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Supplemental Data

A Powerful Approach to Estimating Annotation-Stratified Genetic Covariance via GWAS Summary Statistics

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Supplementary Figures

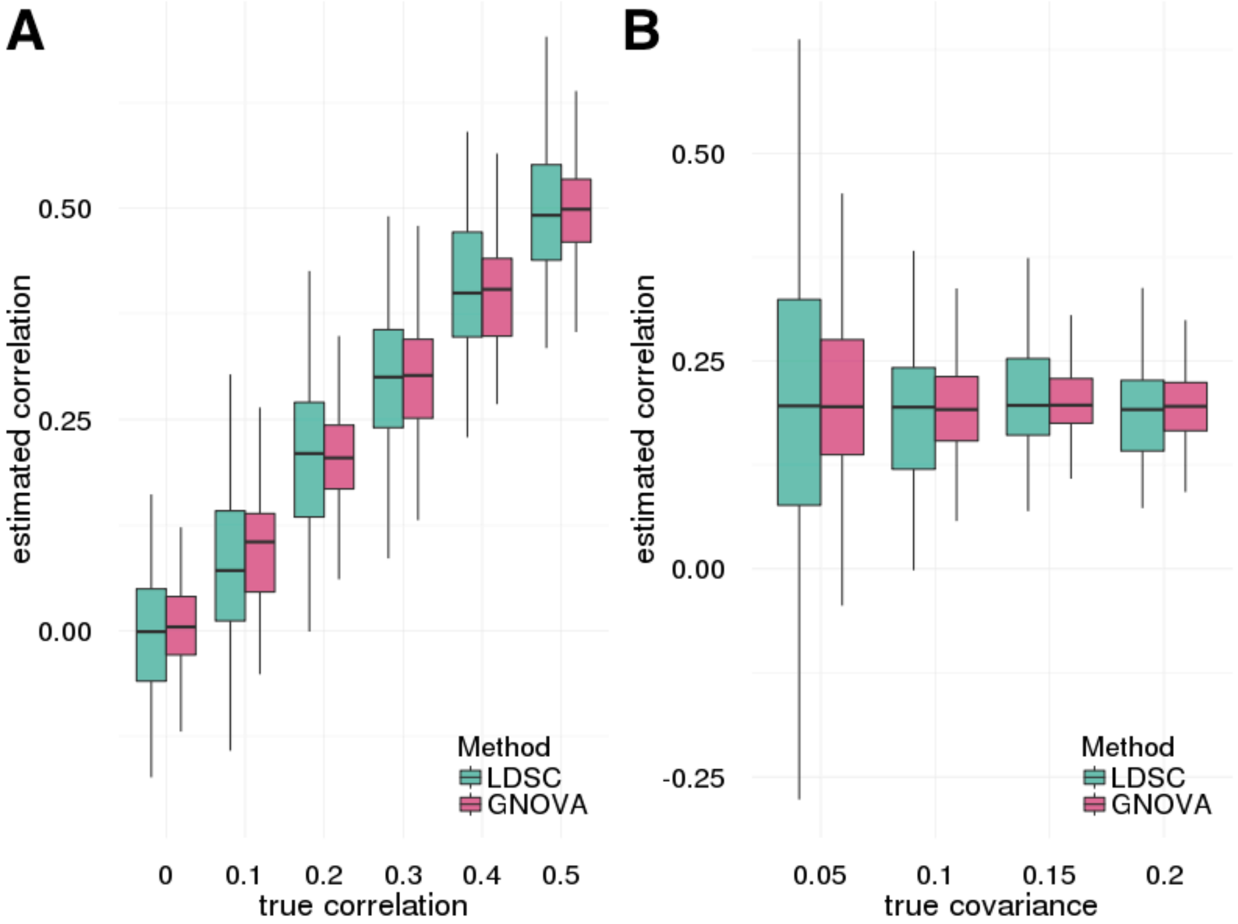

Figure S1. Compare genetic correlation estimates through numerical simulations. See Methods section for details of the simulation settings. **(A)** Simulation setting 1: fixed heritability to be 0.5 for both traits; varied genetic correlation from 0 to 0.5. **(B)** Simulation setting 2: fixed genetic correlation to be 0.2; varied genetic covariance from 0.05 to 0.2.

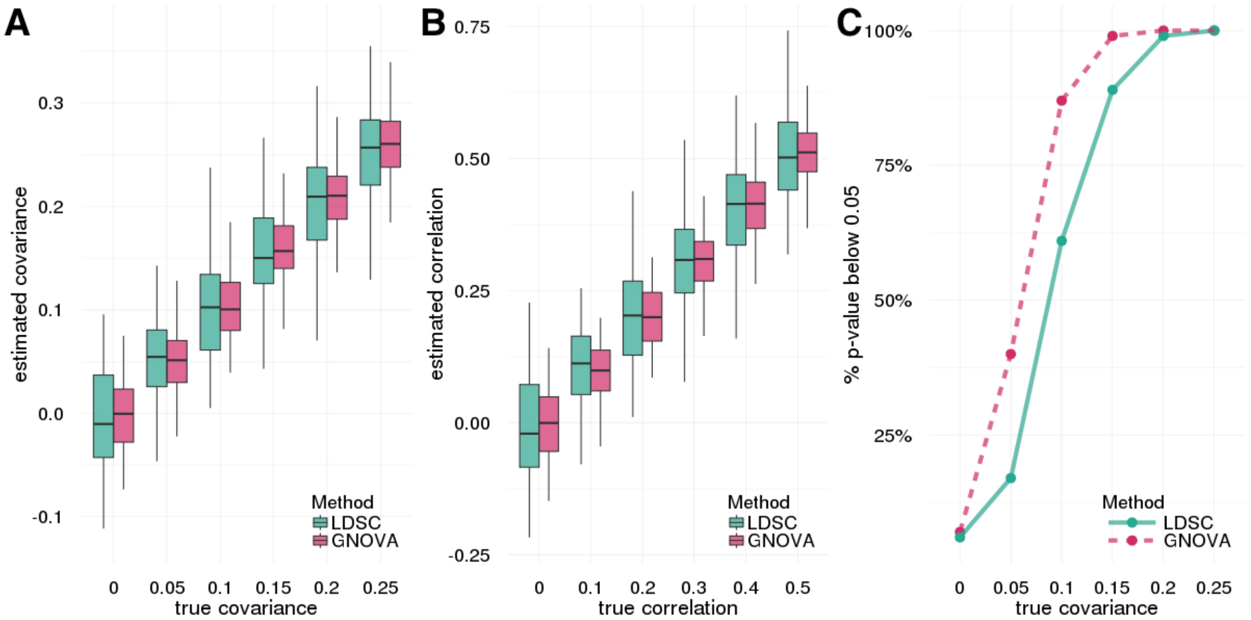

Figure S2. Compare GNOVA and LDSC using two traits simulated on the same cohort. Sample overlap correction was applied when estimating genetic covariance. See simulation setting 3 in the **Methods** section for details on the analysis. Panels **(A-C)** show the genetic covariance estimates, genetic correlation estimates, and power calculation, respectively.

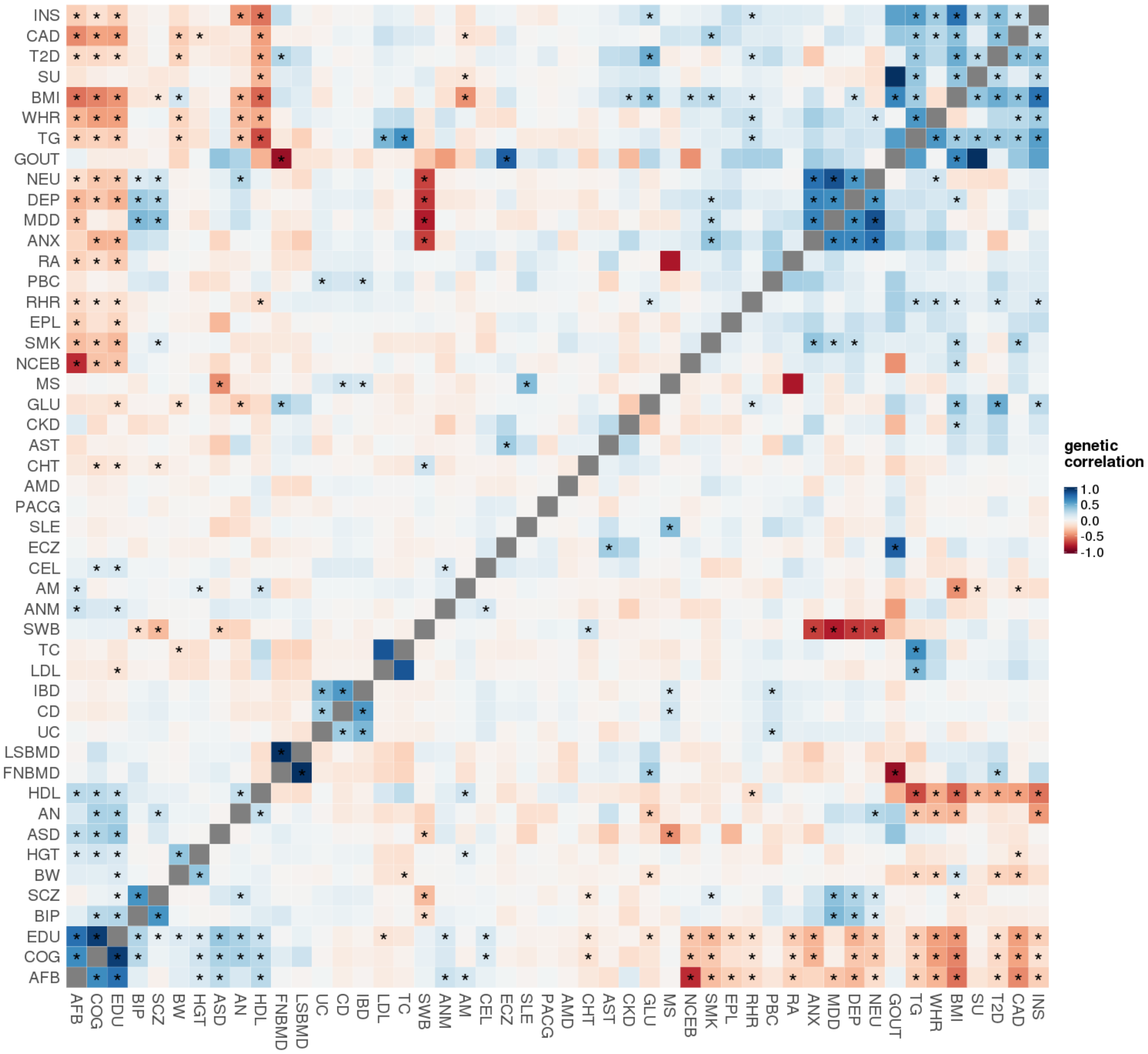

Figure S3. Genetic correlations of 48 complex traits estimated GNOVA. Asterisks highlight significant genetic correlations after Bonferroni correction ($p < 4.4\times10^{-5}$). The order of traits is determined by hierarchical clustering. Sample overlap correction was applied to trait pairs with substantial sample sharing (**Figure S8**). Correlation estimates above 1 or below -1 were truncated.

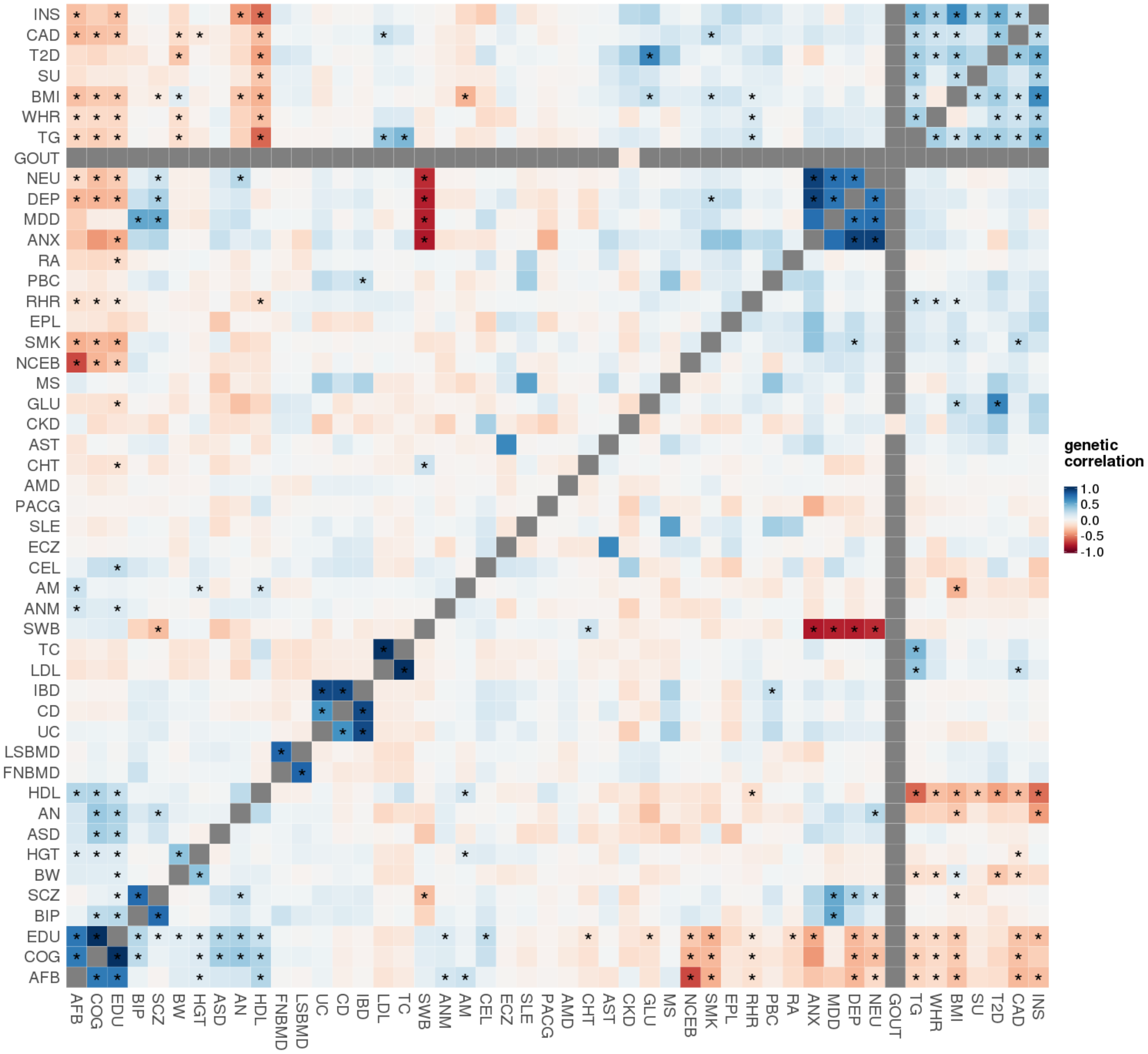

Figure S4. Genetic correlations of 48 complex traits estimated by LDSC. Asterisks highlight significant genetic correlations after Bonferroni correction ($p < 4.4\times10^{-5}$). The order of traits is the same as shown in **Figure S3**. LDSC output p-value=NA for most pairs that involve gout due to its negative heritability estimate. Those blocks are colored in grey.

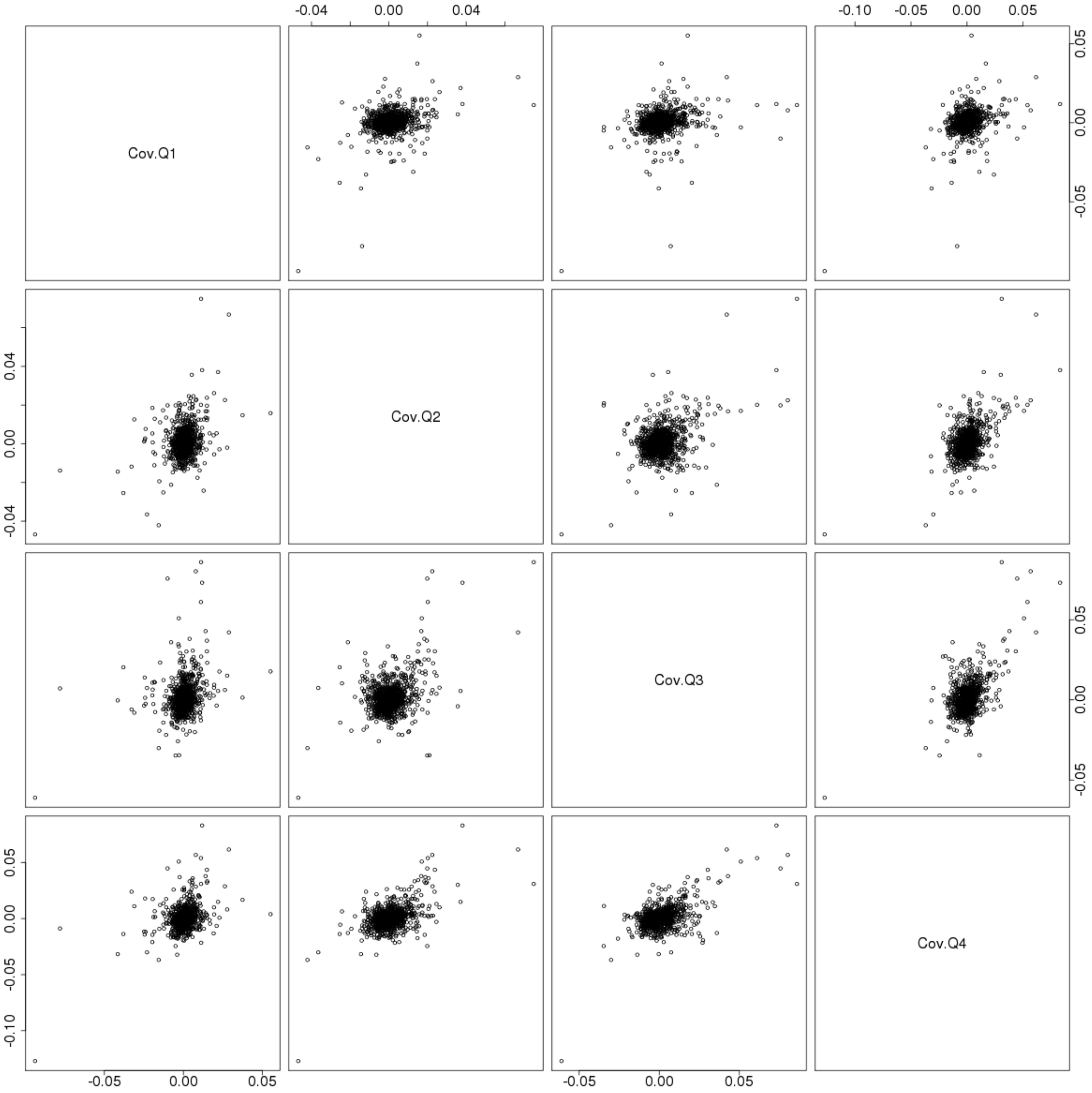

Figure S5. Scatter plot matrix for MAF-stratified genetic covariance estimates. Q1, Q2, Q3, and Q4 denote the MAF quarters (from lowest to highest).

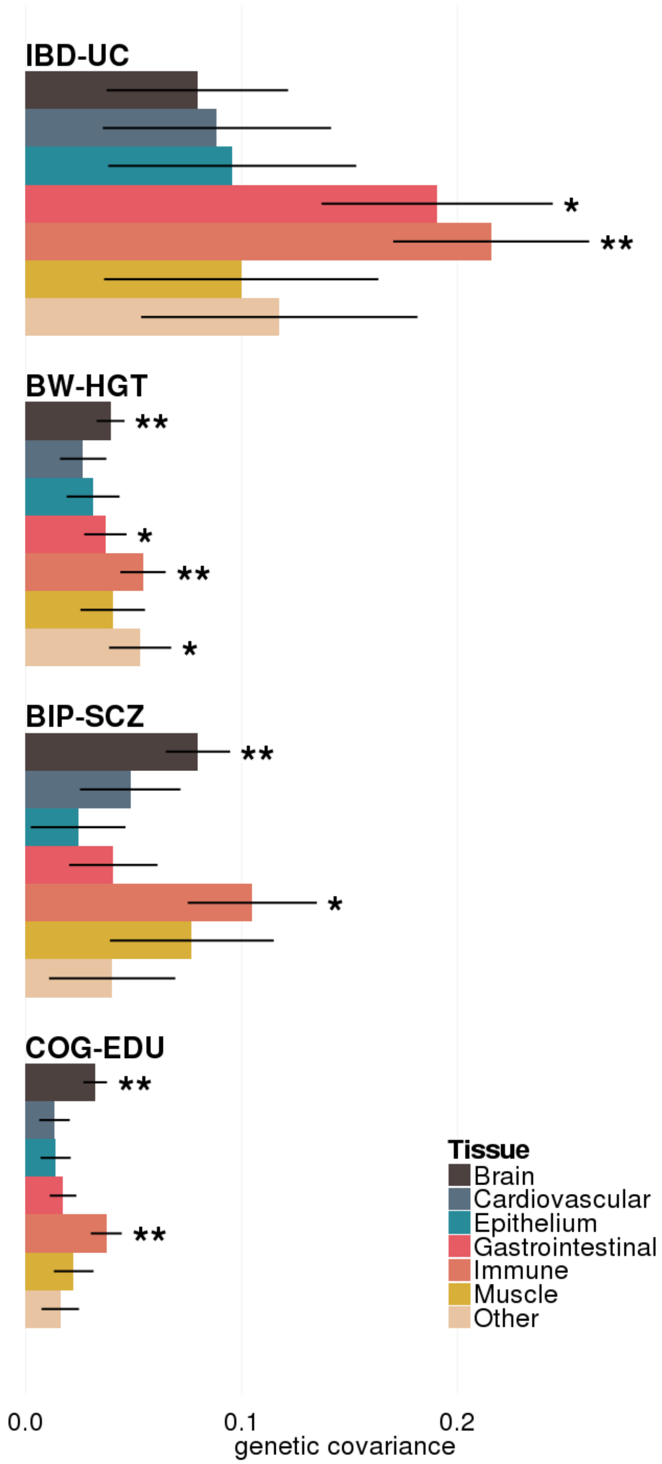

Figure S6. Stratify genetic covariance by tissue type. Intervals show the standard error of covariance estimates. Single asterisks indicate p-values below 0.05/(4*7) = 0.0018. Double asterisks indicate p-values below $0.05/(7\times1225) = 5.8\times10^{-6}$.

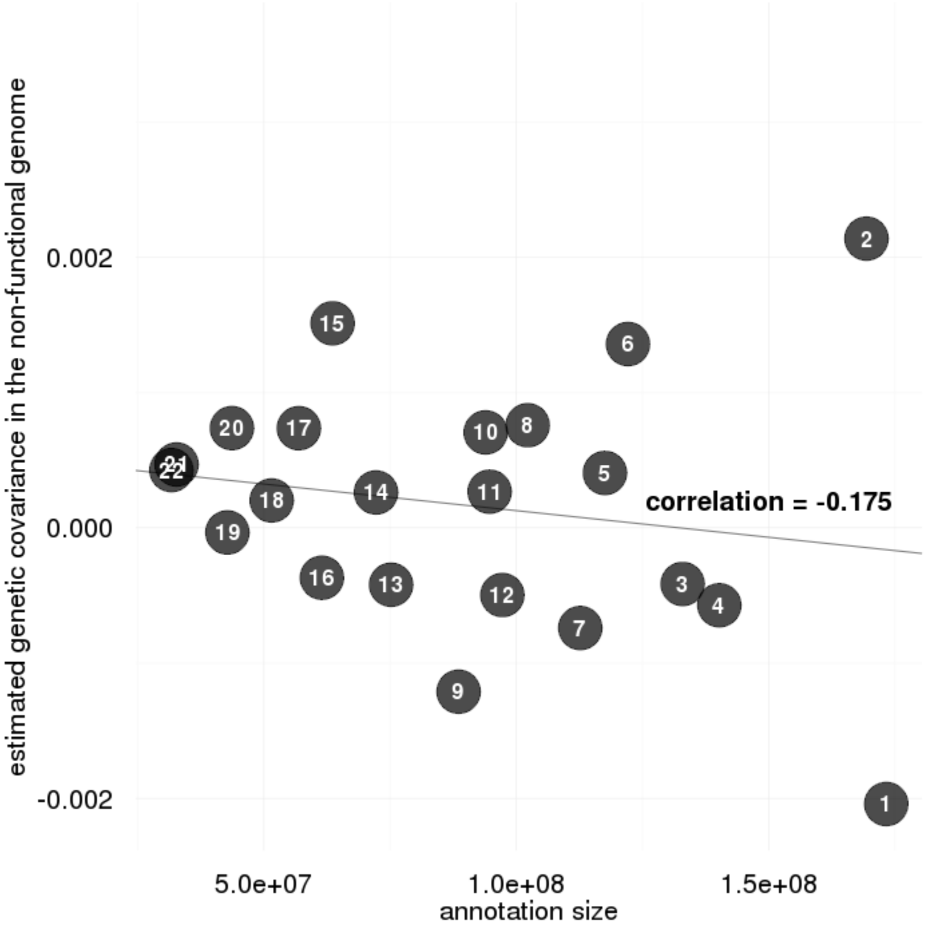

Figure S7. Compare the estimated genetic covariance in the predicted non-functional genome on each chromosome with size of the non-functional genome.

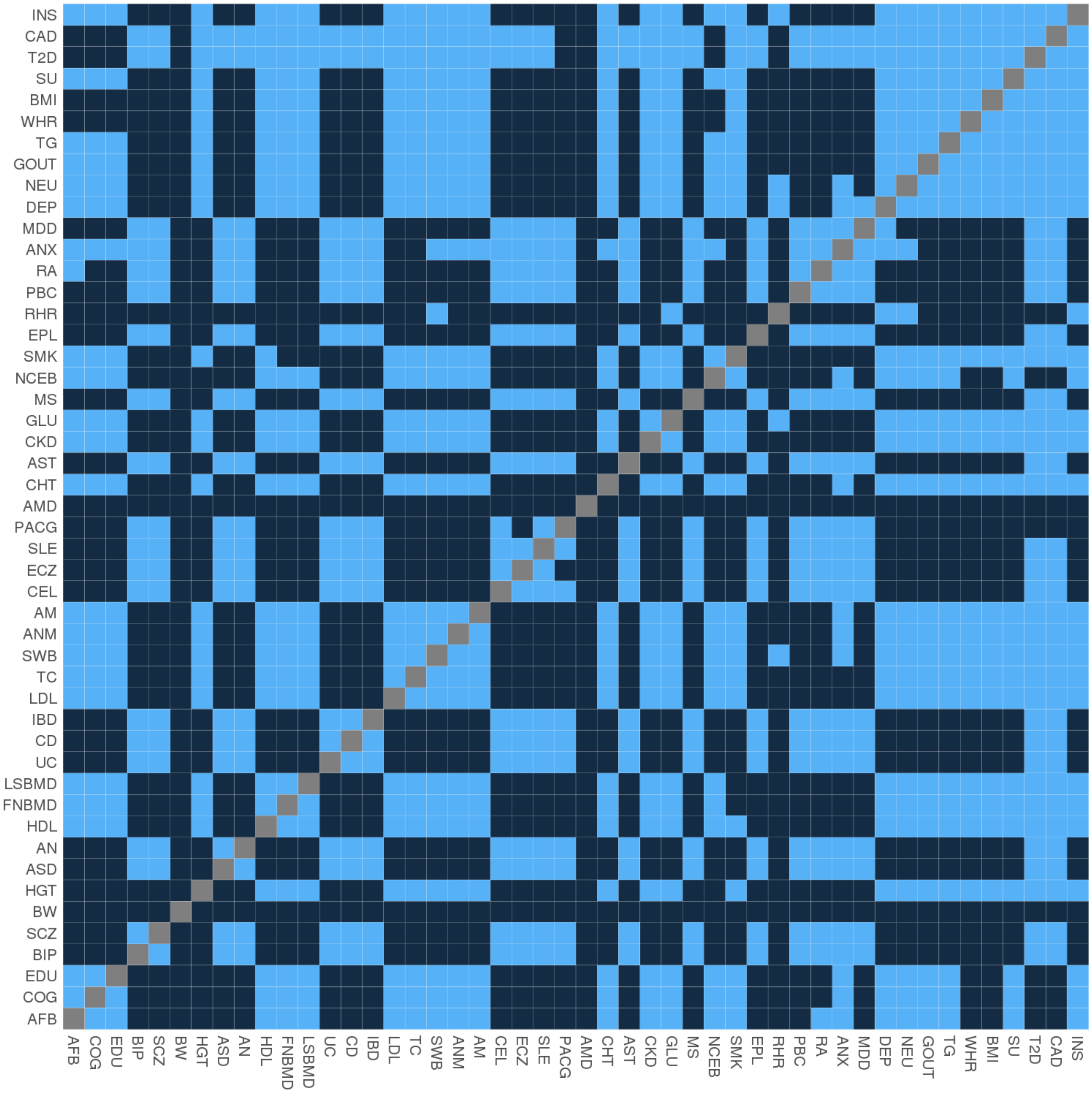

Figure S8. Pairs of traits with sample overlap correction. Some studies among the 48 GWASs have substantial sample overlap. Therefore, we applied sample overlap correction (See **Methods** section) when analyzing those traits throughout the paper. Those trait pairs are highlighted in light blue.

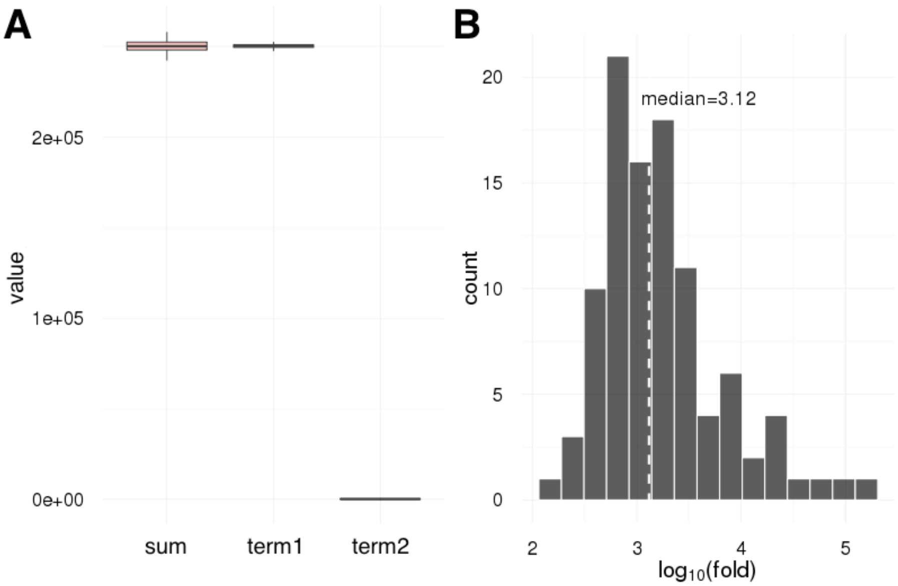

Figure S9. Numerical justifications to the theoretical proof – numerical study 1. Analysis details are described in **Appendix**. **(A)** Labels "term1" and "term2" denote $tr(A^T H_1 A H_2)$ and $tr(A^T \Theta A^T \Theta)$, respectively; "sum" denotes the summation of both, i.e. $tr(A^T H_1 A H_2) + tr(A^T \Theta A^T \Theta)$. **(B)** Histogram of $\log_{10}(|tr(A^T H_1 A H_2)/tr(A^T \Theta A^T \Theta)|)$.

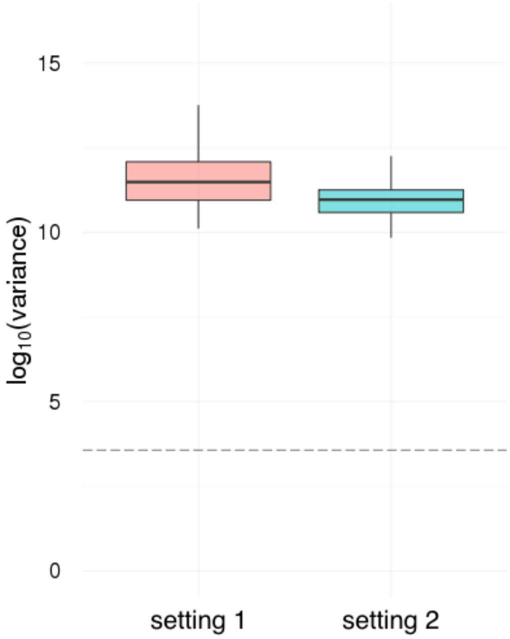

Figure S10. Numerical justifications to the theoretical proof – numerical study 2. Analysis details are described in **Appendix**. Boxplots under settings 1 and 2 denote the sample variance $\widehat{Var}(y_1^T A y_2)$ and $\widehat{Var}(y_1^T A' y_2)$, respectively (with 100 repeats). The dotted line marks the sample variance $\widehat{Var}(y_1^T \tilde{A} y_2)$.

Supplementary Tables

Table S1. Details of 48 GWAS.

Trait	Acronym	Sample Size[a]	Ref.	URL
Age at First Birth	AFB	241,781	1	http://www.thessgac.org/data
Age at Menarche	AM	132,989	2	http://www.reprogen.org/data_download.html
Age at Natural Menopause	ANM	69,360	3	http://www.reprogen.org/data_download.html
Age-related Macular Degeneration	AMD	33,976	4	http://csg.sph.umich.edu/abecasis/public/amd2015/
Anorexia Nervosa	AN	14,477	5	https://www.med.unc.edu/pgc/downloads
Anxiety Disorder	ANX	17,310	6	https://www.med.unc.edu/pgc/downloads
Asthma	AST	26,475	7	http://www.cng.fr/gabriel/index.html
Autism Spectrum Disorder	ASD	10,610	8	https://www.med.unc.edu/pgc/downloads
Bipolar Disorder	BIP	16,731	9	https://www.med.unc.edu/pgc/downloads
Birth Weight	BW	143,677	10	http://egg-consortium.org/birth-weight-2016.html
Body Mass Index	BMI	234,069	11	http://www.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium_data_files
Celiac Disease	CEL	15,283	12	https://www.immunobase.org/downloads/protected_data/GWAS_Data/
Chronic Kidney Disease	CKD	118,147	13	https://www.nhlbi.nih.gov/research/intramural/researchers/ckdgen
Chronotype	CHT	127,898	14	http://www.t2diabetesgenes.org/data/
Cognitive Performance	COG	106,736	15	http://www.thessgac.org/data
Coronary Artery Disease	CAD	184,305	16	http://www.cardiogramplusc4d.org/downloads/
Crohn's Disease	CD	27,726	17	http://www.ibdgenetics.org
Depressive Symptoms	DEP	161,460	18	http://www.thessgac.org/data
Eczema	ECZ	40,835	19	http://data.bris.ac.uk/data/dataset/28uchsdpmub118uex26ylacqm
Education Years	EDU	293,723	20	http://www.thessgac.org/data
Epilepsy	EPL	34,853	21	http://www.epigad.org/page/show/homepage
Fasting Glucose	GLU	58,074	22	http://www.magicinvestigators.org/downloads/
Fasting Insulin	INS	51,750	22	http://www.magicinvestigators.org/downloads/
Femoral Neck Bone Mineral Density	FNBMD	32,961	23	http://www.gefos.org/?q=content/data-release-2012
Gout	GOUT	69,374	24	http://metabolomics.helmholtz-muenchen.de/gugc/
HDL Cholesterol	HDL	99,900	25	http://csg.sph.umich.edu/abecasis/public/lipids2010/
Height	HGT	253,288	26	http://www.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium_data_files
Inflammatory Bowel Disease	IBD	34,694	17	http://www.ibdgenetics.org
LDL Cholesterol	LDL	95,454	25	http://csg.sph.umich.edu/abecasis/public/lipids2010/
Lumbar Spine Bone Mineral Density	LSBMD	31,800	23	http://www.gefos.org/?q=content/data-release-2012
Major Depressive Disorder	MDD	18,759	27	https://www.med.unc.edu/pgc/downloads
Multiple Sclerosis	MS	27,148	28	https://www.immunobase.org/downloads/protected_data/GWAS_Data/
Neuroticism	NEU	170,911	18	http://www.thessgac.org/data
Number of Children Ever Born	NCEB	318,463	1	http://www.thessgac.org/data
Primary Angle Closure Glaucoma	PACG	26,454	29	Supplementary data in the original GWAS paper
Primary Billary Cirrhosis	PBC	13,239	30	https://www.immunobase.org/downloads/protected_data/GWAS_Data/
Resting Heart Rate	RHR	134,251	31	http://www.cardiomics.net/download-data
Rheumatoid Arthritis	RA	58,284	32	http://plaza.umin.ac.jp/~yokada/datasource/software.htm
Schizophrenia	SCZ	82,315	33	https://www.med.unc.edu/pgc/downloads
Serum Urate	SU	110,347	24	http://metabolomics.helmholtz-muenchen.de/gugc/
Smoking Behavior	SMK	74,053	34	https://www.med.unc.edu/pgc/downloads
Subjective Well-being	SWB	298,420	18	http://www.thessgac.org/data
Systemic Lupus Erythematosus	SLE	14,267	35	https://www.immunobase.org/downloads/protected_data/GWAS_Data/
Total Cholesterol	TC	100,184	25	http://csg.sph.umich.edu/abecasis/public/lipids2010/
Triglycerides	TG	96,598	25	http://csg.sph.umich.edu/abecasis/public/lipids2010/
Type-II Diabetes	T2D	69,033	36	http://diagram-consortium.org/downloads.html
Ulcerative Colitis	UC	28,738	17	http://www.ibdgenetics.org
Waist Hip Ratio adjusted for BMI	WHR	142,762	37	http://www.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium_data_files
Total		4,563,942[b]		

[a] Due to technical reasons, sample size may be slightly different from what is reported in the reference.

[b] Calculation for total sample size did not take sample overlap between studies into account.

Table S2. Pair-wise genetic correlation of 48 complex traits.

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Table S3. Compare genetic correlations estimated by GNOVA and LDSC.

			GNOVA		LDSC	
Significance	**Trait 1**	**Trait 2**	**Correlation**	**P**	**Correlation**	**P**
GNOVA+; LDSC-	AFB	ASD	0.2571	1.37E-06	0.1617	2.80E-03
	AFB	EPL	-0.2418	4.22E-05	-0.1067	1.65E-01
	AFB	MDD	-0.2779	3.90E-09	-0.2425	1.20E-03
	AFB	RA	-0.2347	5.89E-11	-0.1799	2.00E-04
	AFB	T2D	-0.1902	5.60E-08	-0.1647	3.00E-04
	AM	CAD	-0.1434	4.22E-06	-0.1108	2.00E-04
	AM	SU	-0.1272	2.03E-06	-0.0822	9.50E-03
	AN	GLU	-0.2545	8.77E-06	-0.2959	8.00E-04
	AN	HDL	0.2354	1.10E-05	0.2575	7.00E-04
	AN	TG	-0.2848	3.23E-08	-0.2292	4.00E-04
	AN	WHR	-0.3156	2.78E-06	-0.2195	5.83E-05
	ANM	CEL	0.1669	5.65E-07	0.0736	3.54E-01
	ANX	COG	-0.3417	1.55E-07	-0.4370	6.00E-04
	ANX	MDD	0.6657	1.14E-09	0.7597	6.58E-05
	ANX	SMK	0.3947	4.25E-05	0.3960	4.30E-03
	ASD	MS	-0.4704	4.13E-11	-0.2531	6.61E-02
	ASD	SWB	-0.2304	4.18E-05	-0.2648	6.00E-04
	AST	ECZ	0.3537	6.71E-06	0.6475	4.98E-05
	BIP	DEP	0.3620	1.43E-18	0.2163	9.86E-05
	BIP	NEU	0.1400	1.55E-05	0.0963	3.97E-02
	BIP	SWB	-0.1773	2.08E-05	-0.2174	9.00E-04
	BMI	CKD	0.2453	4.76E-06	0.1748	1.80E-03
	BMI	DEP	0.2136	6.63E-08	0.1220	9.37E-05
	BMI	NCEB	0.2533	4.20E-11	0.1111	7.70E-05
	BW	GLU	-0.1563	4.17E-05	-0.1246	9.90E-03
	BW	TC	-0.1400	1.29E-05	-0.1269	1.30E-03
	CD	MS	0.1943	3.03E-06	0.2097	1.79E-01
	CEL	COG	0.1438	2.71E-06	0.2218	1.90E-03
	CHT	COG	-0.1491	1.03E-08	-0.1439	1.30E-03
	CHT	SCZ	-0.1047	1.26E-05	-0.1180	4.00E-04
	COG	INS	-0.1511	1.36E-05	-0.2396	1.00E-04
	COG	RA	-0.1809	4.47E-11	-0.1921	1.37E-02
	COG	T2D	-0.1913	1.31E-07	-0.1984	2.00E-04
	EDU	EPL	-0.2099	4.39E-07	-0.1883	1.60E-03
	EDU	LDL	-0.1332	2.98E-06	-0.1319	3.00E-04
	EDU	T2D	-0.1738	1.39E-08	-0.1359	1.00E-04
	FNBMD	GLU	0.3400	1.89E-05	0.1457	6.40E-03
	FNBMD	T2D	0.2976	1.31E-05	0.1734	8.00E-04
	GLU	INS	0.2633	2.52E-05	0.2956	1.50E-03
	GLU	RHR	0.1433	5.34E-06	0.1390	3.90E-03
	IBD	MS	0.1712	1.29E-05	0.3092	9.07E-02
	INS	RHR	0.1834	6.18E-06	0.2228	4.76E-05
	MDD	SMK	0.2738	3.76E-06	0.2000	3.94E-02
	MS	SLE	0.4343	7.13E-16	0.5394	1.29E-02
	NEU	WHR	0.1907	6.79E-06	0.1222	3.00E-04
	PBC	UC	0.2047	9.22E-06	0.2490	1.10E-03
	RHR	T2D	0.1932	9.89E-07	0.1779	2.00E-04
	SCZ	SMK	0.1371	2.84E-06	0.1093	4.60E-03
	SU	T2D	0.2753	1.16E-17	0.2783	2.00E-04
	SU	TG	0.3822	4.58E-09	0.3301	4.12E-05
GNOVA-; LDSC+	CAD	LDL	0.2140	7.01E-03	0.2242	4.40E-06
	LDL	TC	0.8596	7.69E-05	0.9905	0.00E+00
	T2D	WHR	0.2643	1.10E-04	0.2525	1.48E-07

[a] p-value output in LDSC log file was 0.

Table S4. Genetic correlation between eight pairs of physiologically or epidemiologically related traits.

Trait 1	Trait 2	Covariance	SE	Correlation	P
FNBMD	LSBMD	0.1553	0.0156	1.7719	2.01E-23
DEP	MDD	0.0562	0.0058	0.6270	5.95E-22
SCZ	SWB	-0.0309	0.0034	-0.3176	2.50E-19
ANX	SWB	-0.0287	0.0037	-0.6927	5.71E-15
NEU	SWB	-0.0299	0.0023	-0.6799	3.60E-38
DEP	SWB	-0.0221	0.0016	-0.7139	3.03E-42
MDD	SWB	-0.0516	0.0039	-0.7952	3.58E-39

Table S5. Stratify genetic covariance by genome functionality.

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Table S6. Stratify genetic covariance by SNPs' MAF in 1000 Genomes Project.

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Table S7. Stratify genetic covariance by tissue type.

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Table S8. Details of LOAD and ALS GWASs.

Trait	Sample Size	Ref.	URL
Late-onset Alzheimer's disease	54,162	[38]	http://web.pasteur-lille.fr/en/recherche/u744/igap/igap_download.php
Amyotrophic lateral sclerosis	36,052	[39]	http://databrowser.projectmine.com

Table S9. Tissue-stratified covariance estimates of LOAD and ALS.

Tissue	Covariance	SE	P
Brain	0.0087	0.0081	0.283
Cardiovascular	0.0087	0.0106	0.412
Epithelium	0.0038	0.0126	0.762
Gastrointestinal	0.0001	0.0110	0.996
Immune	0.0254	0.0103	0.014
Muscle	0.0008	0.0097	0.938
Other	0.0006	0.0139	0.964

Table S10. Genetic correlation between LOAD, ALS, and 48 complex traits.

	LOAD				ALS			
Trait	**Covariance**	**SE**	**Correlation**	**P**	**Covariance**	**SE**	**Correlation**	**P**
AFB	-0.0095	0.0021	-0.1595	7.07E-06	-0.0060	0.0022	-0.1003	6.07E-03
AM	0.0014	0.0037	0.0129	7.05E-01	0.0070	0.0033	0.0642	3.42E-02
AMD	-0.0051	0.0065	-0.0333	4.33E-01	-0.0033	0.0051	-0.0220	5.19E-01
AN	0.0109*	0.0078	0.0813	1.61E-01	0.0148	0.0078	0.2981*	5.86E-02
ANM	-0.0031	0.0041	-0.0332	4.49E-01	0.0030	0.0038	0.0314	4.32E-01
ANX	0.0078*	0.0075	0.0892	2.98E-01	-0.0083	0.0064	-0.0444*	1.96E-01
ASD	0.0019*	0.0089	0.0136	8.29E-01	-0.0152	0.0087	-0.0761*	8.18E-02
AST	0.0250	0.0063	0.1956	7.97E-05	0.0159	0.0070	0.3405*	2.41E-02
BIP	0.0079*	0.0073	0.0505	2.82E-01	-0.0015	0.0073	0.2364*	8.42E-01
BMI	-0.0034	0.0030	-0.0494	2.71E-01	0.0043	0.0026	0.0626	9.59E-02
BW	-0.0019	0.0029	-0.0203	5.23E-01	0.0051	0.0029	0.0578	7.78E-02
CAD	-0.0012*	0.0026	-0.0223	6.40E-01	-0.0028	0.0023	0.2042*	2.30E-01
CD	-0.0073*	0.0063	-0.0468	2.49E-01	-0.0014	0.0058	0.2603*	8.06E-01
CEL	-0.0110*	0.0099	-0.0455	2.68E-01	0.0284	0.0090	0.5444*	1.52E-03
CHT	0.0046	0.0035	0.0510	1.91E-01	-0.0082	0.0029	-0.0916	5.25E-03
CKD	0.0014	0.0031	0.0346	6.52E-01	0.0017	0.0026	0.0409	5.05E-01
COG	-0.0234	0.0034	-0.2547	1.05E-11	-0.0007	0.0031	-0.0079	8.08E-01
DEP	0.0027	0.0029	0.0479	3.56E-01	0.0035	0.0025	0.0644	1.74E-01
ECZ	0.0117	0.0053	0.1365	2.79E-02	0.0082	0.0046	0.0994	7.56E-02
EDU	-0.0186	0.0027	-0.1988	3.41E-12	-0.0045	0.0024	-0.0501	6.06E-02
EPL	0.0056*	0.0043	0.0899	1.87E-01	0.0012	0.0042	0.6557*	7.68E-01
FNBMD	0.0093	0.0059	0.1131	1.17E-01	0.0010	0.0051	0.0117	8.50E-01
GLU	0.0106	0.0044	0.1284	1.59E-02	0.0042	0.0041	0.0505	3.07E-01
GOUT	0.0007	0.0031	0.0317	8.20E-01	0.0010	0.0030	0.0429	7.32E-01
HDL	0.0014	0.0037	0.0189	7.06E-01	-0.0025	0.0033	-0.0337	4.38E-01
HGT	-0.0174	0.0044	-0.1043	6.67E-05	0.0004	0.0038	0.0025	9.12E-01
IBD	-0.0113*	0.0057	-0.0727	4.93E-02	-0.0029	0.0046	0.3208*	5.20E-01
INS	0.0014	0.0044	0.0175	7.56E-01	-0.0041	0.0042	-0.0530	3.27E-01
LDL	0.0085	0.0040	0.1194	3.25E-02	0.0027	0.0032	0.0365	3.94E-01
LSBMD	0.0188	0.0062	0.2331	2.26E-03	-0.0045	0.0050	-0.0542	3.64E-01
MDD	0.0030*	0.0083	0.0244	7.15E-01	-0.0035	0.0069	0.2029*	6.13E-01
MS	-0.0100*	0.0078	-0.0686	2.02E-01	0.0283	0.0081	0.3924*	4.55E-04
NCEB	0.0013	0.0019	0.0339	4.89E-01	0.0017	0.0018	0.0412	3.62E-01
NEU	0.0064	0.0035	0.0759	6.95E-02	0.0037	0.0036	0.0456	3.02E-01
PACG	0.0062	0.0059	0.0443	2.96E-01	0.0141	0.0055	0.1185	9.67E-03
PBC	-0.0494*	0.0107	-0.2354	4.36E-06	0.0030	0.0170	0.5388*	8.61E-01
RA	-0.0066*	0.0050	-0.0652	1.81E-01	-0.0196	0.0087	0.0211*	2.52E-02
RHR	0.0011	0.0030	0.0101	7.27E-01	0.0054	0.0034	0.0538	1.10E-01
SCZ	0.0005*	0.0047	0.0029	9.13E-01	0.0128	0.0048	0.2516*	7.53E-03
SLE	-0.0009*	0.0094	-0.0034	9.24E-01	0.0243	0.0142	0.0738*	8.75E-02
SMK	-0.0007	0.0036	-0.0095	8.46E-01	0.0054	0.0036	0.0720	1.28E-01
SU	-0.0015	0.0036	-0.0154	6.80E-01	-0.0050	0.0033	-0.0509	1.27E-01
SWB	-0.0015	0.0021	-0.0347	4.71E-01	0.0016	0.0019	0.0353	3.97E-01
T2D	-0.0002*	0.0041	-0.0024	9.62E-01	-0.0028	0.0040	0.2045*	4.82E-01
TC	0.0095	0.0044	0.1258	3.12E-02	0.0004	0.0035	0.0050	9.09E-01
TG	0.0058	0.0037	0.0788	1.17E-01	-0.0027	0.0043	-0.0350	5.27E-01
UC	-0.0148*	0.0054	-0.1061	5.68E-03	-0.0064	0.0047	0.3328*	1.75E-01
WHR	0.0017	0.0025	0.0335	5.02E-01	0.0027	0.0030	0.0508	3.74E-01

* Sample overlap correction was applied.

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The authors declare no conflict of interests.

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