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Supplemental Data

Mixed Model with Correction for Case-Control Ascertainment Increases Association Power

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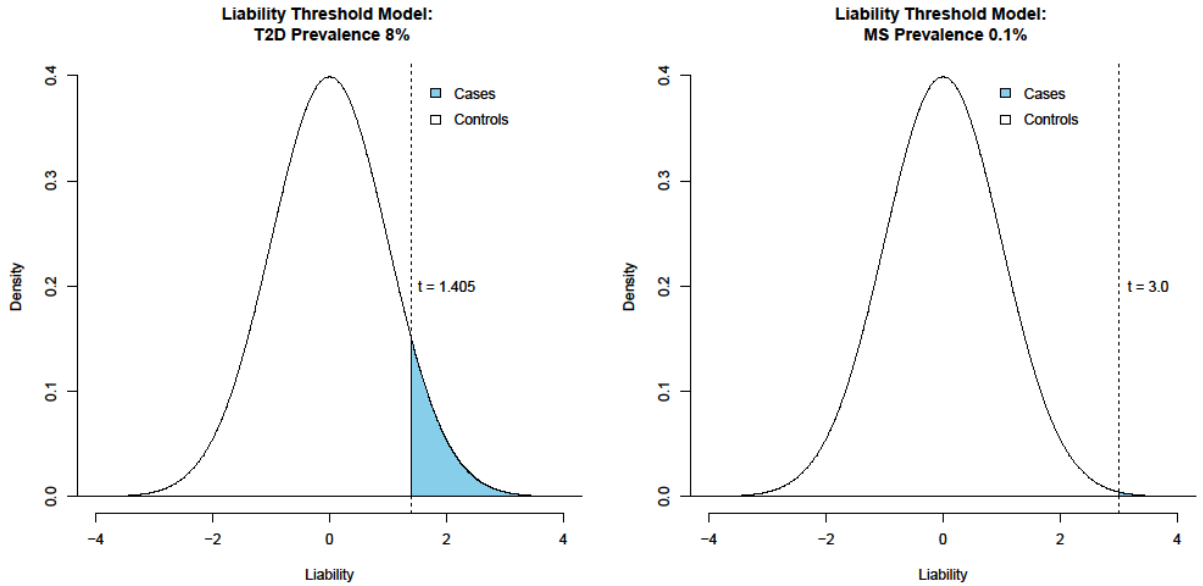

Figure S1. Liability Threshold Model. The liability threshold model performs a transformation based on disease prevalence. As ascertainment becomes more drastic so does the difference between the PML for cases versus controls. In Figure S1, the portion of the population above the threshold is a case (blue). For T2D, at a prevalence of 8% (blue), the threshold is set to 1.405. In this region, the expected value for the posterior liability is 1.85 and the expected value for the controls is -0.14. Comparing T2D to MS with disease prevalence around 0.1% and t around 3.00, the PML_{indiv} for a control is 0.00 and 3.33 for a case. As the disease prevalence goes down the difference in the PML_{indiv} for cases versus controls increases, the transformation plays a larger role for rare diseases and results in a power gain for the LTMLM.

A **B**

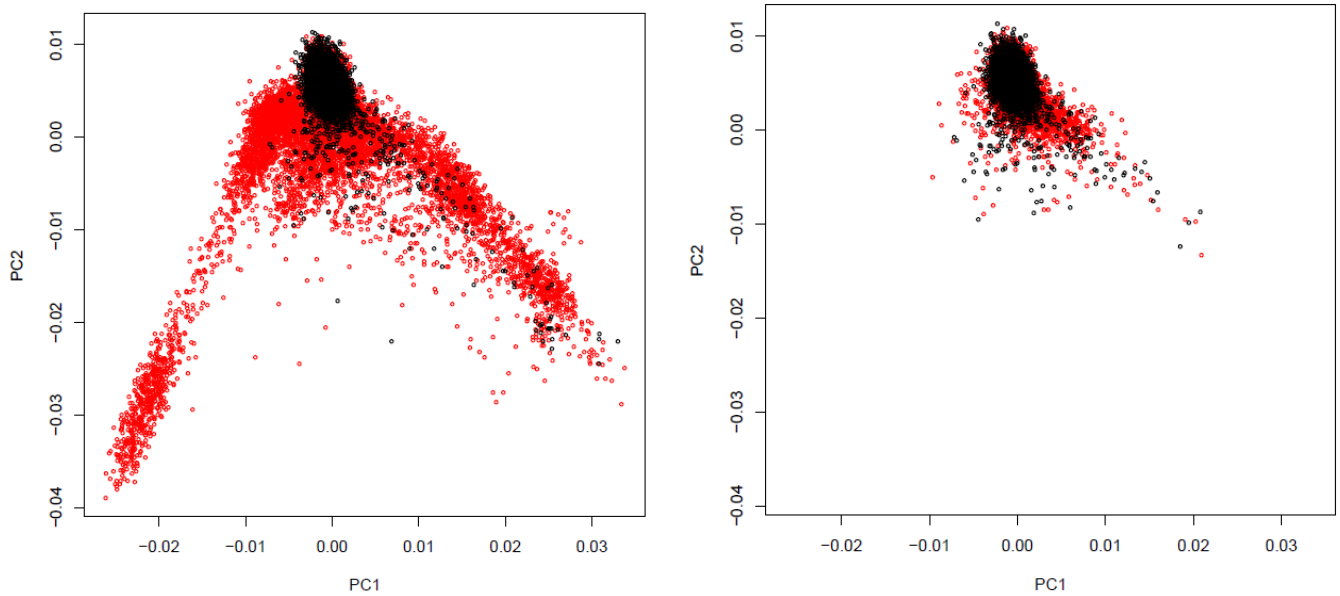

Figure S2. Mismatch in ancestry between MS cases and controls. We plot the first two principal components for (a) unmatched data with a severe mismatch (5,429 MS cases and 10,204controls), (b) stringently matched data using the first 20 PC(4,094 MS cases and 4,094 controls). The controls are depicted in red and cases in black. After PC matching the remaining samples show considerably less population stratification differentiation between cases and controls.

Term	Description
φ	Quantitative liability, the unobserved trait
β	Effect Size of the SNP
x	Genotype values of candidate SNP, normalized to mean 0 variance 1
u	Genetic random effect excluding the candidate SNP
e	Environmental component
X	Matrix of genotype values of non-candidate SNPs, normalized to mean 0 and variance 1
π	Observed binary case control phenotype.
t	Threshold corresponding to the disease prevalence
K	Prevalence of the disease in the population
P	Proportion of cases in the sample
$\widehat{\boldsymbol{\Theta}}$	Genetic Relationship Matrix (GRM) computed from the data
Θ	True underlying Genetic Relationship Matrix (GRM)
V	Phenotypic covariance matrix
I	Identity matrix
h^2	Heritability parameter

Table S1: Description of notation used and a brief description of the terms.

Computation	ATT	MLM	LTMLM
GRM and V^{-1}	NA	$O(MN^2)$	$O(MN^2)$
PML	NA	NA	$O(MN^2)$
Assoc. Statistic	$O(MN)$	$O(MN)$ or $O(MN^2)$	$O(MN)$
Overall	$O(MN)$	$O(MN^2)$	$O(MN^2)$

Table S2. Computational cost. M is the number of SNPs and N is the number of individuals. We assume that $M > N >$ #MCMC iterations. The details of the computational costs of MLM are provided in Table 1 of ref[11].

N	M	Prev	α	set	ATT Liability	MLM Liability	ATT	LogR	MLM	LTMLM
1000	1000	50%	0.05	causal	0.732(0.015)	0.741(0.015)	0.663(0.016)	0.663(0.016)	0.671(0.016)	0.670(0.016)
			0.001	causal	0.548(0.017)	0.562(0.017)	0.444(0.017)	0.443(0.017)	0.447(0.017)	0.444(0.017)
			$1x10^{-6}$	causal	0.331(0.016)	0.353(0.016)	0.227(0.014)	0.224(0.014)	0.236(0.014)	0.234(0.014)
			$5x10^{-8}$	causal	0.275(0.015)	0.287(0.015)	0.179(0.013)	0.175(0.013)	0.177(0.013)	0.178(0.013)
			0.05	null	0.050(0.001)	0.049(0.001)	0.051(0.001)	0.051(0.001)	0.051(0.001)	0.051(0.001)
			0.001	null	$0.001(1x10^{-4})$	$0.001(1x10^{-4})$	$0.001(2x10^{-4})$	$0.001(2x10^{-4})$	$0.001(2x10^{-4})$	$0.001(2x10^{-4})$
			$1x10^{-6}$	null	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)
			$5x10^{-8}$	null	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)
		25%	0.05	causal	0.704(0.015)	0.712(0.015)	0.648(0.016)	0.648(0.016)	0.652(0.016)	0.653(0.016)
			0.001	causal	0.544(0.017)	0.557(0.017)	0.456(0.017)	0.455(0.017)	0.460(0.017)	0.466(0.017)
			$1x10^{-6}$	causal	0.379(0.016)	0.383(0.016)	0.271(0.015)	0.268(0.015)	0.267(0.015)	0.272(0.015)
			$5x10^{-8}$	causal	0.318(0.016)	0.334(0.016)	0.219(0.014)	0.215(0.014)	0.226(0.014)	0.224(0.014)
			0.05	null	0.051(0.001)	0.051(0.001)	0.050(0.001)	0.049(0.001)	0.050(0.001)	0.049(0.001)
			0.001	null	$0.001(1x10^{-4})$	$0.001(1x10^{-4})$	$0.001(1x10^{-4})$	$0.001(1x10^{-4})$	$0.001(1x10^{-4})$	$0.001(1x10^{-4})$
			$1x10^{-6}$	null	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)
			$5x10^{-8}$	null	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)
		10%	0.05	causal	0.761(0.014)	0.752(0.014)	0.708(0.015)	0.708(0.015)	0.708(0.015)	0.711(0.015)
			0.001	causal	0.589(0.016)	0.601(0.016)	0.51(0.017)	0.509(0.017)	0.514(0.017)	0.516(0.017)
			$1x10^{-6}$	causal	0.410(0.016)	0.417(0.016)	0.325(0.016)	0.323(0.016)	0.325(0.016)	0.330(0.016)
			$5x10^{-8}$	causal	0.362(0.016)	0.377(0.016)	0.266(0.015)	0.259(0.015)	0.268(0.015)	0.277(0.015)
			0.05	null	0.050(0.001)	0.051(0.001)	0.049(0.001)	0.049(0.001)	0.050(0.001)	0.050(0.001)
			0.001	null	$0.001(2x10^{-4})$	$0.001(1x10^{-4})$	$0.001(1x10^{-4})$	$0.001(1x10^{-4})$	$0.001(1x10^{-4})$	$0.001(1x10^{-4})$
			$1x10^{-6}$	null	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)
			$5x10^{-8}$	null	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)
		1%	0.05	causal	0.803(0.013)	0.796(0.013)	0.767(0.014)	0.767(0.014)	0.753(0.014)	0.769(0.014)
			0.001	causal	0.666(0.016)	0.665(0.016)	0.632(0.016)	0.632(0.016)	0.619(0.016)	0.638(0.016)
			$1x10^{-6}$	causal	0.548(0.016)	0.543(0.016)	0.496(0.017)	0.491(0.017)	0.477(0.017)	0.501(0.017)
			$5x10^{-8}$	causal	0.504(0.016)	0.500(0.016)	0.449(0.016)	0.447(0.016)	0.433(0.016)	0.451(0.016)
			0.05	null	0.050(0.001)	0.048(0.001)	0.050(0.001)	0.050(0.001)	0.049(0.001)	0.050(0.001)
			0.001	null	$0.001(1x10^{-4})$	$0.001(1x10^{-4})$	$0.001(1x10^{-4})$	$0.001(1x10^{-4})$	$0.001(1x10^{-4})$	$0.001(1x10^{-4})$
			$1x10^{-6}$	null	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)
			$5x10^{-8}$	null	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)

		0.1%	0.05	causal	0.820(0.013)	0.811(0.013)	0.815(0.013)	0.815(0.013)	0.801(0.013)	0.818(0.013)
			0.001	causal	0.727(0.015)	0.689(0.015)	0.697(0.015)	0.697(0.015)	0.656(0.016)	0.695(0.015)
			$1x10^{-6}$	causal	0.585(0.016)	0.559(0.016)	0.551(0.016)	0.547(0.016)	0.510(0.017)	0.559(0.016)
			$5x10^{-8}$	causal	0.548(0.016)	0.511(0.016)	0.512(0.016)	0.510(0.016)	0.475(0.017)	**0.525(0.016)**
			0.05	null	0.050(0.001)	0.046(0.001)	0.050(0.001)	0.049(0.001)	0.048(0.001)	0.050(0.001)
			0.001	null	0.001($1x10^{-4}$)	0.001($1x10^{-4}$)	0.001($1x10^{-4}$)	0.001($1x10^{-4}$)	0.001($1x10^{-4}$)	0.001($1x10^{-4}$)
			$1x10^{-6}$	null	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)
			$5x10^{-8}$	null	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)
5000	1000	50%	0.05	causal	0.700(0.016)	0.700 (0.016)	0.642(0.017)	0.639(0.017)	0.637(0.017)	0.636(0.017)
			0.001	causal	0.526(0.017)	0.529(0.017)	0.422(0.017)	0.420(0.017)	0.424(0.017)	0.424(0.017)
			$1x10^{-6}$	causal	0.337(0.016)	0.341(0.016)	0.234(0.015)	0.231(0.015)	0.240(0.015)	0.241(0.015)
			$5x10^{-8}$	causal	0.290(0.015)	0.288(0.015)	0.19(0.014)	0.185(0.013)	0.191(0.014)	0.190(0.013)
			0.05	null	0.050($4x10^{-4}$)	0.050($4x10^{-4}$)	0.050($4x10^{-4}$)	0.050($4x10^{-4}$)	0.050($4x10^{-4}$)	0.050($4x10^{-4}$)
			0.001	null	0.001($6x10^{-5}$)	0.001($6x10^{-5}$)	0.001($6x10^{-5}$)	0.001($6x10^{-5}$)	0.001($6x10^{-5}$)	0.001($6x10^{-5}$)
			$1x10^{-6}$	null	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)
			$5x10^{-8}$	null	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)
		25%	0.05	causal	0.727(0.015)	0.723(0.015)	0.649(0.016)	0.649(0.016)	0.647(0.016)	0.646(0.016)
			0.001	causal	0.534(0.017)	0.537(0.017)	0.446(0.017)	0.444(0.017)	0.443(0.017)	0.445(0.017)
			$1x10^{-6}$	causal	0.369(0.016)	0.376(0.016)	0.271(0.015)	0.269(0.015)	0.270(0.015)	0.270(0.015)
			$5x10^{-8}$	causal	0.324(0.016)	0.324(0.016)	0.228(0.014)	0.227(0.014)	0.228(0.014)	0.228(0.014)
			0.05	null	0.050($4x10^{-4}$)	0.050($4x10^{-4}$)	0.050($4x10^{-4}$)	0.050($4x10^{-4}$)	0.050($4x10^{-4}$)	0.050($4x10^{-4}$)
			0.001	null	0.001($6x10^{-5}$)	0.001($6x10^{-5}$)	0.001($6x10^{-5}$)	0.001($6x10^{-5}$)	0.001($6x10^{-5}$)	0.001($6x10^{-5}$)
			$1x10^{-6}$	null	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)
			$5x10^{-8}$	null	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)
		10%	0.05	causal	0.741(0.015)	0.747(0.015)	0.691(0.016)	0.690(0.016)	0.694(0.016)	0.694(0.016)
			0.001	causal	0.579(0.016)	0.586(0.016)	0.518(0.017)	0.516(0.017)	0.520(0.017)	0.516(0.017)
			$1x10^{-6}$	causal	0.405(0.016)	0.403(0.016)	0.305(0.016)	0.303(0.016)	0.305(0.016)	0.307(0.016)
			$5x10^{-8}$	causal	0.349(0.016)	0.355(0.016)	0.248(0.015)	0.245(0.015)	0.249(0.015)	0.249(0.015)
			0.05	null	0.050($4x10^{-4}$)	0.050($4x10^{-4}$)	0.051($4x10^{-4}$)	0.050($4x10^{-4}$)	0.050($4x10^{-4}$)	0.051($4x10^{-4}$)

			0.001	null	0.001($6x10^{-5}$)	0.001($6x10^{-5}$)	0.001($7x10^{-5}$)	0.001($6x10^{-5}$)	0.001($6x10^{-5}$)	0.001($7x10^{-5}$)
			$1x10^{-6}$	null	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)
			$5x10^{-8}$	null	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)
		1%	0.05	causal	0.827(0.012)	0.834(0.012)	0.806(0.013)	0.806(0.013)	0.801(0.013)	0.807(0.013)
			0.001	causal	0.700(0.015)	0.700(0.015)	0.668(0.016)	0.664(0.016)	0.66(0.016)	0.663(0.016)
			$1x10^{-6}$	causal	0.555(0.016)	0.551(0.016)	0.499(0.017)	0.496(0.017)	0.494(0.017)	0.503(0.017)
			$5x10^{-8}$	causal	0.514(0.016)	0.509(0.016)	0.443(0.016)	0.441(0.016)	0.44(0.016)	0.446(0.016)
			0.05	null	0.050($4x10^{-4}$)	0.050($4x10^{-4}$)	0.050($4x10^{-4}$)	0.050($4x10^{-4}$)	0.050($4x10^{-4}$)	0.050($4x10^{-4}$)
			0.001	null	0.001($6x10^{-5}$)	0.001($6x10^{-5}$)	0.001($6x10^{-5}$)	0.001($6x10^{-5}$)	0.001($6x10^{-5}$)	0.001($6x10^{-5}$)
			$1x10^{-6}$	null	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)
			$5x10^{-8}$	null	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)
		0.1%	0.05	causal	0.845(0.012)	0.854(0.012)	0.852(0.012)	0.852(0.012)	0.848(0.012)	0.852(0.012)
			0.001	causal	0.771(0.014)	0.770(0.014)	0.775(0.014)	0.775(0.014)	0.770(0.014)	0.770(0.014)
			$1x10^{-6}$	causal	0.689(0.015)	0.667(0.015)	0.657(0.016)	0.657(0.016)	0.631(0.016)	**0.688(0.015)**
			$5x10^{-8}$	causal	0.666(0.016)	0.654(0.016)	0.620(0.016)	0.593(0.016)	0.555(0.016)	0.590(0.016)
			0.05	null	0.049($4x10^{-4}$)	0.049($4x10^{-4}$)	0.051($4x10^{-4}$)	0.051($4x10^{-4}$)	0.049($4x10^{-4}$)	0.051($4x10^{-4}$)
			0.001	null	0.001($7x10^{-5}$)	0.001($6x10^{-5}$)	0.001($6x10^{-5}$)	0.001($6x10^{-5}$)	0.001($6x10^{-5}$)	0.001($6x10^{-5}$)
			$1x10^{-6}$	null	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)
			$5x10^{-8}$	null	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)
5000	5000	50%	0.05	causal	0.696(0.007)	0.703(0.007)	0.630(0.007)	0.629(0.007)	0.633(0.007)	0.632(0.007)
			0.001	causal	0.519(0.008)	0.530(0.008)	0.415(0.008)	0.415(0.008)	0.424(0.008)	0.424(0.008)
			$1x10^{-6}$	causal	0.332(0.007)	0.344(0.007)	0.229(0.006)	0.229(0.006)	0.236(0.007)	0.235(0.007)
			$5x10^{-8}$	causal	0.285(0.007)	0.295(0.007)	0.186(0.006)	0.184(0.006)	0.191(0.006)	0.190(0.006)
			0.05	null	0.0491($4x10^{-4}$)	0.049($4x10^{-4}$)	0.049($4x10^{-4}$)	0.049($4x10^{-4}$)	0.049($4x10^{-4}$)	0.049($4x10^{-4}$)
			0.001	null	0.001 ($6x10^{-5}$)	0.001($6x10^{-5}$)	0.001($6x10^{-5}$)	0.001($6x10^{-5}$)	0.001($6x10^{-5}$)	0.001($6x10^{-5}$)
			$1x10^{-6}$	null	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)
			$5x10^{-8}$	null	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)
		25%	0.05	causal	0.694(0.007)	0.700(0.007)	0.628(0.007)	0.628(0.007)	0.632(0.007)	0.632(0.007)
			0.001	causal	0.512(0.008)	0.523(0.008)	0.427(0.008)	0.427(0.008)	0.434(0.008)	0.434(0.008)

		$1x10^{-6}$	causal	0.344(0.007)	0.355(0.007)	0.260(0.007)	0.260(0.007)	0.265(0.007)	0.265(0.007)
		$5x10^{-8}$	causal	0.297(0.007)	0.307(0.007)	0.211(0.006)	0.211(0.006)	0.215(0.006)	0.215(0.006)
		0.05	null	$0.050(4x10^{-4})$	$0.050(4x10^{-4})$	$0.050(4x10^{-4})$	$0.050(4x10^{-4})$	$0.050(4x10^{-4})$	$0.050(4x10^{-4})$
		0.001	null	$0.001\ (7x10^{-5})$	$0.001(6x10^{-5})$	$0.001\ (6x10^{-5})$	$0.001(6x10^{-5})$	$0.001(6x10^{-5})$	$0.001(6x10^{-5})$
		$1x10^{-6}$	null	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)
		$5x10^{-8}$	null	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)
	10%	0.05	causal	0.751(0.006)	0.758(0.006)	0.704(0.007)	0.703(0.007)	0.706(0.007)	0.709(0.007)
		0.001	causal	0.592(0.007)	0.597(0.007)	0.516(0.008)	0.516(0.008)	0.517(0.008)	0.520(0.008)
		$1x10^{-6}$	causal	0.428(0.007)	0.434(0.007)	0.335(0.007)	0.334(0.007)	0.335(0.007)	0.339(0.007)
		$5x10^{-8}$	causal	0.373(0.007)	0.384(0.007)	0.278(0.007)	0.277(0.007)	0.280(0.007)	0.285(0.007)
		0.05	null	$0.049(4x10^{-4})$	$0.049(4x10^{-4})$	$0.049(4x10^{-4})$	$0.049(4x10^{-4})$	$0.049(4x10^{-4})$	$0.050(4x10^{-4})$
		0.001	null	$0.001\ (6x10^{-5})$	$0.001(6x10^{-5})$	$0.001\ (6x10^{-5})$	$0.001(6x10^{-5})$	$0.001(6x10^{-5})$	$0.001(6x10^{-5})$
		$1x10^{-6}$	null	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)
		$5x10^{-8}$	null	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)
	1%	0.05	causal	0.805(0.006)	0.803(0.006)	0.775(0.006)	0.775(0.006)	0.773(0.006)	0.780(0.006)
		0.001	causal	0.668(0.007)	0.664(0.007)	0.626(0.007)	0.626(0.007)	0.618(0.007)	0.631(0.007)
		$1x10^{-6}$	causal	0.526(0.007)	0.516(0.007)	0.479(0.007)	0.479(0.007)	0.468(0.007)	0.485(0.007)
		$5x10^{-8}$	causal	0.482(0.007)	0.469(0.007)	0.429(0.007)	0.428(0.007)	0.415(0.007)	0.433(0.007)
		0.05	null	$0.050(4x10^{-4})$	$0.045(4x10^{-4})$	$0.050(4x10^{-4})$	$0.050(4x10^{-4})$	$0.050(4x10^{-4})$	$0.050(4x10^{-4})$
		0.001	null	$0.001(6x10^{-5})$	$0.001(5x10^{-5})$	$0.001(6x10^{-5})$	$0.001(6x10^{-5})$	$0.001(6x10^{-5})$	$0.001(6x10^{-5})$
		$1x10^{-6}$	null	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)
		$5x10^{-8}$	null	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)
	0.1%	0.05	causal	0.833(0.005)	0.812(0.006)	0.818(0.006)	0.818(0.006)	0.799(0.006)	0.821(0.006)
		0.001	causal	0.726(0.007)	0.697(0.007)	0.702(0.007)	0.702(0.007)	0.670(0.007)	0.705(0.007)
		$1x10^{-6}$	causal	0.599(0.007)	0.554(0.007)	0.562(0.007)	0.560(0.007)	0.516(0.007)	0.564(0.007)
		$5x10^{-8}$	causal	0.554(0.007)	0.510(0.007)	0.516(0.007)	0.516(0.007)	0.470(0.007)	0.519(0.007)
		0.05	null	$0.050(4x10^{-4})$	$0.0324(4x10^{-4})$	$0.050(4x10^{-4})$	$0.050(4x10^{-4})$	$0.040(4x10^{-4})$	$0.050(4x10^{-4})$
		0.001	null	$0.001\ (6x10^{-5})$	$3x10^{-4}(4x10^{-5})$	$0.001(6x10^{-5})$	$0.001(6x10^{-5})$	$0.001(5x10^{-5})$	$0.001(6x10^{-5})$

			$1x10^{-6}$	null	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)
			$5x10^{-8}$	null	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)
5000	50000	50%	0.05	causal	0.702(0.007)	0.703(0.007)	0.631(0.007)	0.631(0.007)	0.631(0.007)	0.631(0.007)
			0.001	causal	0.518(0.008)	0.520(0.008)	0.418(0.008)	0.418(0.008)	0.419(0.008)	0.420(0.008)
			$1x10^{-6}$	causal	0.331(0.007)	0.333(0.007)	0.231(0.006)	0.230(0.006)	0.232(0.006)	0.231(0.006)
			$5x10^{-8}$	causal	0.278(0.007)	0.280(0.007)	0.183(0.006)	0.182(0.006)	0.183(0.006)	0.184(0.006)
			0.05	null	$0.050(1x10^{-4})$	$0.050(1x10^{-4})$	$0.050(1x10^{-4})$	$0.050(1x10^{-4})$	$0.050(1x10^{-4})$	$0.050(1x10^{-4})$
			0.001	null	$0.001(2x10^{-5})$	$0.001(2x10^{-5})$	$0.001(2x10^{-5})$	$0.001(2x10^{-5})$	$0.001(2x10^{-5})$	$0.001(2x10^{-5})$
			$1x10^{-6}$	null	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)
			$5x10^{-8}$	null	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)
		25%	0.05	causal	0.706(0.007)	0.710(0.007)	0.652(0.007)	0.652(0.007)	0.652(0.007)	0.652(0.007)
			0.001	causal	0.539(0.008)	0.540(0.008)	0.450(0.008)	0.449(0.008)	0.450(0.008)	0.450(0.008)
			$1x10^{-6}$	causal	0.362(0.007)	0.363(0.007)	0.259(0.007)	0.259(0.007)	0.262(0.007)	0.261(0.007)
			$5x10^{-8}$	causal	0.308(0.007)	0.312(0.007)	0.207(0.006)	0.206(0.006)	0.209(0.006)	0.209(0.006)
			0.05	null	$0.050(1x10^{-4})$	$0.050(1x10^{-4})$	$0.050(1x10^{-4})$	$0.050(1x10^{-4})$	$0.050(1x10^{-4})$	$0.050(1x10^{-4})$
			0.001	null	$0.001(2x10^{-5})$	$0.001(2x10^{-5})$	$0.001(2x10^{-5})$	$0.001(2x10^{-5})$	$0.001(2x10^{-5})$	$0.001(2x10^{-5})$
			$1x10^{-6}$	null	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)
			$5x10^{-8}$	null	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)
		10%	0.05	causal	0.751(0.006)	0.755(0.006)	0.726(0.007)	0.726(0.007)	0.725(0.007)	0.720(0.007)
			0.001	causal	0.629(0.007)	0.631(0.007)	0.548(0.008)	0.545(0.008)	0.555(0.007)	0.551(0.007)
			$1x10^{-6}$	causal	0.466(0.007)	0.474(0.007)	0.355(0.007)	0.355(0.007)	0.355(0.007)	0.355(0.007)
			$5x10^{-8}$	causal	0.381(0.007)	0.385(0.007)	0.272(0.007)	0.270(0.007)	0.274(0.007)	0.273(0.007)
			0.05	null	$0.050(1x10^{-4})$	$0.050(1x10^{-4})$	$0.050(1x10^{-4})$	$0.050(1x10^{-4})$	$0.050(1x10^{-4})$	$0.050(1x10^{-4})$
			0.001	null	$0.001(2x10^{-5})$	$0.001(2x10^{-5})$	$0.001(2x10^{-5})$	$0.001(2x10^{-5})$	$0.001(2x10^{-5})$	$0.001(2x10^{-5})$
			$1x10^{-6}$	null	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)
			$5x10^{-8}$	null	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)
		1%	0.05	causal	0.793(0.006)	0.795(0.006)	0.770(0.006)	0.770(0.006)	0.769(0.006)	0.770(0.006)
			0.001	causal	0.671(0.007)	0.671(0.007)	0.634(0.007)	0.634(0.007)	0.634(0.007)	0.637(0.007)
			$1x10^{-6}$	causal	0.526(0.007)	0.526(0.007)	0.477(0.007)	0.476(0.007)	0.476(0.007)	0.480(0.007)

		$5x10^{-8}$	causal	0.484(0.007)	0.485(0.007)	0.431(0.007)	0.431(0.007)	0.429(0.007)	0.432(0.007)
		0.05	null	$0.050(1x10^{-4})$	$0.050(1x10^{-4})$	$0.050(1x10^{-4})$	$0.050(1x10^{-4})$	$0.050(1x10^{-4})$	$0.050(1x10^{-4})$
		0.001	null	$0.001(2x10^{-5})$	$0.001(2x10^{-5})$	$0.001(2x10^{-5})$	$0.001(2x10^{-5})$	$0.001(2x10^{-5})$	$0.001(2x10^{-5})$
		$1x10^{-6}$	null	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)
		$5x10^{-8}$	null	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)
	0.1%	0.05	causal	0.835(0.005)	0.833(0.005)	0.821(0.006)	0.820(0.006)	0.817(0.006)	0.821(0.006)
		0.001	causal	0.719(0.007)	0.717(0.007)	0.697(0.007)	0.697(0.007)	0.688(0.007)	0.697(0.007)
		$1x10^{-6}$	causal	0.588(0.007)	0.587(0.007)	0.561(0.007)	0.560(0.007)	0.557(0.007)	0.560(0.007)
		$5x10^{-8}$	causal	0.547(0.007)	0.545(0.007)	0.517(0.007)	0.517(0.007)	0.508(0.007)	0.518(0.007)
		0.05	null	$0.050(1x10^{-4})$	$0.050(1x10^{-4})$	$0.050(1x10^{-4})$	$0.050(1x10^{-4})$	$0.050(1x10^{-4})$	$0.050(1x10^{-4})$
		0.001	null	$0.001(2x10^{-5})$	$0.001(2x10^{-5})$	$0.001(2x10^{-5})$	$0.001(2x10^{-5})$	$0.001(2x10^{-5})$	$0.001(2x10^{-5})$
		$1x10^{-6}$	null	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)
		$5x10^{-8}$	null	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)

Table S3. Percentage of SNPs achieving alpha levels for simulated genotypes and simulated phenotypes. We report the true positive and false positives at different α levels. For completeness, we also report ATT and MLM statistics computed using the underlying liability, where we again observe a loss in power for MLM at lower prevalence. In bold are the settings where LTMLM demonstrates at least a 5% power improvement over MLM.

N	M	Prev	Set	Statistic	ATT Liability	MLM Liability	ATT	LogR	MLM	LTMLM
1000	1000	50%	causal	average	25.716(1.091)	26.947(1.132)	16.847(0.715)	16.367(0.675)	17.254(0.735)	17.229(0.736)
			null	average	1.005(0.005)	1.003(0.005)	1.008(0.005)	1.006(0.005)	1.008(0.005)	1.007(0.005)
			all	average	1.252(0.014)	1.262(0.015)	1.166(0.010)	1.160(0.009)	1.171(0.010)	1.169(0.01)
			all	λ_{GC}	1.034(0.008)	1.033(0.008)	1.031(0.009)	1.031(0.009)	1.033(0.008)	1.032(0.008)
		25%	causal	average	28.716(1.229)	30.022(1.275)	19.112(0.824)	18.475(0.773)	19.553(0.849)	19.571(0.849)
			null	average	1.003(0.005)	1.004(0.005)	1.000(0.004)	0.998(0.004)	1.002(0.004)	1.001(0.004)
			all	average	1.280(0.016)	1.294(0.016)	1.181(0.011)	1.173(0.010)	1.187(0.011)	1.187(0.011)
			all	λ_{GC}	1.019(0.007)	1.021(0.007)	1.014(0.007)	1.013(0.007)	1.026(0.007)	1.02(0.007)
		10%	causal	average	34.541(1.501)	35.559(1.539)	23.777(1.021)	22.821(0.943)	24.084(1.053)	24.738(1.098)
			null	average	1.001(0.005)	1.004(0.005)	1.001(0.004)	0.999(0.004)	1.004(0.004)	1.003(0.004)
			all	average	1.336(0.019)	1.349(0.019)	1.229(0.013)	1.217(0.012)	1.235(0.014)	1.241(0.014)
			all	λ_{GC}	1.021(0.008)	1.028(0.008)	1.025(0.008)	1.025(0.008)	1.030(0.008)	1.029(0.008)
		1%	causal	average	55.732(2.12)	54.012(2.06)	42.316(1.565)	39.858(1.421)	40.611(1.539)	**45.336(1.756)**
			null	average	1.002(0.004)	0.988(0.004)	0.999(0.004)	0.997(0.004)	0.992(0.004)	0.999(0.004)
			all	average	1.550(0.028)	1.518(0.027)	1.412(0.021)	1.386(0.019)	1.388(0.020)	1.443(0.023)
			all	λ_{GC}	1.027(0.008)	1.012(0.007)	1.02(0.008)	1.019(0.008)	1.009(0.008)	1.018(0.008)
		0.1%	causal	average	73.159(2.847)	63.052(2.549)	58.946(2.157)	54.625(1.924)	51.507(2.045)	**65.991(2.656)**
			null	average	0.997(0.004)	0.974(0.004)	0.996(0.004)	0.994(0.004)	0.978(0.004)	0.996(0.004)
			all	average	1.718(0.037)	1.595(0.032)	1.575(0.029)	1.53(0.026)	1.483(0.026)	1.646(0.034)
			all	λ_{GC}	1.035(0.009)	1.008(0.007)	1.023(0.007)	1.023(0.007)	1.000(0.007)	1.014(0.008)
5000	1000	50%	causal	average	25.224(1.076)	25.503(1.084)	16.488(0.703)	16.029(0.666)	16.652(0.713)	16.625(0.714)
			null	average	1.002(0.002)	1.002(0.002)	1.000(0.002)	0.998(0.002)	1.000(0.002)	0.999(0.002)
			all	average	1.050(0.003)	1.051(0.003)	1.031(0.003)	1.028(0.003)	1.032(0.003)	1.031(0.003)
			all	λ_{GC}	1.006(0.003)	1.007(0.003)	1.005(0.003)	1.005(0.003)	1.006(0.003)	1.005(0.004)
		25%	causal	average	28.012(1.156)	28.279(1.163)	18.545(0.767)	17.985(0.726)	18.707(0.778)	18.757(0.783)
			null	average	1.004(0.002)	1.004(0.002)	1.002(0.002)	1.000(0.002)	1.002(0.002)	1.002(0.002)

			all	average	1.058(0.004)	1.059(0.004)	1.037(0.003)	1.034(0.003)	1.038(0.003)	1.037(0.003)
			all	λ_{GC}	1.010(0.003)	1.011(0.003)	1.003(0.003)	1.003(0.003)	1.004(0.003)	1.004(0.003)
		10%	causal	average	32.953(1.379)	33.282(1.395)	22.883(0.948)	22.028(0.886)	23.065(0.965)	23.497(0.996)
			null	average	1.005(0.002)	1.005(0.002)	1.004(0.002)	1.002(0.002)	1.004(0.002)	1.003(0.002)
			all	average	1.069(0.004)	1.070(0.004)	1.047(0.003)	1.044(0.003)	1.048(0.003)	1.048(0.003)
			all	λ_{GC}	1.009(0.003)	1.009(0.004)	0.999(0.003)	0.999(0.003)	1.003(0.003)	1.001(0.003)
		1%	causal	average	57.101(2.112)	56.546(2.100)	43.459(1.570)	40.939(1.426)	43.546(1.611)	**46.302(1.760)**
			null	average	1.002(0.002)	1.002(0.002)	1.001(0.002)	0.999(0.002)	1.001(0.002)	1.001(0.002)
			all	average	1.115(0.006)	1.113(0.006)	1.086(0.005)	1.079(0.004)	1.086(0.005)	1.091(0.005)
			all	λ_{GC}	1.007(0.004)	1.009(0.003)	1.003(0.003)	1.002(0.003)	1.005(0.003)	1.003(0.004)
		0.1%	causal	average	74.089(2.623)	68.943(2.51)	61.561(2.057)	57.182(1.828)	58.752(2.08)	**67.284(2.450)**
			null	average	0.997(0.002)	0.993(0.002)	0.996(0.002)	0.995(0.002)	0.991(0.002)	0.996(0.002)
			all	average	1.143(0.007)	1.129(0.007)	1.117(0.006)	1.107(0.005)	1.106(0.006)	1.128(0.007)
			all	λ_{GC}	1.004(0.001)	0.994(0.002)	0.989(0.001)	0.988(0.001)	1.005(0.002)	0.996(0.002)
5000	5000	50%	causal	average	25.372(0.496)	26.69(0.52)	16.492(0.325)	16.399(0.321)	16.88(0.332)	16.867(0.332)
			null	average	0.993(0.002)	0.994(0.002)	0.988(0.002)	0.988(0.002)	0.99(0.002)	0.989(0.002)
			all	average	1.237(0.006)	1.251(0.007)	1.143(0.004)	1.142(0.004)	1.148(0.004)	1.148(0.004)
			all	λ_{GC}	1.010(0.004)	1.01(0.003)	1.010(0.003)	1.010(0.003)	1.014(0.003)	1.014(0.003)
		25%	causal	average	28.119(0.588)	29.56(0.617)	18.637(0.388)	18.509(0.383)	19.014(0.396)	19.056(0.398)
			null	average	1.001(0.002)	1.001(0.002)	1.000(0.002)	1.000 (0.002)	1.000(0.002)	1.001(0.002)
			all	average	1.272(0.007)	1.287(0.008)	1.177(0.005)	1.175(0.005)	1.180(0.005)	1.181(0.005)
			all	λ_{GC}	1.019(0.004)	1.017(0.004)	1.012(0.004)	1.012(0.004)	1.013(0.004)	1.013(0.004)
		10%	causal	average	36.38(0.716)	37.626(0.742)	25.235(0.501)	25.014(0.492)	25.386(0.506)	25.778(0.514)
			null	average	0.996(0.002)	0.994(0.002)	0.993(0.002)	0.992(0.002)	0.991(0.002)	0.992(0.002)
			all	average	1.350(0.009)	1.361(0.009)	1.235(0.006)	1.233(0.006)	1.235(0.006)	1.240(0.007)
			all	λ_{GC}	1.016(0.003)	1.017(0.004)	1.005(0.003)	1.005(0.003)	1.007(0.003)	1.008(0.003)
		1%	causal	average	58.172(1.131)	55.473(1.077)	45.376(0.878)	44.682(0.852)	42.594(0.825)	**46.691(0.913)**
			null	average	1.000(0.002)	0.954(0.002)	1.000 (0.002)	0.999(0.002)	0.990(0.002)	1(0.002)

			all	average	1.571(0.014)	1.499(0.013)	1.444(0.011)	1.436(0.011)	1.406(0.010)	1.457(0.011)
			all	λ_{GC}	1.020(0.003)	0.970(0.005)	1.020(0.003)	1.020(0.003)	1.011(0.003)	1.019(0.003)
		0.1%	causal	average	81.745(1.565)	66.716(1.29)	68.648(1.301)	67.099(1.248)	56.303(1.082)	**70.81(1.364)**
			null	average	1.001(0.002)	0.840(0.002)	1.000(0.002)	1.000(0.002)	0.918(0.002)	1.000 (0.002)
			all	average	1.809(0.019)	1.499(0.016)	1.677(0.016)	1.661(0.016)	1.472(0.013)	1.698(0.017)
			all	λ_{GC}	1.022(0.003)	0.861(0.006)	1.026(0.003)	1.026(0.003)	0.942(0.005)	1.025(0.003)
5000	50000	50%	causal	average	25.501(0.504)	25.642(0.507)	16.624(0.331)	16.529(0.327)	16.673(0.332)	16.69(0.333)
			null	average	0.999(0.001)	0.999(0.001)	1.000 (0.001)	0.999(0.001)	1.000 (0.001)	1.000 (0.001)
			all	average	1.023(0.001)	1.024(0.001)	1.015(0.001)	1.015(0.001)	1.016(0.001)	1.015(0.001)
			all	λ_{GC}	0.999(0.001)	1.000 (0.001)	1.003(0.001)	1.002(0.001)	0.999(0.001)	0.999(0.001)
		25%	causal	average	28.475(0.555)	28.638(0.557)	18.965(0.37)	18.843(0.366)	19.03(0.372)	19.04(0.372)
			null	average	1.003(0.001)	1.003(0.001)	1.003(0.001)	1.003(0.001)	1.003(0.001)	1.003(0.001)
			all	average	1.030(0.001)	1.031(0.001)	1.021(0.001)	1.020(0.001)	1.021(0.001)	1.021(0.001)
			all	λ_{GC}	1.004(0.001)	1.004(0.001)	1.006(0.001)	1.006(0.001)	1.003(0.001)	1.003(0.001)
		10%	causal	average	34.358(0.639)	34.704(0.647)	23.71(0.444)	23.528(0.437)	23.868(0.449)	23.910(0.450)
			null	average	0.999(0.001)	1.000 (0.001)	1.001(0.001)	1.000 (0.001)	1.001(0.001)	1.001(0.001)
			all	average	1.033(0.001)	1.034(0.001)	1.023(0.001)	1.023(0.001)	1.024(0.001)	1.024(0.001)
			all	λ_{GC}	1.006(0.001)	1.008(0.002)	1.007(0.001)	1.007(0.001)	1.005(0.001)	1.004(0.001)
		1%	causal	average	60.112(1.139)	59.863(1.135)	46.683(0.883)	45.969(0.859)	46.44(0.881)	47.368(0.905)
			null	average	1.000 (0.001)	1.000 (0.001)	0.999(0.001)	0.999(0.001)	0.999(0.001)	0.999(0.001)
			all	average	1.059(0.002)	1.058(0.002)	1.045(0.001)	1.044(0.001)	1.045(0.001)	1.045(0.001)
			all	λ_{GC}	1.002(0.001)	1.002(0.001)	1.004(0.001)	1.004(0.001)	1.001(0.001)	1.000 (0.001)
		0.1%	causal	average	79.864(1.54)	77.754(1.502)	67.059(1.278)	65.561(1.225)	65.232(1.251)	**68.618(1.333)**
			null	average	1.000 (0.001)	0.999(0.001)	0.999(0.001)	0.999(0.001)	0.999(0.001)	0.999(0.001)
			all	average	1.078(0.002)	1.076(0.002)	1.065(0.002)	1.063(0.002)	1.063(0.002)	1.067(0.002)
			all	λ_{GC}	1.002(0.001)	1.001(0.001)	1.004(0.001)	1.004(0.001)	1.000(0.001)	1.000(0.001)

Table S4. Complete results on simulated genotypes and simulated phenotypes. Results are analogous to Table 2, but are reported for other values of *M* and *N* and consist of the same simulations as S3. For completeness, we also report ATT and MLM statistics computed using the underlying liability, where we again

observe a loss in power for MLM at lower prevalence. In bold are the settings where LTMLM demonstrates at least a 5% power improvement over MLM.

M	Prev	Set	Statistic	ATT Liability	MLM Liability	ATT	ATT+PCs	LogR	LogR +PCs	MLM	LTMLM
1000	10%	**causal**	average	36.835(1.515)	16.352(0.683)	24.736(1.002)	23.406(0.951)	23.622(0.93)	22.399(0.883)	13.222(0.553)	12.172(0.536)
		null	average	2.238(0.032)	0.789(0.014)	1.814(0.022)	1.632(0.020)	1.780(0.020)	1.601(0.019)	0.849(0.012)	0.753(0.011)
		all	average	2.584(0.036)	0.944(0.016)	2.043(0.025)	1.849(0.023)	1.999(0.023)	1.809(0.022)	0.973(0.013)	0.867(0.013)
		all	λ_{GC}	1.376(0.042)	0.373(0.006)	1.240(0.028)	1.064(0.010)	1.239(0.028)	1.062(0.010)	0.518(0.007)	0.458(0.011)
10000	10%	**causal**	average	33.100(1.375)	29.318(1.217)	22.606(0.943)	21.99(0.919)	21.672(0.876)	21.104(0.854)	20.412(0.867)	19.817(0.874)
		null	average	1.342(0.004)	0.965(0.003)	1.232(0.003)	1.084(0.003)	1.226(0.003)	1.078(0.002)	0.976(0.002)	0.948(0.002)
		all	average	1.374(0.004)	0.993(0.003)	1.253(0.003)	1.104(0.003)	1.246(0.003)	1.098(0.003)	0.995(0.003)	0.967(0.003)
		all	λ_{GC}	1.258(0.036)	0.882(0.003)	1.174(0.025)	1.023(0.003)	1.174(0.025)	1.023(0.003)	0.920(0.003)	0.893(0.013)
20000	10%	**causal**	average	34.93(1.481)	32.625(1.39)	24.098(1.037)	23.592(1.014)	23.031(0.963)	22.568(0.943)	22.892(1.003)	22.811(1.006)
		null	average	1.281(0.002)	0.982(0.002)	1.187(0.002)	1.042(0.001)	1.182(0.002)	1.038(0.001)	0.986(0.001)	0.981(0.001)
		all	average	1.298(0.002)	0.998(0.002)	1.198(0.002)	1.053(0.002)	1.193(0.002)	1.048(0.001)	0.997(0.002)	0.992(0.002)
		all	λ_{GC}	1.247(0.029)	0.939(0.002)	1.168(0.020)	1.013(0.002)	1.167(0.020)	1.013(0.002)	0.958(0.002)	0.953(0.006)

Table S5. Results on simulated genotypes and simulated phenotypes with population structure. We report average χ^2 statistics for simulations with population structure averaged across 100 simulations for each parameter setting (see main text).

N	M	Prev	α	set	ATT Liability	MLM Liability	ATT	ATT+PCs	LogR	LogR +PCs	MLM	LTMLM
1000	1000	10%	0.05	causal	0.758(0.014)	0.661(0.016)	0.719(0.015)	0.715(0.015)	0.719(0.015)	0.716(0.015)	0.611(0.017)	0.596(0.017)
			0.001	causal	0.623(0.016)	0.421(0.017)	0.541(0.017)	0.535(0.017)	0.540(0.017)	0.530(0.017)	0.36(0.017)	0.334(0.016)
			$1x10^{-6}$	causal	0.435(0.016)	0.220(0.014)	0.323(0.016)	0.316(0.016)	0.315(0.016)	0.307(0.016)	0.183(0.013)	0.153(0.013)
			$5x10^{-8}$	causal	0.373(0.016)	0.176(0.013)	0.274(0.015)	0.261(0.015)	0.265(0.015)	0.256(0.015)	0.143(0.012)	0.116(0.011)
			0.05	null	0.097(0.001)	0.020(0.001)	0.086(0.001)	0.069(0.001)	0.085(0.001)	0.069(0.001)	0.022(0.001)	0.020(0.001)
			0.001	null	0.022(0.001)	0.012(0.001)	0.018(0.001)	0.016(0.001)	0.018(0.001)	0.016(0.001)	0.011(0.001)	0.010(0.001)
			$1x10^{-6}$	null	$0.012(5x10^{-4})$	$0.006(4x10^{-4})$	0.010 ($4x10^{-4}$)	$0.009(4x10^{-4})$	0.009 ($4x10^{-4}$)	$0.009(4x10^{-4})$	$0.005(4x10^{-4})$	$0.004(3x10^{-4})$
			$5x10^{-8}$	null	$0.011(5x10^{-4})$	$0.005(4x10^{-4})$	0.008 ($4x10^{-4}$)	$0.008(4x10^{-4})$	$0.008(4x10^{-4})$	$0.007(4x10^{-4})$	$0.004(3x10^{-4})$	$0.003(3x10^{-4})$
1000	10000		0.05	causal	0.745(0.015)	0.729(0.015)	0.707(0.015)	0.702(0.016)	0.707(0.015)	0.702(0.016)	0.682(0.016)	0.674(0.016)
			0.001	causal	0.587(0.016)	0.557(0.017)	0.495(0.017)	0.492(0.017)	0.494(0.017)	0.492(0.017)	0.475(0.017)	0.451(0.017)
			$1x10^{-6}$	causal	0.411(0.016)	0.380(0.016)	0.322(0.016)	0.314(0.016)	0.316(0.016)	0.311(0.016)	0.295(0.016)	0.280(0.015)
			$5x10^{-8}$	causal	0.347(0.016)	0.315(0.016)	0.270(0.015)	0.269(0.015)	0.266(0.015)	0.259(0.015)	0.245(0.015)	0.225(0.014)
			0.05	null	$0.08(4x10^{-4})$	$0.038(3x10^{-4})$	0.071 ($4x10^{-4}$)	$0.054(3x10^{-4})$	$0.071(4x10^{-4})$	$0.053(3x10^{-4})$	$0.042(3x10^{-4})$	$0.04(3x10^{-4})$
			0.001	null	$0.006(1x10^{-4})$	$0.002(7x10^{-5})$	0.004 ($9x10^{-5}$)	$0.003(7x10^{-5})$	$0.004(9x10^{-5})$	$0.003(7x10^{-5})$	$0.002(6x10^{-5})$	$0.002(7x10^{-5})$
			$1x10^{-6}$	null	$0.001(5x10^{-5})$	$0.001(5x10^{-5})$	0.001 ($4x10^{-5}$)	$0.001(4x10^{-5})$	$0.001(4x10^{-5})$	$0.001(4x10^{-5})$	$0.001(4x10^{-5})$	$0.001(4x10^{-5})$
			$5x10^{-8}$	null	$0.001(5x10^{-5})$	$0.001(5x10^{-5})$	0.001 ($4x10^{-5}$)	$0.001(4x10^{-5})$	$0.001(4x10^{-5})$	$0.001(4x10^{-5})$	$0.001(4x10^{-5})$	$0.001(4x10^{-5})$
1000	20000		0.05	causal	0.762(0.014)	0.753(0.014)	0.690(0.016)	0.687(0.016)	0.690(0.016)	0.686(0.016)	0.686(0.016)	0.682(0.016)
			0.001	causal	0.588(0.016)	0.578(0.017)	0.512(0.017)	0.506(0.017)	0.511(0.017)	0.505(0.017)	0.490(0.017)	0.488(0.017)
			$1x10^{-6}$	causal	0.412(0.016)	0.400(0.016)	0.315(0.016)	0.309(0.016)	0.311(0.016)	0.306(0.016)	0.297(0.015)	0.300(0.016)
			$5x10^{-8}$	causal	0.356(0.016)	0.340(0.016)	0.264(0.015)	0.262(0.015)	0.260(0.015)	0.258(0.015)	0.254(0.015)	0.254(0.015)
			0.05	null	$0.078(3x10^{-4})$	$0.043(2x10^{-4})$	0.069 ($2x10^{-5}$)	$0.052(2x10^{-4})$	$0.068(2x10^{-4})$	$0.051(2x10^{-4})$	$0.046(2x10^{-4})$	$0.045(2x10^{-4})$
			0.001	null	$0.005(7x10^{-5})$	$0.002(4x10^{-5})$	0.003 ($6x10^{-5}$)	$0.002(4x10^{-5})$	$0.003(5x10^{-5})$	$0.002(4x10^{-5})$	$0.002(4x10^{-5})$	$0.002(4x10^{-5})$
			$1x10^{-6}$	null	$0.001(3x10^{-5})$	$0.001(3x10^{-5})$	0.001 ($2x10^{-5}$)	0 (NA)	0 (NA)	0 (NA)	0 (NA)	0 (NA)

	$5x10^{-8}$	null	$0.001(2x10^{-5})$	$0.001(2x10^{-5})$	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)

Table S6. Percentage of SNPs achieving alpha levels for simulated genotypes and simulated phenotypes with population structure. We report the true positive and false positives at different α levels for the same simulations as in Table S5 (see main text).

		Liability		Observed	
M	Prevalence	H-E	REML	H-E	REML
1000	50%	0.259(0.013)	0.252(0.01)	0.165(0.008)	0.161(0.006)
	25%	0.241(0.010)	0.238(0.008)	0.173(0.007)	0.171(0.006)
	10%	0.245(0.011)	0.242(0.007)	0.233(0.010)	0.230(0.007)
10000	50%	0.236(0.014)	0.245(0.013)	0.150(0.009)	0.156(0.008)
	25%	0.250(0.014)	0.264(0.013)	0.180(0.010)	0.190(0.010)
	10%	0.259(0.012)	0.261(0.009)	0.246(0.011)	0.248(0.009)

Table S7. Heritability parameter estimates on simulated genotypes and phenotypes. Results are analogous to Table 3, under different settings of *M* and *N*.

		Liability		Observed	
M	Prevalence	H-E	REML	H-E	REML
1000	10%	0.470(0.013)	0.415(0.005)	0.446(0.012)	0.394(0.005)
10000	10%	0.407(0.031)	0.526(0.011)	0.438(0.044)	0.500(0.010)
20000	10%	0.383(0.030)	0.531(0.013)	0.408(0.040)	0.505(0.012)

Table S8. Heritability parameter estimates on simulated genotypes and phenotypes with population structure. These results are from the same simulations used to generate Table S5 and S6. We report results on both liability and observed scales. The true h^2 explained by the SNPs used to build the GRM is 25% on the liability scale for all simulations.

N	M	True Prev	Specified Prev	Set	Statistic	ATT Liablity	MLM Liability	ATT	LogR	MLM	LTMLM
1000	1000	1%	1%	causal	average	55.732(2.12)	54.012(2.06)	42.316(1.565)	39.858(1.421)	40.611(1.539)	45.336(1.756)
				null	average	1.002(0.004)	0.988(0.004)	0.999(0.004)	0.997(0.004)	0.992(0.004)	0.999(0.004)
				all	average	1.550(0.028)	1.518(0.027)	1.412(0.021)	1.386(0.019)	1.388(0.020)	1.443(0.023)
				all	λGC	1.027(0.008)	1.012(0.007)	1.020(0.008)	1.019(0.008)	1.009(0.008)	1.018(0.008)
			3.4%	causal	average	As Above	As Above	As Above	As Above	As Above	44.441(1.805)
				null	average	As Above	As Above	As Above	As Above	As Above	1.009(0.005)
				all	average	As Above	As Above	As Above	As Above	As Above	1.444(0.023)
				all	λGC	As Above	As Above	As Above	As Above	As Above	1.035(0.008)
			0.2%	causal	average	As Above	As Above	As Above	As Above	As Above	45.532(1.851)
				null	average	As Above	As Above	As Above	As Above	As Above	1.002(0.004)
				all	average	As Above	As Above	As Above	As Above	As Above	1.448(0.024)
				all	λGC	As Above	As Above	As Above	As Above	As Above	1.023(0.008)
		0.1%	0.1%	causal	average	73.159(2.847)	63.052(2.549)	58.946(2.157)	54.625(1.924)	51.507(2.045)	65.991(2.656)
				null	average	0.997(0.004)	0.974(0.004)	0.996(0.004)	0.994(0.004)	0.978(0.004)	0.996(0.004)
				all	average	1.718(0.037)	1.595(0.032)	1.575(0.029)	1.530(0.026)	1.483(0.026)	1.646(0.034)
				all	λGC	1.035(0.009)	1.008(0.007)	1.023(0.007)	1.023(0.007)	1.000(0.007)	1.014(0.008)
			0.5%	causal	average	As Above	As Above	As Above	As Above	As Above	65.281(2.617)
				null	average	As Above	As Above	As Above	As Above	As Above	0.998(0.004)
				all	average	As Above	As Above	As Above	As Above	As Above	1.641(0.033)
				all	λGC	As Above	As Above	As Above	As Above	As Above	1.022(0.007)
			0.02%	causal	average	As Above	As Above	As Above	As Above	As Above	68.616(2.729)
				null	average	As Above	As Above	As Above	As Above	As Above	1.003(0.005)
				all	average	As Above	As Above	As Above	As Above	As Above	1.679(0.035)
				all	λGC	As Above	As Above	As Above	As Above	As Above	1.022(0.008)

Table S9. Simulated genotypes and phenotypes with mis-specification of the liability threshold. LTMLM was run at prevalence of 1% and 0.1% under mis-specification of the threshold, t=true +/- 0.5.

N	M	True Prev	Specified Prev	α	set	ATT Liability	LogR Liability	ATT	LogR	MLM	LTMLM
5000	5000	1%	1%	0.05	causal	0.803(0.013)	0.796(0.013)	0.767(0.014)	0.767(0.014)	0.753(0.014)	0.769(0.014)
				0.001	causal	0.666(0.016)	0.665(0.016)	0.632(0.016)	0.632(0.016)	0.619(0.016)	0.638(0.016)
				1x10-6	causal	0.548(0.016)	0.543(0.016)	0.496(0.017)	0.491(0.017)	0.477(0.017)	0.501(0.017)
				5x10-8	causal	0.504(0.016)	0.500(0.016)	0.449(0.016)	0.447(0.016)	0.433(0.016)	0.451(0.016)
				0.05	null	0.050(0.001)	0.048(0.001)	0.050(0.001)	0.050(0.001)	0.049(0.001)	0.050(0.001)
				0.001	null	0.001($1x10^{-4}$)	0.001($1x10^{-4}$)	0.001($1x10^{-4}$)	0.001($1x10^{-4}$)	0.001($1x10^{-4}$)	0.001($1x10^{-4}$)
				1x10-6	null	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)
				5x10-8	null	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)
			3.4%	0.05	causal	As Above	As Above	As Above	As Above	As Above	0.783(0.014)
				0.001	causal	As Above	As Above	As Above	As Above	As Above	0.647(0.016)
				1x10-6	causal	As Above	As Above	As Above	As Above	As Above	0.469(0.017)
				5x10-8	causal	As Above	As Above	As Above	As Above	As Above	0.428(0.016)
				0.05	null	As Above	As Above	As Above	As Above	As Above	0.051(0.001)
				0.001	null	As Above	As Above	As Above	As Above	As Above	0.001($1x10^{-4}$)
				1x10-6	null	As Above	As Above	As Above	As Above	As Above	0(NA)
				5x10-8	null	As Above	As Above	As Above	As Above	As Above	0(NA)
			0.2%	0.05	causal	As Above	As Above	As Above	As Above	As Above	0.774(0.014)
				0.001	causal	As Above	As Above	As Above	As Above	As Above	0.638(0.016)
				1x10-6	causal	As Above	As Above	As Above	As Above	As Above	0.491(0.017)
				5x10-8	causal	As Above	As Above	As Above	As Above	As Above	0.439(0.016)
				0.05	null	As Above	As Above	As Above	As Above	As Above	0.050(0.001)
				0.001	null	As Above	As Above	As Above	As Above	As Above	0.001($1x10^{-4}$)
				1x10-6	null	As Above	As Above	As Above	As Above	As Above	0(NA)
				5x10-8	null	As Above	As Above	As Above	As Above	As Above	0(NA)
		0.1%	0.1%	0.05	causal	0.820(0.013)	0.811(0.013)	0.815(0.013)	0.815(0.013)	0.801(0.013)	0.818(0.013)
				0.001	causal	0.727(0.015)	0.689(0.015)	0.697(0.015)	0.697(0.015)	0.656(0.016)	0.695(0.015)
				1x10-6	causal	0.585(0.016)	0.559(0.016)	0.551(0.016)	0.547(0.016)	0.510(0.017)	0.559(0.016)

		5x10-8	causal	0.548(0.016)	0.511(0.016)	0.512(0.016)	0.510(0.016)	0.475(0.017)	0.525(0.016)
		0.05	null	0.050(0.001)	0.046(0.001)	0.050(0.001)	0.049(0.001)	0.048(0.001)	0.050(0.001)
		0.001	null	0.001($1x10^{-4}$)	0.001($1x10^{-4}$)	0.001($1x10^{-4}$)	0.001($1x10^{-4}$)	0.001($1x10^{-4}$)	0.001($1x10^{-4}$)
		1x10-6	null	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)
		5x10-8	null	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)
	0.5%	0.05	causal	As Above	As Above	As Above	As Above	As Above	0.823(0.013)
		0.001	causal	As Above	As Above	As Above	As Above	As Above	0.717(0.015)
		1x10-6	causal	As Above	As Above	As Above	As Above	As Above	0.569(0.016)
		5x10-8	causal	As Above	As Above	As Above	As Above	As Above	0.526(0.016)
		0.05	null	As Above	As Above	As Above	As Above	As Above	0.049(0.001)
		0.001	null	As Above	As Above	As Above	As Above	As Above	0.001($2x10^{-4}$)
		1x10-6	null	As Above	As Above	As Above	As Above	As Above	0(NA)
		5x10-8	null	As Above	As Above	As Above	As Above	As Above	0(NA)
	0.02%	0.05	causal	As Above	As Above	As Above	As Above	As Above	0.824(0.012)
		0.001	causal	As Above	As Above	As Above	As Above	As Above	0.716(0.015)
		1x10-6	causal	As Above	As Above	As Above	As Above	As Above	0.573(0.016)
		5x10-8	causal	As Above	As Above	As Above	As Above	As Above	0.523(0.016)
		0.05	null	As Above	As Above	As Above	As Above	As Above	0.050(0.001)
		0.001	null	As Above	As Above	As Above	As Above	As Above	0.001($1x10^{-4}$)
		1x10-6	null	As Above	As Above	As Above	As Above	As Above	0(NA)
		5x10-8	null	As Above	As Above	As Above	As Above	As Above	0(NA)

Table S10. Percentage of SNPs achieving alpha levels for simulated genotypes and simulated phenotypes with mis-specification of the liability threshold.
This corresponds to the same set of simulations as table S9.

	Prevalence		Liability		Observed	
M	True	Specified	H-E	REML	H-E	REML
1000	1%	1%	0.246(0.007)	0.206(0.005)	0.445(0.013)	0.373(0.008)
		3.4%	0.350(0.012)	0.290(0.007)	0.462(0.016)	0.383(0.010)
		0.2%	0.182(0.006)	0.152(0.004)	0.445(0.014)	0.373(0.009)
	0.1%	0.1%	0.247(0.008)	0.175(0.004)	0.701(0.023)	0.498(0.011)
		0.5%	0.324(0.009)	0.234(0.004)	0.689(0.019)	0.499(0.009)
		0.02%	0.184(0.006)	0.132(0.003)	0.677(0.022)	0.486(0.011)

Table S11. Heritability parameter estimates on simulated genotypes and phenotypes with misspecification of the liability threshold. This corresponds to the same set of simulations as Table S9 and S10.

N	M	Prev	Set	Statistic	ATT	LogR	MLM	LTMLM
1000	1000	50%	causal	average	18.085(0.248)	17.859(0.242)	18.582(0.252)	18.576(0.254)
			null	average	0.997(0.004)	0.996(0.004)	0.998(0.004)	0.997(0.004)
			all	average	1.168(0.007)	1.164(0.007)	1.174(0.008)	1.173(0.008)
			all	λ_{GC}	1.023(0.007)	1.022(0.007)	1.026(0.008)	1.02(0.007)
		25%	causal	average	18.531(0.246)	18.295(0.24)	18.987(0.251)	18.954(0.253)
			null	average	1.005(0.005)	1.003(0.004)	1.005(0.005)	1.004(0.005)
			all	average	1.180(0.008)	1.176(0.007)	1.185(0.008)	1.183(0.008)
			all	λ_{GC}	1.037(0.007)	1.036(0.007)	1.036(0.007)	1.035(0.007)
		10%	causal	average	20.926(0.268)	20.628(0.26)	21.259(0.272)	21.347(0.272)
			null	average	1.005(0.004)	1.003(0.004)	1.005(0.004)	1.004(0.004)
			all	average	1.204(0.008)	1.200(0.008)	1.207(0.008)	1.207(0.008)
			all	λ_{GC}	1.031(0.007)	1.031(0.007)	1.036(0.008)	1.037(0.008)
		1%	causal	average	28.421(0.326)	27.886(0.314)	27.697(0.323)	28.974(0.338)
			null	average	1.009(0.005)	1.007(0.005)	1.008(0.005)	1.008(0.005)
			all	average	1.283(0.010)	1.276(0.010)	1.275(0.010)	1.288(0.010)
			all	λ_{GC}	1.027(0.008)	1.027(0.008)	1.025(0.008)	1.028(0.008)
		0.1%	causal	average	35.927(0.358)	35.100(0.342)	33.172(0.347)	36.654(0.373)
			null	average	0.999(0.004)	0.997(0.004)	0.992(0.004)	0.998(0.004)
			all	average	1.348(0.012)	1.338(0.012)	1.314(0.012)	1.355(0.013)
			all	λ_{GC}	1.031(0.007)	1.031(0.007)	1.012(0.007)	1.022(0.007)

Table S12. Simulated genotypes and phenotypes generated from a logit distribution. We report average χ^2 statistics for simulations with phenotypes generated from a logit distribution averaged across 100 simulations for each parameter setting (see main text).

N	M	Prev	α	set	ATT	LogR	MLM	LTMLM
1000	1000	50%	0.05	causal	0.988(0.003)	0.988(0.003)	0.988(0.003)	0.988(0.003)
			0.001	causal	0.827(0.012)	0.821(0.012)	0.832(0.012)	0.832(0.012)
			$1x10^{-6}$	causal	0.210(0.013)	0.198(0.013)	0.227(0.013)	0.230(0.013)
			$5x10^{-8}$	causal	0.077(0.008)	0.072(0.008)	0.089(0.009)	0.088(0.009)
			0.05	null	0.049(0.001)	0.049(0.001)	0.050(0.001)	0.050(0.001)
			0.001	null	$0.001(1x10^{-4})$	$0.001(1x10^{-4})$	$0.001(1x10^{-4})$	$0.001(1x10^{-4})$
			$1x10^{-6}$	null	0(NA)	0(NA)	0(NA)	0(NA)
			$5x10^{-8}$	null	0(NA)	0(NA)	0(NA)	0(NA)
		25%	0.05	causal	0.997(0.002)	0.997(0.002)	0.997(0.002)	0.995(0.002)
			0.001	causal	0.832(0.012)	0.830(0.012)	0.849(0.011)	0.844(0.011)
			$1x10^{-6}$	causal	0.225(0.013)	0.209(0.013)	0.243(0.014)	0.245(0.014)
			$5x10^{-8}$	causal	0.090(0.009)	0.081(0.009)	0.098(0.009)	0.093(0.009)
			0.05	null	0.050(0.001)	0.050(0.001)	0.050(0.001)	0.050(0.001)
			0.001	null	$0.001(1x10^{-4})$	$0.001(1x10^{-4})$	$0.001(1x10^{-4})$	$0.001(1x10^{-4})$
			$1x10^{-6}$	null	0(NA)	0(NA)	0(NA)	0(NA)
			$5x10^{-8}$	null	0(NA)	0(NA)	0(NA)	0(NA)
		10%	0.05	causal	0.997(0.002)	0.997(0.002)	0.998(0.001)	0.998(0.001)
			0.001	causal	0.893(0.010)	0.892(0.010)	0.894(0.010)	0.894(0.010)
			$1x10^{-6}$	causal	0.344(0.015)	0.334(0.015)	0.357(0.015)	0.365(0.015)
			$5x10^{-8}$	causal	0.140(0.011)	0.129(0.011)	0.154(0.011)	0.160(0.012)
			0.05	null	0.051(0.001)	0.051(0.001)	0.051(0.001)	0.050(0.001)
			0.001	null	$0.001(1x10^{-4})$	$0.001(1x10^{-4})$	$0.001(1x10^{-4})$	$0.001(1x10^{-4})$
			$1x10^{-6}$	null	0(NA)	0(NA)	0(NA)	0(NA)
			$5x10^{-8}$	null	0(NA)	0(NA)	0(NA)	0(NA)
		1%	0.05	causal	1(NA)	1(NA)	1(NA)	1(NA)
			0.001	causal	0.978(0.005)	0.977(0.005)	0.973(0.005)	0.980(0.004)
			$1x10^{-6}$	causal	0.640(0.015)	0.623(0.015)	0.613(0.015)	0.658(0.015)
			$5x10^{-8}$	causal	0.397(0.015)	0.378(0.015)	0.376(0.015)	0.419(0.016)

		0.05	null	0.051(0.001)	0.050(0.001)	0.051(0.001)	0.051(0.001)
		0.001	null	0.001($2x10^{-4}$)	0.001($2x10^{-4}$)	0.001($2x10^{-4}$)	0.001($2x10^{-4}$)
		$1x10^{-6}$	null	0(NA)	0(NA)	0(NA)	0(NA)
		$5x10^{-8}$	null	0(NA)	0(NA)	0(NA)	0(NA)
	0.1%	0.05	causal	1(NA)	1(NA)	1(NA)	1(NA)
		0.001	causal	0.996(0.002)	0.996(0.002)	0.995(0.002)	0.997(0.002)
		$1x10^{-6}$	causal	0.868(0.011)	0.860(0.011)	0.797(0.013)	0.880(0.01)
		$5x10^{-8}$	causal	0.685(0.015)	0.664(0.015)	0.584(0.016)	0.702(0.014)
		0.05	null	0.050(0.001)	0.050(0.001)	0.049(0.001)	0.050(0.001)
		0.001	null	0.001($1x10^{-4}$)	0.001($1x10^{-4}$)	0.001($1x10^{-4}$)	0.001($1x10^{-4}$)
		$1x10^{-6}$	null	0(NA)	0(NA)	0(NA)	0(NA)
		$5x10^{-8}$	null	0(NA)	0(NA)	0(NA)	0(NA)

Table S13. Percentage of SNPs achieving alpha levels for simulated genotypes and phenotypes generated from a logistic distribution. Results are the same simulations as described in Table S12

M	Prev	Set	Statistic	ATT Liability	MM Liability	ATT	ATT+PCs	LogR	LogR+PCs	MLM	LTMLM
1000	50%	causal	average	25.684(1.137)	29.055(1.26)	16.234(0.723)	15.775(0.705)	15.566(0.674)	15.14(0.658)	17.480(0.780)	17.412(0.775)
		null	average	1.698(0.015)	1.792(0.017)	1.444(0.011)	1.425(0.010)	1.433(0.010)	1.415(0.010)	1.472(0.011)	1.471(0.011)
		all	average	1.938(0.021)	2.065(0.023)	1.592(0.014)	1.569(0.013)	1.574(0.013)	1.552(0.013)	1.632(0.015)	1.630(0.015)
		all	λ_{GC}	1.274(0.018)	1.278(0.019)	1.214(0.017)	1.224(0.017)	1.214(0.017)	1.223(0.017)	1.234(0.017)	1.226(0.016)
	25%	causal	average	30.169(1.211)	33.771(1.343)	19.277(0.771)	18.581(0.754)	18.47(0.721)	17.822(0.706)	20.493(0.82)	20.642(0.831)
		null	average	1.821(0.017)	1.917(0.019)	1.551(0.012)	1.507(0.011)	1.538(0.012)	1.495(0.011)	1.571(0.012)	1.577(0.013)
		all	average	2.104(0.023)	2.236(0.025)	1.728(0.015)	1.678(0.014)	1.707(0.015)	1.658(0.014)	1.761(0.016)	1.768(0.016)
		all	λ_{GC}	1.290(0.018)	1.288(0.019)	1.256(0.016)	1.245(0.017)	1.255(0.016)	1.245(0.017)	1.241(0.015)	1.243(0.015)
	10%	causal	average	34.865(1.45)	37.861(1.551)	22.838(0.961)	21.406(0.878)	21.618(0.881)	20.336(0.808)	23.865(1.022)	24.661(1.064)
		null	average	1.973(0.020)	2.039(0.021)	1.664(0.014)	1.583(0.012)	1.647(0.014)	1.568(0.012)	1.668(0.014)	1.695(0.015)
		all	average	2.302(0.027)	2.397(0.028)	1.876(0.018)	1.781(0.016)	1.846(0.017)	1.756(0.015)	1.890(0.019)	1.925(0.019)
		all	λ_{GC}	1.301(0.017)	1.302(0.018)	1.271(0.016)	1.285(0.015)	1.270(0.016)	1.284(0.015)	1.251(0.017)	1.270(0.016)
10000	50%	causal	average	26.781(1.104)	27.44(1.129)	16.898(0.702)	16.815(0.698)	16.229(0.659)	16.156(0.655)	17.279(0.725)	17.26(0.725)
		null	average	1.114(0.002)	1.114(0.002)	1.078(0.002)	1.083(0.002)	1.074(0.002)	1.078(0.002)	1.078(0.002)	1.076(0.002)
		all	average	1.14(0.003)	1.140(0.003)	1.094(0.002)	1.099(0.002)	1.089(0.002)	1.094(0.002)	1.095(0.002)	1.092(0.002)
		all	λ_{GC}	1.046(0.005)	1.042(0.005)	1.039(0.005)	1.047(0.005)	1.039(0.005)	1.046(0.005)	1.039(0.005)	1.035(0.005)
	25%	causal	average	27.208(1.154)	27.938(1.178)	17.573(0.726)	17.293(0.696)	16.856(0.679)	16.61(0.654)	17.976(0.749)	18.077(0.758)
		null	average	1.112(0.002)	1.11(0.002)	1.076(0.002)	1.078(0.002)	1.071(0.002)	1.073(0.002)	1.074(0.002)	1.073(0.002)
		all	average	1.138(0.003)	1.137(0.003)	1.092(0.002)	1.094(0.002)	1.087(0.002)	1.089(0.002)	1.091(0.002)	1.090(0.002)
		all	λ_{GC}	1.048(0.005)	1.043(0.005)	1.040(0.004)	1.045(0.004)	1.040(0.004)	1.044(0.004)	1.040(0.004)	1.039(0.004)
	10%	causal	average	35.911(1.500)	36.598(1.525)	24.379(1.026)	24.116(1.014)	23.127(0.944)	22.894(0.934)	24.987(1.071)	25.399(1.091)
		null	average	1.161(0.003)	1.156(0.003)	1.112(0.002)	1.115(0.002)	1.107(0.002)	1.110(0.002)	1.108(0.002)	1.111(0.002)
		all	average	1.196(0.003)	1.192(0.003)	1.136(0.003)	1.138(0.003)	1.129(0.002)	1.132(0.002)	1.131(0.003)	1.135(0.003)
		all	λ_{GC}	1.059(0.005)	1.050(0.004)	1.051(0.005)	1.059(0.004)	1.050(0.005)	1.058(0.004)	1.044(0.004)	1.047(0.004)

Table S14. Complete results on real genotypes and simulated phenotypes. Results include results from Table 4 but we also report ATT and MLM statistics computed using the underlying liability. We report average χ^2 statistics for simulations with real genotypes and simulated phenotypes averaged across 100 simulations for each parameter setting.

M	Prev	α	ATT Liability	MLM Liability	ATT	ATT+PCs	LogR	LogR +PCs	MLM	LTMLM
1000	50%	0.05	0.689(0.016)	0.717(0.015)	0.614(0.017)	0.602(0.017)	0.614(0.017)	0.603(0.017)	0.630(0.017)	0.625(0.017)
		0.001	0.504(0.017)	0.533(0.017)	0.409(0.017)	0.408(0.017)	0.405(0.017)	0.403(0.017)	0.415(0.017)	0.415(0.017)
		$1x10^{-6}$	0.320(0.016)	0.348(0.016)	0.235(0.015)	0.227(0.014)	0.229(0.014)	0.218(0.014)	0.256(0.015)	0.256(0.015)
		$5x10^{-8}$	0.289(0.015)	0.309(0.016)	0.185(0.013)	0.178(0.013)	0.179(0.013)	0.172(0.013)	0.205(0.014)	0.200(0.014)
		0.05	0.095(0.001)	0.099(0.001)	0.084(0.001)	0.083(0.001)	0.084(0.001)	0.083(0.001)	0.085(0.001)	0.085(0.001)
		0.001	0.002(0.001)	0.022(0.001)	0.014(0.001)	$0.013(5x10^{-4})$	0.013(0.001)	$0.013(5x10^{-4})$	0.014(0.001)	0.014(0.001)
		$1x10^{-6}$	$0.007(4x10^{-4})$	$0.009(4x10^{-4})$	$0.003(3x10^{-4})$	$0.003(2x10^{-4})$	$0.003(3x10^{-4})$	$0.003(2x10^{-4})$	$0.004(3x10^{-4})$	$0.004(3x10^{-4})$
		$5x10^{-8}$	$0.005(3x10^{-4})$	$0.006(3x10^{-4})$	$0.002(2x10^{-4})$	$0.002(2x10^{-4})$	$0.002(2x10^{-4})$	$0.002(2x10^{-4})$	$0.003(2x10^{-4})$	$0.003(2x10^{-4})$
	25%	0.05	0.737(0.015)	0.750(0.014)	0.682(0.016)	0.671(0.016)	0.680(0.016)	0.671(0.016)	0.689(0.016)	0.692(0.016)
		0.001	0.579(0.017)	0.603(0.016)	0.491(0.017)	0.482(0.017)	0.486(0.017)	0.479(0.017)	0.498(0.017)	0.496(0.017)
		$1x10^{-6}$	0.405(0.016)	0.437(0.017)	0.294(0.016)	0.278(0.015)	0.281(0.015)	0.266(0.015)	0.314(0.016)	0.311(0.016)
		$5x10^{-8}$	0.336(0.016)	0.387(0.016)	0.231(0.014)	0.216(0.014)	0.218(0.014)	0.208(0.014)	0.248(0.015)	0.251(0.015)
		0.05	0.102(0.001)	0.104(0.001)	0.091(0.001)	0.09(0.001)	0.091(0.001)	0.090(0.001)	0.091(0.001)	0.092(0.001)
		0.001	0.023(0.001)	0.026(0.001)	0.016(0.001)	0.015(0.001)	0.016(0.001)	0.015(0.001)	0.017(0.001)	0.018(0.001)
		$1x10^{-6}$	$0.009(4x10^{-4})$	$0.01(4x10^{-4})$	$0.005(3x10^{-4})$	$0.004(3x10^{-4})$	$0.005(3x10^{-4})$	$0.004(3x10^{-4})$	$0.005(3x10^{-4})$	$0.005(3x10^{-4})$
		$5x10^{-8}$	$0.006(3x10^{-4})$	$0.007(4x10^{-4})$	$0.003(3x10^{-4})$	$0.003(2x10^{-4})$	$0.003(2x10^{-4})$	$0.003(2x10^{-4})$	$0.004(3x10^{-4})$	$0.004(3x10^{-4})$
	10%	0.05	0.730(0.015)	0.740(0.015)	0.678(0.016)	0.678(0.016)	0.678(0.016)	0.678(0.016)	0.684(0.016)	0.694(0.016)
		0.001	0.575(0.017)	0.593(0.016)	0.498(0.017)	0.492(0.017)	0.494(0.017)	0.490(0.017)	0.510(0.017)	0.517(0.017)
		$1x10^{-6}$	0.410(0.016)	0.435(0.017)	0.332(0.016)	0.328(0.016)	0.324(0.016)	0.316(0.016)	0.340(0.016)	0.343(0.016)
		$5x10^{-8}$	0.374(0.016)	0.388(0.016)	0.271(0.015)	0.265(0.015)	0.261(0.015)	0.251(0.015)	0.276(0.015)	0.281(0.015)
		0.05	0.106(0.001)	0.107(0.001)	0.096(0.001)	0.095(0.001)	0.095(0.001)	0.094(0.001)	0.095(0.001)	0.097(0.001)
		0.001	0.027(0.001)	0.028(0.001)	0.019(0.001)	0.016(0.001)	0.019(0.001)	0.016(0.001)	0.020(0.001)	0.020(0.001)
		$1x10^{-6}$	$0.01(4x10^{-4})$	$0.011(5x10^{-4})$	$0.007(4x10^{-4})$	$0.005(3x10^{-4})$	$0.006(3x10^{-4})$	$0.005(3x10^{-4})$	$0.007(4x10^{-4})$	$0.007(4x10^{-4})$
		$5x10^{-8}$	$0.008(4x10^{-4})$	$0.008(4x10^{-4})$	$0.005(3x10^{-4})$	$0.004(3x10^{-4})$	$0.005(3x10^{-4})$	$0.003(3x10^{-4})$	$0.005(3x10^{-4})$	$0.005(3x10^{-4})$
10000	50%	0.05	0.713(0.015)	0.72(0.015)	0.653(0.016)	0.652(0.016)	0.652(0.016)	0.651(0.016)	0.656(0.016)	0.657(0.016)
		0.001	0.535(0.017)	0.551(0.017)	0.427(0.017)	0.428(0.017)	0.422(0.017)	0.426(0.017)	0.432(0.017)	0.433(0.017)
		$1x10^{-6}$	0.356(0.016)	0.365(0.016)	0.245(0.015)	0.244(0.015)	0.238(0.015)	0.237(0.015)	0.248(0.015)	0.245(0.015)
		$5x10^{-8}$	0.306(0.015)	0.311(0.016)	0.187(0.013)	0.191(0.013)	0.181(0.013)	0.178(0.013)	0.190(0.013)	0.189(0.013)
		0.05	$0.058(3x10^{-4})$	$0.058(3x10^{-4})$	$0.057(3x10^{-4})$	$0.057(3x10^{-4})$	$0.056(3x10^{-4})$	$0.057(3x10^{-4})$	$0.057(3x10^{-4})$	$0.056(3x10^{-4})$

		0.001	0.004($9x10^{-5}$)	0.004($9x10^{-5}$)	0.003($7x10^{-5}$)	0.003($7x10^{-5}$)	0.003($7x10^{-5}$)	0.003($7x10^{-5}$)	0.003($8x10^{-5}$)	0.003($8x10^{-5}$)
		$1x10^{-6}$	0.001($4x10^{-5}$)	0.001($4x10^{-5}$)	0.001($3x10^{-5}$)	0.001($3x10^{-5}$)	0.001($3x10^{-5}$)	0.001($3x10^{-5}$)	0.001($3x10^{-5}$)	0.001($3x10^{-5}$)
		$5x10^{-8}$	0.001($4x10^{-5}$)	0.001($4x10^{-5}$)	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)
	25%	0.05	0.725(0.015)	0.726(0.015)	0.635(0.017)	0.633(0.017)	0.635(0.017)	0.632(0.017)	0.635(0.017)	0.635(0.017)
		0.001	0.529(0.017)	0.538(0.017)	0.440(0.017)	0.438(0.017)	0.438(0.017)	0.437(0.017)	0.448(0.017)	0.445(0.017)
		$1x10^{-6}$	0.352(0.016)	0.362(0.016)	0.266(0.015)	0.261(0.015)	0.256(0.015)	0.254(0.015)	0.270(0.015)	0.267(0.015)
		$5x10^{-8}$	0.303(0.015)	0.309(0.016)	0.209(0.014)	0.206(0.014)	0.198(0.014)	0.197(0.014)	0.215(0.014)	0.216(0.014)
		0.05	0.057($3x10^{-4}$)	0.057($3x10^{-4}$)	0.056($3x10^{-4}$)	0.056($3x10^{-4}$)	0.055($3x10^{-4}$)	0.056($3x10^{-4}$)	0.056($3x10^{-4}$)	0.055($3x10^{-4}$)
		0.001	0.004($9x10^{-5}$)	0.004($9x10^{-5}$)	0.003($7x10^{-5}$)	0.003($7x10^{-5}$)	0.003($7x10^{-5}$)	0.003($7x10^{-5}$)	0.003($7x10^{-5}$)	0.003($7x10^{-5}$)
		$1x10^{-6}$	0.001($5x10^{-5}$)	0.001($5x10^{-5}$)	0.001($3x10^{-5}$)	0.001($3x10^{-5}$)	0.001($3x10^{-5}$)	0.001($3x10^{-5}$)	0.001($3x10^{-5}$)	0.001($3x10^{-5}$)
		$5x10^{-8}$	0.001($4x10^{-5}$)	0.001($4x10^{-5}$)	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)
	10%	0.05	0.752(0.014)	0.756(0.014)	0.711(0.015)	0.711(0.015)	0.709(0.015)	0.706(0.015)	0.713(0.015)	0.715(0.015)
		0.001	0.597(0.016)	0.603(0.016)	0.519(0.017)	0.528(0.017)	0.518(0.017)	0.523(0.017)	0.520(0.017)	0.517(0.017)
		$1x10^{-6}$	0.437(0.017)	0.438(0.017)	0.329(0.016)	0.330(0.016)	0.322(0.016)	0.322(0.016)	0.328(0.016)	0.336(0.016)
		$5x10^{-8}$	0.380(0.016)	0.388(0.016)	0.281(0.015)	0.275(0.015)	0.266(0.015)	0.264(0.015)	0.283(0.015)	0.284(0.015)
		0.05	0.061($3x10^{-4}$)	0.06($3x10^{-4}$)	0.059($3x10^{-4}$)	0.059($3x10^{-4}$)	0.058($3x10^{-4}$)	0.059($3x10^{-4}$)	0.058($3x10^{-4}$)	0.058($3x10^{-4}$)
		0.001	0.005($1x10^{-4}$)	0.005($1x10^{-4}$)	0.004($8x10^{-5}$)	0.004($8x10^{-5}$)	0.003($8x10^{-5}$)	0.003($8x10^{-5}$)	0.004($8x10^{-5}$)	0.004($8x10^{-5}$)
		$1x10^{-6}$	0.001($5x10^{-5}$)	0.001($5x10^{-5}$)	0.001($4x10^{-5}$)	0.001($4x10^{-5}$)	0.001($4x10^{-5}$)	0.001($4x10^{-5}$)	0.001($4x10^{-5}$)	0.001($4x10^{-5}$)
		$5x10^{-8}$	0.001($5x10^{-5}$)	0.001($5x10^{-5}$)	0.001($4x10^{-5}$)	0.001($3x10^{-5}$)	0.001($4x10^{-5}$)	0.001($3x10^{-5}$)	0.001($4x10^{-5}$)	0.001($4x10^{-5}$)

Table S15. Percentage of SNPs achieving alpha levels for real genotypes and simulated phenotypes. Results include results for Table 4, but we also report results for ATT and MLM computed using the underlying liability.

Category	Controlling λ_{GC}	α	ATT	ATT+PCs	LogR	LogR+PCs	MLM	LTMLM
Genome Wide	No	0.05	0.093($5x10^{-4}$)	0.068($4x10^{-4}$)	0.093($5x10^{-4}$)	0.067($4x10^{-4}$)	0.067($4x10^{-4}$)	0.07($4x10^{-4}$)
Genome Wide	No	0.001	0.006($1x10^{-4}$)	0.003($9x10^{-5}$)	0.006($1x10^{-4}$)	0.003($9x10^{-5}$)	0.003($9x10^{-5}$)	0.003($1x10^{-4}$)
Genome Wide	No	$1x10^{-6}$	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)
Genome Wide	No	$5x10^{-8}$	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)
Published	No	0.05	0.747(0.050)	0.733(0.051)	0.747(0.050)	0.747(0.050)	0.707(0.053)	0.747(0.05)
Published	No	0.001	0.427(0.057)	0.387(0.056)	0.427(0.057)	0.387(0.056)	0.387(0.056)	0.360(0.055)
Published	No	$1x10^{-6}$	0.107(0.036)	0.080(0.031)	0.107(0.036)	0.067(0.029)	0.080(0.031)	0.093(0.034)
Published	No	$5x10^{-8}$	0.053(0.026)	0.040(0.023)	0.053(0.026)	0.027(0.019)	0.027(0.019)	0.053(0.026)
Genome Wide	Yes	0.05	0.053($4x10^{-4}$)	0.053($4x10^{-4}$)	0.053($4x10^{-4}$)	0.053($4x10^{-4}$)	0.053($4x10^{-4}$)	0.053($4x10^{-4}$)
Genome Wide	Yes	0.001	0.002($7x10^{-5}$)	0.002($7x10^{-5}$)	0.002($7x10^{-5}$)	0.002($7x10^{-5}$)	0.002($7x10^{-5}$)	0.002($7x10^{-5}$)
Genome Wide	Yes	$1x10^{-6}$	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)
Genome Wide	Yes	$5x10^{-8}$	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)	0(NA)
Published	Yes	0.05	0.720(0.052)	0.693(0.053)	0.720(0.052)	0.707(0.053)	0.693(0.053)	0.733(0.051)
Published	Yes	0.001	0.320(0.054)	0.347(0.055)	0.320(0.054)	0.333(0.054)	0.347(0.055)	0.347(0.055)
Published	Yes	$1x10^{-6}$	0.040(0.023)	0.053(0.026)	0.040(0.023)	0.067(0.029)	0.040(0.023)	0.053(0.026)
Published	Yes	$5x10^{-8}$	0.013(0.013)	0.013(0.013)	0.013(0.013)	0.013(0.013)	0.013(0.013)	0.013(0.013)

Table S16. Proportion of SNPs achieving alpha levels for WTCCC2 MS data set. The number of known associated SNPs that are significant for LTMLM but not MLM (or vice versa) after controlling for λ_{GC} are 3(0) at $\alpha = 0.05$, 1(1) at $\alpha = 0.001$, 1(0) at $\alpha = 1x10^{-6}$, 0(0) at $\alpha = 5x10^{-8}$.

SNP Set	ATT	PCA	MLM	LTMLM
Genome Wide AVERAGE	1.38	1.16	1.14	1.17
Genome Wide LD Score INTERCEPT	1.29	1.09	1.08	1.10
Published SNPs AVERAGE	11.64	9.97	9.92	10.59
Published SNPs/Genome Wide Average	8.44	8.61	8.67	9.03
Published SNPs/LD score INTERCEPT	9.06	9.17	9.20	9.66

Table S17: Results on WTCCC2 MS data set with calibration via LD Score regression. We report the genome wide χ^2 averages using 10,034 individuals over 360,557 SNPs and the average across 75 published SNPs standardized by the genome wide average and LD Score regression intercept.

SNP Set	N	ATT	MLM	LTMLM	LTMLM REML
Genome Wide AVERAGE	8188	1.16	1.11	1.14	1.14
Published SNPs AVERAGE		8.94	8.26	8.76	8.82
Published SNPs/Genome Wide Average		7.73	7.45	7.71	7.73
Genome Wide AVERAGE	10034	1.38	1.14	1.17	1.24
Published SNPs AVERAGE		11.64	9.92	10.59	11.04
Published SNPs/Genome Wide Average		8.44	8.67	9.03	8.92
Genome Wide AVERAGE	15633	3.95	1.23	1.08	1.50
Published SNPs AVERAGE		18.54	11.30	5.76	13.76
Published SNPs/Genome Wide Average		4.69	9.20	5.32	9.15

Table S18: Results on WTCCC2 MS data set at different levels of QC. We report results for stringently matched (N = 8,188), partially matched (N = 10,034) and unmatched (N = 15,633) data sets (see main text). The additional column is for the LTMLM REML statistic calculated using the REML estimate of h^2. LTMLM using the REML estimate for h^2 produces inflated test statistics and it is not recommended.

	Liability		Observed	
N	HE	REML	HE	REML
8188	0.363 (0.0017)	0.260 (0.001)	0.979 (0.005)	0.702 (0.003)
10034	0.704 (0.009)	0.279 (0.001)	1.901 (0.025)	0.753 (0.002)
15633	2.792 (0.010)	0.293 (0.001)	7.543 (0.0266)	0.792 (0.002)

Table S19: Heritability parameter estimates on WTCCC2 MS data set at different levels of QC. We report results for stringently matched (N = 8,188), partially matched (N = 10,034) and unmatched (N = 15,633) data sets (see main text).