Experimental design

Validation cohort 3 (GUSTO children) — Age 6

Discovery cohort (GUSTO & S-PRESTO) — Age 33.98 ± 5.72

Validation cohort 1 (UKB) — Age 56.77 ± 8.03

Validation cohort 2 (ATTRaCT) — Age 62.95 ± 7.18

♥ Diseased cases

Postnatal Year 8
Preconception

Age (years): 0 5 10 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90

● Northeast Asian ● Southeast Asian ● Southwest Asian ● Northern European

Development

Candidate SNP markers pool

17 GWAS summary statistics were obtained from the PGS catalog for 5 MetS-related traits:

Waist circumference
Glucose
Blood pressure
HDL cholesterol
Triglycerides

N=102,431 SNPs

SNP	Allele
rs5	0
rs26	1
rs54	1
...	
rs9837	2

Input data for model training/testing

Discovery cohort (N=1368)

Total of 32,090 SNPs after QC & LD pruning

10-fold cross validation

Training set (80%) — Test set (20%)

Determination of the best prediction model and optimal parameters

GenMetS

SNPs (N=7,850) and trained weights

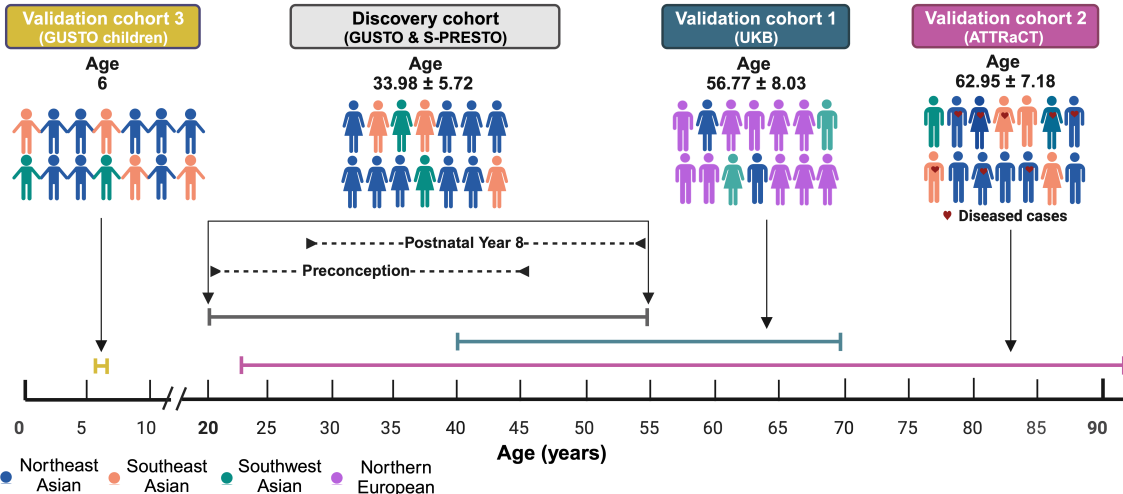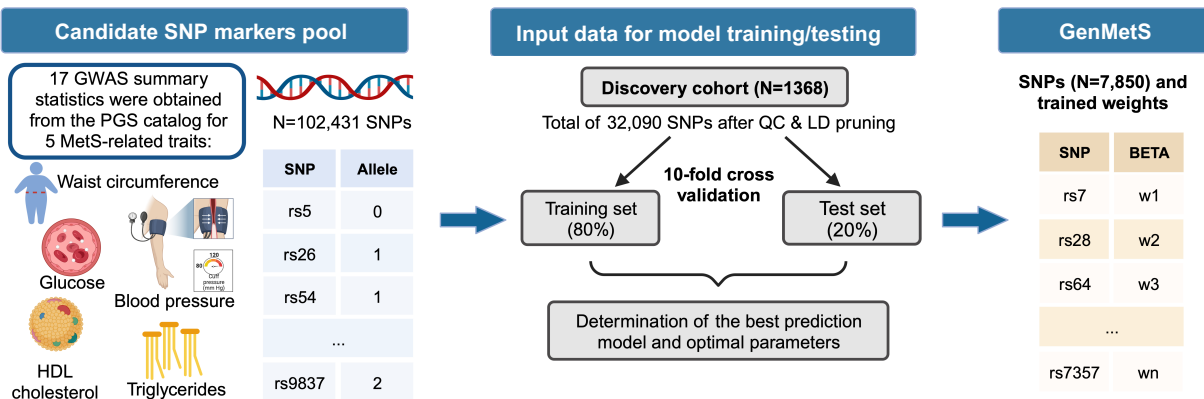| SNP	BETA
rs7	w1
rs28	w2
rs64	w3
...	
rs7357	wn

Cross-cohort validation

Evaluation of GenMetS prediction model performance and outcome of interest

Coefficient of determination (R^2) of GenMetS prediction for MetS traits

| Clinical measures | HDL, clinical observed MetS, BMI, fasting glucose ... |

| Conventional factors | **Demographic**: age, education **Lifestyle**: Physical activity, sleep hours, social economic status ... |

Validation cohort 1
N=195,665(F); 169,830(M)

Validation cohort 2
N=820(F); 1,490(M)

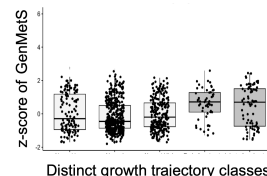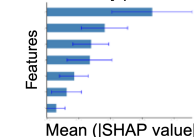Validation cohort 3
N=508(F); 565(M)

Prediction of cardiometabolic diseases and age-of-onset

| ICD-10 | Hypertension, heart failure, T2DM ... |

Prediction of child growth trajectory

Feature importance in cardiometabolic multimorbidity prediction

Features — Mean (|SHAP value|)

z-score of GenMetS — Distinct growth trajectory classes