Evaluating Predictors and Moderators of Smoking Abstinence in Individuals with Major Depressive Disorder: Insights from Behavioral and Pharmacological Interventions

Yunan Chen

2024-11-10

Abstract

This report examines data from a clinical trial exploring smoking abstinence treatments for individuals with major depressive disorder (MDD), who face unique challenges in quitting smoking. The study evaluates two behavioral treatments: Behavioral Activation for Smoking Cessation (BASC) and standard treatment (ST), paired with either varenicline or placebo. Results indicate that varenicline improves smoking abstinence rates compared to placebo, underscoring its effectiveness in this population. BASC, designed to counter depressive symptoms by encouraging engagement in meaningful activities, shows promise, especially when combined with varenicline. However, certain baseline factors, such as nicotine dependence and active depressive symptoms, appear to influence the behavioral treatment effectiveness. Higher nicotine dependence slightly reduces BASC's impact, while current MDD symptoms can act as a barrier to successful abstinence. Exploratory analyses highlight that demographic and behavioral factors like education, income, and age affect somking abstinence. Regression analysis reveals predictors of abstinence, suggesting that individuals with higher education, lower nicotine dependence, and certain income levels have greater odds of quitting. The model's classification accuracy indicates reliable performance, though calibration issues on test data suggest potential for improvement. These findings emphasize the need for tailored interventions for smokers with MDD, particularly combining BASC and varenicline, to enhance long-term cessation success.

Introduction

Major depressive disorder (MDD), or clinical depression, is a mood disorder characterized by a persistent feeling of sadness and loss of interest, impacting individuals' emotions, thoughts, and behaviors and potentially leading to various emotional and physical complications. Research indicates that smokers with a history of depression are less likely to quit successfully and are more susceptible to relapse than those without depression (Cook et al., 2010). Previous studies have shown that smokers with MDD tend to smoke more heavily, find smoking more pleasurable than other rewarding activities, exhibit higher nicotine dependence, and experience more severe withdrawal symptoms than smokers without MDD (Hitsman et al., 2023). Varenicline, a prescription drug specifically designed to help the general population quit smoking. However, unlike smokers without mental health disorders, those with mental health disorders, including MDD, are less likely to be prescribed varenicline than nicotine replacement therapy, despite the greater effectiveness of varenicline (Evins et al., 2019). This discrepancy has prompted researchers to explore targeted treatments for individuals with depression who wish to quit smoking. One promising approach is behavioral activation (BA), a therapeutic intervention aimed at enhancing motivation and engagement in rewarding and meaningful activities, which may address both anhedonia and depressive symptoms. However, the combined effect of behavioral activation for smoking cessation BASC and varenicline on smoking abstinence remains underexplored. In light of this, Hitsman et al. (2023) hypothesized that Behavioral Activation for Smoking

Cessation (BASC) would lead to higher long-term abstinence rates compared to standard treatment (ST), and that varenicline would increase long-term abstinence compared to placebo. To test these hypotheses, they conducted a clinical trial.

This report analyzes data from that clinical trial with the objectives of examining baseline variables as potential moderators of the effects of behavioral treatment on end-of-treatment abstinence. Additionally, this analysis assesses baseline variables as predictors of abstinence, while controlling for both behavioral treatment and pharmacotherapy, to identify factors that may enhance cessation outcomes for people with Major Depressive Disorder (MDD).

Data Collection and Data Preprocessing

The data used in this report was provided by Dr. George Papandonatos and derived from a randomized placebo-controlled trial that investigated smoking cessation interventions in individuals with a history of major depressive disorder (MDD) (Hitsman et al., 2023). In this trial, 300 adults who smoked daily (at least one cigarette per day) and had a lifetime diagnosis of MDD were recruited. Participants were randomized to receive one of two behavioral treatments, Behavioral Activation for Smoking Cessation (BASC) or Standard Treatment (ST), alongside either varenicline or placebo. The intervention period lasted 12 weeks. Medication blister packs were dispensed in two sets: at week 3 (for weeks 3–7) and at week 7 (for weeks 8–13). Both BA treatment arms involved eight 45-minute sessions, conducted weekly for the first 4 weeks and biweekly for the remaining 8 weeks, with a strong focus on stress reduction, loss of reward, and social-environmental strategies to support abstinence. Abstinence from smoking was assessed at a follow-up visit during week 27. Baseline demographic, smoking, and psychiatric history data were collected at the start of the study.

`Table 1` shows the baseline characteristics of participants by treatment group and overall sample. The treatment groups are combinations of pharmacotherapy (placebo vs varenicline) and behavioral treatment (ST vs BASC). Participants were approximately equally assigned to each of the four treatment groups. In the groups receiving varenicline (ST + varenicline group and BASC + varenicline group), a higher percentage of participants achieved smoking cessation (32% and 31%, respectively) compared to the placebo group (12% in the ST + placebo group and 5.9% in the BASC + placebo group). This suggests that varenicline may be more effective than placebo in helping participants achieve smoking cessation. Looking at the distribution of education levels across the four groups, only a very small number of participants had Grade school education, with only one participant in the BASC + placebo group. The high school level group was also underrepresented in all groups, ranging from 2.9% to 8.4% in each group. Given the low representation of the "Grade school" group and the "Some of the high school" group, it would be reasonable to combine these two groups into the "High school and below" group. This would reduce the sparsity within each treatment group. Similar to education levels, we could also consider combining the income levels "$50,001-$75,000" and "$75,000 and over" into "$50,000 and over" and merging "blacks and Hispanics" with "Hispanic" in race. Missing values indicate the need for imputation. Therefore, multiple imputation was performed and the imputed data were used in the regression analyses.

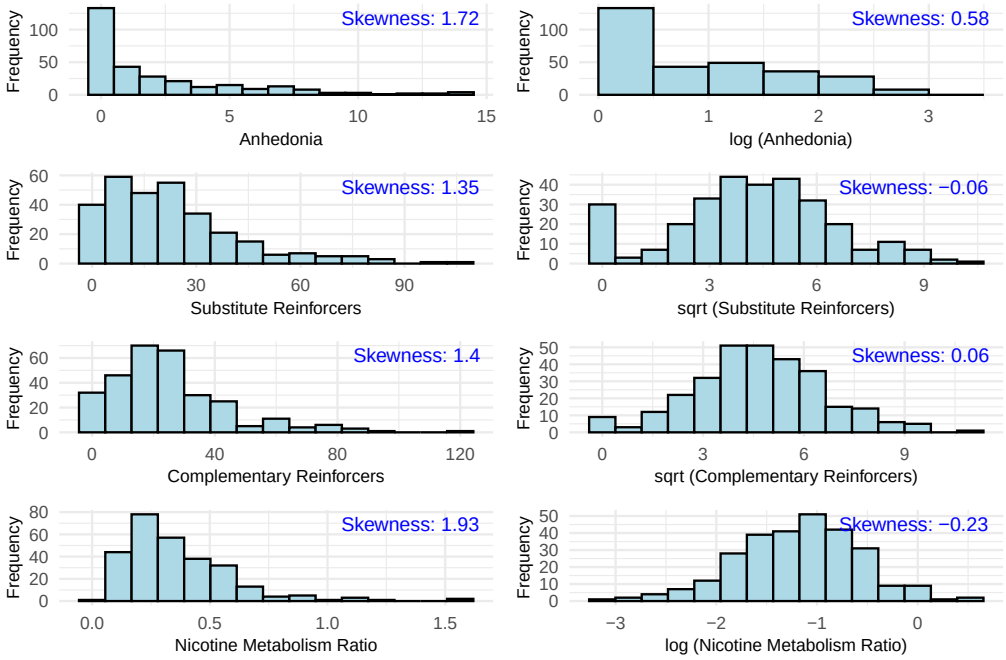
Table 1: Baseline Characteristics by Treatment Group

Characteristic	ST + placebo N = 68[1]	BASC + placebo N = 68[1]	ST + varenicline N = 81[1]	BASC + varenicline N = 83[1]	Overall N = 300[1]
Smoking Abstinence	8 (12%)	4 (5.9%)	26 (32%)	26 (31%)	64 (21%)
Age	50.3 (10.8)	50.7 (13.5)	48.7 (12.7)	50.3 (13.2)	50.0 (12.6)
Sex (% female)	39 (57%)	38 (56%)	44 (54%)	44 (53%)	165 (55%)
Income /yr					
Less than $20,000	26 (38%)	25 (37%)	29 (36%)	30 (37%)	110 (37%)
$20,000–35,000	14 (21%)	16 (24%)	21 (26%)	17 (21%)	68 (23%)
$35,001–50,000	14 (21%)	8 (12%)	11 (14%)	13 (16%)	46 (15%)
$50,001–75,000	8 (12%)	12 (18%)	6 (7.5%)	12 (15%)	38 (13%)
More than $75,000	6 (8.8%)	6 (9.0%)	13 (16%)	10 (12%)	35 (12%)
Missing	0	1	1	1	3
Education					
Grade school	0 (0%)	1 (1.5%)	0 (0%)	0 (0%)	1 (0.3%)
Some high school	2 (2.9%)	3 (4.4%)	4 (4.9%)	7 (8.4%)	16 (5.3%)
High school graduate or GED	11 (16%)	23 (34%)	27 (33%)	15 (18%)	76 (25%)
Some college/technical school	38 (56%)	22 (32%)	24 (30%)	32 (39%)	116 (39%)
College graduate	17 (25%)	19 (28%)	26 (32%)	29 (35%)	91 (30%)
FTCD score	5.4 (2.1)	5.3 (2.0)	5.2 (2.1)	5.1 (2.3)	5.2 (2.1)
Missing	1	0	0	0	1
Smoking with 5 mins of waking up	35 (51%)	32 (47%)	38 (47%)	33 (40%)	138 (46%)
BDI score	18.5 (10.8)	19.0 (12.3)	19.5 (12.2)	18.0 (10.6)	18.7 (11.5)
Cigarettes /day	15.0 (7.2)	15.6 (9.1)	14.4 (6.6)	15.5 (8.5)	15.1 (7.9)
Cigarette reward value	7.0 (3.7)	7.4 (3.8)	7.1 (3.5)	7.2 (3.9)	7.2 (3.7)
Missing	8	1	6	3	18
Substitute reinforcers	20.8 (20.1)	23.2 (20.3)	23.4 (19.5)	22.9 (19.0)	22.6 (19.6)
Complementary reinforcers	27.4 (19.9)	27.7 (21.5)	25.0 (19.4)	22.4 (17.0)	25.4 (19.4)
Anhedonia	2.5 (3.4)	2.2 (3.2)	2.1 (3.0)	2.3 (3.1)	2.2 (3.2)
Missing	1	2	0	0	3
Lifetime DSM-5 diagnosis	28 (41%)	35 (51%)	40 (49%)	30 (36%)	133 (44%)
Taking antidepressant medication	15 (22%)	28 (41%)	15 (19%)	24 (29%)	82 (27%)
Current vs past MDD	31 (46%)	32 (47%)	44 (54%)	40 (48%)	147 (49%)
Nicotine Metabolism Ratio	0.4 (0.3)	0.3 (0.2)	0.4 (0.2)	0.4 (0.2)	0.4 (0.2)
Missing	2	7	9	3	21
Exclusive Mentholated Cigarette User	43 (64%)	40 (59%)	47 (58%)	48 (59%)	178 (60%)
Missing	1	0	0	1	2
Readiness to quit smoking	7.0 (1.3)	6.8 (1.4)	6.7 (1.1)	6.7 (1.2)	6.8 (1.2)
Missing	4	4	4	5	17
Race					
Balck	40 (61%)	36 (55%)	43 (59%)	36 (49%)	155 (56%)
Hispanic	4 (6.1%)	4 (6.2%)	5 (6.8%)	3 (4.1%)	16 (5.8%)
White	22 (33%)	24 (37%)	25 (34%)	34 (46%)	105 (38%)
Balck and Hispanic	0 (0%)	1 (1.5%)	0 (0%)	1 (1.4%)	2 (0.7%)
Missing	2	3	8	9	22

[1] n (%); Mean (SD)

Examining through the distribution of the continuous variables, four variables were found to have skewed distribution, therefore variable transformations were performed (`Figure 1`). Log transformation was performed on Anhedonia (`shaps_score_pq1_log`), and Nicotine Metabolism Ratio (`NMR`). Square root transformations were performed on Substitute Reinforcers (`hedonsum_n_pq1`), and Complementary Reinforcers (`hedonsum_y_pq1`). These transformations effectively reduce the skewness of each variable, making the distributions look more normally distributed. This adjustment is beneficial for statistical analyses that assume normality, as it helps the transformed data align more closely with these assumptions.

Figure 1: Variable Distribution Before and After Transformations



Exploratory Data Analysis

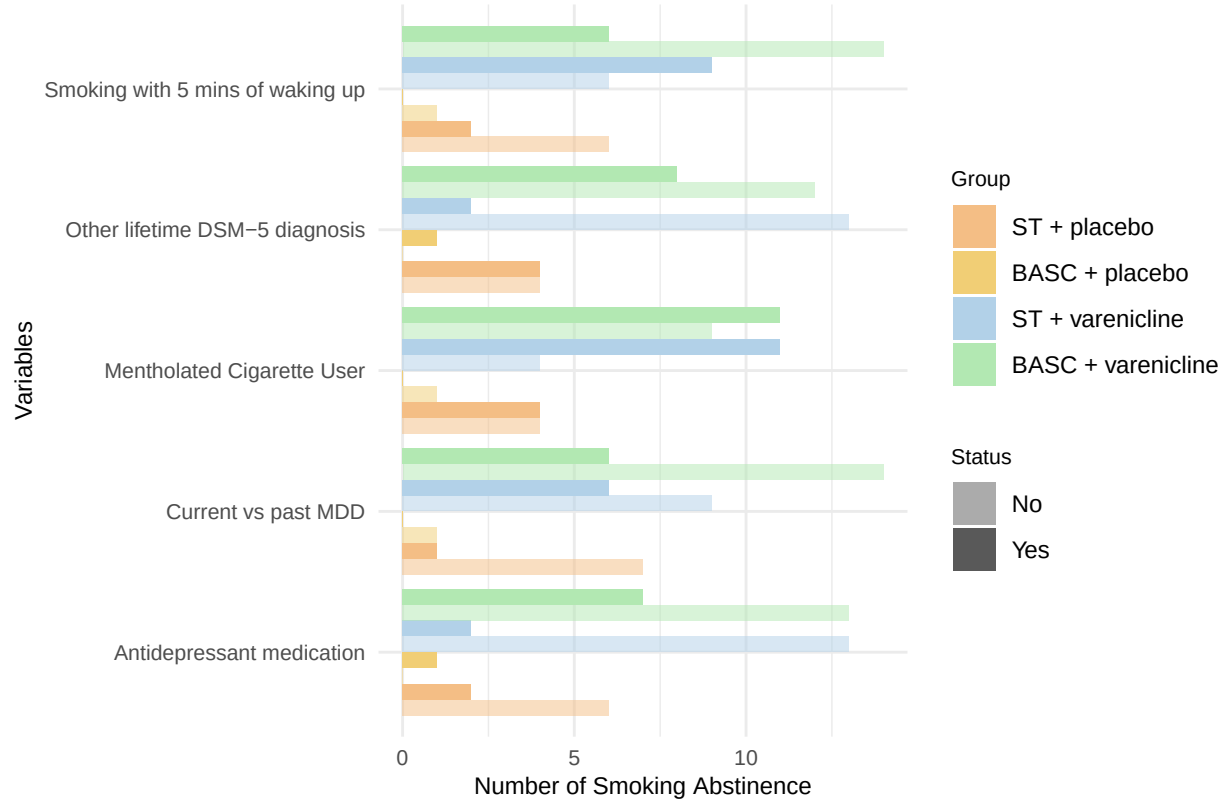
An exploratory analysis was conducted to identify patterns and relationships within the data prior to performing regression analysis. This preliminary investigation aimed to uncover potential trends and insights that could inform the subsequent modeling approach and enhance the interpretation of the regression results.

`Figure 2` visualizes the number of participants who achieved smoking abstinence, broken down by clinically relevant variables, such as smoking behavior and mental health diagnoses, and colored by the four treatment groups. The "ST + varenicline" and "BASC + varenicline" groups generally show higher smoking abstinence rates across, indicating that varenicline, either alone or with behavioral activation support (BASC), may be more effective than placebo in helping participants achieve smoking abstinence. This trend appears across a variety of behavioral and mental health variables, suggesting potential benefits of the varenicline treatment for a general smoking population. Focusing on depression-related variables — Other lifetime DSM-5 diagnosis, Current vs past MDD, and antidepressant medication — we observe differences in smoking abstinence counts between the two varenicline treatment groups: BASC + varenicline and ST + varenicline. Across these variables, the count of smoking abstinence instances is generally equal or higher in the BASC + varenicline group compared to the ST + varenicline group. This could indicate a possible interaction between the behavioral activation (BASC) approach and varenicline in supporting smoking abstinence for individuals with depressive symptoms or related diagnoses and highlighting the potential need for tailored interventions or additional support for participants with these characteristics. For variables related to smoking behavior, 5 minutes after waking up and menthol cigarette user, the bars show that the number of smoking abstinence cases was generally higher in the varenicline group (ST+varenicline and BASC+varenicline) compared with the placebo group, suggesting that pharmacotherapy is an important factor in achieving smoking abstinence. However, there was no indication that the type of behavioral treatment (ST vs. BASC) affected outcomes in each pharmacotherapy condition.

Table 2: Number and proportion of smokers who have achieved cessation

Variables	ST + placebo	BASC + placebo	ST + varenicline	BASC + varenicline
Education Level				
Grade school	-	1 (100%)	-	-
Some high school	-	-	2 (50%)	1 (14%)
High school graduate or GED	-	-	11 (41%)	5 (33%)
Some college/technical school	3 (8%)	-	3 (12%)	13 (41%)
College graduate	5 (29%)	3 (16%)	10 (38%)	7 (24%)
Income Level				
Less than $20,000	2 (11%)	-	7 (35%)	6 (26%)
$20,000–35,000	2 (17%)	-	2 (13%)	5 (38%)
$35,001–50,000	-	-	2 (29%)	4 (40%)
$50,001–75,000	2 (40%)	1 (10%)	2 (50%)	1 (11%)
More than $75,000	2 (33%)	-	2 (20%)	4 (50%)

Figure 2: Number of Smoking Abstinence by Group



`Table 2` summarizes the number and percentage of smokers who achieved cessation across various education and income levels within four treatment groups. Generally, the "ST + varenicline" and "BASC + varenicline" groups had higher cessation rates across both education and income categories, suggesting the efficacy of varenicline in aiding smoking cessation. Among education levels, "College graduate" and "Some college/technical school" participants showed particularly high cessation rates in the "ST + varenicline" and "BASC + varenicline" groups, while "High school graduate or GED" individuals also had notable cessation rates, especially within "ST + varenicline." In terms of income, higher income brackets, especially those earning "$35,001–50,000" and "More than More than $75,000" had higher cessation rates within the "BASC + varenicline" group, while the "ST + varenicline" group showed consistent cessation rates across various income levels, including lower-income categories. These results suggest that varenicline may be effective across a diverse range of demographic groups.

Table 3: Summary of Continuous Variables by Group and Smoking Abstinence

	ST + placebo		BASC + placebo		ST + varenicline		BASC + varenicline	
	No	Yes	No	Yes	No	Yes	No	Yes
Anhedonia	2.68	1.25	2.16	2.00	2.38	1.54	2.46	1.81
Cigarette reward value	7.04	6.62	7.44	7.50	6.89	7.55	7.43	6.75
Cigarettes per day	15.28	13.12	16.06	8.75	14.53	14.23	16.33	13.81
FTCD score	5.71	3.00	5.41	3.75	5.18	5.15	5.54	4.04
Nicotine Metabolism Ratio	0.37	0.36	0.34	0.35	0.33	0.41	0.34	0.46
Pleasurable Events Scale at baseline–complementary reinforcers	27.52	26.50	27.39	32.50	25.60	23.73	23.09	20.88
Pleasurable Events Scale at baseline–substitute reinforcers	18.47	37.88	23.06	25.50	25.62	18.81	20.63	27.92
Readiness to quit smoking	6.96	6.88	6.75	7.67	6.83	6.43	6.66	6.72

`Table 3` summarizes continuous variables related to smoking behavior, psychological factor (Anhedonia), and readiness to quit, stratified by treatment group and smoking abstinence status ("Yes" or "No"). The comparison between participants who successfully quit smoking and those who did not reveals a consistent pattern across treatment groups: successful smoking cessation is associated with lower nicotine dependence (as measured by FTCD scores), fewer cigarettes smoked per day, and lower anhedonia scores. This trend holds true regardless of the type of treatment group, suggesting that these factors may be the key predictors of smoking cessation success across both pharmacological and behavioral interventions. The Nicotine Metabolism Ratio (NMR) is a measure of how quickly an individual metabolizes nicotine. Faster nicotine metabolizers tend to experience shorter-lasting effects of nicotine, which can lead to smoking more frequently to maintain nicotine levels. NMR is often considered when assessing an individual's likelihood to quit smoking, as those with a higher metabolism rate might find it more challenging to quit due to the need for more frequent dosing. In this table, we observe that the NMR is generally higher in the smoking abstinence ("Yes") group compared to the non-abstinent ("No") group across most treatment conditions, with the exception of the ST + placebo group. This pattern suggests that, for most treatments, individuals with a higher nicotine metabolism rate had better success in achieving abstinence.

Regression Analysis

Methods

Lasso (Least Absolute Shrinkage and Selection Operator) is well-suited for achieving the goals of this project, as it enables the identification of baseline variables that act as significant predictors or moderators of end-of-treatment (EOT) abstinence while effectively managing the complexity of the data. In this context, the trial data includes a large number of baseline variables, some of which may be highly correlated or only marginally relevant to abstinence outcomes. Lasso helps in this setting by applying a regularization penalty that shrinks less relevant coefficients to zero, effectively selecting only the most predictive and informative variables. This approach addresses the issue of overfitting and improves the model's interpretability by reducing the number of predictors to those most strongly associated with abstinence.

The regression analysis involved several key steps: First, missing data was handled through multiple imputations, creating five complete datasets. Each imputed dataset was then split into training (70%) and testing (30%) sets while maintaining the proportion of the treatment combination of the behavior and pharmacotherapy treatment maintained in both the training and testing sets. This helps us to make sure that both training and testing sets have a similar distribution of each category. LASSO regression with 10-fold cross-validation was applied to the training data to identify the optimal regularization parameter (lambda), which minimized the cross-validation error and selected important features by shrinking irrelevant coefficients to zero. The best-fit LASSO model was then applied to the test data, with model performance assessed through AUC (Area Under the Curve) scores and ROC (Receiver Operating Characteristic) curves for both training and testing datasets. Finally, coefficients from each imputed dataset were averaged to summarize feature importance across imputations, providing a robust model evaluation that accounts for

Table 4: Summary of Non-Zero Coefficient Estimates in Exponential Scale

Covariate	**Imputation 1**	**Imputation 2**	**Imputation 3**	**Imputation 4**	**Imputation 5**	Average	Proportion Non-Zero
Edu (College graduate)	1.0894	1.0373	1.0881	1.0875	1.0416	1.0685	1.00
FTCD score	0.8488	0.8534	0.8489	0.8491	0.8546	0.8510	1.00
Race (Non-hispanic White)	1.0550	-	1.0530	1.0518	-	1.0316	0.60
BASC :FTCD score	0.9960	-	0.9960	0.9959	0.9991	0.9974	0.80
BASC : Current vs past MDD	0.8434	0.8838	0.8439	0.8443	0.9045	0.8636	1.00
Varenicline : Age	1.0132	1.0112	1.0131	1.0131	1.0115	1.0124	1.00
Varenicline : Income ($35,001–50,000)	1.1644	1.1168	1.1637	1.1636	1.2993	1.1800	1.00
Varenicline : Cigarette reward value	-	1.0090	-	-	-	1.0018	0.20

missing data, regularization, and performance validation.

Results

`Table 4` summarizes the exponentiated non-zero coefficient estimates obtained from a Lasso logistic regression model predicting the likelihood of smoking abstinence based on various covariates and interaction terms between treatment groups and baseline characteristics. The estimates shown are in odds ratio, with an odds ratio greater than 1 suggesting a positive association with smoking abstinence, while an odds ratio less than 1 indicates a negative association. The "Proportion Non-Zero" column in the table provides insight into the stability and importance of each covariate across multiple imputations in the Lasso logistic regression model, reflecting its significance as a predictor of smoking abstinence. A higher proportion suggests that the variable is more important and stable across imputations, while a lower proportion indicates a less consistent association with the outcome. The variables Education Level (College graduate), FTCD score, BASC : Current vs past MDD, and Varenicline: Age, and Varenicline : Income ($35,001–50,000) were significant across all five imputations, suggesting that they have a strong and stable association with smoking abstinence. These covariates likely play a meaningful role in predicting abstinence and may be considered reliable predictors in the model. In contrast, BASC :FTCD score, Race (Non-Hispanic White), and Varenicline : Cigarette reward value showed less consistent association with the outcome, with being significant 0.8, 0.6 and 0.2 percent of the time.

Focusing initially on the primary effects, education level demonstrates a positive association with smoking abstinence, as indicated by an odds ratio of 1.07. This suggests that individuals with a college degree have 7% greater odds of achieving smoking abstinence compared to those with lower education levels, while accounting for other covariates. The FTCD score, which assesses nicotine dependence, presents an odds ratio of 0.85; thus, each additional point increase in FTCD score corresponds to a 15% reduction in the odds of smoking abstinence. This finding underscores the need for more intensive support for individuals with higher levels of dependence. Additionally, the odds ratio for race (Non-Hispanic White) at 1.03 suggests that Non-Hispanic White smokers have a 3% greater likelihood of achieving smoking abstinence compared to smokers of other racial/ethnic backgrounds.

Turning to the interactions involving the Behavioral Activation for Smoking Cessation (BASC) intervention, the data indicate moderating effects from both nicotine dependence, as measured by the FTCD score, and depression status (current versus past MDD). The interaction between BASC and FTCD score has an average odds ratio of 0.9974, implying that with each additional unit increase in FTCD score, representing higher nicotine dependence, the odds of smoking abstinence slightly decline by 0.3% when the BASC intervention is in place. From a moderation perspective, this implies that while higher nicotine dependence marginally weakens the association between BASC and smoking abstinence, the impact may be modest. Similarly, the interaction between BASC and current versus past major depressive disorder (MDD) status has an average odds ratio of 0.86. This implies that participants with current MDD may have about 14% lower odds of

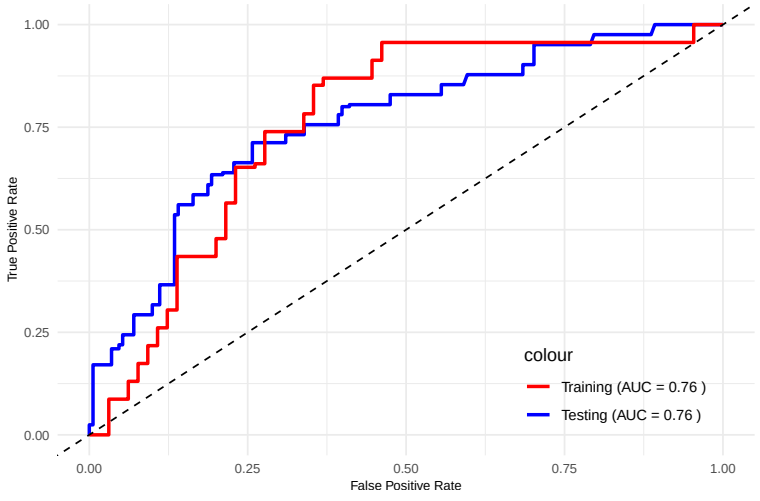
achieving smoking abstinence when compared to those with past MDD, within the context of the BASC intervention, consistent with patterns shown in `Figure 2`. This moderating effect suggests that current MDD may act as a psychological barrier to the effectiveness of the BASC intervention, potentially due to factors associated with active depressive symptoms, such as reduced motivation or higher levels of stress.

In examining pharmacotherapy-related interactions, three interactions involving age, income level, and cigarette reward value appeared as significant predictors of smoking abstinence in the context of Varenicline use. The average odds ratio for the interaction between Varenicline and age is 1.0124, indicating that with each additional year of age, the odds of smoking abstinence among individuals using Varenicline increase by approximately 1.24%, adjusted for other covariates. Older individuals might experience slightly enhanced benefits from Varenicline, potentially due to factors such as greater motivation or life stage considerations related to health. For the interaction between Varenicline and income within the range of $35,001–$50,000, the average odds ratio is 1.1800, indicating that individuals in this income bracket who use Varenicline have an 18% higher likelihood of achieving smoking abstinence compared to those outside this income range. This is consistent with patterns shown in `Table 2`. The interaction between Varenicline and cigarette reward value has an average odds ratio of 1.0018, which is very close to 1, suggesting a negligible effect on smoking abstinence. The proportion non-zero value of 0.20 indicates that this interaction was non-zero in only 20% of imputations, suggesting a weak and inconsistent effect. This implies that the perceived reward value of cigarettes has minimal impact on the effectiveness of Varenicline in achieving smoking cessation. The low impact and inconsistency may be due to Varenicline's strong pharmacological effects, which could diminish the relevance of the reward value perception associated with smoking.

Model Performance

To evaluate the model's performance, ROC and calibration plots were generated, and the area under the ROC curve (AUC) was calculated. The ROC curve and AUC assess the model's classification performance, while the calibration plot evaluates how well the predicted probabilities align with the observed outcome probabilities. Predictions were made using the average coefficient estimates and combined train and test sets from five imputed datasets. As illustrated in `Figure 3`, both the training and testing sets achieved an AUC of 0.76, indicating that, on average, the model has a 76% likelihood of correctly distinguishing between positive and negative cases. This AUC reflects a robust and reliable ability to predict smoking abstinence. The consistency of the AUC between training and testing sets suggests that the model has good generalizability, with no substantial drop in classification performance when applied to unseen data.

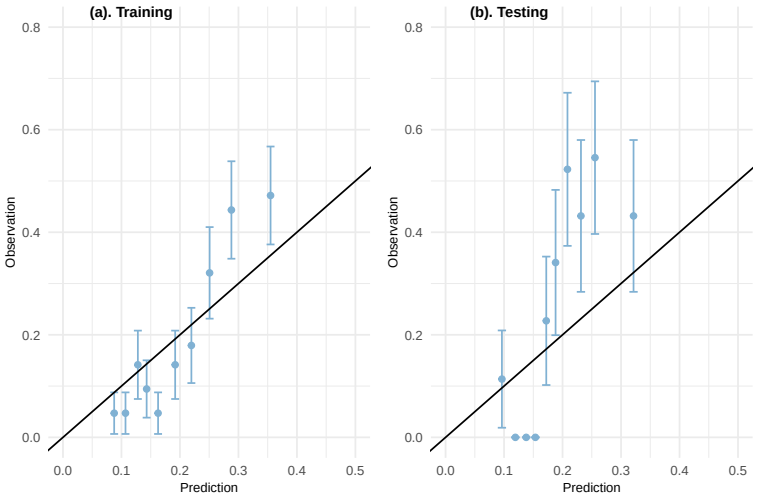
Figure 3: ROC Curve Using Average Coefficients



The calibration plot further examines the alignment between predicted and observed probabilities (`Figure 4`). The 45-degree line in the plot represents perfect calibration, where predicted probabilities match the

observed outcomes. In the training set, the points are generally close to the calibration line, indicating that the model is well-calibrated. However, there is a slight deviation below the line at higher predicted probability levels, suggesting a mild tendency to over predict the likelihood of smoking abstinence in these cases. In contrast, the calibration plot for the testing set shows greater deviation from the diagonal line, indicating that the model is less well-calibrated on the test data than on the training data. Specifically, the model underpredicts probabilities at lower levels (with points falling below the line) and overpredicts at higher levels (with points above the line). These discrepancies suggest that while the model is reasonably well-calibrated on the training data, it exhibits calibration issues when applied to new, unseen data.

Figure 4: Calibration Plots



Discussion

The EDA revealed that demographic and behavioral factors such as age, education, and baseline nicotine dependence influence cessation outcomes. For instance, higher education levels and moderate income level were associated with greater smoking abstinence rates, suggesting socioeconomic factors may play a role in treatment efficacy. Additionally, individuals with lower nicotine dependence scores and fewer current depressive symptoms exhibited better outcomes, highlighting the importance of addressing dependence levels and mental health symptoms in smoking cessation strategies.

The regression analysis identified education level (college graduate), FTCD score, BASC with current FTCD score, BASC with current MDD, Varenicline with age, and Varenicline with income ($35,001–$50,000) as strong predictors of smoking abstinence. College graduates had 7% higher odds of abstinence, while higher nicotine dependence reduced abstinence likelihood by 15% per unit increase. BASC's effectiveness was slightly reduced by high nicotine dependence and active MDD, while varenicline's effectiveness improved with age and moderate income. The model achieved an AUC of 0.76, indicating reliable classification performance; however, calibration issues in the test data suggest that further refinement of the predictive model may be necessary.

However, several limitations should be considered. First, the sample size, while adequate for initial findings, may limit the generalizability of results. Specific subgroups, such as those with varying income levels or education backgrounds, may respond differently to BASC and varenicline, but the sample size in each subgroup was relatively small, potentially affecting the robustness of subgroup analyses. In addition, the need to split the data into training and testing sets, followed by further division of the training set for cross-validation to tune model parameters, reduces the effective data in each subset. The limited data per subset may decrease model stability and generalizability, suggesting that results should be interpreted with caution. A larger sample size in future studies would improve the robustness and predictive reliability of the analysis. Another limitation, rooted in the constraints of the clinical trial, was low treatment adherence,

particularly in the BASC-alone group. This low adherence affects the analysis by potentially underestimating the effectiveness of BASC, as participants may not have received sufficient intervention exposure to achieve meaningful outcomes. As a result, the study's findings may not fully reflect the treatment's potential impact, limiting the generalizability and strength of the conclusions.

References

Hitsman, B., Papandonatos, G. D., Gollan, J. K., Huffman, M. D., Niaura, R., Mohr, D. C., Veluz-Wilkins, A. K., Lubitz, S. F., Hole, A., Leone, F. T., Khan, S. S., Fox, E. N., Bauer, A., Wileyto, E. P., Bastian, J., & Schnoll, R. A. (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 × 2 factorial, randomized, placebo-controlled trial. Addiction, 118(9), 1710–1725. https://doi.org/10.1111/add.16209

Cook, J. W., Spring, B., McChargue, D., & Doran, N. (2010). Effects of anhedonia on days to relapse among smokers with a history of depression: A brief report. Nicotine & Tobacco Research, 12(9), 978–982. https://doi.org/10.1093/ntr/ntq118

Evins, A. E., Benowitz, N. L., West, R., Russ, C., McRae, T., Lawrence, D., Krishen, A., St Aubin, L., Maravic, M. C., & Anthenelli, R. M. (2019). Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with psychotic, anxiety, and mood disorders in the EAGLES trial. Journal of Clinical Psychopharmacology, 39(2), 108–116. https://doi.org/10.1097/jcp.0000000000001015

Code Appendix

```
knitr::opts_chunk$set(echo = FALSE, warning = FALSE, message = FALSE)
# Data manipulation
library(dplyr)
library(tidyr)
library(mice)
library(caret)

# Tables
#library(kableExtra)
library(gtsummary)
library(gt)

# Plots
library(ggplot2)
library(ggpubr)
library(moments)
library(predtools)
library(pROC)
library(gridExtra)
library(ggExtra)


# Models
library(glmnet)
library(boot)
library(ISLR)
project2 <- read.csv("~/Desktop/PHP 2550/Data/project2.csv")

# Modify variables
## Binary variables
project2$sex_ps <- ifelse(project2$sex_ps == 1, 0, 1)
binary_vars <- sapply(project2, function(x) {
  unique_vals <- unique(x[!is.na(x)])
  (all(unique_vals %in% c(0, 1)) | all(unique_vals %in% c(1, 2))) & is.numeric(x)
})
project2[binary_vars] <- lapply(project2[binary_vars], function(x) as.factor(x))

## Ordinal variabl
project2 <- project2 %>%
  mutate(edu = factor(edu, levels = 1:5,
                labels = c("Grade school", "Some high school", "High school graduate or GED",
                           "Some college/technical school", "College graduate"), ordered = TRUE),
         inc = factor(inc, levels = 1:5,
                labels = c("Less than $20,000", "$20,000-35,000", "$35,001-50,000",
                           "$50,001-75,000", "More than $75,000"), ordered = TRUE))

# Categorical variables
project2 <-  project2 %>%
  mutate(Group = case_when(Var == 0 & BA == 0 ~ "ST + placebo", Var == 0 & BA == 1 ~ "BASC + placebo",
                           Var == 1 & BA == 0 ~ "ST + varenicline", Var == 1 & BA == 1 ~ "BASC + vareni
         Race = case_when(Black == 1 & Hisp == 0 & NHW == 0 ~ "Balck",
```

```
                          Hisp == 1 & Black == 0 & NHW == 0 ~ "Hispanic",
                          NHW == 1 & Black == 0 & Hisp == 0 ~ "White",
                          Black == 1 & Hisp == 1 & NHW == 0 ~ "Balck and Hispanic")) %>%
  mutate(Group = factor(Group, levels = c("ST + placebo", "BASC + placebo", "ST + varenicline", "BASC +
         Race = factor(Race, levels = c("Balck", "Hispanic", "White", "Balck and Hispanic"))) %>%
  mutate(
    abst = factor(abst, levels = c(0, 1), labels = c("No", "Yes")),
    ftcd.5.mins = factor(ftcd.5.mins, levels = c(0, 1), labels = c("No", "Yes")),
    otherdiag = factor(otherdiag, levels = c(0, 1), labels = c("No", "Yes")),
    antidepmed = factor(antidepmed, levels = c(0, 1), labels = c("No", "Yes")),
    mde_curr = factor(mde_curr, levels = c(0, 1), labels = c("No", "Yes")),
    Only.Menthol = factor(Only.Menthol, levels = c(0, 1), labels = c("No", "Yes")),
    sex_ps = factor(sex_ps, levels = c(0, 1), labels = c("No", "Yes"))
  )
project2 %>%
  dplyr::select(-c(id, Var, BA, Black, Hisp, NHW)) %>%
  tbl_summary(
    by = Group,                              # Group by the treatment groups
    label = list(abst ~ "Smoking Abstinence",
                 age_ps ~ "Age",
                 sex_ps ~ "Sex (% female)",
                 inc ~ "Income /yr",
                 edu ~ "Education",
                 ftcd_score ~ "FTCD score",
                 ftcd.5.mins ~ "Smoking with 5 mins of waking up",
                 cpd_ps ~ "Cigarettes /day",
                 crv_total_pq1 ~ "Cigarette reward value",
                 hedonsum_n_pq1 ~ "Substitute reinforcers",
                 hedonsum_y_pq1 ~ "Complementary reinforcers",
                 shaps_score_pq1 ~ "Anhedonia",
                 otherdiag ~ "Lifetime DSM-5 diagnosis",
                 antidepmed ~ "Taking antidepressant medication",
                 mde_curr ~ "Current vs past MDD",
                 NMR ~ "Nicotine Metabolism Ratio",
                 Only.Menthol ~ "Exclusive Mentholated Cigarette User",
                 readiness ~"Readiness to quit smoking",
                 bdi_score_w00 ~ "BDI score"),
    type = list(readiness ~ "continuous"),
    statistic = list(all_continuous() ~ "{mean} ({sd})",
                     all_categorical() ~ "{n} ({p}%)"),
    missing = "ifany",
              missing_text = "Missing",
    digits = all_continuous() ~ 1
  ) %>%
  add_overall(last=TRUE) %>%
  modify_header(label = "**Characteristic**") %>%
  bold_labels() %>%
  as_gt() %>%
  tab_header(
    title = md("Table 1: Baseline Characteristics by Treatment Group")) %>%
  tab_options(
    table.font.size = px(8),
    heading.title.font.size = px(8)
```

```
  ) %>%
  cols_width(
        vars(label) ~ px(170),
    everything() ~ px(100),
    starts_with("stat_") ~ px(120)
  ) %>%
    tab_style(
      style = cell_text(weight = "bold", align = "center"),
      locations = cells_column_labels(everything())
    )
# Apply log/sqrt transformations to the specified variables
project2_trans <- project2 %>%
  mutate(shaps_score_pq1_log = log(shaps_score_pq1+1),
    hedonsum_n_pq1_sqrt = sqrt(hedonsum_n_pq1),
         hedonsum_y_pq1_sqrt = sqrt(hedonsum_y_pq1),
         NMR_log = log(NMR))

vars_trans <- list("shaps_score_pq1", "hedonsum_n_pq1", "hedonsum_y_pq1", "NMR",
                   "shaps_score_pq1_log", "hedonsum_n_pq1_sqrt", "hedonsum_y_pq1_sqrt", "NMR_log")

vars_name_trans <- list("shaps_score_pq1" = "Anhedonia",
                        "hedonsum_n_pq1" = "Substitute Reinforcers",
                        "hedonsum_y_pq1" = "Complementary Reinforcers",
                        "NMR" = "Nicotine Metabolism Ratio",
                        "shaps_score_pq1_log" = "log (Anhedonia)",
                        "hedonsum_n_pq1_sqrt" = "sqrt (Substitute Reinforcers)",
                        "hedonsum_y_pq1_sqrt" = "sqrt (Complementary Reinforcers)",
                        "NMR_log" = "log (Nicotine Metabolism Ratio)")

plot_list <- list()
for (var in vars_trans) {
  # Set bin specifications
  skew_score <- round(skewness(project2_trans[[var]], na.rm = TRUE), 2)
  if (var == "shaps_score_pq1_log") {
    plot <- ggplot(project2_trans, aes_string(x = var)) +
      geom_histogram(color = "black", fill = "lightblue", breaks = seq(0, max(3.5, na.rm = TRUE), by = (
      labs(x = vars_name_trans[[var]], y = "Frequency")
  } else {
    plot <- ggplot(project2_trans, aes_string(x = var)) +
      geom_histogram(color = "black", fill = "lightblue", bins = 15) +
      labs(x = vars_name_trans[[var]], y = "Frequency")
  }

  plot <- plot +
    annotate("text", x = Inf, y = Inf, label = paste("Skewness:", skew_score),
             hjust = 1.1, vjust = 1.5, size = 3, color = "blue") +
    theme_minimal() +
    theme(
      plot.title = element_text(size = 8),
      axis.title = element_text(size = 8),
      axis.text = element_text(size = 8))
  plot_list[[var]] <- plot
}
```

```r
plot_trans <- ggarrange(plot_list[["shaps_score_pq1"]], plot_list[["shaps_score_pq1_log"]],
                        plot_list[["hedonsum_n_pq1"]],
                        plot_list[["hedonsum_n_pq1_sqrt"]],
                        plot_list[["hedonsum_y_pq1"]],
                        plot_list[["hedonsum_y_pq1_sqrt"]],
                        plot_list[["NMR"]], plot_list[["NMR_log"]],
                        ncol=2, nrow=4)
annotate_figure(plot_trans,
                top = text_grob("Figure 1: Variable Distribution Before and After Transformations", fac
# Missing Data Imputation
project2_s <- project2 %>%
  dplyr::select(-c(id, Group, Race))
project2_imp <- mice(project2_s, m = 5, method = 'pmm', seed = 2550, printFlag = FALSE)
project2_imp_trans <- list()

for (i in 1:5) {
  # Extract each imputed dataset
  imputed_data <- complete(project2_imp, action = i)

  # Apply transformations
  imputed_data <- imputed_data %>%
    mutate(
      shaps_score_pq1_log = log(shaps_score_pq1+1),
      hedonsum_n_pq1_sqrt = sqrt(hedonsum_n_pq1),
      hedonsum_y_pq1_sqrt = sqrt(hedonsum_y_pq1),
      NMR_log = log(NMR)) %>%
    mutate(Group = case_when(Var == 0 & BA == 0 ~ "ST + placebo", Var == 0 & BA == 1 ~ "BASC + placebo"
                             Var == 1 & BA == 0 ~ "ST + varenicline", Var == 1 & BA == 1 ~ "BASC + vareni
           Race = case_when(Black == 1 & Hisp == 0 & NHW == 0 ~ "Balck",
                            Hisp == 1 & Black == 0 & NHW == 0 ~ "Hispanic",
                            NHW == 1 & Black == 0 & Hisp == 0 ~ "Non-hispanic White",
                            Black == 1 & Hisp == 1 & NHW == 0 ~ "Other",
                            Black == 0 & Hisp == 0 & NHW == 0 ~ "Other")) %>%
    mutate(Group = factor(Group, levels = c("ST + placebo", "BASC + placebo", "ST + varenicline", "BASC
           edu = factor(case_when(edu=="Grade school" | edu=="Some high school"~ "High school and below
                      edu=="High school graduate or GED"~ "High school graduate or GED",
                      edu=="Some college/technical school"~ "Some college/technical school",
                      edu=="College graduate"~ "College graduate")),
    inc = factor(case_when(inc=="Less than $20,000" ~ "Less than $20,000",
                           inc=="$20,000-35,000" ~ "$20,000-35,000",
                           inc=="$35,001-50,000" ~ "$35,001-50,000",
                           inc=="$50,001-75,000" | inc=="More than $75,000" ~ "$More than $50,000"))
    ) %>%
  mutate(edu = factor(edu, levels = c("High school and below", "High school graduate or GED", "Some col
                      Race = factor(Race, levels = c("Balck", "Hispanic", "Non-hispanic White", "Other"
                      inc = factor(inc, levels = c("Less than $20,000", "$20,000-35,000", "$35,001-50,0
    dplyr::select(-c(shaps_score_pq1, hedonsum_n_pq1, hedonsum_y_pq1, NMR, Black, Hisp, NHW))
  # Store the transformed dataset
  project2_imp_trans[[i]] <- imputed_data
}
# Prepare data by selecting binary variables and reshaping to long format
project2_bi_summary <- na.omit(project2) %>%
  dplyr::select(abst, ftcd.5.mins, otherdiag, antidepmed, mde_curr, Only.Menthol, Group) %>%
```

```r
  rename(`Other lifetime DSM-5 diagnosis` = otherdiag,
         `Smoking with 5 mins of waking up` = ftcd.5.mins,
         `Antidepressant medication` = antidepmed,
         `Current vs past MDD` = mde_curr,
         `Mentholated Cigarette User` = Only.Menthol) %>%
  pivot_longer(
    cols = -c(abst, Group),
    names_to = "Variable",
    values_to = "Value"
  ) %>%
  group_by(Group, Variable, Value) %>%
  summarize(sum_abst = sum(abst=="Yes"), .groups = "drop") %>%
  arrange(Group, Variable, Value)

# Create the plot
ggplot(data = project2_bi_summary, aes(x = Variable, y = sum_abst, fill = Group, alpha = as.factor(Valu
  geom_bar(stat = "identity", position = "dodge") +
  scale_fill_manual(values = c("#F4BE85", "#F1CE75", "#B2D1E8", "#B2E8B2"), name = "Group") +
  scale_alpha_manual(values = c("Yes" = 1, "No" = 0.5),name = "Status", labels = c( "No", "Yes")) +  #
  coord_flip() +  # Flip coordinates for horizontal layout
  labs(
    x = "Variables",
    y = "Number of Smoking Abstinence",
    title = "Figure 2: Number of Smoking Abstinence by Group"
  ) +
  theme_minimal() +
  theme(
    plot.title = element_text(size = 10, face = "bold"),
    axis.text.x = element_text(size = 8),
    axis.text.y = element_text(size = 8),
    axis.title.x = element_text(size = 9),  # Make x-axis title smaller
    axis.title.y = element_text(size = 9),
    legend.title = element_text(size = 8)
  )
# Create summary table for count and percentage of smoking abstinence by Education Level and Income Lev

abstinence_by_edu_group <- project2 %>%
  group_by(edu, Group) %>%
  # Calculate count of abstinent individuals and percentage within each group
  summarize(
    Count_Abstinent = sum(abst == "Yes", na.rm = TRUE),
    Proportion_Abstinent = round(sum(abst == "Yes", na.rm = TRUE)/sum(abst == "Yes" | abst == "No", na.
    .groups = 'drop'
  ) %>%
  mutate(Proportion_Abstinent = paste0(Count_Abstinent, " (", Proportion_Abstinent, "%)")) %>%
  dplyr::select(-Count_Abstinent) %>%
  pivot_wider(names_from = Group, values_from = Proportion_Abstinent, values_fill = "0 (0%)") %>%
  rename(Variables = edu) %>%
  dplyr::select(Variables, `ST + placebo`, `BASC + placebo`, `ST + varenicline`, `BASC + varenicline`) %
  mutate(across(c(`ST + placebo`, `BASC + placebo`,`ST + varenicline`, `BASC + varenicline`),
                ~ ifelse(. == "0 (0%)", "-", .))) %>%
  as.data.frame()
```

```r
header_row <- as.data.frame(matrix(" ", nrow = 1, ncol = ncol(abstinence_by_edu_group)))
colnames(header_row) <- colnames(abstinence_by_edu_group)
header_row$Variables <- "Education Level"
abstinence_by_edu_group <- rbind(header_row, abstinence_by_edu_group)

abstinence_by_inc_group <- na.omit(project2) %>%
  group_by(inc, Group) %>%
  # Calculate count of abstinent individuals and percentage within each group
  summarize(
    Count_Abstinent = sum(abst == "Yes", na.rm = TRUE),
    Proportion_Abstinent = round(mean(abst == "Yes", na.rm = TRUE) * 100, 0),
    .groups = 'drop'
  ) %>%
  mutate(Proportion_Abstinent = paste0(Count_Abstinent, " (", Proportion_Abstinent, "%)")) %>%
  dplyr::select(-Count_Abstinent) %>%
  pivot_wider(names_from = Group, values_from = Proportion_Abstinent, values_fill = "0 (0%)") %>%
  rename(Variables = inc) %>%
  dplyr::select(Variables, `ST + placebo`, `BASC + placebo`, `ST + varenicline`, `BASC + varenicline`) %
  mutate(across(c( `ST + placebo`, `BASC + placebo`,`ST + varenicline`, `BASC + varenicline`),
                ~ ifelse(. == "0 (0%)", "-", .))) %>%
  as.data.frame()
header_row <- as.data.frame(matrix(" ", nrow = 1, ncol = ncol(abstinence_by_inc_group)))
colnames(header_row) <- colnames(abstinence_by_inc_group)
header_row$Variables <- "Income Level"
abstinence_by_inc_group <- rbind(header_row, abstinence_by_inc_group)

# Combine tables
combined_table <- rbind(abstinence_by_edu_group, abstinence_by_inc_group)

# Format combined table
combined_table %>%
  gt() %>%
  tab_header(title = md("Table 2: Number and proportion of smokers who have achieved cessation")) %>%
  tab_options(
    table.font.size = px(8),
    heading.title.font.size = px(8)
  ) %>%
  cols_width(
    Variables ~ px(120),
    everything() ~ px(60)

  ) %>%
tab_style(
    style = cell_text(weight = "bold"),
    locations = cells_body(
      columns = vars(Variables),
      rows = Variables %in% c("Education Level", "Income Level")
    )
  )
# Create summary table for continuous variables stratified by those who achieved smoking abstinence and
project2_con_summary <- project2 %>%
  dplyr::select(abst, Group, ftcd_score, cpd_ps, crv_total_pq1,
                hedonsum_n_pq1, hedonsum_y_pq1, shaps_score_pq1,
```

```
                NMR, readiness) %>%
  rename(`FTCD score` = ftcd_score,
         `Cigarettes per day` = cpd_ps,
         `Cigarette reward value` = crv_total_pq1,
         `Pleasurable Events Scale at baseline-substitute reinforcers` = hedonsum_n_pq1,
         `Pleasurable Events Scale at baseline-complementary reinforcers` = hedonsum_y_pq1,
         `Anhedonia` = shaps_score_pq1,
         `Nicotine Metabolism Ratio` = NMR,
         `Readiness to quit smoking` = readiness) %>%
  pivot_longer(
    cols = -c(abst, Group),
    names_to = "Variable",
    values_to = "Value"
  ) %>%
  group_by(Group, abst, Variable) %>%
  summarize(mean_value = mean(Value, na.rm = TRUE), .groups = "drop") %>%
  pivot_wider(
    names_from = c(Group, abst),
    values_from = mean_value,
    names_glue = "{Group}_{abst}"
  )

# Format the summary table
project2_con_summary %>%
  gt(rowname_col = "Variable") %>%
  tab_header(title = "Table 3: Summary of Continuous Variables by Group and Smoking Abstinence") %>%
  fmt_number(
    columns = everything(),
    decimals = 2
  ) %>%
  cols_label(
    `ST + placebo_No` = "No",
    `ST + placebo_Yes` = "Yes",
    `BASC + placebo_No` = "No",
    `BASC + placebo_Yes` = "Yes",
    `ST + varenicline_No` = "No",
    `ST + varenicline_Yes` = "Yes",
    `BASC + varenicline_No` = "No",
    `BASC + varenicline_Yes` = "Yes"
  ) %>%
  tab_spanner(
    label = "ST + placebo",
    columns = c(`ST + placebo_No`, `ST + placebo_Yes`)
  ) %>%
  tab_spanner(
    label = "BASC + placebo",
    columns = c(`BASC + placebo_No`, `BASC + placebo_Yes`)
  ) %>%
  tab_spanner(
    label = "ST + varenicline",
    columns = c(`ST + varenicline_No`, `ST + varenicline_Yes`)
  ) %>%
  tab_spanner(
```

```
    label = "BASC + varenicline",
    columns = c(`BASC + varenicline_No`, `BASC + varenicline_Yes`)
  )%>%
  tab_options(
    table.font.size = px(8),
    heading.title.font.size = px(8)
  ) %>%
  cols_width(
    Variable ~ px(200),
    everything() ~ px(50)
  ) %>%
    tab_style(
      style = cell_text(weight = "bold", align = "center"),
      locations = cells_column_labels(everything())
    )
# Define the function
perform_cv_lasso_mod <- function(data, seed = 2550) {

  # Initialize lists to store results
  best_lambdas <- list()
  coef_list <- list()
  auc_list <- list()
  roc_plots <- list()
  train_data_full <- NULL
  test_data_full <- NULL

  # Loop through each imputed dataset
  for (i in 1:5) {
    # Complete the imputed dataset
    project2_imputed_s <- data[[i]]

    # Split data into training and testing sets
    set.seed(seed)
    train_index <- createDataPartition(project2_imputed_s$Group, p = 0.7, list = FALSE)
    train_data <- project2_imputed_s[train_index, ]
    test_data <- project2_imputed_s[-train_index, ]
    train_data_full <- bind_rows(train_data_full, train_data)
    test_data_full <- bind_rows(test_data_full, test_data)

    train_data$foldid <- NA
    for (group in unique(train_data$Group)) {
      group_data <- train_data[train_data$Group == group, ]
      fold_idex <- sample(rep(1:10, length.out = nrow(group_data)))
      train_data$foldid[train_data$Group == group] <- fold_idex
    }

    # Create model matrices for the training data
    x_mat <- model.matrix(abst ~ BA * (age_ps + sex_ps + inc + edu + ftcd_score + ftcd.5.mins + bdi_sco
    y <- train_data$abst

    # Perform LASSO cross-validation to find the best lambda
    lasso_model_cv <- cv.glmnet(x_mat, y, alpha = 1, nfolds = 10, foldid = train_data$foldid, family =
```

```r
  #  Fit LASSO model with the optimal lambda
  best_lambda <- lasso_model_cv$lambda.min
  best_lambdas[[i]] <- best_lambda  # Store the best lambda for this iteration
  lasso_model <- glmnet(x_mat, y, alpha = 1, lambda = best_lambda, family = "binomial")

  # Store the coefficients with names
  coef_list[[i]] <- as.matrix(coef(lasso_model))[, , drop = FALSE]  # Exclude intercept, keep names

  #  Calculate AUC and create ROC plots for both training and test data
  x_mat_test <- model.matrix(abst ~ BA * (age_ps + sex_ps + inc + edu + ftcd_score + ftcd.5.mins + bdi
  y_test <- test_data$abst

  # Predict probabilities on the training and test data
  train_predictions <- predict(lasso_model, newx = x_mat, type = "response")
  test_predictions <- predict(lasso_model, newx = x_mat_test, type = "response")

  # Calculate AUC and ROC curves
  train_roc <- roc(y, as.vector(train_predictions))
  test_roc <- roc(y_test, as.vector(test_predictions))
  train_auc <- auc(train_roc)
  test_auc <- auc(test_roc)
  auc_list[[i]] <- list(train_auc = train_auc, test_auc = test_auc)

  # Extract specificity and sensitivity for plotting
  train_roc_data <- data.frame(
    specificity = rev(train_roc$specificities),
    sensitivity = rev(train_roc$sensitivities)
  )
  test_roc_data <- data.frame(
    specificity = rev(test_roc$specificities),
    sensitivity = rev(test_roc$sensitivities)
  )

  # Generate the ROC plot
  roc_plot <- ggplot() +
    geom_line(data = train_roc_data, aes(x = 1 - specificity, y = sensitivity, color = "Training"), si
    geom_line(data = test_roc_data, aes(x = 1 - specificity, y = sensitivity, color = "Testing"), size
    geom_abline(slope = 1, intercept = 0, linetype = "dashed", color = "black") +
    scale_color_manual(values = c("Training" = "blue", "Testing" = "red"),
                       labels = c(paste("Training (AUC =", round(train_auc, 2), ")"),
                                  paste("Testing (AUC =", round(test_auc, 2), ")"))) +
    labs(title = paste("Imputation", i, "- ROC Curve"),
         x = "False Positive Rate",
         y = "True Positive Rate") +
    theme_minimal() +
    theme(legend.position = c(0.75, 0.15))

  # Store the plot in the list
  roc_plots[[i]] <- roc_plot
}

# Combine the coefficient lists into a matrix and calculate the average coefficients
coef_matrix <- do.call(cbind, coef_list)  # Combine list of named vectors into a matrix
```

```r
  avg_coef <- rowMeans(coef_matrix, na.rm = TRUE)

  # Return results as a list,
  list(
    best_lambdas = best_lambdas,
    coef_list = coef_list,
    auc_list = auc_list,
    coef_matrix = coef_matrix,
    avg_coef = avg_coef,
    train_data_full = train_data_full,  # Return the combined dataset
    test_data_full = test_data_full,
    roc_plots = roc_plots  # List of ROC plots
  )
}

# Run the function on imputed dataset
results_mod <- perform_cv_lasso_mod(data = project2_imp_trans, seed = 1234)
# Extract coef_matrix from the results
coef_mat_exp_mod <- exp(cbind(results_mod$coef_matrix[-1,], results_mod$avg_coef[-1]))

# Create a data frame to summarize non-zero coefficients
tbl_coef_mod_non_zero <- data.frame(Covariate = rownames(coef_mat_exp_mod))

# Add columns for each imputation's coefficients
for (i in 1:6) {
  tbl_coef_mod_non_zero[[paste("Imputation", i)]] <- coef_mat_exp_mod[, i]
}

# Calculate the proportion of non-zero coefficients for each covariate
tbl_coef_mod_non_zero$Proportion_Non_Zero <- rowMeans(results_mod$coef_matrix[-1,] != 0)

# Filter to show only covariates that have non-zero coefficients
tbl_coef_mod_non_zero <- tbl_coef_mod_non_zero[tbl_coef_mod_non_zero$Proportion_Non_Zero >= 0.2, ]

# Rename name of covariates
tbl_coef_mod_non_zero <- tbl_coef_mod_non_zero %>%
  mutate(Covariate = case_when( Covariate=="eduCollege graduate" ~ "Edu (College graduate)",
    Covariate=="ftcd_score" ~ "FTCD score",
                                #Covariate=="shaps_score_pq1_log" ~ "log(Anhedonia)",
                                #Covariate=="NMR_log" ~ "log(NMR)",
                                Covariate=="RaceNon-hispanic White" ~ "Race (Non-hispanic White)",
                                Covariate=="BA1:ftcd_score" ~ "BASC :FTCD score",
                                Covariate=="BA1:mde_currYes" ~ "BASC : Current vs past MDD",
                                Covariate=="age_ps:Var1" ~ "Varenicline : Age",
                                Covariate=="inc$35,001-50,000:Var1" ~ "Varenicline : Income ($35,001-50,
     Covariate=="crv_total_pq1:Var1" ~ "Varenicline : Cigarette reward value"
    ))

# Create summary table
tbl_coef_mod_non_zero %>%
  mutate(across(starts_with("Imputation"),
                ~ ifelse(. == 1, "-", sprintf("%.4f", .)))) %>%
  mutate(Proportion_Non_Zero = sprintf("%.2f", Proportion_Non_Zero)) %>%
```

```
  gt() %>%
  cols_label(
    Covariate = "Covariate",
    `Imputation 1` = "Imputation 1",
    `Imputation 2` = "Imputation 2",
    `Imputation 3` = "Imputation 3",
    `Imputation 4` = "Imputation 4",
    `Imputation 5` = "Imputation 5",
    `Imputation 6` = "Average",
    Proportion_Non_Zero = "Proportion Non-Zero"
  ) %>%
  tab_header(
    title = "Table 4: Summary of Non-Zero Coefficient Estimates in Exponential Scale"
  ) %>%
  tab_style(
    style = list(
      cell_text(weight = "bold")
    ),
    locations = cells_column_labels()
  ) %>%
  tab_options(
    table.font.size = px(10),
    heading.title.font.size = px(10)
  ) %>%
  cols_width(
    Covariate ~ px(150),
    everything() ~ px(60)
  ) %>%
    tab_style(
      style = cell_text(weight = "bold", align = "center"),
      locations = cells_column_labels(everything())
    )
# Plot ROC and AUC
# 1. Prepare model matrices for train and test data
x_mat_train_full <- model.matrix(abst ~ BA * (age_ps + sex_ps + inc + edu + ftcd_score
                                              + ftcd.5.mins + bdi_score_w00 + cpd_ps +
                                                crv_total_pq1 + hedonsum_n_pq1_sqrt +
                                                hedonsum_y_pq1_sqrt +
                                                shaps_score_pq1_log + otherdiag +
                                                antidepmed + mde_curr + NMR_log +
                                                Only.Menthol + readiness + Race) + Var * (age_ps + s
                                 data = results_mod$train_data_full)

x_mat_test_full <- model.matrix(abst ~ BA * (age_ps + sex_ps + inc + edu + ftcd_score + ftcd.5.mins +
                                               bdi_score_w00 + cpd_ps + crv_total_pq1 +
                                               hedonsum_n_pq1_sqrt + hedonsum_y_pq1_sqrt +
                                               shaps_score_pq1_log + otherdiag + antidepmed +
                                               mde_curr + NMR_log + Only.Menthol + readiness + Race) + Var
                           data = results_mod$test_data_full)

# 2. Calculate predictions for training and testing data using avg_coef
train_linear_predictor <- x_mat_train_full %*% results_mod$avg_coef
test_linear_predictor <- x_mat_test_full %*% results_mod$avg_coef
```

```r
train_predicted_prob <- 1 / (1 + exp(-train_linear_predictor))
test_predicted_prob <- 1 / (1 + exp(-test_linear_predictor))

# 3: Calculate AUC and ROC
train_roc <- roc(results_mod$train_data_full$abst, as.vector(train_predicted_prob))
test_roc <- roc(results_mod$test_data_full$abst, as.vector(test_predicted_prob))
train_auc <- auc(train_roc)
test_auc <- auc(test_roc)

# Plot ROC for Train and Test Data
roc_plots <- ggplot() +
  geom_line(data = data.frame(specificity = rev(train_roc$specificities),
                              sensitivity = rev(train_roc$sensitivities)),
            aes(x = 1 - specificity, y = sensitivity, color = "Training"), size = 1) +
  geom_line(data = data.frame(specificity = rev(test_roc$specificities),
                              sensitivity = rev(test_roc$sensitivities)),
            aes(x = 1 - specificity, y = sensitivity, color = "Testing"), size = 1) +
  geom_abline(slope = 1, intercept = 0, linetype = "dashed", color = "black") +
  scale_color_manual(values = c("Training" = "blue", "Testing" = "red"),
                     labels = c(paste("Training (AUC =", round(train_auc, 2), ")"),
                                paste("Testing (AUC =", round(test_auc, 2), ")"))) +
  labs(
       x = "False Positive Rate",
       y = "True Positive Rate") +
  theme_minimal() +
    theme(
      axis.title = element_text(size = 8),
      axis.text = element_text(size = 8)) +
  theme(legend.position = c(0.8, 0.15))

annotate_figure(roc_plots,
                top = text_grob("Figure 3: ROC Curve Using Average Coefficients", face = "bold", size =
# Create a data frame for calibration plot
calibration_data_train <- results_mod$train_data_full %>%
  mutate(abst = ifelse(abst=="Yes", 1, 0),
    pred = train_predicted_prob)
calibration_data_test <- results_mod$test_data_full %>%
  mutate(abst = ifelse(abst=="Yes", 1, 0),
         pred = test_predicted_prob)

calibration_plot_train <- calibration_plot(data = calibration_data_train, obs = "abst", pred = "pred")$
  annotate("text", x = -Inf, y = Inf, label = "(a). Training", hjust = -0.5, vjust = 1, size = 3, fontfa
  xlim(0, 0.5) +
  ylim(0, 0.8) +
  theme_minimal() +
    theme(
      axis.title = element_text(size = 8),
      axis.text = element_text(size = 8))

calibration_plot_test <- calibration_plot(data = calibration_data_test, obs = "abst", pred = "pred")$cal
  annotate("text", x = -Inf, y = Inf, label = "(b). Testing", hjust = -0.5, vjust = 1, size = 3, fontfac
  xlim(0, 0.5) +
  ylim(0, 0.8) +
```

```
  theme_minimal() +
    theme(
      axis.title = element_text(size = 8),
      axis.text = element_text(size = 8))

# Arrange plots
grid.arrange(calibration_plot_train, calibration_plot_test, ncol = 2) %>%
  annotate_figure(top = text_grob("Figure 4: Calibration Plots", face = "bold", size = 10))
```