Assessing Interventions Effects on Alcohol Dependence and Alcohol Relapse

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Abstract

Alcohol consumption becomes a major risk factor for various diseases and even worse, death, nowadays. In our study, we conducted a longitudinal study on comparing three different treatments effect on alcohol-use disorder-i.e., alcohol dependence and harmful use of alcohol. We built up marginal model as well as Generalized Linear Mixed Effect (GLME) model to assess their effects over time on alcohol dependence and relapse after. We found out that treatment effects over time differ from each other and male and female respond to treatments effect differently.

Keywords: alcohol-use disorder; longitudinal analysis; GEE; GLME; marginal model;

Introduction

Alcohol is viewed a risk factor for the global burden of disease and injury, especially for the so-called alcohol-use disorders. The average volume of alcohol consumption and patterns of drinking, especially heavy drinking occasions, contribute to this disease burden.

Motivated by the urgent needs, we conducted a longitudinal study employing three different treatments which aiming on helping reduce alcohol dependence. We built up models and evaluated their effects over time on alcohol dependence. We also evaluated the differences in treatments effects between genders.

Data and Methods

Data. We enrolled 314 subjects known to suffer from alcohol dependence were recruited. The total number of drinks consumed in the 30 days immediately prior to randomization was recorded. After the assignment of treatment, the total number of drinks consumed in the past 30 days were recorded at 30 days and 60 days since the beginning of treatment (i.e. each observation is the total number of drinks consumed in the last 30 days preceding the day of reporting). The subjects were also followed up 6 months after the end of treatment. Based on an a priori set criteria, the researchers classified the subjects as having relapsed into alcohol dependence or not.

Randomization. The subjects were randomly assigned into one of three treatment groups as follows:

1. Treatment 1: Subjects were given DVD, pamphlets and other instructional materials related alcohol dependency. The subjects kept track of their daily alcohol consumption and reported the total number of drinks consumed in the last 30 days on the 30^{th} and 60^{th} day.
2. Treatment 2: Subjects were given DVD, pamphlets and other instructional materials related alcohol dependency but were also required to report the number of drinks consumed at the end of every week.
3. Treatment 3: Subjects were given DVD, pamphlets and other instructional materials related alcohol dependency but were also required to report the number of drinks consumed daily using a toll-free phone number.

Variable		N
Gender	Male	171
	Female	143
Treatment	1	106
	2	107
	3	101
Relapse	Yes	150
	No	164

Table 1. Recruitment Characteristics. N(total) = 314.

Marginal Model. To assess the treatments effects over time on alcohol consumption, gender effects on alcohol consumption and interaction between gender and treatment, we build up a marginal model with unstructured correlation matrix:

$$Consumption = Treatment \cdot Time + Gender \cdot Time$$

Assuming the consumptions follow Gaussian distribution.

Generalized Linear Mixed Effect Model. To assess the treatments effects on alcohol dependence relapse between subjects, we build up a GLME model with random intercept:

$$Relapse = Treatment + (1 \mid subject\ id)$$

Assuming the relapses follow binomial distribution and the random intercept follow Gaussian distribution. We didn't include gender covariate because as we tested, the gender effect and interaction between gender and treatments are not significant.

Results

Exploratory Data Analysis (EDA). We first ran EDA on the dataset, mainly to test the correlation. Fig.1 shows that outcome pattern varies between treatments and treatment effects varies between male and female. Fig.2 would give us some rough idea of whether the outcome is correlated or not, Fig.2C shows us that outcome varies between time points.

Marginal Model. In Table 2, we can see that most of the parameters are significant except 'Treatment2:TimeND30', these tell us a lot of information. First is that, there is enough evidence to support treatment2's and treatment3's effects on alcohol consumption differ from treatment1's in a given 30-day period. Second is that, combing the results of EDA and marginal model, there is enough evidence to support that treatment2's and treatment3's pattern of change in the number of drinks consumed over the duration of the study differ from treatment1's. Third is that, there is enough evidence to support that males tend to have a higher alcohol dependence than females. Fourth is that, there is enough evidence to support that male and female respond differently to treatments.

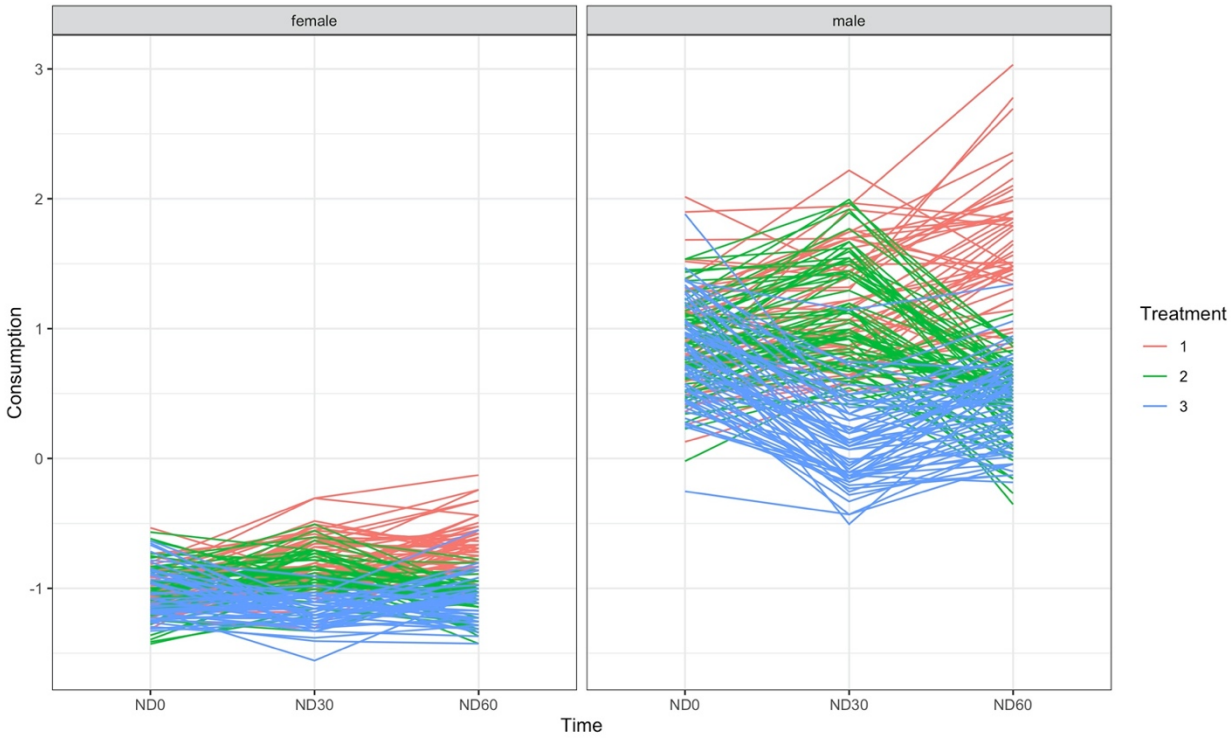

Figure 1. Spaghetti Plot for Consumption Over Time.

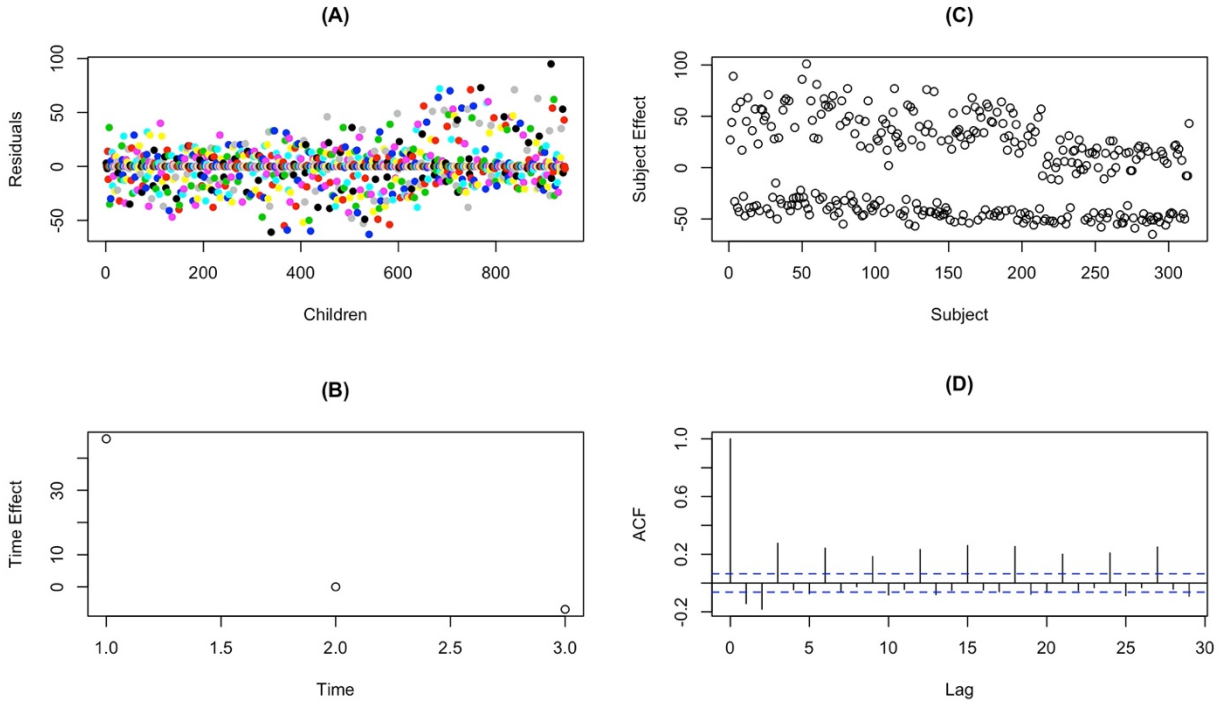

Figure 2. (A) Residuals Using Median Polish. (B) Time Effect from Median Polish. (C) Children Effect from Median Polish. (D) Correlation in alcohol Data

parameters	Estimate	Robust S.E.	CI	p-value
(Intercept)	80.27160494	2.075406809	(78.196, 82.347)	0
Treatment2	5.866158994	3.219466116	(2.647, 9.086)	0.068
Treatment3	9.649037126	3.571382595	(6.078, 13.22)	0.007
TimeND30	-40.9245283	2.663604937	(-43.588, -38.261)	0
TimeND60	-42.5754717	2.665694895	(-45.241, -39.91)	0
Gendermale	92.6194207	2.061062349	(90.558, 94.68)	0
Treatment2:TimeND30	-3.88855581	3.712653294	(-7.601, -0.176)	0.295
Treatment3:TimeND30	-30.40220437	4.104320698	(-34.507, -26.298)	0
Treatment2:TimeND60	-31.24695821	3.829063981	(-35.076, -27.418)	0
Treatment3:TimeND60	-29.63244909	4.06310421	(-33.696, -25.569)	0
Treatment2:Gendermale	-9.873303618	2.877043205	(-12.75, -6.996)	0.001
Treatment3:Gendermale	-19.79459348	3.044507951	(-22.839, -16.75)	0

Table 2. Marginal Model Coefficients Estimation

GLME Model. The results in Table 3 show us that, there is enough evidence to support that treatment differ in their effects on subjects with regard to relapsing into alcohol dependence.

And since the estimations for treatment 2 and 3 are all negative, it suggests that treatment 1 might leads to an overall the least chance to relapse into alcohol consumption. We also did another exploratory model including covariate gender and the interaction between gender and treatment, but neither showed significant result.

parameters	Estimate	Std. Error	CI	Pr(>|z|)
(Intercept)	1.521469081	0.253504035	(1.268, 1.775)	1.95E-09
Treatment2	-1.690091834	0.319298633	(-2.009, -1.371)	1.20E-07
Treatment3	-3.3483199	0.384258503	(-3.733, -2.964)	2.94E-18

grp	var1	var2	vcov	sdcor
sid	(intercept)	NA	1.00E-07	0.0002327

Table 3. GLME Model Coefficients Estimation and Within Subject Correlation Estimation.

Discussion

In our study, the marginal model results told us that treatments effects differ from each other with regard to alcohol consumption, and male and female respond to treatments effect differently. The GLME model results told us that treatments effects differ on subjects with regard to relapsing into alcohol consumption. We also found out that among these three treatments, treatment 1 has the best overall performance to reduce alcohol dependence.

Surprisingly, we found out that, treatments effects are the same for both male and female with regard to relapse into alcohol dependence, but differ with regard to alcohol consumption with 30-day periods. This means that, the interventions have more effects on female during study period, but the difference shrink once study is over.

This study also suffers from limitations in several way. First is we don't have a control arm, so we need to be careful when interpret the result and state that treatments can be effective clinically.

Second is there might be some unknow covariates that can affect outcomes, like age and cardiovascular disease history, which requires future work to lean more into that.

Alcohol consumption is a major risk factor for burden of disease, it is of urgent need to find clinical meaningful and effective interventions to reduce alcohol dependence. The future work may need to focus more on setting a passive control arm and include more potential covariates.

Appendix

Code:

```
# standardized time plot
alcohol2 <- sweep(alcohol[,c(4:6)], 2, apply(alcohol[,c(4:6)], 2, mean))
sd1 <- apply(alcohol[,c(4:6)], 2, sd)
alcohol2 <- sweep(alcohol2, 2, sd1, FUN = "/")
alcohol2 <- cbind(alcohol[,c(1:3)], alcohol2)
alcohol2 %>% gather(ND0:ND60, key = "Time", value = "Consumption") %>%
  ggplot(aes(x = Time, y = Consumption, group = sid, color = Treatment)) +
  geom_line() +
  facet_grid(. ~ Gender)

# median polish
junk1 <- medpolish(alcohol[, c(4:6)])
res <- junk1$res
cols <- rep(1:314, rep(3, 314))
par(mfcol = c(2, 2))
plot(as.vector(t(res)), col = cols, pch = 19, cex = 0.8,
    xlab = "Children", ylab = "Residuals", main = "(A)")
plot(junk1$col ,xlab = "Time", ylab = "Time Effect", main = "(B)")
plot(junk1$row, xlab = "Subject", ylab = "Subject Effect", main = "(C)")
acf(as.vector(t(res)), xlab = "Lag", main = "(D)")

# GEE model regarding alcohol consumption
alcohol3 <- alcohol %>%
  gather(ND0:ND60, key = "Time", value = "Consumption")
fit.gee <- gee(Consumption ~ Treatment * Time + Treatment * Gender,
            data = alcohol3, family = "gaussian",
            id = sid, corstr = "unstructured")
sum.gee <- summary(fit.gee)
gee.coef <- sum.gee$coefficients %>%
```

```
  as_tibble() %>%
  mutate(parameters = rownames(sum.gee$coefficients),
         CIlow = Estimate - `Robust S.E.`,
         CIup = Estimate + `Robust S.E.`,
         CI = paste("(", round(CIlow, 3), ", ", round(CIup, 3), ")", sep = ""),
         pvalue = pnorm(`Robust z`, lower.tail = F) * 2) %>%
  select(parameters, Estimate, `Robust S.E.`, CI, pvalue)
gee.coef %>% write.csv("gee.coef.csv", na = "")

# GLME model regarding relapse
fit.glme <- glmer(Relapse ~ Treatment + (1 | sid),
                  data = alcohol, family = "binomial")
sum.glme <- summary(fit.glme)
glme.coef <- sum.glme$coefficients %>%
  as_tibble() %>%
  mutate(parameters = rownames(sum.glme$coefficients),
         CIlow = Estimate - `Std. Error`,
         CIup = Estimate + `Std. Error`,
         CI = paste("(", round(CIlow, 3), ", ", round(CIup, 3), ")", sep = "")) %>%
  select(parameters, Estimate, `Std. Error`, CI, `Pr(>|z|)`)
glme.coef %>% write.csv("glme.coef.csv", na = "")
```