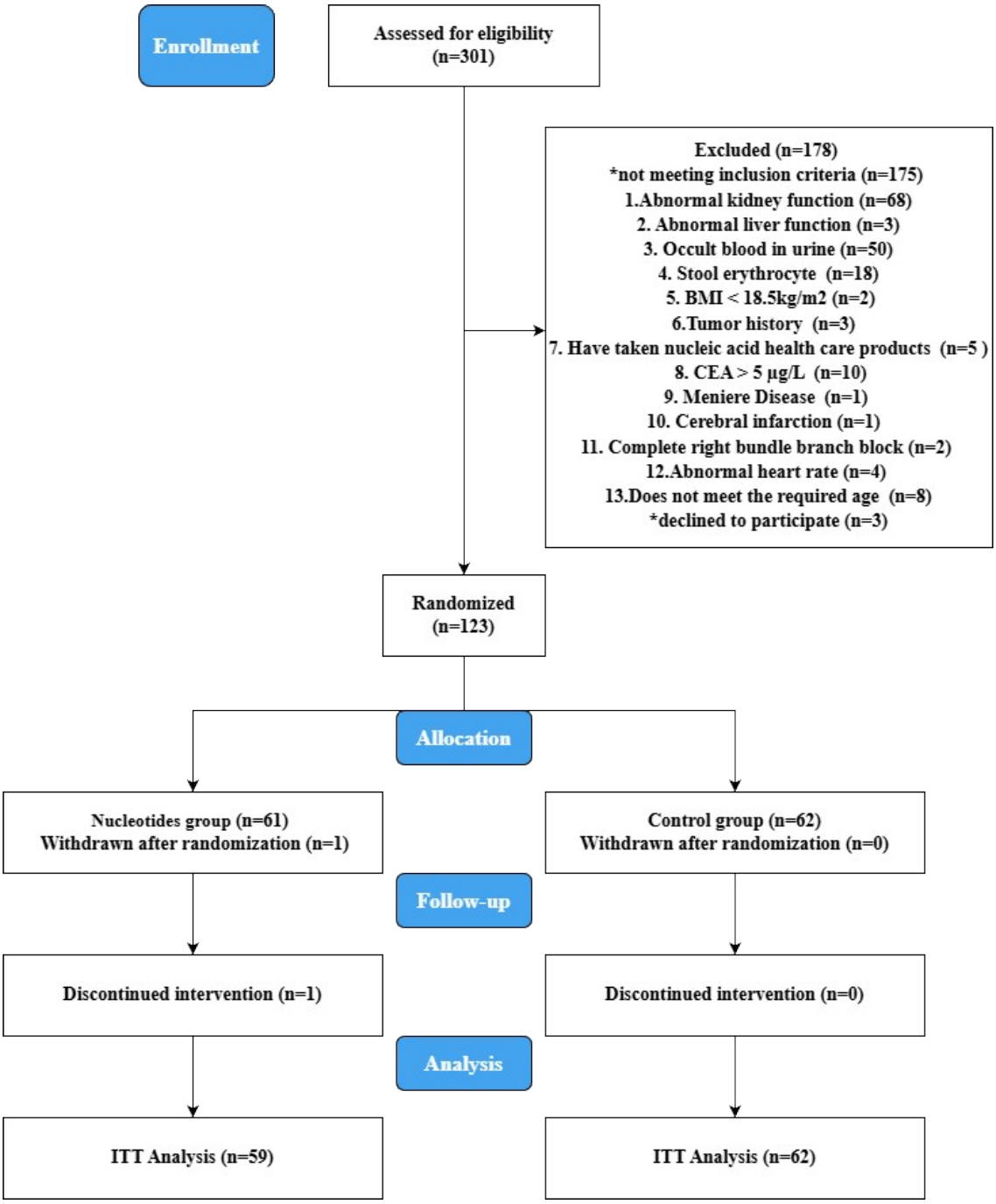
Supplementary Contents

Supplementary Figure 1. Participant Flowchart



Supplementary Table 1. Overview of Study Assessments

Category	Outcome（Units）	Source/Method
Genetic risk score	SNPs	Venous blood draw (fasted)
Dietary Assessment	Accurate food and nutrient intake (g /day)	Photo-Assisted three-day 24-hour Dietary Intake Assessment
Glycolipid metabolic profile	HOMA-IR	Venous blood draw (fasted)
	FBG (mmol/L)	Venous blood draw (fasted)
	INS (uIU/ml)	Venous blood draw (fasted)
	HBA1c (%)	Venous blood draw (fasted)
Body composition	Skeletal muscle mass(kg)	Bioelectrical Impedance Analyzer
	Limbs of muscle mass(kg)	Bioelectrical Impedance Analyzer
	Body fat rate (%)	Bioelectrical Impedance Analyzer
	Visceral fat grade	Bioelectrical Impedance Analyzer
Omics profiling	Metabolome	Venous blood draw (fasted)
	Transcriptome	Venous blood draw (fasted)

* SNPs, single nucleotide polymorphisms; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; FBG, fasting blood glucose; INS, insulin; HbA1c, glycated hemoglobin A1c.

Supplementary Table 2. Associations between FBG-PRS and baseline glucose metabolism indicators

Time point	Markers of glucose metabolism	N	B (95%CI)	*p*
Baseline	FBG (mmol/L)	121	2.74 (0.14, 5.35)	**0.0394**
	Fasting blood insulin (uIU/ml)	121	5.97 (0.25, 11.7)	**0.0411**
	HbA1c (%)	121	1.08 (-0.49, 2.66)	0.1759
	HOMA-IR	121	3.65 (1.28, 6.02)	**0.0028**
	QUICKI	121	-0.17 (-0.31, -0.02)	**0.0272**
	HOMA-B	121	-43.45 (-100.29, 13.39)	0.1327

* Multivariable linear regression models were adjusted for age, sex, and BMI. β values (B) with 95% confidence intervals (CIs) and p values are presented.

* Bolded entries fall below the significance threshold of $p < 0.05$.

* FBG, fasting blood glucose; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; QUICKI, Quantitative Insulin Sensitivity Check Index; HOMA-B, Homeostatic Model Assessment of β-cell function.

Supplementary Table 3. Characteristics of the participants in the High-PRS and Low-PRS group

Variable	Time	High-PRS				*p*	Low-PRS				*p*
		NTs group		CON group			NTs group		CON group		
		N	Mean±SD	N	Mean±SD		N	Mean±SD	N	Mean±SD	
HOMAIR	T0	25	2.78 ± 2.70	35	2.18 ± 1.33	0.31	34	1.83 ± 1.06	27	2.31 ± 1.29	0.12
	T1	24	2.30 ± 1.51	34	2.49 ± 1.49	0.64	33	1.94 ± 0.97	27	2.64 ± 1.39	**0.032**
	T2	25	2.12 ± 1.30	34	2.41 ± 1.33	0.4	32	1.87 ± 0.79	27	2.39 ± 1.26	0.069
	T1-T0	24	-0.44 ± 1.92	34	0.28 ± 0.73	0.094	33	0.13 ± 0.86	27	0.33 ± 0.78	0.35
	T2-T0	25	-0.66 ± 2.01	34	0.28 ± 0.70	**0.032**	32	0.04 ± 0.68	27	0.08 ± 0.78	0.83
	T2-T1	24	-0.30 ± 0.67	33	-0.01 ± 0.81	0.14	31	-0.06 ± 0.78	27	-0.25 ± 0.87	0.39
BF%	T0	24	30.64 ± 6.92	35	28.53 ± 7.38	0.27	34	28.92 ± 6.11	27	32.40 ± 8.25	0.073
	T1	15	30.93 ± 6.55	22	26.61 ± 6.53	0.058	25	27.96 ± 6.70	19	33.71 ± 8.02	**0.016**
	T2	25	30.65 ± 6.95	34	28.87 ± 7.03	0.34	32	29.18 ± 6.93	27	33.14 ± 8.31	0.055
	T1-T0	14	-0.84 ± 2.30	22	-0.66 ± 1.57	0.8	25	0.01 ± 1.72	19	-0.16 ± 0.80	0.66
	T2-T0	24	-0.60 ± 3.06	34	0.68 ± 2.36	0.095	32	0.23 ± 1.74	27	0.74 ± 1.59	0.24
	T2-T1	15	0.05 ± 2.80	21	0.85 ± 2.29	0.37	23	0.74 ± 1.28	19	1.04 ± 1.67	0.52
VFG	T0	24	14.04 ± 2.68	35	12.97 ± 2.83	0.15	34	13.15 ± 2.27	27	14.67 ± 3.44	0.054

	T1	15	14.13 ± 2.53	22	12.23 ± 2.29	**0.027**	25	12.84 ± 2.49	19	15.32 ± 3.25	**0.0094**
	T2	25	13.92 ± 2.61	34	13.21 ± 2.74	0.31	32	13.31 ± 2.52	27	15.04 ± 3.31	0.031
	T1-T0	14	-0.50 ± 1.02	22	-0.23 ± 0.75	0.4	25	0.08 ± 0.81	19	0.00 ± 0.33	0.66
	T2-T0	24	-0.33 ± 1.17	34	0.35 ± 0.98	**0.023**	32	0.16 ± 0.72	27	0.37 ± 0.63	0.23
	T2-T1	15	0.07 ± 1.03	21	0.38 ± 0.92	0.35	23	0.35 ± 0.65	19	0.37 ± 0.60	0.92
	T0	24	38.90 ± 7.39	35	40.34 ± 6.11	0.44	34	39.34 ± 7.29	27	40.21 ± 6.88	0.63
	T1	15	37.67 ± 6.71	22	40.78 ± 6.71	0.18	25	39.63 ± 7.31	19	38.90 ± 6.46	0.73
SMM	T2	25	39.54 ± 7.56	34	40.38 ± 6.23	0.65	32	39.42 ± 7.42	27	39.96 ± 6.72	0.77
(kg)	T1-T0	14	0.48 ± 0.92	22	-0.03 ± 0.81	0.11	25	0.05 ± 1.77	19	0.12 ± 0.34	0.86
	T2-T0	24	0.59 ± 1.46	34	-0.03 ± 0.94	0.075	32	0.19 ± 1.84	27	-0.26 ± 0.91	0.23
	T2-T1	15	0.25 ± 1.59	21	-0.08 ± 0.75	0.47	23	0.07 ± 0.62	19	-0.48 ± 0.87	**0.027**
	T0	24	17.21 ± 3.56	35	17.89 ± 3.04	0.45	34	17.29 ± 3.71	27	17.67 ± 3.25	0.68
LMM	T1	15	16.59 ± 3.26	22	18.08 ± 3.29	0.19	25	17.54 ± 3.56	19	17.09 ± 3.11	0.65
(kg)	T2	25	17.50 ± 3.60	34	17.88 ± 3.06	0.67	32	17.43 ± 3.59	27	17.62 ± 3.26	0.83
	T1-T0	14	0.19 ± 0.41	22	-0.07 ± 0.66	0.15	25	0.16 ± 1.82	19	0.09 ± 0.30	0.84
LMM	T2-T0	24	0.28 ± 0.57	34	-0.05 ± 0.61	**0.038**	32	0.20 ± 1.67	27	-0.04 ± 0.52	0.44
(kg)	T2-T1	15	0.16 ± 0.60	21	-0.03 ± 0.32	0.27	23	0.03 ± 0.27	19	-0.21 ± 0.40	**0.036**

* **T0** refers to the baseline measurement, **T2** represents the endpoint measurement. **T1-T0** represents the change from **T0** to **T1**, **T2-T0** represents the change from **T0** to **T2** and **T2-T1** represents the change from **T1** to **T2**.
* The ***p-values*** are derived from *t*-tests that compare the changes between exogenous nucleotides group and Control group.
* Bolded entries fall below the significance threshold of $p < 0.05$.
* HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; BF%, body fat percentage; VFG, visceral fat grade; SMM, skeletal muscle mass; LMM, limb muscle mass.

Supplementary Table 4. Generalized Estimating Equations of outcomes include baseline and 19-week.

Variable	Time	Mean difference in change between group (NTs group vs Control group)					
		High-PRS			Low-PRS		
		β	95%CI	*p*	β	95%CI	*p*
HOMA-IR	T2vsT0	**-0.94**	**(-1.75, -0.14)**	**0.022**	0.27	(-0.28, 0.82)	0.34
BF%	T2vsT0	-1.29	(-2.70, 0.12)	0.073	-0.48	(-1.29, 0.33)	0.25
VFG	T2vsT0	**-0.70**	**(-1.26, -0.14)**	**0.014**	-0.19	(-0.53, 0.14)	0.25
SMM(kg)	T2vsT0	0.62	(-0.03, 1.27)	0.060	0.44	(-0.24, 1.12)	0.20
LMM(kg)	T2vsT0	**0.33**	**(0.04, 0.63)**	**0.028**	0.23	(-0.34, 0.80)	0.42

* T0 refers to the baseline measurement, T2 indicates the endpoint measurement, T2vsT0 represents the change from T0 to T2.

* *P* values are based on repeated measures analysis using generalized estimating equations (GEE), with models including the interaction between group assignment and time. Covariates adjusted in the models were baseline values of the outcomes, age, sex, and dietary nucleotide intake.

* Primary assessment timepoints include baseline and 19-week.

* Bolded entries fall below the significance threshold of $p < 0.05$.

* HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; BF%, body fat percentage; VFG, visceral fat grade; SMM, skeletal muscle mass; LMM, limb muscle mass.

Supplementary Table 5. Differentially expressed genes in the High-PRS group (|log2FoldChange| > 1 and adjusted p-value < 0.05)

Variable	Gene	Log2 Fold Change	*p*	p_{adj}	Expression Trend (NTs vs Control)
NM_001318028	PPP4R2	-2.00	1.34×10^{-17}	2.81×10^{-13}	Down-regulated
NM_001144001	SEC14L1	-1.26	4.16×10^{-17}	4.36×10^{-13}	Down-regulated
NM_001204410	SEC14L1	-1.07	3.27×10^{-12}	2.29×10^{-8}	Down-regulated
NM_001366058	OTUD4	-2.22	6.41×10^{-9}	7.07×10^{-6}	Down-regulated
NM_001025107	ADAR	-1.04	3.48×10^{-8}	2.36×10^{-5}	Down-regulated
NM_001003810	HNRNPD	-1.04	1.55×10^{-7}	6.52×10^{-5}	Down-regulated
NM_001330451	ETS1	-2.10	4.06×10^{-7}	1.37×10^{-4}	Down-regulated
NM_001321358	NRBP1	-1.13	7.27×10^{-7}	2.03×10^{-4}	Down-regulated
NM_001345968	ZNF394	-1.08	7.44×10^{-7}	2.04×10^{-4}	Down-regulated
NM_181747	ORC5	-1.55	1.22×10^{-6}	2.75×10^{-4}	Down-regulated
NM_001348745	KIDINS220	-1.00	4.71×10^{-6}	7.54×10^{-4}	Down-regulated
NM_001320597	DDX5	-1.27	1.14×10^{-5}	1.42×10^{-3}	Down-regulated

NM_003576	STK24	-1.23	3.28×10^{-5}	3.08×10^{-3}	Down-regulated
NM_001005526	SF3B1	-1.90	4.36×10^{-5}	3.67×10^{-3}	Down-regulated
NM_001127236	GPBP1	1.32	5.92×10^{-5}	4.59×10^{-3}	Up-regulated
NM_001349437	APOBEC3G	-1.08	1.32×10^{-4}	7.85×10^{-3}	Down-regulated
NM_001352891	DENND3	-2.32	1.84×10^{-4}	9.79×10^{-3}	Down-regulated
NM_001270841	CRIP2	-1.34	2.70×10^{-4}	1.26×10^{-2}	Down-regulated
NM_001330417	INTS2	-1.23	3.57×10^{-4}	1.55×10^{-2}	Down-regulated
NM_001031746	VSTM4	1.09	4.08×10^{-4}	1.69×10^{-2}	Up-regulated
NM_001164098	VCAN	-1.65	4.16×10^{-4}	1.70×10^{-2}	Down-regulated
NM_001289971	ZNF84	1.28	4.51×10^{-4}	1.80×10^{-2}	Up-regulated
NM_001385305	PTPRA	-1.15	4.89×10^{-4}	1.92×10^{-2}	Down-regulated
NM_001321982	PRKAR2A	-1.12	5.23×10^{-4}	2.02×10^{-2}	Down-regulated
NM_012134	LMOD1	1.34	5.77×10^{-4}	2.17×10^{-2}	Up-regulated
NM_001362848	NAGA	1.10	6.02×10^{-4}	2.22×10^{-2}	Up-regulated
NM_001278623	NFXL1	-1.32	6.67×10^{-4}	2.38×10^{-2}	Down-regulated
NM_001352803	TACC1	-1.23	7.26×10^{-4}	2.51×10^{-2}	Down-regulated
NM_182543	NSUN6	1.10	7.70×10^{-4}	2.61×10^{-2}	Up-regulated

NM_007013	WWP1	-1.09	9.19×10^{-4}	2.90×10^{-2}	Down-regulated
NM_021070	LTBP3	1.44	1.04×10^{-3}	3.12×10^{-2}	Up-regulated
NM_001195555	CLINT1	1.04	1.26×10^{-3}	3.50×10^{-2}	Up-regulated
NM_004719	SCAF11	1.25	1.51×10^{-3}	3.90×10^{-2}	Up-regulated
NM_001282408	IL1RL1	-1.36	1.59×10^{-3}	4.03×10^{-2}	Down-regulated
NM_001277163	CEACAM3	-1.46	1.68×10^{-3}	4.15×10^{-2}	Down-regulated
NM_001190965	ZMYM2	-1.11	1.87×10^{-3}	4.41×10^{-2}	Down-regulated
NM_006511	RSC1A1	1.02	2.04×10^{-3}	4.62×10^{-2}	Up-regulated
NM_001385402	IRF9	-1.79	2.09×10^{-3}	4.69×10^{-2}	Down-regulated
NM_001199381	RNF145	-1.00	2.11×10^{-3}	4.72×10^{-2}	Down-regulated

* Differential gene expression analysis was performed using DESeq2.

* *P* values were calculated based on Wald tests within the DESeq2 model. Adjusted *p* values were corrected for multiple testing using the Benjamini–Hochberg false discovery rate (FDR) procedure.

Supplementary Table 6. Differentially expressed genes in the Low-PRS group (|log2FoldChange| > 1 and adjusted *p*-value < 0.05)

Variable	Gene	Log2 Fold Change	*p*	p_{adj}	Expression Trend (NTs vs Control)
NM_001201404	WASF2	-1.62	9.05×10^{-5}	0.026	Up-regulated

* Differential gene expression analysis was performed using DESeq2, which applies a negative binomial distribution framework as described by Love et al[1].

* *P* values were calculated based on Wald tests within the DESeq2 model. Adjusted *p* values were corrected for multiple testing using the Benjamini–Hochberg false discovery rate (FDR) procedure.

Supplementary Table 7. Generalized Estimating Equations of outcomes include baseline and 19-week in the High-PRS group

Variable	Time	Expression Trend (NTs vs Control)	Mean difference in change between group (NTs group vs Control group)		
			β	95%CI	*p*
5-Methoxyindole-3-acetic acid (nmol/L)	T2vsT0	Up-regulated	0.84	(0.36, 1.33)	0.00066
L-Alanine (nmol/L)	T2vsT0	Down-regulated	-14745.52	(-23638.80, -5852.24)	0.0012
Benzoic acid (nmol/L)	T2vsT0	Up-regulated	210.44	(56.70, 364.18)	0.0073
L-3,4-dihydroxyphenylalanine (nmol/L)	T2vsT0	Down-regulated	-49.48	(-86.19, -12.78)	0.0082
Indole-3-acetic acid (nmol/L)	T2vsT0	Down-regulated	-455.05	(-794.63, -115.47)	0.0086
Deoxyuridine (nmol/L)	T2vsT0	Up-regulated	3.71	(0.86, 6.56)	0.011
7-Dehydrocholesterol (nmol/L)	T2vsT0	Down-regulated	-226.00	(-415.26, -36.74)	0.019
Glyceric acid (nmol/L)	T2vsT0	Down-regulated	-28960.53	(-54609.75, -3311.32)	0.027
Uric acid (nmol/L)	T2vsT0	Down-regulated	-68304.80	(-129364.60, -7245.00)	0.028
Phenylglyoxylic acid (nmol/L)	T2vsT0	Down-regulated	-9.33	(-17.90, -0.76)	0.033
Epinephrine (nmol/L)	T2vsT0	Up-regulated	923.93	(69.80, 1778.07)	0.034
Acetoacetic acid (nmol/L)	T2vsT0	Down-regulated	-1.33	(-2.59, -0.08)	0.037
5'-Deoxy-5'-methylthioadenosine (nmol/L)	T2vsT0	Up-regulated	20.56	(1.10, 40.03)	0.038

N6-Acetyl-L-lysine (nmol/L)	T2vsT0	Down-regulated	-8.73	(-16.96, -0.49)	0.038
Cyclic AMP (nmol/L)	T2vsT0	Down-regulated	-4.20	(-8.25, -0.16)	0.041
L-Valine (nmol/L)	T2vsT0	Down-regulated	-33024.25	(-65673.49, -375.02)	0.047
Pseudouridine (nmol/L)	T2vsT0	Up-regulated	37849.32	(217.42, 75481.23)	0.049

* T0 refers to the baseline measurement, T2 indicates the endpoint measurement, T2vsT0 represents the change from T0 to T2.

* *P* values are based on repeated measures analysis using generalized estimating equations (GEE), with models including the interaction between group assignment and time. Covariates adjusted in the models were baseline values of the outcomes, age, sex, and dietary nucleotide intake.

* Primary assessment timepoints include baseline and 19-week.

Supplementary Table 8. Generalized Estimating Equations of outcomes include baseline and 19-week in the Low-PRS group

Variable	Time	Expression Trend (NTs vs Control)	Mean difference in change between group (NTs group vs Control group)		
			β	95%CI	*p*
3-Ureidopropionic acid (nmol/L)	T2vsT0	Up-regulated	1.13	(0.44, 1.83)	0.0014
Testosterone (nmol/L)	T2vsT0	Down-regulated	-3.20	(-5.19, -1.21)	0.0016
2-Piperidone (nmol/L)	T2vsT0	Down-regulated	-1222.49	(-2037.64, -407.33)	0.0033
L-Glutamine (nmol/L)	T2vsT0	Up-regulated	61068.40	(15774.52, 106362.29)	0.0082
L-Argininosuccinic Acid (nmol/L)	T2vsT0	Up-regulated	27.84	(7.12, 48.55)	0.0085
Corticosterone (nmol/L)	T2vsT0	Down-regulated	-2.33	(-4.17, -0.48)	0.014
Sucrose (nmol/L)	T2vsT0	Down-regulated	-234.21	(-427.57, -40.84)	0.018
L-Serine (nmol/L)	T2vsT0	Up-regulated	10304.47	(1616.41, 18992.52)	0.020
Gentiobiose (nmol/L)	T2vsT0	Down-regulated	-2356.89	(-4418.30, -295.47)	0.025
Ectoine (nmol/L)	T2vsT0	Down-regulated	-11.43	(-21.59, -1.27)	0.028
N6-Acetyl-L-lysine (nmol/L)	T2vsT0	Down-regulated	-7.66	(-14.52, -0.81)	0.028
Caffeine (nmol/L)	T2vsT0	Up-regulated	27.90	(2.32, 53.49)	0.033
Guanidoacetic acid (nmol/L)	T2vsT0	Down-regulated	-316.37	(-613.94, -18.79)	0.037

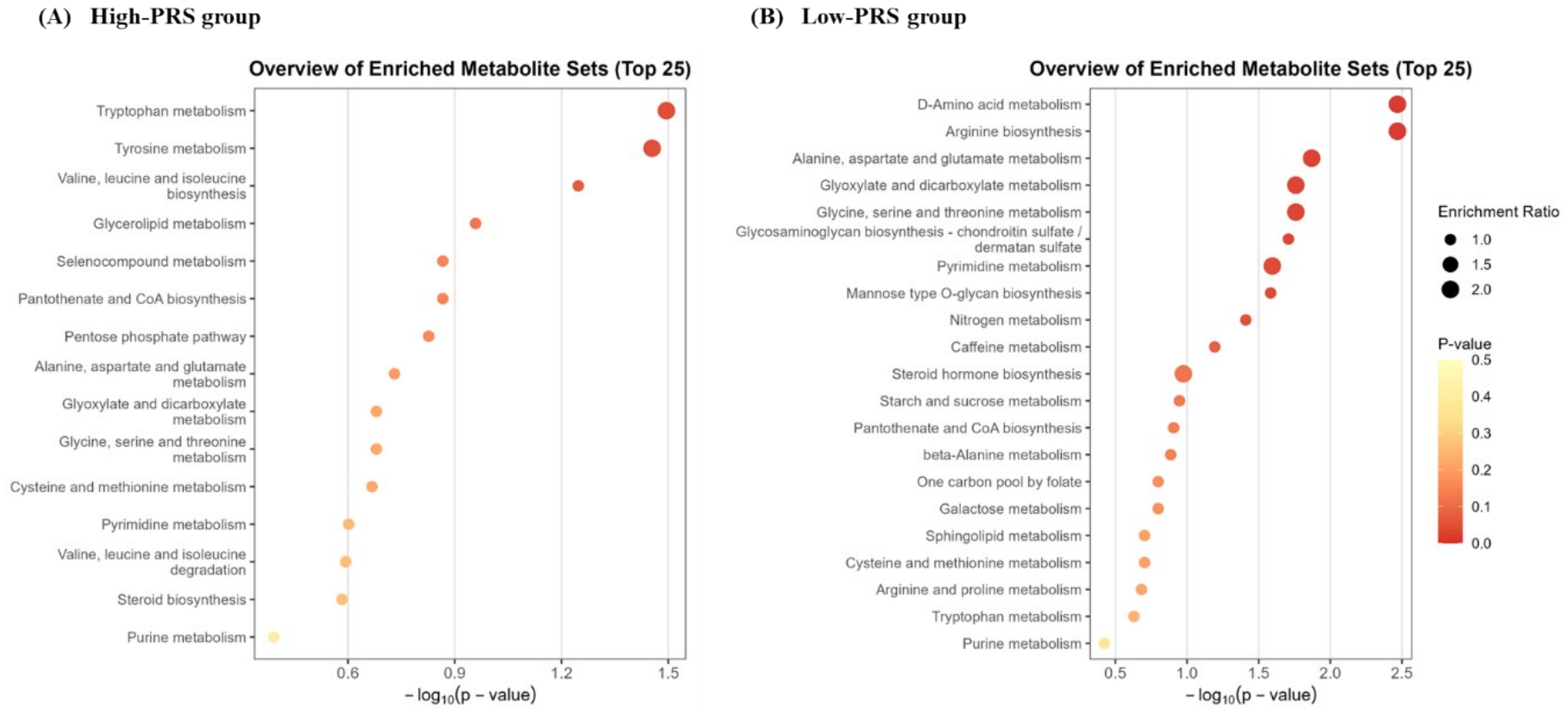
Aspartame (nmol/L)	T2vsT0	Down-regulated	-271.51	(-530.94, -12.08)	0.040
Aminohippuric acid (nmol/L)	T2vsT0	Up-regulated	26.73	(0.67, 52.78)	0.044
Indole-3-acetic acid (nmol/L)	T2vsT0	Up-regulated	329.15	(9.23, 649.08)	0.044
N4-Acetylcytidine (nmol/L)	T2vsT0	Down-regulated	-5.14	(-10.23, -0.04)	0.048

* T0 refers to the baseline measurement, T2 indicates the endpoint measurement, T2vsT0 represents the change from T0 to T2.

* *P* values are based on repeated measures analysis using generalized estimating equations (GEE), with models including the interaction between group assignment and time. Covariates adjusted in the models were baseline values of the outcomes, age, sex, and dietary nucleotide intake.

* Primary assessment timepoints include baseline and 19-week.

Supplementary Figure 2. Metabolic pathway enrichment analysis (KEGG) of different FBG-PRS risk groups



* (A) Top 25 enriched pathways in the High-PRS group(n=60). (B) Top 25 enriched pathways in the Low-PRS group(n=61).

Supplementary Table 9. Overlapping enriched pathways between SMPDB and KEGG in the High-PRS group

SMPDB metabolite set name	KEGG pathway name	Match
Tryptophan Metabolism	Tryptophan Metabolism	Exact
Tyrosine Metabolism	Tyrosine Metabolism	Exact
Glycerolipid Metabolism	Glycerolipid Metabolism	Exact
Valine, Leucine and Isoleucine Degradation	Valine, Leucine and Isoleucine Degradation	Exact
Steroid Biosynthesis	Steroid Biosynthesis	Exact
Purine Metabolism	Purine Metabolism	Exact
Pyrimidine Metabolism	Pyrimidine Metabolism	Exact
Glycine and Serine Metabolism	Glycine, serine and threonine metabolism	Related
Methionine Metabolism	Cysteine and methionine metabolism	Related
Glutamate Metabolism	Alanine, aspartate and glutamate metabolism	Related
Selenoamino Acid Metabolism	Selenocompound metabolism	Related

[1] Love M I, Huber W, Anders S. Moderated estimation of fold change and dispersion for RNA-seq data with DESeq2 [J]. Genome Biol, 2014, 15(12): 550.