

Supplementary Tables

Table S1. Type 1 error rates of omnibus tests in null models of logistic regression when assuming dependent G-E relationship.

	Dependent G-E		
	SNP ^a (N)		
	10	100	300
(P-value threshold)			
$P < 0.5$	0.506	0.555	0.737
$P < 0.1$	0.102	0.118	0.227
$P < 0.05$	0.052	0.059	0.128
$P < 0.01$	0.011	0.012	0.028
$P < 0.005$	0.005	0.006	0.014
$P < 0.0005$	4.0E-04	7.0E-04	0.001

^a Common variants (RAF = 1 – 99%)

Table S2. Genomic inflation factors (λ) under the null hypothesis of no interaction for six interaction tests with normally distributed and moderately correlated exposures.

		Independent G-E			Dependent G-E		
		SNP (N)			SNP (N)		
		10	100	300	10	100	300
Linear regression							
Rare SNP ^a	Omnibus	1.02	0.98	0.99	0.96	0.98	1.01
	MultiE-uGRS	1.04	0.98	1.00	1.04	0.97	1.02
	MultiE-wGRS	0.98	0.95	0.98	0.99	0.96	0.99
	MultiSNP-ERS	1.02	0.96	1.01	1.00	0.98	1.02
	uGRS-ERS	1.02	1.01	0.98	1.02	1.01	1.03
	wGRS-ERS	1.00	1.00	1.03	1.02	1.02	1.00
Common SNP ^b	Omnibus	0.96	1.01	1.01	1.00	0.95	0.99
	MultiE-uGRS	1.00	1.03	1.03	1.01	1.03	1.01
	MultiE-wGRS	1.00	1.03	1.03	1.00	0.98	1.01
	MultiSNP-ERS	1.01	1.01	0.98	1.00	0.99	0.98
	uGRS-ERS	0.98	1.04	1.02	1.00	1.01	1.03
	wGRS-ERS	1.01	1.03	0.98	0.97	1.01	0.99
Logistic regression							
Rare SNP ^a	Omnibus [§]	1.13	1.58	3.56 ^c	1.12	1.59	3.28 ^c
	MultiE-uGRS	0.95	1.00	0.98	1.01	0.98	1.06
	MultiE-wGRS	1.00	0.98	1.01	1.00	0.98	1.02
	MultiSNP-ERS [§]	1.05	1.19	1.65	1.00	1.20	1.55
	uGRS-ERS	1.01	1.02	0.99	1.02	1.00	1.05
	wGRS-ERS	0.99	1.03	0.99	0.98	0.99	1.03
Common SNP ^b	Omnibus [§]	1.05	1.28	2.67 ^c	1.04	1.26	2.80 ^c
	MultiE-uGRS	1.02	1.00	1.02	1.03	0.96	1.03
	MultiE-wGRS	1.00	0.97	1.01	1.02	1.01	0.98
	MultiSNP-ERS [§]	1.04	1.07	1.39	1.05	1.06	1.42
	uGRS-ERS	0.98	1.00	0.97	1.01	1.04	1.00
	wGRS-ERS	1.01	0.98	0.98	0.98	0.98	1.00

^a Rare SNP: RAF = [0.1-1% or 99-99.9%]

^b Common SNP: RAF = [1-99%]

^c 1,000 replicates

Table S3. Genomic inflation factors (λ) under the null hypothesis of no interaction for six interaction tests with non-normally distributed and moderately correlated exposures.

		Independent G-E			Dependent G-E		
		SNP (N)			SNP (N)		
		10	100	300	10	100	300
Linear regression							
Rare SNP ^a	Omnibus	0.98	0.99	0.99	1.02	0.99	1.02
	MultiE-uGRS	1.02	1.01	1.04	1.02	0.99	1.04
	MultiE-wGRS	1.00	0.97	1.00	1.00	0.94	0.95
	MultiSNP-ERS	0.95	1.00	1.01	1.03	0.98	0.97
	uGRS-ERS	0.98	0.99	1.01	1.02	0.97	1.02
	wGRS-ERS	0.99	1.01	0.96	1.00	1.01	1.01
Common SNP ^b	Omnibus	1.00	1.02	1.02	1.04	0.99	1.01
	MultiE-uGRS	1.02	1.01	0.97	1.02	1.02	0.99
	MultiE-wGRS	1.00	1.01	0.96	1.06	0.99	0.99
	MultiSNP-ERS	1.00	0.97	1.06	1.00	0.99	0.96
	uGRS-ERS	1.01	1.00	0.99	1.01	1.06	1.05
	wGRS-ERS	1.00	1.01	1.00	1.00	1.03	1.03
Logistic regression							
Rare SNP ^a	Omnibus	1.14	1.60	3.55 ^c	1.16	1.63	3.55 ^c
	MultiE-uGRS	1.00	1.01	1.03	1.05	1.00	1.00
	MultiE-wGRS	1.03	1.00	1.00	1.01	0.97	0.99
	MultiSNP-ERS	1.04	1.19	1.67	1.04	1.16	1.56
	uGRS-ERS	0.99	1.02	1.04	1.00	1.02	0.95
	wGRS-ERS	0.96	1.00	1.04	1.00	1.00	0.97
Common SNP ^b	Omnibus	0.98	1.22	2.93 ^c	1.00	1.31	2.82 ^c
	MultiE-uGRS	1.00	1.03	1.03	1.00	0.99	0.99
	MultiE-wGRS	0.99	1.06	0.97	0.98	0.99	1.04
	MultiSNP-ERS	1.01	1.03	1.42	1.00	1.05	1.37
	uGRS-ERS	1.01	0.99	1.00	1.01	0.97	1.02
	wGRS-ERS	1.03	1.00	0.98	1.01	0.98	0.96

^a Rare SNP: RAF = [0.1-1% or 99-99.9%]

^b Common SNP: RAF = [1-99%]

^c 1,000 replicates

Table S4. Sample sizes and the numbers of SNPs tested in cohort data (NHS I, NHS II, and HPFS).

	Sample size (N)			SNP (N)
	Cases	Controls	Total	
(Trait)				
Type 2 diabetes	6,150	31,512	37,662	65
Obesity	8,909	25,534	34,443	76
Hypertension	17,873	5,940	23,813	27
Coronary heart disease	2,030	24,743	26,773	48

Table S5. Marginal associations of exposures and genetic risk scores with four traits.

(Trait)	T2D (<i>p</i> -value)	Obesity (<i>p</i> -value)	Hypertension (<i>p</i> -value)	CHD (<i>p</i> -value)
Exposure				
HEI (score)	2.7E-32	1.4E-21	6.2E-09	1.6E-04
Total calorie intake (kcal)	1.1E-04	1.9E-03	0.83	0.43
MET-hour/week	1.6E-23	1.8E-54	1.8E-11	0.22
Smoking ever (yes/no)	1.1E-04	1.5E-07	1.4E-04	4.2E-13
uGRS^a				
T2D	4.1E-20	0.45	0.37	0.11
BMI	4.8E-04	1.9E-13	0.021	0.30
Blood pressure	0.10	0.14	1.5E-11	3.4E-03
Coronary heart disease	0.23	0.63	4.7E-02	9.5E-20
wGRS^a				
T2D	1.0E-23	8.6E-01	0.23	0.22
BMI	4.5E-04	4.9E-17	0.015	0.30
Blood pressure	0.048	0.034	1.8E-10	0.029
CHD	0.85	0.17	0.56	2.9E-21

Abbreviations: T2D, type 2 diabetes; CHD, coronary heart disease; HEI, healthy eating index, MET, metabolic equivalent for task; BMI, body mass index.

^auGRS and wGRS were calculated based on beta coefficients and risk allele counts of top SNPs identified by genome-wide association studies of the four traits listed below.

Table S6. Correlation coefficients between four exposures.

Exposures	HEI	Total calorie intake	MET-hour/week	Smoking ever
HEI	1.0			
Total calorie intake	-0.08	1.0		
MET-hour/week	0.17	0.06	1.0	
Smoking ever	0.04	-0.03	-0.02	1.0

Abbreviations: HEI, healthy eating index, MET, metabolic equivalent for task.

Table S7. Meta-analysis results for 48 loci previously identified to be associated with coronary artery disease.

SNP	CHR	Position	Gene	Effect_allele	Other_allele	Beta ^a	SE ^a	OR (95% CI)	P-value
rs11206510	1	55,030,366	<i>PCSK9</i>	T	C	0.076961041	0.013979068	1.08 (1.05, 1.11)	2.34E-08
rs9970807	1	56,499,992	<i>PPAP2B</i>	C	T	0.122217633	0.017748018	1.13 (1.10, 1.17)	5.00E-14
rs7528419	1	109,274,570	<i>SORT1</i>	A	G	0.113328685	0.013486356	1.12 (1.10, 1.15)	1.97E-23
rs6689306	1	154,423,470	<i>IL6R</i>	A	G	0.058268908	0.009536803	1.06 (1.04, 1.08)	2.60E-09
rs67180937	1	222,650,401	<i>MIA3</i>	G	T	0.076961041	0.013979068	1.08 (1.06, 1.11)	1.01E-12
rs16986953	2	19,742,712	<i>AK097927</i>	A	G	0.086177696	0.013852545	1.09 (1.06, 1.12)	1.45E-08
chr2:21378433:D	2	21,378,433	<i>APOB</i>	D	I	0.067658648	0.014107924	1.07 (1.04, 1.10)	2.89E-08
chr2:44074126:D	2	44,074,126	<i>ABCG5-ABCG8</i>	I	D	0.058268908	0.014239178	1.06 (1.04, 1.09)	2.60E-08
rs7568458	2	85,561,052	<i>VAMP5-VAMP8-GGCX</i>	A	T	0.058268908	0.009536803	1.06 (1.04, 1.08)	3.62E-10
rs17678683	2	144,528,992	<i>ZEB2-ACO74093.1</i>	G	T	0.09531018	0.018223512	1.10 (1.07, 1.14)	3.00E-09
chr2:203828796:I	2	203,828,796	<i>WDR12</i>	I	D	0.139761942	0.013139029	1.15 (1.11, 1.18)	2.15E-18
chr3:138099161:I	3	138,099,161	<i>MRAS</i>	I	D	0.076961041	0.009361805	1.08 (1.05, 1.10)	2.89E-09
rs4593108	4	147,359,849	<i>EDNRA</i>	C	G	0.067658648	0.014107924	1.07 (1.05, 1.10)	8.82E-10
rs72689147	4	155,718,736	<i>GUCY1A3</i>	G	T	0.067658648	0.014107924	1.07 (1.05, 1.10)	6.07E-09
rs273909	5	132,331,660	<i>SLC22A4-SLC22A5</i>	G	A	0.058268908	0.014239178	1.06 (1.03, 1.09)	1.24E-04
rs6903956	6	11,774,350	<i>ADTRP-C6orf105</i>	A	G	0	0.010103381	1.00 (0.98, 1.02)	0.96
rs9349379	6	12,903,725	<i>PHACTR1</i>	G	A	0.131028262	0.008873338	1.14 (1.12, 1.16)	1.81E-42
rs17609940	6	35,067,023	<i>ANKS1A</i>	G	C	0.029558802	0.009811919	1.03 (1.00, 1.05)	0.03
rs56336142	6	39,166,323	<i>KCNK5</i>	T	C	0.067658648	0.009448494	1.07 (1.04, 1.09)	1.85E-08
rs12202017	6	133,852,013	<i>TCF21</i>	A	G	0.067658648	0.009448494	1.07 (1.05, 1.09)	1.98E-11
rs55730499	6	160,584,578	<i>SLC22A3-LPAL2-LPA</i>	T	C	0.31481074	0.02542468	1.37 (1.31, 1.44)	5.39E-39
rs4252185	6	160,702,419	<i>PLG</i>	C	T	0.292669614	0.025979638	1.34 (1.28, 1.41)	1.64E-32
rs2107595	7	19,009,765	<i>HDAC9</i>	A	G	0.076961041	0.009361805	1.08 (1.05, 1.10)	8.05E-11
rs10953541	7	107,604,100	<i>7q22</i>	C	T	0.048790164	0.014372896	1.05 (1.03, 1.08)	1.02E-05
rs11556924	7	130,023,656	<i>ZC3HC1</i>	C	T	0.076961041	0.009361805	1.08 (1.05, 1.10)	5.34E-11
rs264	8	19,955,669	<i>LPL</i>	G	A	0.058268908	0.014239178	1.06 (1.03, 1.09)	1.06E-05
rs2954029	8	125,478,730	<i>TRIB1</i>	A	T	0.039220713	0.009718467	1.04 (1.03, 1.06)	2.61E-06
rs2891168	9	22,098,620	<i>9p21</i>	G	A	0.19062036	0.012495418	1.21 (1.19, 1.24)	2.29E-98
rs2519093	9	133,266,456	<i>ABO</i>	T	C	0.076961041	0.013979068	1.08 (1.06, 1.11)	1.19E-11
rs2487928	10	30,034,963	<i>KIAA1462</i>	A	G	0.058268908	0.009536803	1.06 (1.04, 1.08)	4.41E-11
rs1870634	10	43,985,363	<i>CXCL12</i>	G	T	0.076961041	0.009361805	1.08 (1.06, 1.10)	5.55E-15
rs1412444	10	89,243,170	<i>LIPA</i>	T	C	0.067658648	0.009448494	1.07 (1.05, 1.09)	5.15E-12
rs11191416	10	102,845,159	<i>CYP17A1-CNNM2-NT5C2</i>	T	G	0.076961041	0.013979068	1.08 (1.05, 1.11)	4.65E-09
rs2128739	11	103,802,549	<i>PDGFD</i>	A	C	0.067658648	0.009448494	1.07 (1.05, 1.09)	7.05E-11
rs964184	11	116,778,201	<i>ZNF259-APOA5-APOA1</i>	G	C	0.048790164	0.014372896	1.05 (1.03, 1.08)	5.60E-05
rs2681472	12	89,615,182	<i>ATP2B1</i>	G	A	0.076961041	0.009361805	1.08 (1.05, 1.10)	6.17E-11
rs3184504	12	111,446,804	<i>SH2B3</i>	T	C	0.067658648	0.009448494	1.07 (1.04, 1.09)	1.03E-09
rs9319428	13	28,399,484	<i>FLT1</i>	A	G	0.039220713	0.009718467	1.04 (1.02, 1.06)	7.13E-05
rs11838776	13	110,388,334	<i>COL4A1/A2</i>	A	G	0.067658648	0.009448494	1.07 (1.05, 1.09)	1.83E-10
rs10139550	14	99,679,373	<i>HHLPL1</i>	G	C	0.058268908	0.009536803	1.06 (1.04, 1.08)	1.38E-08
rs4468572	15	78,832,133	<i>ADAMTS7</i>	C	T	0.076961041	0.009361805	1.08 (1.06, 1.10)	4.44E-16

rs17514846	15	90,873,320	<i>FURIN-FES</i>	A	C	0.048790164	0.009626778	1.05 (1.03, 1.07)	3.10E-07
rs216172	17	2,223,210	<i>SMG6</i>	C	G	0.048790164	0.009626778	1.05 (1.03, 1.07)	5.07E-07
rs12936587	17	17,640,408	<i>RAI1-PEMT-RASD1</i>	G	A	0.029558802	0.009811919	1.03 (1.01, 1.05)	8.24E-04
rs46522	17	48,911,235	<i>UBE2Z</i>	T	C	0.039220713	0.009718467	1.04 (1.02, 1.06)	1.84E-05
rs56289821	19	11,077,571	<i>LDLR</i>	G	A	0.131028262	0.017594988	1.14 (1.11, 1.18)	4.44E-15
rs4420638	19	44,919,689	<i>APOE-APOC1</i>	G	A	0.09531018	0.013728292	1.10 (1.07, 1.13)	7.07E-11
rs28451064	21	34,221,526	<i>KCNE2 (gene desert)</i>	A	G	0.131028262	0.013252799	1.14 (1.10, 1.17)	1.33E-15

This GWAS meta-analysis was conducted among 185,000 coronary artery disease cases and controls and the majority (77%) were European ancestry (Nikpay et al. 2015).

^aBeta and SE were estimated using OR and 95% CI.

Table S8. Meta-analysis results of 65 novel and established susceptible loci to the risk of type 2 diabetes.

SNP	CHR	Position	Gene	Risk_allele	Other_allele	Beta ^a	SE ^a	OR (95% CI)	P-value
rs10923931	1	120,319,482	<i>NOTCH2</i>	T	G	0.09531018	0.031476311	1.10 (1.04-1.17)	5.8E-04
rs2075423	1	212,221,342	<i>PROX1</i>	G	T	0.076961041	0.01855492	1.08 (1.04-1.12)	1.6E-04
rs780094	2	27,594,741	<i>GCKR</i>	C	T	0.039220713	0.019255269	1.04 (1.00-1.08)	3.2E-02
rs10203174	2	43,543,534	<i>THADA</i>	C	T	0.139761942	0.025948172	1.15 (1.08-1.21)	4.7E-06
rs243019	2	60,439,310	<i>BCL11A</i>	C	T	0.086177696	0.013852545	1.09 (1.05-1.12)	8.2E-06
rs7593730	2	160,879,700	<i>RBMS1</i>	C	T	0.104360015	0.018062208	1.11 (1.06-1.15)	4.3E-06
rs13389219	2	165,237,122	<i>GRB14</i>	C	T	0.048790164	0.019075271	1.05 (1.01-1.09)	1.3E-02
rs7578326	2	226,728,897	<i>IRS1</i>	A	G	0.09531018	0.022679471	1.10 (1.06-1.15)	4.3E-06
rs1801282	3	12,368,125	<i>PPARG</i>	C	G	0.148420005	0.029894982	1.16 (1.10-1.23)	1.7E-08
rs1496653	3	23,429,794	<i>UBE2E2</i>	A	G	0.076961041	0.023090098	1.08 (1.04-1.13)	3.0E-04
rs12497268	3	64,065,403	<i>PSMD6</i>	G	C	0.039220713	0.023957644	1.04 (1.00-1.09)	6.6E-02
rs6795735	3	64,680,405	<i>ADAMTS9</i>	C	T	0.067658648	0.014107924	1.07 (1.03-1.10)	4.4E-04
rs11708067	3	124,548,468	<i>ADCY5</i>	A	G	0.09531018	0.022679471	1.10 (1.06-1.15)	1.1E-05
rs4402960	3	186,994,381	<i>IGF2BP2</i>	T	G	0.122217633	0.017748018	1.13 (1.09-1.17)	1.8E-10
rs17301514	3	188,096,103	<i>ST6GAL1</i>	A	G	0.104360015	0.039776297	1.11 (1.03-1.20)	5.8E-03
rs6819243	4	1,283,245	<i>MAEA</i>	T	C	0.104360015	0.060603845	1.11 (0.99-1.25)	8.4E-02
rs4458523	4	6,340,887	<i>WFS1</i>	G	T	0.086177696	0.018387723	1.09 (1.06-1.13)	5.7E-07
rs459193	5	55,842,508	<i>ANKRD55</i>	G	A	0.048790164	0.023734702	1.05 (1.01-1.10)	2.7E-02
rs4457053	5	76,460,705	<i>ZBED3</i>	G	A	0.122217633	0.026395752	1.13 (1.08-1.19)	1.5E-06
rs9368222	6	20,794,975	<i>CDKAL1</i>	A	C	0.19062036	0.016593465	1.21 (1.16-1.25)	9.2E-22
rs4299828	6	38,285,645	<i>ZFAND3</i>	A	G	0.058268908	0.018898608	1.06 (1.01-1.10)	1.3E-02
rs3734621	6	39,412,189	<i>KCNK16</i>	C	A	0.09531018	0.056991831	1.10 (0.99-1.23)	8.4E-02
rs6960043	7	15,019,385	<i>DGKB</i>	C	T	0.067658648	0.018725187	1.07 (1.03-1.11)	1.7E-04
rs849135	7	28,162,938	<i>JAZF1</i>	G	A	0.113328685	0.022283196	1.12 (1.08-1.17)	1.90E-09
rs10278336	7	44,211,888	<i>GCK</i>	A	G	0.048790164	0.019075271	1.05 (1.01-1.09)	2.60E-02
rs17867832	7	126,784,073	<i>GCC1</i>	T	G	0.09531018	0.031476311	1.10 (1.03-1.17)	3.90E-03
rs13233731	7	130,088,229	<i>KLF14</i>	G	A	0.09531018	0.013728292	1.10 (1.06-1.13)	1.70E-07
rs516946	8	41,638,405	<i>ANK1</i>	C	T	0.09531018	0.022679471	1.10 (1.06-1.15)	2.10E-06
rs896854	8	96,029,687	<i>TP53INP1</i>	T	C	0.086177696	0.018387723	1.09 (1.05-1.13)	1.40E-05
rs3802177	8	118,254,206	<i>SLC30A8</i>	G	A	0.148420005	0.025730027	1.16 (1.11-1.22)	1.30E-10
rs10758593	9	4,282,083	<i>GLIS3</i>	A	G	0.058268908	0.023515871	1.06 (1.02-1.11)	1.30E-03
rs16927668	9	8,359,533	<i>PTPRD</i>	T	C	0.039220713	0.019255269	1.04 (0.99-1.08)	1.40E-01
rs10811661	9	22,124,094	<i>CDKN2A/B</i>	T	C	0.165514438	0.025304562	1.18 (1.13-1.24)	1.20E-12
rs17791513	9	81,095,410	<i>TLE4</i>	A	G	0.19062036	0.040513662	1.21 (1.13-1.31)	4.30E-07
rs2796441	9	83,498,768	<i>TLE1</i>	G	A	0.067658648	0.023301039	1.07 (1.03-1.12)	4.80E-04
rs12779790	10	12,368,016	<i>CDC123/CAMK1D</i>	G	A	0.076961041	0.023090098	1.08 (1.03-1.13)	2.00E-03
rs12242953	10	70,535,348	<i>VPS26A</i>	G	A	0.104360015	0.039776297	1.11 (1.04-1.20)	3.30E-03
rs12571751	10	80,612,637	<i>ZMIZ1</i>	A	G	0.086177696	0.018387723	1.09 (1.06-1.13)	7.00E-07
rs5015480	10	94,455,539	<i>HHEX/IDE</i>	C	T	0.139761942	0.017444574	1.15 (1.11-1.19)	5.40E-15
rs7903146	10	114,748,339	<i>TCF7L2</i>	T	C	0.336472237	0.021410306	1.40 (1.35-1.46)	1.80E-59
rs2334499	11	1,653,425	<i>DUSP8</i>	T	C	0.067658648	0.018725187	1.07 (1.03-1.11)	1.30E-03

rs231362	11	2,648,047	KCNQ1	G	A	0.104360015	0.022479587	1.11 (1.07-1.16)	5.80E-07
rs5215	11	17,365,206	KCNJ11	C	T	0.076961041	0.01855492	1.08 (1.04-1.12)	1.10E-05
rs1552224	11	72,110,746	ARAP1 (CENTD2)	A	C	0.122217633	0.026395752	1.13 (1.08-1.19)	1.50E-06
rs10830963	11	92,348,358	MTNR1B	G	C	0.104360015	0.022479587	1.11 (1.06-1.16)	2.40E-06
rs11063069	12	4,244,634	CCND2	G	A	0.09531018	0.022679471	1.10 (1.04-1.15)	3.20E-04
rs10842994	12	27,856,417	KLHDC5	C	T	0.086177696	0.018387723	1.09 (1.04-1.13)	3.00E-04
rs2261181	12	64,498,585	HMG2	T	C	0.148420005	0.029894982	1.16 (1.10-1.23)	3.90E-07
rs7955901	12	69,719,560	TSPAN8/LGR5	C	T	0.086177696	0.018387723	1.09 (1.05-1.13)	9.00E-06
rs12427353	12	119,911,284	HNF1A (TCF1)	G	C	0.113328685	0.026625384	1.12 (1.07-1.18)	2.80E-06
rs1359790	13	79,615,157	SPRY2	G	A	0.09531018	0.018223512	1.10 (1.05-1.14)	3.10E-06
rs4502156	15	60,170,447	C2CD4A	T	C	0.058268908	0.023515871	1.06 (1.02-1.11)	1.90E-03
rs7177055	15	75,619,817	HMG20A	A	G	0.076961041	0.01855492	1.08 (1.04-1.12)	1.2E-04
rs11634397	15	78,219,277	ZFAND6	G	A	0.086177696	0.018387723	1.09 (1.05-1.13)	1.80E-05
rs2028299	15	88,175,261	AP3S2	C	A	0.039220713	0.023957644	1.04 (1.00-1.09)	4.40E-02
rs8042680	15	89,322,341	PRC1	A	C	0.067658648	0.018725187	1.07 (1.03-1.11)	2.00E-04
rs9936385	16	52,376,670	FTO	C	T	0.122217633	0.022090207	1.13 (1.09-1.18)	3.20E-10
rs7202877	16	73,804,746	BCAR1	T	G	0.139761942	0.034312361	1.15 (1.07-1.23)	5.00E-05
rs2447090	17	2,245,724	SRR	A	G	0.029558802	0.019438697	1.03 (0.99-1.07)	2.00E-01
rs4430796	17	33,172,153	HNF1B (TCF2)	G	A	0.122217633	0.026395752	1.13 (1.07-1.19)	6.50E-06
rs12970134	18	56,035,730	MC4R	A	G	0.076961041	0.01855492	1.08 (1.03-1.12)	2.30E-04
rs10401969	19	19,268,718	CILP2	C	T	0.122217633	0.03489935	1.13 (1.05-1.21)	9.20E-04
rs3786897	19	38,584,848	PEPD	A	G	0.019802627	0.019625653	1.02 (0.98-1.06)	3.30E-01
rs8108269	19	50,850,353	GIPR	G	T	0.058268908	0.023515871	1.06 (1.02-1.11)	5.00E-03
rs4812829	20	42,422,681	HNF4A	A	G	0.067658648	0.023301039	1.07 (1.01-1.12)	1.20E-02

This meta-analysis was conducted in 12,171 type 2 diabetes cases and 56,862 controls of European descent (Morris et al. 2012).

^aBeta and SE were estimated using OR and 95% CI.

Table S9. European meta-analysis results of 77 body mass index loci reaching genome-wide significance.

SNP	CHR	Position	Gene	Effect_allele	Other_allele	Beta ^a	SE ^a	P-value
rs657452	1	49,362,434	AGBL4	A	G	0.023	0.003	5.48E-13
rs11583200	1	50,332,407	ELAVL4	C	T	0.018	0.003	1.48E-08
rs3101336	1	72,523,773	NEGR1	C	T	0.033	0.003	2.66E-26
rs12566985	1	74,774,781	FPGT-TNNI3K	G	A	0.024	0.003	3.28E-15
rs12401738	1	78,219,349	FUBP1	A	G	0.021	0.003	1.15E-10
rs11165643	1	96,696,685	PTBP2	T	C	0.022	0.003	2.07E-12
rs17024393	1	109,956,211	GNAT2	C	T	0.066	0.009	7.03E-14
rs543874	1	176,156,103	SEC16B	G	A	0.048	0.004	2.62E-35
rs2820292	1	200,050,910	NAV1	C	A	0.020	0.003	1.83E-10
rs13021737	2	622,348	TMEM18	G	A	0.060	0.004	1.11E-50
rs10182181	2	25,003,800	ADCY3	G	A	0.031	0.003	8.78E-24
rs11126666	2	26,782,315	KCNK3	A	G	0.021	0.003	1.33E-09
rs1016287	2	59,159,129	LINC01122	T	C	0.023	0.003	2.25E-11
rs11688816	2	62,906,552	EHBP1	G	A	0.017	0.003	1.89E-08
rs2121279	2	142,759,755	LRP1B	T	C	0.025	0.004	2.31E-08
rs1528435	2	181,259,207	UBE2E3	T	C	0.018	0.003	1.20E-08
rs7599312	2	213,121,476	ERBB4	G	A	0.022	0.003	1.17E-10
rs6804842	3	25,081,441	RARB	G	A	0.019	0.003	2.48E-09
rs2365389	3	61,211,502	FHIT	C	T	0.020	0.003	1.63E-10
rs3849570	3	81,874,802	GBE1	A	C	0.019	0.003	2.60E-08
rs13078960	3	85,890,280	CADM2	G	T	0.030	0.004	1.74E-14
rs16851483	3	142,758,126	RASA2	T	G	0.048	0.008	3.55E-10
rs1516725	3	187,306,698	ETV5	C	T	0.045	0.005	1.89E-22
rs10938397	4	44,877,284	GNPDA2	G	A	0.040	0.003	3.21E-38
rs17001654	4	77,348,592	SCARB2	G	C	0.031	0.005	7.76E-09
rs13107325	4	103,407,732	SLC39A8	T	C	0.048	0.007	1.83E-12
rs11727676	4	145,878,514	HHIP	T	C	0.036	0.006	2.55E-08
rs2112347	5	75,050,998	POC5	T	G	0.026	0.003	6.19E-17
rs205262	6	34,671,142	C6orf106	G	A	0.022	0.004	1.75E-10
rs2033529	6	40,456,631	TDRG1	G	A	0.019	0.003	1.39E-08
rs2207139	6	50,953,449	TFAP2B	G	A	0.045	0.004	4.13E-29
rs9400239	6	109,084,356	FOXO3	C	T	0.019	0.003	1.61E-08
rs13191362	6	162,953,340	PARK2	A	G	0.028	0.005	7.34E-09
rs1167827	7	75,001,105	HIP1	G	A	0.020	0.003	6.33E-10
rs2245368	7	76,446,079	PMS2L11	C	T	0.032	0.006	3.19E-08
rs17405819	8	76,969,139	HNF4G	T	C	0.022	0.003	2.07E-11
rs2033732	8	85,242,264	RALYL	C	T	0.019	0.004	4.89E-08
rs4740619	9	15,624,326	C9orf93	T	C	0.018	0.003	4.56E-09
rs10968576	9	28,404,339	LINGO2	G	A	0.025	0.003	6.61E-14
rs6477694	9	110,972,163	EPB41L4B	C	T	0.017	0.003	2.67E-08
rs1928295	9	119,418,304	TLR4	T	C	0.019	0.003	7.91E-10

rs10733682	9	128,500,735	<i>LMX1B</i>	A	G	0.017	0.003	1.83E-08
rs7899106	10	87,400,884	<i>GRID1</i>	G	A	0.040	0.007	2.96E-08
rs17094222	10	102,385,430	<i>HIF1AN</i>	C	T	0.025	0.004	5.94E-11
rs11191560	10	104,859,028	<i>NT5C2</i>	C	T	0.031	0.005	8.45E-09
rs7903146	10	114,748,339	<i>TCF7L2</i>	C	T	0.023	0.003	1.11E-11
rs4256980	11	8,630,515	<i>TRIM66</i>	G	C	0.021	0.003	2.90E-11
rs11030104	11	27,641,093	<i>BDNF</i>	A	G	0.041	0.004	5.56E-28
rs2176598	11	43,820,854	<i>HSD17B12</i>	T	C	0.020	0.004	2.97E-08
rs3817334	11	47,607,569	<i>MTCH2</i>	T	C	0.026	0.003	5.15E-17
rs12286929	11	114,527,614	<i>CADM1</i>	G	A	0.022	0.003	1.31E-12
rs7138803	12	48,533,735	<i>BCDIN3D</i>	A	G	0.032	0.003	8.15E-24
rs11057405	12	121,347,850	<i>CLIP1</i>	G	A	0.031	0.006	2.02E-08
rs12016871	13	26,915,782	<i>MTIF3</i>	T	C	0.030	0.005	2.29E-10
rs12429545	13	53,000,207	<i>OLFM4</i>	A	G	0.033	0.005	1.09E-12
rs10132280	14	24,998,019	<i>STXBP6</i>	C	A	0.023	0.003	1.14E-11
rs12885454	14	28,806,589	<i>PRKD1</i>	C	A	0.021	0.003	1.94E-10
rs11847697	14	29,584,863	<i>PRKD1</i>	T	C	0.049	0.008	3.99E-09
rs7141420	14	78,969,207	<i>NRXN3</i>	T	C	0.024	0.003	1.23E-14
rs3736485	15	49,535,902	<i>DMXL2</i>	A	G	0.018	0.003	7.41E-09
rs16951275	15	65,864,222	<i>MAP2K5</i>	T	C	0.031	0.004	1.91E-17
rs758747	16	3,567,359	<i>NLRC3</i>	T	C	0.023	0.004	7.47E-10
rs12446632	16	19,842,890	<i>GPRC5B</i>	G	A	0.040	0.005	1.48E-18
rs2650492	16	28,240,912	<i>SBK1</i>	A	G	0.021	0.004	1.92E-09
rs3888190	16	28,796,987	<i>ATP2A1</i>	A	C	0.031	0.003	3.14E-23
rs9925964	16	31,037,396	<i>KAT8</i>	A	G	0.019	0.003	8.11E-10
rs1558902	16	52,361,075	<i>FTO</i>	A	T	0.082	0.003	7.51E-153
rs1000940	17	5,223,976	<i>RABEP1</i>	G	A	0.019	0.003	1.28E-08
rs12940622	17	76,230,166	<i>RPTOR</i>	G	A	0.018	0.003	2.49E-09
rs1808579	18	19,358,886	<i>C18orf8</i>	C	T	0.017	0.003	4.17E-08
rs7243357	18	55,034,299	<i>GRP</i>	T	G	0.022	0.004	3.86E-08
rs6567160	18	55,980,115	<i>MC4R</i>	C	T	0.056	0.004	3.93E-53
rs17724992	19	18,315,825	<i>PGPEP1</i>	A	G	0.019	0.004	3.42E-08
rs29941	19	39,001,372	<i>KCTD15</i>	G	A	0.018	0.003	2.41E-08
rs2075650	19	50,087,459	<i>TOMM40</i>	A	G	0.026	0.005	1.25E-08
rs2287019	19	50,894,012	<i>QPCTL</i>	C	T	0.036	0.004	4.59E-18
rs3810291	19	52,260,843	<i>ZC3H4</i>	A	G	0.028	0.004	4.81E-15

This meta-analysis of 322,154 European-descent individuals identified 77 loci at genome-wide significance defined as $p < 5 \times 10^{-8}$ (Locke et al. 2015).

^aBeta and SE were previously reported in the GWAS.

Table S10. Genome-wide meta-analysis results of 29 blood pressure loci.

SNP	CHR	Position	Gene	Risk_allele	Other_allele	Beta ^a	SE ^a	P-value
rs2932538	1	113,018,066	<i>MOV10</i>	G	A	4.86E-02	9.50E-03	2.89E-07
rs13082711	3	27,512,913	<i>SLC4A7</i>	C	T	3.47E-02	9.70E-03	3.56E-04
rs419076	3	170,583,580	<i>MECOM</i>	T	C	3.09E-02	8.60E-03	3.06E-04
rs13107325	4	103,407,732	<i>SLC39A8</i>	C	T	1.05E-01	2.08E-02	4.89E-07
rs13139571	4	156,864,963	<i>GUCY1A3-GUCY1B3</i>	C	A	4.20E-02	0.01	2.50E-05
rs1173771	5	32,850,785	<i>NPR3-C5orf23</i>	G	A	6.20E-02	9.90E-03	3.23E-10
rs11953630	5	157,777,980	<i>EBF1</i>	C	T	5.22E-02	1.00E-02	1.68E-07
rs1799945	6	26,199,158	<i>HFE</i>	G	C	9.47E-02	1.48E-02	1.76E-10
rs805303	6	31,724,345	<i>BAT2-BAT5</i>	G	A	5.37E-02	8.30E-03	1.12E-10
rs4373814	10	18,459,978	<i>CACNB2(5')</i>	C	G	4.63E-02	8.60E-03	8.53E-08
rs932764	10	95,885,930	<i>PLCE1</i>	G	A	5.51E-02	9.60E-03	9.35E-09
rs7129220	11	10,307,114	<i>ADM</i>	A	G	4.45E-02	1.36E-02	1.11E-03
rs633185	11	100,098,748	<i>FLJ32810-TMEM133</i>	C	G	7.02E-02	1.07E-02	5.41E-11
rs2521501	15	89,238,392	<i>FURIN-FES</i>	T	A	5.87E-02	1.18E-02	7.02E-07
rs17608766	17	42,368,270	<i>GOSR2</i>	C	T	2.47E-02	1.41E-02	8.00E-02
rs1327235	20	10,917,030	<i>JAG1</i>	G	A	3.42E-02	9.80E-03	4.57E-04
rs6015450	20	57,184,512	<i>GNAS-EDN3</i>	G	A	1.10E-01	1.46E-02	4.18E-14
rs17367504	1	11,785,365	<i>MTHFR-NPPB</i>	A	G	1.03E-01	1.63E-02	2.34E-10
rs3774372	3	41,852,418	<i>ULK4</i>	C	T	1.70E-02	1.27E-02	1.80E-01
rs1458038	4	81,383,747	<i>FGF5</i>	T	C	7.17E-02	1.38E-02	1.85E-07
rs1813353	10	18,747,454	<i>CACNB2(3')</i>	T	C	7.78E-02	1.26E-02	6.24E-10
rs4590817	10	63,137,559	<i>C10orf107</i>	G	C	9.61E-02	1.68E-02	9.82E-09
rs11191548	10	104,836,168	<i>CYP17A1-NT5C2</i>	T	C	9.72E-02	2.24E-02	1.40E-05
rs381815	11	16,858,844	<i>PLEKHA7</i>	T	C	6.17E-02	1.33E-02	3.41E-06
rs17249754	12	88,584,717	<i>ATP2B1</i>	G	A	1.26E-01	1.63E-02	1.13E-14
rs3184504	12	110,368,991	<i>SH2B3</i>	T	C	5.57E-02	1.19E-02	2.62E-06
rs10850411	12	113,872,179	<i>TBX5-TBX3</i>	T	C	4.50E-02	0.01	5.20E-06
rs1378942	15	72,864,420	<i>CYP1A1-ULK3</i>	C	A	7.26E-02	1.27E-02	1.04E-08
rs12940887	17	44,757,806	<i>ZNF652</i>	T	C	4.56E-02	8.60E-03	1.20E-07

This GWAS of 200,000 European descent individuals identified 29 independent SNPs associated with systolic or diastolic blood pressure or both in a meta-analysis (International Consortium for Blood Pressure Genome-Wide Association et al. 2011).

^aBeta and SE were previously reported.

Table S11. The number of omnibus tests with lower p-values than the given significance thresholds (< 0.1, 0.05, or 0.01)

Omnibus P-value	Permutation test ^a			Standard omnibus test ^b		
	LRT	Wald	Score	LRT	Wald	Score
< 0.1	93	89	91	491	0	121
< 0.05	35	36	36	361	0	53
< 0.01	8	6	7	146	0	9

^aPermutation test: P-values were the ratios of the number permutations that observe more extreme statistics than the statistic observed in the simulation to the total number of permutations.

^bStandard omnibus test: P-values were obtained based on chi-square distributions of the test statistics.

The table above showed results from simulations of null hypothesis (no G-E interaction). In each simulation, we generated 1,000 replicates of 5,000 samples with 50 common SNPs (RAF: 1-99%) and 10 exposures that were moderately correlated and normally distributed, assuming some marginal effects of G and E and independence between G and E. Then we calculated test statistics of omnibus test of G-E interactions using the three test statistics (*LRT*, *Wald*, and *Score*). For permutations, we shuffled the outcome group (cases and controls) 1,000 times and derived the empirical p-values.

Table S12. P-values^a of six G-E interaction approaches in NHSI, NHSII, and HPFS cohorts

Test	T2D	Obesity	Hypertension	CHD
Omnibus	0.023	0.005	0.346	0.506
MultiE-uGRS	0.248	0.507	0.101	0.364
MultiE-wGRS	0.566	0.554	0.128	0.977
MultiSNP-ERS	0.047	0.215	0.010	0.571
uGRS-ERS	0.473	0.038	0.048	0.437
wGRS-ERS	0.681	0.031	0.020	0.523

^aP-values were obtained from 1000 permutations by shuffling case and control status.

We applied the same permutation procedure (in Table S11) to the real data analysis. Using the three cohort data, we performed permutations for six G-E interaction approaches (omnibus, multiE-uGRS, multiE-wGRS, multiSNP-ERS, uGRS-ERS, and wGRS-ERS) using *Score* test statistic.

Table S13. Type 1 error rates of omnibus test at three α thresholds using correlated SNPs

α threshold	Standard omnibus test		
	LRT	Wald	Score
< 0.1	1.000	0.640	0.228
< 0.05	1.000	0.640	0.131
< 0.01	0.998	0.640	0.030

We simulated 1,000 series data of 5,000 samples with 50 common SNPs in moderate LD (derived from our real cohort data (chr6: 3,944,096 - 3,949,896) after removing SNPs with perfect linkage disequilibrium ($r^2 = 1.0$) and 10 correlated and normally distributed exposures under the null hypothesis (no G-E interaction) in logistic regression, assuming no G-E correlations and 30% prevalence.

Reference

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