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# An one-factor copula mixed model for joint meta-analysis of multiple diagnostic tests

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## Abstract

As meta-analysis of multiple diagnostic tests impacts clinical decision making and patient health, there is an increasing body of research in models and methods for meta-analysis of studies comparing multiple diagnostic tests. The application of the existing models to compare the accuracy of three or more tests suffers from the curse of multi-dimensionality, that is, either the number of model parameters increases rapidly or high dimensional integration is required. To overcome these issues in joint meta-analysis of studies comparing $T > 2$ diagnostic tests in a multiple tests design with a gold standard, we propose a model that assumes the true positives and true negatives for each test are conditionally independent and binomially distributed given the $2T$-variate latent vector of sensitivities and specificities. For the random effects distribution, we employ a one-factor copula that provides tail dependence or tail asymmetry. Maximum likelihood estimation of the model is straightforward as the derivation of the likelihood requires bi-dimensional instead of $2T$-dimensional integration. Our methodology is demonstrated with an extensive simulation study and an application example that determines which is the best test for the diagnosis of rheumatoid arthritis.

**KEYWORDS**

diagnostic tests, factor copulas, mixed models, multivariate meta-analysis, sensitivity/specificity, summary receiver operating characteristic curves

# 1 | INTRODUCTION

The identification of the most accurate diagnostic test for a particular disease contributes to the prevention of unnecessary risks to patients and healthcare costs. Diagnostic test accuracy studies aim to quantify the diagnostic accuracy of a new test in relation to the current perfect reference standard, also known as gold standard.

Clinical and policy decisions are usually made on the basis of the results from many diagnostic test accuracy studies on the same research question. The considerably large number of diagnostic test accuracy studies has led to the use of meta-analysis. The purpose of a meta-analysis of diagnostic test accuracy studies is to combine information over different studies, and provide an integrated analysis that will have more statistical power to detect an accurate diagnostic test than an analysis based on a single study. As the accuracy of a diagnostic test is commonly measured by a pair of indices such as sensitivity and specificity, synthesis of diagnostic test accuracy studies is the most common medical application of multivariate meta-analysis (Jackson et al., 2011). Most of the existing meta-analysis models and methods, when a perfect reference standard is available, have mainly focused on a single test (e.g., Chu & Cole, 2006; Reitsma et al., 2005; Rutter & Gatsonis, 2001).

However, as the understanding of a particular disease increases, along with technological advances, the comparative test accuracy of more than one diagnostic test is of interest. As summarized by Takwoingi et al. (2013), diagnostic test accuracy studies can be comparative when they assess two or more tests or non-comparative when they assess one diagnostic test. Estimates of comparative test accuracy can be obtained from either category of studies, but the ones from the latter category are confounded by the study setting. The robust comparative studies of diagnostic test accuracy use either a multiple test (also called paired or crossover) design, in which all patients undergo all tests together with the perfect reference standard, or more rarely, a randomized (also called parallel) design, in which all patients undergo the perfect reference standard test but are randomly allocated to have only one of the other tests. A multiple test design is statistically much more efficient, in that one needs much smaller sample sizes to detect a given difference in test accuracy, compared with a randomized design.

As meta-analysis of multiple diagnostic tests impacts clinical decision making and patient health, there is an increasing body of research that focuses on the development of meta-analysis models and methods for the synthesis of studies comparing multiple diagnostic tests. Trikalinos et al. (2014) were the first who developed a model for the joint meta-analysis of studies comparing two diagnostic tests in a multiple tests design with a gold standard. They proposed a multinomial generalized linear mixed model (GLMM) which assumes independent multinomial distributions for the counts of each combination of test results in diseased patients and the counts of each combination of test results in non-diseased patients, conditional on the transformed latent true positive rate (TPR) and false positive rate (FPR) for each test, and latent joint TPR and FPR, which capture information on the agreement between the two tests in each study. Dimou et al. (2016) extended the bivariate model of Reitsma et al. (2005), which jointly meta-analyses the study-estimates of sensitivity and specificity for the case of a single test, to the case of two tests. They modelled the transformed study-estimates of TPR and FPR of the two tests using a quadrivariate normal distribution, with the information on the agreement between the two tests incorporated in the calculation of the within-study covariance matrix which is assumed fixed. Nikoloulopoulos (2020c) proposed a multinomial 1-truncated D-vine copula mixed model for the joint meta-analysis of studies comparing two diagnostic tests, which assumes independent multinomial distributions for the counts of each combination of test results in diseased and

non-diseased patients, conditional on the latent vector of probabilities of each combination of test results in diseased and non-diseased patients. Their proposed model includes the multinomial GLMM (Trikalinos et al., 2014) as a special case, but can also operate on the original scale of the latent proportions.

As the information on the agreement between the two tests is usually not available from all the primary studies, Hoyer and Kuss (2018) proposed a model that is solely based on the information from the two (one per test) $2 \times 2$ tables with the number of true positives, true negatives, false negatives and false positives per study. They extended the bivariate generalized mixed model (GLMM) proposed by Chu and Cole (2006) to the quadrivariate case. The proposed quadrivariate GLMM assumes that the true positives and true negatives from the two tests are conditionally independent and binomially distributed given the bivariate latent pairs of transformed sensitivity and specificity, which are quadrivariate normally distributed. Nikoloulopoulos (2019) generalised the quadrivariate GLMM by proposing a model that instead links the four random effects using a quadrivariate D-vine copula rather than the quadrivariate normal distribution.

However, for a particular disease there may be three (or more) diagnostic tests developed, where each of the tests is subject to several studies (e.g., Takwoingi et al., 2013). The extension of the aforementioned models (Dimou et al., 2016; Hoyer & Kuss, 2018; Nikoloulopoulos, 2019, 2020c; Trikalinos et al., 2014) to compare the accuracy of more than two tests suffers from the curse of multi-dimensionality, i.e., either the number of model parameters increases rapidly or high dimensional integration is required. The quadrivariate GLMM (Hoyer & Kuss, 2018) and D-vine copula mixed model (Nikoloulopoulos, 2019) although they can have a moderate number of model parameters, they require $2T$-dimensional integration, where $T$ is the number of tests. The multinomial GLMM (Trikalinos et al., 2014) and 1-truncated D-vine copula mixed model (Nikoloulopoulos, 2020c) that both consider the case the test results are cross-classified do not only require high-dimensional integration, but also their model parameters increase rapidly. For example they have $2(2^T - 1)$ parameters to only model the probabilities of each combination of tests results in diseased and non-diseased patients.

In this paper to overcome the drawbacks in existing models for the joint meta-analysis of studies comparing $T > 2$ diagnostic tests in a multiple test design with a gold standard, we propose a model that assumes the true positives and true negatives for each test are conditionally independent and binomially distributed given the $2T$-variate latent (random) vector of (transformed) sensitivities and specificities. For the random effects distribution, we employ an one-factor copula (Kadhem & Nikoloulopoulos, 2021; Krupskii & Joe, 2013; Nikoloulopoulos & Joe, 2015). The one-factor copula can provide, with appropriately chosen linking copulas, asymmetric dependence structure as well as tail dependence (dependence among extreme values) as it is an 1-truncated C-vine copula (Brechmann et al., 2012) rooted at the latent variable/factor. Joe et al. (2010) have shown that by choosing bivariate linking copulas appropriately, vine copulas can have a flexible range of lower/upper tail dependence, and different lower/upper tail dependence parameters for each bivariate margin. Hence, the factor copula random effects model will be useful when there exists tail asymmetry or tail dependence in the latent sensitivities and specificities, so that the multivariate normality assumption is not valid. With an one-factor copula, dimension reduction is achieved as the dependence among the latent sensitivities and specificities is explained by one other latent variable/factor. Hence, the proposed model has $2T$ dependence parameters instead of $T(2T - 1)$, but more importantly its derivation requires bi-dimensional instead of $2T$-dimensional integration.

The remainder of the paper proceeds as follows. Section 2 introduces the one-factor copula mixed model for the comparison of multiple diagnostic tests in a multiple tests design with

a gold standard and Section 3 discusses its relationship with the $2T$-variate GLMM. Section 4 deduces summary receiver operating characteristic (SROC) curves from the proposed model through quantile regression techniques. Section 5 provides a fast and efficient maximum likelihood (ML) estimation technique based on dependent Gauss-Legendre quadrature points that have an one-factor copula distribution and Section 6 contains small-sample efficiency calculations to investigate the effect of misspecifying the random effects distribution on parameter estimators and standard errors. Section 7 applies our methodology to data from a meta-analysis of diagnostic tests for rheumatoid arthritis. We conclude with some discussion in Section 8, followed by a brief section with software details.

## 2 | THE ONE-FACTOR COPULA MIXED MODEL

We first introduce the notation used in this paper. Let $i$ be an index for the individual studies, $j$ an index for the test outcome (0:negative; 1:positive), $k$ an index for the disease status (0: non-diseased; 1:diseased) and $t$ an index for the diagnostic test. The frequency data $y_{ijkt},\ i = 1, \dots, N,\ j = 0, 1,\ k = 0, 1,\ t = 1, \dots, T$, corresponding to a combination of index test and disease in study $i$ for test $t$, form a $2 \times 2T$ table (Table 1), that is $T$ 'classic' $2 \times 2$ tables. We assume that the gold standard is the same for the $T$ tests, i.e. $y_{i+01} = \cdots = y_{i+0T}$ and $y_{i+11} = \cdots = y_{i+1T}$.

The within-study model assumes that the number of true positives $Y_{i11t}$ and true negatives $Y_{i00t}$ for $t = 1, \dots, T$ are conditionally independent and binomially distributed given $(X_{1t}, X_{0t}) = (x_{1t}, x_{0t})$, where $(X_{1t}, X_{0t})$ denotes the bivariate latent pair of (transformed) sensitivity and specificity for the test $t$. That is

$$\begin{aligned} Y_{i11t}|X_{1t} = x_{1t} &\sim \text{Binomial}\left(y_{i+1t}, l^{-1}(x_{1t})\right); \\ Y_{i00t}|X_{0t} = x_{0t} &\sim \text{Binomial}\left(y_{i+0t}, l^{-1}(x_{0t})\right), \end{aligned} \tag{1}$$

for $t = 1, \dots, T$, where $l(\cdot)$ is a link function. We prefer to use notation that distinguishes unobserved from observed variables. For the observed variables $Y_{i11t}, Y_{i00t}$ we use the index $i$ since they are observed per individual study $i$, but this is not the case for the latent variables (random effects) $X_{1t}, X_{0t}$ and thus we suppress index $i$.

For the between studies model, there are different latent variables $(X_{1t}, X_{0t})$ for each test $t$, but they are dependent. To model the dependence among the latent variables $X_{kt},\ k = 0, 1,\ t = 1, \dots, T$ we employ copulas. A copula is a multivariate cumulative distribution function (cdf) with uniform $U(0, 1)$ margins (Joe, 1997, 2014). The power of copulas for dependence modelling is due to the dependence structure being considered separate from the univariate margins; see, for example, section 1.6 of Joe (1997). For $k = 0, 1$, $t = 1, \dots, T$ denote the univariate cdf of $X_{kt}$ by $F(\cdot; l(\pi_{kt}), \delta_{kt})$, where $\pi_{kt}$ is the meta-analytic parameter of sensitivity ($k = 1$) or specificity ($k = 0$)

**TABLE 1** Data from an individual study in a $2 \times 2T$ table

| | Disease | | | | Disease | | | | Disease | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Test 1** | − | + | … | **Test *t*** | − | + | … | **Test *T*** | − | + |
| − | $y_{i001}$ | $y_{i011}$ | … | − | $y_{i00t}$ | $y_{i01t}$ | … | − | $y_{i00T}$ | $y_{i01T}$ |
| + | $y_{i101}$ | $y_{i111}$ | … | + | $y_{i10t}$ | $y_{i11t}$ | … | + | $y_{i10T}$ | $y_{i11T}$ |
| Total | $y_{i+01}$ | $y_{i+11}$ | … | Total | $y_{i+0t}$ | $y_{i+1t}$ | … | Total | $y_{i+0T}$ | $y_{i+1T}$ |

**TABLE 2** The choices of the $F(\cdot; l(\pi), \delta)$ and $l$ in the one-factor copula mixed model

| $F(\cdot; l(\pi), \delta)$ | $l$ | $\pi$ | $\delta$ |
|---|---|---|---|
| $N(\mu, \sigma)$ | Logit | $l^{-1}(\mu)$ | $\sigma$ |
| Beta$(\pi, \gamma)$ | Identity | $\pi$ | $\gamma$ |

for test $t$, $\delta_{kt}$ is the between-study variability for sensitivity ($k = 1$) or specificity ($k = 0$) for test $t$; the choices of $F(\cdot; l(\pi), \delta)$ and $l$ that are given in Table 2. In multivariate models with copulas, a copula or multivariate uniform distribution is combined with a set of univariate margins. That is, if a $2T$-dimensional parametric family of copulas $C(\cdot; \boldsymbol{\theta})$ is combined with the parametric model $F(\cdot; l(\pi_{kt}), \delta_{kt})$, then

$$C\left(F(x_{11}; l(\pi_{11}), \delta_{11}), \ \dots \ , F(x_{1T}; l(\pi_{1T}), \delta_{1T}), F(x_{01}; l(\pi_{01}), \delta_{01}), \ \dots \ , F(x_{0T}; l(\pi_{0T}), \delta_{0T}); \boldsymbol{\theta}\right)$$

is a multivariate parametric model with univariate margins $F(\cdot; l(\pi_{kt}), \delta_{kt}), \ k = 0, 1, \ t = 1, \dots, T$. This is equivalent to assuming that the latent variables $X_{kt}, \ k = 0, 1, \ t = 1, \dots, T$ have been transformed to standard uniform latent variables $U_{kt} = F(X_{kt}; l(\pi_{kt}), \delta_{kt}), \ k = 0, 1, \ t = 1, \dots, T$. So we assume that $(U_{11}, \dots, U_{1T}, U_{01}, \dots, U_{0T})$ is a random vector with $U_{kt} \sim U(0, 1)$ and joint cdf given by $C(u_{11}, \dots, u_{1T}, u_{01}, \dots, u_{0T}; \boldsymbol{\theta})$. To this end, the stochastic representation of the between studies model takes the form

$$\begin{aligned}&\big(F(X_{11}; l(\pi_{11}), \delta_{11}), \ \dots \ , F(X_{1t}; l(\pi_{1t}), \delta_{1t}), \ \dots \ , F(X_{1T}; l(\pi_{1T}), \delta_{1T}),\\ &F(X_{01}; l(\pi_{01}), \delta_{01}), \ \dots \ , F(X_{0t}; l(\pi_{0t}), \delta_{0t}), \ \dots \ , F(X_{0T}; l(\pi_{0T}), \delta_{0T})\big) \ \sim C(\cdot; \boldsymbol{\theta}).\end{aligned} \tag{2}$$

The models in (1) and (2) together specify a copula mixed model with joint likelihood

$$\begin{aligned}&L(\boldsymbol{\pi}_1, \boldsymbol{\pi}_0, \boldsymbol{\delta}_1, \boldsymbol{\delta}_0, \boldsymbol{\theta})\\ &= \prod_{i=1}^{N} \int_{[0,1]^{2T}} \left\{ \prod_{t=1}^{T} \left[ g\left(y_{i11t}; y_{i+1t}, l^{-1}\left(F^{-1}(u_{1t}; l(\pi_{1t}), \delta_{1t})\right)\right) g\left(y_{i00t}; y_{i+0t}, l^{-1}\left(F^{-1}\left(u_{0t};\right.\right.\right.\right.\\ &\left.\left.\left.\left. l(\pi_{0t}), \delta_{0t}\right)\right)\right)\right] \right\} dC(u_{11}, \dots, u_{1T}, u_{01}, \dots, u_{0T}; \boldsymbol{\theta})\end{aligned} \tag{3}$$

where $g(y; n, \pi) = \binom{n}{y} \pi^y (1 - \pi)^{n-y}, \ y = 0, 1, \dots, n, \ 0 < \pi < 1$, is the binomial probability mass function (pmf). As the joint likelihood in Equation (3) involves $2T$-dimensional numerical integration, we avoid multidimensional integration via an 1-factor copula model to account for the between-studies dependence.

In the one-factor copula model, the latent variables $U_{11}, \dots, U_{1T}, U_{01}, \dots, U_{0T}$ are assumed to be conditionally independent given a univariate latent variable $V \sim U(0, 1)$. The univariate latent variable $V$ drives the dependence between the latent variables $X_{kt}, \ k = 0, 1, \ t = 1, \dots, T$, corresponding to the latent sensitivity ($k = 1$) and latent specificity ($k = 0$) for test $t$. For $k = 0, 1, \ t = 1, \dots, T$ denote the bivariate cdf and density of $(U_{kt}, V)$ by $C_{kt,V}(u_{kt}, v; \theta_{kt})$ and $c_{kt,V}(u_{kt}, v; \theta_{kt}) = \frac{\partial C_{kt,V}(u_{kt}, v; \theta_{kt})}{\partial u_{kt} \partial v}$, respectively, and the conditional copula cdf of $U_{kt}|V$ by $C_{kt|V}(u_{kt}|v; \theta_{kt}) = \Pr(U_{kt} \leq u_{kt}|V = v) = \frac{\partial C_{kt,V}(u_{kt}, v; \theta_{kt})}{\partial v}$; the parameter $\theta_{kt}$ is the bivariate copula parameter, denoting the association between $X_{kt}$ and the latent variable $V$, and is separated

from the marginal parameters $\pi_{kt}, \delta_{kt}$ as the copula $C_{kt,V}(u_{kt}, v; \theta_{kt})$ associated with the latent pair $(X_{kt}, V)$ is invariant by monotone increasing transformations of the margins. Then, the $2T$-dimensional one-factor copula cdf and density with dependence parameter vector $\boldsymbol{\theta} = (\theta_{11}, \ldots, \theta_{1t}, \ldots, \theta_{1T}, \theta_{01}, \ldots, \theta_{0t}, \ldots, \theta_{0T})$ are

$$C(u_{11}, \ldots, u_{1t}, \ldots, u_{1T}, u_{01}, \ldots, u_{0t}, \ldots, u_{0T}; \boldsymbol{\theta}) = \int_0^1 \prod_{t=1}^{T} C_{1t|V}(u_{1t}|v; \theta_{1t}) C_{0t|V}(u_{0t}|v; \theta_{0t}) dv, \quad (4)$$

and

$$c(u_{11}, \ldots, u_{1t}, \ldots, u_{1T}, u_{01}, \ldots, u_{0t}, \ldots, u_{0T}; \boldsymbol{\theta}) = \int_0^1 \prod_{t=1}^{T} c_{1t,V}(u_{1t}, v; \theta_{1t}) c_{0t,V}(u_{0t}, v; \theta_{0t}) dv, \quad (5)$$

respectively (Krupskii & Joe, 2013). It is seen that the $2T$-variate density/cdf decomposes in an one-dimensional integral of a product of $2T$ bivariate copula densities/cdfs. Using the one-factor copula density in Equation (5) the joint likelihood in Equation (3) takes the form

$$\begin{aligned}
&L(\boldsymbol{\pi}_1, \boldsymbol{\pi}_0, \boldsymbol{\delta}_1, \boldsymbol{\delta}_0, \boldsymbol{\theta}) \\
&= \prod_{i=1}^{N} \int_{[0,1]^{2T}} \left\{ \prod_{t=1}^{T} \left[ g\left( y_{i11t}; y_{i+1t}, l^{-1}\left( F^{-1}\left( u_{1t}; l(\pi_{1t}), \delta_{1t} \right) \right) \right) g\left( y_{i00t}; y_{i+0t}, l^{-1}\left( F^{-1}\left( u_{0t}; \right. \right. \right. \right. \right. \\
&\quad \left. \left. \left. \left. \left. l(\pi_{0t}), \delta_{0t} \right) \right) \right) \right] \int_0^1 \left\{ \prod_{t=1}^{T} \left[ c_{1t,V}(u_{1t}, v; \theta_{1t}) c_{0t,V}(u_{0t}, v; \theta_{0t}) \right] \right\} dv \right\} du_{11}, \ldots, du_{1T}\, du_{01}, \ldots, du_{0T} \\
&= \prod_{i=1}^{N} \int_0^1 \left\{ \prod_{t=1}^{T} \left[ \int_0^1 \left\{ g\left( y_{i11t}; y_{i+1t}, l^{-1}\left( F^{-1}\left( u_{1t}; l(\pi_{1t}), \delta_{1t} \right) \right) \right) c_{1t,V}(u_{1t}, v; \theta_{1t}) \right\} du_{1t} \right. \right. \\
&\quad \left. \left. \int_0^1 \left\{ g\left( y_{i00t}; y_{i+0t}, l^{-1}\left( F^{-1}\left( u_{0t}; l(\pi_{0t}), \delta_{0t} \right) \right) \right) c_{0t,V}(u_{0t}, v; \theta_{0t}) \right\} du_{0t} \right] \right\} dv. \qquad (6)
\end{aligned}$$

It is shown that the joint likelihood is represented as an one-dimensional integral of a function which in turn is a product of $2T$ one-dimensional integrals. As a result, $2T$-dimensional numerical integration has been avoided.

In addition to the computational advancements the proposed model offers, it can provide, with appropriately chosen linking copulas, asymmetric dependence structure as well as tail dependence. The one-factor copula can be explained as an 1-truncated C-vine rooted at the latent variable $V$ (Kadhem & Nikoloulopoulos, 2021; Krupskii & Joe, 2013; Nikoloulopoulos & Joe, 2015). $2T$-dimensional C-vine copulas can cover flexible dependence structures through the specification of $2T$ bivariate marginal copulas at level 1 and $T(2T-1)$ bivariate conditional copulas at higher levels (Nikoloulopoulos et al., 2012). For the $2T$-dimensional one-factor copula, the pairs at level 1 are $V, U_{kt}$, for $k = 0, 1$, $t = 1, \ldots, T$, and for higher levels the (conditional) copula pairs are set to independence. That is the 1-factor copula has $2T$ bivariate copulas $C_{kt,V}(\cdot; \theta_{kt})$ that link $U_{kt}$, $k = 0, 1$, $t = 1, \ldots, T$ with $V$ in the 1st level of the vine and independence copulas in all the remaining levels of the vine (truncated after the 1st level). Figure 1 depicts the graphical representation of the 1-factor copula model. Joe et al. (2010) have shown that in order for a vine copula to have (tail) dependence for all bivariate margins, it is only necessary for the bivariate copulas in level 1 to have (tail) dependence and it is not necessary for the conditional bivariate copulas

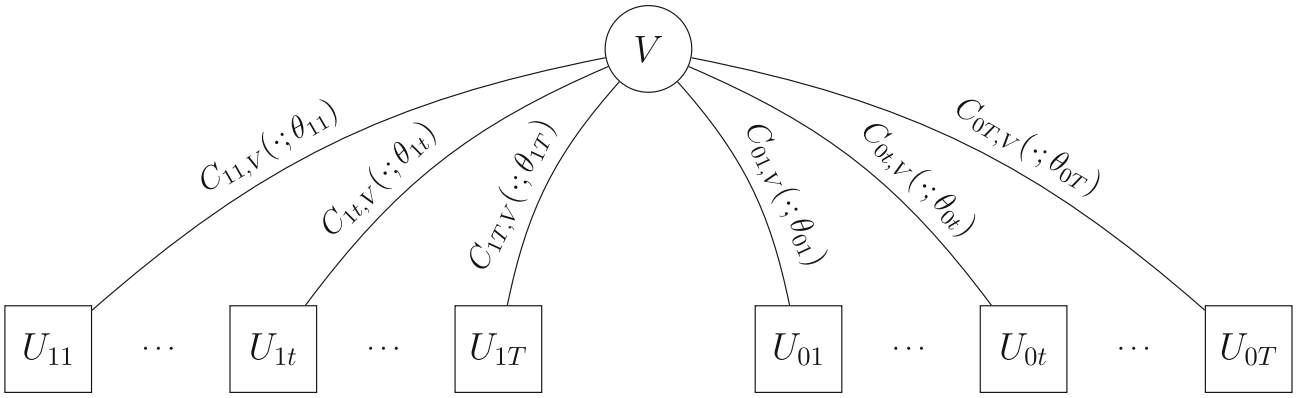


**FIGURE 1** Graphical representation of the 1-factor copula model which consists on $2T + 1$ nodes with the latent variables $V, U_{kt} = F(X_{kt}),\ k = 0, 1,\ t = 1, \ldots, T$ and $2T$ edges. Each edge is allied with a copula $C_{kt,V}(;\theta_{kt})$ associated with the latent pair $(X_{kt}, V)$ with $\theta_{kt}$ being the bivariate copula parameter denoting the association between $X_{kt}$, corresponding to the latent sensitivity ($k = 1$) and latent specificity ($k = 0$) for each test $t$, and the latent variable $V$

in levels $2, \ldots, 2T$ to have (tail) dependence. Hence, the (tail) dependence between the latent variable $V$ and each of the latent variables $U_{kt},\ k = 0, 1,\ t = 1, \ldots, T$ is inherited to the (tail) dependence between the latent variables $U_{kt},\ k = 0, 1,\ t = 1, \ldots, T$, i.e., between the untransformed latent variables $X_{kt},\ k = 0, 1,\ t = 1, \ldots, T$, corresponding to the latent sensitivity ($k = 1$) and latent specificity ($k = 0$) for test $t$, through the dependence invariance property of copulas.

## 3 | RELATIONSHIP WITH THE $2T$-VARIATE GLMM

We show what happens when all the bivariate copulas $C_{kt,V}(;\theta_{kt})$ are BVN and the univariate distribution of the random effects is the $N(\mu, \sigma)$ distribution.

One can easily deduce that the within-study model in (1) is the same as in the $2T$-variate GLMM. Furthermore, when $C_{kt,V}(;\theta_{kt})$ are all BVN copulas, then (4) becomes the copula of the multivariate normal distribution with an one-factor correlation structure. Let $C_{kt,V}(;\theta_{kt})$ be the BVN copula with correlation parameter $\theta_{kt}$. Let $\Phi$ and $\phi$ denote the standard normal cdf and density function, and let $\Phi_2(\cdot;\rho)$ be the BVN cdf with correlation $\rho$. Then $C_{kt,V}(u, v) = \Phi_2(\Phi^{-1}(u), \Phi^{-1}(v); \theta_{kt})$ and $C_{kt|V}(u|v) = \Phi\left(\frac{\Phi^{-1}(u)-\theta_{kt}\Phi^{-1}(v)}{\sqrt{1-\theta_{kt}^2}}\right)$. For (4), let $u_{kt} = \Phi(z_{kt})$, where $z_{kt} = \frac{x_{kt}-l(\pi_{kt})}{\sigma_{kt}}$, to get a $2T$-variate distribution with $N(0, 1)$ margins. Then

$$
\begin{aligned}
&C\big(\Phi(z_{11}), \ldots, \Phi(z_{1t}), \ldots, \Phi(z_{1T}), \Phi(z_{01}), \ldots, \Phi(z_{0t}), \ldots, \Phi(z_{0T}); \boldsymbol{\theta}\big) \\
&= \int_0^1 \prod_{t=1}^{T} \left\{ \Phi\left( \frac{z_{1t} - \theta_{1t}\Phi^{-1}(v)}{\sqrt{1-\theta_{1t}^2}} \right) \Phi\left( \frac{z_{0t} - \theta_{0t}\Phi^{-1}(v)}{\sqrt{1-\theta_{0t}^2}} \right) \right\} dv \\
\text{or}\quad &C\left(\Phi(z_{11}), \ldots, \Phi(z_{1t}), \ldots, \Phi(z_{1T}), \Phi(z_{01}), \ldots, \Phi(z_{0t}), \ldots, \Phi(z_{0T}); \boldsymbol{\theta}\right) \\
&= \int_{-\infty}^{\infty} \prod_{t=1}^{T} \left\{ \Phi\left( \frac{z_{1t} - \theta_{1t} w}{\sqrt{1-\theta_{1t}^2}} \right) \Phi\left( \frac{z_{0t} - \theta_{0t} w}{\sqrt{1-\theta_{0t}^2}} \right) \right\} \phi(w) dw. \qquad (7)
\end{aligned}
$$

This model is the same as the $2T$-variate normal model with an one-factor correlation structure

$$\mathbf{R} = \begin{pmatrix} 1 & \cdots & \rho_{11,1T} & \rho_{11,01} & \cdots & \rho_{11,0T} \\ \vdots & \ddots & \vdots & \vdots & \vdots & \vdots \\ \rho_{1T,11} & \cdots & 1 & \rho_{1T,01} & \cdots & \rho_{1T,0T} \\ \rho_{01,11} & \cdots & \rho_{01,1T} & 1 & \cdots & \rho_{1T,0T} \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ \rho_{0T,11} & \cdots & \rho_{0T,1T} & \rho_{0T,01} & \cdots & 1 \end{pmatrix}$$

with

$$\rho_{k_1t_1,k_2t_2} = \theta_{k_1t_1}\theta_{k_2t_2}, \quad k_1, k_2 = 0, 1,\ t_1, t_2 = 1, \ldots, T. \tag{8}$$

This occurs because the multivariate cdf in Equation (7) comes from the representation

$$Z_{kt} = \frac{X_{kt} - l(\pi_{kt})}{\sigma_{kt}} = \theta_{kt}W + \sqrt{1-\theta_{kt}^2}\epsilon_{kt}, \quad k = 0, 1,\ t = 1, \ldots, T, \tag{9}$$

where $W, \epsilon_{kt}$ are i.i.d. $N(0, 1)$ random variables (Krupskii & Joe, 2013; Nikoloulopoulos & Joe, 2015) and the partial correlation $\rho_{k_1t_1,k_2t_2|W} = \frac{\rho_{k_1t_1,k_2t_2} - \theta_{k_1t_1}\theta_{k_2t_2}}{\sqrt{1-\theta_{k_1t_1}^2}\sqrt{1-\theta_{k_2t_2}^2}}$ is zero due to the assumption of conditional independence. As we assume conditional independence a structured correlation matrix is exploited with $2T$ instead of $T(2T-1)$ correlation parameters.

The resulting random effects distribution for $(X_{11}, \ldots, X_{1t}, \ldots, X_{1T}, X_{01}, \ldots, X_{0t}, \ldots, X_{0T})$ is the $2T$-variate normal distribution with mean vector $\boldsymbol{\mu} = (l(\boldsymbol{\pi}_1), l(\boldsymbol{\pi}_0))$ and variance-covariance matrix

$$\boldsymbol{\Sigma} = \begin{pmatrix} \sigma_{11}^2 & \cdots & \theta_{11}\theta_{1T}\sigma_{11}\sigma_{1T} & \theta_{11}\theta_{01}\sigma_{11}\sigma_{01} & \cdots & \theta_{11}\theta_{0T}\sigma_{11}\sigma_{0T} \\ \vdots & \ddots & \vdots & \vdots & \vdots & \vdots \\ \theta_{1T}\theta_{11}\sigma_{1T}\sigma_{11} & \cdots & \sigma_{1T}^2 & \theta_{1T}\theta_{01}\sigma_{1T}\sigma_{01} & \cdots & \theta_{1T}\theta_{0T}\sigma_{1T}\sigma_{0T} \\ \theta_{01}\theta_{11}\sigma_{01}\sigma_{11} & \cdots & \theta_{01}\theta_{1T}\sigma_{01}\sigma_{1T} & \sigma_{01}^2 & \cdots & \theta_{1T}\theta_{0T}\sigma_{1T}\sigma_{0T} \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ \theta_{0T}\theta_{11}\sigma_{0T}\sigma_{11} & \cdots & \theta_{0T}\theta_{1T}\sigma_{0T}\sigma_{1T} & \theta_{0T}\theta_{01}\sigma_{0T}\sigma_{01} & \cdots & \sigma_{0T}^2 \end{pmatrix}$$

Hence, the proposed model has as special case the $2T$-variate GLMM with an one-factor correlation structure that has a latent additive structure as seen in Equation (9). Nevertheless, if other bivariate copulas are used, then the one-factor copula mixed model has a latent structure that is non-additive.

## 4 | SUMMARY RECEIVER OPERATING CHARACTERISTIC CURVES

Though typically the focus of meta-analysis has been to derive the summary-effect estimates, there is increasing interest in alternative summary outputs, such as summary receiver operating

characteristic (SROC) curves (e.g., Arends et al., 2008; Rücker & Schumacher, 2009). For the $2T$-variate GLMM in the preceding section with the linear additive structure and dependence, the SROC curve can be obtained through a characterization of the estimated BVN margin by a line (Chu & Guo, 2009; Chu et al., 2010, 2012). Therefore, the model parameters control the shape of the GLMM SROC curve which is restricted to be linear. Our general statistical model allows for selection of bivariate copulas and univariate margins independently, i.e., there are no constraints in the choices of parametric bivariate copulas and univariate margins, hence can allow for a non-linear shape of the SROC curves.

In line with our previous contributions in copula mixed models (Nikoloulopoulos, 2015, 2017, 2018a, 2018b, 2019, 2020a, 2020b, 2020c) in addition to the BVN copula with intermediate tail dependence, we use Frank with tail independence and Clayton with positive lower tail dependence. For the latter we also use its rotated versions to provide negative upper-lower tail dependence (Clayton rotated by 90°), positive upper tail dependence (Clayton rotated by 180°) and negative lower-upper tail dependence (Clayton rotated by 270°). We next proceed with the derivation of the SROC curves from the one-factor copula mixed model. For the one-factor copula mixed model, the univariate parameters $\pi_{kt}, \delta_{kt},\ k = 0, 1,\ t = 1, \ldots, T$, the copula parameters $\theta_{kt},\ k = 0, 1,\ t = 1, \ldots, T$, the choice of the copula, and the choice of the univariate margin will affect the shape of the SROC curves.

Let the joint cdf of $(U_{1t}, U_{0t})$ be given by the copula $C_{1t,0t}(\cdot; \theta_{1t,0t})$. The copula parameters $\theta_{1t,0t},\ t = 1, \ldots, T$ can be derived using the following steps:

1. Convert the copula parameters $\theta_{1t}$ and $\theta_{0t}$ of Frank or (rotated) Clayton copulas to Kendall's $\tau_{1t}$ and $\tau_{0t}$ via the relations

$$\tau = \begin{cases} 1 - 4\theta^{-1} - 4\theta^{-2}\int_{\theta}^{0} \frac{t}{e^t - 1} dt, & \theta < 0 \\ 1 - 4\theta^{-1} + 4\theta^{-2}\int_{0}^{\theta} \frac{t}{e^t - 1} dt, & \theta > 0 \end{cases}, \tag{10}$$

   or

$$\tau = \begin{cases} \theta/(\theta + 2), & \text{by } 0^\circ \text{ or } 180^\circ \\ -\theta/(\theta + 2), & \text{by } 90^\circ \text{ or } 270^\circ \end{cases}, \tag{11}$$

   in Genest (1987), or Genest and MacKay (1986), respectively.
2. Convert the Kendall's $\tau_{1t}$ and $\tau_{0t}$ to BVN copula parameters $\theta_{1t}$ and $\theta_{0t}$ using the inverse of the relation

$$\tau = \frac{2}{\pi} \arcsin(\theta), \tag{12}$$

   in Hult and Lindskog (2002).
3. Convert the BVN copula parameters $\theta_{1t}$ and $\theta_{0t}$ to the correlation parameter $\rho_{1t,0t}$ via the relation in Equation (8).
4. Convert the correlation parameter $\rho_{1t,0t}$ to Kendall's $\tau_{1t,0t}$ via the relation (12).
5. Convert the Kendall's $\tau_{1t,0t}$ to the copula parameter $\theta_{1t,0t}$ of Frank or (rotated) Clayton copula via the inverses of the relations in Equations (10) or (11).

For the special case, when all the bivariate copulas are BVN, step 3 is sufficient to get the BVN copula parameter $\theta_{1t,0t} = \rho_{1t,0t}$.

Then, the SROC curves for the latent pair $(X_{1t}, X_{0t})$ for test $t$ can be deduced through the quantile regression techniques proposed by Nikoloulopoulos (2015):

1. Set $C_{1t|0t}(u_{1t}|u_{0t}; \theta_{1t,0t}) = q$;
2. Solve for the quantile regression curve $u_{1t} := \tilde{u}_{1t}(u_{0t}, q; \theta_{1t,0t}) = C^{-1}_{1t|0t}(q|u_{0t}; \theta_{1t,0t})$;
3. Replace $u_{kt}$ by $F(x_{kt}; l(\pi_{kt}), \delta_{kt})$;
4. Plot $x_{1t} := \tilde{x}_{1t}(x_{0t}, q)$ versus $x_{0t}$.

As there is no priori reason to regress $X_{1t}$ on $X_{0t}$ instead of the other way around (Arends et al., 2008), quantile regression curves of $X_{0t}$ on $X_{1t}$ are also derived in a similar manner. We use the median regression curves ($q = 0.5$), along with the quantile regression curves with a focus on high ($q = 0.99$) and low quantiles ($q = 0.01$), which are strongly associated with the upper and lower tail dependence, respectively, imposed from each parametric family of bivariate copulas. These can be seen as confidence regions, as per the terminology in Rücker and Schumacher (2009), of the median regression curves. Finally, in order to reserve the nature of a bivariate response instead of a univariate response along with a covariate, we plot the corresponding contour graph of the bivariate copula density. The contour plot can be seen as the predictive region (analogously to Reitsma et al., 2005) of the estimated pair $(\pi_{1t}, \pi_{0t})$ of the meta-analytic parameters of sensitivity and specificity at test $t$.

To depict the different shapes of the SROC curves that are related to the tail dependence behaviour of each parametric bivariate copula, in Figure 2 we plot the SROC curves and summary

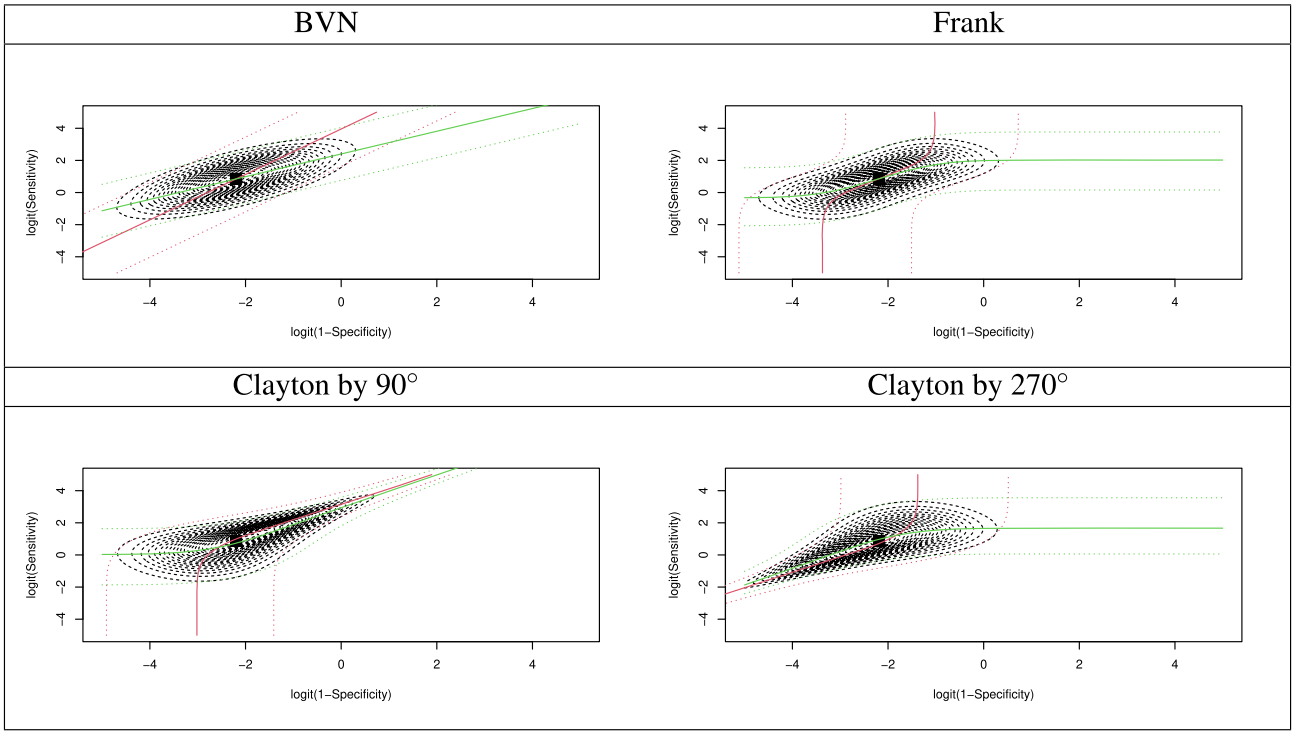


**FIGURE 2** Summary receiver operating characteristic curves and summary operating points at $(\pi_{1t}, 1 - \pi_{0t})$ along with their confidence and predictive regions from the one-factor copula mixed model with BVN, Frank, Clayton by 90° and 270° copulas and normal margins with the same model parameters $\{\pi_{1t} = 0.7, \pi_{0t} = 0.9, \sigma_{1t} = 1, \sigma_{0t} = 1, \tau_{1t,0t} = -0.5\}$ for test $t$. ■: summary operating point; red and green lines represent the quantile regression curves $x_{1t} := \tilde{x}_{1t}(x_{0t}, q)$ and $x_{0t} := \tilde{x}_{0t}(x_{1t}, q)$, respectively; for $q = 0.5$ solid lines and for $q \in \{0.01, 0.99\}$ dotted lines (confidence region) [Colour figure can be viewed at wileyonlinelibrary.com]

operating points at $(\pi_{1t}, 1-\pi_{0t})$ along with their confidence and predictive regions from the one-factor copula mixed model with BVN, Frank, Clayton by 90° and 270° copulas and normal margins with the same model parameters $\left\{\pi_{1t}=0.7, \pi_{0t}=0.9, \sigma_{1t}=2, \sigma_{0t}=1, \tau_{1t,0t}=-0.5\right\}$ for test $t$. Since the copula parameter $\theta_{1t,0t}$ of each family has different range, we use the Kendall's $\tau_{1t,0t}$ in order to be the same among the different parametric bivariate copulas. It is shown that as the form of the copulas changes, typically the middle part of the SROC is similar as they have the same dependence in the middle ($\tau_{1t,0t}=-0.5$), but differs more for extreme values of the latent sensitivity and specificity because of different tail behaviour of the bivariate copulas. The SROC curve and its confidence region from the one-factor copula mixed model with BVN copulas and normal margins are represented by lines and the shape of the predictive region is elliptical. Other bivariate copulas provide non-elliptical shapes and the relationship between the latent sensitivity and specificity is non-linear. Sharper corners of the predictive region (relative to ellipse) indicate tail dependence.

## 5 | MAXIMUM LIKELIHOOD ESTIMATION AND COMPUTATIONAL DETAILS

The parameters $(\pi_{11}, \dots, \pi_{1t}, \dots, \pi_{1T}) := \boldsymbol{\pi}_1$ and $(\pi_{01}, \dots, \pi_{0t}, \dots, \pi_{0T}) := \boldsymbol{\pi}_0$ denote the meta-analytic parameters for the sensitivities and specificities, respectively, while the univariate parameters $(\delta_{11}, \dots, \delta_{1t}, \dots, \delta_{1T}) := \boldsymbol{\delta}_1$ and $(\delta_{01}, \dots, \delta_{0t}, \dots, \delta_{0T}) := \boldsymbol{\delta}_0$ denote the between-study variabilities for the sensitivities and specificities, respectively. The parameter vector $\boldsymbol{\theta}$ of the random effects model is separated from the univariate parameters $\boldsymbol{\pi}_1, \boldsymbol{\pi}_0, \boldsymbol{\delta}_1, \boldsymbol{\delta}_0$ as the random effects model is an 1-factor copula model with dependence parameter vector $\boldsymbol{\theta}$ that does not involve the parameters of the within-studies model $\boldsymbol{\pi}_1, \boldsymbol{\pi}_0, \boldsymbol{\delta}_1, \boldsymbol{\delta}_0$. Estimation of the model parameters $(\boldsymbol{\pi}_1, \boldsymbol{\pi}_0, \boldsymbol{\delta}_1, \boldsymbol{\delta}_0, \boldsymbol{\theta})$ can be approached by the standard maximum likelihood (ML) method, by maximizing the logarithm of the joint likelihood in Equation (3). The estimated parameters can be obtained by using a quasi-Newton (Nash, 1990) method applied to the logarithm of the joint likelihood. This numerical method requires only the objective function, i.e., the logarithm of the joint likelihood, while the gradients are computed numerically and the Hessian matrix of the second order derivatives is updated in each iteration. The standard errors (SE) of the ML estimates can be also obtained via the gradients and the Hessian computed numerically during the maximization process.

For one-factor copula mixed models of the form with joint likelihood as in Equation (3), numerical evaluation of the joint pmf can be achieved with the following steps:

1. Calculate Gauss-Legendre (Stroud & Secrest, 1966) quadrature points $\{u_q : q=1, \dots, N_q\}$ and weights $\{w_q : q=1, \dots, N_q\}$ in terms of standard uniform.
2. Numerically evaluate the joint pmf

$$\int_0^1 \left\{ \prod_{t=1}^{T} \left[ \int_0^1 \left\{ g\left(y_{i11t}; y_{i+1t}, l^{-1}\left(F^{-1}\left(u_{1t}; l(\pi_{1t}), \delta_{1t}\right)\right)\right) c_{1t,V}(u_{1t}, v; \theta_{1t}) \right\} du_{1t} \right. \right.$$

$$\left. \left. \int_0^1 \left\{ g\left(y_{i00t}; y_{i+0t}, l^{-1}\left(F^{-1}\left(u_{0t}; l(\pi_{0t}), \delta_{0t}\right)\right)\right) c_{0t,V}(u_{0t}, v; \theta_{0t}) \right\} du_{0t} \right] \right\} dv$$

in a double sum:

$$\sum_{q_1=1}^{N_q}\left\{w_{q_1}\prod_{t=1}^{T}\left[\sum_{q_2=1}^{N_q}\left\{w_{q_2}g\left(y_{i11t};y_{i+1t},l^{-1}\left(F^{-1}\left(C^{-1}_{1t|V}(u_{q_2}|u_{q_1};\theta_{1t});l(\pi_{1t}),\delta_{1t}\right)\right)\right)\right\}\right.\right.$$
$$\left.\left.\sum_{q_2=1}^{N_q}\left\{w_{q_2}g\left(y_{i00t};y_{i+0t},l^{-1}\left(F^{-1}\left(C^{-1}_{0t|V}(u_{q_2}|u_{q_1};\theta_{0t});l(\pi_{0t}),\delta_{0t}\right)\right)\right)\right\}\right]\right\},$$

where $C^{-1}_{kt|V}(u|v;\theta_{kt})$ is the inverse conditional bivariate copula cdf. Note that the independent quadrature points $\{u_{q_1} : q_1 = 1, \dots, N_q\}$ and $\{u_{q_2} : q_2 = 1, \dots, N_q\}$ have been converted to dependent quadrature points that have an one-factor copula distribution $C(\cdot;\boldsymbol{\theta})$.

With Gauss-Legendre quadrature, the same nodes and weights are used for different functions; this helps in yielding smooth numerical derivatives for numerical optimization via quasi-Newton (Nash, 1990). Our one-factor copula mixed model for meta-analysis of multiple diagnostic tests is straightforward computationally as it requires the calculation of a double summation over the quadrature points.

## 6 | SMALL-SAMPLE EFFICIENCY—MISSPECIFICATION OF THE RANDOM EFFECTS DISTRIBUTION

In this section, we study the small-sample efficiency and robustness of the ML estimation of the one-factor copula mixed model. In Section 6.1, we gauge the small-sample efficiency of the ML method in Section 5 and investigate the misspecification of either the parametric margin or bivariate copula of the random effects distribution. In Section 6.2, we investigate the mixed model misspecification by using the D-vine copula mixed model proposed by Nikoloulopoulos (2019) as the true model. That is we include a sensitivity analysis to the conditional independence assumption.

### 6.1 | Misspecification of the parametric margin or bivariate pair-copulas

We randomly generate 10,000 meta-analysis data sets with $N = \{10, 20, 50\}$ studies in each data set from an one-factor copula mixed model with both normal and beta margins that jointly meta-analyses $T = \{2, 3, 4\}$ diagnostic tests.

The simulation process is as below:

1. Simulate $(u_{11}, \dots, u_{1T}, u_{01}, \dots, u_{0T})$ from an one-factor copula $C(;\boldsymbol{\tau})$; $\boldsymbol{\tau}$ is converted to the copula parameter vector $\boldsymbol{\theta}$ of Frank, (rotated) Clayton or BVN copulas via the inverses of the relations in Equations (10) and (11 or 12), respectively.
2. For each test $t$ in $1, \dots, T$ convert to proportions via

$$x_{1t} = l^{-1}\left(F^{-1}\left(u_{1t};l(\pi_{1t}),\delta_{1t}\right)\right)$$
$$x_{0t} = l^{-1}\left(F^{-1}\left(u_{0t};l(\pi_{0t}),\delta_{0t}\right)\right).$$

3. Simulate the study size $n$ from a shifted gamma distribution, i.e., $n \sim$ sGamma ($\alpha = 1.2$, $\beta = 0.01$, lag $= 30$) and round off to the nearest integer.
4. Draw the number of diseased $n_1$ from a $B(n, 0.4)$ distribution and set $n_0 = n - n_1$.
5. For each test $t$ in 1, … , $T$ generate $y_{11t}$ and $y_{00t}$ from a $B(n_1, x_{1t})$ and $B(n_0, x_{0t})$ distribution, respectively, and set $y_{01t} = n_1 - y_{11t}, y_{10t} = n_0 - y_{00t}$.

Representative summaries of findings on the performance of the ML method in Section 5 are given in Table 3 and Supplementary Table 1 for 6-dimensional ($T = 3$) one-factor copula models with normal and beta margins, respectively. The true (simulated) bivariate copulas are the Clayton and the Clayton copula rotated by 270° to handle the positive and negative dependencies, respectively. True sensitivity $\boldsymbol{\pi}_1$ and specificity $\boldsymbol{\pi}_0$ vectors are (0.8, 0.7, 0.8) and (0.7, 0.8, 0.7), respectively, the variability parameter vectors are $\boldsymbol{\delta}_1 = \boldsymbol{\delta}_0 = (1, 1, 1)$ or $\boldsymbol{\delta}_1 = \boldsymbol{\delta}_0 = (0.1, 0.1, 0.1)$ for normal or beta margin, respectively, and the Kendall's $\boldsymbol{\tau} = (0.6, 0.7, 0.5, -0.3, -0.4, -0.2)$. Under each margin, 10,000 meta-analysis data sets are simulated with $N = 50$ studies in each data set. We have estimated the one-factor copula mixed model with different bivariate copulas and margins. Table 3 and Supplementary Table 1 contain the resultant biases, root mean square errors (RMSEs) and standard deviations (SDs), along with average standard errors (ASEs), scaled by 100, for the MLEs under different copula choices and margins. The standard errors of the MLEs are obtained via the gradients and the Hessian that were computed numerically during the maximization process.

Conclusions from the values in Table 1 and Supplementary Table 1 are the following:

- ML with the true one-factor copula mixed model is highly efficient according to the simulated biases, SDs and RMSEs.
- The MLEs of $\boldsymbol{\pi}_1, \boldsymbol{\pi}_0$ are not robust to margin misspecification, e.g., in Table 3 (Supplementary Table 1) where the true univariate margins are normal (beta) the scaled biases for the MLEs of $\pi_{02}$ for the various one-factor copula mixed models with beta (normal) margins range from −4.16 (3.21) to −1.86 (4.70).
- The MLEs of $\boldsymbol{\pi}_1, \boldsymbol{\pi}_0$ are rather robust to bivariate copula misspecification, but their biases increase when the assumed bivariate copulas have different tail dependence behaviour. For example, in Table 3 (Supplementary Table 1) the scaled biases for the MLEs of $\pi_{11}$ for the various one-factor copula mixed models with normal (beta) margins increase to −1.38 (−0.92) and −3.71 (−2.27) when rotated Clayton copulas with opposite direction tail dependence and Frank copulas with tail independence, respectively, are called.
- The MLEs of $\boldsymbol{\delta}_1, \boldsymbol{\delta}_0$ are rather robust to bivariate copula misspecification, but their biases increase when the assumed bivariate copula has tail dependence of opposite direction from the true bivariate copula. For example, in Table 3 (Supplementary Table 1) the scaled biases for the MLEs of $\sigma_{02}$ ($\gamma_{02}$) for the various one-factor copula mixed models with normal (beta) margins range from −0.83 (−0.25) to 1.75 (0.05), but the scaled bias increases to 6.85 (1.01) when rotated Clayton copulas with opposite direction tail dependence are called.
- The ML estimates of $\tau$'s are robust to margin misspecification, as the copula remains invariant under any series of strictly increasing transformations of the components of the random vector, for example, in Table 3 the scaled bias of $\hat{\tau}_{13}$ is 1.81 for the true one-factor copula mixed model and 1.57 for an one-factor copula mixed model with the true bivariate copulas but beta margins.

**TABLE 3** Simulation results when 10,000 meta-analysis data sets are generated with $N = 50$ studies in each data set from the one-factor copula mixed model with Clayton and Clayton rotated by 270° copulas to handle the positive and negative dependencies, respectively and normal margins

| | Margin | Copula | $\pi_{11}$ | $\pi_{12}$ | $\pi_{13}$ | $\pi_{01}$ | $\pi_{02}$ | $\pi_{03}$ | $\sigma_{11}$ | $\sigma_{12}$ | $\sigma_{13}$ | $\sigma_{01}$ | $\sigma_{02}$ | $\sigma_{03}$ | $\tau_{11}$ | $\tau_{12}$ | $\tau_{13}$ | $\tau_{01}$ | $\tau_{02}$ | $\tau_{03}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Bias | Normal | BVN | −0.35 | −0.43 | −0.32 | −0.03 | 0.04 | −0.04 | −3.56 | −2.72 | −2.94 | −0.43 | 0.61 | −0.83 | 4.93 | 1.94 | 4.88 | −2.01 | −1.45 | −1.75 |
| | | **Cln** {0°, 270°} | **−0.31** | **−0.40** | **−0.31** | **0.05** | **0.08** | **0.02** | **−0.83** | **−0.91** | **−0.76** | **−0.96** | **−0.83** | **−0.97** | **2.49** | **2.59** | **1.81** | **−0.75** | **−1.26** | **−0.46** |
| | | Cln {180°, 90°} | −1.38 | −1.98 | −1.12 | 0.30 | 0.50 | 0.08 | 3.64 | 6.30 | 3.37 | 3.70 | 6.85 | 1.46 | 4.27 | 3.31 | −0.07 | 5.52 | 7.56 | 3.65 |
| | | Frank | −3.71 | −4.92 | −3.42 | 2.40 | 2.28 | 1.64 | 0.70 | 1.48 | 0.48 | 0.64 | 1.75 | −0.16 | 6.42 | 3.70 | 6.36 | −3.32 | −3.67 | −2.43 |
| | Beta | BVN | −3.99 | −3.25 | −4.01 | −3.38 | −4.16 | −3.33 | – | – | – | – | – | – | 5.80 | 2.63 | 5.81 | −1.43 | −0.16 | −1.39 |
| | | Cln {0°, 270°} | −4.28 | −3.57 | −4.31 | −3.21 | −3.92 | −3.24 | – | – | – | – | – | – | 2.85 | 3.46 | 1.57 | −0.08 | 0.07 | −0.20 |
| | | Cln {180°, 90°} | −5.42 | −5.02 | −5.21 | −3.28 | −4.14 | −3.30 | – | – | – | – | – | – | 4.59 | 3.71 | 0.59 | 6.71 | 9.89 | 4.73 |
| | | Frank | −7.03 | −7.04 | −6.82 | −1.21 | −1.86 | −1.88 | – | – | – | – | – | – | 6.89 | 3.92 | 6.87 | −2.63 | −2.90 | −1.85 |
| SD | Normal | BVN | 2.51 | 3.25 | 2.50 | 3.13 | 2.45 | 3.14 | 12.50 | 12.18 | 12.55 | 12.09 | 12.79 | 11.84 | 12.28 | 13.01 | 11.35 | 11.24 | 11.30 | 11.54 |
| | | **Cln** {0°, 270°} | **2.55** | **3.31** | **2.55** | **3.15** | **2.47** | **3.16** | **12.30** | **11.77** | **12.35** | **11.79** | **12.21** | **11.75** | **12.46** | **13.93** | **10.67** | **10.39** | **10.78** | **10.34** |
| | | Cln {180°, 90°} | 2.90 | 3.77 | 2.84 | 3.29 | 2.59 | 3.23 | 16.30 | 16.66 | 15.73 | 14.17 | 15.81 | 13.12 | 21.58 | 22.46 | 17.94 | 12.96 | 13.73 | 13.30 |
| | | Frank | 3.58 | 4.49 | 3.52 | 3.65 | 2.81 | 3.53 | 14.00 | 13.67 | 13.91 | 12.54 | 13.28 | 12.13 | 11.93 | 12.00 | 11.71 | 12.02 | 11.98 | 12.19 |
| | Beta | BVN | 2.46 | 2.86 | 2.46 | 2.77 | 2.44 | 2.79 | 2.82 | 2.91 | 2.84 | 2.83 | 2.85 | 2.79 | 11.16 | 11.62 | 10.56 | 10.52 | 10.24 | 11.06 |
| | | Cln {0°, 270°} | 2.54 | 2.95 | 2.56 | 2.81 | 2.48 | 2.82 | 2.91 | 2.85 | 2.91 | 2.71 | 2.65 | 2.75 | 12.13 | 13.44 | 10.50 | 9.67 | 9.89 | 9.88 |
| | | Cln {180°, 90°} | 2.92 | 3.31 | 2.87 | 2.81 | 2.47 | 2.82 | 3.82 | 4.12 | 3.71 | 3.28 | 3.47 | 3.02 | 20.57 | 21.25 | 16.83 | 12.63 | 13.24 | 12.91 |
| | | Frank | 3.47 | 3.88 | 3.43 | 3.10 | 2.63 | 3.06 | 3.35 | 3.40 | 3.32 | 2.86 | 2.83 | 2.82 | 10.82 | 10.45 | 10.89 | 11.41 | 11.19 | 11.86 |

**TABLE 3** (Continued)

| | Margin | Copula | $\pi_{11}$ | $\pi_{12}$ | $\pi_{13}$ | $\pi_{01}$ | $\pi_{02}$ | $\pi_{03}$ | $\sigma_{11}$ | $\sigma_{12}$ | $\sigma_{13}$ | $\sigma_{01}$ | $\sigma_{02}$ | $\sigma_{03}$ | $\tau_{11}$ | $\tau_{12}$ | $\tau_{13}$ | $\tau_{01}$ | $\tau_{02}$ | $\tau_{03}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ASE | Normal | BVN | 2.40 | 3.09 | 2.41 | 3.08 | 2.40 | 3.07 | 11.73 | 11.43 | 11.93 | 11.36 | 11.85 | 11.22 | 10.09 | 11.13 | 9.26 | 9.47 | 9.25 | 9.86 |
| | | **Cln** $\{0°, 270°\}$ | **2.32** | **2.95** | **2.34** | **2.95** | **2.25** | **2.99** | **10.79** | **10.39** | **11.08** | **10.77** | **10.95** | **10.86** | **10.47** | **12.64** | **9.04** | **8.59** | **8.86** | **8.83** |
| | | Cln $\{180°, 90°\}$ | 2.66 | 3.45 | 2.64 | 3.18 | 2.48 | 3.14 | 13.57 | 13.52 | 13.50 | 12.68 | 13.58 | 12.18 | 12.37 | 12.28 | 11.66 | 10.17 | 10.23 | 10.75 |
| | | Frank | 2.66 | 3.27 | 2.68 | 3.00 | 2.22 | 3.06 | 12.57 | 12.12 | 12.66 | 11.50 | 12.00 | 11.28 | 9.20 | 9.49 | 9.08 | 9.80 | 9.36 | 10.39 |
| | Beta | BVN | 2.29 | 2.70 | 2.30 | 2.69 | 2.29 | 2.67 | 2.52 | 2.73 | 2.56 | 2.68 | 2.51 | 2.65 | 9.96 | 10.92 | 9.04 | 9.43 | 9.21 | 9.83 |
| | | Cln $\{0°, 270°\}$ | 2.17 | 2.54 | 2.19 | 2.55 | 2.13 | 2.59 | 2.33 | 2.46 | 2.38 | 2.46 | 2.20 | 2.51 | 10.89 | 13.21 | 9.33 | 8.52 | 8.82 | 8.76 |
| | | Cln $\{180°, 90°\}$ | 2.56 | 2.99 | 2.55 | 2.74 | 2.36 | 2.72 | 3.04 | 3.32 | 3.03 | 3.06 | 3.01 | 2.91 | 12.24 | 12.41 | 11.36 | 10.36 | 10.44 | 10.91 |
| | | Frank | 2.45 | 2.77 | 2.48 | 2.60 | 2.10 | 2.65 | 2.79 | 2.96 | 2.80 | 2.64 | 2.42 | 2.60 | 9.22 | 9.65 | 9.05 | 9.86 | 9.47 | 10.44 |
| RMSE | Normal | BVN | 2.54 | 3.28 | 2.52 | 3.13 | 2.45 | 3.14 | 13.00 | 12.48 | 12.89 | 12.10 | 12.80 | 11.87 | 13.23 | 13.16 | 12.36 | 11.42 | 11.39 | 11.67 |
| | | **Cln** $\{0°, 270°\}$ | **2.57** | **3.33** | **2.57** | **3.15** | **2.47** | **3.16** | **12.33** | **11.81** | **12.37** | **11.83** | **12.24** | **11.79** | **12.70** | **14.17** | **10.82** | **10.42** | **10.85** | **10.35** |
| | | Cln $\{180°, 90°\}$ | 3.21 | 4.26 | 3.05 | 3.31 | 2.64 | 3.23 | 16.70 | 17.81 | 16.09 | 14.64 | 17.22 | 13.20 | 22.00 | 22.70 | 17.94 | 14.08 | 15.67 | 13.80 |
| | | Frank | 5.15 | 6.66 | 4.91 | 4.37 | 3.62 | 3.89 | 14.02 | 13.75 | 13.91 | 12.56 | 13.39 | 12.13 | 13.55 | 12.56 | 13.32 | 12.47 | 12.53 | 12.43 |
| | Beta | BVN | 4.69 | 4.33 | 4.70 | 4.37 | 4.83 | 4.34 | – | – | – | – | – | – | 12.58 | 11.91 | 12.05 | 10.62 | 10.24 | 11.14 |
| | | Cln $\{0°, 270°\}$ | 4.97 | 4.63 | 5.01 | 4.27 | 4.64 | 4.29 | – | – | – | – | – | – | 12.46 | 13.88 | 10.62 | 9.67 | 9.89 | 9.88 |
| | | Cln $\{180°, 90°\}$ | 6.15 | 6.01 | 5.95 | 4.32 | 4.83 | 4.34 | – | – | – | – | – | – | 21.08 | 21.57 | 16.84 | 14.30 | 16.53 | 13.75 |
| | | Frank | 7.84 | 8.03 | 7.64 | 3.33 | 3.23 | 3.59 | – | – | – | – | – | – | 12.82 | 11.16 | 12.88 | 11.71 | 11.56 | 12.00 |

The biases, root mean square errors (RMSEs) and standard deviations (SDs), along with average standard errors (ASEs) for the MLEs are boldfaced under the true model and scaled by 100 under the various copula choices and margins; Cln $\{\omega_1^\circ, \omega_2^\circ\}$: The bivariate copulas are the Clayton rotated by $\omega_1^\circ$ and $\omega_2^\circ$ to handle the positive and negative dependencies, respectively; $N_q = 25$ quadrature points have been used.

**TABLE 4** Number of times each fitted one-factor copula mixed model under different copula choices and margins has been selected when 10,000 meta-analysis data sets are generated with $N = 50$ studies in each data set from the one-factor copula mixed model with Clayton and Clayton rotated by 270° copulas to handle the positive and negative dependencies, respectively and normal or beta margins

| | | True (simulated) margin | |
|---|---|---|---|
| **Margin** | **Copula** | **Normal** | **Beta** |
| Normal | BVN | 184 | 43 |
| | Cln $\{0°, 270°\}$ | **8125** | 1518 |
| | Cln $\{180°, 90°\}$ | 0 | 1 |
| | Frank | 80 | 18 |
| Beta | BVN | 58 | 221 |
| | Cln $\{0°, 270°\}$ | 1508 | **8040** |
| | Cln $\{180°, 90°\}$ | 0 | 1 |
| | Frank | 45 | 158 |

The numbers of correct choices are boldfaced; Cln $\{\omega_1^\circ, \omega_2^\circ\}$; The bivariate copulas are the Clayton rotated by $\omega_1^\circ$ and $\omega_2^\circ$ to handle the positive and negative dependencies, respectively.

We have chosen $N = 50$ studies as the chosen number of tests is $T = 3$, i.e., there are $3 \times 2T = 18$ parameters to be estimated. Our summaries agree with what we see in simulated data sets with fewer studies as regard as to main parameters of interest. Nevertheless, the SDs and ASEs for the Kendall's $\tau$'s and variability parameters are larger for smaller sample sizes as $2T$ variability and $2T$ Kendall's $\tau$ parameters have to be estimated on the top of the $2T$ probability parameters that are of the main interest. Trikalinos et al. (2014) also acknowledged these parameters are often not well estimated for small sample sizes.

Because the number of parameters is the same between the models, we can use the log-likelihood at the maximum likelihood estimates as a rough diagnostic measure for model selection between the models. For vine copulas (one-factor copula is an 1-truncated C-vine copula), Dissmann et al. (2013) found that pair-copula selection based on likelihood seems to be better than even using bivariate goodness-of-fit tests. The goodness-of-fit procedures involve a global distance measure between the model-based and empirical distribution, hence they might not be sensitive to tail behaviours and are not diagnostic in the sense of suggesting improved parametric models in the case of small $p$-values (Joe, 2014, p. 254). A larger likelihood value indicates a model that better approximates both the dependence structure of the data and the strength of dependence in the tails. Table 4 presents the number of times each fitted model was chosen over the 10,000 simulation runs and reveals the true (simulated) model has been chosen for a considerable large number of times.

## 6.2 | Misspecification of the copula-mixed model—Sensitivity analysis to the conditional independence

We show a sensitivity analysis to the conditional independence assumption. We randomly generate 10,000 meta-analysis datasets from the D-vine copula mixed model with both normal (Table 5)

**TABLE 5** Simulation results when 10,000 meta-analysis data sets are generated with $N = 22$ studies in each data set from the D-vine copula mixed model with normal margins and Clayton copulas rotated by 270° at level 1 and Clayton copulas at levels 2 and 3

| | Margin | Copula | $\pi_{11}$ | $\pi_{12}$ | $\pi_{01}$ | $\pi_{02}$ | $\sigma_{11}$ | $\sigma_{12}$ | $\sigma_{01}$ | $\sigma_{02}$ |
|---|---|---|---|---|---|---|---|---|---|---|
| Bias | Normal | BVN | −0.07 | −0.29 | −0.21 | −0.05 | −3.29 | −4.01 | −2.07 | −1.70 |
| | | Cln {0°, 270°} | −0.10 | −0.29 | −0.32 | −0.06 | −2.76 | −3.36 | −1.11 | −2.07 |
| | | Cln {180°, 90°} | −0.68 | −0.87 | −0.10 | −0.03 | −0.15 | −1.04 | −0.84 | 0.14 |
| | | Frank | −1.33 | −1.47 | 0.06 | 0.03 | −2.53 | −3.21 | −1.69 | −1.69 |
| | Beta | BVN | −1.58 | −1.71 | −4.31 | −1.22 | – | – | – | – |
| | | Cln {0°, 270°} | −1.64 | −1.75 | −4.46 | −1.24 | – | – | – | – |
| | | Cln {180°, 270°} | −2.39 | −2.50 | −4.08 | −1.16 | – | – | – | – |
| | | Frank | −2.64 | −2.73 | −4.14 | −1.15 | – | – | – | – |
| SD | Normal | BVN | 3.61 | 3.48 | 3.39 | 0.84 | 12.80 | 12.27 | 18.92 | 19.00 |
| | | Cln {0°, 270°} | 3.62 | 3.50 | 3.42 | 0.84 | 12.84 | 12.35 | 19.79 | 19.23 |
| | | Cln {180°, 90°} | 3.89 | 3.76 | 3.49 | 0.86 | 15.16 | 14.69 | 19.73 | 20.00 |
| | | Frank | 4.06 | 3.93 | 3.58 | 0.88 | 13.43 | 12.89 | 19.19 | 19.18 |
| | Beta | BVN | 3.35 | 3.25 | 3.58 | 1.06 | 2.68 | 2.55 | 4.02 | 1.51 |
| | | Cln {0°, 270°} | 3.37 | 3.28 | 3.65 | 1.10 | 2.76 | 2.63 | 4.26 | 1.57 |
| | | Cln {180°, 90°} | 3.72 | 3.62 | 3.61 | 1.09 | 3.38 | 3.23 | 4.11 | 1.62 |
| | | Frank | 3.74 | 3.67 | 3.83 | 1.13 | 2.89 | 2.76 | 4.20 | 1.55 |
| ASE | Normal | BVN | 3.38 | 3.31 | 3.22 | 0.80 | 12.07 | 11.84 | 17.15 | 17.57 |
| | | Cln {0°, 270°} | 3.22 | 3.15 | 3.04 | 0.77 | 10.75 | 10.51 | 15.55 | 16.50 |
| | | Cln {180°, 90°} | 3.26 | 3.19 | 3.15 | 0.81 | 11.78 | 11.55 | 16.34 | 16.85 |
| | | Frank | 3.34 | 3.25 | 3.11 | 0.78 | 11.95 | 11.67 | 16.55 | 17.34 |
| | Beta | BVN | 3.14 | 3.08 | 3.17 | 0.94 | 2.64 | 2.56 | 3.48 | 1.26 |
| | | Cln {0°, 270°} | 2.97 | 2.91 | 2.89 | 0.88 | 2.32 | 2.25 | 3.04 | 1.12 |
| | | Cln {180°, 90°} | 3.04 | 2.98 | 3.06 | 0.95 | 2.57 | 2.47 | 3.31 | 1.25 |
| | | Frank | 3.07 | 3.01 | 3.01 | 0.90 | 2.63 | 2.55 | 3.27 | 1.19 |
| RMSE | Normal | BVN | 3.61 | 3.49 | 3.40 | 0.84 | 13.22 | 12.91 | 19.03 | 19.07 |
| | | Cln {0°, 270°} | 3.62 | 3.51 | 3.43 | 0.85 | 13.14 | 12.80 | 19.82 | 19.34 |
| | | Cln {180°, 90°} | 3.95 | 3.86 | 3.49 | 0.86 | 15.16 | 14.73 | 19.75 | 20.00 |
| | | Frank | 4.27 | 4.19 | 3.58 | 0.88 | 13.67 | 13.28 | 19.27 | 19.25 |
| | Beta | BVN | 3.71 | 3.67 | 5.60 | 1.62 | – | – | – | – |
| | | Cln {0°, 270°} | 3.74 | 3.71 | 5.76 | 1.65 | – | – | – | – |
| | | Cln {180°, 90°} | 4.43 | 4.40 | 5.59 | 1.64 | – | – | – | – |
| | | Frank | 4.58 | 4.57 | 5.64 | 1.61 | – | – | – | – |

The biases, root mean square errors (RMSEs) and standard deviations (SDs), along with average standard errors (ASEs) for the MLEs of the one-factor copula mixed model under different copula choices and margins are scaled by 100; Cln $\{\omega_1^\circ, \omega_2^\circ\}$: The bivariate copulas are the Clayton rotated by $\omega_1^\circ$ and $\omega_2^\circ$ to handle the positive and negative dependencies, respectively; $N_q = 25$ quadrature points have been used.

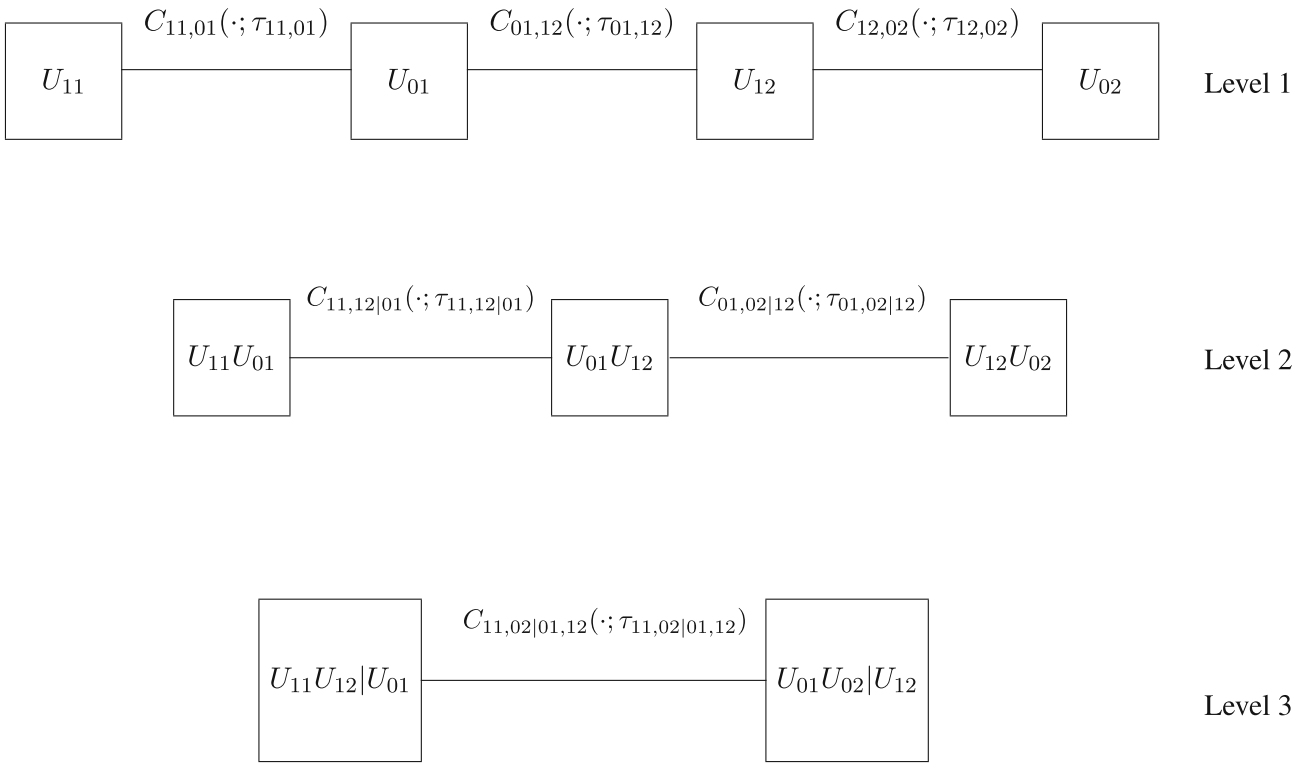


**FIGURE 3** Graphical representation of the 4-dimensional D-vine copula model with 3 levels. Level $\ell$ has $5-\ell$ nodes and $4-\ell$ edges. At level 1 there are three bivariate copulas $C_{11,01}(\cdot;\tau_{11,01})$, $C_{01,12}(\cdot;\tau_{01,12})$ and $C_{12,02}(\cdot;\tau_{12,02})$ associated with the latent pairs $(U_{11},U_{01})$, $(U_{01},U_{12})$ and $(U_{12},U_{02})$ with $\tau_{11,01}$, $\tau_{01,12}$ and $\tau_{12,02}$ being the bivariate copula parameters in Kendall's $\tau$ scale. At level $\ell$ for $\ell=2,3$ there are $4-\ell$ bivariate conditional copulas that condition on $\ell-1$ variables

and beta (Supplementary Table 2) margins for joint meta-analysis and comparison of two diagnostic tests using the algorithm in Nikoloulopoulos (2019). The D-vine copula mixed model assumes full dependence among the tests as the D-vine copula is not truncated, i.e., there are bivariate copulas not only at level 1 of the D-vine. At level 1 there are three bivariate copulas $C_{11,01}(\cdot;\tau_{11,01})$, $C_{01,12}(\cdot;\tau_{01,12})$ and $C_{12,02}(\cdot;\tau_{12,02})$ associated with the latent pairs $(U_{11},U_{01})$, $(U_{01},U_{12})$ and $(U_{12},U_{02})$ with $\tau_{11,01}$, $\tau_{01,12}$ and $\tau_{12,02}$ being the bivariate copula parameters in Kendall's $\tau$ scale. At level $\ell$ for $\ell=2,3$ there are $4-\ell$ bivariate conditional copulas that condition on $\ell-1$ variables and model the conditional dependence. Figure 3 depicts the representation of the D-vine copula model. The true (simulated) D-vine copula mixed model uses Clayton copulas rotated by 270° at level 1 and Clayton copulas at levels 2 and 3.

We set the number of studies $N$, the study size $n$, the disease prevalence, and the true univariate and Kendall's $\tau$ parameters to mimic the rheumatoid arthritis data in Nishimura et al. (2007). True sensitivity $\boldsymbol{\pi}_1$ and specificity $\boldsymbol{\pi}_0$ vectors are (0.679, 0.680) and (0.826, 0.959), respectively, the variability parameter vectors are $\boldsymbol{\delta}_1=(0.711,0.698)$ and $\boldsymbol{\delta}_0=(1.033,0.780)$ or $\boldsymbol{\delta}_1=(0.10,0.10)$ and $\boldsymbol{\delta}_0=(0.15,0.02)$ for normal or beta margin, respectively, and the Kendall's $\tau$'s as shown in Figure 3 are $(\tau_{11,01},\tau_{01,12},\tau_{12,02},\tau_{11,12|01},\tau_{01,02|12},\tau_{11,02|01,12})=(-0.156,-0.115,-0.243,0.597,0.331,0.127)$, as estimated in Nikoloulopoulos (2019) who has previously fitted the D-vine copula mixed model to the rheumatoid arthritis data. Converting the Kendall's $\tau$'s to BVN copula parameters (correlations at level 1 and partial correlations at levels 2 and 3) via the inverse of the relation in (12) and then via the relations in (Joe, 2014, p. 297) to a correlation matrix, viz.,

$$\mathbf{R} = \begin{array}{c} \\ X_{11} \\ X_{01} \\ X_{12} \\ X_{02} \end{array} \begin{array}{c} \begin{array}{cccc} X_{11} & X_{01} & X_{12} & X_{02} \end{array} \\ \begin{pmatrix} 1.00 & -0.24 & 0.81 & -0.26 \\ -0.24 & 1.00 & -0.18 & 0.52 \\ 0.81 & -0.18 & 1.00 & -0.37 \\ -0.26 & 0.52 & -0.37 & 1.00 \end{pmatrix} \end{array}$$

reveals the implied strength of association between the tests.

We have estimated the one-factor copula mixed model with different bivariate copulas and margins. Table 5 and Supplementary Table 2 contain the resultant biases, RMSEs and SDs, along with ASEs, scaled by 100, for the MLEs of the common parameters under different copula choices and margins. The standard errors of the MLEs are obtained via the gradients and the Hessian that were computed numerically during the maximization process. From Table 5 (Supplementary Table 2) it is seen that the one-factor copula mixed model with normal (beta) margins led to unbiased and efficient estimates when the bivariate copulas are a combination of Clayton and rotated Clayton by 270° to model the positive and negative dependencies, respectively. These are the same with the true (simulated) copulas of the D-vine copula mixed model which imply that the sensitivity and specificity of each test have tail dependence. Hence, the tail dependence between the factor $V$ and each of the latent sensitivities/specificities $X_{kt},\ k = 0, 1,\ t = 1, 2$ is inherited to the tail dependence between the latent sensitivities and specificities $X_{kt},\ k = 0, 1,\ t = 1, 2$, and thus, the conditional independence assumption has no impact on the estimation of the meta-analytic parameters of sensitivity and specificity of each test when this assumption is violated. This is due the fact that the one-factor copula can be explained as an 1-truncated C-vine rooted at the factor (Kadhem & Nikoloulopoulos, 2021; Krupskii & Joe, 2013; Nikoloulopoulos & Joe, 2015). Note also that in line with the results in the preceding subsection, the biases of the estimates increase when the assumed bivariate copulas have tail dependence of opposite direction from the true copulas or tail independence. When the BVN copulas with intermediate tail dependence are used to link the factor with the latent sensitivities/specificities, the estimates are robust to misspecification of the copula mixed model as long as the univariate margins are correctly specified.

Finally in order to study the relative performance of the one-factor copula mixed model over the quadrivariate vine copula mixed model as the number of quadrature points increase we randomly generated 20 meta-analysis datasets with $N = 22$ studies in each dataset from the D-vine copula mixed model. The number of studies $N$, the study size $n$, the disease prevalence, and the true univariate and Kendall's $\tau$ parameters are set as in the 10,000 simulation runs. The simulations were carried out on a Broadwell E5-2680 v4@2.40GHz. Table 6 summarizes the computing times (averaged over 20 replications) in seconds. Clearly the D-vine copula mixed approach requires a much higher computing time. Hence it is demonstrated that even for the case of $T = 2$ tests, the computational improvement of the one-factor copula mixed model is substantial, as

**TABLE 6** Average computing times in seconds of the one-factor and quadrivariate D-vine copula mixed approaches for a varying number of quadrature points $N_q$ when 20 meta-analysis data sets are generated with $N = 22$ studies in each data set from the quadrivariate D-vine copula mixed model

| $N_q$ | One-factor | D-vine |
|---|---|---|
| 15 | 35.4 | 799.8 |
| 30 | 65.7 | 7355.4 |
| 50 | 126.2 | 42,997.6 |

one has to calculate numerically bivariate integrals instead of much more difficult quadrivariate integrals.

## 7 | APPLICATION

Nishimura et al. (2007) contacted a systematic review and summarized data of rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibodies for diagnosing rheumatoid arthritis. They included $N = 22$ studies that assessed both RF and anti-CCP2 antibody for diagnosing rheumatoid arthritis and used the 1987 revised American College of Rheumatology (ACR) criteria as the perfect reference standard of rheumatoid arthritis (Arnett et al., 1988). These data have been frequently used as an example for methodological papers on joint meta-analysis of diagnostic accuracy studies in a multiple tests design with a gold standard (e.g., Dimou et al., 2016; Nikoloulopoulos, 2019). Liu et al. (2015) in one of their examples deal with the same data, but as they propose models for the meta-analysis of the accuracy of a diagnostic test under evaluation and an imperfect reference test, they use only the the RF test as the index test for detection of rheumatoid arthritis and assume that the ACR 1987 revised criteria are an imperfect reference test for classification. Their analysis confirmed that the ACR 1987 revised criteria are a prefect reference test as the estimates of sensitivity and specificity of the ACR 1987 criteria (reference test) were 1, suggesting that such reference test is in fact a gold standard.

We use the one-factor copula mixed model in order to determine whether anti-CCP antibody identifies more accurately patients with rheumatoid arthritis than RF does. We fit the one-factor copula mixed model for all choices of parametric families of copulas and margins. To make it easier to compare strengths of dependence, we convert the copula parameters $\hat{\theta}_{kt}$ to $\hat{\tau}_{kt}$ for $k = 0, 1$, $t = 1$ (RF), 2 (anti-CCP2) via the relations in Equations (10)–(12).

The log-likelihoods showed that an one-factor copula mixed model with Clayton and Clayton rotated by 270° degrees copulas with normal margins to join the factor $V$ with each of the latent sensitivities/specificities $X_{kt}$ provides the best fit (Table 7). For this particular example it is revealed that an one-factor copula mixed model with the sensitivities and specificities on the transformed scale provides better fit than an one-factor copula mixed model with beta margins, which models the latent sensitivity and specificity on the original scale.

The estimated meta-analytic sensitivity and specificity parameters $\hat{\pi}_{kt}$, $k = 0, 1, t = 1$ (RF), 2 (anti-CCP2) show that the anti-CCP2 antibody is better compared with RF. Both tests have fairly similar sensitivity but the anti-CCP2 is much more specific. On the one hand, the estimated univariate parameters and standard errors are in line with the ones in Nikoloulopoulos (2019), but the implementation of the proposed model is much faster, since a numerically time-consuming four-dimensional integral calculation is replaced with a numerically fast two-dimensional integral calculation on the other.

From the Kendall's tau estimates and standard errors there is strong evidence of dependence between the two diagnostic tests. The estimated $\tau_{1t}(\tau_{0t})$, $t = 1$ (RF), 2 (anti-CCP2) indicate a positive (negative) association between each of the latent sensitivities $X_{1t}$ (specificities $X_{0t}$) with the latent variable $V$ implying a negative association $\tau_{1t,0t}$ between the latent sensitivity $X_{1t}$ and specificity $X_{0t}$ within each test $t$. The fact that the best-fitting bivariate copulas are Clayton and Clayton rotated by 270° reveals that there is tail dependence among the latent sensitivities and specificities. This can be further seen trough the SROC curves. Figure 4 depicts the SROC curves and summary operating points (a pair of average sensitivity and specificity) with a confidence region and a predictive region for each test from the best fitted one-factor copula mixed model. Sharper corners

**TABLE 7** Maximized log-likelihoods, estimates and standard errors (SE) of the parameters $\pi_{kt}, \sigma_{kt}$ (normal margins), $\gamma_{kt}$ (beta margins), $\tau_{kt}$, $k = 0, 1, t = 1$ (RF), 2 (anti-CCP2) of the one-factor copula mixed models for the rheumatoid arthritis data

| | **BVN** | | **Frank** | | **Cln{0°, 90°}** | | **Cln{0°, 270°}** | | **Cln{180°, 270°}** | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **Est.** | **SE** | **Est.** | **SE** | **Est.** | **SE** | **Est.** | **SE** | **Est.** | **SE** |
| Normal margins | | | | | | | | | | |
| $\pi_{11}$ | 0.681 | 0.034 | 0.660 | 0.033 | 0.678 | 0.033 | 0.681 | 0.036 | 0.676 | 0.034 |
| $\pi_{12}$ | 0.684 | 0.034 | 0.655 | 0.031 | 0.673 | 0.032 | 0.675 | 0.034 | 0.674 | 0.035 |
| $\pi_{01}$ | 0.825 | 0.033 | 0.834 | 0.032 | 0.827 | 0.033 | 0.826 | 0.033 | 0.827 | 0.033 |
| $\pi_{02}$ | 0.960 | 0.008 | 0.962 | 0.000 | 0.960 | 0.008 | 0.960 | 0.008 | 0.960 | 0.008 |
| $\sigma_{11}$ | 0.685 | 0.128 | 0.698 | 0.134 | 0.691 | 0.122 | 0.722 | 0.133 | 0.687 | 0.129 |
| $\sigma_{12}$ | 0.697 | 0.124 | 0.675 | 0.123 | 0.657 | 0.112 | 0.687 | 0.121 | 0.722 | 0.134 |
| $\sigma_{01}$ | 1.028 | 0.181 | 1.028 | 0.177 | 1.037 | 0.183 | 1.029 | 0.181 | 1.027 | 0.178 |
| $\sigma_{02}$ | 0.790 | 0.175 | 0.795 | 0.164 | 0.794 | 0.184 | 0.792 | 0.170 | 0.797 | 0.171 |
| $\tau_{11}$ | 0.644 | 0.168 | 0.680 | 0.119 | 0.719 | 0.137 | 0.716 | 0.124 | 0.818 | 0.223 |
| $\tau_{12}$ | 0.802 | 0.395 | 0.839 | 0.152 | 0.750 | 0.149 | 0.826 | 0.144 | 0.466 | 0.136 |
| $\tau_{01}$ | −0.125 | 0.168 | −0.218 | 0.160 | −0.149 | 0.161 | −0.213 | 0.148 | −0.227 | 0.162 |
| $\tau_{02}$ | −0.201 | 0.182 | −0.289 | 0.183 | −0.228 | 0.333 | −0.272 | 0.203 | −0.278 | 0.221 |
| $-\log(L)$ | 322.4 | | 321.0 | | 320.1 | | 318.9 | | 325.3 | |
| Beta margins | | | | | | | | | | |
| $\pi_{11}$ | 0.667 | 0.031 | 0.648 | 0.032 | 0.664 | 0.033 | 0.665 | 0.031 | 0.661 | 0.032 |
| $\pi_{12}$ | 0.670 | 0.032 | 0.646 | 0.032 | 0.661 | 0.032 | 0.661 | 0.030 | 0.658 | 0.033 |
| $\pi_{01}$ | 0.782 | 0.034 | 0.789 | 0.033 | 0.783 | 0.034 | 0.784 | 0.033 | 0.785 | 0.033 |
| $\pi_{02}$ | 0.949 | 0.009 | 0.950 | 0.009 | 0.949 | 0.009 | 0.949 | 0.009 | 0.949 | 0.009 |
| $\gamma_{11}$ | 0.087 | 0.028 | 0.092 | 0.030 | 0.089 | 0.030 | 0.097 | 0.029 | 0.089 | 0.029 |
| $\gamma_{12}$ | 0.091 | 0.028 | 0.092 | 0.027 | 0.083 | 0.028 | 0.091 | 0.026 | 0.098 | 0.032 |
| $\gamma_{01}$ | 0.132 | 0.039 | 0.132 | 0.039 | 0.133 | 0.039 | 0.132 | 0.039 | 0.130 | 0.039 |
| $\gamma_{02}$ | 0.025 | 0.012 | 0.026 | 0.013 | 0.025 | 0.012 | 0.026 | 0.013 | 0.027 | 0.013 |
| $\tau_{11}$ | 0.635 | 0.226 | 0.937 | 0.004 | 0.723 | 0.140 | 0.731 | 0.128 | 0.815 | 0.231 |
| $\tau_{12}$ | 0.849 | 0.644 | 0.651 | 0.103 | 0.764 | 0.168 | 0.811 | 0.126 | 0.497 | 0.134 |
| $\tau_{01}$ | −0.111 | 0.169 | −0.175 | 0.167 | −0.120 | 0.164 | −0.217 | 0.144 | −0.234 | 0.173 |
| $\tau_{02}$ | −0.203 | 0.179 | −0.195 | 0.187 | −0.212 | 0.290 | −0.248 | 0.192 | −0.278 | 0.221 |
| $-\log(L)$ | 323.3 | | 322.8 | | 321.2 | | 320.1 | | 326.3 | |

Cln $\{\omega_1^\circ, \omega_2^\circ\}$: The bivariate copulas are the Clayton rotated by $\omega_1^\circ$ and $\omega_2^\circ$ to handle the positive and negative dependencies, respectively.

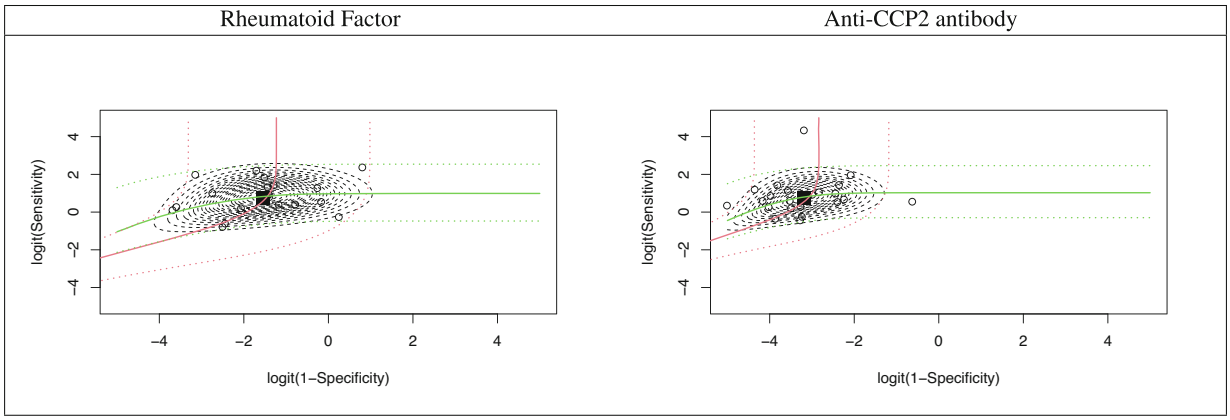


**FIGURE 4** Summary receiver operating characteristic curves and summary operating points at $(\pi_{1t}, 1-\pi_{0t})$ along with their confidence and predictive regions from the best fitted one-factor copula mixed model for the rheumatoid arthritis data. ■: summary operating point; ∘: study estimate; red and green lines represent the quantile regression curves $x_{1t} := \tilde{x}_{1t}(x_{0t}, q)$ and $x_{0t} := \tilde{x}_{0t}(x_{1t}, q)$, respectively; for $q = 0.5$ solid lines and for $q \in \{0.01, 0.99\}$ dotted lines (confidence region); the axes are in logit scale since we also plot the estimated contour plot of the random effects distribution as predictive region [Colour figure can be viewed at wileyonlinelibrary.com]

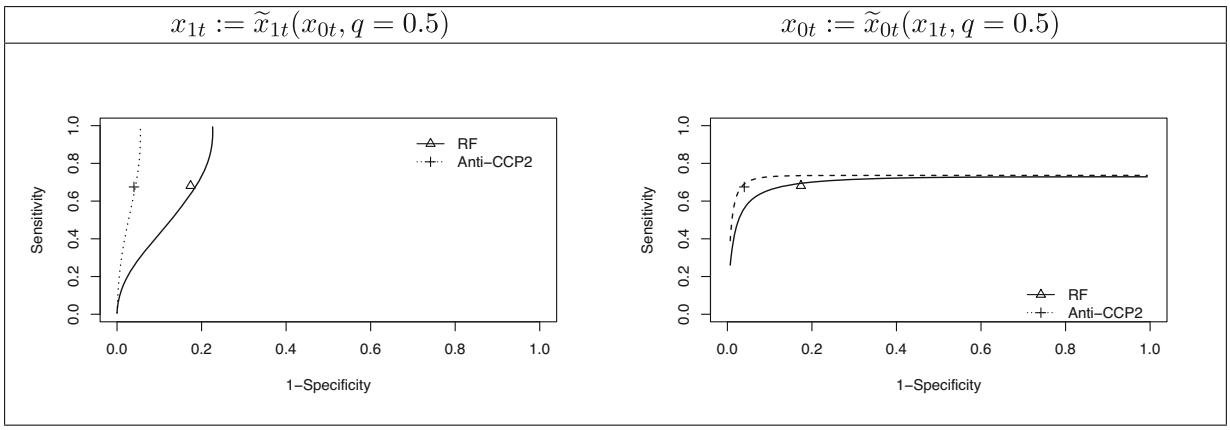


**FIGURE 5** Summary receiver operating characteristic curves and summary operating points at $(\pi_{1t}, 1-\pi_{0t})$ for each test backtransformed to the original scale of sensitivity and specificity for the rheumatoid arthritis data

in the predictive region indicate tail dependence. For the graphs the Kendall's $\tau_{11,01} = -0.191$ and $\tau_{12,02} = -0.261$ have been calculated using the steps 1–5 in Section 4, while the sensitivity and specificity at study $i$ for test $t$ (point estimate) have been calculated with the typical definitions of sensitivity and specificity, viz.,

$$\frac{y_{i11t}}{y_{i+1t}} \quad \text{and} \quad \frac{y_{i00t}}{y_{i+0t}},$$

respectively. Figure 5 provides a direct and visual comparison between the two competing diagnostic tests and reveals that the anti-CCP2 antibody is better compared with RF.

## 8 | DISCUSSION

We have proposed an one-factor copula mixed model for joint meta-analysis and comparison of multiple diagnostic tests in a multiple tests design with a gold standard. This is a parsimonious

meta-analytic model that (a) has the $2T$-variate GLMM with an additive latent structure as a special case when the BVN copulas are used, (b) can have a latent structure that is not additive if other than BVN copulas are called, (c) can model the latent sensitivities and specificities on the original scale rather than a transformed scale as in the $2T$-variate GLMM (d) enables the meta-analytic parameters of interest to be separated from the copula (dependence) parameters which are interpretable as dependence of the latent sensitivity/specificity with another latent variable, (e) avoids the issues of multi-dimensionality and (f) models adequately the dependence among the latent sensitivities and specificities as it can be explained as an 1-truncated C-vine copula.

Our model can provide an improvement over the $2T$-variate GLMM with an additive latent structure as the random effects distribution is expressed via an one-factor copula that provides a wide range of dependence with $2T$ dependence parameters and allow for different types of tail behaviour, different from assuming simple linear correlation structures, normality and tail independence. This strength of multivariate meta-analysis approaches that use copulas has been pointed out by Jackson and White (2018) and Jackson et al. (2020) and it has also been exploited in network meta-analysis (Phillippo et al., 2020).

The $2T$-variate D-vine copula mixed model (Nikoloulopoulos, 2019), which it has as special case the $2T$-variate GLMM with an unstructured correlation structure, provides full dependence and can also provide tail dependence, but it is intractable as the number of competing tests increases. The $2T$-variate one-factor copula mixed model solves this problem since the joint likelihood reduces to an one-dimensional integral of a function which in turn is a product of $2T$ one-dimensional integrals, hence the method avoids $2T$-dimensional integration which is time consuming even for $T = 2$ tests. Its parsimony is not a distributional concern about the dependence between the tests due to the main result in Joe et al. (2010): all the bivariate margins of the vine copula have (tail) dependence if the bivariate copulas at level 1 have (tail) dependence. This is satisfied by the one-factor copula as it is an 1-truncated C-vine. Hence, the proposed model can form the vehicle for conducting meta-analysis of comparative accuracy studies with three or more tests.

Building on the basic model proposed in this paper, the inclusion of covariates is straightforward. One can carry out the model building process in two steps: (a) the selection of the univariate margins with the parameters as functions of some explanatory variables and, (b) the selection of the bivariate copulas to build the one-factor copula model according to the actual dependence among the latent sensitivities and specificities. If the interest is to study the effect of explanatory variables on the dependence structure, one-factor copulas are suitable since allow the use of covariate functions for the copula dependence parameters; this is not the case for the GLMM, because of the joint constraints for the correlation parameters.

When the focus is on estimates of the meta-analytic univariate parameters of interest, the benefit of joint analysis is modest, in that the differences in the summary estimates and standard errors from separate meta-analyses for each test are not that distinct. The most striking differences between separate and joint meta-analyses arise when one deduces comparative diagnostic accuracy, that is, an SROC curve. An SROC curve makes much more sense and will help decision makers to assess the actual diagnostic accuracy of the competing diagnostic tests. In an era of evidence-based medicine, decision makers need high-quality procedures such as the SROC curves to support decisions about whether or not to use a diagnostic test in a specific clinical situation and, if so, which test. We have deduced SROC curves from the one-factor copula mixed model. The model parameters (including dependence parameters), the choice of the copula, and the choice of the margin affect the shape of the SROC curves. On the one hand a series of independence models cannot be used to produce the SROC curves, since the dependence parameters

affect the shape of the SROC curve and these are set to independence, and the GLMM SROC curves are restricted to be linear on the other. Hence our approach brings additional insights into the diagnostic accuracy data with SROC curves that can be non-linear as it allows dependence among the extreme values of the latent sensitivities and specificities.

Comparative accuracy studies with paired designs where each test is applied to the same patients should report the data as separate $2 \times 2$ tables. Authors of primary studies of diagnostic accuracy that assess three or more tests in the same patients should be encouraged to report sufficient data to extract separate $2 \times 2$ tables of test results as in Table 1. Comparative accuracy studies should rightly use a multiple tests designs so that patients receive each test in order to reduce biases and ensure the clinical relevance of the resulting inferences (Trikalinos et al., 2014).

Nevertheless, in practice there exist comparative studies in a randomized design or even non-comparative studies (Takwoingi et al., 2013) and for some of them the reference test might be imperfect. Future research will focus on extending the one-factor copula mixed model to incorporate randomized designs and non-comparative studies with or without a gold standard. Ma et al. (2018) and Lian et al. (2019) proposed methods for comparing multiple diagnostic tests that can incorporate studies with different designs and studies with our without gold standard. As their methods assume that the between-studies model is the multivariate normal distribution that suffers from the computational burden of multidimensionality when the number of tests increases, we will exploit the use of the one-factor copula distribution. The one-factor copula distribution will provide computational and distributional improvements when adapted to the setting of Ma et al. (2018) and Lian et al. (2019).

## SOFTWARE

`R` functions to implement the one-factor copula mixed model for meta-analysis of multiple diagnostic tests are part of the `R` package `CopulaREMADA` (Nikoloulopoulos, 2022).

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