THE USE OF COPULAS IN COST-EFFECTIVENESS ANALYSIS

THE USE OF COPULAS IN COST-EFFECTIVENESS ANALYSIS

By JUAN PABLO DÍAZ-MARTÍNEZ, B. Sc.

A thesis submitted to the School of Graduate Studies in Partial Fulfillment of the Requirements

Master University MASTER OF SCIENCE (2017) Hamilton, Ontario (Health Research Methodology)

TITLE: The Use of Copulas in Cost-Effectiveness Analysis

AUTHOR: Juan Pablo Díaz-Martínez, B.Sc. (UNAM)

SUPERVISOR: Professor Lehana Thabane

NUMBER OF PAGES: vii, 43

Declaration of academic achievement

This thesis project encompasses the work undertaken during 6 months of research and coding.

Abstract

Background: Copula methods have been proposed as a way of modeling dependence between random variables because it lies in the flexibility of the assumption on marginals. As previous authors stated, "A copula is a function which joins or “couples” a multivariate distribution function to its one-dimensional marginal distribution functions. Given that cost and effectiveness are often related to each other and therefore they show statistical dependence, the use of copulas to handle uncertainty caused by sampling variation could be potentially useful when cost-effectiveness analyses (CEA) are performed using patient-level data.

The objective of this study was to empirically compare various copula distributions with two traditional methods, namely, the bootstrapping approach and the Bayesian approach assuming that incremental cost and LYs gained are bivariate normally distributed.

Methods: The patient-level data from a previously published observational study were analyzed using four copula distributions: independent, Farlie-Gumbel-Morgenstern (FGM), Frank and Clayton copulas. Using the results from the traditional methods previously published, models were compared in terms of incremental cost, incremental life years (LYs) gained and the cost-effectiveness acceptability curves (CEACs) based on the net monetary benefit (NMB).

Results: Using the traditional methods provided similar results. The most pronounced impact was the improvement in precision given that the confidence intervals were so much narrower for the copulas methods in comparison to the traditional methods. Consequently, the probability of being optimal derived from the Frank and Clayton copulas were close to 1.0 at a willingness to pay (λ) of CA$20,000. By contrast, the traditional methods were optimal for a λ of $100,000 CAD.

Conclusions: The results of this study demonstreate the potential impact and importance of copulas in patient-level cost-effectiveness analysis. This approach could be particularly important in those situations where the data suggests some kind of dependence and some restrictions on the marginals, as observed in our case study.

Acknowledgments

The last two years have been filled with new experiences, new friends, and in incredible new knowledge base. Thank you to my supervisor, Dr. Lehana Thabane, for your mentorship during the whole time that I was part of the HRM program. I want to acknowledge the support of my committee members, Dr. Jean-Eric Tarride and Dr. Feng Xie whose expertise throughout this project has been much valued. I would like to thank my friends, who have been an important source of help and entertainment in my life. Thanks to Mom, Pepe and Tita for all their love and for always believing in me. Additionally, I want to thank my mentor and friend Herman Soto. Part of my academic achievements are because of him. Last but certainly not least, I want to thank Him whose spilled blood gave us eternal life.

Table of Contents

List of figures

List of tables

Chapter 1 Introduction

1.1 Background

Healthcare economic evaluations have been used with increasing frequency in recent years for the following reasons: (1) the population is aging; (2) the number and the type of the professionals in the health sector increase; (3) the medical techniques in every field develop; (4) the financial limitations impose the control of health expenses. In particular, there is a considerable interest from health providers worldwide in assessing the cost-effectiveness of new treatments. Pharmacoeconomic analyses are being used increasingly as the basis for reimbursement of the costs of new drugs. Reports of these analyses are often published in peer-reviewed journals. However, the analyses are complex and difficult to evaluate and very little guidance is given to researchers on exactly how the assessment of the implications of uncertainty should be done and how the results of the analysis should be presented **(A. H. Briggs, 2004)**. The problem is more serious for the economic evaluations conducted alongside a trial (i.e. using patient-level data) for two reasons:

- sampling uncertainty can arise since the results are derived from a single sample of trial participants.
- most of the time cost and effectiveness are often related to each other and therefore they show statistical dependence.

So, it is considered very interesting to focus our study on handling the sampling uncertainty in the case of cost-effectiveness analysis (CEA), this type of evaluations being more frequently used by the researchers than other types of evaluation, such as cost utility and cost benefit analysis **(C. Pitt, Goodman, & Hanson, 2016)**. Earlier attempts to address this issue regarding sampling uncertainty used parametric methods and then moved onto non-parametric methods; these methods are described below.

1.1.1 Common methods used for handling uncertainty caused by sampling variation

Many authors have proposed parametric and non-parametric methods to handle uncertainty caused by sampling variation **(Glick, Doshi, Sonnad, & Polsky, 2014)**. These methods can be grouped in two: i) methods based on the assumption of normality and ii) the non-parametric bootstrapping method.

Methods based on the assumption of normality

1. Fieller's theorem – When the statistic of interest is the incremental cost-effectiveness ratio (ICER), the Fieller theorem covers a general situation in that the nominator and the denominator are dependent with a covariance different than **0 (Willan & O'Brien, 1996)**.
2. Regression method – This method is useful to capture more distributional information, as well as the association between jointly dependent cost and outcome. In addition, it allows for the adjustment of covariates **(Willan, Briggs, & Hoch, 2004)**.
3. Bayesian methods – Using Bayesian estimation, different authors have proposed the bivariate normal distribution for the likelihood to model cost and effect simultaneously **(C. E. McCarron, Pullenayegum, Marshall, Goeree, & Tarride, 2009)**.

Even though that the previous methods invoke the central limit theorem (CLT), one of the limitations is that cost data are often highly skewed: additionally, effectiveness data could be bounded and hence not normally distributed.

The non-parametric bootstrapping method

The bootstrapping method is a nonparametric technique which involves large numbers of repetitive computations to estimate the shape of a statistic's sampling distribution empirically **(Efron & Tibshirani, 1994)**. This method resamples with replacement from the original sample data to build an empirical estimate of the sampling distribution for the parameter of interest. Some problems arise from this method; Heitjan et al. (2004) found out that coverage probabilities for this method are less satisfactory than the Fieller's method and deteriorates very rapidly as the true values of the ICER get closer to the vertical axis **(Heitjan & Li, 2004)**. Additionally, even with these modifications, the use of the nonparametric bootstrap is not recommended for samples of fewer than 100 observations **(Good & Hardin, 2012)**.

1.1.2 The potential use of copulas

A bivariate approach that imposes no distributional restrictions and measures dependence between cost and effectiveness regardless of the form (or skew, or kurtosis) of the marginals distribution is preferred. We think that copulas could be used to model dependence between random variables.

Copula is a function that connects marginal distributions with a joint distribution. Let's consider a continuous *m*-variate distribution function $F(y_1, \dots, y_m)$ with univariate marginal distributions $F(y_1), \dots, F(y_m)$ and inverse functions$F_1^{-1}, \dots, F_m^{-1}$. Then $y_1 = F_1^{-1}(u_1) \sim F_1, \dots, y_m = F_m^{-1}(u_m) \sim F_m$ where $u_1, \dots, u_m$ are uniformly distributed variates. Hence

$$\begin{aligned} F(y_1, \dots, y_m) &= F\left(F_1^{-1}(u_1), \dots, F_m^{-1}(u_m)\right) \\ &= \mathbb{P}[U_1 \leq u_1, \dots, U_m \leq u_m] \\ &= C(u_1, \dots, u_m) \end{aligned}$$

is the unique copula associated with the distribution function.

For an *m*-variate function F, the copula associated with F is a distribution function $C: [0,1]^m \rightarrow [0,1]$ that satisfies

$$F(y_1, \dots, y_m) = C(F_1(x_1), \dots, F_m(x_m): \theta)$$

From a practical point of view, input distributions can be linked through a suitable copula that can be selected regardless of the marginal distributions **(Nelsen, 2006**). This way dependence among inputs can be captured. In fact, copula is a multivariate distribution with uniform marginals on [0, 1]. No restrictions are placed on the marginal distributions; either continuous or discrete distributions can be used, and even empirical distributions.

1.2 Objective

The aim of this thesis was to use the copulas as an alternative to handle uncertainty caused by sampling variation in a CEA setting. A published trial-based economic evaluation comparing endovascular aneurysm repair (EVAR) with open surgical repair (OSR) was used **(Tarride et al., 2008**). We empirically compared the results of the bootstrapping method and assuming that the incremental cost and effectiveness are bivariate normally distributed to the copula approach using patient-level data from

1.3 Scope of the report

In the following chapters, I will introduce and discuss the copula method in order to do the empirical comparison. These chapters will lead to an analysis of the results and related issues, followed by some concluding statements. In Chapter 2, a literature review was done searching for patient-level CEA that used copulas to handle uncertainty caused by sampling variation. This search will be valuable for the thesis given that it will show the strengths and limitations of the copula method. A manuscript prepared for publication in a peer-reviewed journal is presented in Chapter 3. In this manuscript, I used patient-level data from a previously published observational study and analyzed it using different copula distributions. Comparisons are made with traditional methods previously published in terms of incremental total cost, incremental life years (LYs) gained and the cost-effectiveness acceptability curves (CEACs) based on the net monetary benefit (NMB). Lastly, a discussion on the key findings and concluding remarks lies in Chapter 4. Interpretations of our results, comparisons to similar studies, limitations, and future research are included in this chapter.

Chapter 2 Literature review

2.1 Data sources and search strategy

We conducted a comprehensive search to identify all the relevant literature regarding the use of copulas in CEA (up to May 12th, 2017). We developed the search strategy in MEDLINE (appendix 1) and modify it for other databases. Ovid MEDLINE In-Process & Other Nonindexed Citations, Web of Science, EMBASE, and JSTOR databases were searched. In addition, we searched the reference sections of relevant papers for potentially eligible studies.

Search terms were based on mapping keywords for copulas, sampling uncertainty and economic evaluation to indexed subject headings within the respective databases. Terms also were based on investigator-nominated terms and keywords from the titles and abstracts of potentially relevant studies. Relevant keywords and subject headings were combined allowing for alternative spellings and suffixes. Operators denoting the proximity of various search terms in relation to others were used to derive a comprehensive retrieval strategy.

2.2 Eligibility criteria and study selection

We did two stages in order to screen citation records. Firstly, the titles and abstracts of retrieved articles were screened for potential inclusion or exclusion. Secondly, those records not excluded at the first stage underwent a full-text review. We included studies if they met the following criteria: (1) the study analyzes the copulas method for handling sampling uncertainty in healthcare economic evaluations when patient level data was available, (2) the study analyzed the copulas method using one of the following approaches: methodologically, empirically, using simulations or a combination of these, and (3) the study was published in English or Spanish. We excluded those studies that assessed methods for purposes other than the incorporation and assessment of sampling variation (e.g., evidence synthesis, value of information analysis, model-based economic evaluation). Eligible articles citations were saved in EndnoteX8 library **(Clarivate Analytics)**.

2.3 Data synthesis

In the context of the current analysis, a descriptive synthesis of the included studies was undertaken.

The study data was collected in standardized online data extraction forms (Google forms) according to prespecified instructions. The data extraction form included information pertaining

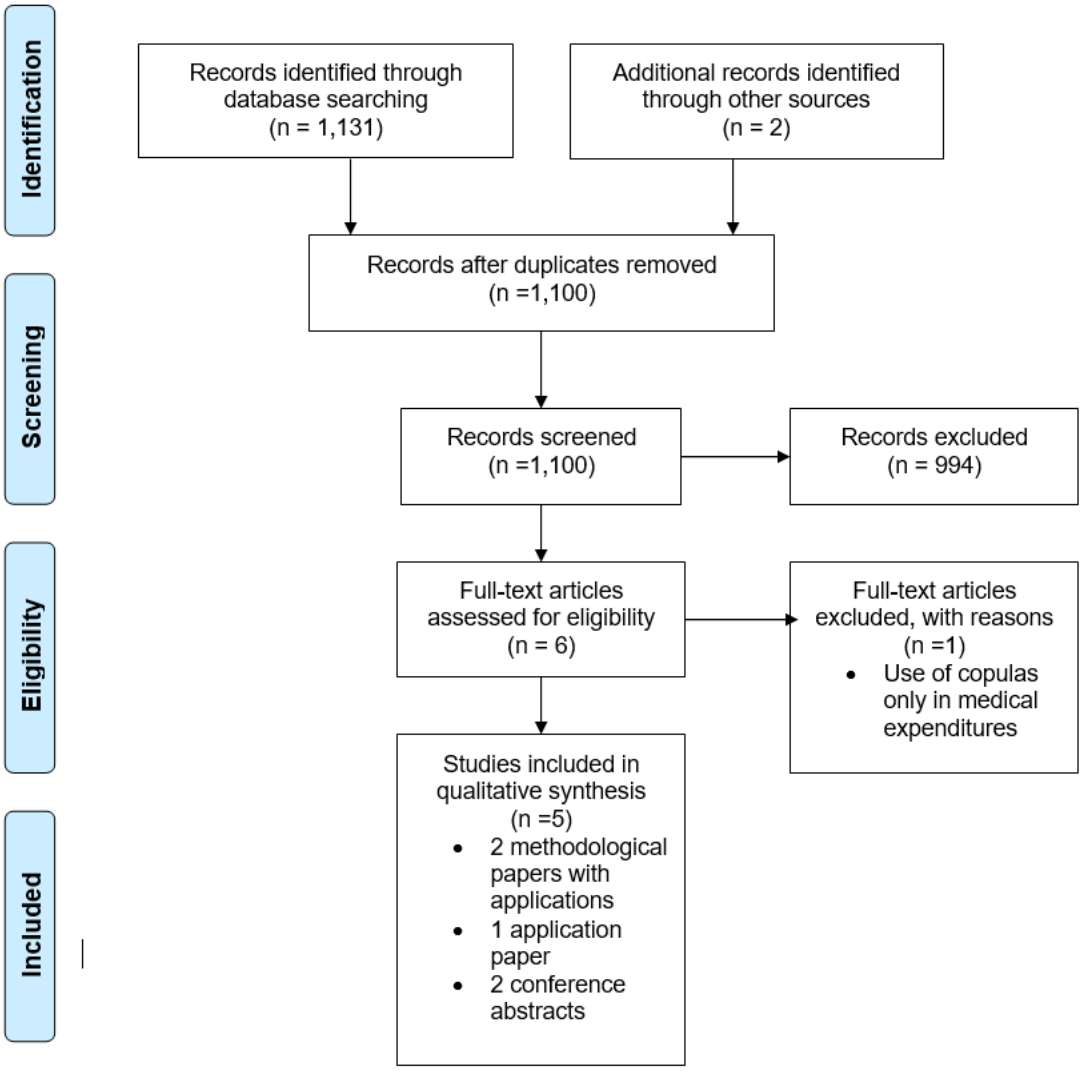
to study background, language of publication and funding sources. Additionally, we captured the following information: (1) statistical approach (Bayesian or frequentist); (2) type of economic evaluation; (3) type of article (paper or abstract); and (4) strengths and limitations of the analysis.

The data extraction form was pilot tested by all reviewers independently before its use. One reviewer performed data extraction (JPD). Finally, the data was synthesized to provide an overall description of the use of statistical methods to handle uncertainty in economic evaluations of patient-level data.

2.4 Results

The literature search yielded 1,133 potentially relevant bibliographic records (Figure 1). From the 1,133 citations, six articles were retrieved for relevance assessment. Only five studies met the final inclusion criteria **(Crespo et al., 2013; Fontaine, Daures, & Landais, 2017; Ibuka & Russell, 2009; Khan, Morris, Hackshaw, & Lee, 2015; Quinn, 2007)**. Two of these studies were classified as methodological papers with applications (Fontaine et al., 2017; Quinn, 2007), one was classified as application papers (Khan et al., 2015) and the last two were conference abstracts **(Crespo et al., 2013; Ibuka & Russell, 2009)**. For the purpose of this review, the methodological papers classification pertains to those papers that used applications merely for illustrative purposes. The application papers classification refers to those papers whose primary objective was an economic evaluation, where the copula method was used to incorporate sampling uncertainty.

Figure 1 PRISMA flowchart



Khan et al. conducted a cost-utility analysis using patient-level data of erlotinib versus supportive care (placebo) overall and within a predefined rash subgroup in elderly patients with advanced non-small-cell lung cancer who are unfit for chemotherapy and receive only active supportive care due to their poor performance status or presence of comorbidities **(Khan et al., 2015)**. Using the Gaussian copula, they found that erlotinib had about 80% chance of being cost-effective at thresholds between £50 000– £60 000 in a subset of elderly poor performance patients with NSCLC unfit for chemotherapy who develop first cycle (28 days) rash.

The two methodological papers with applications aimed to make its own contributions to the development of copulas as a methodology for the individual level data CEA. Quinn provided a

generalizable systematic approach to the estimation of copulas in a CEA context **(Quinn, 2007)**. Using a randomized controlled trial, Quinn compared the use of different copulas (FGM, Frank, Product) to the assumption that cost and effectiveness followed a bivariate normal distribution; he found that the use of copulas the can improve estimation of the treatment effect resulting in either incremental cost-effectiveness ratios (ICER) or incremental net benefit (INB) more accurately estimated. The other paper explored the modeling of the joint density and an estimation method of the costs, and quality adjusted life years (QALY) in a cost-effectiveness analysis in case of censoring **(Fontaine et al., 2017)**. Using different copula distributions, Fontaine et al. found that uncertainty is reduced when copulas are used in comparison to standard regression models (I.e. normality assumption). Additionally, they provided a procedure to find INB and ICER and their confidence intervals (CIs), even in case of censoring.

Finally, the two conference abstracts used observational data in order to analyze the applicability of copulas distribution in economic evaluations **(Crespo et al., 2013; Ibuka & Russell, 2009)**. Crespo et al. analyzed data from a study of patients with allergic rhinitis in Spain. The main findings were that using copulas allowed to adjust better the non-lineal relation between cost and effectiveness; furthermore, this approach could improve probabilistic sensitivity analyses. Ibuka et al. used different copula distributions to model dependence at the patient level using the National Health and Nutrition Examination Survey (NHANES I) I Epidemiologic Follow-up Study who experienced at least 1 hospital stay from 1971 to 1992; given the nature of the survey, Both cost and effectiveness were conditioned on age, systolic blood pressure, and the number of major chronic conditions; they concluded that the use of copulas could improve dependence in CEA when patient-level data is available.

2.5 Conclusion

The results of this review are intended to provide, for the first time, a comprehensive description of the use of copula methods to handle uncertainty due to sampling variation in patient-level CEA. The review was limited to published studies identified from three databases and relied on a single reviewer. However, the search strategy covered the largest databases and was designed in consultation with a trained research librarian. The review was limited to patient-level economic evaluations using information from a single source and did not consider decision analytic models using several data sources.

To the extent that important health policy decisions are informed by the results of economic evaluations, and that these results are subject to uncertainty, a new comprehensive and robust approach is required. This would include the use of all copulas to inform decision makers. Our review found that the use of copulas in CEA reduce uncertainty (i.e. narrower confidence intervals) regardless the copula distribution chosen, suggesting that copulas methods may offer certain advantages over traditional methods.

Chapter 3 The use of copulas in cost-effectiveness analysis using patient-level data: An empirical comparison against traditional methods

Diaz-Martinez Juan Pablo, Tarride Jean-Eric, Xie Feng, Soto-Molina Herman, Thabane Lehana.

Background

Economic evaluations are often used to compare health technology interventions and inform health care decisions. Worldwide, the most common economic evaluation is cost-effectiveness analysis or cost-utility analysis (incorporates quality of life) **(Drummond, Sculpher, Claxton, Stoddart, & Torrance, 2015)**. The purpose of cost-effectiveness analysis is to compare the differences in increments of cost and effectiveness between two or more interventions **(Drummond et al., 2015; Glick et al., 2014)**. However, when cost-effectiveness analysis (CEA) is conducted alongside a trial (i.e. patient-level analysis), sampling or stochastic uncertainty can arise since the results are derived from a single sample of trial participants. If the experiment is repeated with a different sample, it is likely that a different point estimate would be obtained **(Glick et al., 2014)**. In addition, dependency between cost and effectiveness should be accounted when conducting a CEA given that both variables are often related to each other (ie. correlated with each other).

When conducting a CEA based on a trial, many authors have proposed parametric and nonparametric methods to handle the uncertainty caused by sampling variation **(Drummond et al., 2015; Glick et al., 2014; Gray, Clarke, & Wolstenholme, 2011)**. The first attempt to handle this issue was using parametric methods (assuming that the incremental costs and effectiveness follows a bivariate normal distribution) and then moved onto non-parametric methods (bootstrapping). **(A. H. Briggs, 2012; Glick et al., 2014)**. The bootstrapping method is a nonparametric technique which involves large numbers of repetitive computations to estimate the shape of a statistic's sampling distribution empirically **(Efron & Tibshirani, 1994; Mooney, Duval, & Duvall, 1993; Stine, 1989)**. This method resamples with replacement from the original sample data to build an empirical estimate of the sampling distribution for the parameter of interest. Even though bootstrapping does not assume any form of distribution, if the average (sample mean) is the chosen statistic of interest, the results will be similar to those based on a normality assumption **(Thompson & Nixon, 2005)**. If the original sample is small, bootstrapping is problematic **(Good & Hardin, 2012)**. Another limitation of the bootstrapping method include the assumption on the existence of the second moment that may be questionable if there is a distinct possibility of obtaining a zero or near-zero value on the denominator of the incremental cost-effectiveness ratio (ICER).

Assuming that the incremental cost and incremental effectiveness have a bivariate normal distribution is the second approach. This assumption invokes the central limit theorem (CLT); for any population distribution of costs and effects, the distributions of the sample means will converge to normal distributions as the sample size increases **(Pagano & Gauvreau, 1994)**. Parametric methods such as the Fieller's method based on the bivariate normal distribution assumption have been developed to estimate a confidence interval for the ICER **(Willan & O'Brien, 1996)**. Additionally, a regression method was derived allowing for the adjustment for covariates **(Willan et al., 2004)**. This regression method has been useful to capture more distributional information, as well as the association between jointly dependent cost and outcome. A Bayesian approach based on the same assumption has also been explored. A literature review on the use of Bayesian methods to handle uncertainty in economic evaluations using patient level data **(C. E. McCarron et al., 2009)** found that the most common distributional form of likelihood to model cost and effect simultaneously was the bivariate normal distribution. There are some limitations of this approach. First, even though the CLT is invoked, as an example, effectiveness could be bounded between zero and one (i.e. the support of this random variable lies between these values), implying that if the effectiveness is normally distributed, there will be some observations that could be greater than one. Second, the normality assumption is not always appropriate for cost data that is often skewed. Third, assuming that both costs and effectiveness come from a bivariate normal distribution will result in dependence that is symmetric in both tails of the distribution, which could not be the case.

A bivariate approach that imposes no distributional restrictions and measures dependence (we represent this dependence using the greek letter θ) between cost and effectiveness regardless of the form (or skew, or kurtosis) of the marginals distribution[1] is preferred. The copula method has long been advocated as a better tool for modeling dependence between random variables **(Nelsen, 2006)** because it lies in the flexibility of the assumption on the marginals; thus, each marginal could be precisely defined according to the nearest approximation to the data. According to Nelsen, "A copula is a function which joins or "couples" a multivariate distribution function to its one-dimensional marginal distribution functions". The study of copulas started in probability and statistics **(Joe, 1997)**, and application of copulas to finance **(McNeil, Frey, & Embrechts, 2010)**

[1] The marginal distribution of a subset of a collection of random variables is the probability distribution of the variables contained in the subset. In other words, you are only interested in one of the random variables.

and survival analysis **(Romeo, Tanaka, & Pedroso-de-Lima, 2006)** has been increasing in the recent years. Through copula, dependence among inputs can be captured. In fact, a copula is a multivariate distribution with uniform marginals on [0, 1].

The aim of this study was to use copulas as an alternative to handle uncertainty caused by sampling variation when a CEA is conducted using patient-level data. We empirically compared the results of the bootstrapping method and assuming that the incremental cost and effectiveness are bivariate normally distributed (i.e. traditional method) to the copula approach using patient-level data from a published trial-based economic evaluation comparing endovascular aneurysm repair (EVAR) with open surgical repair (OSR) **(Tarride et al., 2008)**. For the purposes of this study, the outcomes compared in this paper were: 1) the incremental cost, 2) the incremental effectiveness and 3) the cost-effectiveness acceptability curve (CEAC) based on the net monetary benefit (NMB). We also explored in much detail the use of different copulas distributions in the analysis of the comparisons mentioned previously.

Methods

Overview of the trial used in the analysis

Patient-level cost and effectiveness data from a 1-year prospective observational study conducted at London Health Sciences Centre, London, Ontario, Canada, was used to determine the incremental cost per life-year gained from EVAR as compared to OSR for the treatment of abdominal aortic aneurysms for patients at high surgical risk **(Tarride et al., 2008)**. Costs were expressed in 2006 Canadian dollars (CAD) and life years at 1-year were reported for 140 EVAR patients and 52 OSR patients. There was no significant difference in terms of clinical characteristics at baseline between both interventions. The estimated mean costs showed that EVAR ($34,147) was less expensive than OSR ($34,170) and the estimated mean life years indicated that EVAR (0.96) was more effective than OSR (0.85). The authors concluded that EVAR dominated OSR in terms of incremental cost per life year gained. Sampling uncertainty in the trial data was handled using the nonparametric bootstrapping method. Additionally, using the same data, other authors **(C. Elizabeth McCarron, Pullenayegum, Thabane, Goeree, & Tarride, 2013)** proposed a Bayesian bivariate normal model using vague and informative priors and compared it to the bootstrapping method in order to assess the impact of incorporating additional information into a cost-effectiveness analysis in terms of the net monetary benefit

(NMB) and cost-effectiveness acceptability curves (CEAC); this analysis found that the bootstrapping and Bayesian analyses using vague priors provided similar results **(C. Elizabeth McCarron et al., 2013)**.

Descriptive statistics

As mentioned before, 140 patients classified as high risk in the observational study were treated with EVAR and 52 with OSR **(Tarride et al., 2008)**. Table 1 describes cost and effects data from the study and Figure 4 (appendix) shows the scatterplot of the two variables. The outcomes of interest here are the incremental cost and the life years (LY) gained per patient.

Table 1 Mean incremental cost and LY gained

	EVAR: n = 140 **Mean (SD)**	**OSR: n = 52** **Mean (SD)**
LYs gained over a year	0.96 (0.014)	0.85 (0.046)
Incremental cost ($CAD)	$34,147 ($966.32)	$34,170 ($5,310.01)

LY – Life years. CAD – Canadian dollars.

We confirmed that neither costs nor effects are normally distributed. Figures 5 and 6 in the appendix show the kernel densities[2] and Q-Q plots[3] comparing the distributions of incremental cost and LYs gained with the normal distribution. In addition, Kendall's tau coefficient was -0.138, implying a negative dependence.

Given that health utilities are restricted to take value between zero and one and the time horizon was 1 year, we propose that effets will be beta distributed. The choice of this distribution is because it accounts directy for the skewness and bounded responses. In order to be consistent with McCarron's et al. study, the incremental cost is going to be gamma distributed.

[2] Kernel density estimation is a non-parametric way to estimate the probability density function of a random variable.

[3] Q-Q plot is a probability plot, which is a graphical method for comparing two probability distributions by plotting their quantiles against each other

Overview of the traditional methods for handling uncertainty caused by sampling variation used for the same data previously.

For the bootstrapping method, incremental cost and LY gained were sampled simultaneously to generate 1000 bootstrap replicates to estimate the sampling distribution for the sample mean costs and effects for both the EVAR and OSR groups as well as for the incremental costs and effects of EVAR compared to OSR. Using the percentile method, we estimate the 95% confidence intervals (CIs) around the various statistics of interest based on the sampled values **(C. Elizabeth McCarron et al., 2013; Tarride et al., 2008)**.

For the assumption that cost and effectiveness are bivariate normally distributed McCarron et al. (2013) made inferences using a Bayesian perspective. Incremental cost and LY gained were first modeled using bivariate normal distributions accommodating for the correlation between costs and life years observed for both interventions (EVAR and OSR). Likewise, invoking the CLT, both incremental cost and LY gained are normally distributed with means and standards deviations estimated from the sample means of the data. Their model also allowed the correlation between costs and life years to be different in the two study interventions.

Copulas method

Copulas are joint distributions generated from given marginals **(Nelsen, 2006) (Joe, 1997)**. In economic evaluations, they represent an improvement in modelling costs and effects simultaneously in two ways:

1. by enabling a range of probability distributions to be accomodated to each marginal.
2. by allowing the association between the random variables in a multivariate distribution to be specified separately for each bivariate pair of marginal distributions.

Sklar's theorem **(Sklar, 1959)** states that an *m*-dimensional copula (or *m*-copula[4]), is a function *C* from the unit *m*-cube $[0,1]^{m}$ to the unit interval $[0,1]$. From this, it follows that an *m*-copula is an *m*-dimensional distribution function with all *m* univariate marginals being uniformly distributed $U(0,1)$. Thus, the joint distribution is expressed in terms of its respective marginal distributions and a function *C* that binds them together. In this manner, copulas separate the joint association of two or more random variables from their marginal distributions, since all the information on the

[4] We are only interested in the case when *m*=2.

dependence structure should be contained within the copula itself, through θ. Once the marginal distributions have been specified, an appropriate copula is selected. Because copulas separate marginal distributions from dependence structures, the appropriate copula for a particular application is the one which best captures dependence features of the data. For the purposes of our study, we propose the next copulas functions given the dependence structure on the data **(Nelsen, 2006)**; we denote u_1 and u_2 as the marginals uniformly distributed.

Product copula

The simplest copula, the product copula, has the form

Equation 1

$$C(u_1, u_2) = u_1 u_2$$

As you can see, the product copula corresponds to the case when both marginals are independent.

Farlie–Gumbel–Morgenstern copula

The Farlie–Gumbel–Morgenstern (FGM) **(Morgenstern, 1956)** copula takes the form

Equation 2

$$C(u_1, u_2; \theta) = u_1 u_2(1 + \theta(1 - u_1)(1 - u_2))$$

This copula is attractive due to its simplicity. However, it is restrictive because this copula is only useful when dependence between the two marginals is modest in magnitude. If the dependence parameter equals zero, then the FGM copula changes to the product copula.

Frank copula

The Frank copula **(Frank, 1979)** takes the form

Equation 3

$$C(u_1, u_2; \theta) = -\theta^{-1} \ln\left\{1 + \frac{(e^{-\theta u_1} - 1)((e^{-\theta u_2} - 1)}{e^{-\theta} - 1}\right\}$$

It is popular for two reasons. First, unlike some other copulas, it permits negative dependence between the marginals. Second, dependence is symmetric in both tails. However, dependence in the tails of the Frank copula tends to be relatively weak.

Clayton copula

The Clayton copula **(Clayton, 1978)** takes the form:

Equation 4

$$C(u_1, u_2; \theta) = [\max\{u_1^{-\theta} + u_2^{-\theta} - 1, 0\}]^{-1/\theta}$$

with $\theta \in [-1, \infty) \backslash 0$. Notice that as θ approaches to zero, the marginals become independent. This copula has been used to study random variables that exhibits strong left tail dependence and relatively weak right tail dependence.

Once the copula has been selected, the next step is to estimate the parameters for each copula proposed above. The next section describes the method used in our analysis.

Estimation

As mentioned before, we were interested in modelling dependence between incremental cost and LY gained when these marginals are conditional on covariates. Simultaneous estimation of all parameters using the full maximum likelihood (FML) approach is the most direct estimation method **(Yan, 2007)**. Once we have chosen the copula to be estimated, we derived the likelihood for the case of a bivariate model (i.e. *m*=2). For our analysis, we denoted each marginal distribution as $F_j(y_j \mid \mathbf{x}_1; \beta_j), j = i, 2$, conditioned on a covariate denoted as $\mathbf{x}_1$. Now let's denote the marginal density functions as $f_j(y_j \mid \mathbf{x}_1; \beta_j) = \partial F_j(y_j \mid \mathbf{x}_1; \beta_j)/\partial y_j$ and the copula derivative as $C_j(F_1(y_1 \mid \mathbf{x}_1; \beta_1), F_2(y_2 \mid \mathbf{x}_1; \beta_2); \theta)/\partial F_j$. Then the copula density is

$$c(F_1(y_j \mid \mathbf{x}_1; \beta_1), F_2(y_2 \mid \mathbf{x}_1; \beta_2); \theta) = \frac{\partial^2 C(F_1(y_1 \mid \mathbf{x}_1; \beta_1), F_2(y_2 \mid \mathbf{x}_1; \beta_2); \theta)}{\partial y_1 \partial y_2}$$
$$= C_{12}(F_1(y_1 \mid \mathbf{x}_1; \beta_1), F_2(y_2 \mid \mathbf{x}_1; \beta_2); \theta)\, f_1(y_1 \mid \mathbf{x}_1; \beta_1)\, f_2(y_2 \mid \mathbf{x}_1; \beta_2)$$

where

$$C_{12}(F_1(y_1 \mid \mathbf{x}_1; \beta_1), F_2(y_2 \mid \mathbf{x}_1; \beta_2); \theta) = \partial C(F_1(y_1 \mid \mathbf{x}_1; \beta_1), F_2(y_2 \mid \mathbf{x}_1; \beta_2); \theta)/\partial F_1 \partial F_2$$

With the information above we were able to construct the likelihood function

$\ell((y_1 \mid \mathbf{x}_1;\beta_1),(y_2 \mid \mathbf{x}_1;\beta_2);\theta)$=$C_{12}(F_1(y_1 \mid \mathbf{x}_1;\beta_1),F_2(y_2 \mid \mathbf{x}_1;\beta_2);\theta)\ f_1(y_1 \mid \mathbf{x}_1;\beta_1)\ f_2(y_2 \mid \mathbf{x}_1;\beta_2)$

and the log-likelihood function is

$$\log\big(\ell(\cdot)\big) = \sum_{i=1}^{n}\sum_{j=1}^{2}\log\big(\ f_{ji}(y_{ji} \mid \mathbf{x}_{1i};\beta_j\ \big) + \sum_{i=1}^{n}\ \log(C_{12}(F_1(y_{1i} \mid \mathbf{x}_{1i};\beta_1),F_2(y_{2i} \mid \mathbf{x}_{1i};\beta_2);\theta))^{5}$$

FML estimates are obtained by solving the score equations $\partial\log\big(\ell(\cdot)\big)/\partial\boldsymbol{\alpha} = 0$ where $\boldsymbol{\alpha} = (\beta_1,\beta_2,\theta)$. These equations will be nonlinear in general, but standard quasi-Newton iterative algorithms are available in any programming language. The estimation process can be summarized as follows

1. Specify the functional forms of each marginal distribution $F_j\big(y_j \mid \mathbf{x}_1;\beta_j\big), j = 1,2$, each with some vector of parameters β_j. For our analysis, while incremental cost is given one distribution and LYs gained another, we adjusted each marginal with the same covariate $\mathbf{x}_1$ (i.e. using a dummy variable as a treatment indicator). For the effect, given that is beta distributed, we performed a regression analysis in which the dependent variable was the LYs gained. Since the model is based on the assumption that the response is beta distributed, it has been called the beta regression model. The beta regression model is based on an alternative parameterization of the beta density in terms of the variate mean and a precision parameter (Ferrari & Cribari-Neto, 2004). Let's $Y \sim Be(p,q)$, Ferrari and Cribari-Neto proposed a different parametrization by setting $\mu = p/(p+q)$ and $\phi = p+q$. Hence the beta density is expressed as

$$f(y;\mu,\phi) = \frac{\Gamma(\phi)}{\Gamma(\mu\phi)\Gamma((1-\mu)\phi}y^{\mu\phi-1}(1-y)^{\ (1-\mu)\phi-1}, 0<y<1$$

[5] Given that a copula is a distribution function with uniformly margins, the log-likelihood of the copula density expressed here will contained the marginals information using the probability integral transformation.

with $0 < \mu < 1$ and $\phi > 0$. Hence $Y \sim Be(\mu, \phi)$. Using our data, the beta regression model is defined as

$$g(\mu_i) = \beta_1 x_{i1} + \beta_2 x_{i2}, i = 1,2, \dots, 192.$$

where $x_{i1} = 1$ for all i so that the model has an intercept and $x_{i2} = 0 \; or \; 1$ being the treatment covariate. $g(\cdot)$ is a link function, For our analysis we chose the logit function as the link.

For the incremental cost, we used a generalized linear model (GLM) to model this dependent variable using the gamma distribution for the error distribution. Let's $Y \sim Gamma(\alpha, \beta)$, with α being the shape and β being the rate. Usually for GLM, there is alternative parameterization through mean (μ) and shape. Let's take $\mu = \alpha/\beta$ and put it into place of rate as $\beta = \alpha/\mu$. The gamma density with the previous alternative parameterization is expressed as

$$f(y; \mu, \alpha) = \frac{\alpha^{\mu}}{\Gamma(\mu)} y^{\mu-1} e^{-\alpha y}, 0 < y < \infty$$

with $\mu > 0$ and $\alpha > 0$. Hence $Y \sim Gamma(\mu, \alpha)$. Using our data, the gamma regression model is defined as

$$g(\mu_i) = \beta_1 x_{i1} + \beta_2 x_{i2}, i = 1,2, \dots, 192.$$

where $x_{i1} = 1$ for all i so that the model has an intercept and $x_{i2} = 0 \; or \; 1$ being the treatment covariate. $g(\cdot)$ is a link function, For our analysis we chose the identity function as the link.

2. Specify the functional form of the copula, $C(F_1(y_1), F_2(y_2); \theta)$. This can be done according to some knowledge of the dependence structure or any characteristics desired of the joint distribution. Given that our data showed a negative dependence we chose the FGM, Clayton and Frank copulas to model our data. In addition we also selected the product copula to show the case when independence is assumed.
3. Construct the copula density $c\big(F_1(y_j \mid \mathbf{x}_1; \beta_1), F_2(y_2 \mid \mathbf{x}_1; \beta_2); \theta\big)$ as well as the likelihood and log-likelihood functions.
4. The copula log-likelihood can be estimated according to any maximum likelihood procedure. We did it using the programming language R **(R Development Core Team, 2016)** through the function `optim`. The function `optim` requires starting values in order

to return a desirable solution; we used the estimates from step 1 and the Kendall's coefficient as the starting values for our analysis.

Copula selection

In the previous section we mentioned that one way to specify the functional form of the copula could be done by some knowledge of the dependence structure or any characteristics desired of the joint distribution. Another way is to use either the log-likelihood directly, or information criteria such as the Akaike Information Criterion (AIC), given by $AIC = 2k - 2\ln(L)$ for likelihood L and k free parameters, or Bayesian Information Criterion (BIC), given by $k\ln(n) - 2\ln(L)$ and where n is the sample size. Models do not need to be nested for this comparison; with each copula model, as well as the bivariate normal, containing an equal number of free parameters, the punitive approach taken towards parameterization is also not necessary **(Joe, 1997)**. The advantage of having immediate access to the log of the log-likelihood function, post-estimation, is an advantage over other methods. For both information criteria, the smaller they are the better the fit of the model is (from a statistical perspective) as they reflect a trade-off between the lack of fit and the number of parameters in the model.

The net benefit framework

The objective of this analysis is to compare the different methods to handle uncertainty caused by sample variation in cost-effectiveness analysis; to do this and in order to be consistent with the previous analysis from the same data, we compared the cost-effectiveness acceptability curve (CEAC) for each method described previously (i.e. bootstrapping, assumption of bivariate normality and copulas). The CEAC was constructed by identifying the range of values of λ over which each intervention had the highest mean NMB **(Fenwick, Claxton, & Sculpher, 2001)**. The frontier indicates the probability that the intervention with the highest NMB will be cost-effective **(C. Elizabeth McCarron et al., 2013)**.

For the traditional methods, the CEACs have already been constructed and the methods have been discussed elsewhere **(C. Elizabeth McCarron et al., 2013)**. For the copula method, once the parameters for the margins and the dependence were estimated, we estimated $\mu_{\Delta E}$ and $\mu_{\Delta C}$ using Monte Carlo integration **(Doucet, de Freitas, & Gordon, 2001)**; this procedure was done using the library `copula` in `R` **(Kojadinovic & Yan, 2010)**. We drew 1000 simulations for each

intervention and using the Monte Carlo algorithm we estimated $\mu_{\Delta E}$,$\mu_{\Delta C}$ and thus the NMB and the CEAC.

Results

The trial point estimates showed that EVAR has slightly a lower 1-year cost of $24 and provides more benefits. In terms of effects EVAR had 0.11 more LYs gained compared with OSR for high-risk patients **(Tarride et al., 2008)**. Looking at the point estimates only, EVAR dominated OSR in terms of incremental cost per LY gained.

The bootstrapping method

Using the bootstrapping method, the estimated values for mean costs and LY for both the EVAR and OSR groups and incremental costs and LYs and their associated 95% CIs are presented in Table 2. The results correspond to those from the previous analyses **(Tarride et al., 2008) (C. Elizabeth McCarron et al., 2013)**. The estimated mean NMB at a willingness to pay (λ) of $10,000 was $2,785 (95% CI: $-6,610 - $14,134). The positive NMB measure indicates that EVAR is optimal compared to OSR at λ equal to $10,000.

Assumption that cost and effectiveness are bivariate normally distributed

The posterior mean estimates and 95% CrIs obtained from the Bayesian bivariate normal analysis with vague priors[6] and a gamma distribution for the incremental cost were similar to the mean estimates and 95% CIs from the nonparametric bootstrap **(C. Elizabeth McCarron et al., 2013)** (Table 2). The CEACs were also similar (Figure 3). These results reflect that more weight that was given to the data (i.e. more weight to the likelihood than the priors).

Even though a normal distribution for the incremental cost was not part of this analysis, McCarron et al. showed that the main impact between these two distributions was in terms of the estimated precision for the mean costs in the OSR group. The gamma distribution increased this precision relative to the normal distribution. This increased precision around the mean costs was due to lower estimates for the variance in the data compared to what was estimated using a normal distribution and what was observed in the trial data itself **(C. Elizabeth McCarron et al., 2013)**.

[6] It is well known that the use of vague or noninformative priors in a Bayesian model will give the same results as the frequentist approach **(Samaniego, 2010)**.

Copula method

Table 4 shows that the Frank copula is the copula with the highest log-likelihood value (-1549.29); if we had to rank the copulas distribution based on the information criteria the rank would be the following: first - Frank, second - FGM and Clayton and third - independent. The estimates given by the FML procedure of the joint distribution are in Table 3. The FGM, Frank, Clayton and product copulas contain gamma distributed intervention incremental cost and beta distributed LYs gained. In addition, appendix 1 presents the densities and contours plots for each copula used in the analysis.

The Clayton copula and the product copula have the same estimates except for the α parameter (i.e. rate). Because the rate has a strong impact on the shape of the gamma distribution, the product copula resulted in a longer tail than the Clayton copula. As for the other copulas, the greatest impact on the treatment in terms of the effectiveness (i.e. LYs gained) was observed in the Frank copula. Subject to evaluation of the relative performance of the copula models, the evidence of the efficacy of the EVAR procedure is the same for the copulas used in this model.

Using the estimates in Table 3 and the Monte Carlo algorithm explained in the methods section, we were able to perform the cost-effectiveness analysis using the copulas method. The estimated values for mean incremental cost and LY for both the EVAR and OSR groups and incremental cost and LYs and their associated 95% CIs are presented in Table 2. Additionally, the estimated mean NMB for each copula at a willingness to pay of $10,000 and its 95% CI are also presented.

When comparing the bootstrapping and the bivariate normal methods with the copulas method (Figure 1 and Table 2), some key distinctions can be observed. In terms of the point estimates of the incremental cost, the three methods produced similar results for both EVAR and OSR interventions. The main difference was the precision of the estimates, specifically for the OSR group. While the bootstrapping and the bivariate normal methods resulted in wider CIs, the FGM, Frank, FGM and product copulas returned narrower CIs. Consequently, the incremental cost emanates the same improvement in precision. For the LYs gained, the precision of the estimates was improved using the copulas method for both interventions. Additionally, the point estimates employing the copula method for the EVAR group were lower as compared to the other methods due to the skewness and multimodality of the beta distribution which is not supported by the normal distribution. Because of this, the incremental LYs gained were shorter and remained

statistically significant. Finally, the estimated mean NMB at a willingness to pay of $10,000 through the copulas method were positive except for the FGM copula ($-697.00), However, all methods produced results that were not statistically significant.

As mentioned earlier, the CEACs present the range of values for λ over which EVAR or OSR had the highest NMB. The type of copula impacted the decision uncertainty. Looking at the CEACs in Figure 3, the curves indicate that the copulas method result in a shorter range over which OSR is optimal compared to EVAR except for the FGM copula. It is interesting that the probability of being optimal derived from the Frank and Clayton copulas are almost one for a λ of $20,000: this contrasts the previous results produced by the bootstrapping and the bivariate normal methods, where the probability get closer to one when λ is $100,000 approximately. Again, it is important to notice that the FGM copula, the bootstrapping method and the bivariate normal method showed that the probability that EVAR was optimal compared to OSR decreased for all λs, and consequently, the decision uncertainty increased.

Discussion

In recent years, considerable research has focused on issues of uncertainty **(Andrew H Briggs, 2004; Carayanni, 2009)**. However, there is a paucity of guidance that is given to analysts on exactly how this should be done and how the results of any analysis of sampling uncertainty should be presented. The bootstrapping method and assuming a bivariate normal distribution seem to be the most common approaches to handling uncertainty caused by sampling variation **(Glick et al., 2014; Gray et al., 2011)**; limitations of these methods have been explained above.

Moreover, regression-based approaches to cost-effectiveness have the potential to overcome a lot of the limiting assumptions made using non-parametric approaches **(A. H. Briggs, 2012)**. By using known information on covariates, more precise estimates of the parameters used in standard cost-effectiveness analysis, more precise posterior information, and more precise posterior probabilities can be obtained. This should help decision makers decide whether an intervention should be targeted at a specific population subgroup leading to efficient allocation of health resources, appropriate treatments for individuals without inefficiency, and cost-savings for the decision maker. As mentioned earlier, this regression approach relies on the assumption that the data comes from a bivariate normal distribution - an assumption which is not always true.

Our analysis compared the bootstrapping method and the bivariate normal method in cost-effectiveness analysis to a new approach (i.e., copulas) to model the dependence between cost and effectiveness. How to choose the appropriate copula for our data? A valid empirical approach is to estimate several different copulas and choose the model that yields the largest penalized log-likelihood value. According to our results, estimates of the Frank and FGM copulas indicate that dependence is negative, with the Frank copula attaining the highest likelihood value (Table 4). Hence, the most appropriate copula given the data is the Frank copula.

Theoretically speaking, copulas performed at least as well or better than standard bivariate normal model, with the advantage to accommodate distributional assumptions on the marginals not accommodated in the bivariate normal technique. We have shown that decision makers analyzing cost-effectiveness would benefit from the use of copulas to obtain covariate explanation of intervention incremental cost and effectiveness at an individual level, conditioning on more precisely estimated joint dependence and distribution. Even using a copula with a relatively simple functional form such as the product copula provided reliable estimates of parameters by reducing the uncertainty than restricting analysis to bivariate normality.

Our study has sought to show the potential impact of the use of copulas in trial-based economic evaluations. While the bootstrapping method and the bivariate normal method using a Bayesian approach with vague priors produced similar results, our study has demonstrated the potential use of copulas to influence both the decisions regarding intervention. Based on the copula chosen and depending on a decision maker's willingness to pay for a life year gained, this could result in very different reimbursement decisions. Given that decision makers look to maximize the health benefits subject to a budget constraint, the impact on uncertainty observed in the CEACs suggests the use of copulas could play a new role in decisions about future research, ensuring that resources are used efficiently. In our analysis the FGM copula showed something interesting; looking at Figure 3, the probability of being cost-effective for different thresholds of EVAR was lower as compared to other copulas and traditional methods. This is one of the main reasons of using different copulas for our analysis.

Inference about dependence can be implemented in a fully parametric or a partially parametric framework. However, as Hougaard has observed **(Hougaard, 2000)**, ". . . strictly speaking, copulas are not important from a statistical point of view. It is extremely rare that marginal

distributions are known. Assuming the marginals are known is in almost all cases in conflict with reality. Copulas make sense, however, in a more broad perspective, first of all as part of the combined approach . . . where the model is parameterized by means of the marginal distributions and the copula. Second, they make sense for illustrating dependence. . . ". Because of this, modeling marginal distributions should be done with care so that gross misspecification is avoided.

This study focused on the use of different copulas to handle sampling uncertainty in a cost-effectiveness analysis. McCarron et al (2013). concluded that ignoring specific sources of evidence could undermine cost-effectiveness results. An improvement to the use of copulas in cost-effectiveness analysis could be making inferences based on Bayesian approach. An example is a study that used a Gaussian copula to model the joint distribution of six count measures of health care **(M. Pitt, Chan, & Kohn, 2006)**. Future research could be done using this approach, letting all available evidence taken into consideration and subsequently, making well-informed health care decisions.

One limitation of our analysis is that we did not account for the long-term consequences. In one of the previous analysis, the 1-year mortality rates observed in the trial were extrapolated up to 5 years. However, these extrapolations did not account for quality of life differences or cost-effects associated with long-term comorbidities such as stroke, renal failure, and myocardial infarction **(Tarride et al., 2008)**. Furthermore, the previous study did not consider scenarios with different costs for endovascular devices for the initial procedure or the reinterventions because it was assumed that the prices would remained constant **(Tarride et al., 2008)**. With long-term data, the copula approach is still advantageous; one can choose a marginal distribution that suits the survival data (i.e. Weibull, exponential,etc.) and adjust the log-likelihood if censored observations are presented.

In the previous studies, in an empirical cost-effectiveness analysis, the true form of the distributions for the costs and effects remains unknown. If correct about the true population distributions, efficiency in estimating the population means could be gained. However, the use of estimators based on incorrect distributional assumptions can lead to misleading conclusions. Given that our analysis came from only one trial, future research could be based in Monte Carlo experiments in order to analyze the effects of model misspecification.

As we mentioned earlier, even though the sample mean performs well **(A. Briggs, Nixon, Dixon, & Thompson, 2005)**, LYs gained are bounded between zero one and hence, assuming a normal distribution to the effectiveness will be incorrect given the nature of the marginal distribution. We think that copulas overcame this issue.

Even though copulas narrowed the variation in the estimates of incremental cost and LYs gained overall, there was still consistent evidence of poor identification and missing information due to omitted variables. However, with more information, it is the copula that can improve on its approximation of the true NMB. Satisfying the requirements for reliable point estimation of cost and effectiveness for individuals is the first step towards reliable stochastic inference of new treatments and technologies. For this, more information, both individual and environmental, must be collected in clinical trials.

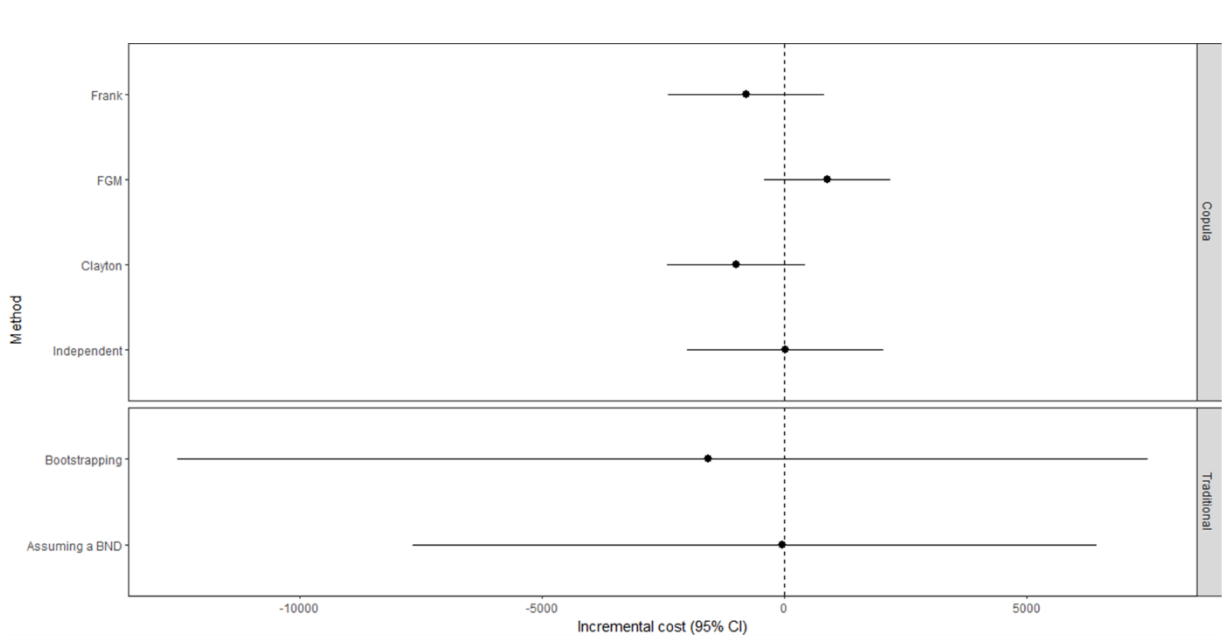
Table 2 Results for the three methndods used in the cost-effectiveness analysis

Uncertainty	Mean incremental cost, $ (95% CI)		Incremental cost, $ (95% CI)	Mean LYs gained, (95% CI)		Incremental LYs gained, (95% CI)	Mean NMB at $\lambda = 10,000$, $ (95% CI)
	EVAR	OSR		EVAR	OSR		
Bootstrapping	32,472 (31,123 - 34,090)	34,035 (25,079 - 45,098)	-1,563 (-12,518 - 7,509)	0.97 (0.94 – 0.99)	0.85 (0.75 – 0.94)	0.12 (0.02 – 0.22)	2,785 (-6,610 - 14,134)
Bivariate normal*	34,150 (32,600 - 35,760)	34,180 (28,010 - 41,660)	-35 (-7,660 - 6,437)	0.96 (0.94 – 0.99)	0.85 (0.76 – 0.94)	0.11 (0.01 – 0.21)	1,125 (-5,494 - 8,986)
Copula							
Frank	33,665 (32,549 - 34,782)	34,447 (33,280 - 35,613)	-781 (-2,390 - 828)	0.92 (0.91 – 0.93)	0.84 (0.83 – 0.86)	0.08 (0.06 – 0.10)	1,558 (-1,169 - 3,285)
FGM	34,517 (31,123 - 34,090)	33,635 (32,734 - 34,536)	882 (-418 - 2,183)	0.85 (0.84 – 0.86)	0.83 (0.82 – 0.85)	0.02 (0.01 – 0.04)	-697 (-2,049 - 656)
Clayton	33,926 (32,967 - 34,885)	34,922 (33,897 - 35,946)	-995 (-2,419 - 428)	0.88 (0.87 – 0.89)	0.86 (0.84 – 0.87)	0.02 (0.01 – 0.04)	1,226 (-214 - 2,665)
Independent	34,449 (33,074 - 35,824)	34,427 (32,969 - 35,886)	22 (-2,005 – 2,049)	0.89 (0.88 – 0.90)	0.85 (0.84– 0.86)	0.04 (0.02 – 0.05)	352 (-1,683 - 2,387)

* Credible intervals. The table shows the point and interval estimates for the incremental cost, LYs gained and NMB regarding the three methods used in our analysis. LY-Life years. NMB-Net monetary benefit. CI- Confidence interval. λ- Willingness-to-pay.

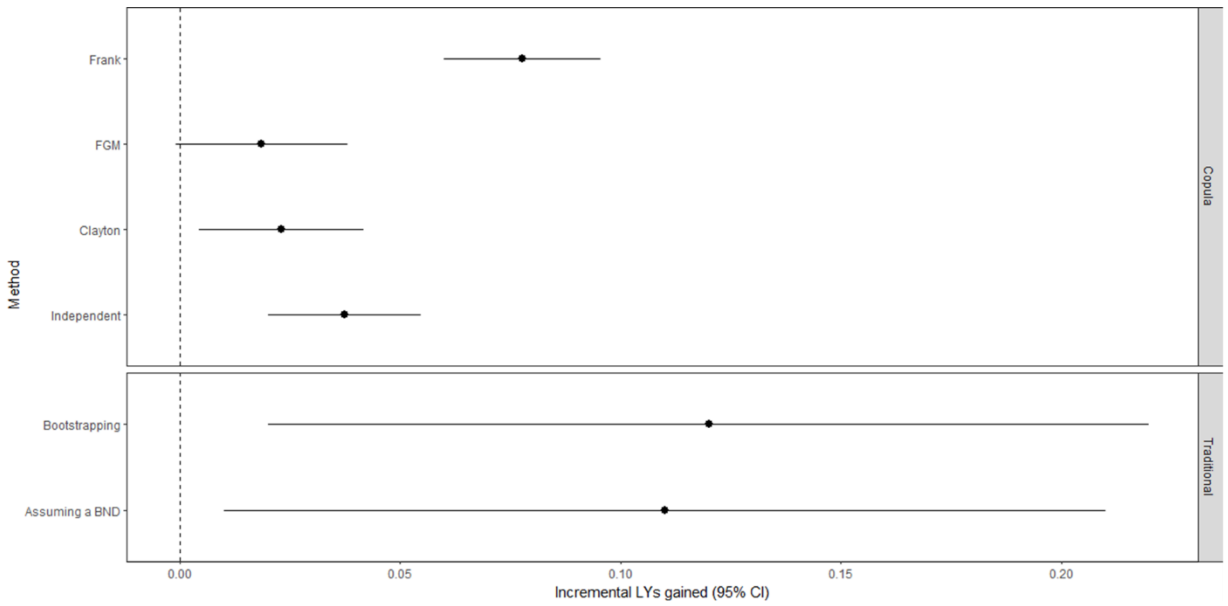
Figure 2 Forest plot: Comparison of the methods in terms of the incremental cost, LYs gained and mean NMB at λ=10,000.

A)



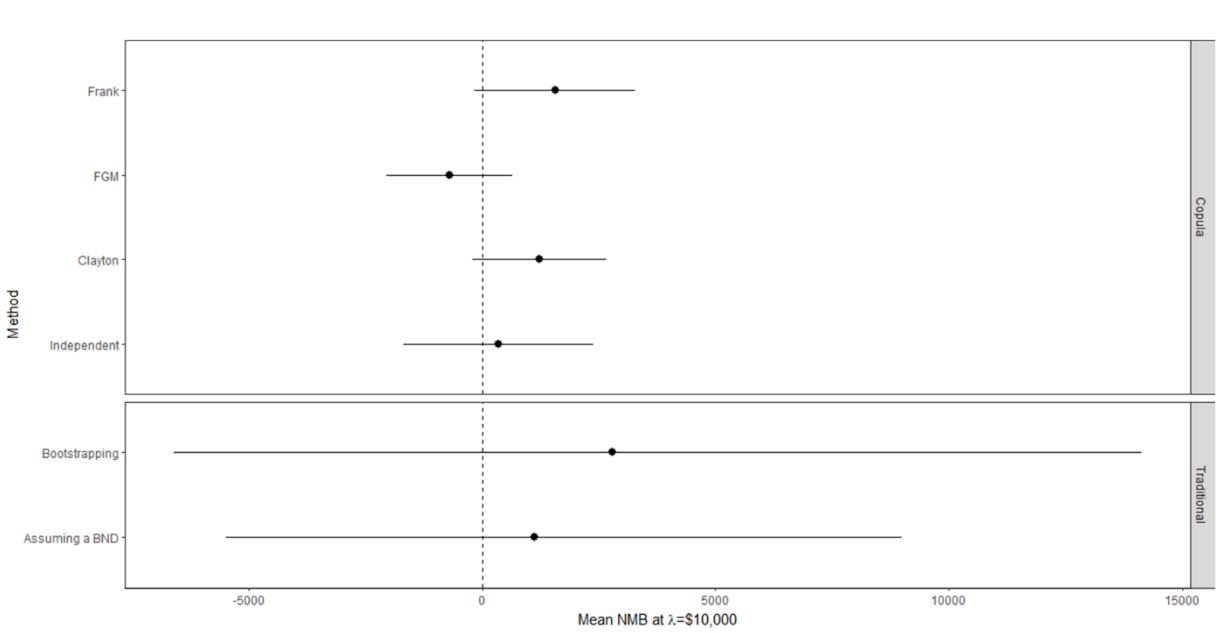
	Estimate	95% CI
Frank	-781.29	(-2,390.16 – 827.59)
FGM	882.39	(-417.97 – 2,182.74)
Clayton	-995.34	(-2,418. – 428.17)
Independent	21.57	(-2005.43 – 2,048.57)
Bootstrapping	-1563	(-12,518 – 7,509)
Assuming a BND	-35	(-7,660 – 6,437)

B)



	Estimate	95% CI
Frank	0.08	(0.06 – 0.10)
FGM	0.02	(0.00 – 0.04)
Clayton	0.02	(0.01 – 0.04)
Independent	0.04	(0.02 – 0.05)
Bootstrapping	0.12	(0.02 – 0.22)
Assuming a BND	0.11	(0.01 – 0.21)

C)



	Estimate	95% CI
Frank	1,558.09	(-2,168.77 – 3,284.96)
FGM	-696.84	(-2,049.49 – 655.80)
Clayton	1,225.58	(-214.23 – 2,665.40)
Independent	325.06	(-1,682.97 – 2,387.09)
Bootstrapping	2,785	(-6,610 – 14,134)
Assuming a BND	1,125	(-5,494 – 8,986)

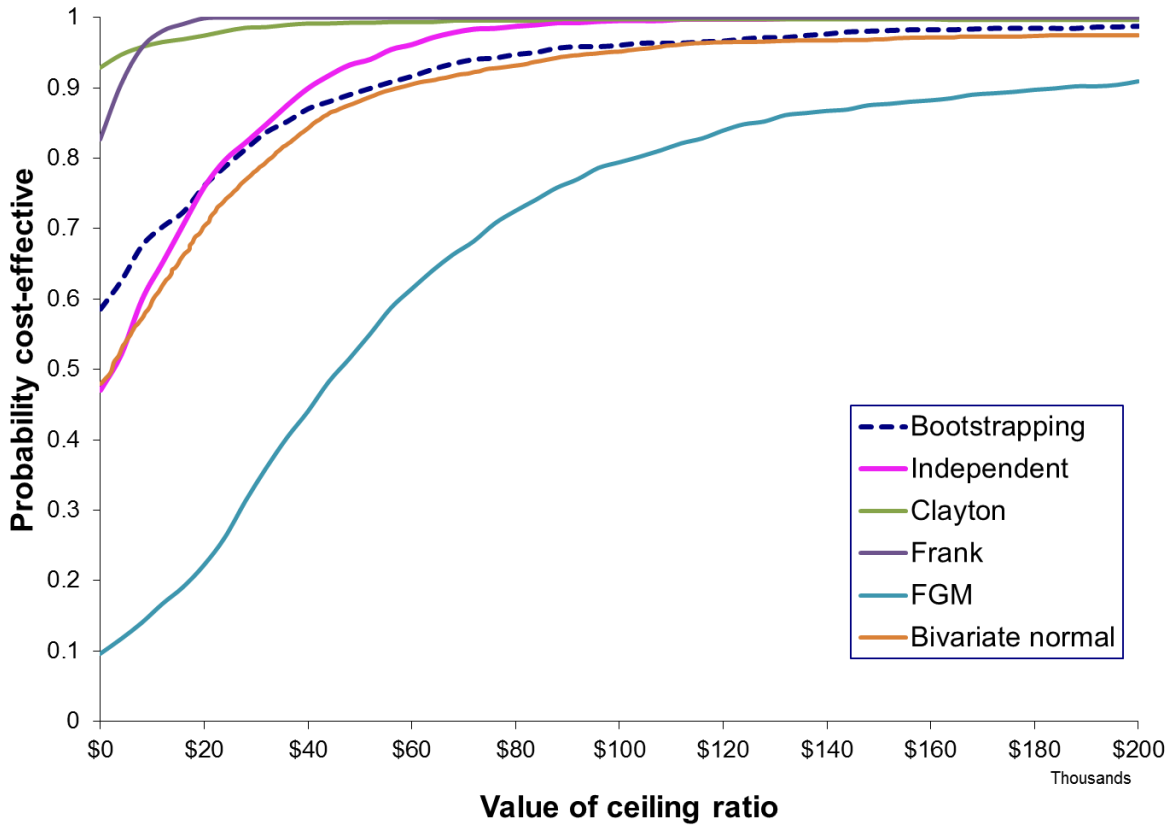
A) Incremental cost. B) Incremental LYs gained. C) Mean NMB at $\lambda = \$10{,}000$ CAD. NMB - Net monetary benefit. BND - Bivariate normal distribution. The reference is OSR.

Table 3 Log-likelihoods and information criteria from copulas used in the model

	Clayton	Frank	FGM	Independent
Log-likelihood	-1587.108	-1549.29	-1582.192	-1607.27
AIC	3188.22	3112.58	3178.38	3226.54
BIC	3211.02	3135.38	3201.19	3246.08

AIC – Akaike criteria information. BIC – Bayesian criteria information.

Figure 3 Cost-effectiveness acceptability curves for the three methods



Appendix

Figure 4 Cost and effectiveness per patient

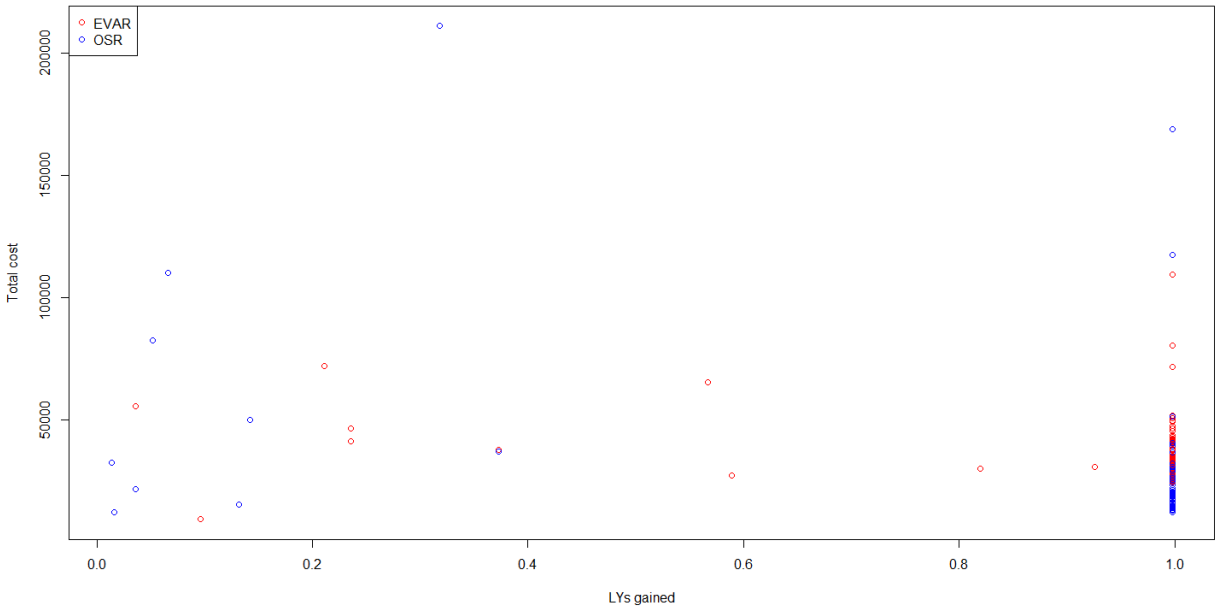


Figure 5 Kernel densities and quantile plots for cost

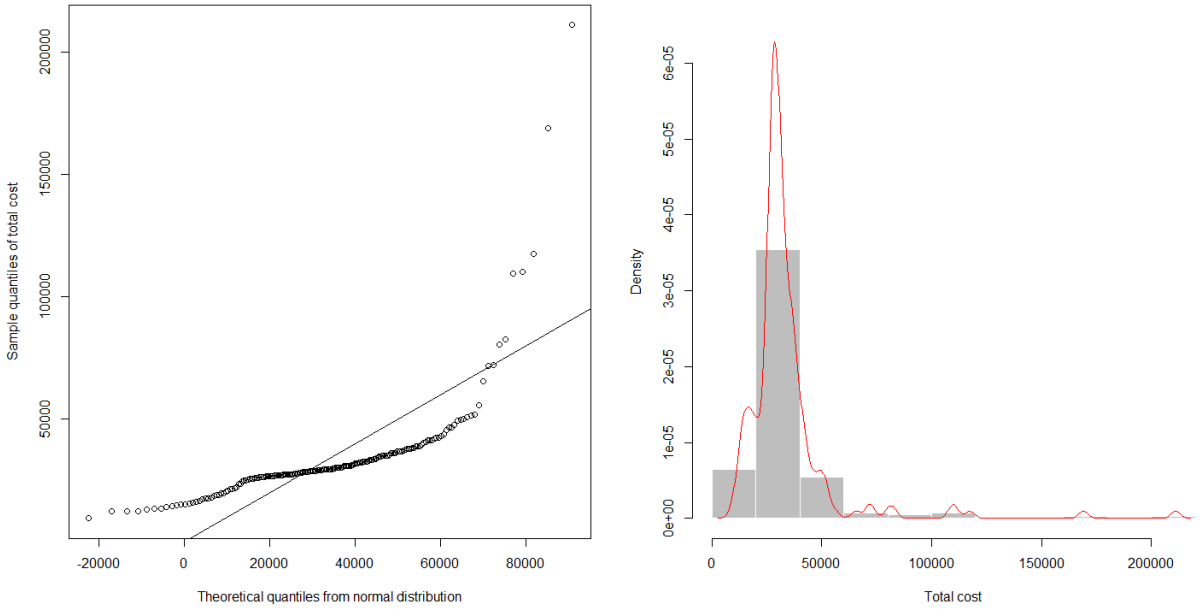


Figure 6 Kernel densities and quantile plots for effectiveness

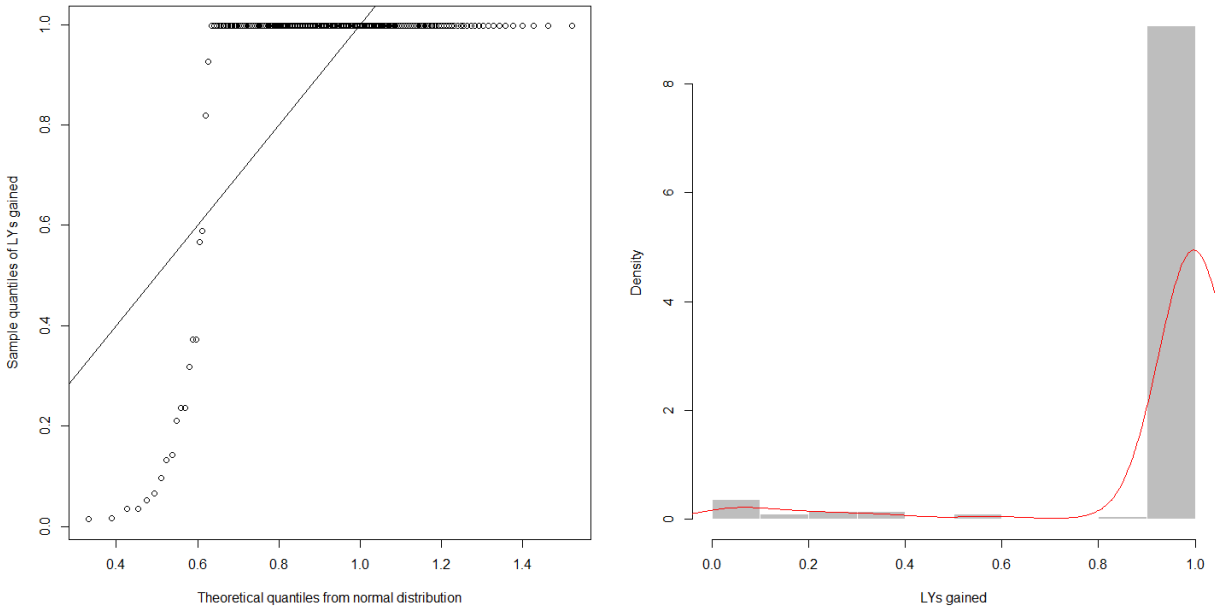


Figure 7 Copula densities and contour plots of the copulas used in the analysis.

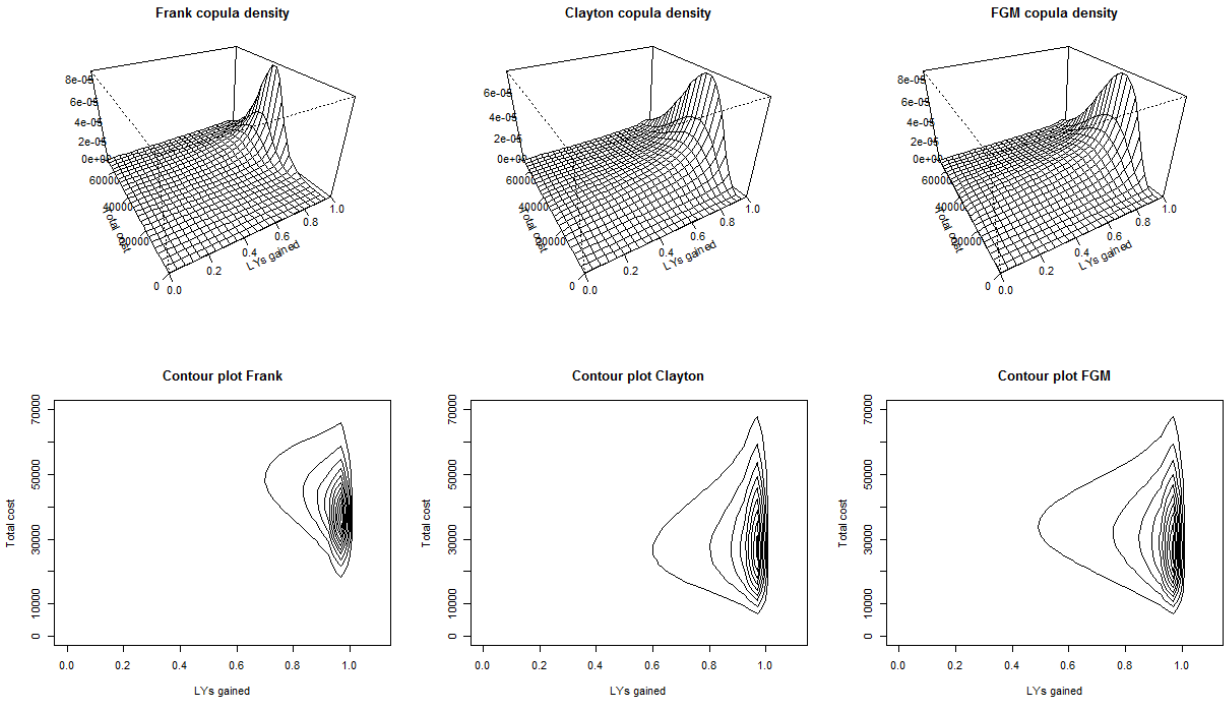


Table 4 Estimates from the copula method for incremental cost and LYs gained

	Clayton		**Frank**		**FGM**		**Product**	
	LYs gained	**Incremental cost**	**LYs gained**	**Incremental cost**	**LYs gained**	**Incremental cost**	**LYs gained**	**Incremental cost**
Intercept	1.78	34169.75	1.67	34169.75	1.66	34169.75	1.77	34169.75
Treatment	0.21	-23.16	0.66	-23.16	0.36	-23.16	0.21	-23.16
$\boldsymbol{\phi/\alpha}$	1.59	4.76	1.49	3.48	1.60	4.96	1.59	2.38
$\boldsymbol{\theta}$	0.015		-8.1		-0.73		NA	

Chapter 4 Conclusions

The economic evaluation of health technologies plays an important role in informed health care decision making. Similarly, the associated methodological issues and challenges offer important opportunities to advance knowledge in the field of health technology assessment by providing a new approach. This thesis has addressed issues related to the use of copulas in CEA. This final chapter offers a summary of the findings of the thesis as well as identifying potential areas for future research. The implications and contributions of the thesis research are also discussed.

In Chapter 3, we explored the use of copulas to handle uncertainty caused by sampling variation using an existing patient-level economic evaluation comparing EVAR and OSR in high risk patients **(Tarride et al., 2008)**; we empirically compared this approach to two traditional methods. In terms of the point estimates of the incremental, the three methods produced similar results for both EVAR and OSR interventions. The main difference was the precision of the estimates, specifically for the OSR group. While the bootstrapping and the bivariate normal methods resulted in wider CIs, the FGM, Frank, FGM and product copulas returned narrower CIs. Consequently, the incremental total cost emanates the same improvement in precision. For the LYs gained, the precision of the estimates was improved using the copulas method for both interventions. This research provides an applied example of the potential importance of accommodating appropriate distribution functions for the cost and effectiveness. Using an actual economic evaluation that was used to inform decision making regarding reimbursement of EVAR in high risk patients in the province of Ontario, this chapter outlines how copulas could play a new role in decisions about future research, ensuring that resources are used efficiently. However, a key limitation is the choice of the marginal distribution. Because of this, modeling marginal distributions should be done with care so that gross misspecification is avoided.

In Chapter 3 we have described, sometimes in a sketchy manner, the state of some, if not most, of the known results about copula theory. It is hard to foresee the future, but there certainly are a few directions that we feel the investigations about copulas and its application to CEA are likely to take. Running the risk of being completely, or even

partially, proved wrong, we venture to put forward the following suggestions for likely directions of future investigations:

New constructions of copulas. The search for families of copulas having properties desirable for specific applications in economic evaluation ought to continue to be important. Having at one's disposal several families of copulas (spanning different behaviour) is essential in order to create a wider spectrum of possible scenarios for the stochastic model at hand. This is of special interest to assist in decision making the policy makers. In particular, we think that special emphasis need and will be devoted to the search for copulas exhibiting different asymmetries, (non-exchangeable copulas, copulas with different tail behaviour, etc.).

The compatibility problem. Given that one just has some vague idea about the dependence of a random variable (for example, one knows the lower dimensional marginals of or some dependence measures among its components), the question is whether one can describe the set of all possible copulas of this random variable, compatible with the given information.

The research presented in this thesis has important implications for the future of health care decision making. This thesis focused on the development and use of a method capable of modeling dependence between cost and effectiveness in order to handle uncertainty caused by sampling variation. Despite limitations, this thesis research provides insights and ideas as well as a practical example of how to address some of the challenges faced in this topic. In an empirical cost-effectiveness analysis, the true form of the distributions for the costs and effectiveness remains unknown. If correct about the true population distributions, efficiency in estimating the population means could be gained. However, the use of estimators based on incorrect distributional assumptions can lead to misleading conclusions. As health care is of such vital importance both individually and collectively, the evidence upon which decisions are based must be carefully considered.

References

Briggs, A., Nixon, R., Dixon, S., & Thompson, S. (2005). Parametric modelling of cost data: some simulation evidence. *Health Economics, 14*(4), 421-428. doi:10.1002/hec.941

Briggs, A. H. (2004). Statistical approaches to handling uncertainty in health economic evaluation. *European Journal of Gastroenterology & Hepatology, 16*(6), 551-561.

Briggs, A. H. (2012). Statistical Methods for Cost-effectiveness Analysis Alongside Clinical Trials. In. Cheltenham, UK: 'Edward Elgar Publishing, Inc.'.

Carayanni, V. (2009). Handling Uncertainty in the Cost Effectiveness Healthcare Evaluations. A Review of Statistical Approaches. *Communications in Statistics - Theory and Methods, 38*(8), 1224-1240. doi:10.1080/03610920802393079

Clayton, D. G. (1978). A Model for Association in Bivariate Life Tables and Its Application in Epidemiological Studies of Familial Tendency in Chronic Disease Incidence. *Biometrika, 65*(1), 141-151. doi:10.2307/2335289

Crespo, C., Monleon, A., Díaz, W., Rodriguez, C., Brosa, M., & Rios, M. (2013). Application of Copulas in Economic Evaluation. *Value in Health, 16*(7), A609. doi:10.1016/j.jval.2013.08.1749

Doucet, A., de Freitas, N., & Gordon, N. (2001). An Introduction to Sequential Monte Carlo Methods. In A. Doucet, N. de Freitas, & N. Gordon (Eds.), *Sequential Monte Carlo Methods in Practice* (pp. 3-14). New York, NY: Springer New York.

Drummond, M. F., Sculpher, M. J., Claxton, K., Stoddart, G. L., & Torrance, G. W. (2015). *Methods for the Economic Evaluation of Health Care Programmes*: Oxford University Press.

Efron, B., & Tibshirani, R. J. (1994). *An Introduction to the Bootstrap*: Taylor & Francis.

Fenwick, E., Claxton, K., & Sculpher, M. (2001). Representing uncertainty: the role of cost-effectiveness acceptability curves. *Health Economics, 10*(8), 779-787.

Ferrari, S., & Cribari-Neto, F. (2004). Beta Regression for Modelling Rates and Proportions. *Journal of Applied Statistics, 31*(7), 799-815. doi:10.1080/0266476042000214501

Fontaine, C., Daures, J. P., & Landais, P. (2017). On the censored cost-effectiveness analysis using copula information. *BMC Medical Research Methodology, 17*(1), 27. doi:https://dx.doi.org/10.1186/s12874-017-0305-9

Frank, M. J. (1979). On the simultaneous associativity ofF(x, y) andx+y−F(x, y). *aequationes mathematicae, 19*(1), 194-226. doi:10.1007/bf02189866

Glick, H. A., Doshi, J. A., Sonnad, S. S., & Polsky, D. (2014). *Economic Evaluation in Clinical Trials*: Oxford University Press.

Good, P. I., & Hardin, J. W. (2012). *Common Errors in Statistics (and How to Avoid Them)*: Wiley.

Gray, A. M., Clarke, P. M., & Wolstenholme, J. L. (2011). *Applied Methods of Cost-effectiveness Analysis in Healthcare*: OUP Oxford.

Heitjan, D. F., & Li, H. (2004). Bayesian estimation of cost-effectiveness: an importance-sampling approach. *Health Economics, 13*(2), 191-198. doi:10.1002/hec.825

Hougaard, P. (2000). *Analysis of Multivariate Survival Data*: Springer New York.

Ibuka, Y., & Russell, L. (2009). 30th Annual Meeting of the Society for Medical Decision Making Abstracts. *Medical Decision Making, 29*(1), E1-E98. doi:doi:10.1177/0272989X0902900102012

Joe, H. (1997). *Multivariate Models and Multivariate Dependence Concepts*: Taylor & Francis.

Khan, I., Morris, S., Hackshaw, A., & Lee, S.-M. (2015). Cost-effectiveness of first-line erlotinib in patients with advanced non-small-cell lung cancer unsuitable for chemotherapy. *BMJ Open, 5*(7). doi:10.1136/bmjopen-2014-006733

Kojadinovic, I., & Yan, J. (2010). Modeling Multivariate Distributions with Continuous Margins Using the copula R Package. *Journal of Statistical Software, 34*(9), 20. doi:10.18637/jss.v034.i09

McCarron, C. E., Pullenayegum, E. M., Marshall, D. A., Goeree, R., & Tarride, J. E. (2009). Handling uncertainty in economic evaluations of patient level data: a review of the use of Bayesian methods to inform health technology assessments. *Int J Technol Assess Health Care, 25*(4), 546-554. doi:10.1017/s0266462309990316

McCarron, C. E., Pullenayegum, E. M., Thabane, L., Goeree, R., & Tarride, J.-E. (2013). The Impact of Using Informative Priors in a Bayesian Cost-Effectiveness Analysis. *Medical Decision Making, 33*(3), 437-450. doi:doi:10.1177/0272989X12458457

McNeil, A. J., Frey, R., & Embrechts, P. (2010). *Quantitative Risk Management: Concepts, Techniques, and Tools: Concepts, Techniques, and Tools*: Princeton University Press.

Mooney, C. Z., Duval, R. D., & Duvall, R. (1993). *Bootstrapping: A Nonparametric Approach to Statistical Inference*: SAGE Publications.

Morgenstern, D. (1956). Einfache Beispiele Zweidimensionaler Verteilungen. *Mitteilingsblatt fur Mathematische Statistik, 8*, 234-235.

Nelsen, R. B. (2006). *An Introduction to Copulas*: Springer.

Pagano, M., & Gauvreau, K. (1994). *Principles of Biostatistics*: Duxbury Press.

Pitt, C., Goodman, C., & Hanson, K. (2016). Economic Evaluation in Global Perspective: A Bibliometric Analysis of the Recent Literature. *Health Economics, 25*, 9-28. doi:10.1002/hec.3305

Pitt, M., Chan, D., & Kohn, R. (2006). Efficient Bayesian inference for Gaussian copula regression models. *Biometrika, 93*(3), 537-554. doi:10.1093/biomet/93.3.537

Quinn, C. (2007). *Improving precision in cost-effectiveness analysis using copulas*. Retrieved from

R Development Core Team. (2016). R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing. Retrieved from https://www.R-project.org/

Romeo, J. S., Tanaka, N. I., & Pedroso-de-Lima, A. C. (2006). Bivariate survival modeling: a Bayesian approach based on Copulas. *Lifetime Data Analysis, 12*(2), 205-222. doi:10.1007/s10985-006-9001-5

Samaniego, F. J. (2010). *A Comparison of the Bayesian and Frequentist Approaches to Estimation*: Springer New York.

Sklar, A. (1959). *Fonctions de répartition à n dimensions et leurs marges*.

Stine, R. (1989). An Introduction to Bootstrap Methods. *Sociological Methods & Research, 18*(2-3), 243-291. doi:doi:10.1177/0049124189018002003

Tarride, J. E., Blackhouse, G., De Rose, G., Novick, T., Bowen, J. M., Hopkins, R., . . . Goeree, R. (2008). Cost-effectiveness analysis of elective endovascular repair compared with open surgical repair of abdominal aortic aneurysms for patients at a high surgical risk: A 1-year patient-level analysis conducted in Ontario, Canada. *J Vasc Surg, 48*(4), 779-787. doi:10.1016/j.jvs.2008.05.064

Thompson, S. G., & Nixon, R. M. (2005). How sensitive are cost-effectiveness analyses to choice of parametric distributions? *Med Decis Making, 25*(4), 416-423. doi:10.1177/0272989x05276862

Willan, A. R., Briggs, A. H., & Hoch, J. S. (2004). Regression methods for covariate adjustment and subgroup analysis for non-censored cost-effectiveness data. *Health Economics, 13*(5), 461-475. doi:10.1002/hec.843

Willan, A. R., & O'Brien, B. J. (1996). Confidence intervals for cost-effectiveness ratios: an application of Fieller's theorem.[Erratum appears in Health Econ 1999 Sep;8(6):559]. *Health Economics, 5*(4), 297-305. doi:https://dx.doi.org/10.1002/(SICI)1099-1050(199607)5:4<297::AID-HEC216>3.0.CO;2-T

Yan, J. (2007). Enjoy the Joy of Copulas: With a Package copula. *Journal of Statistical Software, 21*(4), 21. doi:10.18637/jss.v021.i04

Appendix 1 Medline search strategy

1. (cost$ or budget$ or economic or pharmacoeconomic$ or pharmaco economic$ or price$).ti.

2. (cost$ adj2 (benefit$ or effective$ or minimi#ation or utilit$)).ti,ab.

3. (econom$ adj5 (analy##s or evaluat$ or impact$)).ti,ab.

4. exp Costs/ and Cost Analysis/

5. or/1-4

6. copula$.mp.

7. (sampl$ adj2 uncertainty).mp.

8. exp Uncertainty/

9. or/6-8

10. 5 and 9

11. (animals not human).sh.

12. 10 not 11

13. remove duplicates from 12