

Cell Genomics, Volume 4

Supplemental information

**Novel insights into the genetic architecture
of pregnancy glycaemic traits
from 14,744 Chinese maternities**

Huanhuan Zhu, Han Xiao, Linxuan Li, Meng Yang, Ying Lin, Jieqiong Zhou, Xinyi Zhang, Yan Zhou, Xianmei Lan, Jiuying Liu, Jingyu Zeng, Lin Wang, Yuanyuan Zhong, Xiaobo Qian, Zhongqiang Cao, Panhong Liu, Hong Mei, Mingzhi Cai, Xiaonan Cai, Zhuangyuan Tang, Liqin Hu, Rui Zhou, Xun Xu, Huanming Yang, Jian Wang, Xin Jin, and Aifen Zhou

Figure S1. The basic information of study participants, related to Table 1

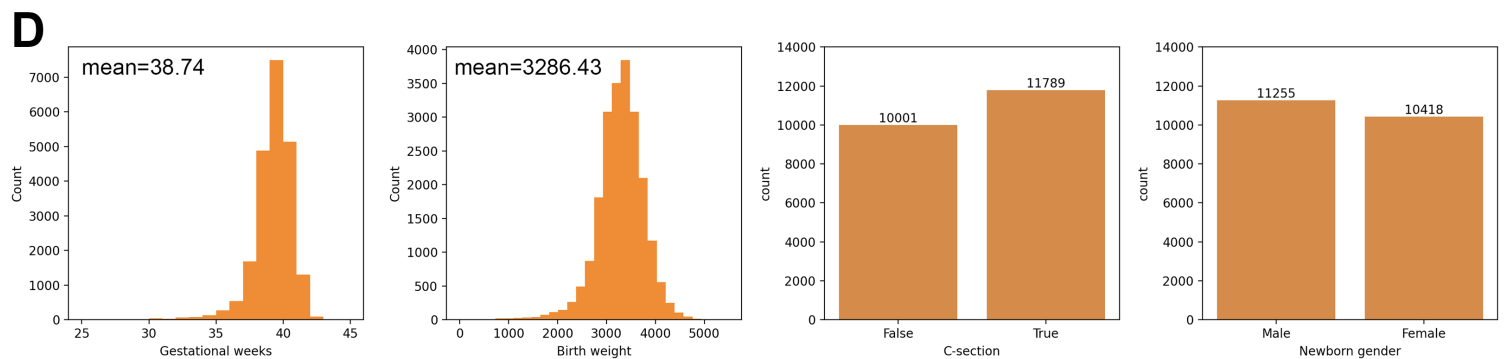
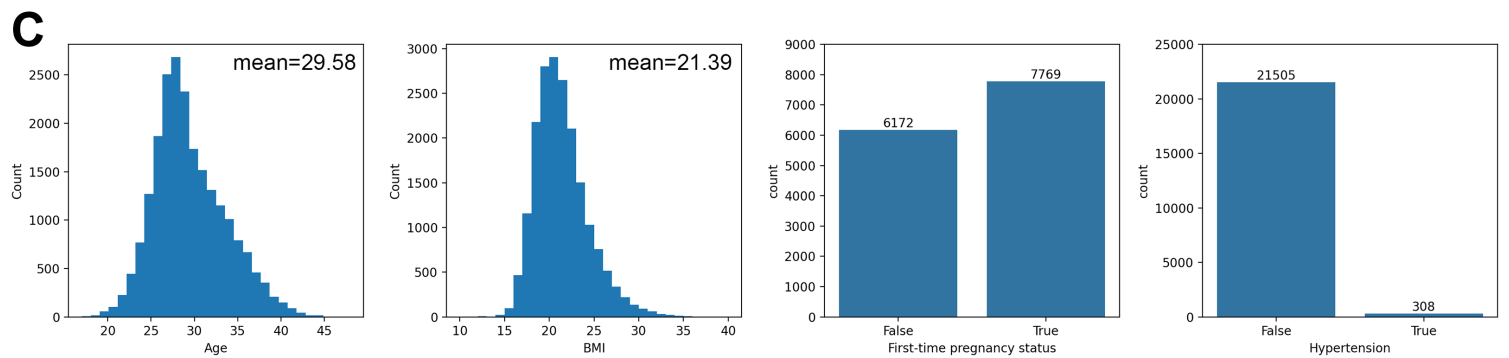
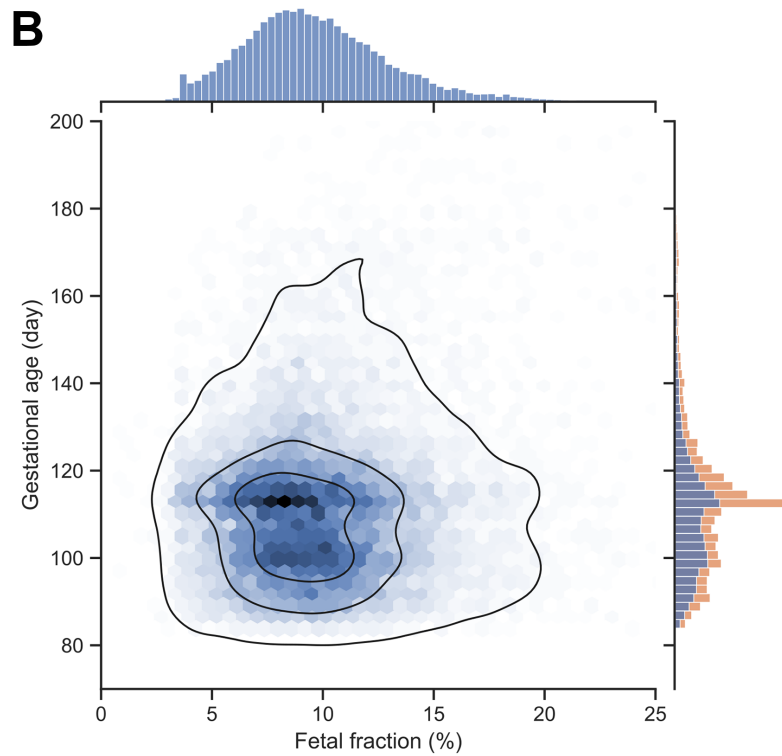
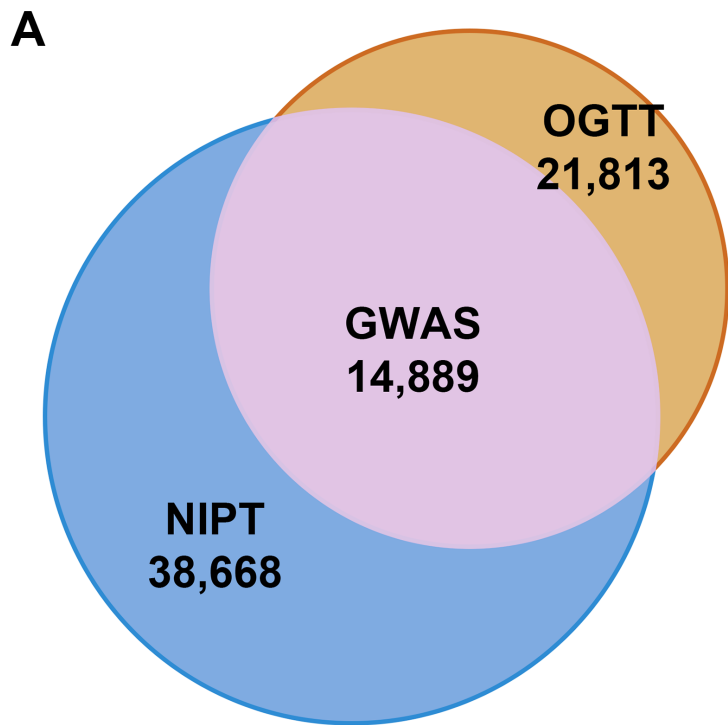


Figure S2. Statistics on glyceimic traits and regression analysis with laboratory features, related to Table 1

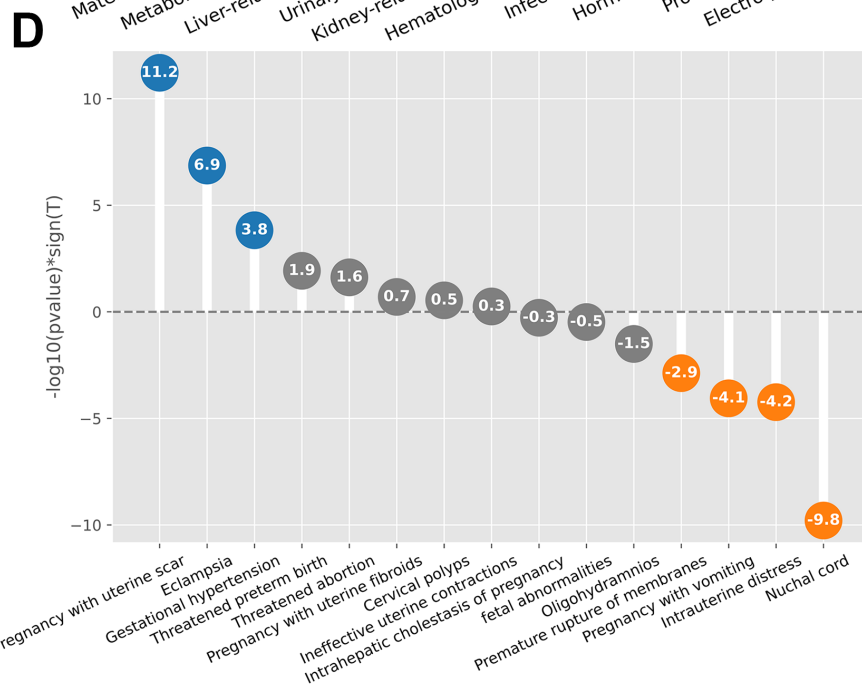
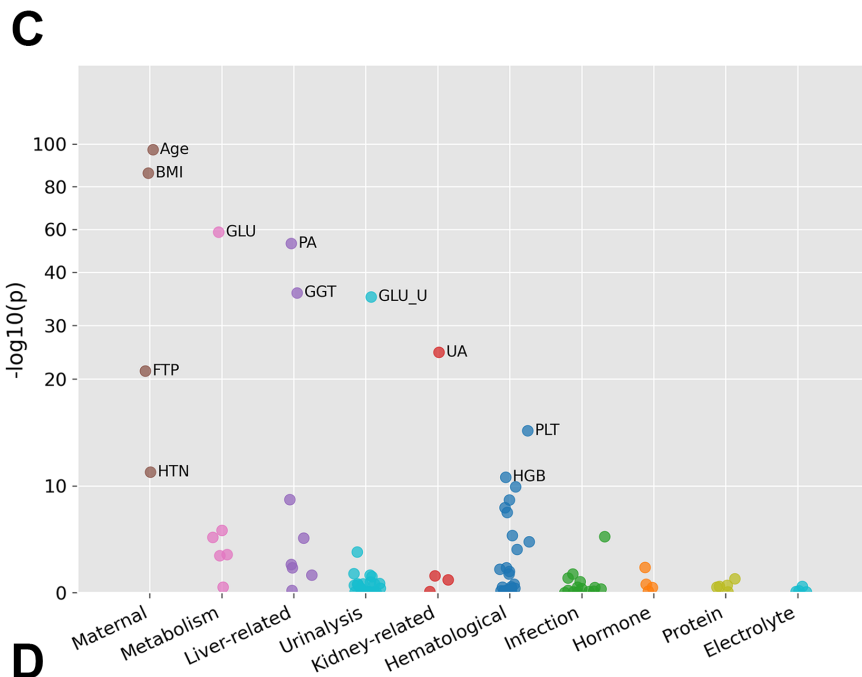
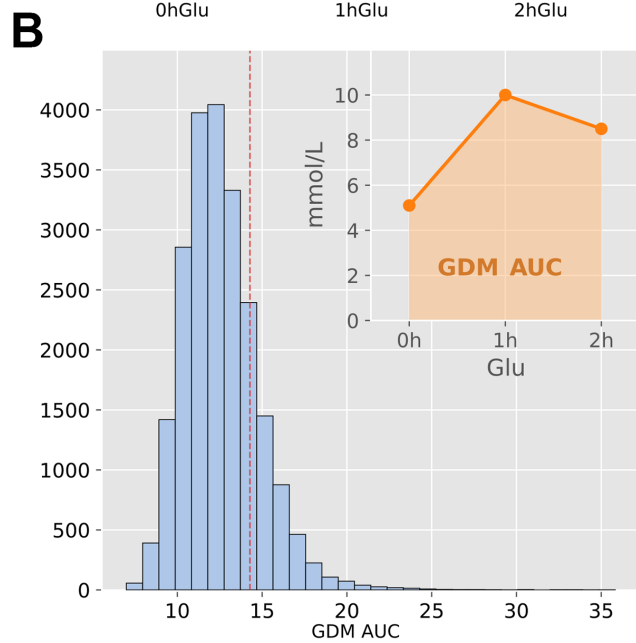
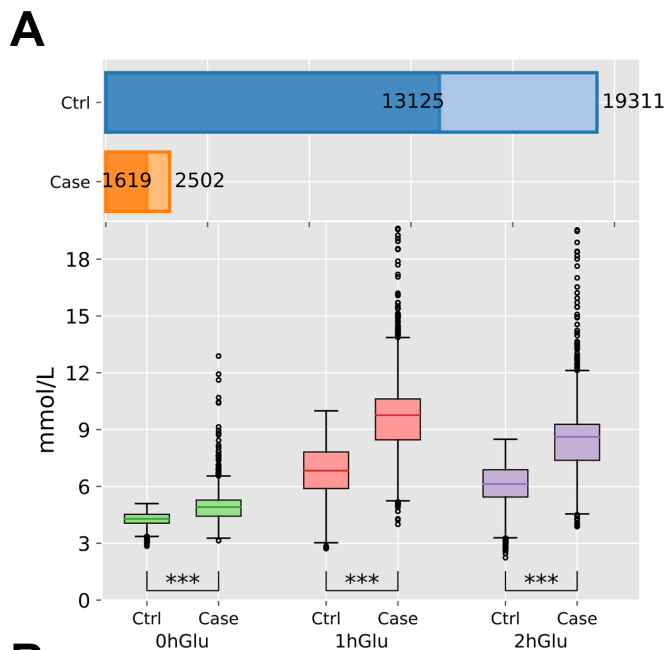


Figure S3. The assessment of sequencing and genotype imputation, related to STAR Methods

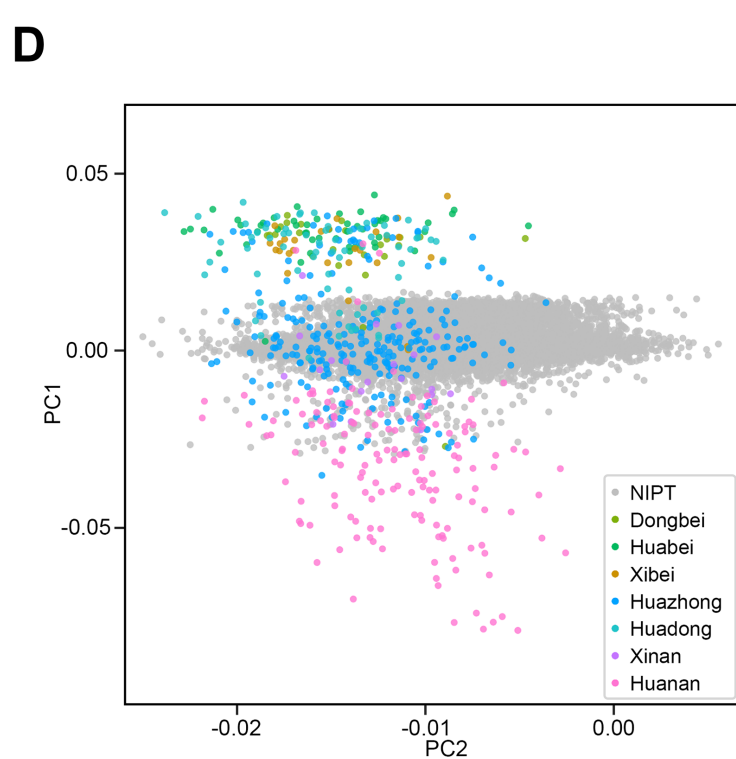
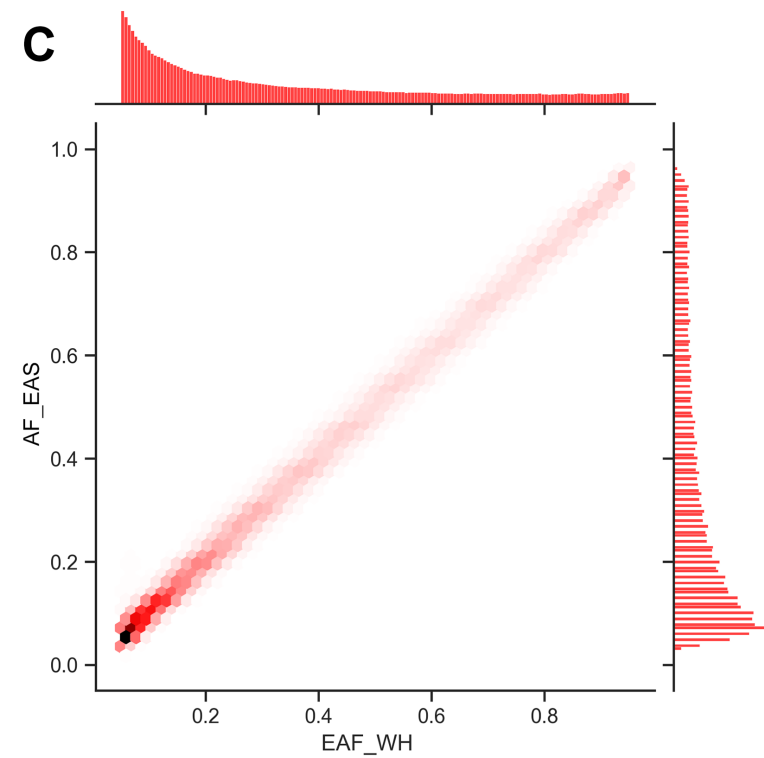
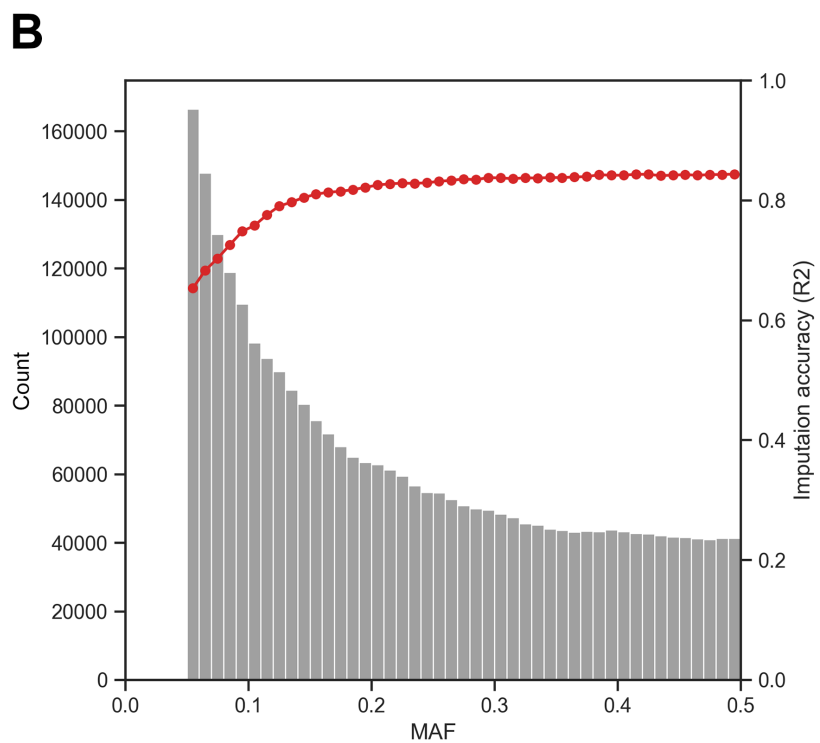
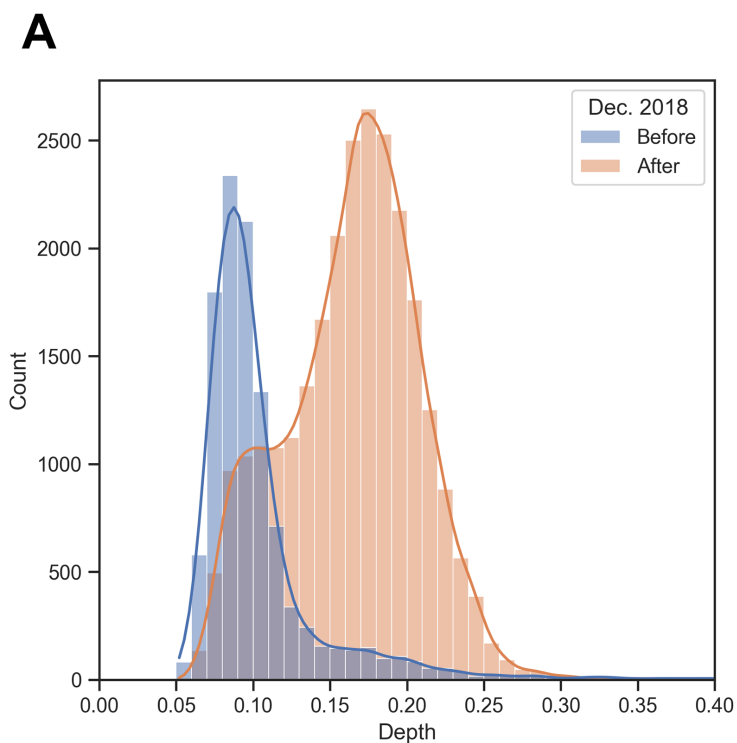


Figure S4. The results of colocalization analysis between discovery and replication studies in the region of gene *ESR1*, related to Figure 1

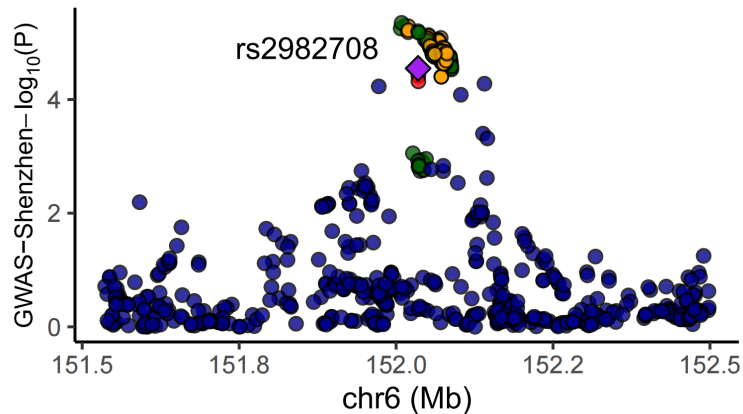
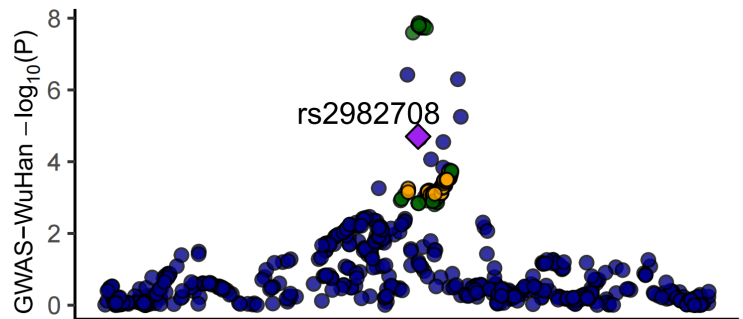
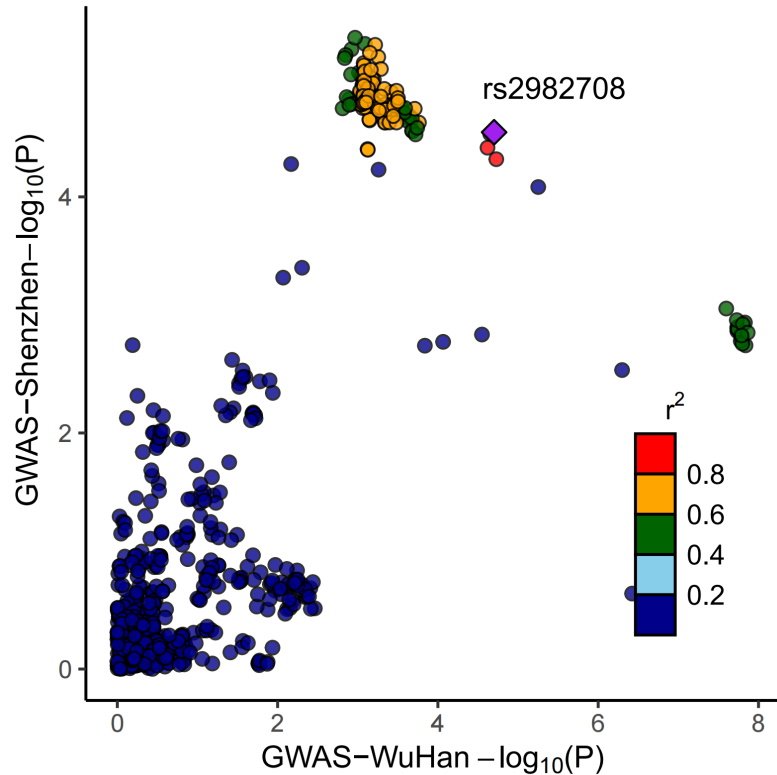


Figure S5. The TWAS results between GTEx data and glycemic traits, related to STAR Methods

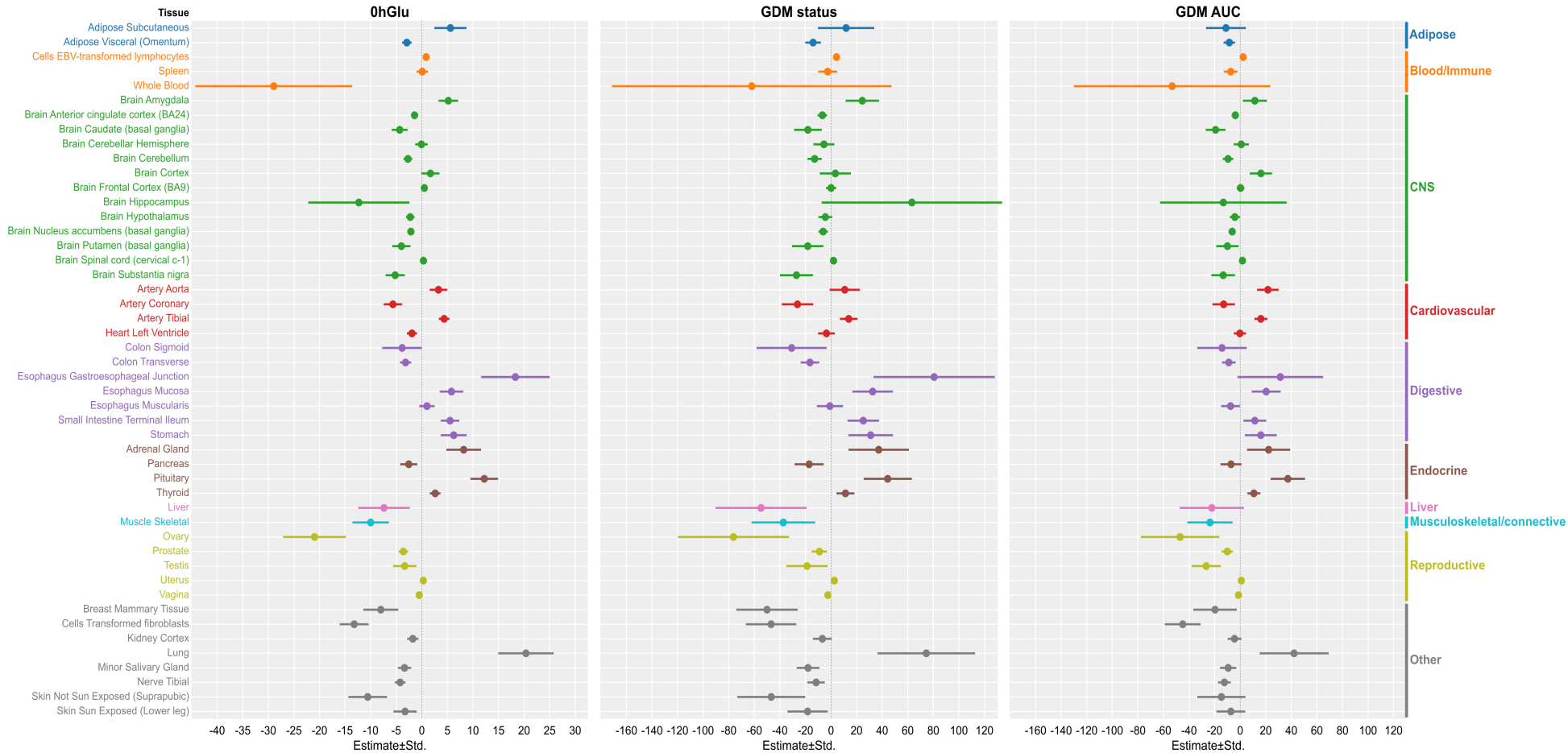
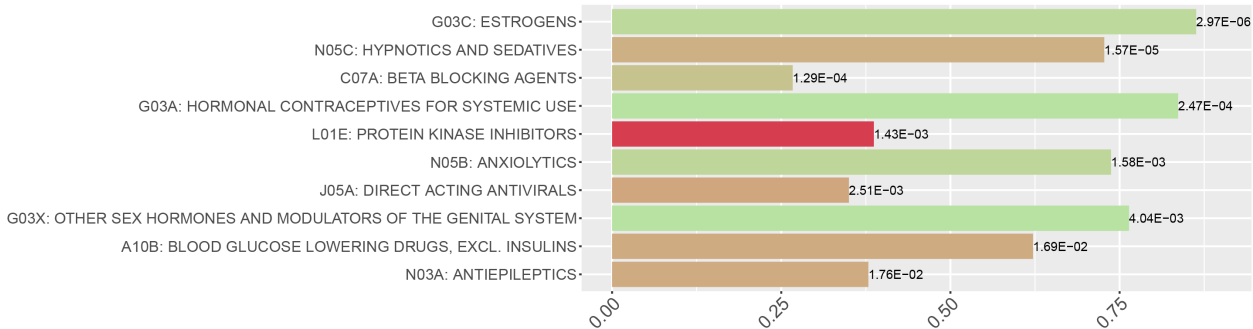


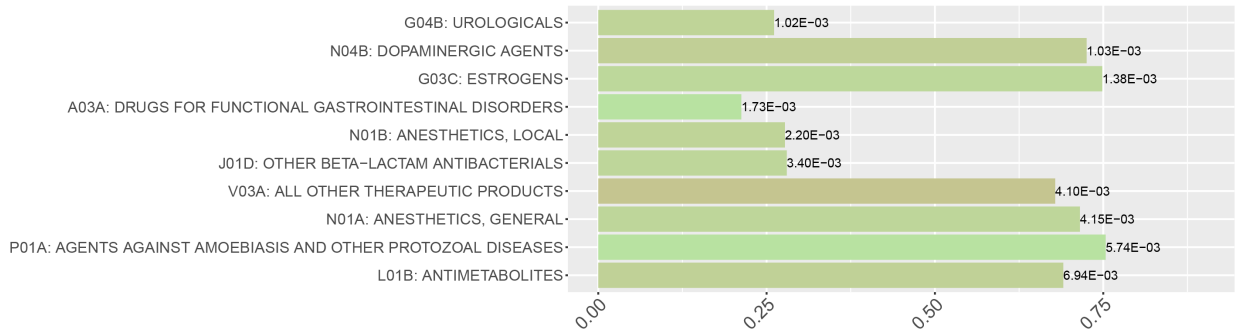
Figure S6. The top ten drug ATC classifications from DTEA analysis, related to STAR Methods

Anatomical therapeutic chemical classification

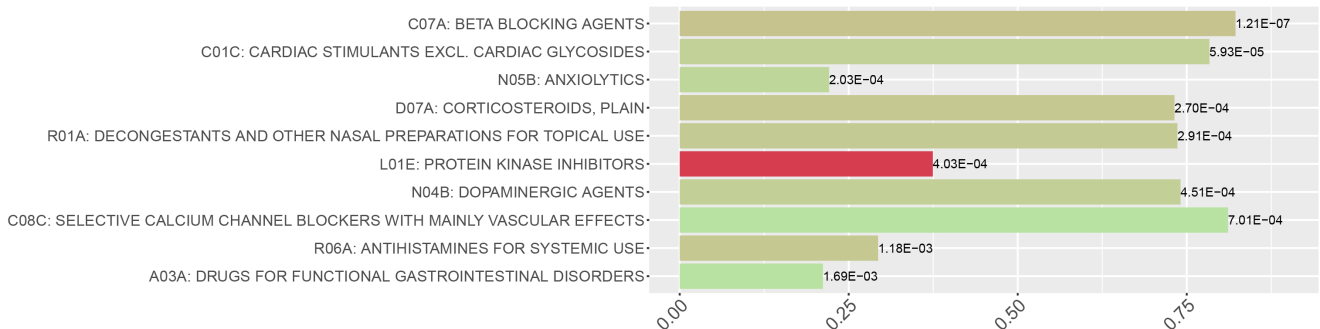
0hGlu



GDM status



GDM AUC



Area under the curve

Table S1. The univariate regression analysis of GDM status and GDM AUC on early-stage laboratory traits, related to Table 1

Trait information					GDM status univariate regression			GDM AUC univariate regression		
Category	Trait	Abbreviation	n	mean±std case(%)	beta	std.	pvalue	beta	std.	pvalue
Metabolism	Blood glucose	GLU	11557	4.51±0.48	1.101	0.068	1.75E-59	1.219	0.048	3.29E-140
Liver-related	Prealbumin	PA	17417	224.17±36.74	0.011	0.001	3.26E-54	0.011	0.001	1.83E-114
Liver-related	γ -glutamyl transferase	GGT	17417	14.30±10.11	0.027	0.002	7.36E-37	0.033	0.002	1.74E-67
Urinalysis	Urine glucose	GLU U	18619	2187(11.75%)	0.825	0.066	4.29E-36	0.957	0.056	3.77E-65
Kidney-related	Uric acid	UA	17807	212.06±48.87	0.005	0.001	9.21E-26	0.005	0.000	2.45E-44
Hematological	Platelet count	PLT	18790	237.63±55.22	0.004	0.000	6.86E-16	0.004	0.000	2.09E-30
Hematological	Hemoglobin	HGB	18790	125.17±10.25	0.017	0.003	1.55E-11	0.015	0.002	6.46E-18
Hematological	White blood cell count	WBC	18790	9.17±2.13	0.076	0.012	1.21E-10	0.077	0.008	1.91E-19
Liver-related	Alkaline phosphatase	ALP	17417	44.24±10.41	0.015	0.002	1.94E-09	0.018	0.002	5.60E-24
Hematological	Plateletcrit	PCT	15752	0.23±0.06	2.866	0.478	2.02E-09	2.698	0.341	2.63E-15
Hematological	Red blood cell count	RBC	18790	4.26±0.38	0.380	0.067	1.12E-08	0.367	0.047	9.55E-15
Hematological	Hematocrit	HCT	18790	37.67±2.98	0.048	0.009	2.97E-08	0.047	0.006	1.47E-14
Metabolism	Oral glucose tolerance test-fasting	OGTT0h	102	5.02±1.07	4.227	0.877	1.43E-06	2.925	0.270	3.04E-18
Hematological	platelet larger cell ratio	P-LCR	15646	28.46±7.90	-0.017	0.004	4.30E-06	-0.014	0.003	3.71E-08
Infection	Herpes simplex virus type 2 specific IgG antibody	HSV-2 IgG	6591	474(7.19%)	0.640	0.141	5.48E-06	0.410	0.121	6.86E-04
Metabolism	Hemoglobin A1c	HbA1C	230	5.20±0.56	2.527	0.560	6.38E-06	3.758	0.328	7.14E-23
Liver-related	Alanine aminotransferase	ALT	17419	16.92±16.50	0.006	0.001	7.99E-06	0.010	0.001	5.51E-18
Hematological	Neutrophil count	NEU	12698	6.64±1.81	0.073	0.017	1.75E-05	0.079	0.012	8.34E-11
Hematological	Lymphocyte count	LYM	12698	1.81±0.50	0.245	0.063	9.11E-05	0.192	0.044	1.36E-05
Urinalysis	Urine PH level	pH	18619	6.54±0.71	-0.143	0.038	1.53E-04	-0.082	0.026	1.71E-03
Metabolism	Oral glucose tolerance test-1 hour	OGTT1h	68	9.75±2.81	0.734	0.201	2.68E-04	1.496	0.056	2.87E-37
Metabolism	Oral glucose tolerance test-2 hour	OGTT2h	68	8.16±2.65	0.727	0.204	3.54E-04	1.499	0.087	4.95E-26
Liver-related	Total bilirubin	TBIL	17417	8.43±3.47	-0.025	0.008	2.24E-03	-0.027	0.005	8.34E-07
Hormone	Free triiodothyronine	FT3	17500	3.39±0.77	0.086	0.030	4.32E-03	0.082	0.024	5.72E-04
Liver-related	Direct bilirubin	DBIL	17417	3.06±1.20	-0.068	0.024	4.49E-03	-0.090	0.016	8.04E-09
Hematological	Monocyte count	MONO	12698	0.51±0.18	0.471	0.167	4.66E-03	0.360	0.118	2.29E-03
Hematological	Platelet size deviation width	PDW	18634	13.03±2.44	-0.030	0.011	6.56E-03	-0.025	0.007	6.60E-04
Hematological	Mean platelet volume	MPV	18634	9.95±1.45	-0.046	0.018	1.00E-02	-0.049	0.013	9.50E-05
Urinalysis	Ketones in urine	KET	18619	6057(32.53%)	0.131	0.054	1.62E-02	0.102	0.039	9.13E-03
Hematological	Mean corpuscular hemoglobin concentration	MCHC	18790	332.57±15.96	0.004	0.002	1.75E-02	0.002	0.001	5.56E-02
Infection	C-reactive protein	CRP	4134	5.17±6.45	0.017	0.007	1.80E-02	0.014	0.007	3.31E-02
Urinalysis	Crystals in Urine	X'TAL U	18453	7.97±117.71	0.001	0.000	2.21E-02	0.000	0.000	9.79E-02
Liver-related	Aspartate aminotransferase	AST	17417	17.70±8.81	0.006	0.003	2.22E-02	0.010	0.002	1.08E-06
Kidney-related	Serum creatinine	Cr	17807	43.45±6.23	-0.010	0.004	2.63E-02	-0.015	0.003	3.17E-07
Urinalysis	Small round epithelial cells in urine	SRC U	18453	3.48±4.76	0.013	0.006	3.18E-02	0.009	0.005	5.27E-02
Infection	Hepatitis B envelope antibody	HBeAb	17851	1.41±0.76	-0.079	0.039	4.33E-02	-0.063	0.024	9.01E-03
Protein	Ferritin	Ferr	938	82.26±66.15	0.003	0.002	5.09E-02	0.001	0.001	3.06E-01
Kidney-related	Cystatin C	CysC	17624	0.67±0.16	0.325	0.173	6.07E-02	0.287	0.119	1.62E-02
Infection	Hepatitis B core antibody	HBeAb	17851	1.46±0.86	-0.051	0.030	9.61E-02	-0.073	0.022	7.44E-04
Urinalysis	Urine specific gravity	SG	18619	1.02±0.01	5.653	3.430	9.93E-02	1.187	2.405	6.22E-01
Urinalysis	Leukocytes esterase in urine	LEU	18619	9282(49.85%)	-0.076	0.052	1.42E-01	-0.089	0.037	1.56E-02
Urinalysis	Casts in urine	CAST U	18452	3.17±4.20	-0.010	0.007	1.44E-01	-0.014	0.005	1.79E-03
Urinalysis	Urine clarity	Clarity	18608	8491(45.63%)	-0.076	0.052	1.46E-01	-0.086	0.037	1.97E-02
Urinalysis	Urine conductivity	Cond	18452	18.07±8.34	-0.004	0.003	1.52E-01	-0.003	0.002	2.08E-01
Hormone	Free thyroxine	FT4	17501	2.81±5.19	-0.007	0.005	1.62E-01	-0.005	0.004	1.98E-01
Hematological	Mean corpuscular volume	MCV	18790	88.61±5.43	-0.006	0.005	1.69E-01	-0.004	0.003	1.93E-01

Urinalysis	Protein in urine	PRO	18602	11542(62.05%)	0.072	0.054	1.86E-01	0.047	0.038	2.11E-01
Protein	Albumin/globulin ratio	AGR	17417	1.68±0.24	-0.147	0.115	1.99E-01	-0.110	0.080	1.69E-01
Urinalysis	Unlysed red blood cell percentage in urine	Unlysed RBC(%)	18453	68.27±22.97	-0.001	0.001	2.03E-01	0.000	0.001	8.09E-01
Electrolyte	Sodium	Na	150	137.15±2.33	0.209	0.183	2.54E-01	-0.013	0.076	8.69E-01
Protein	Globulin	GLB	17417	26.73±3.16	0.010	0.008	2.56E-01	0.008	0.006	1.78E-01
Hematological	Neutrophil percentage	NEU%	12698	72.67±5.89	0.006	0.006	2.84E-01	0.009	0.004	2.23E-02
Protein	Total protein	TP	17417	70.89±3.83	0.007	0.007	2.97E-01	0.005	0.005	3.48E-01
Metabolism	Vitamin D	Vit D	1401	19.60±6.93	-0.012	0.012	2.98E-01	0.000	0.009	9.74E-01
Hematological	Red cell distribution width-coefficient of variation	RDW-CV	18782	13.31±1.37	-0.020	0.020	3.07E-01	-0.016	0.013	2.37E-01
Infection	Cytomegalovirus IgG antibody	CMV IgG	6928	6445(93.03%)	0.176	0.174	3.11E-01	0.133	0.118	2.57E-01
Infection	Hepatitis B envelope antigen	HBeAg	17851	10.88±140.44	0.000	0.000	3.18E-01	0.000	0.000	3.44E-01
Hormone	β-human chorionic gonadotropin	β-hCG	8250	36380.08±48609.71	0.000	0.000	3.24E-01	0.000	0.000	2.72E-01
Urinalysis	Bacteria count in urine	BACT U	18606	1037.48±2397.54	0.000	0.000	3.74E-01	0.000	0.000	2.32E-02
Urinalysis	Bilirubin in urine	BIL	18619	129(0.69%)	0.242	0.279	3.85E-01	-0.372	0.215	8.39E-02
Hematological	Lymphocyte percentage	LYM%	12698	20.41±5.07	-0.005	0.006	3.96E-01	-0.009	0.004	4.06E-02
Hematological	Eosinophil percentage	EOS%	12698	1.05±1.01	-0.028	0.033	3.98E-01	-0.013	0.022	5.50E-01
Infection	Rubella IgM antibody	Rub IgM	8675	72(0.83%)	-0.381	0.467	4.15E-01	-0.160	0.278	5.66E-01
Infection	Rubella IgG antibody	Rub IgG	7250	5765(79.52%)	-0.074	0.099	4.58E-01	-0.066	0.071	3.54E-01
Hematological	Monocyte percentage	MONO%	12698	5.67±1.77	-0.012	0.018	4.95E-01	-0.021	0.012	9.51E-02
Urinalysis	White blood cell count in urine	WBC U	18607	72.35±270.76	0.000	0.000	5.04E-01	0.000	0.000	5.69E-01
Infection	Herpes simplex virus type 2 specific IgM antibody	HSV-2 IgM	6592	18(0.27%)	0.371	0.770	6.30E-01	-0.539	0.627	3.90E-01
Liver-related	Total bile acid	TBA	230	2.36±2.82	-0.069	0.150	6.46E-01	0.037	0.078	6.39E-01
Electrolyte	Calcium	Ca	150	2.36±0.10	1.504	3.602	6.76E-01	-2.491	1.669	1.38E-01
Hematological	Mean corpuscular hemoglobin	MCH	18790	29.45±1.94	0.005	0.013	6.87E-01	0.001	0.009	9.20E-01
Hematological	Basophil count	BASO	12698	0.02±0.04	0.237	0.596	6.91E-01	1.095	0.544	4.43E-02
Hematological	Eosinophil count	EOS	12698	0.10±0.10	0.110	0.322	7.31E-01	0.170	0.225	4.48E-01
Infection	Hepatitis B surface antibody	HBsAb	17851	335.96±390.31	0.000	0.000	7.42E-01	0.000	0.000	6.38E-01
Hormone	Thyroid-stimulating hormone	TSH	17627	1.52±2.16	-0.004	0.014	7.50E-01	-0.005	0.008	5.80E-01
Urinalysis	Red blood cell count in urine	RBC U	18607	28.61±176.91	0.000	0.000	7.88E-01	0.000	0.000	3.11E-01
Urinalysis	Epithelial cell count in urine	EC U	18452	36.36±44.17	0.000	0.001	7.90E-01	0.000	0.000	4.56E-01
Kidney-related	Blood urea nitrogen	BUN	17807	2.77±0.74	0.009	0.036	8.00E-01	0.007	0.025	7.85E-01
Infection	Toxoplasma gondii IgG antibody	TOX IgG	6974	553(7.93%)	-0.043	0.171	8.01E-01	-0.071	0.121	5.55E-01
Electrolyte	Chloride	CL	150	100.65±3.02	0.031	0.126	8.07E-01	0.093	0.057	1.07E-01
Infection	Hepatitis C virus antibody	Anti-HCV	18244	0.19±3.01	0.002	0.009	8.28E-01	0.004	0.006	5.64E-01
Urinalysis	Nitrites in urine	NIT	18619	176(0.95%)	0.053	0.267	8.43E-01	-0.079	0.192	6.81E-01
Urinalysis	Fibers in urine	FIBERS	18608	2.03±8.55	0.001	0.003	8.55E-01	0.000	0.002	9.90E-01
Urinalysis	Yeast-like cell in urine	YLC	18608	3.39±24.87	0.000	0.001	8.57E-01	0.000	0.001	9.85E-01
Protein	Albumin	ALB	17417	44.17±2.52	0.002	0.011	8.74E-01	-0.002	0.007	7.92E-01
Electrolyte	Potassium	K	150	3.92±0.40	0.128	0.821	8.76E-01	0.276	0.403	4.96E-01
Urinalysis	Urinary tract infection	UTI	18453	13304(72.10%)	0.009	0.058	8.78E-01	0.019	0.041	6.46E-01
Urinalysis	Lysed red blood cell percentage in urine	Lysed RBC(%)	18453	5.18±13.95	0.000	0.002	8.80E-01	0.000	0.001	7.52E-01
Infection	Toxoplasma gondii IgM antibody	TOX IgM	6975	19(0.27%)	-0.128	1.055	9.03E-01	0.213	0.718	7.66E-01
Hematological	Basophil percentage	BASO%	12698	0.20±0.24	0.014	0.114	9.04E-01	0.153	0.085	7.25E-02
Hematological	Red cell distribution width-standard deviation	RDW-SD	15799	41.60±3.24	-0.001	0.009	9.26E-01	0.000	0.006	9.64E-01
Urinalysis	Urobilinogen	UBG	18619	1376(7.39%)	-0.006	0.100	9.51E-01	-0.161	0.070	2.22E-02
Urinalysis	Blood in urine	BLD	18619	4787(25.71%)	-0.003	0.059	9.54E-01	0.052	0.042	2.14E-01
Infection	Cytomegalovirus IgM antibody	CMV IgM	6929	36(0.52%)	-0.013	1.062	9.90E-01	0.806	0.757	2.87E-01

Table S2. The multiple regression results of GDM status with potential risk factors, related to Table 1

Model:	Logit			
Method:	Maximum Likelihood Estimation			
Df Model:	20			
No. Observations:	3472			
Pseudo R-squared:	0.132			
Log-Likelihood:	-872.266			
LL-Null:	-970.913			
Prob (F-statistic):	3.86E-31			
variables	coef	stderr	z	P> z
Intercept	-12.524	1.597	-7.841	4.46E-15
Age	0.122	0.019	6.311	2.78E-10
GLU U	0.907	0.176	5.156	2.52E-07
GGT	0.031	0.006	4.721	2.35E-06
UA	0.006	0.001	4.075	4.61E-05
PA	0.007	0.002	3.555	3.78E-04
ALT	-0.016	0.006	-2.701	6.90E-03
BMI	0.032	0.02	1.556	1.20E-01
HTN	0.533	0.406	1.312	1.89E-01
ALP	0.009	0.007	1.294	1.96E-01
FTP	-0.166	0.146	-1.135	2.56E-01
HGB	0.016	0.017	0.941	3.47E-01
NEU	0.18	0.229	0.788	4.31E-01
WBC	-0.148	0.219	-0.674	5.01E-01
RBC	-0.195	0.32	-0.61	5.42E-01
PLT	0.004	0.008	0.53	5.96E-01
LYM	0.153	0.297	0.514	6.07E-01
pH	0.046	0.095	0.478	6.33E-01
P-LCR	0.008	0.023	0.34	7.34E-01
PCT	-2.755	8.146	-0.338	7.35E-01
HCT	0.007	0.06	0.12	9.05E-01

Notes: HTN, FTP, Age and BMI are abbreviations for hypertension, first-time pregnancy, maternal age and body mass index, respectively. The full names of other abbreviations are provided in [Table S1](#).

Table S3. The multiple regression analysis of GDM AUC with potential risk factors, related to Table 1

Model:	Ordinary Least Square			
Method:	Least Squares			
Df Model:	24			
No. Observations:	3472			
R-squared:	0.132			
F-statistic:	21.783			
Prob (F-statistic):	4.50E-88			
variables	coef	stderr	z	P> z
Intercept	4.202	2.287	1.837	6.62E-02
Age	0.123	0.011	11.186	1.47E-28
UA	0.005	0.001	6.193	6.61E-10
PA	0.006	0.001	5.559	2.92E-08
GLU U	0.625	0.114	5.491	4.28E-08
Cr	-0.032	0.006	-5.416	6.52E-08
GGT	0.023	0.005	5.035	5.02E-07
DBIL	-0.387	0.095	-4.074	4.73E-05
BMI	0.046	0.012	3.887	1.04E-04
TBIL	0.115	0.033	3.477	5.14E-04
AST	-0.029	0.009	-3.036	2.41E-03
ALT	0.014	0.005	2.727	6.43E-03
FTP	-0.096	0.075	-1.277	2.02E-01
HGB	0.008	0.009	0.902	3.67E-01
PLT	0.004	0.005	0.872	3.83E-01
HTN	0.247	0.316	0.780	4.35E-01
PCT	-3.295	4.788	-0.688	4.91E-01
MPV	0.186	0.294	0.633	5.27E-01
ALP	-0.002	0.004	-0.615	5.39E-01
NEU	0.053	0.131	0.403	6.87E-01
P-LCR	-0.013	0.035	-0.375	7.07E-01
WBC	-0.033	0.125	-0.266	7.90E-01
LYM	-0.015	0.165	-0.089	9.29E-01
HCT	0.002	0.031	0.059	9.53E-01
RBC	0.007	0.159	0.047	9.63E-01

Notes: HTN, FTP, Age and BMI are abbreviations for hypertension, first-time pregnancy, maternal age and body mass index, respectively. The full names of other abbreviations are provided in [Table S1](#).

Table S4. Correlation tests between GDM traits and clinical diagnosis, related to Table 1

Traits info	n(%)			GDM status		GDM AUC	
	Name	All samples	In GDM control	In GDM case	OR	Pvalue	T
Pregnancy with uterine scar, n(%)	1844(11.34%)	1583(10.98%)	261(14.22%)	1.344	4.50E-05	6.883	6.08E-12
Premature rupture of membranes, n(%)	2469(15.19%)	2266(15.72%)	203(11.06%)	0.667	1.95E-07	-3.211	1.33E-03
Intrauterine distress, n(%)	1419(8.73%)	1306(9.06%)	113(6.15%)	0.658	4.02E-05	-4.023	5.77E-05
Threatened preterm birth, n(%)	404(2.49%)	348(2.41%)	56(3.05%)	1.272	1.16E-01	2.516	1.19E-02
Threatened abortion, n(%)	319(1.96%)	278(1.93%)	41(2.23%)	1.162	4.25E-01	2.256	2.41E-02
Eclampsia, n(%)	220(1.35%)	182(1.26%)	38(2.07%)	1.653	6.67E-03	5.272	1.37E-07
Gestational hypertension, n(%)	224(1.38%)	198(1.37%)	26(1.42%)	1.032	9.66E-01	3.795	1.48E-04
Ineffective uterine contractions, n(%)	287(1.77%)	266(1.84%)	21(1.14%)	0.616	4.00E-02	0.583	5.60E-01
Oligohydramnios, n(%)	371(2.28%)	346(2.40%)	25(1.36%)	0.561	6.49E-03	-2.156	3.11E-02
Nuchal cord, n(%)	773(4.76%)	758(5.26%)	15(0.82%)	0.148	6.22E-17	-6.399	1.61E-10
Intrahepatic cholestasis of pregnancy, n(%)	112(0.69%)	98(0.68%)	14(0.76%)	1.123	7.99E-01	-0.631	5.28E-01
Pregnancy with vomiting, n(%)	132(0.81%)	120(0.83%)	12(0.65%)	0.784	5.06E-01	-3.924	8.75E-05
Pregnancy with uterine fibroids, n(%)	96(0.59%)	83(0.58%)	13(0.71%)	1.232	5.92E-01	1.282	2.00E-01
fetal abnormalities, n(%)	122(0.75%)	110(0.76%)	12(0.65%)	0.856	7.13E-01	-0.969	3.32E-01
Cervical polyps, n(%)	68(0.42%)	56(0.39%)	12(0.65%)	1.687	1.43E-01	1.061	2.89E-01

Table S5. Identified associated loci from GWAS, related to Figures 1-2

Trait	Locus INFO						Top SNP INFO						
	name	chrom	start	end	width	snp_count	locus_gene	pos	SNP	gene	pvalue	beta/log(OR)	se
GDM		6	20623948	20724019	100072	54	CDKAL1	20675561	rs35261542	CDKAL1	3.88E-12	0.306	0.044
GDM		11	92980604	92980604	1	1	MTNR1B	92980604	rs3781637	MTNR1B	3.29E-09	-0.676	0.114
GDM_AUC		6	20614483	20829886	215404	76	CDKAL1	20680447	rs9348441	CDKAL1	1.40E-30	0.155	0.013
GDM_AUC		7	128203335	128217273	13939	13	MIR129-1	128212012	rs11981584	<MIR129-1	2.74E-10	0.284	0.045
GDM_AUC		9	4291435	4307369	15935	3	RNU6-694P	4307369	rs79321323	RNU6-694P>	2.41E-12	0.262	0.037
GDM_AUC		10	92492827	92664301	171475	12	IDE, KIF11, EIF2S2P3	92627577	rs1573051	KIF11	8.97E-11	0.090	0.014
GDM_AUC		11	92934966	92994860	59895	11	SNRPGP16, MTNR1B	92980604	rs3781637	MTNR1B	2.09E-31	-0.378	0.032
0hGlu		2	168797218	168956919	159702	3	NOSTRIN, ABCB11	168797218	rs12612019	NOSTRIN>	1.05E-08	-0.707	0.123
0hGlu		5	96379021	96428986	49966	9	PCSK1	96383972	rs10213823	PCSK1>	3.72E-11	-0.091	0.014
0hGlu		6	20664850	20713683	48834	11	CDKAL1	20680447	rs9348441	CDKAL1	1.57E-09	0.083	0.014
0hGlu		6	152026723	152047623	20901	15	ESR1	152036096	rs3020430	ESR1	1.36E-08	0.074	0.013
0hGlu		7	44078957	44137627	58671	8	POLM, POLD2, RNA5SP230, MYL7	44124463	rs3217944	<POLD2	3.57E-13	-0.116	0.016
0hGlu		9	627420	679916	52497	23	KANK1	655864	rs75885458	KANK1	4.78E-09	0.171	0.029
0hGlu		9	4291435	4291435	1	1	RNU6-694P	4291435	rs57132962	RNU6-694P>	1.07E-09	0.306	0.050
0hGlu		11	92948256	92994860	46605	5	SNRPGP16, MTNR1B	92980604	rs3781637	MTNR1B	9.10E-16	-0.264	0.033
0hGlu		20	22540023	22625059	85037	48	LINC00261, FOXA2, LNCNEF	22580744	rs6048206	FOXA2>	2.34E-11	-0.122	0.018
1hGlu		6	20620906	20724019	103114	58	CDKAL1	20675561	rs35261542	CDKAL1	7.41E-25	0.139	0.014
1hGlu		7	128205603	128212012	6410	7	MIR129-1	128212012	rs11981584	<MIR129-1	5.58E-09	0.264	0.045
1hGlu		9	4307369	4307369	1	1	RNU6-694P	4307369	rs79321323	RNU6-694P>	9.89E-09	0.215	0.037
1hGlu		10	92492827	92664301	171475	12	IDE, KIF11, EIF2S2P3	92627577	rs1573051	KIF11	1.50E-10	0.090	0.014
1hGlu		11	92936503	92994860	58358	10	SNRPGP16, MTNR1B	92980604	rs3781637	MTNR1B	5.09E-27	-0.351	0.033
2hGlu		6	20620906	20829886	208981	63	CDKAL1	20680447	rs9348441	CDKAL1	4.61E-25	0.140	0.014
2hGlu		9	4291435	4307369	15935	3	RNU6-694P	4291435	rs57132962	RNU6-694P>	7.22E-13	0.357	0.050
2hGlu		10	69215297	69215297	1	1	HKDC1	69215297	rs58433451	HKDC1>	6.64E-09	-0.638	0.110
2hGlu		11	92948256	92994245	45990	5	SNRPGP16, MTNR1B	92980604	rs3781637	MTNR1B	5.31E-18	-0.281	0.032

Table S6. The summary of GDM associated SNP, related to Figure 2

SNP	rs35261542	rs3781637	rs7754840	rs9348441	rs10830962	rs10830963
Chr	6	11	6	6	11	11
Pos	20675561	92980604	20661019	20680447	92965261	92975544
Gene	<i>CDKALI</i>	<i>MTNR1B</i>	<i>CDKALI</i>	<i>CDKALI</i>	<i>MTNR1B</i>	<i>MTNR1B</i>
A1	A	C	C	A	G	G
A1 freq	0.3729	0.1409	0.3875	0.3606	0.4322	0.4207
Freq EAS	0.3859	0.1349	0.4008	0.3869	0.4296	0.4226
Freq EUR	0.2793	0.0089	0.3181	0.2783	0.4125	0.2883
pv in GDM status	3.88E-12	3.29E-09	4.90E-11	4.00E-12	NA	NA
pv in GDM_{AUC}	1.97E-30	2.09E-31	3.22E-27	1.40E-30	NA	NA
pv in GCST90239750	2.36E-14	2.97E-01	1.51E-11	1.57E-14	3.01E-37	4.30E-54
HWE	1.33E-02	8.31E-02	1.59E-03	4.24E-01	0.00E+00	0.00E+00
Note					removed due to HWE	removed due to HWE

Notes : A1 freq indicates the allele frequency of A1 allele, and HWE indicates hardy-Weinberg equilibrium p-value for each SNP. The Freq EAS and Freq EUR are allele frequencies in EAS and EUR population, respectively, obtained from 1000 genomes project phase 3.

Table S7. Detailed information of studies downloaded from the GWAS catalog, related to Figures 5-6

Index	GWAS catalog study ID	Trait name	Journal	Title	Population	Publication date	URL
1	GCST90018959	Height	Nat Genet	A cross-population atlas of genetic associations for 220 human phenotypes. ¹	360,388 European ancestry individuals, 165,056 East Asian ancestry individuals	2021/9/30	http://ftp.ebi.ac.uk/pub/databases/gwas/summary_statistics/GCST90018001-GCST90019000/GCST90018959
2	GCST90018949	Weight	Nat Genet	A cross-population atlas of genetic associations for 220 human phenotypes. ¹	360,116 European ancestry individuals, 165,419 East Asian ancestry individuals	2021/9/30	http://ftp.ebi.ac.uk/pub/databases/gwas/summary_statistics/GCST90018001-GCST90019000/GCST90018949
3	GCST90000025	Appendicular lean mass	Commun Biol	The genetic architecture of appendicular lean mass characterized by association analysis in the UK Biobank study. ²	450243 European	2020/10/23	http://ftp.ebi.ac.uk/pub/databases/gwas/summary_statistics/GCST90000001-GCST90001000/GCST90000025
4	GCST90020028	Hip circumference adjusted for BMI	Sci Rep	GWAS of allometric body-shape indices in UK Biobank identifies loci suggesting associations with morphogenesis, organogenesis, adrenal cell renewal and cancer. ³	219872 European	2021/5/21	http://ftp.ebi.ac.uk/pub/databases/gwas/summary_statistics/GCST90020001-GCST90021000/GCST90020028
5	GCST006979	Heel bone mineral density	Nat Genet	An atlas of genetic influences on osteoporosis in humans and mice. ⁴	426824 European	2018/12/31	http://ftp.ebi.ac.uk/pub/databases/gwas/summary_statistics/GCST006001-GCST007000/GCST006979
6	GCST006655	Breast size	Sci Rep	Japanese GWAS identifies variants for bust-size, dysmenorrhea, and menstrual fever that are eQTLs for relevant protein-coding or long non-coding RNAs. ⁵	5,609 Japanese ancestry female individuals	2018/5/31	http://ftp.ebi.ac.uk/pub/databases/gwas/summary_statistics/GCST006001-GCST007000/GCST006655
7	GCST90018972	Systolic blood pressure	Nat Genet	A cross-population atlas of genetic associations for 220 human phenotypes. ¹	340,159 European ancestry individuals, 145,505 East Asian ancestry individuals	2021/9/30	http://ftp.ebi.ac.uk/pub/databases/gwas/summary_statistics/GCST90018001-GCST90019000/GCST90018972
8	GCST90018952	Diastolic blood pressure	Nat Genet	A cross-population atlas of genetic associations for 220 human phenotypes. ¹	340,162 European ancestry individuals, 145,515 East Asian ancestry individuals	2021/9/30	http://ftp.ebi.ac.uk/pub/databases/gwas/summary_statistics/GCST90018001-GCST90019000/GCST90018952
9	GCST90018970	Pulse pressure	Nat Genet	A cross-population atlas of genetic associations for 220 human phenotypes. ¹	360,863 European ancestry individuals, 145,445 East Asian ancestry individuals	2021/9/30	http://ftp.ebi.ac.uk/pub/databases/gwas/summary_statistics/GCST90018001-GCST90019000/GCST90018970
10	GCST90019516	Serum phosphate levels	Nat Genet	Genetics of 35 blood and urine biomarkers in the UK Biobank. ⁶	312888 European, 5568 African unspecified, 6685 South Asian	2021/1/18	http://ftp.ebi.ac.uk/pub/databases/gwas/summary_statistics/GCST90019001-GCST90020000/GCST90019516
11	GCST90018976	Serum total protein level	Nat Genet	A cross-population atlas of genetic associations for 220 human phenotypes. ¹	314,921 European ancestry individuals, 133,321 East Asian ancestry individuals	2021/9/30	http://ftp.ebi.ac.uk/pub/databases/gwas/summary_statistics/GCST90018001-GCST90019000/GCST90018976
12	GCST90019511	Insulin-like growth factor 1 levels	Nat Genet	Genetics of 35 blood and urine biomarkers in the UK Biobank. ⁶	340,567 European ancestry individuals, 5,974 African ancestry individuals, 7,283 South Asian ancestry individuals	2021/1/18	http://ftp.ebi.ac.uk/pub/databases/gwas/summary_statistics/GCST90019001-GCST90020000/GCST90019511
13	GCST90018799	Breast cancer	Nat Genet	A cross-population atlas of genetic associations for 220 human phenotypes. ¹	17,389 European ancestry cases, 240,341 European ancestry controls, 6,325 East Asian ancestry cases, 73,225 East Asian ancestry controls	2021/9/30	http://ftp.ebi.ac.uk/pub/databases/gwas/summary_statistics/GCST90018001-GCST90019000/GCST90018799
14	GCST90000047	Age at first sexual intercourse	Nat Hum Behav	Identification of 371 genetic variants for age at first sex and birth linked to externalising behaviour. ⁷	397338 European	2021/7/1	http://ftp.ebi.ac.uk/pub/databases/gwas/summary_statistics/GCST90000001-GCST90001000/GCST90000047
15	GCST90011804	Breast cancer	Nat Commun	Pan-cancer study detects genetic risk variants and shared genetic basis in two large cohorts. ⁸	428231 European	2020/9/4	http://ftp.ebi.ac.uk/pub/databases/gwas/summary_statistics/GCST90011001-GCST90012000/GCST90011804

Table S8. Genetic correlation between glycemc traits and ESR1-associated traits, related to Figure 5

Traits info		0hGlu				GDM status				GDM AUC			
GWAS catalog study ID	Traits name	Rg	Stderr.	Zscore	Pvalue	Rg	Stderr.	Zscore	Pvalue	Rg	Stderr.	Zscore	Pvalue
GCST90018952	Diastolic blood pressure	0.259	0.080	3.219	1.30E-03	0.483	0.377	1.280	2.01E-01	0.190	0.070	2.734	6.30E-03
GCST90018972	Systolic blood pressure	0.244	0.069	3.512	4.00E-04	0.358	0.289	1.236	2.17E-01	0.185	0.070	2.662	7.80E-03
GCST90018949	Weight	0.169	0.060	2.810	5.00E-03	0.202	0.187	1.082	2.80E-01	0.037	0.062	0.598	5.50E-01
GCST006979	Heel bone mineral density	0.069	0.058	1.194	2.33E-01	0.164	0.200	0.817	4.14E-01	0.044	0.058	0.754	4.51E-01
GCST90000047	Age at first sexual intercourse	-0.062	0.061	-1.012	3.12E-01	-0.121	0.154	-0.786	4.32E-01	-0.029	0.052	-0.553	5.80E-01
GCST90019516	Serum phosphate levels	-0.455	0.282	-1.613	1.07E-01	-0.240	0.307	-0.781	4.35E-01	-0.012	0.127	-0.091	9.27E-01
GCST90018970	Pulse pressure	0.129	0.064	2.005	4.50E-02	0.098	0.156	0.626	5.31E-01	0.110	0.070	1.565	1.18E-01
GCST90018976	Serum total protein level	-0.032	0.080	-0.393	6.94E-01	-0.108	0.174	-0.619	5.36E-01	0.026	0.075	0.344	7.31E-01
GCST90019511	Insulin-like growth factor 1 levels	-0.120	0.072	-1.662	9.66E-02	-0.116	0.217	-0.533	5.94E-01	-0.022	0.071	-0.308	7.58E-01
GCST90000025	Appendicular lean mass	0.038	0.054	0.704	4.82E-01	-0.056	0.116	-0.482	6.30E-01	-0.023	0.056	-0.415	6.78E-01
GCST90018959	Height	0.041	0.057	0.717	4.73E-01	0.038	0.116	0.325	7.45E-01	-0.030	0.057	-0.536	5.92E-01
GCST90020028	Hip circumference adjusted for BMI	-0.025	0.067	-0.367	7.14E-01	-0.038	0.154	-0.245	8.06E-01	-0.062	0.068	-0.916	3.60E-01
GCST006655	Breast size	-0.365	0.380	-0.963	3.36E-01	-0.059	0.465	-0.128	8.98E-01	0.223	0.319	0.699	4.84E-01
GCST90018799	Breast cancer	-0.055	0.130	-0.421	6.74E-01	-0.031	0.257	-0.120	9.05E-01	-0.132	0.129	-1.023	3.06E-01

Table S9. Mendelian randomization of ESRI-associated traits on glycemic traits, related to Figure 6

Exposure info		Outcome: 0hGlu						Outcome: GDM status					Outcome: GDM AUC						
GWAS catalog study ID	Traits name	Estimate	Stderr.	Zvalue	OR	Pvalue	(95% CI)	Estimate	Stderr.	Zvalue	OR	Pvalue	(95% CI)	Estimate	Stderr.	Zvalue	OR	Pvalue	(95% CI)
GCST006979	Heel bone mineral density	0.076	0.227	0.334	1.079	7.38E-01	(0.69, 1.68)	0.206	1.640	0.125	1.228	9.00E-01	(0.05, 30.60)	0.090	1.142	0.079	1.094	9.37E-01	(0.12, 10.26)
GCST90000025	Appendicular lean mass	-0.747	0.259	-2.886	0.474	3.91E-03	(0.29, 0.79)	-3.878	1.875	-2.069	0.021	3.86E-02	(0.00, 0.82)	-3.123	1.302	-2.400	0.044	1.64E-02	(0.00, 0.56)
GCST90000047	Age at first sexual intercourse	-0.004	0.037	-0.095	0.996	9.24E-01	(0.93, 1.07)	-0.014	0.270	-0.051	0.986	9.59E-01	(0.58, 1.67)	-0.091	0.188	-0.485	0.913	6.28E-01	(0.63, 1.32)
GCST90011804	Breast cancer	-0.131	0.117	-1.118	0.877	2.64E-01	(0.70, 1.10)	-0.719	0.777	-0.925	0.487	3.55E-01	(0.11, 2.24)	-0.935	0.540	-1.730	0.393	8.36E-02	(0.14, 1.13)
GCST90019516	Serum phosphate levels	0.422	0.144	2.930	1.525	3.40E-03	(1.15, 2.02)	0.402	1.038	0.387	1.495	6.99E-01	(0.20, 11.44)	0.111	0.724	0.153	1.117	8.79E-01	(0.27, 4.62)
GCST90020028	Hip circumference adjusted for BMI	-0.043	0.022	-1.997	0.958	4.59E-02	(0.92, 1.00)	0.130	0.155	0.835	1.138	4.03E-01	(0.84, 1.54)	-0.069	0.108	-0.632	0.934	5.27E-01	(0.75, 1.15)
GCST90018959	Height	0.437	0.196	2.224	1.548	2.61E-02	(1.05, 2.28)	1.598	1.714	0.933	4.943	3.51E-01	(0.17, 142.15)	3.366	1.185	2.840	28.963	4.51E-03	(2.84, 295.49)
GCST90018970	Pulse pressure	0.409	0.111	3.703	1.506	2.14E-04	(1.21, 1.87)	0.499	0.970	0.515	1.647	6.07E-01	(0.25, 11.03)	1.740	0.670	2.597	5.700	9.41E-03	(1.53, 21.20)

Table S10. Transcriptome-wide association study for glycemic traits, related to STAR Methods

Tissue info		0hGlu			GDM status			GDM AUC			
Category	Tissue	Beta	Stderr.	Pvalue	Beta	Stderr.	Pvalue	Beta	Stderr.	Pvalue	
Adipose	Adipose Subcutaneous	5.594	2.950	5.80E-02	11.784	21.243	5.79E-01	-11.120	14.835	4.54E-01	
	Adipose Visceral (Omentum)	-2.922	0.739	7.77E-05	-14.039	5.319	8.31E-03	-8.498	3.720	2.24E-02	
Blood/Immune	Cells EBV-transformed lymphocytes	0.851	0.252	7.48E-04	4.321	1.816	1.73E-02	2.335	1.270	6.59E-02	
	Spleen	0.089	0.918	9.23E-01	-2.579	6.655	6.98E-01	-7.382	4.619	1.10E-01	
	Whole Blood	-28.945	15.127	5.57E-02	-61.981	108.560	5.68E-01	-53.266	76.046	4.84E-01	
CNS	Brain Amygdala	5.180	1.720	2.60E-03	24.459	12.324	4.72E-02	11.483	8.646	1.84E-01	
	Brain Anterior cingulate cortex (BA24)	-1.414	0.412	5.95E-04	-6.762	2.958	2.23E-02	-3.831	2.071	6.43E-02	
	Brain Caudate (basal ganglia)	-4.321	1.380	1.74E-03	-18.077	10.047	7.20E-02	-19.259	6.942	5.54E-03	
	Brain Cerebellar Hemisphere	-0.065	1.032	9.50E-01	-5.569	7.425	4.53E-01	0.849	5.186	8.70E-01	
	Brain Cerebellum	-2.715	0.666	4.57E-05	-12.835	4.799	7.48E-03	-9.493	3.350	4.61E-03	
	Brain Cortex	1.688	1.579	2.85E-01	3.383	11.420	7.67E-01	16.232	7.942	4.10E-02	
	Brain Frontal Cortex (BA9)	0.496	0.449	2.69E-01	0.035	3.241	9.91E-01	0.302	2.257	8.94E-01	
	Brain Hippocampus	-12.308	9.696	2.04E-01	63.231	69.789	3.65E-01	-13.170	48.767	7.87E-01	
	Brain Hypothalamus	-2.257	0.640	4.22E-04	-4.449	4.601	3.34E-01	-4.158	3.220	1.97E-01	
	Brain Nucleus accumbens (basal ganglia)	-2.137	0.408	1.69E-07	-6.178	2.919	3.43E-02	-6.236	2.056	2.43E-03	
	Brain Putamen (basal ganglia)	-3.997	1.587	1.18E-02	-18.198	11.534	1.15E-01	-9.970	7.985	2.12E-01	
	Brain Spinal cord (cervical c-1)	0.318	0.218	1.45E-01	1.960	1.576	2.14E-01	1.764	1.099	1.09E-01	
	Brain Substantia nigra	-5.209	1.684	1.99E-03	-27.008	12.140	2.61E-02	-13.290	8.475	1.17E-01	
	Cardiovascular	Artery Aorta	3.261	1.522	3.22E-02	10.779	11.085	3.31E-01	21.671	7.660	4.67E-03
		Artery Coronary	-5.648	1.605	4.34E-04	-26.222	11.520	2.28E-02	-12.912	8.073	1.10E-01
Artery Tibial		4.367	0.858	3.61E-07	13.848	6.157	2.45E-02	16.170	4.318	1.81E-04	
Heart Atrial Appendage		1.106	1.711	5.18E-01	-6.927	12.338	5.75E-01	7.991	8.596	3.53E-01	
Heart Left Ventricle		-1.919	0.803	1.68E-02	-3.601	5.781	5.33E-01	-0.204	4.041	9.60E-01	
Colon Sigmoid		-3.848	3.696	2.98E-01	-30.791	26.708	2.49E-01	-14.250	18.585	4.43E-01	
Digestive	Colon Transverse	-3.170	0.908	4.86E-04	-16.483	6.535	1.17E-02	-8.894	4.570	5.17E-02	
	Esophagus Gastroesophageal Junction	18.303	6.506	4.91E-03	80.647	46.713	8.43E-02	31.393	32.730	3.37E-01	
	Esophagus Mucosa	5.802	2.101	5.75E-03	32.588	15.131	3.13E-02	20.353	10.566	5.41E-02	
	Esophagus Muscularis	1.008	1.311	4.42E-01	-0.880	9.480	9.26E-01	-7.531	6.598	2.54E-01	
	Small Intestine Terminal Ileum	5.524	1.615	6.26E-04	25.208	11.580	2.95E-02	11.449	8.124	1.59E-01	
	Stomach	6.243	2.339	7.61E-03	31.010	16.714	6.35E-02	16.135	11.754	1.70E-01	
	Adrenal Gland	8.190	3.202	1.05E-02	37.301	22.863	1.03E-01	22.234	16.093	1.67E-01	
Endocrine	Pancreas	-2.558	1.479	8.38E-02	-17.109	10.611	1.07E-01	-7.161	7.434	3.35E-01	
	Pituitary	12.214	2.518	1.24E-06	44.345	18.084	1.42E-02	37.282	12.682	3.29E-03	
	Thyroid	2.616	0.865	2.50E-03	11.291	6.244	7.06E-02	10.724	4.353	1.38E-02	
	Liver	-7.394	4.853	1.28E-01	-54.706	34.872	1.17E-01	-22.213	24.392	3.62E-01	
Musculoskeletal/connective	Muscle Skeletal	-10.001	3.362	2.94E-03	-37.286	24.057	1.21E-01	-23.627	16.902	1.62E-01	
Reproductive	Ovary	-20.964	5.951	4.28E-04	-76.249	42.746	7.45E-02	-47.004	29.927	1.16E-01	
	Prostate	-3.601	0.740	1.15E-06	-9.072	5.291	8.64E-02	-10.074	3.723	6.82E-03	
	Testis	-3.334	2.109	1.14E-01	-18.805	15.407	2.22E-01	-26.571	10.610	1.23E-02	
	Uterus	0.290	0.219	1.84E-01	2.592	1.575	9.99E-02	0.858	1.099	4.35E-01	
	Vagina	-0.498	0.150	9.18E-04	-2.448	1.081	2.35E-02	-1.328	0.755	7.88E-02	
	Breast Mammary Tissue	-8.010	3.230	1.32E-02	-50.069	23.264	3.14E-02	-19.646	16.245	2.27E-01	

Other

Cells Transformed fibroblasts	-13.224	2.630	5.00E-07	-46.871	18.969	1.35E-02	-44.936	13.242	6.92E-04
Kidney Cortex	-1.762	0.924	5.65E-02	-6.758	6.599	3.06E-01	-4.428	4.644	3.40E-01
Lung	20.361	5.216	9.53E-05	74.485	37.386	4.63E-02	42.162	26.222	1.08E-01
Minor Salivary Gland	-3.379	1.122	2.61E-03	-17.953	8.067	2.60E-02	-9.387	5.643	9.62E-02
Nerve Tibial	-4.228	0.844	5.58E-07	-11.668	6.036	5.32E-02	-12.328	4.247	3.70E-03
Skin Not Sun Exposed (Suprapubic)	-10.573	3.592	3.25E-03	-46.750	25.791	6.99E-02	-14.686	18.055	4.16E-01
Skin Sun Exposed (Lower leg)	-3.269	2.084	1.17E-01	-18.319	14.996	2.22E-01	-7.293	10.477	4.86E-01

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