

**Supporting Information for “Meta-Analysis of Gene-Environment Interaction  
Exploiting Gene-Environment Independence Across Multiple Case-Control  
Studies”**

Supporting Information: Modeling  $P(G_{ki}|E_{ki}, \mathbf{S}_{ki})$  under HWE

Under HWE, we have  $P(G_{ki} = 0|E_{ki}, \mathbf{S}_{ki}) = (1 - q_{ki})^2$ ,  $P(G_{ki} = 1|E_{ki}, \mathbf{S}_{ki}) = 2q_{ki}(1 - q_{ki})$  and  $P(G_{ki} = 2|E_{ki}, \mathbf{S}_{ki}) = q_{ki}^2$  where  $q_{ki}$  is the minor allele frequency for a given  $(E_{ki}, \mathbf{S}_{ki})$ . Thus,

$$\log \left\{ \frac{P(G_{ki} = 1|E_{ki}, \mathbf{S}_{ki})}{P(G_{ki} = 0|E_{ki}, \mathbf{S}_{ki})} \right\} = \log(2) + \log \left\{ \frac{q_{ki}}{1 - q_{ki}} \right\} \text{ and}$$

$$\log \left\{ \frac{P(G_{ki} = 2|E_{ki}, \mathbf{S}_{ki})}{P(G_{ki} = 0|E_{ki}, \mathbf{S}_{ki})} \right\} = 2 \log \left\{ \frac{q_{ki}}{1 - q_{ki}} \right\}.$$

One can then use the logistic model  $q_{ki} = H\{\eta_{0k} + \eta_k \mathbf{S}_{ki}^T + \theta_k E_{ki}\}$  which reduces to  $q_{ki} = H\{\eta_{0k}^0 + \eta_k^0 \mathbf{S}_{ki}^T\}$  under  $G$ - $E$  independence conditional on  $\mathbf{S}_{ki}$ .

Supporting Information: Approximation of  $(\boldsymbol{\theta}\boldsymbol{\theta}^T)(\boldsymbol{\theta}\boldsymbol{\theta}^T)^+$

LEMMA 1. Let  $\mathbf{x} = (x_1, \dots, x_K)^T$  be a real  $K \times 1$  column vector such that  $\mathbf{x} \neq \mathbf{0}$ . Then  $\mathbf{y} = \mathbf{x}\mathbf{x}^T(\mathbf{x}^T\mathbf{x})^{-2}$  is the Moore-Penrose inverse of  $\mathbf{x}\mathbf{x}^T$ .

*Proof.* We establish the result by showing that the following holds

$$\begin{aligned} (i) \quad & (\mathbf{x}\mathbf{x}^T)\mathbf{y}(\mathbf{x}\mathbf{x}^T) = \mathbf{x}\mathbf{x}^T \\ (ii) \quad & \mathbf{y}(\mathbf{x}\mathbf{x}^T)\mathbf{y} = \mathbf{y} \\ (iii) \quad & \{(\mathbf{x}\mathbf{x}^T)\mathbf{y}\}^T = (\mathbf{x}\mathbf{x}^T)\mathbf{y} \\ (iv) \quad & \{\mathbf{y}(\mathbf{x}\mathbf{x}^T)\}^T = \mathbf{y}(\mathbf{x}\mathbf{x}^T) \end{aligned}$$

To show (i), we note that  $(\mathbf{x}\mathbf{x}^T)\mathbf{y}(\mathbf{x}\mathbf{x}^T) = (\mathbf{x}\mathbf{x}^T)\mathbf{x}\mathbf{x}^T(\mathbf{x}\mathbf{x}^T)(\mathbf{x}^T\mathbf{x})^{-2}$ . Using the property of associativity, it follows that  $(\mathbf{x}\mathbf{x}^T)\mathbf{x}\mathbf{x}^T(\mathbf{x}\mathbf{x}^T)(\mathbf{x}^T\mathbf{x})^{-2} = \mathbf{x}(\mathbf{x}^T\mathbf{x})(\mathbf{x}^T\mathbf{x})\mathbf{x}^T(\mathbf{x}^T\mathbf{x})^{-2} = \mathbf{x}\mathbf{x}^T$ . Similar calculations will establish (ii), (iii), and (iv).

LEMMA 2. Let  $X \sim N(0, \tau^2)$ . Then  $E[X(X^2 + c)^{-1}] = 0$  where  $c \neq 0$ .

*Proof.* The result follows since  $x(x^2 + c)^{-1}$  defines a bounded continuous odd function of  $x$  over the entire real line e.g.  $|x(x^2 + c)^{-1}| \leq \frac{1}{2}c^{-1/2}$  for all  $x \in \mathbb{R}$ .

THEOREM 1. Let  $\boldsymbol{\theta} = (\theta_1, \dots, \theta_K)^T \sim N(\mathbf{0}, \tau^2 \mathbf{I}_K)$  and  $\boldsymbol{\Theta} = (\boldsymbol{\theta}\boldsymbol{\theta}^T)(\boldsymbol{\theta}\boldsymbol{\theta}^T)^+$  where  $\mathbf{M}^+$  denotes the Moore-Penrose inverse of the matrix  $\mathbf{M}$ . Then  $E[\boldsymbol{\Theta}] = K^{-1}\mathbf{I}_K$  and  $\text{Var}[\boldsymbol{\Theta}] = (K^{-1} - K^{-2})\mathbf{I}_K$  where  $\mathbf{I}_K$  is the identity matrix of dimension  $K \times K$ .

*Proof.* From Lemma 1,  $\boldsymbol{\Theta} = (\boldsymbol{\theta}\boldsymbol{\theta}^T)^2(\boldsymbol{\theta}^T\boldsymbol{\theta})^{-2}$ . But  $(\boldsymbol{\theta}\boldsymbol{\theta}^T)^2(\boldsymbol{\theta}^T\boldsymbol{\theta})^{-2} = \boldsymbol{\theta}(\boldsymbol{\theta}^T\boldsymbol{\theta})\boldsymbol{\theta}^T(\boldsymbol{\theta}^T\boldsymbol{\theta})^{-2} = \boldsymbol{\theta}\boldsymbol{\theta}^T(\boldsymbol{\theta}^T\boldsymbol{\theta})^{-1}$ . Thus,  $\boldsymbol{\Theta} = (\boldsymbol{\Theta}_{ij})$  where  $\boldsymbol{\Theta}_{ij} = \theta_i\theta_j\{\boldsymbol{\theta}^T\boldsymbol{\theta}\}^{-1}$  for  $i, j \in \{1, \dots, K\}$ . Since  $\text{tr}(\boldsymbol{\Theta}) = \sum_{i=1}^K \boldsymbol{\Theta}_{ii} = \sum_{i=1}^K \theta_i^2\{\boldsymbol{\theta}^T\boldsymbol{\theta}\}^{-1} = 1$ , then  $E\{\text{tr}(\boldsymbol{\Theta})\} = \sum_{i=1}^K E[\boldsymbol{\Theta}_{ii}] = 1$ . But  $\theta_i$  are independent and identically distributed, and so  $E[\boldsymbol{\Theta}_{11}] = \dots = E[\boldsymbol{\Theta}_{KK}]$ . Thus,  $E[\boldsymbol{\Theta}_{ii}] = K^{-1}$  for all  $i$ . Finally, from Lemma 2,  $E[\boldsymbol{\Theta}_{ij}] = E\{\theta_i\theta_j(\boldsymbol{\theta}^T\boldsymbol{\theta})^{-1}\} = E(\theta_j E[\theta_i\{\theta_i^2 + \boldsymbol{\theta}_{(-i)}^T\boldsymbol{\theta}_{(-i)}\}^{-1} \mid \boldsymbol{\theta}_{(-i)}]) = E[\theta_j \cdot 0] = 0$  for  $i \neq j$  where  $\boldsymbol{\theta}_{(-i)}$  denotes the random vector  $\boldsymbol{\theta}$  with the  $i$ th component removed. Therefore,  $E[\boldsymbol{\Theta}] = K^{-1}\mathbf{I}_K$ . Since  $\boldsymbol{\Theta}^2 = \boldsymbol{\Theta}$ , then  $\text{Var}[\boldsymbol{\Theta}] = K^{-1}\mathbf{I}_K - (K^{-1}\mathbf{I}_K)^2 = (K^{-1} - K^{-2})\mathbf{I}_K$ .

COROLLARY 1. Let  $\boldsymbol{\theta} = (\theta_1, \dots, \theta_k)^T \sim N(\mathbf{0}, \boldsymbol{\Sigma})$  and  $\boldsymbol{\Theta} = (\boldsymbol{\theta}\boldsymbol{\theta}^T)(\boldsymbol{\theta}\boldsymbol{\theta}^T)^+$  where  $\boldsymbol{\Sigma}$  is a diagonal matrix with non-zero diagonal  $\{\tau_1^2, \dots, \tau_k^2\}$  and  $\mathbf{M}^+$  denotes the moore-penrose inverse of the matrix  $\mathbf{M}$ . Then  $E[\boldsymbol{\Theta}] = \boldsymbol{\xi}$  where  $\boldsymbol{\xi} = \text{diag}\{\xi_1, \dots, \xi_K\}$ ,  $\xi_1 + \dots + \xi_K = 1$  and  $\text{Var}[\boldsymbol{\Theta}] = \boldsymbol{\xi} - \boldsymbol{\xi}^2$ .

*Proof.* The results follow immediately from the details in the proof of Theorem 1.

#### Supporting Information: Variance estimates of MSEB estimators

Our EB estimators are of the form  $\mathbf{W}\hat{\boldsymbol{\beta}} + (\mathbf{I}_K - \mathbf{W})\hat{\boldsymbol{\beta}}^0$  where  $\mathbf{W}$  is a  $K \times K$  weight matrix. Thus, a crude estimate of the variance of the EB estimators are given by  $\mathbf{W}\text{Var}(\hat{\boldsymbol{\beta}})\mathbf{W}^T + 2\mathbf{W}\text{Cov}(\hat{\boldsymbol{\beta}}, \hat{\boldsymbol{\beta}}^0)(\mathbf{I}_K - \mathbf{W})^T + (\mathbf{I}_K - \mathbf{W})\text{Var}(\hat{\boldsymbol{\beta}}^0)(\mathbf{I}_K - \mathbf{W})^T$  where  $\mathbf{W}$  is treated as a constant matrix. However, since  $\mathbf{W}$  are random matrices, the crude estimates are typically not appropriate. Thus, we derive an approximation that adjusts for this variation using the notation

of Section 2.2.1 where only the full variance covariance matrix  $Cov(\hat{\boldsymbol{\beta}}, \hat{\boldsymbol{\beta}}^0, \hat{\boldsymbol{\theta}})$  is fixed at its estimate. Our MSEB estimators are of the form

$$\hat{\Delta}^T \hat{\mathbf{A}} \hat{\Delta} \{ \hat{\mathbf{V}}_{\hat{\boldsymbol{\beta}}} + \hat{\Delta}^T \hat{\mathbf{A}} \hat{\Delta} \}^{-1} \hat{\boldsymbol{\beta}} + \hat{\mathbf{V}}_{\hat{\boldsymbol{\beta}}} \{ \hat{\mathbf{V}}_{\hat{\boldsymbol{\beta}}} + \hat{\Delta}^T \hat{\mathbf{A}} \hat{\Delta} \}^{-1} \hat{\boldsymbol{\beta}}^0 \quad (1)$$

where  $\hat{\Delta}^T \hat{\mathbf{A}} \hat{\Delta} = (K\hat{\tau})^2 (\hat{\boldsymbol{\theta}}^T \hat{\boldsymbol{\theta}})^{-1} (\hat{\boldsymbol{\beta}} - \hat{\boldsymbol{\beta}}^0) (\hat{\boldsymbol{\beta}} - \hat{\boldsymbol{\beta}}^0)^T$ . Using the identity  $\hat{\Delta}^T \hat{\mathbf{A}} \hat{\Delta} \{ \hat{\mathbf{V}}_{\hat{\boldsymbol{\beta}}} + \hat{\Delta}^T \hat{\mathbf{A}} \hat{\Delta} \}^{-1} = \mathbf{I}_K - \hat{\mathbf{V}}_{\hat{\boldsymbol{\beta}}} \{ \hat{\mathbf{V}}_{\hat{\boldsymbol{\beta}}} + \Delta^T \mathbf{A} \Delta \}^{-1}$ , our estimator in (1) can be written as

$$\hat{\boldsymbol{\beta}} - \hat{\mathbf{V}}_{\hat{\boldsymbol{\beta}}} \{ \hat{\mathbf{V}}_{\hat{\boldsymbol{\beta}}} + (K\hat{\tau})^2 (\hat{\boldsymbol{\theta}}^T \hat{\boldsymbol{\theta}})^{-1} (\hat{\boldsymbol{\beta}} - \hat{\boldsymbol{\beta}}^0) (\hat{\boldsymbol{\beta}} - \hat{\boldsymbol{\beta}}^0)^T \}^{-1} (\hat{\boldsymbol{\beta}} - \hat{\boldsymbol{\beta}}^0). \quad (2)$$

By the Sherman-Morrison formula,  $\{ \hat{\mathbf{V}}_{\hat{\boldsymbol{\beta}}} + (K\hat{\tau})^2 (\hat{\boldsymbol{\theta}}^T \hat{\boldsymbol{\theta}})^{-1} (\hat{\boldsymbol{\beta}} - \hat{\boldsymbol{\beta}}^0) (\hat{\boldsymbol{\beta}} - \hat{\boldsymbol{\beta}}^0)^T \}^{-1} = \hat{\mathbf{V}}_{\hat{\boldsymbol{\beta}}}^{-1} - \{ 1 + (K\hat{\tau})^2 (\hat{\boldsymbol{\theta}}^T \hat{\boldsymbol{\theta}})^{-1} (\hat{\boldsymbol{\beta}} - \hat{\boldsymbol{\beta}}^0)^T \hat{\mathbf{V}}_{\hat{\boldsymbol{\beta}}}^{-1} (\hat{\boldsymbol{\beta}} - \hat{\boldsymbol{\beta}}^0) \}^{-1} \hat{\mathbf{V}}_{\hat{\boldsymbol{\beta}}}^{-1} (K\hat{\tau})^2 (\hat{\boldsymbol{\theta}}^T \hat{\boldsymbol{\theta}})^{-1} (\hat{\boldsymbol{\beta}} - \hat{\boldsymbol{\beta}}^0) (\hat{\boldsymbol{\beta}} - \hat{\boldsymbol{\beta}}^0)^T \hat{\mathbf{V}}_{\hat{\boldsymbol{\beta}}}^{-1}$  which allows (2) to be written as

$$\hat{\boldsymbol{\beta}} - \left\{ 1 + (K\hat{\tau})^2 (\hat{\boldsymbol{\theta}}^T \hat{\boldsymbol{\theta}})^{-1} (\hat{\boldsymbol{\beta}} - \hat{\boldsymbol{\beta}}^0)^T \hat{\mathbf{V}}_{\hat{\boldsymbol{\beta}}}^{-1} (\hat{\boldsymbol{\beta}} - \hat{\boldsymbol{\beta}}^0) \right\}^{-1} (\hat{\boldsymbol{\beta}} - \hat{\boldsymbol{\beta}}^0). \quad (3)$$

Our first estimate  $K^{-1} (\hat{\boldsymbol{\theta}}^T \hat{\boldsymbol{\theta}}) \mathbf{I}_K$  of  $\mathbf{A} = \tau^2 \mathbf{I}_K$  reduces our MSEB estimator in (3) to  $\hat{\boldsymbol{\beta}}_{\text{EB1}} = \hat{\boldsymbol{\beta}} - \left\{ 1 + K (\hat{\boldsymbol{\beta}} - \hat{\boldsymbol{\beta}}^0)^T \hat{\mathbf{V}}_{\hat{\boldsymbol{\beta}}}^{-1} (\hat{\boldsymbol{\beta}} - \hat{\boldsymbol{\beta}}^0) \right\}^{-1} (\hat{\boldsymbol{\beta}} - \hat{\boldsymbol{\beta}}^0)$ . Consider the function  $f_1 : \mathbb{R}^{2p} \rightarrow \mathbb{R}^p$  defined by  $f_1(\hat{\boldsymbol{\beta}}, \hat{\boldsymbol{\beta}}^0) = \hat{\boldsymbol{\beta}} - \left\{ 1 + K (\hat{\boldsymbol{\beta}} - \hat{\boldsymbol{\beta}}^0)^T \hat{\mathbf{V}}_{\hat{\boldsymbol{\beta}}}^{-1} (\hat{\boldsymbol{\beta}} - \hat{\boldsymbol{\beta}}^0) \right\}^{-1} (\hat{\boldsymbol{\beta}} - \hat{\boldsymbol{\beta}}^0)$  where  $p$  is the length of the column vectors  $\hat{\boldsymbol{\beta}}$  and  $\hat{\boldsymbol{\beta}}^0$ . Then, by a first-order multivariate Taylor's expansion of  $f_1(\hat{\boldsymbol{\beta}}, \hat{\boldsymbol{\beta}}^0)$  about  $(\boldsymbol{\beta}, \boldsymbol{\beta}^0)$ , an estimate of the variance-covariance matrix of  $\hat{\boldsymbol{\beta}}_{\text{EB1}}$  is given by  $\{ \nabla f_1(\hat{\boldsymbol{\beta}}, \hat{\boldsymbol{\beta}}^0) \}^T \text{Var}(\hat{\boldsymbol{\beta}}, \hat{\boldsymbol{\beta}}^0) \nabla f_1(\hat{\boldsymbol{\beta}}, \hat{\boldsymbol{\beta}}^0)$  where  $\nabla f_1(\hat{\boldsymbol{\beta}}, \hat{\boldsymbol{\beta}}^0) = (\mathbf{I}_p - \mathbf{C}_1 | \mathbf{C}_1)^T$  is the  $2p \times p$  augmented gradient matrix of  $f_1$  with respect to  $(\hat{\boldsymbol{\beta}}, \hat{\boldsymbol{\beta}}^0)$ ,  $\mathbf{C}_1 = w_1 \mathbf{I}_p - 2(w_1)^2 K (\hat{\boldsymbol{\beta}} - \hat{\boldsymbol{\beta}}^0) (\hat{\boldsymbol{\beta}} - \hat{\boldsymbol{\beta}}^0)^T \hat{\mathbf{V}}_{\hat{\boldsymbol{\beta}}}^{-1}$ ,  $w_1 = \{ 1 + K (\hat{\boldsymbol{\beta}} - \hat{\boldsymbol{\beta}}^0)^T \hat{\mathbf{V}}_{\hat{\boldsymbol{\beta}}}^{-1} (\hat{\boldsymbol{\beta}} - \hat{\boldsymbol{\beta}}^0) \}^{-1}$ ,  $\text{Var}(\hat{\boldsymbol{\beta}}, \hat{\boldsymbol{\beta}}^0)$  is the block matrix  $[\mathbf{V}_{11}, \mathbf{V}_{12}; \mathbf{V}_{21}, \mathbf{V}_{22}]$ ,  $\mathbf{V}_{11} = \text{Var}(\hat{\boldsymbol{\beta}})$ ,  $\mathbf{V}_{12} = \mathbf{V}_{21}^T = \text{Cov}(\hat{\boldsymbol{\beta}}, \hat{\boldsymbol{\beta}}^0)$  and  $\mathbf{V}_{22} = \text{Var}(\hat{\boldsymbol{\beta}}^0)$  are replaced with their estimates.

Our second estimate  $K^{-1} \{ \hat{\boldsymbol{\theta}}^T \hat{\boldsymbol{\theta}} - \text{tr}(\hat{\mathbf{V}}_{\hat{\boldsymbol{\theta}}}) \} \mathbf{I}_K$  of  $\mathbf{A} = \tau^2 \mathbf{I}_K$  reduces our MSEB estimator in (3) to  $\hat{\boldsymbol{\beta}}_{\text{EB2}} = \hat{\boldsymbol{\beta}} - [1 + K \{ 1 - \text{tr}(\hat{\mathbf{V}}_{\hat{\boldsymbol{\theta}}}) (\hat{\boldsymbol{\theta}}^T \hat{\boldsymbol{\theta}})^{-1} \} (\hat{\boldsymbol{\beta}} - \hat{\boldsymbol{\beta}}^0)^T \hat{\mathbf{V}}_{\hat{\boldsymbol{\beta}}}^{-1} (\hat{\boldsymbol{\beta}} - \hat{\boldsymbol{\beta}}^0)]^{-1} (\hat{\boldsymbol{\beta}} - \hat{\boldsymbol{\beta}}^0)$ . Consider the function  $f_2 : \mathbb{R}^{2p+K} \rightarrow \mathbb{R}^p$  defined by  $f_2(\hat{\boldsymbol{\beta}}, \hat{\boldsymbol{\beta}}^0, \hat{\boldsymbol{\theta}}) = \hat{\boldsymbol{\beta}} - [1 + K \{ 1 - \text{tr}(\hat{\mathbf{V}}_{\hat{\boldsymbol{\theta}}}) (\hat{\boldsymbol{\theta}}^T \hat{\boldsymbol{\theta}})^{-1} \} (\hat{\boldsymbol{\beta}} -$

$\hat{\beta}^0)^T \widehat{\mathbf{V}}_{\hat{\beta}}^{-1} (\hat{\beta} - \hat{\beta}^0)]^{-1} (\hat{\beta} - \hat{\beta}^0)$ . Then, by a first-order multivariate Taylor's expansion of  $f_2(\hat{\beta}, \hat{\beta}^0, \hat{\theta})$  about  $(\beta, \beta^0, \mathbf{0})$ , an estimate of the variance-covariance matrix of  $\hat{\beta}_{\text{EB2}}$  is given by  $\{\nabla f_2(\hat{\beta}, \hat{\beta}^0, \hat{\theta})\}^T \text{Var}(\hat{\beta}, \hat{\beta}^0, \hat{\theta}) \nabla f_2(\hat{\beta}, \hat{\beta}^0, \hat{\theta})$  where  $\nabla f_2(\hat{\beta}, \hat{\beta}^0, \hat{\theta}) = (\mathbf{I}_p - \mathbf{C}_2 | \mathbf{C}_2 | \mathbf{D})^T$  is the  $(2p + K) \times p$  augmented gradient matrix of  $f_2$  with respect to  $(\hat{\beta}, \hat{\beta}^0, \hat{\theta})$ ,  $\mathbf{C}_2 = w_2 \mathbf{I}_p - 2(w_2)^2 K \{1 - \text{tr}(\widehat{\mathbf{V}}_{\hat{\theta}} (\hat{\theta}^T \hat{\theta})^{-1})\} (\hat{\beta} - \hat{\beta}^0) (\hat{\beta} - \hat{\beta}^0)^T \widehat{\mathbf{V}}_{\hat{\beta}}^{-1}$ ,  $\mathbf{D} = \{2K(w_2)^2 \text{tr}(\widehat{\mathbf{V}}_{\hat{\theta}} (\hat{\theta}^T \hat{\theta})^{-2}) (\hat{\beta} - \hat{\beta}^0)^T \widehat{\mathbf{V}}_{\hat{\beta}}^{-1} (\hat{\beta} - \hat{\beta}^0)\} (\hat{\beta} - \hat{\beta}^0) \hat{\theta}^T$ ,  $w_2 = [1 + K \{1 - \text{tr}(\widehat{\mathbf{V}}_{\hat{\theta}} (\hat{\theta}^T \hat{\theta})^{-1})\} (\hat{\beta} - \hat{\beta}^0)^T \widehat{\mathbf{V}}_{\hat{\beta}}^{-1} (\hat{\beta} - \hat{\beta}^0)]^{-1}$ ,  $\text{Var}(\hat{\beta}, \hat{\beta}^0, \hat{\theta})$  is the block matrix  $[\mathbf{V}_{11}, \mathbf{V}_{12}, \mathbf{V}_{13}; \mathbf{V}_{21}, \mathbf{V}_{22}, \mathbf{V}_{23}; \mathbf{V}_{31}, \mathbf{V}_{32}, \mathbf{V}_{33}]$ ,  $\mathbf{V}_{11} = \text{Var}(\hat{\beta})$ ,  $\mathbf{V}_{22} = \text{Var}(\hat{\beta}^0)$ ,  $\mathbf{V}_{33} = \text{Var}(\hat{\theta})$ ,  $\mathbf{V}_{12} = \mathbf{V}_{21}^T = \text{Cov}(\hat{\beta}, \hat{\beta}^0)$ ,  $\mathbf{V}_{13} = \mathbf{V}_{31}^T = \text{Cov}(\hat{\beta}, \hat{\theta})$ , and  $\mathbf{V}_{23} = \mathbf{V}_{32}^T = \text{Cov}(\hat{\beta}^0, \hat{\theta})$  are replaced with their estimates.

Let  $\hat{\tau}^2 \mathbf{I}_K$  denote our third estimate of  $\mathbf{A} = \tau^2 \mathbf{I}_K$ . Then from (3), we can write  $\hat{\beta}_{\text{EB3}} = \hat{\beta} - \left\{1 + (K\hat{\tau})^2 (\hat{\theta}^T \hat{\theta})^{-1} (\hat{\beta} - \hat{\beta}^0)^T \widehat{\mathbf{V}}_{\hat{\beta}}^{-1} (\hat{\beta} - \hat{\beta}^0)\right\}^{-1} (\hat{\beta} - \hat{\beta}^0)$ . Consider the function  $f_3 : \mathbb{R}^{2p+K} \rightarrow \mathbb{R}^p$  defined by  $f_3(\hat{\beta}, \hat{\beta}^0, \hat{\theta}) = \hat{\beta} - \left\{1 + (K\hat{\tau})^2 (\hat{\theta}^T \hat{\theta})^{-1} (\hat{\beta} - \hat{\beta}^0)^T \widehat{\mathbf{V}}_{\hat{\beta}}^{-1} (\hat{\beta} - \hat{\beta}^0)\right\}^{-1} (\hat{\beta} - \hat{\beta}^0)$ . Then, by a first-order multivariate Taylor's expansion of  $f_3(\hat{\beta}, \hat{\beta}^0, \hat{\theta})$  about  $(\beta, \beta^0, \mathbf{0})$ , an estimate of the variance-covariance matrix of  $\hat{\beta}_{\text{EB3}}$  is given by  $\{\nabla f_3(\hat{\beta}, \hat{\beta}^0, \hat{\theta})\}^T \text{Var}(\hat{\beta}, \hat{\beta}^0, \hat{\theta}) \nabla f_3(\hat{\beta}, \hat{\beta}^0, \hat{\theta})$  where  $\nabla f_3(\hat{\beta}, \hat{\beta}^0, \hat{\theta}) = (\mathbf{I}_p - \mathbf{C}_3 | \mathbf{C}_3 | \mathbf{E})^T$  is the  $(2p + K) \times p$  augmented gradient matrix of  $f_3$  with respect to  $(\hat{\beta}, \hat{\beta}^0, \hat{\theta})$ ,  $\mathbf{C}_3 = w_3 \mathbf{I}_p - 2(w_3)^2 (K\hat{\tau})^2 (\hat{\theta}^T \hat{\theta})^{-1} (\hat{\beta} - \hat{\beta}^0) (\hat{\beta} - \hat{\beta}^0)^T \widehat{\mathbf{V}}_{\hat{\beta}}^{-1}$ ,  $\mathbf{E} = \{-2(w_3)^2 (K\hat{\tau})^2 (\hat{\theta}^T \hat{\theta})^{-2} (\hat{\beta} - \hat{\beta}^0)^T \widehat{\mathbf{V}}_{\hat{\beta}}^{-1} (\hat{\beta} - \hat{\beta}^0)\} (\hat{\beta} - \hat{\beta}^0) \hat{\theta}^T$ ,  $w_3 = [1 + (K\hat{\tau})^2 (\hat{\theta}^T \hat{\theta})^{-1} (\hat{\beta} - \hat{\beta}^0)^T \widehat{\mathbf{V}}_{\hat{\beta}}^{-1} (\hat{\beta} - \hat{\beta}^0)]^{-1}$ ,  $\text{Var}(\hat{\beta}, \hat{\beta}^0, \hat{\theta})$  is the block matrix  $[\mathbf{V}_{11}, \mathbf{V}_{12}, \mathbf{V}_{13}; \mathbf{V}_{21}, \mathbf{V}_{22}, \mathbf{V}_{23}; \mathbf{V}_{31}, \mathbf{V}_{32}, \mathbf{V}_{33}]$ ,  $\mathbf{V}_{11} = \text{Var}(\hat{\beta})$ ,  $\mathbf{V}_{22} = \text{Var}(\hat{\beta}^0)$ ,  $\mathbf{V}_{33} = \text{Var}(\hat{\theta})$ ,  $\mathbf{V}_{12} = \mathbf{V}_{21}^T = \text{Cov}(\hat{\beta}, \hat{\beta}^0)$ ,  $\mathbf{V}_{13} = \mathbf{V}_{31}^T = \text{Cov}(\hat{\beta}, \hat{\theta})$ , and  $\mathbf{V}_{23} = \mathbf{V}_{32}^T = \text{Cov}(\hat{\beta}^0, \hat{\theta})$  are replaced with their estimates.

An estimate of the variance-covariance matrix of  $\hat{\beta}_{\text{EB4}}$  is identically derived as the estimate of the variance-covariance matrix  $\hat{\beta}_{\text{EB3}}$  above. For variance-covariance estimates of  $\tilde{\beta}_{\text{EB1}}, \tilde{\beta}_{\text{EB2}}, \tilde{\beta}_{\text{EB3}}$  and  $\tilde{\beta}_{\text{EB4}}$  we use the formulas derived for  $\hat{\beta}_{\text{EB1}}, \hat{\beta}_{\text{EB2}}, \hat{\beta}_{\text{EB3}}$  and  $\hat{\beta}_{\text{EB4}}$  except that  $\text{Cov}(\tilde{\beta}, \tilde{\beta}^0) = (\sum_k \tilde{\mathbf{V}}_{\tilde{\beta}_k}^{-1})^{-1} [\sum_k \tilde{\mathbf{V}}_{\tilde{\beta}_k}^{-1} \text{Cov}(\tilde{\beta}_k, \tilde{\beta}_k^0) (\tilde{\mathbf{V}}_{\tilde{\beta}_k^0}^{-1})^T] \{(\sum_k \tilde{\mathbf{V}}_{\tilde{\beta}_k^0}^{-1})^{-1}\}^T$ ,  $\text{Cov}(\tilde{\beta}, \tilde{\theta}) = (\sum_k \tilde{\mathbf{V}}_{\tilde{\beta}_k}^{-1})^{-1} [\sum_k \tilde{\mathbf{V}}_{\tilde{\beta}_k}^{-1} \text{Cov}(\tilde{\beta}_k, \tilde{\theta})]$  and  $\text{Cov}(\tilde{\beta}^0, \tilde{\theta}) = (\sum_k \tilde{\mathbf{V}}_{\tilde{\beta}_k^0}^{-1})^{-1} [\sum_k \tilde{\mathbf{V}}_{\tilde{\beta}_k^0}^{-1} \text{Cov}(\tilde{\beta}_k^0, \tilde{\theta})]$ .

It is important to note that the statistical package used to perform the likelihood estimation may not report all estimated covariances between the UML and CML parameter estimates which can impact the variance approximation formulas. In this case, one might consider replacing all unknown covariances with 0 or resort to a bootstrap estimate of the standard errors, which we found to be easy to implement.

Table S1: Bias (BIAS), standard errors (SE1), empirical standard errors (SE2) and  $100 \times$  MSE (MSE) of  $\hat{\gamma}_E$ ,  $\hat{\gamma}_G$  and  $\hat{\gamma}_{GE}$  resulting from standard logistic regression (LOG), unconstrained maximum likelihood (UML), constrained maximum likelihood (CML), empirical Bayes (EB) and our proposed multi-study empirical Bayes estimators EB1 - EB4 in both IPD and summary statistic meta-analysis (META) simulation settings with  $K = 2$  individual studies and small individual study sample sizes randomly generated from  $[100, 300]$  under  $G$ - $E$  independence over 1,000 Monte Carlo runs. In the meta-analysis setting, we use the inverse variance-covariance weighted approach to obtain the standard logistic, unconstrained, constrained and empirical Bayes results.

	Main Effect of $E$				Main Effect of $G$				$G \times E$ Interaction			
IPD	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE
LOG	.016	.1467	.1543	2.405	.021	.1592	.1570	2.506	.015	.1682	.1770	3.152
UML	.021	.1425	.1472	2.209	.015	.1565	.1528	2.354	.006	.1579	.1609	2.589
CML	.023	.1265	.1280	1.687	.011	.1557	.1523	2.331	-.006	.0987	.1012	1.027
EB	.021	.1319	.1345	1.850	.012	.1559	.1528	2.348	.006	.1345	.1369	1.877
EB1	.021	.1374	.1391	1.979	.014	.1563	.1526	2.345	.003	.1394	.1373	1.885
EB2	.022	.1363	.1344	1.853	.013	.1563	.1526	2.344	.000	.1302	.1255	1.574
EB3	.022	.1296	.1354	1.881	.013	.1560	.1526	2.345	.000	.1107	.1273	1.619
EB4	.022	.1296	.1350	1.869	.013	.1560	.1526	2.344	.000	.1106	.1266	1.601
META	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE
LOG	.014	.1490	.1507	2.288	.015	.1607	.1544	2.403	.009	.1710	.1725	2.981
UML	.017	.1438	.1449	2.128	.010	.1574	.1510	2.289	.003	.1591	.1592	2.534
CML	.020	.1274	.1259	1.622	.011	.1562	.1512	2.295	-.004	.0992	.1004	1.009
EB	.021	.1327	.1304	1.740	.009	.1566	.1514	2.297	-.002	.1330	.1254	1.571
EB1	.019	.1378	.1368	1.907	.012	.1569	.1511	2.294	.001	.1377	.1351	1.822
EB2	.018	.1329	.1304	1.733	.012	.1567	.1512	2.297	.001	.1191	.1186	1.406
EB3	.020	.1313	.1331	1.809	.012	.1566	.1512	2.298	-.001	.1139	.1230	1.512
EB4	.020	.1315	.1322	1.784	.012	.1566	.1512	2.298	.000	.1148	.1214	1.472

Table S2: Bias (BIAS), estimated standard errors (SE1), empirical standard errors (SE2) and  $100 \times \text{MSE}$  (MSE) of  $\hat{\gamma}_E$ ,  $\hat{\gamma}_G$  and  $\hat{\gamma}_{GE}$  resulting from standard logistic regression, unconstrained maximum likelihood, constrained maximum likelihood, empirical Bayes and our proposed multi-study empirical Bayes estimators in both IPD and summary statistic meta-analysis (META) simulation settings with  $K = 2$  individual studies and small individual study sample sizes randomly generated from  $[100, 300]$  when  $G$ - $E$  independence is violated. In the meta-analysis setting, we use the inverse variance-covariance weighted approach to obtain the standard logistic, unconstrained, constrained and empirical Bayes results.

$\theta_k = .1$ for all $k$													
		Main Effect of $E$				Main Effect of $G$				GxE Interaction			
IPD	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE	
LOG	.011	.1526	.1568	2.470	.016	.1552	.1588	2.546	.024	.1619	.1677	2.865	
UML	.017	.1474	.1485	2.233	.010	.1525	.1544	2.391	.014	.1516	.1506	2.286	
CML	-.019	.1289	.1320	1.775	.012	.1519	.1535	2.369	.067	.0950	.0933	1.315	
EB	-.007	.1368	.1387	1.927	.013	.1520	.1538	2.379	.043	.1304	.1297	1.863	
EB1	.007	.1426	.1423	2.029	.010	.1523	.1540	2.381	.029	.1352	.1296	1.760	
EB2	.000	.1422	.1403	1.967	.011	.1523	.1539	2.377	.039	.1294	.1215	1.630	
EB3	.000	.1344	.1403	1.967	.011	.1520	.1539	2.377	.039	.1100	.1221	1.644	
EB4	.000	.1344	.1403	1.966	.011	.1520	.1539	2.377	.039	.1099	.1219	1.637	
META	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE	
LOG	.009	.1547	.1529	2.344	.009	.1565	.1560	2.441	.016	.1648	.1637	2.703	
UML	.013	.1485	.1465	2.161	.005	.1533	.1527	2.334	.009	.1526	.1498	2.249	
CML	-.021	.1296	.1305	1.748	.011	.1524	.1524	2.333	.067	.0956	.0926	1.309	
EB	-.014	.1367	.1348	1.834	.009	.1527	.1525	2.331	.043	.1272	.1206	1.638	
EB1	.004	.1429	.1405	1.973	.008	.1529	.1525	2.330	.026	.1354	.1287	1.723	
EB2	-.005	.1387	.1380	1.905	.009	.1527	.1523	2.325	.041	.1201	.1189	1.584	
EB3	-.003	.1355	.1382	1.910	.009	.1526	.1523	2.326	.039	.1126	.1200	1.588	
EB4	-.004	.1355	.1382	1.908	.009	.1526	.1523	2.325	.040	.1124	.1196	1.584	
$\theta_k = -.5$ for all $k$													
		Main Effect of $E$				Main Effect of $G$				GxE Interaction			
IPD	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE	
LOG	.008	.1231	.1290	1.670	.017	.1970	.1950	3.830	.014	.2279	.2216	4.927	
UML	.010	.1224	.1284	1.657	.011	.1941	.1907	3.643	.006	.2174	.2065	4.262	
CML	.102	.1164	.1240	2.584	-.051	.1877	.1860	3.716	-.342	.1382	.1407	13.699	
EB	.062	.1203	.1272	1.997	-.036	.1907	.1885	3.682	-.080	.2329	.2207	5.507	
EB1	.024	.1235	.1296	1.736	.003	.1937	.1903	3.618	-.046	.2250	.2109	4.656	
EB2	.032	.1265	.1320	1.845	-.001	.1943	.1905	3.625	-.074	.2400	.2246	5.590	
EB3	.032	.1213	.1318	1.838	-.001	.1927	.1905	3.624	-.073	.2039	.2237	5.532	
EB4	.032	.1213	.1318	1.838	-.001	.1927	.1905	3.624	-.073	.2039	.2235	5.526	
META	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE	
LOG	.005	.1249	.1257	1.581	.008	.1992	.1903	3.625	.007	.2314	.2134	4.554	
UML	.006	.1239	.1255	1.578	.003	.1958	.1868	3.489	.001	.2187	.2028	4.109	
CML	.099	.1176	.1210	2.449	-.047	.1886	.1838	3.599	-.333	.1378	.1394	13.048	
EB	.073	.1199	.1230	2.051	-.051	.1915	.1842	3.650	-.146	.2149	.2022	6.204	
EB1	.023	.1252	.1270	1.663	-.003	.1950	.1865	3.474	-.055	.2253	.2076	4.609	
EB2	.035	.1255	.1301	1.812	-.008	.1952	.1865	3.479	-.095	.2262	.2221	5.834	
EB3	.034	.1219	.1300	1.806	-.008	.1939	.1865	3.482	-.094	.1972	.2222	5.808	
EB4	.034	.1220	.1299	1.801	-.008	.1940	.1865	3.481	-.092	.1979	.2210	5.729	

Table S3: Bias (BIAS), standard errors (SE1), empirical standard errors (SE2) and  $100 \times$  MSE (MSE) of  $\hat{\gamma}_E$ ,  $\hat{\gamma}_G$  and  $\hat{\gamma}_{GE}$  resulting from standard logistic regression (LOG), unconstrained maximum likelihood (UML), constrained maximum likelihood (CML), empirical Bayes (EB) and our proposed multi-study empirical Bayes estimators EB1 - EB4 in both IPD and summary statistic meta-analysis (META) simulation settings with  $K = 5$  individual studies and small individual study sample sizes randomly generated from  $[100, 300]$  under  $G$ - $E$  independence over 1,000 Monte Carlo runs. In the meta-analysis setting, we use the inverse variance-covariance weighted approach to obtain the standard logistic, unconstrained, constrained and empirical Bayes results.

	Main Effect of $E$				Main Effect of $G$				$G \times E$ Interaction			
IPD	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE
LOG	.014	.0927	.0907	.841	.006	.1026	.1065	1.136	.008	.1068	.1083	1.178
UML	.017	.0909	.0886	.815	.001	.1012	.1031	1.062	.002	.1017	.1026	1.052
CML	.018	.0808	.0794	.664	-.001	.1009	.1026	1.052	-.004	.0638	.0647	.420
EB	.017	.0835	.0810	.684	.000	.1009	.1030	1.060	.003	.0844	.0830	.690
EB1	.017	.0895	.0861	.771	.001	.1012	.1030	1.060	.001	.0963	.0940	.883
EB2	.017	.0898	.0831	.719	.000	.1014	.1029	1.058	.000	.0900	.0829	.687
EB3	.018	.0836	.0832	.724	.000	.1010	.1029	1.058	-.001	.0744	.0832	.691
EB4	.017	.0836	.0832	.721	.000	.1010	.1029	1.058	.000	.0743	.0832	.691
META	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE
LOG	.010	.0952	.0867	.761	-.005	.1041	.1033	1.069	-.003	.1099	.1026	1.053
UML	.012	.0924	.0863	.757	-.007	.1021	.1010	1.025	-.006	.1029	.1003	1.008
CML	.014	.0819	.0775	.619	-.002	.1015	.1011	1.021	-.002	.0645	.0635	.404
EB	.015	.0844	.0784	.635	-.006	.1017	.1011	1.024	-.007	.0821	.0748	.564
EB1	.014	.0901	.0836	.717	-.005	.1020	.1010	1.022	-.005	.0950	.0905	.820
EB2	.013	.0857	.0807	.667	-.003	.1017	.1010	1.020	.000	.0786	.0762	.581
EB3	.015	.0852	.0804	.668	-.003	.1017	.1011	1.022	-.004	.0769	.0757	.575
EB4	.014	.0852	.0806	.668	-.003	.1017	.1010	1.020	-.002	.0769	.0762	.580



Table S4: Bias (BIAS), estimated standard errors (SE1), empirical standard errors (SE2) and  $100 \times \text{MSE}$  (MSE) of  $\hat{\gamma}_E$ ,  $\hat{\gamma}_G$  and  $\hat{\gamma}_{GE}$  resulting from standard logistic regression, unconstrained maximum likelihood, constrained maximum likelihood, empirical Bayes and our proposed multi-study empirical Bayes estimators in both IPD and summary statistic meta-analysis (META) simulation settings with  $K = 5$  individual studies and small individual study sample sizes randomly generated from  $[100, 300]$  when  $G$ - $E$  independence is violated. In the meta-analysis setting, we use the inverse variance-covariance weighted approach to obtain the standard logistic, unconstrained, constrained and empirical Bayes results.

$\theta_k = .1$ for all $k$												
	Main Effect of $E$				Main Effect of $G$				$G \times E$ Interaction			
IPD	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE
LOG	.012	.1147	.1203	1.461	.010	.1157	.1184	1.411	.015	.1199	.1275	1.646
UML	.018	.1114	.1141	1.333	.003	.1138	.1154	1.330	.005	.1128	.1160	1.346
CML	-.021	.0972	.0989	1.023	.008	.1135	.1153	1.335	.066	.0713	.0725	.961
EB	-.007	.1038	.1064	1.136	.008	.1136	.1155	1.340	.034	.0980	.1023	1.160
EB1	.013	.1102	.1120	1.270	.004	.1138	.1154	1.332	.013	.1090	.1097	1.218
EB2	.002	.1108	.1103	1.216	.005	.1139	.1155	1.336	.030	.1036	.1031	1.149
EB3	.003	.1032	.1104	1.219	.005	.1136	.1155	1.336	.028	.0871	.1046	1.174
EB4	.003	.1031	.1103	1.217	.005	.1136	.1155	1.336	.028	.0867	.1038	1.158
META	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE
LOG	.007	.1184	.1124	1.266	-.004	.1180	.1144	1.308	.000	.1241	.1183	1.399
UML	.010	.1134	.1094	1.205	-.006	.1151	.1129	1.278	-.003	.1146	.1126	1.267
CML	-.027	.0986	.0954	.981	.005	.1144	.1134	1.288	.067	.0724	.0712	.957
EB	-.020	.1036	.0981	1.002	.000	.1147	.1133	1.282	.042	.0934	.0868	.927
EB1	.007	.1111	.1069	1.145	-.003	.1150	.1130	1.276	.007	.1093	.1062	1.132
EB2	-.009	.1051	.1052	1.114	.002	.1147	.1137	1.291	.037	.0902	.0986	1.106
EB3	-.005	.1050	.1049	1.102	.001	.1147	.1135	1.288	.030	.0900	.1004	1.099
EB4	-.006	.1049	.1049	1.103	.001	.1147	.1136	1.289	.032	.0897	.0996	1.095
$\theta_k = -.5$ for all $k$												
	Main Effect of $E$				Main Effect of $G$				$G \times E$ Interaction			
LOG	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE
LOG	.007	.0683	.0698	.491	.005	.1098	.1070	1.145	.002	.1259	.1317	1.734
UML	.007	.0680	.0695	.488	.001	.1087	.1055	1.111	-.002	.1220	.1255	1.573
CML	.098	.0648	.0674	1.413	-.054	.1056	.1015	1.320	-.338	.0780	.0799	12.084
EB	.039	.0686	.0705	.647	-.037	.1077	.1042	1.220	-.039	.1327	.1372	2.037
EB1	.010	.0683	.0697	.495	-.001	.1087	.1054	1.111	-.010	.1237	.1269	1.619
EB2	.011	.0685	.0702	.504	-.001	.1087	.1054	1.111	-.014	.1253	.1301	1.709
EB3	.011	.0682	.0702	.504	-.001	.1086	.1055	1.111	-.014	.1234	.1304	1.717
EB4	.011	.0682	.0702	.504	-.001	.1086	.1055	1.111	-.014	.1234	.1301	1.710
META	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE
LOG	.002	.0695	.0673	.453	-.007	.1114	.1036	1.078	-.007	.1287	.1242	1.545
UML	.003	.0692	.0674	.454	-.009	.1100	.1027	1.061	-.008	.1231	.1216	1.482
CML	.094	.0657	.0654	1.305	-.049	.1063	.1005	1.252	-.326	.0776	.0798	11.236
EB	.070	.0669	.0669	.942	-.061	.1077	.1003	1.380	-.160	.1198	.1271	4.161
EB1	.006	.0695	.0677	.461	-.010	.1099	.1027	1.062	-.017	.1253	.1235	1.554
EB2	.008	.0696	.0691	.484	-.010	.1099	.1027	1.065	-.026	.1259	.1313	1.790
EB3	.009	.0691	.0699	.496	-.011	.1098	.1028	1.066	-.030	.1215	.1352	1.912
EB4	.009	.0691	.0692	.486	-.010	.1098	.1027	1.065	-.027	.1218	.1318	1.807

Table S5: Bias (BIAS), standard errors (SE1), empirical standard errors (SE2) and  $100 \times$  MSE (MSE) of  $\hat{\gamma}_E$ ,  $\hat{\gamma}_G$  and  $\hat{\gamma}_{GE}$  resulting from standard logistic regression (LOG), unconstrained maximum likelihood (UML), constrained maximum likelihood (CML), empirical Bayes (EB) and our proposed multi-study empirical Bayes estimators EB1 - EB4 in both IPD and summary statistic meta-analysis (META) simulation settings ( $K = 10$  individual studies with sample sizes  $n_k = 1000 + 100(k - 1)$ ,  $k = 1, \dots, K$ ) with  $MAF = 5\%$  under  $G$ - $E$  independence over 1,000 Monte Carlo runs. In the meta-analysis setting, we use the inverse variance-covariance weighted approach to obtain the standard logistic, unconstrained, constrained and empirical Bayes results.

	Main Effect of $E$				Main Effect of $G$				$G \times E$ Interaction			
IPD	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE
LOG	.008	.0181	.0181	.039	.005	.0508	.0508	.260	.005	.0517	.0547	.302
UML	.008	.0181	.0181	.040	.004	.0507	.0507	.259	.002	.0503	.0525	.276
CML	.009	.0176	.0177	.039	.003	.0506	.0506	.256	-.003	.0298	.0307	.095
EB	.009	.0176	.0177	.039	.003	.0506	.0506	.256	.002	.0413	.0422	.179
EB1	.008	.0180	.0180	.039	.004	.0507	.0507	.259	.001	.0487	.0501	.251
EB2	.008	.0182	.0179	.039	.004	.0507	.0507	.258	.001	.0447	.0441	.194
EB3	.008	.0178	.0179	.039	.004	.0506	.0507	.258	-.001	.0369	.0440	.193
EB4	.008	.0178	.0179	.039	.004	.0506	.0507	.258	.000	.0368	.0441	.194
META	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE
LOG	.007	.0182	.0180	.037	.000	.0511	.0502	.252	-.003	.0523	.0531	.283
UML	.007	.0181	.0180	.038	-.001	.0510	.0502	.251	-.004	.0505	.0518	.270
CML	.008	.0177	.0176	.037	.005	.0507	.0502	.254	.003	.0297	.0306	.094
EB	.008	.0177	.0177	.037	.002	.0508	.0502	.252	-.001	.0379	.0365	.133
EB1	.008	.0181	.0179	.038	.001	.0510	.0502	.252	-.003	.0480	.0489	.240
EB2	.008	.0179	.0178	.037	.004	.0509	.0503	.254	.002	.0380	.0401	.161
EB3	.008	.0178	.0178	.038	.003	.0509	.0504	.255	-.002	.0376	.0400	.161
EB4	.008	.0178	.0178	.038	.004	.0509	.0503	.254	.000	.0377	.0403	.163

Table S6: Bias (BIAS), estimated standard errors (SE1), empirical standard errors (SE2) and  $100 \times \text{MSE}$  (MSE) of  $\hat{\gamma}_E$ ,  $\hat{\gamma}_G$  and  $\hat{\gamma}_{GE}$  resulting from standard logistic regression, unconstrained maximum likelihood, constrained maximum likelihood, empirical Bayes and our proposed multi-study empirical Bayes estimators in both IPD and summary statistic meta-analysis (META) simulation settings ( $K = 10$  individual studies with sample sizes  $n_k = 1000 + 100(k - 1)$ ,  $k = 1, \dots, K$ ) with  $MAF = 5\%$  when  $G$ - $E$  independence is violated. In the meta-analysis setting, we use the inverse variance-covariance weighted approach to obtain the standard logistic, unconstrained, constrained and empirical Bayes results.

$\theta_k = .1$ for all $k$												
	Main Effect of $E$				Main Effect of $G$				$G \times E$ Interaction			
IPD	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE
LOG	.009	.0184	.0189	.044	.008	.0482	.0483	.240	.005	.0468	.0479	.232
UML	.010	.0184	.0189	.045	.007	.0481	.0481	.237	.002	.0455	.0464	.215
CML	.002	.0178	.0182	.034	.010	.0480	.0480	.240	.063	.0267	.0271	.471
EB	.004	.0180	.0184	.035	.010	.0480	.0480	.240	.022	.0443	.0449	.248
EB1	.009	.0184	.0189	.044	.008	.0481	.0481	.237	.005	.0458	.0462	.216
EB2	.008	.0190	.0191	.043	.008	.0481	.0481	.237	.015	.0501	.0512	.285
EB3	.008	.0182	.0190	.043	.008	.0481	.0481	.237	.013	.0404	.0504	.271
EB4	.008	.0182	.0191	.043	.008	.0481	.0481	.237	.014	.0402	.0508	.277
META	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE
LOG	.008	.0185	.0188	.042	.004	.0484	.0479	.231	-.003	.0472	.0469	.220
UML	.009	.0184	.0187	.043	.003	.0483	.0478	.229	-.003	.0458	.0459	.211
CML	.001	.0178	.0181	.033	.010	.0482	.0478	.238	.067	.0267	.0270	.525
EB	.001	.0179	.0181	.033	.008	.0482	.0476	.233	.042	.0352	.0350	.295
EB1	.008	.0184	.0187	.042	.004	.0483	.0478	.230	.000	.0461	.0462	.213
EB2	.006	.0182	.0189	.039	.007	.0482	.0481	.235	.025	.0380	.0546	.360
EB3	.007	.0183	.0188	.040	.006	.0482	.0480	.234	.014	.0404	.0534	.306
EB4	.007	.0182	.0188	.040	.006	.0482	.0481	.235	.018	.0391	.0543	.328
$\theta_k = -.5$ for all $k$												
	Main Effect of $E$				Main Effect of $G$				$G \times E$ Interaction			
IPD	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE
LOG	.008	.0174	.0174	.037	.007	.0691	.0689	.480	.011	.0829	.0826	.693
UML	.009	.0174	.0175	.038	.006	.0689	.0685	.472	.006	.0808	.0797	.638
CML	.024	.0172	.0173	.088	-.059	.0661	.0648	.763	-.333	.0498	.0505	11.371
EB	.017	.0174	.0174	.059	-.026	.0690	.0685	.534	-.008	.0856	.0845	.721
EB1	.009	.0174	.0175	.038	.005	.0689	.0685	.471	.004	.0811	.0799	.639
EB2	.009	.0174	.0175	.038	.005	.0689	.0685	.471	.004	.0811	.0800	.642
EB3	.009	.0174	.0175	.038	.005	.0689	.0685	.471	.004	.0811	.0801	.642
EB4	.009	.0174	.0175	.038	.005	.0689	.0685	.471	.004	.0811	.0801	.642
META	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE
LOG	.008	.0175	.0173	.036	-.003	.0700	.0672	.453	-.003	.0846	.0790	.625
UML	.008	.0175	.0173	.036	-.002	.0699	.0671	.450	-.002	.0816	.0788	.621
CML	.023	.0173	.0172	.084	-.050	.0666	.0646	.664	-.321	.0495	.0508	10.577
EB	.022	.0173	.0173	.080	-.064	.0677	.0643	.822	-.148	.0799	.0811	2.855
EB1	.008	.0175	.0173	.036	-.002	.0699	.0671	.450	-.004	.0820	.0791	.628
EB2	.008	.0175	.0173	.036	-.002	.0699	.0671	.450	-.005	.0821	.0795	.635
EB3	.008	.0175	.0174	.036	-.002	.0698	.0671	.451	-.006	.0815	.0805	.651
EB4	.008	.0175	.0173	.036	-.002	.0698	.0671	.451	-.006	.0815	.0797	.638

Table S7: Bias (BIAS), standard errors (SE1), empirical standard errors (SE2) and  $100 \times$  MSE (MSE) of  $\hat{\gamma}_E$ ,  $\hat{\gamma}_G$  and  $\hat{\gamma}_{GE}$  resulting from standard logistic regression (LOG), unconstrained maximum likelihood (UML), constrained maximum likelihood (CML), empirical Bayes (EB) and our proposed multi-study empirical Bayes estimators EB1 - EB4 in both IPD and summary statistic meta-analysis (META) simulation settings ( $K = 10$  individual studies with sample sizes  $n_k = 1000 + 100(k - 1)$ ,  $k = 1, \dots, K$ ) with  $MAF = 10\%$  under  $G$ - $E$  independence over 1,000 Monte Carlo runs. In the meta-analysis setting, we use the inverse variance-covariance weighted approach to obtain the standard logistic, unconstrained, constrained and empirical Bayes results.

	Main Effect of $E$				Main Effect of $G$				$G \times E$ Interaction			
IPD	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE
LOG	.009	.0193	.0188	.044	.007	.0371	.0375	.145	.001	.0379	.0375	.141
UML	.010	.0192	.0188	.044	.006	.0370	.0373	.142	-.001	.0369	.0367	.135
CML	.010	.0183	.0183	.044	.005	.0369	.0372	.141	-.005	.0221	.0219	.051
EB	.010	.0184	.0182	.043	.005	.0369	.0372	.141	-.002	.0302	.0282	.080
EB1	.010	.0192	.0187	.044	.006	.0370	.0373	.142	-.002	.0360	.0348	.122
EB2	.010	.0195	.0184	.043	.006	.0370	.0373	.142	-.003	.0339	.0297	.089
EB3	.010	.0186	.0184	.044	.006	.0369	.0373	.142	-.004	.0269	.0295	.089
EB4	.010	.0186	.0184	.044	.006	.0369	.0373	.142	-.003	.0268	.0296	.089
META	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE
LOG	.008	.0194	.0187	.042	.003	.0372	.0373	.140	-.004	.0381	.0367	.136
UML	.009	.0193	.0187	.042	.003	.0371	.0371	.138	-.004	.0370	.0363	.134
CML	.009	.0183	.0182	.042	.006	.0370	.0371	.140	-.003	.0221	.0219	.049
EB	.009	.0184	.0182	.042	.004	.0370	.0371	.139	-.005	.0280	.0256	.067
EB1	.009	.0192	.0185	.042	.004	.0371	.0371	.139	-.004	.0354	.0341	.118
EB2	.009	.0188	.0182	.041	.005	.0370	.0371	.140	-.002	.0285	.0275	.076
EB3	.009	.0187	.0183	.042	.005	.0370	.0371	.140	-.004	.0282	.0278	.079
EB4	.009	.0187	.0182	.042	.005	.0370	.0371	.140	-.003	.0282	.0277	.078

Table S8: Bias (BIAS), estimated standard errors (SE1), empirical standard errors (SE2) and  $100 \times \text{MSE}$  (MSE) of  $\hat{\gamma}_E$ ,  $\hat{\gamma}_G$  and  $\hat{\gamma}_{GE}$  resulting from standard logistic regression, unconstrained maximum likelihood, constrained maximum likelihood, empirical Bayes and our proposed multi-study empirical Bayes estimators in both IPD and summary statistic meta-analysis (META) simulation settings ( $K = 10$  individual studies with sample sizes  $n_k = 1000 + 100(k - 1)$ ,  $k = 1, \dots, K$ ) with  $MAF = 10\%$  when  $G$ - $E$  independence is violated. In the meta-analysis setting, we use the inverse variance-covariance weighted approach to obtain the standard logistic, unconstrained, constrained and empirical Bayes results.

$\theta_k = .1$ for all $k$												
	Main Effect of $E$				Main Effect of $G$				$G \times E$ Interaction			
IPD	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE
LOG	.010	.0199	.0200	.050	.006	.0355	.0353	.128	.006	.0350	.0355	.130
UML	.011	.0198	.0200	.052	.005	.0353	.0350	.125	.003	.0339	.0343	.119
CML	-.004	.0186	.0188	.037	.008	.0353	.0350	.130	.064	.0202	.0203	.457
EB	.002	.0194	.0194	.038	.008	.0353	.0350	.130	.019	.0351	.0356	.164
EB1	.011	.0199	.0200	.051	.005	.0353	.0350	.125	.005	.0342	.0346	.122
EB2	.009	.0210	.0205	.051	.006	.0354	.0350	.126	.010	.0397	.0392	.164
EB3	.009	.0197	.0204	.051	.006	.0353	.0350	.126	.010	.0325	.0385	.157
EB4	.009	.0197	.0204	.051	.006	.0353	.0350	.126	.010	.0325	.0387	.159
META	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE
LOG	.010	.0200	.0199	.049	.003	.0356	.0351	.124	.001	.0352	.0352	.124
UML	.010	.0199	.0199	.050	.003	.0354	.0349	.122	.000	.0340	.0342	.117
CML	-.005	.0187	.0187	.037	.009	.0354	.0350	.129	.066	.0203	.0202	.481
EB	-.004	.0188	.0188	.037	.007	.0354	.0349	.127	.043	.0268	.0271	.255
EB1	.010	.0199	.0199	.049	.003	.0354	.0349	.123	.002	.0345	.0347	.120
EB2	.006	.0196	.0206	.047	.005	.0354	.0350	.125	.017	.0306	.0443	.226
EB3	.008	.0196	.0206	.048	.004	.0354	.0349	.124	.012	.0314	.0421	.192
EB4	.007	.0196	.0206	.047	.004	.0354	.0350	.124	.014	.0309	.0432	.207
$\theta_k = -.5$ for all $k$												
	Main Effect of $E$				Main Effect of $G$				$G \times E$ Interaction			
LOG	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE
LOG	.007	.0178	.0179	.037	.008	.0490	.0493	.250	.005	.0580	.0569	.325
UML	.007	.0178	.0179	.038	.007	.0488	.0494	.249	.002	.0569	.0557	.310
CML	.040	.0175	.0175	.187	-.054	.0470	.0481	.520	-.335	.0352	.0350	11.340
EB	.015	.0179	.0181	.054	-.015	.0493	.0494	.268	-.005	.0591	.0576	.334
EB1	.007	.0178	.0179	.038	.007	.0488	.0494	.249	.001	.0570	.0557	.311
EB2	.008	.0178	.0179	.038	.007	.0488	.0494	.249	.001	.0570	.0558	.311
EB3	.008	.0178	.0179	.038	.007	.0488	.0494	.249	.001	.0570	.0558	.311
EB4	.008	.0178	.0179	.038	.007	.0488	.0494	.249	.001	.0570	.0558	.311
META	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE
LOG	.006	.0179	.0178	.036	.002	.0493	.0485	.236	-.002	.0587	.0556	.309
UML	.006	.0179	.0178	.036	.002	.0491	.0487	.237	-.002	.0571	.0550	.303
CML	.039	.0176	.0174	.180	-.050	.0471	.0478	.482	-.328	.0351	.0350	10.876
EB	.031	.0177	.0177	.128	-.052	.0479	.0473	.498	-.093	.0601	.0649	1.278
EB1	.007	.0179	.0179	.036	.002	.0491	.0487	.237	-.003	.0572	.0551	.305
EB2	.007	.0179	.0179	.036	.002	.0491	.0487	.237	-.003	.0573	.0552	.306
EB3	.007	.0179	.0179	.036	.002	.0491	.0487	.237	-.003	.0571	.0552	.306
EB4	.007	.0179	.0179	.036	.002	.0491	.0487	.237	-.003	.0571	.0552	.306

Table S9: Bias (BIAS), standard errors (SE1), empirical standard errors (SE2) and  $100 \times$  MSE (MSE) of  $\hat{\gamma}_E$ ,  $\hat{\gamma}_G$  and  $\hat{\gamma}_{GE}$  resulting from standard logistic regression (LOG), unconstrained maximum likelihood (UML), constrained maximum likelihood (CML), empirical Bayes (EB) and our proposed multi-study empirical Bayes estimators EB1 - EB4 in both IPD and summary statistic meta-analysis (META) simulation settings ( $K = 10$  individual studies with sample sizes  $n_k = 1000 + 100(k - 1)$ ,  $k = 1, \dots, K$ ) with marginal disease prevalence 10% under  $G$ - $E$  independence over 1,000 Monte Carlo runs. In the meta-analysis setting, we use the inverse variance-covariance weighted approach to obtain the standard logistic, unconstrained, constrained and empirical Bayes results.

	Main Effect of $E$				Main Effect of $G$				$G \times E$ Interaction			
IPD	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE
LOG	.007	.0233	.0231	.059	.005	.0264	.0270	.075	.005	.0273	.0260	.070
UML	.009	.0230	.0229	.061	.003	.0262	.0267	.072	.001	.0264	.0250	.063
CML	.017	.0205	.0209	.073	.002	.0262	.0266	.071	-.015	.0165	.0157	.046
EB	.013	.0215	.0213	.064	.002	.0262	.0266	.071	-.003	.0236	.0219	.049
EB1	.010	.0229	.0227	.061	.003	.0262	.0267	.072	.000	.0261	.0242	.059
EB2	.012	.0234	.0223	.065	.003	.0263	.0267	.072	-.005	.0253	.0233	.057
EB3	.012	.0216	.0223	.065	.003	.0262	.0267	.072	-.005	.0208	.0233	.057
EB4	.012	.0216	.0223	.065	.003	.0262	.0267	.072	-.005	.0208	.0233	.057
META	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE
LOG	.007	.0234	.0228	.057	.003	.0265	.0269	.073	.002	.0274	.0257	.066
UML	.008	.0231	.0227	.059	.002	.0263	.0267	.071	.000	.0265	.0248	.062
CML	.017	.0206	.0207	.070	.002	.0262	.0266	.071	-.014	.0165	.0157	.044
EB	.015	.0210	.0209	.067	.001	.0262	.0266	.071	-.010	.0206	.0181	.042
EB1	.009	.0230	.0225	.059	.002	.0263	.0266	.071	-.001	.0258	.0239	.057
EB2	.013	.0219	.0222	.065	.002	.0262	.0266	.071	-.007	.0215	.0219	.053
EB3	.013	.0217	.0219	.065	.002	.0262	.0266	.071	-.008	.0210	.0214	.052
EB4	.013	.0218	.0220	.065	.002	.0262	.0266	.071	-.007	.0212	.0218	.052

Table S10: Bias (BIAS), estimated standard errors (SE1), empirical standard errors (SE2) and  $100 \times \text{MSE}$  (MSE) of  $\hat{\gamma}_E$ ,  $\hat{\gamma}_G$  and  $\hat{\gamma}_{GE}$  resulting from standard logistic regression, unconstrained maximum likelihood, constrained maximum likelihood, empirical Bayes and our proposed multi-study empirical Bayes estimators in both IPD and summary statistic meta-analysis (META) simulation settings ( $K = 10$  individual studies with sample sizes  $n_k = 1000 + 100(k - 1)$ ,  $k = 1, \dots, K$ ) with marginal disease prevalence 10% when  $G$ - $E$  independence is violated. In the meta-analysis setting, we use the inverse variance-covariance weighted approach to obtain the standard logistic, unconstrained, constrained and empirical Bayes results.

$\theta_k = .1$ for all $k$		Main Effect of $E$				Main Effect of $G$				$G \times E$ Interaction			
IPD	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE	
LOG	.011	.0247	.0254	.076	.005	.0258	.0251	.066	.003	.0264	.0270	.074	
UML	.013	.0244	.0252	.081	.004	.0256	.0249	.063	.000	.0254	.0259	.067	
CML	-.017	.0213	.0216	.076	.008	.0256	.0249	.069	.052	.0159	.0161	.294	
EB	.000	.0245	.0250	.062	.008	.0256	.0249	.068	.014	.0270	.0277	.095	
EB1	.012	.0245	.0253	.079	.004	.0256	.0249	.063	.001	.0258	.0262	.069	
EB2	.011	.0257	.0265	.081	.004	.0257	.0249	.064	.004	.0280	.0293	.088	
EB3	.011	.0243	.0264	.081	.004	.0256	.0249	.064	.004	.0250	.0291	.086	
EB4	.011	.0243	.0264	.081	.004	.0256	.0249	.064	.004	.0250	.0292	.087	
META	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE	
LOG	.011	.0248	.0252	.075	.003	.0259	.0250	.064	.001	.0265	.0268	.072	
UML	.012	.0244	.0250	.078	.002	.0256	.0248	.062	-.002	.0255	.0258	.067	
CML	-.018	.0213	.0215	.077	.008	.0256	.0249	.068	.052	.0159	.0161	.296	
EB	-.013	.0222	.0221	.065	.007	.0256	.0248	.067	.033	.0208	.0208	.151	
EB1	.012	.0245	.0251	.077	.003	.0257	.0248	.062	.000	.0259	.0261	.068	
EB2	.007	.0240	.0274	.080	.004	.0256	.0250	.063	.008	.0241	.0328	.114	
EB3	.008	.0240	.0270	.079	.003	.0256	.0249	.063	.006	.0241	.0318	.105	
EB4	.008	.0239	.0272	.080	.003	.0256	.0249	.063	.007	.0239	.0323	.109	
$\theta_k = -.5$ for all $k$		Main Effect of $E$				Main Effect of $G$				$G \times E$ Interaction			
LOG	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE	
LOG	.006	.0194	.0192	.040	.005	.0316	.0318	.104	.003	.0361	.0357	.129	
UML	.006	.0194	.0191	.041	.004	.0315	.0315	.100	.001	.0355	.0347	.121	
CML	.096	.0185	.0184	.955	-.049	.0306	.0306	.336	-.337	.0225	.0219	11.377	
EB	.010	.0195	.0193	.047	-.008	.0319	.0320	.110	.000	.0364	.0359	.129	
EB1	.007	.0194	.0191	.041	.004	.0315	.0315	.100	.001	.0355	.0347	.121	
EB2	.007	.0194	.0191	.041	.004	.0315	.0315	.100	.001	.0355	.0347	.121	
EB3	.007	.0194	.0191	.041	.004	.0315	.0315	.100	.001	.0355	.0347	.121	
EB4	.007	.0194	.0191	.041	.004	.0315	.0315	.100	.001	.0355	.0347	.121	
META	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE	
LOG	.005	.0195	.0190	.039	.003	.0317	.0316	.100	.001	.0363	.0353	.124	
UML	.006	.0194	.0190	.039	.002	.0315	.0313	.098	.000	.0355	.0345	.119	
CML	.095	.0185	.0182	.938	-.048	.0306	.0305	.327	-.334	.0225	.0218	11.210	
EB	.034	.0196	.0195	.153	-.039	.0312	.0309	.248	-.033	.0381	.0374	.249	
EB1	.006	.0194	.0190	.039	.002	.0315	.0313	.098	-.001	.0356	.0345	.119	
EB2	.006	.0194	.0190	.039	.002	.0315	.0313	.098	-.001	.0356	.0345	.119	
EB3	.006	.0194	.0190	.039	.002	.0315	.0313	.098	-.001	.0355	.0345	.119	
EB4	.006	.0194	.0190	.039	.002	.0315	.0313	.098	-.001	.0355	.0345	.119	

Table S11: Bias (BIAS), standard errors (SE1), empirical standard errors (SE2) and  $100 \times$  MSE (MSE) of  $\hat{\gamma}_E$ ,  $\hat{\gamma}_G$  and  $\hat{\gamma}_{GE}$  resulting from standard logistic regression (LOG), unconstrained maximum likelihood (UML), constrained maximum likelihood (CML), empirical Bayes (EB) and our proposed multi-study empirical Bayes estimators EB1 - EB4 in both IPD and summary statistic meta-analysis (META) simulation settings ( $K = 10$  individual studies with sample sizes  $n_k = 1000 + 100(k - 1)$ ,  $k = 1, \dots, K$ ) with marginal disease prevalence 20% under  $G$ - $E$  independence over 1,000 Monte Carlo runs. In the meta-analysis setting, we use the inverse variance-covariance weighted approach to obtain the standard logistic, unconstrained, constrained and empirical Bayes results.

	Main Effect of $E$				Main Effect of $G$				$G \times E$ Interaction			
IPD	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE
LOG	.006	.0229	.0235	.059	.004	.0266	.0256	.067	.003	.0276	.0279	.079
UML	.008	.0227	.0233	.061	.002	.0264	.0254	.065	-.001	.0267	.0269	.073
CML	.021	.0203	.0208	.088	.000	.0263	.0253	.064	-.028	.0167	.0165	.107
EB	.014	.0218	.0219	.068	.000	.0264	.0253	.064	-.007	.0260	.0259	.072
EB1	.009	.0227	.0232	.062	.002	.0264	.0254	.065	-.003	.0268	.0267	.072
EB2	.012	.0235	.0233	.068	.001	.0265	.0254	.064	-.009	.0276	.0280	.086
EB3	.012	.0217	.0233	.069	.001	.0264	.0254	.064	-.009	.0227	.0281	.087
EB4	.012	.0217	.0233	.068	.001	.0264	.0254	.064	-.009	.0227	.0281	.087
META	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE
LOG	.005	.0230	.0233	.057	.002	.0267	.0254	.065	.001	.0277	.0277	.077
UML	.007	.0228	.0232	.059	.001	.0265	.0253	.064	-.002	.0268	.0269	.073
CML	.021	.0204	.0207	.085	-.001	.0264	.0252	.064	-.028	.0167	.0165	.103
EB	.019	.0208	.0208	.078	-.001	.0264	.0252	.064	-.019	.0212	.0198	.077
EB1	.008	.0229	.0232	.061	.001	.0265	.0253	.064	-.004	.0267	.0266	.072
EB2	.013	.0218	.0229	.069	.000	.0264	.0253	.064	-.013	.0226	.0263	.086
EB3	.014	.0216	.0229	.071	.000	.0264	.0253	.064	-.014	.0220	.0263	.088
EB4	.013	.0217	.0229	.070	.000	.0264	.0253	.064	-.013	.0222	.0264	.087



Table S12: Bias (BIAS), estimated standard errors (SE1), empirical standard errors (SE2) and  $100 \times \text{MSE}$  (MSE) of  $\hat{\gamma}_E$ ,  $\hat{\gamma}_G$  and  $\hat{\gamma}_{GE}$  resulting from standard logistic regression, unconstrained maximum likelihood, constrained maximum likelihood, empirical Bayes and our proposed multi-study empirical Bayes estimators in both IPD and summary statistic meta-analysis (META) simulation settings ( $K = 10$  individual studies with sample sizes  $n_k = 1000 + 100(k - 1)$ ,  $k = 1, \dots, K$ ) with marginal disease prevalence 20% when  $G$ - $E$  independence is violated. In the meta-analysis setting, we use the inverse variance-covariance weighted approach to obtain the standard logistic, unconstrained, constrained and empirical Bayes results.

$\theta_k = .1$ for all $k$		Main Effect of $E$				Main Effect of $G$				$G \times E$ Interaction			
IPD	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE	
LOG	.007	.0243	.0248	.067	.004	.0260	.0257	.068	.002	.0266	.0266	.071	
UML	.010	.0240	.0246	.071	.002	.0258	.0254	.065	-.002	.0256	.0254	.065	
CML	-.011	.0211	.0220	.061	.005	.0257	.0254	.067	.036	.0160	.0161	.157	
EB	-.002	.0232	.0237	.057	.005	.0257	.0254	.067	.013	.0256	.0254	.081	
EB1	.009	.0241	.0246	.070	.002	.0258	.0254	.065	-.001	.0259	.0256	.066	
EB2	.006	.0262	.0257	.070	.003	.0259	.0254	.065	.005	.0296	.0287	.085	
EB3	.007	.0235	.0256	.070	.003	.0258	.0254	.065	.004	.0240	.0285	.083	
EB4	.007	.0235	.0257	.070	.003	.0258	.0254	.065	.004	.0239	.0286	.084	
META	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE	
LOG	.007	.0244	.0247	.066	.002	.0261	.0256	.066	.000	.0267	.0264	.070	
UML	.009	.0240	.0245	.069	.001	.0258	.0253	.064	-.003	.0257	.0253	.065	
CML	-.012	.0211	.0220	.063	.005	.0258	.0253	.067	.036	.0161	.0161	.159	
EB	-.009	.0217	.0221	.057	.005	.0258	.0253	.066	.024	.0204	.0199	.096	
EB1	.009	.0241	.0245	.067	.001	.0258	.0253	.064	-.002	.0261	.0257	.067	
EB2	.002	.0232	.0260	.068	.002	.0258	.0254	.065	.010	.0228	.0305	.102	
EB3	.004	.0232	.0258	.068	.002	.0258	.0255	.065	.008	.0230	.0300	.095	
EB4	.003	.0232	.0259	.068	.002	.0258	.0255	.065	.008	.0228	.0303	.099	
$\theta_k = -.5$ for all $k$		Main Effect of $E$				Main Effect of $G$				$G \times E$ Interaction			
LOG	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE	
LOG	.005	.0193	.0194	.040	.004	.0320	.0318	.102	.001	.0366	.0357	.127	
UML	.006	.0193	.0194	.041	.002	.0318	.0316	.100	-.001	.0359	.0348	.121	
CML	.094	.0184	.0186	.925	-.053	.0309	.0305	.371	-.345	.0228	.0232	11.983	
EB	.009	.0194	.0195	.047	-.010	.0323	.0320	.112	-.003	.0369	.0359	.129	
EB1	.006	.0193	.0194	.041	.002	.0318	.0316	.100	-.002	.0360	.0348	.121	
EB2	.006	.0193	.0194	.041	.002	.0318	.0316	.100	-.002	.0360	.0348	.121	
EB3	.006	.0193	.0194	.041	.002	.0318	.0316	.100	-.002	.0360	.0348	.121	
EB4	.006	.0193	.0194	.041	.002	.0318	.0316	.100	-.002	.0360	.0348	.121	
META	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE	
LOG	.004	.0194	.0194	.039	.001	.0321	.0316	.100	-.001	.0368	.0352	.124	
UML	.005	.0194	.0193	.040	.000	.0319	.0315	.099	-.003	.0360	.0345	.120	
CML	.094	.0185	.0186	.909	-.052	.0309	.0303	.360	-.343	.0228	.0232	11.801	
EB	.033	.0195	.0198	.147	-.042	.0315	.0309	.269	-.036	.0386	.0372	.265	
EB1	.005	.0194	.0194	.040	.000	.0319	.0315	.099	-.003	.0360	.0345	.120	
EB2	.005	.0194	.0194	.040	.000	.0319	.0315	.099	-.003	.0360	.0345	.120	
EB3	.005	.0194	.0194	.040	.000	.0319	.0315	.099	-.003	.0360	.0345	.120	
EB4	.005	.0194	.0194	.040	.000	.0319	.0315	.099	-.003	.0360	.0345	.120	

Table S13: Bias (BIAS), standard errors (SE1), empirical standard errors (SE2) and  $100 \times$  MSE (MSE) of  $\hat{\gamma}_E$ ,  $\hat{\gamma}_G$  and  $\hat{\gamma}_{GE}$  resulting from standard logistic regression (LOG), unconstrained maximum likelihood (UML), constrained maximum likelihood (CML), empirical Bayes (EB) and our proposed multi-study empirical Bayes estimators EB1 - EB4 in both IPD and summary statistic meta-analysis (META) simulation settings ( $K = 10$  individual studies with sample sizes  $n_k = 1000 + 100(k - 1)$ ,  $k = 1, \dots, K$ ) with individual study case-control ratios 1:2 under  $G$ - $E$  independence over 1,000 Monte Carlo runs. In the meta-analysis setting, we use the inverse variance-covariance weighted approach to obtain the standard logistic, unconstrained, constrained and empirical Bayes results.

	Main Effect of $E$				Main Effect of $G$				$G \times E$ Interaction			
IPD	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE
LOG	.008	.0240	.0235	.062	.003	.0275	.0270	.074	.002	.0269	.0261	.068
UML	.009	.0237	.0233	.062	.002	.0273	.0267	.072	.001	.0259	.0252	.064
CML	.012	.0220	.0220	.062	.002	.0273	.0268	.072	-.005	.0194	.0189	.038
EB	.011	.0224	.0221	.060	.002	.0273	.0268	.072	-.001	.0226	.0214	.046
EB1	.009	.0236	.0231	.062	.002	.0273	.0268	.072	.000	.0255	.0242	.059
EB2	.010	.0238	.0225	.061	.002	.0273	.0268	.072	-.002	.0248	.0218	.048
EB3	.010	.0226	.0225	.061	.002	.0273	.0267	.072	-.002	.0216	.0219	.048
EB4	.010	.0226	.0225	.061	.002	.0273	.0268	.072	-.002	.0216	.0219	.048
META	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE
LOG	.009	.0242	.0234	.062	.002	.0275	.0269	.072	.000	.0271	.0257	.066
UML	.009	.0238	.0232	.062	.002	.0273	.0267	.071	.000	.0260	.0251	.063
CML	.012	.0220	.0220	.062	.002	.0273	.0267	.072	-.004	.0194	.0189	.037
EB	.011	.0223	.0220	.062	.002	.0273	.0268	.072	-.003	.0220	.0204	.042
EB1	.010	.0236	.0229	.062	.002	.0273	.0267	.071	-.001	.0251	.0239	.057
EB2	.011	.0228	.0224	.062	.002	.0273	.0267	.072	-.002	.0222	.0211	.045
EB3	.011	.0227	.0224	.062	.002	.0273	.0267	.072	-.002	.0219	.0212	.046
EB4	.011	.0227	.0224	.062	.002	.0273	.0267	.072	-.002	.0219	.0212	.045

Table S14: Bias (BIAS), estimated standard errors (SE1), empirical standard errors (SE2) and  $100 \times \text{MSE}$  (MSE) of  $\hat{\gamma}_E$ ,  $\hat{\gamma}_G$  and  $\hat{\gamma}_{GE}$  resulting from standard logistic regression, unconstrained maximum likelihood, constrained maximum likelihood, empirical Bayes and our proposed multi-study empirical Bayes estimators in both IPD and summary statistic meta-analysis (META) simulation settings ( $K = 10$  individual studies with sample sizes  $n_k = 1000 + 100(k - 1)$ ,  $k = 1, \dots, K$ ) with individual study case-control ratios 1:2 when  $G$ - $E$  independence is violated. In the meta-analysis setting, we use the inverse variance-covariance weighted approach to obtain the standard logistic, unconstrained, constrained and empirical Bayes results.

$\theta_k = .1$ for all $k$												
	Main Effect of $E$				Main Effect of $G$				$G \times E$ Interaction			
IPD	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE
LOG	.009	.0256	.0255	.072	.003	.0269	.0272	.075	.003	.0259	.0261	.069
UML	.010	.0252	.0252	.074	.003	.0267	.0271	.074	.001	.0249	.0250	.062
CML	-.025	.0230	.0232	.118	.006	.0267	.0270	.077	.061	.0186	.0192	.405
EB	-.003	.0258	.0256	.066	.006	.0267	.0270	.076	.013	.0270	.0271	.091
EB1	.010	.0252	.0252	.073	.003	.0267	.0271	.074	.002	.0251	.0251	.063
EB2	.009	.0255	.0256	.074	.003	.0268	.0271	.074	.003	.0257	.0263	.070
EB3	.009	.0252	.0256	.073	.003	.0267	.0271	.074	.003	.0251	.0262	.070
EB4	.009	.0252	.0256	.074	.003	.0267	.0271	.074	.003	.0250	.0262	.070
META	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE
LOG	.009	.0257	.0252	.072	.002	.0270	.0271	.074	.001	.0261	.0257	.066
UML	.010	.0252	.0251	.073	.002	.0268	.0270	.073	.000	.0250	.0249	.062
CML	-.025	.0230	.0232	.118	.006	.0268	.0270	.076	.061	.0187	.0192	.410
EB	-.018	.0238	.0237	.088	.005	.0268	.0270	.076	.036	.0224	.0230	.183
EB1	.010	.0253	.0251	.072	.002	.0268	.0270	.073	.001	.0252	.0250	.063
EB2	.008	.0252	.0261	.074	.002	.0268	.0270	.074	.004	.0250	.0279	.080
EB3	.008	.0251	.0259	.074	.002	.0268	.0270	.074	.004	.0247	.0272	.075
EB4	.008	.0251	.0259	.073	.002	.0268	.0270	.074	.004	.0247	.0273	.076
$\theta_k = -.5$ for all $k$												
	Main Effect of $E$				Main Effect of $G$				$G \times E$ Interaction			
IPD	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE
LOG	.004	.0200	.0200	.042	.005	.0324	.0322	.106	.003	.0359	.0364	.133
UML	.005	.0199	.0199	.042	.004	.0322	.0319	.103	.002	.0352	.0354	.125
CML	.092	.0192	.0193	.875	-.041	.0317	.0310	.261	-.324	.0265	.0267	10.577
EB	.009	.0200	.0201	.048	-.011	.0325	.0324	.116	-.001	.0360	.0366	.134
EB1	.005	.0199	.0199	.042	.004	.0322	.0319	.103	.001	.0352	.0354	.125
EB2	.005	.0199	.0199	.042	.004	.0322	.0319	.103	.001	.0352	.0354	.125
EB3	.005	.0199	.0199	.042	.004	.0322	.0319	.103	.001	.0352	.0354	.125
EB4	.005	.0199	.0199	.042	.004	.0322	.0319	.103	.001	.0352	.0354	.125
META	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE
LOG	.005	.0201	.0198	.041	.004	.0325	.0320	.104	.001	.0361	.0359	.129
UML	.005	.0200	.0198	.041	.004	.0323	.0318	.102	.001	.0353	.0352	.124
CML	.092	.0193	.0192	.874	-.038	.0317	.0309	.242	-.321	.0264	.0266	10.386
EB	.035	.0202	.0200	.159	-.033	.0320	.0313	.208	-.034	.0375	.0376	.254
EB1	.005	.0200	.0198	.041	.004	.0323	.0318	.102	.001	.0353	.0352	.124
EB2	.005	.0200	.0198	.041	.004	.0323	.0318	.102	.001	.0353	.0352	.124
EB3	.005	.0200	.0198	.041	.004	.0323	.0318	.102	.001	.0353	.0352	.124
EB4	.005	.0200	.0198	.041	.004	.0323	.0318	.102	.001	.0353	.0352	.124

Table S15: Bias (BIAS), standard errors (SE1), empirical standard errors (SE2) and  $100 \times$  MSE (MSE) of  $\hat{\gamma}_E$ ,  $\hat{\gamma}_G$  and  $\hat{\gamma}_{GE}$  resulting from standard logistic regression (LOG), unconstrained maximum likelihood (UML), constrained maximum likelihood (CML), empirical Bayes (EB) and our proposed multi-study empirical Bayes estimators EB1 - EB4 in both IPD and summary statistic meta-analysis (META) simulation settings ( $K = 10$  individual studies with sample sizes  $n_k = 1000 + 100(k - 1)$ ,  $k = 1, \dots, K$ ) with individual study case-control ratios 1:4 under  $G$ - $E$  independence over 1,000 Monte Carlo runs. In the meta-analysis setting, we use the inverse variance-covariance weighted approach to obtain the standard logistic, unconstrained, constrained and empirical Bayes results.

IPD	Main Effect of $E$				Main Effect of $G$				$G \times E$ Interaction			
	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE
LOG	.003	.0276	.0277	.078	.005	.0323	.0312	.099	.003	.0300	.0311	.097
UML	.005	.0273	.0273	.076	.004	.0321	.0310	.097	.000	.0289	.0298	.089
CML	.008	.0261	.0257	.073	.004	.0321	.0310	.097	-.006	.0245	.0254	.068
EB	.007	.0263	.0260	.072	.004	.0321	.0310	.097	-.002	.0266	.0272	.074
EB1	.005	.0272	.0269	.075	.004	.0321	.0310	.097	-.001	.0287	.0289	.083
EB2	.006	.0272	.0262	.073	.004	.0321	.0310	.097	-.003	.0280	.0269	.074
EB3	.007	.0265	.0262	.073	.004	.0321	.0310	.097	-.004	.0260	.0269	.074
EB4	.006	.0265	.0262	.073	.004	.0321	.0310	.097	-.004	.0260	.0269	.074
META	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE
LOG	.006	.0277	.0273	.078	.005	.0323	.0309	.098	.000	.0303	.0306	.093
UML	.006	.0273	.0271	.077	.004	.0321	.0309	.097	.000	.0290	.0297	.088
CML	.009	.0261	.0256	.074	.005	.0321	.0309	.098	-.005	.0244	.0254	.067
EB	.009	.0262	.0258	.075	.004	.0321	.0308	.097	-.004	.0261	.0262	.071
EB1	.007	.0272	.0268	.076	.005	.0321	.0309	.097	-.001	.0284	.0285	.081
EB2	.008	.0266	.0260	.074	.005	.0321	.0309	.098	-.003	.0264	.0266	.071
EB3	.008	.0266	.0259	.074	.005	.0321	.0309	.098	-.003	.0262	.0264	.071
EB4	.008	.0266	.0260	.074	.005	.0321	.0309	.098	-.003	.0262	.0265	.071

Table S16: Bias (BIAS), estimated standard errors (SE1), empirical standard errors (SE2) and  $100 \times \text{MSE}$  (MSE) of  $\hat{\gamma}_E$ ,  $\hat{\gamma}_G$  and  $\hat{\gamma}_{GE}$  resulting from standard logistic regression, unconstrained maximum likelihood, constrained maximum likelihood, empirical Bayes and our proposed multi-study empirical Bayes estimators in both IPD and summary statistic meta-analysis (META) simulation settings ( $K = 10$  individual studies with sample sizes  $n_k = 1000 + 100(k - 1)$ ,  $k = 1, \dots, K$ ) with individual study case-control ratios 1:4 when  $G$ - $E$  independence is violated. In the meta-analysis setting, we use the inverse variance-covariance weighted approach to obtain the standard logistic, unconstrained, constrained and empirical Bayes results.

$\theta_k = .1$ for all $k$												
	Main Effect of $E$				Main Effect of $G$				$G \times E$ Interaction			
LOG	.004	.0292	.0292	.087	.003	.0317	.0322	.105	.001	.0287	.0282	.080
UML	.006	.0288	.0286	.085	.003	.0315	.0319	.102	-.001	.0277	.0271	.073
CML	-.029	.0273	.0270	.155	.004	.0315	.0319	.103	.057	.0235	.0228	.377
EB	-.009	.0292	.0293	.095	.004	.0315	.0319	.103	.013	.0296	.0292	.102
EB1	.005	.0289	.0286	.084	.003	.0315	.0319	.102	.000	.0278	.0272	.074
EB2	.004	.0296	.0288	.085	.003	.0315	.0319	.102	.002	.0294	.0280	.079
EB3	.005	.0289	.0288	.085	.003	.0315	.0319	.102	.001	.0279	.0279	.078
EB4	.005	.0289	.0288	.085	.003	.0315	.0319	.102	.001	.0279	.0280	.078
META	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE
LOG	.007	.0294	.0289	.088	.003	.0318	.0320	.103	-.001	.0290	.0276	.076
UML	.007	.0289	.0285	.086	.003	.0315	.0318	.102	-.001	.0278	.0270	.073
CML	-.027	.0273	.0269	.147	.005	.0315	.0318	.103	.058	.0234	.0227	.389
EB	-.021	.0278	.0272	.116	.004	.0315	.0317	.102	.035	.0260	.0251	.184
EB1	.006	.0289	.0285	.085	.003	.0315	.0318	.102	.000	.0279	.0271	.074
EB2	.005	.0289	.0289	.086	.003	.0315	.0318	.102	.002	.0280	.0284	.081
EB3	.005	.0288	.0288	.086	.003	.0315	.0318	.102	.002	.0277	.0282	.080
EB4	.005	.0288	.0288	.086	.003	.0315	.0318	.102	.002	.0277	.0282	.080
$\theta_k = -.5$ for all $k$												
	Main Effect of $E$				Main Effect of $G$				$G \times E$ Interaction			
LOG	.003	.0230	.0232	.055	.001	.0375	.0385	.148	.001	.0404	.0399	.159
UML	.003	.0230	.0232	.055	.000	.0373	.0381	.145	-.001	.0397	.0390	.152
CML	.087	.0224	.0224	.807	-.038	.0370	.0375	.283	-.319	.0336	.0333	10.283
EB	.009	.0231	.0232	.061	-.018	.0375	.0386	.180	-.004	.0406	.0401	.162
EB1	.003	.0230	.0232	.055	.000	.0373	.0381	.145	-.001	.0397	.0390	.152
EB2	.003	.0230	.0232	.055	.000	.0373	.0381	.145	-.001	.0397	.0390	.152
EB3	.003	.0230	.0232	.055	.000	.0373	.0381	.145	-.001	.0397	.0390	.152
EB4	.003	.0230	.0232	.055	.000	.0373	.0381	.145	-.001	.0397	.0390	.152
META	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE	BIAS	SE1	SE2	MSE
LOG	.004	.0231	.0231	.055	.003	.0377	.0381	.146	.000	.0408	.0392	.154
UML	.004	.0231	.0231	.055	.003	.0374	.0378	.144	.000	.0398	.0389	.152
CML	.088	.0224	.0223	.830	-.033	.0371	.0374	.246	-.315	.0334	.0335	10.013
EB	.040	.0231	.0229	.213	-.031	.0372	.0376	.239	-.045	.0421	.0407	.368
EB1	.005	.0231	.0231	.055	.003	.0374	.0378	.144	.000	.0398	.0390	.152
EB2	.005	.0231	.0231	.055	.003	.0374	.0378	.144	.000	.0398	.0390	.152
EB3	.005	.0231	.0231	.055	.003	.0374	.0378	.144	.000	.0397	.0390	.152
EB4	.005	.0231	.0231	.055	.003	.0374	.0378	.144	.000	.0397	.0390	.152