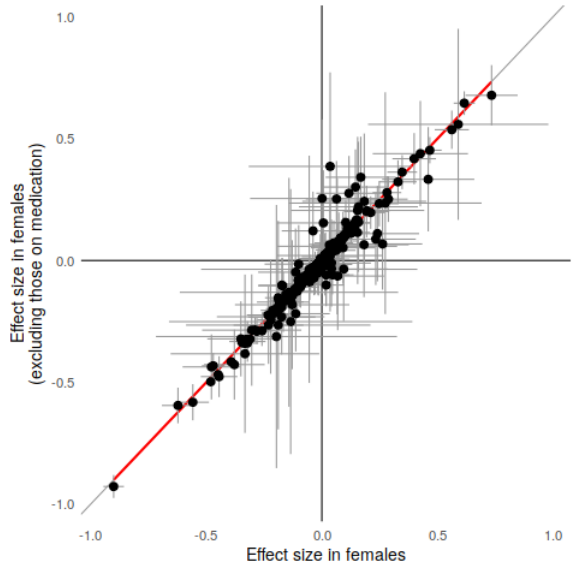
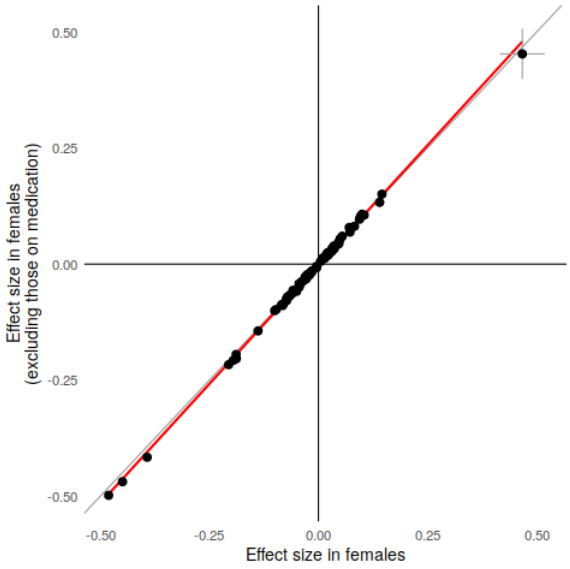
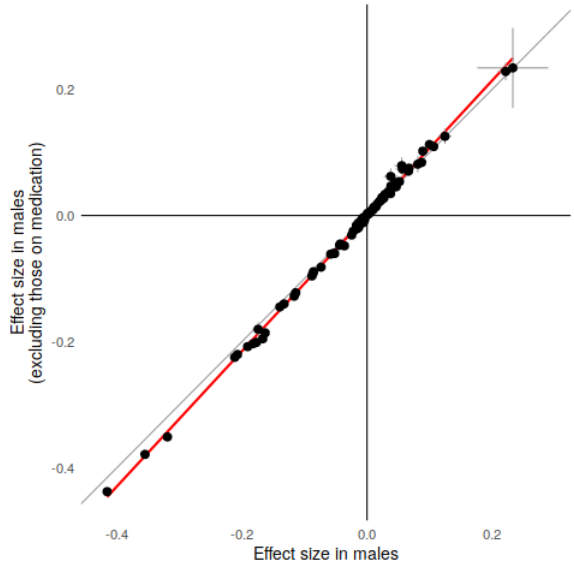
A. Females (all index variants)



B. Females (only variants with significant difference by sex)



C. Males (all index variants)



D. Males (only variants with significant difference by sex)

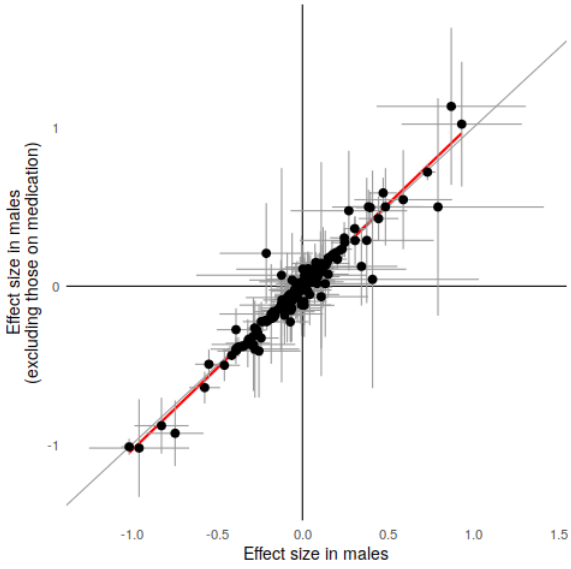


Figure S10. Comparison of effect sizes for trans-ancestry index variants excluding cholesterol-lowering medication. Grey lines show the y=x diagonal while red lines are from linear regression. Effect sizes were slightly larger after excluding individuals on cholesterol-lowering medication.

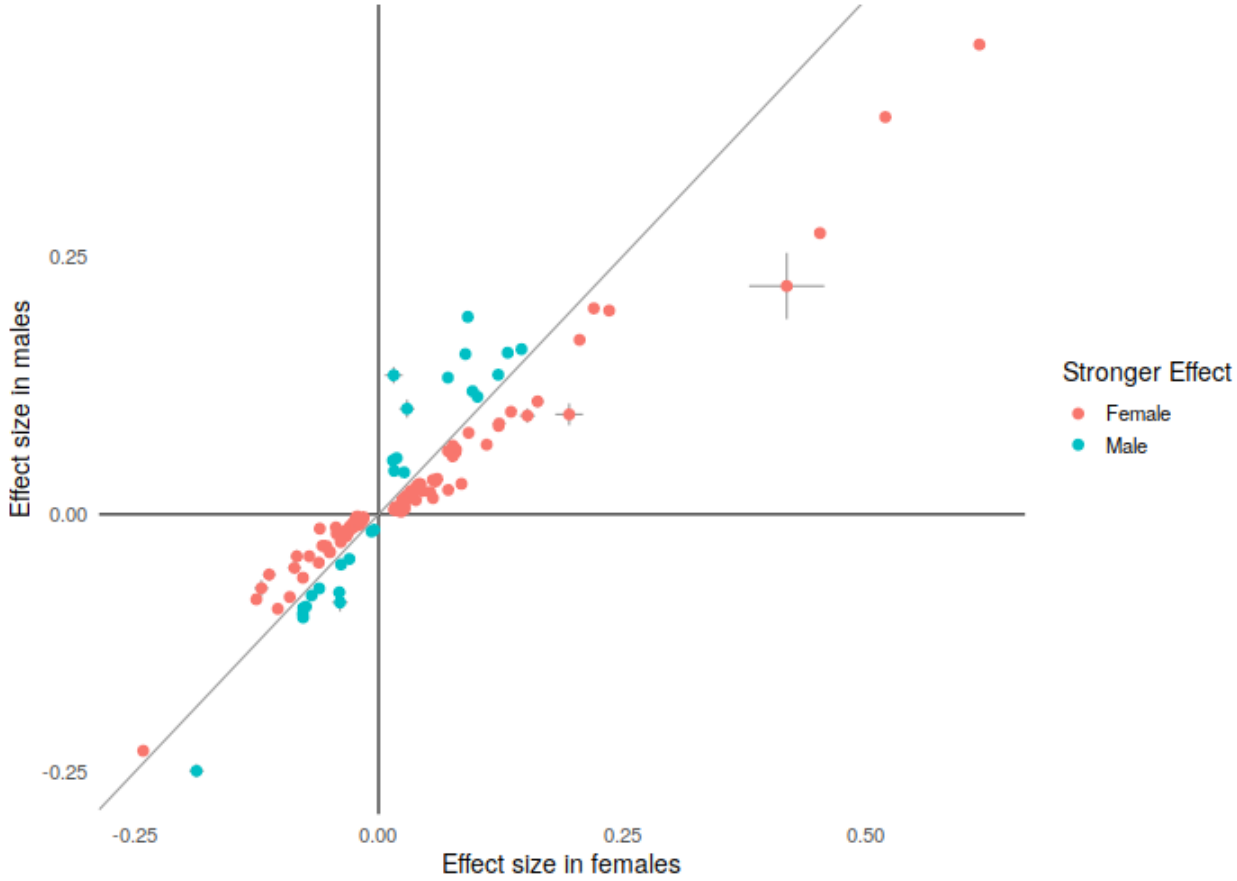


Figure S9. **Comparison of effect size estimates between males and females for index variants showing a significant difference in effect size between sexes.** Effect size estimates are from trans-ancestry meta-analysis in each sex and were more often stronger in females relative to males.

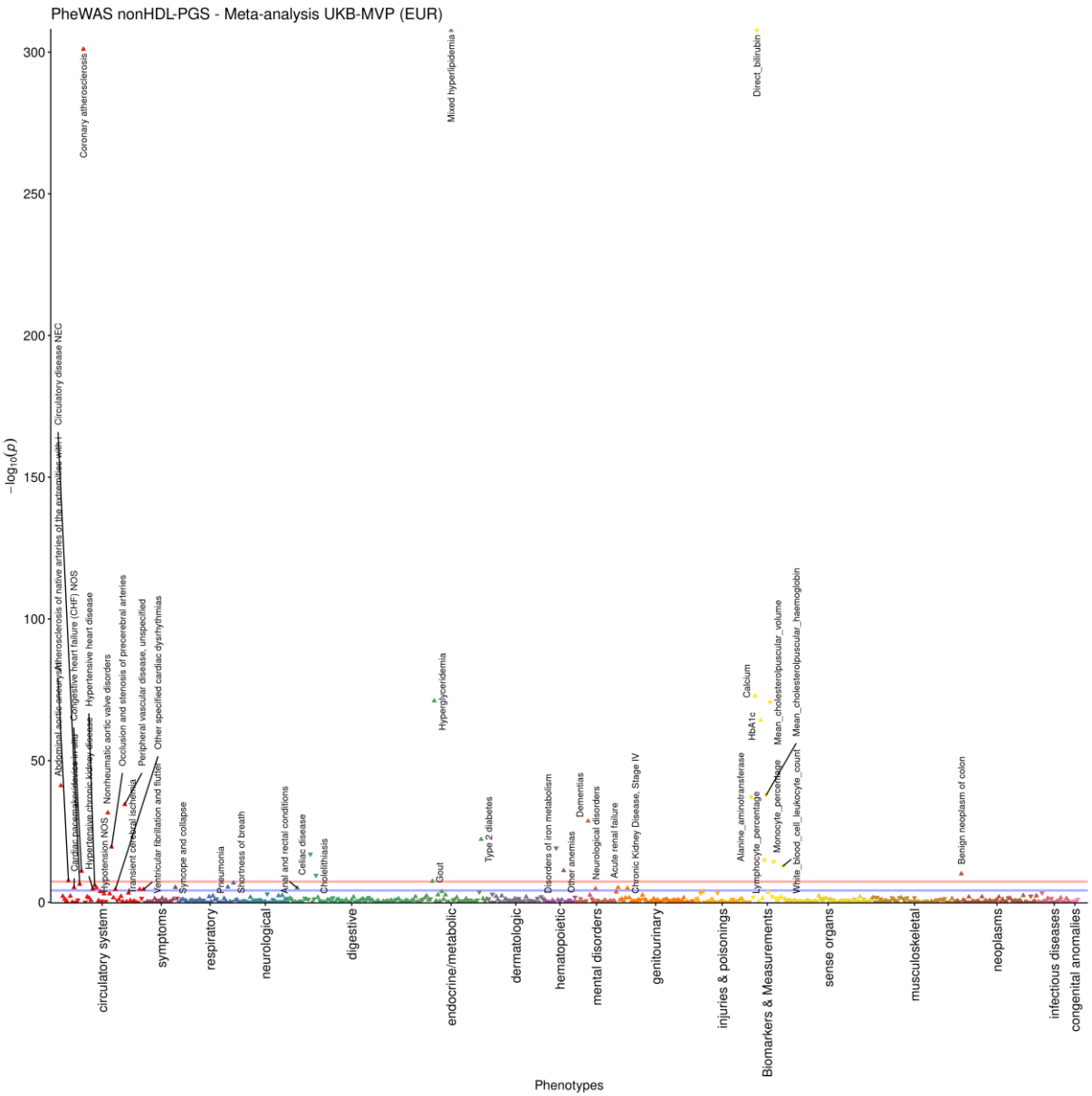


Figure S8. **PheWAS meta-analysis results for the trans-ethnic nonHDL-C PGS in UK Biobank and MVP.** The blue horizontal line denotes phenome-wide significance ($p<=6.5x10^{-05}$) and the red line is genome-wide significance ($p<=5x10^{-08}$). Phenotypes have been pruned, so that the most significant one per correlated phenotype group (correlation coefficient > 0.2) is retained. Pairwise correlations were estimated with chi-square test and Cramer's V for the dichotomous phenotypes and Pearson's correlation for the continuous phenotypes. Full phenome-wide significant results are presented in **Additional file 12: Table S8**.

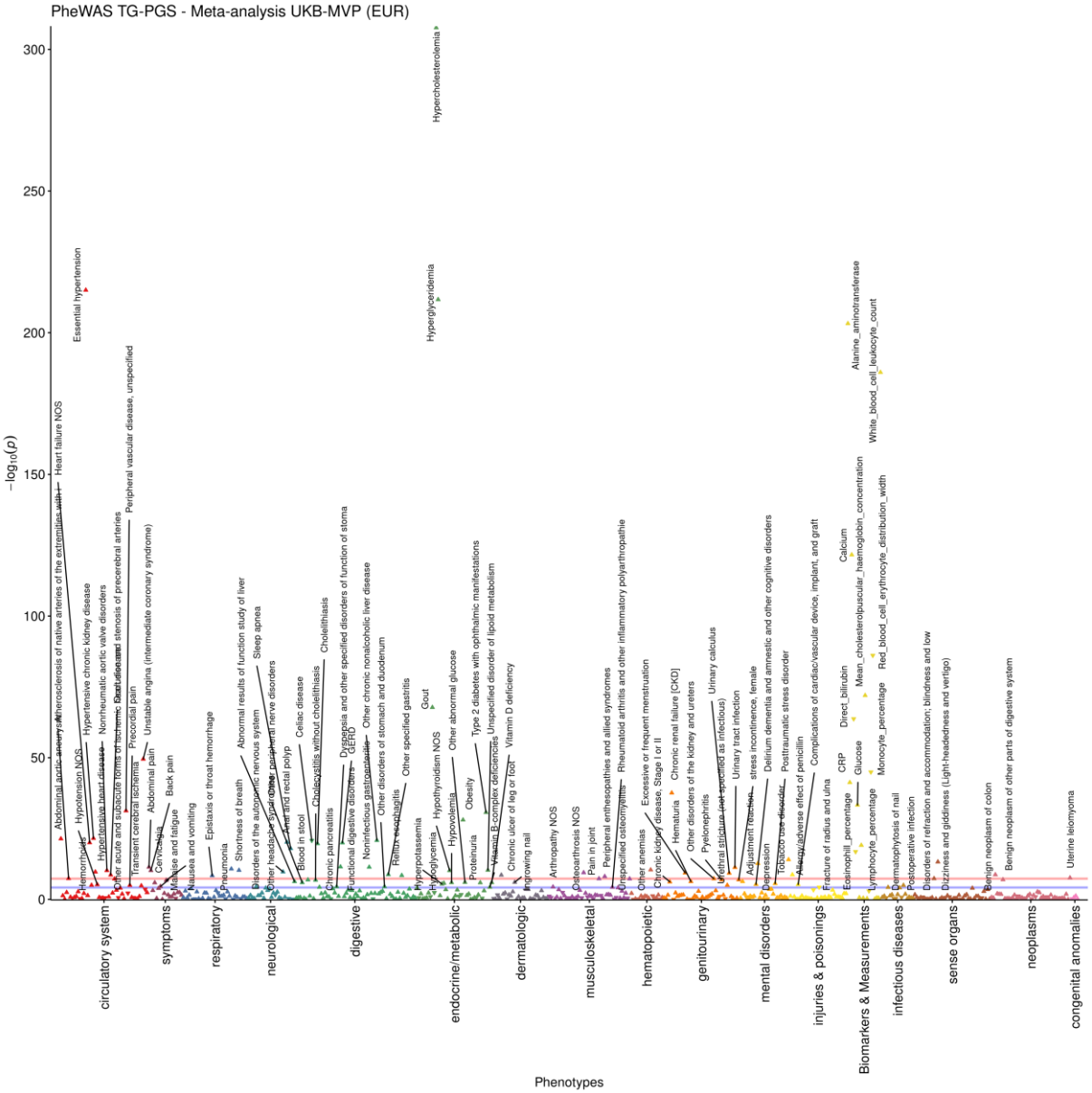


Figure S7. **PheWAS meta-analysis results for the trans-ethnic TG PGS in UK Biobank and MVP.** The blue horizontal line denotes phenome-wide significance ($p<=6.5x10^{-05}$) and the red line is genome-wide significance ($p<=5x10^{-08}$). Phenotypes have been pruned, so that the most significant one per correlated phenotype group (correlation coefficient > 0.2) is retained. Pairwise correlations were estimated with chi-square test and Cramer's V for the dichotomous phenotypes and Pearson's correlation for the continuous phenotypes. Full phenome-wide significant results are presented in **Additional file 12: Table S8**.

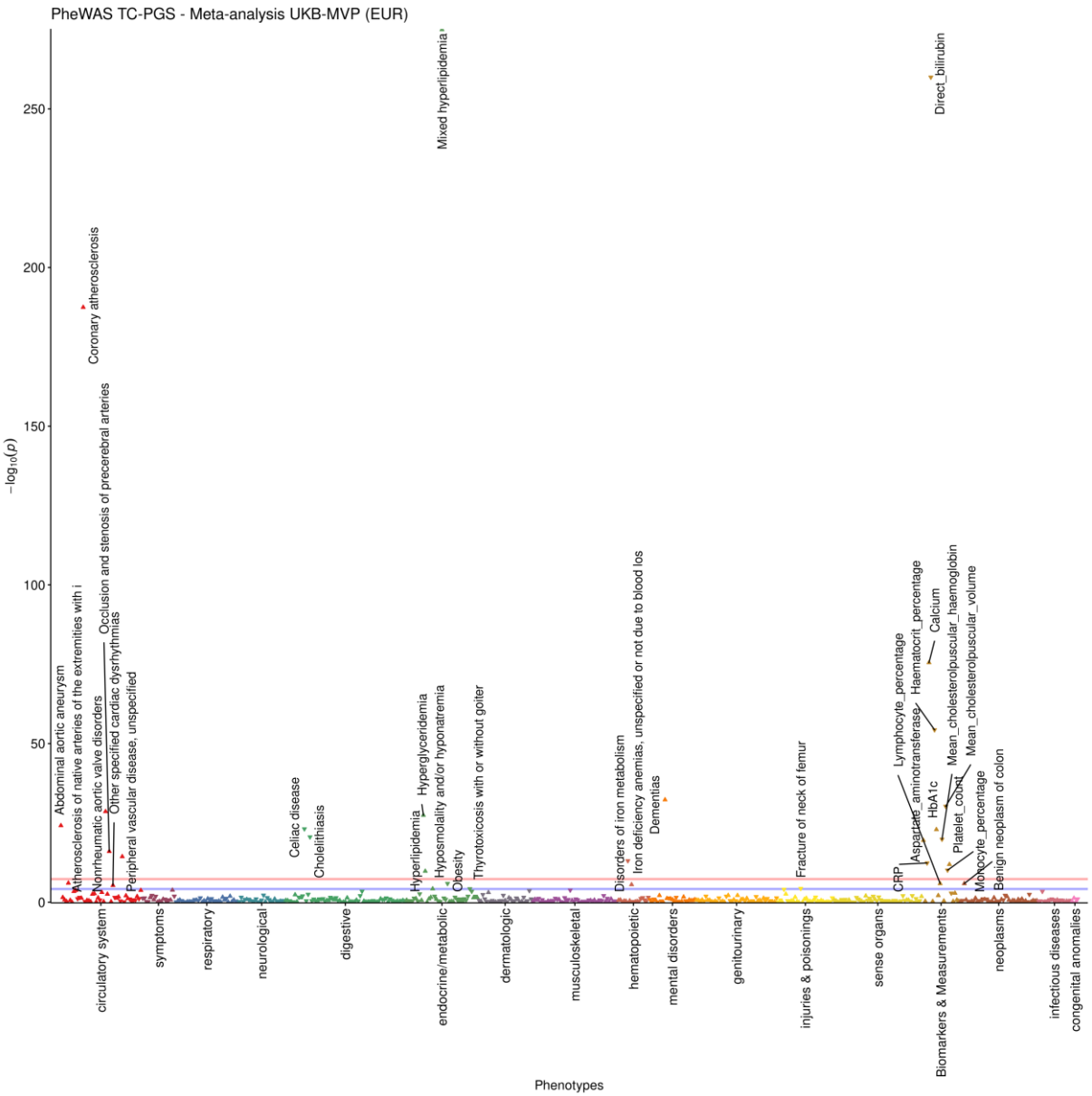


Figure S6. **PheWAS meta-analysis results for the trans-ethnic TC PGS in UK Biobank and MVP.** The blue horizontal line denotes phenome-wide significance ($p<=6.5x10^{-05}$) and the red line is genome-wide significance ($p<=5x10^{-08}$). Phenotypes have been pruned, so that the most significant one per correlated phenotype group (correlation coefficient > 0.2) is retained. Pairwise correlations were estimated with chi-square test and Cramer's V for the dichotomous phenotypes and Pearson's correlation for the continuous phenotypes. Full phenome-wide significant results are presented in **Additional file 12: Table S8**.

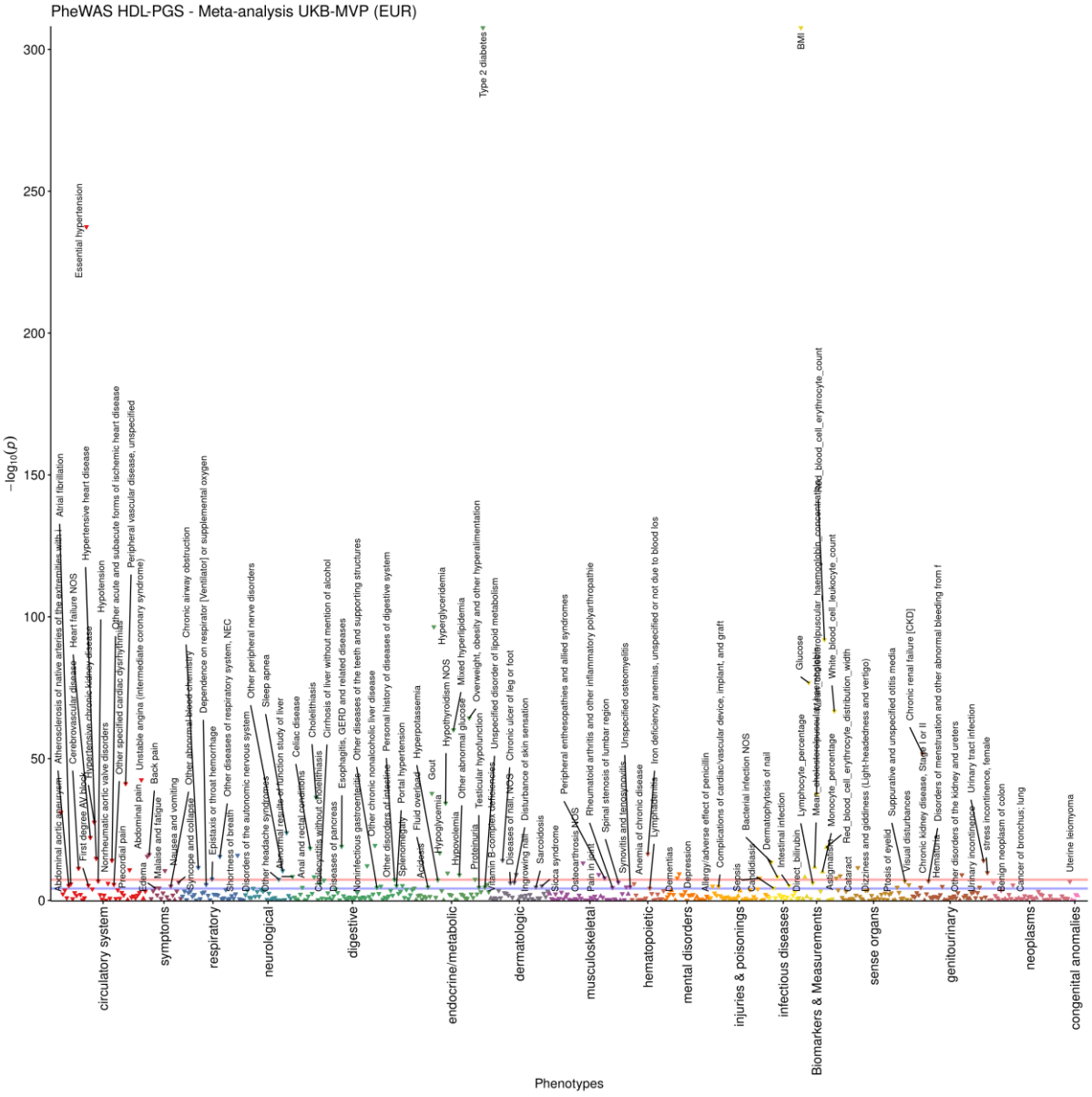


Figure S5. **PheWAS meta-analysis results for the trans-ethnic HDL-C PGS in UK Biobank and MVP.** The blue horizontal line denotes phenome-wide significance ($p<=6.5x10^{-05}$) and the red line is genome-wide significance ($p<=5x10^{-08}$). Phenotypes have been pruned, so that the most significant one per correlated phenotype group (correlation coefficient > 0.2) is retained. Pairwise correlations were estimated with chi-square test and Cramer's V for the dichotomous phenotypes and Pearson's correlation for the continuous phenotypes. Full phenome-wide significant results are presented in **Additional file 17: Table S8**.

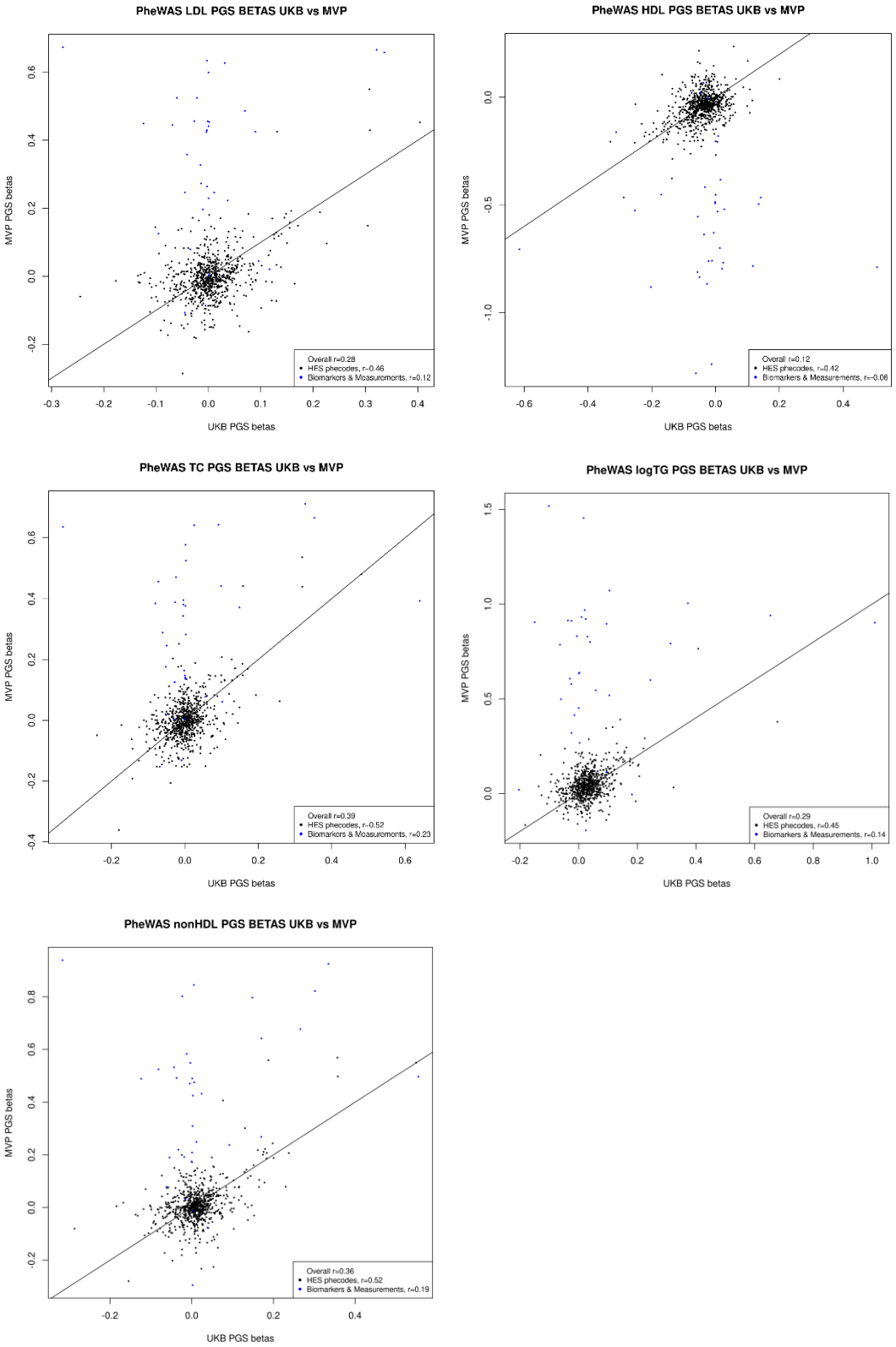
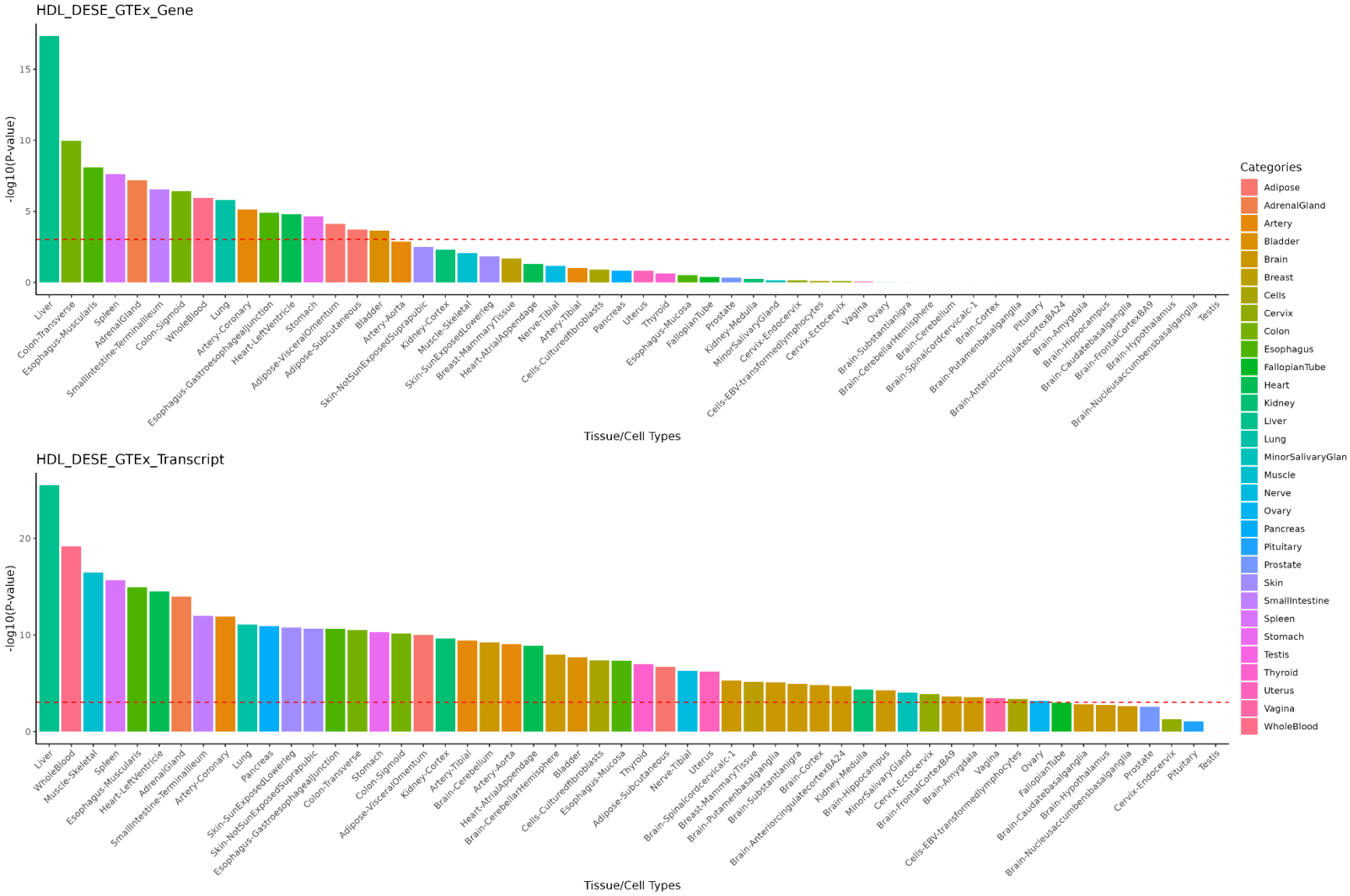


Figure S4. **Comparison of PheWAS results in UKB and MVP for the LDL-C PGS, HDL-C PGS, TC PGS, TG PGS and nonHDL-C PGS.** Effect sizes (betas) for the association of each PGS with each phecode and biomarker are plotted for UK Biobank (x-axis) versus MVP (y-axis). Black points represent ICD10-derived phecodes and blue points represent biomarkers.

A


HDL_DESE_GTEx_Gene
-log10(P-value)
Tissue/Cell Types
HDL_DESE_GTEx_Transcript
-log10(P-value)
Tissue/Cell Types
Categories
Adipose
AdrenalGland
Artery
Bladder
Brain
Breast
Cells
Cervix
Colon
Esophagus
FallopianTube
Heart
Kidney
Liver
Lung
MinorSalivaryGlan
Muscle
Nerve
Ovary
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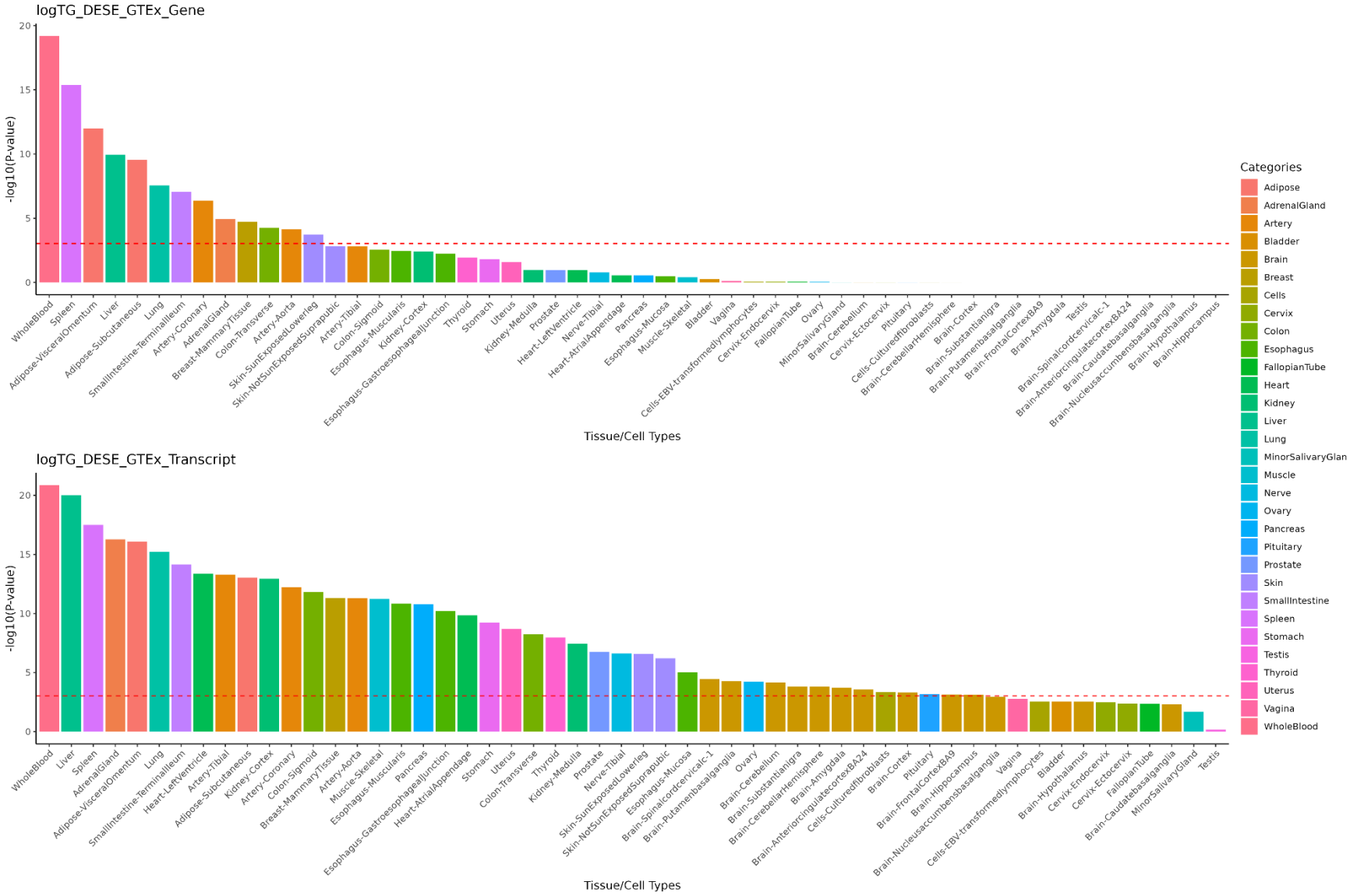
Spleen
Stomach
Testis
Thyroid
Uterus
Vagina
WholeBlood

B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-log10(P-value)
Tissue/Cell Types
logTG_DESE_GTEx_Transcript
-log10(P-value)
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Cervix
Colon
Esophagus
FallopianTube
Heart
Kidney
Liver
Lung
MinorSalivaryGlan
Muscle
Nerve
Ovary
Pancreas
Pituitary
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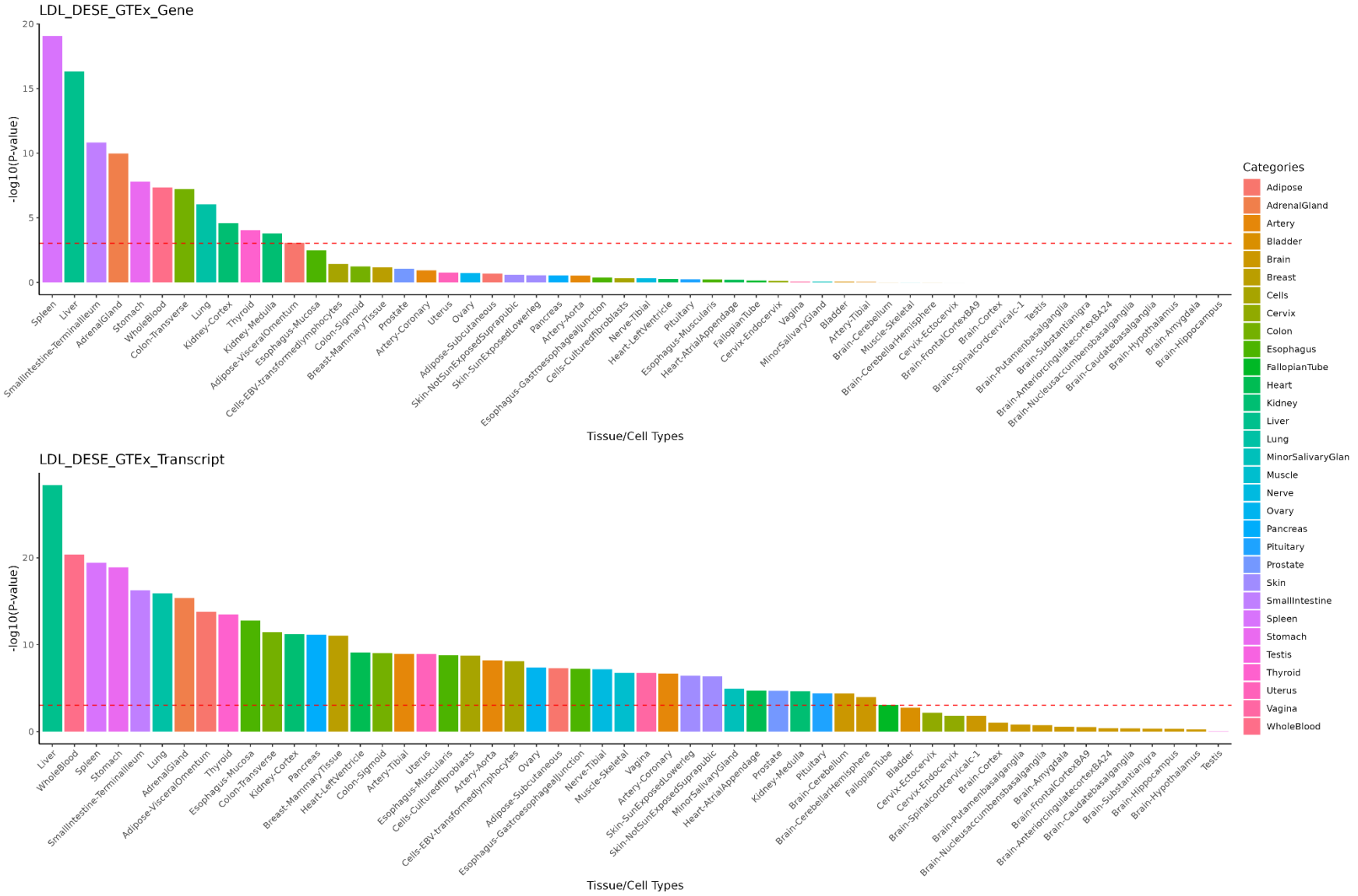
Spleen
Stomach
Testis
Thyroid
Uterus
Vagina
WholeBlood

C


LDL_DESE_GTEx_Gene
-log10(P-value)
Tissue/Cell Types
LDL_DESE_GTEx_Transcript
-log10(P-value)
Tissue/Cell Types
Categories
Adipose
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Artery
Bladder
Brain
Breast
Cells
Cervix
Colon
Esophagus
FallopianTube
Heart
Kidney
Liver
Lung
MinorSalivaryGlan
Muscle
Nerve
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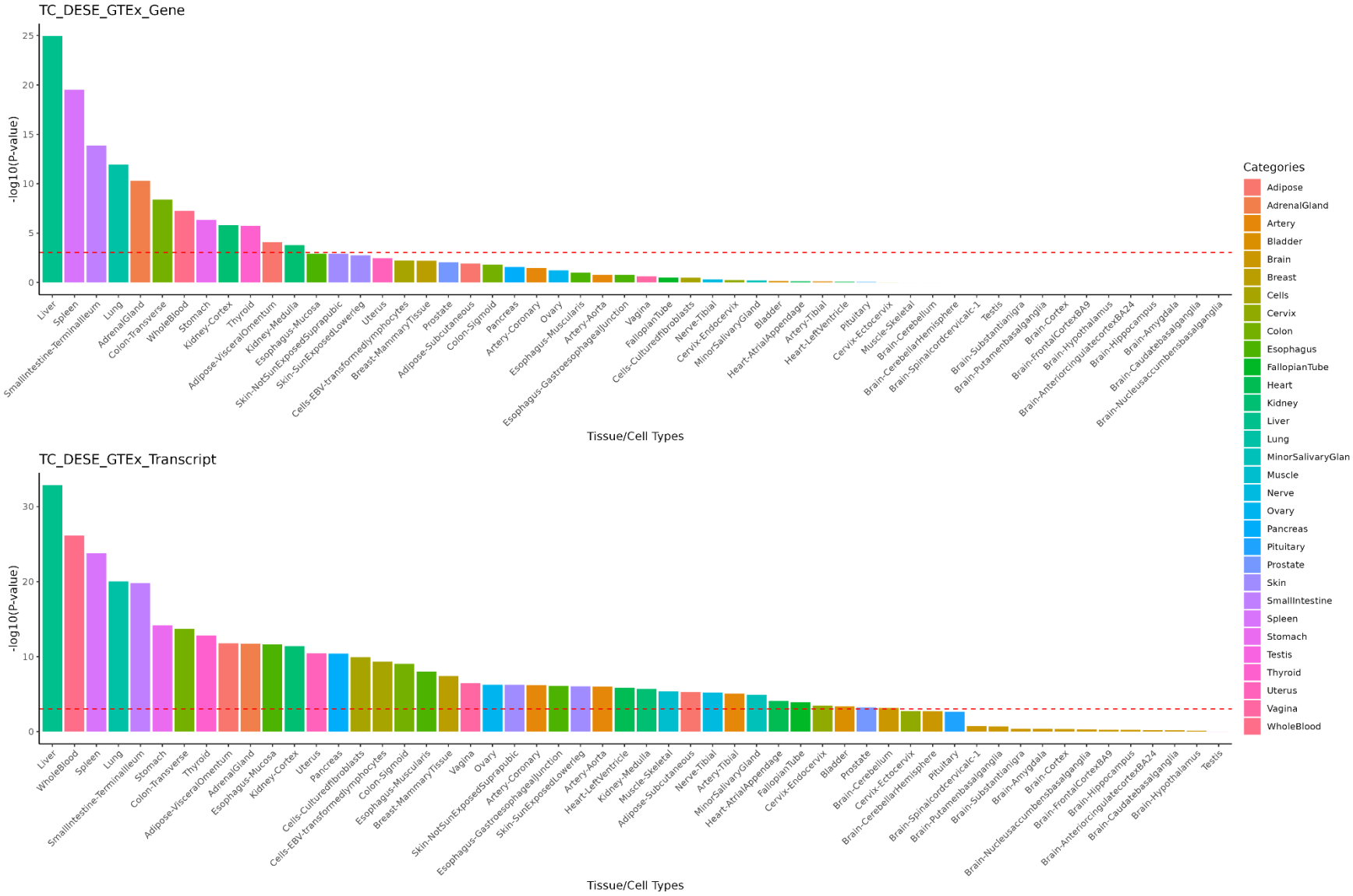
Uterus
Vagina
WholeBlood

D


TC_DESE_GTEx_Gene
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Tissue/Cell Types
TC_DESE_GTEx_Transcript
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Tissue/Cell Types
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Kidney
Liver
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MinorSalivaryGlan
Muscle
Nerve
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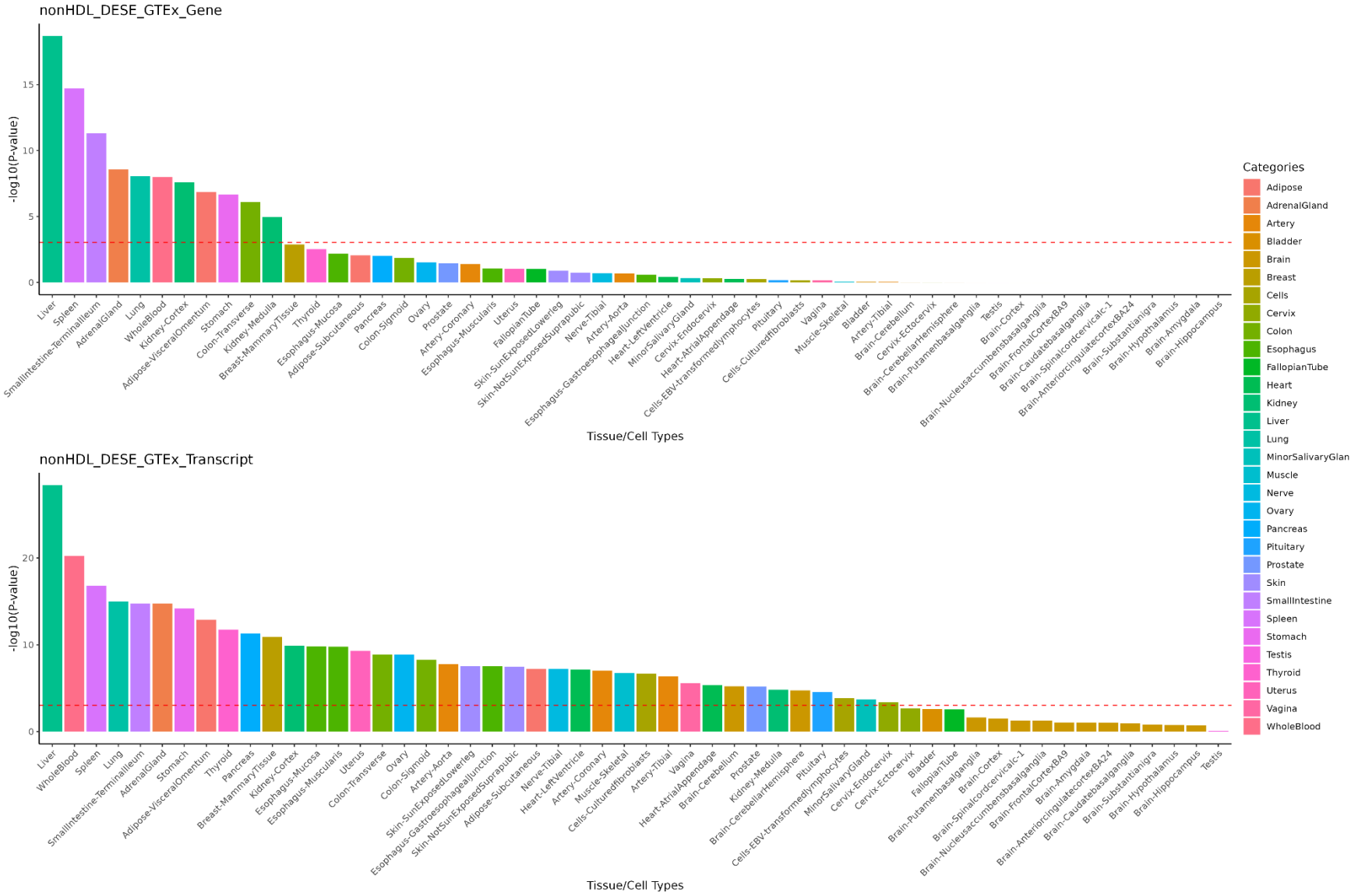
Thyroid
Uterus
Vagina
WholeBlood

E


nonHDL_DESE_GTEx_Gene
-log10(P-value)
Tissue/Cell Types
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Tissue/Cell Types
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Esophagus
FallopianTube
Heart
Kidney
Liver
Lung
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Muscle
Nerve
Ovary
Pancreas
Pituitary
Prostate
Skin
SmallIntestine
Spleen
Stomach
Testis
Thyroid
Uterus
Vagina
WholeBlood

Figure S3. **Lipid traits – tissue/cell type associations estimated by DESE according to GTEx gene-level and GTEx transcript-level selective expression.**

We performed phenotype-tissue association tests in five lipid traits: (**A**) HDL-C, (**B**) TG, (**C**) LDL-C, (**D**) TC, and (**E**) nonHDL-C with 54 GTEx tissues. For each lipid traits, the upper panel showed the estimated driver tissues according to GTEx gene-level selective expression and the bottom panel showed estimated driver tissues according to GTEx transcript-level selective expression. The tissues were ranked by their association significance (-log10(P-value)) with each lipid traits. The red horizontal line denoted the significance threshold using a Bonferroni correction.

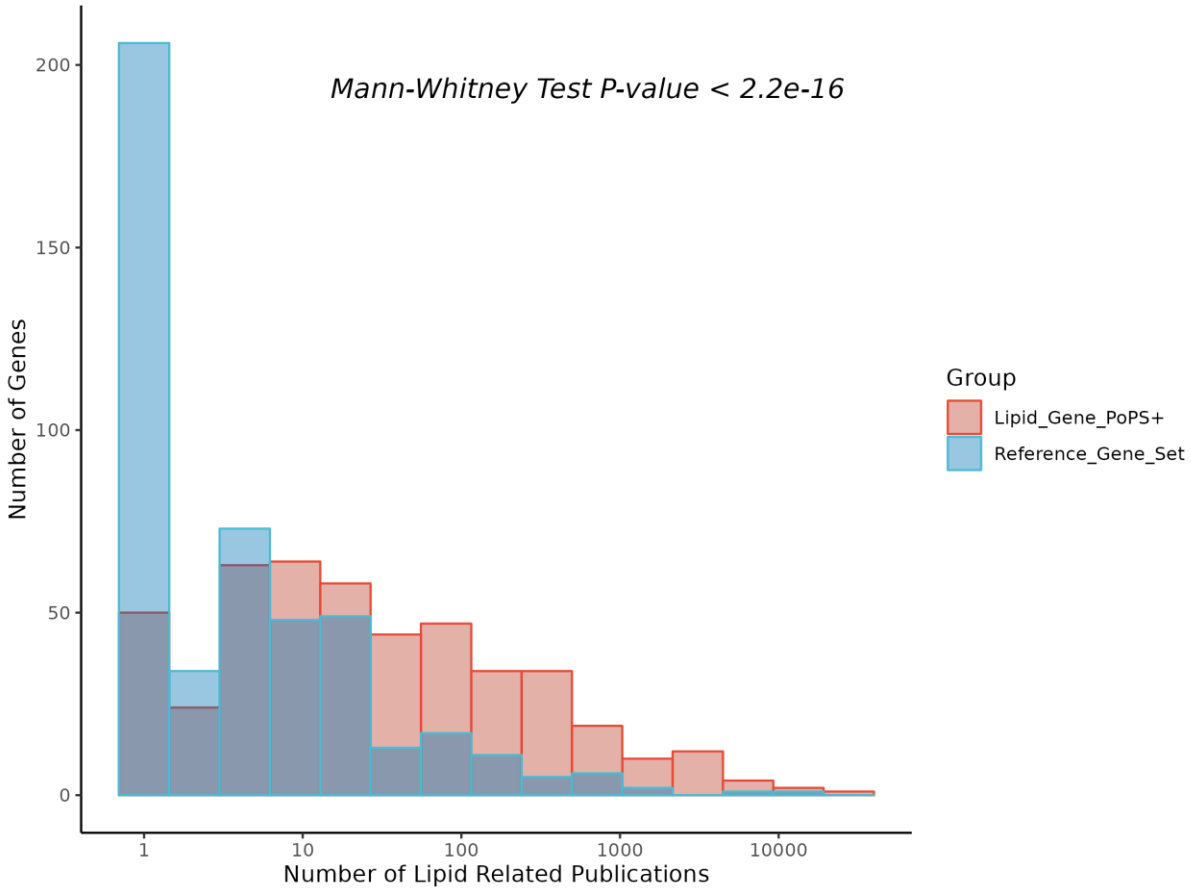
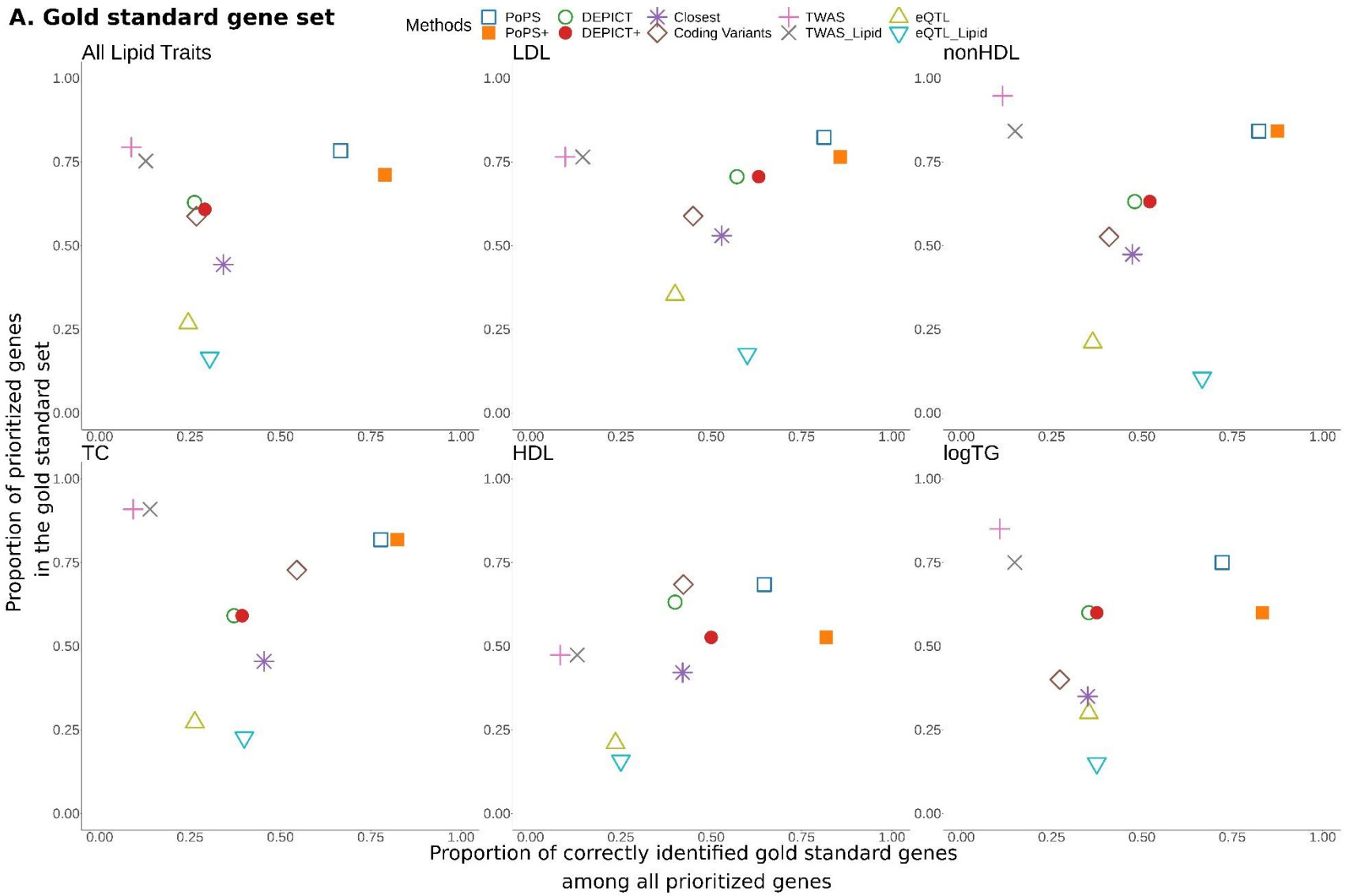


Figure S2. Frequency distribution of the lipid-related publications for both high confidence genes and the baseline genes. The A Mann-Whitney U test showed that there was a significant difference (W = 52353, p-value < 2.2e-16) between the high confidence gene group compared to the baseline group. The exact numbers of lipid-related publications for the high confidence prioritized genes can be found in **Additional file 7: Table S5**.


A. Gold standard gene set
Methods
PoPS
PoPS+
DEPICT
DEPICT+
Closest
Coding Variants
TWAS
TWAS_Lipid
eQTL
eQTL_Lipid
All Lipid Traits
LDL
nonHDL
TC
HDL
logTG
Proportion of prioritized genes in the gold standard set
Proportion of correctly identified gold standard genes among all prioritized genes
0.00
0.25
0.50
0.75
1.00

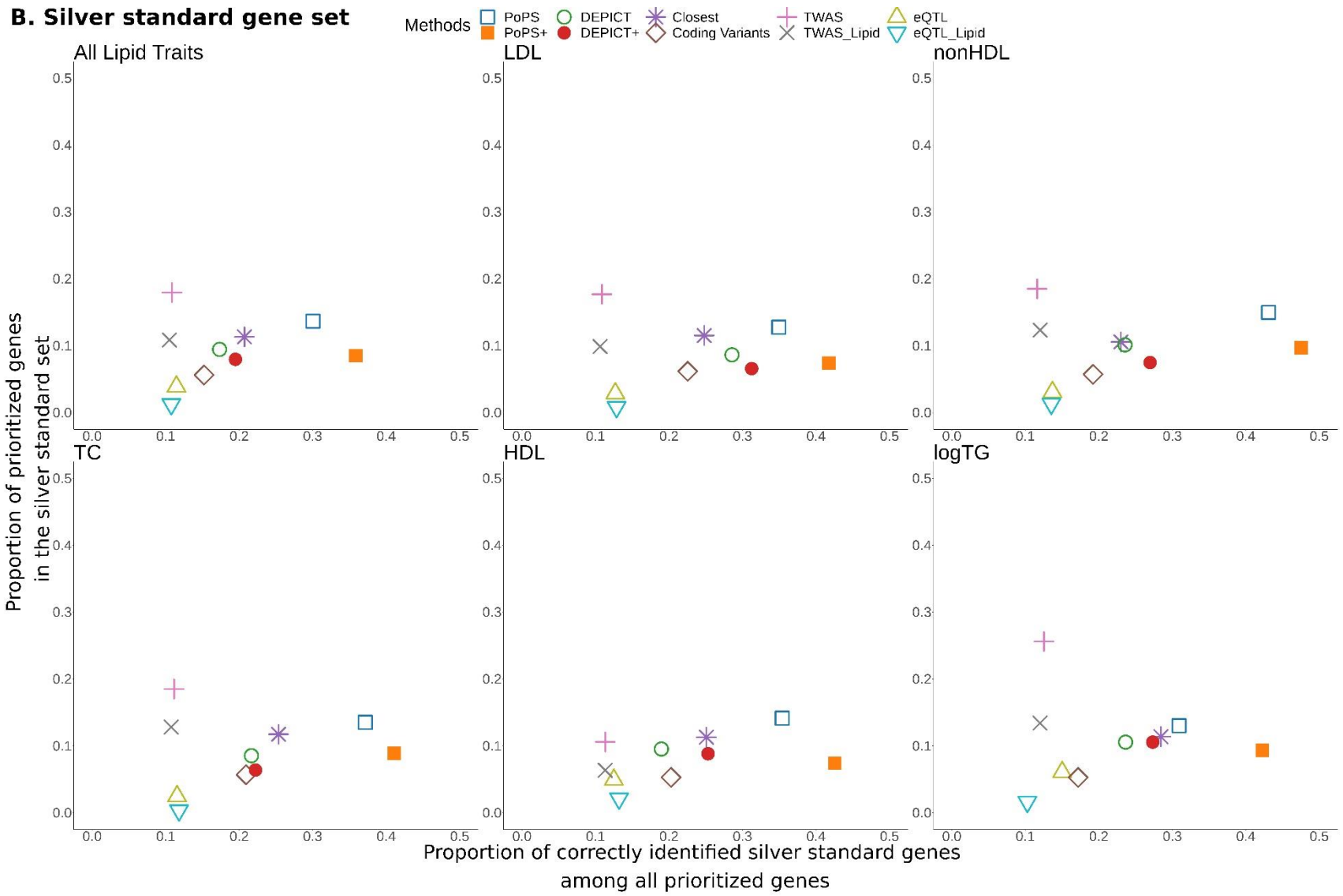

B. Silver standard gene set
Methods
PoPS
PoPS+
DEPICT
DEPICT+
Closest
Coding Variants
TWAS
TWAS_Lipid
eQTL
eQTL_Lipid
All Lipid Traits
LDL
nonHDL
TC
HDL
logTG
Proportion of prioritized genes in the silver standard set
Proportion of correctly identified silver standard genes among all prioritized genes

Figure S1. **Summary of prioritizing genes for A. Mendelian and B. mouse model genes separately by trait.**

We determined the proportion of prioritized genes in the gold standard set (y-axis) and proportion of correctly identified gold standard genes among all prioritized genes (x-axis) for each gene prioritization methods utilizing the gold-standard (**A**) and silver-standard (**B**) gene sets. We calculated the overall proportions and separately by trait.