Individualized treatment effects of CPAP on secondary cardiovascular outcomes in non-sleepy obstructive sleep apnea patients

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Online Data Supplement

Supplementary Tables and Figures:

Supplementary Table 1. Variables Included in Model Development

Duration of ApneaLink recording (ApneaLink)	Heart Rate IQR (MATLAB)	HADS Anxiety
Duration of flow analysis (ApneaLink)	Average Heart Rate (MATLAB)	HADS Depression
SpO_2 Evaluation Period (ApneaLink)	Heart Rate SD (MATLAB)	SF36 Limit Physical subscale
Risk Indicator (ApneaLink)	Mean NN interval (milliseconds; MATLAB)	SF36 Limit emotion subscale
Apnea Index (ApneaLink)	SD NN Interval (milliseconds; MATLAB)	SF36 Vitality subscale
Hypopnea Index (ApneaLink)	Heart rate variability measured using RMSSD (MATLAB)	SF36 Mental subscale
Total flow limited breaths without snoring (ApneaLink)	T90, minutes (MATLAB)	SF36 Social subscale
Flow limited breaths without snoring, % (ApneaLink)	T90/TST (MATLAB)	SF36 Body Pain subscale
Total flow limited breaths with snoring (ApneaLink)	T90 Area (MATLAB)	SF36 General Health subscale
Flow limited breaths with snoring, % (ApneaLink)	T90 Area/TST (MATLAB)	SF36 Trans
Average breaths per minute of evaluation (ApneaLink)	Median Desaturation Integral (MATLAB)	SF36 Physical Health baseline
Total number of breaths (ApneaLink)	Median Desaturation Duration (MATLAB)	SF36 Mental Health baseline
Total number of snoring events in evaluation (ApneaLink)	Median Desaturation Amplitude (MATLAB)	European Quality of Life utility score
Average Saturation (ApneaLink)	Median nadir desaturation (MATLAB)	Country
Lowest Desaturation (ApneaLink)	Median desaturation/resaturation time ratio (MATLAB)	Sex
Baseline Saturation (ApneaLink)	Median desaturation/resaturation Integral Ratio (MATLAB)	Age
Total desaturating events (ApneaLink)	Baseline Hypoxic Load (MATLAB)	Race
Minimum Pulse Frequency (ApneaLink)	Desat hypoxic load (MATLAB)	Height
Cheyne-Stokes, %Epochs (ApneaLink)	Anti-hypertensive medication	BMI

SpO_2 Evaluation Minutes (ApneaLink)	Lipid Lowering Agent	Waist
Time spent <90% SpO_2, % (ApneaLink)	Oral anti-diabetic medications	Hip
Time spent <85% SpO_2, % (ApneaLink)	Insulin	Waist/hip ratio
Time spent <80% SpO_2, % (ApneaLink)	Antiplatelet and antithrombotic agents	Neck circumference
Median AH Duration	Organic nitrates	SBP
Heart Rate, second quartile (MATLAB)	Other cardiac medications	DBP
Median Heart Rate (MATLAB)	Traditional Chinese medicines	Heart Rate
ESS	Alimentary tract and metabolism medications	ODI
AHI (ApneaLink)	Smoking Status	Coronary artery bypass graft
Snoring loudness	CAD only	Stroke
Snoring frequency	TIA, STROKE, or CAD	TIA
Snoring bothers others	Previous or current medication for cardiovascular disease or diabetes	Atrial Fibrillation
Frequency of breathing pauses notice	Hypertension	Other form of cardiovascular disease
> 100 cigarettes in lifetime	Diabetes	Subgroup based on BMI
Drink alcohol at least once a week	Any heart disease	Valvular heart disease
Number of vigorously exercise (>15 minutes)	Prior MI	Prior coronary revascularization
Number of moderate exercise (>15 minutes)	Angina	Heart Failure
Number of mild exercise (>15 minutes)		

Supplementary Table 1 lists all features included in model development. Variables obtained directly from the ApneaLink sleep testing devices are noted, in contrast to non-standard sleep study variables, which were processed and derived in MATLAB by the SAVE study team. AH Apnea Hypopnea; AHI Apnea Hypopnea Index; BMI Body Mass Index; CAD Coronary Artery Disease; DBP Diastolic Blood Pressure; ESS Epworth Sleepiness Scale; HADS Hospital Anxiety Depression Scale; IQR Interquartile Range; MI Myocardial Infraction; NN Normal-to-Normal; ODI Oxygen Desaturation Index; RMSSD Root Mean Square of Successive Differences; SBP Systolic Blood Pressure; SD Standard Deviation; SF36 Short Form Questionnaire; SpO_2 Oxygen Saturation; T90 Time Under 90% Oxygen Saturation; TIA Transient Ischemic Attack; TST Total Sleep Time

Supplementary Table 2. Variables Excluded During Pre-Processing

Excluded Variables	Reason for exclusion
Snoring frequency	No Variance
Smoke cigars everyday	No Variance
Current pipe smoker	No Variance
Carotid endarterectomy or percutaneous stent	No Variance
Intracerebral stent	No Variance
Pipe per day	20 % Missing
Time since last cigarette	20 % Missing
Smoke cigarettes after awake for 30 minutes	20 % Missing
Average wine per week	20 % Missing
Average spirits per week	20 % Missing
Number of cigars per day	20 % Missing
Number of cigarettes per day	20 % Missing
Smoke cigarettes everyday	20 % Missing
Average beer per week	20 % Missing
Blood glucose lowering drugs: Ratio dose/DDD at baseline	20 % Missing
Number of Blood glucose lowering drug agents	20 % Missing
Sum of Blood glucose lowering drugs DDD	20 % Missing
Sum of Blood glucose lowering drugs daily dose	20 % Missing
Diuretics: Ratio dose/DDD at baseline	20 % Missing
Number of Diuretics agents	20 % Missing
Sum of Diuretics DDD	20 % Missing
Sum of Diuretics daily dose	20 % Missing
Calcium channel blockers: Ratio dose/DDD at baseline	20 % Missing
Number of Calcium channel blockers agents	20 % Missing
Sum of Calcium channel blockers DDD	20 % Missing
Sum of Calcium channel blockers daily dose	20 % Missing
Beta blocking agents: Ratio dose/DDD at baseline	20 % Missing
Number of Beta blocking agents	20 % Missing
Sum of Beta blocking agents DDD	20 % Missing
Sum of Beta blocking agents daily dose	20 % Missing
Lipid modifying agents: Ratio dose/DDD at baseline	20 % Missing
Number of Lipid modifying agents	20 % Missing
Sum of Lipid modifying agents DDD	20 % Missing
Sum of Lipid modifying agents daily dose	20 % Missing
Antihypertensive drugs Ratio dose/DDD	20 % Missing
Number of Antihypertensive drug agents	20 % Missing
Sum of Antihypertensive drugs DDD	20 % Missing
Sum of Antihypertensive drugs daily dose	20 % Missing

ACE inhibitors: Ratio dose/DDD at baseline	20 % Missing
Number of ACE inhibitor agents	20 % Missing
Sum of ACE inhibitors DDD	20 % Missing
Sum of ACE inhibitors daily dose	20 % Missing
Triglycerides	20 % Missing
Total Cholesterol	20 % Missing
Insulin: Ratio dose/DDD at baseline	20 % Missing
Insulin: Sum of DDD at baseline	20 % Missing
Insulin: Sum of daily dose at baseline	20 % Missing
Insulin: Number of agents at baseline	20 % Missing
LDL	20 % Missing
HDL	20 % Missing
Total flow limited breaths with snoring (ApneaLink)	Correlated
Total number of apneas in evaluation (ApneaLink)	Correlated
Total number of hypopneas in evaluation (ApneaLink)	Correlated
Lowest SpO_2 during a marked desaturation event (ApneaLink)	Correlated
Time spent below 90% SpO_2, minutes (ApneaLink)	Correlated
Time spent below 85% SpO_2, minutes (ApneaLink)	Correlated
Time spent below 80% SpO_2, minutes (ApneaLink)	Correlated
Average pulse frequency (ApneaLink)	Correlated
Total Cheyne Stokes epochs (ApneaLink)	Correlated
Average AH duration	Correlated
Heart Rate, third quartile (MATLAB)	Correlated
Usable sleep time (MATLAB)	Correlated
Number of desaturations (MATLAB)	Correlated
ODI (MATLAB)	Correlated
Baseline SpO_2 (MATLAB)	Correlated
Total Hypoxic Load (MATLAB)	Correlated
Average SpO_2 (MATLAB)	Correlated
HADS Total	Correlated
SF36 Physical subscale	Correlated
Country	Correlated
Established coronary disease confirmed as eligibility criterion	Correlated
Established cerebrovascular disease confirmed as eligibility criterion	Correlated
Calculated ESS at screening	Correlated
Ethnicity	Correlated
Weight	Correlated
TIA only	Correlated
TIA or Stroke	Correlated
Subgroup of region	Correlated
Subgroup of age	Correlated

Subgroup of ODI	Correlated
Subgroup of ESS	Correlated
Subgroup of CV history	Correlated
Subgroup of diabetes history/known at baseline	Correlated

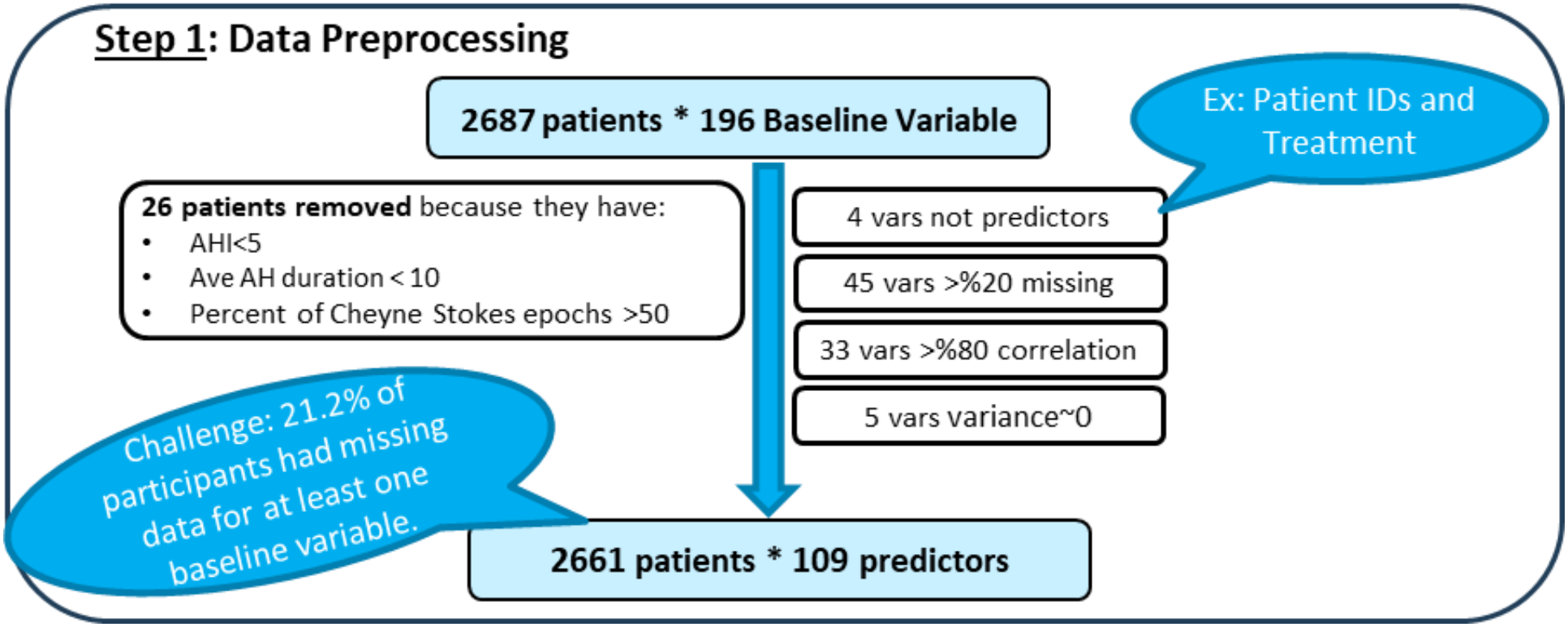
Supplementary Table 2 lists all features excluded during pre-processing and the reason for exclusion. Variables obtained directly from the ApneaLink sleep testing devices are noted, in contrast to non-standard sleep study variables, which were processed and derived in MATLAB by the SAVE study team. ACE Angiotensin-Converting Enzyme; AH Apnea Hypopnea; CV Cardiovascular; DDD Defined Daily Dose; ESS Epworth Sleepiness Scale; HADS Hospital Anxiety Depression Scale; HDL High Density Lipoprotein; LDL Low Density Lipoprotein; ODI Oxygen Desaturation Index; SF36 Short Form Questionnaire; SpO_2 Oxygen Saturation; TIA Transient Ischemic Attack

Supplementary Table 3. Key Features Included in the Final Model

Variable	Number of Imputed Models
Prior coronary revascularization	98
Smoking Status	80
Lipid Lowering Agent Use	53
Time spent <90% SpO_2, % (ApneaLink)	22
ODI	8
Median nadir desaturation (MATLAB)	6
SF36 physical health baseline	4
Desaturation hypoxic load (MATLAB)	4
SF36 Mental Health baseline	4
Total desaturating events (ApneaLink)	4
SF36 Limit Physical subscale	4
SF36 Body Pain subscale	4
SF36 General Health subscale	4
SF36 Social subscale	4
SF36 Mental subscale	4
SF36 Limit emotion subscale	4
Race	4
Heart Rate SD	2
Total number of breaths (ApneaLink)	2
Baseline Hypoxic Load (MATLAB)	1
Median desaturation/resaturation time ratio (MATLAB)	1
Heart rate variability measure by RMSSD (MATLAB)	1
Duration of flow analysis (ApneaLink)	1

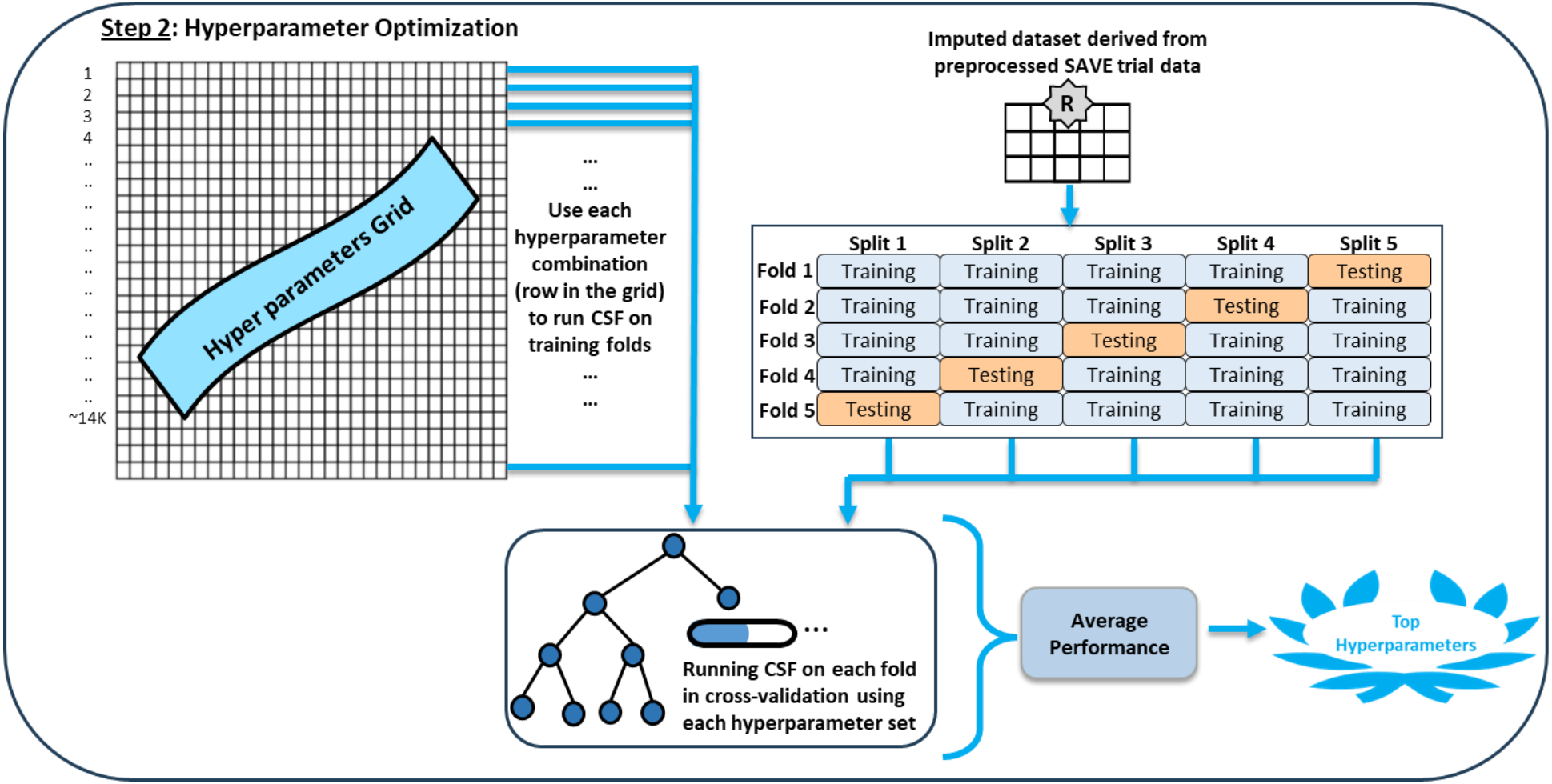
Supplementary Table 3 lists all features included in the final model training. Variables obtained directly from the ApneaLink sleep testing devices are noted, in contrast to non-standard sleep study variables, which were processed and derived in MATLAB by the SAVE study team. ODI Oxygen Desaturation Index; RMSSD Root Mean Square of Successive Differences; SD Standard Deviation; SF36 Short Form Questionnaire; SpO_2 Oxygen Saturation

Supplementary Figure 1. Data Preprocessing



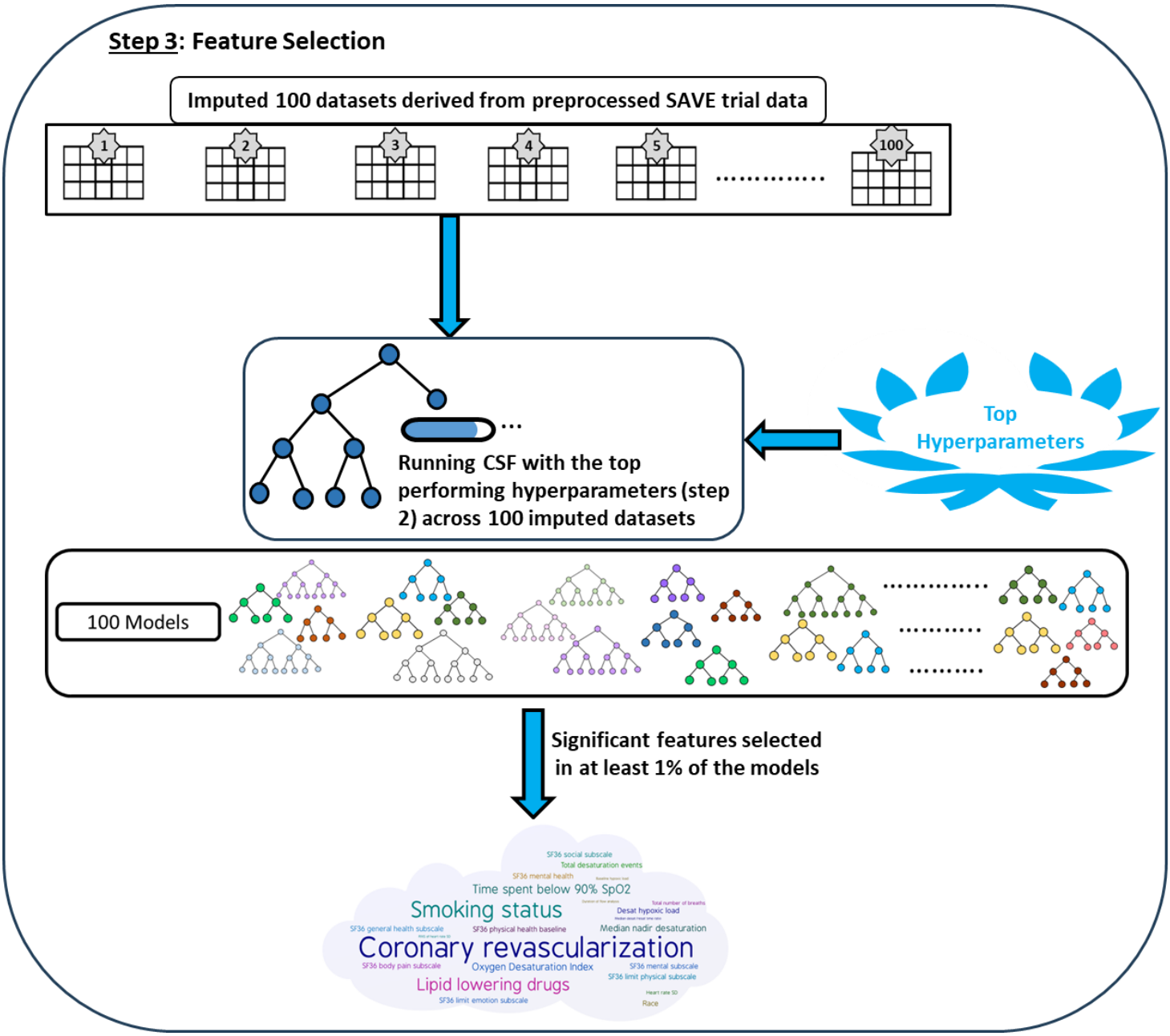
Step 1 in model development involved data preprocessing to ensure that both participants and predictor variables were appropriate for model training. We excluded variables that were not baseline predictors, had more than 20% missingness, exhibited collinearity with other variables in the model, or showed little to no variance. Despite these preprocessing steps, 21.2% of participants still had at least one missing value among the retained variables. Therefore, additional methods were required to identify a parsimonious feature set that preserved predictive performance while minimizing participant exclusion due to missing data (see Step 3 below for feature selection methods). AH Apnea-Hypopnea; AHI Apnea-Hypopnea Index; Ave Average; Vars Variables

Supplementary Figure 2. Hyperparameter Optimization



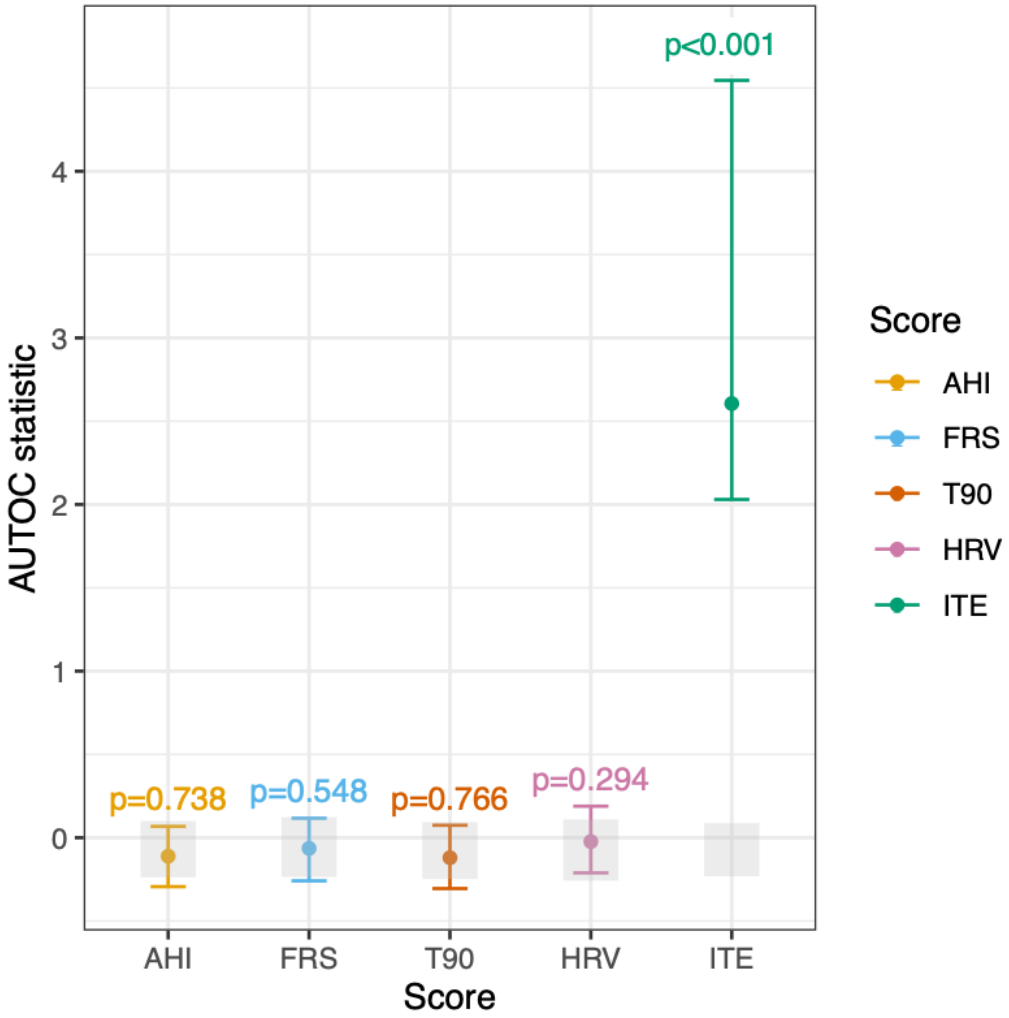
Prior to model development, we employed a data-driven strategy to identify the optimal hyperparameter set. In Step 2, we constructed a grid comprising all possible combinations of model hyperparameters. Using an imputed version of the preprocessed dataset from Step 1, we implemented a 5-fold cross-validation framework with causal survival forest models. Each hyperparameter combination was evaluated across all five folds, and performance metrics were averaged. The hyperparameter set yielding the highest average performance was selected for subsequent feature selection and the final model. CSF Causal Survival Forest

Supplementary Figure 3. Feature Selection



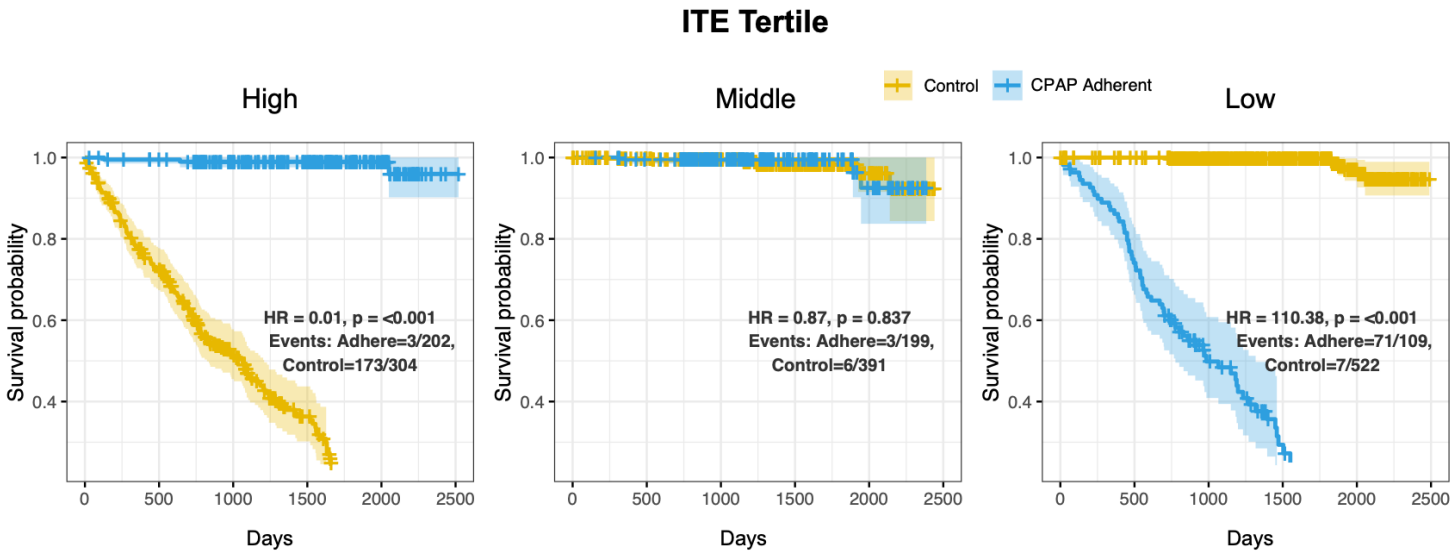
After preprocessing (Step 1) and hyperparameter tuning (Step 2), we performed feature selection (Step 3). We generated 100 imputed datasets from the preprocessed SAVE data and applied causal survival forest modeling to each using the optimal hyperparameter set identified in Step 2. Features that appeared in any of the 100 resulting models were selected as the final set of predictors. A total of 23 key features were identified. This approach ensured an informative set of variables for individualized treatment effect estimation in the final model, while avoiding the exclusion of 21.2% of participants with at least one missing variable. Among the 2,661 participants in the preprocessed SAVE dataset 2,603 had complete data for the 23 key features. CSF Causal Survival Forest

Supplementary Figure 4. Identifying heterogeneity in CPAP treatment effects by our ITE model, AHI, FRS, T90, and HRV



Our ITE model (n = 2603) predicts heterogeneity of treatment effects significantly better than the AHI (n = 2603), FRS (n = 2498), T90 (n = 2603), and HRV (n = 2603). All error bars represent 95% confidence intervals. p-values for AUTOC plots used a one-sided bootstrap percentile test. AHI Apnea-Hypopnea Index; AUTOC Area Under the Target Operator Characteristic; FRS Framingham Risk Score; HRV Heart Rate Variability; ITE Individualized Treatment Effect; T90 Time Spent Below SpO_2 90%

Supplementary Figure 5. Survival analysis by ITE tertile for those adherent to CPAP as compared to usual care



Per protocol survival analysis for time-to-CVD event for SAVE participants partitioned by ITE tertiles into top third (benefit HR = 0.01, p = 8.11×10^{-14}), middle third (no effect HR = 0.87, p = 0.837), and bottom third (harm HR = 110.38, p = 1.33×10^{-34}). Comparison is between those randomized to CPAP that adhered to therapy for more than 4 hours per night versus those from the usual care arm that did not use CPAP at all. All error bands represent 95% confidence intervals. p-value for survival plots are calculated using a two-sided Wald z-test. Cardiovascular Disease CVD; CPAP Continuous Positive Airway Pressure; HR Hazard Ratio; ITE Individualized Treatment Effect