Letter to the editor

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We congratulate Harbord *and others* (2007) for identifying the very closely related and sometimes identical relationship between the hierarchical summary receiver operating characteristic (HSROC) model (Rutter and Gatsonis, 2001) and the bivariate random-effects meta-analysis (Van Houwelingen *and others*, 2002; Macaskill, 2004; Reitsma *and others*, 2005; Chu and Cole, 2006) from a meta-analysis of diagnostic accuracy studies. However, the formulas for constructing the summary receiver operating characteristic (SROC) curve from the HSROC model presented in equation (5.1) by Harbord *and others* (2007), in p. 2870 by Rutter and Gatsonis (2001), and in p. 927 by Macaskill (2004) are incorrect and potentially misleading.

To simplify the discussion, we focus on models without any covariates. Let n_{11}^i , n_{00}^i , n_{01}^i , and n_{10}^i be the number of true positives, true negatives, false positives, and false negatives and $n_{1.}^i$ and $n_{.0}^i$ be the number of diseased and nondiseased patients in the i th diagnostic accuracy studies from a meta-analysis, respectively. Conditional on the number of diseased and nondiseased patients in each study, the bivariate random-effects meta-analysis model assumes the following: $n_{00}^i \sim \text{Binomial}(n_{.0}^i, \text{Sp}_i)$, $n_{11}^i \sim \text{Binomial}(n_{1.}^i, \text{Se}_i)$, $\text{logit}(\text{Se}_i) = \mu_0 + \mu_i$, and $\text{logit}(\text{Sp}_i) = \nu_0 + \nu_i$, where the random effects $(\mu_i, \nu_i)^T$ are bivariate normally distributed with mean 0. The expected sensitivity for a chosen specificity is given by

$$\text{logit}(\text{Se}) = \mu_0 + \rho\sigma_u/\sigma_v[\text{logit}(\text{Sp}) - \nu_0] = (\mu_0 - \rho\nu_0\sigma_u/\sigma_v) + \rho\sigma_u/\sigma_v[\text{logit}(\text{Sp})]. \quad (1.1)$$

Let $\theta = (\mu_0, \nu_0, \rho, \sigma_u, \sigma_v)$ be the parameters of interests from the bivariate random-effects meta-analysis model and $\hat{\theta}$ be the maximum likelihood estimate (MLE) of θ with estimated variance–covariance $\hat{\Sigma}$. Let $\mathbf{Q} = \{1, -\rho\sigma_u/\sigma_v, \sigma_u/\sigma_v[\text{logit}(\text{Sp}) - \nu_0], \rho/\sigma_v[\text{logit}(\text{Sp}) - \nu_0], -\rho\sigma_u/\sigma_v^2[\text{logit}(\text{Sp}) - \nu_0]\}$, then based on the delta method, the variance of the expected sensitivity for a chosen specificity in logit scale is given by $\hat{\mathbf{Q}}\hat{\Sigma}\hat{\mathbf{Q}}^T$, where $\hat{\mathbf{Q}}$ is the MLE of $\mathbf{Q}$. The variance of the predicted sensitivity for an individual study with a given specificity in logit scale is $\hat{\mathbf{Q}}\hat{\Sigma}\hat{\mathbf{Q}}^T + \hat{\sigma}_\mu^2(1 - \hat{\rho}^2)$.

The HSROC model (Rutter and Gatsonis, 2001) assumes the following: $n_{01}^i \sim \text{Binomial}(n_{.0}^i, \pi_{i0})$, $n_{11}^i \sim \text{Binomial}(n_{1.}^i, \pi_{i1})$, and $\text{logit}(\pi_{ij}) = (\theta_i + \alpha_i X_{ij}) \exp(-\beta X_{ij})$, where $\theta_i \sim N(\theta_0, \sigma_\theta^2)$ and $\alpha_i \sim N(\alpha_0, \sigma_\alpha^2)$ are independent and X_{ij} is a dummy variable coded as $X_{ij} = 0.5$ for those with

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disease ($j = 1$) and -0.5 for those without disease ($j = 0$). According to the HSROC model, $\text{logit}(\text{Se}_i) = \text{logit}(\pi_{i1}) = \exp(-\beta/2)(\theta_i + 0.5\alpha_i)$ and $\text{logit}(\text{Sp}_i) = -\text{logit}(\pi_{i0}) = -\exp(\beta/2)(\theta_i - 0.5\alpha_i)$. Let $J = \begin{bmatrix} \exp(-\beta/2) & 0.5\exp(-\beta/2) \\ -\exp(\beta/2) & 0.5\exp(\beta/2) \end{bmatrix}$, thus $[\text{logit}(\text{Se}_i) \quad \text{logit}(\text{Sp}_i)]^T = J \times [\theta_i \quad \alpha_i]^T$. Since θ_i and α_i are assumed to be independently normally distributed as $\theta_i \sim N(\theta_0, \sigma_\theta^2)$ and $\alpha_i \sim N(\alpha_0, \sigma_\alpha^2)$, the joint distribution of $[\text{logit}(\text{Se}_i) \quad \text{logit}(\text{Sp}_i)]^T$ is a bivariate normal with mean $J \times \begin{pmatrix} \theta_0 \\ \alpha_0 \end{pmatrix} = \begin{bmatrix} \exp(-\beta/2)(\theta_0 + 0.5\alpha_0) \\ -\exp(\beta/2)(\theta_0 - 0.5\alpha_0) \end{bmatrix}$ and variance-covariance matrix $J \times \begin{pmatrix} \sigma_\theta^2 & 0 \\ 0 & \sigma_\alpha^2 \end{pmatrix} \times J^T = \begin{bmatrix} \exp(-\beta)(0.25\sigma_\alpha^2 + \sigma_\theta^2) & 0.25\sigma_\alpha^2 - \sigma_\theta^2 \\ 0.25\sigma_\alpha^2 - \sigma_\theta^2 & \exp(\beta)(0.25\sigma_\alpha^2 + \sigma_\theta^2) \end{bmatrix}$. It then follows from the assumed independent normal distributions for θ_i and α_i that the HSROC model also assumes a linear relationship between the expected sensitivity and the specificity in the logit scale, namely

$$\begin{aligned} \text{logit}(\text{Se}) &= \exp(-\beta/2)(0.5\alpha_0 + \theta_0) + \frac{0.25\sigma_\alpha^2 - \sigma_\theta^2}{0.25\sigma_\alpha^2 + \sigma_\theta^2} \\ &\quad \times \exp(-\beta) \times [\text{logit}(\text{Sp}) - \exp(\beta/2)(0.5\alpha_0 - \theta_0)]. \end{aligned} \quad (1.2)$$

This is equivalent to equation (5.1) in Harbord *and others* (2007) only when $\sigma_\alpha^2 = 0$, which corresponds to a HSROC model with fixed “accuracy” parameter, that is, $\text{logit}(\pi_{ij}) = (\theta_i + \alpha_0 X_{ij}) \exp(-\beta X_{ij})$. Using equations (4.11) to (4.15) presented in Harbord *and others* (2007), one can easily prove that (1.2) is exactly the same as (1.1). Thus, the 2 approaches can lead to the same form of model output.

We present an example here to compare the SROC curves constructed from (1.1) in this article and equation (5.1) in Harbord *and others* (2007). In this example of the 17 studies of lymphangiography for the diagnosis of lymph node metastasis in women with cervical cancer (Scheidler *and others*, 1997), the estimated correlation coefficient between sensitivity and specificity in logit scale (i.e. μ_i and ν_i) is 0.24 with a standard error of 0.46. Figure 1 shows the estimates of sensitivity and specificity from the individual studies in the conventional receiver operating characteristic (ROC) space. There is substantial difference

Fig. 1. SROC curve in the conventional receiver operating characteristic (ROC) space for the data on the 17 studies of lymphangiography for the diagnosis of lymph node metastasis in women with cervical cancer (Scheidler *and others*, 1997). The area of the circles is in proportion to the number of patients in each study. The solid lines present the SROC curve based on (1.1), with dotted lines denoting their 95% confidence intervals. The dashed lines present the SROC curve using equation (5.1) as presented in Harbord *and others* (2007).

between the SROC curves constructed from (1.1) in this article and equation (5.1) by Harbord *and others* (2007).

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