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Supplemental information

GWAS of longitudinal trajectories at biobank scale

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Supplemental Material for "GWAS of Longitudinal Trajectories at Biobank Scale"

Seyoon Ko[1,2,8], Christopher A. German[2,8], Aubrey Jensen[2], Judong Shen[3], Anran Wang[3], Devan V. Mehrotra[3], Yan V. Sun[4], Janet S. Sinsheimer[1,2,5], Hua Zhou[1,2,**], Jin J. Zhou[2,6,7,*]

[1]Department of Computational Medicine, University of California, Los Angeles, CA 90095, U.S.A.
[2]Department of Biostatistics, University of California, Los Angeles, CA 90095, U.S.A.
[3]Biostatistics and Research Decision Sciences, Merck & Co., Inc., Kenilworth, NJ 07033, U.S.A.
[4]Department of Epidemiology, Emory University, Atlanta, GA 30322, U.S.A.
[5]Department of Human Genetics, University of California, Los Angeles, CA 90095, U.S.A.
[6]Department of Medicine, University of California, Los Angeles, CA 90095, U.S.A.
[7]Department of Epidemiology and Biostatistics, University of Arizona, Tucson, AZ 85721, U.S.A.
[8]These author contributed equally to this work.
[*]Correspondence: jinjinzhou@ucla.edu
[**]Correspondence: huazhou@ucla.edu

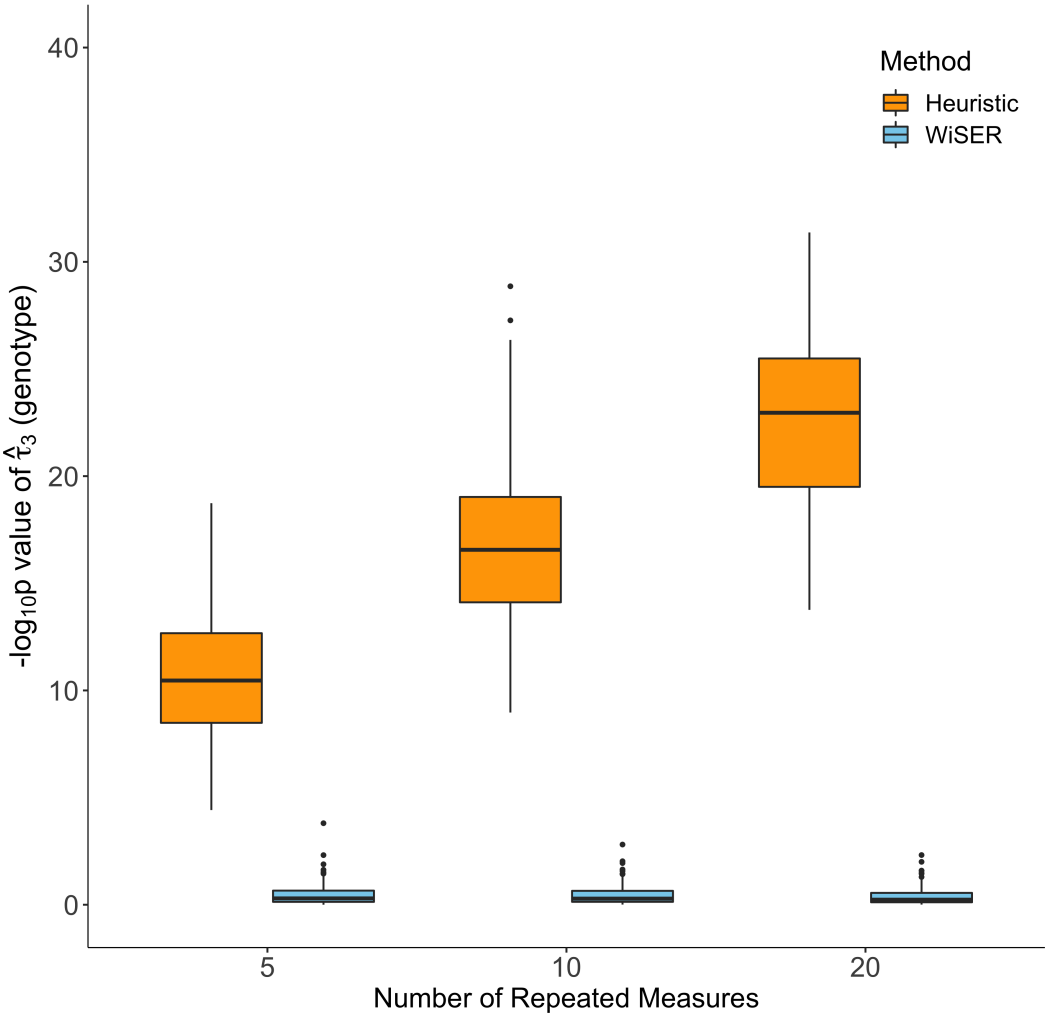

Figure S1: **Boxplots of $-\log_{10}$(p values) for testing a null effect genotype by WiSER (adjusting for time-varying covariates) and the heuristic method of using standard deviation of the residuals as the outcome**
The sample size is $m = 6,000$ and the number of replicates is 100. The heuristic method leads to incorrect inference – false positives due to systematically inflated p values.

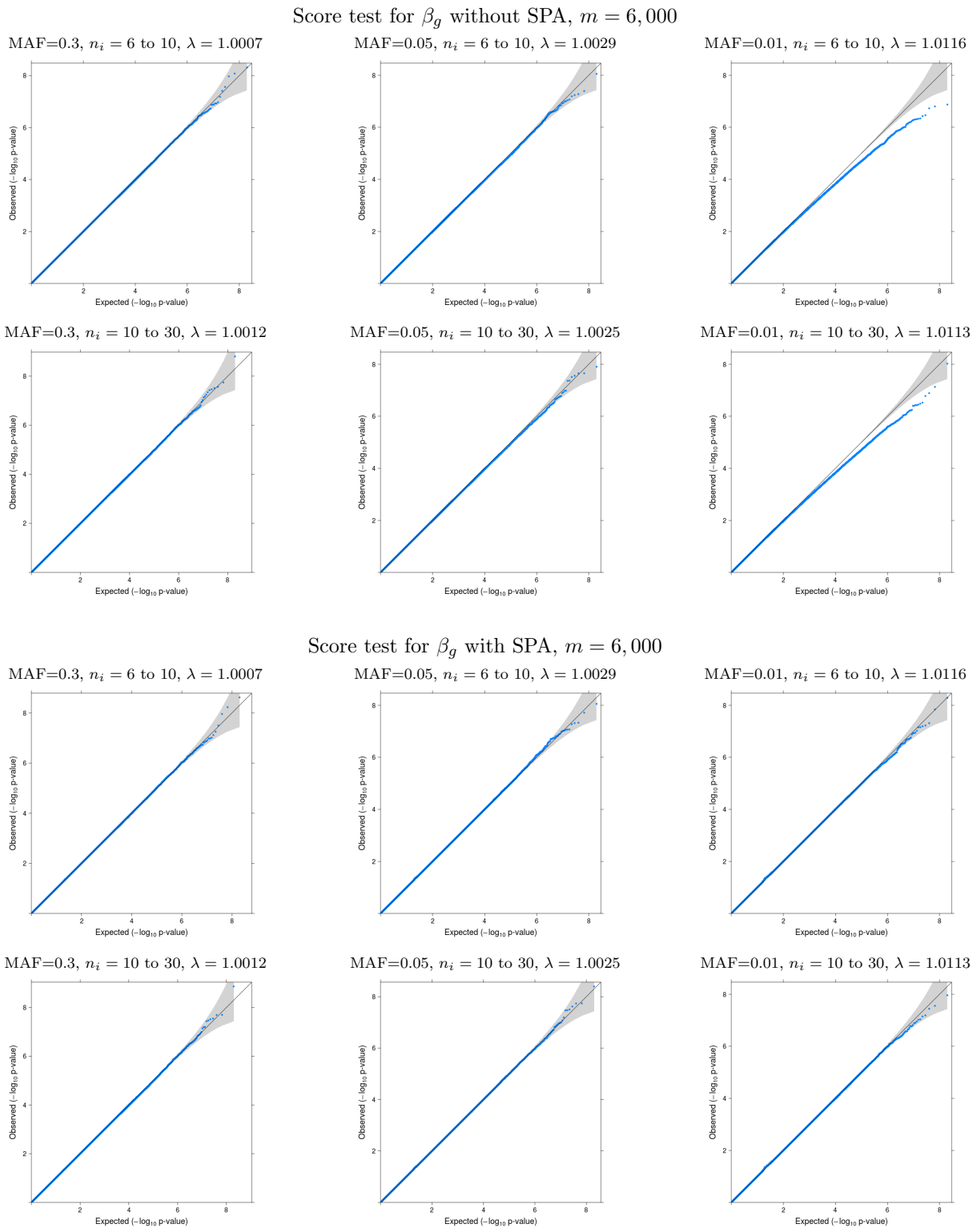

Figure S2: **Quantile-Quantile (QQ) plots of p values for testing β_g from the score test and SPA of the simulation studies,** $m = 6,000$
QQ plots from score test without SPA (row 1-2) and SPA (row 3-4) for testing β_g, where $m = 6,000$, $n_i = 6$ to 10 (row 1 and row 3) and $n_i = 10$ to 30 (row 2 and row 4), MAF = 0.3 (column 1), 0.05 (column 2), and 0.01 (column 3), based on 10^9 replicates.

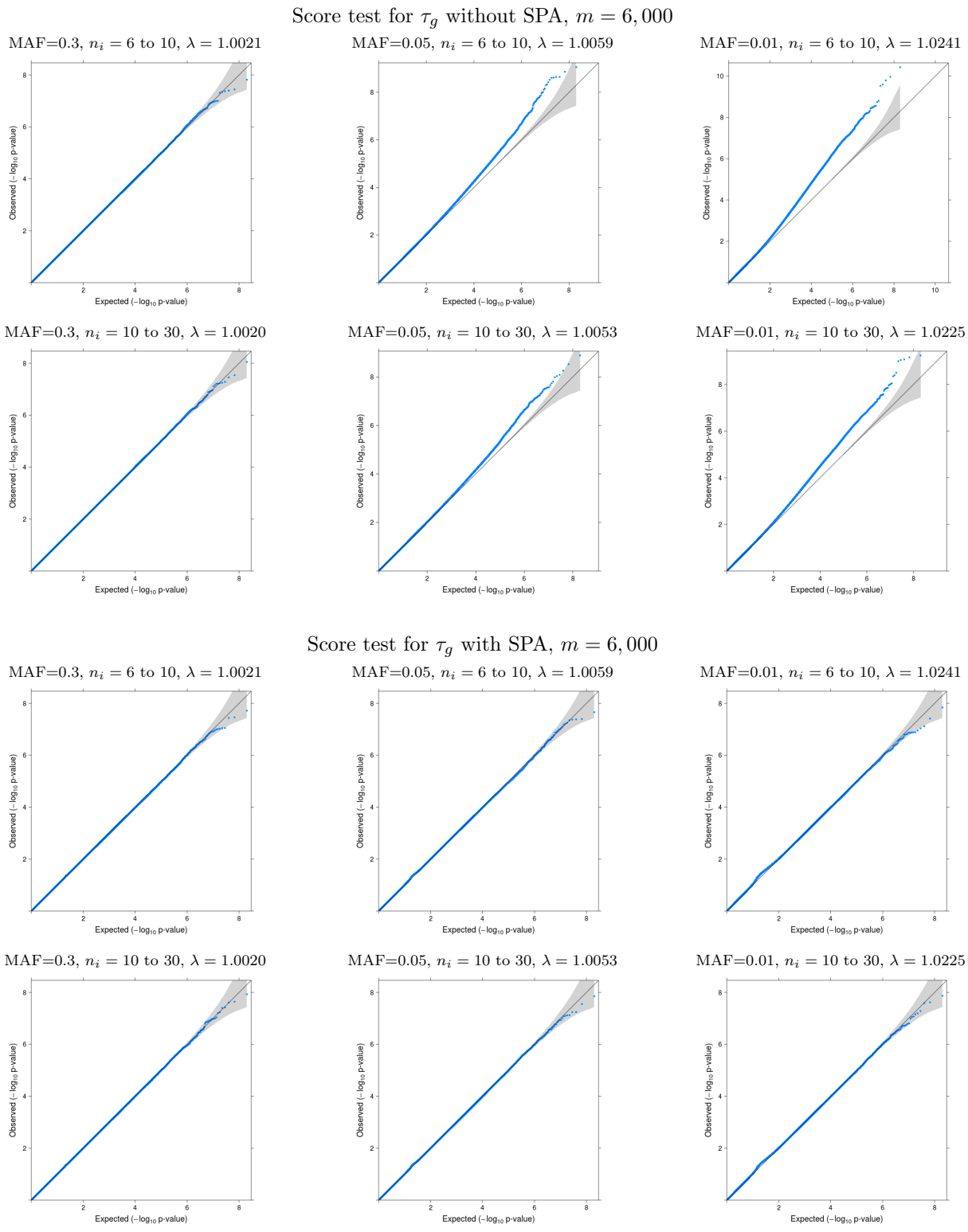

Figure S3: **Quantile-Quantile (QQ) plots of p values for testing τ_g from the score test and SPA of the simulation studies,** $m = 6,000$

QQ plots of p values from score test (row 1-2) and SPA (row 3-4) for testing τ_g, where $m = 6,000$, $n_i = 6$ to 10 (row 1 and row 3) and $n_i = 10$ to 30 (row 2 and row 4), MAF = 0.3 (column 1), 0.05 (column 2), and 0.01 (column 3), based on 10^9 replicates.

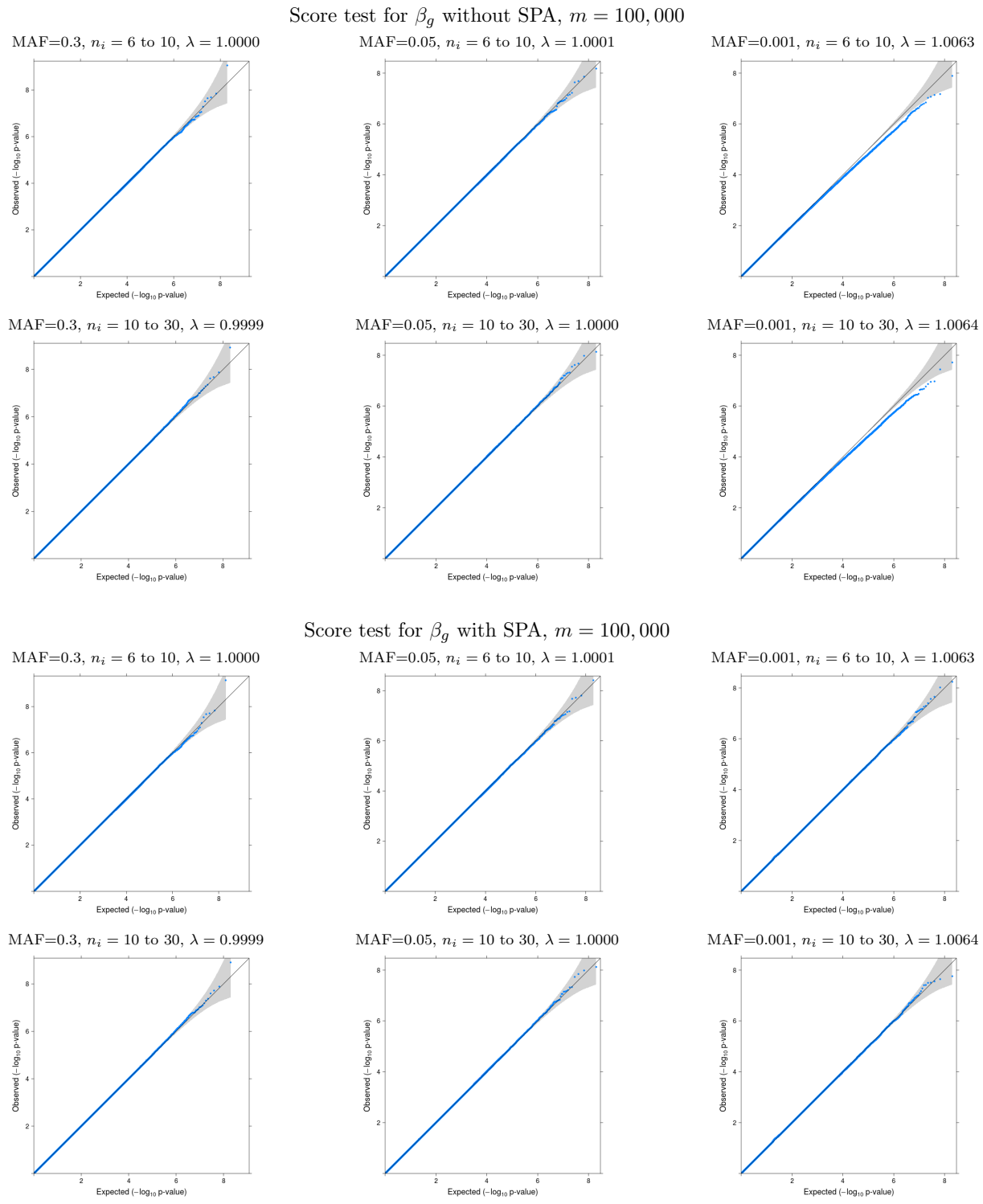

Figure S4: **Quantile-Quantile (QQ) plots of p values for testing β_g from the score test and SPA of the simulation studies,** $m = 100,000$

QQ plots of p values from score test (row 1-2) and SPA (row 3-4) for testing β_g, where $m = 100,000$, $n_i = 6$ to 10 (row 1 and row 3) and $n_i = 10$ to 30 (row 2 and row 4), MAF = 0.3 (column 1), 0.05 (column 2), and 0.001 (column 3), based on 10^9 replicates.

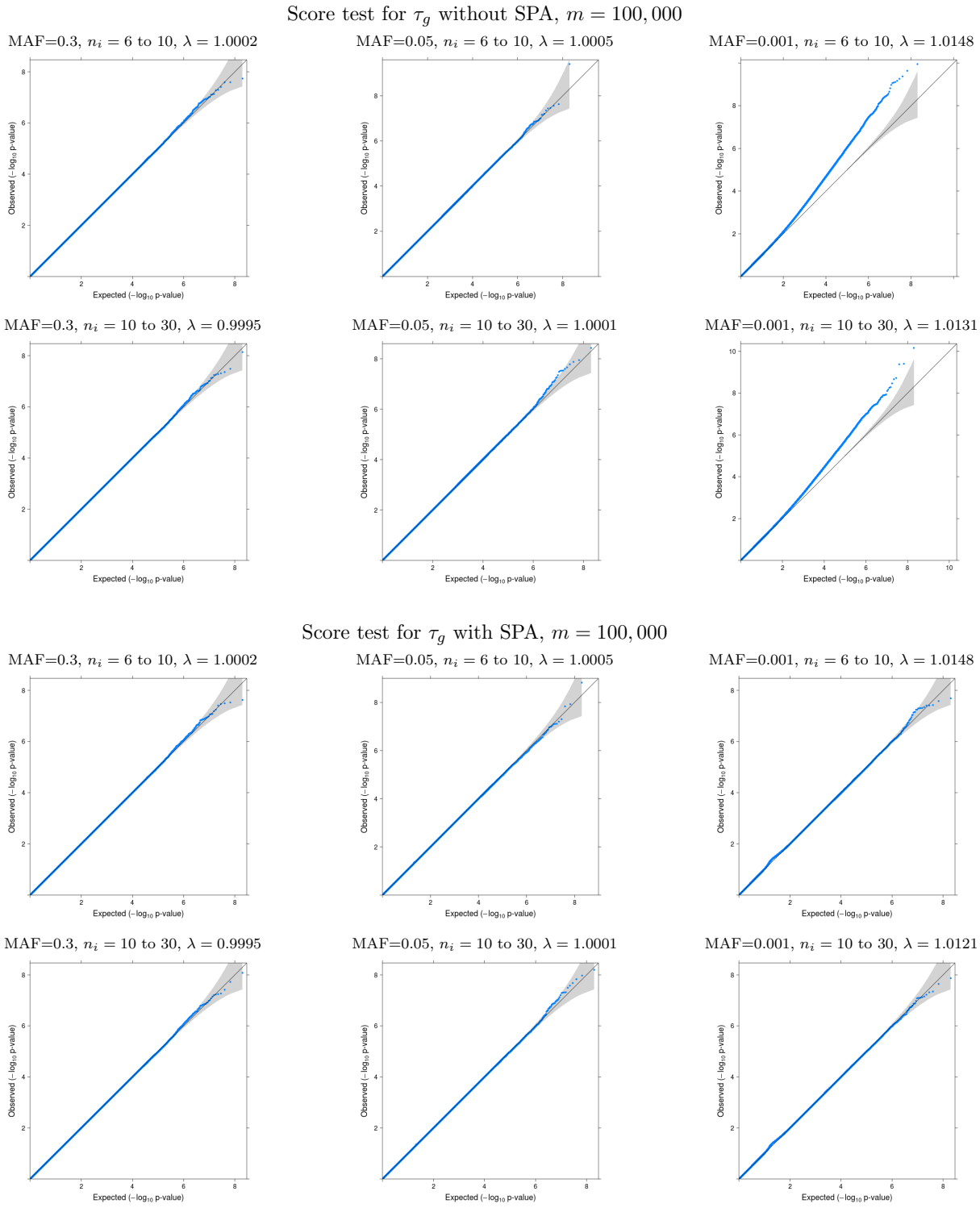

Figure S5: **Quantile-Quantile (QQ) plots of p values for testing τ_g from the score test and SPA of the simulation studies,** $m = 10,000$

QQ plots of p values from score test (row 1-2) and SPA (row 3-4) for testing τ_g, where $m = 10,000$, $n_i = 6$ to 10 (row 1 and row 3) and $n_i = 10$ to 30 (row 2 and row 4), MAF = 0.3 (column 1), 0.05 (column 2), and 0.001 (column 3), based on 10^9 replicates.

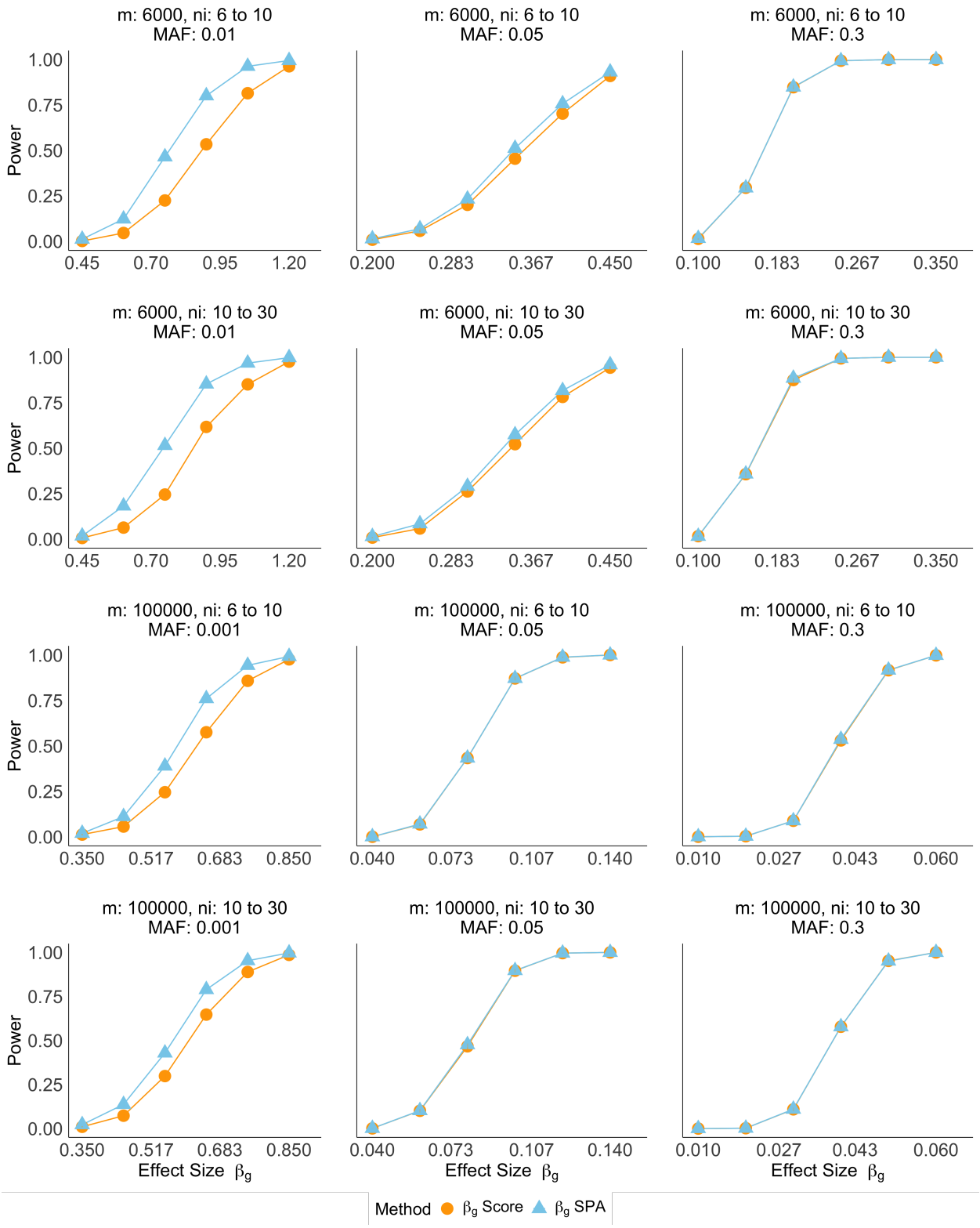

Figure S6: **Empirical powers of testing β_g with score test and SPA**
Each row contains the same sample size m and number of observations per individual n_i. Power is evaluated at the significance level $\alpha = 5 \times 10^{-8}$. Each scenario is based on 1,000 replicates.

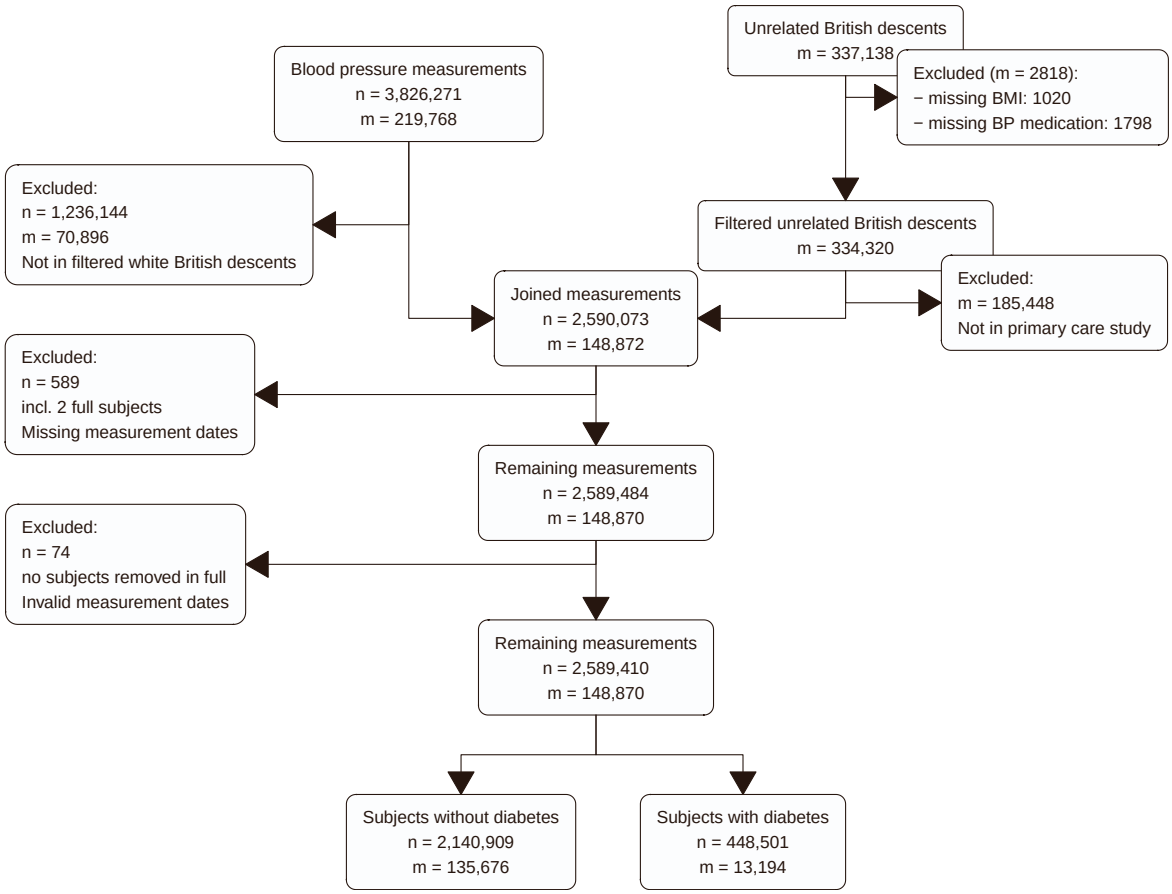

Figure S7: **Cohort curation for blood pressure `TrajGWAS` analysis from UK Biobank primary care data.**

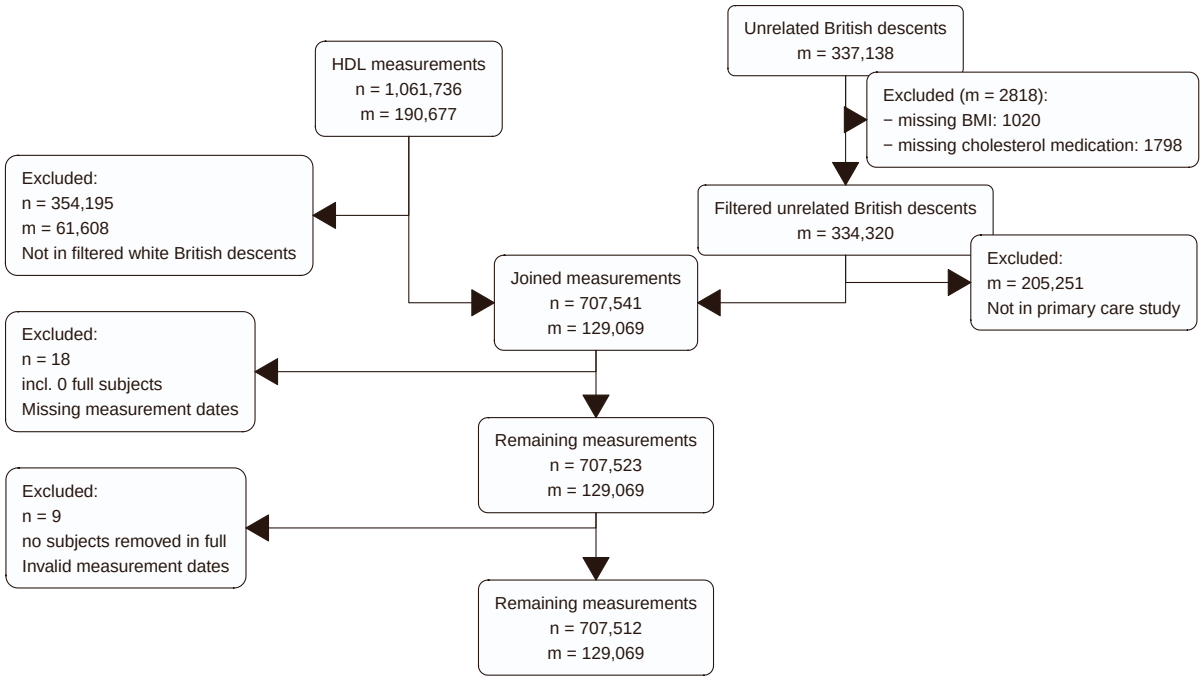

Figure S8: **Cohort curation for HDL `TrajGWAS` analysis from UK Biobank primary care data.**

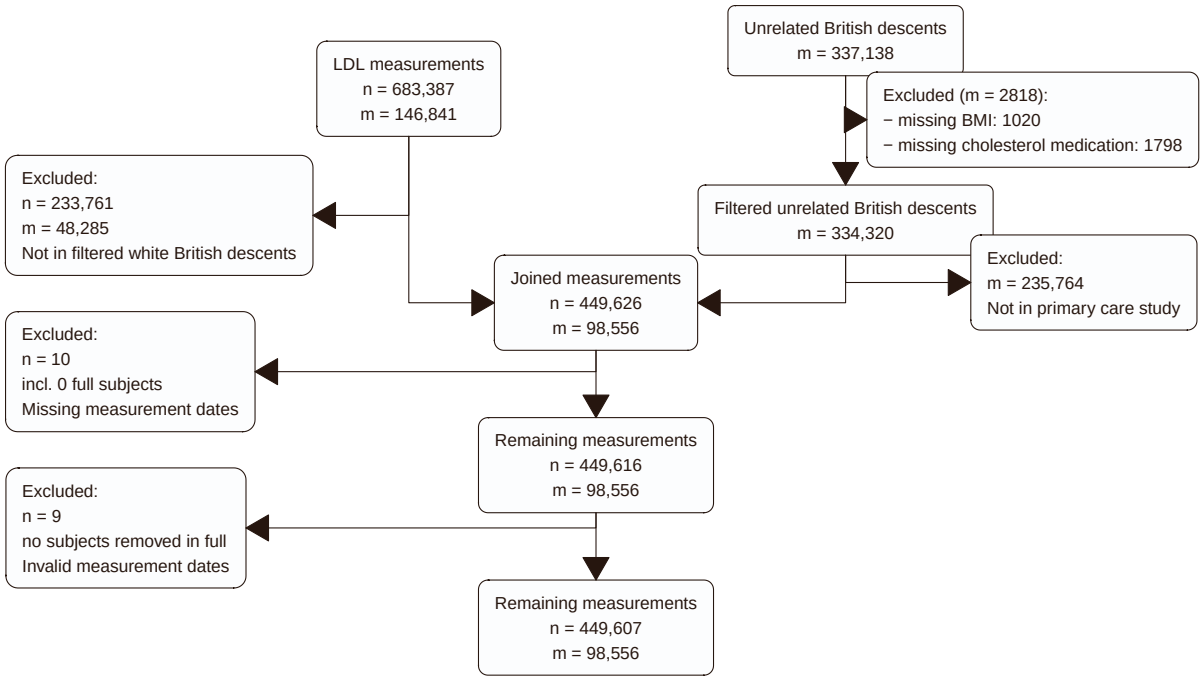

Figure S9: **Cohort curation for LDL `TrajGWAS` analysis from UK Biobank primary care data.**

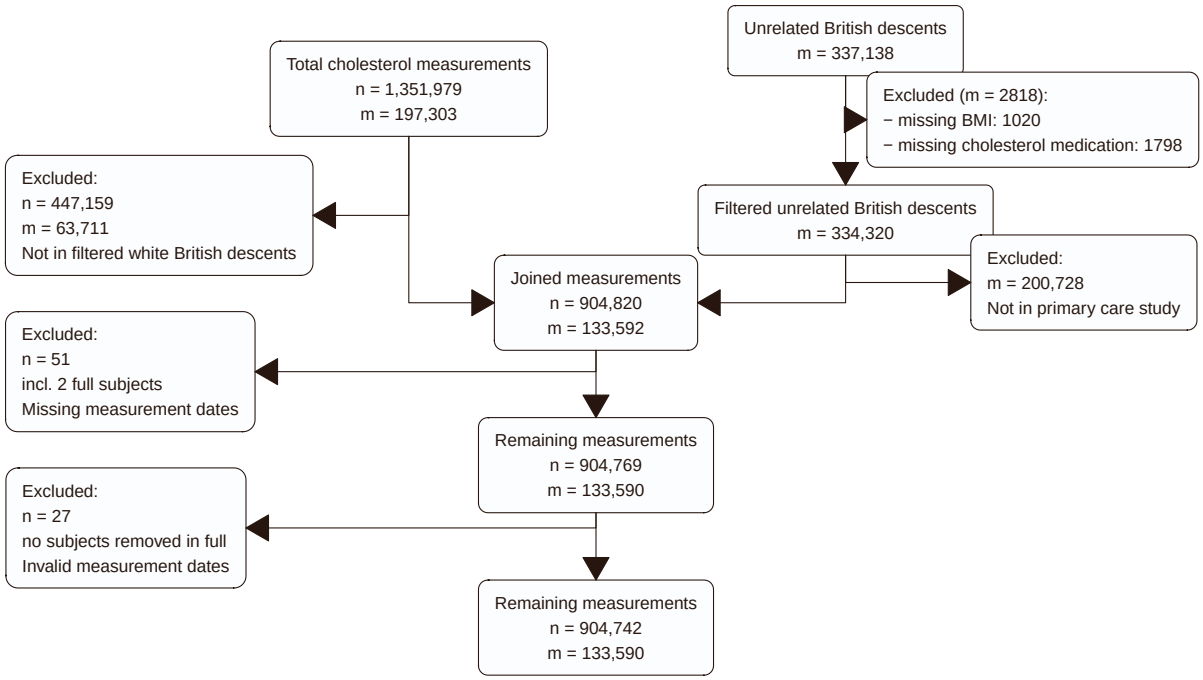

Figure S10: **Cohort curation for total cholesterol `TrajGWAS` analysis from UK Biobank primary care data.**

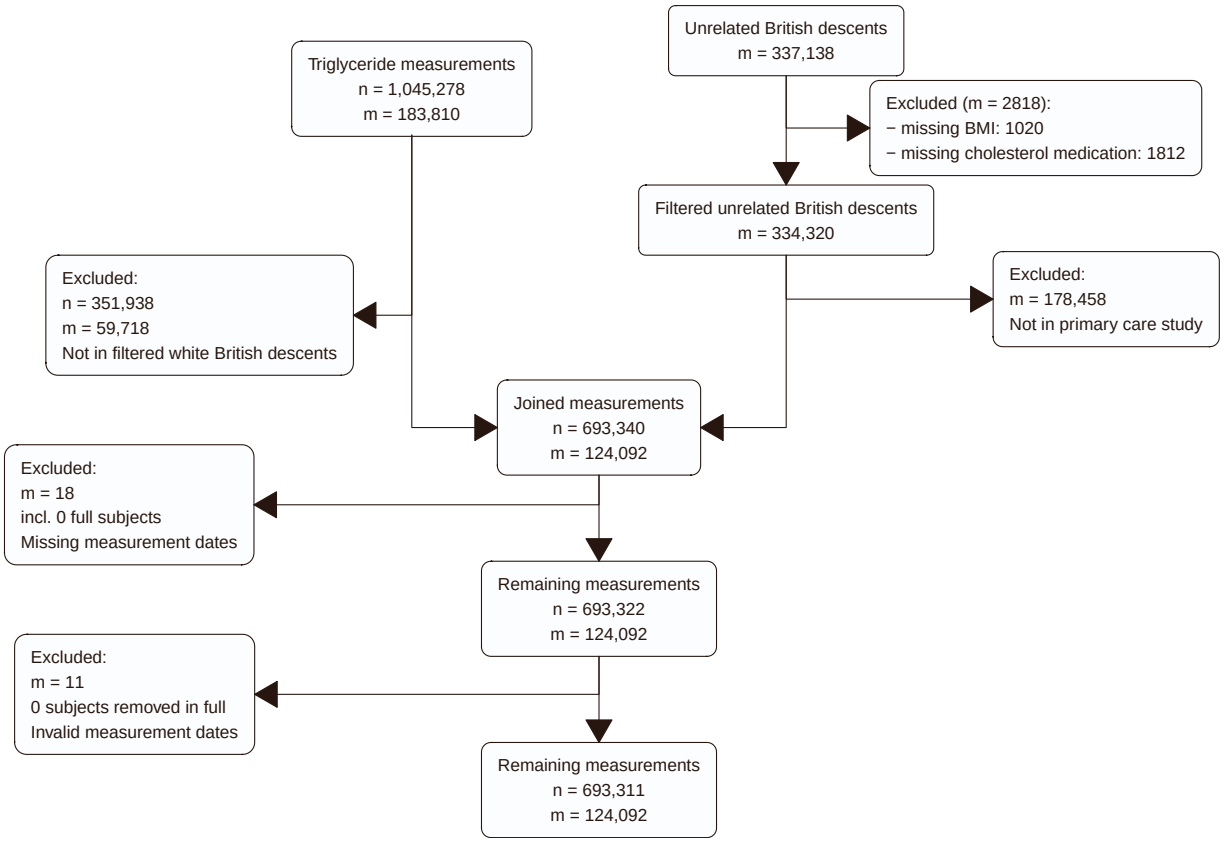

Figure S11: **Cohort curation for triglycerides `TrajGWAS` analysis from UK Biobank primary care data.**

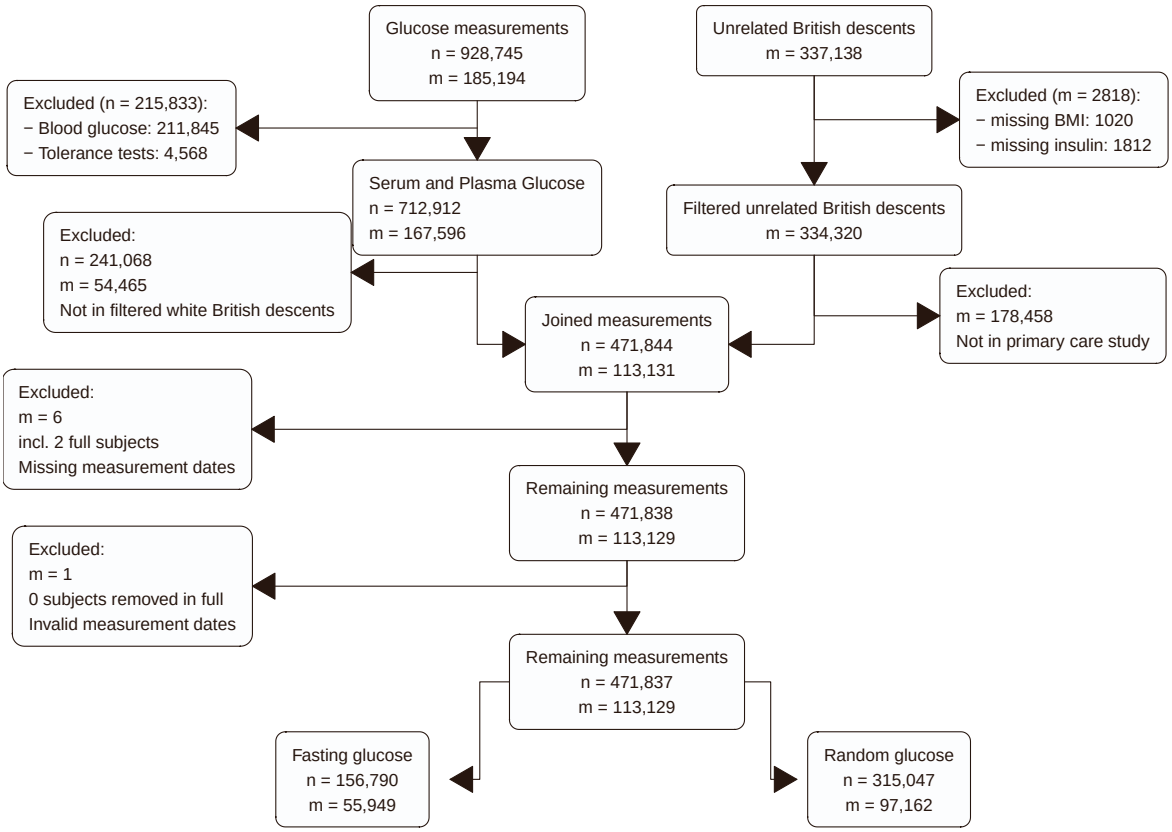

Figure S12: **Cohort curation for glucose `TrajGWAS` analysis from UK Biobank primary care data.**

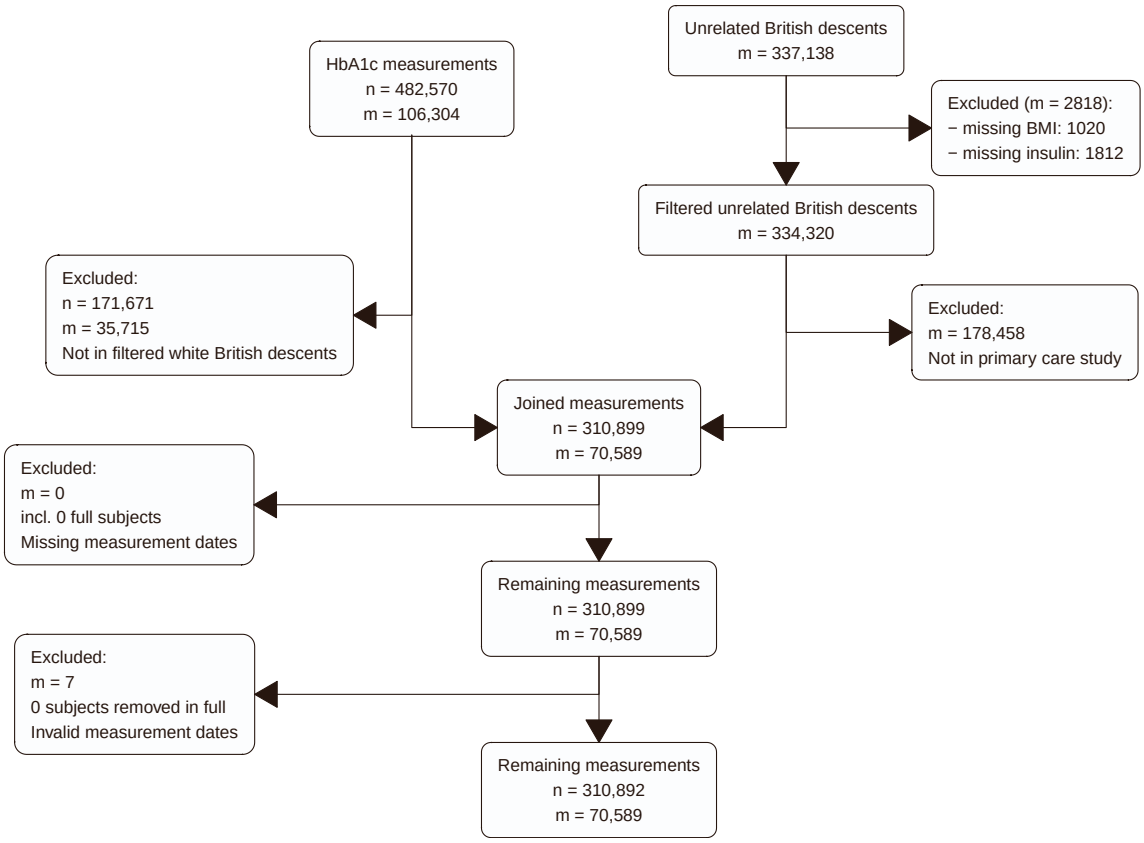

Figure S13: **Cohort curation for HbA1c `TrajGWAS` analysis from UK Biobank primary care data.**

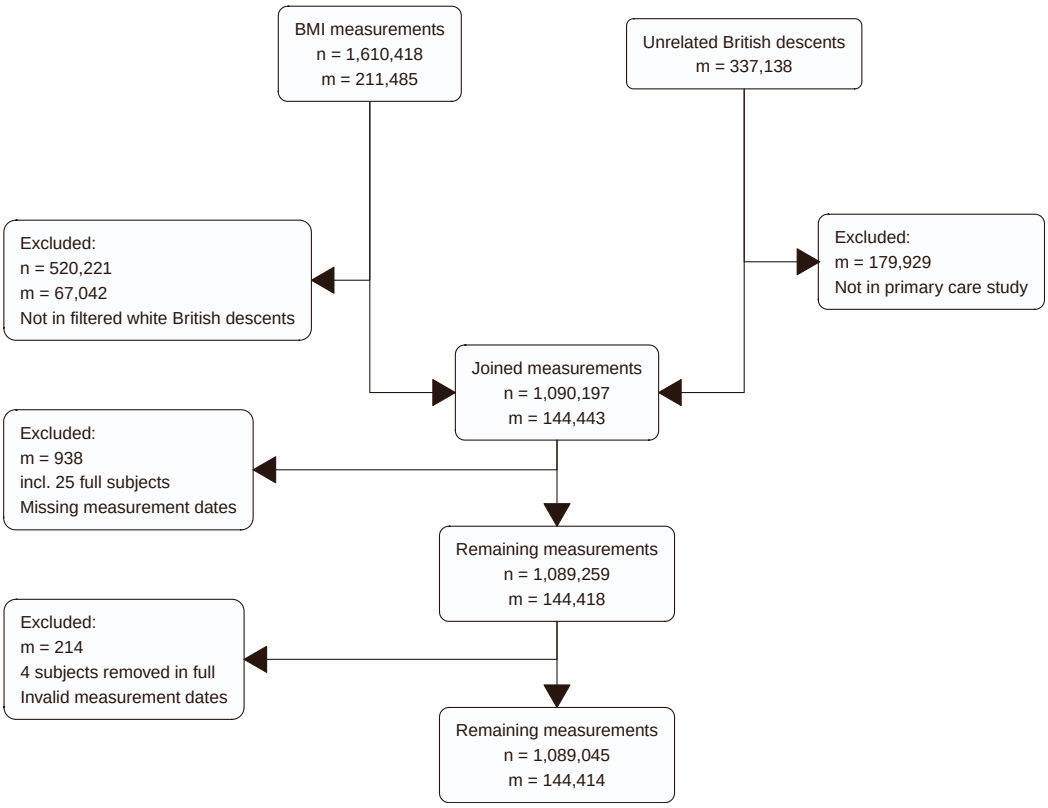

Figure S14: **Cohort curation for BMI `TrajGWAS` analysis from UK Biobank primary care data.**

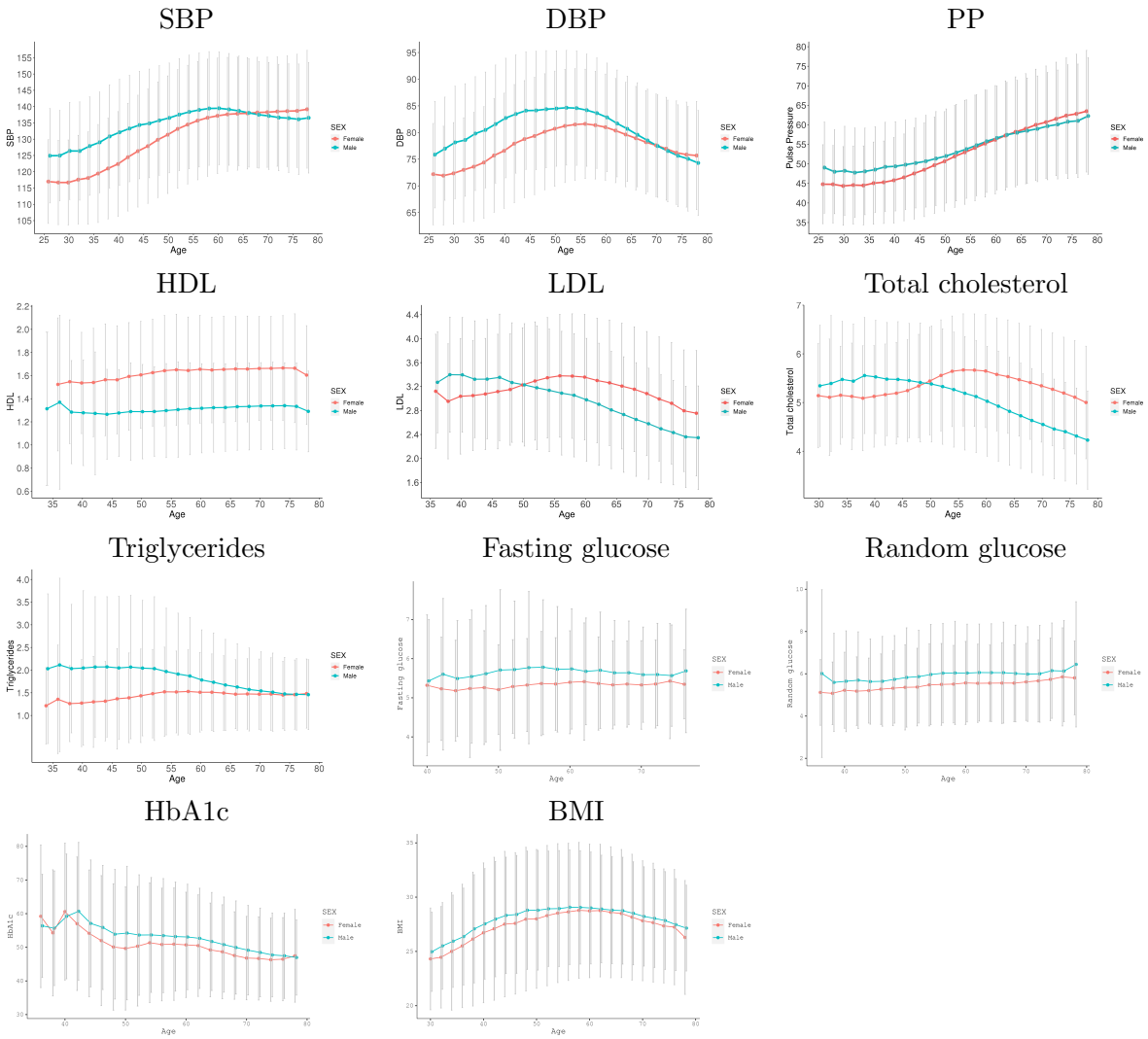

Figure S15: **Mean profile plot over age groups for biomarker measures extracted from the UK Biobank primary care data.**

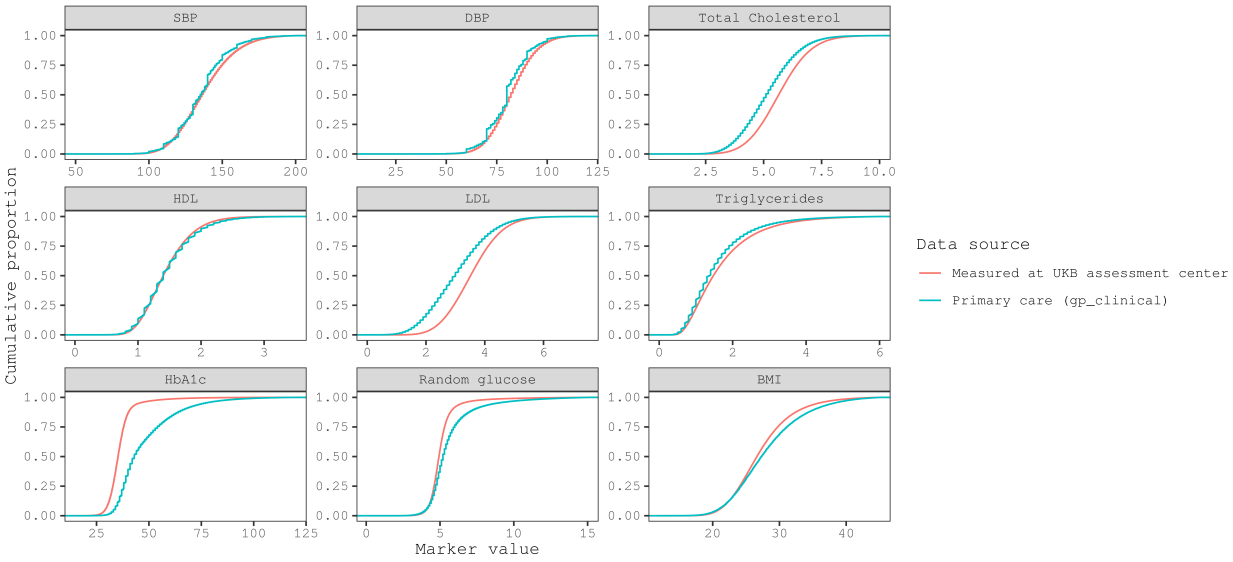

Figure S16: **Empirical cumulative distribution functions (eCDFs) of biomarker measures from UK Biobank primary care data (blue curve) and assessment centers (red curve) respectively.**
Agreement between the eCDFs provides quality control for the extraction procedure from the primary care data.

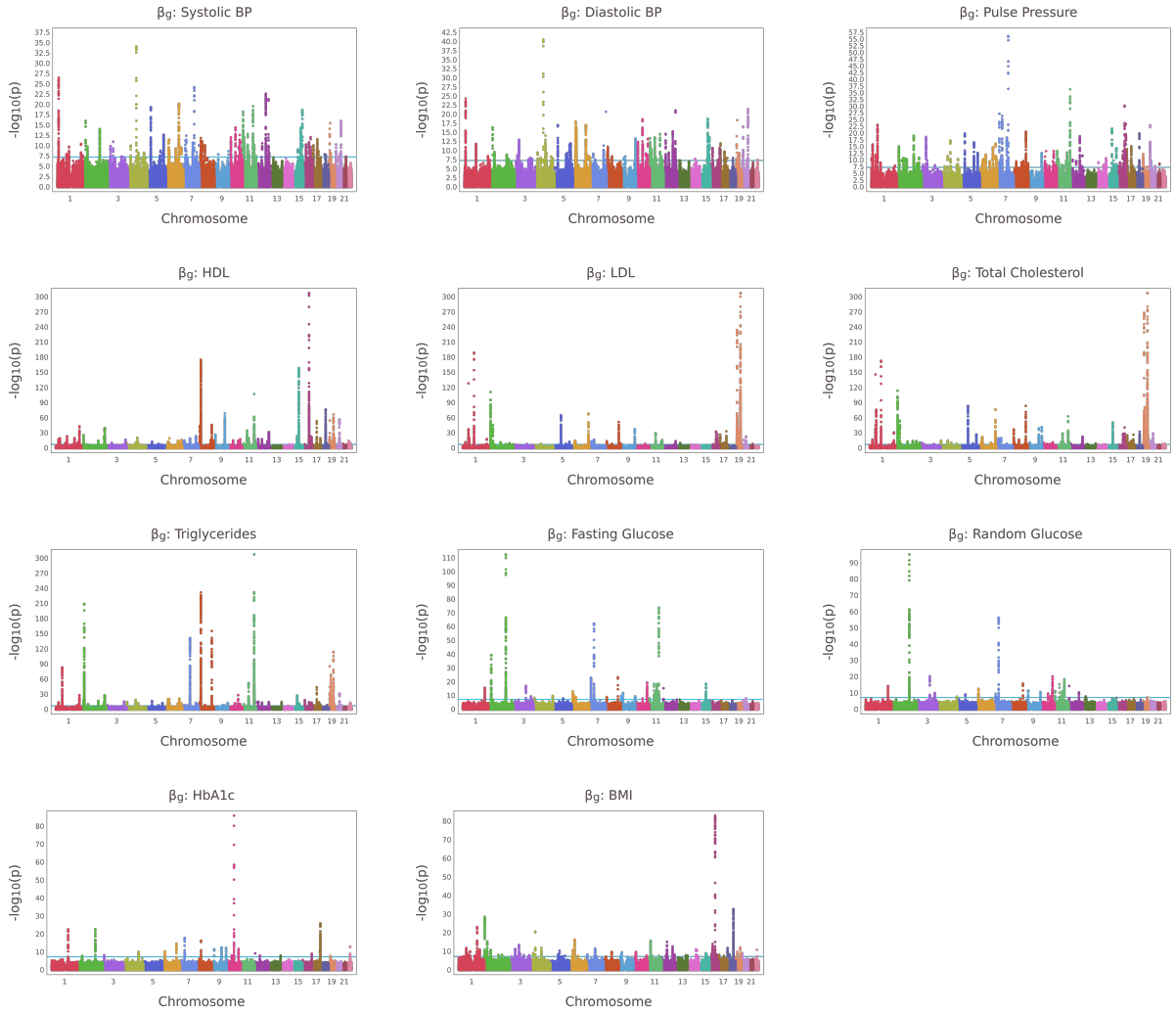

Figure S17: **Manhattan plots for testing β_g for longitudinal markers in the UK Biobank study**

Manhattan plots for testing β_g, effects to the mean, for 11 longitudinal biomarkers in the UK Biobank study. The blue line represents the genome-wide significance level, 5×10^{-8}.

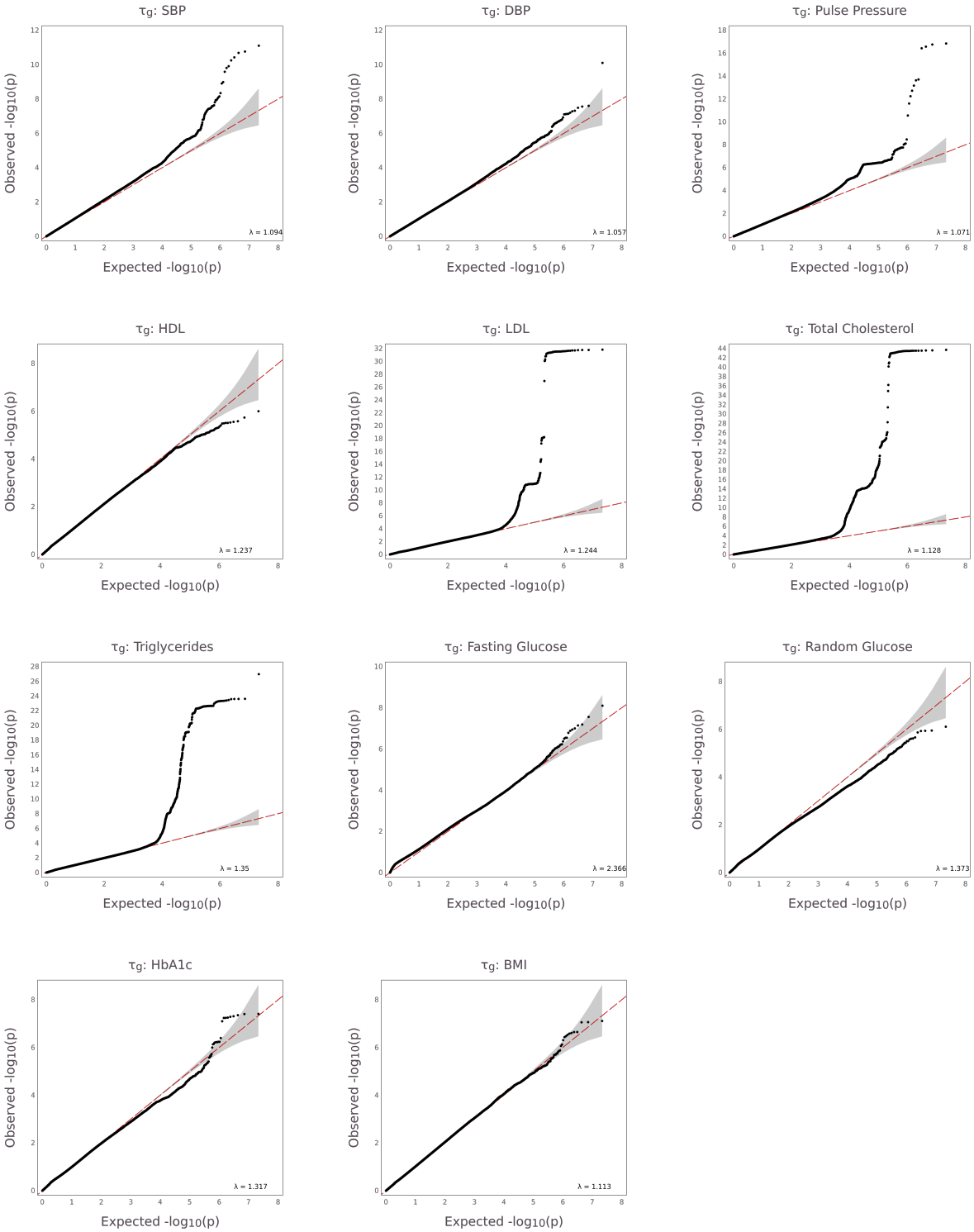

Figure S18: `TrajGWAS` **QQ plots for testing τ_g, effects on the WS variability, on 11 longitudinal biomarkers in the UK Biobank study**

Genomic control factor, λ, is based on the median p value, where SPA is not applied. See Supplementary Table S3 for the λ values at different p value quantiles.

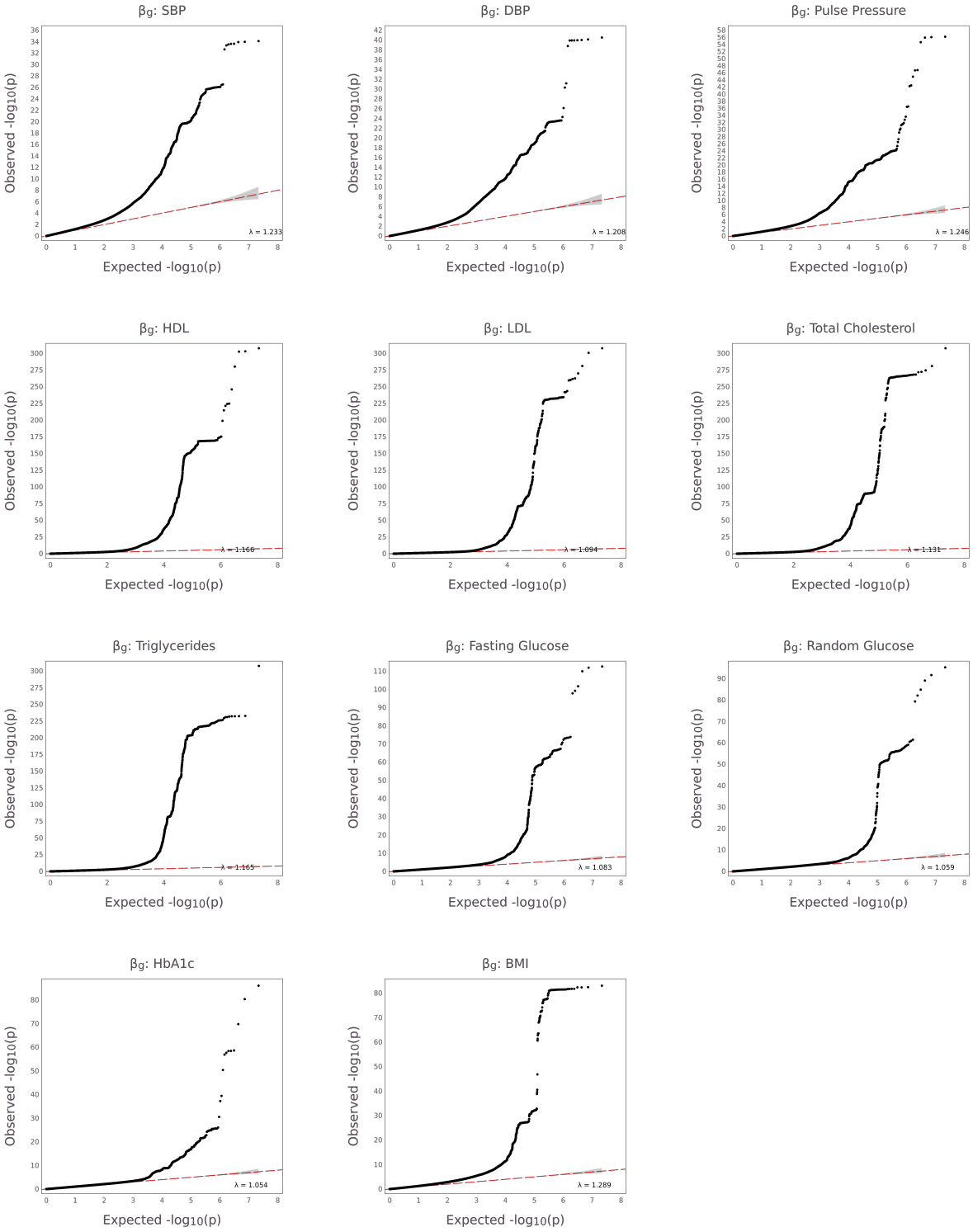

Figure S19: `TrajGWAS` **QQ plots for β_g, effects to the mean, on 11 longitudinal biomarkers in the UK Biobank study**

Genomic control factor, λ, is based off the median p value, where the score test is often applied. See Supplementary Table S3 for different p value quantile cutoffs.

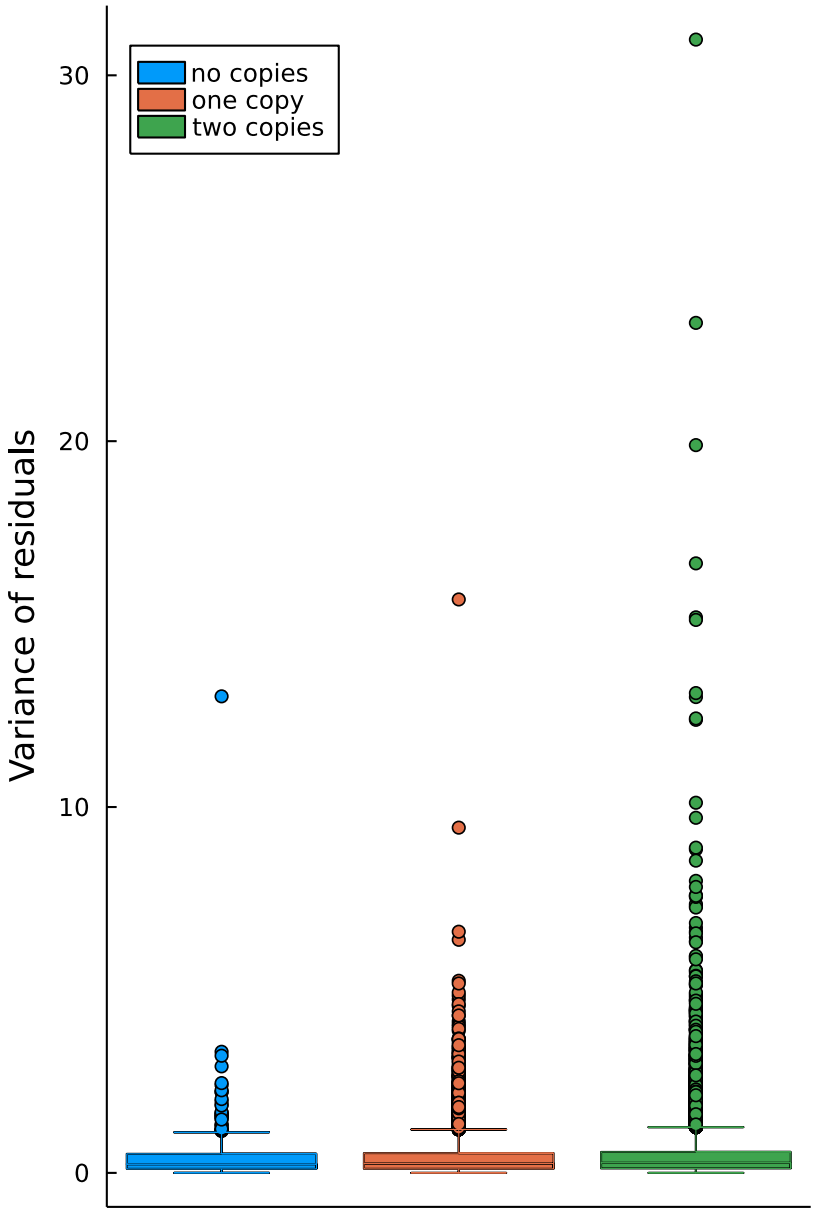

Figure S20: **Boxplots of within-sample variance of residuals of a SNP significant in terms of τ_g**
Boxplots of within-sample variance of residuals (regressed out mean part covariates other than the SNP count) of total cholesterol for different reference allele counts (0, 1, or 2) of rs6993414, the SNP with the lowest p value in terms of τ_g on the *LPL* gene. Note that the phenotype is standardized before the analysis.

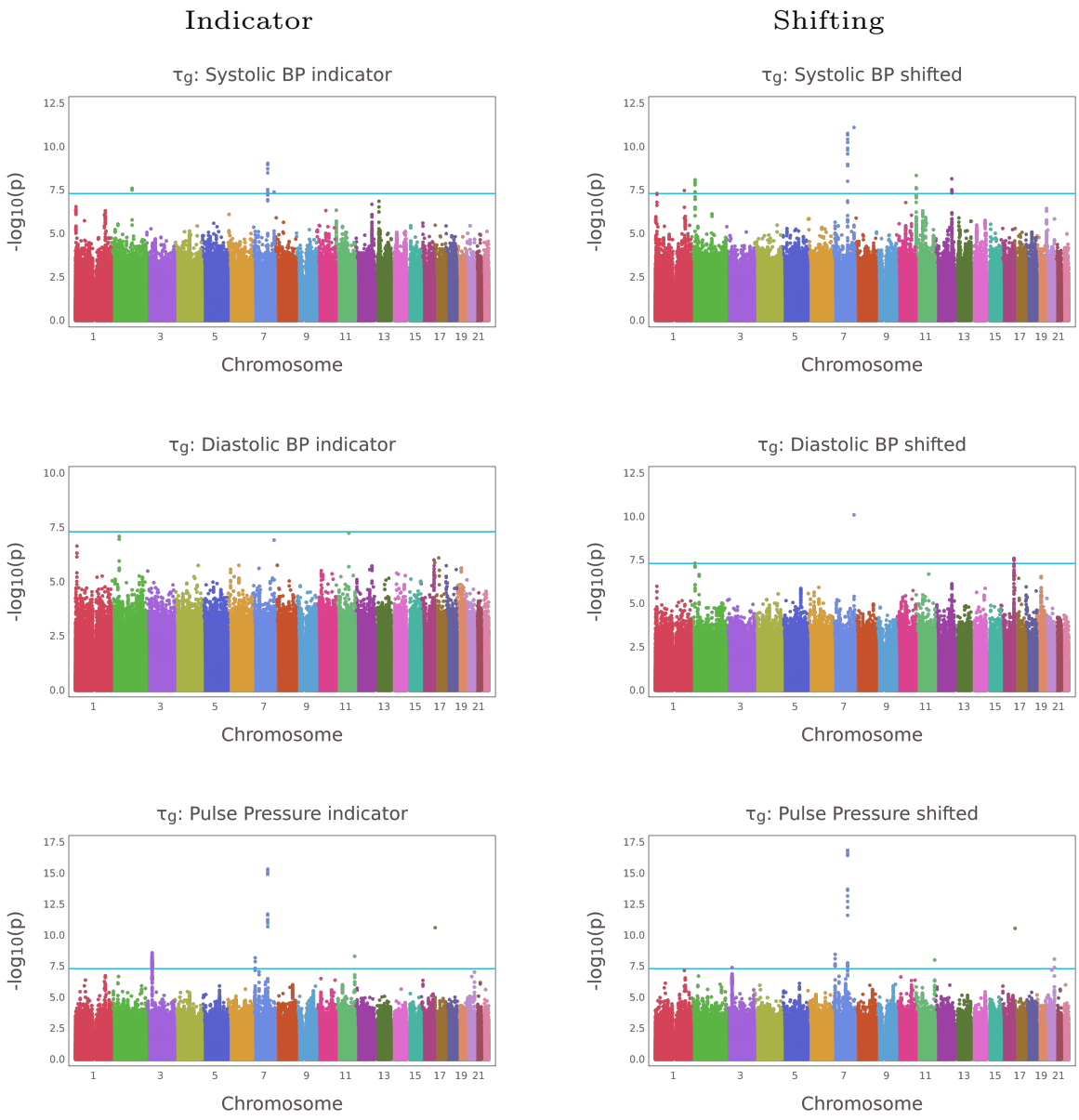

Figure S21: **Comparison of the medication adjustment methods in the blood pressure `TrajGWAS` analysis.**
We plot Manhattan plots for τ_g in the blood pressure `TrajGWAS` analysis, effects to the WS variability for SBP, DBP, and PP in UK Biobank study. (Left) Medication adjusted by an additional indicator covariate reflecting on or off medication in both β_g and τ_g. (Right) A sensible constant is added to the observed measures.

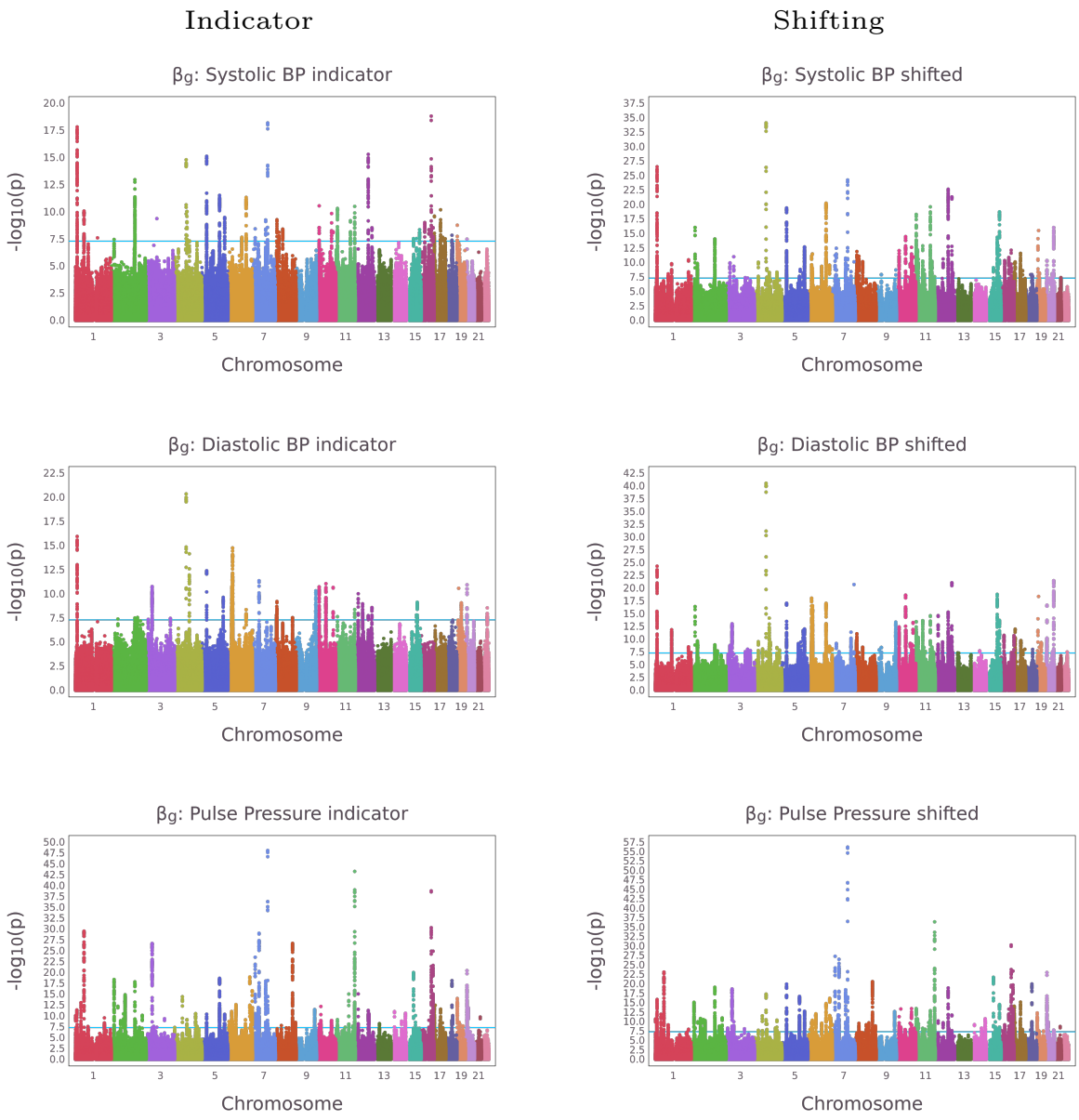

Figure S22: **Comparisons of medication adjustment methods in the blood pressures `TrajGWAS` analysis.**
We plot Manhattan plots for β_g in the `TrajGWAS`, effects to the mean for SBP, DBP, and PP, in UK Biobank study. (Left) Medication is adjusted by an additional indicator covariate to reflect on medication or not in both β_g and τ_g. (Right) A sensible constant is added to the observed measures.

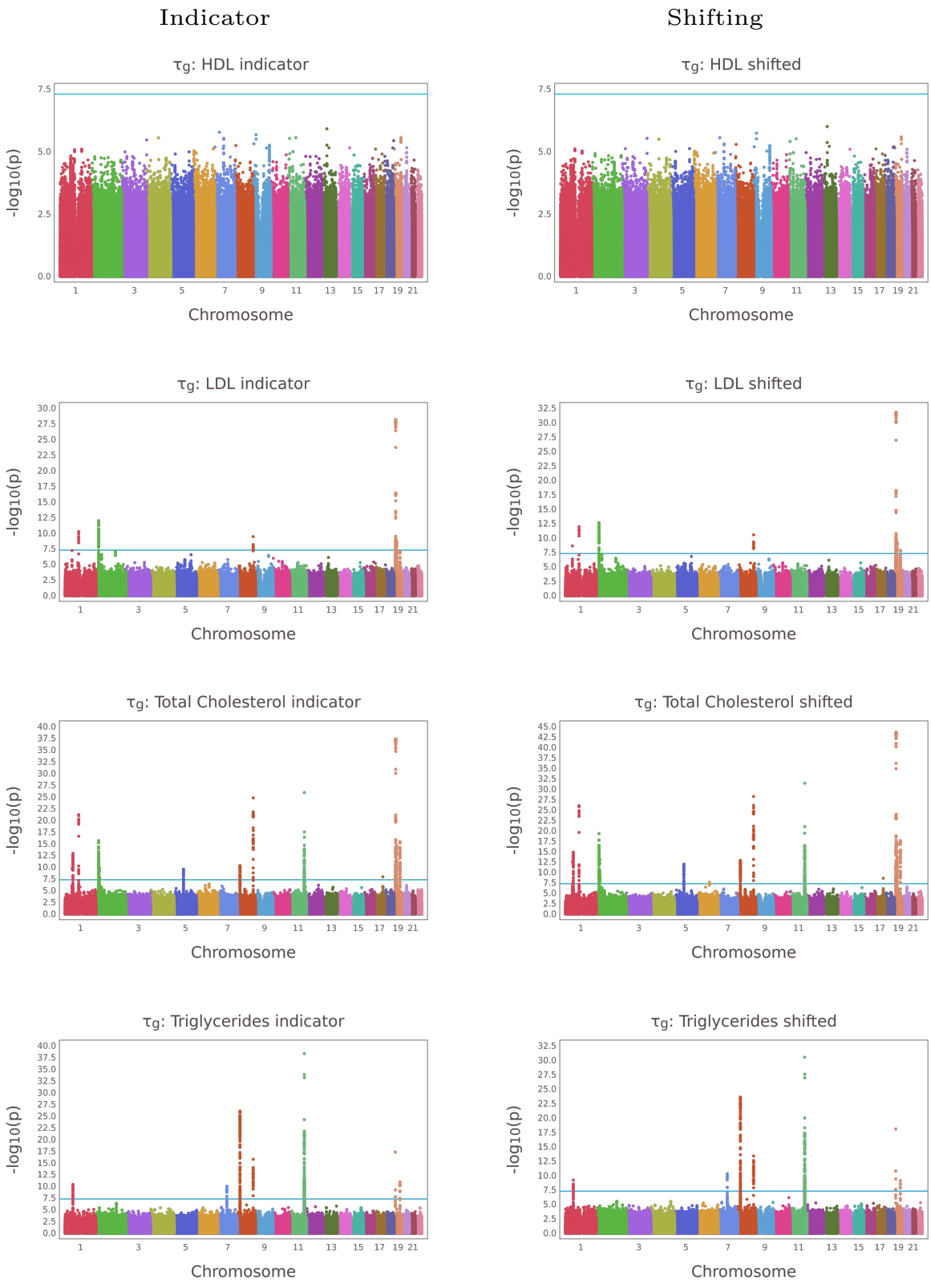

Figure S23: **Comparisons of the effects of medication adjustment in the lipid `TrajGWAS` analysis.**
We plot Manhattan plots for β_g in the `TrajGWAS` analysis, effects to the mean for HDL, LDL, total cholesterol, and triglyceride in UK Biobank study. (Left) Medication adjusted by an additional indicator covariate reflecting on and off medications in both β_g and τ_g. (Right) A sensible constant is added to the observed measures.

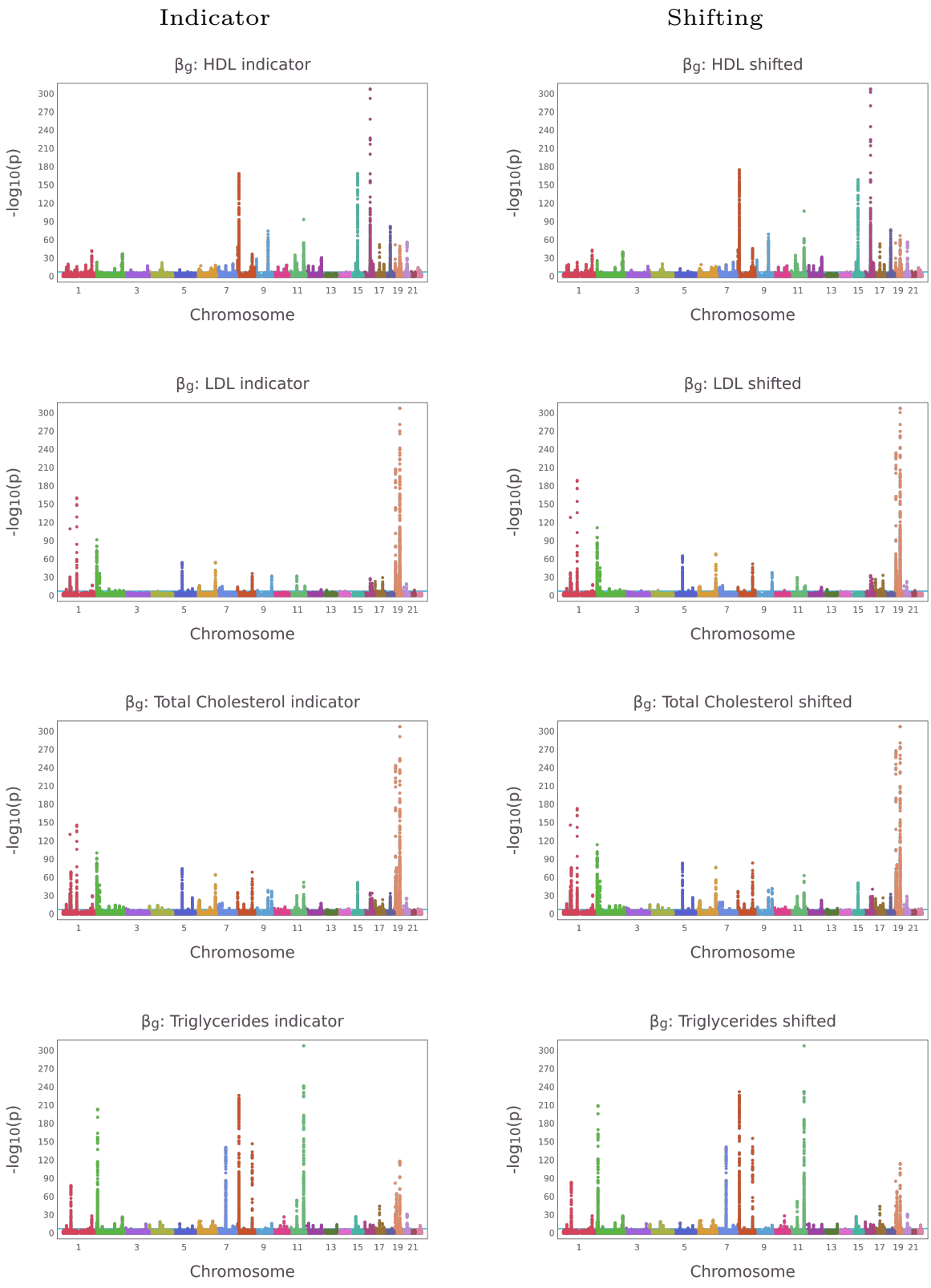

Figure S24: **Comparisons of the effects of medication adjustment in the lipid `TrajGWAS` analysis.**
We plot Manhattan plots for β_g in the `TrajGWAS` analysis, effects to the mean for HDL, LDL, total cholesterol, and triglyceride in UK Biobank study. (Left) Medication adjusted by an additional indicator covariate reflecting on or off medication in both β_g and τ_g. (Right) A sensible constant is added to the observed measures.

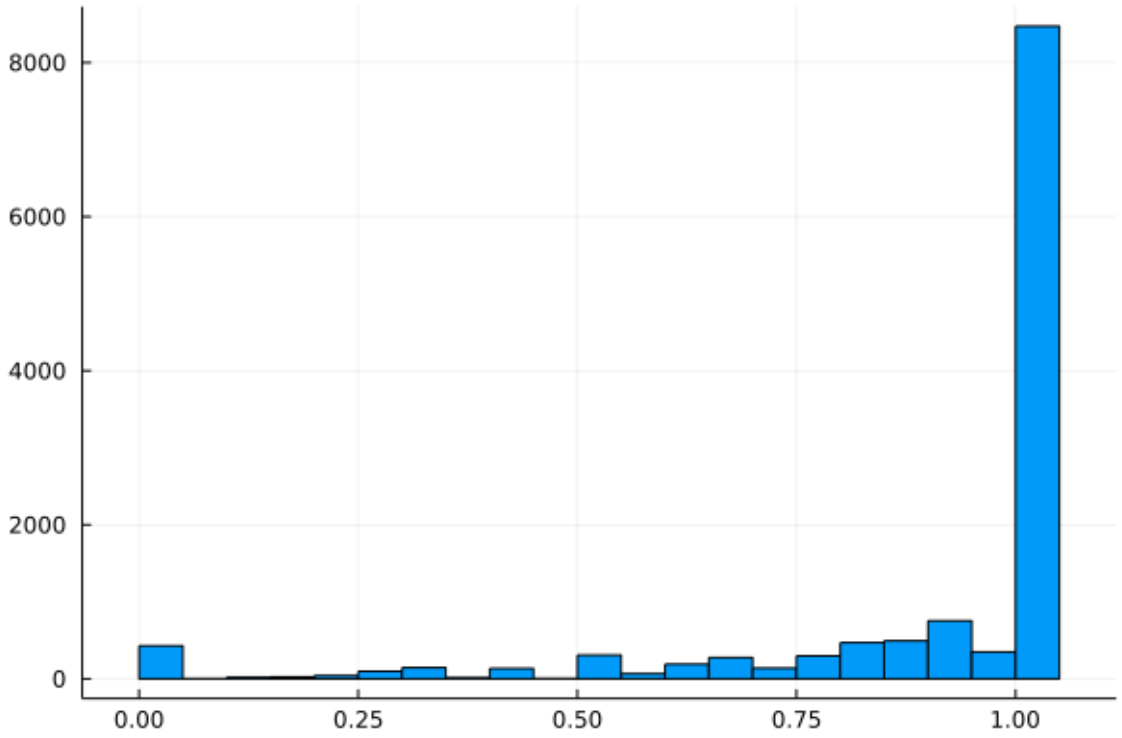

Figure S25: **Histogram of the proportion of observation after the diagnosis of diabetes**

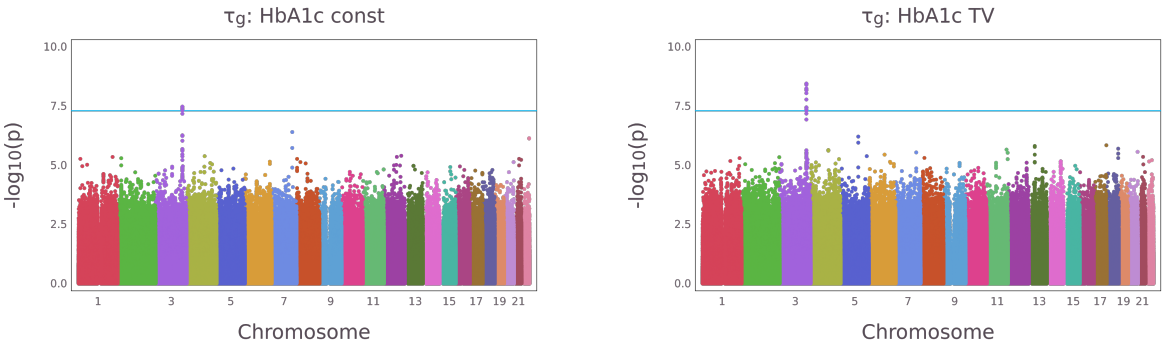

Figure S26: **Manhattan plots for testing τ_g for HbA1c with different adjustments for disease status**

Manhattan plots for testing τ_g, the effects of the WS variability, for HbA1c. Adjustment for diabetes status is performed on both mean and WS variation component: (left) adjustment using a constant indicator, (right) adjustment using a time-varying indicator. The blue line represents the genome-wide significance level, 5×10^{-8}.

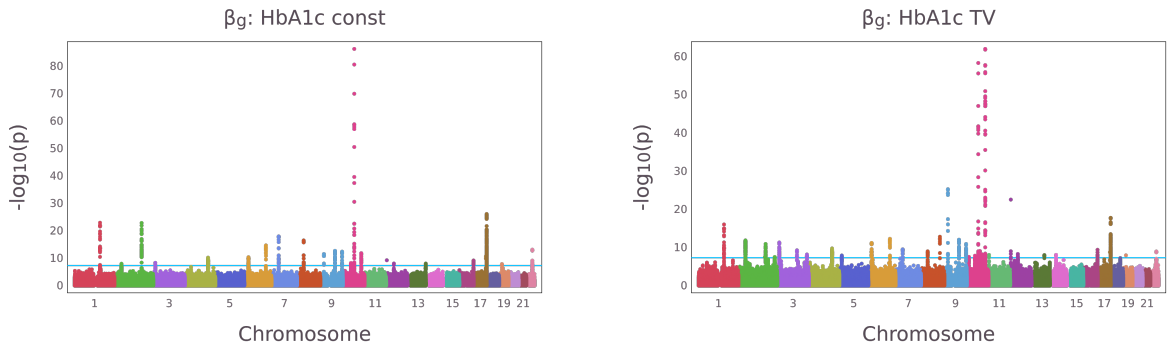

Figure S27: **Manhattan plots for testing β_g for HbA1c with different adjustments for disease status**

Manhattan plots for testing β_g, the effects of the WS variability, for HbA1c. Adjustment for diabetes status is performed on both mean and WS variation component: (left) adjustment using a constant indicator, (right) adjustment using a time-varying indicator. The blue line represents the genome-wide significance level, 5×10^{-8}.

Table S1: **Variables in the UK Biobank primary care clinical event records table (`clinical_table`) by source and the unified UK Biobank variable names.**

Column name	Description
eid	Participant identifier
data_provider	1 = England (Vision), 2 = Scotland, 3 = England (TPP), 4 = Wales
event_dt	Date clinical code was entered
read_2	Read v2
read_3	CTV3 (Read v3)
value1	Value recorded 1
value2	Value recorded 2
value3	Value recorded 3

Table S2: **Clinical terms used to extract biomarkers from UK Biobank primary care data and the UK Biobank field numbers being compared to in Figure S16.**

Biomarker	Units	Terminology	Terms	UK Biobank field
Systolic Blood Pressure	mmHg	Read v2/CTV3	246.., 246[012345679BCDEFGJNQSWYdg], G20.., XaF4[FLO], XaJ2[EG], XaKFx	93
Diastolic Blood Pressure	mmHg	Read v2/CTV3	246.., 246[01234567ABCDEFGJPRTVXcg], G20.., XaF4[Sab], XaJ2[FH], XaKFw	94
Total Cholesterol	mmol/L	Read v2/CTV3	44P.., 44P[12349HJKZ], XE2eD, XaJe9, XSK14, XaLux, XaFs9, XaIRd	30690
HDL	mmol/L	Read v2/CTV3	XaEVr, X772M, 44d[23], 44P[5BC]	30760
LDL	mmol/L	Read v2/CTV3	XaEVs, 44d[45], 44P[6DE]	30780
Triglycerides	mmol/L	Read v2/CTV3	44e, X772O, 44Q[.12345Z], XE2q9	30870
Random Glucose	mmol/L	Read v2/CTV3	44f.., 44f0., 44g.., 44g0., 44TA., XM0ly	30740
Fasting Glucose	mmol/L	Read v2/CTV3	44f1, 44g1	
HbA1c	mmol/mol	Read v2/CTV3	XaPbt, XaERp, X772q, 42W.., 42W[12345Z], 44TB.	30750
Height	m	Read v2/CTV3	229.., 229[1234Z]	50
Weight	kg	Read v2/CTV3	1622., 22A.., 22A[1234567AZ], X76CG, XE1h4, XM01G, Xa7wI	21002
BMI	kg/m^2	Read v2/CTV3	22K.., 22K[12345678], XaCDR, XaJJH, XaJqk, XaZcl	21001

"[·]" represents any one letter or number among the content provided in "[·]" can be used.

Table S3: **Genomic control factor λ at various p value quantiles for the UK Biobank analyses.**
Because SPA is only applied to score test statistics in the right tail, the genomic control factor calculated based on the median p values, which is not SPA adjusted, may appear inflated.

		Genomic control factor at q^{th} p value quantile		
Phenotype	Parameter	$q = 0.5$ (median)	$q = 0.05$	$q = 0.01$
Systolic blood pressure	β_g	1.23	1.32	1.48
	τ_g	1.09	1.07	1.07
Diastolic blood pressure	β_g	1.21	1.29	1.48
	τ_g	1.06	1.04	1.03
Pulse pressure	β_g	1.25	1.34	1.50
	τ_g	1.07	1.06	1.07
HDL	β_g	1.166	1.253	1.451
	τ_g	1.237	1.023	1.013
LDL	β_g	1.094	1.12	1.193
	τ_g	1.244	1.011	1.007
Total Cholesterol	β_g	1.131	1.203	1.386
	τ_g	1.128	1.04	1.055
Triglycerides	β_g	1.165	1.229	1.419
	τ_g	1.35	1.01	0.985
Random Glucose	β_g	1.08	1.08	1.10
	τ_g	1.19	1.01	1.01
Fasting Glucose	β_g	1.08	1.09	1.12
	τ_g	2.37	1.12	1.07
HbA1c	β_g	1.05	1.05	1.06
	τ_g	1.32	0.99	0.99
BMI	β_g	1.29	1.39	1.53
	τ_g	1.11	1.02	1.02

Table S4: **Previously reported traits associated with novel SNPs of systolic blood pressure from NHGRI GWAS Catalog.**

Gene	Chromosome	Number of SNPs (β_g / τ_g)	Trait(s)
BCL2	18	1 / 0	Body mass index High light scatter reticulocyte count Modified Stumvoll Insulin Sensitivity Index (BMI interaction) Modified Stumvoll Insulin Sensitivity Index (model adjusted for BMI) Reticulocyte count Systolic blood pressure Triglyceride levels Triglycerides Type 2 diabetes Waist-hip ratio Waist-to-hip ratio adjusted for BMI Waist-to-hip ratio adjusted for BMI (adjusted for smoking behaviour) Waist-to-hip ratio adjusted for BMI x sex x age interaction (4df test) Waist-to-hip ratio adjusted for body mass index

Table S5: **Previously reported traits associated with novel SNPs of diastolic blood pressure from NHGRI GWAS Catalog.**

Gene	Chromosome	Number of SNPs (β_g / τ_g)	Trait(s)
CLOCK	4	3 / 0	Height
			Red blood cell count
			Waist-to-hip ratio adjusted for BMI x sex interaction
			Waist-to-hip ratio adjusted for BMI x sex x age interaction (4df test)
PDCL2	4	1 / 0	Height
HAND2	4	1 / 0	Atrial fibrillation
HCG15	6	1 / 0	Depression (broad)
SAR1P1	6	1 / 0	Blood protein levels
XXbac-BPG308J9.3	6	4 / 0	Breast cancer
			Heel bone mineral density
			Intelligence (MTAG)
			Schizophrenia
OR11A1	6	1 / 0	Estimated glomerular filtration rate in diabetes
HLA-F	6	1 / 0	Psoriatic arthritis
HLA-F-AS1	6	2 / 0	Mixed cellularity Hodgkin lymphoma
			Psoriatic arthritis
HLA-V	6	1 / 0	Sarcoidosis (Lofgren's syndrome vs non-Lofgren's syndrome)
MCCD1P1	6	1 / 0	Non-small cell lung cancer
HCG4P5	6	1 / 0	Hemoglobin levels
HLA-A	6	2 / 0	Blood protein levels
			Hemoglobin levels
ZNRD1	6	1 / 0	AIDS progression
			Autism spectrum disorder, attention deficit-hyperactivity disorder, bipolar disorder, major depressive disorder, and schizophrenia (combined)
VDR	12	1 / 0	Cardiovascular disease
			Medication use (diuretics)
SEPT9	17	1 / 0	Cardiovascular disease
			Heel bone mineral density
			Medication use (diuretics)
			Systolic blood pressure

Table S6: **Previously reported traits associated with novel SNPs of pulse pressure from NHGRI GWAS Catalog.**

Gene	Chromosome	Number of SNPs (β_g / τ_g)	Trait(s)
EBF2	8	2 / 0	Cardiovascular disease Medication use (agents acting on the renin-angiotensin system) Systolic blood pressure
SORCS3	10	1 / 0	Systolic blood pressure

Table S7: **Previously reported traits associated with novel SNPs of HDL from NHGRI GWAS Catalog.**

Gene	Chromosome	Number of SNPs (β_g / τ_g)	Trait(s)
BCL2	18	1 / 0	Body mass index High light scatter reticulocyte count Modified Stumvoll Insulin Sensitivity Index (BMI interaction) Modified Stumvoll Insulin Sensitivity Index (model adjusted for BMI) Reticulocyte count Systolic blood pressure Triglyceride levels Triglycerides Type 2 diabetes Waist-hip ratio Waist-to-hip ratio adjusted for BMI Waist-to-hip ratio adjusted for BMI (adjusted for smoking behaviour) Waist-to-hip ratio adjusted for BMI x sex x age interaction (4df test) Waist-to-hip ratio adjusted for body mass index

Table S8: Previously reported traits associated with novel SNPs of total cholesterol from NHGRI GWAS Catalog.

Gene	Chromosome	Number of SNPs (β_g / τ_g)	Trait(s)
ZNRD1	6	1 / 0	AIDS progression
			Autism spectrum disorder, attention deficit-hyperactivity disorder, bipolar disorder, major depressive disorder, and schizophrenia (combined)
TRIM31	6	1 / 0	Beta-2 microglubulin plasma levels
TRIM31-AS1	6	2 / 0	Beta-2 microglubulin plasma levels
			Cold sores
TRIM15	6	1 / 0	Blood protein levels
PAIP1P1	6	1 / 0	Help-seeking from a GP (without major depressive disorder symptoms)
			Help-seeking from a psychiatrist
TRIM26	6	5 / 0	Asthma (adult onset)
			Asthma (childhood onset)
			Autism spectrum disorder, attention deficit-hyperactivity disorder, bipolar disorder, major depressive disorder, and schizophrenia (combined)
			Help-seeking from a GP (without major depressive disorder symptoms)
			Help-seeking from a psychiatrist
			Medication use (anti-inflammatory and antirheumatic products, non-steroids)
			Schizophrenia
HCG17	6	3 / 0	General cognitive ability
			LDL cholesterol levels
LPL	8	0 / 17	Apolipoprotein A1 levels
			Apolipoprotein B levels
			Cholesterol efflux capacity
			Coronary artery disease
			Eosinophil counts
			HDL Cholesterol - Triglycerides (HDLC-TG)
			HDL cholesterol
			HDL cholesterol levels
			HDL cholesterol levels in current drinkers
			HDL cholesterol levels x alcohol consumption (drinkers vs non-drinkers) interaction (2df)
			HDL cholesterol levels x alcohol consumption (regular vs non-regular drinkers) interaction (2df)
			HDL cholesterol levels x long total sleep time interaction (2df test)
			HDL cholesterol levels x short total sleep time interaction (2df test)
			Height
			High density lipoprotein cholesterol levels
			Lipid metabolism phenotypes
			Lipid traits
			Lipoprotein phospholipase A2 activity in cardiovascular disease
			Low density lipoprotein cholesterol levels
			Medication use (HMG CoA reductase inhibitors)
			Metabolic syndrome
			Metabolic syndrome (bivariate traits)
			Metabolite levels
			Parental longevity (father's age at death or father's attained age)
			Peripheral artery disease
			Red cell distribution width
			Serum metabolite levels
			Serum metabolite levels (CMS)
			Triacylglyceride levels
			Triglyceride levels
			Triglyceride levels in current drinkers
			Triglyceride levels x alcohol consumption (drinkers vs non-drinkers) interaction (2df)
			Triglyceride levels x alcohol consumption (regular vs non-regular drinkers) interaction (2df)
			Triglycerides

			Triglycerides x physical activity interaction (2df test)
			Triglycerides-Blood Pressure (TG-BP)
			Type 2 diabetes
			Type 2 diabetes (adjusted for BMI)
			Waist-hip ratio
			Waist-to-hip ratio adjusted for BMI
AC100802.3	8	0 / 1	High density lipoprotein cholesterol levels

Table S9: **Previously reported traits associated with novel SNPs of triglycerides from NHGRI GWAS Catalog.**

Gene	Chromosome	Number of SNPs (β_g / τ_g)	Trait(s)
NR5A2	1	1 / 0	Waist-hip ratio
CCND2	12	1 / 0	Appendicular lean mass
			Birth weight
			Body mass index
			Cardiovascular disease
			Heel bone mineral density
			Height
			Low density lipoprotein cholesterol levels
			Medication use (HMG CoA reductase inhibitors)
			Medication use (drugs used in diabetes)
			Offspring birth weight
			Pulse pressure
			Systolic blood pressure
			Triglyceride levels
			Type 2 diabetes
			Waist circumference adjusted for body mass index

Table S10: **Previously reported traits associated with novel SNPs of random glucose from NHGRI GWAS Catalog.**

Gene	Chromosome	Number of SNPs (β_g / τ_g)	Trait(s)
HK1	10	6 / 0	Apolipoprotein B levels
			Glycated hemoglobin levels
			HDL cholesterol levels
			Hematocrit
			Hemoglobin
			Hemoglobin A1c levels
			Hemoglobin concentration
			Hemoglobin levels
			High light scatter reticulocyte count
			High light scatter reticulocyte percentage of red cells
			Immature fraction of reticulocytes
			LDL cholesterol levels
			Low density lipoprotein cholesterol levels
			Mean corpuscular hemoglobin
			Mean corpuscular volume
			Red blood cell count
			Red blood cell traits
			Red cell distribution width
			Reticulocyte count
			Reticulocyte fraction of red cells
CCND2	12	1 / 0	Appendicular lean mass
			Birth weight
			Body mass index
			Cardiovascular disease
			Heel bone mineral density
			Height
			Low density lipoprotein cholesterol levels
			Medication use (HMG CoA reductase inhibitors)
			Medication use (drugs used in diabetes)
			Offspring birth weight
			Pulse pressure
			Systolic blood pressure
			Triglyceride levels
			Type 2 diabetes
			Waist circumference adjusted for body mass index
CCND2-AS1	12	1 / 0	Appendicular lean mass
			Birth weight
			Body mass index
			Cardiovascular disease
			Heel bone mineral density
			Height
			Low density lipoprotein cholesterol levels
			Medication use (HMG CoA reductase inhibitors)
			Medication use (drugs used in diabetes)
			Offspring birth weight
			Pulse pressure
			Systolic blood pressure
			Triglyceride levels
			Type 2 diabetes
			Waist circumference adjusted for body mass index

Table S11: **Previously reported traits associated with novel SNPs of fasting glucose from NHGRI GWAS Catalog.**

Gene	Chromosome	Number of SNPs (β_g / τ_g)	Trait(s)
WFS1	4	1 / 0	Type 2 diabetes
ACSL1	4	4 / 0	Type 2 diabetes
GPSM1	9	9 / 0	Birth weight
			Insulinogenic index
			Offspring birth weight
			Type 2 diabetes
			Type 2 diabetes (adjusted for BMI)
			Waist-to-hip ratio adjusted for BMI
			White blood cell count
HK1	10	2 / 0	Apolipoprotein B levels
			Glycated hemoglobin levels
			HDL cholesterol levels
			Hematocrit
			Hemoglobin
			Hemoglobin A1c levels
			Hemoglobin concentration
			Hemoglobin levels
			High light scatter reticulocyte count
			High light scatter reticulocyte percentage of red cells
			Immature fraction of reticulocytes
			LDL cholesterol levels
			Low density lipoprotein cholesterol levels
			Mean corpuscular hemoglobin
			Mean corpuscular volume
			Red blood cell count
			Red blood cell traits
			Red cell distribution width
			Reticulocyte count
			Reticulocyte fraction of red cells
KCNQ1	11	2 / 0	Birth weight
			Type 2 diabetes
CCND2	12	1 / 0	Appendicular lean mass
			Birth weight
			Body mass index
			Cardiovascular disease
			Heel bone mineral density
			Height
			Low density lipoprotein cholesterol levels
			Medication use (HMG CoA reductase inhibitors)
			Medication use (drugs used in diabetes)
			Offspring birth weight
			Pulse pressure
			Systolic blood pressure
			Triglyceride levels
			Type 2 diabetes
			Waist circumference adjusted for body mass index
CCND2-AS1	12	1 / 0	Appendicular lean mass
			Birth weight
			Body mass index
			Cardiovascular disease
			Heel bone mineral density
			Height
			Low density lipoprotein cholesterol levels
			Medication use (HMG CoA reductase inhibitors)
			Medication use (drugs used in diabetes)
			Offspring birth weight
			Pulse pressure
			Systolic blood pressure
			Triglyceride levels
			Type 2 diabetes
			Waist circumference adjusted for body mass index
ZHX3	20	2 / 0	Balding type 1
			Depressive symptoms (MTAG)
			Fasting blood glucose adjusted for BMI
			Heel bone mineral density
			Height
			Male-pattern baldness
			Resting heart rate
			Type 2 diabetes
			Type 2 diabetes (adjusted for BMI)

Supplementary Methods

A WiSER Score Test

In this section we derive the score test for the WiSER model. Let $\boldsymbol{X}_{i,1} \in \mathbb{R}^{n_i \times r_1}$ be the covariates to be tested for the mean component of subject i, and $\boldsymbol{W}_{i,1} \in \mathbb{R}^{n_i \times r_2}$ be the covariates to be tested for the WS variability of subject i. Let $r = r_1 + r_2$ and $\widetilde{\boldsymbol{\theta}} = (\boldsymbol{0}_r, \widehat{\boldsymbol{\theta}}_2)^T \in \mathbb{R}^{r+p+\ell+q(q+1)/2}$, where $\widehat{\boldsymbol{\theta}}_2 = \left(\boldsymbol{\beta}^T, \boldsymbol{\tau}^T, \mathbf{vech}\left(\boldsymbol{L}_{\boldsymbol{\gamma}}^T\right)\right)^T$ is the WiSER estimator under the null model, where **vech** is the half-vectorization function and $\boldsymbol{L}_{\boldsymbol{\gamma}}$ is the Cholesky factor of $\boldsymbol{\Sigma}_{\boldsymbol{\gamma}}$. We use $\boldsymbol{\psi}_{H_1} \in \mathbb{R}^r$ and $\boldsymbol{\psi}_{H_0} \in \mathbb{R}^{p+\ell+q(q+1)/2}$ to represent the gradient vectors derived under the full model and the null model respectively. Then the chi-square score test statistic for testing $\boldsymbol{\theta}_1 = \boldsymbol{0}_r$ takes the form

$$S = \frac{1}{m}\left[\boldsymbol{\psi}_{H_1}(\widetilde{\boldsymbol{\theta}})\right]^T \boldsymbol{V}^{-1}_{\boldsymbol{\psi}_{H_1}(\widetilde{\boldsymbol{\theta}})}\left[\sum_i \boldsymbol{\psi}_{H_1}(\widetilde{\boldsymbol{\theta}})\right],$$

where $\boldsymbol{V}_{\boldsymbol{\psi}_{H_1}(\widetilde{\boldsymbol{\theta}})}$ is the covariance matrix of score $\boldsymbol{\psi}_{H_1}(\widetilde{\boldsymbol{\theta}})$. The score test statistic S is asymptotically distributed as χ^2_r under H_0. The score is given by $\boldsymbol{\psi}_{H_1}(\widetilde{\boldsymbol{\theta}}) = \sum_{i=1}^n \boldsymbol{\psi}_{iH_1}(\widetilde{\boldsymbol{\theta}})$, where $\boldsymbol{\psi}_{iH_1}(\widetilde{\boldsymbol{\theta}})$ is estimated by

$$\widehat{\boldsymbol{\psi}}_{iH_1}(\widetilde{\boldsymbol{\theta}}) = \begin{pmatrix} \boldsymbol{X}_{i,1}^T[\boldsymbol{V}_i^{(0)}]^{-1}\widehat{\boldsymbol{r}}_i \\ -\boldsymbol{W}_{i,1}^T \operatorname{diag}\left[\begin{pmatrix} e^{\boldsymbol{w}_{i1}^T\widehat{\boldsymbol{\tau}}} & & \\ & \ddots & \\ & & e^{\boldsymbol{w}_{in_i}^T\widehat{\boldsymbol{\tau}}} \end{pmatrix}\left(\boldsymbol{V}_i^{(0)}\right)^{-1}\widehat{\boldsymbol{R}}_i\left(\boldsymbol{V}_i^{(0)}\right)^{-1}\right] \end{pmatrix} \in \mathbb{R}^r,$$

where $\widehat{\boldsymbol{r}}_i$, $\widehat{\boldsymbol{R}}_i$, and $\widehat{\boldsymbol{\tau}}$ are from the fitted null model. For genotypes, which is assumed to be constant through time, it reduces to a scalar S_{β_g} for testing $\beta_g = 0$ ($r_1 = 1$ and $r_2 = 0$), and S_{τ_g} for testing $\tau_g = 0$ ($r_1 = 0$ and $r_2 = 1$).

To calculate $\widehat{\boldsymbol{V}}_{\boldsymbol{\psi}_{H_1}}(\widetilde{\boldsymbol{\theta}})$, we note that from Boos and Stefanski Chapter 7,[1]. $\boldsymbol{V}_{\boldsymbol{\psi}_{H_1}}(\widetilde{\boldsymbol{\theta}})$ can be represented by

$$\boldsymbol{V}_{\boldsymbol{\psi}_{H_1}}(\widetilde{\boldsymbol{\theta}}) = \boldsymbol{B}_{11} - \boldsymbol{A}_{12}\boldsymbol{A}_{22}^{-1}\boldsymbol{B}_{21} - \boldsymbol{B}_{12}\boldsymbol{A}_{22}^{-1}\boldsymbol{A}_{21} + \boldsymbol{A}_{12}\boldsymbol{A}_{22}^{-1}\boldsymbol{B}_{22}\boldsymbol{A}_{22}^{-1}\boldsymbol{A}_{21} \in \mathbb{R}^{r\times r},$$

where

$$\boldsymbol{A}(\widetilde{\boldsymbol{\theta}}) = \mathbb{E}\left[-\frac{\partial\boldsymbol{\psi}}{\partial\boldsymbol{\theta}}\right] = \begin{bmatrix}\boldsymbol{A}_{11} & \boldsymbol{A}_{12}\\ \boldsymbol{A}_{21} & \boldsymbol{A}_{22}\end{bmatrix}$$

and

$$\boldsymbol{B}(\widetilde{\boldsymbol{\theta}}) = \mathbb{E}\left[\boldsymbol{\psi}\boldsymbol{\psi}^T\right] = \begin{bmatrix}\boldsymbol{B}_{11} & \boldsymbol{B}_{12}\\ \boldsymbol{B}_{21} & \boldsymbol{B}_{22}\end{bmatrix}.$$

Here $\boldsymbol{\psi} = \begin{bmatrix}\boldsymbol{\psi}_{H_1}\\ \boldsymbol{\psi}_{H_0}\end{bmatrix}$, $\boldsymbol{A}_{11}$, $\boldsymbol{B}_{11} \in \mathbb{R}^{r\times r}$, $\boldsymbol{A}_{12}$, $\boldsymbol{B}_{12} \in \mathbb{R}^{r\times[p+\ell+q(q+1)/2]}$, and $\boldsymbol{A}_{22}$, $\boldsymbol{B}_{22} \in \mathbb{R}^{[p+\ell+q(q+1)/2]\times[p+\ell+q(q+1)/2]}$. $\widehat{\boldsymbol{A}}_{22}^{-1}$ and $\widehat{\boldsymbol{A}}_{22}^{-1}\widehat{\boldsymbol{B}}_{22}\widehat{\boldsymbol{A}}_{22}^{-1}$ are readily available from the estimation and inference of the null model.

$\boldsymbol{A}_{22}$ is estimated from the Fisher Information Matrix of the null model and $\boldsymbol{B}_{22}$ is estimated from the null model as

$$\widehat{\boldsymbol{B}}_{22} = \frac{1}{m}\sum_{i=1}^m \widehat{\boldsymbol{\psi}}_{iH_0}(\widehat{\boldsymbol{\theta}}_2)\widehat{\boldsymbol{\psi}}_{iH_0}^T(\widehat{\boldsymbol{\theta}}_2) \in \mathbb{R}^{[p+\ell+q(q+1)/2]\times[p+\ell+q(q+1)/2]},$$

where $\boldsymbol{\psi}_{iH_0}(\widehat{\boldsymbol{\theta}}_2)$ is the score vector under the null model for sample i. We estimate $\boldsymbol{B}_{11}$ by

$$\widehat{\boldsymbol{B}}_{11} = \frac{1}{m}\sum_{i=1}^m \widehat{\boldsymbol{\psi}}_{iH_1}(\widetilde{\boldsymbol{\theta}})\widehat{\boldsymbol{\psi}}_{iH_1}^T(\widetilde{\boldsymbol{\theta}}) \in \mathbb{R}^{r\times r}$$

and $\boldsymbol{B}_{12}$ by

$$\widehat{\boldsymbol{B}}_{12} = \frac{1}{m}\sum_{i=1}^m \widehat{\boldsymbol{\psi}}_{iH_1}(\widetilde{\boldsymbol{\theta}})\widehat{\boldsymbol{\psi}}_{iH_0}(\widetilde{\boldsymbol{\theta}})^T \in \mathbb{R}^{r\times[p+\ell+q(q+1)/2]}.$$

Let

$$\widehat{\boldsymbol{A}}_{i,21} = \begin{pmatrix} \boldsymbol{X}_i^T[\boldsymbol{V}_i^{(0)}]^{-1}\boldsymbol{X}_{i,1} & \boldsymbol{O}_{p\times r_2} \\ \boldsymbol{O}_{\ell\times r_1} & \boldsymbol{W}_i^T \begin{pmatrix} e^{\boldsymbol{w}_{i1}^T\widehat{\boldsymbol{\tau}}} & & \\ & \ddots & \\ & & e^{\boldsymbol{w}_{in_i}^T\widehat{\boldsymbol{\tau}}} \end{pmatrix} \left(\boldsymbol{V}_i^{(0)}\right)^{-1} \widehat{\boldsymbol{R}}_i \left(\boldsymbol{V}_i^{(0)}\right)^{-1} \begin{pmatrix} e^{\boldsymbol{w}_{i1}^T\widehat{\boldsymbol{\tau}}} & & \\ & \ddots & \\ & & e^{\boldsymbol{w}_{in_i}^T\widehat{\boldsymbol{\tau}}} \end{pmatrix} \boldsymbol{W}_{i,1} \\ \boldsymbol{O}_{[q(q+1)/2]\times r_1} & 2\boldsymbol{C}_q^T \cdot \left(\boldsymbol{\ell}_\gamma^T \boldsymbol{Z}_i^T \left(\boldsymbol{V}_i^{(0)}\right)^{-1} \odot \boldsymbol{Z}_i^T \left(\boldsymbol{V}_i^{(0)}\right)^{-1}\right) \cdot \begin{pmatrix} e^{\boldsymbol{w}_{i1}^T\widehat{\boldsymbol{\tau}}} & & \\ & \ddots & \\ & & e^{\boldsymbol{w}_{in_i}^T\widehat{\boldsymbol{\tau}}} \end{pmatrix} \cdot \boldsymbol{W}_{i,1} \end{pmatrix}$$

$$\in \mathbb{R}^{[p+\ell+q(q+1)/2]\times r},$$

where $\odot$ represents the Khatri-Rao (column-wise Kronecker) product, and $\boldsymbol{C}_q \in \mathbb{R}^{q^2\times q(q+1)/2}$ is the copy matrix such that $\boldsymbol{C}_q\mathbf{vech}\boldsymbol{M} = \mathbf{vec}\boldsymbol{M}$, the vectorization of $\boldsymbol{M}$. The estimates $\widehat{\boldsymbol{\tau}}$ and $\widehat{\boldsymbol{R}}_i$ are from the fitted null model. We estimate $\boldsymbol{A}_{21} = \boldsymbol{A}_{12}^T$ by

$$\widehat{\boldsymbol{A}}_{21} = \frac{1}{m}\sum_{i=1}^{m} \widehat{\boldsymbol{A}}_{i,21}.$$

B Derivation of saddlepoint approximation (SPA)

The score test statistic for testing β_g is

$$S_{\beta_g} = \sum_{i=1}^{m} g_i \left\{\mathbf{1}_{n_i}^T[\boldsymbol{V}_i^{(0)}]^{-1}\widehat{\boldsymbol{r}}_i\right\} =: \boldsymbol{g}^T\boldsymbol{c}_{\beta_g}, \tag{1}$$

where $\boldsymbol{g}$ is the normalized genotype vector. The score test statistic for testing τ_g is

$$S_{\tau_g} = -\sum_{i=1}^{m} g_i \left[\mathbf{1}_{n_i}^T \operatorname{diag}\left[\begin{pmatrix} e^{\boldsymbol{w}_{i1}^T\widehat{\boldsymbol{\tau}}} & & \\ & \ddots & \\ & & e^{\boldsymbol{w}_{in_i}^T\widehat{\boldsymbol{\tau}}} \end{pmatrix} \left(\boldsymbol{V}_i^{(0)}\right)^{-1} \widehat{\boldsymbol{R}}_i \left(\boldsymbol{V}_i^{(0)}\right)^{-1}\right]\right] =: \boldsymbol{g}^T\boldsymbol{c}_{\tau_g}. \tag{2}$$

First, we construct the empirical cumulant generating function (CGF) of $\boldsymbol{c} \in \{\boldsymbol{c}_{\tau_g}, \boldsymbol{c}_{\beta_g}\}$. The empirical moment generating function (MGF) of $\boldsymbol{c}$ is

$$\widehat{M}_0(z) := \frac{1}{m}\sum_{i=1}^{m}\exp(c_i z)$$

with the first two derivatives

$$\widehat{M}_0'(z) = \frac{1}{m}\sum_{i=1}^{m} c_i\exp(c_i z), \quad \widehat{M}_0''(z) = \frac{1}{m}\sum_{i=1}^{m} c_i^2\exp(c_i z).$$

The empirical CGF of $\boldsymbol{c}$ is defined as the logarithm of empirical MGF, $\widehat{K}_0(z) = \log\widehat{M}_0(z)$. Its first two derivatives are

$$\widehat{K}_0'(z) = \frac{\widehat{M}_0'(z)}{\widehat{M}_0(z)}, \quad \widehat{K}_0''(z) = \frac{\widehat{M}_0''(z)\widehat{M}_0(z) - \left[\widehat{M}_0'(z)\right]^2}{\left[\widehat{M}_0(z)\right]^2}.$$

Then, the empirical CGF and the first two derivatives of the observed score $S = \sum_{i=1}^m g_i c_i$ are

$$\widehat{K}(z) = \sum_{i=1}^{m}\widehat{K}_0(g_i z), \quad \widehat{K}'(z) = \sum_{i=1}^{m} g_i\widehat{K}_0'(g_i z), \quad \text{and } \widehat{K}''(z) = \sum_{i=1}^{m} g_i^2\widehat{K}_0''(g_i z).$$

To apply the saddlepoint approximation for an observed score $S = s$, we first find a "saddlepoint" ζ such that $\widehat{K}'(\zeta) = s$ and retrieve

$$\omega = \text{sign}(\zeta)\sqrt{2(\zeta s - \widehat{K}(\zeta))},$$
$$\nu = \zeta\sqrt{\widehat{K}''(\zeta)}.$$

The cumulative distribution function of S at s is approximated by

$$P(S < s) \approx \Phi\left(\omega + \frac{1}{\omega}\log(\frac{\nu}{\omega})\right),$$

where $\Phi(\cdot)$ denotes the cumulative distribution function of the standard normal distribution[2]. The p value for the score test with the statistic $S = s$ is given by $P(S < -|s|) + (1 - P(S < |s|))$.

C Heuristic method inflates the type I error

Failure to properly control for time-varying covariates that are correlated with genotypes can lead to biased results. We conduct a small scale simulation in order to demonstrate this. The heuristic approach involves regressing per-subject residual standard deviations on a set of covariates. We simulate data from Model (1) and Model (2). We set $\boldsymbol{\beta}_{\text{true}} = (0.1, 6.5, 0.0, 1.0, 5.0)^T$, $\boldsymbol{\tau}_{\text{true}} = (0.0, 0.3, 0.0, 0.5, 0.25)^T$, and the covariance of $(\boldsymbol{\gamma}_i, \omega_i)$ to be

$$\boldsymbol{\Sigma}_{\boldsymbol{\gamma}\omega} = \begin{pmatrix} 2.0 & 0.0 & 0.2 \\ 0.0 & 1.2 & 0.1 \\ 0.2 & 0.1 & 1.0 \end{pmatrix}.$$

For each subject, the mean level covariates $\boldsymbol{X}$ are the same as the WS variability covariates $\boldsymbol{W}$. W_1 is the intercept. W_2 and W_3 are time-invariant covariates with effect sizes $\tau_2 = 0.3$ and $\tau_3 = 0.0$ respectively. W_2 acts as sex and is drawn from Bernoulli(0.5) per subject. W_3 is the simulated genotype with MAF $= 0.3$ following Hardy-Weinberg equilibrium. W_4 is a time-varying covariate with effect size $\tau_4 = 0.5$; it is correlated with W_3 (the genotype) with its entries generated from $N(0, 0.5) \cdot I\{W_3 < 0\} + N(0, 2) \cdot I\{W_3 > 0\}$. W_5 is time-varying with entries generated from independent standard normals. Since the heuristic method involves one outcome per subject, time-varying covariates cannot be incorporated as-is, so we use their per-subject mean to control for them.

Figure S1 displays the $-\log_{10}$(p value) of τ_3 (the genotype with no effect on WS variability) based on 100 replicates per scenario with a sample size of 6,000. The number of repeated measurements per subject range from 5 to 20. The heuristic method leads to significantly inflated type I error. Inadequately controlling for time-varying covariates results in false positives when using standard deviation of the residuals as the outcome.

D Clinical measurement extraction from the UK Biobank primary data

We extract HbA1c data using the HbA1c code list by Denaxas et al.[3], omitting the terms: 42c and 44TC (tests of HbA1), XE24t (no occurrences), and X80U3 (no values accompanying term). We convert between DCCT (Diabetes Control and Complications Trial) align and IFCC (International Federation of Clinical Chemistry) standardized measurements, and keep values between 4-18% (20-173 mmol/mol). The distribution of resulting values is then compared against that of HbA1c available from UK Biobank field 30750.

To extract blood pressure records, we require values to be specified as systolic or diastolic in pairs. We look for codes relating to blood pressure or primary hypertension in "read v2" and "CTV3 (read v3)" dictionaries, and exclude codes related to ambulatory care or hypertension secondary to a transient cause. The terms included are 246.., 2461 - 2467, 2469, 246[A-G], 246J, 246N, 246[P-S], 246[V-Y], 246c, 246d, 246g, XaF4F, XaF4L, XaF4O, XaF4S,

XaF4a, XaF4b, XaJ2[E-H], XaKFw, XaKFx, and G20.. All units are assumed to be mmHg. Blood pressure readings are assigned as diastolic or systolic according to the attached term, where possible. Otherwise, where two unique values are given for an individual and date, the higher is assumed to be the systolic blood pressure, while the lower is assumed to be the diastolic blood pressure. For all pairs of blood pressure readings, systolic blood pressure is required to lie between 45 and 300, diastolic blood pressure is required to be greater than 30 mmHg but less than the associated systolic blood pressure. The distribution of resulting values is compared against that of systolic and diastolic blood pressure from UK Biobank field numbers 93 and 94, respectively.

HDL cholesterol is extracted from primary care using the code list prepared by Denaxas et al. [3], with the addition of terms XaEVr (Plasma HDL cholesterol level), 44d2 (Plasma random HDL cholesterol level), 44d3 (Plasma fasting HDL cholesterol level), and X772M (High density lipoprotein cholesterol level). Units are assumed to be mmol/L, and the records (n=819) that explicitly indicate a different unit are excluded. Values are required to be less than 10. The distribution of resulting values is compared against that of HDL cholesterol values from UK Biobank field number 30760.

LDL cholesterol is extracted from primary care using terms 44P6, 44PD, 44PE, 44d4, 44d5, and XaEVs. Units are assumed to be mmol/L, and the records (n=21) that explicitly indicated a different unit are excluded. Values are required to be less than 30. The distribution of resulting values is compared against that of LDL cholesterol values from UK Biobank field number 30780.

Total cholesterol is extracted from primary care using the code list prepared by Denaxas et al. [3], with the addition of terms XaFs9 (Fasting cholesterol level) and XaIRd (Plasma total cholesterol level). Units are assumed to be mmol/L. Records (n=45) that explicitly indicate a different unit are excluded. Values are required to be less than 30. The distribution of resulting values is compared against that of total cholesterol values from UK Biobank field number 30690. Triglyceride records are extracted from primary care using the code list prepared by Denaxas et al. [3], with the addition of the code X772O (Triglyceride level) and the code prefix 44e (Plasma triglyceride level). Units are assumed to be mmol/L, and the records (n=249) that explicitly indicate a different unit are excluded. Values are required to be less than 30. The distribution of resulting values is compared against that of triglyceride levels from UK Biobank field number 30870.

Serum and plasma random glucose levels are extracted from primary care data using codes 44TA, 44f.., 44f0, 44g.., 44g0, and XM0ly. Serum and plasma fasting glucose levels are extracted using codes 44f1 and 44g1. Units are assumed to be mmol/L, and records (n=39) that explicitly indicate a different unit are excluded. Values are required to be less than 60. The distribution of random glucose is compared against that of glucose from UK Biobank field number 30740.

BMI is extracted from primary care using codes XaCDR, XaJJH, XaJqk, XaZcl, and prefix 22K. Values are required to lie between 12 and 75 kg/m^2. Height records are extracted using code prefix 229, and values are required to lie between 125 and 210 cm. Weight records are extracted using codes X76CG, XM01G, XE1h4, Xa7wI, 1622, and prefix 22A. Values are required to lie between 30 and 200 kg. Height, weight, and BMI measures are then matched by individual and date. Missing values for height are filled in from previous or subsequent measurements, where possible. BMI is calculated from height and weight at each date. If a value for BMI is already recorded for that individual and date, and the reported BMI differs from the calculated BMI by more than 1.5 (0.27% of records), both measures are excluded, otherwise, the calculated BMI is retained. If a BMI record is reported for a date where height or weight is not available, the reported BMI is retained.

E Covariate adjustment for β_g and τ_g in UK Biobank `TrajGWAS` analyses

- Blood pressures, i.e., SBP, DBP, and PP (if on medication, add 15 mmHg for SBP, 10 mmHg for DBP, and 5 mmHg for PP [4])
  - β_g: age, age^2, sex, age×sex, 10 PCs;

  - τ_g: age, age^2, sex, age×sex

- HDL (if on medication, -0.060 mmol/L[5])
  - β_g: age, age^2, BMI, sex, age×BMI, age×sex, 10 PCs
  - τ_g: age, age^2, BMI, sex, age×BMI, age×sex
- LDL (if on medication, add 1.290 mmol/L[5])
  - β_g: age, age^2, BMI, sex, age×BMI, age×sex, 10 PCs
  - τ_g: age, age^2, BMI, sex, age×BMI, age×sex
- Total cholesterol (if on medication, add 1.347 mmol/L[5])
  - β_g: age, age^2, BMI, sex, age×BMI, age×sex, 10 PCs
  - τ_g: age, age^2, BMI, sex, age×BMI, age×sex
- Triglycerides (if on medication, add 0.208 mmol/L[5])
  - β_g: age, age^2, BMI, sex, age×BMI, age×sex, cholesrol_drug, 10 PCs
  - τ_g: age, age^2, BMI, sex, age×BMI, age×sex, cholesrol_drug
- Glucose, i.e., fasting glucose and random glucose
  - β_g: age, age^2, BMI, sex, age×BMI, age×sex, self_insulin, diabetes_status, 10 PCs
  - τ_g: age, age^2, BMI, sex, age×BMI, age×sex, diabetes_status
- HbA1c
  - β_g: age, age^2, BMI, sex, age×BMI, age×sex, diabetes_status, self_insulin, 10 PCs
  - τ_g: age, age^2, BMI, sex, age×BMI, age×sex, diabetes_status
- BMI
  - β_g: age, age^2, sex, age×sex, 10 PCs
  - τ_g: age, age^2, sex, age×sex

F Considerations of Diabetes Diagnosis in `TrajGWAS` Analysis

One of the advantages of `TrajGWAS` is that it can incorporate time-varying covariates, e.g., diseases developed after the first observation. To fully explore how the occurrence of the related disease influences the genetic contribution to WS variability, we now include disease status as a time-varying covariates. We extracted first occurrence of diabetes from their primary care, hospital records, and registry data and include it as a time-varying covariate when analyzing HbA1c, given that HbA1c has abundant sample size as well as the larger number of repeated measurements than glucose measures. We compare the results with the those when including disease status as a time-fixed covariate.

For time-varying indicator, we use 0 for measurements before first diagnosis of diabetes, and 1 for measurements after the diagnosis. Percentage of observations after the diagnosis averaged over subjects is 95.8%. 66.6% of the subjects had all the observations after the diagnosis, and 85.1% had at least 75% of the observations after the diagnosis. Histogram of proportion of observation after diagnosis is shown in Figure S25. The results with time-varying indicator have magnified some of the signals compared to constant indicator, as shown in Figures S26-S27. For β_g, the SNPs magnified in Chromosome 2 maps to *THADA* (OMIM: 611800)[6,7], the one on Chromosme 8 to *SLC30A8* (OMIM: 611145)[8,9], and the last peak of Chromosome 10 to *TCF7L2* (OMIM: 602228), all of which are reported to be highly correlated to type 2 diabetes, glycemic changes, and beta-cell function.

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