Supplemental Figure Legends:

Figure 1: Sensitivity of the Empirical Bayes estimation to the number of bins chosen.

10,000 Z-scores were simulated from a mixture of three unit variance normal distributions with means at -1, 0 and 1. The probabilities of a Z-score coming from the zero-mean component – representing SNPs that are not associated with disease - was either 0.99 (top panel) or 0.9 (bottom panel). We used the Empirical Bayes algorithm described in the main manuscript to estimate the posterior mean for given Z-scores, given differing numbers of bins, b. Here we display the relationship between the Z-score and the estimated posterior mean, for each choice of b.

Figure 2: Average Mean Squared error on Simulated Data using a threshold of $p < 0.05$

A-C: Estimated mean and associated 95% confidence interval for the quantity $(\hat{\beta}_{1,i}^{\ cor} - \beta_{1,i})^2$, where $\hat{\beta}_{1,i}^{\ cor}$ is the corrected estimate for the log-OR for a particular SNP and $\beta_{1,i}$ is the true underlying OR for the same SNP. The average was taken over nominally significant SNPs (having $p < 0.05$) in 100 simulations of a given scenario. 6 methods were used to correct the log-ORs: Empircal Bayes (EB), Conditional Likelihood (CL), Conditional Mean (CM), the Average of CL and CM (Ave), the Empirical Bayes estimator using all 100 simulations to estimate the marginal distribution (EB_100), and the Combination estimator (Comb). The distribution of the true log-ORs were simulated according to a Contaminated Normal distribution (A), Double Exponential (B) or Normal Distribution (C). The number of non zero log-ORs was either 100 or 1000.

Figure 3: Estimated Mean Square error at different Z-scores

A-B: Estimated mean $(\hat{\beta}_{1,i}^{\ cor} - \beta_{1,i})^2$, regressed against the observed Z-score for each particular SNP using local regression (the loess function in R). Genotype data for 1000 cases and 1000 controls for 100000 SNPs was simulated, assuming 3 population level log-ORs of 0.4, 0.8 and 1.2, 997 population

level log-ORs were simulated from a normal distribution with standard deviation 0.07, and the remainder of the SNPs (99,000) having no association with disease. Similar plots were obtained from other disease models. One can see that Empirical Bayes and the Combination estimator have excellent performance when correcting the log-OR for weakly associated SNPs. For highly associated SNPs, the performance of Empirical Bayes deteriorates rapidly due to the difficulty of estimating the log marginal density function for these SNPs. However, the combination estimator still shows near optimal peformance. A: Conditional likelihood and Combination estimators assume a nominal significance threshold of 0.05 for the selection of SNPs B: . Conditional likelihood and Combination estimators assume a genome wide significance, $p < \frac{0.05}{10^6}$, for the selection of SNPs

Figure 4: Average Mean Bias

A-C: Estimated mean and associated 95% confidence interval for the quantity $(\hat{\beta}_{1,i}^{\ cor} - \beta_{1,i})$, where $\hat{\beta}_{1,i}^{\ cor}$ is the corrected estimate for the log-OR for a particular SNP and $\beta_{1,i}$ is the true underlying OR for the same SNP. The average was taken over genome wide significant SNPs (having $p < 0.05 / 10^6$) in 100 simulations of a given scenario. 6 methods were used to correct the log-ORs: Empircal Bayes (EB), Conditional Likelihood (CL), Conditional Mean (CM), the Average of CL and CM (Ave), the Empirical Bayes estimator using all 100 simulations to estimate the marginal distribution (EB_100), and the Combination estimator (Comb). The distribution of the true log-ORs were simulated according to a Contaminated Normal distribution (A), Double Exponential (B) or Normal Distribution (C). The number of non zero log-ORs was either 100 or 1000.

Figure 5: Comparison of Empirical Bayes, Conditional Likelihood and BR-Squared in terms of shrinkage on real GWAS data.

To compare the shrinkage performance for BR-Squared to other methods, we use a scaled version of the BR-squared adjusted log-ORs, defined for a given SNP as, $\hat{\mu}^{BR} = \frac{\hat{\beta}^{BR}}{SE(\hat{\beta})}$, where $\hat{\beta}^{BR}$ is the original corrected log-OR coming from the BR-squared software and $SE(\hat{\beta})$ is the estimated standard error of the originally estimated log-OR. We plot this quantity against the Z-scores, defined for each SNP as $Z = \frac{\hat{\beta}}{SE(\hat{\beta})}$, for both Schizophrenia and Crohn's Disease. We show similar relationships for Conditional Likelihood and Empirical Bayes on the same plot.