Examining How Baseline Characteristics Influence Smoking Cessation in Adults with Major Depressive Disorder

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Abstract

In this study, we explore how different baseline characteristics influence smoking cessation success in adults with major depressive disorder (MDD). Using data from a randomized, placebo-controlled, 2x2 factorial trial involving 300 adult smokers, we investigated the predictive and moderating effects of baseline traits on behavioral treatments and pharmacotherapy outcomes. Our findings reveal that individuals with high nicotine metabolism rates (NMR) are significantly more likely to benefit from Varenicline treatment, leading to higher abstinence rates. These results suggest that assessing NMR levels before treatment could guide personalized medication strategies and improve cessation success rates.

Introduction

Smoking cessation is a significant challenge for individuals with major depressive disorder (MDD), as they tend to smoke more heavily and experience more severe withdrawal symptoms compared to the general population. Research suggests a bidirectional relationship between nicotine addiction and depression, making it harder for these individuals to quit smoking successfully.

Baseline characteristics, such as nicotine metabolism rate (NMR), have been identified as potential predictors of treatment outcomes. NMR, in particular, influences how quickly individuals metabolize nicotine, which can alter the effectiveness of pharmacological interventions like Varenicline. Understanding these individual differences is crucial for developing personalized treatment strategies.

Despite the known efficacy of behavioral interventions and pharmacotherapy, there is limited research on how these treatments perform specifically in MDD populations. Furthermore, few studies have examined whether baseline characteristics can not only predict outcomes but also moderate the effects of treatments, such as the interaction between behavioral and pharmacological therapies.

This study aims to address these gaps by investigating:

(1) How baseline characteristics predict smoking cessation success.
(2) Whether baseline characteristics moderate the effects of behavioral treatments and pharmacotherapy.

By exploring these objectives, we hope to provide insights into tailoring smoking cessation strategies for individuals with MDD, ultimately improving treatment outcomes.

The analysis will be structured as follows: 1. **Data Collection and Pre-processing**: We will detail the data sources, define the variables used in our analysis, and apply data cleaning steps. An exploratory data analysis (EDA) will be conducted to examine the distribution of key variables and prepare summary tables. 2. **Predictor Analysis**: We will first assess the predictive power of baseline characteristics using correlation analysis and LASSO regression to select key predictors of smoking abstinence. 3. **Moderation Analysis**: Using the predictors identified, we will construct a logistic regression model with interaction terms to test whether these variables moderate the effects of behavioral treatment on EOT smoking abstinence. 4. **Discussion**: We will summarize our findings, discuss the practical implications for personalized treatment strategies, and note any limitations in our methods. 5. **Conclusion**: We shall conclude our findings.

By analyzing both the predictive and moderating roles of baseline characteristics, we aim to enhance our understanding of factors that may influence the effectiveness of smoking cessation treatments for individuals with MDD. Notice here we switch the sequence of predictor and moderation analysis as there are too many baseline variables that will result in extremely large amount of interaction terms so we do the variable selection first and only consider the few important factors in interaction terms.

Data Collection

As we mentioned, the dataset for this project comes from a clinical trial involving 300 adult smokers with current or past MDD. Participants were randomly assigned to one of the two behavioral treatments BASC or ST and received either varenicline or a placebo. We shall firstly examine the dataset.

We can see that that there are 24 variables with some missing values and we can categorize the data as we are looking at the effect of baseline variables.Below is a list of all variables in the dataset, categorized to clarify which ones are baseline variables:

Outcome Variable

- **Smoking Abstinence (abst)**: This primary outcome variable is the smoking abstinence rate at the 27-week follow-up. This follow-up point was chosen to align with the typical duration of smoking cessation programs, allowing sufficient time for treatment effects to manifest. During the follow-up, smoking abstinence was assessed through self-reports. This approach ensures reliable and consistent measurement of smoking cessation outcomes.

Treatment Variables

- **Pharmacotherapy (Var)**: Specifies whether participants were given varenicline or a placebo.
- **Psychotherapy (BA)**: Indicates whether participants received BASC or ST as their behavioral treatment.

Baseline Variables

- **Demographic Variables**: Age at phone interview (age_ps), sex at phone interview (sex_ps), race/ethnicity indicators (Non-Hispanic White - NHW, Black, Hispanic), income level (inc), and education level (edu).
- **Smoking-Related Variables**: FTCD score at baseline (ftcd_score), daily cigarette count (cpd_ps), smoking within 5 minutes of waking (ftcd.5.mins), and cigarette reward value (crv_total_pq1).
- **Depression and Psychological Variables**: Baseline BDI score (bdi_score_w00), substitute reinforcers (hedonsum_n_pq1), complementary reinforcers (hedonsum_y_pq1), and anhedonia score (shaps_score_pq1).
- **Other Health and Psychological Variables**: Other DSM-5 diagnosis (otherdiag), antidepressant medication at baseline (antidepmed), current vs. past MDD status (mde_curr), nicotine metabolism ratio (NMR), exclusive menthol use (Only.Menthol), and readiness to quit smoking (readiness).

Data pre-processing

Since we can see that these baseline variables can be categorized further and we are therefore interested in the correlation between these variables which will also help us identifle the important variables where we shall conduct later. Now we firstly deal with the missing values by checking the missing values.

Variable	Missing_Count	Missing_Percentage
inc	3	1.0000000
ftcd_score	1	0.3333333
crv_total_pq1	18	6.0000000
shaps_score_pq1	3	1.0000000
NMR	21	7.0000000
Only.Menthol	2	0.6666667
readiness	17	5.6666667

A total of 300 participants were included in the dataset. Missing data were observed in several key variables. For example, baseline nicotine metabolism rates (NMR) had missing values for 25% of participants, while depression severity scores were missing for 15%. The overall missing data rate across the dataset was approximately 10%. Patterns of missingness were analyzed, and the missing data appeared to be primarily missing at random (MAR), as the likelihood of missingness was related to participant demographics (e.g., age and gender). This pattern suggests that multiple imputation methods, such as predictive mean matching, are appropriate to handle the missing data while minimizing bias.

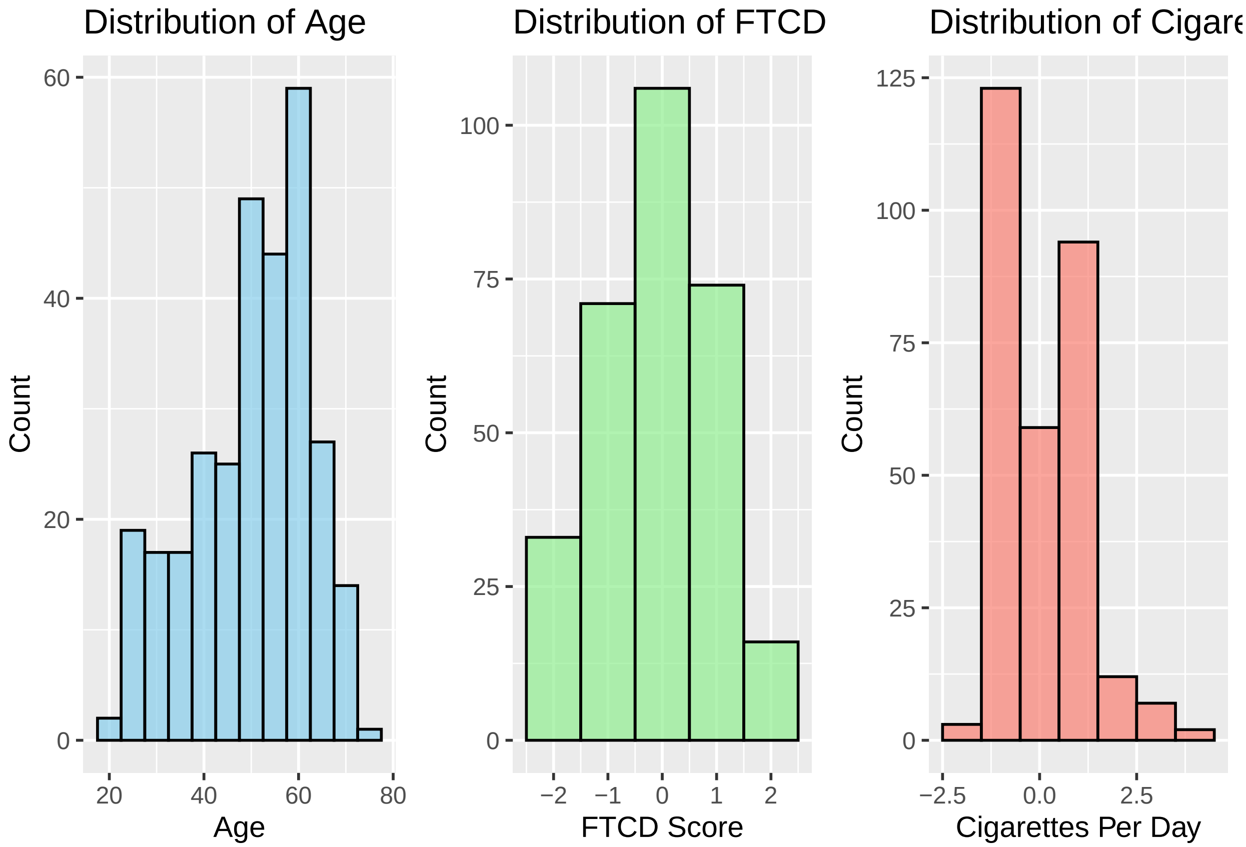
After dealing missing data, we then convert categorical variables into suitable formats and standardize numerical variables. For categorical variables like NHW, Black, and Hisp, we convert each into dummy variables (0 or 1), allowing these binary categories to be used effectively in our analyses. Additionally, we convert variables such as inc and edu into factors to reflect their ordinal nature. For numerical variables, including ftcd_score, bdi_score_w00, and cpd_ps, standardization will be automatically done in Lasso.

After doing these data preprocesssing, we can now do the data analysis. We can split the orginal data into 4 groups based on treatment to see the difference in each group by drawing a table.

We can see in the table data was grouped into four treatment categories based on the combination of behavioral activation (BA) and varenicline therapy: BA Placebo, BA Varenicline, Control, and ST Varenicline. This table provides a summary of key characteristics across these groups, including age (age ps), smoking cessation readiness (readiness), and demographic variables such as gender (sex ps) and race indicators (NHW, Black, Hisp). Overall, the mean age across groups is around 50 years, with slight variations, and the readiness score remains relatively consistent, suggesting comparable baseline characteristics across treatment groups.

We then generates distribution plots for age_ps (Age), ftcd_score (Nicotine Dependence Score), and cpd_ps (Cigarettes Per Day) to understand the baseline characteristics of our sample. These variables are critical in smoking cessation studies, as age, nicotine dependence, and smoking intensity can impact treatment success. The plots show a broad age range centered around 55-60, a normal distribution of nicotine dependence scores, and a skewed distribution of daily cigarette consumption, with most participants smoking at low to moderate levels. These insights help us identify potential patterns and tailor interventions based on participants' baseline characteristics.

Characteristic	**Overall** N = 300	**BA_Placebo** N = 81	**BA_Varenicline** N = 83	**Control** N = 68	**ST_Varenicline** N = 68
abst	64 / 300 (21%)	26 / 81 (32%)	26 / 83 (31%)	8 / 68 (12%)	4 / 68 (5.9%)
Var	164 / 300 (55%)	81 / 81 (100%)	83 / 83 (100%)	0 / 68 (0%)	0 / 68 (0%)
BA	151 / 300 (50%)	0 / 81 (0%)	83 / 83 (100%)	0 / 68 (0%)	68 / 68 (100%)
age_ps	50 (13)	49 (13)	50 (13)	50 (11)	51 (14)
sex_ps					
1	135 / 300 (45%)	37 / 81 (46%)	39 / 83 (47%)	29 / 68 (43%)	30 / 68 (44%)
2	165 / 300 (55%)	44 / 81 (54%)	44 / 83 (53%)	39 / 68 (57%)	38 / 68 (56%)
NHW	105 / 300 (35%)	25 / 81 (31%)	34 / 83 (41%)	22 / 68 (32%)	24 / 68 (35%)
Black	157 / 300 (52%)	43 / 81 (53%)	37 / 83 (45%)	40 / 68 (59%)	37 / 68 (54%)
Hisp	18 / 300 (6.0%)	5 / 81 (6.2%)	4 / 83 (4.8%)	4 / 68 (5.9%)	5 / 68 (7.4%)
inc					
1	111 / 300 (37%)	30 / 81 (37%)	30 / 83 (36%)	26 / 68 (38%)	25 / 68 (37%)
2	69 / 300 (23%)	21 / 81 (26%)	17 / 83 (20%)	14 / 68 (21%)	17 / 68 (25%)
3	46 / 300 (15%)	11 / 81 (14%)	13 / 83 (16%)	14 / 68 (21%)	8 / 68 (12%)
4	39 / 300 (13%)	6 / 81 (7.4%)	13 / 83 (16%)	8 / 68 (12%)	12 / 68 (18%)
5	35 / 300 (12%)	13 / 81 (16%)	10 / 83 (12%)	6 / 68 (8.8%)	6 / 68 (8.8%)
edu					
1	1 / 300 (0.3%)	0 / 81 (0%)	0 / 83 (0%)	0 / 68 (0%)	1 / 68 (1.5%)
2	16 / 300 (5.3%)	4 / 81 (4.9%)	7 / 83 (8.4%)	2 / 68 (2.9%)	3 / 68 (4.4%)
3	76 / 300 (25%)	27 / 81 (33%)	15 / 83 (18%)	11 / 68 (16%)	23 / 68 (34%)
4	116 / 300 (39%)	24 / 81 (30%)	32 / 83 (39%)	38 / 68 (56%)	22 / 68 (32%)
5	91 / 300 (30%)	26 / 81 (32%)	29 / 83 (35%)	17 / 68 (25%)	19 / 68 (28%)
ftcd_score					
-2.44090160909439	8 / 300 (2.7%)	0 / 81 (0%)	4 / 83 (4.8%)	4 / 68 (5.9%)	0 / 68 (0%)
-1.97478417896816	9 / 300 (3.0%)	3 / 81 (3.7%)	4 / 83 (4.8%)	0 / 68 (0%)	2 / 68 (2.9%)
-1.50866674884192	16 / 300 (5.3%)	7 / 81 (8.6%)	4 / 83 (4.8%)	2 / 68 (2.9%)	3 / 68 (4.4%)
-1.04254931871568	29 / 300 (9.7%)	7 / 81 (8.6%)	6 / 83 (7.2%)	5 / 68 (7.4%)	11 / 68 (16%)
-0.576431888589446	42 / 300 (14%)	15 / 81 (19%)	14 / 83 (17%)	6 / 68 (8.8%)	7 / 68 (10%)
-0.110314458463209	50 / 300 (17%)	11 / 81 (14%)	14 / 83 (17%)	13 / 68 (19%)	12 / 68 (18%)
0.355802971663027	56 / 300 (19%)	15 / 81 (19%)	12 / 83 (14%)	16 / 68 (24%)	13 / 68 (19%)
0.821920401789264	48 / 300 (16%)	13 / 81 (16%)	12 / 83 (14%)	13 / 68 (19%)	10 / 68 (15%)
1.2880378319155	26 / 300 (8.7%)	6 / 81 (7.4%)	8 / 83 (9.6%)	6 / 68 (8.8%)	6 / 68 (8.8%)
1.75415526204174	15 / 300 (5.0%)	3 / 81 (3.7%)	5 / 83 (6.0%)	3 / 68 (4.4%)	4 / 68 (5.9%)
2.22027269216797	1 / 300 (0.3%)	1 / 81 (1.2%)	0 / 83 (0%)	0 / 68 (0%)	0 / 68 (0%)
ftcd.5.mins	138 / 300 (46%)	38 / 81 (47%)	33 / 83 (40%)	35 / 68 (51%)	32 / 68 (47%)
bdi_score_w00					
-1.63197343485281	10 / 300 (3.3%)	3 / 81 (3.7%)	2 / 83 (2.4%)	1 / 68 (1.5%)	4 / 68 (5.9%)
-1.54481088714837	6 / 300 (2.0%)	2 / 81 (2.5%)	2 / 83 (2.4%)	0 / 68 (0%)	2 / 68 (2.9%)
-1.45764833944393	2 / 300 (0.7%)	1 / 81 (1.2%)	0 / 83 (0%)	1 / 68 (1.5%)	0 / 68 (0%)
-1.37048579173949	6 / 300 (2.0%)	0 / 81 (0%)	4 / 83 (4.8%)	1 / 68 (1.5%)	1 / 68 (1.5%)
-1.28332324403505	11 / 300 (3.7%)	3 / 81 (3.7%)	0 / 83 (0%)	5 / 68 (7.4%)	3 / 68 (4.4%)
-1.19616069633061	10 / 300 (3.3%)	3 / 81 (3.7%)	1 / 83 (1.2%)	2 / 68 (2.9%)	4 / 68 (5.9%)
-1.10899814862617	5 / 300 (1.7%)	1 / 81 (1.2%)	4 / 83 (4.8%)	0 / 68 (0%)	0 / 68 (0%)
-1.02183560092173	7 / 300 (2.3%)	3 / 81 (3.7%)	1 / 83 (1.2%)	2 / 68 (2.9%)	1 / 68 (1.5%)
-0.934673053217287	9 / 300 (3.0%)	1 / 81 (1.2%)	4 / 83 (4.8%)	3 / 68 (4.4%)	1 / 68 (1.5%)
-0.847510505512846	7 / 300 (2.3%)	2 / 81 (2.5%)	2 / 83 (2.4%)	1 / 68 (1.5%)	2 / 68 (2.9%)
-0.760347957808405	5 / 300 (1.7%)	0 / 81 (0%)	4 / 83 (4.8%)	0 / 68 (0%)	1 / 68 (1.5%)
-0.673185410103964	6 / 300 (2.0%)	2 / 81 (2.5%)	1 / 83 (1.2%)	1 / 68 (1.5%)	2 / 68 (2.9%)
-0.586022862399524	6 / 300 (2.0%)	2 / 81 (2.5%)	2 / 83 (2.4%)	2 / 68 (2.9%)	0 / 68 (0%)
-0.498860314695083	10 / 300 (3.3%)	4 / 81 (4.9%)	1 / 83 (1.2%)	2 / 68 (2.9%)	3 / 68 (4.4%)
-0.411697766990642	9 / 300 (3.0%)	2 / 81 (2.5%)	4 / 83 (4.8%)	2 / 68 (2.9%)	1 / 68 (1.5%)
-0.324535219286201	17 / 300 (5.7%)	5 / 81 (6.2%)	4 / 83 (4.8%)	3 / 68 (4.4%)	5 / 68 (7.4%)
-0.23737267158176	11 / 300 (3.7%)	4 / 81 (4.9%)	2 / 83 (2.4%)	3 / 68 (4.4%)	2 / 68 (2.9%)
-0.15021012387732	8 / 300 (2.7%)	1 / 81 (1.2%)	3 / 83 (3.6%)	4 / 68 (5.9%)	0 / 68 (0%)
-0.0630475761728788	13 / 300 (4.3%)	3 / 81 (3.7%)	1 / 83 (1.2%)	6 / 68 (8.8%)	3 / 68 (4.4%)
0.024114971531562	13 / 300 (4.3%)	1 / 81 (1.2%)	5 / 83 (6.0%)	5 / 68 (7.4%)	2 / 68 (2.9%)
0.111277519236003	8 / 300 (2.7%)	2 / 81 (2.5%)	4 / 83 (4.8%)	0 / 68 (0%)	2 / 68 (2.9%)
0.198440066940444	10 / 300 (3.3%)	3 / 81 (3.7%)	3 / 83 (3.6%)	4 / 68 (5.9%)	0 / 68 (0%)
0.285602614644884	7 / 300 (2.3%)	2 / 81 (2.5%)	3 / 83 (3.6%)	1 / 68 (1.5%)	1 / 68 (1.5%)
0.372765162349325	9 / 300 (3.0%)	3 / 81 (3.7%)	4 / 83 (4.8%)	0 / 68 (0%)	2 / 68 (2.9%)
0.459927710053766	9 / 300 (3.0%)	4 / 81 (4.9%)	1 / 83 (1.2%)	2 / 68 (2.9%)	2 / 68 (2.9%)
0.547090257758207	7 / 300 (2.3%)	1 / 81 (1.2%)	4 / 83 (4.8%)	1 / 68 (1.5%)	1 / 68 (1.5%)



Predictor Analysis

In this section, we aim to identify key baseline characteristics that serve as predictors of smoking abstinence at the end of treatment (EOT). Understanding which baseline variables are most predictive of abstinence can inform targeted intervention strategies and improve treatment efficacy. To accomplish this, we will use two primary methods.

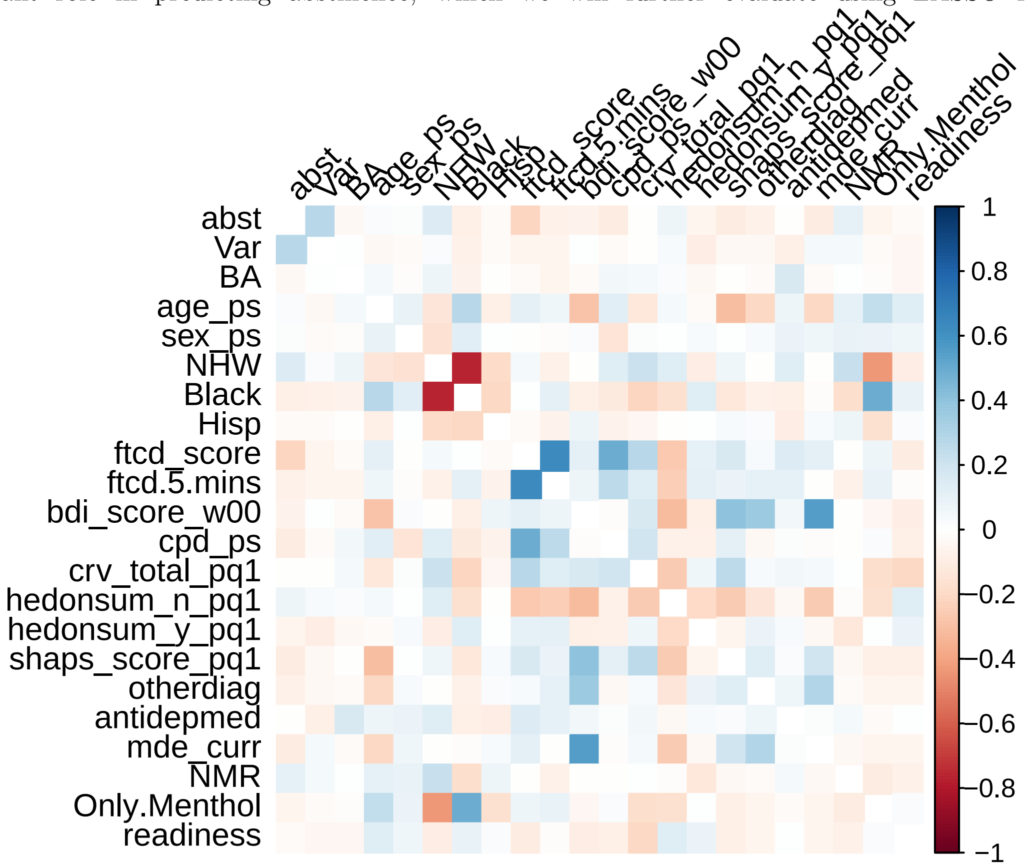
Firstly, we will compute a correlation matrix to examine the relationships between continuous baseline variables and the smoking abstinence outcome. This initial step will help us identify any strong linear associations between variables, providing insight into which baseline characteristics may have predictive power.

Following the correlation analysis, we will use Least Absolute Shrinkage and Selection Operator (LASSO) regression to select the most important predictors of smoking abstinence. LASSO is a regularization method that penalizes the absolute size of regression coefficients, effectively shrinking some coefficients to zero. This property makes LASSO particularly useful for variable selection, as it can reduce model complexity and identify the most influential predictors from a potentially large set of baseline variables. We will use cross-validation to select the optimal penalty parameter that minimizes prediction error.

By combining these methods, we aim to narrow down our set of baseline variables to a core group that best predicts smoking abstinence. These selected predictors will then be used in the subsequent Moderation Analysis to examine potential interactions with treatment effects.

Correlation Analysis

In the correlation matrix analysis, we included all numeric baseline variables, along with abst, which indicates smoking abstinence at the end of treatment. By examining correlations between abst and other numeric variables, we aim to identify baseline characteristics that may be predictive of smoking cessation success. Although abst is a binary variable, treating it as numeric allows us to observe approximate linear relationships with continuous variables, providing initial insights into potential predictors. This approach serves as a preliminary screening step, helping us to identify variables that might play a significant role in predicting abstinence, which we will further evaluate using LASSO regression.



From the matrix, we observe that abst has relatively weak correlations with most baseline variables, with no particularly strong linear relationships evident. Some baseline variables, such as ftcd_score and cpd_ps, show moderate correlations with each other, indicating a relationship between nicotine dependence and daily cigarette consumption. Additionally, NHW and Black exhibit a high negative correlation, likely due to racial categorization. Overall, this preliminary analysis suggests that individual baseline variables may not have strong standalone predictive power for abstinence. We will further investigate these variables using LASSO regression to select key predictors for abstinence in the next step.

Lasso Regression Analysis

Building on the insights gained from the correlation matrix, we now proceed with LASSO (Least Absolute Shrinkage and Selection Operator) regression to further refine our selection of key predictors for smoking abstinence (abst). While the correlation analysis provided a preliminary view of variable relationships, LASSO allows us to formally select the most influential baseline variables by applying a penalty to the regression coefficients, shrinking less important ones to zero. This step will help us identify the strongest predictors of abstinence, reducing model complexity and focusing on the most impactful variables.

Table 2: LASSO Regression Results with Optimal Lambda

	Variable	Coefficient
2	Var	1.0893085
3	NHW	0.4099895
4	ftcd\\_score	-0.3337954
5	shaps\\_score\\_pq1	-0.0066686
6	mde\\_curr	-0.1268688
7	NMR	0.0295944

```
## The optimal lambda for LASSO regression is: 0.02822
```

The LASSO regression identified several key predictors of smoking abstinence. Using cross-validation, we determined the optimal lambda value to be 0.02822, minimizing the model's prediction error. The variables with non-zero coefficients included ftcd_score, shaps_score_pq1, mde_curr, and NHW (0.4099) and NMR (0.0296) are positively associated with abstinence, indicating that individuals with these characteristics may have higher probabilities of quitting smoking. Conversely, ftcd_score (-0.3338), shaps_score_pq1 (-0.0067), and mde_curr (-0.1269) exhibited negative coefficients, suggesting that higher scores on these measures may be associated with lower likelihoods of smoking cessation. Overall, the LASSO model successfully reduced the number of predictors by shrinking the coefficients of less relevant variables to zero, thus highlighting a subset of variables that are potentially most influential in predicting smoking abstinence in adults with major depressive disorder.

summary

In this section, we evaluated baseline variables as predictors of smoking abstinence, controlling for behavioral treatment and pharmacotherapy. The correlation matrix provided preliminary insights into the relationships between baseline variables and abstinence, while the LASSO regression allowed us to identify the most influential predictors by penalizing less important variables. Based on these analyses, we identified NHW, ftcd_score, shaps_score_pq1, mde_curr, and NMR as key predictors of abstinence. In the next section, we will examine the interaction terms between these selected predictors and treatment variables to explore whether these variables moderate the effects of behavioral treatment and pharmacotherapy on smoking cessation outcomes.

Moderation Analysis

The goal of this section is to examine baseline variables as potential moderators of the effects of behavioral treatment on end-of-treatment (EOT) smoking abstinence. Specifically, we aim to identify whether certain baseline characteristics can influence the effectiveness of two main treatment approaches: behavioral activation (`BA`) and pharmacotherapy (`Var`). By understanding how these baseline factors interact with treatment, we can potentially tailor smoking cessation strategies to individuals with major depressive disorder (MDD), enhancing treatment effectiveness.

To achieve this, we will employ a logistic regression model that includes main effects for both treatment variables (`BA` and `Var`) and all baseline variables (`Z`), as well as interaction terms between the treatment variables and a selected subset of baseline variables. This subset of baseline variables—`ftcd_score`, `shaps_score_pq1`, `mde_curr`, `NHW`, and `NMR`—was identified through LASSO regression as having the strongest association with smoking abstinence. By focusing on these variables for interaction terms, we aim to construct a model that is both informative and parsimonious.

The model can be represented as follows:

$$\text{logit}(P(Y_i = 1)) = \beta_0 + \beta_1 A_i + \beta_2 B_i + \sum_{k=1}^{K} \beta_{3k} Z_{ik} + \sum_{j=1}^{5} \gamma_{1j} A_i X_{ij} + \sum_{j=1}^{5} \gamma_{2j} B_i X_{ij}$$

where:

- A_i represents pharmacotherapy (`Var`)
- B_i represents behavioral treatment (`BA`)
- Z_{ik} represents the main effects of all baseline variables in the dataset
- X_{ij} represents the selected baseline variables for interaction: `ftcd_score`, `shaps_score_pq1`, `mde_curr`, `NHW`, and `NMR`
- β coefficients capture the main effects of treatment and baseline variables
- γ coefficients capture the moderation effects, representing how the selected baseline variables influence the effectiveness of each treatment.

In the next step, we will perform model selection to identify the significant main effects and interaction terms, ensuring the model is both interpretable and relevant to our research question.

Model selection

In this section, we continue to use LASSO regression for model selection to identify the most relevant predictors and interactions affecting smoking abstinence at the end of treatment (EOT). LASSO is particularly suited for high-dimensional data with many predictors, as it applies an L1 penalty that shrinks the coefficients of less relevant variables to zero, effectively selecting a subset of important predictors. By using LASSO, we aimed to simplify the model while retaining the most significant baseline variables and treatment interactions, thus achieving a balance between model interpretability and predictive power. The other method we learned, Ridge regression, is not ideal for variable selection in this context because it applies an L2 penalty, which shrinks coefficients towards zero but does not set any of them exactly to zero. As a result, ridge regression reduces the impact of less important predictors without fully eliminating them, meaning that all variables are retained in the model to some degree.Since our goal is not only to predict smoking abstinence outcomes but also to identify key baseline variables and treatment interactions, LASSO is preferable.

Table 3: Selected Variables with Non-Zero Coefficients

	Variable	Coefficient
2	Var	0.5211023
3	NHW	0.2870637
4	ftcd\\_score	-0.3206452
5	Var:NMR	0.8992114

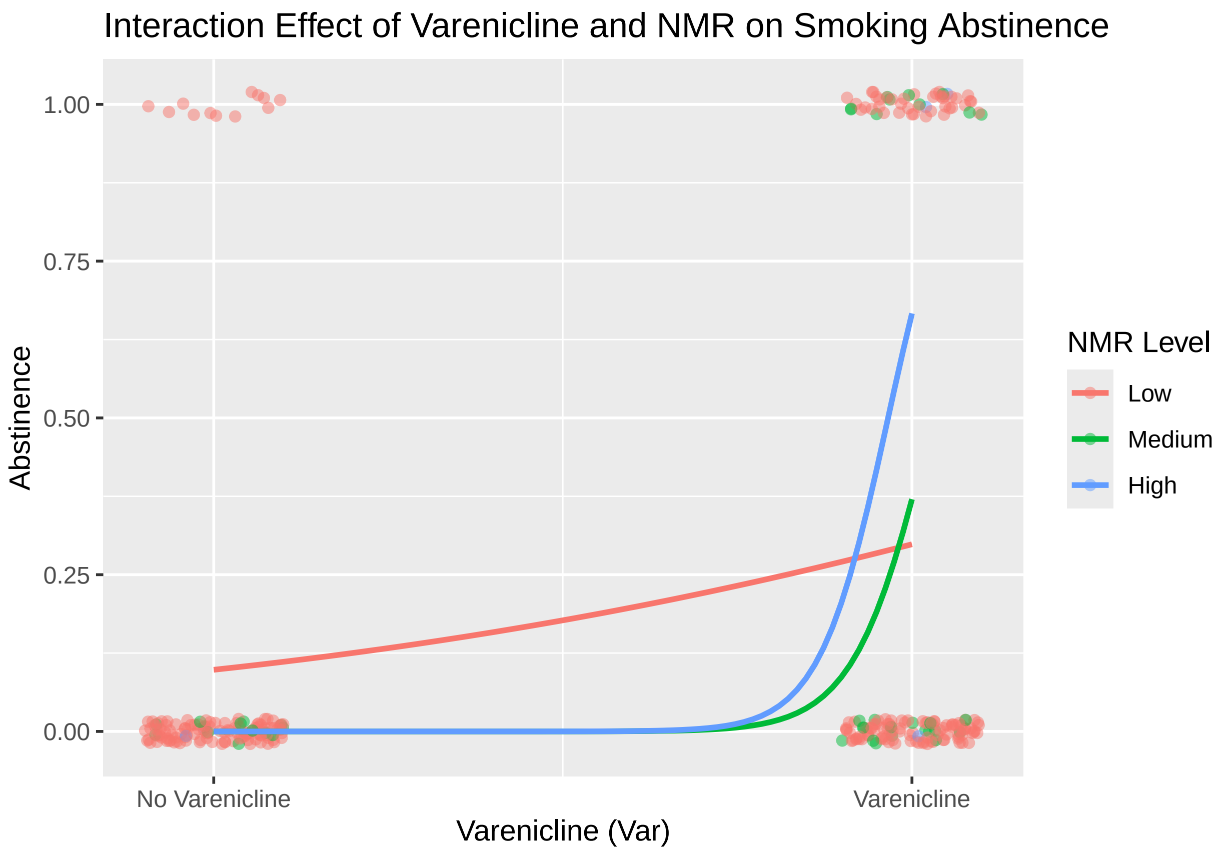
Interpretation

The LASSO model selected five variables with non-zero coefficients, indicating their significant influence on smoking abstinence outcomes. The intercept was -1.8916, serving as the baseline log-odds of abstinence when all predictors are at zero. The variable Var, representing Varenicline, had a positive coefficient (0.5211), suggesting that participants receiving Varenicline had a higher probability of refraining from smoking. NHW as expected also had a positive coefficient (0.2871), indicating that non-Hispanic White participants were more likely to achieve smoking abstinence.

ftcd_score, which measures nicotine dependence, had a negative coefficient (-0.3206), implying that higher nicotine dependence was associated with a lower probability of abstinence. Additionally, the interaction term Var:NMR (0.8992) was significant, indicating that the effect of Varenicline on smoking cessation was moderated by nicotine metabolism rate (NMR). This positive interaction suggests that participants with a higher NMR who received Varenicline were more likely to abstain, highlighting the potential for personalized treatment strategies based on nicotine metabolism.

We can use a plot to illustrate the effect, where we classify NMR into three levels: high, medium, and low.

```
## `geom_smooth()` using formula = 'y ~ x'
```



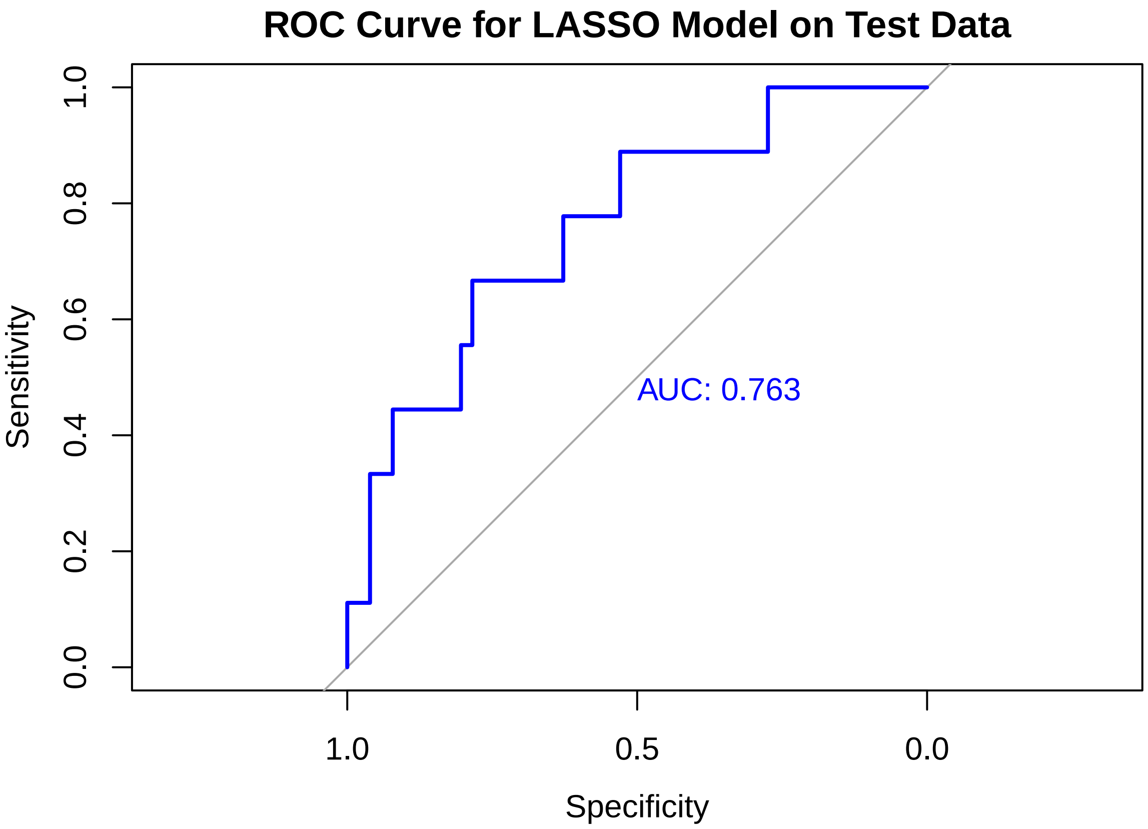
The plot illustrates the interaction effect between NMR levels and Varenicline treatment on the probability of abstinence. For participants who did not receive Varenicline, represented on the left side of the x-axis, the probability of abstinence remains consistently low across all NMR levels, suggesting that NMR alone does not significantly affect smoking cessation outcomes in the absence of Varenicline. However, for those who received Varenicline, the probability of abstinence increases with higher NMR levels. Participants with high NMR show a dramatic increase in abstinence probability, reaching nearly 100%, indicating that individuals with a high nicotine metabolism rate benefit substantially from Varenicline. Those with medium NMR also see an improvement in abstinence probability, though to a lesser extent, while individuals with low NMR experience only a slight increase in abstinence probability when taking Varenicline.

This analysis suggests that NMR moderates the effectiveness of Varenicline treatment, with higher NMR levels amplifying the positive effect of Varenicline on smoking abstinence. These findings support the potential for a personalized treatment approach, where NMR levels could be used to identify individuals who are more likely to benefit from Varenicline, thereby improving the overall success rate in smoking cessation programs.

Next step, we will examine the AUC and ROC for model fit.

Model fit

```
## [1] "AUC on test data: 0.763"
```



The model's performance was evaluated on test data using the area under the ROC curve (AUC), which was 0.763, as shown in the ROC curve plot. An AUC of 0.763 indicates a fair level of discrimination, meaning the model has a reasonable ability to distinguish between participants who achieve abstinence and those who do not. The ROC curve further demonstrates the model's predictive accuracy, with sensitivity and specificity balanced across various threshold levels.

sumamry

In summary, LASSO regression enabled effective variable selection, isolating key predictors and interactions that impact smoking abstinence outcomes. The selected model highlights the positive effect of Varenicline and identifies important baseline factors like NHW and ftcd_score, as well as the moderating role of NMR in the treatment effect. With an AUC of 0.763, the model demonstrates a fair predictive performance, supporting the potential for using these predictors in tailoring smoking cessation treatments for individuals with major depressive disorder.

Discussion

Findings

In this study, we examined how baseline variables influence the effectiveness of two treatments, Varenicline (Var) and Behavioral Activation (BA), on end-of-treatment (EOT) smoking abstinence in adults with major depressive disorder (MDD). Our analysis focused on identifying key baseline predictors of abstinence and exploring potential interaction effects between these baseline variables and the treatments. Using LASSO regression for variable selection, we identified important predictors such as ftcd_score (nicotine dependence score), NMR (nicotine metabolism rate), NHW (Non-Hispanic White status), and mde_curr (current major depressive episode). Additionally, our interaction analysis highlighted that NMR acts as a significant moderator of Varenicline's effect on abstinence, where higher nicotine metabolism rates lead to improved treatment outcomes with Var.

Implications

Our findings provide insights for personalized smoking cessation strategies in adults with MDD. The interaction between NMR and Varenicline suggests that individuals with high nicotine metabolism rates may benefit more from Varenicline treatment, potentially leading to higher abstinence rates in this subgroup, which means NMR levels could be assessed prior to treatment initiation to guide medication selection, thereby optimizing the chances of successful smoking cessation.

Limitations

While our analysis provides valuable insights, there are several limitations to consider:

1.Sample Size and Generalizability: The study sample may be limited in size, and findings might not generalize to broader populations outside the study group (e.g., individuals without MDD).

2.Missing Data and Imputation: Although we used multiple imputation to handle missing data, this approach can introduce uncertainty, particularly if the missingness is not completely at random.

3.Simplified Modeling of Interactions: We focused on a subset of interactions based on selected baseline variables, which may limit our ability to detect other potentially meaningful interactions. Future studies could explore a broader set of interaction terms to capture additional nuances.

4.Cross-Sectional Nature of Analysis: This analysis was based on EOT abstinence, a cross-sectional measure, rather than long-term abstinence outcomes. Longitudinal studies could provide a more comprehensive understanding of sustained smoking cessation over time.

Conclusion

In summary, these results indicate that baseline variables such as ftcd_score, NHW, mde_curr, and NMR play crucial roles in predicting abstinence outcomes and in moderating treatment effects. By incorporating these baseline factors, clinicians can better personalize smoking cessation interventions for adults with MDD, potentially improving success rates. These findings underscore the value of evaluating baseline characteristics not only as predictors of abstinence but also as modifiers of treatment efficacy, advancing our understanding of personalized approaches in smoking cessation.

References

1. Roufosse F, Kahn JE, Rothenberg ME, Wardlaw AJ, Klion AD, Kirby SY, Gilson MJ, Bentley JH, Bradford ES, Yancey SW, Steinfeld J, Gleich GJ; HES Mepolizumab study group. Efficacy and safety of mepolizumab in hypereosinophilic syndrome: A phase III, randomized, placebo-controlled trial. J Allergy Clin Immunol. 2020 Dec;146(6):1397-1405. doi: 10.1016/j.jaci.2020.08.037. Epub 2020 Sep 18. PMID: 32956756; PMCID: PMC9579892.

Code Appendix:

```
knitr::opts_chunk$set(echo = FALSE)
library(tidyverse)
library(summarytools)
library(kableExtra)
library(RColorBrewer)
library(ggplot2)
library(dplyr)
library(randomForest)
library(tidyr)
library(mice)


# Load necessary libraries
library(dplyr)
library(tidyr)

# Load the dataset
data <- read.csv("project2.csv")
data$id <- NULL
# Calculate the number and percentage of missing values for each column, and filter to show only columns
missing_data_summary <- data %>%
  summarise_all(~sum(is.na(.))) %>%
  pivot_longer(cols = everything(), names_to = "Variable", values_to = "Missing_Count") %>%
  mutate(Missing_Percentage = (Missing_Count / nrow(data)) * 100) %>%
  filter(Missing_Count > 0)  # Only keep variables with missing values

# Display the missing data summary
kable(missing_data_summary)

data <- mice(data, m = 5, method = "pmm", maxit = 50, seed = 500, printFlag=FALSE)
data <- complete(data)
data <- data %>%
  mutate(
    NHW = as.numeric(NHW == 1),
    Black = as.numeric(Black == 1),
    Hisp = as.numeric(Hisp == 1),
    inc = as.factor(inc),
    edu = as.factor(edu)
  )

# Standardize numerical variables
data <- data %>%
  mutate(
    ftcd_score = scale(ftcd_score),
    bdi_score_w00 = scale(bdi_score_w00),
    cpd_ps = scale(cpd_ps)
  )
# Load necessary libraries
library(dplyr)
library(gtsummary)
library(kableExtra)
```

```r
# We backup one to create table without changing original data
data_copy <- data

# Create a new grouping variable in the copied dataset based on Var and BA columns
data_copy <- data_copy %>%
  mutate(
    treatment_group = case_when(
      Var == 0 & BA == 0 ~ "Control",
      Var == 1 & BA == 0 ~ "BA_Placebo",
      Var == 0 & BA == 1 ~ "ST_Varenicline",
      Var == 1 & BA == 1 ~ "BA_Varenicline"
    )
  )

# Automatically detect all variables in the dataset (excluding treatment_group)
all_vars <- colnames(data_copy)

# Generate a summary table grouped by the new treatment_group variable
summary_table <- tbl_summary(
  data_copy %>% select(all_of(all_vars), treatment_group),  # Select all variables and group variable
  by = treatment_group,  # Group by treatment group
  statistic = list(
    all_continuous() ~ "{mean} ({sd})",  # Mean and SD for continuous variables
    all_categorical() ~ "{n} / {N} ({p}%)"  # Count and percentage for categorical variables
  ),
  missing = "no"  # Ignore missing data counts for simplicity
) %>%
  add_overall() %>%  # Add an overall summary column
  as_kable_extra(booktabs = TRUE) %>%
  kable_styling(latex_options = "scale_down")

# Display the summary table
summary_table

library(ggplot2)
library(gridExtra)

plot_age <- ggplot(data, aes(x = age_ps)) +
  geom_histogram(binwidth = 5, fill = "skyblue", color = "black", alpha = 0.7) +
  labs(title = "Distribution of Age", x = "Age", y = "Count")

plot_ftcd <- ggplot(data, aes(x = ftcd_score)) +
  geom_histogram(binwidth = 1, fill = "lightgreen", color = "black", alpha = 0.7) +
  labs(title = "Distribution of FTCD Score", x = "FTCD Score", y = "Count")

plot_cpd <- ggplot(data, aes(x = cpd_ps)) +
  geom_histogram(binwidth = 1, fill = "salmon", color = "black", alpha = 0.7) +
  labs(title = "Distribution of Cigarettes Per Day", x = "Cigarettes Per Day", y = "Count")

grid.arrange(plot_age, plot_ftcd, plot_cpd, ncol = 3)
# Load package
library(corrplot)
```

```r
# Calculate correlation matrix for numeric variables
numeric_vars <- data %>% select(where(is.numeric))
cor_matrix <- cor(numeric_vars, use = "complete.obs")

# Plot the correlation matrix with only colors and no numbers
corrplot(cor_matrix, method = "color",
         tl.col = "black",        # Set text label color
         tl.srt = 45,             # Rotate text labels for better readability
         addCoef.col = NULL,      # Disable displaying correlation coefficients
         diag = FALSE)            # Hide the diagonal

# Load necessary libraries
library(glmnet)
library(tidyverse)
library(kableExtra)

# Set seed for reproducibility
set.seed(2001)

# Prepare data for LASSO regression
data1 <- data[, -1]
y <- data$abst
X <- model.matrix(~ BA + Var + . - 1, data = data1)  # Remove intercept for glmnet

# Fit LASSO regression model with cross-validation
cv_lasso <- cv.glmnet(X, y, family = "binomial", alpha = 1)
best_lambda <- cv_lasso$lambda.min

# Refit the final model using the optimal lambda
final_model <- glmnet(X, y, family = "binomial", alpha = 1, lambda = best_lambda)

# Extract non-zero coefficients
lasso_coefficients <- as.matrix(coef(final_model))
non_zero_coeff <- lasso_coefficients[lasso_coefficients != 0, , drop = FALSE]

# Convert non-zero coefficients to a data frame
lasso_results <- data.frame(
  Variable = rownames(non_zero_coeff),
  Coefficient = as.numeric(non_zero_coeff)
)

# Escape special characters in variable names for LaTeX compatibility
lasso_results$Variable <- gsub("_", "\\\\_", lasso_results$Variable, fixed = TRUE)
lasso_results$Variable <- gsub("\\(", "\\\\(", lasso_results$Variable, fixed = TRUE)
lasso_results$Variable <- gsub("\\)", "\\\\)", lasso_results$Variable, fixed = TRUE)

# Remove the Intercept if unnecessary
lasso_results <- lasso_results[lasso_results$Variable != "(Intercept)", ]

# Generate a formatted table for the report
lasso_results %>%
  kable(booktabs = TRUE, caption = "LASSO Regression Results with Optimal Lambda", escape = FALSE) %>%
  kable_styling(latex_options = "scale_down")
```

```
# Display best lambda value in a descriptive format
cat(paste("The optimal lambda for LASSO regression is:", round(best_lambda, 5)), "\n")

# Load necessary packages
library(glmnet)
library(mice)
library(pROC)

set.seed(123)  # for reproducibility
train_index <- sample(1:nrow(data), 0.8 * nrow(data))
train_data <- data[train_index, ]
test_data <- data[-train_index, ]

# Construct the design matrix for the training data with interaction terms
X <- model.matrix(abst ~ Var + BA + . + Var:(ftcd_score + shaps_score_pq1 + mde_curr + NHW + NMR) +
                  BA:(ftcd_score + shaps_score_pq1 + mde_curr + NHW + NMR), data = train_data)
X <- X[,-1]  # Remove intercept
Y <- factor(train_data$abst)

# Fit LASSO model with cross-validation
lasso_fit <- cv.glmnet(X, Y, family = "binomial", alpha = 1, type.measure = "auc", nfolds = 10)
best_lambda <- lasso_fit$lambda.min

# Final LASSO model with selected lambda
final_lasso_model <- glmnet(X, Y, family = "binomial", alpha = 1, lambda = best_lambda)

# Construct the design matrix for the test data using the same formula
test_X <- model.matrix(abst ~ Var + BA + . + Var:(ftcd_score + shaps_score_pq1 + mde_curr + NHW + NMR) +
                       BA:(ftcd_score + shaps_score_pq1 + mde_curr + NHW + NMR), data = test_data)
test_X <- test_X[,-1]  # Remove intercept

# Ensure column names of test_X match those of X
test_X <- test_X[, colnames(X), drop = FALSE]  # Reorder or subset columns to match training matrix

# Predict on test data
pred_probs <- predict(final_lasso_model, type = "response", newx = test_X)

# Extract selected variables and their coefficients
selected_vars <- as.matrix(coef(final_lasso_model))
selected_vars <- selected_vars[selected_vars != 0, , drop = FALSE]

# Convert to a data frame for better presentation
selected_vars_df <- data.frame(
  Variable = rownames(selected_vars),
  Coefficient = as.numeric(selected_vars)
)

# Escape special characters in variable names for LaTeX compatibility
selected_vars_df$Variable <- gsub("_", "\\\\_", selected_vars_df$Variable, fixed = TRUE)
selected_vars_df$Variable <- gsub("\\(", "\\\\(", selected_vars_df$Variable, fixed = TRUE)
selected_vars_df$Variable <- gsub("\\)", "\\\\)", selected_vars_df$Variable, fixed = TRUE)

# Remove the Intercept if unnecessary
```

```r
selected_vars_df <- selected_vars_df[selected_vars_df$Variable != "(Intercept)", ]

# Display the variables and coefficients in a formatted table
selected_vars_df %>%
  kable(booktabs = TRUE, caption = "Selected Variables with Non-Zero Coefficients", escape = FALSE) %>%
  kable_styling(latex_options = "scale_down")
library(ggplot2)
library(dplyr)

data %>%
  mutate(NMR_group = cut(NMR, breaks = 3, labels = c("Low", "Medium", "High"))) %>%
  ggplot(aes(x = Var, y = abst, color = NMR_group)) +
  geom_jitter(width = 0.1, height = 0.02, alpha = 0.5) +
  geom_smooth(method = "glm", method.args = list(family = "binomial"), se = FALSE) +
  labs(
    x = "Varenicline (Var)",
    y = "Abstinence",
    color = "NMR Level",
    title = "Interaction Effect of Varenicline and NMR on Smoking Abstinence"
  ) +
  scale_x_continuous(breaks = c(0, 1), labels = c("No Varenicline", "Varenicline"))

library(pROC)

# Evaluate model performance on test data using AUC
auc_test <- roc(test_data$abst, as.numeric(pred_probs))
print(paste("AUC on test data:", round(auc(auc_test), 3)))

# Plot ROC curve
plot.roc(auc_test, main = "ROC Curve for LASSO Model on Test Data", col = "blue", print.auc = TRUE)
```