

Supplementary Information

Interpretable Machine Learning Predicts Hepatic Fat Response to a Monounsaturated Fat-Enriched Diet in Steatotic Liver Disease

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Supplementary Methods

Detailed methodological information - including the bootstrap variable selection procedure, hyperparameter search spaces, calibration evaluation, and SHAP interpretation pipeline - is documented in the analysis code repository (<https://github.com/Alejandro1149662/hat-masld-predictive-analysis>). Key supplementary procedures are summarized below.

Bootstrap variable selection. We performed 100 bootstrap resamples of the training partition ($n=553$); a Random Forest ($n_estimators=50$) was fit on each resample and per-feature selection frequency was recorded. Features selected in $\geq 60\%$ of resamples were retained for downstream modeling, with multicollinearity-aware top-k truncation applied to mitigate redundancy between Insulin and HOMA-IR (Pearson $r \approx 0.94$).

Hyperparameter optimization. RandomizedSearchCV ($n_iter=50$) with 5-fold stratified cross-validation on the training partition was used to select hyperparameters per model class. Final hyperparameter values are tabulated in Supplementary Table S3.

Calibration assessment. We report Expected Calibration Error (ECE, $n_bins=10$) and Brier score on the held-out test set, with reliability diagrams shown in Supplementary Figure S9.

Decision-curve analysis. Net-benefit curves were computed across treatment thresholds 0.05–0.85; results are shown in Figure 8 (main manuscript).

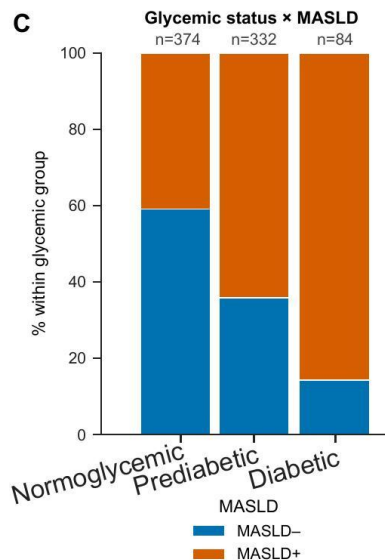
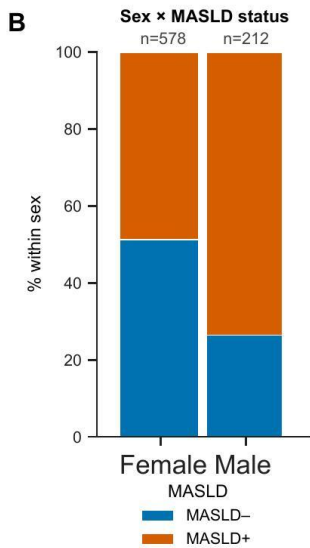
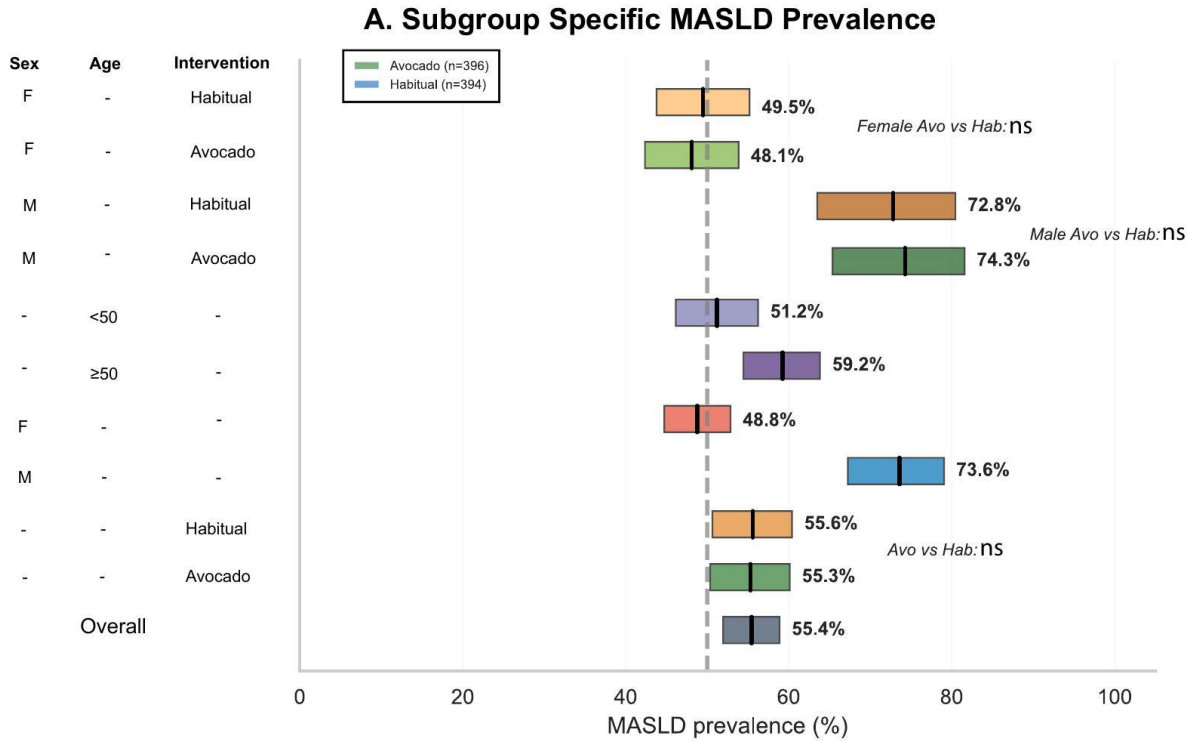
Supplementary Figures

All 10 supplementary figures (S1–S10) are reproduced below.

Supplementary Figure S1

Baseline MASLD prevalence and treatment effects on imaging and inflammatory outcomes.

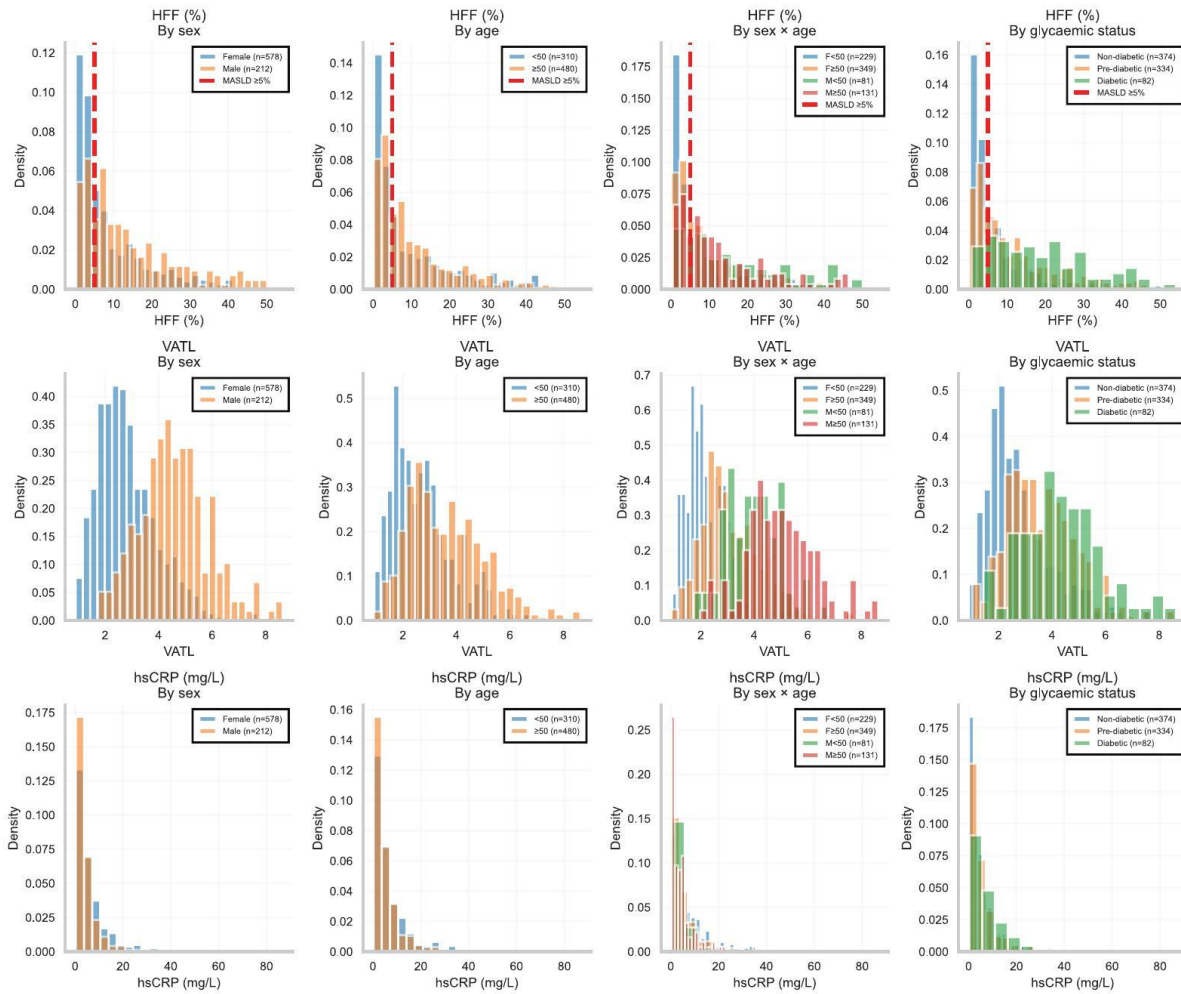
S1. Baseline MASLD Prevalence and Treatment Effects on Imaging & Inflammatory Outcomes



Supplementary Figure S2

Baseline HFF and VAT distributions stratified by sex and glycaemic status.

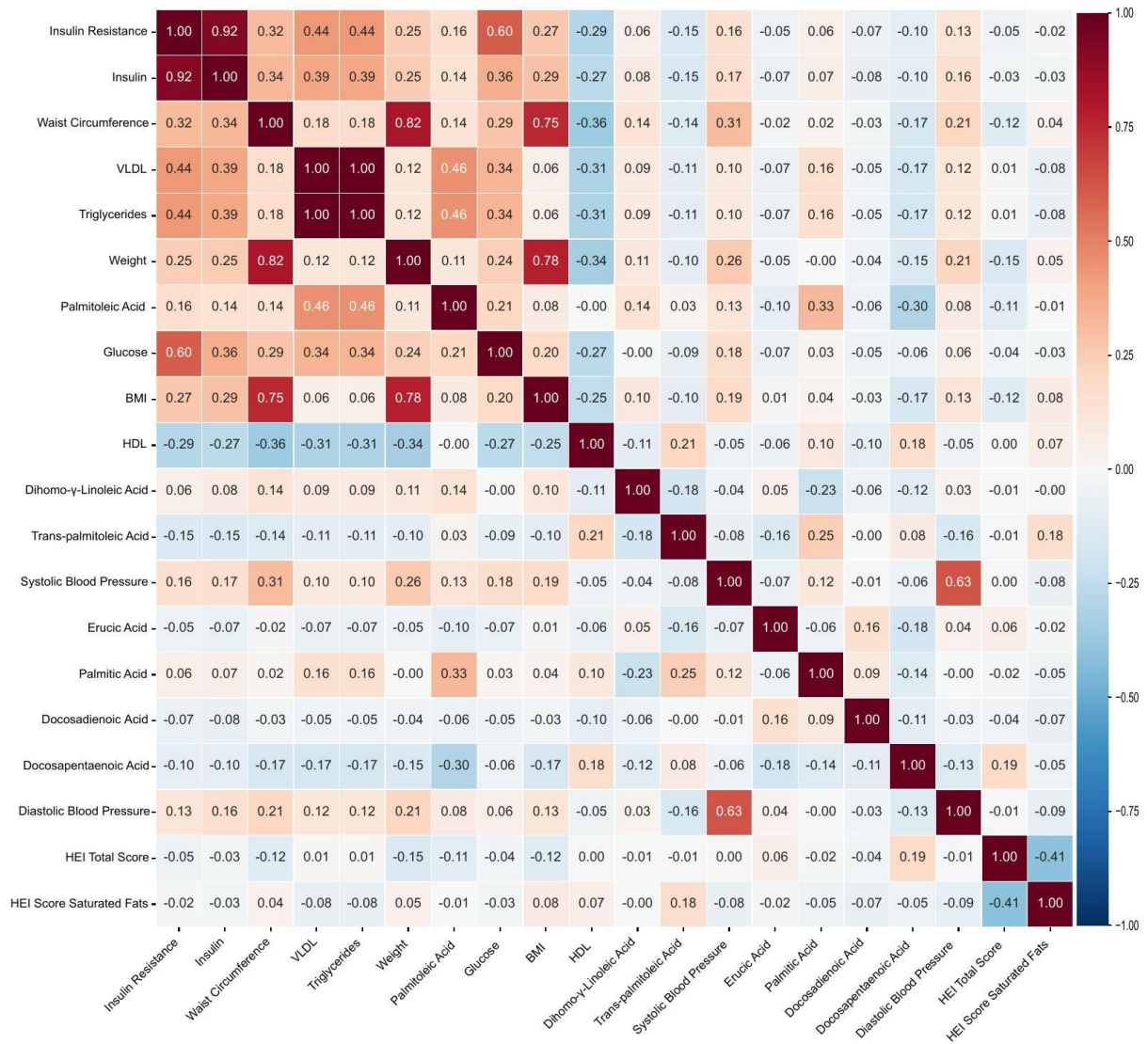
S2: Baseline HFF and VAT distributions stratified by sex and glycaemic status.



Supplementary Figure S3

Correlation matrices among MASLD-status predictors (insulin resistance, anthropometry, lipid panel).

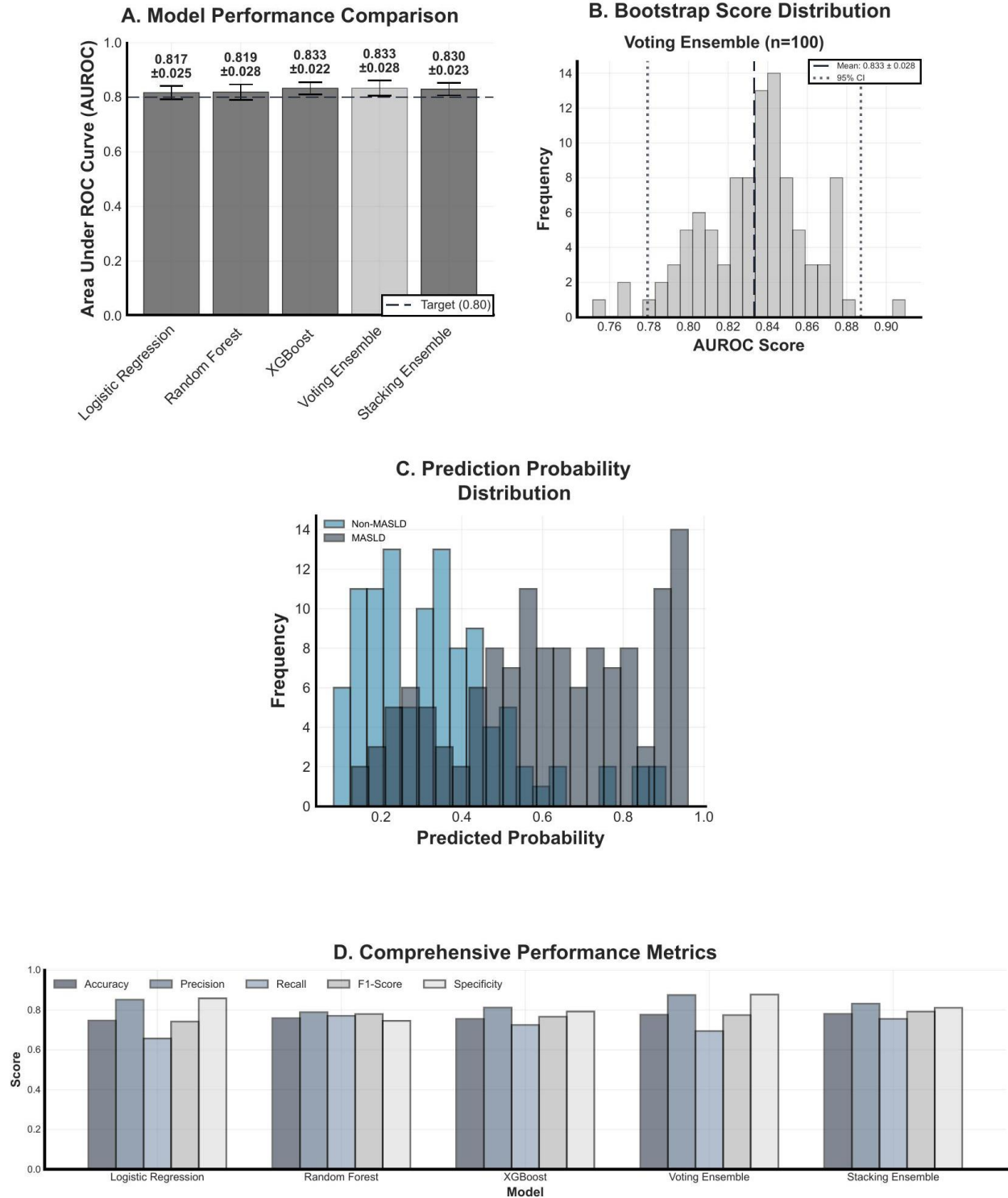
S3: Correlation matrices among MASLD Status predictors



Supplementary Figure S4

MASLD classification: supplementary performance analysis (bootstrap score distributions).

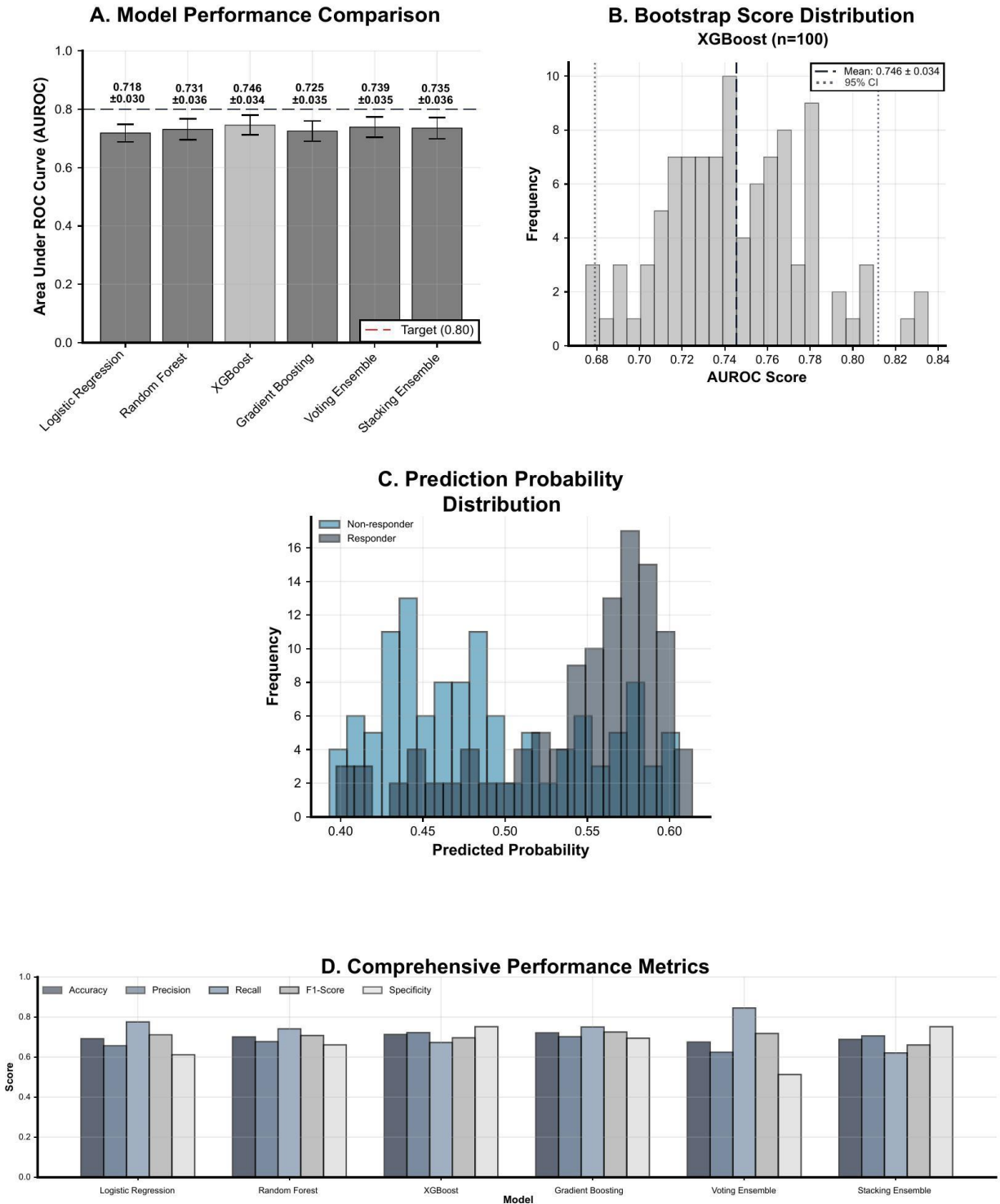
S4. MASLD Classification: Supplementary Performance Analysis



Supplementary Figure S5

HFF-responder classification: supplementary performance analysis (model performance comparison).

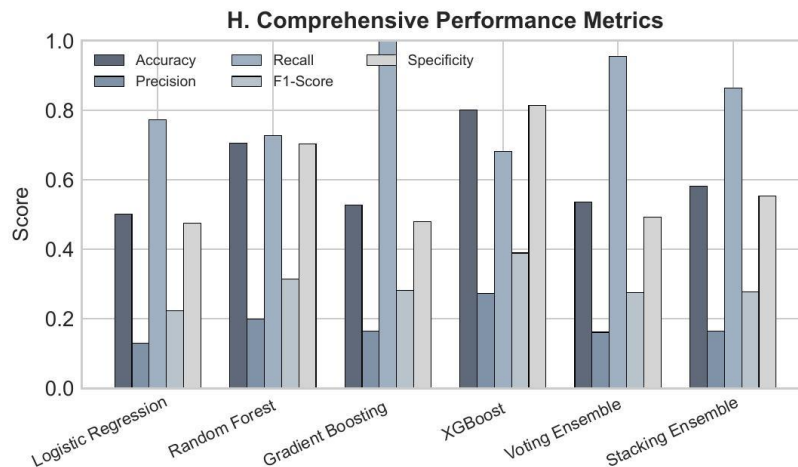
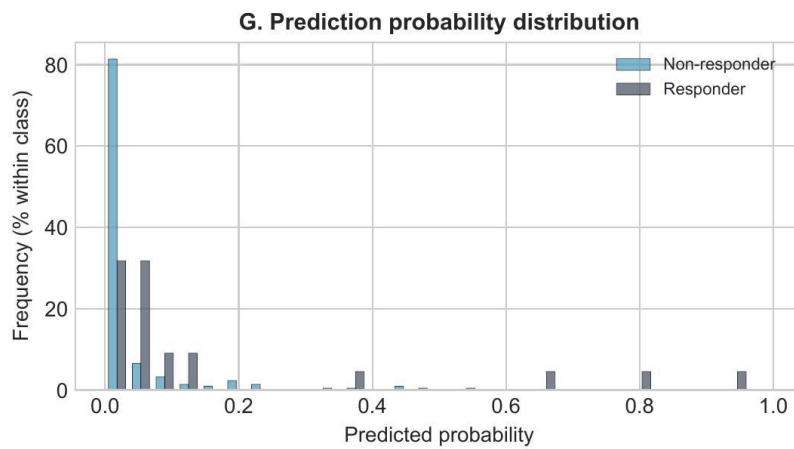
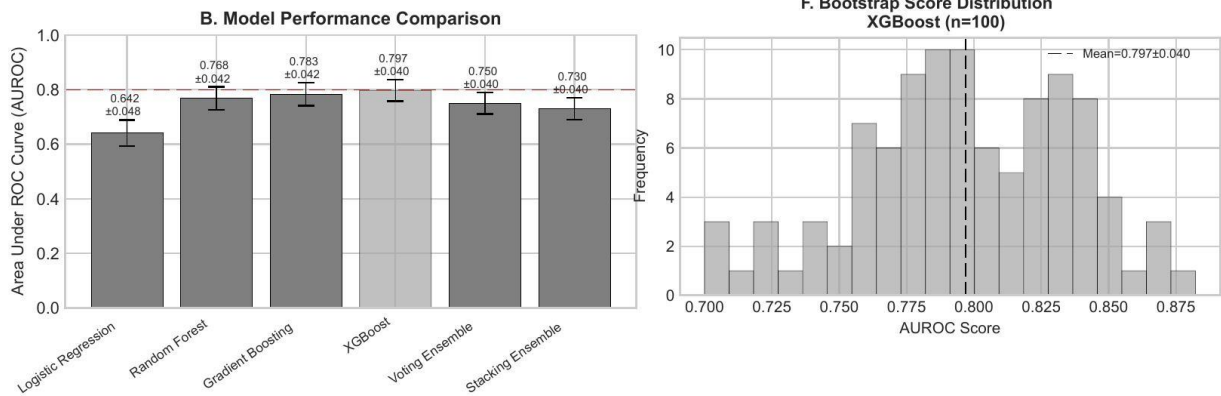
S5. Responders Classification: Supplementary Performance Analysis



Supplementary Figure S6

Positive (reduction-only) responders classification: supplementary performance analysis.

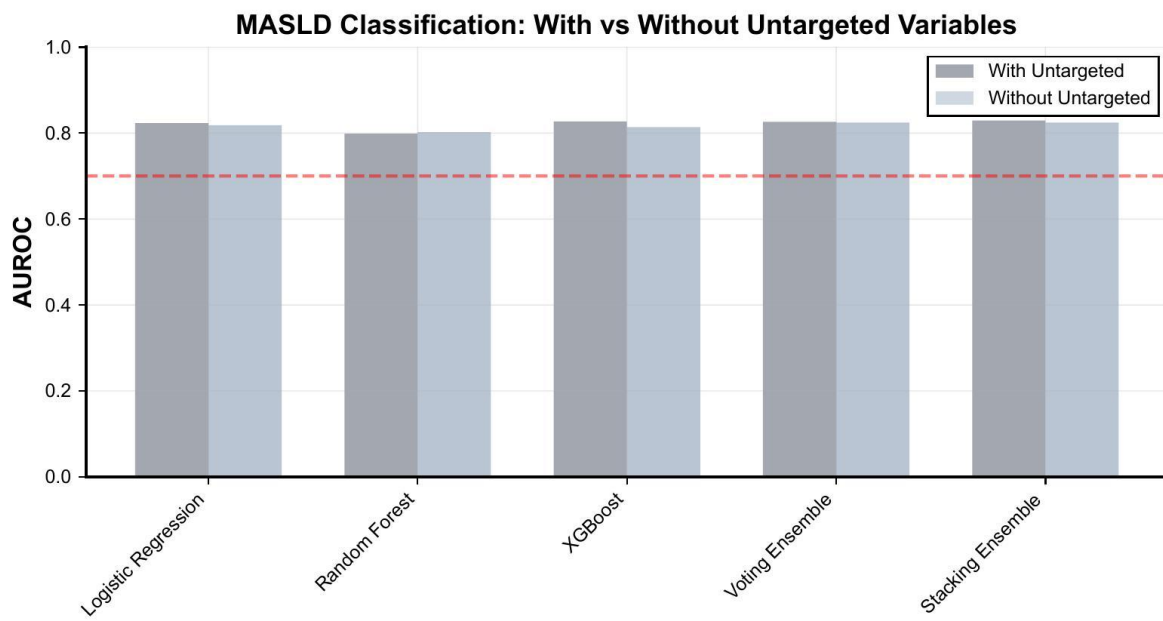
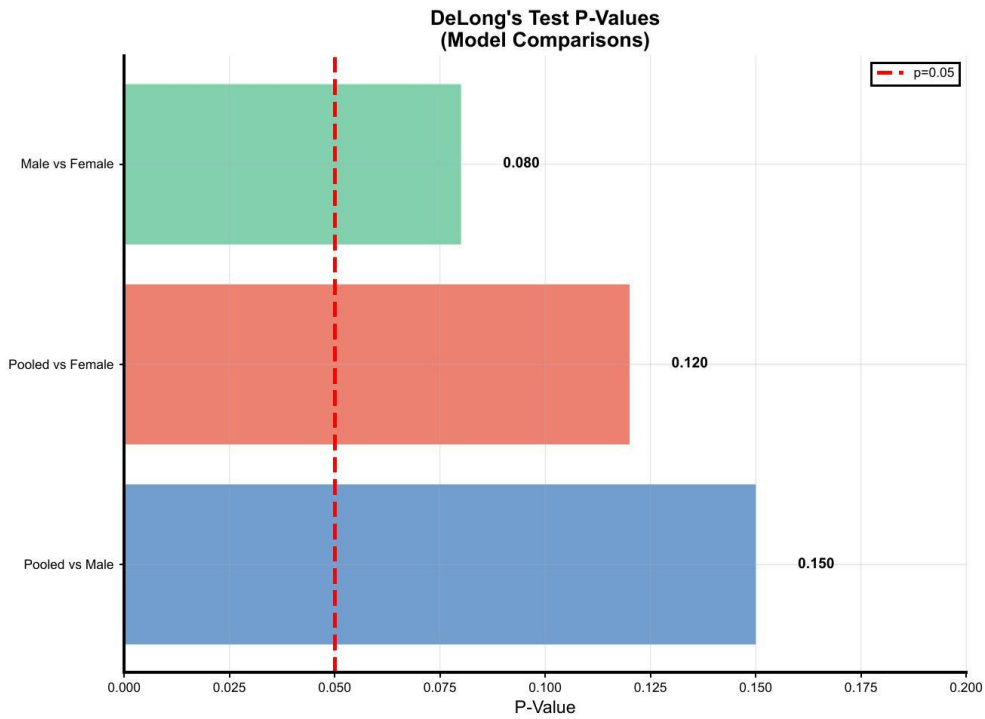
S6. Positive Responders Classification: Supplementary Performance Analysis



Supplementary Figure S7

Sex-specific and untargeted-feature-set effect (DeLong's test p-values).

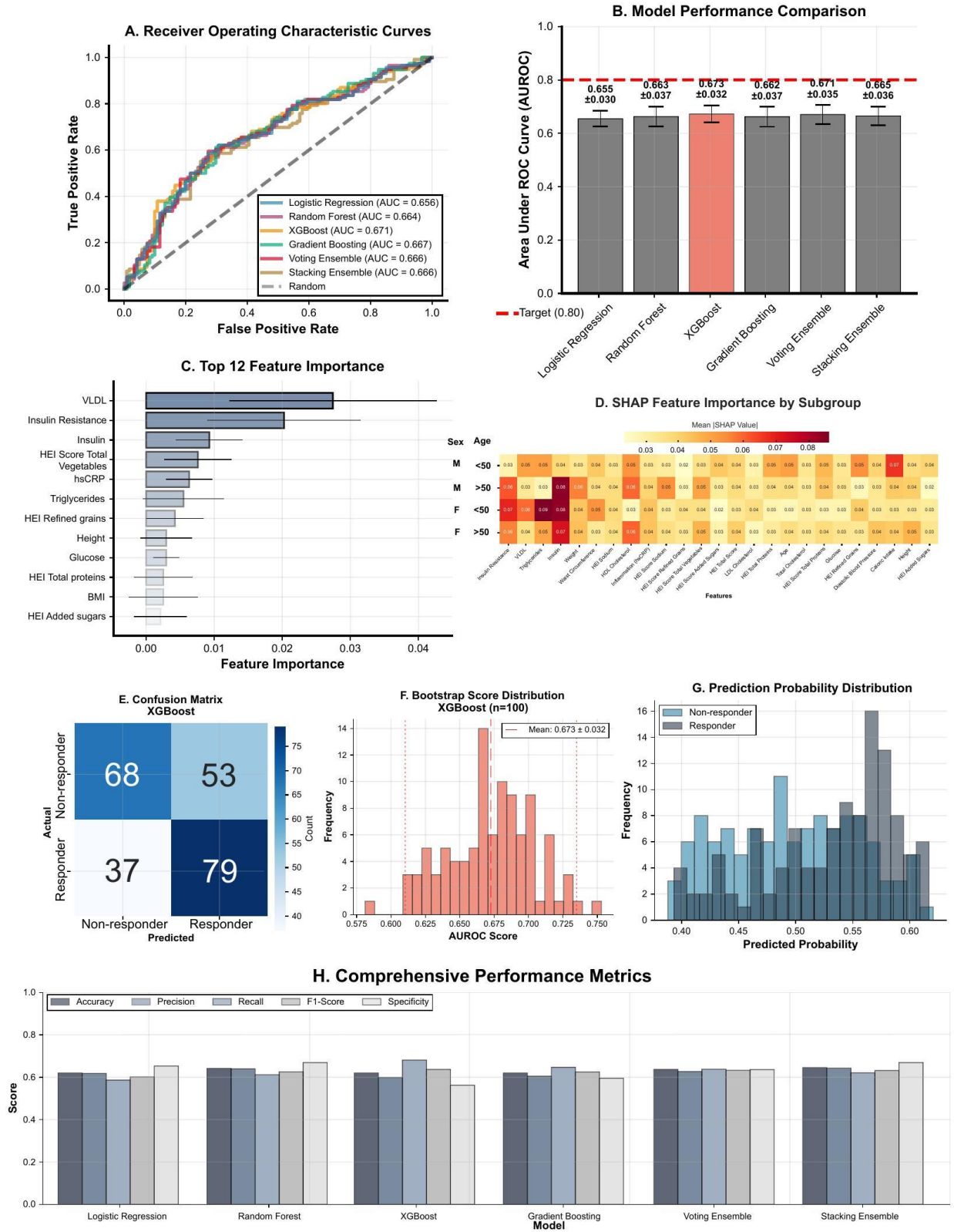
S7: Sex-Specific and Untargeted specific effect



Supplementary Figure S8

MASLD-responder classification performance without baseline MASLD-status feature.

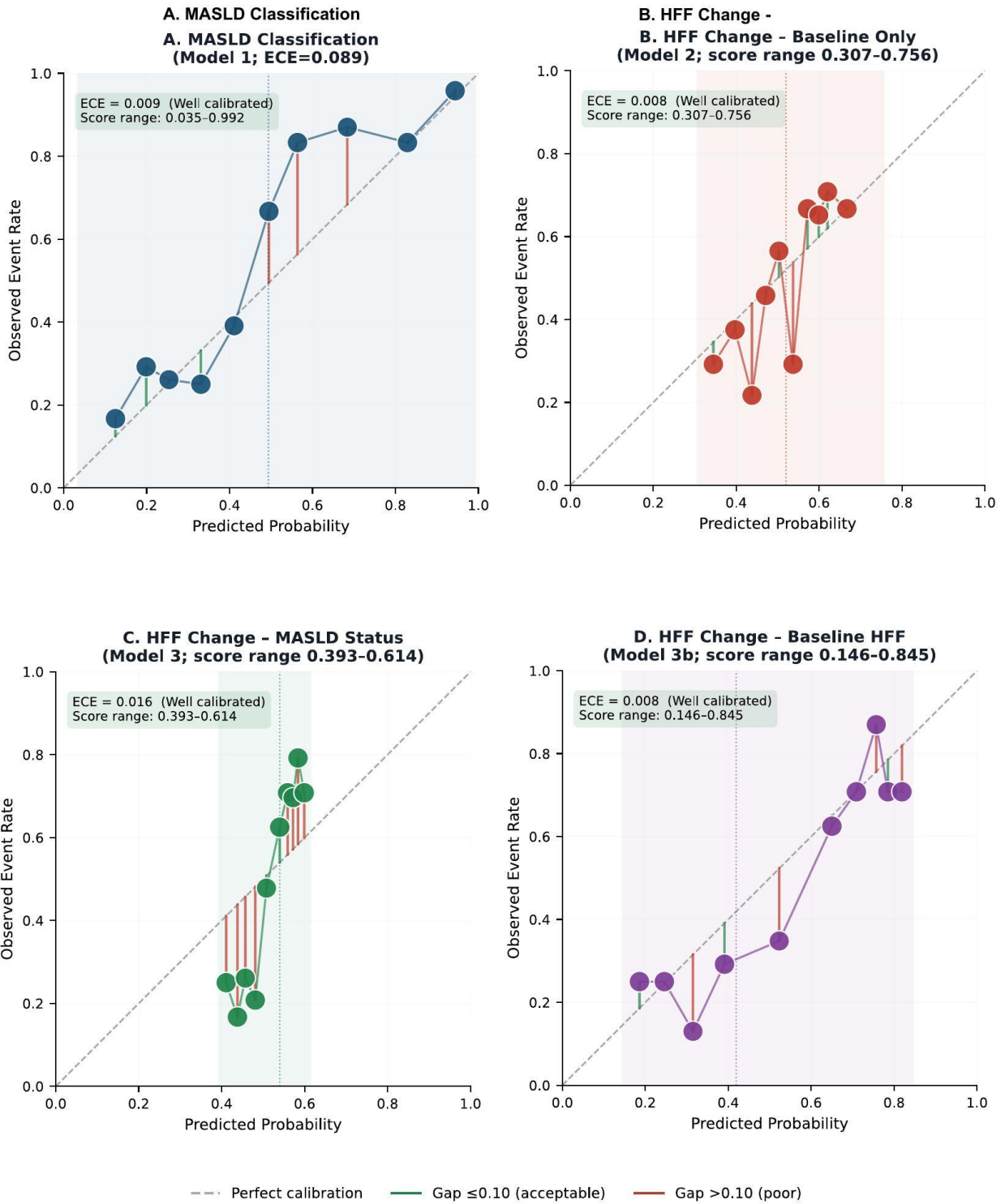
S8. MASLD Responder Classification: Performance Analysis (without baseline MASLD)



Supplementary Figure S9

Calibration and reliability diagrams for MASLD classification.

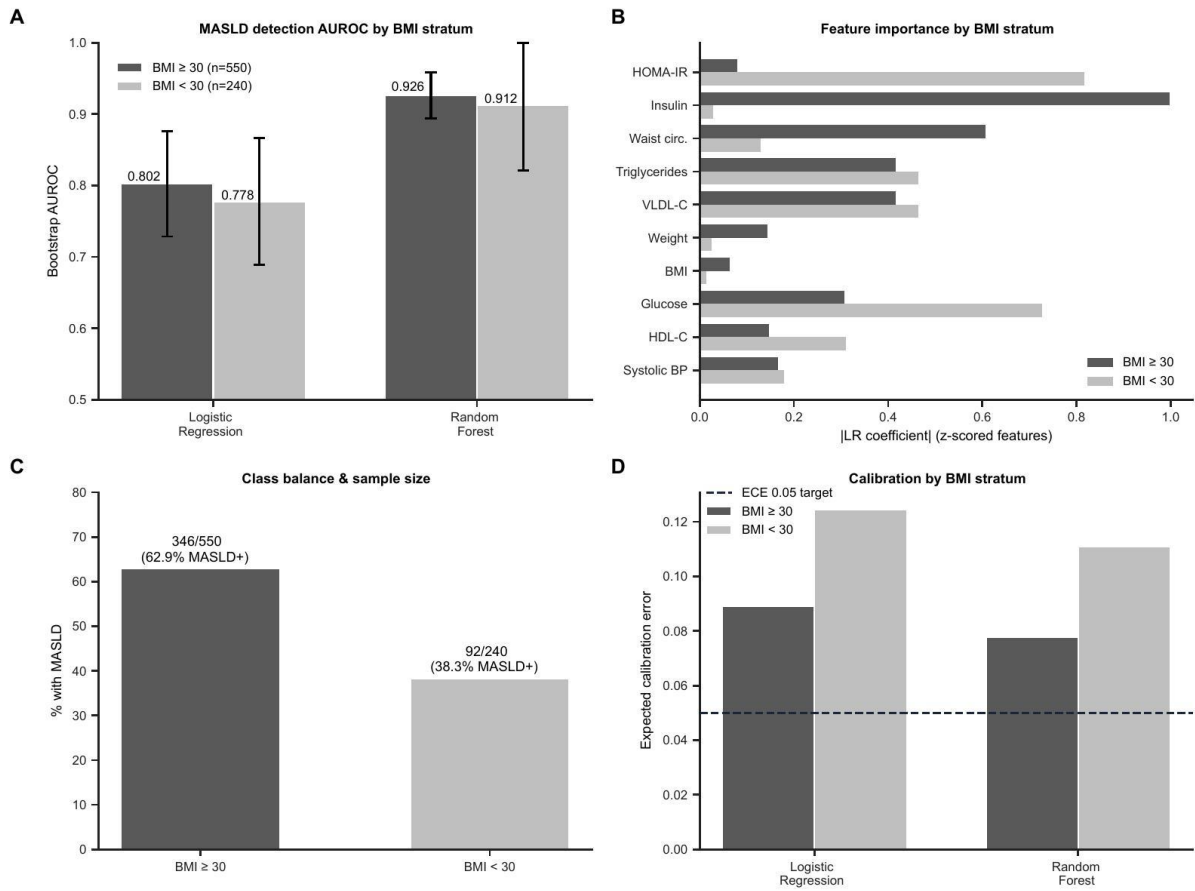
S9. Calibration and Reliability Diagram



Supplementary Figure S10

Obesity-stratified MASLD detection sensitivity analysis (BMI ≥ 30 vs < 30).

S10. Obesity-stratified MASLD detection sensitivity analysis



Supplementary Table S1 - HFF Change Prediction Performance by Feature Set (embedded in main Results)

Bootstrapped AUROC (mean \pm SD, 95% CI) for HFF change prediction (≥ 5 percentage point absolute change vs. stable) across four sequential feature branches. Each branch adds one predictor type to the baseline biomarker panel. Branch 4 adds both; the marginal gain over Branch 3 is minimal, supporting sufficiency of continuous baseline HFF.

Feature Branch	Best Model AUROC	95% CI	Best Algorithm	Δ vs. Branch 1
Branch 1: Baseline biomarker panel only	0.676 \pm 0.038	0.598–0.728	Gradient Boosting	—
Branch 2: + MASLD status (binary, ground truth)	0.746 \pm 0.034	0.674–0.794	XGBoost	+0.070
Branch 3: + Baseline HFF (continuous)	\approx 0.745	0.685–0.805	Multiple	+0.069
Branch 4: + MASLD status and Baseline HFF	\approx 0.747	0.686–0.808	Multiple	+0.071

AUROC = area under the receiver operating characteristic curve; CI = confidence interval; HFF = hepatic fat fraction; MASLD = metabolic dysfunction–associated steatotic liver disease. Δ = difference in best AUROC vs. Branch 1.

Supplementary Table S2. MASLD Classification and HFF Change Prediction: Targeted vs. Untargeted Lipidomic Variables

Bootstrapped AUROC (\pm SD) for MASLD classification and HFF change prediction (≥ 5 percentage point absolute change) using targeted clinical and lipidomic variables only versus the same pipeline with untargeted lipidomic variables additionally included. Both analyses used 10 selected features; n=790 for MASLD classification and n=723 for HFF change prediction.

	Targeted AUROC (\pm SD)	Untargeted AUROC (\pm SD)	Δ AUROC	Interpretation
<u>MASLD Classification</u>				
Logistic Regression	0.807 \pm 0.026	0.813 \pm 0.025	+0.006	Negligible
Random Forest	0.823 \pm 0.026	0.824 \pm 0.026	+0.001	Negligible
XGBoost	0.818 \pm 0.027	0.818 \pm 0.027	0.000	None
Voting Ensemble	0.826 \pm 0.023	0.828 \pm 0.023	+0.002	Negligible
Stacking Ensemble	0.827 \pm 0.027	0.830 \pm 0.027	+0.003	Negligible
<u>HFF Change Prediction</u>				
Logistic Regression	0.653 \pm 0.036	0.674 \pm 0.037	+0.021	Modest
Random Forest	0.663 \pm 0.032	0.695 \pm 0.032	+0.032	Modest
XGBoost	0.658 \pm 0.035	0.689 \pm 0.034	+0.031	Modest
Gradient Boosting	0.676 \pm 0.038	0.690 \pm 0.037	+0.014	Modest
Voting Ensemble	0.670 \pm 0.030	0.694 \pm 0.030	+0.024	Modest

AUROC = area under the receiver operating characteristic curve; SD = standard deviation; Δ = difference (Untargeted minus Targeted). All values from 100-iteration bootstrap validation. "Negligible" = Δ AUROC $<$ 0.01; "Modest" = Δ AUROC 0.01–0.04. Targeted = clinical and targeted lipidomic variables only. Untargeted = same pipeline with untargeted lipidomic metabolites additionally included.

S3 Supplementary Table S3 - Model Hyperparameter and Regularization Specifications

Analysis_function	Task_type	Model	Estimator_base	Search_space	Regularization_or_imbalance	CV_and_scoring	Notes
optimize_hyperparameters	classification	Logistic Regression	LogisticRegression(max_iter=1000, class_weight=balanced for binary)	$C \sim \text{loguniform}(1e-3, 1e3)$; penalty $\in \{1, l2\}$; solver $\in \{\text{liblinear}, \text{saga}\}$	L1/L2 regularization; class_weight and sample_weight balanced.	StratifiedKfold(cv_folds, shuffle=True); scoring=roc_auc or roc_auc_ovr	RandomizedSearch CV (or Optuna TPE when USE_OPTUNA=1); default N_ITER=48, CV=5.
optimize_hyperparameters	classification	Random Forest	RandomForestClassifier(class_weight=balanced, n_jobs=1)	n_estimators $\in [50, 500]$; max_depth $\in \{\text{None}, 5, 50\}$; min_samples_split $\in [2, 20]$; min_samples_leaf $\in [1, 15]$	Implicit regularization via tree depth/split/leaf controls.	StratifiedKfold; scoring=roc_auc/roc_auc_ovr	RandomizedSearch CV (or Optuna TPE when USE_OPTUNA=1); default N_ITER=48, CV=5.
optimize_hyperparameters	classification	XGBoost	XGBClassifier(eval_metric=logloss; scale_pos_weight for binary imbalance)	n_estimators $\in [50, 500]$; max_depth $\in [3, 15]$; learning_rate $\sim \text{loguniform}(1e-3, 0.5)$; subsample $\sim U(0.6, 1.0)$; colsample_bytree $\sim U(0.6, 1.0)$	Imbalance handled via scale_pos_weight + sample_weight.	StratifiedKfold; scoring=roc_auc/roc_auc_ovr	RandomizedSearch CV (or Optuna TPE when USE_OPTUNA=1); default N_ITER=48, CV=5.
optimize_hyperparameters	regression	Ridge	Ridge(random_state=42)	alpha $\sim \text{loguniform}(1e-2, 1e3)$	L2 regularization via alpha.	K-fold cv_folds; scoring=r2	RandomizedSearch CV (or Optuna TPE when USE_OPTUNA=1); default N_ITER=48, CV=5.
optimize_hyperparameters_for_change_models	classification (responder / 3-group)	Logistic Regression	LogisticRegression(max_iter=2000, class_weight=balanced)	$C \sim \text{loguniform}(1e-3, 1e3)$; penalty fixed to l2; solver $\in \{\text{lbfgs}, \text{saga}\}$	L2 regularization; balanced class/sample weighting.	RepeatedStratifiedKfold; scoring=roc_auc or roc_auc_ovr	RandomizedSearch CV (or Optuna TPE); default N_ITER=50 with RepeatedStratifiedKfold (5 folds \times 2 repeats).
optimize_hyperparameters_for_change_models	classification (responder / 3-group)	XGBoost	XGBClassifier(eval_metric=logloss/mlogloss; objective multisoftprob for multiclass)	n_estimators $\in [100, 500]$; max_depth $\in [3, 15]$; learning_rate $\sim \text{loguniform}(1e-3, 0.5)$; subsample $\sim U(0.6, 1.0)$; colsample_bytree $\sim U(0.6, 1.0)$; min_child_weight $\in [1, 10]$	scale_pos_weight for binary imbalance; sample_weight balanced.	RepeatedStratifiedKfold; scoring=roc_auc or roc_auc_ovr	RandomizedSearch CV (or Optuna TPE); default N_ITER=50 with RepeatedStratifiedKfold (5 folds \times 2 repeats).
optimize_hyperparameters_for_change_models	classification (responder / 3-group)	Gradient Boosting	GradientBoostingClassifier(random_state=42)	n_estimators $\in [50, 350]$; max_depth $\in [2, 10]$; learning_rate $\sim \text{loguniform}(1e-3, 0.3)$; min_samples_split $\in [2, 20]$; min_samples_leaf $\in [1, 15]$; subsample $\sim U(0.6, 1.0)$	Regularization via depth/leaf/subsample/learning_rate.	RepeatedStratifiedKfold; scoring=roc_auc or roc_auc_ovr	RandomizedSearch CV (or Optuna TPE); default N_ITER=50 with RepeatedStratifiedKfold (5 folds \times 2 repeats).
ensembles	classification	Voting + Stacking	VotingClassifier(voting=soft) and StackingClassifier(meta=LogisticRegression)	No separate search; built from optimized base estimators	Meta learner class_weight balanced	Stacking cv=3 (main) or cv=5 (change models)	Added when ≥ 2 optimized base models available.

Supplementary Table S4 - Master Variable Codebook and Baseline Missingness

Variable Name	Common Name	Category	Baseline Missing (%)	Description
cuffsize_wk0	Blood Pressure Cuff Size	Anthropometric	0	Feature in category 'Anthropometric' at baseline (week 0).
BMI_wk0	Body Mass Index (BMI)	Anthropometric	0	Feature in category 'Anthropometric' at baseline (week 0).
wstcircavg_wk0	Waist Circumference	Anthropometric	0	Feature in category 'Anthropometric' at baseline (week 0).
weightavg_wk0	Weight (baseline)	Anthropometric	0	Feature in category 'Anthropometric' at baseline (week 0).
diasmean_wk0	diasmean (baseline)	Anthropometric	0	Feature in category 'Anthropometric' at baseline (week 0).
heights_wk0	heights (baseline)	Anthropometric	0	Feature in category 'Anthropometric' at baseline (week 0).
pulsmean_wk0	pulsmean (baseline)	Anthropometric	0	Feature in category 'Anthropometric' at baseline (week 0).
sysmean_wk0	sysmean (baseline)	Anthropometric	0	Feature in category 'Anthropometric' at baseline (week 0).
chol_wk0	Cholesterol (baseline)	Clinical Labs	0	Feature in category 'Clinical Labs' at baseline (week 0).
Insulin_wk0	Fasting Insulin	Clinical Labs	0	Metabolic biomarker (Clinical Labs) at baseline (week 0).
glucose_wk0	Glucose (baseline)	Clinical Labs	0	Metabolic biomarker (Clinical Labs) at baseline (week 0).
hdl_wk0	HDL (baseline)	Clinical Labs	0	Feature in category 'Clinical Labs' at baseline (week 0).
HOMA-IR_wk0	HOMA-IR (baseline)	Clinical Labs	0	Metabolic biomarker (Clinical Labs) at baseline (week 0).
ldl_wk0	LDL (baseline)	Clinical Labs	0	Feature in category 'Clinical Labs' at baseline (week 0).
trig_wk0	Triglycerides (baseline)	Clinical Labs	0	Feature in category 'Clinical Labs' at baseline (week 0).
vldl_wk0	VLDL (baseline)	Clinical Labs	0	Feature in category 'Clinical Labs' at baseline (week 0).
hsCRP_wk0	hsCRP (baseline)	Clinical Labs	0	Feature in category 'Clinical Labs' at baseline (week 0).
rikcal_wk0	rikcal (baseline)	Clinical Labs	0	Feature in category 'Clinical Labs' at baseline (week 0).
age_wk0	age (baseline)	Demographics	0	Demographic covariate (Demographics); encoded for modeling where applicable.
education_wk0	education (baseline)	Demographics	0	Feature in category 'Demographics' at baseline (week 0).
livingsituation_wk0	livingsituation (baseline)	Demographics	0	Feature in category 'Demographics' at baseline (week 0).
occupation_wk0	occupation (baseline)	Demographics	0	Feature in category 'Demographics' at baseline (week 0).
weight_wk0	Weight	Derived/Other	0	Feature in category 'Derived/Other' at baseline (week 0).
xhei_fatacid_wk0	Fatty Acids (HEI component) (RBC, baseline)	HEI Components	0	Feature in category 'HEI Components' at baseline (week 0).
HEI2015_TOTAL_SCORE_wk0	HEI-2015 total (baseline)	HEI Components	0	Feature in category 'HEI Components' at baseline (week 0).
HEIX10_SODIUM_wk0	HEIX10_SODIUM (baseline)	HEI Components	0	Feature in category 'HEI Components' at baseline (week 0).
HEIX11_REFINEDGRAIN_wk0	HEIX11_REFINEDGRAIN (baseline)	HEI Components	0	Feature in category 'HEI Components' at baseline (week 0).
HEIX12_ADDEDSUGARS_wk0	HEIX12_ADDEDSUGARS (baseline)	HEI Components	0	Feature in category 'HEI Components' at baseline (week 0).
HEIX13_SATFATS_wk0	HEIX13_SATFATS (baseline)	HEI Components	0	Feature in category 'HEI Components' at baseline (week 0).
HEIX1_TOTALVEG_wk0	HEIX1_TOTALVEG (baseline)	HEI Components	0	Feature in category 'HEI Components' at baseline (week 0).
HEIX2_GREEN_AND_BEAN_wk0	HEIX2_GREEN_AND_BEAN (baseline)	HEI Components	0	Feature in category 'HEI Components' at baseline (week 0).
HEIX3_TOTALFRUIT_wk0	HEIX3_TOTALFRUIT (baseline)	HEI Components	0	Feature in category 'HEI Components' at baseline (week 0).
HEIX4_WHOLEFRUIT_wk0	HEIX4_WHOLEFRUIT (baseline)	HEI Components	0	Feature in category 'HEI Components' at baseline (week 0).
HEIX5_WHOLEGRAIN_wk0	HEIX5_WHOLEGRAIN (baseline)	HEI Components	0	Feature in category 'HEI Components' at baseline (week 0).
HEIX6_TOTALDAIRY_wk0	HEIX6_TOTALDAIRY (baseline)	HEI Components	0	Feature in category 'HEI Components' at baseline (week 0).
HEIX7_TOTPROT_wk0	HEIX7_TOTPROT (baseline)	HEI Components	0	Feature in category 'HEI Components' at baseline (week 0).
HEIX8_SEAPLANT_PROT_wk0	HEIX8_SEAPLANT_PROT (baseline)	HEI Components	0	Feature in category 'HEI Components' at baseline (week 0).
HEIX9_FATTYACID_wk0	HEIX9_FATTYACID (baseline)	HEI Components	0	Feature in category 'HEI Components' at baseline (week 0).
hei_addedsugars_wk0	hei_addedsugars (baseline)	HEI Components	0	Feature in category 'HEI Components' at baseline (week 0).
hei_dairy_wk0	hei_dairy (baseline)	HEI Components	0	Feature in category 'HEI Components' at baseline (week 0).
hei_greensbeans_wk0	hei_greensbeans (baseline)	HEI Components	0	Feature in category 'HEI Components' at baseline (week 0).
hei_refinedgrains_wk0	hei_refinedgrains (baseline)	HEI Components	0	Feature in category 'HEI Components' at baseline (week 0).
hei_seafoodplantprot_wk0	hei_seafoodplantprot (baseline)	HEI Components	0	Feature in category 'HEI Components' at baseline (week 0).
hei_sodium_wk0	hei_sodium (baseline)	HEI Components	0	Feature in category 'HEI Components' at baseline (week 0).
hei_totfruit_wk0	hei_totfruit (baseline)	HEI Components	0	Feature in category 'HEI Components' at baseline (week 0).
hei_totproteins_wk0	hei_totproteins (baseline)	HEI Components	0	Feature in category 'HEI Components' at baseline (week 0).
hei_wholefruit_wk0	hei_wholefruit (baseline)	HEI Components	0	Feature in category 'HEI Components' at baseline (week 0).
hei_wholegrains_wk0	hei_wholegrains (baseline)	HEI Components	0	Feature in category 'HEI Components' at baseline (week 0).
xhei_addedsugars_wk0	xhei_addedsugars (baseline)	HEI Components	0	Feature in category 'HEI Components' at baseline (week 0).
xhei_dairy_wk0	xhei_dairy (baseline)	HEI Components	0	Feature in category 'HEI Components' at baseline (week 0).
xhei_greensbeans_wk0	xhei_greensbeans (baseline)	HEI Components	0	Feature in category 'HEI Components' at baseline (week 0).
xhei_refinedgrains_wk0	xhei_refinedgrains (baseline)	HEI Components	0	Feature in category 'HEI Components' at baseline (week 0).
xhei_satfats_wk0	xhei_satfats (baseline)	HEI Components	0	Feature in category 'HEI Components' at baseline (week 0).
xhei_seafoodplantprot_wk0	xhei_seafoodplantprot (baseline)	HEI Components	0	Feature in category 'HEI Components' at baseline (week 0).
xhei_sodium_wk0	xhei_sodium (baseline)	HEI Components	0	Feature in category 'HEI Components' at baseline (week 0).
xhei_totfruit_wk0	xhei_totfruit (baseline)	HEI Components	0	Feature in category 'HEI Components' at baseline (week 0).
xhei_totproteins_wk0	xhei_totproteins (baseline)	HEI Components	0	Feature in category 'HEI Components' at baseline (week 0).
xhei_totveg_wk0	xhei_totveg (baseline)	HEI Components	0	Feature in category 'HEI Components' at baseline (week 0).
xhei_wholefruit_wk0	xhei_wholefruit (baseline)	HEI Components	0	Feature in category 'HEI Components' at baseline (week 0).
xhei_wholegrains_wk0	xhei_wholegrains (baseline)	HEI Components	0	Feature in category 'HEI Components' at baseline (week 0).
Diabetes_wk0	Diabetes (baseline)	Health Conditions	0	Feature in category 'Health Conditions' at baseline (week 0).
allergy_food_wk0	allergy_food (baseline)	Health Conditions	0	Feature in category 'Health Conditions' at baseline (week 0).
allergy_meds_wk0	allergy_meds (baseline)	Health Conditions	0	Feature in category 'Health Conditions' at baseline (week 0).
allergy_other_wk0	allergy_other (baseline)	Health Conditions	0	Feature in category 'Health Conditions' at baseline (week 0).
allergy_seasonal_wk0	allergy_seasonal (baseline)	Health Conditions	0	Feature in category 'Health Conditions' at baseline (week 0).
chew_wk0	chew (baseline)	Health Conditions	0	Feature in category 'Health Conditions' at baseline (week 0).
choke_wk0	choke (baseline)	Health Conditions	0	Feature in category 'Health Conditions' at baseline (week 0).
condition_wk0	condition (baseline)	Health Conditions	0	Feature in category 'Health Conditions' at baseline (week 0).
diet_prescribed_wk0	diet_prescribed (baseline)	Health Conditions	0	Feature in category 'Health Conditions' at baseline (week 0).

meals_day_wk0	meals_day (baseline)	Lifestyle	0	Feature in category 'Lifestyle' at baseline (week 0).
meals_delivered_wk0	meals_delivered (baseline)	Lifestyle	0	Feature in category 'Lifestyle' at baseline (week 0).
meals_home_wk0	meals_home (baseline)	Lifestyle	0	Feature in category 'Lifestyle' at baseline (week 0).
meals_other_wk0	meals_other (baseline)	Lifestyle	0	Feature in category 'Lifestyle' at baseline (week 0).
meals_restaurant_wk0	meals_restaurant (baseline)	Lifestyle	0	Feature in category 'Lifestyle' at baseline (week 0).
meals_sites_wk0	meals_sites (baseline)	Lifestyle	0	Feature in category 'Lifestyle' at baseline (week 0).
meals_work_wk0	meals_work (baseline)	Lifestyle	0	Feature in category 'Lifestyle' at baseline (week 0).
nowsmoke_wk0	nowsmoke (baseline)	Lifestyle	0	Feature in category 'Lifestyle' at baseline (week 0).
prepare_special_wk0	prepare_special (baseline)	Lifestyle	0	Feature in category 'Lifestyle' at baseline (week 0).
reg_activity_wk0	reg_activity (baseline)	Lifestyle	0	Feature in category 'Lifestyle' at baseline (week 0).
smoked100_wk0	smoked100 (baseline)	Lifestyle	0	Feature in category 'Lifestyle' at baseline (week 0).
snacks_day_wk0	snacks_day (baseline)	Lifestyle	0	Feature in category 'Lifestyle' at baseline (week 0).
special_diet_wk0	special_diet (baseline)	Lifestyle	0	Feature in category 'Lifestyle' at baseline (week 0).
PUFA22_4n_6_wk0	Adrenic Acid	Targeted_FA	0	Targeted RBC fatty-acid feature at baseline (week 0).
PUFA18_3n_3_wk0	Alpha-linolenic Acid (ALA)	Targeted_FA	0	Targeted RBC fatty-acid feature at baseline (week 0).
SFA20_0_wk0	Arachidic Acid	Targeted_FA	0	Targeted RBC fatty-acid feature at baseline (week 0).
PUFA20_4n_6_wk0	Arachidonic Acid (AA)	Targeted_FA	0	Targeted RBC fatty-acid feature at baseline (week 0).
SFA22_0_wk0	Behenic Acid	Targeted_FA	0	Targeted RBC fatty-acid feature at baseline (week 0).
SFA10_0_wk0	Capric Acid	Targeted_FA	0	Targeted RBC fatty-acid feature at baseline (week 0).
TFA18_2CLA_wk0	Conjugated Linoleic Acid	Targeted_FA	0	Targeted RBC fatty-acid feature at baseline (week 0).
PUFA20_3n_6_wk0	Dihomo-gamma-linolenic Acid (DGLA)	Targeted_FA	0	Targeted RBC fatty-acid feature at baseline (week 0).
PUFA22_2n_6_wk0	Docosadienoic Acid	Targeted_FA	0	Targeted RBC fatty-acid feature at baseline (week 0).
PUFA22_6n_3_wk0	Docosahexaenoic Acid (DHA)	Targeted_FA	0	Targeted RBC fatty-acid feature at baseline (week 0).
PUFA22_5n_3_wk0	Docosapentaenoic Acid (DPA)	Targeted_FA	0	Targeted RBC fatty-acid feature at baseline (week 0).
PUFA20_5n_3_wk0	Eicosapentaenoic Acid (EPA)	Targeted_FA	0	Targeted RBC fatty-acid feature at baseline (week 0).
TFA18_1n_9T_wk0	Elaidic Acid (Trans-oleic acid)	Targeted_FA	0	Targeted RBC fatty-acid feature at baseline (week 0).
MFA22_1n_9_wk0	Erucic Acid	Targeted_FA	0	Targeted RBC fatty-acid feature at baseline (week 0).
PUFA18_3n_6_wk0	Gamma-linolenic Acid (GLA)	Targeted_FA	0	Targeted RBC fatty-acid feature at baseline (week 0).
MFA20_1n_9_wk0	Gondoic Acid	Targeted_FA	0	Targeted RBC fatty-acid feature at baseline (week 0).
SFA12_0_wk0	Lauric Acid	Targeted_FA	0	Targeted RBC fatty-acid feature at baseline (week 0).
SFA24_0_wk0	Lignoceric Acid	Targeted_FA	0	Targeted RBC fatty-acid feature at baseline (week 0).
PUFA18_2n_6_wk0	Linoleic Acid (LA)	Targeted_FA	0	Targeted RBC fatty-acid feature at baseline (week 0).
SFA14_0_wk0	Myristic Acid	Targeted_FA	0	Targeted RBC fatty-acid feature at baseline (week 0).
MFA24_1n_9_wk0	Nervonic Acid	Targeted_FA	0	Targeted RBC fatty-acid feature at baseline (week 0).
MFA18_1n_9_wk0	Oleic Acid	Targeted_FA	0	Targeted RBC fatty-acid feature at baseline (week 0).
PUFA22_5n_6_wk0	Osbond Acid	Targeted_FA	0	Targeted RBC fatty-acid feature at baseline (week 0).
SFA16_0_wk0	Palmitic Acid	Targeted_FA	0	Targeted RBC fatty-acid feature at baseline (week 0).
MFA16_1n_7_wk0	Palmitoleic Acid	Targeted_FA	0	Targeted RBC fatty-acid feature at baseline (week 0).
SFA15_0_wk0	Pentadecanoic Acid	Targeted_FA	0	Targeted RBC fatty-acid feature at baseline (week 0).
MFA16_1n_9_wk0	Sapinic Acid	Targeted_FA	0	Targeted RBC fatty-acid feature at baseline (week 0).
SFA18_0_wk0	Stearic Acid	Targeted_FA	0	Targeted RBC fatty-acid feature at baseline (week 0).
PUFA18_4n_3_wk0	Stearidonic Acid (SDA)	Targeted_FA	0	Targeted RBC fatty-acid feature at baseline (week 0).
PUFA_n_3_wk0	Total Omega-3 Polyunsaturated Fatty Acids	Targeted_FA	0	Targeted RBC fatty-acid feature at baseline (week 0).
PUFA_n_6_wk0	Total Omega-6 Polyunsaturated Fatty Acids	Targeted_FA	0	Targeted RBC fatty-acid feature at baseline (week 0).
SFA_wk0	Total Saturated Fatty Acids	Targeted_FA	0	Targeted RBC fatty-acid feature at baseline (week 0).
Total_trans_wk0	Total Trans Fatty Acids	Targeted_FA	0	Targeted RBC fatty-acid feature at baseline (week 0).
TFA16_1n_9T_wk0	Trans-hexadecenoic Acid (16:1 n-9 trans)	Targeted_FA	0	Targeted RBC fatty-acid feature at baseline (week 0).
TFA18_2T_wk0	Trans-linoleic Acid Isomers (18:2 trans)	Targeted_FA	0	Targeted RBC fatty-acid feature at baseline (week 0).
TFA18_1n10_12T_wk0	Trans-octadecenoic Acid Isomers (18:1 n-10/n-12 trans)	Targeted_FA	0	Targeted RBC fatty-acid feature at baseline (week 0).
TFA16_1n_7T_wk0	Trans-palmitoleic Acid	Targeted_FA	0	Targeted RBC fatty-acid feature at baseline (week 0).
TFA18_1n_7T_wk0	Trans-vaccenic Acid	Targeted_FA	0	Targeted RBC fatty-acid feature at baseline (week 0).
MFA18_1n_7_wk0	Vaccenic Acid	Targeted_FA	0	Targeted RBC fatty-acid feature at baseline (week 0).
MUFA_wk0	monounsaturated fatty acids (RBC, baseline)	Targeted_FA	0	Targeted RBC fatty-acid feature at baseline (week 0).

Supplementary Table S5 - TRIPOD+AI Reporting Checklist

The 27-item TRIPOD+AI completed reporting checklist.

TRIPOD+AI 2024 Checklist — HAT Trial MASLD Predictive Sub-Analysis						
Reference: Collins GS, Moons KGM, Dhiman P, et al. TRIPOD+AI statement: updated guidance for reporting clinical prediction models that use regression or machine learning methods. <i>BMJ</i> 2024;385:e078378.						
Section	Item #	Topic	Requirement (TRIPOD+AI, Collins et al. 2024)	Status	Location in manuscript	Action required
Title	1	Title	Identify the study as a prediction-model study, including target population, outcome, and AI/ML use.	Complete	Title page	Title states machine-learning prediction of hepatic-fat response to MUFA-rich dietary intervention in MASLD and identifies secondary analysis of HAT randomized trial.
Abstract	2	Abstract	Summarize background, objectives, data source, participants, outcomes, predictors, sample size, model type, performance, calibration, and conclusions.	Complete with final consistency check	Abstract	Abstract reports HAT, n=790, MASLD classification AUROC, calibration ECE, HFF responder endpoints, Figure 7 AUROC, TRIPOD+AI, and need for external validation. Ensure endpoint wording matches Results: HFF_Responder vs ≥5 pp reduction-only.
Introduction	3a	Background/rationale	Explain clinical problem, why prediction is needed, and why AI/ML is appropriate.	Complete	Introduction paragraphs 1–4	Introduction describes MASLD heterogeneity, neutral parent trial average effects, precision nutrition rationale, and ML use for nonlinear/heterogeneous response patterns.
Introduction	3b	Objectives and intended use	State study objectives and intended model use/users.	Complete	Final Introduction paragraph	Objectives are listed as MASLD discrimination, HFF response prediction, and subgroup interaction testing; intended users include hepatology, primary care, and dietitian workflows.
Methods	4a	Source of data — design	Describe study design, data source, and dates.	Complete	Methods: Study design and participants	HAT is described as a multicenter randomized controlled trial; enrollment/follow-up dates are in Results Study population.
Methods	4b	Source of data — setting	Describe healthcare/research setting and source population.	Complete	Methods: Study design and participants	Multicenter US academic medical centers and abdominal-obesity trial population described.
Methods	5a	Participants — eligibility	Specify eligibility criteria, exclusions, participant flow, and analytic sample.	Complete	Methods: Study design and participants; Figure 1	Eligibility, exclusions, source participants, and final analytic cohort n=790 are described and visualized in Figure 1.
Methods	5b	Treatments/exposures	Describe interventions/exposures received, especially if randomized.	Complete	Methods: Study design and participants	Randomized 1:1 avocado-supplemented diet vs habitual diet for 26 weeks is reported.
Methods	6a	Outcome definition	Define each outcome being predicted and timing of assessment.	Complete	Methods: Predictive modeling: feature sets and outcomes	Baseline MASLD status, primary HFF_Responder endpoint, and secondary ≥5 percentage-point absolute HFF reduction endpoint are defined with n and positives.
Methods	6b	Outcome ascertainment	Describe outcome measurement method, timing, and blinding where relevant.	Complete	Methods: Imaging and Subgroup Analyses	HFF and VAT MRI-PDFF measurements at baseline and week 26 are described; quality control by readers blinded to randomization arm is stated.
Methods	7a	Predictors	Define candidate predictors, timing, and source.	Complete	Methods: Predictive modeling; Supplementary Table S4	Baseline demographics, anthropometrics, labs, lipidomic measures, fatty acids, and SDoH indicators are described; full codebook/missingness in Supplementary Table S4.
Methods	7b	Predictor measurement and timing	Describe predictor measurement relative to outcome and whether leakage was avoided.	Complete with caveat	Methods: Predictive modeling; Model development; Internal validation	Predictors are baseline variables and imputation/selection are fitted on training folds. Final text could be strengthened by adding: 'All predictors were measured at baseline before week-26 outcome ascertainment.'
Methods	8	Sample size	Explain sample size and number of events/non-events for prediction tasks.	Complete	Methods: Predictive modeling	Reports n=790, 261 HFF_Responder positives, 74 reduction-only positives, and EPV rationale.
Methods	9	Missing data	Describe missing-data exclusions, imputation, and limitations.	Complete	Methods: Study design and participants; Model development	Variables with >50% missingness excluded; retained variables median/mode imputed on training folds; lack of multiple imputation acknowledged.
Methods	10a	Continuous predictors	Describe transformations/scaling/categorization of continuous predictors.	Complete	Methods: Calibration; Supplementary Table S3	Training-fold preprocessing and hyperparameter specifications are reported; continuous clinical variables are handled within model pipelines and detailed in Supplementary Table S3.

Methods	10b	Categorical predictors	Describe handling/encoding of categorical predictors.	Complete	Methods: Predictive modeling; Supplementary Table S3/S4	Categorical SDoH and clinical variables are included; codebook and model preprocessing details are provided in Supplementary Tables S3–S4.
Methods	10c	Model development	Describe algorithms, feature selection, tuning, class imbalance handling, and final fitting.	Complete	Methods: Model development and explainability; Internal validation; Calibration	Bootstrap RF feature selection, logistic regression, random forest, XGBoost, RandomizedSearchCV, cross-validation, sample weights, and no oversampling are described.
Methods	10d	Model specification / hyperparameters	Report model specification, hyperparameters, regularization, and software.	Complete	Methods: Calibration; Supplementary Table S3; Code Availability	Randomized search and software versions are in Methods; final hyperparameters and regularization details in Supplementary Table S3.
Methods	10e	Performance measures	Define discrimination, calibration, threshold metrics, and clinical utility measures.	Complete	Methods: Model development; Calibration; Discussion DCA	AUROC, accuracy, precision, recall, F1-score, specificity, Youden threshold, ECE, Brier score, reliability diagrams, and decision-curve analysis are described.
Methods	11	Risk groups / thresholds	Describe how predictions were converted to groups or decisions.	Complete	Methods: Model development and explainability; Results ML section	Predicted probabilities were dichotomized using Youden-optimal threshold; LR+/LR- and DCA threshold interpretation reported in Discussion/Supplementary Table S3
Methods	12	Development vs validation	Describe validation design and any model updating if applicable.	Complete	Methods: Internal validation strategy	Single stratified 70/30 train/test split, internal cross-validation for tuning, test-set bootstrap, and resample-then-split sensitivity are described. No external validation; limitation acknowledged.
AI extension	13a	Training data transparency	Report train/test split, seed, stratification, leakage prevention, and resampling.	Complete	Methods: Internal validation strategy	70/30 split, seed=42, class stratification, training-fold tuning, bootstrap test resampling, and internal-validation interpretation are stated.
AI extension	13b	Software/environment	Report software, packages, versions, and computing environment.	Complete	Methods: Calibration; Code Availability	Python 3.11, scikit-learn v1.3, xgboost v2.0, shap v0.42, environment file, and repository are described.
AI extension	14	Explainability/interpretability	Describe interpretability approach and clarify whether used for interpretation or selection.	Complete	Methods: Calibration/explainability; Figures 5–7	SHAP and permutation importance are used for feature attribution/interpretation; bootstrap RF was used for feature selection.
AI extension	15	Fairness/subgroup performance	Report or discuss performance and limitations across relevant subgroups.	Complete with caveat	Results subgroup analyses; Clinical interpretability; Discussion limitations; Supplementary Figures	Sex/glycemic subgroup effects and subgroup SHAP summaries are presented; limitations note small diabetes and race/ethnicity subgroups. Formal fairness metrics are not performed.
AI extension	16	Reproducibility — code/data/model	State access to code, data, model artifacts, and restrictions.	Complete with final release check	Data Availability; Code Availability; Supplementary Table S3/S4	Code repository and planned public release/review-token access are stated. Ensure repository is accessible to editors/reviewers before submission.
Results	17	Participant flow	Report participant flow and exclusions.	Complete	Figure 1; Results Study population	Figure 1 gives source cohort, exclusions, analytic cohort, and randomized arms.
Results	18	Sample characteristics	Report baseline participant characteristics and outcome distribution.	Complete	Results: Study population; Table 1; Supplementary Figures S1–S2	Baseline characteristics by MASLD status are in Table 1; baseline HFF range/mean/median and distributions are reported.
Results	19a	Model performance — discrimination	Report discrimination with uncertainty for each model/outcome.	Complete	Results ML section; Figures 5–7; Supplementary Figures S4–S6; Supplementary Tables S1–S2	MASLD AUROC, HFF_Responder AUROC, and reduction-only AUROC are reported with bootstrap summaries in main/supplement.
Results	19b	Model performance — calibration	Report calibration with prespecified thresholds and calibration plots.	Complete	Results ML section; Supplementary Figure S9; Supplementary Table S3	ECE and Brier score are reported; MASLD classifier ECE did not meet target; HFF_Responder ECE met target.
Results	19c	Clinical utility	Report clinical utility analyses when relevant.	Complete	Discussion implementation paragraph; Figure 8	Decision-curve analysis is reported in Figure 8 and discussed conservatively as internal/hypothesis-generating.
Results	20	Model presentation	Present final model features/structure or provide access.	Complete	Figures 5–7; Supplementary Table S3; Code Availability	Final model predictors/importance are in Figures 5–7; hyperparameters and regularization in Supplementary Table S3; model artifacts described in repository.
Discussion	21	Limitations	Discuss limitations including bias, overfitting, calibration, sample size, and generalizability.	Complete	Discussion limitations paragraph	Limitations include single cohort, internal validation only, baseline HFF/MASLD outcome alignment, FRS overlap, small subgroups, calibration failure, and need for external validation.

Discussion	21	Limitations	Discuss limitations including bias, overfitting, calibration, sample size, and generalizability.	Complete	Discussion limitations paragraph	Limitations include single cohort, internal validation only, baseline HFF/MASLD outcome alignment, FRS overlap, small subgroups, calibration failure, and need for external validation.
Discussion	22	Interpretation	Interpret results in light of objectives, limitations, and prior evidence.	Complete	Discussion	Discussion links neutral parent trial average effects, subgroup heterogeneity, and ML interpretability to precision-nutrition hypothesis.
Discussion	23	Implications / implementation	Discuss intended use, clinical actionability, thresholds, and deployment caveats.	Complete	Discussion implementation paragraph	Two-stage diagnostic-to-therapeutic workflow, LR+/LR-, DCA, recalibration, and external validation requirements are described.
Other	24	Funding and funder role	Report funding sources and funder role.	Complete with caveat	Acknowledgements and Funding	Funding sources are reported. Add a funder-role sentence if not already present: 'The funders had no role in the present secondary analysis, model development, interpretation, manuscript preparation, or decision to submit.'
Other	25	Registration	Provide study registration.	Complete	Methods; Ethics	Parent HAT trial registration NCT03528031 is reported.
Other	26	Protocol/statistical analysis plan	State where protocol and analysis plan are available.	Complete	Methods; Supplementary Methods; Code Availability	Parent trial protocol cited [9,10]; secondary-analysis pipeline and code repository are described; TRIPOD+AI checklist provided as Supplementary Table S5.
Other	27	Data/code sharing	Describe data, code, trained models, restrictions, and access process.	Complete with final release check	Data Availability; Code Availability	De-identified data access by request/data-use agreement; code and model artifacts to be public at publication with review-token access for peer review.