FIG. 1

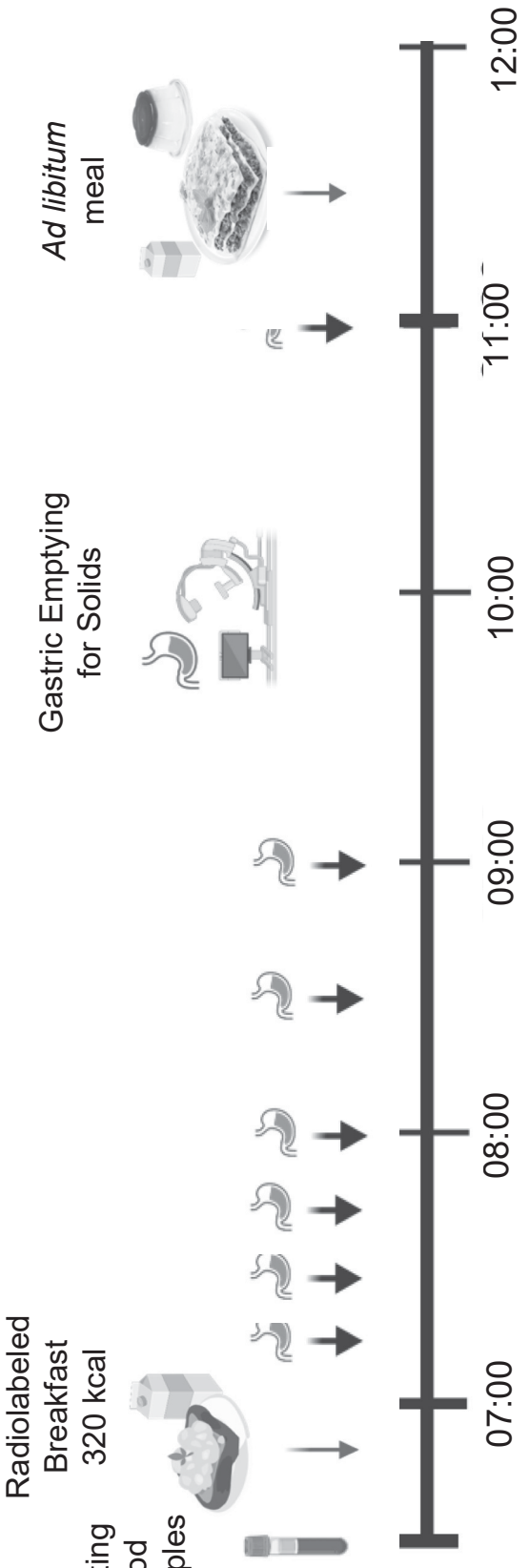

Fasting Blood Samples
Radiolabeled Breakfast 320 kcal
Gastric Emptying for Solids
Ad libitum meal
07:00
08:00
09:00
10:00
11:00
12:00

FIG. 2A

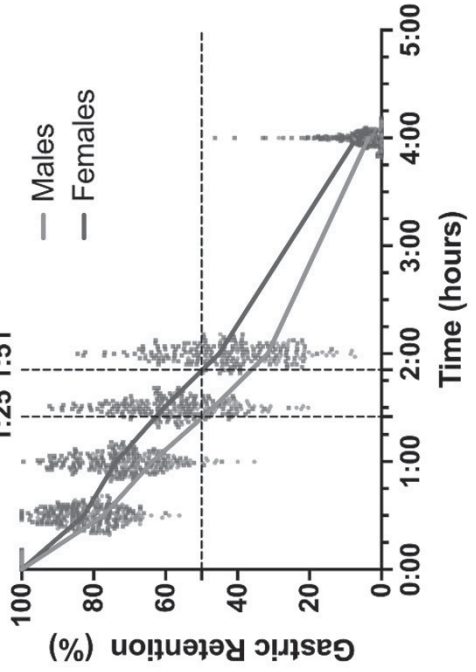


FIG. 2B

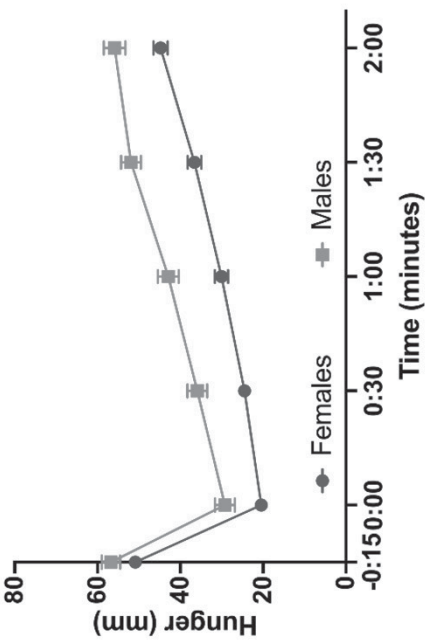


FIG. 2C

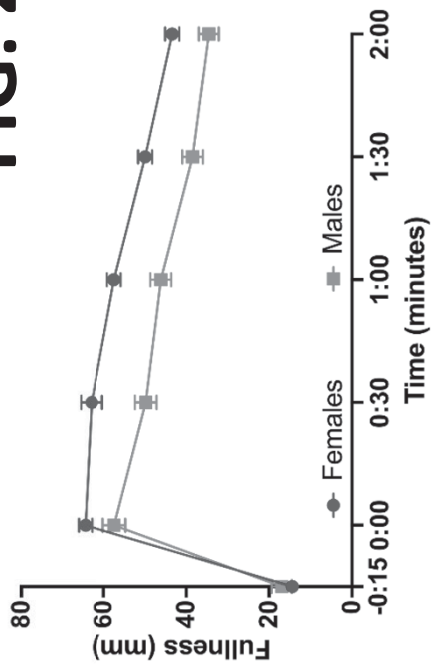


FIG. 2D

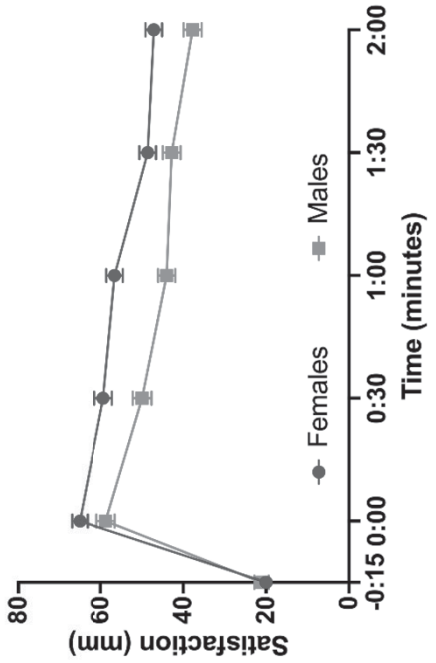


FIG. 2E

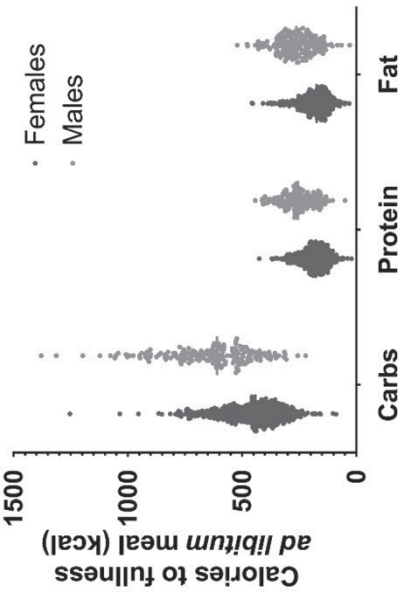


FIG. 2F

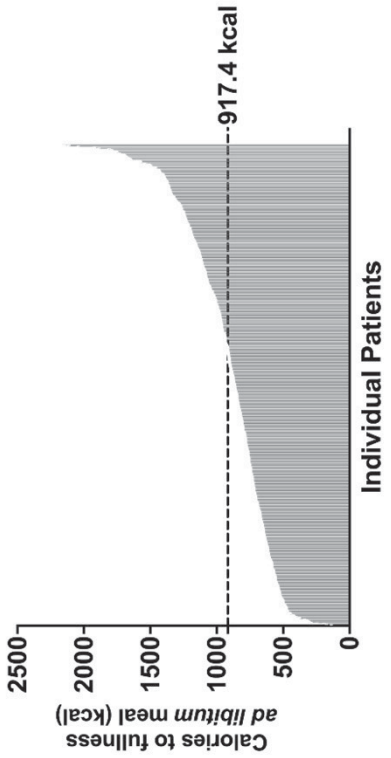


FIG. 2G

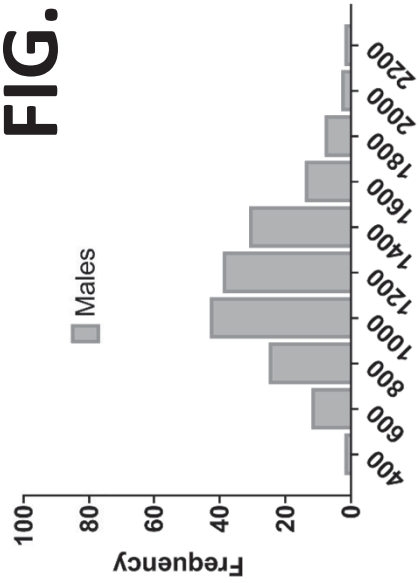


FIG. 2H

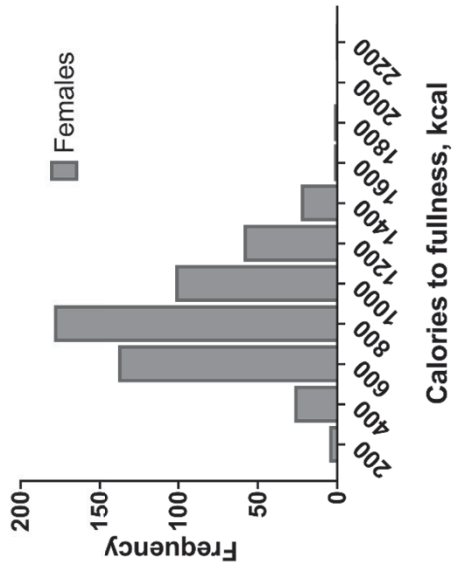


FIG. 3

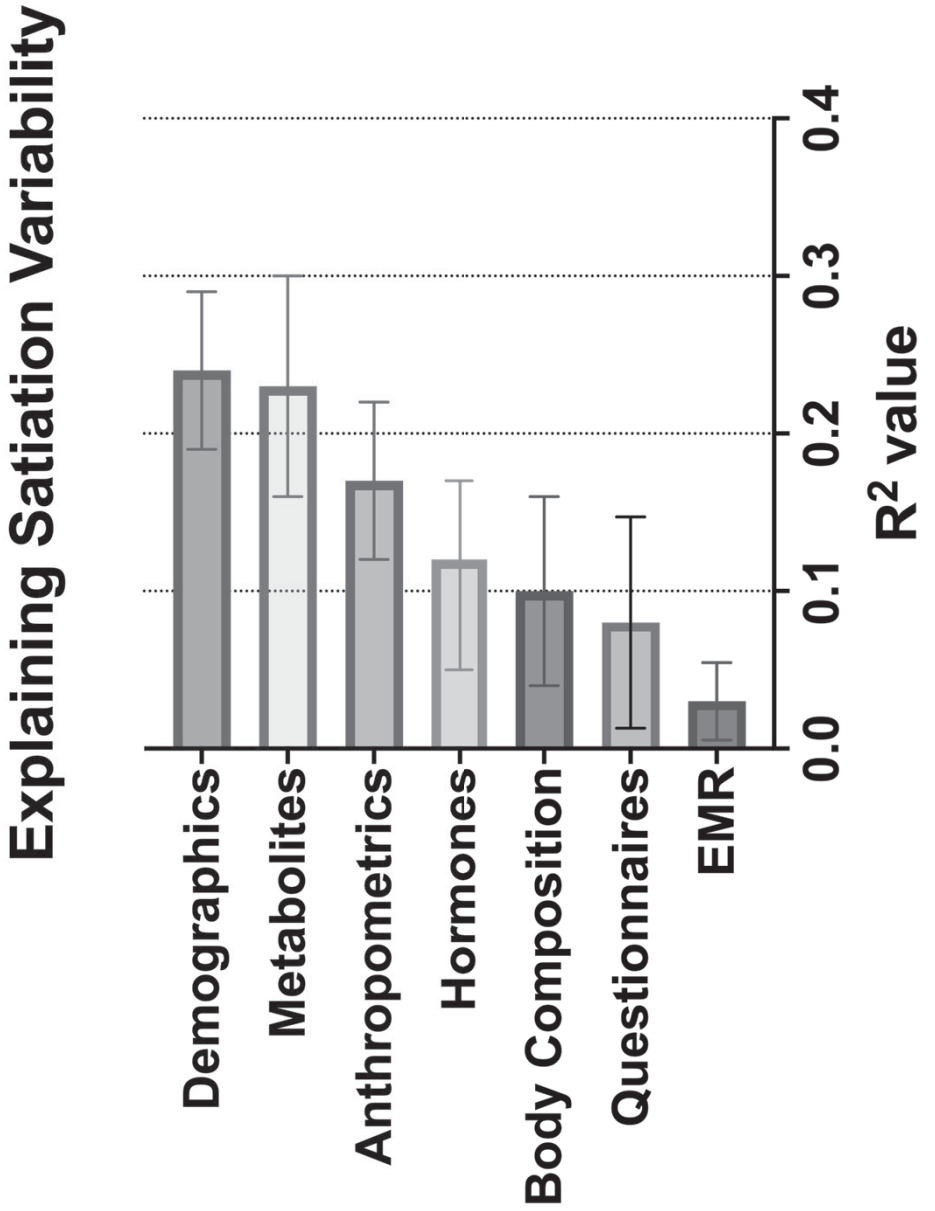

Explaining Satiation Variability
Demographics
Metabolites
Anthropometrics
Hormones
Body Composition
Questionnaires
EMR
0.0
0.1
0.2
0.3
0.4
R2 value

FIG. 4A

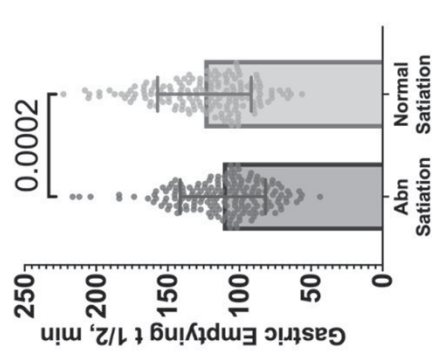


FIG. 4B

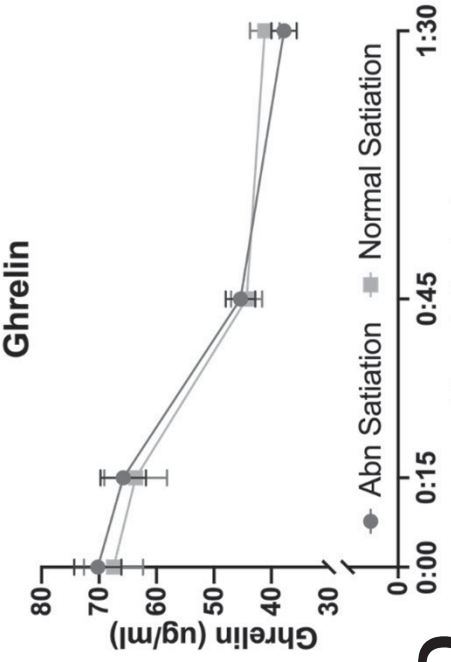


FIG. 4C

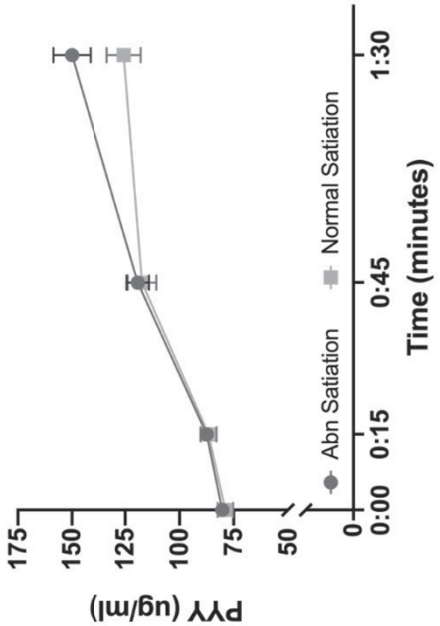


FIG. 4D

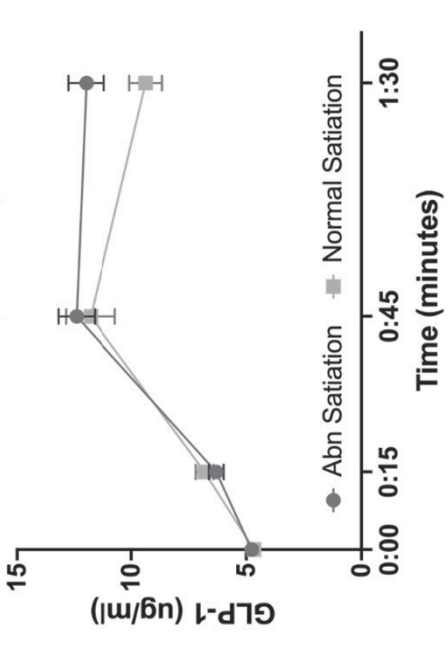


FIG. 4E

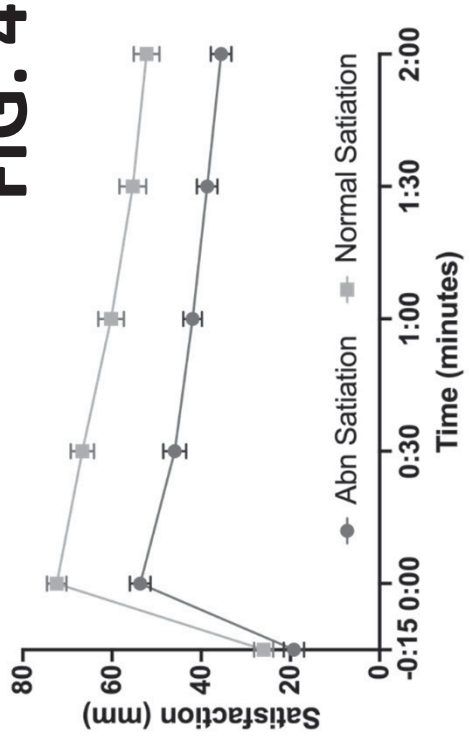


FIG. 4F

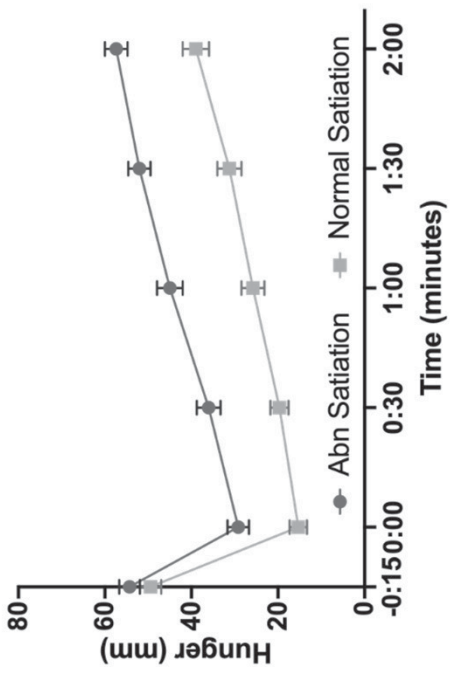


FIG. 4G

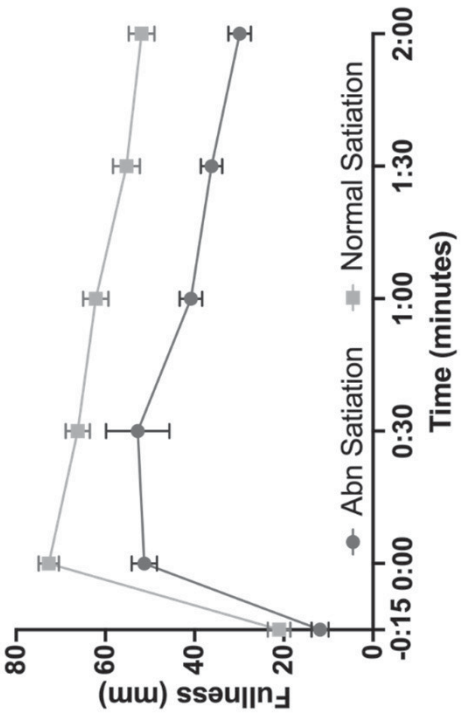


FIG. 4H

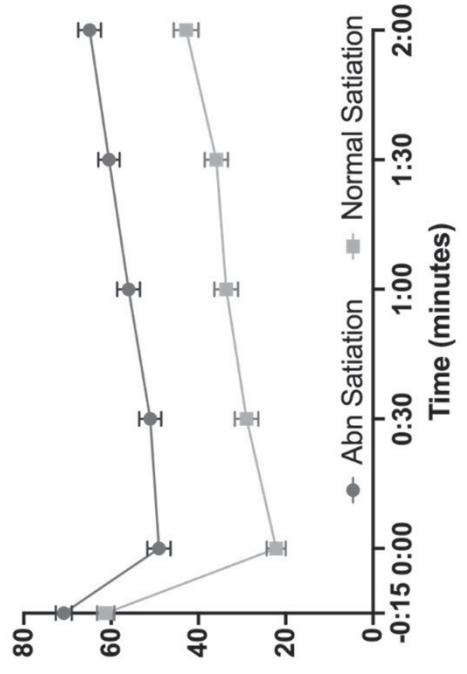
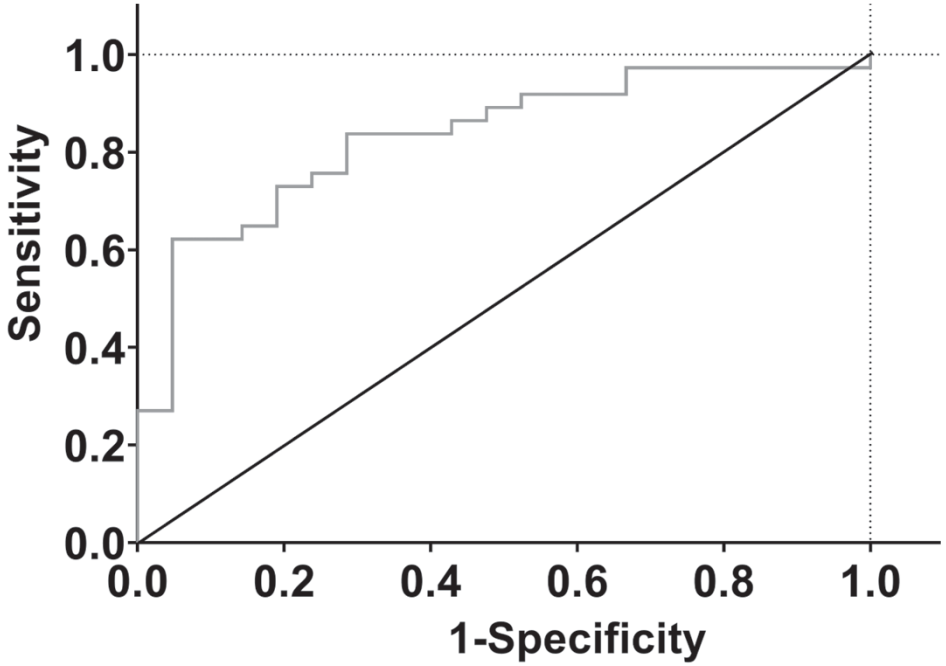


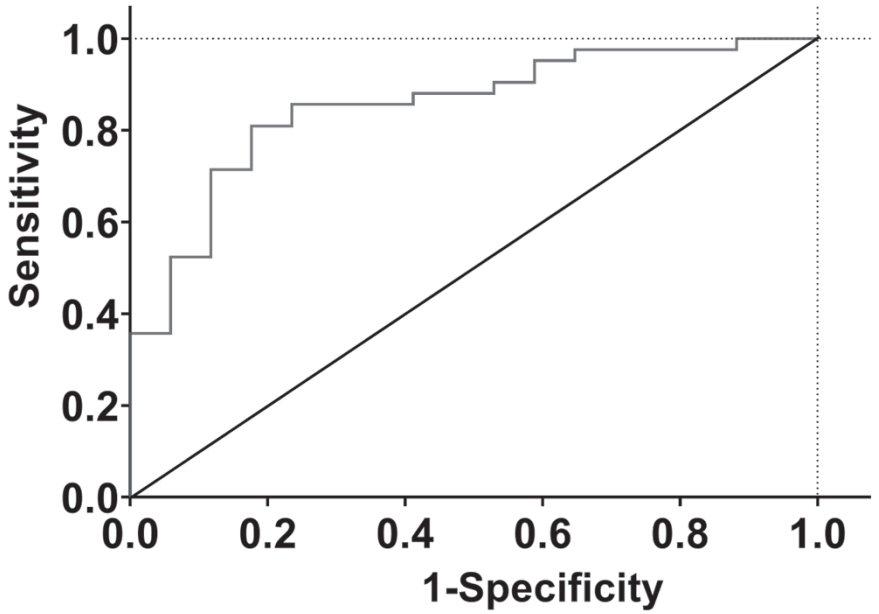
FIG. 5A



	Value
AUC	0.91
Sensitivity	0.92
Specificity	0.71
Accuracy	0.85

PPV	0.86
NPV	0.83
NND	1.57
NNP	1.45

FIG. 5B



	Value
AUC	0.85
Sensitivity	0.71
Specificity	0.82
Accuracy	0.70

PPV	0.91
NPV	0.54
NND	1.86
NNP	2.23

FIG. 6A

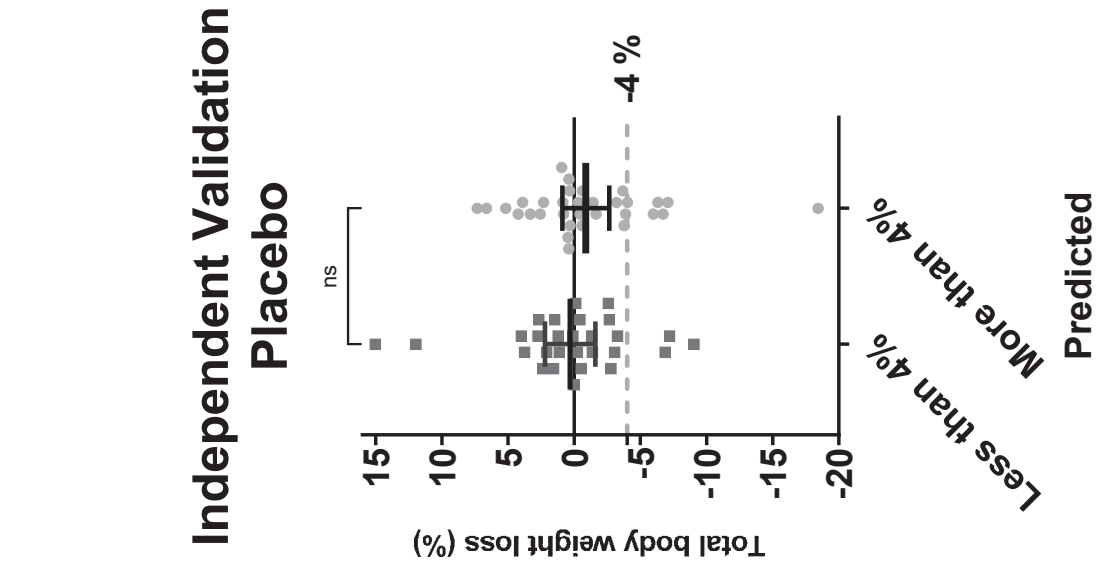

Independent Validation
Placebo
Total body weight loss (%)
15
10
5
0
-5
-10
-15
-20
ns
-4 %
Less than 4%
More than 4%
Predicted

FIG. 6B

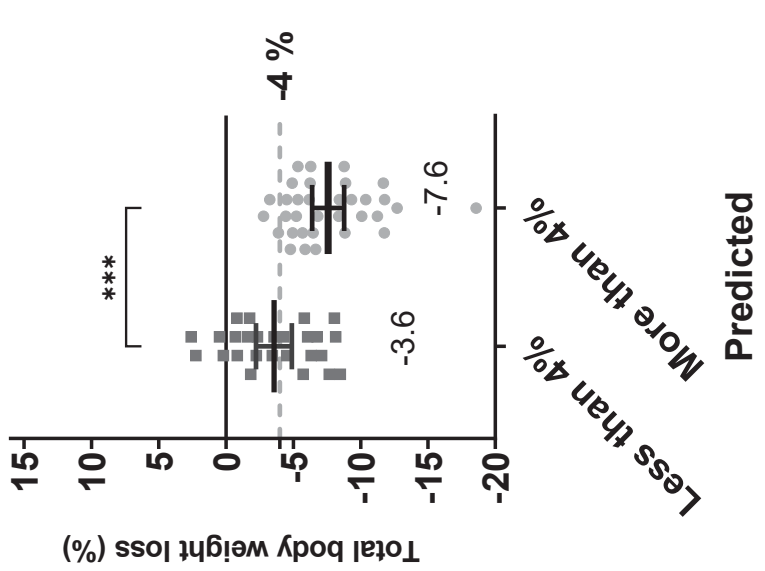

Independent Validation
Liraglutide
Total body weight loss (%)
15
10
5
0
-5
-10
-15
-20
***
-4 %
-3.6
-7.6
Less than 4%
More than 4%
Predicted

FIG. 7

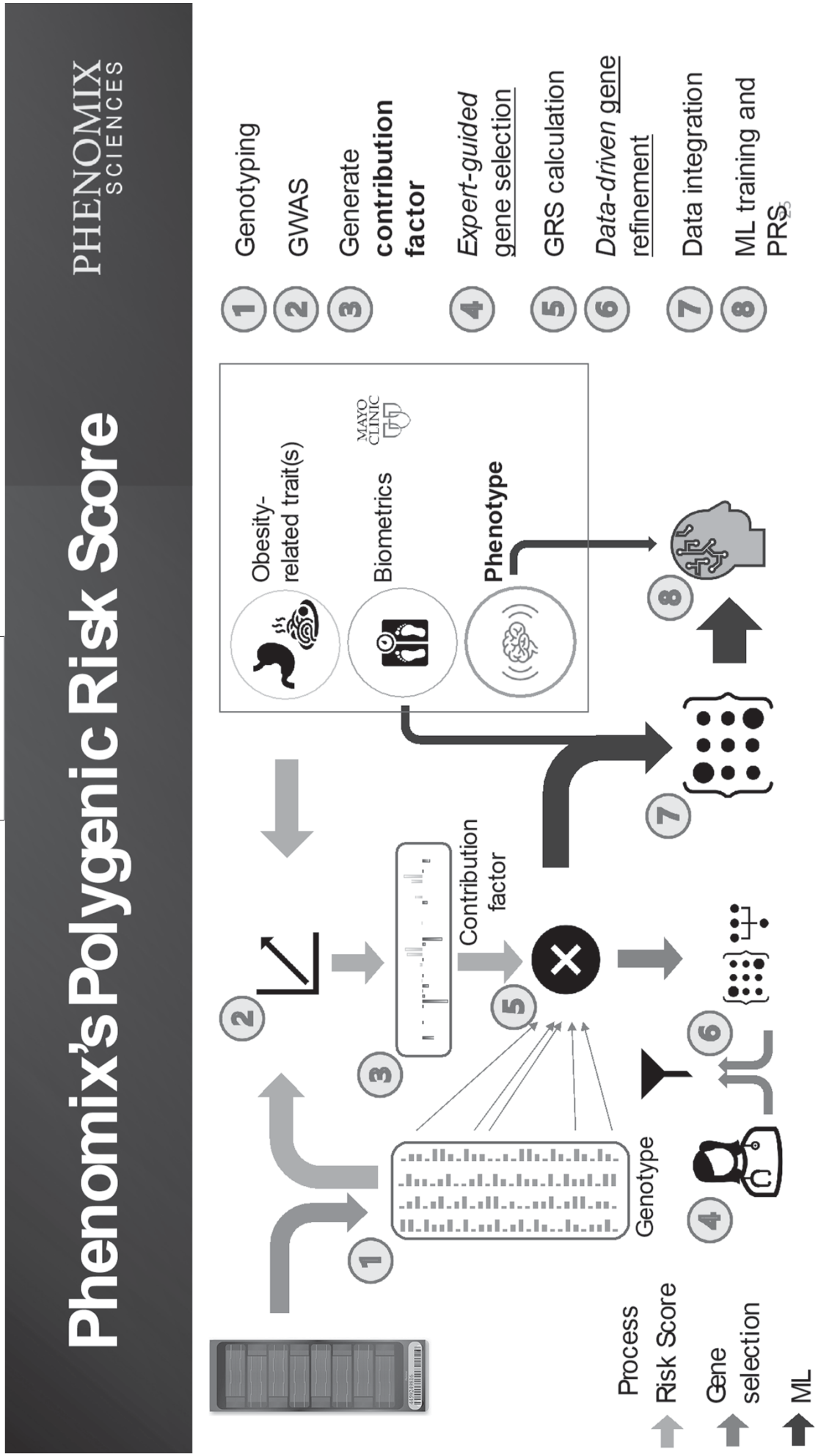
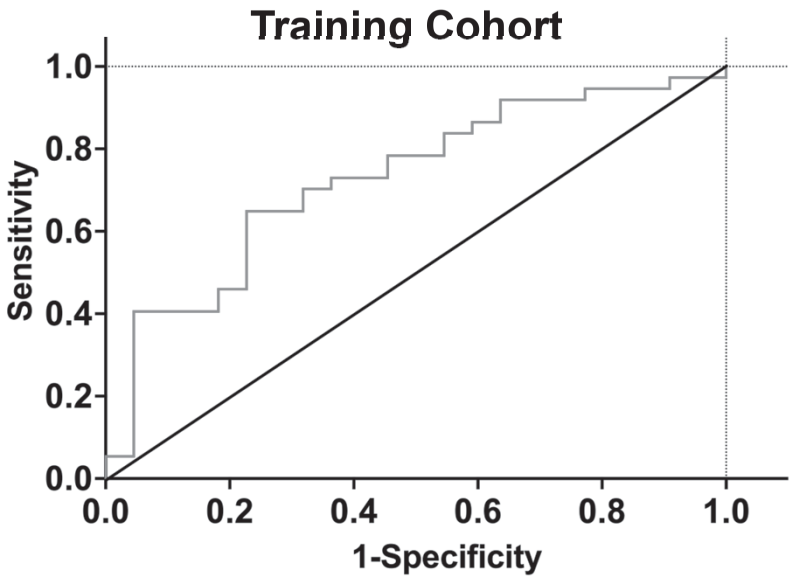

Phenomix's Polygenic Risk Score
PHENOMIX SCIENCES
1 Genotyping
2 GWAS
3 Generate contribution factor
4 Expert-guided gene selection
5 GRS calculation
6 Data-driven gene refinement
7 Data integration
8 ML training and PRS
Obesity-related trait(s)
Biometrics
MAYO CLINIC
Phenotype
Contribution factor
Genotype
Process
Risk Score
Gene selection
ML

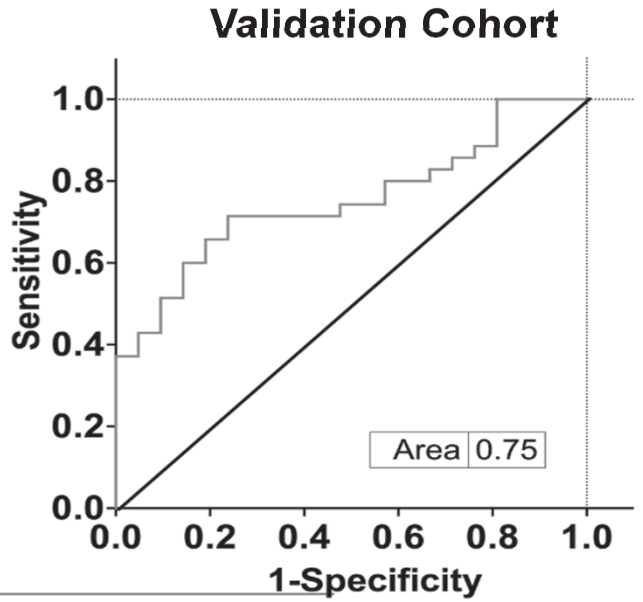
FIG. 8A



	Value
AUC	0.82
Sensitivity	0.79
Specificity	0.67
Accuracy	0.75

PPV	0.85
NPV	0.57
NND	2.21
NNP	2.39

FIG. 8B



	Value
AUC	0.75
Sensitivity	0.89
Specificity	0.67
Accuracy	0.69

PPV	0.26
NPV	0.37
NND	3.91
NNP	2.71

FIG. 8C

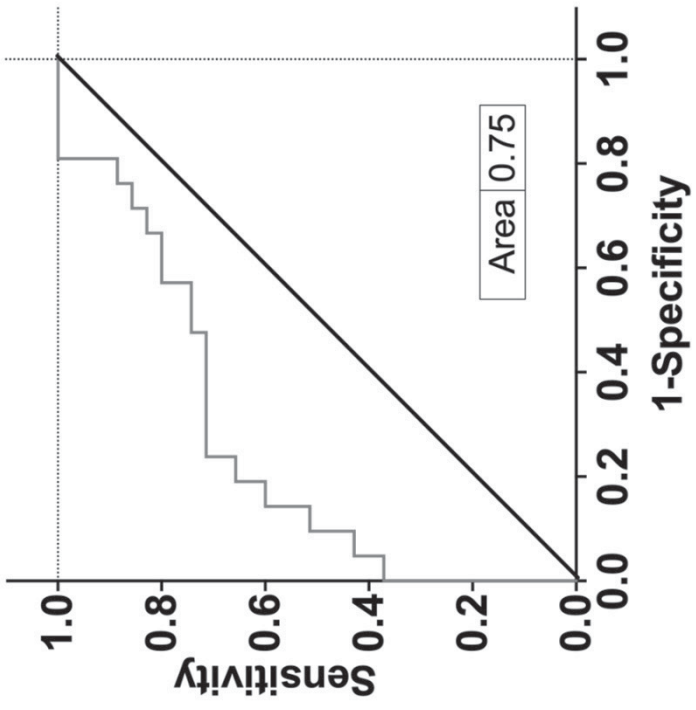

Validation Cohort
Responder to Liraglutide
Sensitivity
1-Specificity
0.0
0.2
0.4
0.6
0.8
1.0
Area 0.75

FIG. 8D

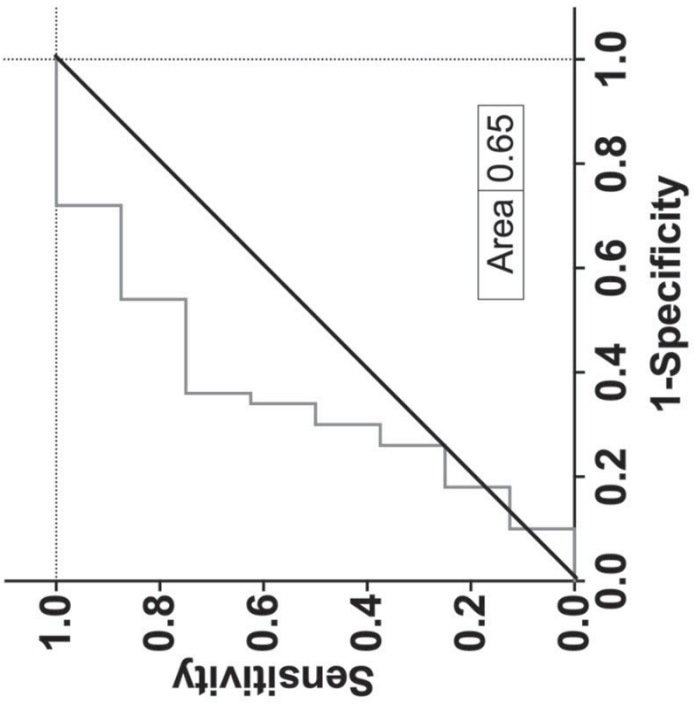

Training Cohort
Responder to Placebo
Sensitivity
1-Specificity
0.0
0.2
0.4
0.6
0.8
1.0
Area 0.65

FIG. 9A

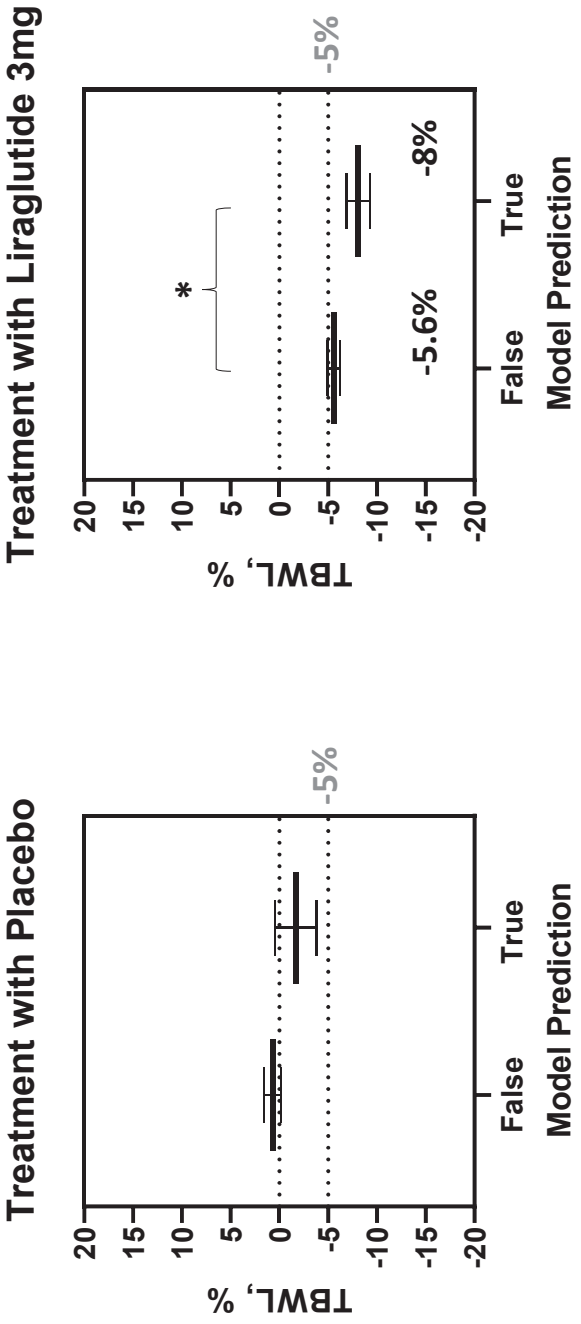

Treatment with Placebo
TBWL, %
20
15
10
5
0
-5
-10
-15
-20
-5%
False
True
Model Prediction

FIG. 9B

Treatment with Liraglutide 3mg
TBWL, %
20
15
10
5
0
-5
-10
-15
-20
-5%
*
-5.6%
-8%
False
True
Model Prediction

FIG. 10A

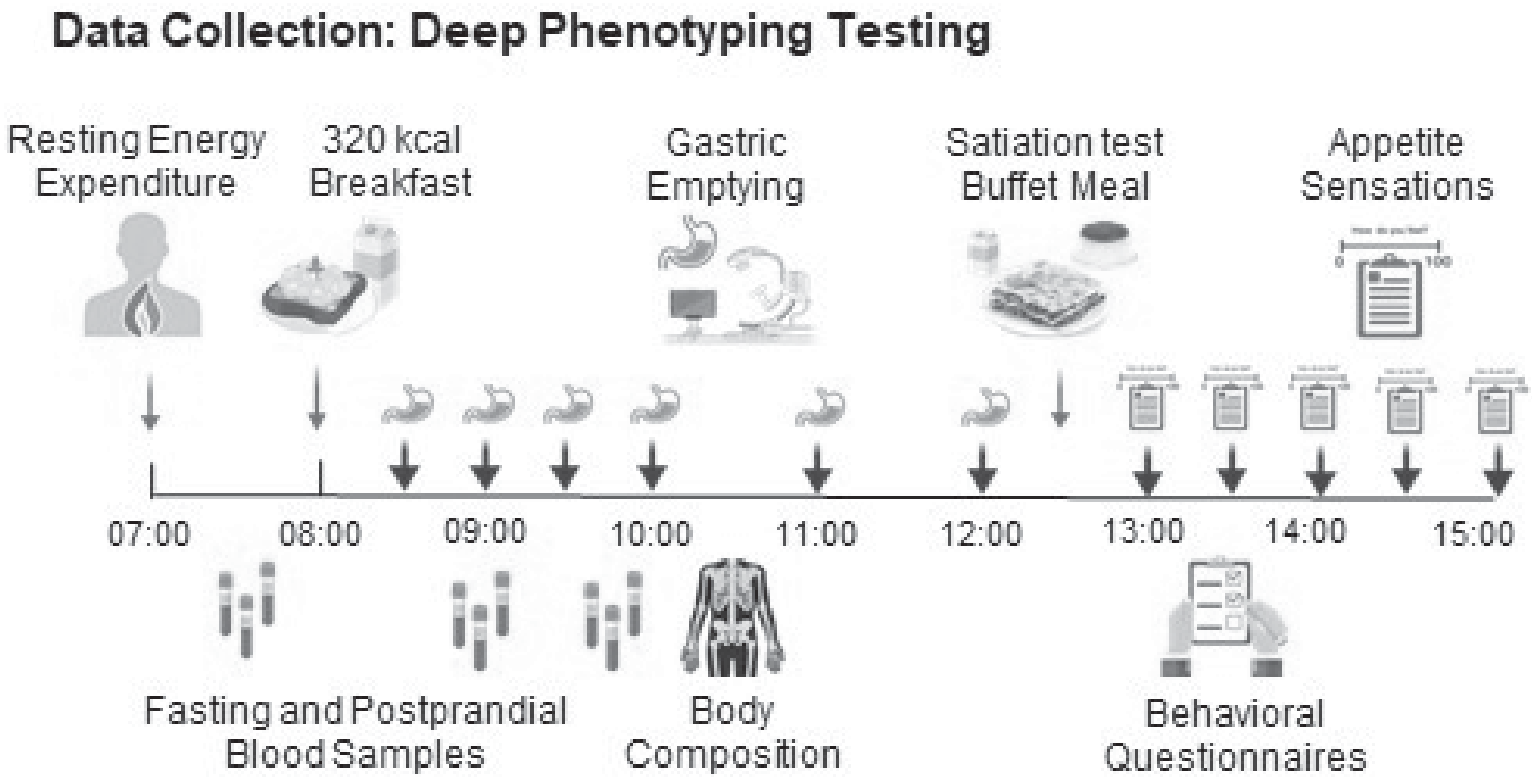
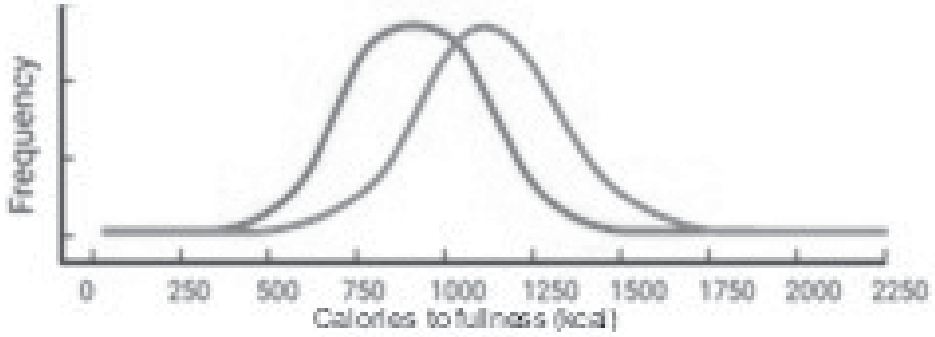

Data Collection: Deep Phenotyping Testing
Resting Energy Expenditure
320 kcal Breakfast
Gastric Emptying
Satiation test Buffet Meal
Appetite Sensations
07:00
08:00
09:00
10:00
11:00
12:00
13:00
14:00
15:00
Fasting and Postprandial Blood Samples
Body Composition
Behavioral Questionnaires

FIG. 10B

Feature extraction: Characterization of Satiation

Measurement of satiation by gender



Genotyping

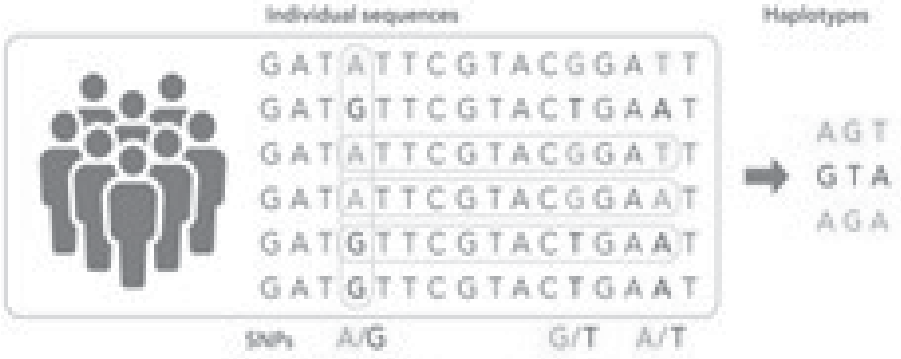


FIG. 10C

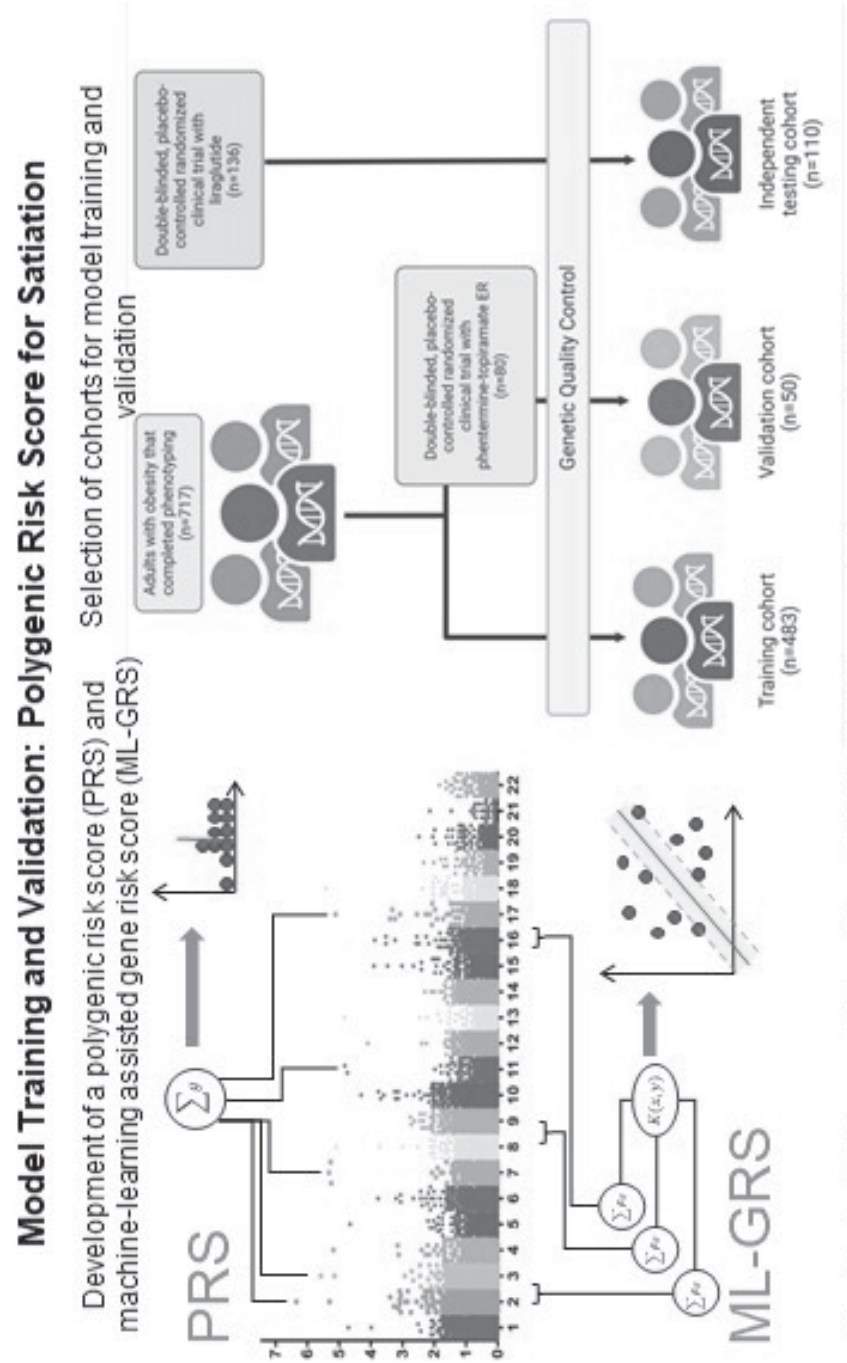

Model Training and Validation: Polygenic Risk Score for Satiation
Development of a polygenic risk score (PRS) and machine-learning assisted gene risk score (ML-GRS)
PRS
ML-GRS
Selection of cohorts for model training and validation
Adults with obesity that completed phenotyping (n=717)
Double-blinded, placebo-controlled randomized clinical trial with liraglutide (n=136)
Double-blinded, placebo-controlled randomized clinical trial with phentermine-topiramate ER (n=80)
Genetic Quality Control
Training cohort (n=483)
Validation cohort (n=50)
Independent testing cohort (n=110)

FIG. 10D

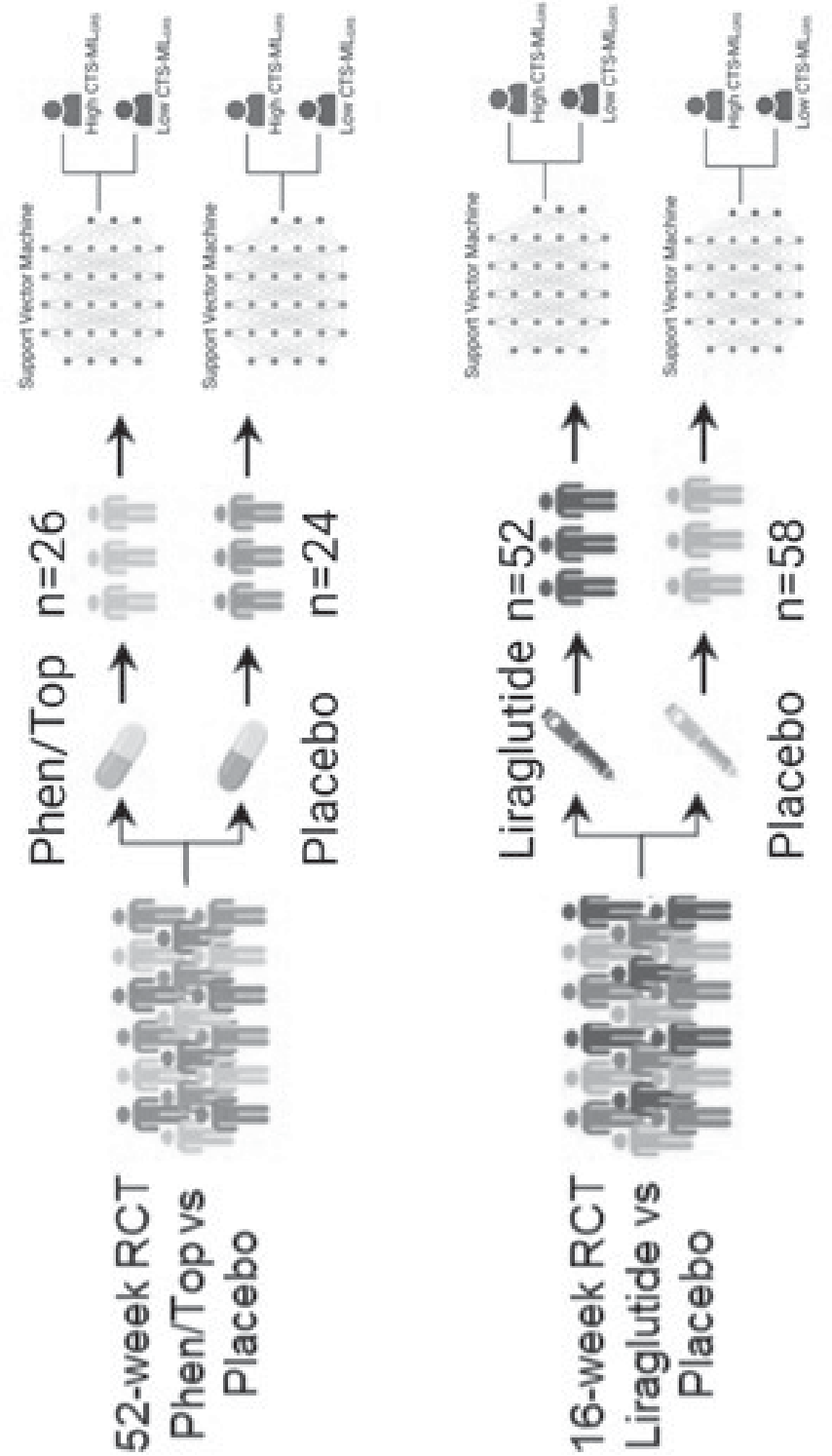

Model Extrapolation: Predict Weight Loss Outcomes to AOM
52-week RCT
Phen/Top vs
Placebo
Phen/Top n=26
Placebo n=24
Support Vector Machine
High CTS-MLoss
Low CTS-MLoss
16-week RCT
Liraglutide vs
Placebo
Liraglutide n=52
Placebo n=58

FIG. 11A

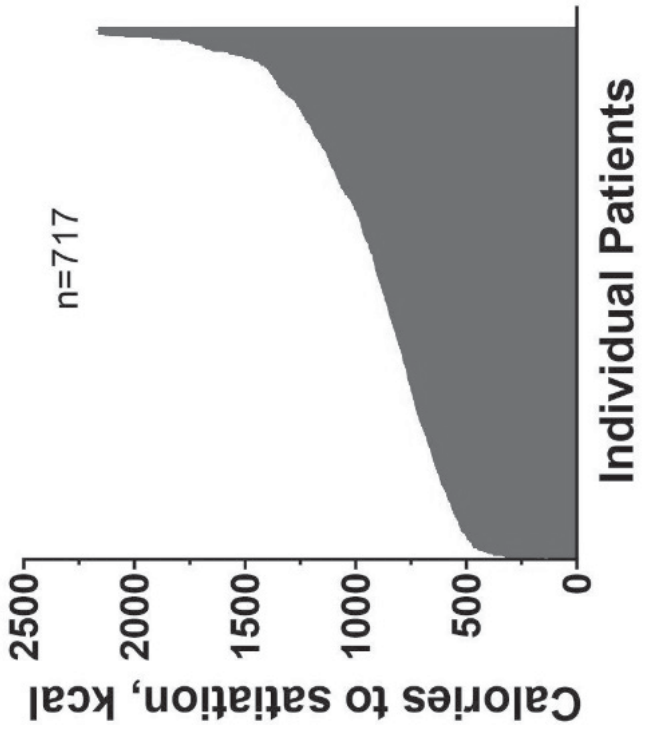


FIG. 11B

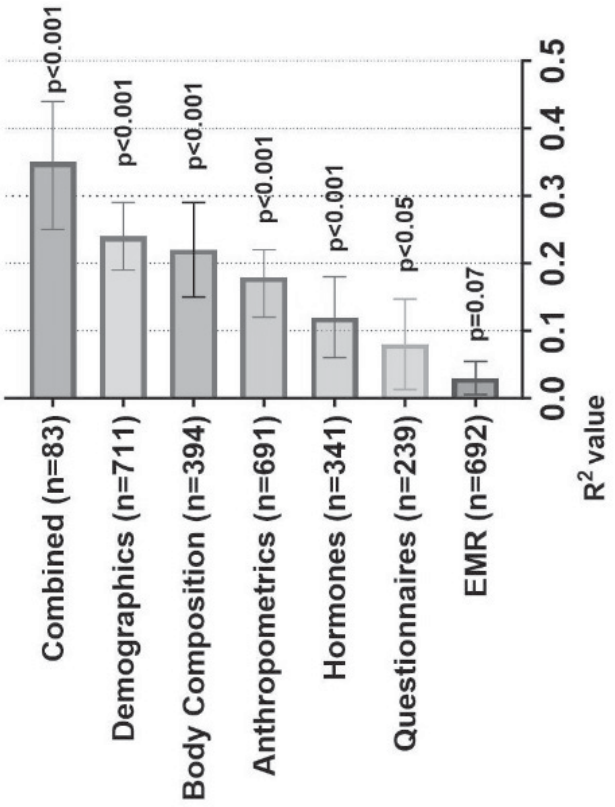


FIG. 11C

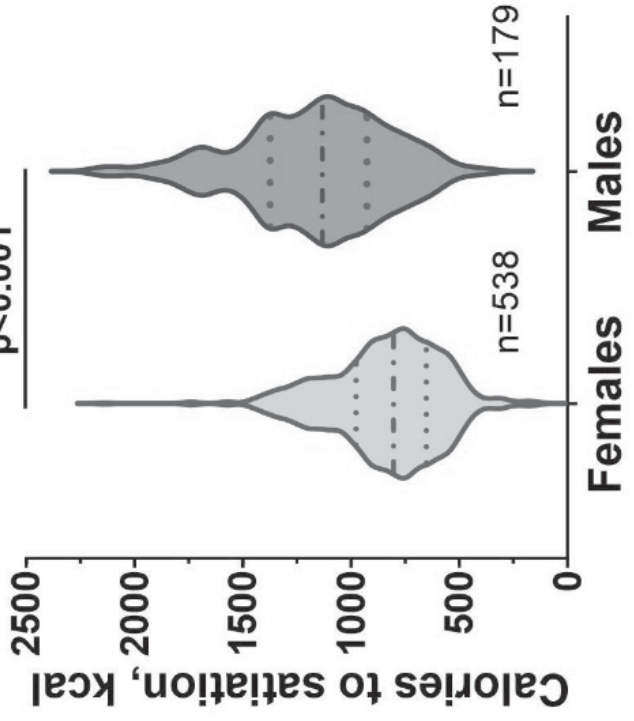


FIG. 11D

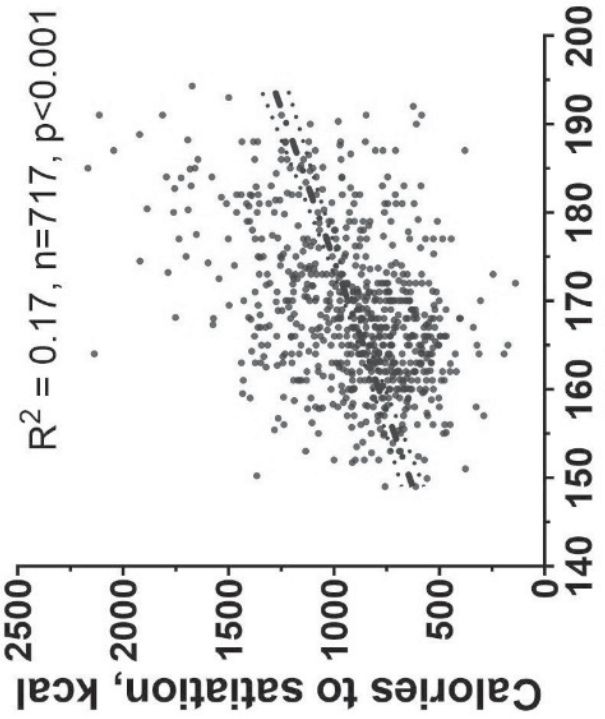


FIG. 11E

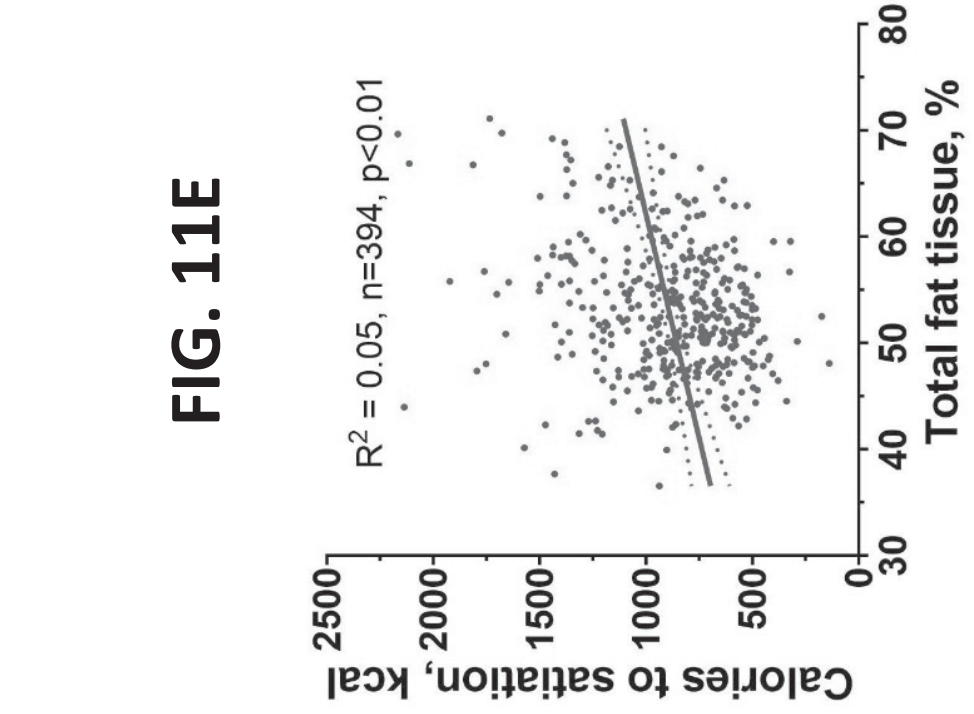


FIG. 11F

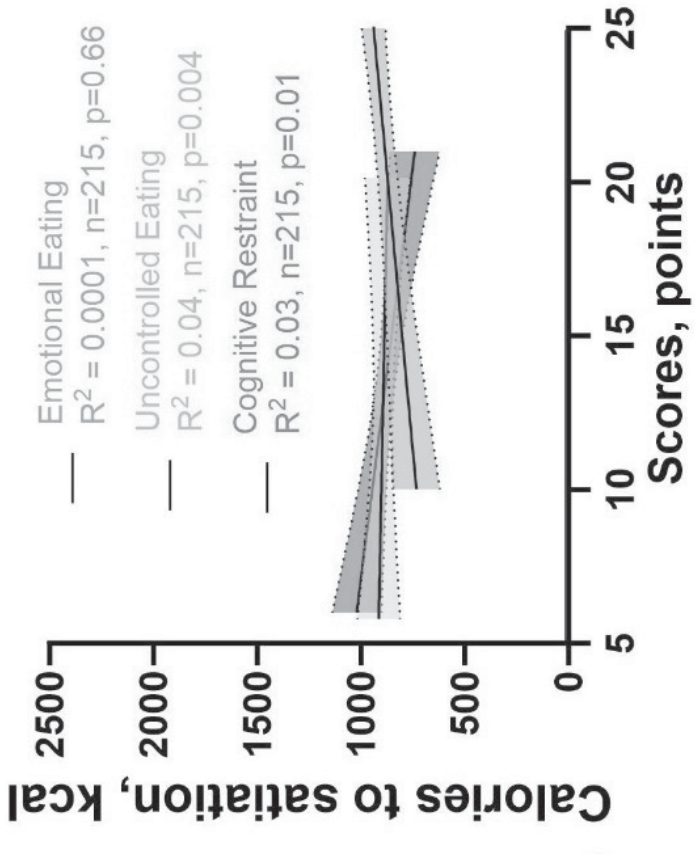


FIG. 12A

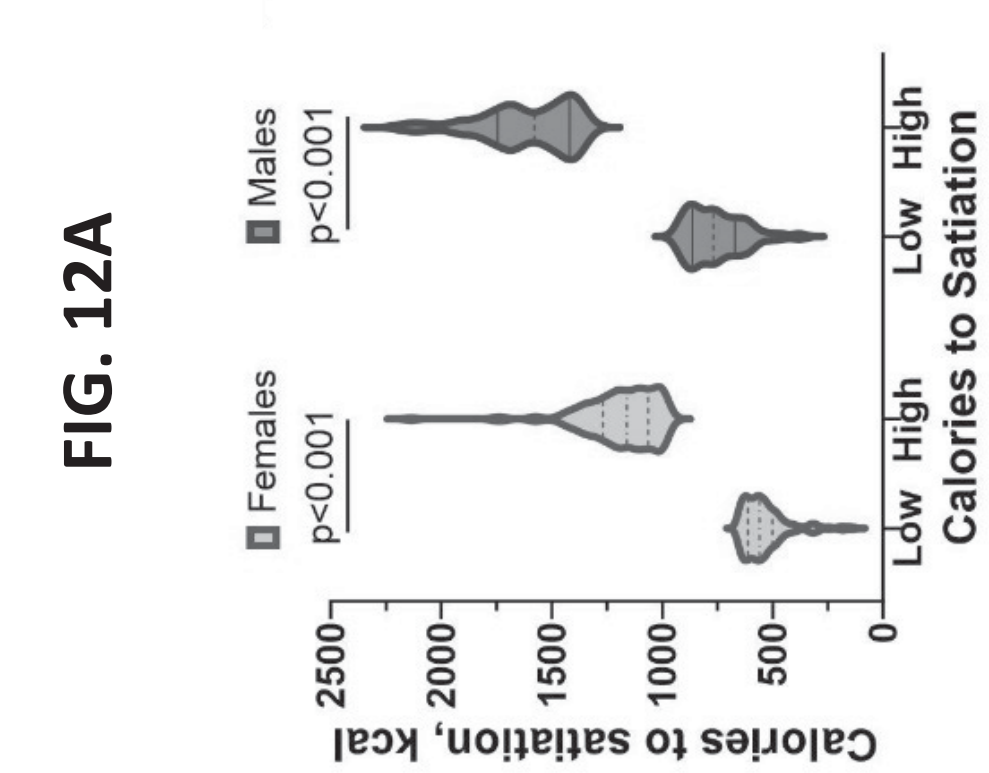


FIG. 12B

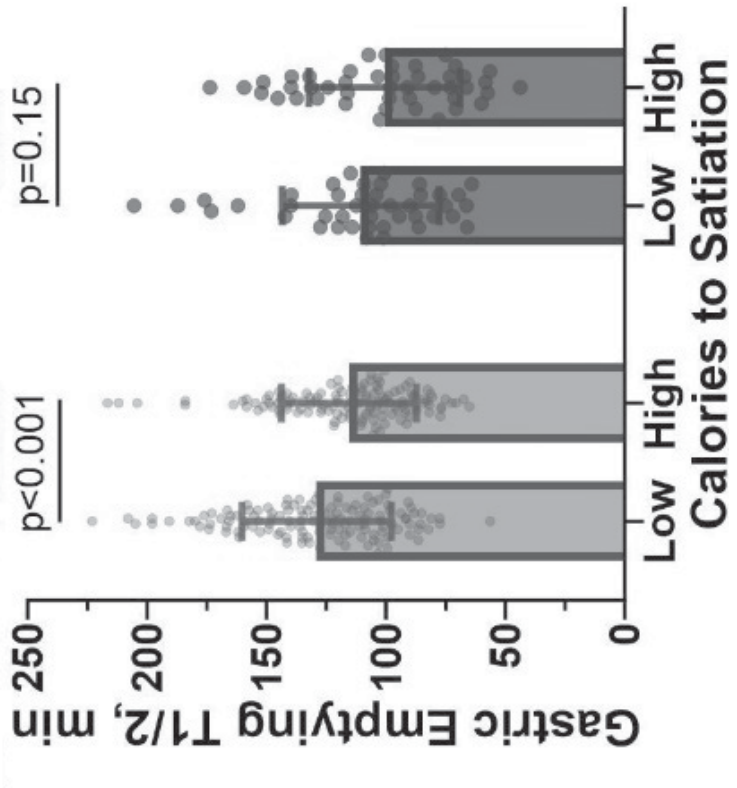


FIG. 12C

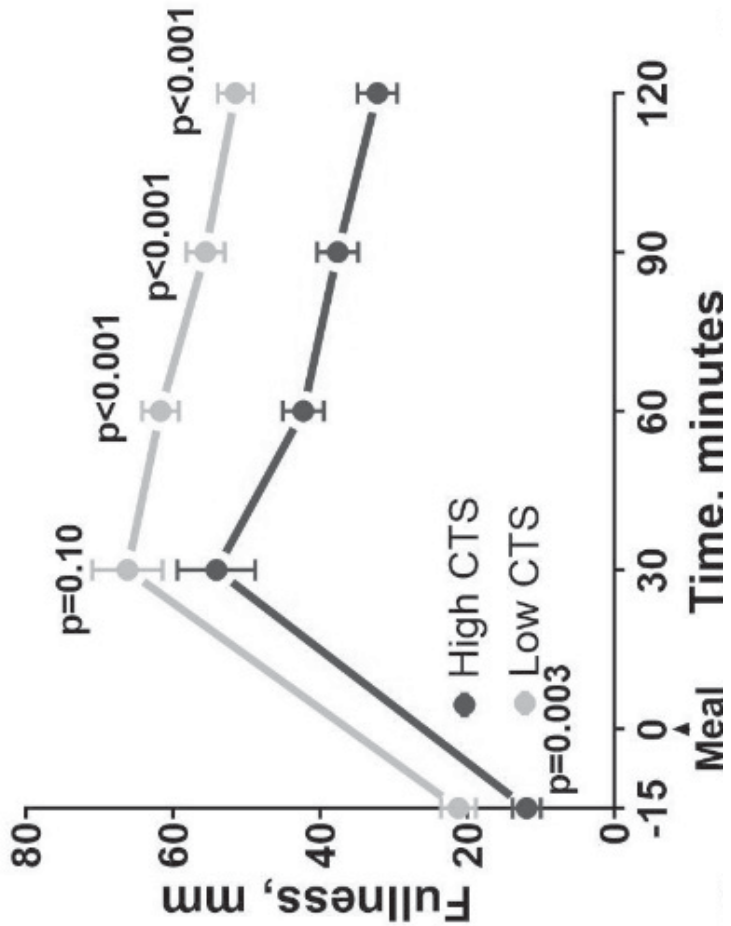


FIG. 12D

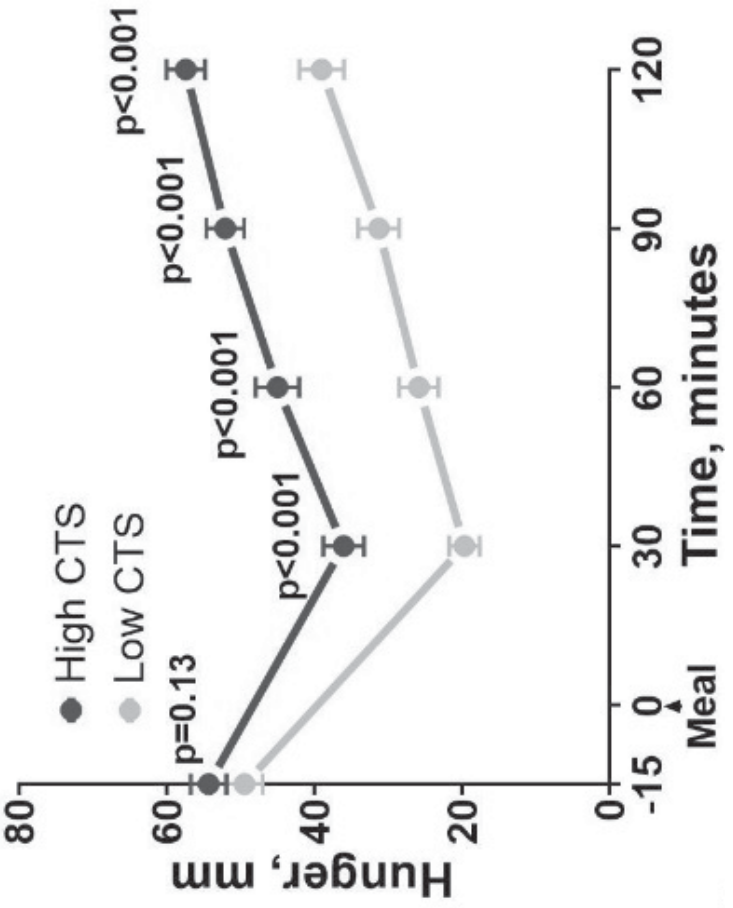


FIG. 12E

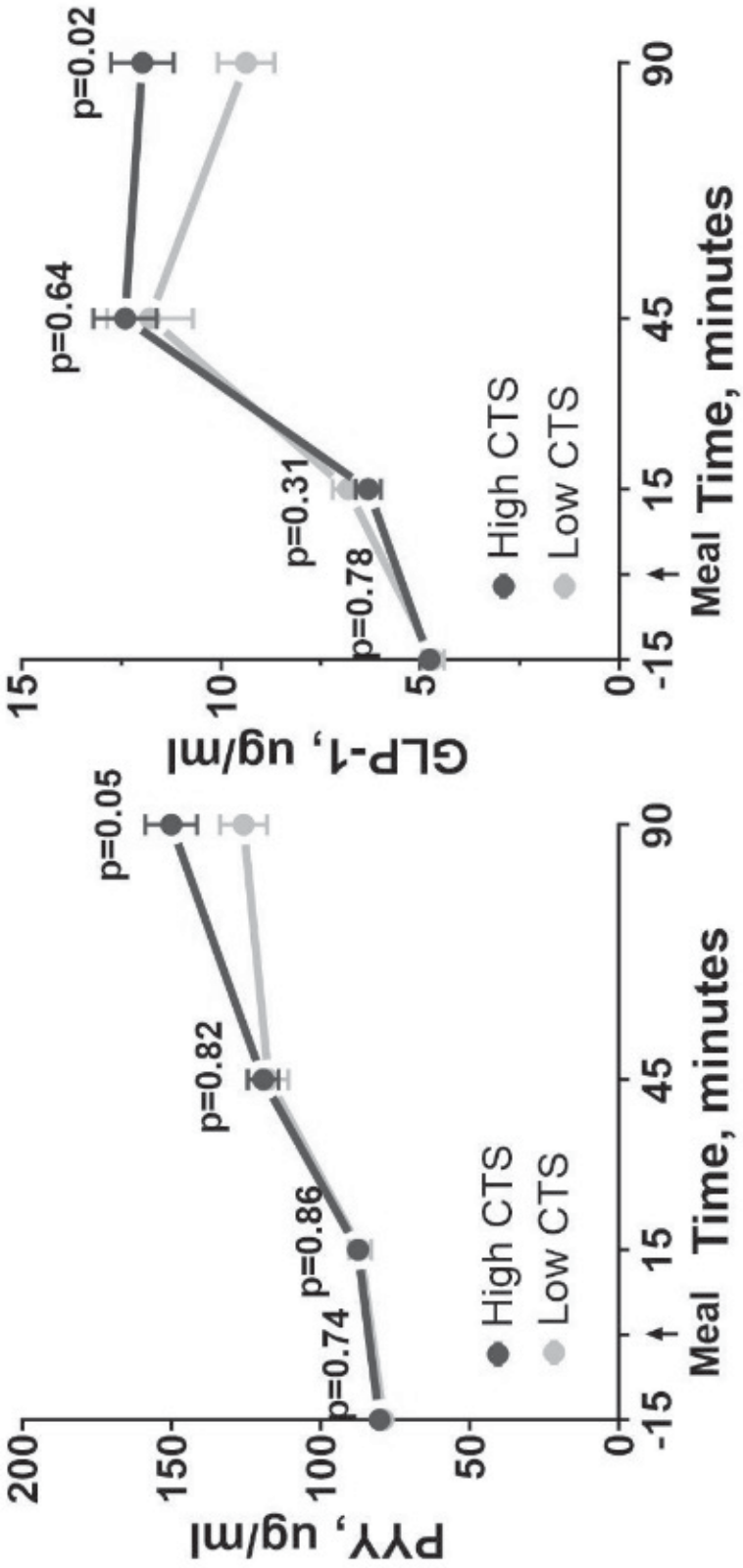


FIG. 12F

FIG. 12G

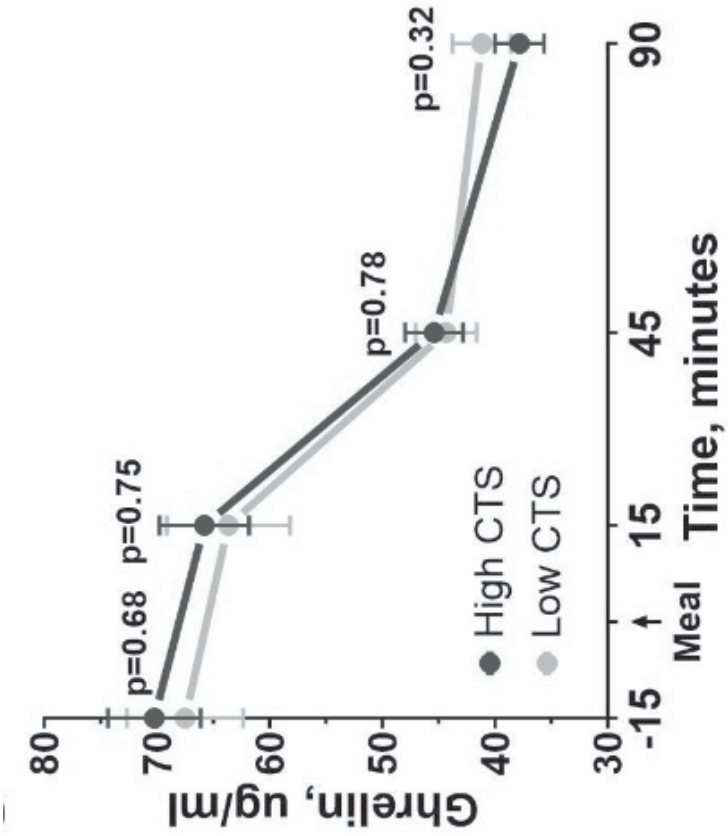


FIG. 12H

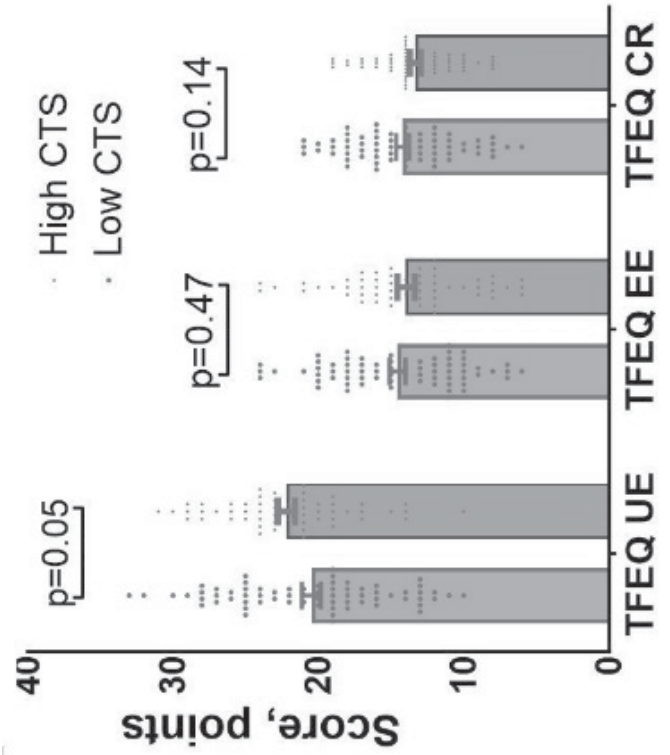
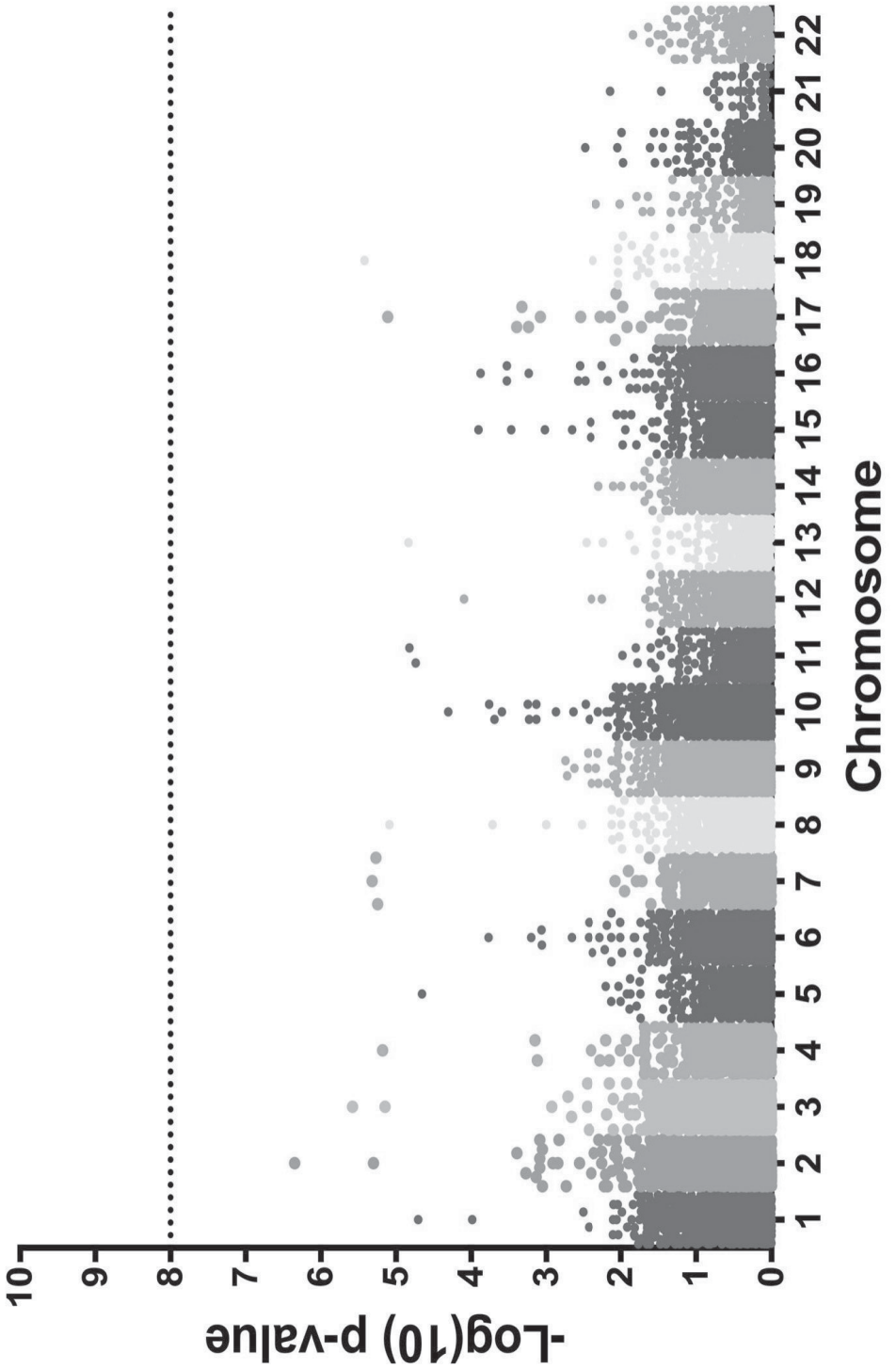


FIG. 13A


-Log(10) p-value
0
1
2
3
4
5
6
7
8
9
10
Chromosome
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22

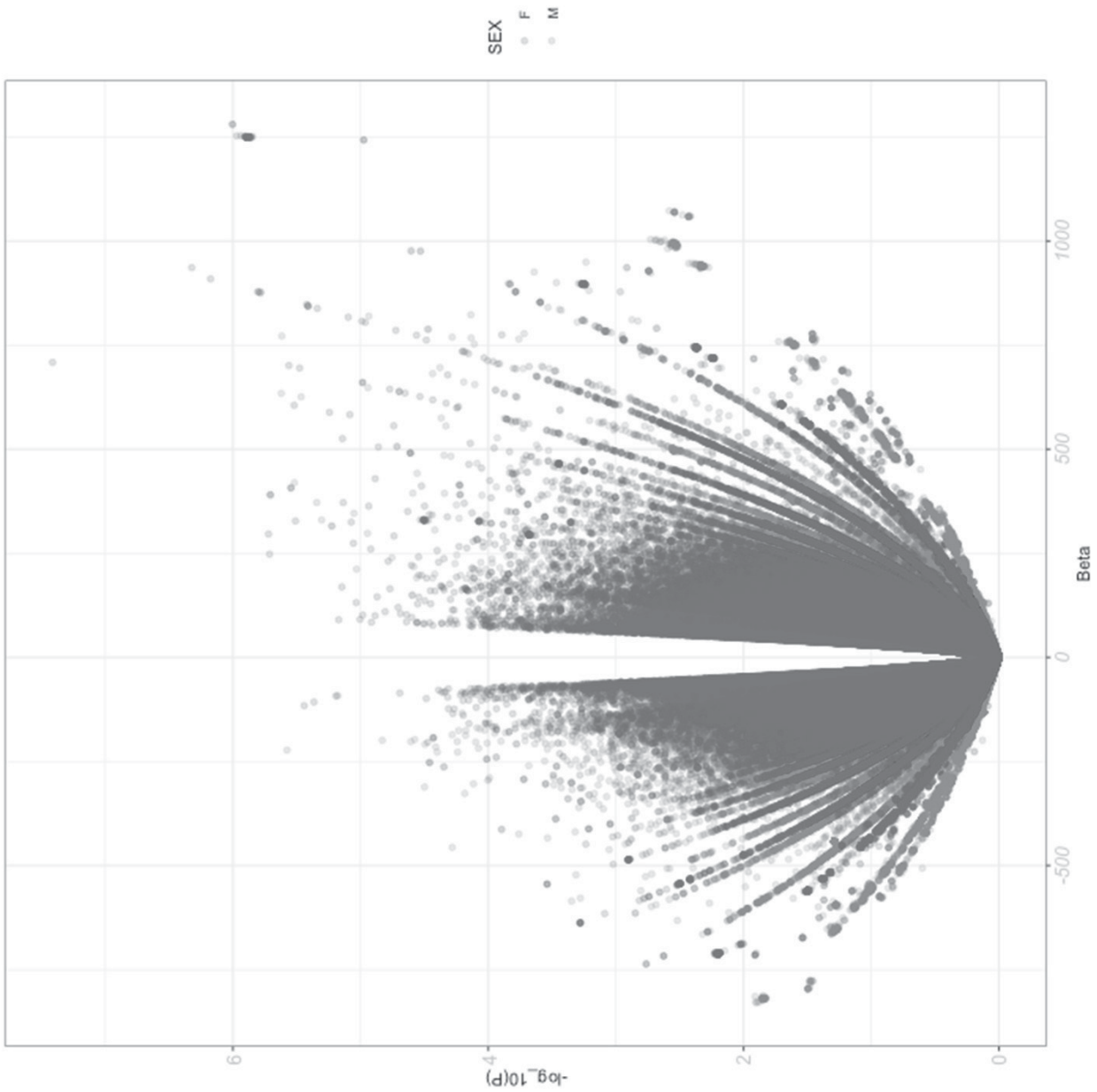


FIG. 13B

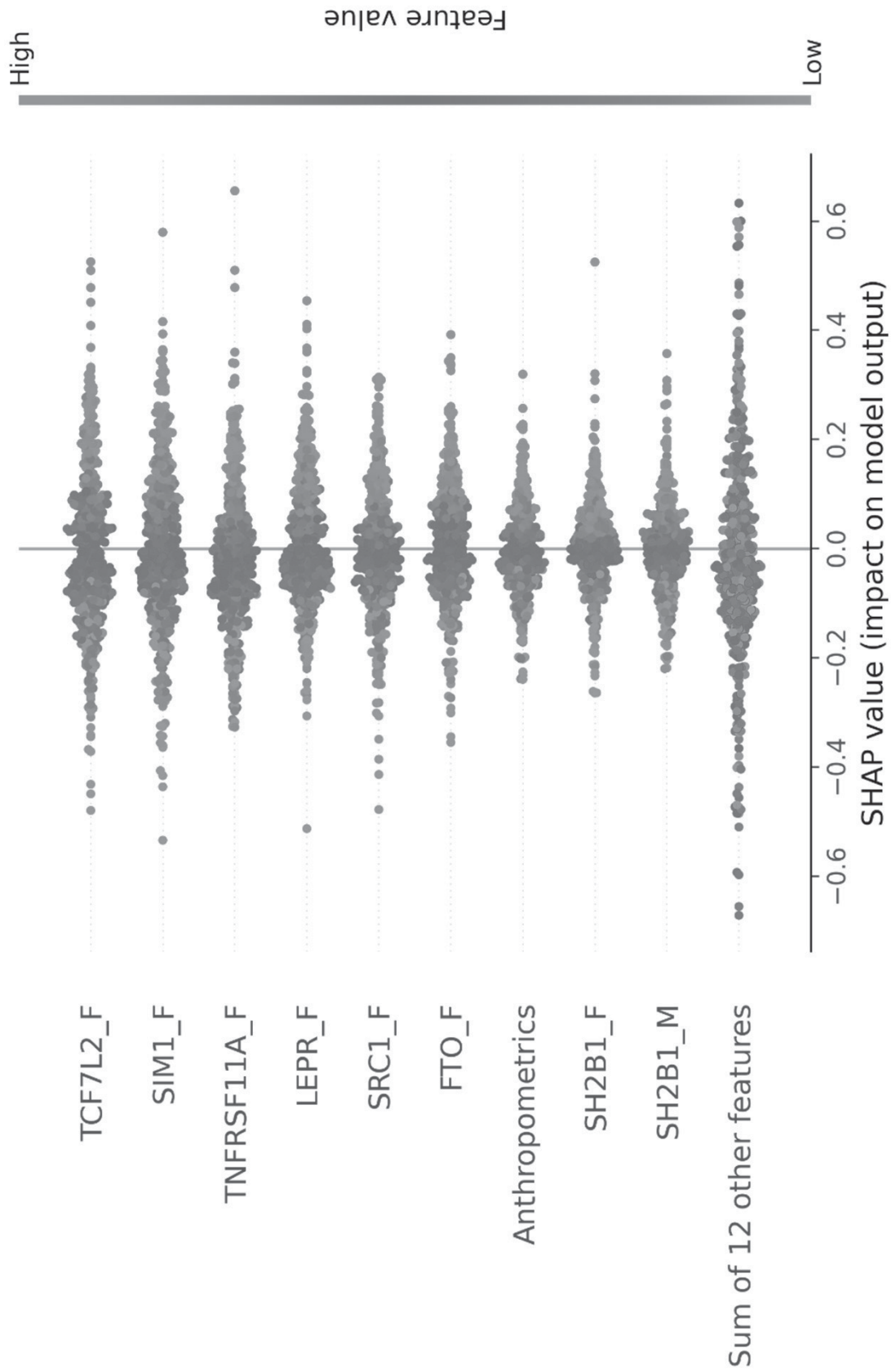

High
Feature value
Low
TCF7L2_F
SIM1_F
TNFRSF11A_F
LEPR_F
SRC1_F
FTO_F
Anthropometrics
SH2B1_F
SH2B1_M
Sum of 12 other features
−0.6
−0.4
−0.2
0.0
0.2
0.4
0.6
SHAP value (impact on model output)

FIG. 13C

FIG. 14A

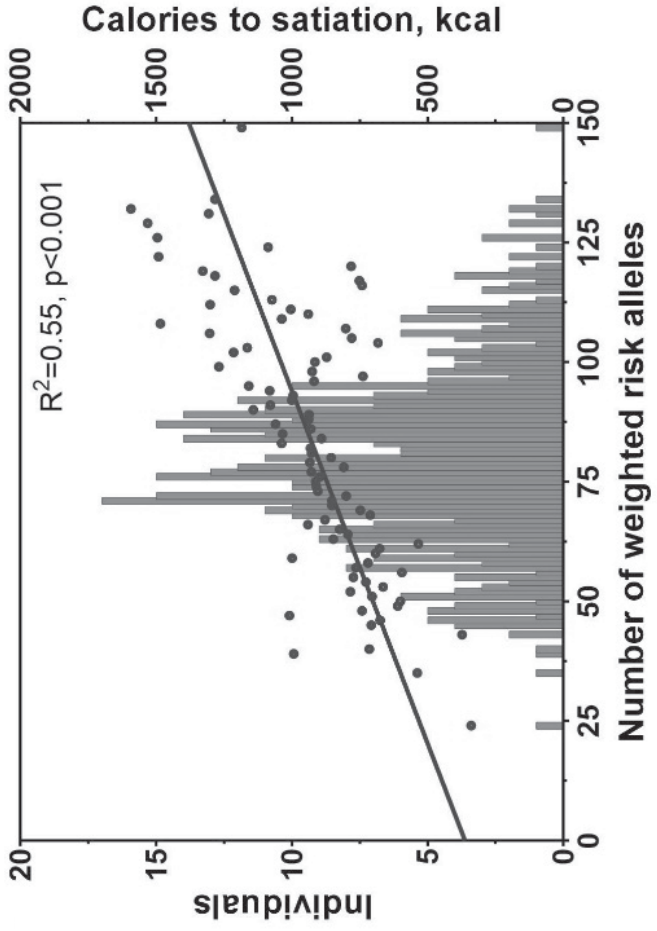


FIG. 14B

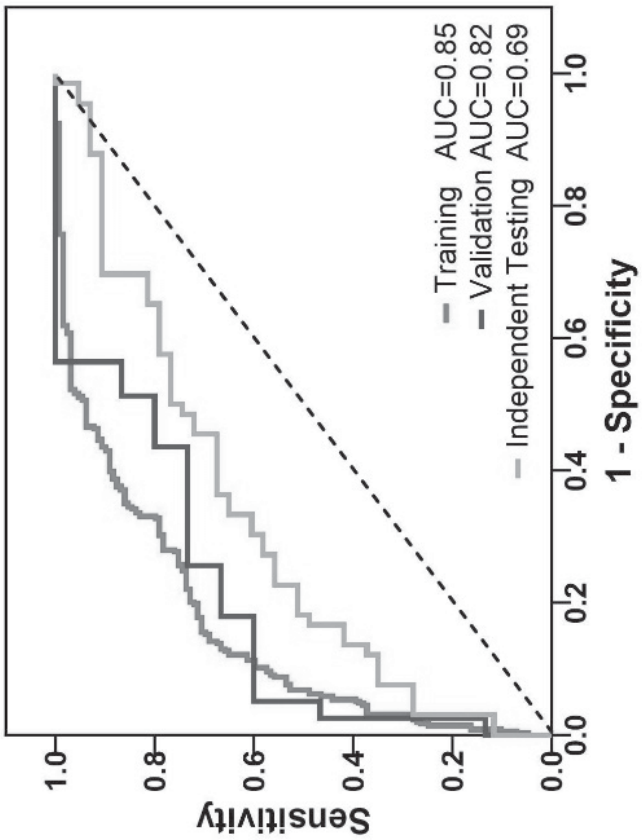


FIG. 14C

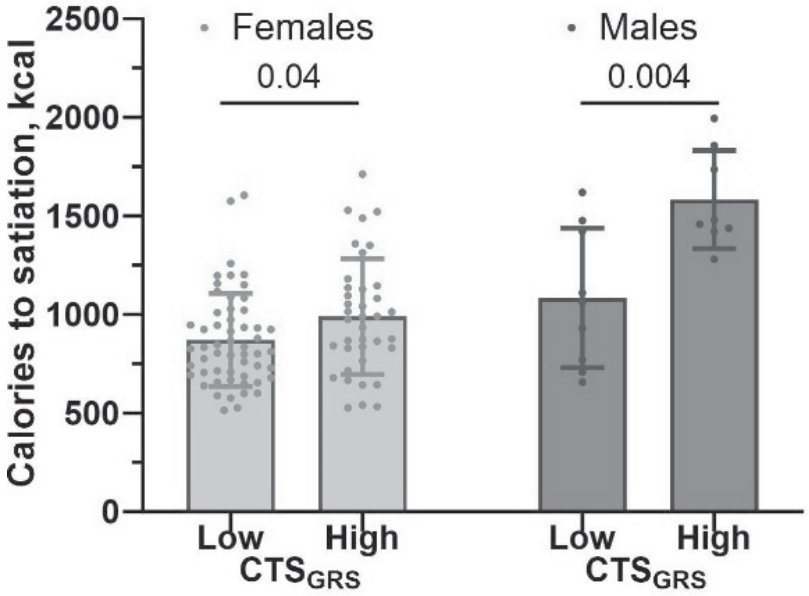


FIG. 14D

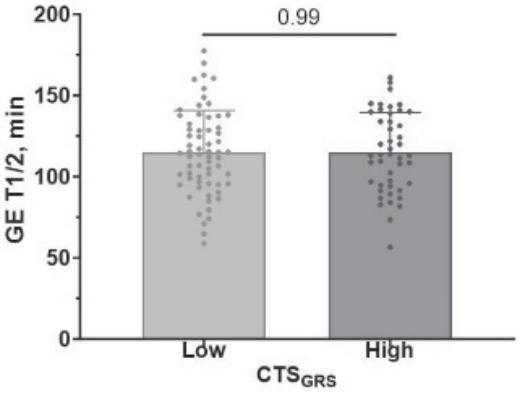
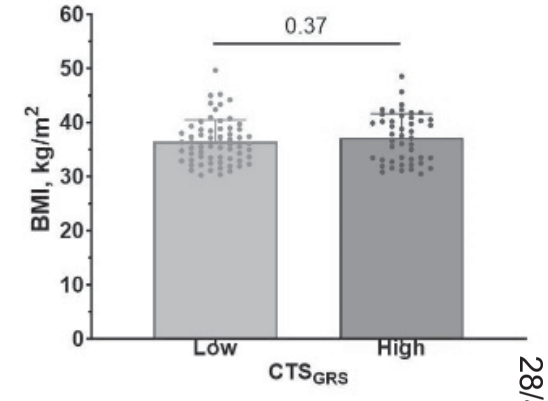


FIG. 14E



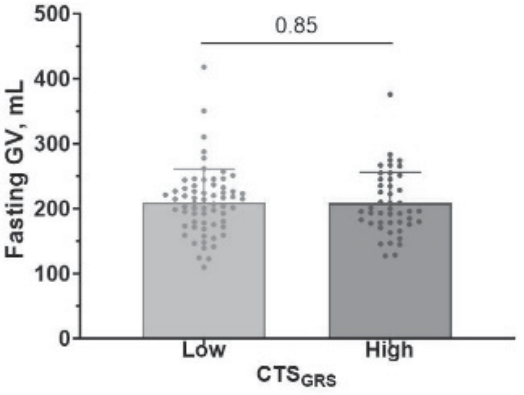


FIG. 14F

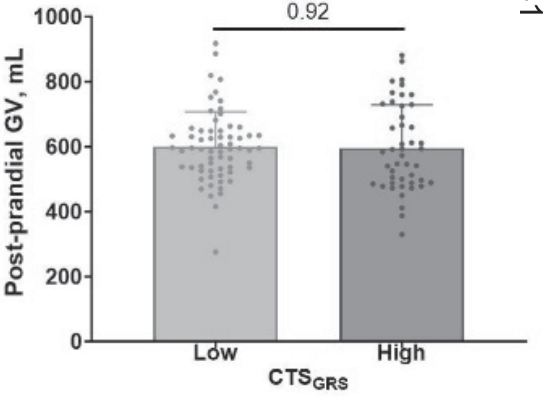
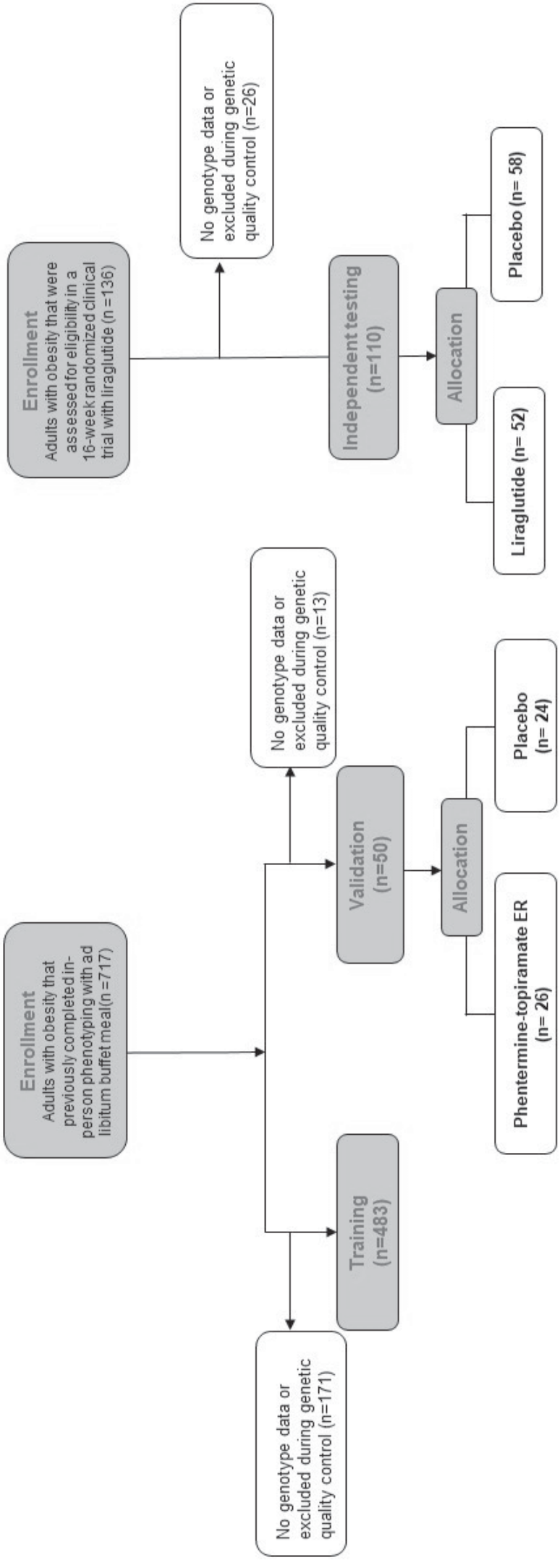


FIG. 14G

FIG. 15


Enrollment
Adults with obesity that previously completed in-person phenotyping with ad libitum buffet meal(n=717)
No genotype data or excluded during genetic quality control (n=171)
Training (n=483)
Validation (n=50)
No genotype data or excluded during genetic quality control (n=13)
Allocation
Phentermine-topiramate ER (n= 26)
Placebo (n= 24)
Enrollment
Adults with obesity that were assessed for eligibility in a 16-week randomized clinical trial with liraglutide (n=136)
No genotype data or excluded during genetic quality control (n=26)
Independent testing (n=110)
Allocation
Liraglutide (n= 52)
Placebo (n= 58)

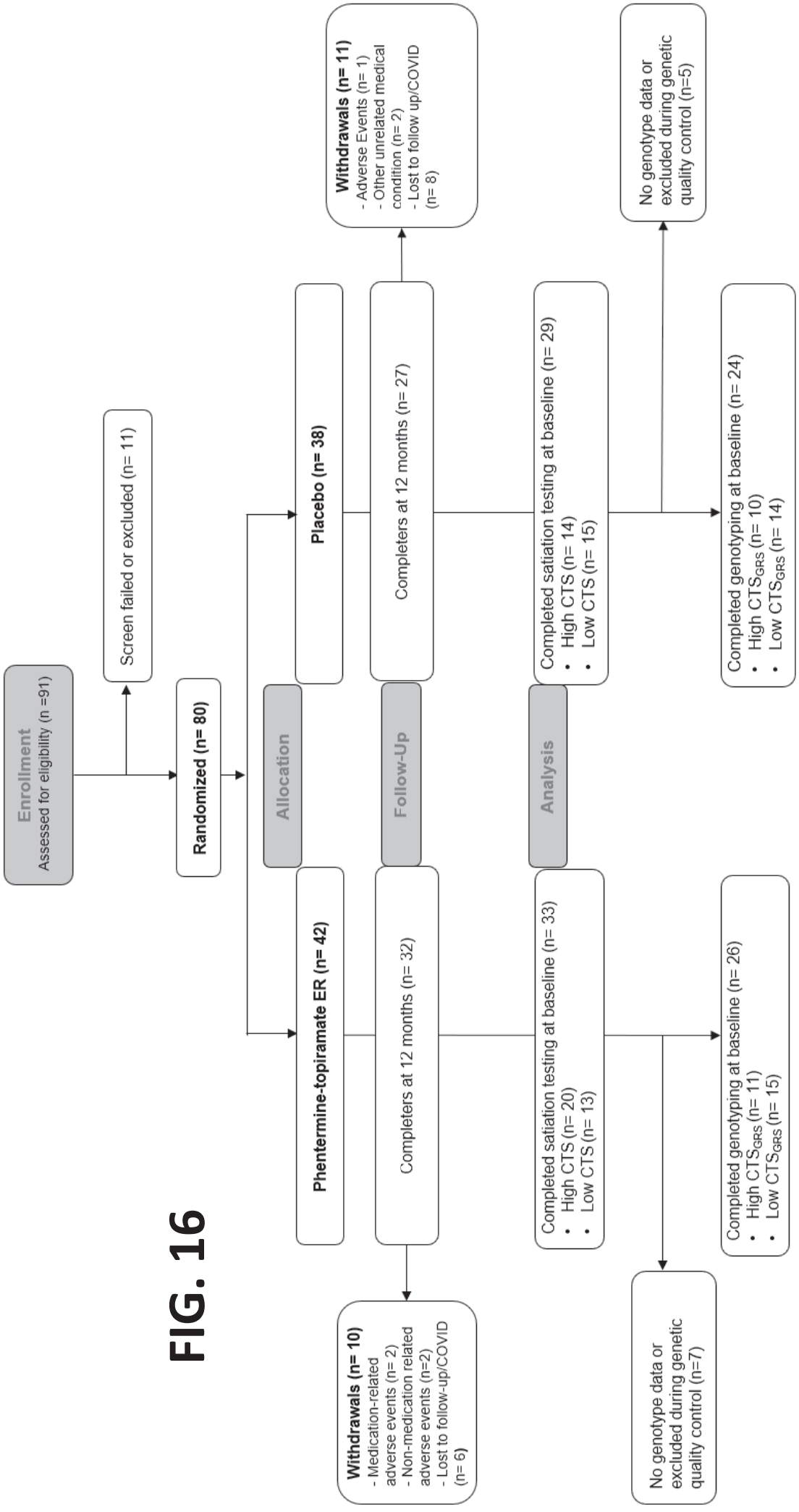

Enrollment
Assessed for eligibility (n =91)
Screen failed or excluded (n= 11)
Randomized (n= 80)
Allocation
Phentermine-topiramate ER (n= 42)
Placebo (n= 38)
Follow-Up
Completers at 12 months (n= 32)
Completers at 12 months (n= 27)
Withdrawals (n= 10)
- Medication-related adverse events (n= 2)
- Non-medication related adverse events (n=2)
- Lost to follow-up/COVID (n= 6)
Withdrawals (n= 11)
- Adverse Events (n= 1)
- Other unrelated medical condition (n= 2)
- Lost to follow up/COVID (n= 8)
Analysis
Completed satiation testing at baseline (n= 33)
• High CTS (n= 20)
• Low CTS (n= 13)
Completed satiation testing at baseline (n= 29)
• High CTS (n= 14)
• Low CTS (n= 15)
No genotype data or excluded during genetic quality control (n=7)
Completed genotyping at baseline (n= 26)
• High CTSGRS (n= 11)
• Low CTSGRS (n= 15)
No genotype data or excluded during genetic quality control (n=5)
Completed genotyping at baseline (n= 24)
• High CTSGRS (n= 10)
• Low CTSGRS (n= 14)

FIG. 16

FIG. 17

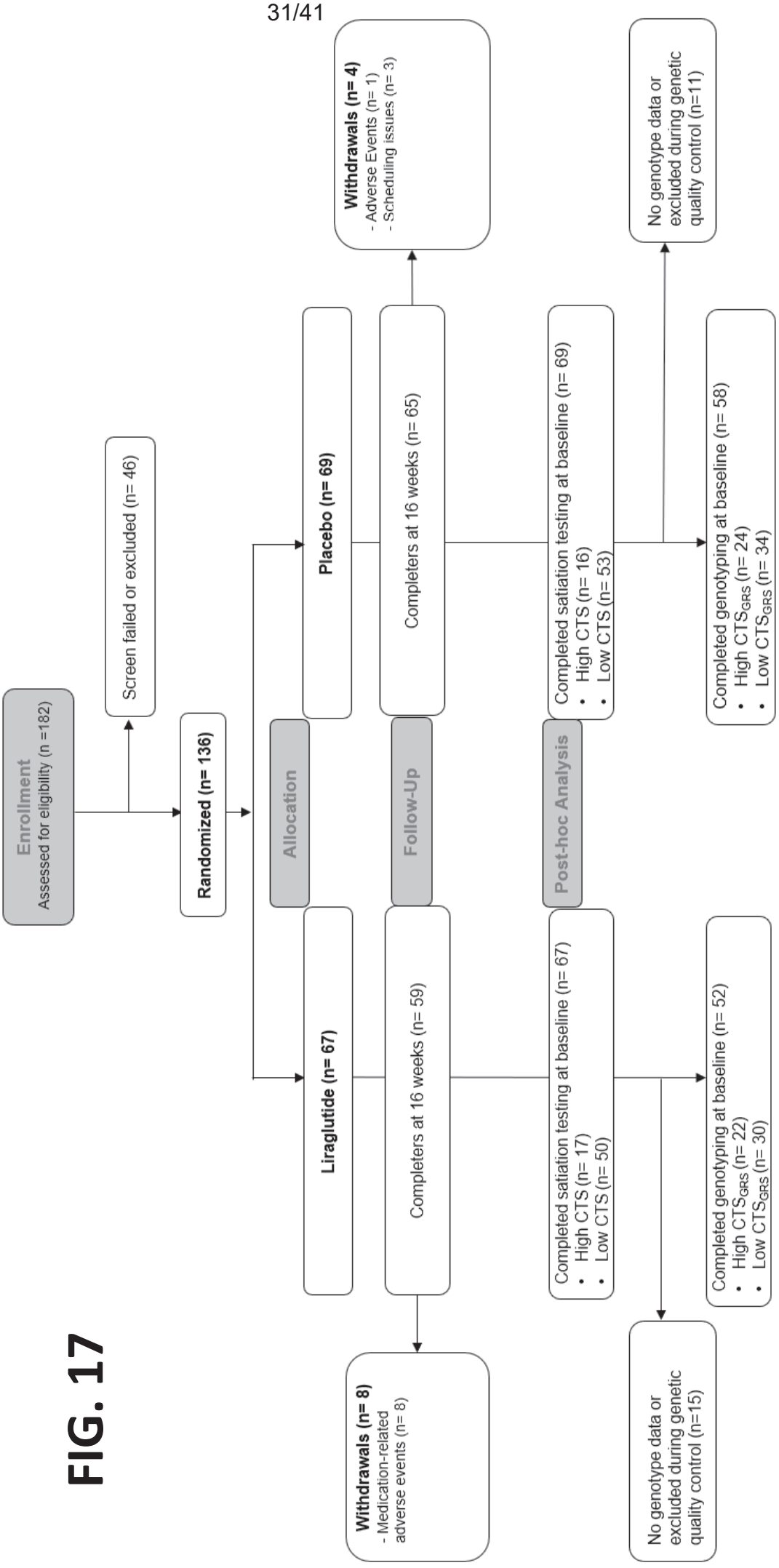

Enrollment
Assessed for eligibility (n =182)
Screen failed or excluded (n= 46)
Randomized (n= 136)
Allocation
Liraglutide (n= 67)
Placebo (n= 69)
Follow-Up
Completers at 16 weeks (n= 59)
Completers at 16 weeks (n= 65)
Withdrawals (n= 8)
- Medication-related adverse events (n= 8)
Withdrawals (n= 4)
- Adverse Events (n= 1)
- Scheduling issues (n= 3)
Post-hoc Analysis
Completed satiation testing at baseline (n= 67)
• High CTS (n= 17)
• Low CTS (n= 50)
Completed satiation testing at baseline (n= 69)
• High CTS (n= 16)
• Low CTS (n= 53)
Completed genotyping at baseline (n= 52)
• High CTSGRS (n= 22)
• Low CTSGRS (n= 30)
Completed genotyping at baseline (n= 58)
• High CTSGRS (n= 24)
• Low CTSGRS (n= 34)
No genotype data or excluded during genetic quality control (n=15)
No genotype data or excluded during genetic quality control (n=11)

FIG. 18A

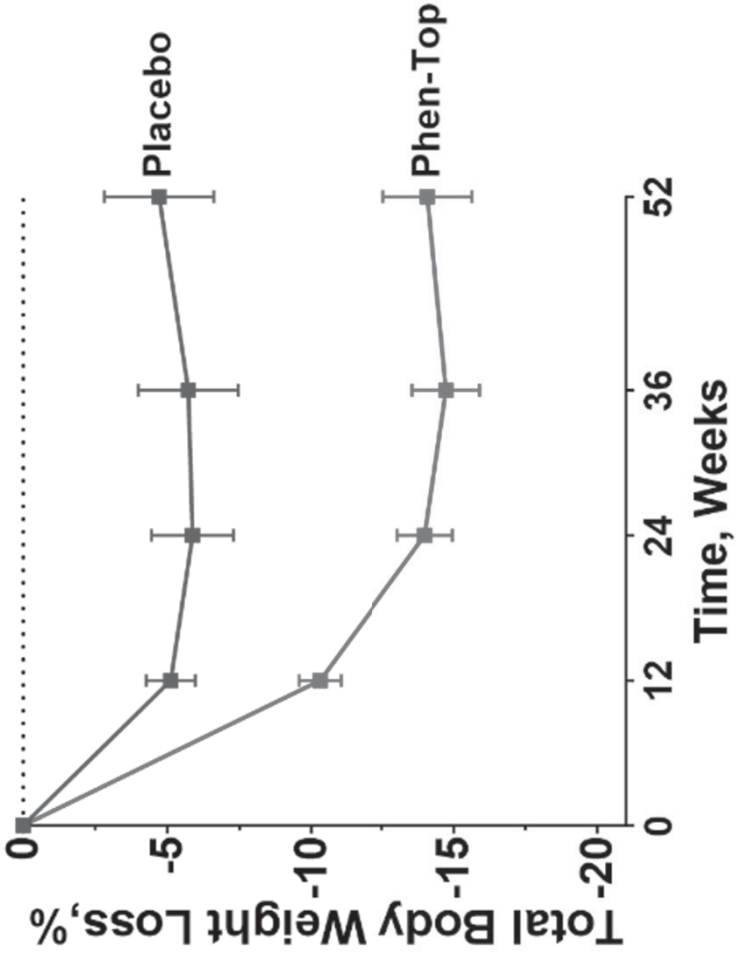


FIG. 18B

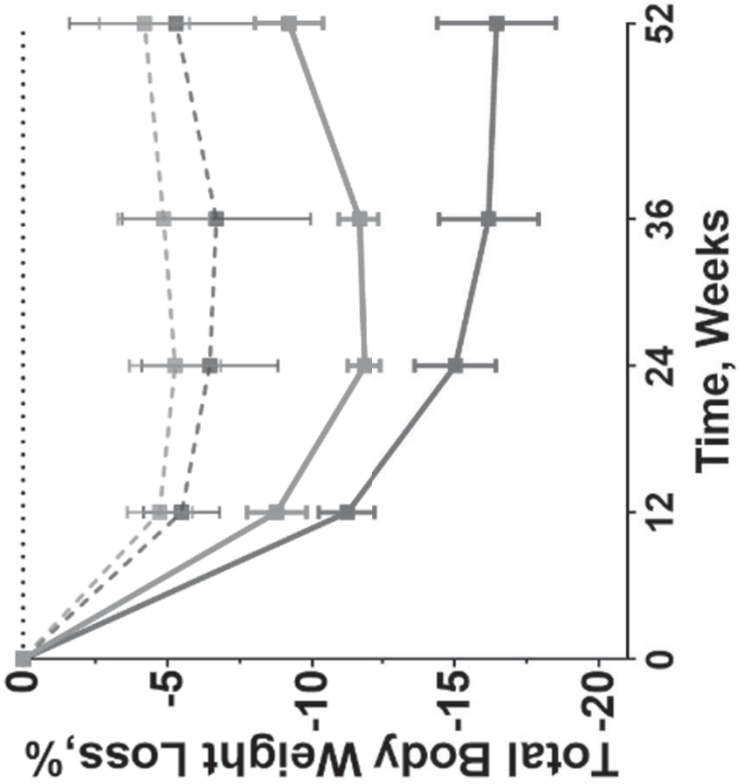


FIG. 18C

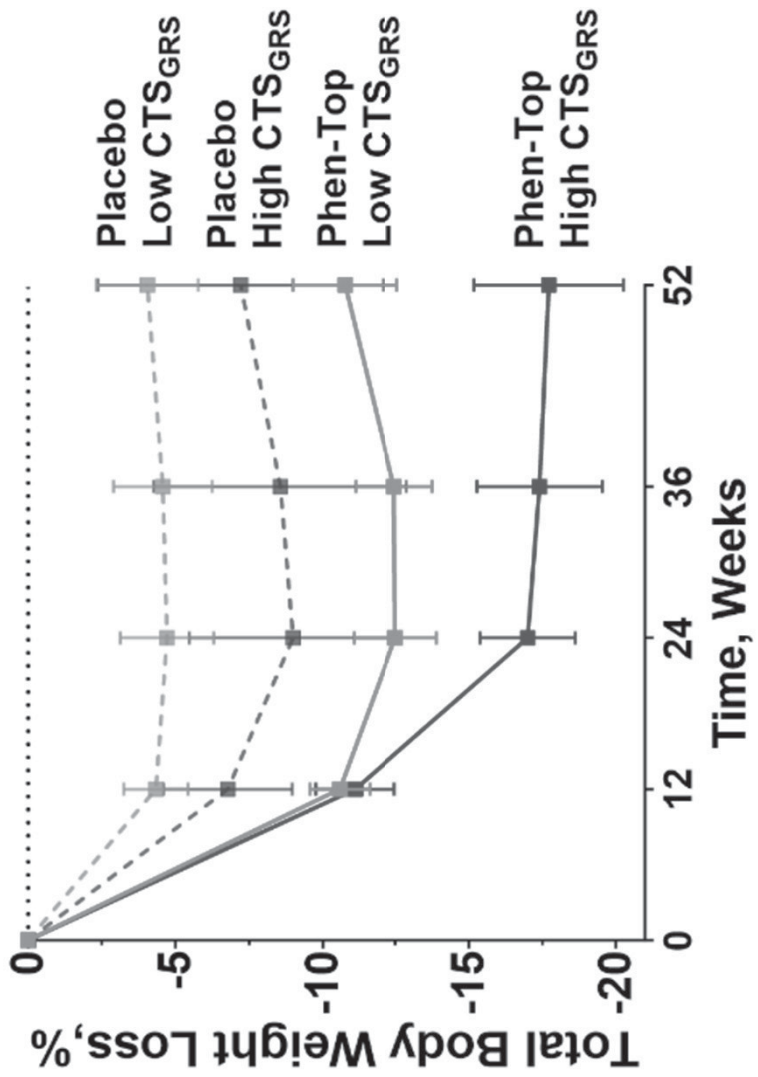

Placebo Low CTS$_{GRS}$
Placebo High CTS$_{GRS}$
Phen-Top Low CTS$_{GRS}$
Phen-Top High CTS$_{GRS}$
Total Body Weight Loss,%
0
-5
-10
-15
-20
0
12
24
36
52
Time, Weeks

FIG. 18D

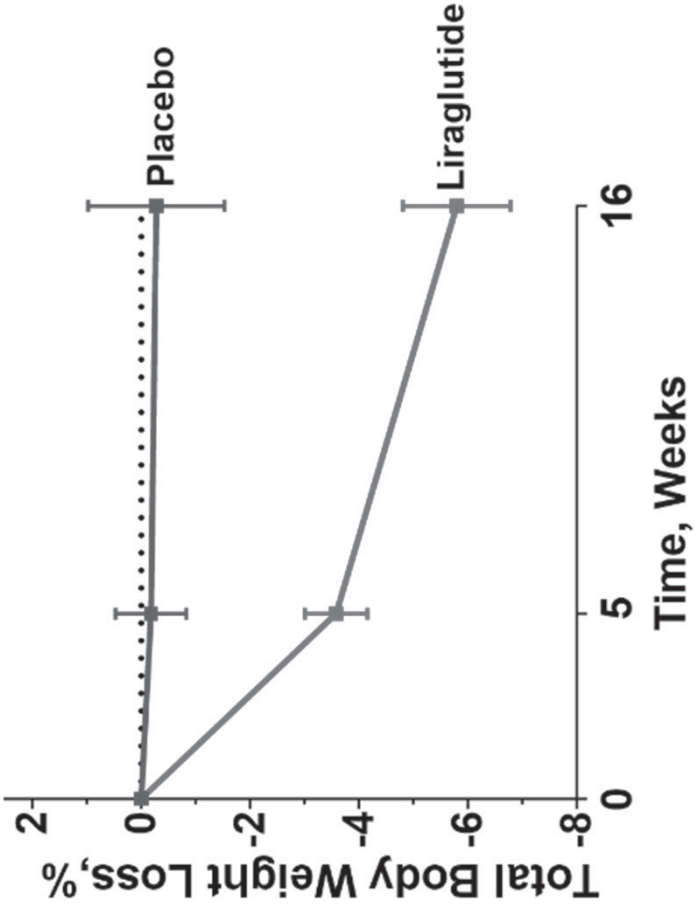


FIG. 18E

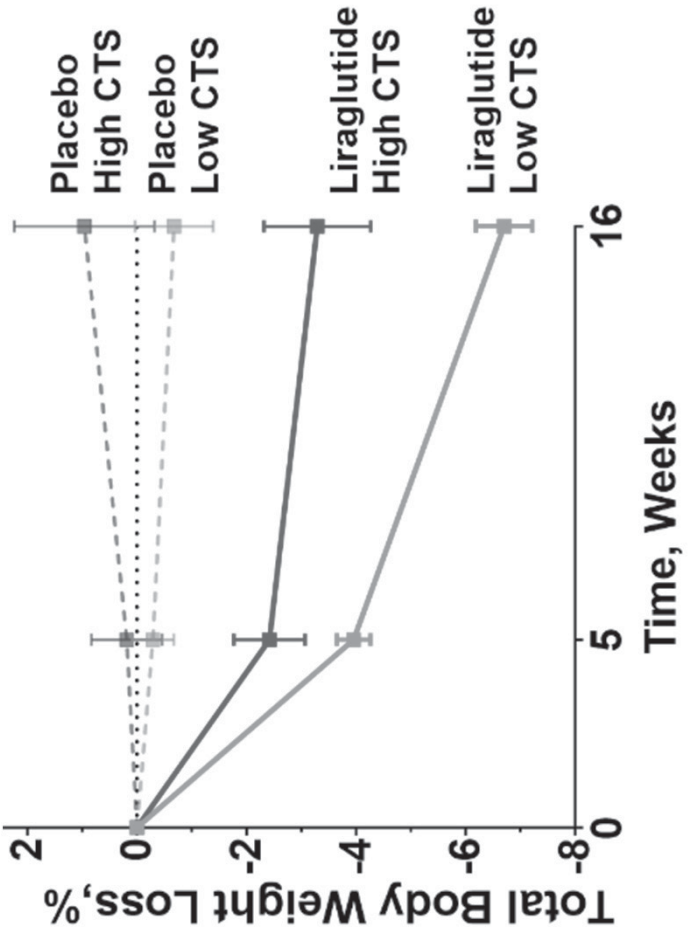


FIG. 18F

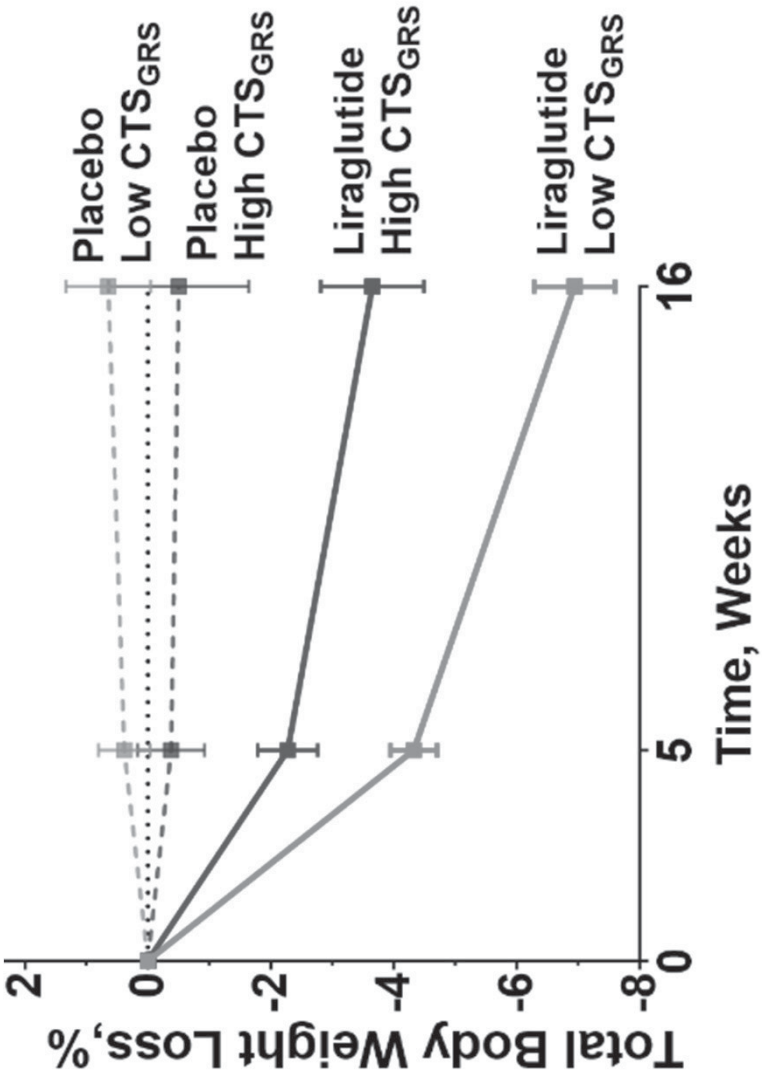

Placebo
Low CTS$_{GRS}$
Placebo
High CTS$_{GRS}$
Liraglutide
High CTS$_{GRS}$
Liraglutide
Low CTS$_{GRS}$
Total Body Weight Loss,%
2
0
-2
-4
-6
-8
0
5
16
Time, Weeks

FIG. 19A

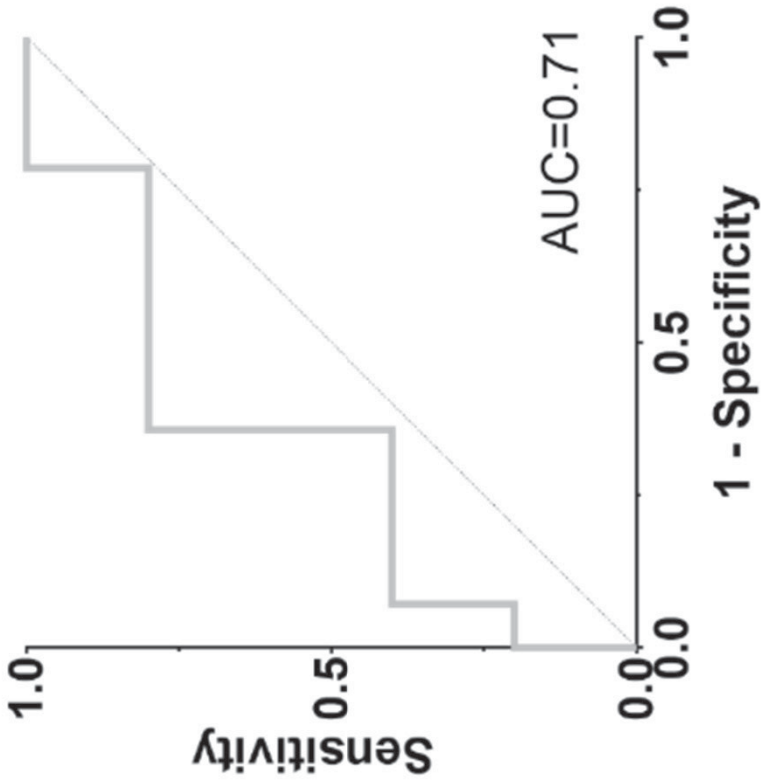


FIG. 19B

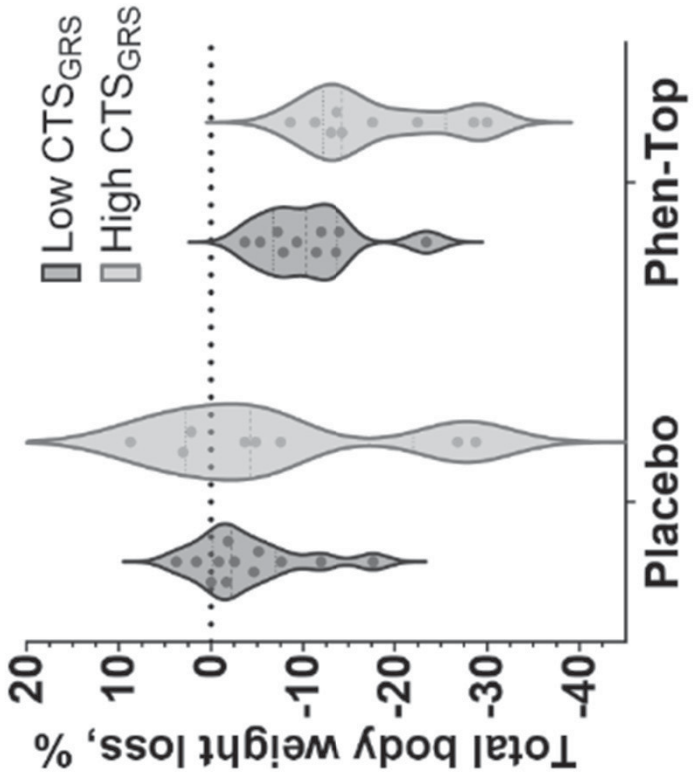


FIG. 19C

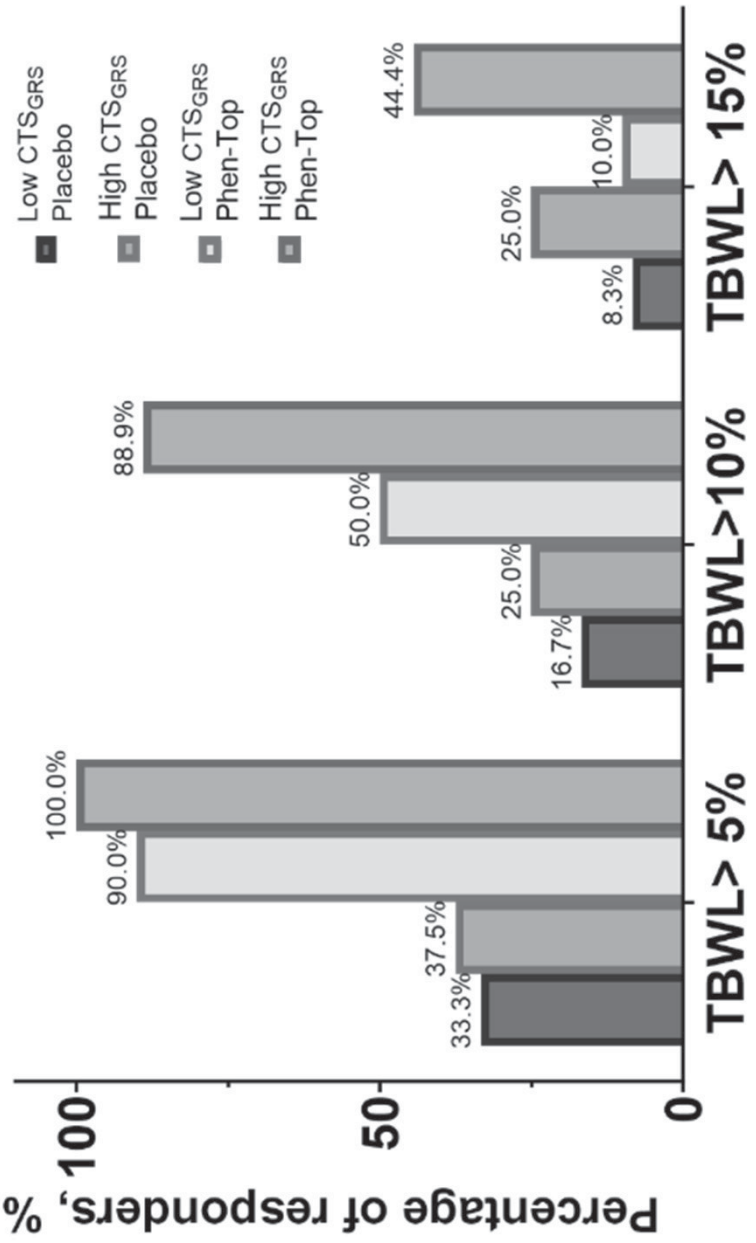

Low CTSGRS Placebo
High CTSGRS Placebo
Low CTSGRS Phen-Top
High CTSGRS Phen-Top
Percentage of responders, %
0
50
100
33.3%
37.5%
90.0%
100.0%
16.7%
25.0%
50.0%
88.9%
8.3%
25.0%
10.0%
44.4%
TBWL> 5%
TBWL>10%
TBWL> 15%

FIG. 20A

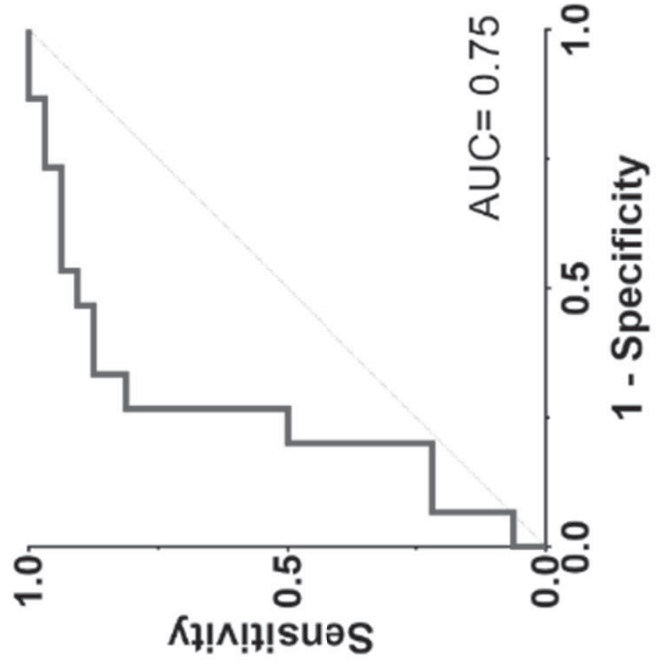


FIG. 20B

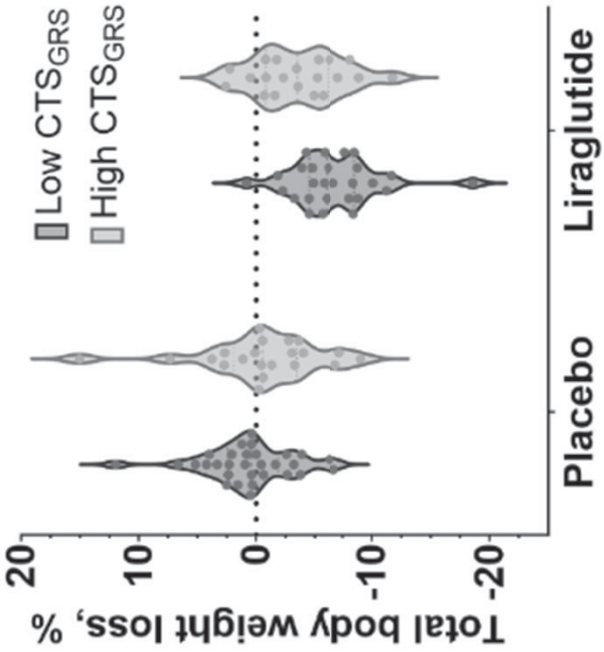


FIG. 20C

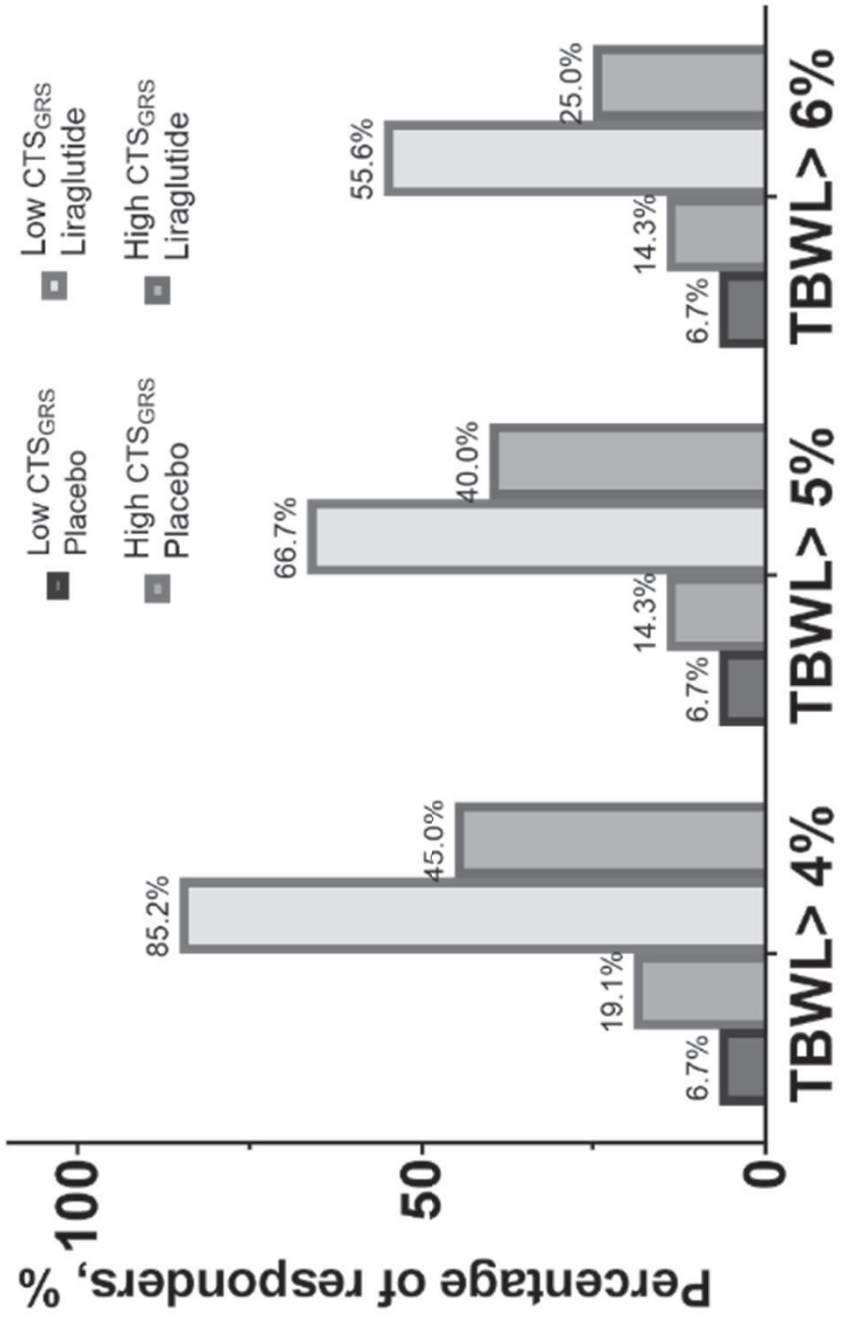

Percentage of responders, %
100
50
0
Low CTSGRS Placebo
High CTSGRS Placebo
Low CTSGRS Liraglutide
High CTSGRS Liraglutide
6.7%
19.1%
85.2%
45.0%
6.7%
14.3%
66.7%
40.0%
6.7%
14.3%
55.6%
25.0%
TBWL> 4%
TBWL> 5%
TBWL> 6%

FIG. 21A

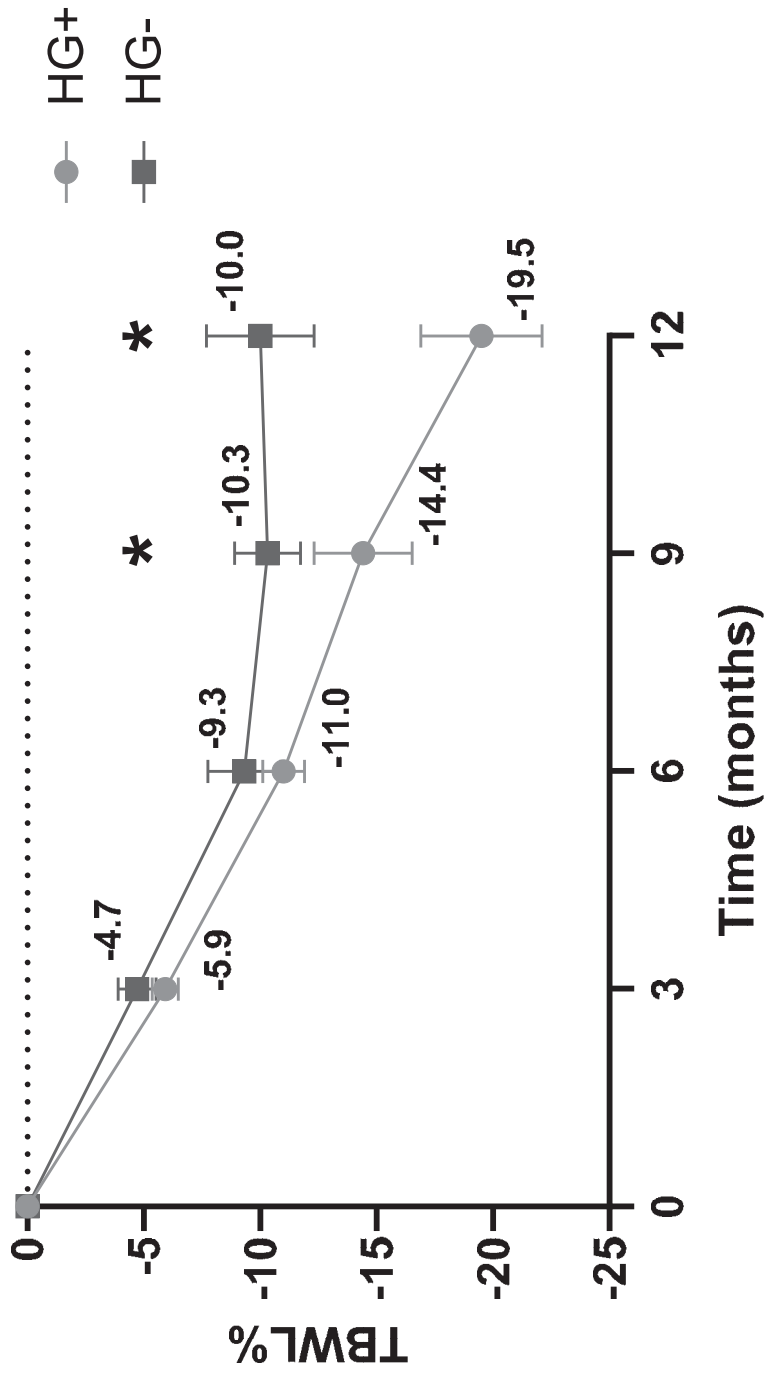

HG+
HG-
TBWL%
Time (months)
0
-5
-10
-15
-20
-25
0
3
6
9
12
-4.7
-5.9
-9.3
-11.0
-10.3
-14.4
-10.0
-19.5
*
*

FIG. 21B

