

Bivariate Random-effects Meta-analysis of Sensitivity and Specificity with SAS PROC GLIMMIX

J. Menke^{1, 2}

¹Gesellschaft für wissenschaftliche Datenverarbeitung Goettingen (GWDG), Goettingen, Germany;

²Diagnostic Radiology, University Hospital, Goettingen, Germany

Keywords

Meta-analysis, sensitivity and specificity, statistical models, software

Summary

Objectives: Meta-analysis allows to summarize pooled sensitivities and specificities from several primary diagnostic test accuracy studies. Often these pooled estimates are indirectly obtained from a hierarchical summary receiver operating characteristics (HSROC) analysis. This article presents a generalized linear random-effects model with the new SAS PROC GLIMMIX that obtains the pooled estimates for sensitivity and specificity directly.

Methods: Firstly, the formula of the bivariate random-effects model is presented in context with the literature. Then its implementation with the new SAS PROC GLIMMIX is empirically evaluated in comparison to the indirect HSROC approach, utilizing the published 2 x 2 count data of 50 meta-analyses.

Results: According to the empirical evaluation the meta-analytic results from the bivariate GLIMMIX approach are nearly identical to the results from the indirect HSROC approach.

Conclusions: A generalized linear mixed model with PROC GLIMMIX offers a straightforward method for bivariate random-effects meta-analysis of sensitivity and specificity.

The bivariate random-effects model offers a straightforward meta-analytic approach for pooling sensitivity and specificity. Additionally it accounts for a possible correlation between sensitivities and specificities of the included primary studies and for randomly distributed unspecified differences between the studies [2, 5]. Alternatively, in the absence of covariates the hierarchical summary receiver operating characteristics (HSROC) model can be indirectly used for bivariate meta-analysis by transforming the resulting HSROC estimates to corresponding bivariate estimates [3, 6, 7].

Several algorithms are used for bivariate meta-analysis [2, 3, 5, 6, 8–14]. This article focuses on the implementation with the statistical software package SAS (SAS Institute, Cary, N.C.). The current SAS version 9.2 incorporates PROC GLIMMIX that implements a generalized linear mixed model. The purpose of this article is to present the application of PROC GLIMMIX for bivariate random-effects meta-analysis of sensitivity and specificity. Additionally it is studied whether this GLIMMIX approach can be used instead of the indirect HSROC approach.

Section 2 describes basics of mixed models; Section 3 specifies the bivariate mixed model for meta-analysis of sensitivity and specificity; Section 4 presents its implementation with PROC GLIMMIX; Section 5 uses a meta-analytic standard example to compare the bivariate GLIMMIX approach to the indirect HSROC NLMIXED approach; Section 6 compares these approaches by using the 2 x 2 contingency data of 50 published meta-analyses; and Section 7 discusses the methods and results. An appendix with SAS code is supplemented.

Correspondence to:

Jan Menke
Gesellschaft für wissenschaftliche Datenverarbeitung
Göttingen (GWDG)
Am Faßberg 11
37077 Göttingen
Germany
E-mail: jmenke@gwdg.de

Methods Inf Med 2010; 49: 54–64

doi: 10.3414/ME09-01-0001

received: January 12, 2009

accepted: July 29, 2009

republished: November 20, 2009

1. Introduction

Meta-analysis allows to summarize the results from similar diagnostic test accuracy studies quantitatively. These primary studies compare an index test with its gold standard, resulting in dichotomous 2 x 2 contingency tables (►Table 1). Most meta-analyses report the diagnostic test accuracy by bivariate pairs of sensitivity and specificity, since these parameters can be readily interpreted. Sensitivity measures the probability of correctly diagnosing a disease or status, while specificity measures the probability of correctly identifying its absence (►Table 1) [1–3].

If several primary studies are conducted then their results usually differ. A meta-analysis of these primary studies intends to find pooled summary estimates for sensitivity and specificity that are more globally valid than the results of a single study. Such meta-analysis can be conducted with either a fixed-effects model or a random-effect model [4]. A fixed-effects model assumes that the variation among the primary studies originates from sampling errors alone [3, 4]. A random-effects model assumes that such variation originates both from sampling errors and true differences between the primary studies, such as differences in patient characteristics or other factors [3, 4].

2. Mixed Models for Meta-analysis

Currently SAS incorporates three different mixed models that can be used for fixed-effects and random-effects meta-analysis.

2.1 Linear Mixed Model (LMM)

PROC MIXED implements a linear mixed model (LMM). The observed data are modeled directly as a linear combination of fixed effects, random effects, and sampling errors. In its general form the linear mixed model may be written as

$$(Y - \epsilon) = X\beta + Zu \tag{2.1}$$

or alternatively as

$$E[Y | u] = X\beta + Zu$$

where Y is the vector of observed data, also termed the “response” of the model; ϵ is the vector of sampling errors; $E[Y | u]$ are the expected values of Y conditional on the random effects u ; X is the known design matrix for the fixed effects resulting from the MODEL statement in PROC MIXED; β is the vector of unknown fixed-effects parameters; Z is the known design matrix for the random effects resulting from the RANDOM statement in PROC MIXED; and u is the vector of unknown random effects [15, 16]. The fixed-effects and random-effects terms on the right-hand side of (2.1) are termed the linear predictor η (eta). The random effects u and the sampling errors e are assumed to be uncorrelated and to be normally distributed with mean zero. Without the random-effects term Zu the linear mixed model reduces to a linear fixed-effects model. In contrast to a standard analysis of variance, PROC MIXED is not implemented with least squares methods. Instead, PROC MIXED utilizes iterative likelihood-based methods. PROC GLIMMIX and PROC NLMIXED are also implemented with likelihood-based methods and are described below. Usually (2.1) is written with its sampling errors ϵ on the right-hand side [15]. Here (2.1) is presented being a special case of the generalized linear mixed model.

2.2 Generalized Linear Mixed Model (GLMM)

PROC GLIMMIX implements a generalized linear mixed model (GLMM) that is a generalization of the linear mixed model (LMM). In addition to the linear mixed model’s properties, the GLMM has a link function that can account for different non-normal distributions of the observed Y data. The equation of the generalized linear mixed model is given by

$$g(E[Y | u]) = X\beta + Zu \tag{2.2}$$

where on the left-hand side $g(\cdot)$ is a differentiable monotonic link function with $g^{-1}(\cdot)$ being the inverse link function; $E[Y | u]$ are the expected values of Y conditional on the random effects u ; and the terms on the right-hand side are termed the linear predictor η (eta) with fixed-effects and random-effects terms as in (2.1) [16, 17]. Similar to PROC MIXED, PROC GLIMMIX also assumes a normal distribution for the unknown random effects [16]. PROC GLIMMIX allows to use a logit link function for the observed 2×2 contingency data of the diagnostic test accuracy studies, and to enter these data directly with an Events/Trial syntax. Without the random-effects term Zu the generalized linear mixed model reduces to a fixed-effects generalized linear model. If the link function g is the identity function, the generalized linear mixed model (2.2) reduces to the linear mixed model (2.1).

2.3 Nonlinear Mixed Model (NLMM)

PROC NLMIXED implements a nonlinear mixed model (NLMM) [15]. In this model the predictors are related to the observed data through a nonlinear function

$$Y = f(X, \beta, Z, u) + \epsilon \tag{2.3}$$

where Y is the vector of observed data; $f(\cdot)$ is a nonlinear function of fixed-effects components X , β and random-effects components Z , u ; and ϵ is a vector of sampling errors. Being an iterative method, PROC NLMIXED needs starting values that are not too different from the final model’s solution. The estimates from a nonlinear fixed-effects model may be used as such starting values for a subsequent nonlinear random-effects model. Due to its nonlinear capabilities PROC NLMIXED (NLMM) has more applications than the linear PROC MIXED (LMM) and PROC GLIMMIX (GLMM). The LMM and the GLMM are special linear cases of the NLMM and can thus also be modeled with PROC NLMIXED. However, the numerical fitting of nonlinear models may be less stable than the fitting of linear models [15]. Thus PROC MIXED and PROC GLIMMIX may have computational advantages over PROC NLMIXED, if they are appropriate for the studied statistical model. Additionally, PROC MIXED and PROC GLIMMIX offer more options for modeling the covariance structure of the random effects [16].

Table 1 2×2 contingency table and diagnostic test accuracy parameters. **TP** (true-positives), **FP** (false-positives), **FN** (false-negatives), **TN** (true-negatives), **RP** (positive reference tests), **RN** (negative reference tests), **IP** (positive index tests), **IN** (negative index tests), **N** (total count), **Sens** (sensitivity), **Spec** (specificity), **PPV** (positive predictive value), **NPV** (negative predictive value); **DOR** (diagnostic odds ratio). If **FP** or **FN** is zero, **DOR** is not defined because of division by zero. A somewhat biased standard solution is to add 0.5 to all cells of the 2×2 table, if any cell is zero [2, 3].

		Reference test			proportions
		positive	negative	total	
Index test	positive	TP	FP	IP = TP + FP	PPV = TP / IP
	negative	FN	TN	IN = FN + TN	NPV = TN / IN
total		RP = TP + FN	RN = FP + TN	N = RP + RN	
proportions		Sens = TP / RP	Spec = TN / RN	DOR = (TP*TN) / (FP*FN)	

Element	Description
i	denotes that the element belongs to study i
TP_i, FP_i, FN_i, TN_i	observed true-positives, false-positives, false-negatives, and true-negatives of study i
$RP_i = TP_i + FN_i$	observed positive reference tests of study i
$RN_i = TN_i + FP_i$	observed negative reference tests of study i
$p_{A,i} = TP_i / RP_i$	observed sensitivity (proportion) of study i
$p_{B,i} = TN_i / RN_i$	observed specificity (proportion) of study i
\sim	stochastic relation
$=$	equality relation
$Binomial(n, \pi)$	binomial distribution with totals n and probability π
$Normal(\mu, V)$	normal distribution with mean μ and variance structure V
$\pi_{A,i}$	true sensitivity (probability) of study i
$\pi_{B,i}$	true specificity (probability) of study i
$\mu_{A,i}$	logit-transformed true sensitivity of study i
$\mu_{B,i}$	logit-transformed true specificity of study i
μ_A	pooled sensitivity of the meta-analysis
μ_B	pooled specificity of the meta-analysis
$U_{A,i}$	random effect for sensitivity of study i
$U_{B,i}$	random effect for specificity of study i
σ_A^2	variance of the $U_{A,i}$
σ_B^2	variance of the $U_{B,i}$
σ_{AB}	covariance of the $U_{A,i}$ and the $U_{B,i}$

3. Specification of the Bivariate Mixed Model

The parameters of the bivariate mixed model are summarized in ►Table 2. In a meta-analysis each primary study contributes observed 2×2 count data, from which the observed proportions p_A for sensitivity and p_B for specificity can be calculated (►Table 1). These observed proportions are usually affected with sampling errors and are thus only estimates for the true but unknown probabilities π . This can be written as

$$E(p_{A,i}) = \pi_{A,i} \text{ for sensitivity} \\ \text{and} \\ E(p_{B,i}) = \pi_{B,i} \text{ for specificity of each study } i \quad (3.1)$$

with $E(\cdot)$ denoting the expected value of the random variable $p_{A,i}$ and $p_{B,i}$, respectively.

Sensitivity and specificity are binomial data. The relation between the 2×2 observations and the estimated probabilities π is a stochastic relation. This is denoted by a “ \sim ” sign:

$$\text{sens: } TP_i \sim \text{Binomial}(RP_i, \pi_{A,i}), \\ \text{with } RP_i = TP_i + FN_i \\ \text{spec: } TN_i \sim \text{Binomial}(RN_i, \pi_{B,i}), \\ \text{with } RN_i = TN_i + FP_i \quad (3.2)$$

Sensitivity and specificity can be linearized by transformation to the logit scale by (3.3):

$$\text{logit}(\pi) = \log(\pi/(1-\pi)). \quad (3.3)$$

$$\pi = \exp(\text{logit}(\pi))/(1 + \exp(\text{logit}(\pi))) \quad (3.4)$$

►Equation 3.4 gives the inverse link. Following the notation of Harbord et al. [6],

Table 2
Parameters for specification of the bivariate mixed model.

$\mu_{A,i} = \text{logit}(\pi_{A,i})$ is defined as the logit-transformed estimated true sensitivity and $\mu_{B,i} = \text{logit}(\pi_{B,i})$ as the logit-transformed estimated true specificity in the i th study. μ_A and μ_B are the according summary statistics of sensitivity and specificity. These are bivariate fixed model effects that can represent all levels of diagnostic accuracy in a two-dimensional ROC space. These pooled summary statistics are usually estimated and described by their mean and 95%-CI (confidence interval). In a random-effects meta-analysis the studies are allowed to contribute additional random effects of unknown origin to the model. According to Harbord et al. the logit-transforms $\mu_{A,i}$ and $\mu_{B,i}$ of the estimated true sensitivity and true specificity in each study are assumed to have a bivariate normal distribution across studies, thereby allowing for a possible correlation between them [6]. This bivariate random-effects model and its covariance structure has been specified by Reitsma et al. [5]:

$$\begin{pmatrix} \mu_{A,i} \\ \mu_{B,i} \end{pmatrix} \sim \text{Normal} \left(\begin{pmatrix} \mu_A \\ \mu_B \end{pmatrix}, \Sigma_{AB} \right), \quad (3.5)$$

with $\Sigma_{AB} = \begin{pmatrix} \sigma_A^2 & \sigma_{AB} \\ \sigma_{AB} & \sigma_B^2 \end{pmatrix}$

In Equation 3.5 $\mu_{A,i}$ and $\mu_{B,i}$ are the logit-transformed estimated true sensitivity and specificity of the i th study. $\text{Normal}(\cdot)$ denotes the bivariate normal distribution. This bivariate normal distribution of Equation 3.5 is determined by the bivariate pooled mean estimates μ_A and μ_B for sensitivity and specificity, and by the bivariate covariance matrix Σ_{AB} . This covariance matrix includes the random-effects between-study variances σ_A^2 and σ_B^2 of the studies' sensitivities and specificities, and their covariance σ_{AB} . With the given definitions Equation 3.5 can be written as

$$\begin{pmatrix} \text{logit}(\mathcal{T}_{A,i}) \\ \text{logit}(\mathcal{T}_{B,i}) \end{pmatrix} \sim \begin{pmatrix} \mu_A \\ \mu_B \end{pmatrix} + \text{Normal} \left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \sigma_A^2 & \sigma_{AB} \\ \sigma_{AB} & \sigma_B^2 \end{pmatrix} \right) \quad (3.6)$$

This can also be written as

$$\begin{pmatrix} \text{logit}(\mathcal{T}_{A,i}) \\ \text{logit}(\mathcal{T}_{B,i}) \end{pmatrix} = \begin{pmatrix} \mu_A \\ \mu_B \end{pmatrix} + \begin{pmatrix} U_{A,i} \\ U_{B,i} \end{pmatrix}, \quad (3.7)$$

```

line code
1  DATA LAG_data;
2  length author $20;
3  input number author $ year TP FP FN TN;
4  RP=TP+FN; RN=TN+FP;
5  study = _N_;
6  datalines;
7  1  Kindermann    1970 19  1 10  81
8  2  Lecart        1971  8  9  2  13
   ... (further data in Appendix A)
23 17 Stellato     1992  4  3  0  14
24 ;run;
25 PROC PRINT data=LAG_data;run;
26
27 DATA LAG_bidata; set LAG_data;
28 status='A_pos'; true=TP; pos=TP; total=RP; output;
29 status='B_neg'; true=TN; pos=FP; total=RN; output;
30 keep study status true pos total; run;

```

Fig. 1 Data code of the example in Section 4

with

$$\begin{pmatrix} U_{A,i} \\ U_{B,i} \end{pmatrix} \sim \text{Normal} \left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \sigma_A^2 & \sigma_{AB} \\ \sigma_{AB} & \sigma_B^2 \end{pmatrix} \right)$$

In conjunction with Equation 3.2 this model (Eq. 3.7) is similar to the bivariate generalized linear mixed model as specified by Chu and Cole [11]. $U_{A,i}$ and $U_{B,i}$ are normally distributed random-effects predictions that may be correlated via their covariance σ_{AB} . Omitting $U_{A,i}$ and $U_{B,i}$ results in a fixed-effects model.

4. Implementation of the Bivariate Mixed Model

4.1 Data Structure

The implementation of the bivariate model is shown for the historical lymphangiography (LAG) data of Scheidler et al. [18]. In this example the data file LAG_DATA contains the 2×2 data of the 17 primary LAG studies with one record per study. LAG_BIDATA splits these data into two records per study and adds a status index to

identify the bivariate data for sensitivity “A_pos” and specificity “B_neg” (► Fig. 1).

4.2 Program Code of the Bivariate Mixed Model with PROC GLIMMIX

The bivariate random-effects model of Equation 3.7 requires a generalized linear mixed model with the binomial link function (Eq. 2.2). This can be implemented with PROC GLIMMIX (► Fig. 2), where line 3 specifies “study” and “status” as classification variables. In line 4 the 2×2 count data of the primary studies are modeled directly with an Events/Trials syntax to specify the binomial proportions of sensitivity and specificity with the logit link as the default link. Line 5 defines the random effects and generates the bivariate covariance matrix of Equation 3.7. “subject=study” identifies the studies as the groups, by which the covariance parameters are varied. Per study this gives a pair of random-effects estimates for the status levels, i.e. one for sensitivity and one for specificity per study. “S” requests the output of these random-effects solutions. The covariance matrix of Equation 3.7 is modeled in terms of its Cholesky parameterization “type=chol”, as proposed by Jones and Huddleston [16]. If the iterative model estimation does not converge, “type=chol” can be replaced by “type=un”. “G” displays the estimated covariance matrix of the random effects. Lines 6 and 7 give the pooled summary estimates μ_A and μ_B of sensitivity and specificity on the logit scale. Additionally, “ilink” requests their output on the original probability scale. Omitting line 5 gives the fixed-effects version of this bivariate generalized linear random-effects model (► Appendix B and C).

```

line code
1  PROC GLIMMIX data=LAG_bidata method=quad;
2  title 'Bivariate generalized linear random-effects model';
3  class study status;
4  model true/total = status / noint s cl corrb covb ddfm=bw;
5  random status / subject=study S type=chol G;
6  estimate "logit_sens" status 1 0 / cl ilink;
7  estimate "logit_spec" status 0 1 / cl ilink; run;

```

Fig. 2
GLIMMIX code of the example in Section 4

Table 3 Fixed-effects meta-analysis of the lymphangiography data. This table gives the mean (and 95% confidence interval) of sensitivity and specificity for the fixed-effects meta-analysis with the GLIMMIX and NLMIXED approaches (Appendix B, D).

approach	SAS PROC	pooled sensitivity	pooled specificity
Bivariate	GLIMMIX	67.1% (61.8–72.1)	80.0% (77.3–82.5)
HSROC	NLMIXED	67.1% (62.0–72.3)	80.0% (77.4–82.7)

Table 4 Random-effects meta-analysis of the lymphangiography data. This table gives the mean (and 95% confidence interval) of sensitivity and specificity for the random-effects meta-analysis with the GLIMMIX and NLMIXED approaches (Appendix C, E).

approach	SAS PROC	pooled sensitivity	pooled specificity
Bivariate	GLIMMIX	67.4% (59.8–74.2)	83.7% (75.1–89.8)
HSROC	NLMIXED	67.4% (60.2–74.6)	83.7% (76.5–91.0)

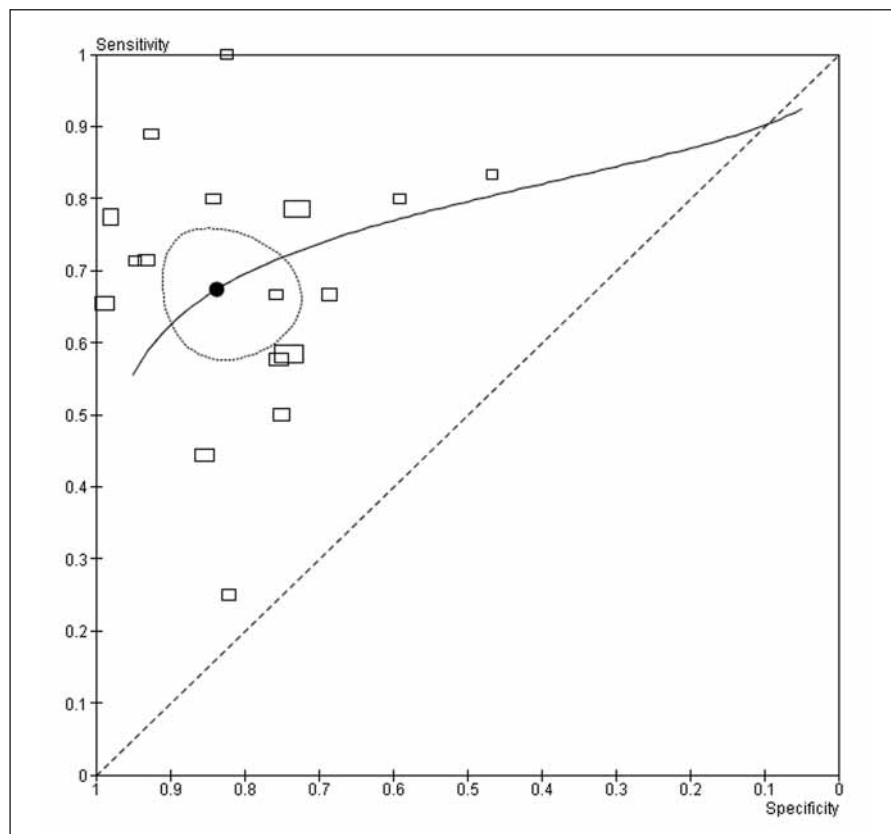


Fig. 3 Bivariate random-effects meta-analysis of sensitivity and specificity with PROC GLIMMIX. Summary ROC space of sensitivity and specificity. This figure visualizes the results of a bivariate random-effects meta-analysis with PROC GLIMMIX for the lymphangiography (LAG) data of Scheidler et al. [18]. Rectangles: Observed bivariate pairs of sensitivity and specificity of the 17 primary LAG studies. Solid line: summary ROC curve. Central point: bivariate summary point. Ellipse: bivariate boundary of the 95% confidence region for the bivariate summary point. Dashed line: line of identity for sensitivity versus $(1 - \text{specificity})$. The plot was generated with Review Manager (RevMan) version 5 [19]. Its input parameters were: $E(\text{logitSe})$ 0.7266; $E(\text{logitSp})$ 1.639; $\text{Var}(\text{logitSe})$ 0.125; $\text{Var}(\text{logitSp})$ 0.8233; $\text{Cov}(\text{logits})$ 0.07664; $\text{SE}(E(\text{logitSe}))$ 0.1545; $\text{SE}(E(\text{logitSp}))$ 0.2505; $\text{Cov}(Es)$ 0.004587; Studies 17. It makes no difference whether to use these bivariate model parameters or their HSROC equivalents: $\text{Lambda} = \text{Alpha}$ 2.1868; Theta 0.07407; beta 0.9491; $\text{Var}(\text{accuracy})$ 0.7797; $\text{Var}(\text{threshold})$ 0.1189.

5. Example

As an example the described bivariate GLIMMIX approach of Section 4 was applied to the meta-analytic lymphangiography data of Scheidler et al. [18]. For comparison the HSROC NLMIXED model of Macaskill was adapted to the terminology of this article (►Appendix D and E) [3]. With the formulae of Harbord et al. this HSROC approach was used to indirectly calculate pooled estimates of sensitivity and specificity [6]. ►Table 3 gives the results for the fixed-effects meta-analyses and ►Table 4 gives the results of the random-effects meta-analyses. In both tables the summary estimates and their confidence intervals are very similar, although they had been calculated with seemingly different models. ►Figure 3 visualizes the results for the bivariate random-effects meta-analysis with PROC GLIMMIX in the two-dimensional summary ROC space [19].

6. Empirical Model Comparison

The bivariate GLIMMIX model was empirically compared with the HSROC NLMIXED model by using the published 2×2 contingency data of 50 meta-analyses about diagnostic test accuracy [20–69]. These meta-analyses were identified from the literature by searching the PubMed database for “meta-analysis”, “systematic review” and related terms from January 2006 to March 2009. Per meta-analysis the 2×2 data of one index test were used, also if two or more index tests had been investigated in that meta-analysis. From each meta-analysis those primary studies were excluded that had not investigated both sensitivity and specificity; for example if only diseased patients had been included so that the specificity of the index test could not be determined. The 2×2 count data of the 50 meta-analyses were recalculated with the bivariate GLIMMIX model (►Appendix B and C) and with the indirect HSROC approach (►Appendix D and E). These meta-analytic models were compared by regression analysis with the question whether the GLIMMIX approach could be used instead of the indirect

HSROC approach for pooling sensitivity and specificity.

The bivariate GLIMMIX approach and the indirect HSROC NLMIXED approach converged in all of the 50 meta-analyses. The average calculation time was 1.4 seconds per meta-analysis on a 2.6 GHz dual core Pentium computer in batch mode. ▶ Figure 4A summarizes the pooled mean estimates for sensitivity and specificity of the fixed-effects versions of the meta-analytic models ($r = 1$, $P = 0$, standard deviation (SD) of residuals = 0). ▶ Figure 4B presents the corresponding standard errors of the pooled sensitivity and specificity ($r = 1$, $P = 0$, SD of residuals = 0). The results of both fixed-effects models are identical. ▶ Figure 5A shows that the pooled mean estimates of both random-effects models are nearly identical ($r = 0.999$, $P < 0.001$, SD of residuals = 0.016). ▶ Figure 5B indicates that the corresponding standard errors are not all identical, but any differences are small ($r = 0.999$, $P < 0.001$, SD of residuals = 0.010). In summary, the bivariate GLIMMIX approach can be used instead of the indirect HSROC NLMIXED approach for calculating fixed-effects or random-effects summary estimates of sensitivity and specificity.

7. Discussion

Diagnostic tests are valuable elements of the clinical diagnosis. In a screening population a diagnostic test intends to identify patients before they become symptomatic. In symptomatic patients a diagnostic test supports the differential diagnosis and allows to assess the extend of a disease. However, similar to traditional diagnostic tests such as inspection and palpation, any other diagnostic test may also not be expected to be completely perfect. To judge the probability that a diagnostic test has given a true result it is necessary to know the accuracy of that test [70]. The diagnostic test accuracy is often assessed by several studies. A meta-analysis intends to quantitatively summarize such primary studies to obtain pooled test accuracy estimates that are more globally valid than the results of one local study.

Most meta-analyses of diagnostic test accuracy studies report their results as bivariate

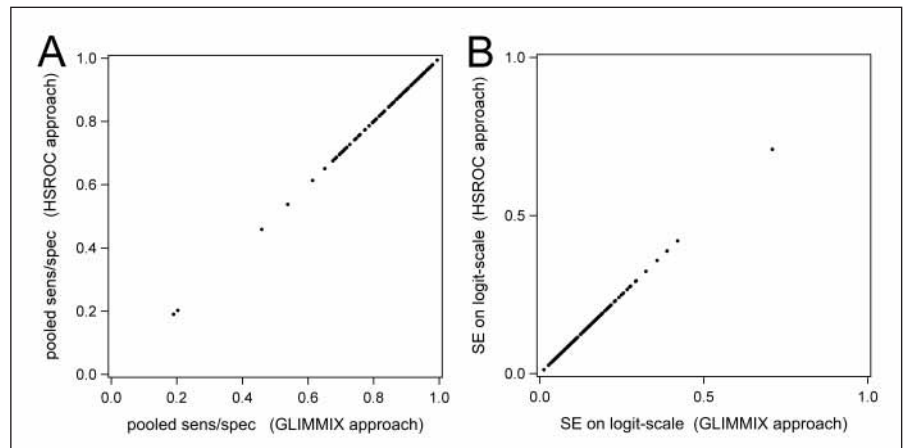


Fig. 4 Comparing fixed-effects models of the bivariate and the HSROC approach. Bivariate summary estimates of 50 meta-analyses: A) pooled mean sensitivities and specificities on the original probability scale; B) their standard errors (SE) on the logit scale

pairs of sensitivity and specificity [20–69]. Sensitivity and specificity are based on binomial 2×2 count data. The binomial distribution is a discrete distribution that approaches the Gaussian normal distribution only with large numbers. However, often the primary studies comprise small 2×2 numbers. PROC GLIMMIX implements a *generalized* linear mixed model (GLMM, Section 2.2) and considers the binomial distribution. Therefore, PROC GLIMMIX is in principle more appropriate for bivariate meta-analysis of sensitivity and specificity than PROC MIXED that implements a linear mixed model (LMM, Section 2.1) [8, 11, 71, 72].

Heterogeneity among the primary studies is a further issue to consider in a

meta-analysis. The reported sensitivities and specificities of the primary studies usually differ, at least because of sampling errors. However, often there is more dispersion (overdispersion) among the studies' sensitivities and/or specificities than what may be expected from sampling errors alone [12, 13, 73]. Such excessive dispersion is termed "heterogeneity" and can be assessed by the Q-test and the I^2 -statistics that are provided by the free meta-analysis program Meta-DiSc [74, 75].

Heterogeneity may arise from unknown differences in the study populations or other factors. A random-effects model accounts for such differences among the primary studies. By its covariance matrix it

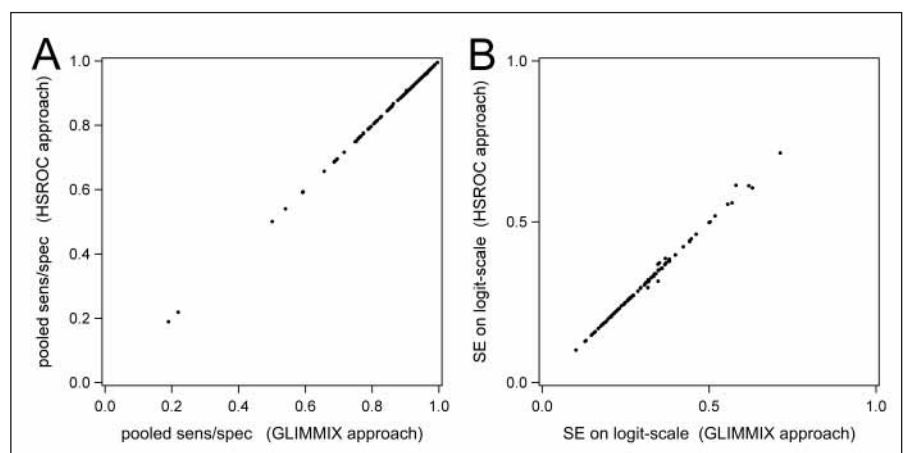


Fig. 5 Comparing random-effects models of the bivariate and the HSROC approach. Bivariate summary estimates of 50 meta-analyses: A) pooled mean sensitivities and specificities on the original probability scale; B) their standard errors (SE) on the logit scale

also accounts for a possible correlation between sensitivity and specificity on the study level [6]. A fixed-effects model is closely related to the random-effects model. It can be regarded as a special case of a random-effects model with the random effects being zero [3]. However, many meta-analyses observe some heterogeneity among their primary studies and thus apply a random-effects model [12, 13].

The HSROC approach (►Appendix E) accounts for random effects and belongs to the more rigorous meta-analytic methods [3, 6, 10, 76]. Macaskill has shown that the empirical Bayes estimates for sensitivity and specificity from the HSROC NLMIXED approach agree closely with those of a full Bayesian analysis [3, 10]. The HSROC approach models the 2×2 count data of the primary studies in terms of diagnostic accuracy (alpha) and threshold (theta). The additional scale parameter (beta) provides for asymmetry in the summary ROC curve by allowing accuracy to vary with threshold [3]. However, most meta-analyses prefer to report their results in terms of sensitivity and specificity [20–69]. With the formulae given by Harbord et al. the HSROC approach can be used to calculate the pooled sensitivity and specificity indirectly [6].

This study has shown that the bivariate GLIMMIX approach offers a straightforward alternative to the indirect HSROC approach. The empirical evaluation of 50 meta-analyses has shown that the results of both meta-analytic approaches are very similar, although being calculated with seemingly different models. Thus the presented GLIMMIX approach has the same accuracy as the indirect HSROC approach. The direct modeling of sensitivity and specificity may be considered an advantage of the bivariate GLIMMIX approach. A further advantage of the GLIMMIX approach is its brief program code that appears to be more comprehensible and more structured than the code of the indirect HSROC NLMIXED approach (►Appendix B to E).

This study is limited to comparing the bivariate GLIMMIX approach and the indirect HSROC NLMIXED approach, which are mathematically equivalent approaches for the bivariate meta-analysis of

sensitivity and specificity [6]. In the empirical evaluation of the 50 meta-analyses (Section 6) the computational performance of these both SAS implementations was similar with fast numerical convergence in all cases [20–69]. A comparison with the different other published meta-analytic approaches was beyond the scope of this study [2, 3, 5, 8–14].

This article has introduced the generalized linear mixed model with PROC GLIMMIX for bivariate random-effects meta-analysis of sensitivity and specificity. The model can also be used for fixed-effects meta-analysis as shown in Sections 4 to 6. Furthermore, the bivariate GLIMMIX approach can be used to obtain the HSROC results when utilizing the equations of Harbord et al. [6]. The results from the bivariate GLIMMIX approach can be applied with the RevMan program to plot bivariate summary estimates and SROC curves, as shown in ►Figure 3 [19]. Among further applications are the bivariate meta-regression and the bivariate comparison of different index tests. For these purposes the PROC MIXED codes of van Houwelingen et al. and Reitsma et al. can be well adapted to the PROC GLIMMIX syntax [2, 5].

In summary, a generalized linear random-effects model with PROC GLIMMIX offers a straightforward method for bivariate meta-analysis of sensitivity and specificity, and is thus an alternative to the closely related indirect HSROC approach.

References

1. Armitage P, Berry G. Statistical methods in medical research. 3rd edition. Oxford: Blackwell Science; 1994.
2. van Houwelingen HC, et al. Advanced methods in meta-analysis: multivariate approach and meta-regression. *Stat Med* 2002; 21: 589–624.
3. Macaskill P. Empirical Bayes estimates generated in a hierarchical summary ROC analysis agreed closely with those of a full Bayesian analysis. *J Clin Epidemiol* 2004; 57: 925–932.
4. Wang MC, Bushman BJ. Integrating results through meta-analytic review using SAS software. Cary, NC: SAS Institute Inc.; 1999.
5. Reitsma JB, et al. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. *J Clin Epidemiol* 2005; 58: 982–990.
6. Harbord RM, Deeks JJ, Egger M, Whiting P, Sterne JA. A unification of models for meta-analysis of diagnostic accuracy studies. *Biostatistics* 2007; 8: 239–251.
7. Leeflang MM, Deeks JJ, Gatsonis C, Bossuyt PM. Systematic reviews of diagnostic test accuracy. *Ann Intern Med* 2008; 149: 889–897.
8. van Houwelingen HC, Zwinderman KH, Stijnen T. A bivariate approach to meta-analysis. *Stat Med* 1993; 12: 2273–2284.
9. Komaroff E, Wolfinger RD. Meta-analysis with linear and nonlinear multilevel models using Proc Mixed and Proc Nlmixed. SAS Conference Proceedings: PharmaSUG 2000. <http://www.lexjansen.com/pharmasug/2000/stats/st09.pdf>. Accessed September 3, 2008.
10. Rutter CM, Gatsonis CA. A hierarchical regression approach to meta-analysis of diagnostic test accuracy evaluations. *Stat Med* 2001; 20: 2865–2884.
11. Chu H, Cole SR. Bivariate meta-analysis of sensitivity and specificity with sparse data: a generalized linear mixed model approach. *J Clin Epidemiol* 2006; 59: 1331–1332.
12. Hamon M, Champ-Rigot L, Morello R, Riddell JW, Hamon M. Diagnostic accuracy of in-stent coronary restenosis detection with multislice spiral computed tomography: a meta-analysis. *Eur Radiol* 2008; 18: 217–225.
13. Kwee TC, Kwee RM. Combined FDG-PET/CT for the detection of unknown primary tumors: systematic review and meta-analysis. *Eur Radiol* 2009; 19: 731–744.
14. Kuss O, Gromann C. An exact test for meta-analysis with binary endpoints. *Methods Inf Med* 2007; 46: 662–668.
15. Littell RC, Milliken GA, Stroup WW, Wolfinger RD, Schabenberger O. SAS for mixed models. Second edition. Cary, NC: SAS Institute Inc; 2006.
16. Jones A, Huddleston E. SAS/STAT 9.2 User's Guide. 1st electronic book. Cary, NC: SAS Institute Inc.; 2008. <http://support.sas.com>. Accessed June 27, 2008.
17. Schabenberger O. Introducing the Glimmix procedure for generalized linear mixed models. *SUGI 30 Proceedings* 2005, Paper 196-30. <http://www2.sas.com/proceedings/sugi30/196-30.pdf>. Accessed August 25, 2008.
18. Scheidler J, Hricak H, Yu KK, Subak L, Segal MR. Radiological evaluation of lymph node metastases in patients with cervical cancer. A meta-analysis. *JAMA* 1997; 278: 1096–1101.
19. Review Manager (RevMan) version 5.0.16. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008. <http://www.ccims.net/RevMan/RevMan5>. Accessed October 1, 2008.
20. van Zaane B, Zuithoff NP, Reitsma JB, Bax L, Nierich AP, Moons KG. Meta-analysis of the diagnostic accuracy of transesophageal echocardiography for assessment of atherosclerosis in the ascending aorta in patients undergoing cardiac surgery. *Acta Anaesthesiol Scand* 2008; 52: 1179–1187.
21. Christou MA, Siontis GC, Katritsis DG, Ioannidis JP. Meta-analysis of fractional flow reserve versus quantitative coronary angiography and noninvasive imaging for evaluation of myocardial ischemia. *Am J Cardiol* 2007; 99: 450–456.
22. Geleijnse ML, Krenning BJ, Soliman OI, Nemes A, Galema TW, ten Cate FJ. Dobutamine stress echocardiography for the detection of coronary artery disease in women. *Am J Cardiol* 2007; 99: 714–717.
23. Gisbert JP, Abaira V. Accuracy of Helicobacter pylori diagnostic tests in patients with bleeding peptic

- ulcer: a systematic review and meta-analysis. *Am J Gastroenterol* 2006; 101: 848–863.
24. Gisbert JP, de la Morena F, Abairra V. Accuracy of monoclonal stool antigen test for the diagnosis of *H. pylori* infection: a systematic review and meta-analysis. *Am J Gastroenterol* 2006; 101: 1921–1930.
 25. Rosman AS, Korsten MA. Meta-analysis comparing CT colonography, air contrast barium enema, and colonoscopy. *Am J Med* 2007; 120: 203–210.
 26. Stein PD, Yeakoub AY, Matta F, Sostman HD. 64-slice CT for diagnosis of coronary artery disease: a systematic review. *Am J Med* 2008; 121: 715–725.
 27. Alvarez S, Anorbe E, Alcorta P, Lopez F, Alonso I, Cortes J. Role of sonography in the diagnosis of axillary lymph node metastases in breast cancer: a systematic review. *Am J Roentgenol* 2006; 186: 1342–1348.
 28. Niemann T, Kollmann T, Bongartz G. Diagnostic performance of low-dose CT for the detection of urolithiasis: a meta-analysis. *Am J Roentgenol* 2008; 191: 396–401.
 29. Meijer AB, O YL, Geleijns J, Kroft LJ. Meta-analysis of 40- and 64-MDCT angiography for assessing coronary artery stenosis. *Am J Roentgenol* 2008; 191: 1667–1675.
 30. Jones AE, Fiechtl JF, Brown MD, Ballew JJ, Kline JA. Procalcitonin test in the diagnosis of bacteremia: a meta-analysis. *Ann Emerg Med* 2007; 50: 34–41.
 31. Shiga T, Wajima Z, Apfel CC, Inoue T, Ohe Y. Diagnostic accuracy of transesophageal echocardiography, helical computed tomography, and magnetic resonance imaging for suspected thoracic aortic dissection: systematic review and meta-analysis. *Arch Intern Med* 2006; 166: 1350–1356.
 32. Vanhoenacker PK, Decramer I, Bladt O, Sarno G, Bevernage C, Wijns W. Detection of non-ST-elevation myocardial infarction and unstable angina in the acute setting: meta-analysis of diagnostic performance of multi-detector computed tomographic angiography. *BMC Cardiovasc Disord* 2007; 7: 39.
 33. Vanhoenacker PK, Decramer I, Bladt O, Sarno G, van Hul E, Wijns W, Dwamena BA. Multidetector computed tomography angiography for assessment of in-stent restenosis: meta-analysis of diagnostic performance. *BMC Med Imaging* 2008; 8: 14.
 34. Pewsner D, Juni P, Egger M, Battaglia M, Sundstrom J, Bachmann LM. Accuracy of electrocardiography in diagnosis of left ventricular hypertrophy in arterial hypertension: systematic review. *BMJ* 2007; 335: 711.
 35. van Vliet EP, Heijenbrok-Kal MH, Hunink MG, Kuipers EJ, Siersema PD. Staging investigations for oesophageal cancer: a meta-analysis. *Br J Cancer* 2008; 98: 547–557.
 36. Vestergaard ME, Macaskill P, Holt PE, Menzies SW. Dermoscopy compared with naked eye examination for the diagnosis of primary melanoma: a meta-analysis of studies performed in a clinical setting. *Br J Dermatol* 2008; 159: 669–676.
 37. Jiang J, Shi HZ, Liang QL, Qin SM, Qin XJ. Diagnostic value of interferon-gamma in tuberculous pleurisy: a metaanalysis. *Chest* 2007; 131: 1133–1141.
 38. Jing JY, Huang TC, Cui W, Xu F, Shen HH. Should FEV1/FEV6 replace FEV1/FVC ratio to detect airway obstruction? A metaanalysis. *Chest* 2009; 135: 991–998.
 39. Pfeiffer CD, Fine JB, Safdar N. Diagnosis of invasive aspergillosis using a galactomannan assay: a meta-analysis. *Clin Infect Dis* 2006; 42: 1417–1427.
 40. Leeftang MM, Debets-Ossenkopp YJ, Visser CE, Scholten RJ, Hooft L, Bijlmer HA, Reitsma JB, Bossuyt PM, Vandenbroucke-Grauls CM. Galactomannan detection for invasive aspergillosis in immunocompromised patients. *Cochrane Database Syst Rev* 2008; 4: CD007394.
 41. Purkayastha S, Tekkis PP, Athanasiou T, Tilney HS, Darzi AW, Heriot AG. Diagnostic precision of magnetic resonance imaging for preoperative prediction of the circumferential margin involvement in patients with rectal cancer. *Colorectal Dis* 2007; 9: 402–411.
 42. de Bondt RB, Nelemans PJ, Hofman PA, Casselman JW, Kremer B, van Engelshoven JM, Beets-Tan RG. Detection of lymph node metastases in head and neck cancer: a meta-analysis comparing US, USgFNAC, CT and MR imaging. *Eur J Radiol* 2007; 64: 266–272.
 43. Lameris W, van Randen A, Bipat S, Bossuyt PM, Boermeester MA, Stoker J. Graded compression ultrasonography and computed tomography in acute colonic diverticulitis: meta-analysis of test accuracy. *Eur Radiol* 2008; 18: 2498–2511.
 44. Liu JL, Wyatt JC, Deeks JJ, Clamp S, Keen J, Verde P, Ohmann C, Wellwood J, Dawes M, Altman DG. Systematic reviews of clinical decision tools for acute abdominal pain. *Health Technol Assess* 2006; 10 (47): 1–167.
 45. Martin JL, Williams KS, Abrams KR, Turner DA, Sutton AJ, Chapple C, Assassa RP, Shaw C, Cheater F. Systematic review and evaluation of methods of assessing urinary incontinence. *Health Technol Assess* 2006; 10 (6): 1–132.
 46. Arbyn M, Sankaranarayanan R, Muwonge R, Keita N, Dolo A, Mbalawa CG, Nouhou H, Sakande B, Wesley R, Somanathan T, Sharma A, Shastri S, Basu P. Pooled analysis of the accuracy of five cervical cancer screening tests assessed in eleven studies in Africa and India. *Int J Cancer* 2008; 123: 153–160.
 47. Ewald B, Ewald D, Thakkinstian A, Attia J. Meta-analysis of B type natriuretic peptide and N-terminal pro B natriuretic peptide in the diagnosis of clinical heart failure and population screening for left ventricular systolic dysfunction. *Intern Med J* 2008; 38: 101–113.
 48. Virgili G, Menchini F, Dimastrogiovanni AF, Rapizzi E, Menchini U, Bandello F, Chiodini RG. Optical coherence tomography versus stereoscopic fundus photography or biomicroscopy for diagnosing diabetic macular edema: a systematic review. *Invest Ophthalmol Vis Sci* 2007; 48: 4963–4973.
 49. Hamon M, et al. Diagnostic performance of multi-slice spiral computed tomography of coronary arteries as compared with conventional invasive coronary angiography: a meta-analysis. *J Am Coll Cardiol* 2006; 48: 1896–1910.
 50. Nandalur KR, et al. Diagnostic performance of stress cardiac magnetic resonance imaging in the detection of coronary artery disease: a meta-analysis. *J Am Coll Cardiol* 2007; 50: 1343–1353.
 51. Morisson P, Neves DD. Evaluation of adenosine deaminase in the diagnosis of pleural tuberculosis: a Brazilian meta-analysis. *J Bras Pneumol* 2008; 34: 217–224.
 52. Gu P, Huang G, Chen Y, Zhu C, Yuan J, Sheng S. Diagnostic utility of pleural fluid carcinoembryonic antigen and CYFRA 21-1 in patients with pleural effusion: a systematic review and meta-analysis. *J Clin Lab Anal* 2007; 21: 398–405.
 53. Houssami N, et al. Accuracy and surgical impact of magnetic resonance imaging in breast cancer staging: systematic review and meta-analysis in detection of multifocal and multicentric cancer. *J Clin Oncol* 2008; 26: 3248–3258.
 54. Terasawa T, et al. Fluorine-18-Fluorodeoxyglucose Positron Emission Tomography for Interim Response Assessment of Advanced-Stage Hodgkin's Lymphoma and Diffuse Large B-Cell Lymphoma: A Systematic Review. *J Clin Oncol*. 2009; 27 (11): 1906–1914.
 55. Morselli-Labate AM, Pezzilli R. Usefulness of serum IgG4 in the diagnosis and follow up of autoimmune pancreatitis: A systematic literature review and meta-analysis. *J Gastroenterol Hepatol* 2009; 24: 15–36.
 56. Sanders S, Barnett A, Correa-Velez I, Coulthard M, Doust J. Systematic review of the diagnostic accuracy of C-reactive protein to detect bacterial infection in nonhospitalized infants and children with fever. *J Pediatr* 2008; 153: 570–574.
 57. Met R, et al. Diagnostic performance of computed tomography angiography in peripheral arterial disease: a systematic review and meta-analysis. *JAMA* 2009; 301: 415–424.
 58. Wang P, et al. A meta-analysis of the accuracy of prostate cancer studies which use magnetic resonance spectroscopy as a diagnostic tool. *Korean J Radiol* 2008; 9: 432–438.
 59. Wardlaw JM, et al. Non-invasive imaging compared with intra-arterial angiography in the diagnosis of symptomatic carotid stenosis: a meta-analysis. *Lancet* 2006; 367: 1503–1512.
 60. Vos MJ, et al. Systematic review of the diagnostic accuracy of 201Tl single photon emission computed tomography in the detection of recurrent glioma. *Nucl Med Commun* 2007; 28: 431–439.
 61. Dong MJ, et al. Role of fluorodeoxyglucose-PET versus fluorodeoxyglucose-PET/computed tomography in detection of unknown primary tumor: a meta-analysis of the literature. *Nucl Med Commun* 2008; 29: 791–802.
 62. Doria AS, et al. US or CT for Diagnosis of Appendicitis in Children and Adults? A Meta-Analysis. *Radiology* 2006; 241: 83–94.
 63. Heijenbrok-Kal MH, et al. Lower extremity arterial disease: multidetector CT angiography meta-analysis. *Radiology* 2007; 245: 433–439.
 64. Hamon M, et al. Coronary arteries: diagnostic performance of 16- versus 64-section spiral CT compared with invasive coronary angiography – meta-analysis. *Radiology* 2007; 245: 720–731.
 65. Peters NH, et al. Meta-analysis of MR imaging in the diagnosis of breast lesions. *Radiology* 2008; 246: 116–124.
 66. Horsthuis K, Bipat S, Bennink RJ, Stoker J. Inflammatory bowel disease diagnosed with US, MR, scintigraphy, and CT: meta-analysis of prospective studies. *Radiology* 2008; 247: 64–79.
 67. Shi HZ, et al. Diagnostic value of carcinoembryonic antigen in malignant pleural effusion: a meta-analysis. *Respirology* 2008; 13: 518–527.
 68. Al-Khayal KA, Al-Omran MA. Computed tomography and ultrasonography in the diagnosis of equivocal acute appendicitis. A meta-analysis. *Saudi Med J* 2007; 28: 173–180.

69. Des Guetz G, et al. Is sentinel lymph node mapping in colorectal cancer a future prognostic factor? A meta-analysis. *World J Surg* 2007; 31: 1304–1312.
70. Gerke O, Vach W, Hoiland-Carlsen PE. PET/CT in cancer: Methodological considerations for comparative diagnostic phase II studies with paired binary data. *Methods Inf Med* 2008; 47: 470–479.
71. Reitsma JB, Zwinderman AH. Response to Chu and Cole: Bivariate meta-analysis of sensitivity and specificity with sparse data. *J Clin Epidemiol* 2006; 59: 1332–1333.
72. Hamza TH, van Houwelingen HC, Stijnen T. The binomial distribution of meta-analysis was preferred to model within-study variability. *J Clin Epidemiol* 2008; 61: 41–51.
73. Cronin P, et al. Solitary pulmonary nodules and masses: a meta-analysis of the diagnostic utility of alternative imaging tests. *Eur Radiol* 2008; 18: 1840–1856.
74. Higgins JP, et al. Measuring inconsistency in meta-analyses. *BMJ* 2003; 327: 557–560.
75. Meta-DiSc version 1.4. <http://www.hrc.es/investigacion/metadisc.html>. Accessed June 2, 2008.
76. Harbord RM, et al. An empirical comparison of methods for meta-analysis of diagnostic accuracy showed hierarchical models are necessary. *J Clin Epidemiol* 2008; 61: 1095–1103.

Appendix

```
ods html body='output.htm' style=statistical;
/*****
/* A. Data Files
/*****
%let nStudies = 17;
%let n_minus1 = 16;
/* n_minus1 is used for degrees of freedom in fixed-effects
   models to accomplish for the fact that LAG_bidata contains 34
   records although these represent only 17 different studies.
   In the random-effects models this is automatically considered
   by the 'random ... subject=study' statements. */
DATA LAG_data;
length author $20;
input number author $ year TP FP FN TN;
RP=TP+FN; RN=TN+FP;
study = _N_;
datalines;
 1 Kindermann 1970 19 1 10 81
 2 Lecart      1971 8 9 2 13
 3 Piver       1971 41 1 12 49
 4 Piver       1973 5 1 2 18
 5 Kolbenstvedt 1975 45 5832165
 6 LemansJr    1975 8 6 2 32
 7 Brown       1979 5 8 1 7
 8 Lagasse     1979 15 17 11 52
 9 Kjorstad    1980 16 11 8 24
10 Ashraf      1982 4 8 2 25
11 deMuylder   1984 8 12 10 70
12 Smales      1986 10 4 4 55
13 Feigen      1987 2 5 6 23
14 Swart       1989 7 10 7 30
15 Heller      1990 44 50 12 135
16 Lafianza    1990 8 3 1 37
17 Stellato    1992 4 3 0 14
;run; PROC PRINT data=LAG_data;run;

DATA LAG_bidata; set LAG_data;
status='A_pos'; true=TP; pos=TP; total=RP; output;
status='B_neg'; true=TN; pos=FP; total=RN; output;
keep study status true pos total; run;
```

```

/*****/
/* B. Bivariate generalized linear fixed-effects model */
/*****/
PROC GLIMMIX data=LAG_bidata method=quad;
title 'Bivariate generalized linear fixed-effects model';
class study status;
model true/total=status/noint s cl corrb covb df=&n_minus1;
estimate 'logit_sens' status 1 0 / cl ilink;
estimate 'logit_spec' status 0 1 / cl ilink;
estimate 'LOR' status 1 1 / cl exp;
run;

/*****/
/* C. Bivariate generalized linear random-effects model */
/*****/
PROC GLIMMIX data=LAG_bidata method=quad;
title 'Bivariate generalized linear random-effects model';
class study status;
model true/total = status / noint s cl corrb covb ddfm=bw;
random status / subject=study S type=chol G;
/* if the model does not converge then replace 'chol' by 'un' */
estimate 'logit_sens' status 1 0 / cl ilink;
estimate 'logit_spec' status 0 1 / cl ilink;
estimate 'LOR' status 1 1 / cl exp;
run;

/*****/
/* D. SROC nonlinear fixed-effects model */
/*****/
PROC NLMIXED data=LAG_bidata tech=quanew df=&n_minus1;
title 'SROC nonlinear fixed-effects model';
parms Theta=0 Alpha=0;
if (status='A_pos') then eta = Theta + Alpha/2;
if (status='B_neg') then eta = Theta - Alpha/2;
pi = exp(eta)/(1+exp(eta));
model pos ~ binomial(total,pi);
/* calculate bivariate parameters */
mu_A = Alpha/2 + Theta;
mu_B = Alpha/2 - Theta;
/* Bivariate model parameters */
estimate 'logit_sens' mu_A;
estimate 'logit_spec' mu_B;
estimate 'LOR' mu_A + mu_B;
estimate 'sens' exp(mu_A)/(1+exp(mu_A));
estimate 'spec' exp(mu_B)/(1+exp(mu_B));
estimate 'DOR' exp(mu_A + mu_B);
run;

```

```

/*****
/* E. HSROC nonlinear random-effects model */
/*****
PROC NL MIXED data=LAG_bidata tech=quanew;
title 'HSROC nonlinear random-effects model';
parms Theta=0 Alpha=0 Beta=0 s2ut=0 s2ua=0;
bounds s2ut >= 0, s2ua >= 0;
if (status='A_pos') then eta = exp(-Beta/2) * (Theta+ut + (Alpha+ua)/2);
if (status='B_neg') then eta = exp( Beta/2) * (Theta+ut - (Alpha+ua)/2);
pi = exp(eta)/(1+exp(eta));
model pos ~ binomial(total,pi);
random ut ua ~ normal([0,0],[s2ut,0,s2ua]) subject=study;
/* calculate bivariate parameters */
mu_A = exp(-Beta/2) * (Alpha/2 + Theta);
mu_B = exp( Beta/2) * (Alpha/2 - Theta);
var_uA = exp(-Beta) * (s2ut + s2ua/4);
var_uB = exp( Beta) * (s2ut + s2ua/4);
cov_uAB = s2ua - s2ut/4;
/* Bivariate model parameters */
estimate 'var_uA' var_uA;
estimate 'var_uB' var_uB;
estimate 'cov_uAB' cov_uAB;
estimate 'logit_sens' mu_A;
estimate 'logit_spec' mu_B;
estimate 'LOR' mu_A + mu_B;
estimate 'sens' exp(mu_A)/(1+exp(mu_A));
estimate 'spec' exp(mu_B)/(1+exp(mu_B));
estimate 'DOR' exp(mu_A + mu_B);
run;

ods html close;

```