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Web-based Supplementary Materials for Multiple Phenotype Association Tests Using Summary Statistics in Genome-Wide Association Studies

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Web Appendix A. Multiple Binary Phenotypes

In this section, we examine whether the correlation among binary phenotypes can be well estimated by the corresponding genome-wide Z-score test statistics,

we conduct simulation study to show the correlation matrix of the Z-scores for multiple phenotypes at a particular genetic locus does not depend on the genotype under the null, and is approximately equal to the correlation of the multiple binary phenotypes. Suppose there are two binary phenotypes $y_{ik}, k = 1, 2$ measured on the ith subject in a study sample of size $n = 2000$. For simplicity, we consider the following null model

$$\log \frac{p_{ik}}{1 - p_{ik}} = -1 + G_i \beta_k$$

where $\beta_k = 0$ and $p_{ik} = E(y_{ik})$. The correlation between the two binary phenotypes was set to be $\rho = 0.3$. We also simulated $M = 10,000$ independent SNPs for each individual with minor allele frequencies being sampled from a uniform distribution between 0.01 and 0.5, with the assumption of Hardy-Weinberg equilibrium. We then perform association testing by running logistic regression of each binary phenotype on each of the SNP and obtain testing statistics $Z_{mk}, m = 1, \ldots, M, k = 1, 2$. We observed that the empirical binary trait correlation is 0.319, which can be approximated through the calculation of the sample correlation (0.315) of test statistics of SNPs corresponding to those two binary traits, and the minor allele frequency does not affect the correlation estimation.

Web Appendix B. Testing for Mixed Effects

B.1 Proof of Independence between U_{μ_0} and U_{τ_0}

Using the following result from the properties of multivariate normal distributions which states that if $\mathbf{Z}$ is a multivariate normal random vector with covariance matrix $\mathbf{\Sigma}$, then $A\mathbf{Z}$ and $B\mathbf{Z}$ are independent of each other if and only if $Cov(A\mathbf{Z}, B\mathbf{Z}) = A\mathbf{\Sigma}B^T = \mathbf{0}$.

In this case, $A = \mathbf{J}^T\mathbf{\Sigma}^{-1}$, and $B = \mathbf{\Sigma}^{-1}(\mathbf{I} - \mathbf{H})$, where $\mathbf{H} = \mathbf{J}(\mathbf{J}^T\mathbf{J})^{-1}\mathbf{J}^T$. So we have

$$\begin{aligned} Cov(A\mathbf{Z}, B\mathbf{Z}) &= A\mathbf{\Sigma}B^T \\ &= \mathbf{J}^T\mathbf{\Sigma}^{-1}\mathbf{\Sigma}(\mathbf{\Sigma}^{-1}(\mathbf{I} - \mathbf{H}))^T \\ &= \mathbf{J}^T\mathbf{\Sigma}^{-1}\mathbf{\Sigma}(\mathbf{I} - \mathbf{H})\mathbf{\Sigma}^{-1} \\ &= \mathbf{J}^T(\mathbf{I} - \mathbf{J}(\mathbf{J}^T\mathbf{J})^{-1}\mathbf{J}^T)\mathbf{\Sigma}^{-\mathbf{1}} \\ &= (\mathbf{J}^T - \mathbf{J}^T)\mathbf{\Sigma}^{-1} \\ &= \mathbf{0}. \end{aligned}$$

Therefore, U_{μ_0} and $\mathbf{\Sigma}^{-1}(\mathbf{I} - \mathbf{H})\mathbf{Z}$ are independent of each other, and note that U_{μ_0} is independent of any measurable function of the elements of $\mathbf{\Sigma}^{-1}(\mathbf{I} - \mathbf{H})\mathbf{Z}$. Hence, this proves that U_{μ_0} and U_{τ_0} are statistically independent.

C.2 Proof of Independence between $U^2_{\mu_0}$ and U_{τ_0}

We could also prove that $U^2_{\mu_0}$ and U_{τ_0} are independent directly using results from quadratic form of norm random variables. The proof is based on the Craig's theorem (Craig, 1943). which says that X^TAX and X^TBX are independent if and only if $A\mathbf{\Sigma}B = 0$, given that $X \sim N(\mu, \mathbf{\Sigma})$. Therefore we only need to check whether $\Lambda_{\mu_0}\mathbf{\Sigma}\Lambda_{\tau_0} = 0$, where $\Lambda_{\mu_0} = \mathbf{\Sigma}^{-1}\mathbf{J}\mathbf{J}^T\mathbf{\Sigma}^{-1}$ and $\Lambda_{\tau_0} = (\mathbf{I} - \mathbf{H})\mathbf{\Sigma}^{-1}\mathbf{\Sigma}^{-1}(\mathbf{I} - \mathbf{H})$. Since we have

$$\begin{aligned} \Lambda_{\mu_0}\mathbf{\Sigma}\Lambda_{\tau_0} &= \mathbf{\Sigma}^{-1}\mathbf{J}\mathbf{J}^T\mathbf{\Sigma}^{-1}\mathbf{\Sigma}(\mathbf{I} - \mathbf{H})\mathbf{\Sigma}^{-1}\mathbf{\Sigma}^{-1}(\mathbf{I} - \mathbf{H}) \\ &= \mathbf{\Sigma}^{-1}\mathbf{J}\mathbf{J}^T(\mathbf{I} - \mathbf{H})\mathbf{\Sigma}^{-1}\mathbf{\Sigma}^{-1}(\mathbf{I} - \mathbf{H}) \\ &= \mathbf{\Sigma}^{-1}\mathbf{J}(\mathbf{J}^T - \mathbf{J}^T)\mathbf{\Sigma}^{-1}\mathbf{\Sigma}^{-1}(\mathbf{I} - \mathbf{H}) \\ &= \mathbf{0}, \end{aligned}$$

therefore $U^2_{\mu_0}$ and U_{τ_0} are independent.

C.3 Comparison of mixFisher and mixTippett

The difference between mixFisher and mixTippett can be better seen by comparing their rejection regions as in Web Figure S1. The point $(0.06, 0.06)$ can be detected by mixFisher but not mixTippett, while the point $(0.02, 0.8)$ can be detected by mixTippett but not mixFisher.

[Figure 1 about here.]

C.4 Graphical Comparison of Tests

In this section, we present the graphical comparison of the nine tests, since mixSD, mixVar and mixTippett were not presented in the main text. We can see that different tests have different rejection boundaries and hence have different favoring alternatives as shown in the Web Figure S2.

[Figure 2 about here.]

C.Simulation Studies

In this section, we report additional simulation results on the other three tests: mixVar, mixSD and mixTippett.

C.1 Type I Error Rates

We set $K = 4$ and the correlation matrix $\mathbf{\Sigma}$ to be exchangeable with $\rho = 0.1, 0.3, 0.5$ respectively. We generated 10^7 multivariate normal random samples with mean $\mathbf{0}$ and covariance matrix equal to $\mathbf{\Sigma}$ as summary statistics. Then we apply our proposed methods to obtain p-values for each sample. The type I error rates are estimated as the proportions of p-values that are less than the pre-specified significance levels. Web Table S1 shows that the type I error rates of our methods are well controlled at $\alpha = 0.05, 0.001$ and even at more stringent threshold 10^{-5} and 10^{-6}.

[Table 1 about here.]

C.2 Power Comparison

Under the same setup as in the main text, we consider the following factors of practical interests: signal sparsity, effect heterogeneity and the correlation structure. We also include MinP test defined as the minimum p-value among the K marginal p-values (Conneely and Boehnke, 2007) and the traditional Wald test $\mathbf{Z}^T\mathbf{\Sigma}^{-1}\mathbf{Z}$ for comparison purpose.

We first consider $K = 3$, mimicking the blood lipids GWAS data conducted by the Global Lipids Genetics Consortium (Teslovich et al., 2010) (by excluding TC since LDL and TC are highly correlated). We consider two correlation matrices: $\mathbf{\Sigma}_1$ is a 3×3 exchangeable correlation matrix with off-diagonal element $\rho = 0.5$ and $\mathbf{\Sigma}_2$ is an unstructured correlation matrix estimated from the summary statistics in the lipids GWAS data

$$\mathbf{\Sigma}_2 = \begin{pmatrix} 1.00 & -0.08 & -0.42 \\ -0.08 & 1.00 & 0.27 \\ -0.42 & 0.27 & 1.00 \end{pmatrix}. \tag{1}$$

We considered the following five alternatives for $K = 3$: $\boldsymbol{\mu}_1 = (2, 2, 2)^T$ with ℓ^2-norm $||\boldsymbol{\mu}_1|| = 3.46$, $\boldsymbol{\mu}_2 = (1.2, 1.2, 1.2)^T$ with $||\boldsymbol{\mu}_2|| = 2.08$, $\boldsymbol{\mu}_3 = (1.63, -0.82, -0.82)^T$ with $||\boldsymbol{\mu}_3|| = 2$ (the third eigenvector direction of $\mathbf{\Sigma}_1$), $\boldsymbol{\mu}_4 = (-1.21, 0.64, -1.46)^T$ with $||\boldsymbol{\mu}_4|| = 2$ (the third eigenvector direction of $\mathbf{\Sigma}_2$), $\boldsymbol{\mu}_5 = (2.38, -1.72, -2.72)^T$ with $||\boldsymbol{\mu}_5|| = 4$ (the first eigenvector direction of $\mathbf{\Sigma}_2$).

We generated $10,000$ multivariate normal random samples with means equal to these five alternatives with one of the two correlation matrices. The power is estimated as the proportions of p-values that are less than pre-specified significance level $\alpha = 0.05$. We summarize the results in the Web Table S2.

As expected, the SUM test has the largest power for homogeneous effects $\boldsymbol{\mu}_1$ and $\boldsymbol{\mu}_2$, regardless of the correlation structures. In these two settings, there exist only shared group

effects, so mixTippett is slightly more powerful than mixFisher. Since there exist a strong signal in $\boldsymbol{\mu}_1$, so MinP also has good power. But the signal gets weaker in $\boldsymbol{\mu}_2$, so MinP has lower power accordingly.

The VC test has the largest power when the mean vectors are on the directions of the last eigenvectors of the correlation matrices. For the alternative $\boldsymbol{\mu}_3$, the SUM test is almost powerless, indicating that there is no shared group effect. Therefore, mixTippett is slightly more powerful than mixFisher. The first signal of $\boldsymbol{\mu}_3$ is relatively strong, so MinP also has some power. For the alternative $\boldsymbol{\mu}_4$, the SUM test has power about 0.48, suggesting that there exist both shared group effect and individual heterogeneous effect. This well explains why mixFisher is more powerful than mixTippett. There is no single strong signal in $\boldsymbol{\mu}_4$, so MinP has low power.

When the mean is $\boldsymbol{\mu}_5$ and the correlation matrix is $\boldsymbol{\Sigma}_2$, both SUM and VC perform poorly since this is not their favoring alternative. It might be surprising that MinP performs better than others in this setting where a genetic variant affects all the phenotypes. This is because the third element of $\boldsymbol{\mu}_5$ is a very strong signal, which explains why MinP has very high power. Since $\boldsymbol{\mu}_5$ is heterogeneous, so U_{τ_0} (not VC) can well detect it. The SUM test has low power but is not powerless, so it still indicates the existence of weak shared group effect.

[Table 2 about here.]

We then consider the setting where a genetic variant affects only one phenotype. For both the exchangeable correlation matrix $\boldsymbol{\Sigma}_1$ and unstructured correlation matrix $\boldsymbol{\Sigma}_2$, we consider the following mean vectors for $\boldsymbol{Z}$: $(2.5, 0, 0)^T$, $(0, 2.5, 0)^T$, $(0, 0, 2.5)^T$. The results are summarized in the Web Figure S3. The power of each test for the three means stay the same when the correlation matrix is exchangeable but changes when the correlation matrix is unstructured, with an exception of the MinP test. We surprisingly found that MinP test can be less powerful than VC, Wald and mix-type tests when there is only one signal.

[Figure 3 about here.]

D.Re-analysis of Global Lipids GWAS Data

To illustrate our proposed tests, we applied them to the global lipids GWAS summary statistics data set. We reported the number of additional significant SNPs identified by various tests before and after LD pruning in the main test, here we present additional Venn diagrams to demonstrate the connections and differences of those tests in Figure S4 and Figure S5. After LD pruning, the SNPs represent independent signals as in Figure S5. Every test can identify some independent loci that other tests cannot identify, this is consistent with the theoretical results that there is no UMP test.

[Figure 4 about here.]

[Figure 5 about here.]

Figure S6 shows the QQ plots of the p-values of the four lipids traits in the summary statistics data set. There are in total 5395 genome-wide significant SNPs that are associated with at least one of the four traits, and the p-values of many SNPs are highly significant. Those p-values are after genomic control correction and the genomic inflation factors are all equal to 1. In Figure S7 and S8, we present QQ plots of the p-values of various tests included in this paper. The genomic inflation factors of those tests were not inflated. Figures S9 - S16 are the Manhattan plots of the p-values of various tests, where the green points represent the additional SNPs identified by the corresponding multivariate test. Table S3 presents the p-values of other multivariate tests, providing complementary information to the Table 3 in the main text.

Table S4 presents analysis results of 5 SNPs as an example to illustrate the consequences when TC is included in the joint analysis in addition to HDL, LDL and TG. SNP rs11669173 located in gene CLPTM1 on chromosome 19 has p-value of 2.01×10^{-16} using mixFisher

test. After including TC, the p-value of SNP rs11669173 using mixFisher test is not genome-wide significant ($p = 1.64 \times 10^{-6}$), which might be explained that TC is not adding any information and the removal of TC can help better detect the signal. While SNP rs874743 in gene RELB on chromosome 19 becomes genome-wide significant after including TC using mixFisher test, which might be due to the fact that the last eigevalue is very small (0.05) and joint analysis with TC included might produce a false positive SNP. Therefore, removing TC should provide more robust results. For SNPs rs5167, rs3094228 and rs474339, they remain genome-wide significant even after including TC into the joint analysis even if the three p-values of those three SNPs show suggestive evidence associated with TC, removing TC does not eliminate the signals because TC does not provide much extra information once we have information on HDL, LDL and TG. In practice, we suggest to pay special attention to those highly-correlated phenotypes before performing joint analysis of them. However, to the best of our knowledge, there is no principled way of determining the cut-off point for defining "high correlation". Substantive knowledge about those phenotypes can provide expert insights on the choice of proper phenotypes to be included in the joint analysis.

[Figure 6 about here.]

[Figure 7 about here.]

[Figure 8 about here.]

[Figure 9 about here.]

[Figure 10 about here.]

[Figure 11 about here.]

[Figure 12 about here.]

[Figure 13 about here.]

[Figure 14 about here.]

[Figure 15 about here.]

[Figure 16 about here.]

[Table 3 about here.]

[Table 4 about here.]

References

Conneely, K. N. and Boehnke, M. (2007). So many correlated tests, so little time! rapid adjustment of p values for multiple correlated tests. *Am J Hum Genet* **81,** 1158–68.

Craig, A. T. (1943). Note on the independence of certain quadratic forms. *The Annals of Mathematical Statistics* **14,** 195–197.

Teslovich, T. M., Musunuru, K., Smith, A. V., Edmondson, A. C., Stylianou, I. M., Koseki, M., Pirruccello, J. P., Ripatti, S., Chasman, D. I., Willer, C. J., et al. (2010). Biological, clinical and population relevance of 95 loci for blood lipids. *Nature* **466,** 707–713.

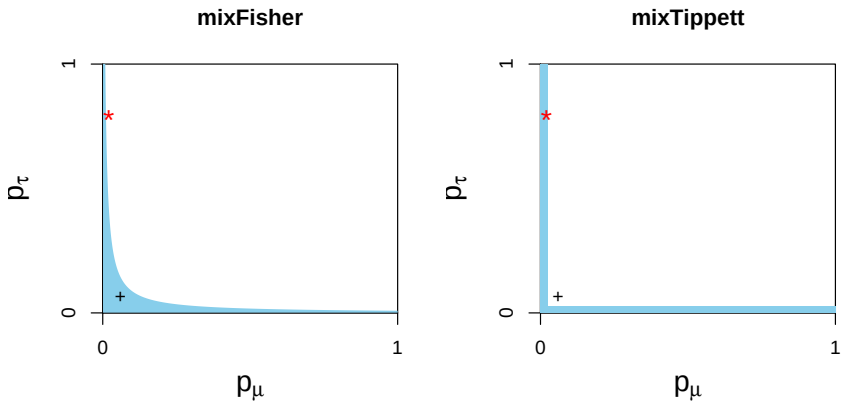


Figure S1. This figure depicts the difference between the rejection regions (shaded areas) of mixFisher and mixTippett at significance level 0.05. The point "+" is $(0.06, 0.06)$ and the point "*" is $(0.02, 0.8)$.

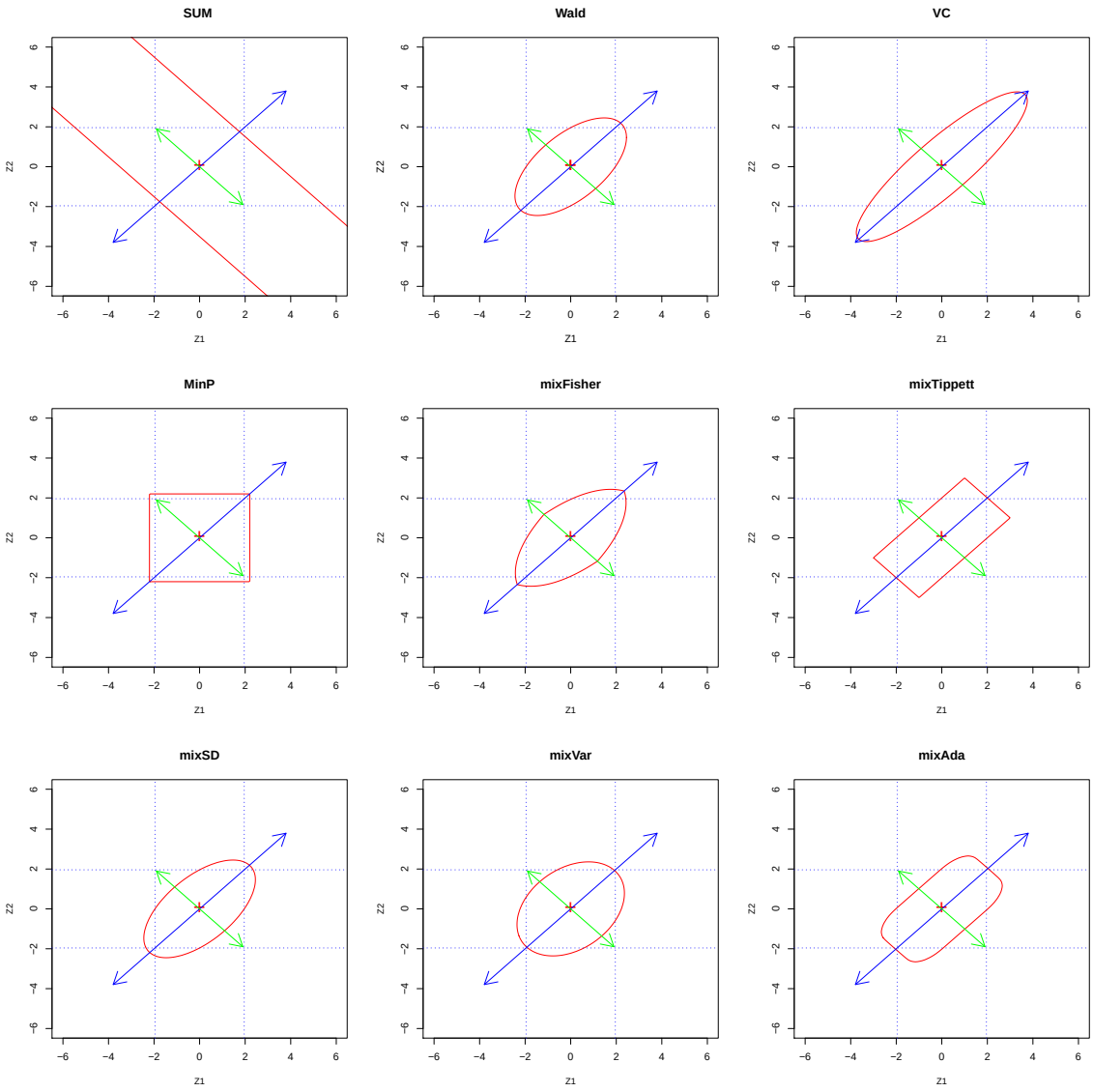


Figure S2. The rejection boundaries (red solid lines or curves) of the nine tests (SUM, VC, mixVar, mixSD, mixAda, mixFisher, mixTippett, Wald and MinP) at the significance level 0.05 for a bivariate normal $\mathbf{Z} = (Z_1, Z_2)^T$ with correlation $\rho = 0.6$ under the null. The blue solid lines with arrows represents the direction where $\mathbf{Z}$ has the largest variation and the green solid lines with arrows represents the direction (orthogonal to blue solid lines) where $\mathbf{Z}$ has the second largest variation under the null. The dotted blue lines mark the univariate critical values at ± 1.96 for Z_1 and Z_2 respectively.

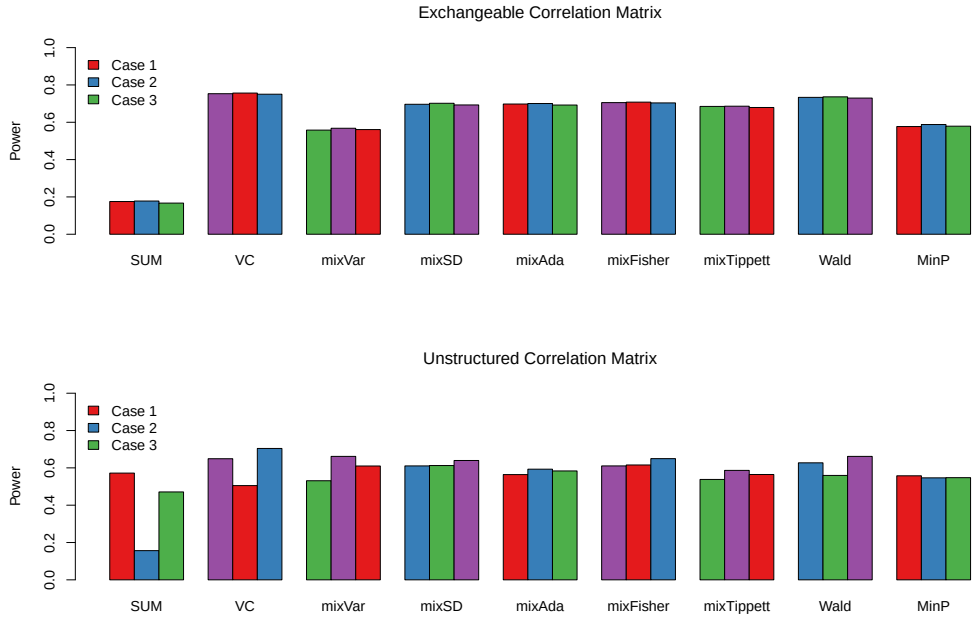


Figure S3. Powers of the tests when a genetic variant affects only one of the three phenotypes. Case j ($j = 1, \cdots, 3$) refers to the case whether a genetic variant has an effect on the jth phenotype, i.e., the jth element of the mean vector $\boldsymbol{\mu}$ is non-zero. The upper panel is for the exchangeable correlation matrix and the lower panel is for the unstructured correlation matrix, both with the non-zero value of the mean vector equal to 2.5.

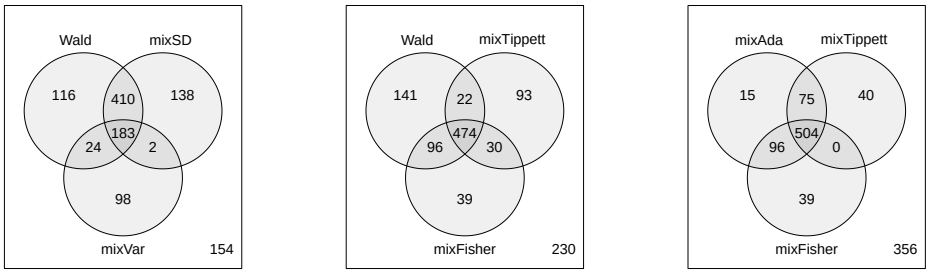


Figure S4. Venn diagram for the number of significant SNPs from the joint analysis of HDL, LDL and TG before LD pruning.

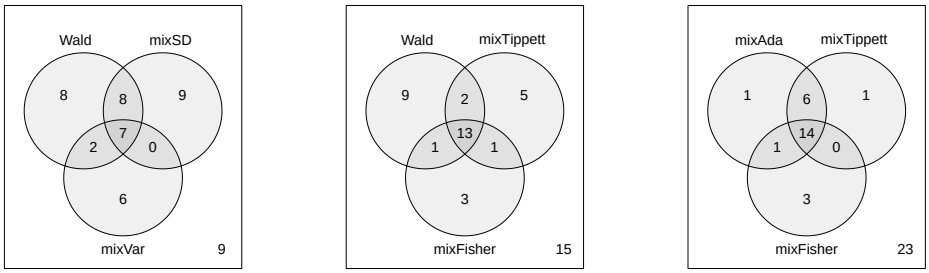
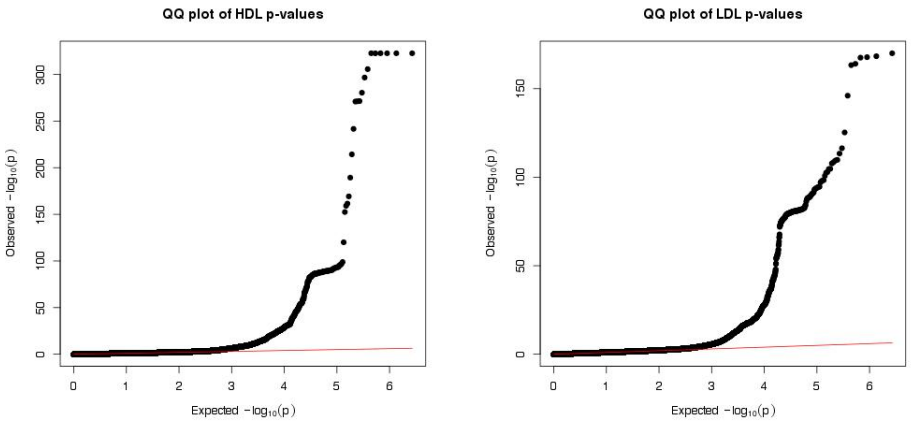
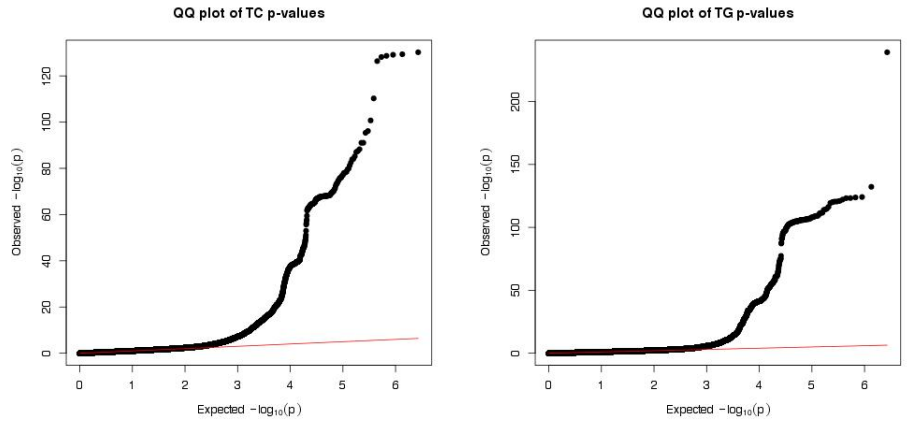


Figure S5. Venn diagram for the number of significant SNPs from the joint analysis of HDL, LDL and TG after LD pruning.



(a) QQ Plot of HDL p-values

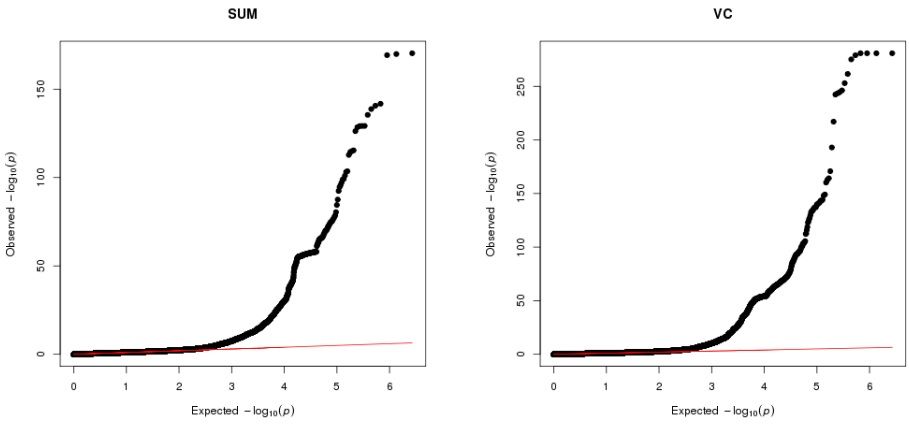
(b) QQ Plot of LDL p-values



(c) QQ Plot of TC p-values

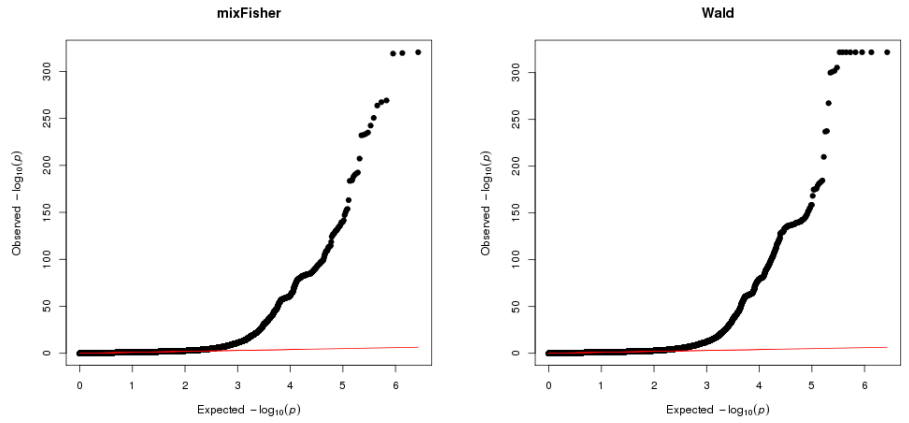
(d) QQ Plot of TG p-values

Figure S6. QQ plots of the p-values of the four lipids. The genomic inflation factors are all equal to 1 since the p-values for the four traits are after genomic control correction already in the public available summary statistics data set.



(a) QQ Plot of the SUM p-values

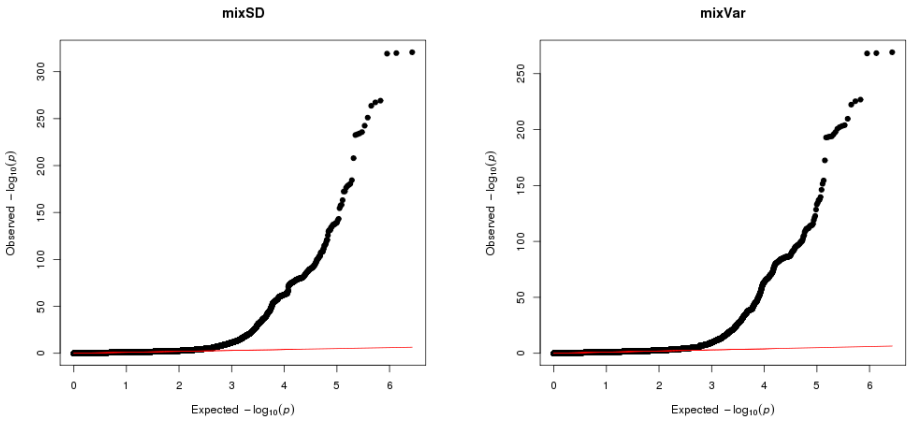
(b) QQ Plot of the VC p-values



(c) QQ Plot of the mixFisher p-values

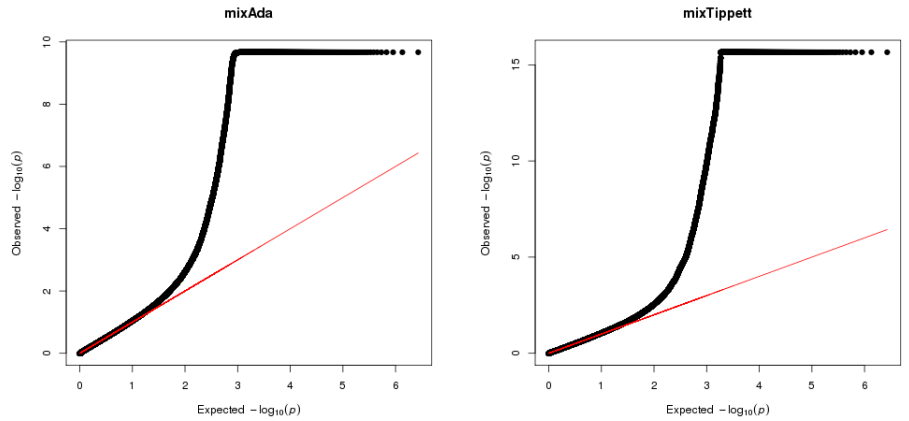
(d) QQ Plot of the Wald p-values

Figure S7. QQ plots of the p-values of the SUM, VC, mixFisher and Wald tests and their genomic inflation factors are 0.98,0.99,0.99 and 0.99 respectively.



(a) QQ Plot of the mixSD p-values

(b) QQ Plot of the mixVar p-values



(c) QQ Plot of the mixAda p-values

(d) QQ Plot of the mixTippett p-values

Figure S8. QQ plots of the p-values of the mixSD, mixVar, mixAda and mixTippett tests and their genomic inflation factors are 0.99,0.99,1.1 and 0.99 respectively. Due to R computing precision, the p-values of mixAda and mixTippett are truncated after certain thresholds.

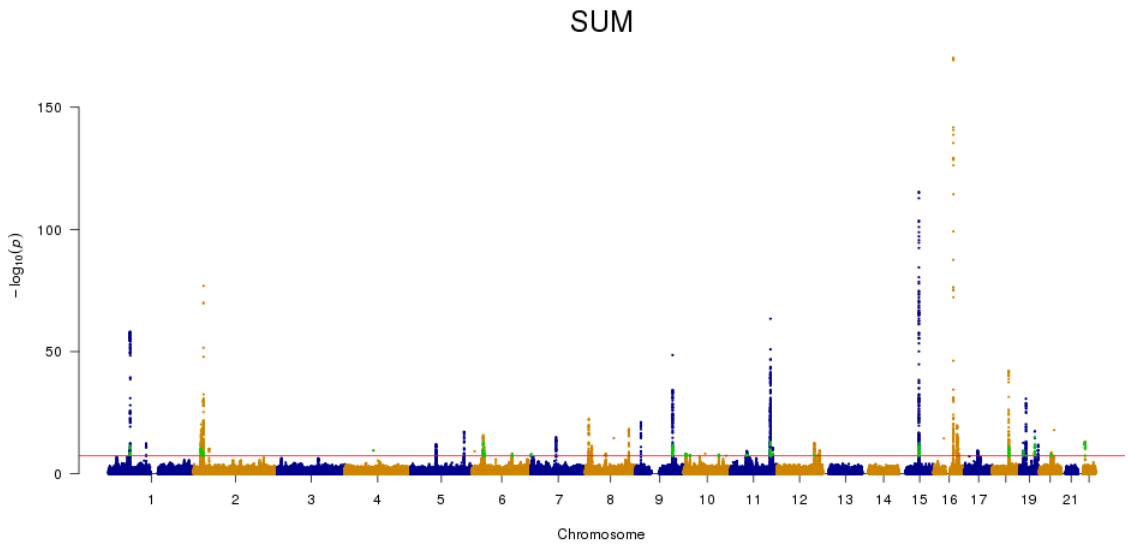


Figure S9. Manhattan plot of the p-values of the SUM test.The green points represent additional SNPs identified by the SUM test.

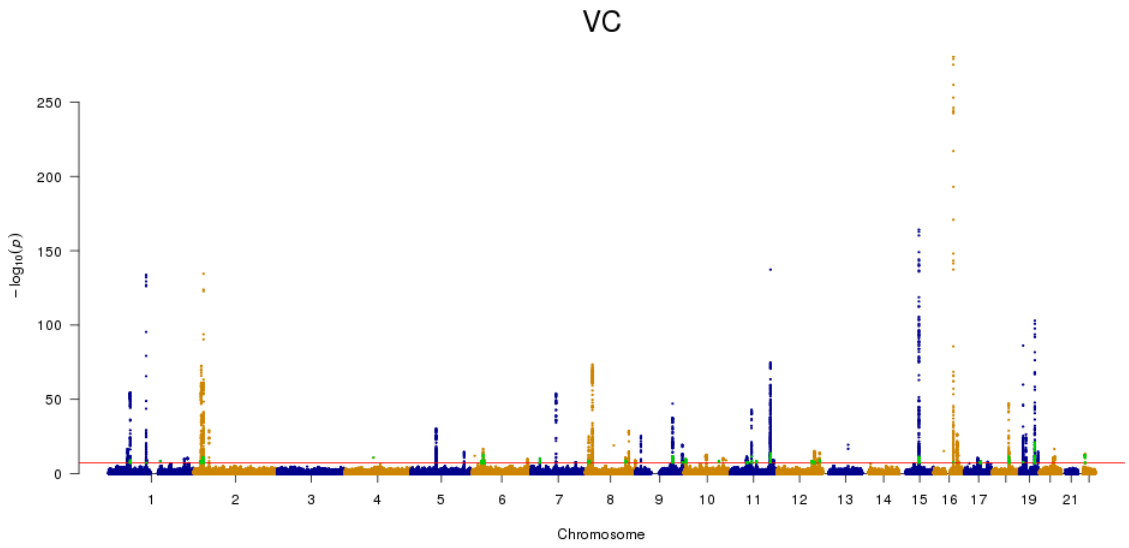


Figure S10. Manhattan plot of the p-values of the VC test.The green points represent additional SNPs identified by the VC test.

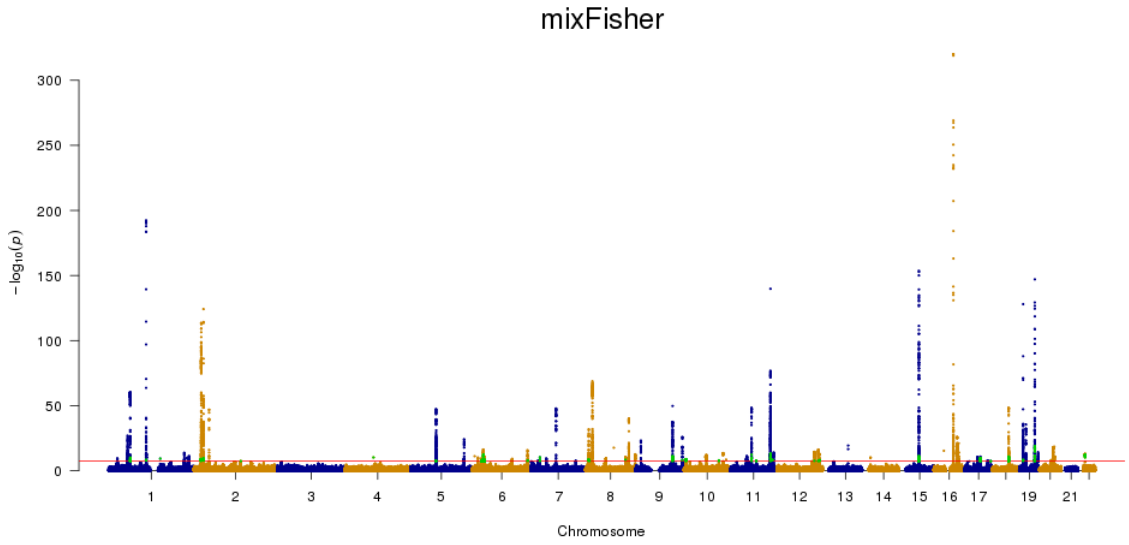


Figure S11. Manhattan plot of the p-values of the mixFisher test. The green points represent additional SNPs identified by the mixFisher test.

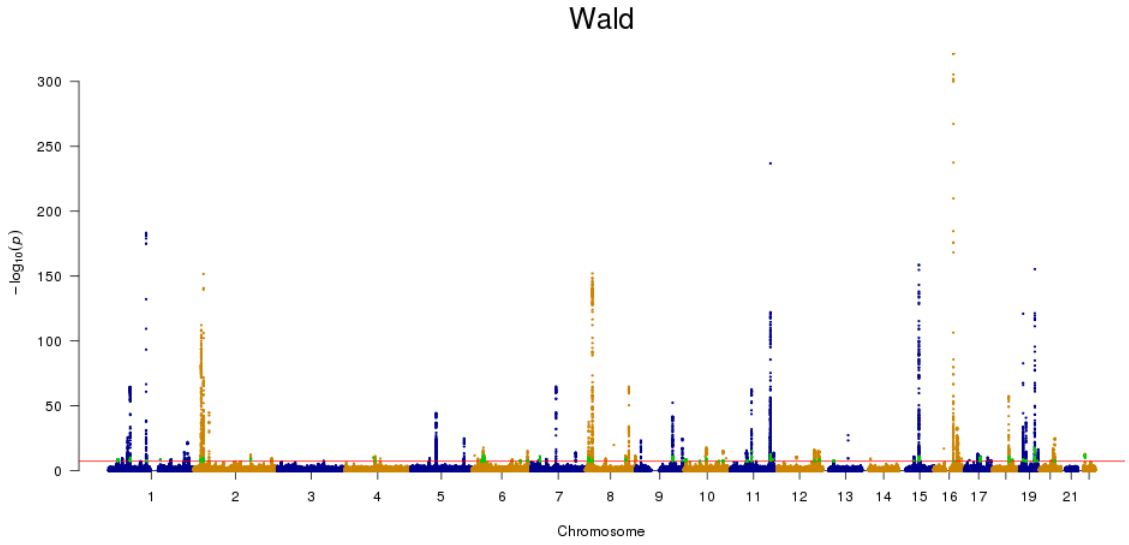


Figure S12. Manhattan plot of the p-values of the Wald test. The green points represent additional SNPs identified by the Wald test.

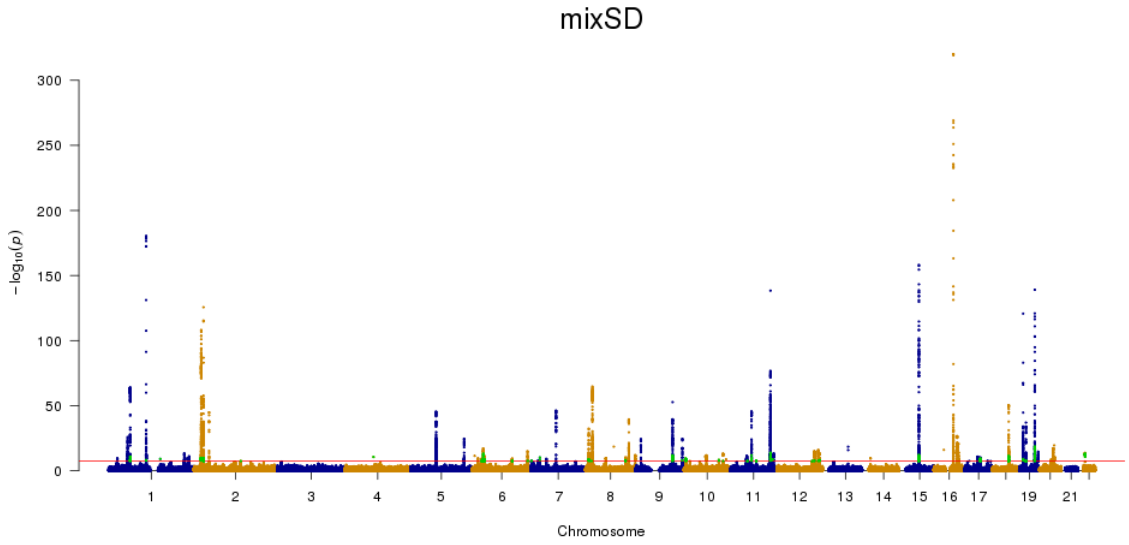


Figure S13. Manhattan plot of the p-values of the mixSD test. The green points represent additional SNPs identified by the mixSD test.

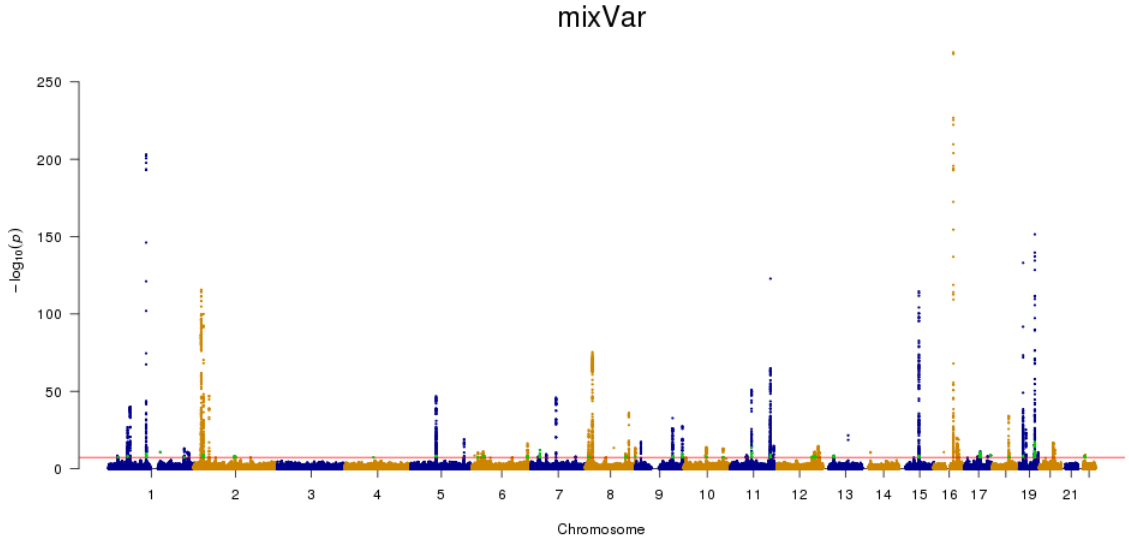


Figure S14. Manhattan plot of the p-values of the mixVar test. The green points represent additional SNPs identified by the mixVar test.

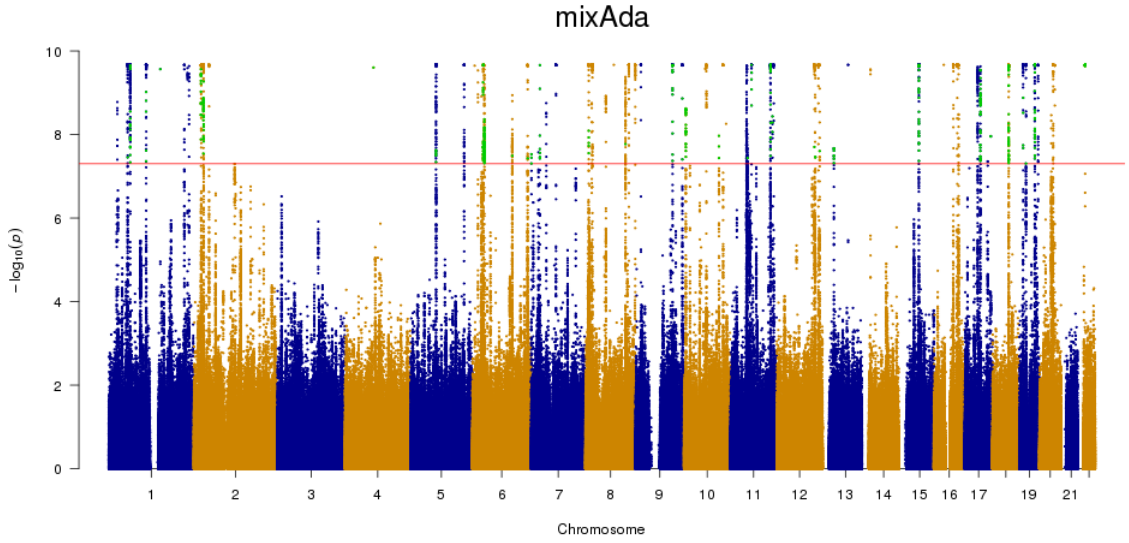


Figure S15. Manhattan plot of the p-values of the mixAda test. The green points represent additional SNPs identified by the mixAda test.

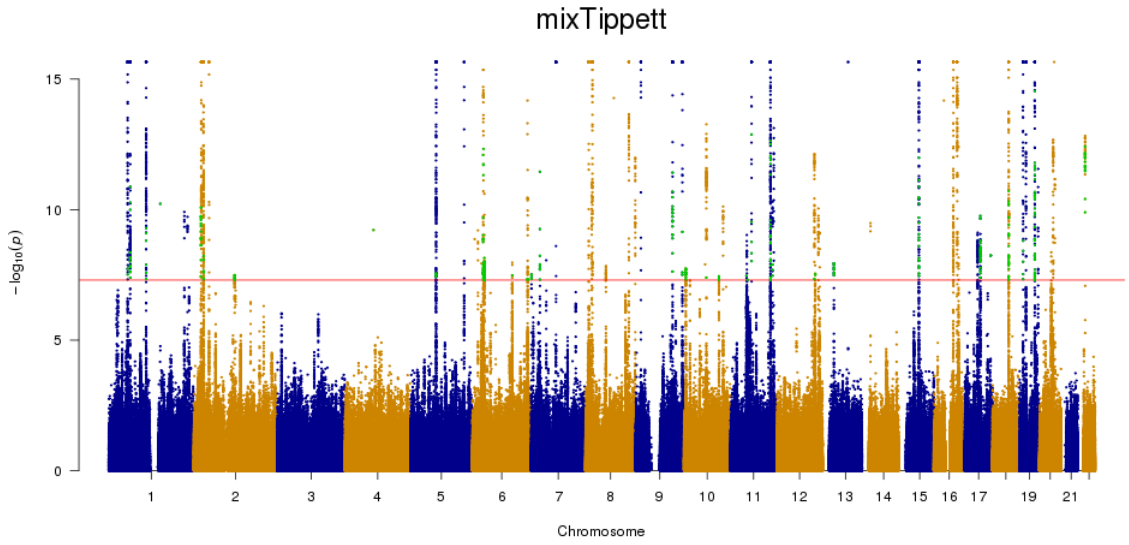


Figure S16. Manhattan plot of the p-values of the mixTippett test. The green points represent additional SNPs identified by the mixTippett test.

Table S1

Type I error estimates of the proposed methods. Each entry represents the type I error estimates as the proportions of p-values less than α under the null hypothesis based on 10^7 simulations. The correlation matrix is exchangeable with off-diagonal element equal to ρ.

K	ρ	α	SUM	VC	mixVar	mixSD	mixAda	mixFisher	mixTippett
4	0.1	0.05	0.049	0.049	0.049	0.049	0.049	0.050	0.050
4	0.3	0.05	0.049	0.050	0.048	0.049	0.049	0.050	0.049
4	0.5	0.05	0.049	0.049	0.049	0.049	0.050	0.049	0.049
4	0.1	10^{-3}	1.0×10^{-3}	1.0×10^{-3}	1.0×10^{-3}	1.0×10^{-3}	1.0×10^{-3}	1.0×10^{-3}	1.0×10^{-3}
4	0.3	10^{-3}	1.0×10^{-3}	1.0×10^{-3}	1.0×10^{-3}	1.0×10^{-3}	1.0×10^{-3}	1.0×10^{-3}	1.0×10^{-3}
4	0.5	10^{-3}	9.9×10^{-3}	1.0×10^{-3}	1.0×10^{-3}	1.0×10^{-3}	1.0×10^{-3}	1.0×10^{-3}	1.0×10^{-3}
4	0.1	10^{-5}	8.4×10^{-6}	8.8×10^{-6}	1.02×10^{-5}	7.7×10^{-6}	8.8×10^{-6}	9.6×10^{-6}	7.5×10^{-6}
4	0.3	10^{-5}	9.1×10^{-6}	8.1×10^{-6}	9.1×10^{-6}	7.2×10^{-6}	9.2×10^{-6}	9.8×10^{-6}	7.6×10^{-6}
4	0.5	10^{-5}	9.3×10^{-6}	6.6×10^{-6}	8.6×10^{-6}	8.3×10^{-6}	9.5×10^{-6}	9.4×10^{-6}	9.6×10^{-6}
4	0.1	10^{-6}	8.3×10^{-7}	8.7×10^{-7}	1.01×10^{-6}	7.8×10^{-7}	8.8×10^{-6}	9.5×10^{-7}	7.5×10^{-7}
4	0.3	10^{-6}	9.2×10^{-7}	8.2×10^{-7}	9.2×10^{-7}	7.3×10^{-7}	9.2×10^{-6}	9.5×10^{-7}	7.7×10^{-7}
4	0.5	10^{-6}	9.3×10^{-7}	6.7×10^{-7}	8.7×10^{-7}	8.4×10^{-7}	9.4×10^{-6}	9.2×10^{-7}	9.3×10^{-7}

Table S2

Power comparisons from simulation studies. Each entry represents the empirical power estimated as the proportions of p-values less than $\alpha = 0.05$ under the specified alternatives based on 10^4 replications. When $K = 2$, the correlation is set to be $0.1, 0.5, 0.8$. Three phenotypes $K = 3$, $\mathbf{\Sigma}_1$ is exchangeable with off-diagonal element $\rho = 0.5$ and $\mathbf{\Sigma}_2$ is unstructured and specified in the main text. In the last row, we set $K = 100$ and $\mathbf{\Sigma}_3$ to be exchangeable with off-diagonal element $\rho = 0.2$.

$\boldsymbol{\mu}^T$	$\mathbf{\Sigma}$	SUM	VC	mixVar	mixSD	mixAda	mixFisher	mixTippett	Wald	MinP
$(1, -1)$	0.1	0.05	0.27	0.29	0.24	0.24	0.24	0.23	0.24	0.22
$(1, -1)$	0.5	0.05	0.54	0.36	0.44	0.44	0.43	0.44	0.44	0.24
$(1, -1)$	0.8	0.06	0.91	0.34	0.82	0.84	0.81	0.83	0.82	0.25
$(2.0, 2.0, 2.0)$	$\mathbf{\Sigma}_1$	0.68	0.13	0.66	0.59	0.59	0.57	0.59	0.52	0.61
$(1.2, 1.2, 1.2)$	$\mathbf{\Sigma}_2$	0.67	0.52	0.41	0.56	0.57	0.55	0.57	0.50	0.33
$(1.63, -0.82, -0.82)$	$\mathbf{\Sigma}_1$	0.05	0.70	0.41	0.59	0.62	0.60	0.62	0.65	0.34
$(-1.21, 0.64, -1.46)$	$\mathbf{\Sigma}_2$	0.48	0.74	0.64	0.67	0.63	0.68	0.61	0.62	0.33
$(2.38, -1.72, -2.72)$	$\mathbf{\Sigma}_2$	0.11	0.48	0.61	0.51	0.51	0.51	0.51	0.78	0.80
$(1.4, \ldots, 1.4, 1.4)$	$\mathbf{\Sigma}_3$	0.87	0.05	0.80	0.86	0.0.80	0.79	0.81	0.15	0.64

Table S3

Top ten SNPs based on the P-value of mixFisher method in the joint analysis of HDL, LDL and TG.

SNP	P_{SUM}	P_{VC}	P_{mixVar}	P_{mixSD}	$P_{mixTippett}$	$P_{mixFisher}$	P_{mixAda}	P_{Wald}
rs5167	1.43E-15	1.77E-16	4.75E-11	1.25E-16	2.89E-15	7.45E-16	2.15E-10	3.33E-15
rs3095326	8.43E-14	1.56E-12	1.06E-08	1.07E-13	1.69E-13	8.10E-13	2.15E-10	1.57E-12
rs2777802	3.77E-11	2.54E-12	2.06E-08	4.30E-12	7.54E-11	1.21E-11	2.20E-10	3.38E-11
rs3786248	2.94E-11	3.30E-12	2.28E-08	4.13E-12	5.87E-11	1.22E-11	2.20E-10	1.98E-11
rs267733	6.77E-01	3.48E-09	1.84E-11	9.03E-10	5.97E-11	5.18E-10	2.72E-10	1.96E-09
rs17134601	1.48E-08	2.39E-10	2.90E-07	8.68E-10	2.96E-08	1.48E-09	2.64E-09	2.52E-09
rs2278426	7.75E-10	1.39E-08	7.24E-06	1.01E-09	1.55E-09	3.50E-09	1.32E-09	1.93E-09
rs11216321	6.93E-09	3.53E-09	7.08E-06	2.87E-09	1.39E-08	6.43E-09	5.27E-09	3.58E-09
rs2304684	2.65E-06	8.53E-10	2.36E-07	9.96E-09	5.30E-06	1.05E-08	5.42E-08	4.90E-09
rs13195279	2.12E-04	1.04E-08	1.65E-07	6.41E-08	1.33E-05	3.01E-08	1.88E-07	3.14E-08

Table S4

Comparison of the Analysis with and without TC included, where suffix M3 denotes the joint analysis of HDL, LDL and TG, and suffix M4 denotes the joint analysis of HDL, LDL, TG and TC.

SNP	CHR	Gene	P_{HDL}	P_{LDL}	P_{TG}	P_{TC}	$P_{mixFisherM3}$	$P_{mixFisherM4}$
rs11669173	19	CLPTM1	1.74E-04	9.31E-03	3.92E-05	9.23E-01	2.01E-16	**1.64E-06**
rs5167	19	APOC2	1.51E-06	7.41E-02	2.68E-05	3.91E-05	7.45E-16	1.51E-13
rs3094228	6	HCP5	1.33E-03	3.91E-02	2.38E-07	1.10E-07	6.53E-14	1.53E-12
rs474339	11	STDT2	3.62E-03	3.54E-02	5.49E-08	7.29E-05	6.79E-14	2.08E-12
rs874743	19	RELB	1.71E-02	8.03E-01	5.51E-04	7.00E-01	**2.60E-07**	1.64E-12