Genetic and Environmental Contributions to the Covariation Between Cardiometabolic Traits

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Background—The variation and covariation for many cardiometabolic traits have been decomposed into genetic and environmental fractions, by using twin or single-nucleotide polymorphism (SNP) models. However, differences in population, age, sex, and other factors hamper the comparison between twin- and SNP-based estimates.

Methods and Results—Twenty-four cardiometabolic traits and 700,000 genotyped SNPs were available in the study base of 10 682 twins from TwinGene cohort. For the 27 highly correlated pairs (absolute phenotypic correlation coefficient ≥0.40), twin-based bivariate structural equation models were performed in 3870 complete twin pairs, and SNP-based bivariate genomic relatedness matrix restricted maximum likelihood methods were performed in 5779 unrelated individuals. In twin models, the model including additive genetic variance and unique/nonshared environmental variance was the best-fitted model for 7 pairs (5 of them were between blood pressure traits); the model including additive genetic variance, common/shared environmental variance, and unique/nonshared environmental variance components was best fitted for 4 pairs, but estimates of shared environment were close to zero; and the model including additive genetic variance, dominant genetic variance, and unique/nonshared environmental variance was best fitted for 16 pairs, in which significant dominant genetic effects were identified for 13 pairs (including all 9 obesity-related pairs). However, SNP models did not identify significant estimates of dominant genetic effects for any pairs. In the paired *t* test, twin- and SNP-based estimates of additive genetic correlation were not significantly different (both were 0.67 on average), whereas the nonshared environmental correlations from these 2 models differed slightly from each other (on average, twin-based estimate=0.64 and SNP-based estimate=0.68).

Conclusions—Beside additive genetic effects and nonshared environment, nonadditive genetic effects (dominance) also contribute to the covariation between certain cardiometabolic traits (especially for obesity-related pairs); contributions from the shared environment seem to be weak for their covariation in TwinGene samples. (***J Am Heart Assoc***. 2018;7:e007806. DOI: 10.1161/JAHA.117.007806.)

Key Words: biomarker • cardiac metabolism • environment • genes • heritability

Levels of cardiometabolic traits vary more between than within individuals, and most of them are normally distributed in the population, indicating complex regulation by both genes and environment. The concept of "heritability" reflects the relative importance of genes (in contrast to environment) for complex traits.[1] Univariate heritability is defined as the proportion of a trait's phenotypic variation explained by genetic effects, whereas bivariate heritability is the proportion of phenotypic covariation between 2 traits explained by genetic effects.[2]

Several methods have been developed to partition the variation and covariation of human complex traits into genetic and environmental components. The twin study is the classic family-based design, relying on comparing the within-pair similarity between monozygotic and dizygotic twins.[3] As a result of genome-wide association studies, many common single-nucleotide polymorphisms (SNPs) associated with complex traits (eg, cardiometabolic biomarker levels) have been identified.[4] Since 2010, several SNP-based methods for heritability estimation have been developed; the genomic relatedness matrix restricted maximum likelihood (GREML) and linkage disequilibrium score regression (LDSC) are the most frequently used SNP-based methods.[5–7]

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Clinical Perspective

What Is New?

- This was a comprehensive investigation about the relative importance of genes and environment for the covariation between cardiometabolic traits, by using both twin- and single-nucleotide polymorphism–based models within the same study base.

What Are the Clinical Implications?

- The contributions of genetic and environmental effects vary by different clusters of cardiometabolic traits.
- Additive genetic effects and nonshared environmental effects influence the covariation between blood pressure traits.
- Beside additive genetic effects and nonshared environmental effects, dominant genetic effects are important for the covariation between obesity traits.
- Contributions from shared environment seem to be weak between these cardiometabolic traits.

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To date, the univariate heritabilities of >17 800 traits/diseases have been estimated from twin studies[8]; SNP-based univariate heritabilities of >700 traits/diseases have been estimated by GREML or LDSC.[9,10] A general finding has been that SNP-based estimates tend to be considerably lower than corresponding estimates from twin studies. The causes of this gap are topics for continuing discussions and investigations.[11] Although heritability often turns out comparable across populations, it varies by the actual distribution of age, sex, and other factors in the investigated population sample.[12] Therefore, the only straightforward and strictly valid way to investigate the "heritability gap" between the twin and SNP model is to compare the twin- and SNP-based estimates in the same population sample at the same time point.

By comparing univariate heritabilities of 18 human complex traits within the same study base, we observed that common SNPs captured 70% of the narrow-sense heritability estimated from twin models, when the power in the twin model was high enough to declare and distinguish the dominant from additive genetic variation.[13] However, similar comparisons for the bivariate estimates between cardiometabolic traits have not been undertaken. This study quantifies the extent of genetic (additive and dominant) and environmental (shared and nonshared) contributions to the covariation between cardiometabolic traits, by applying both twin and SNP models within the same study base.

Methods

The data and study materials are available to other researchers on application and approval from the steering group of the Swedish Twin Registry.[14] Access to the analytic methods may be requested from the corresponding author.

Study Population

All participants in this study were from the TwinGene project, a Swedish population-based cohort of twins born between 1911 and 1958.[15] From 2004 to 2008, 12 614 twins donated venous blood samples after overnight fasting and had a health checkup at their local healthcare facility. Blood samples were sent to Karolinska Institutet Biobank before the weekend by overnight post. The TwinGene project was approved by the local ethics committee at Karolinska Institutet, and all participants gave informed consent.

Phenotypes

Twenty-four continuous cardiometabolic traits were measured or calculated for ≈12 000 TwinGene participants. Serum levels of apolipoprotein (apo) A1 and B, total cholesterol (TC), low- and high-density lipoprotein (LDL and HDL, respectively), triglycerides, hemoglobin, C-reactive protein, and fasting glucose were measured by routine methods on semiautomated biochemistry analyzer (Beckman Coulter, CA). Non-HDL was calculated as TC minus HDL. Hemoglobin A1c was measured by ion exchange chromatography. Creatinine was measured by an enzymatic method using Arcitect c8000 and Arcitect c16000 immunoassay analyzers (Abbott, IL). Cystatin C was measured by particle-reinforced immunoturbidimetric method using Architect ci8200, and estimated glomerular filtration rate was calculated as $79.901 \times (\text{cystatin C [mg/L]})^{-1.4389}$. Height, weight, and waist and hip circumference were measured without shoes and in light clothing. Body mass index was calculated as weight (kg)/height (m)^2, and waist/hip ratio (WHR) was calculated as waist circumference (cm)/hip circumference (cm). Systolic and diastolic blood pressures (SBP and DBP, respectively) were measured in mm Hg, mean arterial pressure (MAP) was calculated as 0.33 SBP+0.67 DBP, and pulse pressure (PP) was calculated as SBP minus DBP. The same transformation was used to make all cardiometabolic traits comparable and to achieve standard normal distribution: the raw values were adjusted for age, sex, and 10 genetic principal components in a linear regression model, after which the residuals were rank order normalized and used as phenotypes in the further analyses. Subjects with missing values (after adjustments) for >5 blood biomarkers or who had unknown zygosity were excluded; finally, 10 682 twins remained to constitute the study base.

Genotypes

Genomic DNA was extracted from whole blood samples by using Puregene extraction kit (Gentra Systems, Minneapolis,

MN). After excluding subjects with DNA concentration <20 ng/mL, DNA samples of other available dizygotic twins and 1 twin from each monozygotic twin pair (n=9896) were sent for genotyping. SNPs were genotyped by using Illumina OmniExpress BeadChip (700K), with quality controls as follows: individual missingness ≤0.03, genotype missingness ≤0.03, minor allele frequency ≥0.01, Hardy-Weinberg equilibrium $P{\geq}10^{-7}$, no sex mismatch, no excess heterozygosity (individuals with an F-statistic beyond 5 SDs from the sample mean), and no cryptic (unknown) relatedness. Finally, 9617 individuals and 644 556 SNPs were kept.

Twin and SNP Models

For each cardiometabolic trait and highly correlated trait pair (absolute phenotypic correlation coefficient |rP|≥0.4), twin-based structural equation model (SEM) and SNP-based GREML (dominant) method were performed to get the twin- and SNP-based estimates, respectively. Paired *t* test was used to test the agreement (or difference) between significant twin- and SNP-based estimates.

From the study base, 3870 complete twin pairs (1088 monozygotic, 1443 same-sex dizygotic, and 1339 opposite-sex dizygotic pairs) were used in twin models. The zygosity was determined by DNA markers (for 57% of the study sample) or by using an algorithm on self-reported childhood resemblance data.[15] Twin studies are based on 3 main assumptions: cotwins within monozygotic pair share 100% while cotwins within dizygotic pair share 50% of segregating genes, and cotwins within the same pair share 100% of the raising environment.[2] By using OpenMx 2.8.3 package in R 3.4.1, twin-based SEMs were constructed to partition phenotypic variation of each trait and covariation between traits into genetic and environmental components.[16] Akaike information criterion was used to compare the goodness of model fitting, in which the parameters of the covariance matrices were estimated by maximum likelihood methods.[17]

The GREML(d) method implemented in genome-wide complex trait analysis tool, version 1.26.0, was used to get SNP-based estimates.[5,18] The method relies on comparisons between measured phenotypic similarities and estimated genetic sharing. All directly genotyped SNPs (passing the quality controls) were fitted as random effects in a mixed linear model. To avoid bias from shared environment, 1 twin from each twin pair was randomly removed first, and remaining related individuals (relatedness >0.025) were further removed on the basis of pair-wise genomic relationship matrix. Finally, 5779 unrelated individuals from the same study base were used in SNP-based GREML(d) model. Restricted maximum likelihood approach was used to calculate the parameter values with the best probability, and likelihood ratio test was used to test for the best model fitting.

For each trait, the phenotypic variation can be mainly partitioned into the following: additive genetic variance (a^2; sum of individual effect of each locus or SNP), dominant genetic variance (d^2; interactions between alleles at the same locus or SNP) or common/shared environmental variance (c^2; contributes to the similarities between relatives who live together, only from twin model), and unique/nonshared environmental variance (e^2; specific to individuals, contributes to the dissimilarities between family members).

To decompose the covariation between 2 correlated traits, bivariate "Cholesky model" was constructed in twin-based SEM,[2] and SNP-based bivariate GREML(d) analyses were performed in genome-wide complex trait analysis.[6] The phenotypic correlation between 2 traits can be decomposed into bivariate a^2 (proportion explained by additive genetic effects), bivariate d^2 (proportion explained by dominant genetic effects) or bivariate c^2 (proportion explained by shared environment, only from twin model), and bivariate e^2 (proportion explained by nonshared environment). The overlaps of genetic and environmental effects (to what extent it is the same effects in action) were investigated by estimating additive and dominant genetic correlations (rA and rD, respectively), as well as shared and nonshared environmental correlations (rE).

Results

General characteristics of 10 682 twins in the study base are presented in Table 1. The distribution of each cardiometabolic trait was similar between the 3870 complete twin pairs and the 5779 unrelated individuals (Table 2). Results from the univariate models for 17 of the 24 traits from the same sample have been published previously (Table S1).[13] In short, for all traits, but not apolipoprotein A1 and height, the intrapair correlation coefficients were more than twice larger in monozygotic than dizygotic twin pairs. In the univariate twin SEM, the model including a^2 and e^2 (AE) was the best-fitted model for HDL, apolipoprotein A1, DBP, MAP, and PP; the model including a^2, c^2, and e^2 components (ACE) was the best-fitted model for height; the model including a^2, d^2, and e^2 (ADE) was the best-fitted model for the remaining 18 traits. SNP-GREML(d) identified significant d^2 for triglycerides and waist circumference. Except for C-reactive protein, waist circumference, and WHR, the twin-based a^2 values were larger than the corresponding SNP-based estimates; SNP-based a^2 was not significant for SBP, DBP, and MAP.

The phenotypic correlation pattern for the investigated cardiometabolic traits was also similar between the complete twin pairs and samples restricted to unrelated individuals (Figure 1). Twenty-seven pairs (9 for blood lipids, 4 for metabolic biomarkers, 9 for obesity traits, and 5 for blood

Table 1. General Characteristics of Participants in the Study Base

Characteristics	All	Men	Women
Participants	10 682 (100)	5074 (47.50)	5608 (52.50)
Age, y*	64.89±8.08	65.45±7.99	64.38±8.13
Triglycerides, mmol/L*	1.20 (0.86–1.60)	1.20 (0.88–1.70)	1.10 (0.84–1.60)
Total cholesterol, mmol/L*	5.77±1.12	5.52±1.10	6.00±1.09
Low-density lipoprotein, mmol/L*	3.76±0.99	3.65±0.98	3.86±0.99
Apolipoprotein B, g/L*	1.08±0.25	1.07±0.24	1.10±0.25
Non-high-density lipoprotein, mmol/L*	4.37±1.07	4.28±1.06	4.44±1.07
High-density lipoprotein, mmol/L*	1.41±0.42	1.24±0.34	1.56±0.42
Apolipoprotein A1, g/L*	1.64±0.30	1.53±0.26	1.75±0.30
Hemoglobin, g/dL*	14.26±1.21	14.87±1.13	13.72±1.00
Hemoglobin A1c, %*	4.82±0.68	4.85±0.74	4.78±0.61
Glucose, mmol/L*	5.59±1.22	5.76±1.33	5.44±1.08
Creatinine, μmol/L*	75 (66–86)	84 (76–93)	68 (62–76)
Cystatin C, mg/L*	0.97 (0.86–1.11)	0.99 (0.88–1.14)	0.95 (0.84–1.09)
eGFR, mL/min per 1.73 m^2*	83.55±21.88	80.74±21.94	86.08±21.53
C-reactive protein, mg/L	1.70 (0.72–3.50)	1.70 (0.73–3.40)	1.70 (0.72–3.60)
Height, m*	1.69±0.10	1.76±0.09	1.63±0.08
Weight, kg*	74.94±13.81	81.77±12.33	68.75±12.05
Body mass index, kg/m^2*	26.31±7.33	26.59±6.83	26.07±7.75
Waist circumference, cm*	91.78±12.18	97.16±10.26	86.91±11.72
Hip circumference, cm	103.26±8.93	103.20±8.06	103.30±9.64
Waist/hip ratio*	0.89±0.15	0.94±0.13	0.84±0.16
Systolic blood pressure, mm Hg*	139.07±19.80	140.10±19.43	138.20±20.10
Diastolic blood pressure, mm Hg*	82.10±10.61	83.19±10.63	81.12±10.49
Mean arterial pressure, mm Hg*	101.09±12.22	102.20±12.11	100.10±12.24
Pulse pressure, mm Hg	56.97±15.94	56.89±15.65	57.04±16.19

Values are in number (percentage) for sex, mean±SD for the normal distribution, or median (25th–75th percentile) for the skewed distribution. eGFR indicates estimated glomerular filtration rate.

*The difference between men and women is statistically significant ($P<0.05$) from *t* test, in which triglycerides, creatinine, cystatin C, and C-reactive protein are log transformed before performing the *t* test.

pressure traits) showed strong or moderate phenotypic correlations ($|rP|\geq0.40$), and they were selected for further investigation in the bivariate analyses.

Negative phenotypic correlation was found between triglycerides and HDL (rP=−0.46), but positive phenotypic correlations were found for the other 8 pairs of blood lipids (average rP=0.85, Table 3). AE was the best-fitted twin model for triglycerides-HDL and TC-apoB. ACE was the best-fitted model for HDL–apolipoprotein A1, LDL-apoB, and apoB–non-HDL, but the estimates of bivariate c^2 were close to zero. In twin models, significant contributions of dominance genetic effects were identified for 3 lipids pairs (TC-LDL, TC–non-HDL, and LDL–non-HDL), and the average bivariate d^2 was 23% and rD was 0.96. For these 9 pairs of blood lipids, the average

estimates of bivariate a^2 were 42% from the twin models, whereas the SNP models provided lower estimates of 16%.

ADE was the best-fitted twin model for 3 of 4 pairs of metabolic biomarkers (hemoglobin A1c–glucose, creatinine–cystatin C, and creatinine–estimated glomerular filtration rate), but bivariate d^2 and rD were only significantly identified for hemoglobin A1c–glucose (Table 4). ACE model was best fitted for cystatin C–estimated glomerular filtration rate, whereas bivariate c^2 was also close to zero. For these 4 pairs of metabolic biomarkers, the average twin- and SNP-based bivariate a^2 values were 43% and 23%, respectively.

For all of the 9 pairs of obesity traits, bivariate d^2 (48% on average) and rD (0.84 on average) were significantly identified from twin models (Table 5). However, bivariate a^2 was not

Table 2. General Characteristics of Subjects in Twin and SNP Models

Characteristics	Complete Twin Pairs in Twin Model		Unrelated Individuals in SNP Model	
	N	Value	N	Value
Men, %	3653	47.20	2755	47.67
Age, y	7740	65.03±7.75	5779	64.91±8.33
Triglycerides, mmol/L	7739	1.20 (0.86–1.60)	5778	1.20 (0.85–1.60)
Total cholesterol, mmol/L	7740	5.78±1.13	5779	5.76±1.11
Low-density lipoprotein, mmol/L	7639	3.77±0.99	5704	3.75±0.98
Apolipoprotein B, g/L	7738	1.09±0.25	5776	1.08±0.25
Non-high-density lipoprotein, mmol/L	7740	4.38±1.07	5779	4.35±1.06
High-density lipoprotein, mmol/L	7740	1.41±0.42	5779	1.41±0.42
Apolipoprotein A1, g/L	7738	1.64±0.30	5776	1.64±0.30
Hemoglobin, g/dL	7726	14.26±1.19	5769	14.26±1.21
Hemoglobin A1c, %	7727	4.82±0.66	5770	4.82±0.68
Glucose, mmol/L	7736	5.59±1.20	5775	5.59±1.19
Creatinine, μmol/L	7534	75 (66–86)	5634	76 (66–87)
Cystatin C, mg/L	7534	0.97 (0.86–1.11)	5634	0.97 (0.86–1.12)
eGFR, mL/min per 1.73 m^2	7534	83.62±21.50	5633	83.09±22.26
C-reactive protein, mg/L	7738	1.70 (0.74–3.50)	5777	1.70 (0.71–3.50)
Height, m	7685	1.69±0.10	5701	1.69±0.10
Weight, kg	7684	74.74±13.67	5699	75.06±13.69
Body mass index, kg/m^2	7679	26.29±7.48	5695	26.26±6.72
Waist circumference, cm	7671	91.70±12.12	5693	91.89±12.13
Hip circumference, cm	7655	103.24±8.83	5680	103.41±8.77
Waist/hip ratio	7652	0.89±0.15	5680	0.89±0.10
Systolic blood pressure, mm Hg	7334	139.11±19.79	5420	139.42±20.01
Diastolic blood pressure, mm Hg	7333	82.14±10.68	5420	82.13±10.67
Mean arterial pressure, mm Hg	7333	101.13±12.30	5420	101.23±12.31
Pulse pressure, mm Hg	7333	56.96±15.78	5420	57.28±16.13

Values are in number (percentage) for sex, mean±SD for the normal distribution, or median (25th–75th percentile) for the skewed distribution. eGFR indicates estimated glomerular filtration rate; SNP, single-nucleotide polymorphism.

significant for weight–WHR, body mass index–WHR, or waist circumference–WHR. For the remaining 6 obesity-related pairs, on average, the twin- and SNP-based bivariate a^2 values were 26% and 21%, respectively.

AE was the best-fitted twin model for all 5 pairs of blood pressure traits (Table 6). The average estimates of bivariate a^2 were ≈40% in the twin models, whereas in SNP models, they were smaller and significant only for SBP-PP (bivariate a^2=11%; 95% confidence interval, 0%–22%). The twin- and SNP-based estimates of rA and rE were similar for SBP-MAP, SBP-PP, and DBP-MAP (>0.80); SNP-based estimates of rA and rE were not significant for SBP-DBP or MAP-PP.

The overall agreements between significant twin- and SNP-based estimates for these highly correlated cardiometabolic pairs are plotted in Figure 2. The twin-based bivariate a^2 (36% on average) was significantly larger than SNP-based estimates (19% on average). The estimates of rA were not significantly different between twin-SEM and SNP-GREML (both were 0.67 on average). However, the twin-based rP (0.66 on average) and rE (0.64 on average) values were slightly but significantly different from the SNP-based rP (0.65 on average) and rE (0.68 on average) values.

Discussion

This study mainly aims to quantify the contribution of genetic and environmental effects to the covariation between cardiometabolic traits and to compare the
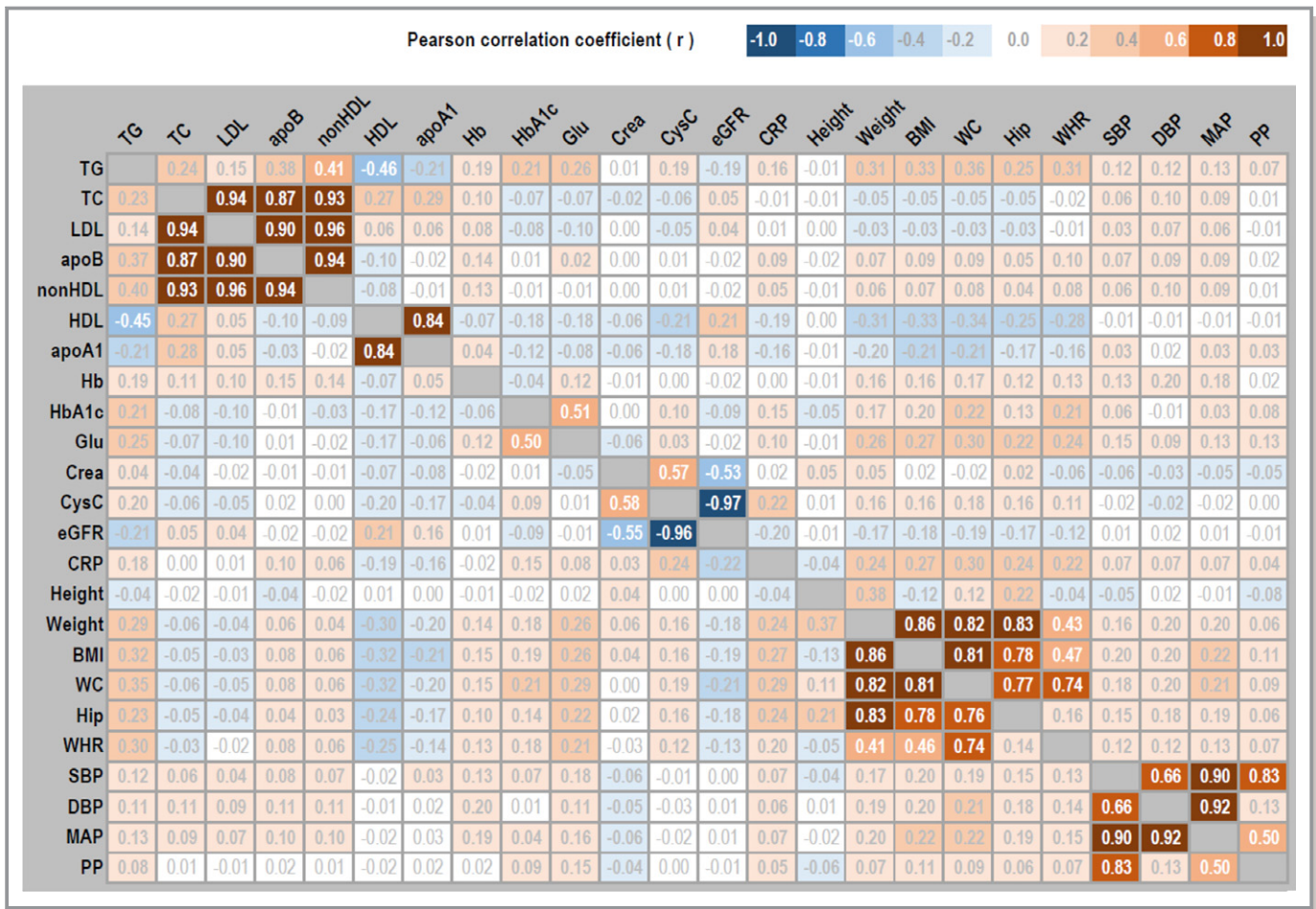
Figure 1. Phenotypic correlation matrix among 24 cardiometabolic traits. Statistically significant (*P*<0.05) estimates of Pearson correlation coefficient (*r*) are boldfaced. Estimates in the top triangle are from the 3870 complete twin pairs used in twin models, and estimates in the bottom triangle are from the 5779 unrelated individuals used in single-nucleotide polymorphism models. apoA1 indicates apolipoprotein A1; apoB, apolipoprotein B; BMI, body mass index; Crea, creatinine; CRP, C-reactive protein; CysC, cystatin C; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; Glu, fasting glucose; Hb, hemoglobin; HDL, high-density lipoprotein; Hip, hip circumference; LDL, low-density lipoprotein; MAP, mean arterial pressure; PP, pulse pressure; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; WC, waist circumference; WHR, waist/hip ratio.

estimates obtained from both twin and SNP models within the same study base. Beside additive genetic effects and nonshared environment, the twin models also find significant contributions of dominant genetic effects to the covariation between certain cardiometabolic traits (especially for obesity-related pairs); contributions of shared environment generally seem to be weak for their covariation. The results show that the twin model captures significantly more bivariate additive genetic variance than SNP model, whereas the estimates of additive genetic correlation from these 2 models are not significantly different.

Twenty-seven highly correlated pairs of cardiometabolic traits were investigated in this study. They were grouped into 4 biological clusters: blood lipids, metabolic biomarkers, obesity traits, and blood pressure traits. The magnitudes of rP,

rA, and rE are similar for each pair (Figure 2), perhaps because the correlated traits are calculated from each other, represent similar features, or are involved in the same biological process. For example, apoB is the primary apolipoprotein of LDL, LDL constitutes the majority of TC, and non-HDL is calculated as TC minus HDL; thus, apoB–LDL–TC–non-HDL are strongly and positively correlated.

ApoA1 is the major component of HDL, and genetic effects contribute more (66%) to their phenotypic correlation than environment in twin model. Similarly, twin model also indicates that 66% of the negative correlation between triglycerides and HDL is explained by genes (Table 3). On the contrary, environmental factors contribute more (≈60%) than genes to the phenotypic correlations for 5 pairs of blood pressure traits (Table 6), perhaps because blood pressure fluctuates more from environmental or behavioral factors (eg,

Table 3. Bivariate Analyses Between Blood Lipids in Twin and SNP Models

Pairs	rP (SE)	BM	Bivariate a^2 (SE), %		Bivariate d^2 (SE), %*		rA (SE)		rD (SE)*		rE (SE)	
			Twin	SNP	Twin	SNP	Twin	SNP	Twin	SNP	Twin	SNP
Triglycerides-HDL	−0.46 (0.01)†	AE	66 (3)†	29 (6)†	...		−0.51 (0.02)†	−0.48 (0.13)†	...		−0.39 (0.02)†	−0.45 (0.11)†
Triglycerides–non-HDL	0.41 (0.01)†	ADE	33 (14)†	11 (6)	23 (15)		0.43 (0.15)†	0.23 (0.20)	0.49 (0.51)		0.38 (0.03)†	0.46 (0.05)†
HDL–apoA1	0.84 (0.02)†	ACE‡	66 (2)†	21 (6)†	...		0.89 (0.01)†	0.88 (0.06)†	...		0.85 (0.01)†	0.84 (0.05)†
TC-LDL	0.94 (0.02)†	ADE	25 (8)†	15 (6)†	21 (9)†		0.92 (0.04)†	0.92 (0.04)†	0.94 (0.06)†		0.95 (0.00)†	0.94 (0.04)†
TC-apoB	0.87 (0.02)†	AE	46 (2)†	14 (6)†	...		0.83 (0.01)†	0.82 (0.09)†	...		0.91 (0.00)†	0.87 (0.07)†
TC–non-HDL	0.93 (0.02)†	ADE	25 (8)†	13 (6)†	22 (9)†		0.88 (0.05)†	0.89 (0.05)†	−0.96 (0.04)†		0.96 (0.00)†	0.94 (0.05)†
LDL-apoB	0.91 (0.02)†	ACE‡	47 (2)†	14 (6)†	...		0.91 (0.01)†	0.89 (0.06)†	...		0.92 (0.00)†	0.91 (0.05)†
LDL–non-HDL	0.97 (0.02)†	ADE	23 (8)†	14 (6)†	25 (9)†		0.94 (0.03)†	0.95 (0.03)†	0.98 (0.02)†		0.96 (0.00)†	0.96 (0.03)†
ApoB–non-HDL	0.94 (0.02)†	ACE‡	47 (2)†	14 (6)†	...		0.95 (0.01)†	0.96 (0.03)†	...		0.95 (0.00)†	0.93 (0.03)†

a^2 Indicates additive genetic variance; ACE, model including a^2, common (c^2), and nonshared environmental (e^2) components; ADE, model including a^2, d^2, and e^2; AE, model including a^2 and e^2; apoA1, apolipoprotein A1; apoB, apolipoprotein B; BM, best-fitted model according to Akaike information criterion; d^2, dominant genetic variance; HDL, high-density lipoprotein; LDL, low-density lipoprotein; rA, additive genetic correlation; rD, dominant genetic correlation; rE, nonshared environmental correlation; rP, phenotypic correlation; SNP, single-nucleotide polymorphism–based genomic relatedness matrix restricted maximum likelihood model; TC, total cholesterol.

*Bivariate d^2 and rD are not significantly identified from SNP models for any pairs.

†Statistically significant estimates (P<0.05).

‡ACE is the best-fitted model, but bivariate c^2=0% (SE=1%).

physical activity, smoking, alcohol drinking, and psychological stress) than genes.[19]

On the basis of different assumptions, twin and SNP models are used to estimate the relative importance of genes and environment for complex traits (represented by the concept of heritability). Twin studies have historically been the most frequently used design to provide estimates of "traditional heritability." By using directly genotyped SNPs in unrelated individuals, GREML(d) estimates the so-called "chip heritability." LDSC uses the summary genome-wide association study results (including both directly genotyped and imputed SNPs) to estimate the "SNP heritability." For most cardiometabolic traits in our study, a trend can be found that the estimates of traditional heritability ≥ chip heritability ≥ SNP heritability (Table S1). A similar significant trend was also observed for bivariate heritabilities (Figure 2). The causes of the gap between twin- and SNP-based estimates of heritability are of direct relevance for the discussions about the "missing" or "hidden" heritability.[11,20]

The issue of missing heritability was raised because of the fact that robustly associated genome-wide significant SNPs generally explain <5% of traits' variation.[20] However, the explained variance becomes larger (≈50%) when all common SNPs are taken into account in GREML methods.[21] Our previous study also indicated that genome-wide common SNPs could capture large proportions (≈70%) of the "traditional narrow-sense heritability (a^2)" if the power in the twin model was enough to identify and discriminate dominant from additive genetic contributions.[13]

Classic twin studies based solely on monozygotic and dizygotic twins reared together are unable to simultaneously estimate shared environmental variance (c^2) and dominant genetic variance (d^2). However, because c^2 and d^2 are likely to coexist in reality, it is fully possible that both of them contribute simultaneously to similarities between twins and relatives. Whenever c^2 and d^2 are both present, their contributions will tend to mask each other in the twin model; thus, the net effect may appear as contribution from neither. Although an extended twin-family study design including more family members (eg, parents, offspring, and nontwin siblings) is the optimal design to detect the existence of nonadditive genetic effects, such materials of adequate sample size are exceptionally rare.[22–24]

The identification of true d^2 depends heavily on the sample size. Most previous twin studies are small, <1000 twin pairs on average.[8] It might lead to inadequate power to significantly declare contributions from less prominent variance components; thus, d^2 or c^2 may be attributed to a^2 instead.[13] This is in line with the observation that most previous twin studies report the estimates from the most parsimonious AE model.[8]

Table 4. Bivariate Analyses Between Metabolic Biomarkers in Twin and SNP Models

Pairs	BM	rP (SE)	Bivariate a² (SE), %		Bivariate d² (SE), %*	rA (SE)		rD (SE)*	rE (SE)	
			Twin	SNP	Twin	Twin	SNP	Twin	Twin	SNP
HbA1c-glucose	ADE	0.51 (0.01)†	29 (11)†	23 (6)†	49 (11)†	0.51 (0.15)†	0.61 (0.16)†	0.76 (0.12)†	0.32 (0.03)†	0.48 (0.14)†
Creatinine-CysC	ADE	0.56 (0.01)†	44 (10)†	22 (6)†	18 (11)	0.65 (0.09)†	0.59 (0.13)†	0.48 (0.16)†	0.53 (0.02)†	0.59 (0.13)†
Creatinine-eGFR	ADE	−0.53 (0.01)†	39 (11)†	25 (6)†	22 (12)	−0.57 (0.11)†	−0.57 (0.13)†	0.54 (0.23)	−0.50 (0.02)†	−0.55 (0.13)†
CysC-eGFR	ACE‡	−0.95 (0.02)†	58 (2)†	...	...	−0.98 (0.00)†	...	...	−0.97 (0.00)†	...

a² Indicates additive genetic variance; ACE, model including a², common (c²), and nonshared environmental (e²) components; ADE, model including a², d², and e²; BM, best-fitted model according to Akaike information criterion; CysC, cystatin C; d², dominant genetic variance; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; rA, additive genetic correlation; rD, dominant genetic correlation; rE, nonshared environmental correlation; rP, phenotypic correlation; SNP, single-nucleotide polymorphism–based genomic relatedness matrix restricted maximum likelihood model.

*Bivariate d² and rD are not significantly identified from SNP models for any pairs.

†Statistically significant estimates (*P*<0.05).

‡ACE is the best-fitted model, but bivariate c²=0% (SE=1%).

There are 3870 complete twin pairs in present study, and bivariate d² is significantly distinguished from bivariate a² for 13 of 16 ADE best-fitted pairs. Among these pairs, the directly genotyped common SNPs captured 75% of twin-based bivariate a² (narrow-sense heritability). Previous genome-wide association studies have identified 47 loci that associated with both LDL and TC[25]; the significant bivariate d² for TC-LDL in our twin model suggests potential interactions between the alleles within the same locus. However, our SNP model did not identify significant dominant genetic effects for any pairs, perhaps because of the inadequate power for bivariate GREML(d). Therefore, more SNPs in larger samples need to test such potential interactions.

For ADE fitted traits or pairs, the separation between additive and dominant genetic variation is important to understand the gap between twin- and SNP-based univariate or bivariate narrow-sense heritability. Even so, the twin-based bivariate a² values are still significantly higher (on average 25% for ADE fitted pairs and 48% for all pairs) than SNP-based estimates. Potential explanations might be the following: twin-based SEM captures all genetic effects, whereas GREML(d) is just based on common SNPs; other mutations, like rare SNPs, copy number variations, insertions, or deletions, will not be taken into account; and violations of the assumptions of twin studies (monozygotic and dizygotic twin pairs share environment to the same extent, minimal gene–environment correlations or interactions) may inflate the twin-based heritability estimation.[26]

For all ACE best-fitted pairs, estimates of bivariate shared environmental variance (c²) are close to zero, perhaps reflecting the relative old age of the participants in our study base (65±8 years on average). It is reasonable to assume that most cotwins of old age live separately and that the influences of shared environment decrease with age. A weaker contribution from c² may lend d² less masked and thus more prominent at older ages. Therefore, the influence on twin similarity stemming from c² can be expected to be largest during childhood, with subsequent diminishing importance with advancing age. However, a thorough investigation of the potential role of age for the relative importance between c² and d² (eg, the age-related changes in contribution from c² and d² to trait covariation) requires even larger sample size.

Previous twin studies, including small numbers of monozygotic twins reared apart, identified that shared environmental effects contribute to the variation of some cardiometabolic traits[27,28]; this occurs perhaps because such study setting allows researchers to directly use ACE decomposing model rather than choosing the best-fitted one among ACE, ADE, and AE models. After removing pairs with relatedness >0.025, it is unlikely to have contributions from c² in GREML(d). Therefore, the estimates from SNP-GREML(d) represent a

Table 5. Bivariate Analyses Between Obesity Traits in Twin and SNP Models

| Pairs | rP (SE) | BM | Bivariate a² (SE), % | | Bivariate d² (SE), %* | rA (SE) | | rD (SE)* | rE (SE) | |
			Twin	SNP	Twin	Twin	SNP	Twin	Twin	SNP
Weight-BMI	0.86 (0.02)[†]	ADE	25 (8)[†]	18 (6)[†]	45 (8)[†]	0.68 (0.08)[†]	0.66 (0.09)[†]	1.00 (0.00)[†]	0.89 (0.01)[†]	0.93 (0.09)[†]
Weight-WC	0.82 (0.02)[†]	ADE	25 (8)[†]	22 (6)[†]	47 (8)[†]	0.83 (0.09)[†]	0.87 (0.06)[†]	0.93 (0.04)[†]	0.74 (0.01)[†]	0.82 (0.06)[†]
Weight-Hip	0.83 (0.02)[†]	ADE	33 (8)[†]	28 (6)[†]	40 (8)[†]	0.91 (0.05)[†]	0.99 (0.04)[†]	0.90 (0.04)[†]	0.70 (0.02)[†]	0.78 (0.04)[†]
Weight-WHR	0.42 (0.01)[†]	ADE	14 (13)	7 (6)	54 (14)[†]	0.26 (0.51)	0.14 (0.19)	0.62 (0.12)[†]	0.38 (0.03)[†]	0.49 (0.20)[†]
BMI-WC	0.81 (0.02)[†]	ADE	21 (8)[†]	17 (6)[†]	50 (8)[†]	0.80 (0.14)[†]	0.76 (0.09)[†]	0.93 (0.04)[†]	0.70 (0.02)[†]	0.83 (0.08)[†]
BMI-Hip	0.77 (0.02)[†]	ADE	26 (8)[†]	21 (6)[†]	46 (9)[†]	0.76 (0.10)[†]	0.78 (0.08)[†]	0.89 (0.05)[†]	0.66 (0.02)[†]	0.78 (0.08)[†]
BMI-WHR	0.47 (0.01)[†]	ADE	15 (12)	10 (6)	56 (13)[†]	0.36 (0.51)	0.24 (0.20)	0.66 (0.11)[†]	0.37 (0.03)[†]	0.52 (0.18)[†]
WC-Hip	0.76 (0.02)[†]	ADE	23 (8)[†]	22 (6)[†]	46 (9)[†]	0.94 (0.09)[†]	0.90 (0.08)[†]	0.80 (0.05)[†]	0.66 (0.02)[†]	0.73 (0.08)[†]
WC-WHR	0.73 (0.01)[†]	ADE	12 (9)	10 (6)	48 (9)[†]	0.64 (0.51)	0.46 (0.19)[†]	0.80 (0.06)[†]	0.72 (0.01)[†]	0.79 (0.19)[†]

a² Indicates additive genetic variance; ADE, model including a², d², and nonshared environmental (e²) components; BM, best-fitted model according to Akaike information criterion; BMI, body mass index; d², dominant genetic variance; Hip, hip circumference; rA, additive genetic correlation; rD, dominant genetic correlation; rE, nonshared environmental correlation; rP, phenotypic correlation; SNP, single-nucleotide polymorphism–based genomic relatedness matrix restricted maximum likelihood model; WC, waist circumference; WHR, waist/hip ratio.
*Bivariate d² and rD are not significantly identified from SNP models for any pairs.
[†]Statistically significant estimates (*P*<0.05).

lower bound of a². In Table S1, the estimates of univariate heritability from SNP-based GREML(d) (22% on average, using 644 556 directly genotyped SNPs in our samples) are significantly higher than LDSC-based estimates (14% on average, including up to ≈10 million directly genotyped and imputed SNPs in LD Hub). Both GREML(d) and LDSC assume that heritability is independent of linkage disequilibrium pattern, which has been suggested to underestimate the SNP-based heritability.[29,30] However, the estimates of rA from LDSC were >1 for 4 pairs of blood lipids, indicating potential inflation in signal, potentially resulting from using overlapped individuals (Table S2) or imputed SNPs to capture the covariation. Recently, a study suggested that rA estimates from LDSC are less accurate than rA obtained by GREML(d), perhaps because of the uncertainty of homogeneity among combined data sets.[31] Still, our twin-SEM and SNP-

GREML(d) models give estimates of rA and rE largely in agreement with each other for most correlated cardiometabolic pairs.

In summary, this study indicates that contributions of genetic and environmental effects vary by different clusters of cardiometabolic traits. Contributions from the shared environment seem to be weak between these cardiometabolic traits. Additive genetic effects and nonshared environmental effects influence the covariation between blood pressure traits. Dominant genetic effects are important between obesity traits, and the gap between twin- and SNP-based bivariate narrow-sense heritability would become smaller if dominance can be significantly distinguished from additive genetic effects. However, larger sample size of unrelated individuals is still required to test the significance of dominant genetic effects from SNP-based models.

Table 6. Bivariate Analyses Between Blood Pressure Traits in Twin and SNP Models

| Pairs | rP (SE) | BM | Bivariate a² (SE), % | | rA (SE) | | rE (SE) | |
			Twin	SNP	Twin	SNP	Twin	SNP
SBP-DBP	0.67 (0.01)*	AE	41 (3)*	7 (6)	0.71 (0.02)*	0.55 (0.34)	0.63 (0.01)*	0.67 (0.50)
SBP-MAP	0.92 (0.02)*	AE	40 (2)*	9 (6)	0.92 (0.01)*	0.88 (0.11)*	0.89 (0.01)*	0.90 (0.16)*
SBP-PP	0.84 (0.02)*	AE	39 (2)*	11 (6)*	0.85 (0.01)*	0.83 (0.13)*	0.81 (0.01)*	0.83 (0.10)*
DBP-MAP	0.93 (0.02)*	AE	38 (2)*	7 (6)	0.93 (0.01)*	0.88 (0.11)*	0.92 (0.00)*	0.92 (0.22)*
MAP-PP	0.51 (0.01)*	AE	42 (3)*	9 (6)	0.57 (0.03)*	0.46 (0.35)	0.46 (0.02)*	0.51 (0.34)

a² Indicates additive genetic variance; AE, model including a² and nonshared environmental components; BM, best-fitted model according to Akaike information criterion; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure; rA, additive genetic correlation; rE, nonshared environmental correlation; rP, phenotypic correlation; SBP, systolic blood pressure; SNP, single-nucleotide polymorphism–based genomic relatedness matrix restricted maximum likelihood model.
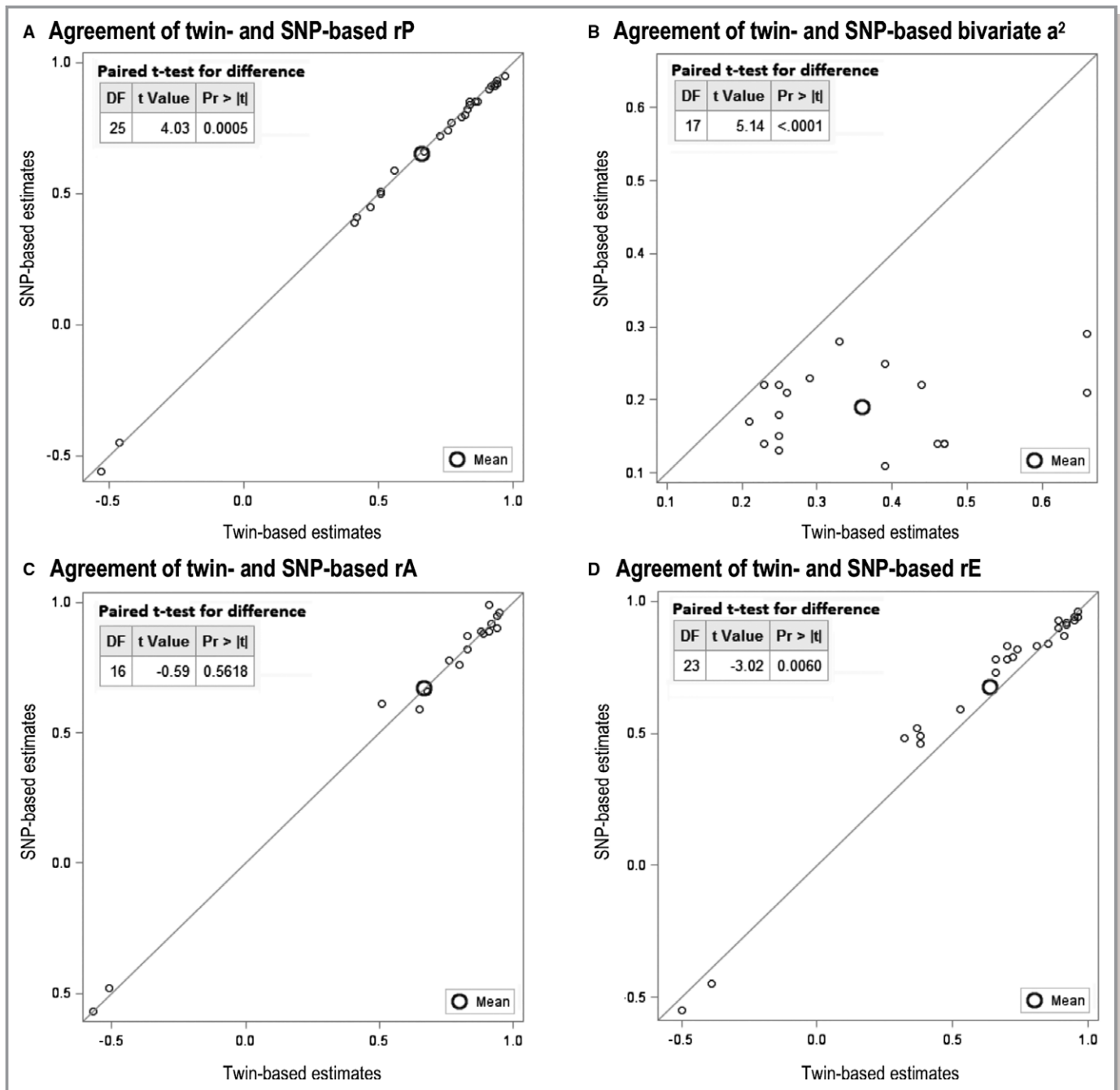*Statistically significant estimates (*P*<0.05).

Figure 2. Paired test for agreement between significant twin- and single-nucleotide polymorphism (SNP)–based estimates. a^2 Indicates additive genetic variance; Pr, probability; rA, additive genetic correlation; rE, nonshared environmental correlation; rP, phenotypic correlation.

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None.

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SUPPLEMENTAL MATERIAL

Table S1. Univariate Analyses in Twin and SNP Models.

Traits	rMZ/rDZ*	BM	a^2 (se)			d^2 (se)	
			Twin	SNP	LDSC†	Twin	SNP
Triglycerides	2.27	ADE	42% (7%)*	31% (6%)*	15% (2%)*	14% (8%)	28% (9%)*
Total cholesterol	2.50	ADE	28% (8%)*	15% (6%)*	15% (2%)*	19% (8%)*	0% (9%)
LDL	2.64	ADE	23% (8%)*	16% (6%)*	13% (2%)*	24% (8%)*	0% (9%)
Apolipoprotein B	2.24	ADE	39% (7%)*	14% (6%)*	11% (3%)*	14% (8%)	0% (9%)
nonHDL	2.61	ADE	24% (8%)*	13% (6%)*	NA	25% (8%)*	0% (9%)
HDL	2.17	AE	66% (2%)*	24% (6%)*	16% (2%)*	-	1% (9%)
Apolipoprotein A1	1.93	AE	66% (2%)*	17% (6%)*	9% (3%)*	-	9% (9%)
Hemoglobin	2.24	ADE	41% (7%)*	21% (6%)*	NA	15% (8%)	0% (9%)
Hemoglobin A1c	2.50	ADE	37% (7%)*	20% (6%)*	7% (1%)*	35% (7%)*	0% (9%)
Glucose	2.55	ADE	24% (7%)*	17% (6%)*	10% (2%)*	30% (8%)*	15% (9%)
Creatinine	2.41	ADE	35% (7%)*	18% (6%)*	11% (2%)*	24% (8%)*	0% (9%)
Cystatin C	2.19	ADE	42% (7%)*	27% (6%)*	NA	18% (8%)*	5% (9%)
eGFR	2.35	ADE	38% (7%)*	32% (6%)*	NA	21% (8%)*	3% (9%)
C-reactive protein	2.19	ADE	30% (7%)*	37% (6%)*	NA	14% (8%)	0% (9%)
Height	1.81	ACE	77% (3%)*	62% (6%)*	27% (1%)*	-	0% (9%)
Weight	2.66	ADE	37% (7%)*	26% (6%)*	NA	35% (7%)*	11% (9%)
Body mass index	2.80	ADE	28% (7%)*	21% (6%)*	19% (1%)*	41% (7%)*	3% (9%)
Waist circumference	3.14	ADE	15% (7%)*	16% (6%)*	12% (0%)*	49% (7%)*	19% (9%)*
Hip circumference	2.86	ADE	24% (7%)*	22% (6%)*	13% (1%)*	40% (8%)*	13% (9%)
Waist-hip ratio	3.12	ADE	13% (7%)	19% (6%)*	11% (1%)*	40% (8%)*	3% (9%)
SBP	2.50	ADE	27% (8%)*	10% (6%)	NA	15% (9%)	0% (9%)
DBP	2.33	AE	37% (2%)*	8% (6%)	NA	-	0% (10%)
MAP	2.50	AE	39% (2%)*	8% (6%)	NA	-	0% (9%)
Pulse pressure	2.17	AE	36% (2%)*	12% (6%)*	NA	-	2% (9%)

rMZ/rDZ, ratio of intra-pair correlation in monozygotic and dizygotic twin pairs; BM, the best-fitted model according to Akaike information criterion; SNP, single nucleotide polymorphism-based genomic-relatedness-matrix restricted maximum likelihood model; LDSC: linkage disequilibrium score regression model; a^2, additive genetic variance; d^2, dominant genetic variance; se, standard error; ADE, model including a^2, d^2 and non-shared environmental (e^2) components; AE, model including a^2 and e^2; ACE, model including a^2, c^2 and e^2; LDL, low-density lipoprotein; HDL, high-density lipoprotein; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; NA, not available from LD Hub.

* Statistically significant estimates (P-value<0.05).

† Estimates are based on the largest European ancestry genome-wide association study reported from LD Hub.

Table S2. LDSC-based Estimates of Cardiometabolic Traits from European Ancestry Data in the LD Hub.

Traits	Consortium	Sample size	N_{SNP}	h^2	SE	λ_{GC}	PMID
Triglycerides	GLGC	96598	2692561	15%	2%	1.1294	20686565
	Kettunen	21545	11820641	12%	3%	1.0195	27005778
Total Cholesterol	GLGC	99900	2692414	15%	2%	1.1232	20686565
	Kettunen	21491	11866342	9%	3%	1.0225	27005778
Low-density lipoprotein	GLGC	95454	2692565	13%	2%	1.1151	20686565
Apolipoprotein B	Kettunen	20690	11813266	11%	3%	1.0255	27005778
High-density lipoprotein	GLGC	100184	2692430	16%	2%	1.1622	20686565
Apolipoprotein A1	Kettunen	20687	11760646	9%	3%	1.0165	27005778
Hemoglobin A1c	MAGIC	46368	2576680	7%	1%	1.0405	20858683
Glucose	MAGIC	58074	2628880	10%	2%	1.0679	22581228
	Kettunen	24679	12052259	9%	2%	1.0315	27005778
Creatinine	Kettunen	24810	12087816	11%	2%	1.0496	27005778
Height	GIANT	133859	2469636	27%	1%	1.4122	20881960
Body mass index	GIANT	123912	2471517	19%	1%	1.3675	20935630
Waist circumference	GIANT	232101	2565409	12%	0%	1.1085	25673412
Hip circumference	GIANT	213038	2559740	13%	1%	1.1085	25673412
Waist-hip ratio	GIANT	212244	2560783	11%	1%	1.1617	25673412

LDSC, linkage disequilibrium score regression model; N_{SNP}, number of single nucleotide polymorphisms; h^2, estimate of heritability; SE, standard error; λ_{GC}, genomic inflation factor; PMID, PubMed Unique Identifier; GLGC, the Global Lipids Genetics Consortium; MAGIC, the Meta-Analyses of Glucose and Insulin-related traits Consortium; GIANT, the Genetic Investigation of ANthropometric Traits consortium.