw())

dev.off()

## png

## 2

# Plotting birth weight-by-time interaction

pdf(file = "plot\_bw.pdf", onefile = TRUE, width = 8, height = 6)

m <- plot\_model(fit.plot.bw, show.values = TRUE,

title = "Mixed-effects modeling - coefficient plot",

auto.label = FALSE,

value.offset = 0.3,

axis.title = c("estimates", "variable"),

vline.color = "darkorchid",

order.terms = c(1,4,2,3),

digits = 3)

n <- plot\_model(fit.plot.bw, type = "pred",

terms = c("time\_week", "birth\_weight"),

title = "Predicted values of wt z score by time")

## Model contains polynomial or cubic / quadratic terms. Consider using `terms="time\_week [all]"` to get smooth plots. See also package-vignette 'Marginal Effects at Specific Values'.

print(m + theme\_bw())

print(n + theme\_bw())

dev.off()

## png

## 2

### 8.1 placental insufficeincy-by-time interaction

require(sjPlot)

# for html Markdown

tab\_model(fit.plot.pla, show.icc = FALSE, auto.label = FALSE,

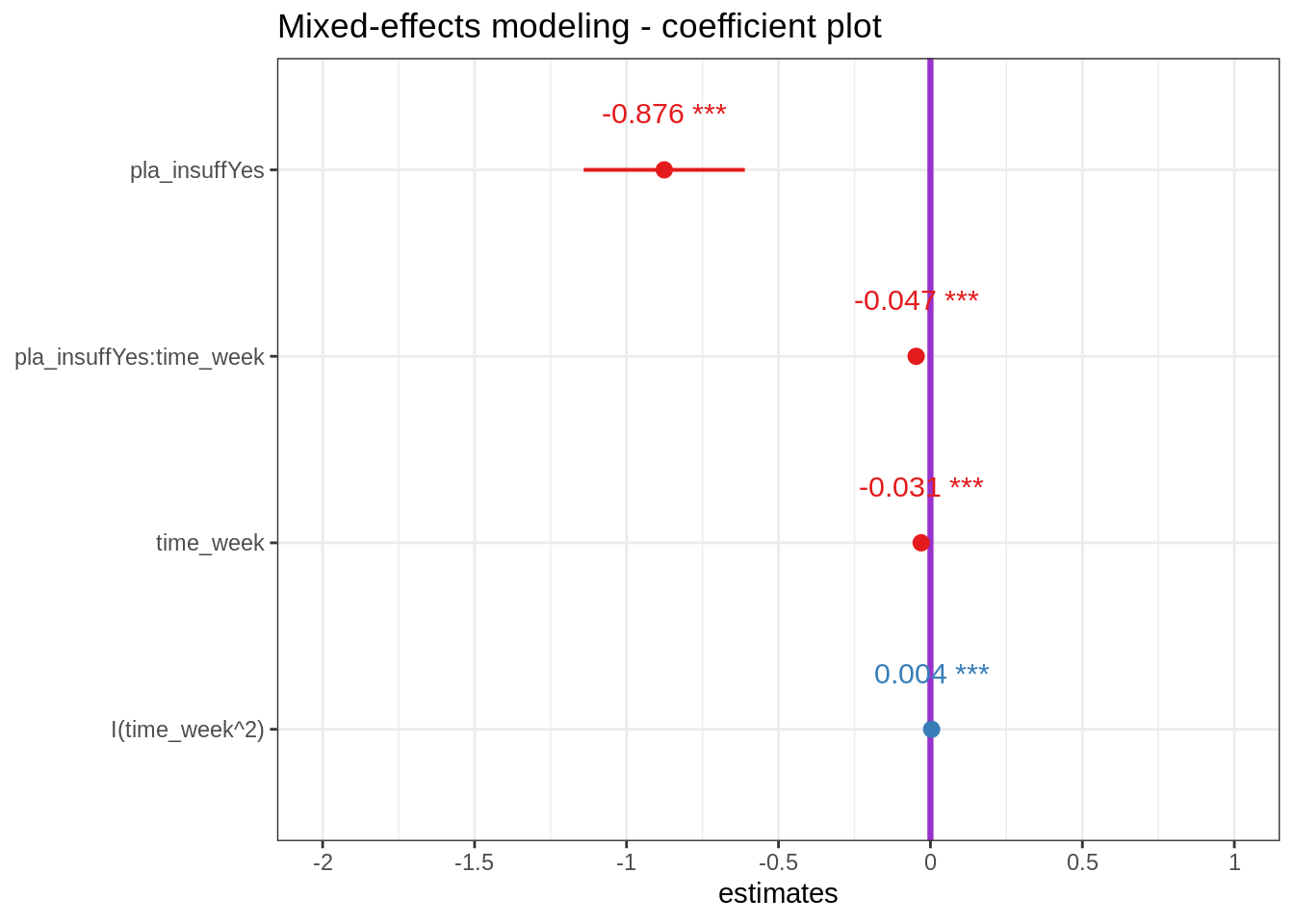
title = "Mixed-effects modeling - coefficient table",

file = "table\_pla.html",

digits = 3)

|  |  |  |  |
| --- | --- | --- | --- |
| **Mixed-effects modeling - coefficient table** | | | |
|  | **wt\_z\_score** | | |
| *Predictors* | *Estimates* | *CI* | *p* |
| (Intercept) | -1.441 | -1.615 – -1.267 | **<0.001** |
| pla\_insuffYes | -0.876 | -1.141 – -0.611 | **<0.001** |
| time\_week | -0.031 | -0.046 – -0.015 | **<0.001** |
| I(time\_week^2) | 0.004 | 0.003 – 0.005 | **<0.001** |
| pla\_insuffYes:time\_week | -0.047 | -0.073 – -0.021 | **0.001** |
| **Random Effects** | | | |
| σ2 | 0.05 | | |
| τ00 id | 0.48 | | |
| τ11 id.time\_week | 0.00 | | |
| τ11 id.I(time\_week^2) | 0.00 | | |
| ρ01 | 0.70 | | |
|  | -0.48 | | |
| N id | 91 | | |
| Observations | 1433 | | |
| Marginal R2 / Conditional R2 | 0.364 / 0.935 | | |

print(k + theme\_bw())



print(l + theme\_bw())



### 8.2 birth weight-by-time interaction

require(sjPlot)

#for html Markdown

tab\_model(fit.plot.bw, show.icc = FALSE, auto.label = FALSE,

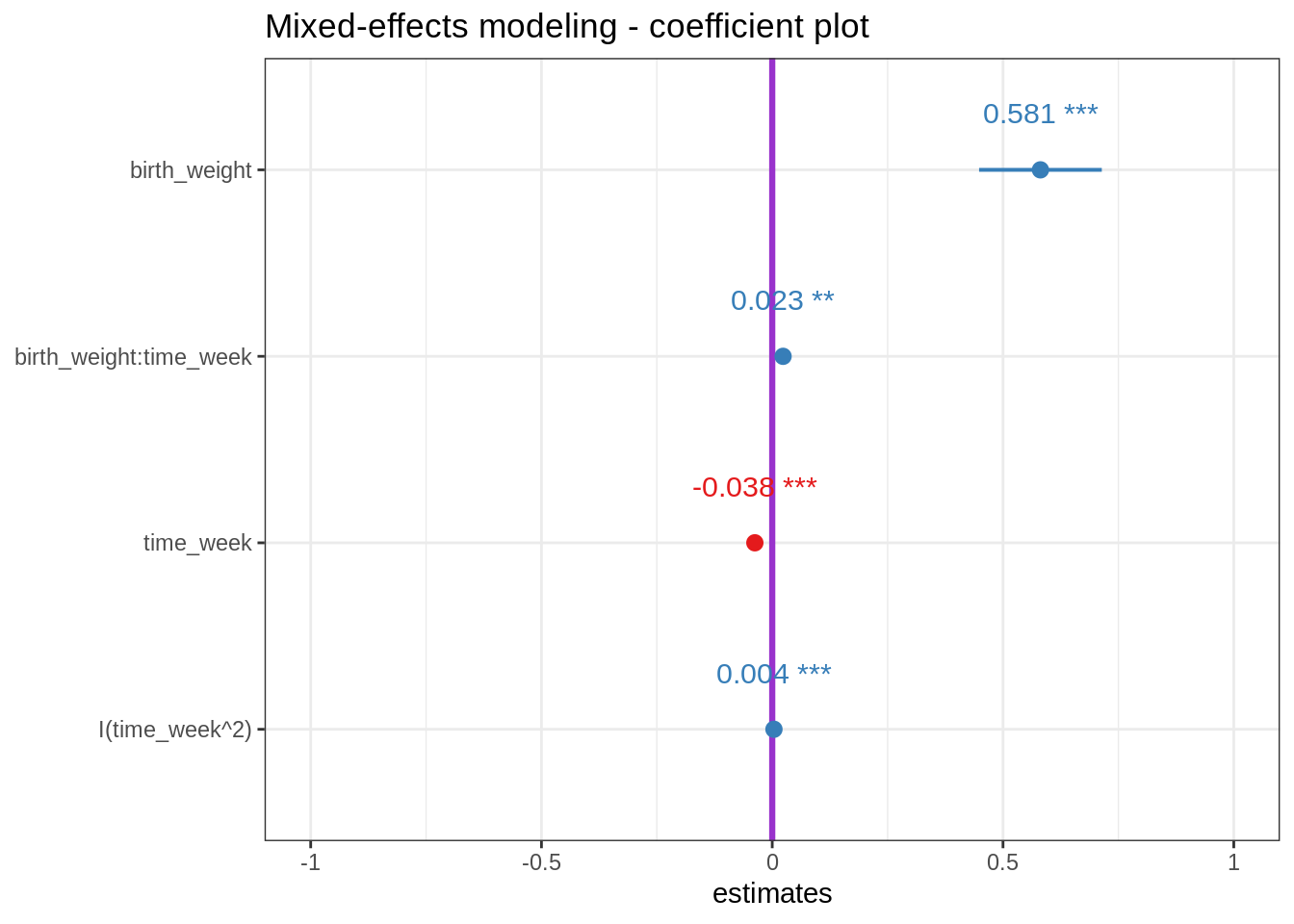
title = "Mixed-effects modeling - coefficient table",

file = "table\_bw.html",

digits = 3)

|  |  |  |  |
| --- | --- | --- | --- |
| **Mixed-effects modeling - coefficient table** | | | |
|  | **wt\_z\_score** | | |
| *Predictors* | *Estimates* | *CI* | *p* |
| (Intercept) | -1.518 | -1.660 – -1.377 | **<0.001** |
| birth\_weight | 0.581 | 0.448 – 0.714 | **<0.001** |
| time\_week | -0.038 | -0.051 – -0.024 | **<0.001** |
| I(time\_week^2) | 0.004 | 0.003 – 0.005 | **<0.001** |
| birth\_weight:time\_week | 0.023 | 0.009 – 0.038 | **0.002** |
| **Random Effects** | | | |
| σ2 | 0.05 | | |
| τ00 id | 0.39 | | |
| τ11 id.time\_week | 0.00 | | |
| τ11 id.I(time\_week^2) | 0.00 | | |
| ρ01 | 0.74 | | |
|  | -0.49 | | |
| N id | 91 | | |
| Observations | 1433 | | |
| Marginal R2 / Conditional R2 | 0.461 / 0.935 | | |

print(m + theme\_bw())



print(n + theme\_bw())



## 9. Session Info

folder.check(folder.name = "Results", getwd())

sink(file = paste0(getwd(), "/seesionInfo.txt"))

sessionInfo()

## R version 3.6.0 (2019-04-26)

## Platform: x86\_64-pc-linux-gnu (64-bit)

## Running under: Ubuntu 18.04.2 LTS

##

## Matrix products: default

## BLAS: /usr/lib/x86\_64-linux-gnu/blas/libblas.so.3.7.1

## LAPACK: /usr/lib/x86\_64-linux-gnu/lapack/liblapack.so.3.7.1

##

## locale:

## [1] LC\_CTYPE=en\_US.UTF-8 LC\_NUMERIC=C

## [3] LC\_TIME=en\_US.UTF-8 LC\_COLLATE=en\_US.UTF-8

## [5] LC\_MONETARY=en\_US.UTF-8 LC\_MESSAGES=en\_US.UTF-8

## [7] LC\_PAPER=en\_US.UTF-8 LC\_NAME=C

## [9] LC\_ADDRESS=C LC\_TELEPHONE=C

## [11] LC\_MEASUREMENT=en\_US.UTF-8 LC\_IDENTIFICATION=C

##

## attached base packages:

## [1] parallel grid stats graphics grDevices utils datasets

## [8] methods base

##

## other attached packages:

## [1] sjPlot\_2.6.3 doParallel\_1.0.14 iterators\_1.0.10

## [4] foreach\_1.4.4 kableExtra\_1.1.0 PropCIs\_0.3-0

## [7] effsize\_0.7.4 optimx\_2018-7.10 ggpubr\_0.2

## [10] magrittr\_1.5 vcd\_1.4-4 psych\_1.8.12

## [13] lmerTest\_3.1-0 lme4\_1.1-21 Matrix\_1.2-17

## [16] forcats\_0.4.0 stringr\_1.4.0 dplyr\_0.8.0.1

## [19] purrr\_0.3.2 readr\_1.3.1 tidyr\_0.8.3

## [22] tibble\_2.1.1 ggplot2\_3.1.1 tidyverse\_1.2.1

##

## loaded via a namespace (and not attached):

## [1] nlme\_3.1-139 lubridate\_1.7.4 RColorBrewer\_1.1-2

## [4] insight\_0.3.0 webshot\_0.5.1 httr\_1.4.0

## [7] numDeriv\_2016.8-1 tools\_3.6.0 TMB\_1.7.15

## [10] backports\_1.1.4 R6\_2.4.0 sjlabelled\_1.0.17

## [13] lazyeval\_0.2.2 colorspace\_1.4-1 withr\_2.1.2

## [16] tidyselect\_0.2.5 gridExtra\_2.3 mnormt\_1.5-5

## [19] emmeans\_1.3.4 compiler\_3.6.0 performance\_0.1.0

## [22] cli\_1.1.0 rvest\_0.3.3 xml2\_1.2.0

## [25] labeling\_0.3 bayestestR\_0.1.0 scales\_1.0.0

## [28] mvtnorm\_1.0-10 lmtest\_0.9-37 digest\_0.6.18

## [31] foreign\_0.8-70 minqa\_1.2.4 rmarkdown\_1.12

## [34] pkgconfig\_2.0.2 htmltools\_0.3.6 highr\_0.8

## [37] rlang\_0.3.4 readxl\_1.3.1 rstudioapi\_0.10

## [40] generics\_0.0.2 zoo\_1.8-5 jsonlite\_1.6

## [43] Rcpp\_1.0.1 munsell\_0.5.0 stringi\_1.4.3

## [46] yaml\_2.2.0 snakecase\_0.9.2 MASS\_7.3-51.1

## [49] plyr\_1.8.4 sjmisc\_2.7.9 crayon\_1.3.4

## [52] lattice\_0.20-38 ggeffects\_0.10.0 haven\_2.1.0

## [55] cowplot\_0.9.4 splines\_3.6.0 sjstats\_0.17.4

## [58] hms\_0.4.2 knitr\_1.22 pillar\_1.3.1

## [61] boot\_1.3-20 estimability\_1.3 codetools\_0.2-16

## [64] glue\_1.3.1 evaluate\_0.13 modelr\_0.1.4

## [67] nloptr\_1.2.1 cellranger\_1.1.0 gtable\_0.3.0

## [70] assertthat\_0.2.1 xfun\_0.6 xtable\_1.8-3

## [73] broom\_0.5.2 coda\_0.19-2 viridisLite\_0.3.0

## [76] glmmTMB\_0.2.3 ellipsis\_0.1.0

sink()