Modeling Cardiovascular Disease Risk: Evaluating Predictive Performance in the NHANES Target Population Using Framingham Heart Study Data

Victoria Grase

2023-12-03

Abstract

This study aimed to develop a prediction model for assessing the risk of cardiovascular disease (CVD) events. Professionals in the healthcare system often rely on these multivariable risk algorithms to estimate the likelihood of specific CVD events in a target population. This investigation utilized data from the Framingham Heart Study through the risk Communicator package to construct a prediction model. Subsequently, it evaluated the model's performance in a target population derived from the National Health and Nutrition Examination Survey (NHANES) data using the nhanesA package. The logistic regression method was employed to assess the probability of CVD event occurrence in a binary setting within the NHANES target population, comprising 2,838 study participants. The study population, with a mean age of 46.65 years and 1,512 women, consisted of individuals who underwent routine examinations between 30 and 62 years of age and were free of any prior stroke or heart occurrences. The sex-specific multivariable risk functions, often referred to as "general CVD" algorithms, incorporated variables such as age, total and high-density lipoprotein cholesterol, systolic and diastolic blood pressure, treatment for hypertension, smoking status, body mass index (BMI), blood pressure medication usage, and diabetes status.The study aimed to comprehensively assess the predictive performance of the model within the NHANES target population. The findings and results of this evaluation show the Monte Carlo simulation, with a high-density cluster around the Brier estimate in the target NHANES population (0.047) and lower densities for brier estimates beyond 0.08, effectively mirrors the observed performance, indicating potential optimism and providing valuable insights into the model's robustness across diverse scenarios in comparison to the Framingham study.

Introduction

The nhanesA package serves as a pivotal tool for researchers and facilitates access to the extensive National Health and Nutrition Examination Survey (NHANES) data. Leveraging the nhanesA package, analysts can seamlessly explore, analyze, and derive valuable insights from this comprehensive dataset, contributing to evidence-based decision-making in healthcare. This study uses demographic, questionnaire, and examination data.

Concurrently, the Framingham Heart Study dataset stands as a benchmark in cardiovascular research, providing a wealth of information crucial for developing predictive models related to cardiovascular diseases.The Framingham data is used evaluate risk prediction models, enabling researchers to assess the likelihood of cardiovascular events based on a multitude of risk factor in which this study will do as well.

The ability of a predictive model to perform effectively when applied to a different population than the one it was developed on, is a critical consideration in model development. One essential metric for evaluating transportability is the Brier score, which quantifies the accuracy of probabilistic predictions. In this context, the Brier score serves as a reliable measure to assess how well a predictive model, initially trained on Framingham data, generalizes its performance to a distinct population represented by NHANES data. This study explores the use of the Brier score to evaluate the transportability of cardiovascular risk prediction

models between these two datasets, shedding light on the model's reliability and robustness across diverse populations.

Aim

The primary aim of this study is to comprehensively evaluate the performance of a cardiovascular risk prediction model in a target population underlying NHANES (National Health and Nutrition Examination Survey). Importantly, the emphasis is placed on the assessment of model performance where we will be comparing brier estimates to help determine transportability of the model.

```
##
## Summary of Framingham Cardiovascular Risk Factors by Sex
```

```
##                        Stratified by SEX
##                         level 1                2                 p      test
##   n                             1110             1468
##   CVD (mean (SD))               0.32 (0.47)      0.16 (0.37)     <0.001
##   TIMECVD (mean (SD))        7226.18 (2402.62) 7952.63 (1830.88) <0.001
##   SEX (mean (SD))               1.00 (0.00)      2.00 (0.00)     <0.001
##   TOTCHOL (mean (SD))         226.34 (41.49)   246.22 (45.91)    <0.001
##   AGE (mean (SD))              60.08 (8.23)     60.62 (8.41)      0.102
##   SYSBP (mean (SD))           138.90 (21.05)   140.02 (23.74)     0.215
##   DIABP (mean (SD))            81.88 (11.41)    80.33 (11.08)     0.001
##   CURSMOKE (mean (SD))          0.39 (0.49)      0.31 (0.46)     <0.001
##   DIABETES (mean (SD))          0.09 (0.28)      0.07 (0.25)      0.049
##   BPMEDS (mean (SD))            0.11 (0.32)      0.18 (0.38)     <0.001
##   HDLC (mean (SD))             43.58 (13.36)    53.03 (15.69)    <0.001
##   BMI (mean (SD))              26.21 (3.49)     25.55 (4.25)     <0.001
```

```
## [1] 2578   14
```

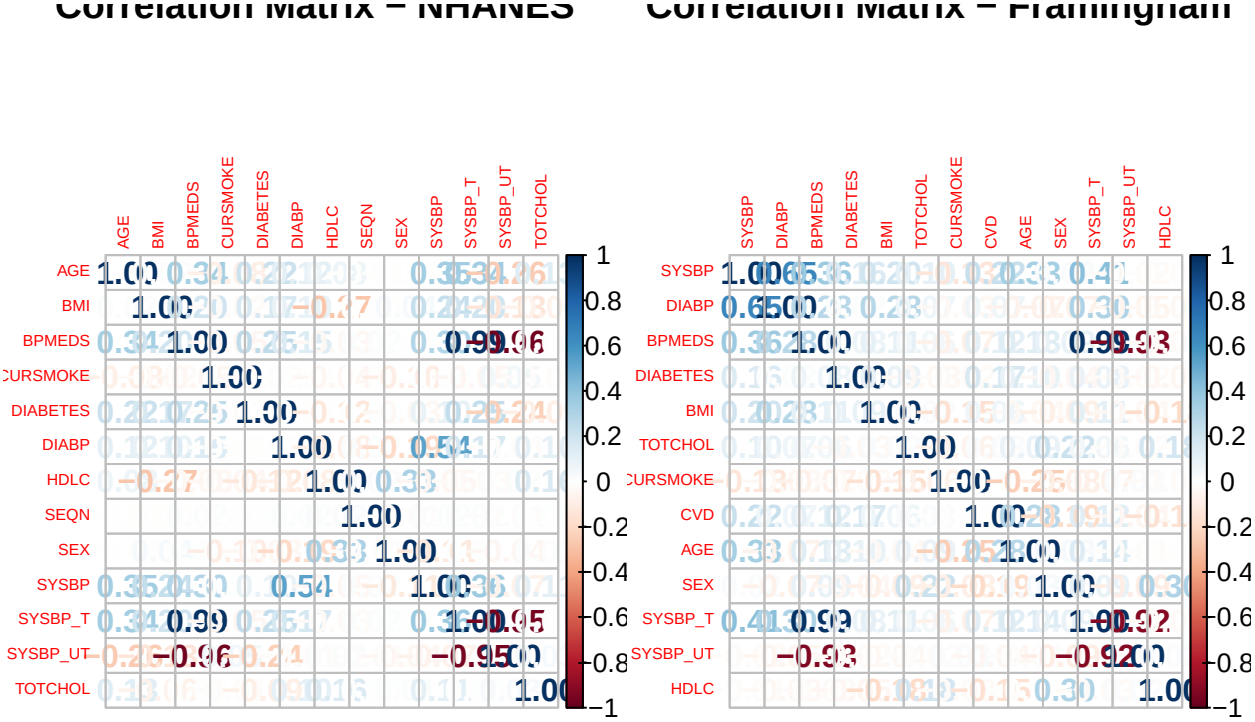
```
## [1] 2539   13
```

```
##
## Summary of NHANES Cardiovascular Risk Factors by Sex
```

```
##                        Stratified by SEX
##                         level 1              2              p      test
##   n                             1326             1512
##   SEX (mean (SD))               1.00 (0.00)      2.00 (0.00)  <0.001
##   TOTCHOL (mean (SD))         194.01 (40.21)   195.22 (38.06)  0.439
##   AGE (mean (SD))              46.65 (9.90)     46.49 (9.85)   0.663
##   SYSBP (mean (SD))           125.62 (16.12)   122.30 (18.71) <0.001
##   DIABP (mean (SD))            77.80 (11.09)    73.20 (12.23) <0.001
##   CURSMOKE (mean (SD))          0.25 (0.43)      0.16 (0.37)  <0.001
##   DIABETES (mean (SD))          0.11 (0.32)      0.10 (0.30)   0.401
##   BPMEDS (mean (SD))            0.22 (0.41)      0.22 (0.41)   0.852
##   HDLC (mean (SD))             47.78 (14.74)    57.72 (16.22) <0.001
##   BMI (mean (SD))              30.10 (6.68)     30.69 (8.34)   0.043
```

The comparison of cardiovascular risk factors between the Framingham and NHANES datasets reveals interesting distinctions in key variables. For instance in the Framingham study, participants having a mean age of 60.35 years, and NHANES participants having a mean age of 46.57 years.A few other differences are observed in blood pressure measurements, where all Framingham participants exhibit higher systolic blood pressure (138.96 mmHg) compared to all NHANES participants (123.79 mmHg),and diastolic blood pressure is higher in Framingham (80.67 mmHg) than in NHANES (77.94).Total cholesterol levels also differ, with Framingham participants having a mean total cholesterol of 236.89 mg/dL, compared to NHANES participants with a lower mean of 194.61 mg/dL. Notably, the Framingham cohort includes the outcome variable of

CVD events.These variations underscore the importance of considering dataset-specific characteristics when interpreting cardiovascular risk profiles, offering insights that can inform tailored preventive strategies in different populations.



In the correlation plot analysis for both the framingham and NHANES target pop, the variables “SEX,” “TOTCHOL,” “AGE,” “SYSBP,” “DIABP,” “CURSMOKE,” “DIABETES,” “BPMEDS,” “HDLC,” and “BMI” exhibit a diagonal value of 1(“CVD,” “TIMECVD,” are included on diagonal for framingham study). This diagonal value represents the correlation of each variable with itself, resulting in a perfect correlation. Essentially, this indicates that each variable is perfectly correlated with its own values, which is expected in a correlation matrix. Moreover, an interesting observation emerges when considering the correlation between “SYSBP” (systolic blood pressure) and “BPMEDS” (blood pressure medication usage). The correlation between these two variables is noteworthy due to the clinical context. Specifically, individuals with systolic and diastolic blood pressures exceeding 140 mmHg and 90 mmHg, respectively, are often prescribed blood pressure medications (“BPMEDS”) to manage hypertension. This relationship contributes to a positive correlation between “SYSBP” and “BPMEDS” in the correlation plot, as elevated blood pressure levels may necessitate medication. The inclusion of “SYSBP_t” (treated systolic blood pressure) and “SYSBP_ut” (untreated systolic blood pressure) further underscores the association, as they represent systolic blood pressure values under different treatment conditions.

Data Generating Mechanism

In an approach to handling missing data in the NHANES dataset,it was decided to employ multiple imputation, particularly focusing on variables DIABP (diastolic blood pressure) and SYSBP (systolic blood pressure). After implementing eligibility criteria and filtering the dataset, it was observed that DIABP and SYSBP exhibited the highest missing rates, each hovering around 15%, while the remaining variables had missingness levels below 10.7%. Given that the missing values were concentrated in specific blood pressure-related variables, and with the understanding that blood pressure measurements are critical indicators in cardiovascular health

Table 1: Brier Score Measures

Population	Brier Score
Framingham	0.157
NHANES	0.047 *estimator for Brier risk in target population

assessments;multiple imputation was deemed an appropriate strategy. By doing so, we aimed to ensure a more comprehensive and accurate representation of cardiovascular risk factors in the NHANES population, facilitating robust analyses.

The process of building a logistic regression model using the Framingham dataset for cardiovascular risk prediction and then extending the model to incorporate imputed data from the NHANES study starts when an 80/20 split is applied to the Framingham dataset for training and testing sets, respectively. Starting with the calculation of predicted probabilities for the source test set. These probabilities are computed using the logistic regression model fitted on the Framingham training data. The Brier score is then calculated for the source test set, providing a measure of the model's accuracy by assessing the mean squared difference between predicted probabilities and actual outcomes. Subsequently, imputed data is processed by averaging across multiple datasets . Variables that are common in both the Framingham and imputed datasets are identified, and a combined dataset is formed by merging these datasets on common variables. A population indicator variable (S) is introduced to differentiate between NHANES (0) and Framingham (1) populations based on the presence or absence of participant identifiers. The final dataset is created, focusing on similar variables that facilitate meaningful comparisons between the two studies. To ensure the reproducibility of the analysis a logistic regression model is then fitted to the training set(with an 80/20 split and a set seed), incorporating key factors. Additionally, a logistic regression model specific to the Framingham population is constructed.

The logistic regression model for the combined dataset is as follows:

$$CVD \sim \log(HDLC+1) + \log(TOTCHOL+1) + \log(AGE+1) + \log(SYSBP\_UT+1) + \log(SYSBP\_T+1) + \text{CURSMOKE} + \text{DIABETES}$$

$$\widehat{\psi}_{\widehat{\beta}} = \frac{\sum_{i=1}^{n} I(S_i = 1, D_{\text{test},i} = 1)\widehat{o}(X_i)\left(Y_i - g_{\widehat{\beta}}(X_i)\right)^2}{\sum_{i=1}^{n} I(S_i = 0, D_{\text{test},i} = 1)}, \tag{3}$$

where $\widehat{o}(X)$ is an estimator for the inverse-odds weights in the test set, $\dfrac{\Pr[S=0|X, D_{\text{test}}=1]}{\Pr[S=1|X, D_{\text{test}}=1]}$.

Next we look at the computation of the Brier score, a metric that quantifies the accuracy of probability predictions made by logistic regression models. To achieve this we are looking at the function and weights above. The numerator of the Brier risk is computed by subtracting the predicted probabilities of cardiovascular disease (CVD) outcomes for the Framingham population from the observed outcomes in the combined test set . This discrepancy is squared to assess the squared differences between predicted probabilities and actual outcomes, forming the basis for the Brier score calculation. Subsequently, the weights for each observation in the combined test set are determined based on the inverse odds of being from the Framingham population (S=1). These weights are essential for estimating the Brier risk in the overall population, considering the NHANES population (S=0) as well. The weighted Brier risk is then calculated as the sum of the squared differences between observed and predicted outcomes, normalized by the total number of NHANES participants. This approach provides an estimation of the Brier risk in the broader population, acknowledging the different origins of the two study populations.

The results are summarized in Table 1, comparing the Brier scores for the Framingham and NHANES

populations. Notably, the Framingham population exhibits a higher Brier score of 0.157, suggesting a greater discrepancy between predicted probabilities and observed outcomes for the logistic regression model applied to this cohort.While, the NHANES population demonstrates a lower Brier score of 0.047, indicating a more accurate prediction based on the model. The Brier score calculated for the NHANES population serves as an estimator for the Brier risk in the broader target population, combining both Framingham and NHANES populations. The lower Brier score for NHANES suggests that the logistic regression model's predictions align more closely with observed outcomes in this population, contributing to its role as an estimator for overall Brier risk.

Estimand:

Brier Scores of a prediction model for assessing the risk of cardiovascular disease (CVD) events

Methods:

Monte Carlo Simulation:

The Monte Carlo simulation aimed to generate individual-level data for binary and continuous covariates, simulating a population that aligns with the observed NHANES data. To achieve this, we leverage two functions, SimulateData_NormalDist and SimulateData_GammaDist, each tailored to draw individual-level data under specific distributions. Firstly, for binary covariates, the function SimulateData_NormalDist uses a Bernoulli distribution (0-1 distribution) to simulate the binary variables. The probability of success in the Bernoulli distribution is determined by the proportion of the corresponding binary covariate in the NHANES data. This approach ensures that the generated data mimics the distribution observed in NHANES. Now, for continuous covariates, two distributions are employed based on the nature of the variable. Therefore normally distributed continuous covariates, the function utilizes a normal distribution. The mean and standard deviation for each stratum are derived from the NHANES data. In addition, for positively skewed continuous covariates, the function adopts a gamma distribution. The shape and rate parameters for the gamma distribution are derived from the NHANES data. The gamma distribution is well-suited for modeling positive continuous covariates. It's to note that the decision to use these specific distributions is driven by the underlying characteristics of the covariates in the NHANES data. The Monte Carlo simulation aims to generate a synthetic population that mirrors the observed NHANES distribution, ensuring that the simulated data is a plausible representation of the population for subsequent analyses.

Next we use the BrierEstimate function which requires a dataset generated by the simulation functions SimulateData_GammaDist or SimulateData_NormalDist functions with parameters(SEQN, proportion of binary variables, mean of continuous variables, SD of the continuous variable, Sex variable for stratification, and proportion of total sample size for sex).It repeats the same steps as above for finding the brier estimate by next merging it with the original Framingham dataset, builds logistic regression models, and calculates a weighted Brier estimate for evaluating the model's performance in a combined dataset.

Next examining the distribution across the NHANES data and the simulated data from both simulation functions is important for ensuring that the generated data adequately represents the characteristics of the target population. In this context, focusing on the distribution for each gender separately is particularly important. In the context of cardiovascular disease risk prediction, where gender-specific risk factors may play a significant role, aligning the distributions becomes essential. If there are notable disparities in the distribution of key variables between the NHANES data and the simulated data, it could lead to biased models and inaccurate predictions. Therefore, a thorough examination of the distribution, particularly across genders, helps researchers identify and address any discrepancies, ensuring the robustness and applicability of their simulation results to diverse subpopulations.

Table 2: Summary of NHANES Data Proportions

SEX	CURSMOKE	DIABETES	BPMEDS
1	0.2503771	0.1123680	0.2150450
2	0.1633598	0.1025811	0.2180294

Table 3: Summary of Simulated Data Proportions-Normal Dist

SEX	CURSMOKE	DIABETES	BPMEDS
1	0.2663848	0.1176885	0.2121212
2	0.1656096	0.0993658	0.2156448

Table 4: Summary of Simulated Data Proportions-Gamma Dist

SEX	CURSMOKE	DIABETES	BPMEDS
1	0.2452431	0.1085271	0.2339676
2	0.1642001	0.1028894	0.2198732

Table 5: Summary of NHANES Data Mean

SEX	AGE	TOTCHOL	SYSBP	DIABP	HDLC	BMI
1	46.64932	194.0119	125.6207	77.80053	47.77749	30.09564
2	46.48743	195.2163	122.2983	73.20284	57.71670	30.69478

Table 6: Summary of Simulated Data Mean-Normal Dist

SEX	AGE	TOTCHOL	SYSBP	DIABP	HDLC	BMI
1	46.74634	193.2880	125.9436	78.15959	47.74334	29.80067
2	46.57130	195.5539	122.0663	72.87118	58.35182	30.56776

Table 7: Summary of Simulated Data Mean-Gamma Dist

SEX	AGE	TOTCHOL	SYSBP	DIABP	HDLC	BMI
1	46.53105	194.9962	125.7190	77.57476	47.73156	30.27631
2	46.54046	195.0227	122.6063	72.62365	57.38103	30.36608

Table 8: Summary of NHANES Data SD

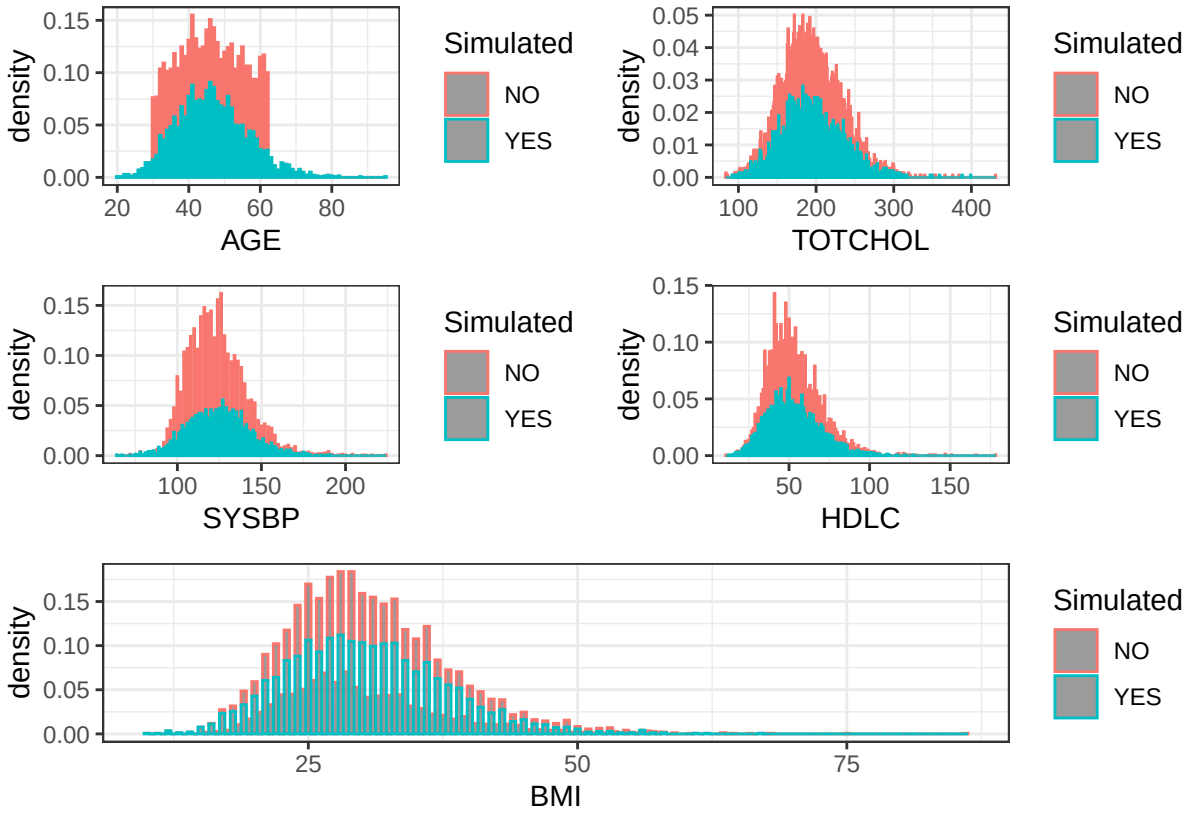
SEX	AGE	TOTCHOL	SYSBP	DIABP	HDLC	BMI
1	9.902541	40.21181	16.12259	11.08689	14.74241	6.682138
2	9.854661	38.05515	18.71080	12.23128	16.21977	8.335072

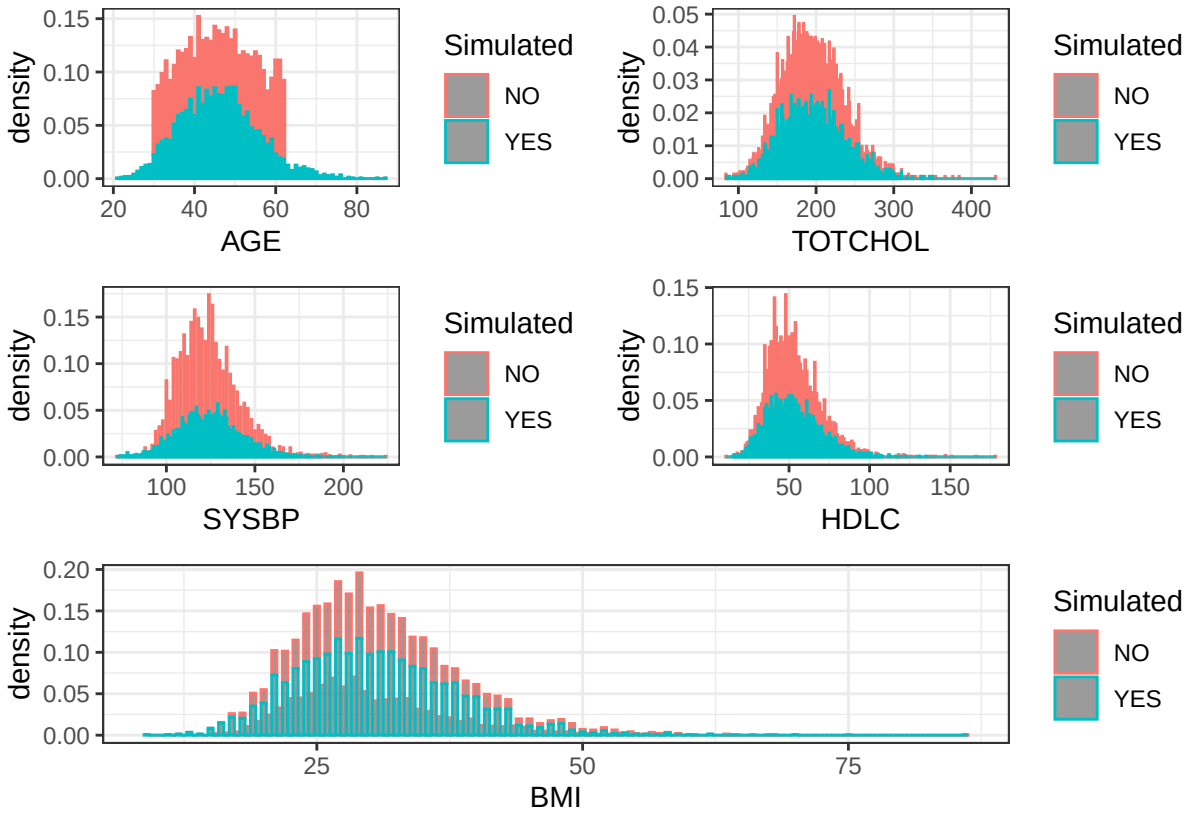
Table 9: Summary of Simulated Data SD-Normal Dist

SEX	AGE	TOTCHOL	SYSBP	DIABP	HDLC	BMI
1	9.746749	41.3486	15.46784	11.17947	14.27114	6.774700
2	9.899403	38.5206	19.02758	11.85954	16.61523	8.625614

Table 10: Summary of Simulated Data SD-Gamma Dist

SEX	AGE	TOTCHOL	SYSBP	DIABP	HDLC	BMI
1	10.314691	39.63185	15.95143	10.69403	15.13247	6.673883
2	9.614214	38.72685	19.70105	12.34789	16.09742	8.114669





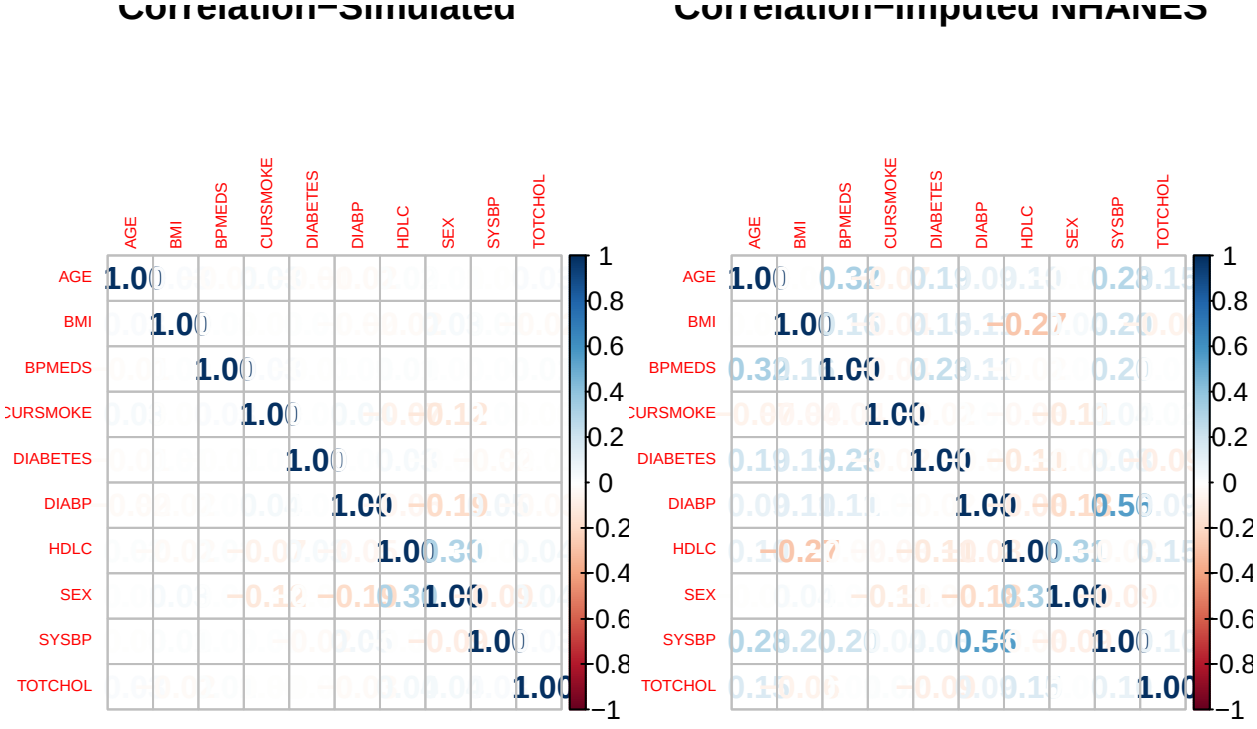
Looking at distributions we first observe the proportions (Tables:2,3,4) of smoking status, blood pressure medication, and diabetes in both of the simulated datasets closely resemble those in the NHANES data for both genders. The differences are minimal, suggesting that the simulated data adequately captures this variable's distribution.

The same thing can be said for the mean(Tables:5,6,7) and standard deviation (Tables:8,9,10) of the continuous variables: systolic blood pressure, age, HDLC, diastolic blood pressure, total cholesterol, and BMI in which the averages from the distribution closely resemble the same as the NHANES data for both genders in which you can see in the summary tables.

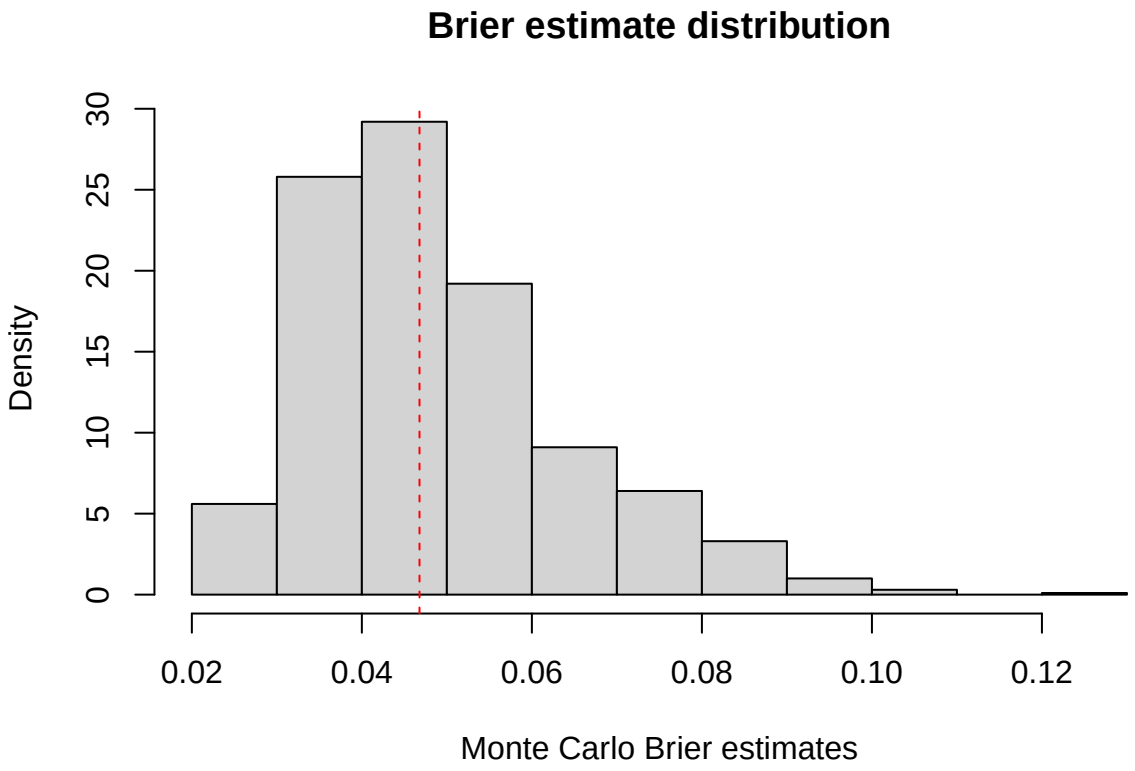
This is important for model tansferability because when distributions are similar as they are in this case, the learned patterns, relationships,and predictive features are more likely to transfer effectively to the new population. Which is essential to check for before continuing on to see how source and target performance measures compare. Not only from the tables but you can see similar distributions in the graph. The first set representing the normal distribution and the second set of graphs modeling the Gamma distribution versus the simulated data. it is evident that the summary statistics of the simulated individual level data is similar to the summary statistics of the nhanes data.

In the following, Monte Carlo Brier estimates is derived. The procedure invloves two steps. (1) Simulate individual level data based on the summary statistics of the nhanesA data and (2) compute the Brier estimates for each Monte Carlo draws. Before proceeding with the Monte Carlo simulations, it is essential to examine the correlation plots comparing the simulated data with the NHANES data. The diagonal values in these plots represent the correlation of each variable with itself, resulting in a perfect correlation as expected in a correlation matrix. In the NHANES imputed data, the correlation between systolic blood pressure (sysbp) and diastolic blood pressure (diabp) is observed, aligning with the physiological relationship between these two components of blood pressure. In the simulated data, a slight correlation is observed between sex and high-density lipoprotein cholesterol (HDLC). This exploration of correlations provides valuable insights into the relationships among variables and helps ensure the fidelity of the simulated data in comparison to the

NHANES dataset.



Results



The above histogram shows the distribution of 1000 Monte Carlo Brier estimates. The vertical red line is the Brier estimate of the model on NHANES individual level data. The bar graph illustrating the Monte Carlo simulation function reveals a compelling pattern, characterized by a concentrated high density around a Brier estimate value similar to the observed estimate in the target population (0.047 in the NHANES data). This clustering implies that the simulated data faithfully mirrors the actual performance observed in the target population, attesting to the robustness and reliability of the simulation in capturing the model's characteristics across various scenarios. The simulation's distinct density concentration around lower Brier estimates, particularly centered around 0.02. This tendency suggests a consistent inclination of the simulated data towards lower Brier scores compared to the actual estimate, indicating a potential optimism in the model's performance. However, as Brier estimates surpass 0.08, the simulation exhibits a lower density, signifying a reduced likelihood of higher Brier scores. This nuanced observation underscores the variability in simulated outcomes, offering valuable insights into the distribution of model performance across a spectrum of Brier estimates. It provides a comprehensive understanding of potential scenarios, contributing to the assessment of the model's robustness in diverse settings.

Performance Measures

The utilization of the Framingham dataset with its established Brier score of 0.157 as a benchmark allows for a comprehensive assessment of the model's predictive capabilities. The Monte Carlo simulation, characterized by a dense concentration around the NHANES target population Brier estimate of 0.047, stands out with a significantly lower Brier score compared to the Framingham data. This notable contrast implies a potential optimism in the model's predictive performance when applied to scenarios beyond the Framingham population. The simulation's consistent propensity to yield lower Brier scores, aligning closely with the target population, further underlines the model's adaptability and reliability across diverse settings. This suggests that the predictive model, when subjected to the Monte Carlo simulation, consistently demonstrates a favorable

outlook, showcasing its robustness and effectiveness in capturing the risk of cardiovascular disease events in a broader context.

Discussion

The Monte Carlo simulation, reflecting a high density around the Brier estimate of 0.047 in the NHANES target population, signifies the potential of the model to generalize well across diverse populations. The simulation's consistent alignment with the observed Brier estimate suggests that the model's performance in the target population closely mirrors its behavior in the Framingham dataset, providing evidence of its transportability.

Furthermore, the comparison with the Framingham dataset, which serves as a benchmark with a Brier score of 0.15, highlights the robustness of the predictive model. The simulation consistently yields lower Brier scores, indicating an optimistic outlook beyond the Framingham population. This observed trend supports the notion that the model maintains its favorable performance and predictive accuracy in scenarios beyond the original study population, substantiating its potential for generalization.

Conclusion

The model's adaptability across different populations is a crucial aspect for healthcare professionals and policymakers, as it suggests that the risk assessment algorithm is not limited to specific cohorts. Instead, it holds promise for widespread application, catering to diverse demographics and contributing to more inclusive and accurate CVD risk assessments. However, ongoing validation and scrutiny across various populations will be essential to strengthen the model's credibility and ensure its reliable performance in real-world applications. Overall, the results underscore the potential for the predictive model to serve as a valuable tool in enhancing risk assessment strategies for cardiovascular diseases across diverse and varied populations.

Limitations

While this study employed a simulation approach using normal and gamma distributions, it's important to acknowledge certain limitations that warrant consideration. Firstly, the choice of normal and gamma distributions for generating simulated data might not fully capture the complexity of the underlying distributions of the covariates in the real-world dataset. Different variables may exhibit diverse distributional characteristics, and utilizing a more diverse set of distributions could provide a more accurate representation of the true population.

Moreover, the logistic regression model employed in this study, while widely used for binary outcomes, is a simplification of the complex relationships that may exist within the data. More sophisticated modeling techniques, such as neural network models, could offer a more flexible representation of the underlying data structure. Neural networks are capable of capturing intricate patterns and interactions among variables, potentially enhancing the accuracy and generalizability of the predictive model.

Furthermore, the study focused on a specific set of variables for cardiovascular risk assessment, and other relevant covariates may exist that were not considered in the simulation. Exploring a broader range of predictors and their potential interactions could contribute to a more comprehensive and realistic simulation.

In conclusion, while the chosen simulation approach provides valuable insights, the study's limitations underscore the need for ongoing refinement and exploration of alternative methodologies. Future research could delve into more diverse distributional assumptions, employ advanced modeling techniques, and expand the scope of considered covariates, ultimately enhancing the study's applicability and robustness in capturing the complexities of cardiovascular risk assessment.

References

1."Transporting a prediction model for use in a new target population" (Jon A. Steingrimsson, Constantine Gatsonis, and Issa J. Dahabreh)-2021

2."General Cardiovascular Risk Profile for Use in Primary Care-The Framingham Heart Study" (Ralph B. D'Agostino, Sr, PhD, Ramachandran S. Vasan, MD, Michael J. Pencina, PhD, Philip A. Wolf, MD, Mark Cobain, PhD, Joseph M. Massaro, PhD, and William B. Kannel, MD)-2008

3. Li, Bing & Gatsonis, Constantine & Dahabreh, Issa & Steingrimsson, Jon. (2022). Estimating the area under the ROC curve when transporting a prediction model to a target population. Biometrics. 79. 10.1111/biom.13796.

Code Appendix

```
library(riskCommunicator)
library(tidyverse)
library(tableone)
library("DescTools")
library(mice)
library(knitr)
library(png)
library(naniar)
library(corrplot)
library(patchwork)
library(tinytex)
library(kableExtra)
library(rmarkdown)
knitr::opts_chunk$set(echo = FALSE,
                      message = FALSE,
                      warning = FALSE)
data("framingham")


framingham_df <- framingham %>% select(c(CVD, TIMECVD, SEX, TOTCHOL, AGE,
                                         SYSBP, DIABP, CURSMOKE, DIABETES, BPMEDS,
                                         HDLC, BMI))
framingham_df <- na.omit(framingham_df)
vars <- c("CVD", "TIMECVD", "SEX", "TOTCHOL", "AGE", "SYSBP", "DIABP", "CURSMOKE", "DIABETES", "BPMEDS"
labels <- c("CVD (mean (SD))", "TIMECVD (mean (SD))", "SEX (mean (SD))",
            "Total Cholesterol (mean (SD))", "Age (mean (SD))",
            "Systolic Blood Pressure (mean (SD))", "Diastolic Blood Pressure (mean (SD))",
            "Current Smoker (mean (SD))", "Diabetes (mean (SD))",
            "Blood Pressure Medication (mean (SD))", "HDL Cholesterol (mean (SD))",
            "BMI (mean (SD))")
table_1<-CreateTableOne(data=framingham_df, strata = c("SEX"), vars = vars)
# Rename the columns with custom labels

cat("\nSummary of Framingham Cardiovascular Risk Factors by Sex\n\n")

print(table_1, label = labels, showAllLevels = TRUE)



framingham_df$SYSBP_UT <- ifelse(framingham_df$BPMEDS == 0,
                                 framingham_df$SYSBP, 0)
framingham_df$SYSBP_T <- ifelse(framingham_df$BPMEDS == 1,
                                framingham_df$SYSBP, 0)

dim(framingham_df)
framingham_df <- framingham_df %>%
  filter(!(CVD == 0 & TIMECVD <= 365*15)) %>%
  select(-c(TIMECVD))
dim(framingham_df)

framingham_df_men <- framingham_df %>% filter(SEX == 1)
framingham_df_women <- framingham_df %>% filter(SEX == 2)
```

```r
mod_men <- glm(CVD~log(HDLC)+log(TOTCHOL)+log(AGE)+log(SYSBP_UT+1)+
                 log(SYSBP_T+1)+CURSMOKE+DIABETES,
      data= framingham_df_men, family= "binomial")


mod_women <- glm(CVD~log(HDLC)+log(TOTCHOL)+log(AGE)+log(SYSBP_UT+1)+
                   log(SYSBP_T+1)+CURSMOKE+DIABETES,
               data= framingham_df_women, family= "binomial")


library(nhanesA)

bpx_2017 <- nhanes("BPX_J") %>%
  select(SEQN, BPXSY1, BPXDI1 ) %>%
  rename(SYSBP = BPXSY1, DIABP=BPXDI1)
demo_2017<- nhanes("DEMO_J") %>%
  select(SEQN, RIAGENDR, RIDAGEYR) %>%
  rename(SEX = RIAGENDR, AGE = RIDAGEYR)

mcq_2017<-nhanes("MCQ_J")%>%
  select(SEQN, MCQ160F,MCQ160E)

bmx_2017 <- nhanes("BMX_J") %>%
  select(SEQN, BMXBMI) %>%
  rename(BMI = BMXBMI)
smq_2017 <- nhanes("SMQ_J") %>%
  mutate(CURSMOKE = case_when(SMQ040 %in% c(1,2) ~ 1,
                              SMQ040 == 3 ~ 0,
                              SMQ020 == 2 ~ 0)) %>%
  select(SEQN, CURSMOKE)
bpq_2017 <- nhanes("BPQ_J") %>%
  mutate(BPMEDS = case_when(
    BPQ020 == 2 ~ 0,
    BPQ040A == 2 ~ 0,
    BPQ050A == 1 ~ 1,
    TRUE ~ NA )) %>%
  select(SEQN, BPMEDS)

tchol_2017 <- nhanes("TCHOL_J") %>%
  select(SEQN, LBXTC) %>%
  rename(TOTCHOL = LBXTC)
hdl_2017 <- nhanes("HDL_J") %>%
  select(SEQN, LBDHDD) %>%
  rename(HDLC = LBDHDD)
diq_2017 <- nhanes("DIQ_J") %>%
  mutate(DIABETES = case_when(DIQ010 == 1 ~ 1,
                              DIQ010 %in% c(2,3) ~ 0,
                              TRUE ~ NA)) %>%
  select(SEQN, DIABETES)



# Join data from different tables
```

```r
df_2017<- bpx_2017 %>%
  full_join(demo_2017, by = "SEQN") %>%
  full_join(bmx_2017, by = "SEQN") %>%
  full_join(hdl_2017, by = "SEQN") %>%
  full_join(smq_2017, by = "SEQN") %>%
  full_join(bpq_2017, by = "SEQN") %>%
  full_join(tchol_2017, by = "SEQN") %>%
  full_join(mcq_2017, by= "SEQN")%>%
  full_join(diq_2017, by = "SEQN")%>%
  filter(AGE >= 30 & AGE <= 62)%>%
  filter(MCQ160F==2 & MCQ160E==2)


df_2017<-df_2017[, -c(11, 12)]

vars <- c("SEX", "TOTCHOL", "AGE", "SYSBP", "DIABP", "CURSMOKE", "DIABETES", "BPMEDS", "HDLC", "BMI")
labels <- c("SEX (mean (SD))",
            "Total Cholesterol (mean (SD))", "Age (mean (SD))",
            "Systolic Blood Pressure (mean (SD))", "Diastolic Blood Pressure (mean (SD))",
            "Current Smoker (mean (SD))", "Diabetes (mean (SD))",
            "Blood Pressure Medication (mean (SD))", "HDL Cholesterol (mean (SD))",
            "BMI (mean (SD))")
table_2<-CreateTableOne(data = df_2017, strata = c("SEX"),vars=vars)
cat("\nSummary of NHANES Cardiovascular Risk Factors by Sex\n\n")

print(table_2, label = labels, showAllLevels = TRUE)

df_2017$SYSBP_UT<- ifelse(df_2017$BPMEDS == 0,
                                df_2017$SYSBP, 0)
df_2017$SYSBP_T<- ifelse(df_2017$BPMEDS == 1,
                               df_2017$SYSBP, 0)

#overall_missing<-miss_var_summary(df_2017)
par(mfrow = c(1, 2), mar = c(2, 1, 1, 1))
commonvar= interaction(colnames(framingham_df),colnames(df_2017))
df_2017 = df_2017 %>%as.data.frame()%>% select(order(commonvar))
m_NHANES= cor(na.omit(df_2017))
nhanes_corr<-corrplot(m_NHANES, method = 'number',title = 'Correlation Matrix - NHANES',tl.cex = 0.5)
framingham_df = framingham_df %>%as.data.frame()%>% select(order(commonvar))
m_framingham = cor(framingham_df)
fram_corr<-corrplot(m_framingham, method = 'number',title = 'Correlation Matrix - Framingham',tl.cex = 

nhanes_mice<- mice(df_2017, m = 5, print = FALSE, seed = 110)
nhanes_imputed<- list()
for (i in 1:5){
  nhanes_imputed[[i]]<-complete(nhanes_mice,i)
}
completed_data<-complete(nhanes_mice)

set.seed(123)
sample_fram<-sample(c(TRUE,FALSE),nrow(framingham_df), replace=TRUE, prob = c(0.8,0.2))
test_fram_17<-framingham_df[sample_fram,]
train_fram_17<-framingham_df[!sample_fram,]
```

```r
model_both<- glm(CVD~log(HDLC)+log(TOTCHOL)+log(AGE)+log(SYSBP_UT+1)+
                 log(SYSBP_T+1)+CURSMOKE+DIABETES,
      data= train_fram_17, family= "binomial")

test_prob<- predict(model_both, newdata = test_fram_17, type = "response")

test_brier<- BrierScore(as.numeric(as.character(test_fram_17$CVD)), test_prob)

imputed_data<- completed_data %>%
  group_by(SEQN) %>%
  summarise_all(mean, na.rm = TRUE)

common_vars <- intersect(names(framingham_df), names(imputed_data))

combine_df <- merge(framingham_df, imputed_data, by = common_vars, all = TRUE)

combine_df$S <- if_else(is.na(combine_df$SEQN), 1, 0)

same_vars <- c("CVD","SEX", "AGE", "TOTCHOL", "SYSBP", "CURSMOKE", "DIABETES", "BPMEDS",
                 "HDLC", "BMI", "S")

combined_df <- combine_df[same_vars]

combined_df$SYSBP_UT <- ifelse(combined_df$BPMEDS == 0, combined_df$SYSBP, 0)
combined_df$SYSBP_T <- ifelse(combined_df$BPMEDS == 1, combined_df$SYSBP, 0)

set.seed(1)

sample <- sample(c(TRUE, FALSE), nrow(combined_df), replace=TRUE, prob=c(0.8,0.2))
combined_train_df  <- combined_df[sample, ]
combined_test_df   <- combined_df[!sample, ]

model_combined <- glm(S~log(HDLC)+log(TOTCHOL)+log(AGE)+log(BMI)+
                 log(SYSBP_UT+1)+log(SYSBP_T+1)+CURSMOKE+DIABETES,
      data= combined_train_df, family= "binomial")

#summary(model_combined)

 model_Y<- glm(CVD~log(HDLC)+log(TOTCHOL)+log(AGE)+log(BMI)+
                 log(SYSBP_UT+1)+log(SYSBP_T+1)+CURSMOKE+DIABETES,
                 data= combined_train_df,
               family= "binomial")

 #summary(model_Y)


combined_test_df_rm = na.omit(combined_test_df)
model_combined_predict_probs <- predict(model_combined, newdata =  combined_test_df_rm, type = "respons
model_Y_predict_probs <- predict(model_Y, newdata = combined_test_df_rm, type = "response")


combined_brier<-(combined_test_df_rm$CVD-model_Y_predict_probs)^2
```

```r
inv_odds_weights<-(1-model_combined_predict_probs)/(model_combined_predict_probs)

brier_estimate<-sum(combined_brier*inv_odds_weights)/sum(combined_test_df$S==0)


brierscores <- data.frame(Population = c("Framingham", "NHANES"), "Brier Score" = c(round(test_brier,3)

kable(brierscores, col.names = c("Population", "Brier Score"), caption = "Brier Score Measures", align =



SimulateData_NormalDist <- function(SEQN,
                proportion_summ,
                mean_summ,
                sd_summ,
                strata_var = "SEX",
                strata_prop =0.5){

  n= length(SEQN)

  Bin = data.frame(SEQN = SEQN)
  aux_binary <- proportion_summ %>%
    select(-all_of(strata_var)) %>%
    colnames()
  rex_sex1_prop <- proportion_summ %>%
    filter(SEX==1) %>%
    select(all_of(aux_binary)) %>%
    as.data.frame()
  rex_sex2_prop <- proportion_summ %>%
    filter(SEX==2) %>%
    select(all_of(aux_binary)) %>%
    as.data.frame()


  for (k in seq_len(length(aux_binary))) {
    Bin[,aux_binary[k]] <- c(rbinom(round(n*strata_prop),size=1, prob = rex_sex1_prop[,aux_binary[k]]),
                             rbinom(round(n-n*strata_prop),size=1, prob = rex_sex2_prop[,aux_binary[k]])
    )
  }
    Bin[,strata_var] <- c(rep(1,round(n*strata_prop)),
                          rep(2,round(n*strata_prop)))

  C <-  data.frame(SEQN = SEQN)
  aux_con<- mean_summ %>%
    select(-all_of(strata_var)) %>%
    colnames()

  rex_sex1_mean <-mean_summ %>%
    filter(SEX==1) %>%
    select(all_of(aux_con)) %>%
    as.data.frame()
  rex_sex1_sd<-  sd_summ %>%
    filter(SEX==1) %>%
```

```
    select(all_of(aux_con)) %>%
    as.data.frame()

  rex_sex2_mean<-  mean_summ %>%
    filter(SEX==2) %>%
    select(all_of(aux_con)) %>%
    as.data.frame()
  rex_sex2_sd<-sd_summ %>%
    filter(SEX==2) %>%
    select(all_of(aux_con)) %>%
    as.data.frame()

  for (k in seq_len(length(aux_con))) {
    C[,aux_con[k]] = c(rnorm(round(n*strata_prop),mean = rex_sex1_mean[,aux_con[k]], sd = rex_sex1_sd[,a
                       rnorm(round(n-n*strata_prop),mean = rex_sex2_mean[,aux_con[k]], sd = rex_sex2_sd[

    }

  SimulatedData = Bin %>% left_join(C,by="SEQN")

# Add constraint to prevent nan due to log()
  SimulatedData[SimulatedData<0] = 0.001

  return(SimulatedData)

}



SimulateData_GammaDist <- function(SEQN,
                                   proportion_summ,
                                   mean_summ,
                                   sd_summ,
                                   strata_var = "SEX",
                                   strata_prop =0.5){

  n= length(SEQN)


    Bin = data.frame(SEQN = SEQN)
    aux_binary <- proportion_summ %>%
      select(-all_of(strata_var)) %>%
      colnames()
    rex_sex1_prop <- proportion_summ %>%
      filter(SEX==1) %>%
      select(all_of(aux_binary)) %>%
      as.data.frame()
    rex_sex2_prop <- proportion_summ %>%
      filter(SEX==2) %>%
      select(all_of(aux_binary)) %>%
      as.data.frame()
```

```
    for (k in seq_len(length(aux_binary))) {
      Bin[,aux_binary[k]] <- c(rbinom(round(n*strata_prop),size=1, prob = rex_sex1_prop[,aux_binary[k]]),
                               rbinom(round(n-n*strata_prop),size=1, prob = rex_sex2_prop[,aux_binary[k]])
      )
    }
      Bin[,strata_var] <- c(rep(1,round(n*strata_prop)),
                            rep(2,round(n*strata_prop)))

      C <-  data.frame(SEQN = SEQN)
      aux_con<-  mean_summ %>%
        select(-all_of(strata_var)) %>%
        colnames()

      rex_sex1_mean <-mean_summ %>%
        filter(SEX==1) %>%
        select(all_of(aux_con)) %>%
        as.data.frame()
      rex_sex1_sd <-sd_summ %>%
        filter(SEX==1) %>%
        select(all_of(aux_con)) %>%
        as.data.frame()

      rex_sex2_mean <-mean_summ %>%
        filter(SEX==2) %>%
        select(all_of(aux_con)) %>%
        as.data.frame()
      rex_sex2_sd<-sd_summ %>%
        filter(SEX==2) %>%
        select(all_of(aux_con)) %>%
        as.data.frame()


      transform_shape_sex1 = rex_sex1_mean^2/rex_sex1_sd^2
      transform_rate_sex1 = rex_sex1_mean/rex_sex1_sd^2
      # Sex==2
      transform_shape_sex2 = rex_sex2_mean^2/rex_sex2_sd^2
      transform_rate_sex2 = rex_sex2_mean/rex_sex2_sd^2



      for (k in seq_len(length(aux_con))) {
        C[,aux_con[k]] = c(rgamma(round(n*strata_prop),shape = transform_shape_sex1[,aux_con[k]], rate =
                           rgamma(round(n-n*strata_prop),shape = transform_shape_sex2[,aux_con[k]], rat

      }

      SimulatedData = Bin %>% left_join(C,by="SEQN")

      return(SimulatedData)

    }

BrierEstimate <- function(DATA){
```

```
  common_vars <- intersect(names(framingham_df), names(DATA))

combine_df<- merge(framingham_df, DATA, by = common_vars, all = TRUE)

combine_df$S <- if_else(is.na(combine_df$SEQN), 1, 0)

same_vars <- c("CVD","SEX", "AGE", "TOTCHOL", "SYSBP", "CURSMOKE", "DIABETES", "BPMEDS",
                "HDLC", "BMI", "S")

combined_df <- combine_df[same_vars]

combined_df$SYSBP_UT <- ifelse(combined_df$BPMEDS == 0, combined_df$SYSBP, 0)
combined_df$SYSBP_T <- ifelse(combined_df$BPMEDS == 1, combined_df$SYSBP, 0)



sample <- sample(c(TRUE, FALSE), nrow(combined_df), replace=TRUE, prob=c(0.8,0.2))
combined_train_df  <- combined_df[sample, ]
combined_test_df   <- combined_df[!sample, ]

model_combined <- glm(S~log(HDLC)+log(TOTCHOL)+log(AGE)+log(BMI)+
                log(SYSBP_UT+1)+log(SYSBP_T+1)+CURSMOKE+DIABETES,
      data= combined_train_df, family= "binomial")

summary(model_combined)

 model_Y<- glm(CVD~log(HDLC)+log(TOTCHOL)+log(AGE)+log(BMI)+
                log(SYSBP_UT+1)+log(SYSBP_T+1)+CURSMOKE+DIABETES,
                data= combined_train_df,
              family= "binomial")

 summary(model_Y)



combined_test_df_rm = na.omit(combined_test_df)


model_combined_predict_probs <- predict(model_combined, newdata =  combined_test_df_rm, type = "respons
model_Y_predict_probs <- predict(model_Y, newdata = combined_test_df_rm, type = "response")


combined_brier <- (combined_test_df_rm$CVD-model_Y_predict_probs)^2

inv_odds_weights <- (1-model_combined_predict_probs)/(model_combined_predict_probs)

brier_estimate <-  sum(combined_brier*inv_odds_weights)/sum(combined_test_df$S==0)

return(brier_estimate)
}
same_vars <- c("SEX", "AGE", "TOTCHOL", "SYSBP","DIABP", "CURSMOKE", "DIABETES", "BPMEDS",
               "HDLC", "BMI")
```

```r
same_vars.ContinouseDistribution = c("AGE", "TOTCHOL", "SYSBP","DIABP",
                                     "HDLC", "BMI")
same_vars.DiscreteDistribution = c("CURSMOKE", "DIABETES", "BPMEDS")

nhanes_summary_prop <-  df_2017[,same_vars] %>%
  group_by(SEX) %>%
  select(all_of(same_vars.DiscreteDistribution)) %>%
  summarise_all(mean,na.rm = T)

nhanes_summary_mean <-  df_2017[,same_vars] %>%
  group_by(SEX) %>%
  select(all_of(same_vars.ContinouseDistribution)) %>%
  summarise_all(mean,na.rm = T)

nhanes_summary_sd <-  df_2017[,same_vars] %>%
  group_by(SEX) %>%
  select(all_of(same_vars.ContinouseDistribution)) %>%
  summarise_all(sd,na.rm = T)



DATA = SimulateData_NormalDist(SEQN = imputed_data$SEQN,
                               proportion_summ=nhanes_summary_prop,
                               mean_summ =nhanes_summary_mean ,
                               sd_summ =nhanes_summary_sd ,
                               strata_var = "SEX",
                               strata_prop =0.5)


same_vars <- c("SEX", "AGE", "TOTCHOL", "SYSBP", "DIABP","CURSMOKE", "DIABETES", "BPMEDS",
               "HDLC", "BMI")
DATA_summary_prop <-  DATA[,same_vars] %>% group_by(SEX) %>%
  select(all_of(same_vars.DiscreteDistribution)) %>% summarise_all(mean,na.rm = T)

DATA_summary_mean <-  DATA[,same_vars] %>% group_by(SEX) %>%
  select(all_of(same_vars.ContinouseDistribution)) %>% summarise_all(mean,na.rm = T)

DATA_summary_sd <-  DATA[,same_vars] %>% group_by(SEX) %>%
  select(all_of(same_vars.ContinouseDistribution)) %>% summarise_all(sd,na.rm = T)



DATA= SimulateData_GammaDist(SEQN = imputed_data$SEQN,
                               proportion_summ=nhanes_summary_prop,
                               mean_summ =nhanes_summary_mean ,
                               sd_summ =nhanes_summary_sd ,
                               strata_var = "SEX",
                               strata_prop =0.5)


same_vars <- c("SEX", "AGE", "TOTCHOL", "SYSBP","DIABP","CURSMOKE", "DIABETES", "BPMEDS",
               "HDLC", "BMI")
```

```r
DATA_summary_prop1<-  DATA[,same_vars] %>%
  group_by(SEX) %>%
  select(all_of(same_vars.DiscreteDistribution)) %>%
  summarise_all(mean,na.rm = T)

DATA_summary_mean1<-  DATA[,same_vars] %>%
  group_by(SEX) %>%
  select(all_of(same_vars.ContinouseDistribution)) %>%
  summarise_all(mean,na.rm = T)

DATA_summary_sd1<-  DATA[,same_vars] %>%
  group_by(SEX) %>%
  select(all_of(same_vars.ContinouseDistribution)) %>%
  summarise_all(sd,na.rm = T)



# For display
kable(nhanes_summary_prop, caption = "Summary of NHANES Data Proportions")
kable(DATA_summary_prop, caption = "Summary of Simulated Data Proportions-Normal Dist")
kable(DATA_summary_prop1, caption = "Summary of Simulated Data Proportions-Gamma Dist")


kable(nhanes_summary_mean, caption = "Summary of NHANES Data Mean")
kable(DATA_summary_mean, caption = "Summary of Simulated Data Mean-Normal Dist")
kable(DATA_summary_mean1, caption = "Summary of Simulated Data Mean-Gamma Dist")


kable(nhanes_summary_sd, caption = "Summary of NHANES Data SD")
kable(DATA_summary_sd, caption = "Summary of Simulated Data SD-Normal Dist")
kable(DATA_summary_sd1, caption = "Summary of Simulated Data SD-Gamma Dist")




# table(DATA$CURSMOKE,imputed_data$CURSMOKE) %>% kable
# table(DATA$DIABETES,imputed_data$DIABETES) %>% kable
# table(DATA$BPMEDS,imputed_data$BPMEDS)%>% kable


DATA2 = DATA %>%
  round  %>%
  mutate(Simulated="YES")
imputed_data2 = imputed_data %>%
  select(colnames(DATA)) %>%
  mutate(Simulated="NO")

ggplotData<-bind_rows(imputed_data2,DATA2)

plt1<-ggplotData %>%
  ggplot() +
  geom_histogram(aes(x=AGE,color=Simulated,y=after_stat(density)),alpha=0.6,binwidth = 0.5)+
  theme_bw()
```

```r
plt2<-ggplotData %>%
  ggplot() +
  geom_histogram(aes(x=TOTCHOL,color=Simulated,y=after_stat(density)),alpha=0.6,binwidth = 0.5)+
  theme_bw()

plt3<-ggplotData %>%
  ggplot() +
  geom_histogram(aes(x=SYSBP,color=Simulated,y=after_stat(density)),alpha=0.6,binwidth = 0.5)+
  theme_bw()
plt4<-ggplotData %>%
  ggplot() +
  geom_histogram(aes(x=HDLC,color=Simulated,y=after_stat(density)),alpha=0.6,binwidth = 0.5)+
  theme_bw()
plt5<-ggplotData %>%
  ggplot() +
  geom_histogram(aes(x=BMI,color=Simulated,y=after_stat(density)),alpha=0.6,binwidth = 0.5)+
  theme_bw()

(plt1|plt2)/(plt3|plt4)/(plt5)

DATA = SimulateData_GammaDist(SEQN = imputed_data$SEQN,
                              proportion_summ=nhanes_summary_prop,
                              mean_summ =nhanes_summary_mean ,
                              sd_summ =nhanes_summary_sd ,
                              strata_var = "SEX",
                              strata_prop =0.5)
DATA2<-DATA %>%
  round  %>%
  mutate(Simulated="YES")
imputed_data2<- imputed_data %>%
  select(colnames(DATA)) %>%
  mutate(Simulated="NO")

ggplotData<- bind_rows(imputed_data2,DATA2)

plt1<-ggplotData %>% ggplot() +
  geom_histogram(aes(x=AGE,color=Simulated,y=after_stat(density)),alpha=0.6,binwidth = 0.5)+
  theme_bw()
plt2<- ggplotData %>% ggplot() +
  geom_histogram(aes(x=TOTCHOL,color=Simulated,y=after_stat(density)),alpha=0.6,binwidth = 0.5)+
  theme_bw()

plt3<- ggplotData %>% ggplot() +
  geom_histogram(aes(x=SYSBP,color=Simulated,y=after_stat(density)),alpha=0.6,binwidth = 0.5)+
  theme_bw()
plt4<-ggplotData %>% ggplot() +
  geom_histogram(aes(x=HDLC,color=Simulated,y=after_stat(density)),alpha=0.6,binwidth = 0.5)+
  theme_bw()
plt5<-ggplotData %>% ggplot() +
  geom_histogram(aes(x=BMI,color=Simulated,y=after_stat(density)),alpha=0.6,binwidth = 0.5)+
  theme_bw()

(plt1|plt2)/(plt3|plt4)/(plt5)
```

```r
DATA = SimulateData_GammaDist(SEQN = imputed_data$SEQN,
                              proportion_summ=nhanes_summary_prop,
                              mean_summ =nhanes_summary_mean ,
                              sd_summ =nhanes_summary_sd ,
                              strata_var = "SEX",
                              strata_prop =0.5)

par(mfrow = c(1, 2), mar = c(2, 1, 1, 1))
DATA = DATA %>%
  as.data.frame()%>%
  select(order(colnames(DATA))) %>%
  select(-SEQN)
M = cor(DATA)
corrplot(M, method = 'number',tl.cex = 0.5, title = 'Correlation-Simulated')
imputed_data2 = imputed_data2[,colnames(DATA)]
M = cor(imputed_data2)
corrplot(M, method = 'number',tl.cex = 0.5, title = 'Correlation-Imputed NHANES')


N=1000

MC_brier_estimate = rep(0,N)


for (l in 1:N) {


DATA = SimulateData_NormalDist(SEQN = imputed_data$SEQN,
                                    proportion_summ=nhanes_summary_prop,
                                    mean_summ =nhanes_summary_mean ,
                                    sd_summ =nhanes_summary_sd ,
                                    strata_var = "SEX",
                                    strata_prop =0.5)

MC_brier_estimate[l] = BrierEstimate(DATA = DATA)

}


hist(MC_brier_estimate,main="Brier estimate distribution",xlab="Monte Carlo Brier estimates",freq = F)
abline(v=brier_estimate,col="red",lty=2)
```