Exploratory Analysis of Linkage with Primary Care and Multi-disciplinary Health Intervention

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Introduction

In the United States, approximately 95,000 people die from alcohol-related instances every year. This makes alcohol the third-leading cause of death in the U.S. (Alcohol Facts and Statistics | National Institute on Alcohol Abuse and Alcoholism (NIAAA), 2021). In addition, alcohol dependency can cause chronic conditions, such as liver disease, heart disease, liver cancer, alcohol use disorder (AUD), and breast cancer, all of which are the greatest contributors to alcohol-related deaths (Alcohol Facts and Statistics | National Institute on Alcohol Abuse and Alcoholism (NIAAA), 2021). Moreover, more than 70,000 Americans died from drug-related overdose in 2019, and overall, deaths caused by drug overdose are increasing in the U.S. (National Institute on Drug, 2021). Although there are many rehabilitation centers across the U.S. for alcohol and drug dependent people, approximately 40-60% of people treated for alcohol and/or drug addiction relapse within a year (Why Do Alcoholics and Addicts Relapse So Often?, 2017). Therefore, it is vital to link these alcohol and drug abusers to primary care, even after they have completed rehabilitation. Linking alcohol and drug dependent people to primary care can improve the patients' overall quality of life by mitigating substance abuse severity, medical issues, and mental health problems, making a patient's chance of relapse significantly lower. In addition, linkage with primary care can prevent a patient's relapse by allowing primary care officials to identify early signs of relapse and mental health problems and to practice prevention techniques (Samet et al., 2001).

In an attempt to link more alcohol and drug abusers to primary care, a multidisciplinary medical clinic was established in a substance abuse treatment unit. Accordingly, this clinic was called the Health Evaluation and Linkage to Primary Care (HELP) Clinic. The clinic's main purpose was to "perform a single comprehensive initial evaluation at the substance abuse treatment facility and then arrange subsequent follow-up with a primary care physician from whom the patient could receive ongoing health care" (Samet et al., 2003). The study randomly assigned patients undergoing detoxification for alcohol and drug problems to the clinic in order to test the clinic's effectiveness in linking the patients with primary care. Using this study's data, we will test our primary hypothesis that alcohol and drug dependent people assigned to the HELP clinic are more likely to link with primary care and will take less time to do so.

In our study, besides looking at the impact of the intervention treatment administered by the HELP clinic, we also examined other variables and their impact on linkage to primary care, including years of education completed, substance use status, and alcohol preference. Based on our exploratory data analysis (see more in the Results section), we predict that alcohol and drug dependent people assigned to the HELP clinic will have a higher hazard of linking to primary care. Additionally, we predict that the hazard of linkage to primary care will decrease as the years of education completed increases and if the patient uses alcohol or any other substance within 6 months of leaving the clinic.

Methods

We used the dataset from the Health Evaluation and Linkage to Primary Care (HELP; Samet et al., 2003) study to examine the variables that affect the time for detoxification clinic patients to link to primary medical care.

We took a survival analysis approach to evaluate whether the primary explanatory variable of interest, intervention through the HELP clinic, significantly impacted the time to link to primary medical care. Our event of interest was linkage to primary medical care, which coincided with our time-to-event variable, which was the number of days it took for a patient to link to primary medical care. We used a censoring indicator to mark when observations of patients ended before they were linked to primary medical care. We created Kaplan-Meier survival curves to determine whether the intervention affected linkage to primary care.

We created a Cox Proportional Hazards (PH) model to model the hazard of the event of interest at given points in time. As explanatory variables, we included type of intervention group (group), years of education (a9), alcohol preference (alcohol), and substance usage (anysubstatus). We included alcohol preference and substance usage in the model as interacting variables. To test whether our variables significantly affected our model, we conducted likelihood ratio tests on each of the variables, starting with the variables with the highest p-values. Thus, we conducted the likelihood ratio tests between the full model and models without the alcohol preference, education, and substance usage variables, in that order. We did not conduct the likelihood ratio test between the full model and the model without the treatment variable, since the treatment variable was the primary explanatory variable of interest. We also conducted a likelihood ratio test between the models that had alcohol preference and substance usage as additive variables and as interactive variables. The Cox PH model assumes proportional hazards, or that the hazard ratios of the variables do not depend on time. Therefore, we checked whether the proportional hazards assumption held for our Cox PH using log-log transformations on the relevant survival curves.

Something New

Kristine's Something New

The cox.zph() function tests the proportionality of each covariate in the model and also runs a global test for the entire model. To find the proportionality of each covariate, the function creates a set of corresponding Schoenfeld residuals, which are residuals for each individual for each covariate. Schoenfeld residuals can be calculated by taking the value of the covariate for the person who died at time t and subtracting the expected value of the covariate for the risk set at t. The expected value is a mean of the covariates, weighted by every person's likelihood of dying at t. The cox.zph() function is essentially a test of whether Schoenfeld residuals interact with time, where the null hypothesis is that there is no interaction and that the hazards are proportional, while the alternative hypothesis is that there is interaction and thus hazards are not proportional. A p-value less than 0.05 indicates that we reject the null hypothesis and that there are significant interactions with time. Proportionality necessitates that the hazard does not change over time, so a significant interaction with time indicates that the model violates the proportional hazards assumptions. Additionally, we can plot the cox.zph() function using plot(cox.zph(. . .)), which plots each covariate on a separate graph. The graphs plot the scaled Schoenfeld residuals, along with a solid line that shows the time varying estimates of the log of the HR (aka the coefficient) and two dashed lines that mark the bounds of the confidence intervals. If proportionality assumptions hold and the covariate does not change over time, the solid line should stay flat and close to y=0, indicating that the coefficient does not change much over time. If the solid line curves a lot, this indicates that the coefficient does vary over time and that the model violates proportional hazard assumptions.

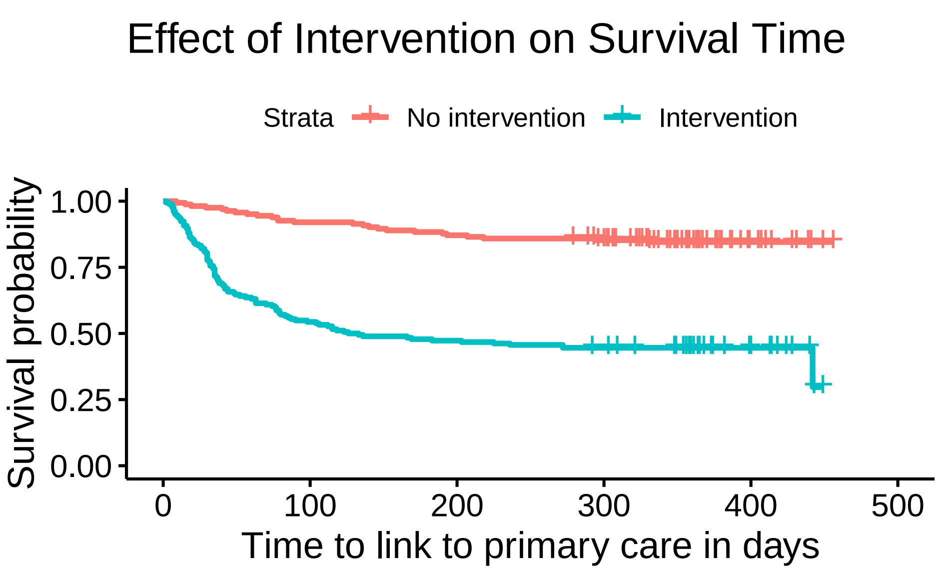
Hanna's Something New

Although the HELP study was well-conducted and the intervention treatment administered by the HELP clinic was ultimately deemed significant, the possibility of there being time-dependent covariates may affect the results of this study. Time-dependent covariates are covariates that are not constant throughout the study. Therefore, a key rule when working with time-dependent covariates in a Cox PH model is that one cannot "look into the future." In other words, a covariate may change in any way based on past data or outcomes, but it may not reach forward in time (Therneau et al., 2021.). A popular example of a time-dependent covariate exists in the Stanford Heart Transplantation Study, in which the receiving of a heart transplant is the time-dependent covariate. The time-dependency manifests because waiting times to get the heart transplant can vary amongst different subjects. This time-dependent covariate changes the Cox PH model, as a normal Cox PH model with time-independent covariates would only compare the survival rates between subjects without a transplant and those with a transplant. Simply put, a subject's transplant status at the end of the study would determine which category they were put in for the Cox model. A Cox model with time-dependent covariates, however, would compare the risk of an event between those with a transplant and those without at each event time, but would reassess which group each subject belonged to based on whether they had a transplant by that specific time (University of California, San Diego Mathematics, n.d.). Therefore, if we add time-dependent covariates to the Cox PH model, it is no longer a "proportional hazards" model, as the time-independence assumption is violated (University of Kentucky Mathematics, n.d.).

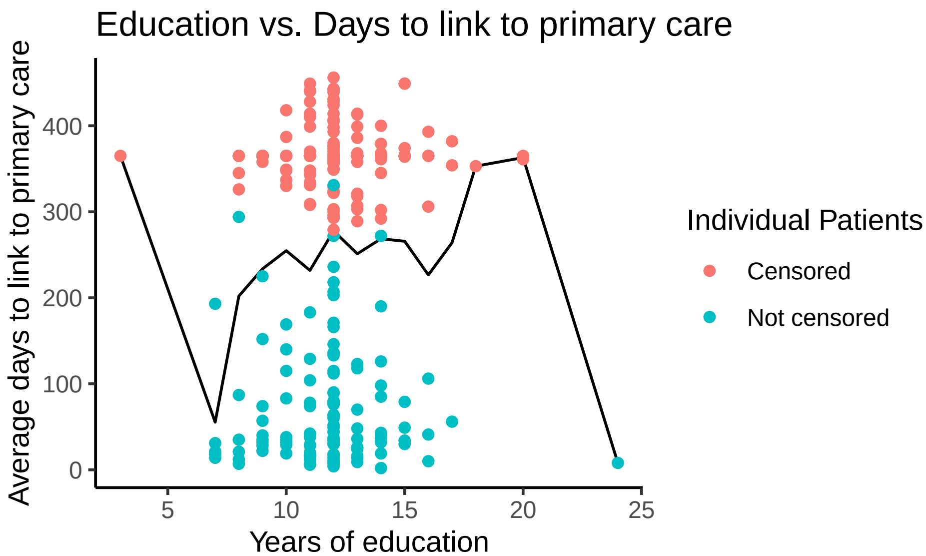
From the cox.zph() function output (seen in the Results section), we observed that the `group` variable has a p-value of 0.005, meaning that the `group` variable significantly interacts with time and the hazard of linking to primary care is not constant amongst the subjects in the treatment groups throughout time. One possible hypothesis that explains why the treatment `group` variable is time-dependent is that the effectiveness of the intervention may "wear off" over time. For example, if a patient is impacted significantly by the HELP clinic and links with primary care relatively quickly, the HELP clinic treatment is positively correlated with the hazard of linking to primary care for this patient and others like them. In contrast, however, if a patient does not link with primary care as quickly, the effectiveness of the intervention may decrease for as long as the patient does not link with primary care. In other words, as more time passes from a patient's attendance at the HELP clinic, the less effective the knowledge obtained from the clinic becomes. Researchers have observed this phenomenon in many aspects of human behavior, where people only act on the things "at the top of their head." For example, when a person is given a lecture about climate change, they may feel very inclined to take action right after the lecture. However, as more time passes from the lecture, the urgency of taking action may slowly decline, especially if they did not take action right away. Knowing now that the `group` variable may be a time-dependent covariate, the Cox PH model may not be the best model to fit the data, as it does not take into account the changing hazard rates over time. Therefore, future studies should take the extra time and effort to check whether their variables are time-dependent and if so, change their models accordingly.

Results

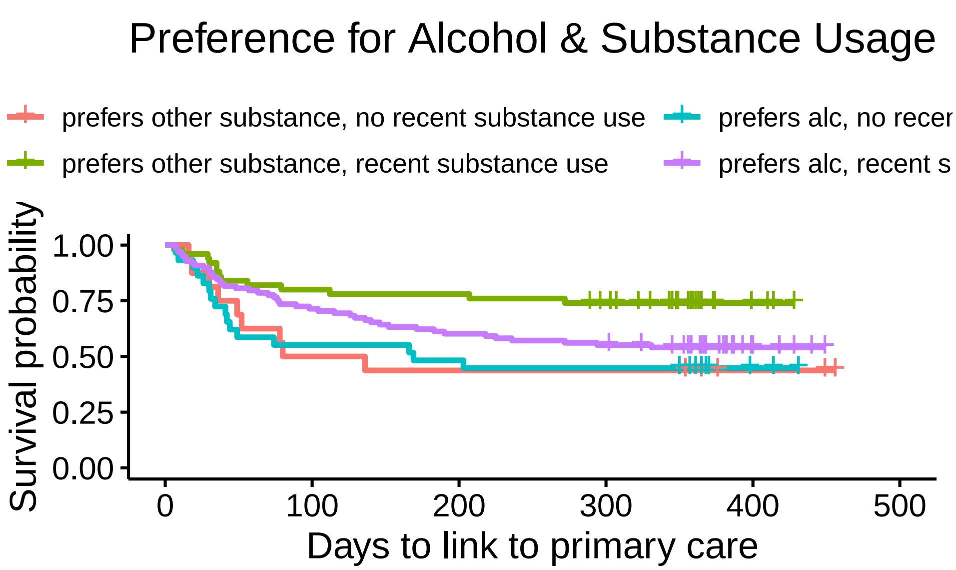
We wanted to see which variables impacted linkage to primary care for alcohol and drug abusers. Our primary variable of interest was intervention through the HELP clinic. Kaplan-Meier survival curves showed that the group which received the intervention had shorter survival times than the control group and took less time to link to primary care. In other words, the intervention was consistently more effective in linking patients to primary care.



Our secondary variables of interest were education, alcohol preference, and substance usage. Exploratory data analysis of the relationship between education and days to link to primary care indicated a generally positive correlation up until 20 years of education, before which the more education a patient had, the more days they took to link to primary care.



We created survival curves to explore the interaction between alcohol preference and substance usage in the past six months. Patients answered yes or no as to whether alcohol was their first/second substance of choice, as well as if they had used cocaine, heroin, or alcohol since leaving the detoxification clinic. The survival curves show that patients who had not used any substances in the past six months were the quickest to connect to primary care, while patients whose first choice of substance was NOT alcohol and who had used substances in the past six months took the longest to connect to primary care.

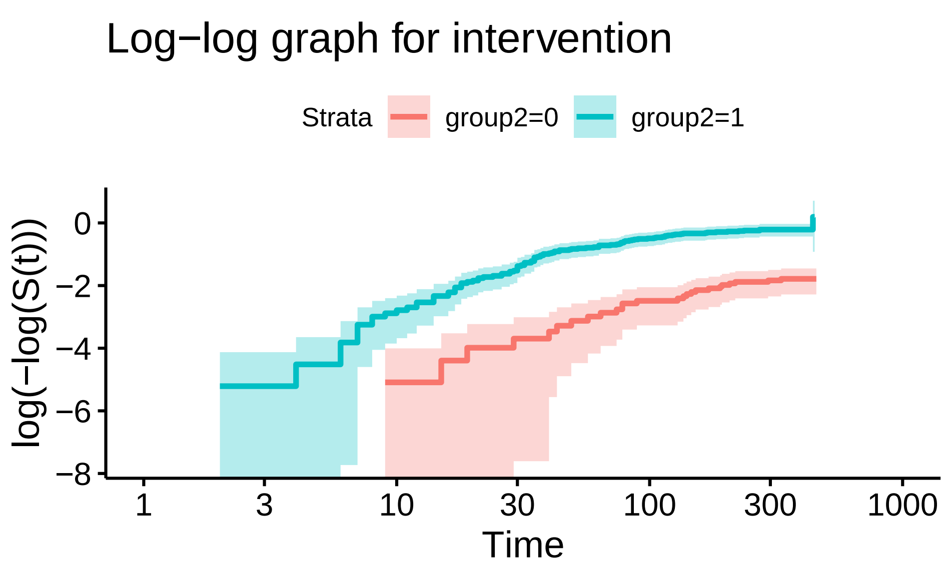


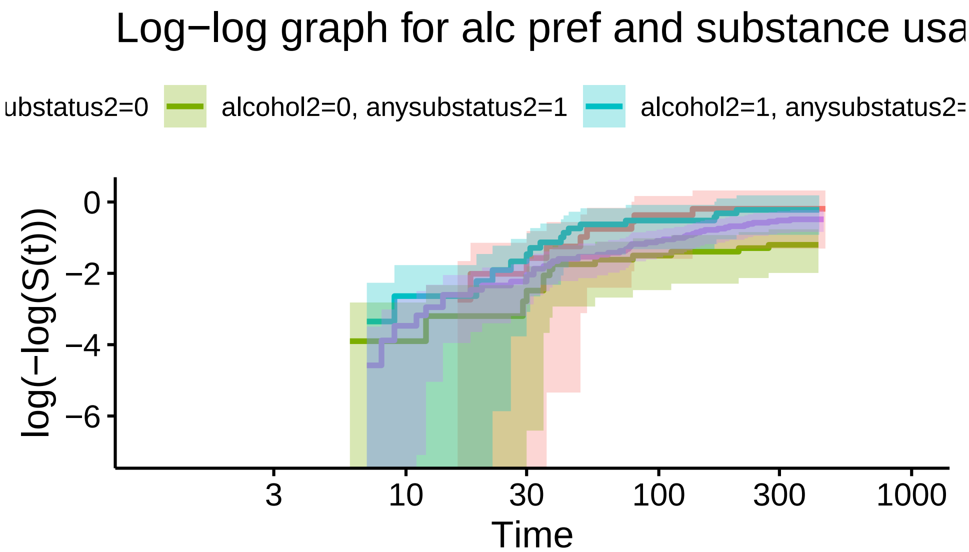
We created a Cox PH model to examine the risk of connecting to primary care based on the following variables: intervention, education, alcohol preference, and substance usage. Our model uses the interaction between alcohol preference and substance usage. Patients who had received the intervention were more likely to connect to primary care (adjusted HR, 5.57; 95% CI, 3.24 to 9.55; P=4x10ˆ-10). Patients were significantly less likely to link to primary care if they had more years of education (HR, 0.85; 95% CI, 0.77 to 0.95; P=0.004) or if they had used substances in the past month (HR, 0.226; 95% CI, 0.09 to 0.54; P=0.0009). Patients were more likely to link to primary care if their first/second choice of substance was alcohol and if they had used substances in the past six months (HR, 3.03; 95% CI, 1.07 to 8.56; P=0.03).

#to show/explain interaction: #for substance abusers calculate: hazard (alc = 1) / hazard (alc = 0) #for non-sub abusers calculate hazard (alc = 1) / hazard (alc = 0) #if those two numbers are (significantly / very) different, then the HR for alcohol or not CHANGES depending on whether or not you use substances #that is the 3rd variable (substance) changes the relationship between the 2nd variable (alcohol) and the 1st variable (seeing doctor = response) #can change 3rd variable and 2nd variable! they are equivalent (if interacts in one way, interacts w other)

```
## # A tibble: 5 x 5
##   term                                    estimate std.error statistic  p.value
##   <chr>                                      <dbl>     <dbl>     <dbl>    <dbl>
## 1 as.factor(anysubstatus)1                  -1.49     0.447     -3.33  8.82e- 4
## 2 as.factor(alcohol)1                       -0.220    0.423     -0.521 6.03e- 1
## 3 as.factor(group)1                          1.72     0.275      6.26  3.92e-10
## 4 a9                                        -0.158    0.0550    -2.86  4.18e- 3
## 5 as.factor(anysubstatus)1:as.factor(alco~   1.11     0.530      2.09  3.68e- 2
```

To check for Cox PH model assumptions, we transformed survival curves for each of the variables we used in the log-log space, both for time and the log of time. Using this method, we found that only the intervention variable did not violate the proportional hazards assumption.




Log−log graph for alc pref and substance usa
ubstatus2=0
alcohol2=0, anysubstatus2=1
alcohol2=1, anysubstatus2=
0
−2
−4
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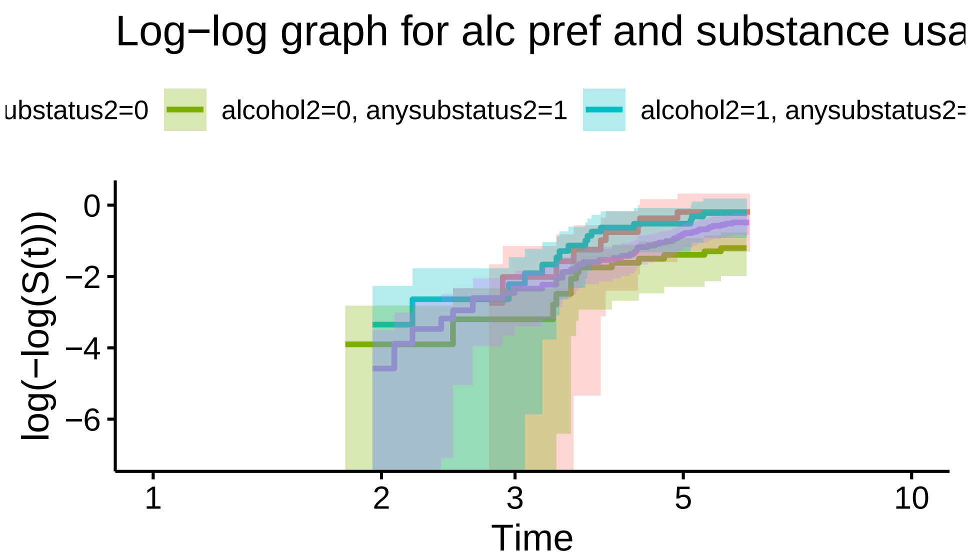
log(−log(S(t)))
3
10
30
100
300
1000
Time


Log−log graph for alc pref and substance usa
ubstatus2=0
alcohol2=0, anysubstatus2=1
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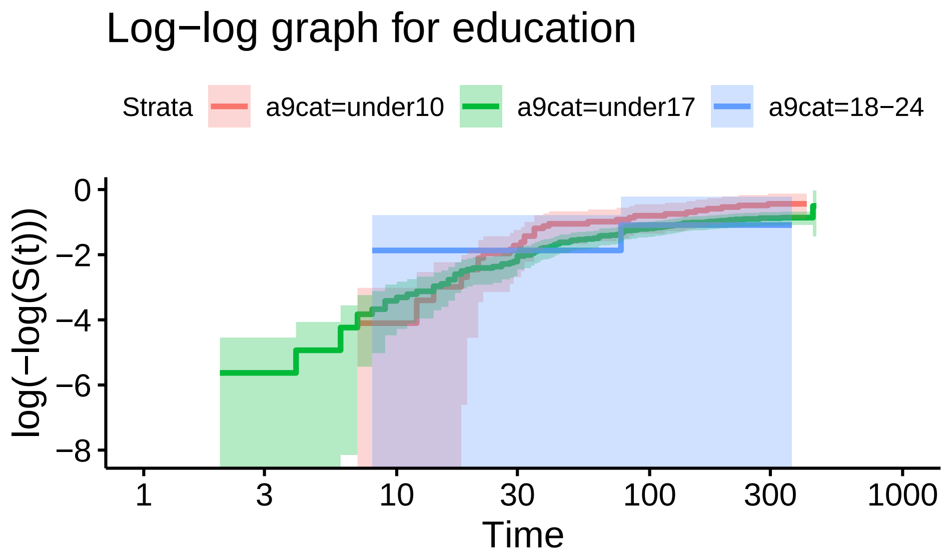
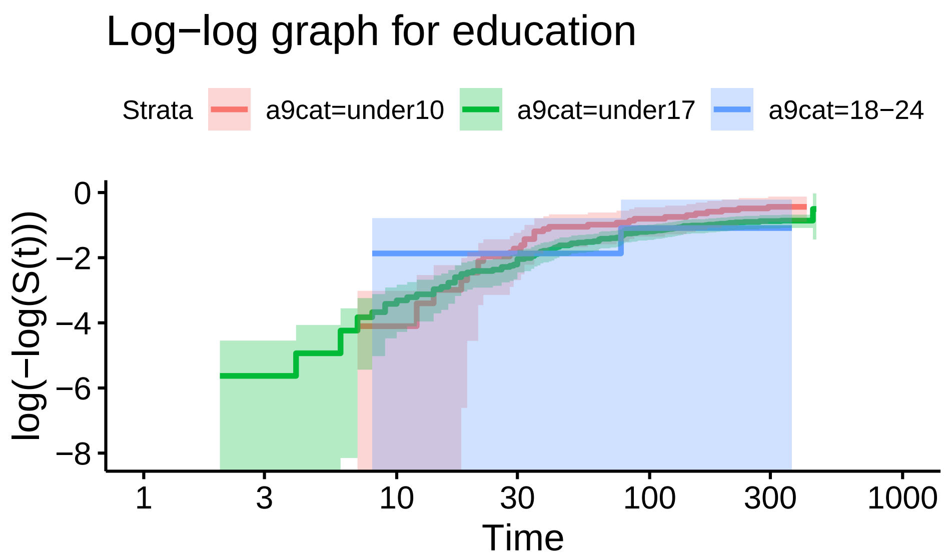
Time



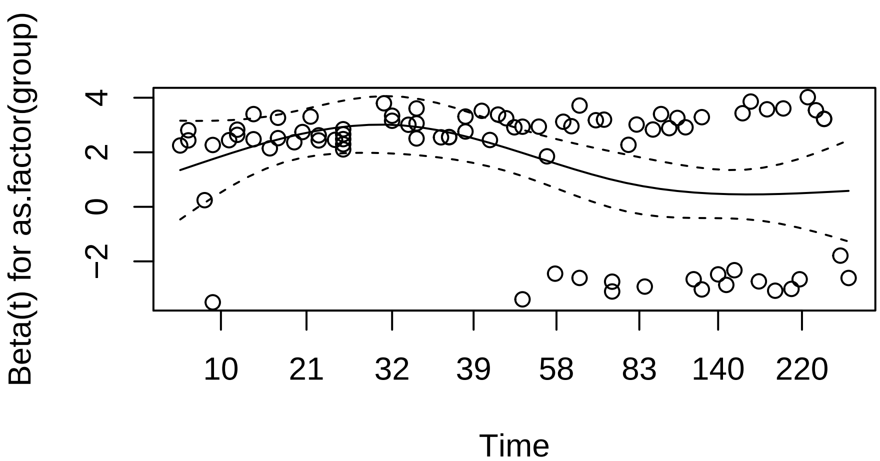


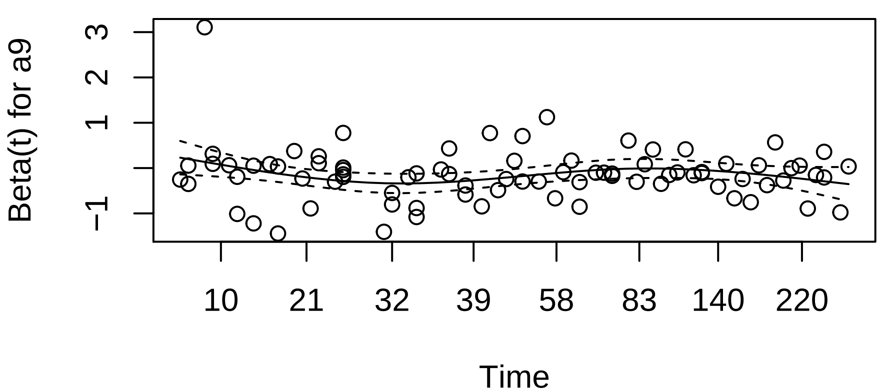
We examined whether the variables interacted with time using Schoenfeld residuals using time and the log of time. Using this method, we found that only the treatment group violated the proportional hazards assumption. We also plotted the scaled Schoenfeld residuals for each covariate in the model. The solid line in the graph for education (variable a9) is the flattest, oscillating around y=0. The graphs for substance usage (anysubstatus), and alcohol preference (alcohol) showed lines that curved away from y=0 but still had confidence intervals that contained y=0. These graphs visually show how these three variables may still uphold the proportionality assumptions when conducting a PH test using the coxzph() function. However, the graph for treatment (group) is the most variable, with y=0 out of the confidence interval for most of the graph. This graph visually shows why the coxzph() function yields a p-value below 0.05 for the treatment group, indicating that it does not uphold the proportionality assumptions.

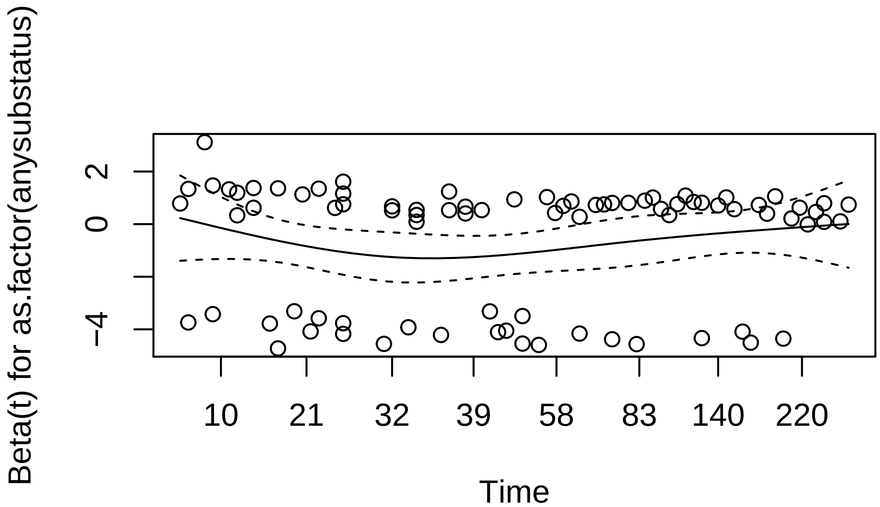
```
##                              chisq df      p
## as.factor(group)             8.777  1 0.0031
## a9                           0.921  1 0.3372
## as.factor(anysubstatus)      0.175  1 0.6760
```

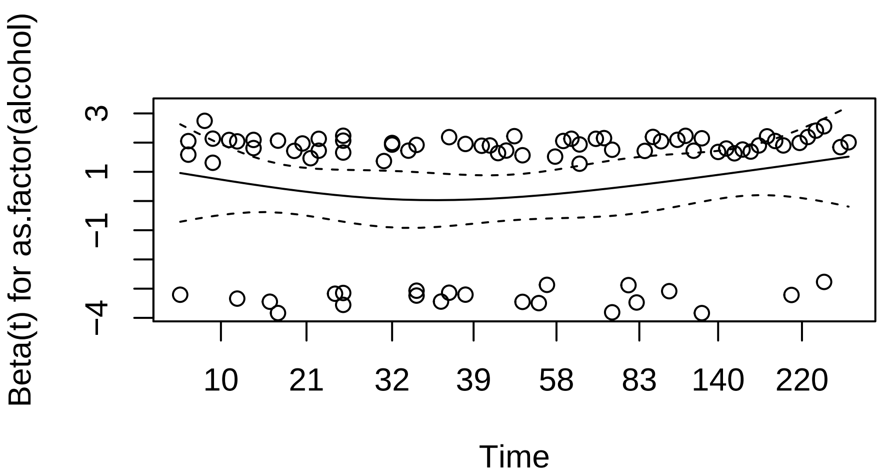
```
## as.factor(alcohol)       1.237  1 0.2660
## GLOBAL                  10.099  4 0.0388
```

```
##                          chisq df      p
## as.factor(group)          7.71  1 0.0055
## a9                        1.49  1 0.2219
## as.factor(anysubstatus)  0.15  1 0.6987
## as.factor(alcohol)        1.18  1 0.2782
## GLOBAL                    9.36  4 0.0527
```









Discussion

Using data from the HELP study, we found that patients who received intervention through the HELP clinic took fewer days to link to primary care. These results suggest that the HELP clinic is effective for connecting patients to primary care and should be offered more extensively to patients in detoxification clinics. Further research should be conducted as to what components of the HELP clinic are most or least helpful for patients.

Additionally, we found that patients were less likely to link to primary care if they had more years of education. We have several hypotheses as to why this might be the case: it is possible that patients with more years of education feel more stigma in their alcohol or drug usage, or that a more-educated person who uses substances regularly has particularly extenuating circumstances that make it more difficult for them to link to primary care. More research should be conducted to examine the reasons for how and why years of education impacts one's substance usage as well as one's process of rehabilitation.

Patients who had not used substances within the past six months of the interview were most likely to link to primary care, especially if their first/second substance of choice was alcohol. These results suggest that patients who relapse with alcohol or do not relapse at all are more likely to link to primary care compared with those who relapse with other substances, including heroin and cocaine. The interaction between substance use and alcohol use indicates that the instantaneous hazard of linking to primary care if one's first/second substance of choice was alcohol is dependent on the instantaneous hazard of linking to primary care if any substance was used in the past 6 months. To further explain, for a patient whose first/second substance of choice is alcohol, the instantaneous hazard of linking to primary care will be impacted by whether or not they used any substance in the past 6 months. If they did not use any substance in the past 6 months, their instantaneous hazard of linking with primary care would increase, even if they reported that their first/second substance of choice is alcohol. Conversely, if a patient whose first/second substance of choice is alcohol did use any substance in the past 6 months, their instantaneous hazard of linking with primary care would decrease.

Because the study is a full randomized clinical trial, we conclude causation; the treatment of the intervention affects the number of days one takes to get linked to primary medical care. We further conclude that the secondary variables of years of education, alcohol preference, and substance usage correlate with the number of days to get linked to primary care, generalizing our results to a larger population of adult inpatients recruited from detoxification clinics. Based on these findings, rehabilitation centers can begin implementing clinics similar to the HELP clinic to prevent relapse amongst their drug/alcohol dependent patients and overall promote linkage to primary care. Additionally, further research focusing on the relationship between years of education and linkage to primary care can be conducted, hopefully revealing how patients with more years of education should be approached to more effectively link them to primary care.

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