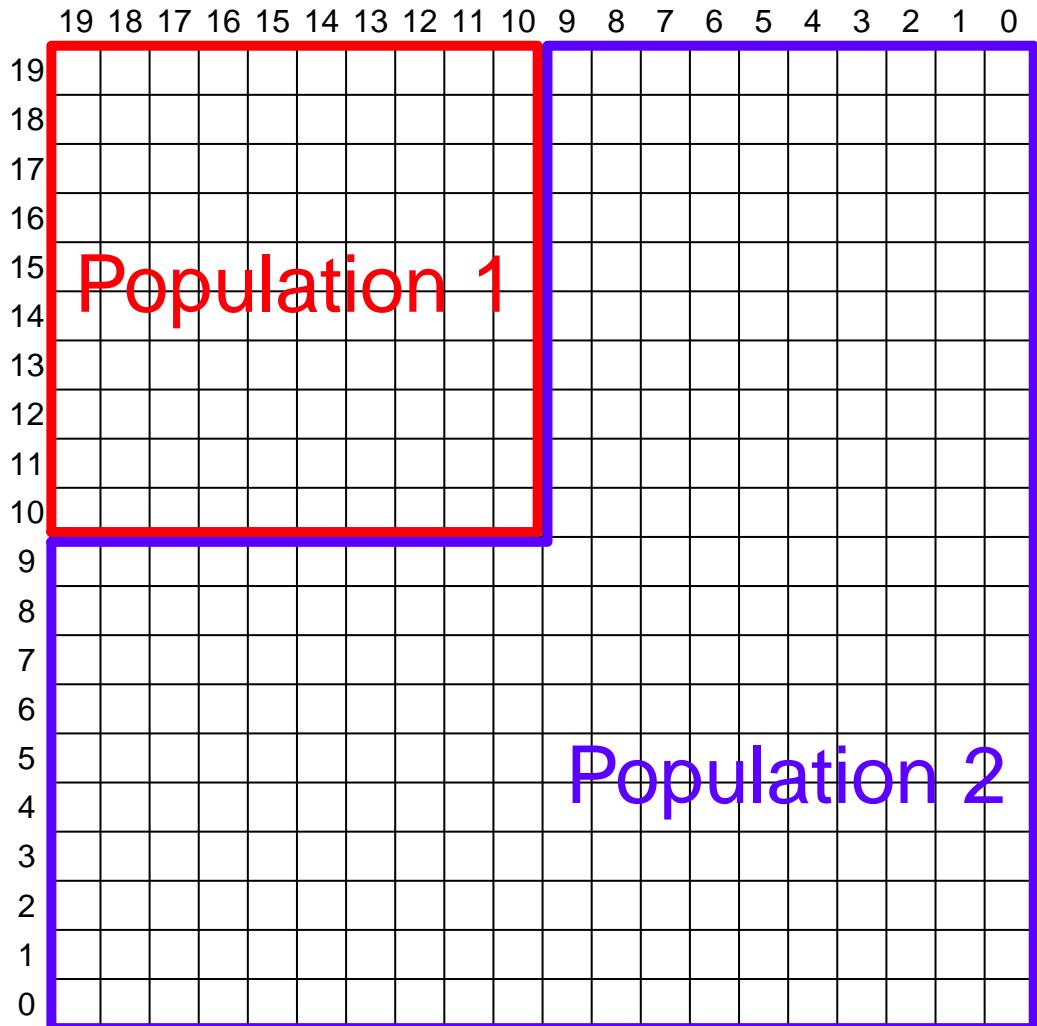


## **Supplemental Data**

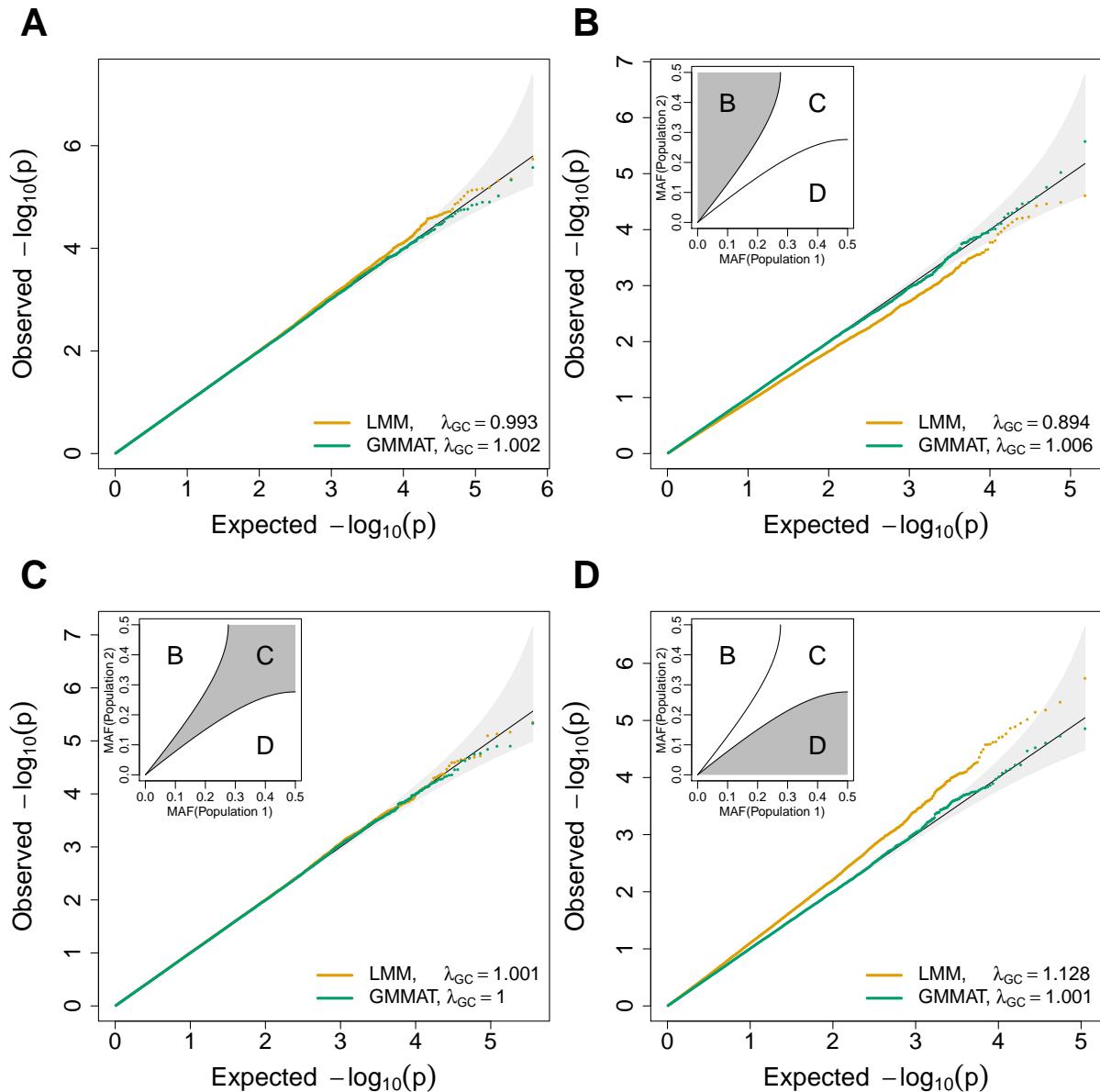
### **Control for Population Structure and Relatedness for Binary Traits in Genetic Association Studies via Logistic Mixed Models**

**Han Chen, Chaolong Wang, Matthew P. Conomos, Adrienne M. Stilp, Zilin Li, Tamar Sofer, Adam A. Szpiro, Wei Chen, John M. Brehm, Juan C. Celedón, Susan Redline, George J. Papanicolaou, Timothy A. Thornton, Cathy C. Laurie, Kenneth Rice, and Xihong Lin**

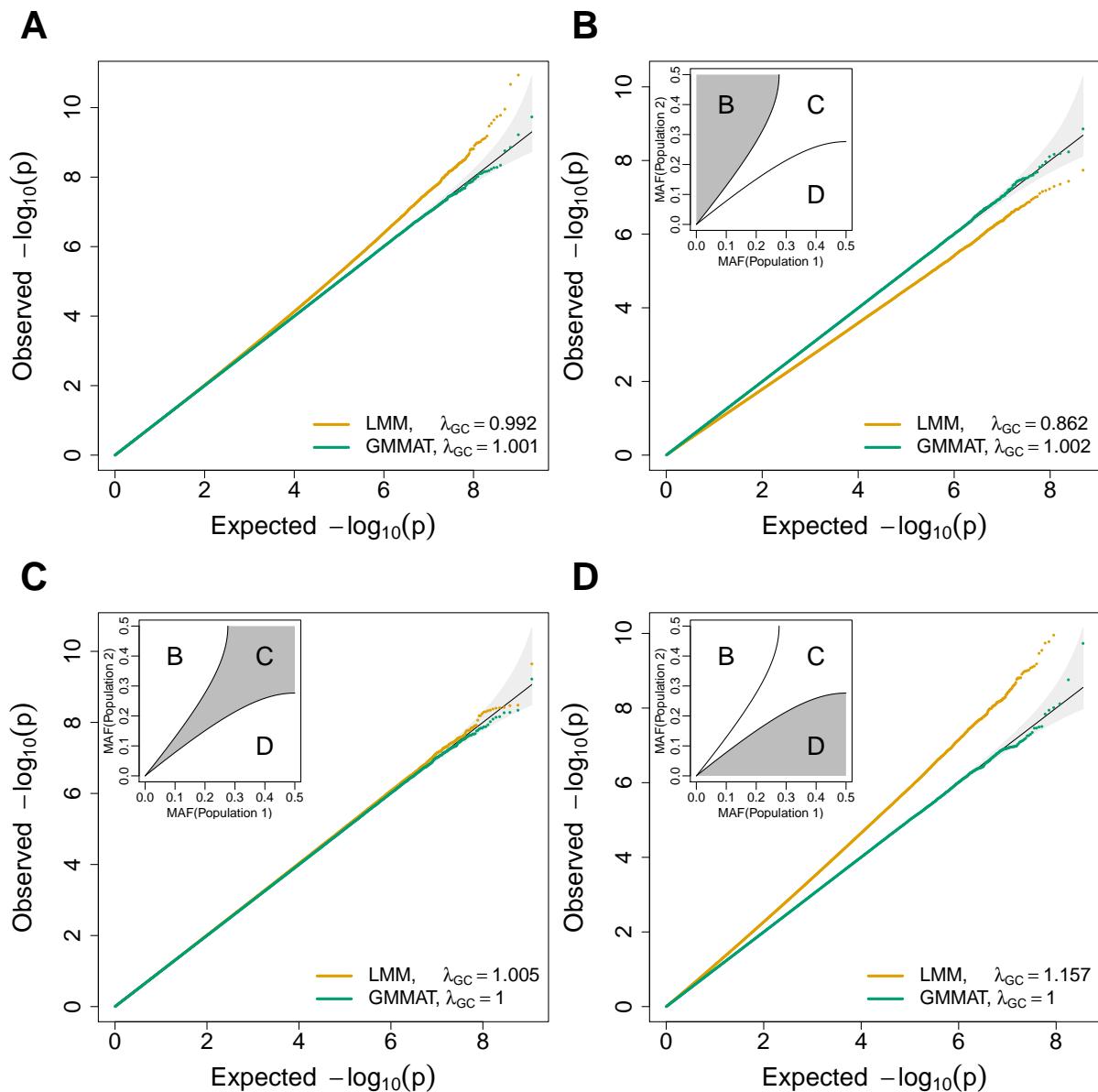
**Figure S1** Map of spatially continuous populations from which we simulate genotypes based on the coalescent model. The red square in the top left indicates Population 1, and cells of the rest regions form Population 2. Row and column coordinates are shown.



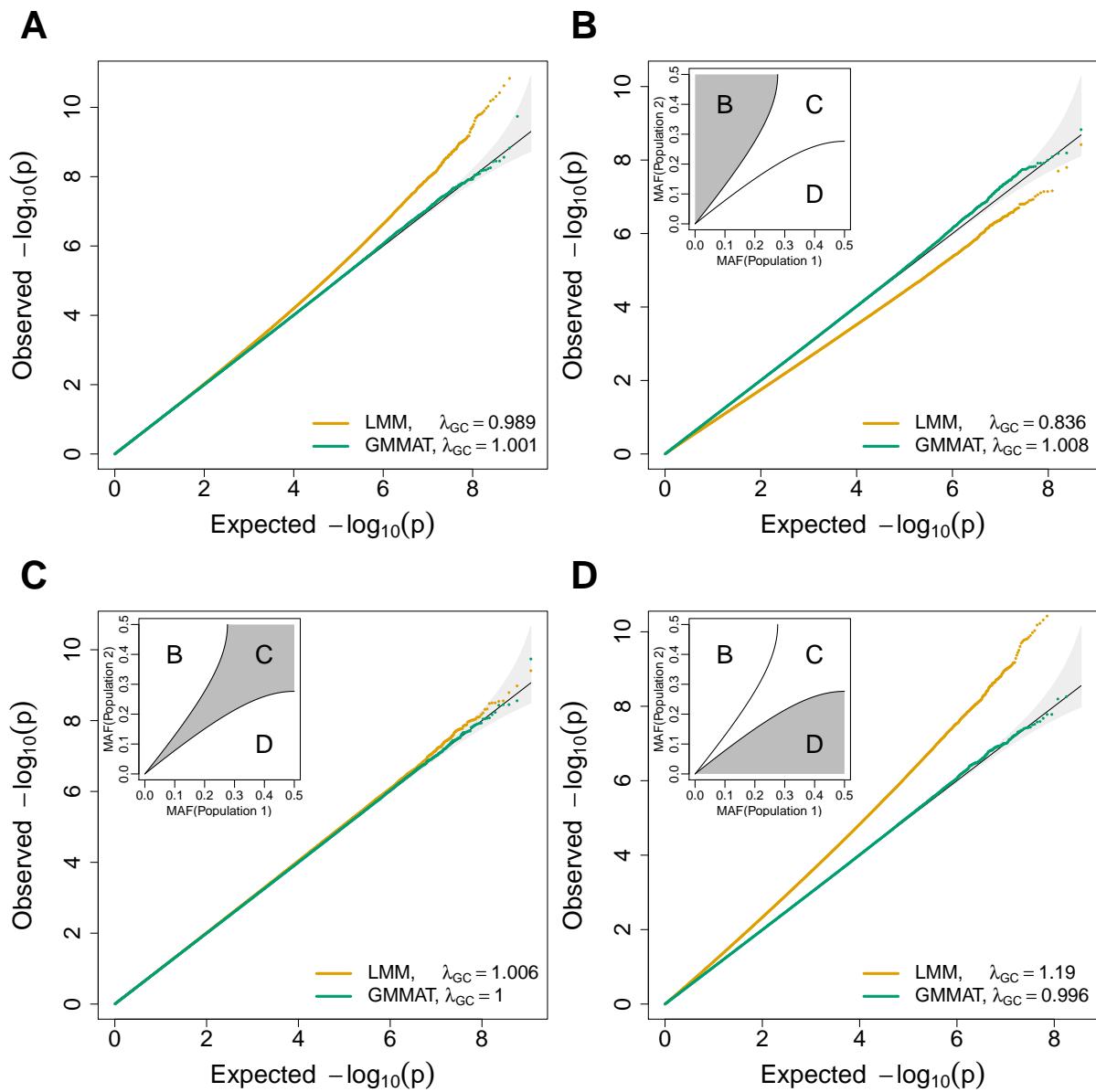
**Figure S2** Comparison of LMM and GMMAT in a simulated cohort study with 10,000 related individuals. Disease prevalence was 28% in Population 1 and 5% in Population 2. Quantile-quantile plots of association test p values from one simulation replicate under the null hypothesis of no genetic association with 625,583 common SNPs were shown. (A) All SNPs. (B) Category 1: SNPs with the ratio of expected variances in Population 1 (high risk) over Population 2 (low risk) less than 0.8. (C) Category 2: SNPs with the ratio of expected variances in Population 1 (high risk) over Population 2 (low risk) between 0.8 and 1.25. (D) Category 3: SNPs with the ratio of expected variances in Population 1 (high risk) over Population 2 (low risk) greater than 1.25.



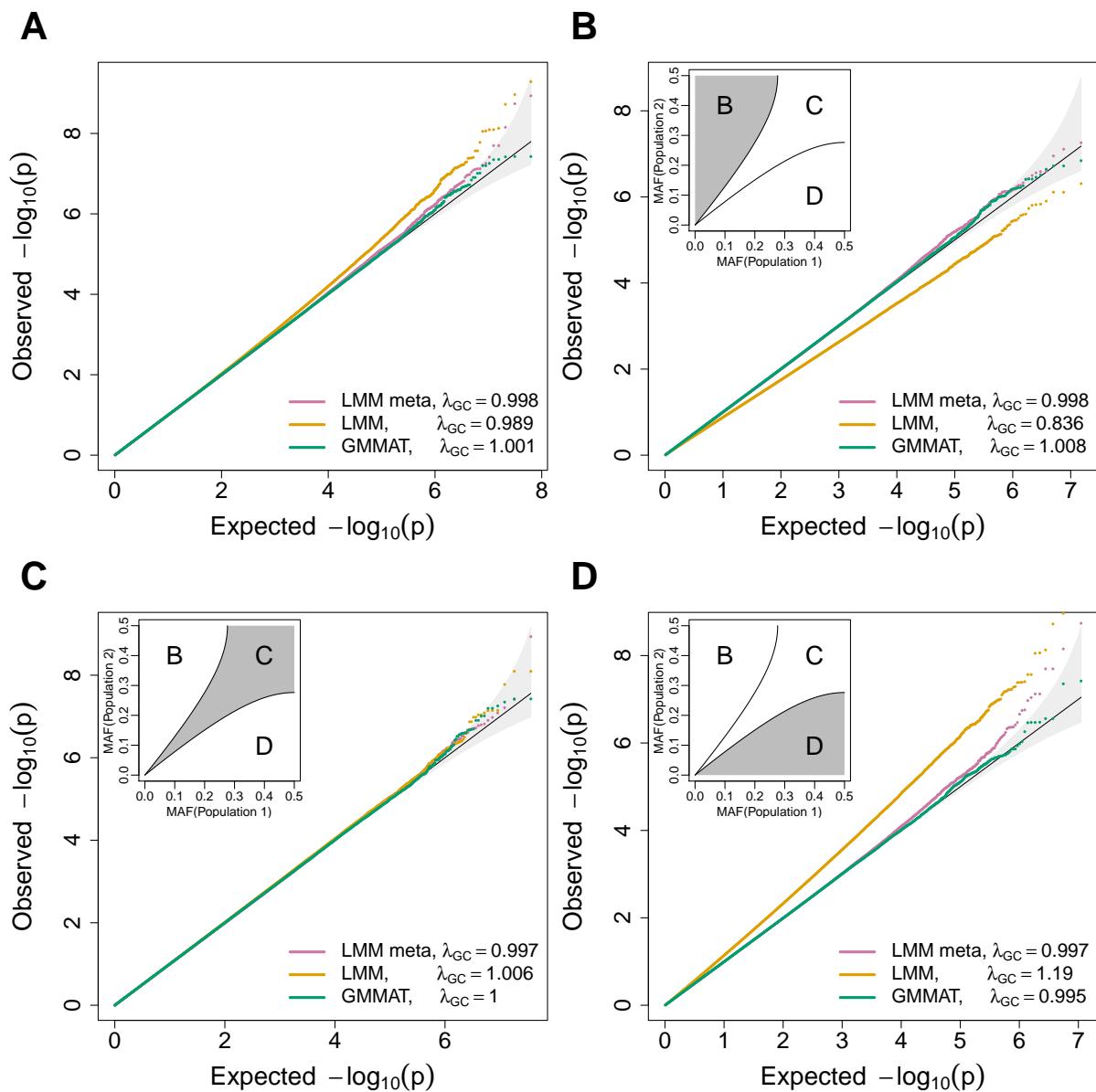
**Figure S3** Comparison of LMM and GMMAT in a simulated case-control study with case-control ratio 1:5 and 10,000 related individuals. Disease prevalence was 4.5% in Population 1 and 0.5% in Population 2. Quantile-quantile plots of association test p values from 3,200 simulation replicates under the null hypothesis of no genetic association, each with 625,583 common SNPs, were combined to get more than 2 billion null p values. (A) All SNPs. (B) Category 1: SNPs with the ratio of expected variances in Population 1 (high risk) over Population 2 (low risk) less than 0.8. (C) Category 2: SNPs with the ratio of expected variances in Population 1 (high risk) over Population 2 (low risk) between 0.8 and 1.25. (D) Category 3: SNPs with the ratio of expected variances in Population 1 (high risk) over Population 2 (low risk) greater than 1.25.



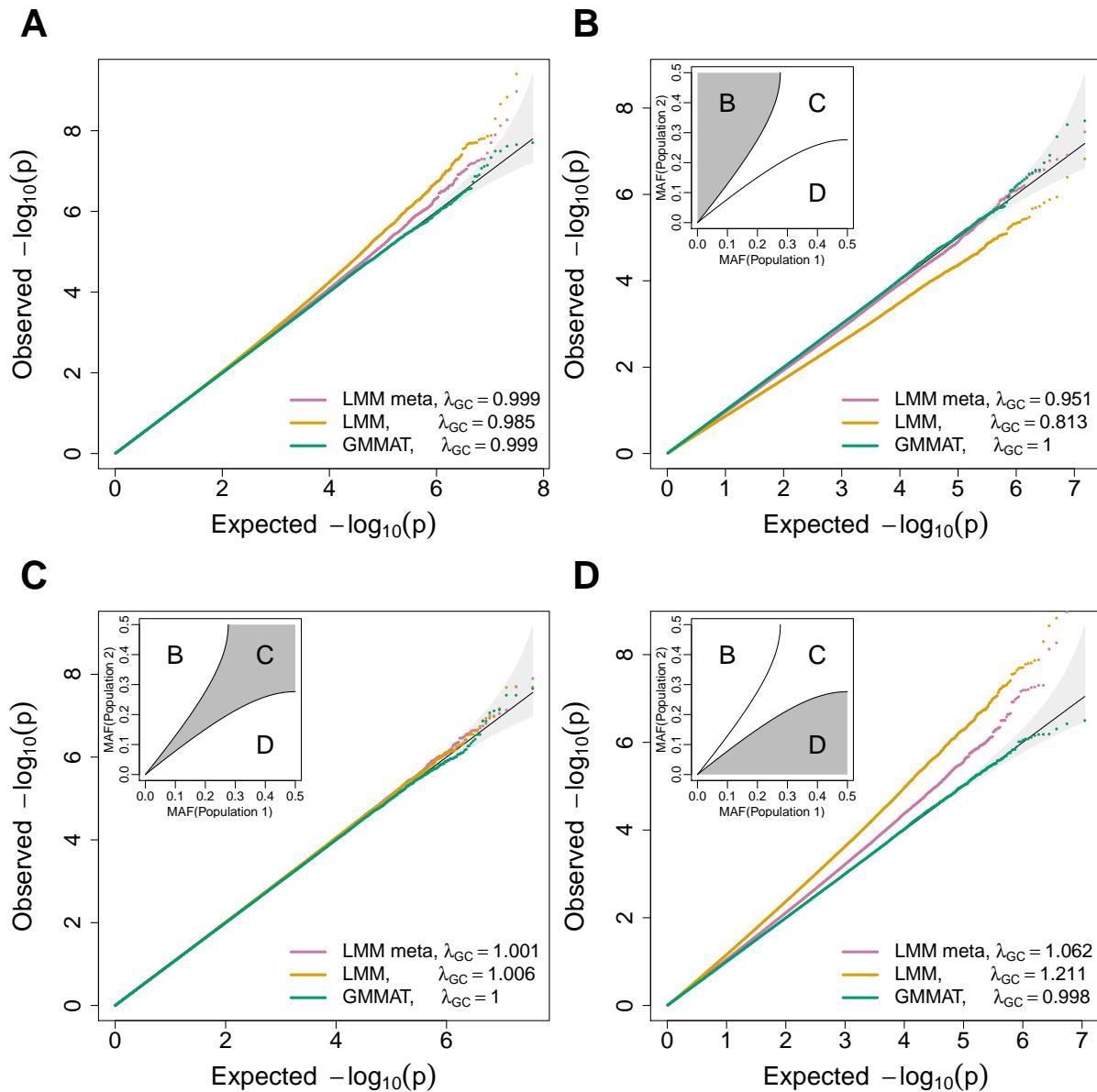
**Figure S4** Comparison of LMM and GMMAT in a simulated cohort study with 10,000 unrelated individuals. Disease prevalence was 28% in Population 1 and 5% in Population 2. Quantile-quantile plots of association test p values from 3,200 simulation replicates under the null hypothesis of no genetic association, each with 625,504 common SNPs, were combined to get more than 2 billion null p values. (A) All SNPs. (B) Category 1: SNPs with the ratio of expected variances in Population 1 (high risk) over Population 2 (low risk) less than 0.8. (C) Category 2: SNPs with the ratio of expected variances in Population 1 (high risk) over Population 2 (low risk) between 0.8 and 1.25. (D) Category 3: SNPs with the ratio of expected variances in Population 1 (high risk) over Population 2 (low risk) greater than 1.25.



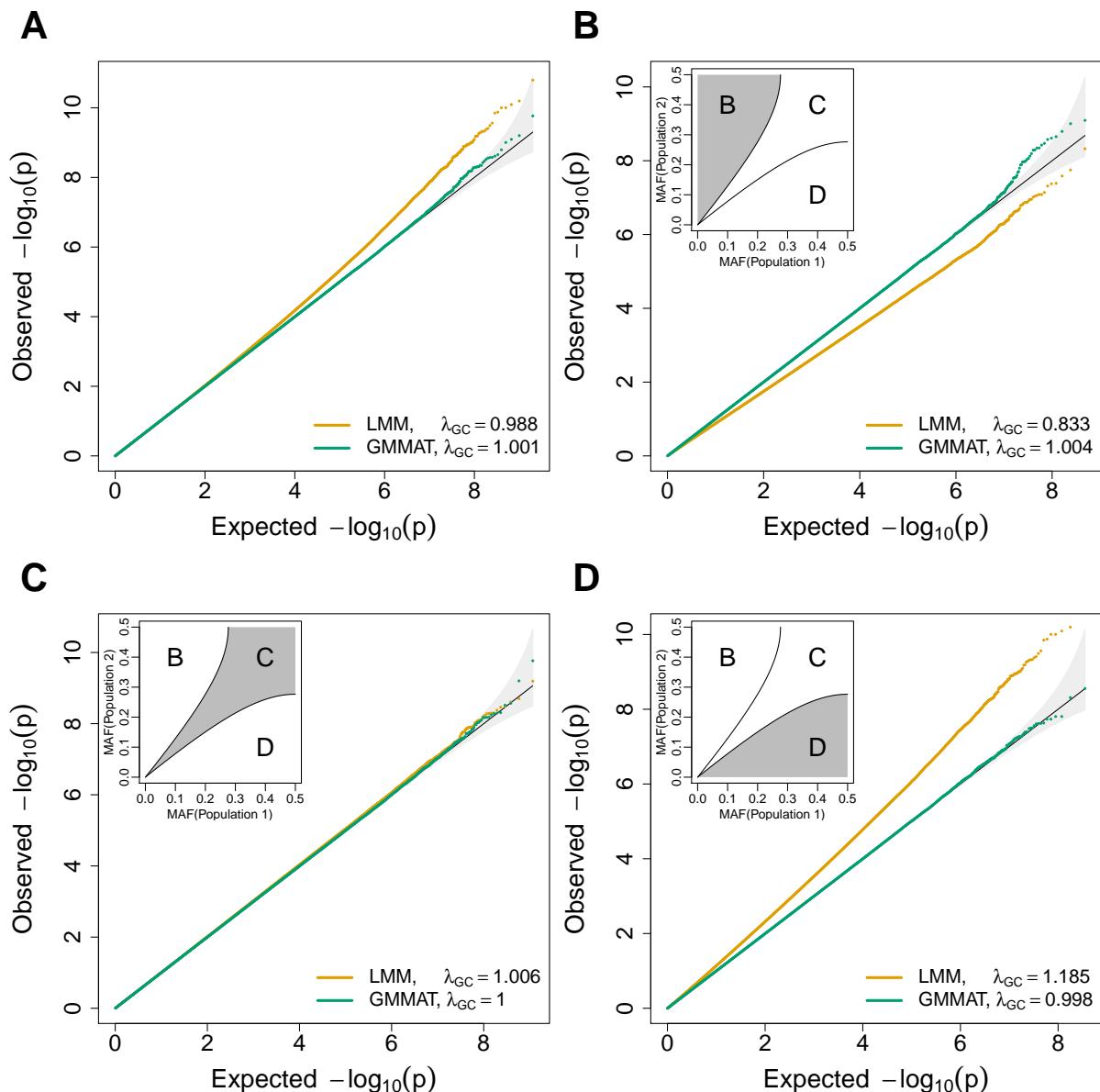
**Figure S5** Comparison of LMM meta-analysis, joint analysis and GMMAT in a simulated cohort study with 10,000 unrelated individuals. Disease prevalence was 28% in Population 1 and 5% in Population 2. Quantile-quantile plots of association test p values from 100 simulation replicates under the null hypothesis of no genetic association, each with 625,504 common SNPs, were shown. (A) All SNPs. (B) Category 1: SNPs with the ratio of expected variances in Population 1 (high risk) over Population 2 (low risk) less than 0.8. (C) Category 2: SNPs with the ratio of expected variances in Population 1 (high risk) over Population 2 (low risk) between 0.8 and 1.25. (D) Category 3: SNPs with the ratio of expected variances in Population 1 (high risk) over Population 2 (low risk) greater than 1.25. LMM meta: a meta-analysis approach to combine LMM results from analyzing Population 1 and Population 2 separately. LMM: a joint analysis using LMM on the combined samples.



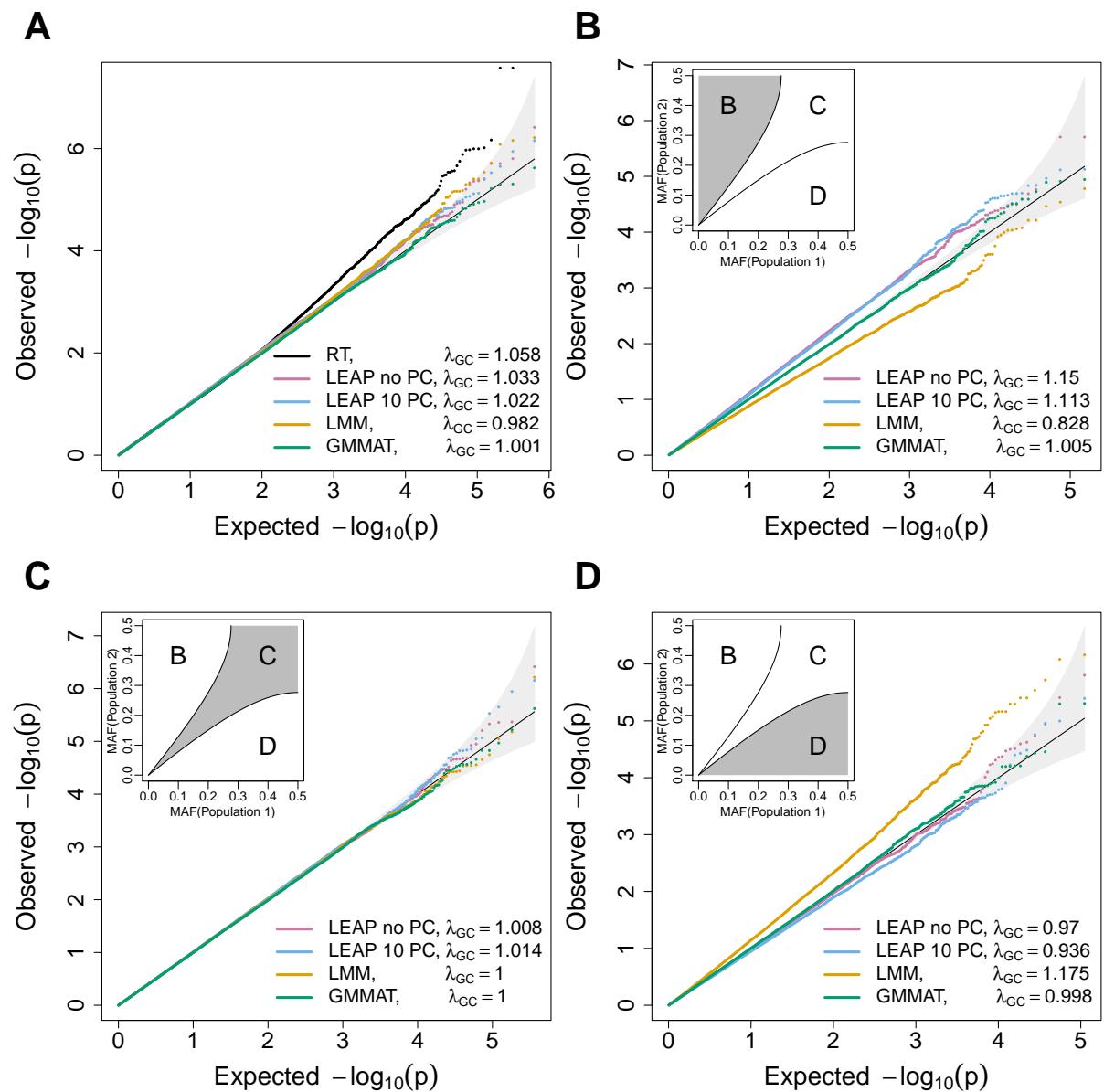
**Figure S6** Comparison of LMM meta-analysis, joint analysis and GMMAT in a simulated cohort study with 10,000 unrelated individuals in the presence of continuous population stratification. Disease prevalence was 2% in the lowest risk populations (with minimum of row and column coordinates equal to 0) and gradually increased to the topleft population. Quantile-quantile plots of association test p values from 100 simulation replicates under the null hypothesis of no genetic association, each with 625,504 common SNPs, were shown. (A) All SNPs. (B) Category 1: SNPs with the ratio of expected variances in Population 1 (high risk) over Population 2 (low risk) less than 0.8. (C) Category 2: SNPs with the ratio of expected variances in Population 1 (high risk) over Population 2 (low risk) between 0.8 and 1.25. (D) Category 3: SNPs with the ratio of expected variances in Population 1 (high risk) over Population 2 (low risk) greater than 1.25. LMM meta: a meta-analysis approach to combine LMM results from analyzing Population 1 and Population 2 separately. LMM: a joint analysis using LMM on the combined samples.



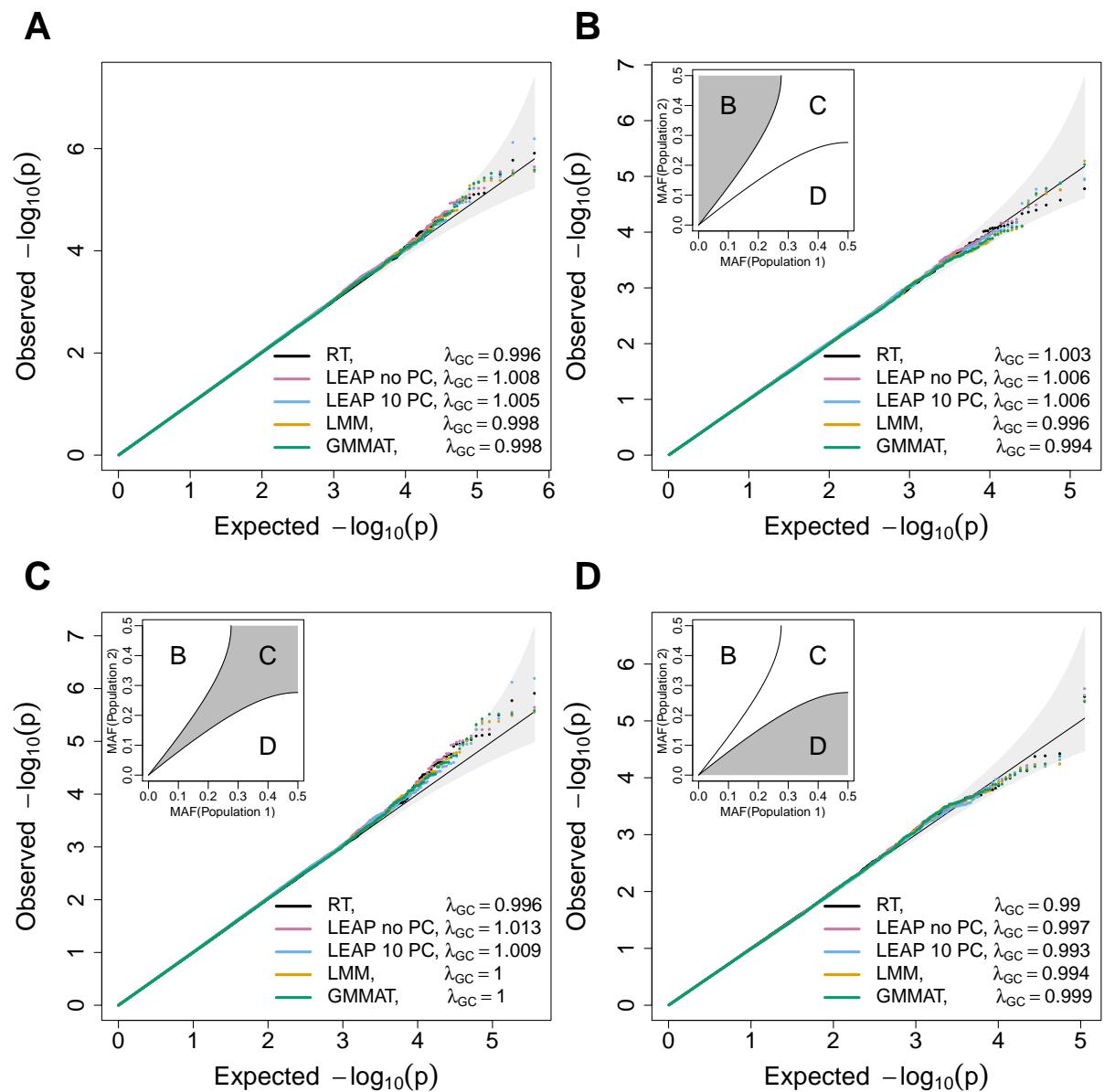
**Figure S7** Comparison of LMM and GMMAT in a simulated case-control study with case-control ratio 1:5 and 10,000 unrelated individuals. Disease prevalence was 4.5% in Population 1 and 0.5% in Population 2. Quantile-quantile plots of association test p values from 3,200 simulation replicates under the null hypothesis of no genetic association, each with 625,504 common SNPs, were combined to get more than 2 billion null p values. (A) All SNPs. (B) Category 1: SNPs with the ratio of expected variances in Population 1 (high risk) over Population 2 (low risk) less than 0.8. (C) Category 2: SNPs with the ratio of expected variances in Population 1 (high risk) over Population 2 (low risk) between 0.8 and 1.25. (D) Category 3: SNPs with the ratio of expected variances in Population 1 (high risk) over Population 2 (low risk) greater than 1.25.



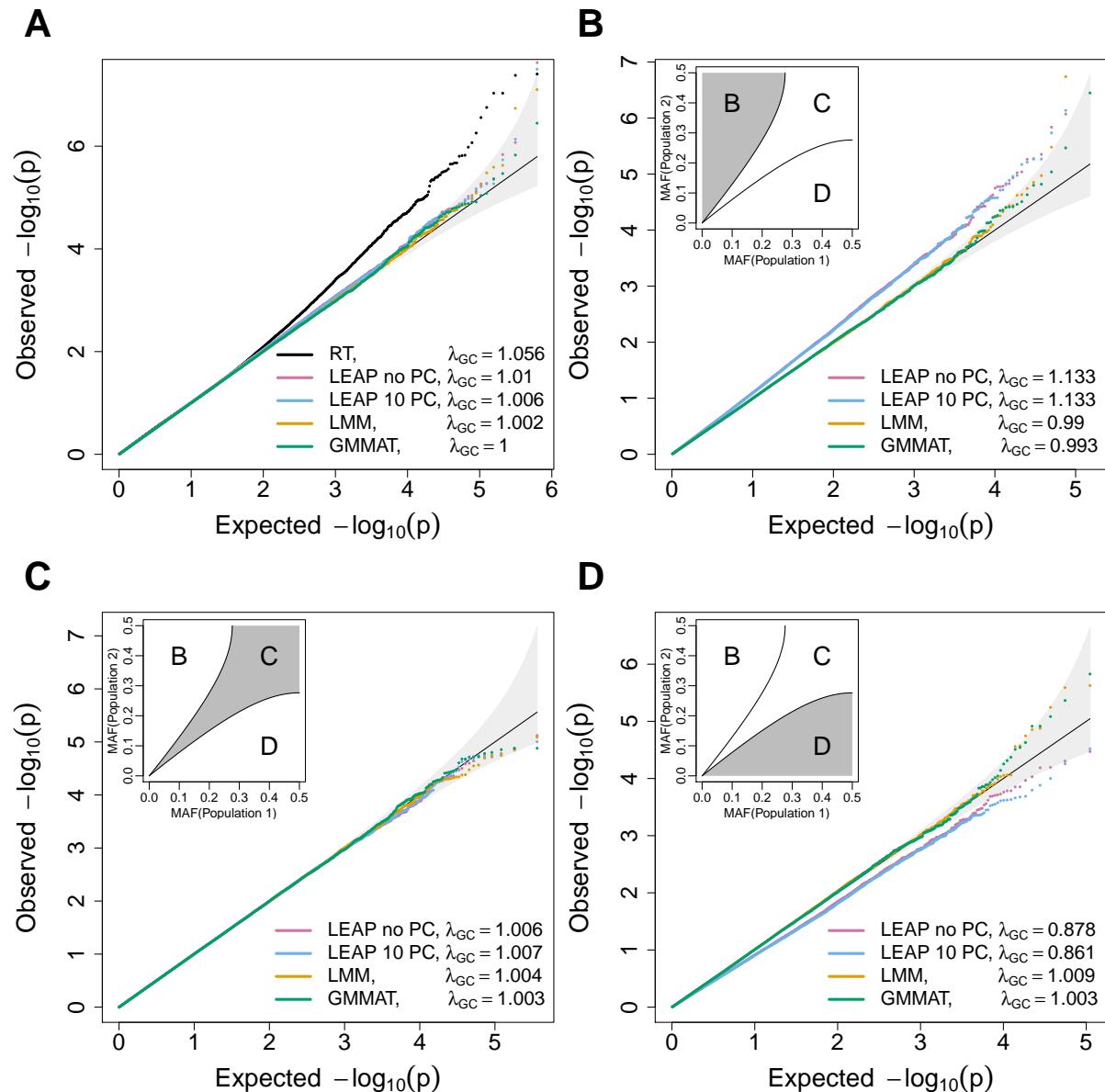
**Figure S8** Comparison of ROADTRIPS, LEAP, LMM and GMMAT in a simulated case-control study with case-control ratio 1:5 and 10,000 unrelated individuals. Disease prevalence was 4.5% in Population 1 and 0.5% in Population 2. Quantile-quantile plots of association test p values from one simulation replicate under the null hypothesis of no genetic association with 625,504 common SNPs were shown. (A) All SNPs. (B) Category 1: SNPs with the ratio of expected variances in Population 1 (high risk) over Population 2 (low risk) less than 0.8. (C) Category 2: SNPs with the ratio of expected variances in Population 1 (high risk) over Population 2 (low risk) between 0.8 and 1.25. (D) Category 3: SNPs with the ratio of expected variances in Population 1 (high risk) over Population 2 (low risk) greater than 1.25. RT: ROADTRIPS. LEAP no PC: LEAP with no covariate adjustment in heritability and liability estimation. LEAP 10 PC: LEAP adjusting for top 10 PCs in heritability and liability estimation.



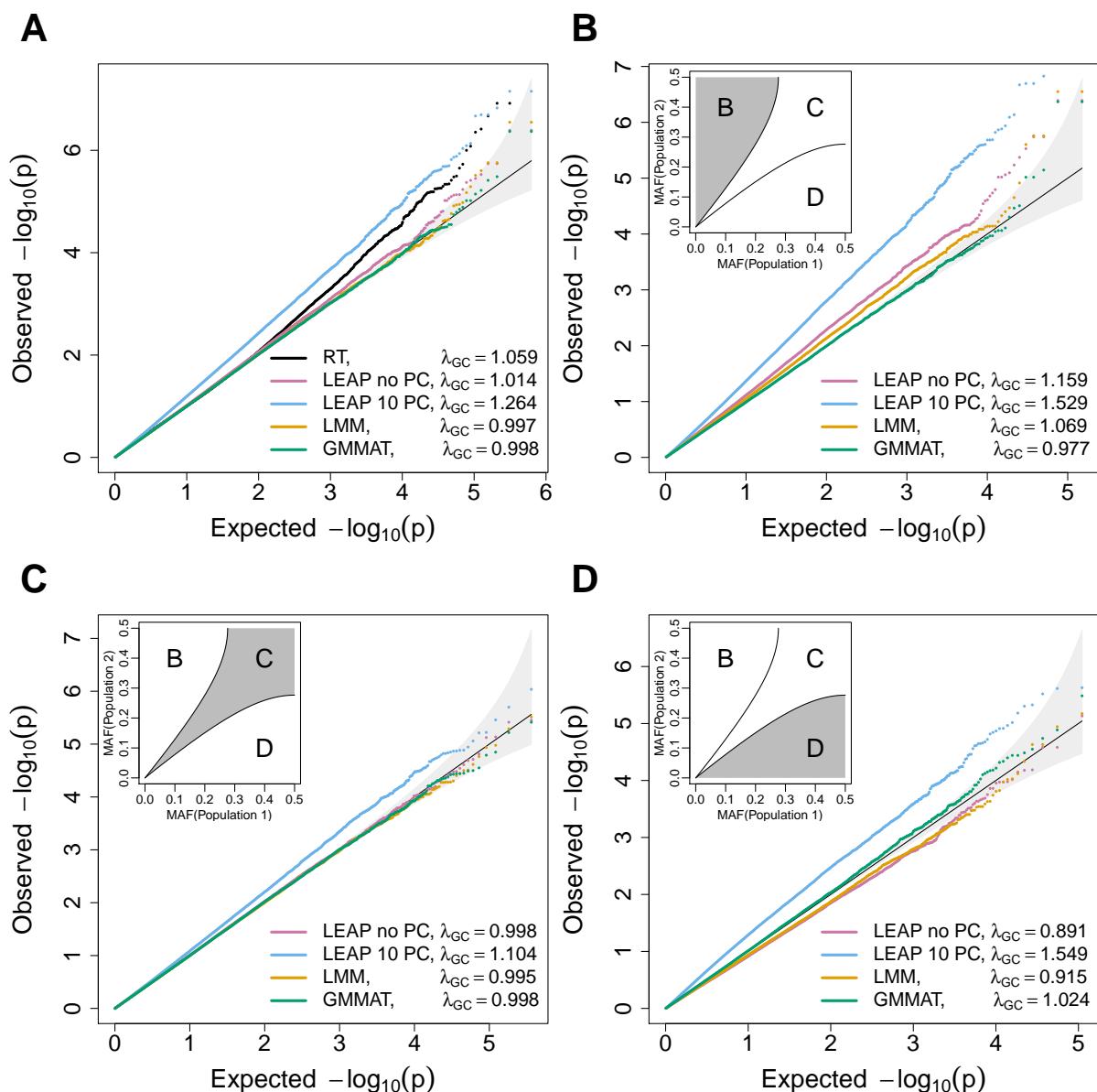
**Figure S9** Comparison of ROADTRIPS, LEAP, LMM and GMMAT in a simulated balanced case-control study with 10,000 unrelated individuals and balanced designs (case-control ratio 1:1) in two population groups. Disease prevalence was 1% in both Population 1 and Population 2. Quantile-quantile plots of association test p values from one simulation replicate under the null hypothesis of no genetic association with 625,504 common SNPs were shown. (A) All SNPs. (B) Category 1: SNPs with the ratio of expected variances in Population 1 over Population 2 less than 0.8. (C) Category 2: SNPs with the ratio of expected variances in Population 1 over Population 2 between 0.8 and 1.25. (D) Category 3: SNPs with the ratio of expected variances in Population 1 over Population 2 greater than 1.25. RT: ROADTRIPS. LEAP no PC: LEAP with no covariate adjustment in heritability and liability estimation. LEAP 10 PC: LEAP adjusting for top 10 PCs in heritability and liability estimation.



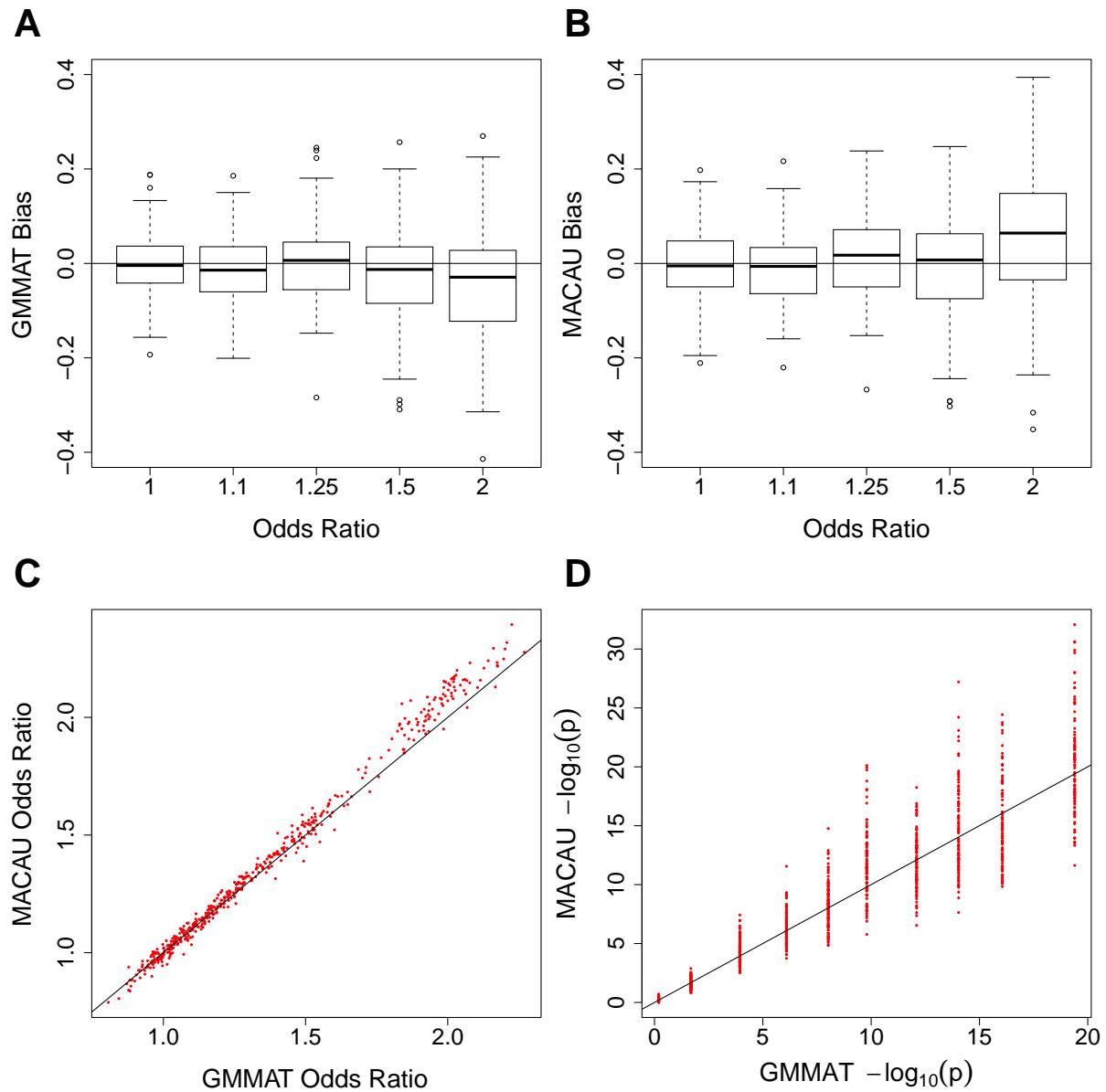
**Figure S10** Comparison of ROADTRIPS, LEAP, LMM and GMMAT in a simulated unbalanced case-control study with 10,000 unrelated individuals and unbalanced designs with equal binary trait variances in two population groups (case-control ratio 4:1 in Population 1, 1:4 in Population 2). Disease prevalence was 1% in both Population 1 and Population 2. Quantile-quantile plots of association test p values from one simulation replicate under the null hypothesis of no genetic association with 625,504 common SNPs were shown. (A) All SNPs. (B) Category 1: SNPs with the ratio of expected variances in Population 1 over Population 2 less than 0.8. (C) Category 2: SNPs with the ratio of expected variances in Population 1 over Population 2 between 0.8 and 1.25. (D) Category 3: SNPs with the ratio of expected variances in Population 1 over Population 2 greater than 1.25. RT: ROADTRIPS. LEAP no PC: LEAP with no covariate adjustment in heritability and liability estimation. LEAP 10 PC: LEAP adjusting for top 10 PCs in heritability and liability estimation.



**Figure S11** Comparison of ROADTRIPS, LEAP, LMM and GMMAT in a simulated balanced case-control study with 10,000 unrelated individuals and unbalanced designs with unequal binary trait variances in two population groups (case-control ratio 25:2 in Population 1, 25:48 in Population 2). Disease prevalence was 1% in both Population 1 and Population 2. Quantile-quantile plots of association test p values from one simulation replicate under the null hypothesis of no genetic association with 625,504 common SNPs were shown. (A) All SNPs. (B) Category 1: SNPs with the ratio of expected variances in Population 1 (low binary trait variance group) over Population 2 (high binary trait variance group) less than 0.8. (C) Category 2: SNPs with the ratio of expected variances in Population 1 (low binary trait variance group) over Population 2 (high binary trait variance group) between 0.8 and 1.25. (D) Category 3: SNPs with the ratio of expected variances in Population 1 (low binary trait variance group) over Population 2 (high binary trait variance group) greater than 1.25. RT: ROADTRIPS. LEAP no PC: LEAP with no covariate adjustment in heritability and liability estimation. LEAP 10 PC: LEAP adjusting for top 10 PCs in heritability and liability estimation.



**Figure S12** Comparison of GMMAT and MACAU in odds ratio estimation and p value calculation. Results from 100 simulation replicates in each odds ratio scenario were shown in (A), (B) and (C). (A) Bias of GMMAT odds ratio estimates. (B) Bias of MACAU odds ratio estimates. (C) Comparison of GMMAT and MACAU odds ratio estimates from combined 500 simulation replicates. (D) Comparison of GMMAT and MACAU p values from 10 simulation replicates with odds ratios ranging from 1 to 1.5. MACAU (with 1,000 Markov chain Monte Carlo iterations) p values from 100 random seeds were shown for each simulation replicate.



**Table S1** Power comparison of logistic regression, LMM and GMMAT in identifying causal genetic variants at the genome-wide significance level  $5 \times 10^{-8}$ . Results from 1,000 simulation replicates in each scenario were shown.

Scenario	Prevalence	Odds Ratio	Power		
			Logistic Regression	LMM	GMMAT
No stratification	0.01	1.25	0.43	0.36	0.36
With stratification <sup>a</sup>	0.11 <sup>b</sup>	1.5	NA <sup>c</sup>	0.66	0.70

<sup>a</sup> Since LMM has inflated type I error rates for genetic variants with a higher MAF in the high risk population group, only results from genetic variants with a lower MAF in the high risk population group were shown. Note that the empirical type I error rate of LMM is below  $5 \times 10^{-8}$  for these genetic variants, and it becomes lower as the ratio of expected genotype variances ( $2\text{MAF}(1-\text{MAF})$ ) in the high risk population group over the low risk population group becomes smaller.

<sup>b</sup> Prevalence 0.28 in the high risk population group, 0.05 in the low risk population group.

<sup>c</sup> Excluded due to inflated type I error rates.

**Table S2** Computation time in seconds of SAS® PROC GLIMMIX (version 9.3, on the Linux 2.6.32-431.17.1.el6.x86\_64 platform) and GMMAT when fitting the null model with 1 variance component (VC) and the null model with 3 VC. The sample size was 2,000 and 10,000, and the comparison was repeated 10 times on a single core of an Intel® Xeon® E5-2690 CPU (2.90 GHz). Score test was performed on 1 million SNPs.

Sample Size	Fit 1 VC Null Model		Fit 3 VC Null Model		1 Million Score Tests
	GMMAT	SAS®	GMMAT	SAS®	GMMAT
2,000	22.3	1784.0	22.6	4471.7	923.3
	22.4	1551.8	22.8	3914.4	861.4
	19.8	1515.0	20.3	3913.6	836.3
	22.2	1580.2	22.8	3932.0	878.4
	22.0	2308.4	22.8	6237.3	844.0
	23.4	1696.3	22.6	4440.3	885.2
	22.4	1513.0	22.8	3937.5	804.1
	21.0	1608.8	20.2	3907.1	803.8
	22.1	1610.2	22.8	3917.5	823.0
	22.0	1521.0	22.3	3918.4	792.3
10,000	1134.2	NA	2982.1	NA	12074.7
	1114.3	NA	2838.0	NA	12096.3
	1061.5	NA	1481.5	NA	12706.0
	1011.9	NA	1468.4	NA	12066.1
	1514.9	NA	3795.2	NA	11850.1
	1051.5	NA	1745.3	NA	12536.3
	1062.5	NA	1466.1	NA	12612.6
	1070.2	NA	1635.2	NA	17861.3
	1007.1	NA	1480.4	NA	12299.2
	1028.6	NA	1618.2	NA	12438.1