## APPENDIX

Some studies use $\chi^2_2$ test that allows different OR estimates for the heterozygote and homozygote for the minor allele. This test involves a quadratic function, $\hat{S}$, of the OR estimates for the heterozygote and homozygote, which is compared to the $\chi^2_2$ distribution quantiles to obtain a p-value. An extension of the bias correction procedure mentioned above for the joint estimation of these two ORs.

Asymptotically, the $\chi^2_2$ test is equivalent to the Wald test of the two coefficients in a logistic regression model with separate parameters for the heterozygote and homozygote, $logit(P) = \beta_0 + \beta_1 1_{[Z=1]} + \beta_2 1_{[Z=2]}$, where $Z$ is the number of minor SNP alleles, and $[\ldots.]$ denotes the indicator function. The null hypothesis that corresponds to no association between the SNP and the disease is $H_0$: $\beta \equiv (\beta_1, \beta_2)^T = \mathbf{0}$. The conditional distribution of $\hat{\beta} \equiv \left(\hat{\beta}_1, \hat{\beta}_2\right)^T$, conditional on $\hat{S} \geq c$, where the constant c is the $\chi^2_2$ quantile value corresponding to the desired p-value cutoff, is

$$f_{\hat{\beta}|\hat{S}\geq c}(\mathbf{x}; \beta, \Sigma) = \frac{f_N(\mathbf{x}; \beta, \Sigma^{-1})}{\int_c^\infty f_{\chi^2}(t; 2, \beta^T \Sigma \beta) dt} 1[\mathbf{x}^T \Sigma \mathbf{x} \geq c] \tag{1}$$

where $\Sigma^{-1}$ denotes the variance covariance matrix of $\hat{\beta}$, $f_N(\mathbf{x}; \beta, \Sigma^{-1})$ denotes the normal density function of with mean $\beta$ and variance $\Sigma^{-1}$) at argument $\mathbf{x}$. $f_{\chi^2}(t; 2, \beta^T \Sigma \beta)$ denotes the density function of a non-central $\chi^2_2$ variate with non-centrality parameter $\beta^T \Sigma \beta$ at argument $t$. $\Sigma$ can be replaced by $\hat{\Sigma}$ to a good approximation, and $\hat{\Sigma}$ can be estimated from $\hat{\sigma_1}$, $\hat{\sigma_2}$, and $P_{2-df}$, because $\hat{\Sigma}$ satisfies:

$$[\hat{\Sigma}^{-1}]_{11} = \hat{\sigma_1}^2$$

$$[\hat{\Sigma}^{-1}]_{22} = \hat{\sigma_2}^2$$

$$\hat{s} \equiv \hat{\beta}^T \hat{\Sigma} \hat{\beta} \quad = \quad F^{-1}(P_{2-df}; 2, 0)$$

where $F^{-1}(P_{2-df}; 2, 0)$ is the $P_{2-df}$ quantile of $\chi^2_2$.

The maximum likelihood adjusted estimator is defined to maximize the conditional likelihood of $\beta$ given $\hat{s}$, that is $\hat{\beta}_{MLE} = argmax_{\beta} \log f_{\hat{\beta}|\hat{S} \geq c}(\hat{\beta}; \beta, \hat{\Sigma})$. When estimating the confidence interval for one $\beta$, we draw its profile likelihood curve. Then its profile confidence limits are the intersection of the log-likelihood curve with a horizontal line $\chi^2_{1,0.95}/2 = 1.92$ units below its maximum. The profile likelihood for each $\beta$ value is estimated as the maximized likelihood value among all possible values for the other $\beta$.

We used a likelihood ratio test to compare if the bias-corrected estimate ($\hat{\beta}_{MLE}$) to the replication estimate of $(\beta_1, \beta_2)$. The test is performed as follows:

The total likelihood containing data from both the GWAS stage and the replication stage is defined as $\log f(\beta_1, \beta_2) = \log f_{\hat{\beta}|\hat{S} \geq c}(\hat{\beta}; \boldsymbol{\beta_1}, \hat{\Sigma}) + \log g(\hat{\beta}_{replication}; \beta_2)$, where $\log f_{\hat{\beta}|\hat{S} \geq c}(\hat{\beta}; \beta, \hat{\Sigma})$ is the conditional likelihood at $\hat{\beta}$ defined in (1) under the true log OR $\beta_1$ in the initial GWAS population. $g(\hat{\beta}_{replication}; \beta_2)$ is the normal likelihood at $\hat{\beta}_{replication}$ under the true log OR $\beta_2$ in the replication population. The total likelihood is the sum of these two statistically independent components.

Under the null hypothesis that the ORs from the two populations are the same, the restricted likelihood is $\log f(\beta_1, \beta_2; \beta_1 = \beta_2 = \beta)$; with the combined estimate is $\hat{\beta}_{combine} = argmax_{\beta} \log f(\beta_1, \beta_2; \beta_1 = \beta_2 = \beta)$. The maximum log-likelihood under $H_0$ is $max_{H_0} logf = logf(\beta_1 = \beta_2 = \hat{\beta}_{combine})$. Without $H_0$ restriction, $\beta_1$ is estimated by $\hat{\beta}_{MLE}$, $\beta_2$ is estimated by $\hat{\beta}_{replication}$. The maximum log-likelihood is $maxlogf = logf(\beta_1 = \hat{\beta}_{MLE}; \beta_2 = \hat{\beta}_{replication})$. The pvalue is thus estimated by comparing $2(maxlogf - max_{H_0} logf)$ to $\chi^2_1$. All the described bias correction procedure and the likelihood ratio test are detailed in Zhong's dissertation (PhD Dissertation, University of Washington, 2008).