**Appendix**

Appendix A: TWAS and the LDA-MR

If for all SNPs, the TWAS and LDA-MR will be proportional to each other by a constant. Recall that:

If , then . Also, recall and , we then have:

Recall that when all the marginal variances are the same and therefore .

The desired result.

Appendix B: Convergence of the LDA MR-Egger Parameters.

Recall from the document that the parameters converge to ().

Recall that:

The expected value of our γ estimate is:

The first term will go to as NE (the sample size used to estimate ) increases. Therefore, as NE →∞, →*βE.* Assume that NE is sufficiently large to reach this convergence boundary. We then have:

Focusing on the second term, it can be rewritten as

The numerator is the sample univariate covariance between and weighted by ***W***, times We’ll treat that as a constant. The denominator is the sample univariate variance of weighted by ***W***times . If is independent of and the mean of is a constant - the term will go to 0 as *JEFF*→∞. JEFF denotes the effective number of SNPs at the loci. We will take the expectation of the numerator conditional on :

If is independent of then and if, the above reduces to:

The above results taken together gives us:

Our estimate of the intercept from the LDA-MR Egger regressions is:

With expectation:

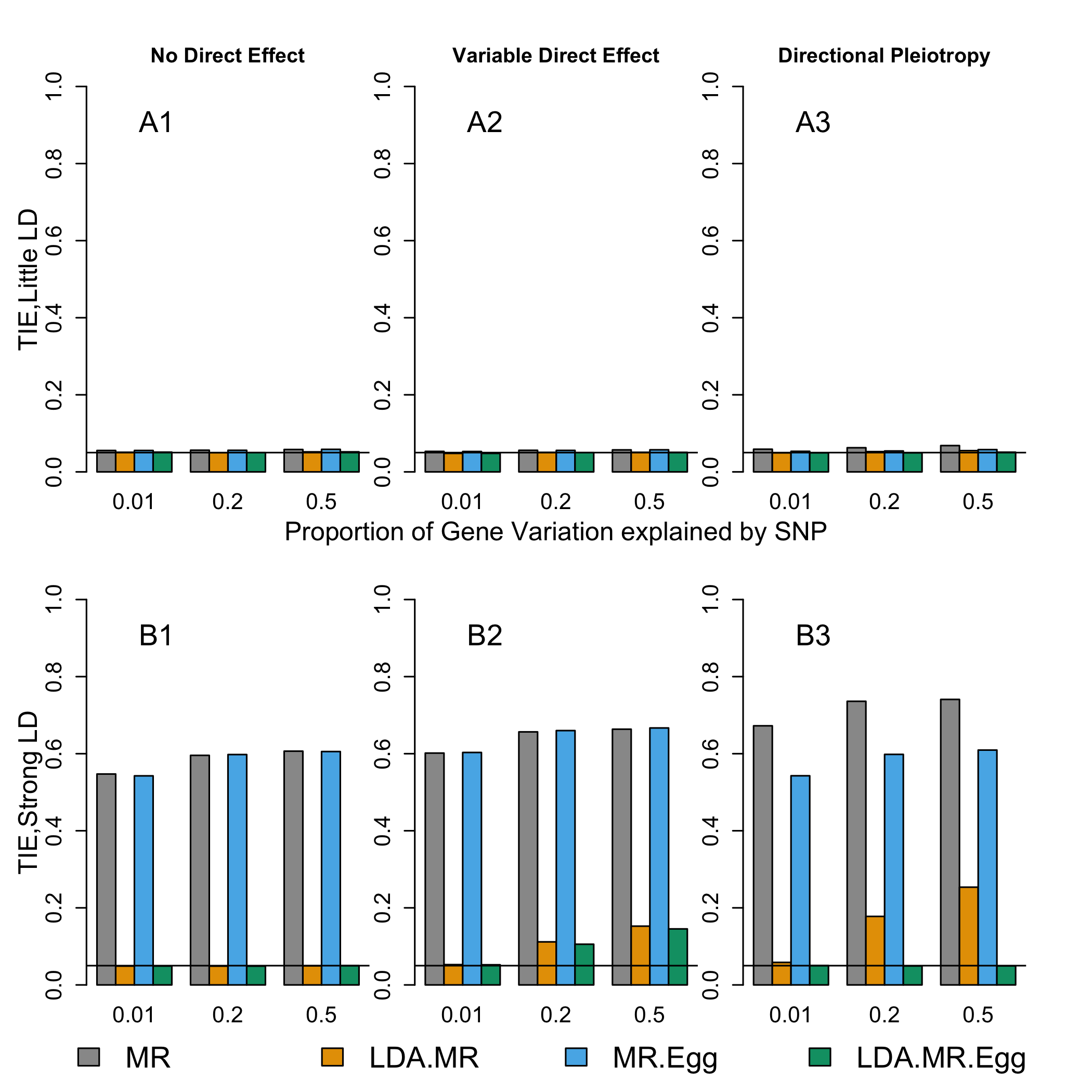
As NE goes to infinity, the first term will go to 0 as

Rewriting this, if we have that is independent of and .

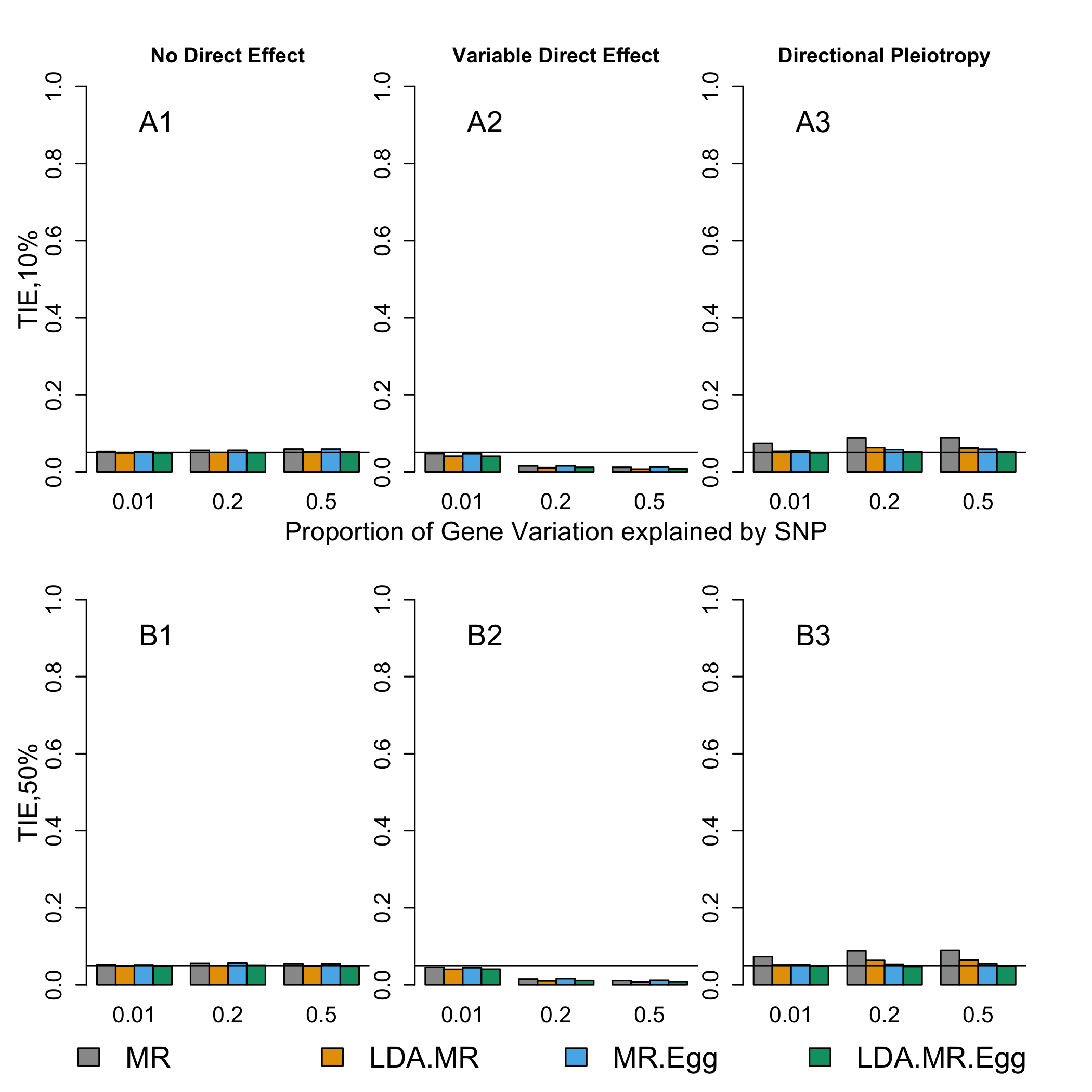
This is if the INSIDE condition holds, and the mean is a constant. Therefore

**Supplementary Figures**

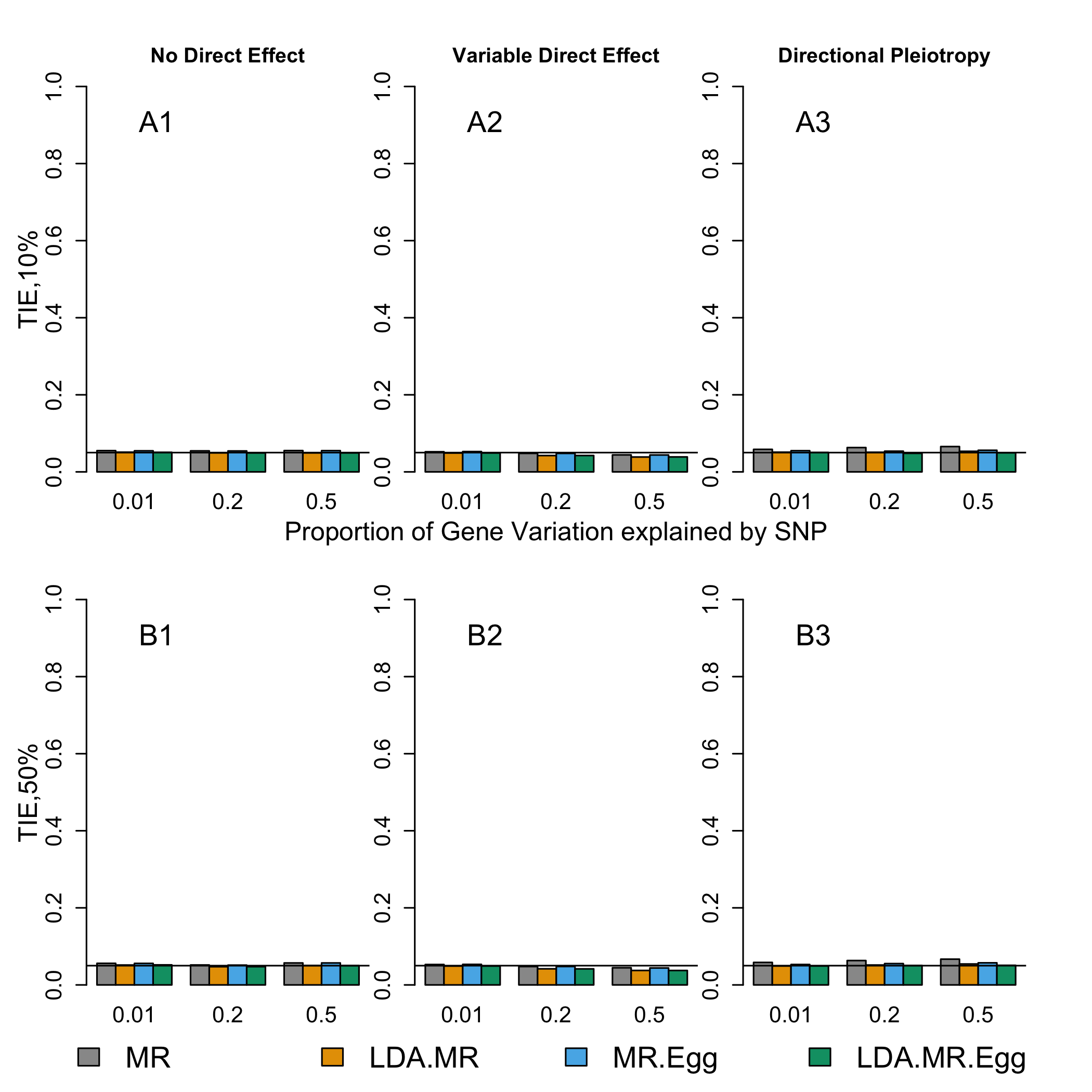
**Supplementary Figure 1: Type I error when J=300.** Each bar represents results over 5x104 simulations. Evaluated at = 0:05. First panel represent when low LD (plots with A). Second panel represents when strong LD (plots with B). From left to right correspond to: no direct effect, variable direct effects with mean 0 across SNPs, and direct effects with mean >0 across SNPs and small variability (directional pleiotropy). When there is a direct effect, the SNPs explain 1% of the variation in the outcome ().



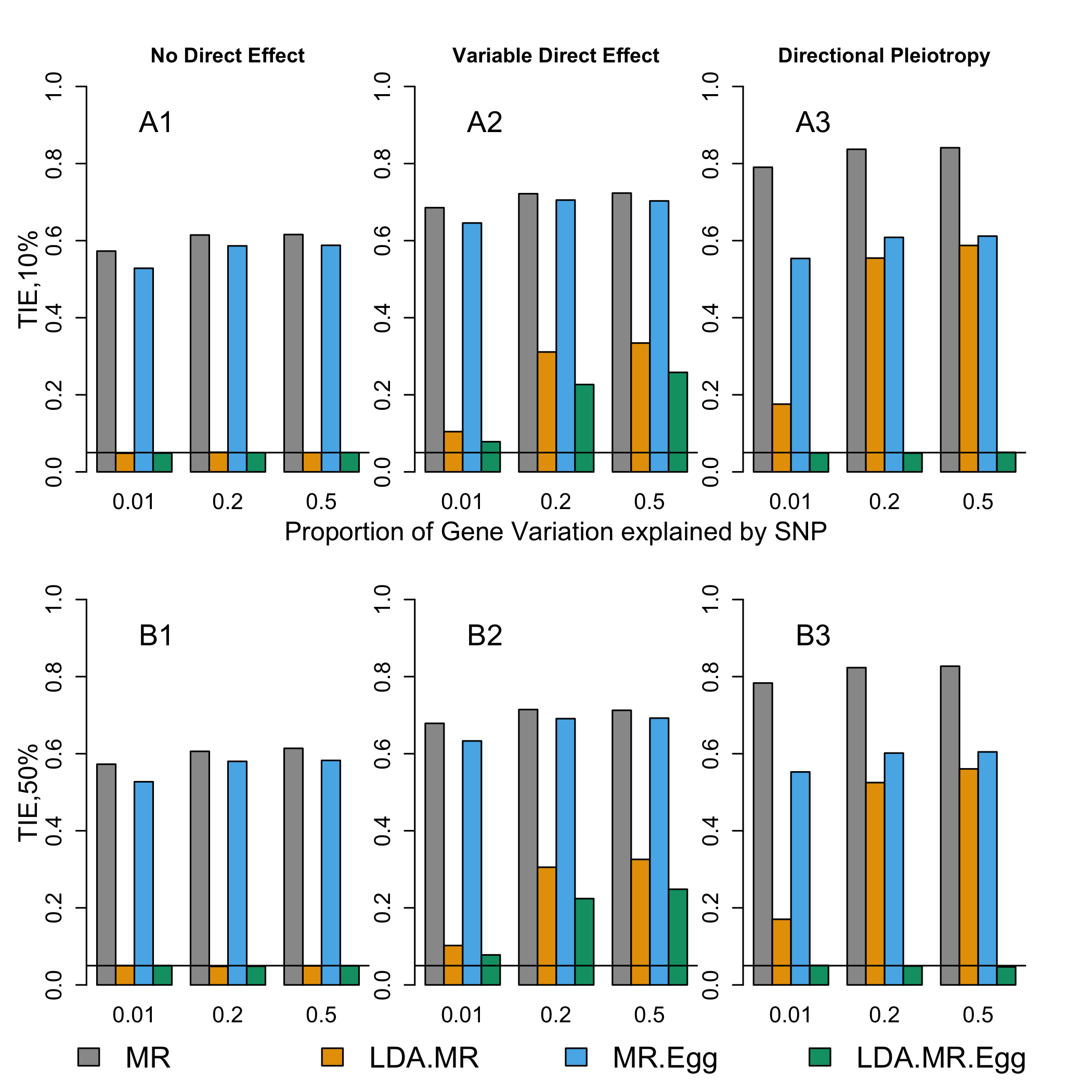
**Supplementary Figure 2: Type I error when J=50, little LD, and co-localization.** Each bar represents results over 5x104 simulations. Evaluated at = 0:05. First panel represent when 10% eQTL and 10% disease SNPs (plots with A). Second panel represents when 50% eQTL and 50% disease SNPs (plots with B). From left to right correspond to: no direct effect, variable direct effects with mean 0 across SNPs, and directional pleiotropy. When there is a direct effect, the SNPs explain 1% of the variation in the outcome ().



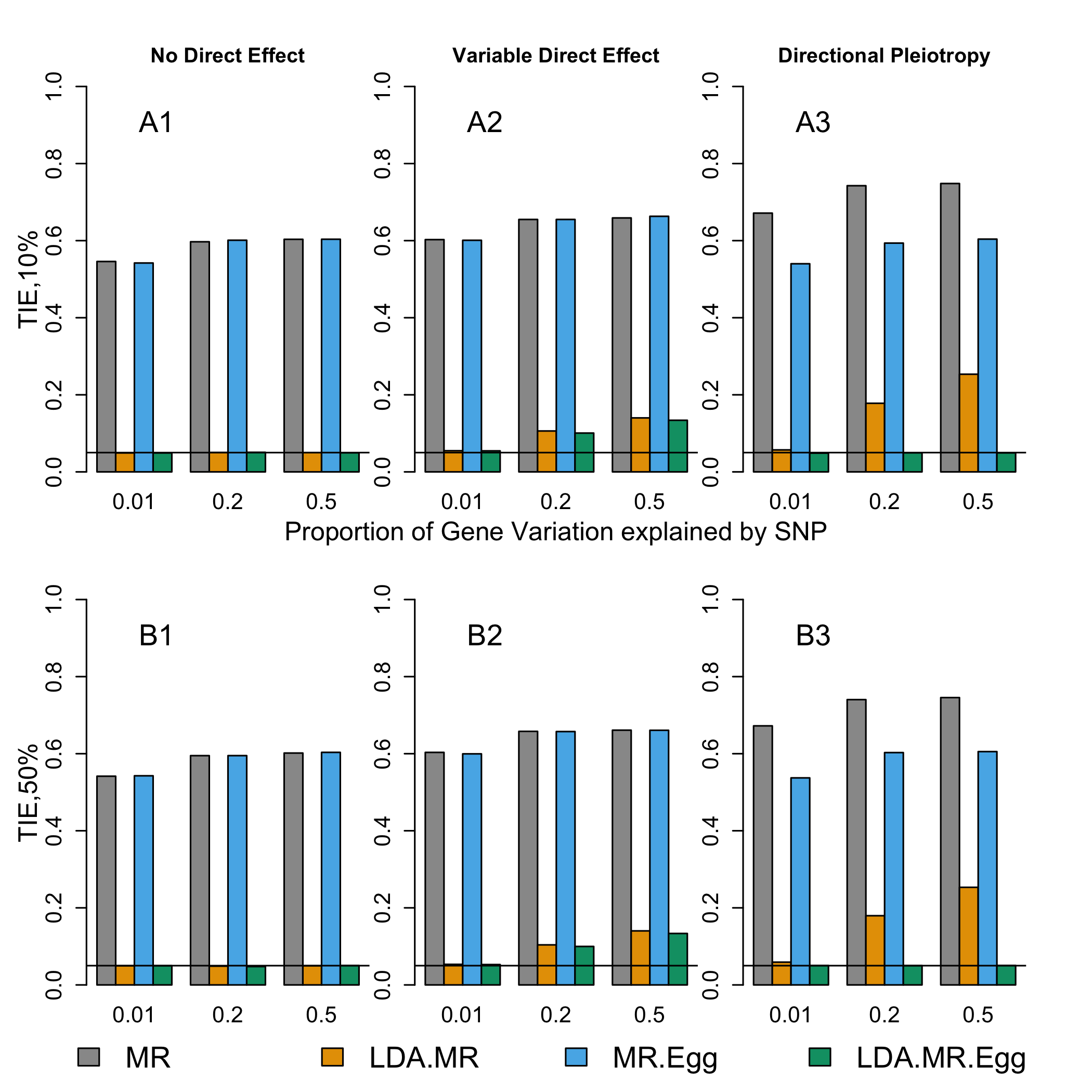
**Supplementary Figure 3: Type I error when J=300, little LD, and co-localization.** Each bar represents results over 5x104 simulations. Evaluated at = 0:05. First panel represent when 10% eQTL and 10% disease SNPs (plots with A). Second panel represents when 50% eQTL and 50% disease SNPs (plots with B). From left to right correspond to: no direct effect, variable direct effects with mean 0 across SNPs, and directional pleiotropy. When there is a direct effect, the SNPs explain 1% of the variation in the outcome ().



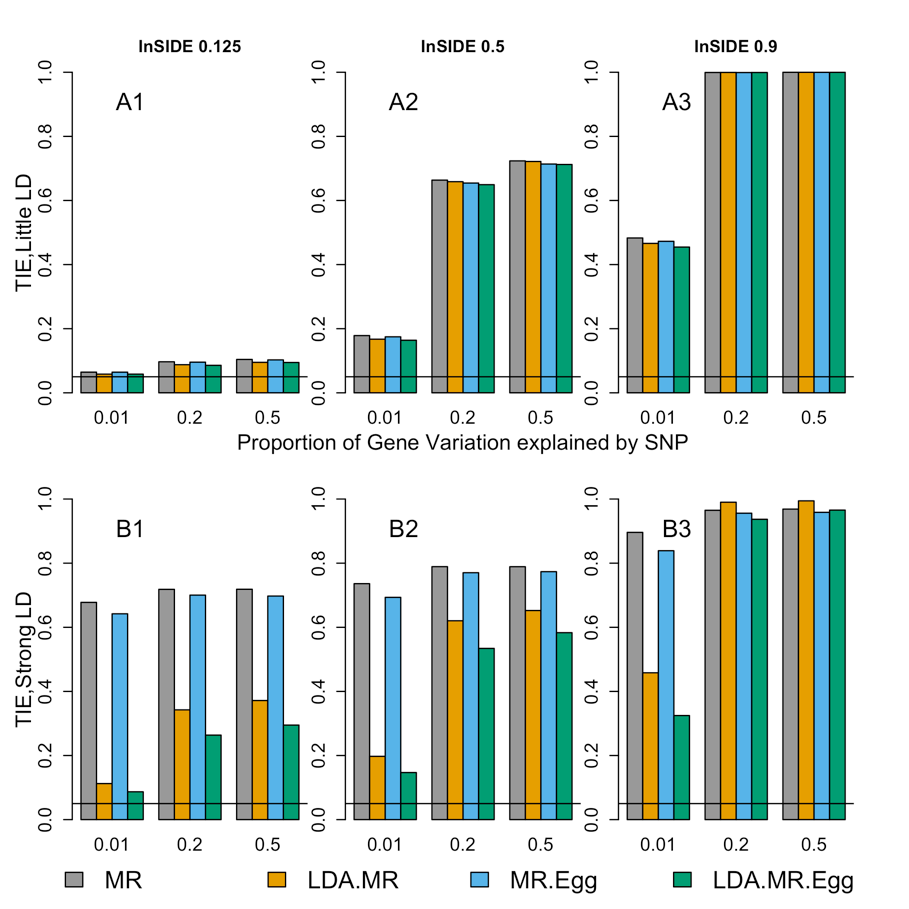
**Supplementary Figure 4: Type I error when J=50, strong LD, and co-localization.** Each bar represents results over 5x104 simulations. Evaluated at = 0:05. First panel represent when 10% eQTL and 10% disease SNPs (plots with A). Second panel represents when 50% eQTL and 50% disease SNPs (plots with B). From left to right correspond to: no direct effect, variable direct effects with mean 0 across SNPs, and directional pleiotropy. When there is a direct effect, the SNPs explain 1% of the variation in the outcome ().



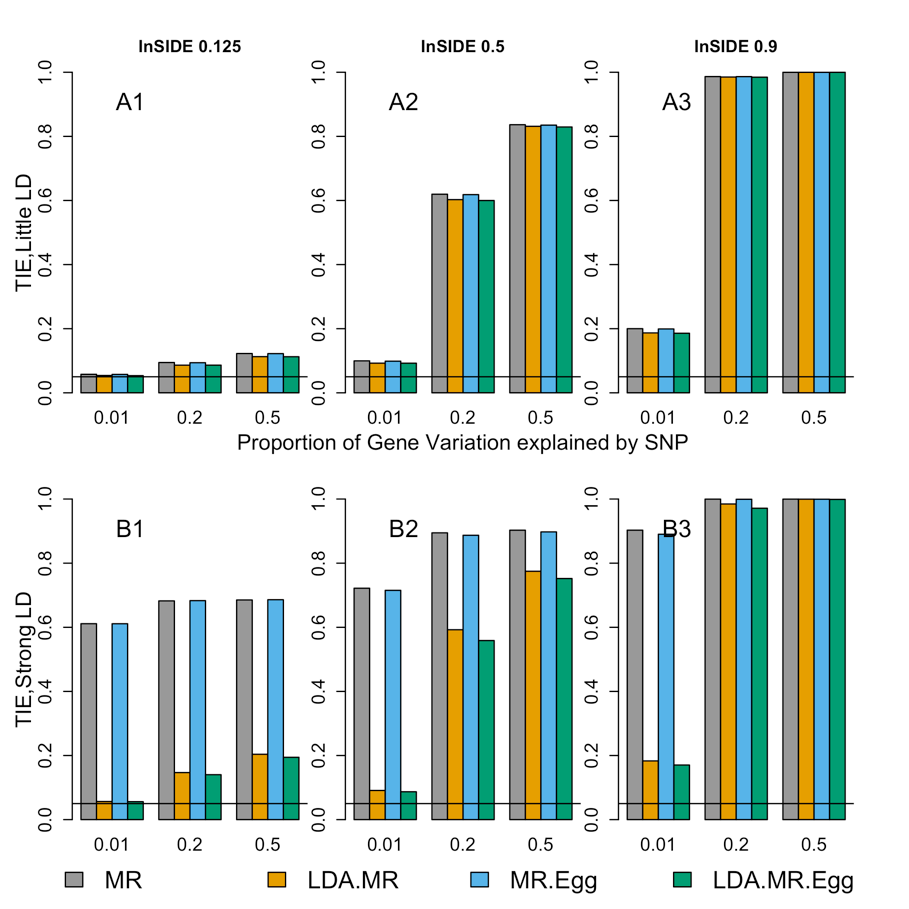
**Supplementary Figure 5: Type I error when J=300, strong LD, and co-localization.** Each bar represents results over 5x104 simulations. Evaluated at = 0:05. First panel represent when 10% eQTL and 10% disease SNPs (plots with A). Second panel represents when 50% eQTL and 50% disease SNPs (plots with B). From left to right correspond to: no direct effect, variable direct effects with mean 0 across SNPs, and directional pleiotropy. When there is a direct effect, the SNPs explain 1% of the variation in the outcome ().



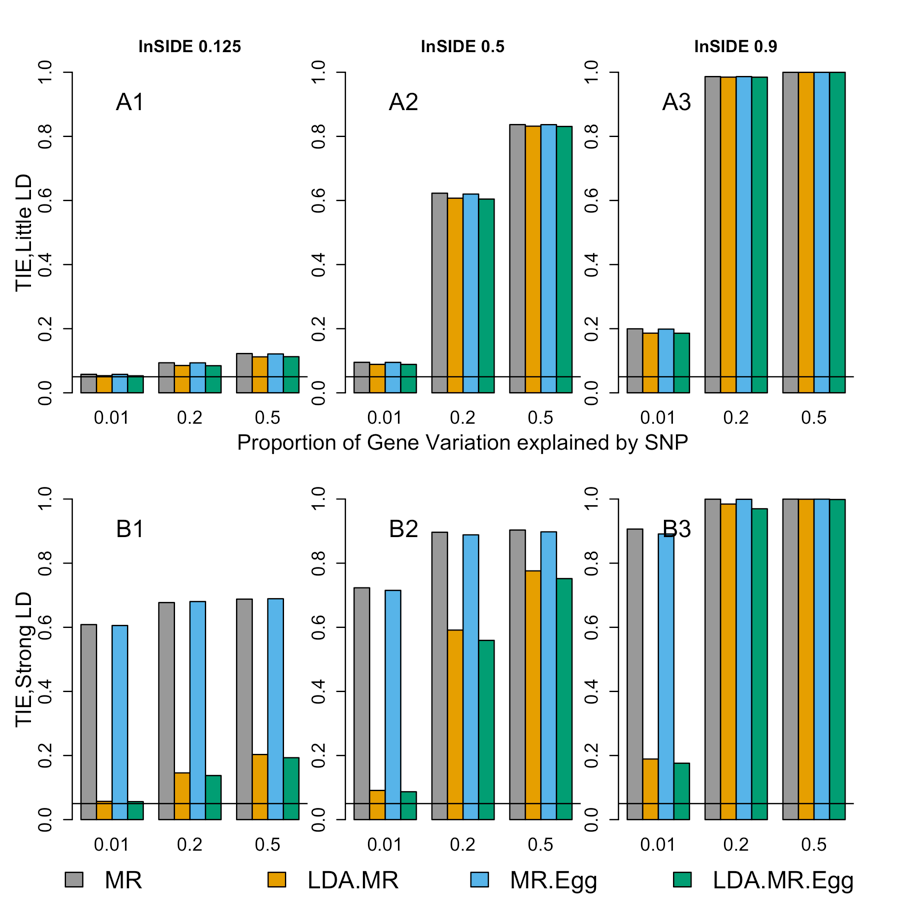
**Supplementary Figure 6: Type I error when J=50, InSIDE condition violated, and variable direct effects with mean 0 across SNPs.** Each bar represents results over 5x104 simulations. Evaluated at α = 0:05. First panel represent when low LD (plots with A). Second panel represents when strong LD (plots with B). From left to right correspond to: correlation between and is 0.125, 0.5, or 0.9.



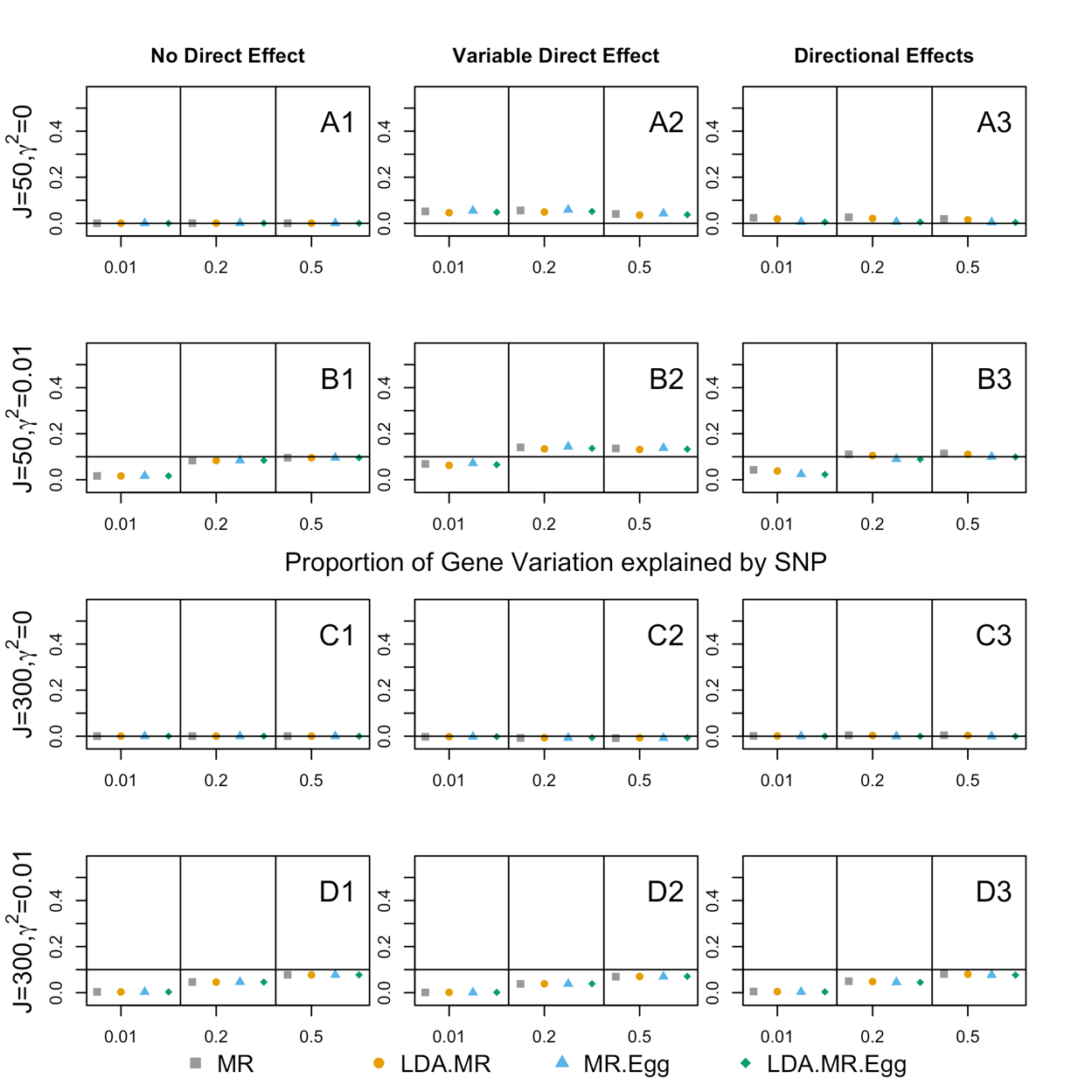
**Supplementary Figure 7: Type I error when J=300, InSIDE condition violated, and directional pleiotropy.** Each bar represents results over 5x104 simulations. Evaluated at α = 0:05. First panel represent when low LD (plots with A). Second panel represents when strong LD (plots with B). From left to right correspond to: correlation between and is 0.125, 0.5, or 0.9.



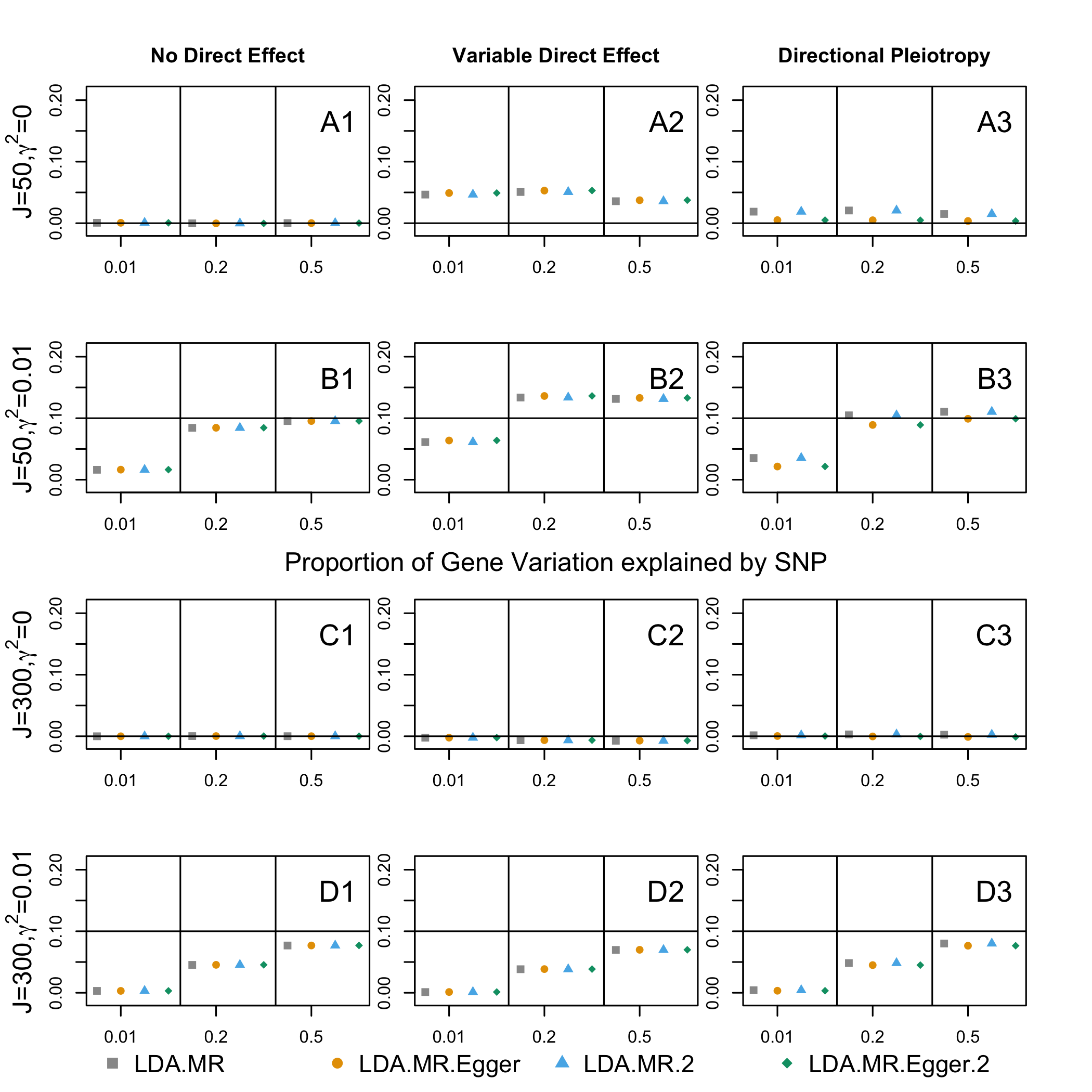
**Supplementary Figure 8: Type I error when J=300, InSIDE condition violated, and variable direct effects with mean 0 across SNPs.** Each bar represents results over 5x104 simulations. Evaluated at α = 0:05. First panel represent when low LD (plots with A). Second panel represents when strong LD (plots with B). From left to right correspond to: correlation between and is 0.125, 0.5, or 0.9.



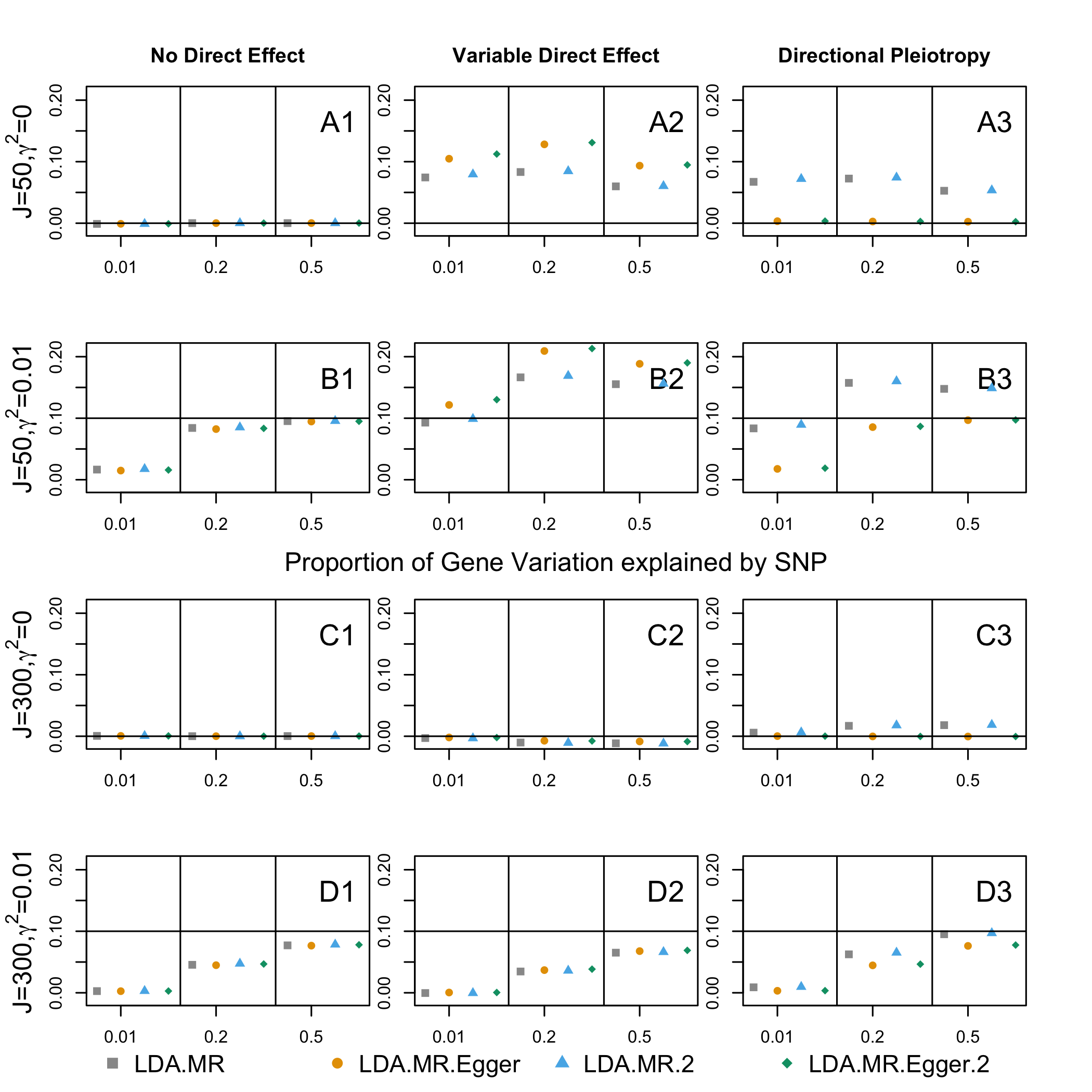
**Supplementary Figure 9: Bias when low LD for J=50, 300.** Bias plots for when there is low LD in the SNP set. First row corresponds to J=50, γ2= 0 (plots with A). Second panel (plots with B) when J = 50 and γ2 = 0.01. Third panel (plots with C) when J = 300 and γ = 0. Final panel (plots with D) J = 300 and γ2 = 0.01. From left to right: no direct effect, variable direct effects with mean 0 across SNPs, and directional pleiotropy. When there is a direct effect, the SNPs explain 1% of the variation in the outcome ().



**Supplementary Figure 10: Bias when low LD for J=50, 300 Comparing LDA method when add 0.1 to diagonal of LD matrix.** Bias plots for when there is low LD in the SNP set. The adjusted LD methods are denoted as .2 in the legend. First row corresponds to J=50, γ2= 0 (plots with A). Second panel (plots with B) when J = 50 and γ2 = 0.01. Third panel (plots with C) when J = 300 and γ = 0. Final panel (plots with D) J = 300 and γ2 = 0.01. From left to right: no direct effect, variable direct effects with mean 0 across SNPs, and directional pleiotropy. When there is a direct effect, the SNPs explain 1% of the variation in the outcome ().



**Supplementary Figure 11: Bias when high LD for J=50, 300 Comparing LDA method when add 0.1 to diagonal of LD matrix.** Bias plots for when there is low LD in the SNP set. The adjusted LD methods are denoted as .2 in the legend. First row corresponds to J=50, γ2= 0 (plots with A). Second panel (plots with B) when J = 50 and γ2 = 0.01. Third panel (plots with C) when J = 300 and γ = 0. Final panel (plots with D) J = 300 and γ2 = 0.01. From left to right: no direct effect, variable direct effects with mean 0 across SNPs, and directional pleiotropy. When there is a direct effect, the SNPs explain 1% of the variation in the outcome ().



**Supplementary Figure 12: Comparing TWAS vs LDA MR.** Comparing test statistics between TWAS (x-axis) and LDA-MR (y-axis) across 683 genes.

