# Evaluating the Impact of Behavioral Activation on Smoking Cessation in Major Depressive Disorder

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## Abstract

Behavioral Activation (BA) has been proposed as a treatment to support smoking cessation in individuals with Major Depressive Disorder (MDD), though evidence regarding its effectiveness remains limited. This study re-evaluates the impact of BA on smoking cessation, utilizing data from a prior 2x2 factorial randomized controlled trial. Our primary objectives are to investigate potential moderators of BA's effect on end-of-treatment (EOT) smoking abstinence and to identify baseline predictors of abstinence while accounting for pharmacotherapy. We first use penalized regression models to select variables and interaction terms, then fit a logistic regression model to estimate the causal effect of BA on smoking cessation. Our results confirm that BA does not significantly influence smoking cessation, consistent with prior findings. However, several baseline predictors, including Non-Hispanic White and FTCD score at baseline, demonstrate strong associations with abstinence. Additionally, Age moderates the effect of pharmacotherapy on cessation. While this model provides valuable insights, limitations such as sample size constraints and potential model dependency suggest a need for further research.

## Introduction

Behavioral Activation (BA) is regarded as a promising intervention for aiding smoking cessation in individuals diagnosed with Major Depressive Disorder (MDD), who are known to be more likely to smoke heavily, exhibit greater nicotine dependence, and experience more severe withdrawal symptoms than those without MDD(Hitsman et al. 2023). However, there has been limited research examining the specific impact of BA on smoking cessation outcomes. In one study, Hitsman et al. (2023) employed a 2x2 randomized factorial design (BA versus standard behavioral treatment (ST) and varenicline versus placebo, which is effect drug to help

smoking cessation) to investigate this effect, concluding that BA did not significantly improve smoking cessation outcomes. This project aims to revisit the influence of BA on smoking cessation, using the same dataset from Hitsman et al. (2023) but with an alternative analytical approach.

Our objective is to explore potential moderators influencing the effectiveness of behavioral treatment on end-of-treatment (EOT) abstinence rates. Additionally, we seek to identify baseline characteristics that may predict abstinence, while accounting for the effects of behavioral treatment and pharmacotherapy(varenicline).

## Data collection

The randomized, placebo-controlled trial recruited 300 adult daily smokers with current or past major depressive disorder (MDD) across research clinics at Northwestern University and the University of Pennsylvania. Initial eligibility screening was conducted via telephone, followed by final eligibility screening, informed consent, randomization, and baseline assessment at an intake session. Randomization, stratified by clinical site, sex, and depression severity, ensured balanced treatment arms. Participants were allocated to one of four groups using a computer-based system with unequal block sizes to maximize assignment to varenicline arms. Behavioral treatment sessions were standardized to eight 45-minute sessions over 12 weeks, with medication (varenicline or placebo) administered according to FDA-approved guidelines. Adherence and outcomes were monitored through multiple in-person and remote assessments over 27 weeks, with bio-verified smoking abstinence as a primary measure. Participants received compensation for participation and travel to enhance study retention and compliance.

A total of 25 variables were collected in the study, including demographic information, smoking history, and psychological assessments. Variable details are provided in Table 1. The primary outcome of interest was end-of-treatment (EOT) abstinence, defined as self-reported 7-day point prevalence abstinence confirmed by expired carbon monoxide (CO) levels of  10 ppm. Secondary outcomes included continuous abstinence, time to first lapse, and time to first relapse.

Table 1: An overview of participant characteristics

| Variable | Description |
|---|---|
| abst | Smoking Abstinence |
| Var (Varenicline) | Pharmacotherapy |
| BA (Behavioral Activation) | Psychotherapy |
| age_ps | Age at phone interview |
| sex_ps | Sex at phone interview |
| NHW | Non-Hispanic White indicator |
| Black | Black indicator |

Table 1: An overview of participant characteristics

| Variable | Description |
|---|---|
| Hisp | Hispanic indicator |
| inc | Income (ordinal categorical, low to high) |
| edu | Education (ordinal categorical, low to high) |
| ftcd_score | FTCD score at baseline |
| ftcd.5.mins | Smoking within 5 mins of waking up |
| bdi_score_pq1 | BDI score at baseline |
| cpd_ps | Cigarettes per day at baseline phone survey |
| crv_total_pq1 | Cigarette reward value at baseline |
| hedonsum_n_pq1 | Pleasurable Events Scale at baseline – substitute reinforcers |
| hedonsum_y_pq1 | Pleasurable Events Scale at baseline – complementary reinforcers |
| shaps_score_pq1 | Anhedonia |
| otherdiag | Other lifetime DSM-5 diagnosis |
| antidepmed | Taking antidepressant medication at baseline |
| mde_curr | Current vs past MDD |
| NMR | Nicotine Metabolism Ratio |
| Only.Menthol | Exclusive Mentholated Cigarette User |
| readiness | Baseline readiness to quit smoking |

## Identifing the causal effect

In Hitsman et al. (2023)'s work, the causal effect was estimated by comparing the abstinence rates between the treatment and control groups, following an intent-to-treat (ITT) approach. Rather than solely examining abstinence rates, this project evaluates the odds of abstinence and estimates the causal effect using the odds ratio of abstinence between the treatment and control groups, while adhering to ITT principles. The causal effect, denoted as $\hat{\tau}$, can be formulated as follows:

$$\hat{\tau} = \frac{odds(E[Y^1])}{odds(E[Y^0])}$$

Where $Y^1$ and $Y^0$ represent the potential outcomes under treatment and control, respectively.

The dataset originates from a 2x2 randomized factorial design, theoretically balancing all covariates across treatment and control groups. As examined in Table 2, baseline covariate distributions confirm that randomization was successful, as covariates appear balanced between groups. The table also reveals some missing data. While the data may not be missing at

random, the low proportion of missing records suggests a minimal impact on the results, allowing us to treat the missingness as random. Therefore, the assumptions for identifying causal effects are met, and we express the causal effect as:

$$\begin{aligned}\hat{\tau} &= \frac{adds(E[Y^1])}{odds(E[Y^0])} \\ &= \frac{odds(E[Y|A=1])}{odds(E[Y|A=0])}\end{aligned}$$

Where $A$ is the whether having behavioral treatment or not. A naive approach to estimate the causal effect is to fit a logistic regression model with the treatment group as the only covariate. The causal effect can be estimated by the coefficient of the treatment group. However, this approach does not consider the potential interaction between the treatment group and other covariates, nor the moderation of other variables. In this project, we fit a logistic regression model with the treatment group and the interaction terms between the treatment group and other covariates.

Except for identifying the causal effect, the logistic regression model can also be used to examine the potential moderators of the effect of behavioral treatment on end-of-treatment (EOT) abstinence and evaluate baseline variables as predictors of abstinence, controlling for behavioral treatment and pharmacotherapy.

## Exploratory Data Analysis

Table 2 summarized the distribution of variables among different groups. Except showing a succeful randomization as discussed in the previous section, the table also shows that the majority of subject did not quit smoking by the end of study.

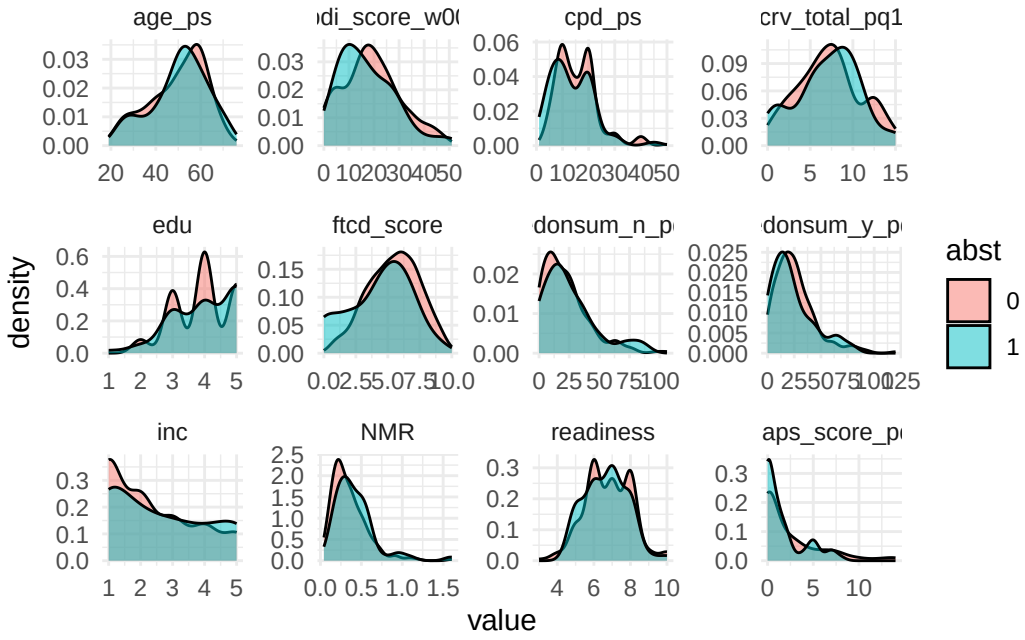
In order to examine the distribution of each variables and their relations with the outcome variable, we first plot the distribution of continuous variables and categorical variables. As shown in Figure 1, most continuous variables' distributions have little change between different outcome, except that the peak of `age` and `bdi_score` is lower among subjects who quit smoking (`abst` = 1). The distribution of binary variables also shows little difference between different outcome, except that the among those who take Varenicline, more people quit smoking. It is worth to notice that the distribution of `BA` among different outcome basically the same, bring the question of whether BA has effect on smoking cessation.

The correlation among variables are also examined, showed in Table 3. The table shows no variables' VIF bigger than 5, indicating that there is no multicollinearity issue among variables.

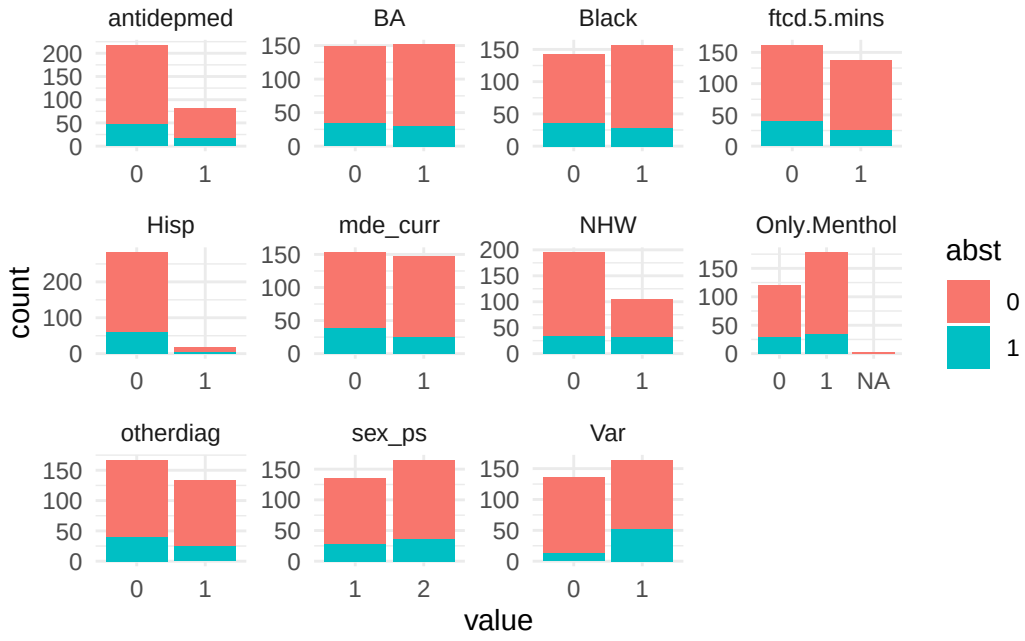
Table 2: Summary of the data

| **Characteristic** | **BA + Placebo** N = 81 | **BA + Varenicline** N = 83 | **Control** N = 68 | **ST + Varenicline** N = 68 |
|---|---|---|---|---|
| abst | | | | |
| 0 | 55 (68%) | 57 (69%) | 60 (88%) | 64 (94%) |
| 1 | 26 (32%) | 26 (31%) | 8 (12%) | 4 (5.9%) |
| age_ps | 52 (41, 59) | 53 (40, 60) | 51 (45, 58) | 54 (42, 61) |
| sex_ps | | | | |
| 1 | 37 (46%) | 39 (47%) | 29 (43%) | 30 (44%) |
| 2 | 44 (54%) | 44 (53%) | 39 (57%) | 38 (56%) |
| NHW | | | | |
| 0 | 56 (69%) | 49 (59%) | 46 (68%) | 44 (65%) |
| 1 | 25 (31%) | 34 (41%) | 22 (32%) | 24 (35%) |
| Black | | | | |
| 0 | 38 (47%) | 46 (55%) | 28 (41%) | 31 (46%) |
| 1 | 43 (53%) | 37 (45%) | 40 (59%) | 37 (54%) |
| Hisp | | | | |
| 0 | 76 (94%) | 79 (95%) | 64 (94%) | 63 (93%) |
| 1 | 5 (6.2%) | 4 (4.8%) | 4 (5.9%) | 5 (7.4%) |
| inc | 2.00 (1.00, 3.00) | 2.00 (1.00, 4.00) | 2.00 (1.00, 3.00) | 2.00 (1.00, 4.00) |
| Unknown | 1 | 1 | 0 | 1 |
| edu | 4.00 (3.00, 5.00) | 4.00 (3.00, 5.00) | 4.00 (4.00, 4.50) | 4.00 (3.00, 5.00) |
| ftcd_score | 5.00 (4.00, 7.00) | 5.00 (4.00, 7.00) | 6.00 (4.00, 7.00) | 5.00 (4.00, 7.00) |
| Unknown | 0 | 0 | 1 | 0 |
| ftcd.5.mins | | | | |
| 0 | 43 (53%) | 50 (60%) | 33 (49%) | 36 (53%) |
| 1 | 38 (47%) | 33 (40%) | 35 (51%) | 32 (47%) |
| bdi_score_w00 | 18 (11, 27) | 18 (10, 25) | 18 (12, 25) | 18 (9, 27) |
| cpd_ps | 15 (10, 20) | 15 (10, 20) | 13 (10, 20) | 15 (10, 20) |
| crv_total_pq1 | 7.0 (5.0, 9.0) | 8.0 (4.5, 10.0) | 7.0 (4.5, 9.0) | 7.0 (5.0, 10.0) |
| Unknown | 6 | 3 | 8 | 1 |
| hedonsum_n_pq1 | 20 (9, 35) | 20 (9, 32) | 14 (9, 27) | 21 (10, 31) |
| hedonsum_y_pq1 | 21 (13, 34) | 17 (11, 31) | 25 (12, 38) | 23 (14, 34) |
| shaps_score_pq1 | 1.00 (0.00, 3.00) | 1.00 (0.00, 4.00) | 1.00 (0.00, 5.00) | 0.00 (0.00, 3.00) |
| Unknown | 0 | 0 | 1 | 2 |
| otherdiag | | | | |
| 0 | 41 (51%) | 53 (64%) | 40 (59%) | 33 (49%) |
| 1 | 40 (49%) | 30 (36%) | 28 (41%) | 35 (51%) |
| antidepmed | | | | |
| 0 | 66 (81%) | 59 (71%) | 53 (78%) | 40 (59%) |
| 1 | 15 (19%) | 24 (29%) | 15 (22%) | 28 (41%) |
| mde_curr | | | | |
| 0 | 37 (46%) | 43 (52%) | 37 (54%) | 36 (53%) |
| 1 | 44 (54%) | 40 (48%) | 31 (46%) | 32 (47%) |
| NMR | 0.29 (0.20, 0.51) | 0.33 (0.22, 0.50) | 0.32 (0.20, 0.43) | 0.32 (0.23, 0.46) |
| Unknown | 9 | 3 | 2 | 7 |
| Only.Menthol | | | | |
| 0 | 34 (42%) | 34 (41%) | 24 (36%) | 28 (41%) |
| 1 | 47 (58%) | 48 (59%) | 43 (64%) | 40 (59%) |
| Unknown | 0 | 1 | 1 | 0 |
| readiness | 7.00 (6.00, 8.00) | 7.00 (6.00, 8.00) | 7.00 (6.00, 8.00) | 7.00 (6.00, 8.00) |
| Unknown | 4 | 5 | 4 | 4 |

[1] n (%); Median (Q1, Q3)




(a) Distribution of continuous variables, stratified by outcome (abst)




(b) Distribution of binary variables, stratified by outcome (abst)

Figure 1: Relationship between continuous variables and the outcome variable

Table 3: Generalized variance inflation factor of the data

| | VIF |
|---|---|
| age_ps | 1.422728 |
| sex_ps | 1.145365 |
| NHW | 4.462106 |
| Black | 4.736099 |
| Hisp | 1.694604 |
| inc | 1.468204 |
| edu | 1.469299 |
| ftcd_score | 2.763104 |
| ftcd.5.mins | 1.953346 |
| bdi_score_w00 | 2.003905 |
| cpd_ps | 1.660048 |
| crv_total_pq1 | 1.569717 |
| hedonsum_n_pq1 | 1.760080 |
| hedonsum_y_pq1 | 1.232178 |
| shaps_score_pq1 | 1.428846 |
| otherdiag | 1.282832 |
| antidepmed | 1.124861 |
| mde_curr | 1.696843 |
| NMR | 1.212831 |
| Only.Menthol | 1.551892 |
| readiness | 1.113905 |

There are missingness in the dataset, showed in Table 4. 7 out of 25 variables have missing values, with the highest missing percentage is 7%. Indicated that the missingness is not severe, and can be treated as random missingness.

Table 4: Missingness of the data

| | Missing Percentage |
|---|---|
| inc | 1.0000 |
| ftcd_score | 0.3333 |
| crv_total_pq1 | 6.0000 |
| shaps_score_pq1 | 1.0000 |
| NMR | 7.0000 |
| Only.Menthol | 0.6667 |
| readiness | 5.6667 |

## Identifing the interactions

Given that many variables in the dataset are categorical, including all possible interaction terms would produce more terms than the sample size allows, leading to model overfitting. To avoid this, we manually select covariates for inclusion based on the their VIF. VIF is a measures how much the variance of a estimated regression coefficient due to correlations among preictors. The higher the value, the less benefit of including the variable into interaction terms as the addtional information brought by the interaction terms may have been already captured by the main effect of other predictors. We only select variables with VIF less than 1.3 to include in the interaction terms. The threshold is set by balancing the trade-off between including more variables and avoiding overfitting, and the gap of VIF values. the selected variables are `readiness`, `antidepmed`, `sex_ps`, `NMR`, `hedonsum_y_pq1` and `otherdiag`, with corresponding VIF values are 1.11 1.12 1.15 1.21 1.23 1.28. Only up to 2 way interaction terms are included in the model, as the number of interaction terms increase exponentially with the number of variables, and the sample size is limited. We also consider the interaction terms between the treatment group and other covariates, as the effect of the treatment group may be moderated by other variables.

Therefor, the model can be written as:

$$logit(E[Y_i]) = \beta_0 + \beta_1 A_i + \beta_2 Z_i + \beta_3 X_i^T + \beta_4 X_i^T A_i + \beta_5 X_i^T Z_i + \beta_6 Z_i A_i + \sum_{k=1}^{K} \beta_7 L_k L_{-k}^T$$

Where $L_k$ is the kth variable with VIF $< 1.3$ showed in the previous paragraph, and $L_{-k}$ is the rest of the variable with VIF $< 1.3$

## Model selection

The primary goal of this project is to identify potential moderators of behavioral treatment effects on end-of-treatment (EOT) abstinence and to assess baseline predictors of abstinence while controlling for behavioral treatment and pharmacotherapy. We employed various variable selection techniques, including Lasso regression and subset selection with L0, L0L1, and L0L2 penalties, all implemented using 10-fold cross-validation.

To address missing values in the dataset, we applied multiple imputation before splitting the data into training and testing sets. This approach was selected due to the limited sample size, as performing imputation after data splitting could result in unreliable outcomes. The multiple imputation process was conducted using the `mice` package in R, generating a total of five imputed datasets. We randomly assigned 80% of the records to the training set and reserved the remaining 20% for testing. Models were fitted to the training set for each imputed dataset, and the coefficients were pooled to obtain the final results. Variables included in the final model were those retained in at least three out of the five imputed datasets.

For subset selection models using L0, L0L1, and L0L2 penalties, the $\lambda$ and $\gamma$ values were chosen to minimize the mean cross-validated error. The coefficients from each model were averaged across imputed datasets to obtain the final results. Using these pooled results, the model was then applied to the test dataset to evaluate its performance.

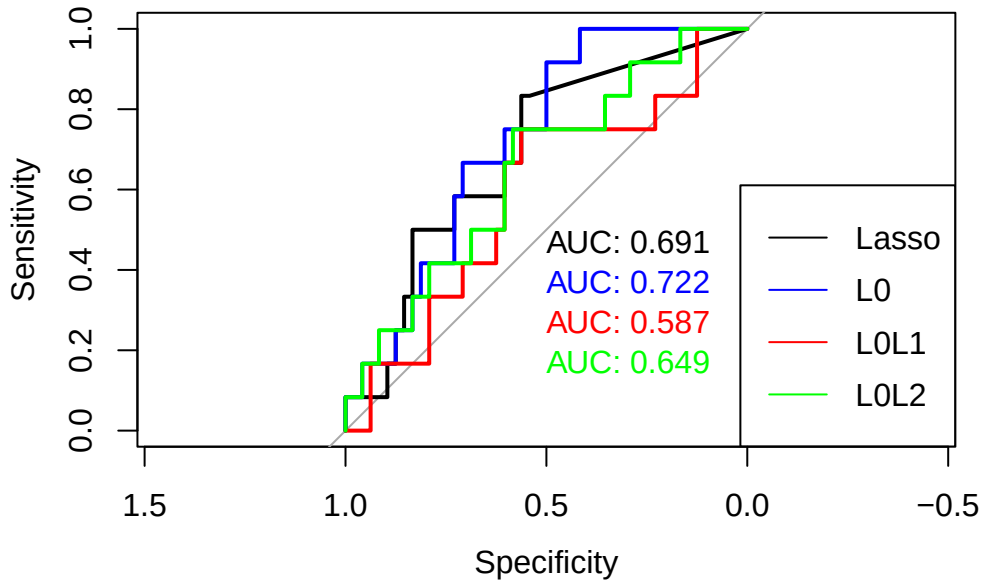


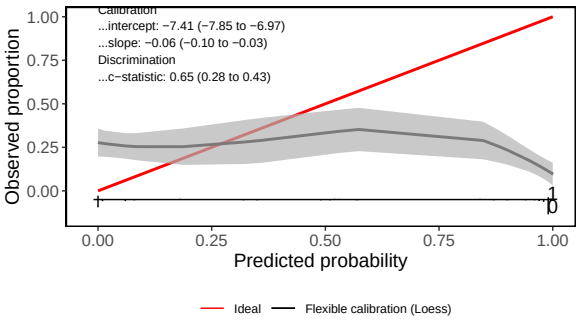

Figure 2: ROC curves of the models in test data

Figure 2 shows the all four models' performance in test data. Subset selection model with L0 penalty have the highest AUC among all models, indicating the model is robust.

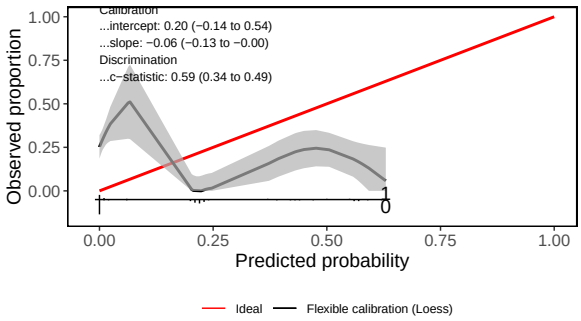
We also examine the calibration curve of the model in the test data, showed in Figure 3. The calibration curve of the L0 model is the closest to the 45 degree line, indicating the model is well calibrated. While the orther model's calibration curve is largely devated from the 45 degree line, indicating the model may not be well calibrated.

Based on the performance of the model in the test data, we use the model with L0 penalty to answer our research question. The model exclude all but 3 terms: `NHW1`, `ftcd_score` and `Var1:age_ps`. All terms with behaviour treatment are excluded from the model, indicating that the behaviour treatment has no effect on addressing smoking cessation among MDD patients.

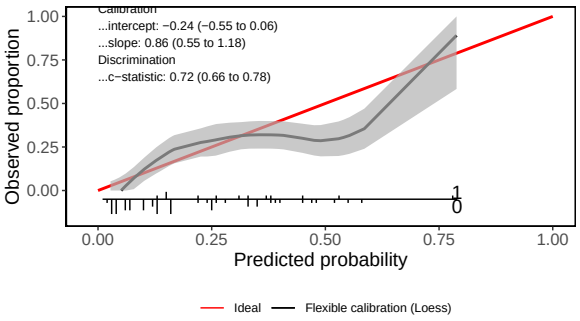
We fit a logistic regression model with the selected terms to examine the effect of the predictors on smoking cessation. As shown in Table 5, the model shows being a non hispanic white(`NHW` = 1) will increase the odds of quitting smoking by 161%, and one unit increase in FTCD score at baseline (`ftcd_score`) will decrease the odds of quitting smoking by 25%. The mean effect



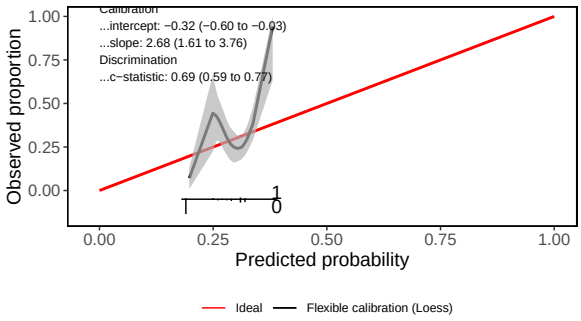

(a) Calibration curve of the L0L2 model




(b) Calibration curve of the L0L1 model




(c) Calibration curve of the L0 model




(d) Calibration curve of the Lasso model

Figure 3: Calibration curves of the models in test data

of `Var` on smoking cessation is negative, but considering the interaction terms, the effect of `Var` on smoking cessation positive when the subject is over 15 years old. Considering that the minimum age in the dataset is 19, exploring the effect of `Var` on smoking cessation for individuals under 19 would be an extrapolation of the model and is not meaningful. Taking varenicline(Var = 1) for a subject with 20 years of old will increase the odds of quitting smoking by 24%. When the subject is 40 years of old, the increase of odds is 177%. Indicating the effect is more significant among older people. However, as the p value of both the main effects and the interaction terms are not significant, the effect of `Var` on smoking cessation is still questionable.

Table 5

| **Characteristic** | **log(OR)**[1] | **95% CI**[1] | **p-value** |
|---|---|---|---|
| NHW | | | |
| 0 | — | — | |
| 1 | 0.96 | 0.33, 1.6 | 0.003 |
| ftcd_score | -0.28 | -0.43, -0.14 | <0.001 |
| Var | | | |
| 0 | — | — | |
| 1 | -0.59 | -3.2, 2.2 | 0.7 |
| age_ps | -0.01 | -0.06, 0.04 | 0.6 |
| Var * age_ps | | | |
| 1 * age_ps | 0.04 | -0.01, 0.10 | 0.10 |

[1]OR = Odds Ratio, CI = Confidence Interval

Coefficients of the best model

There for, we can conclude that both non hispanic white (`NHW`) and FTCD score at baseline (`ftcd_score`) are predictors for smoking cessation, with being a non hispanic white will increase the odds of quitting smoking, and higher FTCD score at baseline will decrease the odds of quitting smoking. The effect of `Var` on smoking cessation is postive and moderated by `age`, with the older the subject is, the more significant the effect is. However, the effect of `Var` on smoking cessation is still questionable as the p value indicates the effect may not be significant.

## Discussion

The result of this project shows that behaviour treatment has no effect on smoking cessation among MDD patients. This finding corresponds with the result of Hitsman et al. (2023), which also found that BA does not have a significant effect on smoking cessation. Possible explanations for this result has already been discussed in Hitsman et al. (2023).

Two important predictors are identified in this project. `ftcd_score` and `NHW` are predictors for smoking cessation. `Age` is identified as the moderator of the effect of `Var` on smoking cessation.

This project has several limitations. First of all, the model selected to use will have a large impact on the result. The subset selection model with L0 penalty is selected as the best model in this project, but other models may have different results. Second, the data set only contains limited sample size, making examining the effect of interaction terms difficult. As shown in the previous section, only limited interaction terms are included in the model while those interaction terms excluded from the model may also have significant effect.

In conclusion, this project re-evaluates the impact of BA on smoking cessation in MDD patients. The results confirm that BA does not significantly influence smoking cessation, consistent with prior findings. Two baseline predictors, including `ftcd_score` and `NHW`, demonstrate strong associations with abstinence, while `Age` moderates the effect of pharmacotherapy on cessation. Despite limitations, this model offers valuable insights into the predictors of smoking cessation in MDD patients, highlighting the need for further research to confirm these findings.

## References

Hitsman, Brian, George D. Papandonatos, Jacqueline K. Gollan, Mark D. Huffman, Raymond Niaura, David C. Mohr, Anna K. Veluz-Wilkins, et al. 2023. "Efficacy and Safety of Combination Behavioral Activation for Smoking Cessation and Varenicline for Treating Tobacco Dependence Among Individuals with Current or Past Major Depressive Disorder: A $2 \times 2$ Factorial, Randomized, Placebo-controlled Trial." *Addiction* 118 (9): 1710–25. https://doi.org/10.1111/add.16209.

## Code Appendix

```
# Example data frame representing the participant characteristics table

participant_characteristics <- data.frame(
  Variable = c("abst", "Var (Varenicline)", "BA (Behavioral Activation)", "age_ps", "sex_ps"
               "inc", "edu", "ftcd_score", "ftcd.5.mins", "bdi_score_pq1", "cpd_ps", "crv_to
               "hedonsum_y_pq1", "shaps_score_pq1", "otherdiag", "antidepmed", "mde_curr", "
               "readiness"),
  Description = c("Smoking Abstinence", "Pharmacotherapy", "Psychotherapy", "Age at phone in
                  "Non-Hispanic White indicator", "Black indicator", "Hispanic indicator", "
                  "Education (ordinal categorical, low to high)", "FTCD score at baseline",
                  "BDI score at baseline", "Cigarettes per day at baseline phone survey", "C
                  "Pleasurable Events Scale at baseline - substitute reinforcers",
```

```
                  "Pleasurable Events Scale at baseline - complementary reinforcers", "Anhedo
                  "Taking antidepressant medication at baseline", "Current vs past MDD", "Nic
                  "Exclusive Mentholated Cigarette User", "Baseline readiness to quit smoking
)

knitr::kable(participant_characteristics)

library(gtsummary)
library(mice)
library(glmnet)
library(pROC)
library(kableExtra)
library(dplyr)
library(LOLearn)
library(ggpubr)
library(tidyr)
library(ggcorrplot)
library(parallel)
library(rms)
library(CalibrationCurves)
# Read data
data <- read.csv("../Data/project2.csv")
num_col <- c(5,12,14:19,23,25)
ordinal_col <- c(10,11)

# Preprocess
data[,num_col] <- lapply(data[,num_col], as.numeric)
data[,ordinal_col] <- lapply(data[,ordinal_col], factor, order = T)
data[,-c(num_col, ordinal_col)] <- lapply(data[,-c(num_col, ordinal_col)], factor)
# summary table
data_tbl <- data[, -1]
data_tbl$group <- paste(data_tbl$Var, data_tbl$BA, sep = "_")
data_tbl$group <- case_when(data_tbl$group == "0_0" ~ "Control",
                            data_tbl$group == "1_0" ~ "BA + Placebo",
                            data_tbl$group == "0_1" ~ "ST + Varenicline",
                            data_tbl$group == "1_1" ~ "BA + Varenicline")
data_tbl <- data_tbl[, -c(2,3)]
data_tbl$inc <- as.numeric(data_tbl$inc)
data_tbl$edu <- as.numeric(data_tbl$edu)
tbl_summary(data_tbl, by = group, type = list(readiness ~ 'continuous',
                                              inc ~ 'continuous',
                                              edu ~ 'continuous')) %>%
```

```r
  as_kable_extra(booktabs = TRUE) %>%
  kableExtra::kable_styling(latex_options = "scale_down")
# continuous variables
par(mfrow=c(2,5))
data_con <- data[,c(num_col)]
data_con$abst <- data$abst
data_ord <- data[,ordinal_col]
data_ord <- apply(data_ord, 2, as.numeric)
data_con <- cbind(data_con, data_ord)
data_cat <- data[,-c(num_col, ordinal_col)]
data_cat <- data_cat[,-1]

pivot_longer(data_con, cols = -abst) %>%
  ggplot(aes(x = value, fill = abst)) +
  geom_density(alpha = 0.5) +
  facet_wrap(~name, scales = "free") +
  theme_minimal()

pivot_longer(data_cat, cols = -abst) %>%
  ggplot(aes(x = value, fill = abst)) +
  geom_bar() +
  facet_wrap(~name, scales = "free") +
  theme_minimal()


# VIF
car::vif(glm(abst ~ . -group, data = data_tbl, family = "binomial")) %>%
  as.data.frame() %>%
  kable(col.names = 'VIF')

# missingness table
missing_df <- apply(data, 2, function(x) sum(is.na(x)))
missing_df <- missing_df[missing_df != 0]
missing_df <- round(missing_df/nrow(data) * 100, 4)
kable(missing_df, col.names = "Missing Percentage")
# Depicted
vif_res <- car::vif(glm(abst ~ . -group, data = data_tbl, family = "binomial"))
vif_res <- as.data.frame(vif_res)
vif_res$var <- rownames(vif_res)
order_vif <- (vif_res[vif_res < 1.3,])
rownames(order_vif) <- NULL
order_vif <- order_vif[order(order_vif$vif_res),]
```

```r
#multiple imputation
data_imp <- mice(data[,-1], m = 5, seed = 2550, printFlag = F)
data_imp <- complete(data_imp, action = 'all')
train_index <- sample(1:nrow(data), 0.8*nrow(data))

# Model selection on all 5 datasets
model_matrix_fun <- function(data, train_id){
  #' @param data: the data set
  #' @param train_id: the index of the training set
  #' @return: a list of model matrix and response variable
  X <- model.matrix(abst ~ . + (readiness + antidepmed + NMR + sex_ps +
                                  hedonsum_y_pq1 + otherdiag)^2
                    + Var*(.) + BA*(.),
                    data = data[train_id,])
  X <- X[,-1]
  Y <- factor(data[train_id,]$abst)

  return(list(X,Y))
}

fit_regression <- function(data, train_id){
  #' @param data: the data set
  #' @param train_id: the index of the training set
  #' @return: a list of the coefficients of the model

  model_data <- model_matrix_fun(data, train_id)

  #model fitting
  lasso_fit <- cv.glmnet(model_data[[1]], model_data[[2]], family = "binomial",
                         alpha = 1, type.measure = "auc",
                         nfolds = 10)

  subset_fit <- L0Learn.cvfit(model_data[[1]], model_data[[2]],
                              nFolds=10, penalty="L0", loss = 'Logistic')
  subset01_fit <- L0Learn.cvfit(model_data[[1]], model_data[[2]],
                                nFolds=10, penalty="L0L1", loss = 'Logistic')
  subset02_fit <- L0Learn.cvfit(model_data[[1]], model_data[[2]],
                                nFolds=10, penalty="L0L2", loss = 'Logistic')

  # Extract variables names and coefficients, Exclude variables with effect size = 0
  var_names <- rownames(coef(lasso_fit))
  lasso_coef_id <- which(coef(lasso_fit) != 0)
```

```
  lasso_res <- data.frame(var_names[lasso_coef_id], coef(lasso_fit)[lasso_coef_id])

  # choose gamma and lambda so that cvmeans are minimized
  # L0
  min_l_subset <- which.min(subset_fit$cvMeans[[1]])
  subset_id <- coef(subset_fit, subset_fit$fit$lambda[[1]][min_l_subset], 0)
  id <- which(subset_id != 0)
  subset_res <- data.frame(var_names[id], subset_id[id])

  # L0L1
  min_l_subset01 <- sapply(1:10, function (x) which.min(subset01_fit$cvMeans[[x]]))
  min_g_subset01 <- sapply(1:10, function (x) subset01_fit$cvMeans[[x]][[min_l_subset01[x]]])
  gamma_id <- which.min(min_g_subset01)
  min_lambda <- min(min_g_subset01)

  subset01_coef <- coef(subset01_fit,
                        min_lambda,
                        subset01_fit$fit$gamma[gamma_id])
  id <- which(subset01_coef != 0)

  subset01_res <- data.frame(var_names[id],
                             subset01_coef[id])

  #L0L2
  min_l_subset02 <- sapply(1:10, function (x) which.min(subset02_fit$cvMeans[[x]]))
  min_g_subset02 <- sapply(1:10, function (x) subset02_fit$cvMeans[[x]][[min_l_subset02[x]]])
  gamma_id <- which.min(min_g_subset02)
  min_lambda <- min(min_g_subset02)
  subset02_coef <- coef(subset02_fit,
                        min_lambda,
                        subset02_fit$fit$gamma[gamma_id])
  id <- which(subset02_coef != 0)
  subset02_res <- data.frame(var_names[id],
                             subset02_coef[id])


  return(list(lasso_res, subset_res, subset01_res, subset02_res))
}
set.seed(2550)

# run selection
fit_res <- mclapply(1:5, function(x) fit_regression(data_imp[[x]], train_index),
```

```
                    mc.cores = 5)

#Manually choose variable and pooled the result
lasso_var <- sapply(1:5, function(x) fit_res[[x]][[1]][,1])
lasso_var <- as.factor(unlist(lasso_var))
lasso_res <- lapply(1:5, function(x) fit_res[[x]][[1]])
lasso_res <- do.call(rbind, lasso_res)
#summary(lasso_var)

lasso_coef <- data.frame(var = c('Intercept', 'Var1:age_ps', 'Var1:NMR'),
                         value = c(mean(lasso_res[lasso_res$var_names.lasso_coef_id. == '(Int
                                   mean(lasso_res[lasso_res$var_names.lasso_coef_id. == 'Var
                                   mean(lasso_res[lasso_res$var_names.lasso_coef_id. == 'Var

subset_var <- sapply(1:5, function(x) fit_res[[x]][[2]][,1])
subset_var <- as.factor(unlist(subset_var))
subset_res <- lapply(1:5, function(x) fit_res[[x]][[2]])
subset_res <- do.call(rbind, subset_res)
#summary(subset_var)
subset_coef <- data.frame(var = c('Intercept', 'ftcd_score', 'NHW1', 'Var1:age_ps'),
                         value = c(mean(subset_res[subset_res$var_names.id. == '(Intercept)'
                                   mean(subset_res[subset_res$var_names.id. == 'ftcd_score',2
                                   mean(subset_res[subset_res$var_names.id. == 'NHW1',2]),
                                   mean(subset_res[subset_res$var_names.id. == 'Var1:age_ps'

subset01_var <- sapply(1:5, function(x) fit_res[[x]][[3]][,1])
subset01_var <- as.factor(unlist(subset01_var))
subset01_res <- lapply(1:5, function(x) fit_res[[x]][[3]])
subset01_res <- do.call(rbind, subset01_res)
#summary(subset01_var)
subset01_coef <- data.frame(var = c('Intercept', 'BA1:bdi_score_w00', 'ftcd_score', 'Var1:age
                         value = c(mean(subset01_res[subset01_res$var_names.id. == '(Intercep
                                   mean(subset01_res[subset01_res$var_names.id. == 'BA1:bdi_s
                                   mean(subset01_res[subset01_res$var_names.id. == 'ftcd_scor
                                   mean(subset01_res[subset01_res$var_names.id. == 'Var1:age_

subset02_var <- sapply(1:5, function(x) fit_res[[x]][[4]][,1])
subset02_var <- as.factor(unlist(subset02_var))
subset02_res <- lapply(1:5, function(x) fit_res[[x]][[4]])
subset02_res <- do.call(rbind, subset02_res)
#summary(subset02_var)
subset02_coef <- data.frame(var = c('Intercept', 'antidepmed1:NMR', 'BA1:bdi_score_w00', 'BA
```

```
                                    'ftcd_score', 'mde_curr1', 'NHW1', 'Var1:age_ps', 'Var1:
                          value = c(mean(subset02_res[subset02_res$var_names.id. == '(Intercep
                                    mean(subset02_res[subset02_res$var_names.id. == 'antidepme
                                    mean(subset02_res[subset02_res$var_names.id. == 'BA1:bdi_s
                                    mean(subset02_res[subset02_res$var_names.id. == 'BA1:inc.
                                    mean(subset02_res[subset02_res$var_names.id. == 'ftcd_scor
                                    mean(subset02_res[subset02_res$var_names.id. == 'mde_curr
                                    mean(subset02_res[subset02_res$var_names.id. == 'NHW1',2])
                                    mean(subset02_res[subset02_res$var_names.id. == 'Var1:age_
                                    mean(subset02_res[subset02_res$var_names.id. == 'Var1:Blac

# test data set
test_data <- lapply(1:5, function(x) data_imp[[x]][-train_index,])
test_data <- do.call(rbind, test_data)

# manually fit model on test dataset
lasso_x <- model.matrix(abst ~ Var:age_ps + Var:NMR, data = test_data)
lasso_x <- lasso_x[,c(1,3,5)] # remove reference level
t <- lasso_coef$value %*% t(lasso_x)
lasso_p <- exp(t)/(1+exp(t)) #expit
auc_test_l <- roc(test_data$abst, lasso_p)

subset_x <- model.matrix(abst ~ ftcd_score + NHW + Var:age_ps, data = test_data)
subset_x <- subset_x[,-4] # remove reference level
t <- subset_coef$value %*% t(subset_x)
subset_p <- exp(t)/(1+exp(t))
auc_test_sub <- roc(test_data$abst, subset_p)

subset01_x <- model.matrix(abst ~ BA:bdi_score_w00 + ftcd_score + Var:age_ps, data = test_dat
subset01_x <- subset01_x[,c(1,2,4,6)] # remove reference level
t <- subset01_coef$value %*% t(subset01_x)
subset01_p <- exp(t)/(1+exp(t))
auc_test_sub01 <- roc(test_data$abst, subset01_p)

subset02_x <- model.matrix(abst ~ antidepmed:NMR + BA:bdi_score_w00 + BA:inc + ftcd_score + m
subset02_x <- subset02_x[,-c(5,7,9,11,13,15,17,19)] # remove reference level
subset02_x <- subset02_x[,-c(8:10)] # remove reference level
t <- subset02_coef$value %*% t(subset02_x)
subset02_p <- exp(t)/(1+exp(t))
auc_test_sub02 <- roc(test_data$abst, subset02_p)

#saveRDS(list(lasso_coef, subset_coef, subset01_coef, subset02_coef), "coef.rds")
```

```r
# Plot Roc curve
plot.roc(auc_test_l, print.auc=TRUE, col = 'black')
plot.roc(auc_test_sub, print.auc=TRUE, col = 'blue', add = TRUE, print.auc.x = 0.5, print.au
plot.roc(auc_test_sub01, print.auc=TRUE, col = 'red', add = TRUE, print.auc.x = 0.5, print.a
plot.roc(auc_test_sub02, print.auc=TRUE, col = 'green', add = TRUE, print.auc.x = 0.5, print
legend("bottomright", legend = c("Lasso", "L0", "L0L1", "L0L2"), col = c("black", "blue","re

# Calibration plots
p1 <- valProbggplot(as.numeric(subset02_p), as.numeric(test_data$abst)-1)
p1$ggPlot
p2 <- valProbggplot(as.numeric(subset01_p), as.numeric(test_data$abst)-1)
p2$ggPlot
p3 <- valProbggplot(as.numeric(subset_p), as.numeric(test_data$abst)-1)
p4 <- valProbggplot(as.numeric(lasso_p), as.numeric(test_data$abst)-1)
p3$ggPlot
p4$ggPlot
# final model
mod <- glm(abst ~ NHW + ftcd_score + Var*age_ps, data = data, family = "binomial")
tbl_regression(mod)
```