

Supplementary Materials

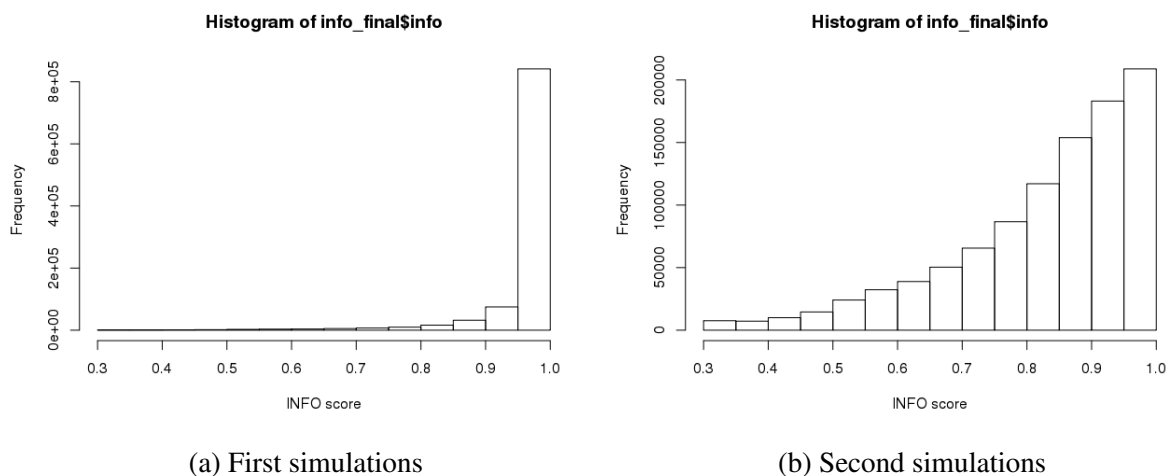


Figure S1: Histogram of INFO scores for the 1M variants used in the simulations.

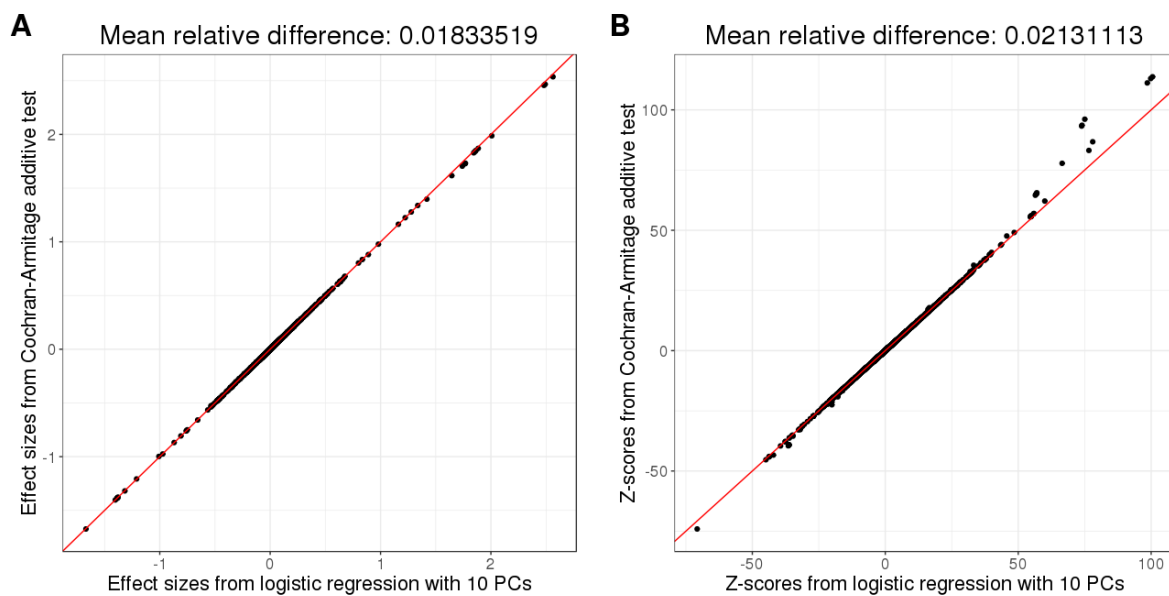


Figure S2: Comparison between logistic regression and Cochran-Armitage additive test. Comparison of estimated effect sizes (**A**) and Z-scores (**B**) if computed using a logistic regression with 10 principal components as covariates, or with a simple Cochran-Armitage additive test. Phenotypes were simulated using 100 causal variants only, allowing for large effects.

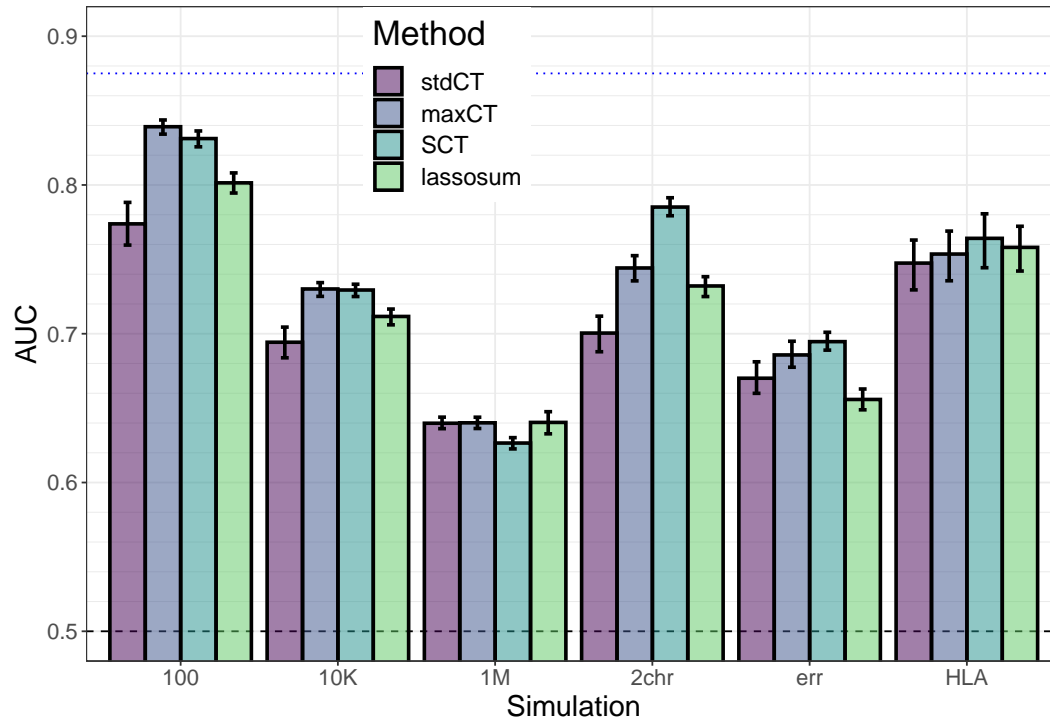


Figure S3: Results of the 6 simulation scenarios with less well imputed variants. Scenarios are (100) 100 random causal variants; (10K) 10,000 random causal variants; (1M) all 1M variants are causal variants; (2chr) 100 variants of chromosome 1 are causal and all variants of chromosome 2, with half of the heritability for both chromosomes; (err) 10,000 random causal variants, but 10% of the GWAS effects are reported with an opposite effect; (HLA) 7105 causal variants in a long-range LD region of chromosome 6. Mean and 95% CI of 10^4 non-parametric bootstrap replicates of the mean AUC of 10 simulations for each scenario. The blue dotted line represents the maximum achievable AUC for these simulations (87.5% for a prevalence of 10% and an heritability of 50% – see equation (3) of¹). See corresponding values in table S3.

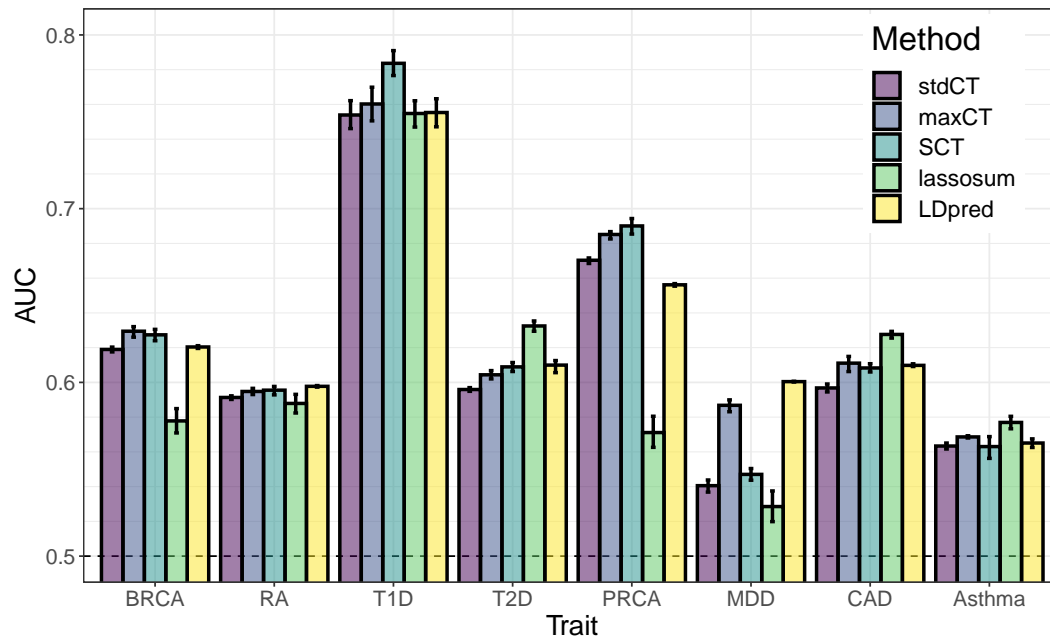
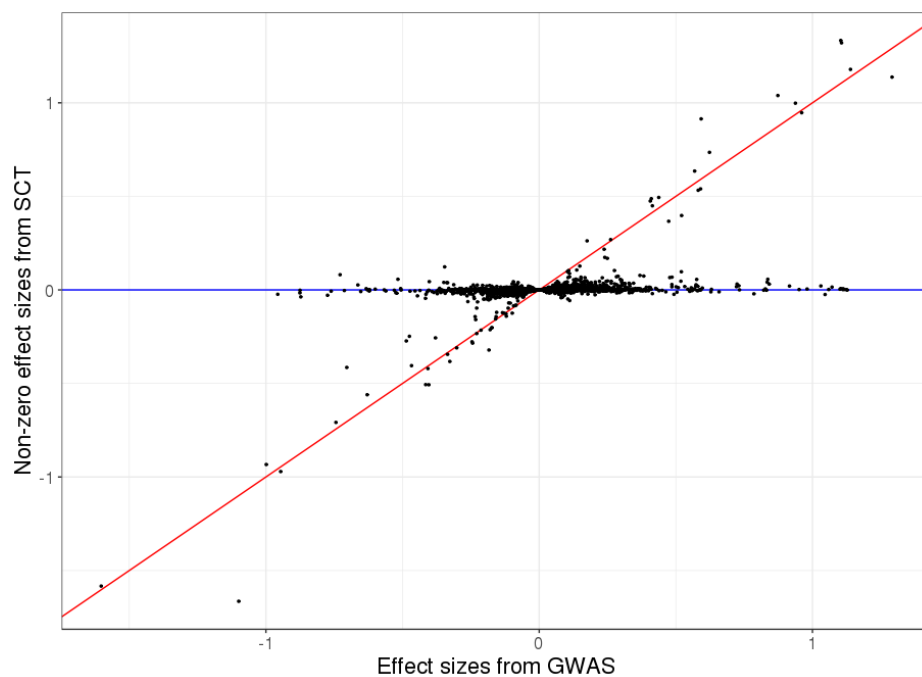
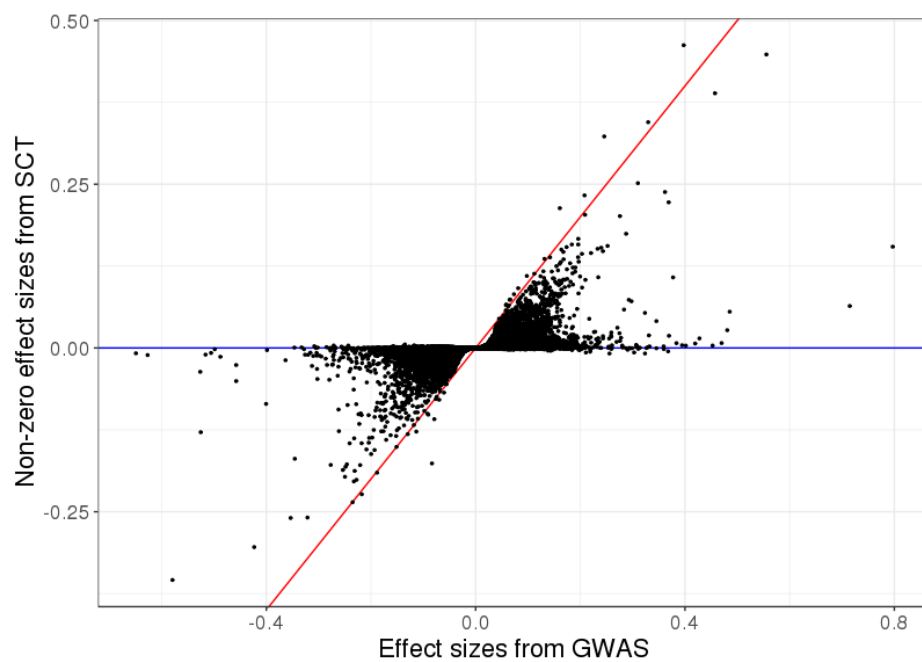


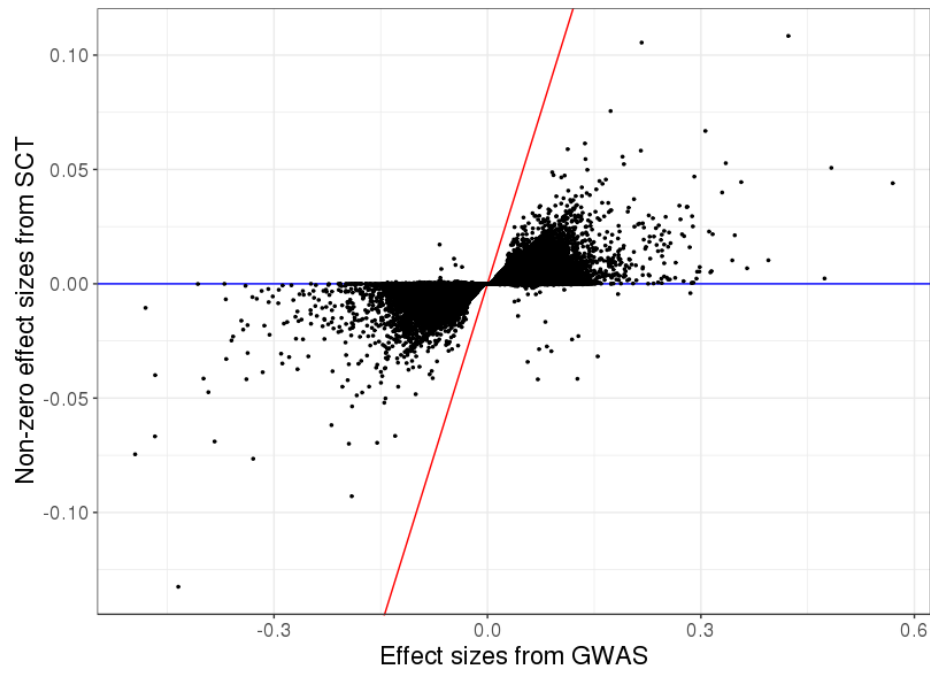
Figure S4: Results of the real data applications with small training size. Mean and 95% CI of 10^4 non-parametric bootstrap replicates of the mean AUC of 6 random splits to define the training set. Training SCT and choosing optimal hyper-parameters for C+T, LDpred and lassosum use 500 cases and 2000 controls only. See corresponding values in table S4.



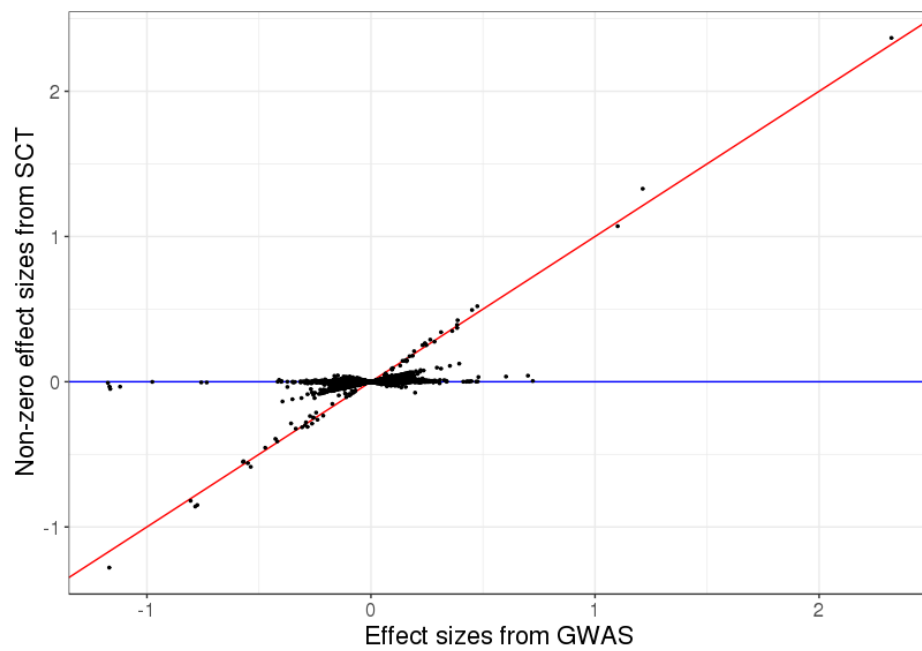
(a) “100”: 100 random causal variants



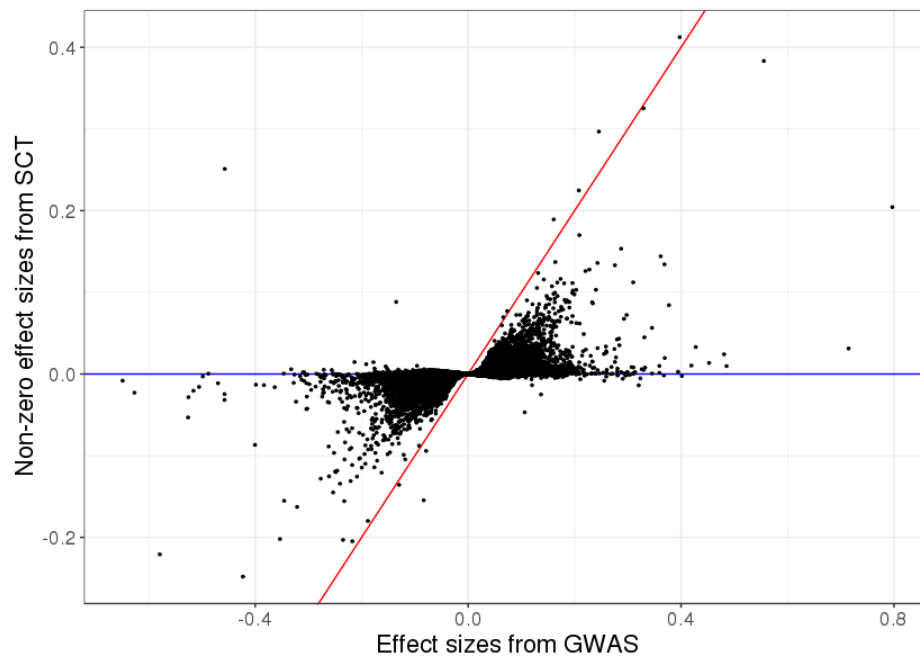
(b) “10K”: 10,000 random causal variants



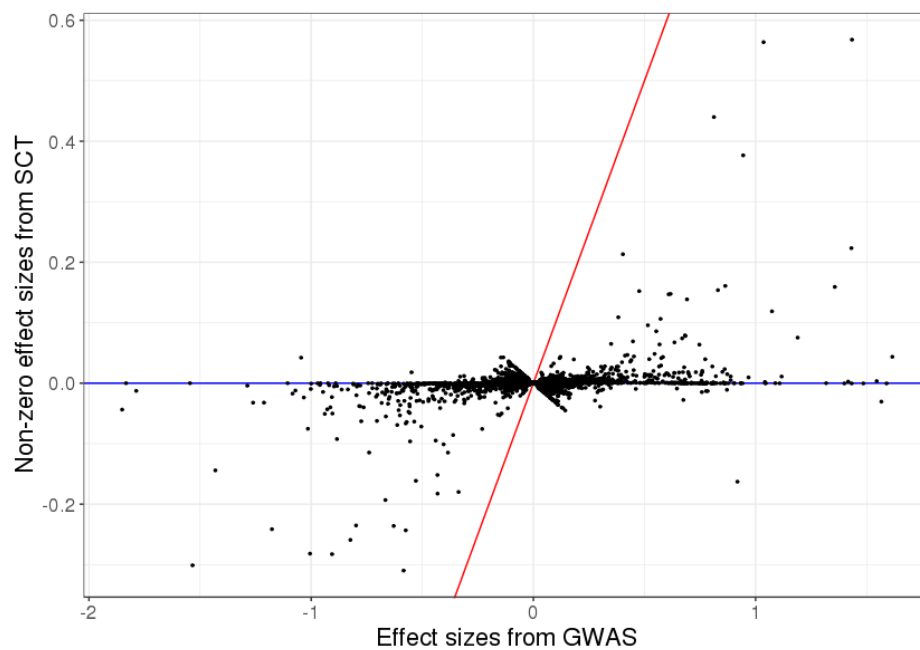
(c) “1M”: all 1M variants are causal variants



(d) “2chr”: Causal variants on chromosomes 1 & 2

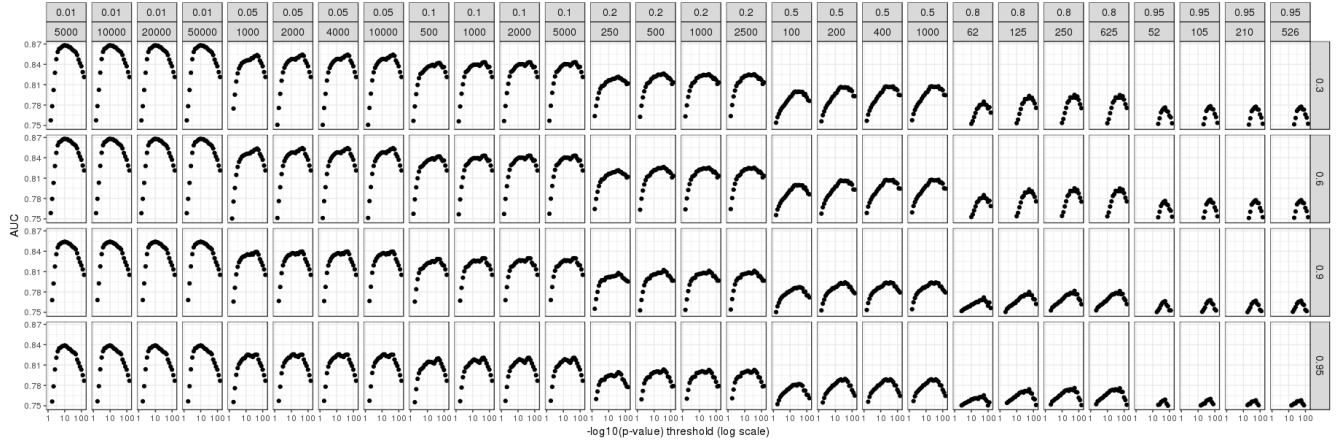


(e) “err”: 10,000 random causal variants, but 10% of the GWAS effects are reported with an opposite effect

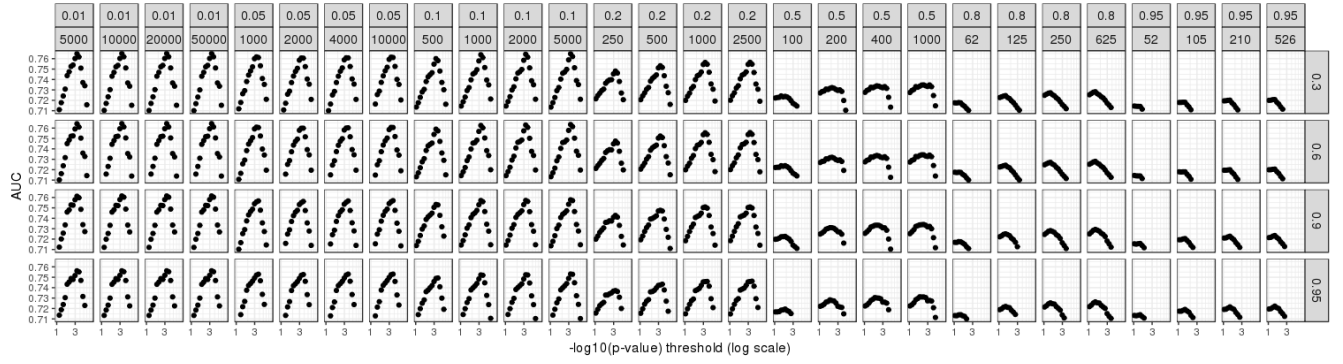


(f) “HLA”: 7105 causal variants in a long-range LD region of chromosome 6

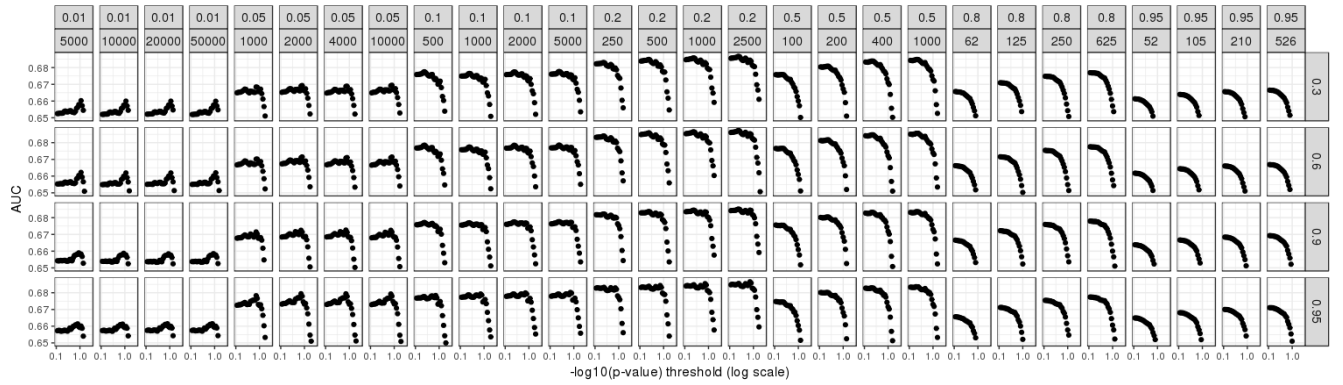
Figure S5: Effect sizes in simulations. New effect sizes resulting from SCT versus initial effect sizes of GWAS in the first simulation of each simulation scenario. Only non-zero effects are represented. Red line corresponds to the 1:1 line.



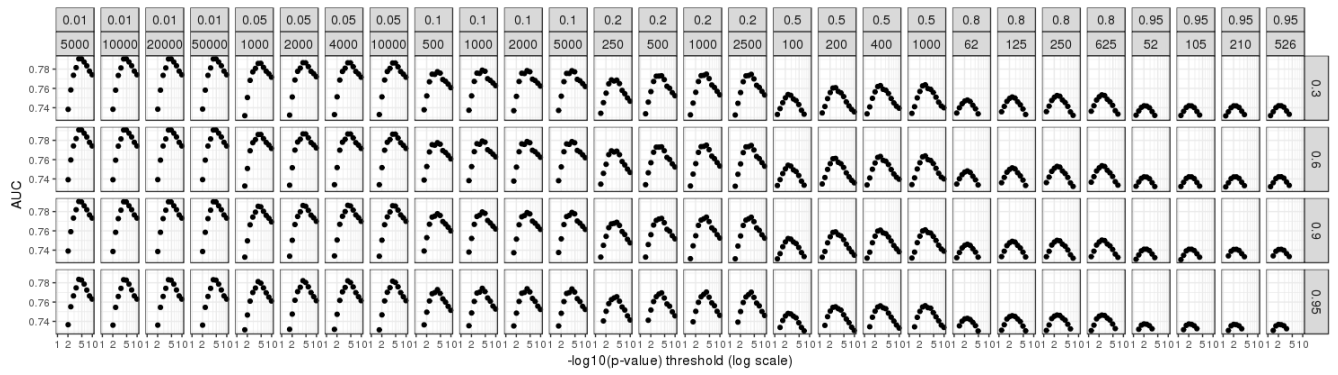
(a) “100”: 100 random causal variants



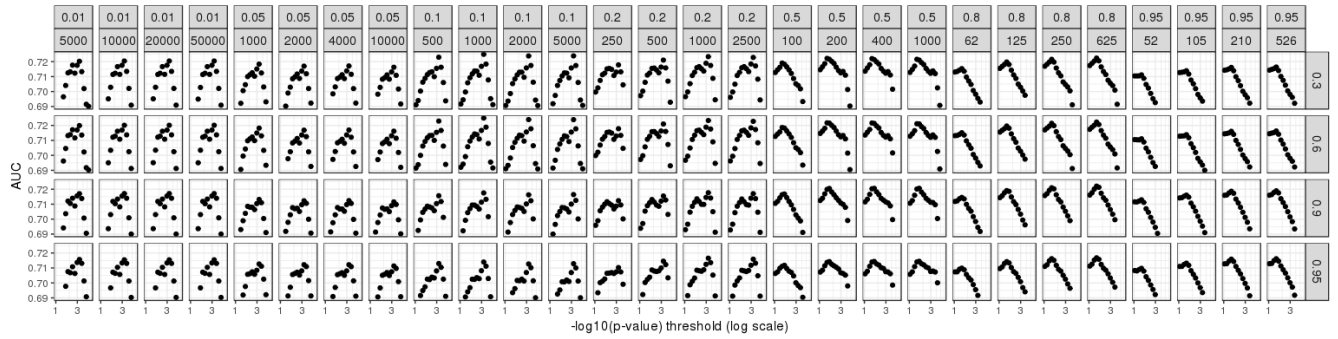
(b) “10K”: 10,000 random causal variants



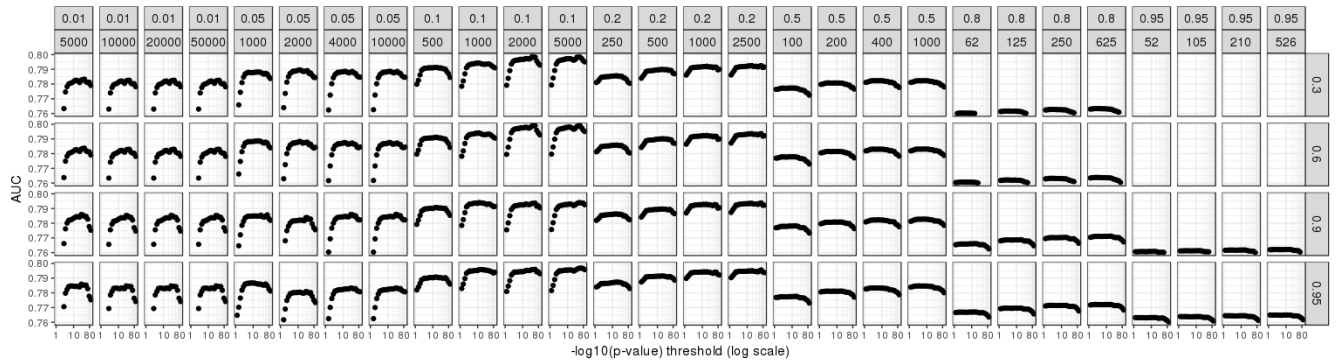
(c) “1M”: all 1M variants are causal variants



(d) “2chr”: Causal variants on chromosomes 1 & 2

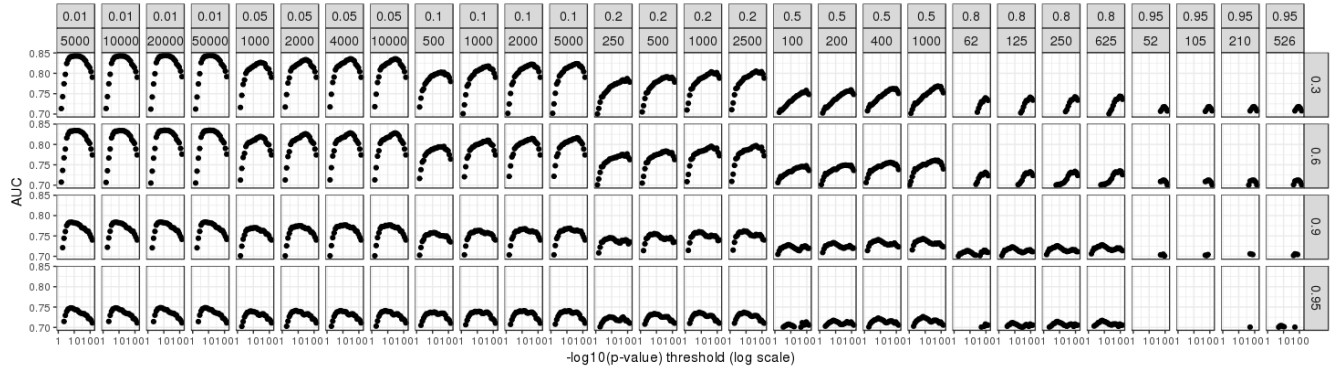


(e) “err”: 10,000 random causal variants, but 10% of the GWAS effects are reported with an opposite effect

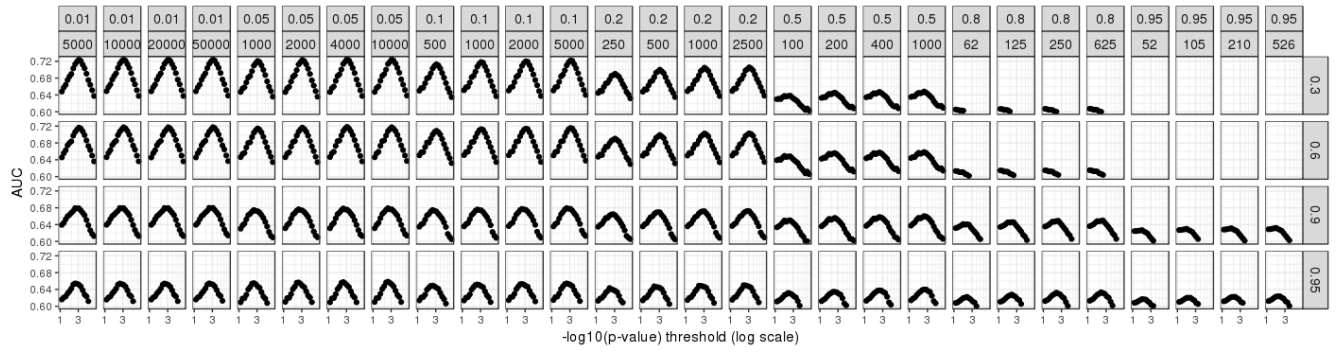


(f) “HLA”: 7105 causal variants in a long-range LD region of chromosome 6

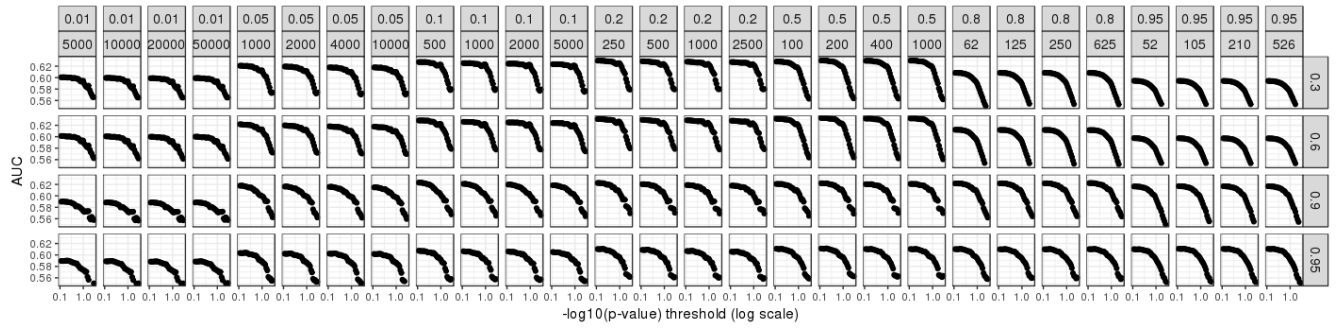
Figure S6: AUC results of all C+T scores in simulations with well imputed variants. AUC values (for the training set) when predicting disease status for many parameters of C+T in the first simulation of each simulation scenario when using well imputed variants. Facets are presenting different clumping thresholds r_c^2 from 0.01 to 0.95, window sizes w_c from 52 to 50,000 kb, and imputation thresholds from 0.3 to 0.95. The x-axis corresponds to the remaining hyper-parameter, the p-value threshold p_T ; here, $-\log_{10}(\text{p-values})$ are represented using a logarithmic scale.



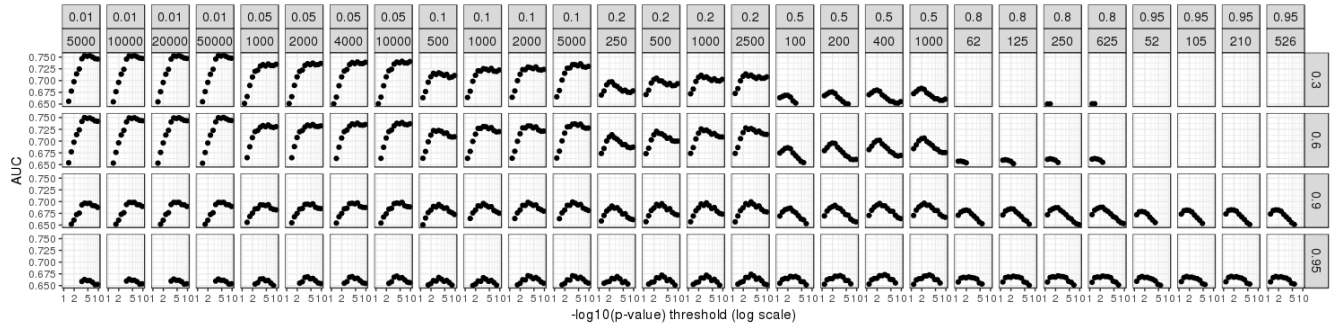
(a) “100”: 100 random causal variants



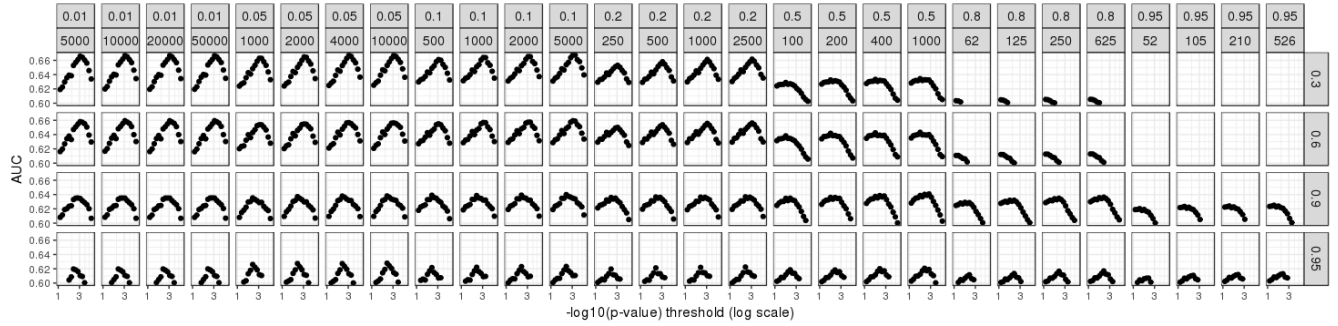
(b) “10K”: 10,000 random causal variants



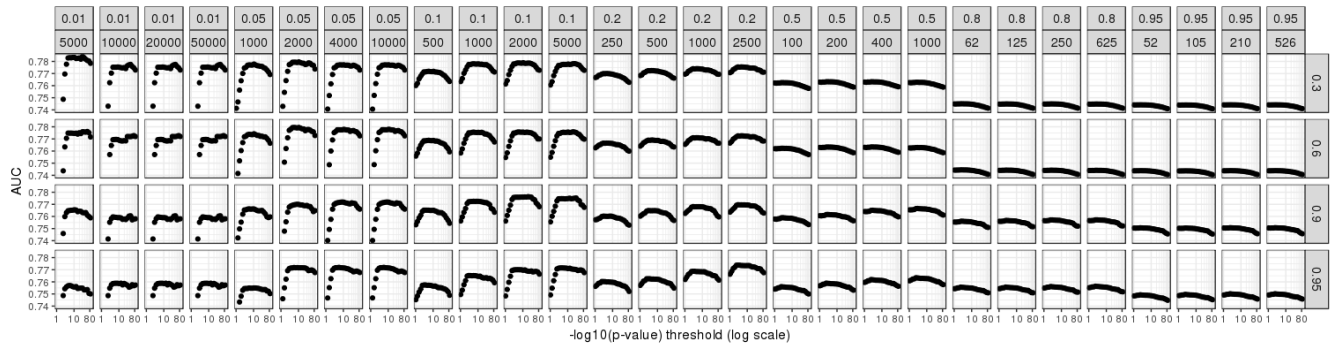
(c) “1M”: all 1M variants are causal variants



(d) “2chr”: Causal variants on chromosomes 1 & 2

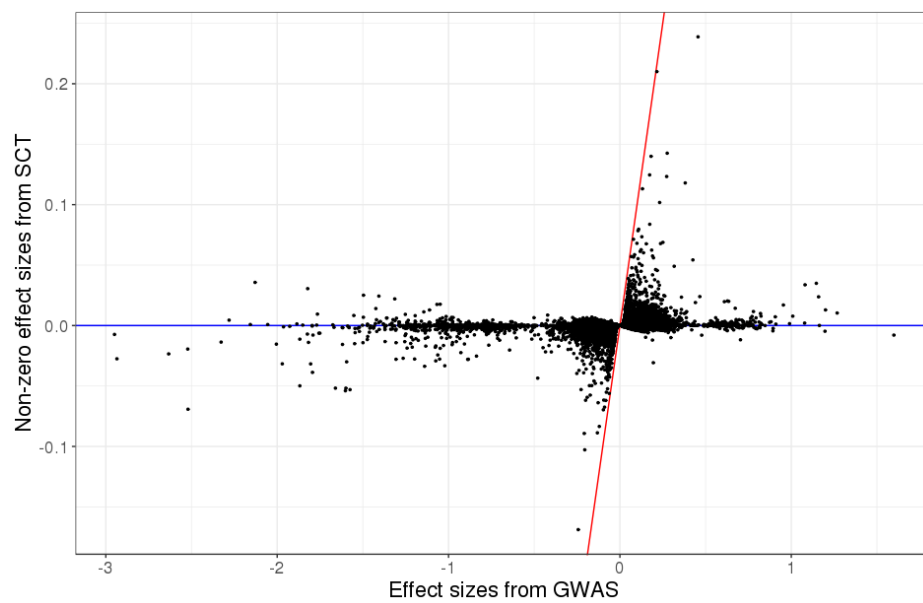


(e) “err”: 10,000 random causal variants, but 10% of the GWAS effects are reported with an opposite effect

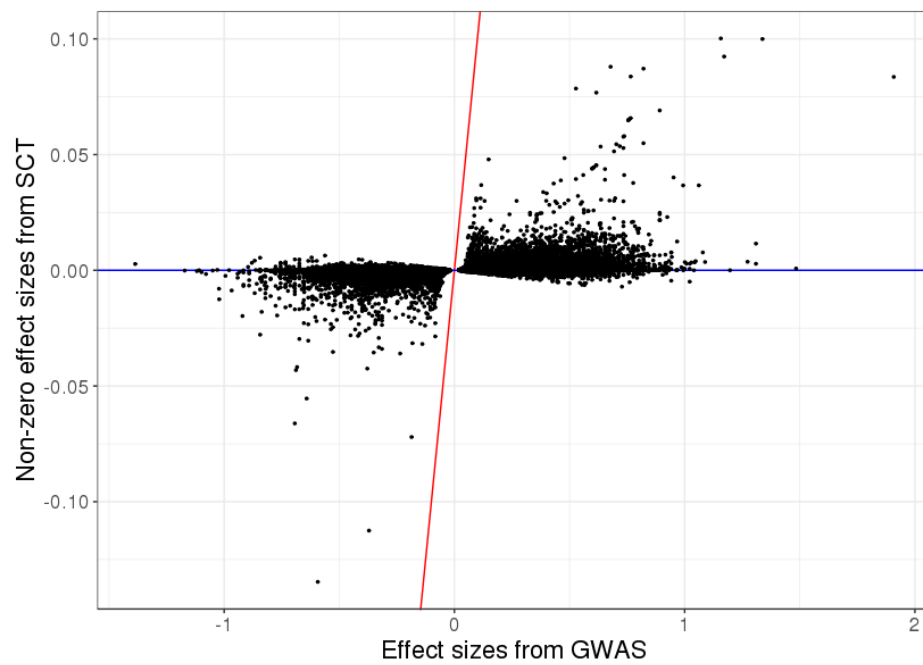


(f) “HLA”: 7105 causal variants in a long-range LD region of chromosome 6

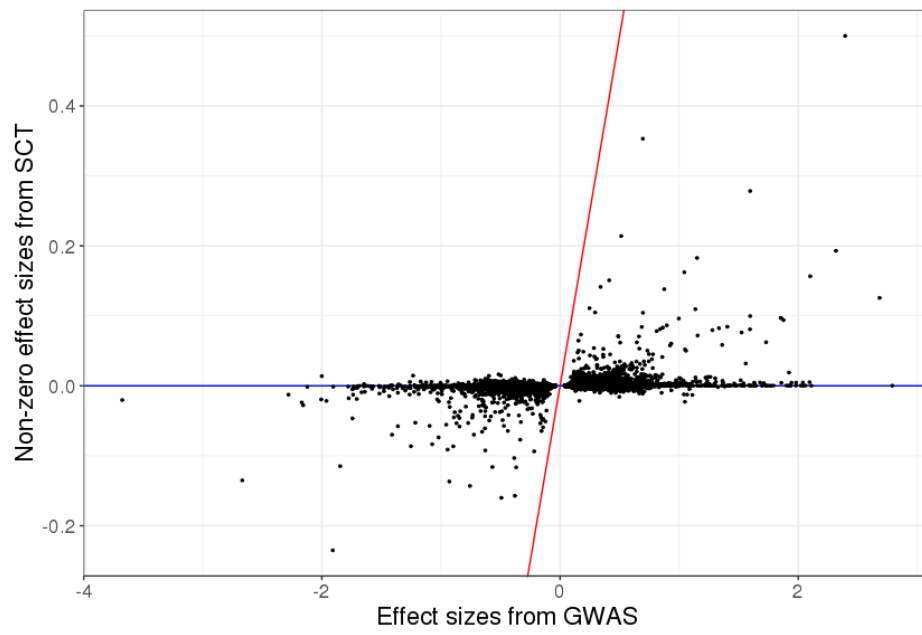
Figure S7: AUC results of all C+T scores in simulations with less well imputed variants. AUC values (for the training set) when predicting disease status for many parameters of C+T in the first simulation of each simulation scenario when using less well imputed variants. Facets are presenting different clumping thresholds r_c^2 from 0.01 to 0.95, window sizes w_c from 52 to 50,000 kb, and imputation thresholds from 0.3 to 0.95. The x-axis corresponds to the remaining hyper-parameter, the p-value threshold p_T ; here, $-\log_{10}(\text{p-values})$ are represented using a logarithmic scale.



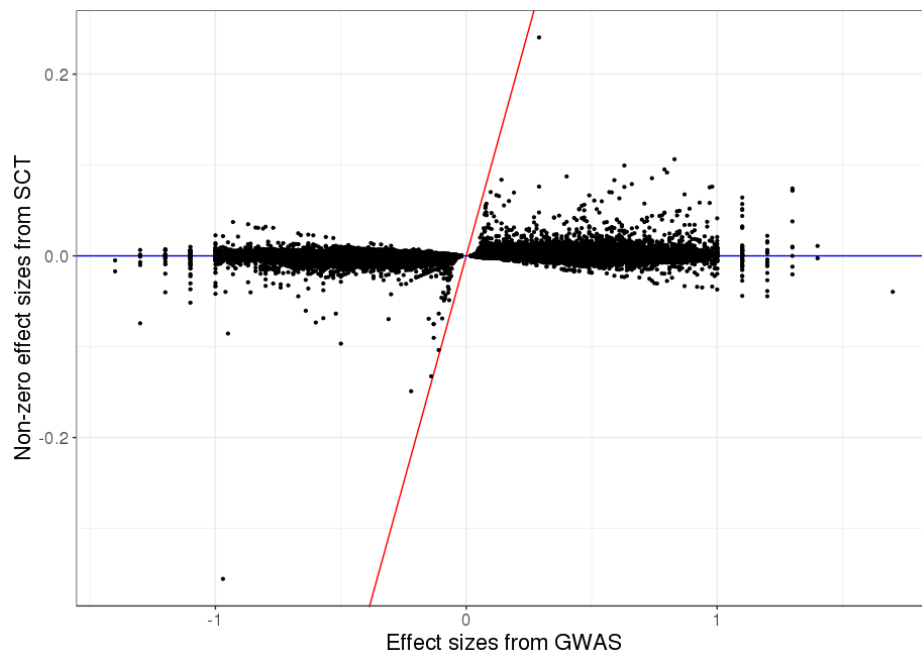
(a) Breast cancer



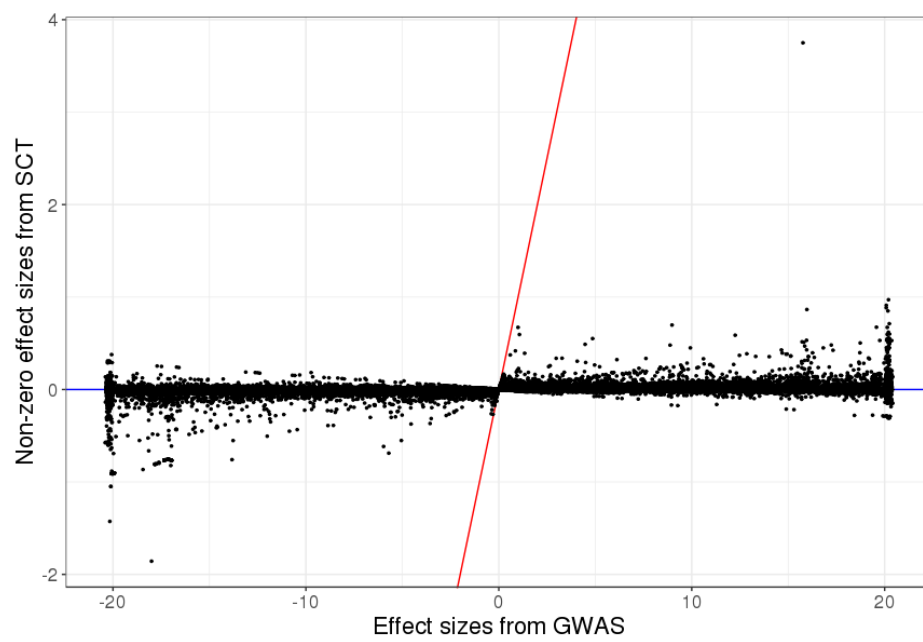
(b) Rheumatoid arthritis



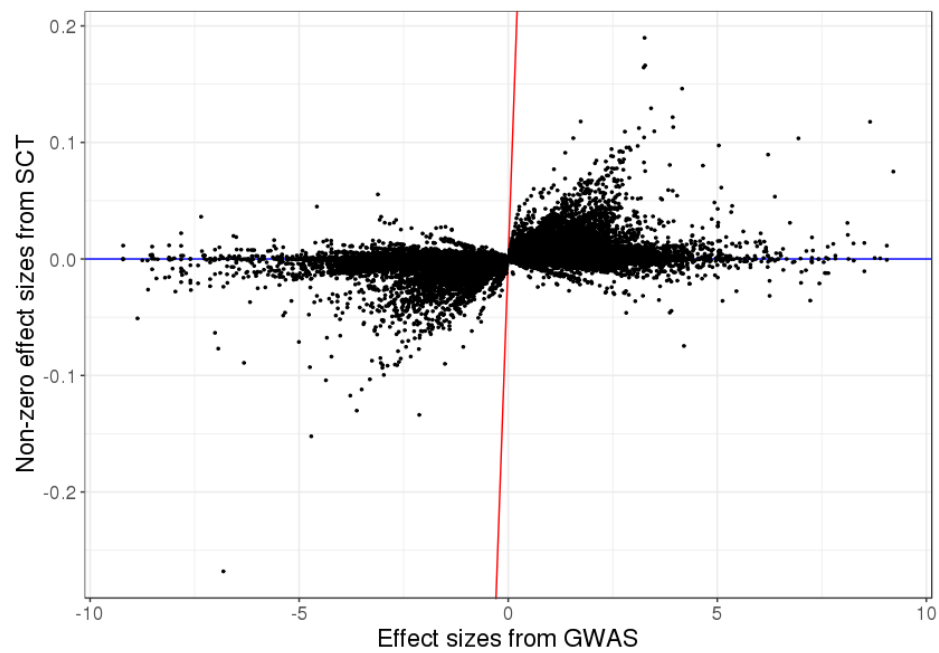
(c) Type 1 diabetes



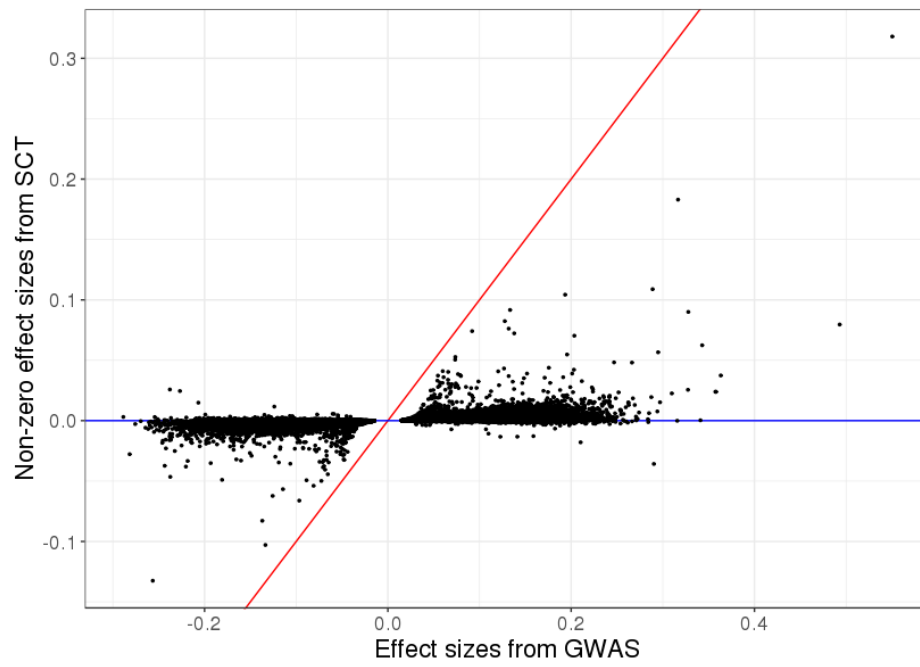
(d) Type 2 diabetes



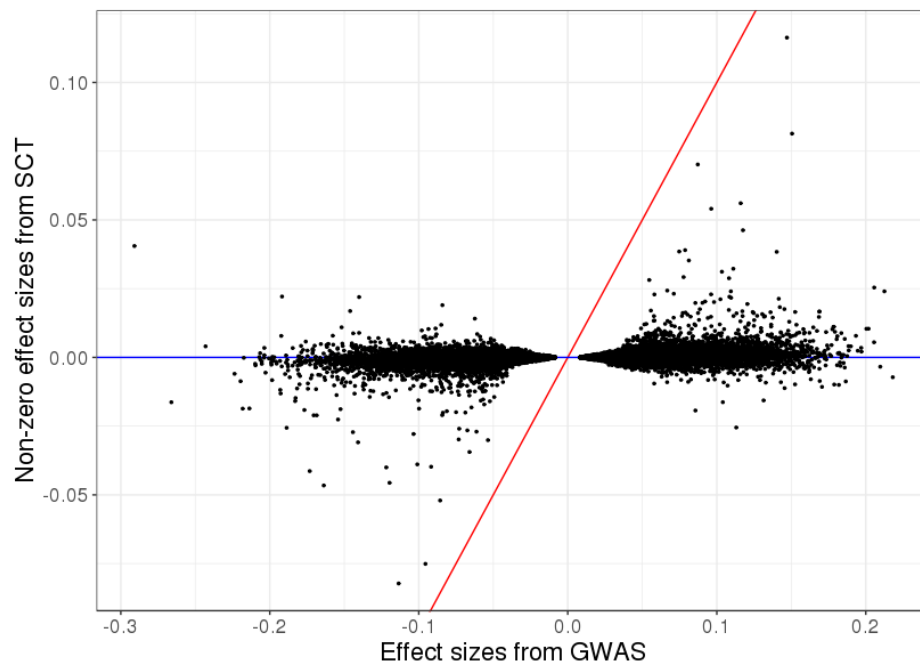
(e) Prostate cancer



(f) Depression

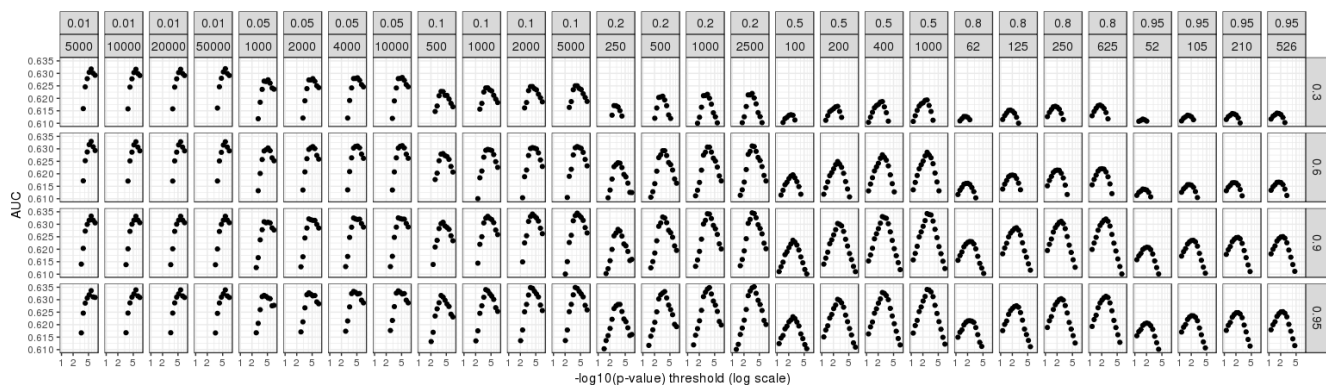


(g) Coronary artery disease

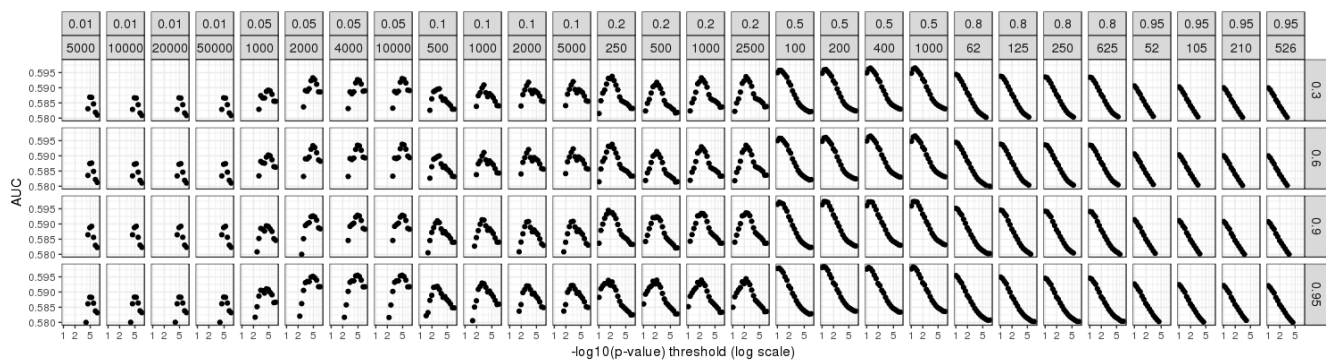


(h) Asthma

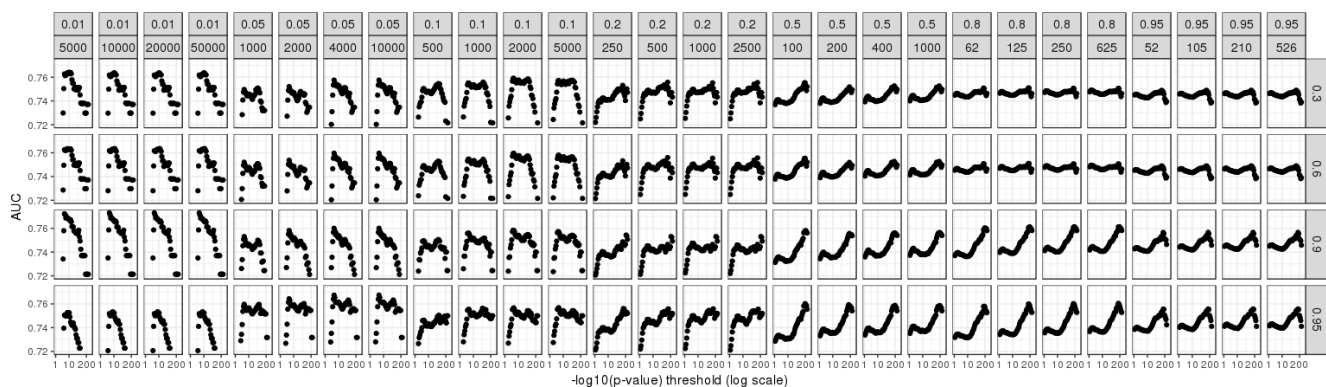
Figure S8: Effect sizes in real data applications. New effect sizes resulting from SCT versus initial effect sizes of GWAS in real data applications. Only non-zero effects are represented. Red line corresponds to the 1:1 line.



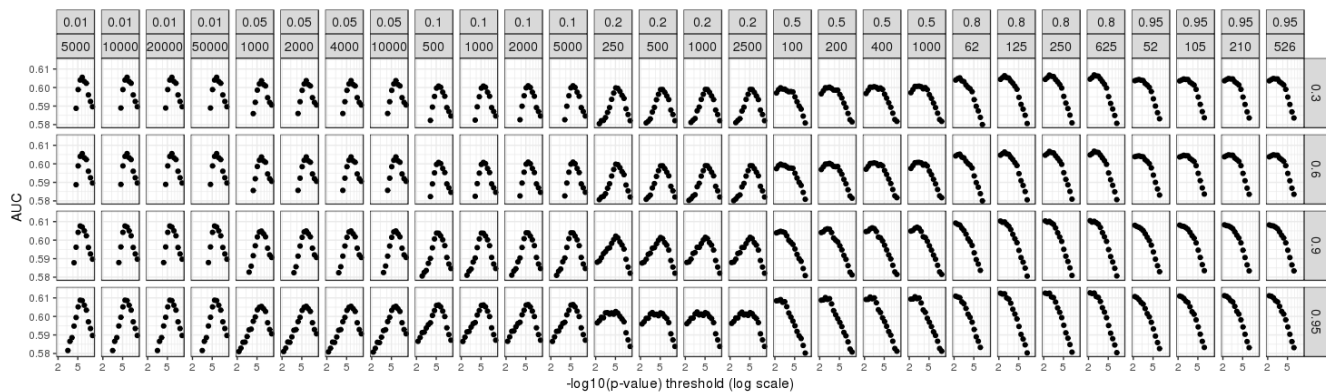
(a) Breast cancer



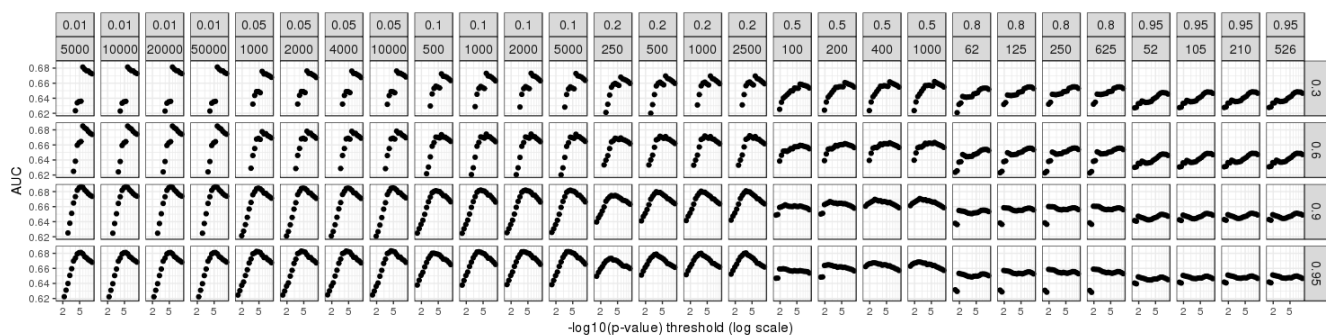
(b) Rheumatoid arthritis



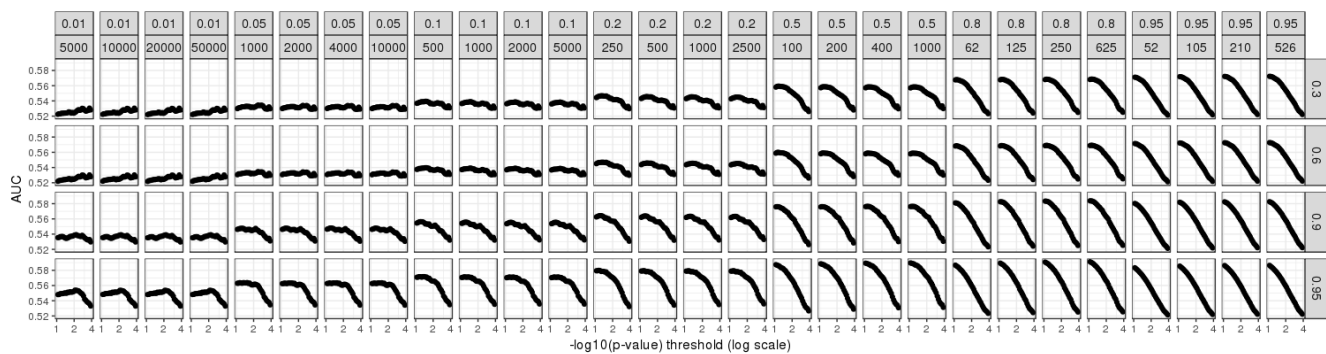
(c) Type 1 diabetes



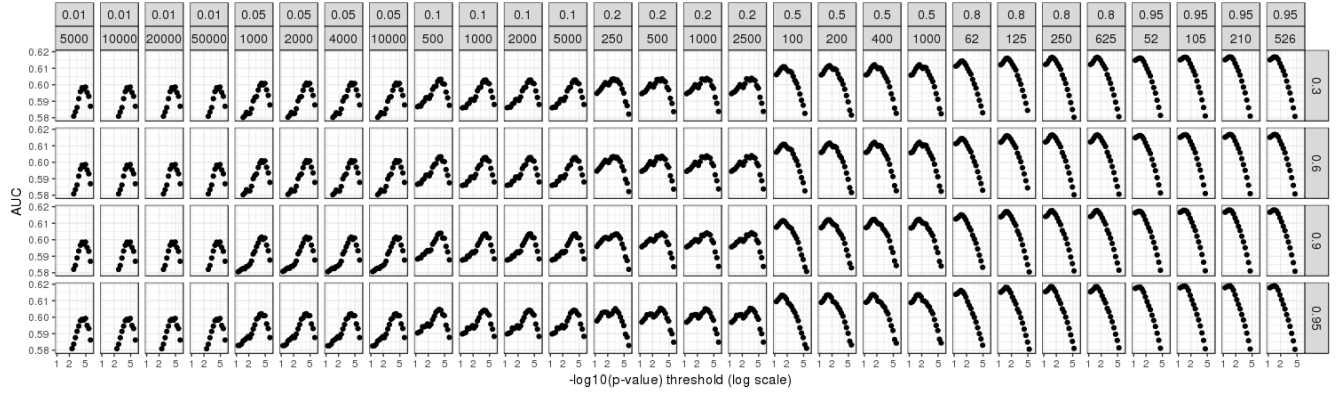
(d) Type 2 diabetes



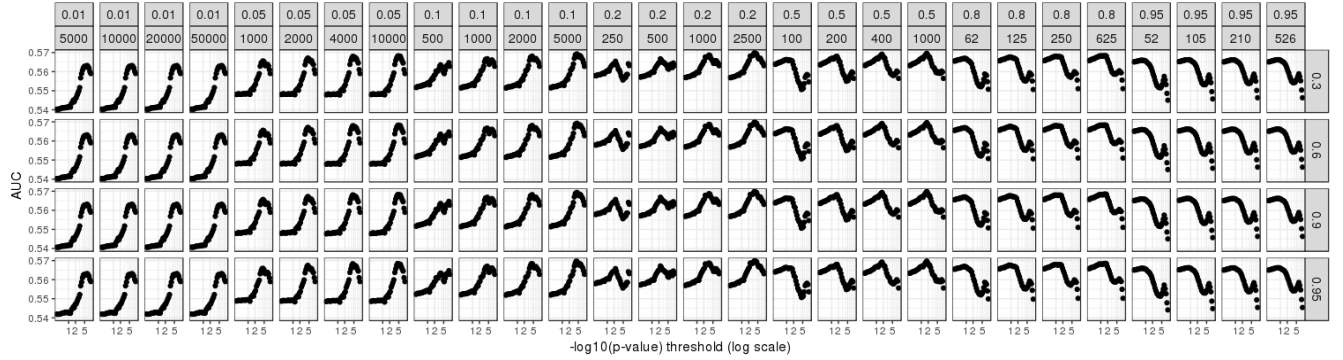
(e) Prostate cancer



(f) Depression



(g) Coronary artery disease



(h) Asthma

Figure S9: AUC results of all C+T scores in real data applications. AUC values (for the training set) when predicting disease status for many parameters of C+T in real data applications. Facets are presenting different clumping thresholds r_c^2 from 0.01 to 0.95, window sizes w_c from 52 to 50,000 kb, and imputation thresholds from 0.3 to 0.95. The x-axis corresponds to the remaining hyper-parameter, the p-value threshold p_T ; here, $-\log_{10}(\text{p-values})$ are represented using a logarithmic scale.

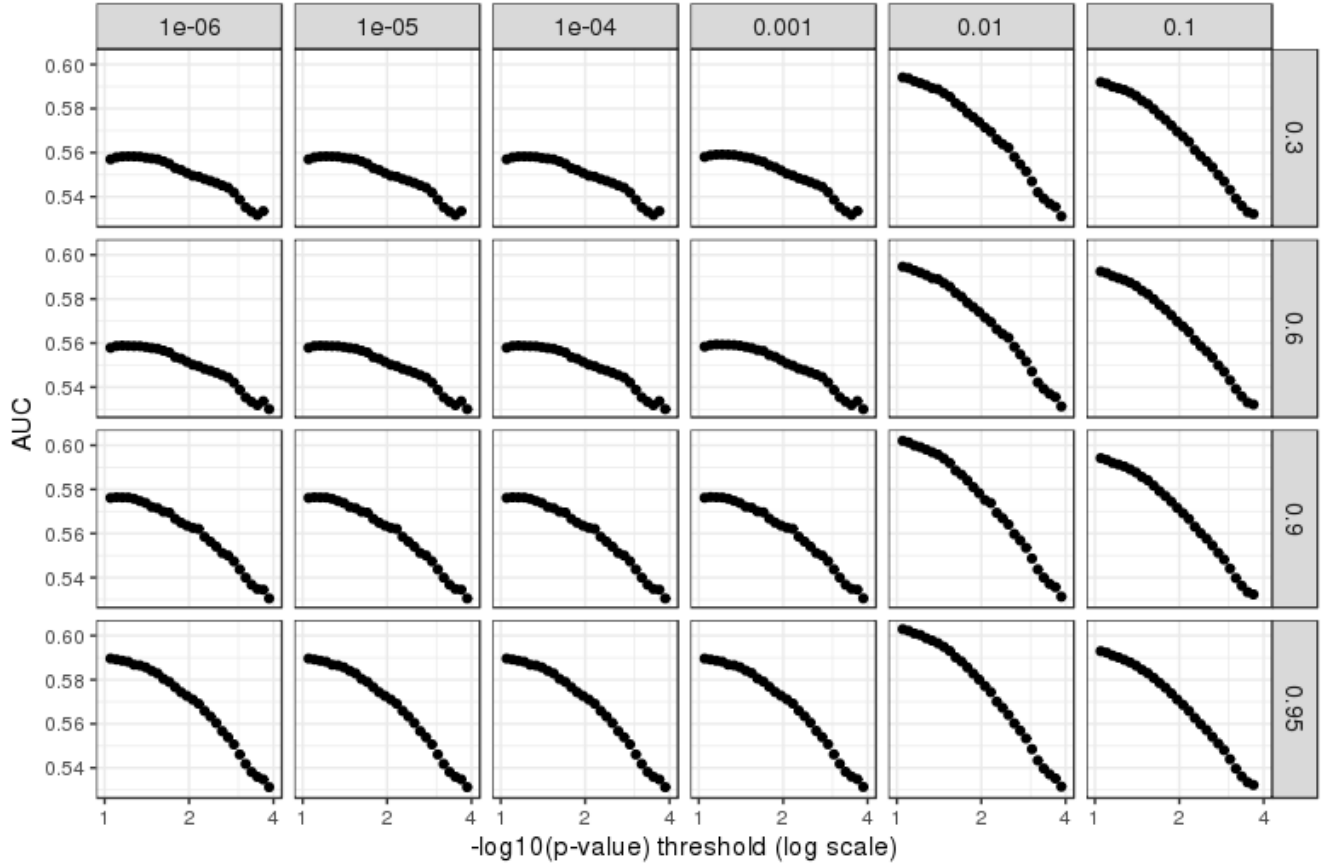


Figure S10: AUC results of all C+T scores for MDD when including MAF. AUC values (for the training set) when predicting MDD status for many parameters of C+T in real data application. Facets are presenting different MAF thresholds (top), and imputation thresholds from 0.3 to 0.95 (right). Parameter r_c^2 was fixed at 0.5 and w_c at 1000 kb. The x-axis corresponds to the remaining hyper-parameter, the p-value threshold p_T ; here, $-\log_{10}(\text{p-values})$ are represented using a logarithmic scale.

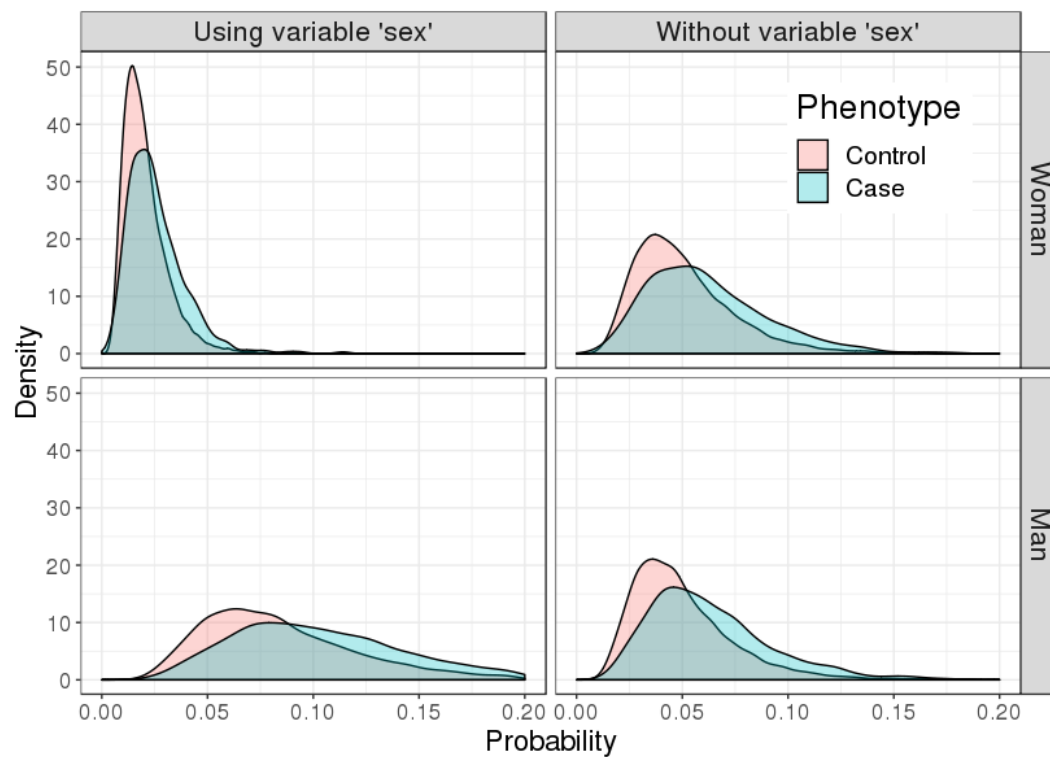


Figure S11: Distribution of CAD predictions. Distribution of predicted probabilities of Coronary Artery Disease (CAD) in the UK Biobank using SCT. Upper / lower panels corresponds to women / men. Left panels correspond to a model using C+T scores and variable 'sex' when fitting penalized logistic regression in the stacking step. Right panels correspond to performing stacking of C+T scores without using variable 'sex'.

Scenario	stdCT	maxCT	SCT	lassosum	LDpred
100	82.0 [81.6-82.5]	86.8 [86.4-87.2]	86.1 [85.7-86.5]	83.9 [83.5-84.4]	76.3 [75.7-77.0]
10K	72.4 [71.5-73.5]	75.6 [75.1-76.1]	76.4 [75.9-77.0]	75.0 [74.4-75.7]	71.2 [70.6-71.9]
1M	68.7 [68.1-69.2]	69.0 [68.3-69.6]	69.1 [68.6-69.6]	70.1 [69.5-70.6]	71.0 [70.3-71.6]
2chr	77.4 [76.9-78.0]	78.8 [78.3-79.4]	82.1 [81.6-82.7]	79.0 [78.3-79.8]	74.6 [73.6-75.8]
err	70.1 [69.3-70.9]	70.9 [70.5-71.5]	73.4 [72.8-74.1]	72.0 [71.3-72.9]	70.7 [70.1-71.4]
HLA	78.7 [78.0-79.5]	79.8 [79.2-80.3]	80.7 [80.2-81.3]	79.4 [78.7-80.2]	76.9 [76.3-77.4]

Table S1: Results of the 6 simulation scenarios with well imputed variants. Scenarios are (100) 100 random causal variants; (10K) 10,000 random causal variants; (1M) all 1M variants are causal variants; (2chr) 100 variants of chromosome 1 are causal and all variants of chromosome 2, with half of the heritability for both chromosomes; (err) 10,000 random causal variants, but 10% of the GWAS effects are reported with an opposite effect; (HLA) 7105 causal variants in a long-range LD region of chromosome 6. Mean and 95% CI of 10^4 non-parametric bootstrap replicates of the mean AUC of 10 simulations for each scenario. These results are plotted in figure 1.

Trait	stdCT	maxCT	SCT	lassosum
Breast cancer (BRCA)	62.1 [60.5-63.6] 6256	63.3 [61.7-64.8] 2572	65.9 [64.4-67.4] 670,050	57.9 [56.3-59.5] 322,003
Rheumatoid arthritis (RA)	59.8 [57.7-61.8] 12,220	60.3 [58.3-62.4] 88,556	61.3 [59.1-63.4] 317,456	59.5 [57.5-61.7] 672,922
Type 1 diabetes (T1D)	75.4 [72.4-78.4] 1112	76.9 [73.9-79.7] 267	78.7 [75.7-81.7] 135,991	75.3 [72.2-78.3] 204,785
Type 2 diabetes (T2D)	59.1 [58.1-60.1] 177	60.7 [59.8-61.7] 33,235	63.8 [62.9-64.7] 548,343	63.2 [62.3-64.1] 256,353
Prostate cancer (PRCA)	68.0 [66.5-69.5] 1035	69.3 [67.8-70.8] 356	71.7 [70.2-73.1] 696,575	58.7 [57.1-60.3] 121,660
Depression (MDD)	55.7 [54.4-56.9] 165,584	59.2 [58.0-60.4] 222,912	59.5 [58.2-60.7] 524,099	52.0 [50.8-53.3] 625,732
Coronary artery disease (CAD)	59.9 [58.6-61.2] 1182	61.1 [59.9-62.4] 87,577	63.9 [62.7-65.1] 315,165	63.0 [61.8-64.2] 290,204
Asthma	56.8 [56.2-57.5] 3034	57.3 [56.7-58.0] 360	60.7 [60.0-61.3] 446,120	58.7 [58.1-59.4] 75,965

Table S2: Results of the real data applications with large training size. AUC values on the test set of UKBB (mean [95% CI] from 10^4 bootstrap samples) and the number of variants used in the final model. Training SCT and choosing optimal hyper-parameters for C+T and lassosum use 63%-90% of the individuals reported in table 1. These results are plotted in figure 2.

Scenario	stdCT	maxCT	SCT	lassosum
100	77.4 [76.0-78.8]	83.9 [83.4-84.4]	83.1 [82.6-83.6]	80.1 [79.5-80.8]
10K	69.4 [68.4-70.5]	73.0 [72.5-73.4]	72.9 [72.5-73.3]	71.2 [70.6-71.7]
1M	64.0 [63.6-64.4]	64.0 [63.6-64.4]	62.7 [62.3-63.0]	64.1 [63.3-64.8]
2chr	70.0 [68.8-71.2]	74.4 [73.6-75.2]	78.5 [77.9-79.1]	73.2 [72.5-73.8]
err	67.0 [66.0-68.1]	68.6 [67.7-69.5]	69.5 [68.9-70.1]	65.6 [64.9-66.3]
HLA	74.8 [72.9-76.3]	75.3 [73.5-76.9]	76.4 [74.5-78.0]	75.8 [74.2-77.2]

Table S3: Results of the 6 simulation scenarios with less well imputed variants. AUC values on the test set for simulations with less well imputed variants (mean [95% CI] from 10^4 bootstrap samples). These results are plotted in figure S3.

Trait	stdCT	maxCT	SCT	lassosum	LDpred
Breast cancer (BRCA)	61.9 [61.8-62.0]	62.9 [62.6-63.2]	62.7 [62.4-63.1]	57.8 [57.1-58.5]	62.0 [62.0-62.1]
Rheumatoid arthritis (RA)	59.1 [59.0-59.2]	59.5 [59.3-59.7]	59.6 [59.3-59.8]	58.8 [58.2-59.3]	59.8 [59.7-59.8]
Type 1 diabetes (T1D)	75.4 [74.6-76.2]	76.0 [75.1-77.0]	78.4 [77.7-79.1]	75.5 [74.7-76.2]	75.5 [74.7-76.3]
Type 2 diabetes (T2D)	59.6 [59.5-59.7]	60.4 [60.2-60.7]	60.9 [60.6-61.1]	63.2 [62.9-63.5]	61.0 [60.6-61.3]
Prostate cancer (PRCA)	67.0 [66.8-67.2]	68.5 [68.3-68.7]	69.0 [68.5-69.4]	57.1 [56.3-58.1]	65.6 [65.5-65.7]
Depression (MDD)	54.1 [53.7-54.4]	58.7 [58.3-59.0]	54.7 [54.4-55.0]	52.9 [52.0-53.8]	60.0 [60.0-60.1]
Coronary artery disease (CAD)	59.7 [59.5-59.9]	61.1 [60.6-61.5]	60.8 [60.6-61.1]	62.8 [62.6-62.9]	61.0 [60.9-61.1]
Asthma	56.3 [56.2-56.5]	56.9 [56.8-56.9]	56.3 [55.6-56.9]	57.7 [57.3-58.0]	56.5 [56.3-56.7]

Table S4: Results of the real data applications with small training size. Mean and 95% CI of 10^4 non-parametric bootstrap replicates of the mean AUC of 6 random splits to define the training set. Training SCT and choosing optimal hyper-parameters for C+T, LDpred and lassosum use 500 cases and 2000 controls only. These results are plotted in figure S4.

Caution on using covariates

For example, because prevalence of CAD is much higher in men than in women in the UKBB (8-9% vs 2%), adding sex in the model amount to fitting two different intercepts, centering distributions of fitted probabilities around disease prevalence (Figure S11). This increases the AUC from 63.9% to 74.4% but results in a model that would classify all women as healthy. A possible solution would be to report AUC figures for each gender separately, or even to fit a model for each gender separately (in the stacking step). Fitting models separately would enable the use of sex chromosomes without introducing bias. As for ancestry concerns, fitting different models for different ancestries might be a way to get more calibrated results and to account for differences in effect sizes and LD. However, here for CAD, fitting two separate models for each gender results in a slight loss of predictive performance, while using variable 'sex' does not change results when they are reported for each gender separately, with an AUC of 64.9% [63.5-66.3] for men and 62.5% [59.8-65.2] for women. Thus, adding 'sex' as a covariate in the model may provide a model with similar discrimination and with better calibration of probabilities (if prevalence in the data is representative of prevalence in the population). Yet, we would like to emphasize again that reporting one AUC figure for all individuals would be misleading in the case of using variable 'sex' in the model.

References

- [1] Wray, N. R., Yang, J., Goddard, M. E., and Visscher, P. M. (2010). The genetic interpretation of area under the ROC curve in genomic profiling. *PLoS genetics* 6, e1000864.