DEPENDENCE BETWEEN THREE DIAGNOSTIC TESTS IN PRESENCE OF VERIFICATION BIAS: A COPULA FUNCTION APPROACH

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▪ *ABSTRACT: The study of the dependence betweenn the outcomes of two medical diagnostic tests is important since that decision about what therapeutic treatment is suitable for diseased individuals, depends of the test results. In this paper, we introduce a Bayesian approach to study the effect of three copula structures to model the dependence effect on the prevalence and performance test parameters, using data obtained within a design with verification bias and three diagnostic tests, two of them with dependent outcomes and the other one independent. We simulated data of three copula models each of them with three dependence levels: weak, moderate and strong inside of two scenaries: sensibilities relatively high with high specificities and sensibilities relatively low with high specificities.*

▪ *KEYWORDS: Dependent diagnostic tests; bayesian analysis; copula functions; Farley Gumbel Morgenstern (FGM) copula; Gumbel copula; Clayton copula.*

1 Introduction

The study of the performance of medical diagnostic tests diagnostics has been of great interest for statistical and medical researchers since the middle of the last century. Classical works on this topic were developed by Neyman (1947), Homburguer *et al.* (1950), Youden (1950), Buck and Gart (1966), among many others. In practical work, there are some diagnostic procedures, where it is important the use of two or more diagnostic tests before the use of one reference

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test or "gold standard". Under those designs we have situations where only part of the individuals are verified by "gold standard". In many cases, if the results of both tests are negative then no further medical diagnostics are applied. If one of the tests has a positive outcome, then the "gold standard" is usually applied to evaluate the correct disease status, a situation that is referred as verification restricted to screen positives and that leads to biased estimations by verification bias presence. The estimation of performance tests parameters within designs with verification bias is perhaps the most studied matter on diagnostic tests, by researchers both in statistics as in medical sciences. In statistics, the problem was initially treated assuming independence between the tests and using maximum likelihood or Bayesian approaches for parameter estimation. There exists a large bibliography about the topic (see for example Hui and Walter (1980), Begg and Greenes (1983), Begg (1987), Schatzkin *et al.* (1987), Begg and McNeil (1988), Joseph *et al.* (1995), Cheng and Macaluso (1997), Walter (1999), Enøe *et al.* (2000), Achcar *et al.* (2005), Martinez *et al.* (2005), Aragon *et al.* (2010) among many others).

In many practical situations, the diagnostic procedure includes the measure of two or more (observable or not), biological traits associated to the disease process. Generally, those traits are expressed on a continuous scale with a necessary limit value (cut point), used for dichotomization which is implicitly given by the threshold of clinical detectability. Given that, the measured traits belongs the same individual, is possible to have dependence between test outcomes with not necessarely linear or concordance structure, therefore, is not possible to study the test dependence with association indicatores commonly used, as the Pearson correlation coefficient, the Kendall's tau or the Spearman coefficient.

In this paper, we assume a model with three diagnostic tests, assuming that the first test is binary and its outcome is known by the doctor before asking for the other two tests, the test 2 and test 3 have dependent continuous outcomes with one of three copula structure models and the individuals with negative results in the three diagnostic tests are not verified by "gold standard". We assume homogenous dependence between diseased and non-diseased populations. Our main goal is to study the effect of three levels of copula structure dependence (weak, moderate, strong) on the prevalence and the performance test parameter estimators, for which we develop a simulation study. Using Bayesian approach, we estimate the performance test parameters and prevalence when the dependent tests have relatively high sensitivities with high specificities and when the tests have relatively low sensibilities with high specificities.

This paper is organized as follows: in section 2 we introduce the model formulation for the proposed design; in section 3, we introduce the results and finally, in section 4, we present a discussion about the obtained results.

2 Model formulation for a design with three diagnostic tests where two of them are dependents

Let us assume a design with three diagnostic tests, two of them dependents and a first one independent whose result is known before asking for the other two tests; in this way, there are eigth combinations of results (Table 1). In this design, the quantities in brackets are the numbers of subjects with negative outcome in the three tests which are not verified by a "gold standard".

Table 1 - Design with three diagnostic tests. Values in brackets are unknown

		$T_1 = 1$			$T_1 = 0$		
		T_3+	T_3-	Total	T_3+	T_3-	Total
Disease	T_2+	$a1$	$a2$	$a1 + a2$	$a5$	$a6$	$a5 + a6$
individuals	T_2-	$a3$	$a4$	$a3 + a4$	$a7$	$[a8]$	$a7 + [a8]$
	Total	$a1 + a3$	$a2 + a4$	$n_{T_1 D}$	$a5 + a7$	$a6 + [a8]$	$[n_{\bar{T}_1 D}]$
Non-disease	T_2+	$b1$	$b2$	$b1 + b2$	$b5$	$b6$	$b5 + b6$
individuals	T_2-	$b3$	$b4$	$b3 + b4$	$b7$	$[b8]$	$b7 + [b8]$
	Total	$b1 + b3$	$b2 + b4$	$n_{T_1 \bar{D}}$	$b5 + b7$	$b6 + [b8]$	$[n_{\bar{T}_1 \bar{D}}]$

Within the design of Table 1, we introduce three different models to get the estimation of the parameters assuming that the two dependent tests have one of three dependence copula structures, namely: Farley Gumbel Morgenstern denoted as "copula1-model", Gumbel copula denoted as "copula2-model" and Clayton copula denoted as "copula3-model".

2.1 Statistical model for the dependence between tests using copula functions

Let us assume that the two dependent test outcomes are realizations of the random variables V_2 and V_3 measured in a positive continuous scale, that is, $V_2 > 0$ and $V_3 > 0$. Also, let us assume that two cut-off values ξ_2 and ξ_3 are chosen for each test in order to determine when an individual is classified as positive or negative. In this way we assume that an individual is classified as positive for test ν if $V_\nu > \xi_\nu$ that is, $T_\nu = 1$ if and only if $V_\nu > \xi_\nu$ for $\nu = 2, 3$. To measure the degree of the dependence structure between the random variables V_2 and V_3, let us consider the use of copula functions. Copula functions has been studied by many authors (Nelsen, 1999; is a classical book on this topic). Copula functions can be used to link marginal distributions with a joint distribution. For specified univariate marginal distribution functions $F_1(v_1), ..., F_m(v_m)$, the function $C(F_1(v_1), ..., F_m(v_m))$ which is defined using a copula function C, results in a multivariate distribution function with univariate marginal distributions specified as $F_1(v_1), ..., F_m(v_m)$. It is important to point out that any multivariate distribution function F can be written in the form of a copula function that is, if $F(v_1, ..., v_m)$ is a joint multivariate distribution function with univariate marginal distribution

functions $F_1(v_1), ..., F_m(v_m)$, thus exists a copula function $C(u_1, ..., u_m)$ such that (Sklar's theorem),

$$F(v_1, ..., v_m) = C(F_1(v_1), ..., F_m(v_m)). \quad (1)$$

Copula functions do not focus on correlation coefficients but on scale invariant measures of association. It is important to point out that these measures of association are functions of a measure of dependence between marginals. This measure of dependence, also known as an association parameter can take many different values depending on the copula, whereas measures of association, such as Pearson's correlation coefficient, are usually bounded. For the special case of bivariate distributions, we have $m = 2$. The approach to formulate a multivariate distribution using a copula is based on the idea that a simple transformation can be made of each marginal variable in such a way that each transformed marginal variable has an uniform distribution. Once this is done, the dependence structure can be expressed as a multivariate distribution on the obtained uniforms and a copula is precisely a multivariate distribution on marginally uniform random variables.

In this way, there are many families of copulas which differ in the detail of the dependence they represent. In the bivariate case, let V_2 and V_3 be two random variables with continuous distribution functions F_2 and F_3. The probability integral transformation is applied separately for the two random variables to define $U = F_2(V_2)$ and $W = F_3(V_3)$ where U and W have uniform $(0, 1)$ distributions, but are usually dependents if V_2 and V_3 are dependents (V_2 and V_3 independents implies that U and W are independents). Specifying dependence between V_2 and V_3 is the same as specifying dependence between U and W, thus the problem reduces to specifying a bivariate distribution between two uniform variables, that is a copula.

2.1.1 One independent test and two tests with Copula1-Model dependence

The first copula model considered for the study of the dependence structure for the two tests conditionally on the true individual status, is based in the Farley Gumbel Morgenstern (FGM) copula function wich has been studied by authors as Amblard and Girard (2002, 2005, 2008), Bairamov and Kotz (2002), Fisher and Klein (2007). The FGM copula is defined by,

$$C_I(u, w) = uw[1 + \varphi(1 - u)(1 - w)], \quad (2)$$

where $u = F_2(v_2)$, $w = F_3(v_3)$ and $-1 \leq \varphi \leq 1$. Observe that, φ measures the dependence between the two marginals, that is, if $\varphi = 0$, we have independent random variables. The parameters φ are related to the well known association coefficients Kendall's Tau ($\tau_{v,w}$) and Spearman's Rho $\rho_{v,w}$ by the equations:

$$\tau_{v,w} = 4 \int \int C(u, w) dC(u, w) - 1 = 4 \left(\frac{\varphi}{18} + \frac{1}{4} \right) - 1 = \frac{2\varphi}{9}, \quad (3)$$

$$\rho_{v,w} = 12 \int\int C(u,w)dC(u,w) - 3 = 12\left(\frac{1}{4} + \frac{\varphi}{36}\right) - 3 = \frac{\varphi}{3}. \quad (4)$$

From (2), the cumulative joint distribution function for the random variables V_2 and V_3 is given by,

$$F_I(v_2, v_3) = C_I(F_2(v_2), F_3(v_3)) = F_2(v_2)F_2(v_2)[1+\varphi(1-F_2(v_2))(1-F_3(v_3))]. \quad (5)$$

The joint survival function for V_2 and V_3 is given by

$$S(v_2, v_3) = P(V_2 > v_2, V_3 > v_3) = 1 - F_2(v_2) - F_3(v_3) + F(v_2, v_3). \quad (6)$$

Given that we have two subpopulations within each population, then we have four association copula coefficients, one for each subpopulation namely: $\varphi_{T_1 D}$ for diseased individuals with first test positive, $\varphi_{T_1^- D}$ for diseased individuals with negative outcome in the test1, $\varphi_{T_1 \bar{D}}$ for non-diseased individuals with positive result in test 1 and $\varphi_{\bar{T_1}\bar{D}}$ for non-diseased individuals with negative outcome in the first test. We obtain the likelihood function components for the first of the subpopulations (diseased individuals with positive result in test 1) and the procedure is similarly applied for the other three subpopulations. In this way and using (5) and (6), we have:

$$\begin{aligned}
P(T_1 = 1|D = 1) &= S_1 \\
P(T_2 = 1|T_1 = 1, D = 1) &= P(V_2 > \xi_2|T_1 = 1, D = 1) = S_2 \\
P(T_3 = 1|T_1 = 1, D = 1) &= P(V_3 > \xi_3|T_1 = 1, D = 1) = S_3 \\
P(D = 1, T_1 = 1, T_2 = 1, T_3 = 1) &= P(D = 1)P(T_1 = 1|D = 1)P(T_2 = 1, T_3 = 1|D = 1, T_1 = 1) \\
&= pS_1 P(V_2 > \xi_2, V_3 > \xi_3|T_1 = 1, D = 1) \\
&= pS_1 S_{T_1 D}(\xi_2, \xi_3) \\
S_{T_1 D} &= 1 - F_2^{T_1 D}(\xi_2) - F_3^{T_1 D}(\xi_3) + F_{T_1 D}(\xi_2, \xi_3) \\
F_2^{T_1 D} &= P(V_2 \leq \xi_2|T_1 = 1, D = 1) = P(V_2 \leq \xi_2|D = 1) = 1 - S_2 \\
F_3^{T_1 D} &= P(V_3 \leq \xi_3|T_1 = 1, D = 1) = P(V_3 \leq \xi_3|D = 1) = 1 - S_3 \\
F_{T_1 D}(\xi_2, \xi_3) &= F_2^{T_1 D}(\xi_2)F_3^{T_1 D}(\xi_3)[1 + \varphi_{T_1 D}(1 - F_2^{T_1 D}(\xi_2))(1 - F_3^{T_1 D}(\xi_3))] \\
&= (1 - S_2)(1 - S_3)(1 + \varphi_{T_1 D} S_2 S_3) \\
S^{T_1, D}(\xi_2, \xi_3) &= 1 - F_2^{T_1 D}(\xi_2) - F_3^{T_1 D}(\xi_3) + F_{T_1 D}(\xi_2, \xi_3) \\
&= 1 - (1 - S_2) - (1 - S_3) + (1 - S_2)(1 - S_3)[1 + \varphi_{T_1 D} S_2 S_3] \\
P(T_1 = 1, T_2 = 1, T_3 = 1, D = 1) &= pS_1[S_2 + S_3 - 1 + (1 - S_2)(1 - S_3)[1 + \varphi_{T_1 D} S_2 S_3]].
\end{aligned}$$

Also,

$$\begin{aligned}
P(T_1 = 1, T_2 = 1, T_3 = 0, D = 1) &= P(D = 1)P(T_1 = 1|D = 1)P(T_2 = 1, T_3 = 0|D = 1) \\
&= pS_1 P(V_2 > \xi_2, V_3 \leq \xi_3|T_1 = 1, D = 1) \\
P(V_2 > \xi_2, V_3 \leq \xi_3|T_1 = 1, D = 1) &= P(V_3 \leq \xi_3|T_1 = 1, D = 1) - P(V_2 \leq \xi_2, V_3 \leq \xi_3|T_1 = 1, D = 1) \\
&= F_3^{T_1 D}(\xi_3) - F_{T_1 D}(\xi_2, \xi_3) \\
&= (1 - S_3) - (1 - S_2)(1 - S_3)[1 + \varphi_{T_1 D} S_2 S_3] \\
&= S_2[1 - S_3[1 - \varphi_{T_1 D} S_3(1 - S_2)]] \\
P(T_1 = 1, T_2 = 1, T_3 = 0, D = 1) &= pS_1 S_2(1 - S_3)[1 - \varphi_{T_1 D} S_3(1 - S_2)].
\end{aligned}$$

Similarly,

$$\begin{aligned}
P(T_1=1,T_2=0,T_3=1,D=1) &= P(D=1)P(T_1=1|D=1)P(T_2=0,T_3=1|T_1=1,D=1)\\
&= pS_1P(V_2\le\xi_2,V_3>\xi_3|T_1=1,D=1)\\
P(V_2\le\xi_2,V_3>\xi_3|T_1=1,D=1) &= P(V_2\le\xi_2|T_1=1,D=1)-P(V_2\le\xi_2,V_3\le\xi_3|T_1=1,D=1)\\
&= F_2^{T_1D}(\xi_2)-F_{T_1D}(\xi_2,\xi_3)\\
&= (1-S_2)-(1-S_2)(1-S_3)[1+\varphi_{T_1D}S_2S_3]\\
&= (1-S_2)S_3[1-\varphi_{T_1D}S_2(1-S_3)]\\
P(T_1=1,T_2=0,T_3=1,D=1) &= pS_1S_3(1-S_2)[1-\varphi_{T_1D}S_2(1-S_3)].
\end{aligned}$$

On the other hand;

$$\begin{aligned}
P(T_1=1,T_2=0,T_3=0,D=1) &= P(D=1)P(T_1=1|D=1)P(T_2=0,T_3=0|T_1=1,D=1)\\
&= pS_1P(V_2\le\xi_2,V_3\le\xi_3|T_1=1,D=1)\\
&= pS_1F_D(\xi_2,\xi_3)\\
&= pS_1(1-S_2)(1-S_3)[1+\varphi_{T_1D}S_2S_3]\\
&= pS_1(1-S_2)(1-S_3)[1+\varphi_{T_1D}S_2S_3]. \qquad (7)
\end{aligned}$$

Within the non-diseased individuals group, we have:

$$\begin{aligned}
P(T_1=1,T_2=1,T_3=1,D=0) &= P(D=0)P(T_2=1,T_3=1|T_1=1,D=0)\\
&= (1-p)P(T_1=1|D=0)P(V_2>\xi_2,V_3>\xi_3|T_1=1,D=0)\\
&= (1-p)(1-E_1)S_{T_1\bar{D}}(\xi_2,\xi_3)\\
F_2^{T_1\bar{D}}(\xi_2) &= P(V_2\le\xi_2|T_1=1,D=0)\\
&= P(T_2=0|D=0)=E_2
\end{aligned}$$

$$\begin{aligned}
F_3^{T_1\bar{D}}(\xi_3) &= P(V_3\le\xi_3|T_1=1,D=0)\\
&= P(T_3=0|D=0)=E_3\\
F_{T_1\bar{D}}(\xi_2,\xi_3) &= P(V_2\le\xi_2,V_3\le\xi_3|T_1=1,D=0)\\
&= F_2^{T_1\bar{D}}(\xi_2)F_3^{T_1\bar{D}}(\xi_3)[1+\varphi_{T_1\bar{D}}(1-F_2^{T_1\bar{D}}(\xi_2))(1-F_3^{T_1\bar{D}}(\xi_3))]\\
&= E_2E_3[1+\varphi_{T_1\bar{D}}(1-E_2)(1-E_3)]\\
S_{T_1\bar{D}}(\xi_2,\xi_3) &= 1-F_2^{T_1\bar{D}}(\xi_2)-F_3^{T_1\bar{D}}+F_{T_1\bar{D}}(\xi_2,\xi_3)\\
&= 1-E_2-E_3+E_2E_3+\varphi_{T_1,\bar{D}}E_2E_3(1-E_2)(1-E_3)\\
P(T_1=1,T_2=1,T_3=1,D=0) &= P(D=0)P(T_1=1|D=0)P(T_2=1,T_3=1|T_1=1,D=0)\\
&= (1-p)(1-E_1)(1-E_2)(1-E_3)[1+\varphi_{T_1\bar{D}}E_2E_3].
\end{aligned}$$

Similarly, we get the other cases. The contributions to the likelihood for all situations with diseased and non-diseased individuals are given in Table 2.1.1.

2.1.2 One independent test and two tests with Copula2-Model dependence

The second considered copula model denoted as "copula2-model", is the Gumbel copula function (Gumbel, 1960) defined as,

$$C_{II}(u,w)=u+w-1+(1-u)(1-w)\exp\{-\phi\ln(1-u)\ln(1-w)\}. \qquad (8)$$

Table 2 - Likelihood contributions of all possible combinations of outcomes of T_1, T_2, T_3 and D within a design with three tests, two of them with "copula1-model" dependence. (y_2 and y_3 are unknown)

D	T_1	T_2	T_3	N. Indiv.$^{(+)}$	"Copula1-model"
1	1	1	1	a1	$pS_1S_2S_3\left[1+\varphi_{T_1D}(1-S_2)(1-S_3)\right]$
1	1	1	0	a2	$pS_1S_2(1-S_3)\left[1-\varphi_{T_1D}(S_3)(1-S_2)\right]$
1	1	0	1	a3	$pS_1(1-S_2)S_3\left[1-\varphi_{T_1D}S_2(1-S_3)\right]$
1	1	0	0	a4	$pS_1(1-S_2)(1-S_3)\left[1+\varphi_{T_1D}S_2S_3)\right]$
1	0	1	1	a5	$p(1-S_1)S_2S_3\left[1+\varphi_{\bar{T}_1D}(1-S_2)(1-S_3)\right]$
1	0	1	0	a6	$p(1-S_1)S_2(1-S_3)\left[1-\varphi_{\bar{T}_1D}(S_3)(1-S_2)\right]$
1	0	0	1	a7	$p(1-S_1)(1-S_2)S_3\left[1-\varphi_{\bar{T}_1D}S_2(1-S_3)\right]$
1	0	0	0	$[y_2]$	$p(1-S_1)(1-S_2)(1-S_3)\left[1+\varphi_{\bar{T}_1D}S_2S_3\right]$
0	1	1	1	b1	$(1-p)(1-E_1)(1-E_2)(1-E_3)\left[1+\varphi_{T_1\bar{D}}E_2E_3\right]$
0	1	1	0	b2	$(1-p)(1-E_1)(1-E_2)E_3\left[1-\varphi_{T_1\bar{D}}E_2(1-E_3)\right]$
0	1	0	1	b3	$(1-p)(1-E_1)E_2(1-E_3)\left[1-\varphi_{T_1\bar{D}}E_3(1-E_2)\right]$
0	1	0	0	b4	$(1-p)(1-E_1)E_2E_3\left[1+\varphi_{T_1\bar{D}}(1-E_2)(1-E_3)\right]$
0	0	1	1	b5	$(1-p)E_1(1-E_2)(1-E_3)\left[1+\varphi_{\bar{T}_1\bar{D}}E_2E_3\right]$
0	0	1	0	b6	$(1-p)E_1(1-E_2)E_3\left[1-\varphi_{\bar{T}_1\bar{D}}E_2(1-E_3)\right]$
0	0	0	1	b7	$(1-p)E_1E_2(1-E_3)\left[1-\varphi_{\bar{T}_1\bar{D}}(1-E_2)E_3\right]$
0	0	0	0	$[y_3]$	$(1-p)E_1E_2E_3\left[1+\varphi_{\bar{T}_1\bar{D}}(1-E_2)(1-E_3)\right]$

$^{(+)}$ N. Ind. = Number of individuals

In this model, the general conditional joint cumulative distribution function for the random variables V_2 and V_3 is given by,

$$F_{\phi_i}(\xi_2,\xi_3)=F_2^{\phi_i}(\xi_3)+F_3^{\phi_i}(\xi_3)-1+(1-F_2^{\phi_i}(\xi_2))[1-F_3^{\phi_i}(\xi_3)]Q_{\phi_i}, \qquad (9)$$

and

$$Q_{\phi_i}=\exp\{-\phi_i\ln(1-F_2^{\phi_i}(\xi_2))\ln(1-F_3^{\phi_i}(\xi_3))\} \qquad i=1,2,3,4,$$

where ϕ_i, is the copula association parameter that identifies each subpopulation of individuals with the combinations between test 1 result and the true disease status.

For this copula model, when $\phi=1$ the Pearson correlation linear coefficient (ρ) takes the value -0.40365 and when the two variables are independents, $\phi=0$. Employing the same arguments considered with the "copula1-model" to find the joint probabilities of all combinations with D, T_1 T_2 and T_3 and using (9) we obtain all the contributions for the likelihood for the "copula2-model" (Table 4).

2.1.3 One independent test and two tests with Copula3-Model dependence

The "copula3-model" was developed from the probabilistic model originally proposed by Clayton (more details in Clayton, 1978). This model is defined as follows:

Table 3 - Likelihood contributions of all possible combinations of outcomes of T_1, T_2, T_3 and D within a design with three independent tests, two of them with "copula2-model" dependence. (y_2 and y_3 are unknown)

D	T_1	T_2	T_3	Number of individuals	"Copula2-model"
1	1	1	1	a1	$pS_1S_2S_3Q_1$
1	1	1	0	a2	$pS_1S_2(1-S_3)Q_1$
1	1	0	1	a3	$pS_1(1-S_2)S_3Q_1$
1	1	0	0	a4	$pS_1(1-S_2)(1-S_3)Q_1$
1	0	1	1	a5	$p(1-S_1)S_2S_3Q_2$
1	0	1	0	a6	$p(1-S_1)S_2(1-S_3)Q_2$
1	0	0	1	a7	$p(1-S_1)(1-S_2)S_3Q_2$
1	0	0	0	$[y_2]$	$p(1-S_1)(1-S_2)(1-S_3)Q_2$
0	1	1	1	b1	$(1-p)(1-E_1)(1-E_2)(1-E_3)Q_3$
0	1	1	0	b2	$(1-p)(1-E_1)(1-E_2)E_3Q_3$
0	1	0	1	b3	$(1-p)(1-E_1)E_2(1-E_3)Q_3$
0	1	0	0	b4	$(1-p)(1-E_1)E_2E_3Q_3$
0	0	1	1	b5	$(1-p)E_1(1-E_2)(1-E_3)Q_4$
0	0	1	0	b6	$(1-p)E_1(1-E_2)E_3Q_4$
0	0	0	1	b7	$(1-p)E_1E_2(1-E_3)Q_4$
0	0	0	0	$[y_3]$	$(1-p)E_1E_2E_3Q_4$

$Q_1 = \exp\left[-\phi_{T_1 D} \ln S_2 \ln S_3\right]$, $Q_2 = \exp\left[-\phi_{\bar{T}_1 D} \ln S_2 \ln S_3\right]$
$Q_3 = \exp\left[-\phi_{T_1 \bar{D}} \ln S_2 \ln S_3\right]$, $Q_4 = \exp\left[-\phi_{\bar{T}_1 \bar{D}} \ln S_2 \ln S_3\right]$

$$C_{III}(u,w) = max\left[\frac{uw}{[u^\alpha + w^\alpha - u^\alpha w^\alpha]^{1/\alpha}}, 0\right], \quad u,w \in (0,1), \quad \alpha \in [-1,\infty)|\{0\}, \tag{10}$$

and

$$F_{\alpha_i}(\xi_2,\xi_3) = F_2^{\alpha_i}(\xi_2)F_3^{\alpha_i}(\xi_3)[(1-F_2^{\alpha_i})^{\alpha_i} + (1-F_3^{\alpha_i})^{\alpha_i} - (1-F_2^{\alpha i})^{\alpha_i}(1-F_3^{\alpha_i})^{\alpha_i}]^{-1/\alpha_i}, \tag{11}$$

where, $\alpha_i, \quad i = 1,2,3,4$ is the copula dependence parameter that indentifies each of the four subpopulations of interest. Employing the same arguments used with the other two copula models, we obtained the joint probabilities of all contributions for the likelihood function using the Clayton copula model (Table 4).

For this copula model, the relationship between the association copula parameter α and the Kendall's tau, is given by;

$$\alpha = \frac{2\tau}{1-\tau}, \tag{12}$$

when $\tau = 0$, then $\alpha = 0$ indicating independence among tests; if $\alpha = -1$, then $\tau = -1$ indicating perfect negative dependence and if α tends to infinite, then τ tends to 1 indicating perfect positive dependence.

Table 4 - Likelihood contributions of all possible combinations of outcomes of T_1, T_2, T_3 and D within a design with three independent tests, two of them with "copula3-model" dependence. (y_2 and y_3 are unknown)

	D	T_1	T_2	Number individuals	"Copula3-model"
1	1	1	1	a1	$pS_1\,[S_2 + S_3 - 1 + (1-S_2)(1-S_3)R_1]$
1	1	1	0	a2	$pS_1(1-S_3)\,[1-(1-S_2)R_1]$
1	1	0	1	a3	$pS_1(1-S_2)\,[1-(1-S_3)R_1]$
1	1	0	0	a4	$pS_1(1-S_2)(1-S_3)R_1$
1	0	1	1	a5	$p(1-S_1)\,[S_2 + S_3 - 1 + (1-S_2)(1-S_3)R_2]$
1	0	1	0	a6	$p(1-S_1)(1-S_3)\,[1-(1-S_2)R_2]$
1	0	0	1	a7	$p(1-S_1)(1-S_2)\,[1-(1-S_3)R_2]$
1	0	0	0	$[y_2]$	$p(1-S_1)(1-S_2)(1-S_3)R_2$
0	1	1	1	b1	$(1-p)(1-E_1)\,[1-E_2-E_3+E_2E_3R_3]$
0	1	1	0	b2	$(1-p)(1-E_1)E_3\,[1-E_2R_3]$
0	1	0	1	b3	$(1-p)(1-E_1)E_2\,[1-E_3R_3]$
0	1	0	0	b4	$(1-p)(1-E_1)E_2E_3R_3$
0	0	1	1	b5	$(1-p)E_1\,[1-E_2-E_3+E_2E_3R_4]$
0	0	1	0	b6	$(1-p)E_1E_3\,[1-E_2R_4]$
0	0	0	1	b7	$(1-p)E_1E_2\,[1-E_3R_4]$
0	0	0	0	$[y_3]$	$(1-p)E_1E_2E_3R_4$

$$R_1 = [(1-S_2)^{\alpha_{T_1D}} + (1-S_3)^{\alpha_{T_1D}} - (1-S_2)^{\alpha_{T_1D}}(1-S_3)^{\alpha_{T_1D}}]^{-1/\alpha_{T_1D}}$$
$$R_2 = [(1-S_2)^{\alpha_{\bar{T}_1D}} + (1-S_3)^{\alpha_{\bar{T}_1D}} - (1-S_2)^{\alpha_{\bar{T}_1D}}(1-S_3)^{\alpha_{\bar{T}_1D}}]^{-1/\alpha_{\bar{T}_1D}}$$
$$R_3 = [E_2^{\alpha_{T_1\bar{D}}} + E_2^{\alpha_{T_1\bar{D}}} - E_1^{\alpha_{T_1\bar{D}}}E_2^{\alpha_{T_1\bar{D}}}]^{-1/\alpha_{T_1\bar{D}}}$$
$$R_4 = [E_2^{\alpha_{\bar{T}_1\bar{D}}} + E_2^{\alpha_{\bar{T}_1\bar{D}}} - E_1^{\alpha_{\bar{T}_1\bar{D}}}E_2^{\alpha_{\bar{T}_1\bar{D}}}]^{-1/\alpha_{\bar{T}_1\bar{D}}}$$

3 Prior distributions elicitation and identifiability issues

When we have information about some distributional moments (for instance, mean or variance) and we can write the hyperparameters as functions of them, we can use the Chebychev formula to obtain the prior hyperparameters values. For parameters as those of dependence, we could use existing subjetive or objetive prior information on some usual related correlation index (for instance, Kendall's τ or Spearman's ρ) to elicit a prior distribution. If we do not have any kind of information, we can divide the parametric range of values in a finite number of subintervals, for each subinterval take the midpoint as the mean $E(\theta)$ and apply the Chebychev's inequality to aproximate the variance $V(\theta)$, as follows:

$$P(|\theta - E(\theta)| \geq k\sigma) \leq \frac{1}{k^2} = \gamma,$$
$$\sigma^2 \leq \frac{(\theta - E(\theta))^2}{k^2} = \gamma(\theta - E(\theta))^2, \tag{13}$$

where γ is the prior probability of θ do not belonging to the constructed interval. The hyperparameter values, are obtained solving an 2 by 2 equations system, made from the mean and variance of a variable with Beta(a, b) distribution.

The "copula1-model" dependence parameter belong to the range $(-1, 1)$ by which it is more dificult to obtain prior distributions, then we take the most frequent case with diagnostic tests assuming positive dependence that is, $P(\varphi \in (-1, 0)) = 0$ and we use $Beta(a, b)$ distributions as informative priors, in the same way we made with the "copula2-model" dependence parameter. For the "copula3-model" we considered the interval $(0, \infty)$ as parametric space to elicit prior distributions. We could assume distributions with that range of values as for example, $Gamma(r, s)$, $Lognormal(t, u)$, or $Weibull(m, n)$ distributions among others. As non-informative priors, we could use large variance values or large scale hyperparameter values. If we can not to use the positive dependence assumption, an option that may be considered is to use a *Generalized* $Gamma(r, s)$ distribution to construct informative and non-informative prior distributions for α dependence parameter.

As we do not have any kind of information about the copula parameters, then, for copula models 1 and 2, we assume that when the dependence is weak, the parameter should belong to the interval $(0, 1/4)$ and we used a $Beta(17, 122)$ as informative prior distribution, when the dependence is moderate the parameter belongs to the interval $(1/4, 3/4)$ and the informative prior distribution would be a $Beta(39.5, 39.5)$ and when the dependence is strong, the parameter belongs to the interval $(3/4, 1)$, then, the informative prior distribution is a $Beta(122, 17)$.

For the Clayton parameter dependence, we have used the relationship between α and the Kendall tau (12) also assuming that τ belongs to each interval built for the other two copula models. Thus, for the α parameter, we have three intervals as follows: $\alpha \in (0, 2/3)$ when $\tau \in (0, 1/4)$, then, the prior informative distribution is a $Gamma(20, 60)$, if $\alpha \in (2/3, 6)$ then $\tau \in (1/4, 3/4)$ so the prior distribution is a $Gamma(20, 7.5)$ and when $\alpha \in (6, 98)$ then $\tau \in (3/4, 0.99)$, therefore $Gamma(20, 0.20833)$ is the informative prior distribution to use in that case. All informative prior distributions were obtained assuming $\gamma = 0.05$ in (13).

For each of the proposed models, we must estimate eleven parameters; three sensitivities, three specificities, one prevalence and four association parameters, one for each combination of status and test 1 result, but we have only seven degrees of freedom for the estimation process; thus, we have a non-identifiable problem. In order to deal with this problem informative priors would be needed on at least as many parameters as would be constrained when using the frequentist approach (Joseph *et al.*, 1995). Then, we used informative priors on dependence parameters and non-informative priors on prevalence and tests performance parameters.

4 Simulation procedure and data analysis

For the simulation procedure, we establish the following conditions:

- We have three dependence levels: weak (0.2), moderate (0.5) and strong (0.9), in each of the three copula structures (FGM, Gumbel and Clayton).

- The first test has moderate sensibility and specificity ($S_1 = E_1 = 0.50$).

- The specificities of the dependent tests are the same ($E_2 = E_3 = 0.95$) and the prevalence is relatively lower ($p = 0.10$).

Besides, we considered two different scenaries as follows:

- The dependent tests have the same relatively high sensititivities ($S_2 = S_3 = 0.85$).
- The dependent tests have the same relatively low sensitivities ($S_2 = S_3 = 0.45$).

The first scenary simulates a situation where the two screening tests are biological traits with outcomes expressed in a continuous scale strongly modificated with the disease presence in the individual while in the second scenary those traits have a lower impact with the illness presence.

To simulate outcomes of the first test, we simulated 1000 samples of a Binomial$(1, 0.5)$ distribution as a diseased population with a binary outcome test, in similar way, we made a simulation with 9000 samples for non-diseased individuals population. The simulated data of "copula1-model" and "copula2-model" were obtained using the algorithms introduced by Johnson (1987) and to "copula3-model" we have used the approach developed by McNeil *et al.* (2005). For each dependence value, we made the simulation procedure and we obtained all values of Table 1 cells, but for the Bayesian analysis we wrote a program using the Winbugs 1.4. software assuming that we only have the total quantity of individuals with negative results in tests 2 and 3.

As we have posterior distributions with not closed forms, we have used MCMC methods with Metropolis-Hastings algorithm to obtain estimates for the parameters. For all models, $60,000$ Gibbs samples were simulated from the conditional distributions for each parameter. From these generated samples, we discarded the first $10,000$ samples to eliminate the effect of the initial values and considering a spacing of size 100. Convergence of the algorithm was verified graphically and also using standard existing methods implemented in the software CODA.

5 Results of the simulated data set

5.1 Three copula model dependences within of scenary 1

Assuming each of the three dependence values considered for the study, we obtained the Bayes estimates to prevalence and performance test parameters, using the informative priors defined in section 3. The results are given in Table 5.

Within of this scenary the "copula1-model" has little effect over one of the dependent tests sensitivities (for $\varphi = 0.2$ and $\varphi = 0.5$ on S_3 and for $\varphi = 0.9$ over S_2). The specificities and the prevalence estimations do not show differences when the dependence increases within this scenary. It is important to observe that, when the dependence level is low, the S_1 and the S_2 tends to be a little understimated

Table 5 - Bayesian estimators of prevalence and performance tests parameters under three dependence levels of three copula functions within a design with verification bias present. (ICr: Credible interval)

Escenary 1: $S_2 = S_3 = 0.85$, $S_1 = E_1 = 0.5$, $E_2 = E_3 = 0.95$

		FGM	Gumbel	Clayton
Dependence	Param.	Mean (95%IC)	Mean(95% ICr)	Mean(95% IC)
	S_1	0.469(0.44-0.50)	0.502(0.47-0.53)	0.512(0.48-0.54)
	S_2	0.838(0.81-0.86)	0.856(0.83-0.88)	0.811(0.78-0.84)
0.2	S_3	0.859(0.84-0.88)	0.894(0.87-0.91)	0.850(0.83-0.87)
$Weak$	E_1	0.507(0.50-0.52)	0.506(0.50-0.52)	0.502(0.49-0.51)
	E_2	0.948(0.94-0.95)	0.957(0.95-0.96)	0.947(0.94-0.95)
	E_3	0.954(0.95-0.96)	0.957(0.95-0.96)	0.943(0.94-0.95)
	p	0.101(0.095-0.107)	0.100(0.094-0.106)	0.102(0.096-0.106)
	S_1	0.508(0.48-0.54)	0.508(0.47-0.54)	0.476(0.44-0.51)
	S_2	0.835(0.81-0.86)	0.909(0.89-0.93)	0.800(0.71-0.83)
0.5	S_3	0.849(0.83-0.87)	0.877(0.86-0.90)	0.812(0.78-0.84)
$Moderate$	E_1	0.503(0.49-0.51)	0.497(0.49-0.51)	0.507(0.50-0.52)
	E_2	0.946(0.94-0.95)	0.962(0.96-0.97)	0.951(0.95-0.96)
	E_3	0.955(0.95-0.96)	0.963(0.96-0.97)	0.949(0.94-0.95)
	p	0.100(0.095-0.107)	0.100(0.094-0.106)	0.105(0.098-0.111)
	S_1	0.509(0.48-0.54)	0.510(0.48-0.54)	0.485(0.45-0.50)
	S_2	0.849(0.82-0.87)	0.909(0.89-0.92)	0.788(0.76-0.82)
0.9	S_3	0.838(0.81-0.86)	0.905(0.89-0.92)	0.802(0.77-0.83)
$Strong$	E_1	0.505(0.49-0.51)	0.500(0.49-0.51)	0.502(0.49-0.51)
	E_2	0.950(0.94-0.95)	0.966(0.96-0.97)	0.951(0.95-0.96)
	E_3	0.947(0.94-0.95)	0.967(0.96-0.97)	0.952(0.95-0.96)
	p	0.101(0.095-0.107)	0.101(0.094-0.106)	0.101(0.099-0.112)

and the S_3 tends be a little overestimated (bias = 0.03 for S_1, 0.01 for S_2 and 0.009 for S_3), being the bias less important in the last two cases whenever, the credibility regions include the true value of the parameter in all cases. For the other two dependence levels, the effect over S_1 is in opposition to the observed in the low level. When we have dependent tests with relatively high sensitivities and with low Gumbel dependence level, the effect of the same tends to overestimate the sensitivity of one of two dependent tests (in this case S_3), while the other two sensitivities and the specificities trends to be unbiased. When the dependence level increases (moderate level), the first test sensitivity and especificity estimators remain unbiased but all other estimators are overestimated. This behavior remains unchanged in the highest dependence level, but for one of the dependent tests (test 2), the bias increases with the dependence while the other one remains in the same biased value. With "copula3-model" dependence, it was observed that, one of the dependent sensitivities is understimate in the three dependence levels and the bias increases with the increasing of dependence. With weak Clayton dependence the independent test sensitivity is unbiased but the same is understimated in the other

two dependence levels while the prevalence and specificities remains unbiased for all dependence levels.

5.2 Three copula model dependences within of scenary 2

The obtained results assuming tests witn relatively low sensibilities inside of a design with three diagnostic tests, to appear in Table 6.

Table 6 - Bayesian estimators of prevalence and performance tests parameters under three dependence levels of three copula functions within a design with verification bias present. (ICr: Credible interval)

Escenary 2: $S_2 = S_3 = 0.45$, $S_1 = E_1 = 0.5$, $E_2 = E_3 = 0.95$

		FGM	Gumbel	Clayton
Dependence	Param.	Mean (95%IC)	Mean(95% ICr)	Mean(95% IC)
	S_1	0.520(0.49-0.56)	0.483(0.45-0.52)	0.450(0.41-0.49)
	S_2	0.425(0.39-0.46)	0.525(0.49-0.56)	0.447(0.41-0.48)
0.2	S_3	0.432(0.40-0.47)	0.511(0.48-0.54)	0.411(0.38-0.45)
Weak	E_1	0.506(0.50-0.52)	0.506(0.50-0.52)	0.505(0.49-0.52)
	E_2	0.948(0.94-0.95)	0.957(0.95-0.96)	0.951(0.95-0.96)
	E_3	0.954(0.95-0.96)	0.957(0.95-0.96)	0.949(0.94-0.95)
	p	0.103(0.096-0.111)	0.100(0.094-0.107)	0.098(0.100-0.120)
	S_1	0.483(0.45-0.52)	0.508(0.47-0.54)	0.463(0.43-0.50)
	S_2	0.442(0.41-0.48)	0.562(0.89-0.93)	0.397(0.36-0.43)
0.5	S_3	0.432(0.40-0.47)	0.510(0.86-0.90)	0.430(0.39-0.47)
Moderate	E_1	0.501(0.49-0.51)	0.498(0.49-0.51)	0.500(0.49-0.52)
	E_2	0.945(0.94-0.95)	0.962(0.96-0.97)	0.951(0.94-0.95)
	E_3	0.955(0.95-0.96)	0.964(0.96-0.97)	0.952(0.95-0.96)
	p	0.103(0.097-0.112)	0.098(0.092-0.104)	0.109(0.100-0.120)
	S_1	0.459(0.42-0.50)	0.516(0.48-0.55)	0.472(0.44-0.51)
	S_2	0.447(0.41-0.48)	0.665(0.63-0.70)	0.409(0.38-0.44)
0.9	S_3	0.389(0.35-0.42)	0.676(0.65-0.71)	0.441(0.41-0.48)
Strong	E_1	0.502(0.49-0.51)	0.502(0.49-0.51)	0.501(0.49-0.51)
	E_2	0.950(0.94-0.95)	0.965(0.96-0.97)	0.949(0.94-0.95)
	E_3	0.947(0.94-0.95)	0.969(0.96-0.97)	0.951(0.94-0.95)
	p	0.107(0.099-0.115)	0.094(0.088-0.099)	0.107(0.100-0.120)

When the FGM dependence is low, the effect of the same over sensibility estimators is more evident than those observed in the other scenary. The S_1 tends to be overestimated, while the other two show a tendency to be underestimated. In the moderate dependence level, the MLE gives unbiased estimates but the Bayes procedure shows a different behavior. In the last dependence level, the S_1 MLE is unbiased but the S_2 tends to be overestimated and the S_3 tends to be underestimated while the Bayes procedure tends to underestimated the S_1 parameter, underestimated broadly the S_3 parameter and the S_2 estimator tends to be unbiased (Table 6). With Gumbel dependence, the estimation behavior is similar

to those observed in the other scenary, the positive bias in the all parameters except to independent test sensibility increases with the increasing of the dependence. When de dependence level increase, the prevalence tends to underestimated. The Clayton dependence shows a behavior similar with these observed in data under FGM dependence (Table 6).

Discussion

In many diagnostic medical studies, factors as the study design and the availability of diagnostic procedures can leads to dependence between diagnostic tests under verification bias, which is an important problem given the implications on medical decision to allocating the therapeutic procedure for a patient. In this paper, we showed these problems considering a simulation study with three diagnostic tests, two of them with continuous dichotomized outcomes and three different dependence levels within three different copula dependence structures. Our simulate design includes two situations; the first one the biological traits measured express important changes in presence of the illness which implies high sensitivity in the test and the another one, that sensitivity is lower and the expression of the traits can be mixtured with other kind of the biological process present in the individual in the moment of the measurement.

When the dependence structure is likes FGM copula regardless the degree of the same, at least one of the tests parameters is underestimated or overestimated and the effect is smaller when we have tests with relatively high sensitivities. In the opposite direction (tests with low sensitivities), the effect is more strong. If the three tests have low sensitivities, it is important to point out that the low dependence level affects the independent test sensitivity estimator even when the other two tests estimates remain unbiased.

If the dependence structure is of the Gumbel type, in general, it has no effect on the independent test parameters but the effect is very evident on all dependent test parameters being very strong when the dependence level is high, and in this case, the sensitivities are widely overestimated and the specificities show a trend in the same way but with lower bias; that result is independent of the tests ability to detect true positive cases.

For dependences type Clayton, the results are similar those obtained under FGM dependence. We observed differences among scenaries and among dependence levels within scenaries. In all cases, at least a test parameter estimator is biased tending to underestimation. In the same way as for the FGM model and in opposition to the Gumbel model, the Clayton dependence tends to underestimate the tests sensitivities without affecting the specificities.

Gupta and Roehrborn (2004) point out that in studies with the type of verification bias considered in this work, the sensitivities increasing and the specificities decreasing but those authores did not quantified the bias. We observed that the effect of the dependence do not have effect on the prevalence estimate but on the performance parameter tests its effect varies in according with the dependence

level and with the test capacity to identify true disease individuals. When the screening tests have high sensitivity, the minimum observed relative estimation bias is 1.4% to low dependence level of the FGM and a maximum of 7.3% to high level of Clayton dependence, while screening tests with relatively low ability to detect positive cases, the relative estimation bias varies among 5.6% and 50%. Therefore, when the design to colect data consideres biological traits with relatively low ability to identify positive cases and verification bias, the dependence copula has an effect on the performance test parameters higer than these observed with tests that have high detection ability.

In agreement with our results, it is important to point out that when the diagnostic procedure includes continuous outcome variables with a cut point, the presence of the dependence structure between variables remains despite the dicotomization process and it could not have the same effect on the estimates as those observed if the tests were strictly binary. So, it is important to make a graphical analysis with the continuous measures to detect trends and behaviors of continuous dependent data, developed in the literature as Kendall plots (Genest and Boies, 2003) for instance. The approach using copula function has some advantages when compared to the other existing approaches introduced in the literature; the test parameters and the prevalence parameters are direct components of the likelihood function and standard existing programs like the Winbugs software can be used to simulate samples for the joint posterior distribution of interest. Other advantage of the copula functions is modeling dependences that not fitted to known linear or concordance forms, using for that different types of copulas each of them with a parameter that identifies a specific dependence structure.

To apply our Bayesian procedure, we assumed informative priors on the copula parameters and non-informative priors on the test parameters; this is a way to address the identifiability problem proposed by Joseph *et al.* (1995).

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TOVAR CUEVAS, J. R.; ACHCAR, J. A. Dependência entre três testes diagnósticos na presença de vício de verificação: Uso de funções cópulas. *Rev. Bras. Biom.*, São Paulo, v.29, n.1, p.74-90, 2011.

▪ RESUMO: O estudo da dependencia entre os resultados de dois testes diagnósticos é importante pois a decisão sobre qual tratamento terapêutico é adequado para a doença depende dos resultados dos testes. Neste artigo, introduzimos um procedimento Bayesiano para estudar o efeito de diferentes níveis de dependência tipo cópula sobre as estimativas da prevalência e dos parâmetros de desempenho de testes diagnósticos. Simulou-se um planejamento com viés de verificação e três testes diagnósticos, dois deles

dependentes e outro independente. Simularam-se dados com estruturas FGM, Gumbel e Clayton cada uma com três níveis de dependência: fraca, moderada e forte sob dois scenários: sensibilidades relativamente altas com especificidades altas e sensibilidades relativamente baixas com altas especificidades.

▪ PALAVRAS-CHAVE: Testes diagnósticos dependentes; análise bayesiana; funções cópulas; cópula Farley Gumbel Morgenstern (FGM); cópula de Gumbel; cópula de Clayton.

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