

# Randomized blood pressure reduction trial

## Appendix

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# 1. Descriptive analysis

## Data cleaning

### Data errors

No missing values

```
# Missing value count  
colSums(is.na(data))
```

No duplicates

```
# Check for duplicate rows  
data[duplicated(data),]
```

### Adherence to the treatment

```
# Summary statistics  
summary(data$comp)  
# Compliance by treatment group  
boxplot(data$comp~data$treatment, data=data,  
        main="Compliance by treatment group",  
        xlab="Treatment group", ylab="Compliance")  
  
# Display observations with a compliance below 80 %  
data <- data[order(data$comp),]  
data_low_dose <- data[data$comp < 0.8,]  
print(data_low_dose)  
# Apply 80 % adherence rule  
data <- data[data$comp >= 0.8,]  
data_raw <- data_raw[data_raw$comp >= 0.8,]
```

### Selection criteria

```
# Diastolic bloodpressure below 90 for a run-in period measure  
data[data$dbp1 < 90 | data$dbp2 < 90 | data$dbp3 < 90,]  
# Remove the outlier of 66 for the 3rd measurement  
data = data[data$dbp3 != 66,]  
# Subsets by treatment group  
treat1 <- data[data$treatment == "Treatment 1",]  
placebo <- data[data$treatment == "Placebo",]  
treat3 <- data[data$treatment == "Treatment 1",]
```

---

## Study population

Based on the Shapiro-Wilk test, weight is normally distributed, the other variables not. Based on the result either the mean or median is chosen to be used in the characteristics of the study population table.

```

# Test the normality of the variables
shapiro.test(treat1$dbpdif)
shapiro.test(placebo$dbpdif)
shapiro.test(treat3$dbpdif)

shapiro.test(data$dbp3)
shapiro.test(data$dbp2)
shapiro.test(data$dbp1)
shapiro.test(data$age)
shapiro.test(data$weight)

# Characteristics of the study population table (assuming normality)
CreateTableOne(data=data)
# By treatment group
mytable(treatment~.,data=data)
CreateTableOne(vars=c("age", "weight", "dose", "dbp1", "dbp2",
                      "dbp3", "dbp_end", "dbpdif", "sex"),
              strata="treatment", data=data, factorVars="")

# Complete descriptives
describe(data)
describe.by(data, data$treatment)

# Amount of removed observations
one <- nrow(original[original$trt==1,]) -
  nrow(data[data$treatment=="Treatment 1",])
two <- nrow(original[original$trt==2,]) -
  nrow(data[data$treatment=="Placebo",])
three <- nrow(original[original$trt==3,]) -
  nrow(data[data$treatment=="Treatment 3",])
one
two
three
one / nrow(original[original$trt==1,])
two / nrow(original[original$trt==2,])
three / nrow(original[original$trt==3,])
(nrow(original) - nrow(data)) / nrow(original)

```

## Evaluating assumptions

### Comparability of the groups

Based on the previously mentioned descriptive statistics the groups are comparable except for the gender distribution.

### Normality

The final DBP measurement and the DBP difference are normally distributed, but the run-in period DBP measurements are not. Due to the limited size of the sample and the difference

between the run-in and final DBP measurement, the result cannot be trusted. Age is not normally distributed, but weight is.

```
# Check normality
par(mfrow=c(3,1))
qqnorm(treat1$dbpdif, main="DBP difference treatment group 1")
qqline(treat1$dbpdif)
qqnorm(placebo$dbpdif, main="DBP difference placebo")
qqline(placebo$dbpdif)
qqnorm(treat3$dbpdif, main="DBP difference treatment group 3")
qqline(treat3$dbpdif)

par(mfrow=c(1,1))

qqnorm(treat1$dbp_end, main="Final DBP treatment group 1")
qqline(treat1$dbp_end)

qqnorm(placebo$dbp_end, main="Final DBP placebo")
qqline(placebo$dbp_end)

qqnorm(treat3$dbp_end, main="Final DBP treatment group 3")
qqline(treat3$dbp_end)

qqnorm(data$dbp3, main="3rd DBP measure");qqline(data$dbp3)

qqnorm(data$age, main="Age");qqline(data$age)

qqnorm(data$weight, main="Weight");qqline(data$weight)
```

## Independence

The observations are independent from one another.

Examining relations between variables:

```
corrplot.mixed(cor(data_raw %>%
  select(sex, weight, age, comp, dbp_mean, dbpdif, dbp_end)),
  lower="number", upper="ellipse", tl.pos="d",
  title = '\n Correlations between variables for all observations')

# By treatment group
corrplot.mixed(cor(data_raw[data_raw$treatment == 1,] %>%
  select(sex, weight, age, comp, dbp_mean, dbpdif, dbp_end)),
  lower="number", upper="ellipse", tl.pos="d",
  title = '\n Correlations between variables for Treatment 1')

corrplot.mixed(cor(data_raw[data_raw$treatment == 2,] %>%
  select(sex, weight, age, comp, dbp_mean, dbpdif, dbp_end)),
  lower="number", upper="ellipse", tl.pos="d",
  title = '\n Correlations between variables for Placebo')

corrplot.mixed(cor(data_raw[data_raw$treatment == 3,] %>%
  select(sex, weight, age, comp, dbp_mean, dbpdif, dbp_end)),
```

```
lower="number", upper="ellipse", tl.pos="d",  
title = '\n Correlations between variables for Treatment 3')
```

## Outliers

There are outliers for the DBP3 measure. In the 3rd treatment group, the final DBP has outliers as well as for DBP difference. There are no outliers in the placebo group for the final DBP measure nor the DBP difference.

```
# Boxplot to check for outliers  
boxplot(data$dbp3, main="Run-in DBP measure 3", ylab="DBP")  
  
boxplot(data$dbpdif~data$treatment, main="DBP difference by group", ylab="DBP")  
  
boxplot(data$dbp_end~data$treatment, main="Final DBP measure by group")
```

## Homogeneity of variances

This was only tested for groups 2 and 3, as only these groups are used in the formal analysis.

```
# Creating a dataset with only treatment 2 and 3  
data23 <- data[which(data$treatment != "Treatment 1"),]  
data23$treatment <- droplevels(data23$treatment)  
  
# Comparing the variances of both groups  
with(data23, tapply(dbpdif, treatment, function(x) round(var(x), digits=2)))  
  
# Formal testing via the F-ratio test  
var.test(dbpdif~treatment, data = data23)
```

The variances seem comparable and the formal test cannot detect a difference

## Sample size

```
# Sample size for each treatment group, for total population, split by gender  
summary(data$treatment)  
summary(data$treatment[data$sex == "Male"])  
summary(data$treatment[data$sex == "Female"])
```

The samples in the total study population are sufficiently large. When split by gender, the groups get somewhat small.

---

## 2. Descriptives for the research question

```

# Columns to rows
data_pop <- melt(data, id.vars='treatment',
                 measure.vars=c('dbp3', 'dbp_end', 'dbpdif'))
data_pop$ID <- seq.int(nrow(data))
# Custom summary table using dplyr
summarycols <-
  list(
    "treatment1" =
      list(
        "mean (sd)" = ~ qwraps2::mean_sd(
          data_pop[data_pop$treatment == "Treatment 1" & data_pop$variable ==
variable,]$value),
        "min" = ~ min(data_pop[data_pop$treatment == "Treatment 1" & data_pop
$variable == variable,]$value),
        "25th" = ~ quantile(data_pop[data_pop$treatment == "Treatment 1" & da
ta_pop$variable == variable,]$value, .25),
        "Median" = ~ median(data_pop[data_pop$treatment == "Treatment 1" & da
ta_pop$variable == variable,]$value),
        "75th" = ~ quantile(data_pop[data_pop$treatment == "Treatment 1" & da
ta_pop$variable == variable,]$value, .75),
        "max" = ~ max(data_pop[data_pop$treatment == "Treatment 1" & data_pop
$variable == variable,]$value)
      ),
    "placebo" =
      list(
        "mean (sd)" = ~ qwraps2::mean_sd(data_pop[data_pop$treatment == "Plac
ebo" & data_pop$variable == variable,]$value),
        "min" = ~ min(data_pop[data_pop$treatment == "Placebo" & data_pop$var
iable == variable,]$value),
        "25th" = ~ quantile(data_pop[data_pop$treatment == "Placebo" & data_p
op$variable == variable,]$value, .25),
        "Median" = ~ median(data_pop[data_pop$treatment == "Placebo" & data_p
op$variable == variable,]$value),
        "75th" = ~ quantile(data_pop[data_pop$treatment == "Placebo" & data_p
op$variable == variable,]$value, .75),
        "max" = ~ max(data_pop[data_pop$treatment == "Placebo" & data_pop$var
iable == variable,]$value)
      ),
    "treatment3" =
      list(
        "mean (sd)" = ~ qwraps2::mean_sd(data_pop[data_pop$treatment == "Trea
tment 3" & data_pop$variable == variable,]$value),
        "min" = ~ min(data_pop[data_pop$treatment == "Treatment 3" & data_pop
$variable == variable,]$value),
        "25th" = ~ quantile(data_pop[data_pop$treatment == "Treatment 3" & da
ta_pop$variable == variable,]$value, .25),
        "Median" = ~ median(data_pop[data_pop$treatment == "Treatment 3" & da
ta_pop$variable == variable,]$value),
        "75th" = ~ quantile(data_pop[data_pop$treatment == "Treatment 3" & da
ta_pop$variable == variable,]$value, .75),

```

```

      "max" = ~ max(data_pop[data_pop$treatment == "Treatment 3" & data_pop
$variable == variable,]$value)
    )
  )
print(summary_table(dplyr::group_by(data_pop, variable), summarycols),
      rtitle = "Summary Statistics",
      cnames = c("dbp3", "dbp_end", "dbpdif"))

```

At first glance we can see that the groups had a similar bp at intake visits, but the treatment groups(1,3) had a lower bp than before at the final visit. The control group(2) remained more or less stable throughout the study. We can see this as a first indication that the treatment groups did achieve a lower bp.

```

# Boxplot: difference between treatment groups
par(mfrow=c(1,3), mar=c(2.5, 2, 2, 1))
plot(data$treatment, data$dbp3, ylim=c(70, 130), levels=c("Treatment 1", "Pla
cebo", "Treatment 3"))
title('DBP at visit 3')
plot(data$treatment, data$dbp_end,
      ylim=c(70, 130))
title('Final DBP')
plot(data$treatment, data$dbpdif)
title('DBP difference')

par(mfrow=c(1,1))

# Histogram comparison of the final dbp by treatment group
ggplot(data, aes(x=dbp_end)) +
  geom_histogram() +
  facet_grid(~treatment) +
  stat_bin(binwidth=5) +
  ggtitle("Final DBP measeurement frequencies by treatment group") +
  labs(x="DBP")

```

Checking the consistency of the decrease in dbp measurements for the 3rd treatment group: not all measures follow the trend

```

# Columns to rows
data_res <- melt(data, id.vars='treatment', measure.vars=c('dbp3', 'dbp_end'))
data_res$ID <- seq.int(nrow(data))
# Profile plot
ggplot(data_res[data_res$treatment == "Treatment 3",], aes(x=variable, y=valu
e, group=ID)) +
  geom_point() +
  geom_line() +
  ggtitle("DBP evolution before and after the experiment for the 3rd treatmen
t group") +
  labs(y="DBP")

```



---

### 3. Formal primary analysis

#### Parametric

Welch Two Sample t-test H0: The difference in diastolic blood pressure is equal in both the third treatment group and the placebo group. Ho:  $\text{mean}(\text{third treatment}) - \text{mean}(\text{placebo}) = \text{diff} = 0$  Ha: The difference in diastolic blood pressure is bigger in the third treatment group compared to the placebo group. Ha:  $\text{mean}(\text{third treatment}) - \text{mean}(\text{placebo}) = \text{diff} \neq 0$

```
t.test(dbpdif~treatment, data = data23, mu=0, alternative = "greater", conf=0.95, var.eq=T, paired=F)
```

The difference between DBP measures is greater for treatment 3. The diastolic blood pressure decreases significantly more when using Treatment 3. Assumptions: scale of measurement, random sampling, normality of data distribution, adequacy of sample size -> Scale is not that large, not sure about normal distribution of both populations

#### Non-parametric

Mann-Whitney U test (because we are not sure about the normal distribution of both populations) Only one assumption, Samples are independent and randomly drawn

```
wilcox.test(formula = dbpdif~treatment, data = data23, mu = 0, alt="greater", correct= TRUE, paired = FALSE, conf.int = TRUE, exact =FALSE)
```

Same conclusion. The diastolic blood pressure decreases significantly more when using Treatment 3. In this case I think it is best to use Mann-Whitney since we are not sure about the normal distribution.

---

## 4. Binary indicator

Binary indicator of whether  $(\text{dbp5}-\text{dbp3}) < 10\text{mmHg}$  between the 2 treatment arms. Use appropriate 5% sign level & conclude, how and why do treatment arms differ? How does this comparison differ from the one above?

The actual succes rate can be seen as a proportion. To test the proportion difference, we can calcalte the Z-value based on the 2 proportions.

However, since the sample sizes do not allow us to assume normality (we observe only 2 proportions), a sampling method is more appropriate

```
data23$binary <- 0
data23$binary[data23$dbpdif<10]<-1
binTr <- data23[data23$treatment == 'Treatment 3',]$binary
binPl <- data23[data23$treatment == 'Placebo',]$binary
pasTr <- sum(binTr)
pasPl <- sum(binPl)
nTr <- length(pasTr)
nPl <- length(pasPl)
n_1 <- length(binTr)
n_2 <- length(binPl)
p_1 <- sum(binTr)/n_1
p_2 <- sum(binPl)/n_2
#P -> the proportion of total passes
p<-(n_1*p_1+n_2*p_2)/(n_1+n_2)
#Z-score
z<-(p_1- p_2)/
  sqrt(p*(1- p)*(1/n_1+1/n_2))
#Get the required z-value of chosen significance level
#1 sided testing, the probability of the trial group passing(P_1) is greater
than that of the placebo group (P_2)
qnorm(0.95, 0, 1)<z
z
#power for this statistic
1- pnorm(z, 0, 1)
#source: https://onlinecourses.science.psu.edu/stat414/node/268/
```

We can reject the 0 hypotheses of the proportions of being under the cut-off being equal at the 95% confidence level. The treatments were compared here on a cut-off value of  $\{\text{dbp5}-\text{dbp3}\} < 10\text{mmHg}$ . Instead of comparing the natural group means, we created a yes or no indicator according to our set benchmark. The strength of this test will rely hugely on how well the cut-off value is chosen, and can not be seen as a complete representation of the difference between the groups. Only the difference in relation to the cut-off can be evaluated here.

The best procedure would be to generate a simulation. Note that from the 80 observations, only 6 did not meet the  $(\text{dbp5}-\text{dbp3}) < 10\text{mmHg}$  mark. Therefore only 7 possible differences

are to be noted. This is by far a smooth distribution and should not be seen as an exact measure.

```
'Using a simulation'
x<-data23$binary
y<-c(as.numeric(1:length(data23$binary)))
allresp <- data.frame(x,y)    #create df with indexes for sampling
size <- nrow(allresp)/2 #original size is 80, divide in even groups
diff<- vector()
for(i in 1:10000){
  a <- allresp[sample(nrow(allresp),40),] #sample 40 randoms
  propa <- sum(a[,1])/size #calc prop 1
  #b <- setdiff(allresp, a) stopped working ??
  b <- allresp[!(allresp$y%in%unique(a$y)),] #get all values not in a
  propb <- sum(b[,1])/size #calc prop 2
  diff[i] <- c(propa-propb)
}
hist(diff)

#observed difference likeliness, p-value
1-sum(c(p_1-p_2)>diff)/length(diff)
```

Although the chance that our observed difference is higher than a random difference is, because of the oneven distribution this should be seen as a raw estimate, not a precise measure.

Since the cutoff defined as (dbp5-dbp3)<10mmHg seemed rather wide to us, we decided to also check if (dbp5-dbp3)< -10mmHg, thereby looking if the Treatment group beats the placebo group with at least 10mmHg.

```
data23$binaryrev <- 0
data23$binaryrev[data23$dbpdif<(-10)]<-1
binTr <-data23[data23$treatment == 'Treatment 3',]$binaryrev
binPl <-data23[data23$treatment == 'Placebo',]$binaryrev
pasTr <- sum(binTr)
pasPl <- sum(binPl)
nTr <- length(pasTr)
nPl <- length(pasPl)
n_1 <- length(binTr)
n_2 <- length(binPl)
p_1 <- sum(binTr)/n_1
p_2 <- sum(binPl)/n_2
#P -> the proportion of total passes
p<-(n_1*p_1+n_2*p_2)/(n_1+n_2)
#Z-score
z<-(p_1- p_2)/
  sqrt(p*(1- p)*(1/n_1+1/n_2))
#Get the required z-value of chosen significance level
#1 sided testing, the probability of the trial group passing(P_1) is greater
than that of the placebo group (P_2)
qnorm(0.95, 0, 1)<z
```

```
1- pnorm(z, 0, 1)
z
```

Here we also see a rejection of the  $H_0$ , but stronger. A z-value of 3.52 relates to a confidence level of 99.98%, whereas in the first case a 1.76 Z-score relates to a 96.08% confidence level.

```
'Using a simulation'
x<-data23$binaryrev
y<-c(as.numeric(1:length(data23$binaryrev)))
allresp <- data.frame(x,y)      #create df with indexes for sampling
size <- nrow(allresp)/2 #original size is 80, divide in even groups
diff<- vector()
for(i in 1:10000){
  a <- allresp[sample(nrow(allresp),40),] #sample 40 randoms
  propa <- sum(a[,1])/size #calc prop 1
  #b <- setdiff(allresp, a) stopped working ??
  b <- allresp[!(allresp$y%in%unique(a$y)),] #get all values not in a
  propb <- sum(b[,1])/size #calc prop 2
  diff[i] <- c(propa-propb)
}
hist(diff)

#observed difference likeliness: p-value
1-sum(c(p_1-p_2)>diff)/length(diff)

sum(data23$binaryrev)
```

---

## 5. Continuous outcome measure

expected evolution in blood pressure between visit 5 en 3 in the placebo group.

Test if mean for Placebo group is different from 0.  $H_0$ : mean difference for placebo group is equal to 0  $H_1$ : mean difference for placebo group is not equal to 0

### Parametric

using one sample t-test

```
t.test(placebo$dbpdif)
```

We do not reject the 0 hypothesis, so we expect no difference in bloodpressure between visit 5 an visit 3 in the placebo group. This shows that the effect of treat 1 and 3 can not be dedicated to a placebo effect. We could also use a paired t-test to compare dbp3 with dbp5; gives exactly the same results.

## Non-parametric

using one sample Wilcoxon test

```
#Samples do not need to be drawn from a population with a normal distribution
qqnorm(placebo$dbpdif)
qqline(placebo$dbpdif)

wilcox.test(placebo$dbpdif, mu=0)
```

Same conclusion:  $H_0$  is not rejected, mean is not different from zero. No placebo effect.

---

## 6 Gender difference

Does the mean difference in dbpdif between group 3 and group 2 depend on gender? Derive a justified answer. 2-way anova to see a possible interaction between treat and gender.

```
str(treat3)

#Nieuw object maken dat enkel data van groepen 2 en 3 bevat
data23 <- data[which(data$treatment != "Treatment 1"),]
data23$treatment <- droplevels(data23$treatment)
data23$treatment <- as.factor(data23$treatment)
```

## Visualization

```
#!require(devtools) install.packages("devtools")
#devtools::install_github("kassambara/ggpubr")
str(data23)

library(ggpubr)

plot <- ggline(data23, x = "treatment", y = "dbpdif", color = "sex",
               add = c("mean_se", "dotplot"),
               palette = c("#00AFBB", "#E7B800"))

plot
```

Two-way ANOVA with interaction Interaction = the effect of one factor on the dependent variable depends on the level of another factor

```
modell1 <- lm(dbpdif ~ sex * treatment, data = data23)
anova(modell1)
```

```
#type 1 because we are interested in the interaction
```

There is no interaction, so the mean difference between group 3 and 2 does not depend on gender.

## Check assumptions of the model

```
#Assumption 1 : Normal distribution of the model residuals  
plot(model1,2)
```

Residuals approximatly normally distributed.

```
#Assumption 2: Homogeneity of variance of the groups  
plot(model1,1)
```

```
leveneTest(dbpdif ~ sex * treatment, data = data23)
```

P-value is larger than 0.05 so variances are approximatly equal. Both assumptions are met.

---

## 7 Power of the gender difference test

```
# Finding the mean of each gender-treatment combination in the real dataset  
mu2f <- mean(data23$dbpdif[data23$treatment == "Placebo" & data23$sex == "Female"])  
mu3f <- mean(data23$dbpdif[data23$treatment == "Treatment 3" & data23$sex == "Female"])  
mu2m <- mean(data23$dbpdif[data23$treatment == "Placebo" & data23$sex == "Male"])  
mu3m <- mean(data23$dbpdif[data23$treatment == "Treatment 3" & data23$sex == "Male"])  
  
mu2_sim <- (mu2f + mu2m)/2  
mu3_sim <- (mu3f + mu3m)/2  
  
# Finding the sd of each gender-treatment combination in the real dataset  
sd2f <- sd(data23$dbpdif[data23$treatment == "Placebo" & data23$sex == "Female"])  
sd3f <- sd(data23$dbpdif[data23$treatment == "Treatment 3" & data23$sex == "Female"])  
sd2m <- sd(data23$dbpdif[data23$treatment == "Placebo" & data23$sex == "Male"])  
sd3m <- sd(data23$dbpdif[data23$treatment == "Treatment 3" & data23$sex == "Male"])  
  
# Simulation study to find the power of the ANOVA-interaction test  
power_data <- vector(,10000)  
set.seed(2018)  
for(i in 1:10000) {  
  sim2f <- rnorm(19, mean = mu2_sim, sd = sd2f)  
  sim3f <- rnorm(20, mean = mu3_sim - 2, sd = sd3f) # mean decreased by 2 for females
```

```

sim2m <- rnorm(22, mean = mu2_sim, sd = sd2m)
sim3m <- rnorm(19, mean = mu3_sim + 2, sd = sd3m) # mean increased by 2 for
males
# The genders now differ 4 mmHg in treatment effect on average

#Creating a dataframe from the simulated values
dbpdif <- c(sim2f, sim3f, sim2m, sim3m)
genders <- as.factor(c(rep("Female", 39), rep("Male", 41)))
treatments <- as.factor(c(rep("placebo", 19), rep("treatment3", 20), rep("p
lacebo", 22), rep("treatment3", 19)))
sim_data <- data.frame (data.frame(dbpdif, genders), treatments)

#Calculating the significance of the interaction in the simulated data
sim_model1 <- lm(dbpdif ~ genders * treatments, data = sim_data)
aov_result <- anova(sim_model1)
x <- aov_result$`Pr(>F)`[[3]]
power_data[i] <- x
}
mean(power_data < 0.05)

```

The ANOVA approach has a power of 13%

---

## Other explorations

Summary table alternative version

```

# Alternative custom summary table using dplyr
summarycols <-
  list(
    "Run-in mean DBP" =
      list(
        "mean (sd)" = ~ qwraps2::mean_sd(dbp_mean),
        "min" = ~ min(dbp_mean),
        "25th" = ~ quantile(dbp_mean, .25),
        "Median" = ~ median(dbp_mean),
        "75th" = ~ quantile(dbp_mean, .75),
        "max" = ~ max(dbp_mean)
      ),
    "Final DBP" =
      list(
        "mean (sd)" = ~ qwraps2::mean_sd(dbp_end),
        "min" = ~ min(dbp_end),
        "25th" = ~ quantile(dbp_end, .25),
        "Median" = ~ median(dbp_end),
        "75th" = ~ quantile(dbp_end, .75),
        "max" = ~ max(dbp_end)
      )
  )

```

```

    ),
    "DBP change" =
      list(
        "mean (sd)" = ~ qwraps2::mean_sd(dbp_mean),
        "min" = ~ min(dbp_mean),
        "25th" = ~ quantile(dbp_mean, .25),
        "Median" = ~ median(dbp_mean),
        "75th" = ~ quantile(dbp_mean, .75),
        "max" = ~ max(dbp_mean)
      )
  )
)
print(summary_table(dplyr::group_by(data, treatment), summarycols),
      rtitle = "Summary Statistics",
      cnames = c("Treatment 1", "Placebo", "Treatment 3"))

```

Change between the run-in period DBP measurements

```

# Columns to rows
data_res <- melt(data, id.vars='treatment', measure.vars=c('dbp1', 'dbp2', 'dbp3'))
data_res$ID <- seq.int(nrow(data))
# Profile plot
ggplot(data_res, aes(x=variable, y=value, group=ID)) +
  geom_point() +
  geom_line()

```