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Stochastic Cost-Effectiveness Analysis: A Simultaneous Marginal-Effect Approach

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ABSTRACT

Objective: The purpose of this study is to develop a cost-effectiveness methodology in the context of a simultaneous modeling framework that provides consistent point and interval estimates.
Methods: A simultaneous model of cost and effectiveness functions was developed to measure the incremental cost-effectiveness ratio for competing medical interventions. A feasible nonlinear least-squares method was suggested to estimate the simultaneous model. Using a series of hypothetical data, a simulation analysis was performed to show the superior performance of the proposed model, relative to the average-effect model, a widely used approach to cost-effectiveness estimation.
Results: The traditional average-effect approach has two shortcomings. First, it assumes two strong conditions: truly random distributions of all the significant nontreatment variables (both observed and unobserved) across study groups, and the independence of cost and effectiveness variables. Second, it does not give the confidence interval, an important measure to assess the stochastic nature and robustness of point estimates. In contrast, the simultaneous modeling approach provides marginal-effect estimates, imposing no restrictions on the random distributions of the individual characteristics across study groups. Furthermore, it takes into account the simultaneity of cost and effectiveness functions being estimated. The simulation analysis showed that the simultaneous modeling approach is significantly more unbiased and efficient in predicting the true cost-effectiveness ratio.
Conclusion: The simultaneous modeling approach is superior to the average-effect approach in the estimation of incremental cost-effectiveness ratios using data with significant nontreatment confounding factors. The advantages of the simultaneous modeling approach are particularly appealing for evaluative studies dealing with large-scale retrospective data at the patient level.
Keywords: average-effect approach; bias; cost-effectiveness analysis; marginal-effect approach.

Introduction

Under the increasing challenges for more efficient allocation and utilization of healthcare resources all around the world, economic assessment of competing alternatives in medical practice has become a vital step in improving the economic efficiency of medical decision-making. As a result, various methods have been developed to help assess the cost-effectiveness of alternative healthcare products and services [1–6].

Conceptually, a cost-effectiveness analysis (CEA) can be performed in two ways, depending on the relationship between the competing alternatives under consideration [7]. If the competing alternatives are not therapeutic substitutes, a treatment-specific cost-effectiveness ratio (C/E ratio) can be estimated, giving an average cost of achieving one unit of a health outcome associated with each treatment intervention. Medical decisions about the use of cost-effective treatment options can then be made using the relative comparison of the treatment-specific C/E ratios. If the treatment alternatives are therapeutically substitutable, however, an incremental C/E ratio should be computed based on the across-group changes in cost and health outcomes. Since most evaluative studies seek to compare substitutable interventions within the same therapeutic area, this study discusses some methodological issues associated with the use of incremental CEA.

In this study, two fundamental issues concerning the validity (degree of bias) and robustness (efficiency) of incremental CEA were investigated. First, the most widely used technique in estimating an incremental C/E ratio is based conventionally

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on an average-effect approach, which is referred to as the method that estimates a C/E ratio using the across-group mean changes in cost and health outcome measures. In this study, it is argued that the average-effect approach is valid on two strong assumptions: 1) Neither cost nor outcome measures are determined systematically by any confounding factors other than treatment interventions; 2) If cost and/or health outcomes are determined by study interventions as well as other factors, then the other factors must be distributed in a truly random fashion across study groups. In other words, the average-effect approach assumes that the observed across-group differences in cost and outcome measures can be attributable entirely to treatment effects. This would be the case if treatment interventions are the only determinants; or if there are any other factors in the determination, they must be identical across study groups. These assumptions, however, are seldom the case in retrospective studies. Even in some randomized controlled trials (RCTs), they may not hold due to the effects of unobserved factors [3,8]. An unobserved factor may introduce a bias to the estimate of the average C/E ratio when its impact on cost and outcomes was not random across the study groups. On the other hand, a random unobserved factor, while it may not bias the estimate, could influence the efficiency of the estimate when it is present as an error term simultaneously in both cost and outcome functions [9].

The second issue this study addresses is the robustness of C/E ratio measures given by the average-effect approach. In particular, a major problem with the average-effect approach is the lack of information on the stochastic nature and confidence interval for its C/E ratio estimates. Generally, the average-effect approach does not lend itself to confidence interval estimation. For this reason, there has recently been a growing literature that addresses the issues of confidence interval estimations in cost-effectiveness studies [10–19].

There are five major approaches suggested in previous research dealing with the stochastic confidence of cost-effectiveness estimates. O'Brien and colleagues suggested a method based upon the Taylor series [10]. Wakker and Klaassen [13] offered a one-sided Bonferroni confidence interval procedure. Willan and O'Brien [15] and Chaudhary and Stearns [14] proposed the application of Fieller's Theorem for the estimation of confidence intervals. Recently, Laska et al. [16] further extended the Bonferroni method to a two-sided confidence interval and established a relationship between the Bonferroni method and the Fieller Method. Polsky et al. [18], Obenchain et al. [17], and Tambour and Zethraeus [19] discussed the estimation of C/E ratios using bootstrap approaches. While the bootstrap approach seems to perform somewhat better overall in comparison with other methods according to Polsky et al. [18], the effectiveness of the bootstrap method is uncertain due to concerns with its stability as noted in previous studies [20,21]. Finally, a stochastic decision model was also proposed to assess the uncertainty of cost-effectiveness estimation [22]. This is a simulation-based model, and can be estimated using either Bayesian inference or resampling approach. Yet the modeling performance of this method, relative to others, was not well documented.

In the study, a simultaneous modeling approach is proposed that makes three major contributions to the estimation methodology of C/E ratios. First, as opposed to the conventional average-effect approach, the simultaneous model measures treatment effects on cost and outcome functions while controlling for the across-group differences in terms of other confounding factors. This approach generally provides unbiased marginal-effect estimates of C/E ratios that otherwise may be confounded by observed nontreatment factors. Second, the simultaneous model takes into account the possibility that cost and outcome functions may be influenced by a common set of unobserved factors. In the conventional average-effect model, cost and effectiveness measures are estimated independently, ignoring any possible correlation between the underlying unobserved error terms. When such a correlation exists, estimation of the simultaneous model improves the efficiency of C/E ratio estimates [9]. A formal exposition on the distinction between the simultaneous model approach and average-effect approach is provided below. Third, this study presents a statistical method that estimates the simultaneous model obtaining both the point and interval estimates of C/E ratios. Specifically, a feasible nonlinear least-squares estimator is suggested to obtain consistent estimates of C/E ratios and their confidence intervals. Finally, a simulation analysis has been conducted to demonstrate the different performance of the marginal-effect model vs. the average-effect model in predicting a given true C/E ratio.

Analytical Framework

Average-Effect Approach

To demonstrate the estimation bias associated with the C/E ratio given by the traditional average-

effect approach, assume that two alternative medications, drug 1 and drug 0, are assessed on the basis of cost-effectiveness. Subjects on drug 1 are defined as being in the treatment group and those on drug 0 as being in the control group. Two major investigation variables for each individual i are considered, the cost variable C_i and the health outcome variable E_i (effectiveness). Further, assume that both the cost and outcome variables are determined by the two study medications indexed by a treatment dummy variable T_i, defined as being 1 for drug 1 and 0 for the alternative drug 0. To maintain generality, it must also be assumed that some nontreatment variables may also influence the cost function by X_{ci} and the outcomes function by X_{ei}. This assumed relationship can be described formally in a system of equations:

$$C_i = \alpha T_i + \gamma_c' X_{ci} + u_{ci} \quad (1)$$

$$E_i = \beta T_i + \gamma_e' X_{ei} + u_{ei} \quad (2)$$

where α and β measure the true treatment effects on the cost and outcomes functions respectively; γ_c' and γ_e' are the vectors of parameters to be estimated, representing the effects of other confounding factors in addition to the treatment effects; and u_{ci} and u_{ei} are used to capture random unobserved factors in each function.

To determine the cost-effectiveness of drug 1 in comparison with the competing drug 0, an incremental C/E ratio can be computed to measure the average cost of obtaining one unit of a health outcome (e.g., cost per quality adjusted life year (QALY)) as if patients were switched from the control group to the treatment group. Using the parameters in Equations (1) and (2), the true C/E ratio is $r = \alpha/\beta$. In practice, however, the true C/E ratio value is not known, and therefore must be estimated using various data sources from clinical, claim, or survey instruments. With regard to the estimation method, the average-effect approach has been widely used that estimates C/E ratio on the basis of across-group mean differences in cost and outcome measures. Following the model specifications in equations (1) and (2), the average-effect C/E ratio $\bar{r}$ can be expressed as follows:

$$\Sigma_i C_{1i}/n_1 = \alpha + \gamma_c' \Sigma_i X_{ci}/n_1 + \Sigma_i u_{ci}/n_1 \quad (3)$$

$$\Sigma_i C_{0i}/n_0 = \gamma_c' \Sigma_i X_{ci}/n_0 + \Sigma_i u_{ci}/n_0 \quad (4)$$

$$\Sigma_i E_{1i}/n_1 = \beta + \gamma_e' \Sigma_i X_{ei}/n_1 + \Sigma_i u_{ei}/n_1 \quad (5)$$

$$\Sigma_i E_{0i}/n_0 = \gamma_e' \Sigma_i X_{ei}/n_0 + \Sigma_i u_{ei}/n_0 \quad (6)$$

$$\bar{r} = \frac{\Delta\bar{C}}{\Delta\bar{E}} = \frac{\Sigma_i C_{1i}/n_1 - \Sigma_i C_{0i}/n_0}{\Sigma_i E_{1i}/n_1 - \Sigma_i E_{0i}/n_0} = \frac{\alpha + \gamma_c'(\bar{X}_{c1} - \bar{X}_{c0}) + (\bar{u}_{c1} - \bar{u}_{c0})}{\beta + \gamma_e'(\bar{X}_{e1} - \bar{X}_{e0}) + (\bar{u}_{e1} - \bar{u}_{e0})} \quad (7)$$

For simplicity, assume the last random term converges to 0 asymptotically, then

$$\lim_{n_1, n_0 \to \infty} \bar{r} = \frac{\Delta\bar{C}}{\Delta\bar{E}} \cong \frac{\alpha + \gamma_c'(\bar{X}_{c1} - \bar{X}_{c0})}{\beta + \gamma_e'(\bar{X}_{e1} - \bar{X}_{e0})} = \frac{\alpha + \gamma_c'\Delta\bar{X}_c}{\beta + \gamma_e'\Delta\bar{X}_e} \neq \frac{\alpha}{\beta} = r \quad (8)$$

Apparently, the average-effect C/E ratio estimator $\bar{r}$ will consistently converge to the true C/E ratio $r = \alpha/\beta$ only if either the across-group mean difference $\Delta\bar{X}_c$,$\Delta\bar{X}_e$, or the coefficients γ_c' and γ_e' are not significantly different from 0. That is, patients in both study groups must be either distributed in a truly random fashion in terms of all observed and unobserved nontreatment factors, or else all nontreatment variables should have no influence on the changes in cost and health outcomes. If these conditions are not met, there would be a systematic bias associated with the average-effect estimator $\bar{r}$. In most retrospective studies, however, these conditions are rarely met. This is a potential problem even in prospective RCT studies. For instance, in some RCT studies, the samples of subjects may be poorly representative of the general population due to self selection, the subjects may have dropped out in a nonrandom fashion across study groups over time, or the subjects may differ systematically across the study groups with respect to observed compliance or health behaviors [3]. Furthermore, the average-effect estimator contains another type of bias. To illustrate this, a strong assumption is made for the sake of simplicity that there is no statistical bias in estimating the true across-group mean difference in cost and effectiveness, i.e., $E(\Delta C) = \alpha$; and $E(\Delta E) = \beta$. Even with such a strong assumption, however, one cannot take for granted that the expected value of the estimated C/E ratio is equal to the true counterpart α/β. More formally, this can be shown as follows:

$$E(\bar{r}) = E\left(\frac{\Delta C}{\Delta E}\right) \neq \frac{E(\Delta C)}{E(\Delta E)} = \frac{\alpha}{\beta} = r \quad (9)$$

Equation (9) holds on a well-established statistical foundation that the expectation of a random-variable ratio is not necessarily equal to the ratio of the expectations [23]. As a consequence, without

making some strong assumptions, the widely used average-effect approach is unlikely to provide statistically unbiased C/E ratio estimates.

Marginal-Effect Approach

In contrast with the conventional average-effect approach that is likely to produce biased estimates of C/E ratios, an alternative approach is to estimate the incremental C/E ratio in the context of a simultaneous modeling framework. This simultaneous model gives a marginal-effect estimate of C/E ratio because it is a direct marginal product of the model system (1) and (2) with respect to treatment effect. The following presentation shows that such a marginal-effect C/E ratio estimate is statistically consistent, as it is measured in a model controlling for the impact of nontreatment variables and the simultaneity of cost and outcomes functions. Let a random vector $u_i = (u_{ci}, u_{ei})'$ be independently distributed across individuals i with a variance-covariance matrix:

$$\Sigma = \begin{pmatrix} \sigma_c^2 & \sigma_{ce} \\ \sigma_{ec} & \sigma_e^2 \end{pmatrix} \tag{10}$$

Define $r = \alpha/\beta$, then substitute $\alpha = r\beta$ into equations (1) and (2):

$$C_i = r\beta T_i + \gamma_c' X_{ci} + u_{ci} \tag{11}$$

$$E_i = \beta T_i + \gamma_e' X_{ei} + u_{ei} \tag{12}$$

It is worth noting that the C/E ratio $r = \alpha/\beta$ can only be measured conditional on the nonzero treatment effect on health outcome function, i.e., $\beta \neq 0$. In order to ensure this condition, a null hypothesis testing should be conducted:

Null Hypothesis Testing: $\beta = 0$. i) This test can be conducted using a standard OLS t-test. If the null hypothesis cannot be rejected in the test, it suggests that the effectiveness outcomes are indifferent across the study groups of patients. As a result, it is appropriate to conduct a cost-minimization analysis. In such a case, the basic decision rule is that the treatment option with the least cost should be chosen over its alternative. ii) If the null hypothesis is rejected significantly, it then suggests the treatment effect to be significant and thus statistically there exists $r = \alpha/\beta$, which can be estimated as follows.

Nonlinear Generalized Least Squares Estimation. Equations (1) and (2) are rewritten together in vector:

$$\begin{pmatrix} C_i \\ E_i \end{pmatrix} = r\beta \begin{pmatrix} T_i \\ 0 \end{pmatrix} + \beta \begin{pmatrix} 0 \\ T_i \end{pmatrix} + \begin{pmatrix} X_{ci}' & 0 \\ 0 & X_{ei}' \end{pmatrix} \begin{pmatrix} \gamma_c \\ \gamma_e \end{pmatrix} + \begin{pmatrix} u_{ci} \\ u_{ei} \end{pmatrix} \tag{13}$$

Assume for now that a variance-covariance matrix Σ is known with a 2×2 nonsingular matrix P such that $P'\Sigma P = I$. Multiply the left of equation (13) by P:

$$P\begin{pmatrix} C_i \\ E_i \end{pmatrix} = r\beta P \begin{pmatrix} T_i \\ 0 \end{pmatrix} + \beta P \begin{pmatrix} 0 \\ T_i \end{pmatrix} + P \begin{pmatrix} X_{ci}' & 0 \\ 0 & X_{ei}' \end{pmatrix} \begin{pmatrix} \gamma_c \\ \gamma_e \end{pmatrix} + P \begin{pmatrix} u_{ci} \\ u_{ei} \end{pmatrix} \tag{14}$$

For convenience, denote:

$$Y_i = P\begin{pmatrix} C_i \\ E_i \end{pmatrix}, Z_{ci} = \begin{pmatrix} T_i \\ 0 \end{pmatrix}, Z_{ei} = \begin{pmatrix} 0 \\ T_i \end{pmatrix},$$

$$X_i = \begin{pmatrix} X_{ci}' & 0 \\ 0 & X_{ei}' \end{pmatrix}, U_i = \begin{pmatrix} u_{ci} \\ u_{ei} \end{pmatrix}, \gamma = \begin{pmatrix} \gamma_c \\ \gamma_e \end{pmatrix}.$$

Equation (14) then becomes

$$Y_i = r\beta P Z_{ci} + \beta P Z_{ei} + P X_i \gamma + P U_i \tag{15}$$

Note that the variance-covariance matrix of PU_i is identity, the nonlinear least-squares estimates of r, β and γ can be obtained by minimizing:

$$S = \sum_{i=1}^{N} (PU_i)'(PU_i) = \sum_{i=1}^{N} U_i' \Sigma^{-1} U_i \tag{16}$$

Solving the first order conditions of equation (16) produces consistent estimates of r, β, γ.

$$\hat{r} = \frac{A_2 C_1 - C_2 A_1}{B_2 A_1 - B_1 A_2} \tag{17}$$

$$\hat{\beta} = \frac{B_2 A_1 - A_2 B_1}{C_1 B_2 - B_1 C_2} \tag{18}$$

$$\hat{\gamma} = \left(\sum_{i=1}^{N} X_i' \Sigma^{-1} X_i\right)^{-1} \left[\sum_{i=1}^{N} X_i' \Sigma^{-1} Y_i - \hat{r}\hat{\beta} \sum_{i=1}^{N} X_i' \Sigma^{-1} Z_{ci} - \hat{\beta} \sum_{i=1}^{N} X_i' \Sigma^{-1} Z_{ei}\right] \tag{19}$$

where $A_1 = \sum_{i=1}^{N} a_i' \Sigma^{-1} Z_{ci}$, $A_2 = \sum_{i=1}^{N} a_i' \Sigma^{-1} Z_{ei}$,

$$B_1 = \sum_{i=1}^{N} b_i'\Sigma^{-1}Z_{ci},\ B_2 = \sum_{i=1}^{N} b_i'\Sigma^{-1}Z_{ei},$$

$$C_1 = \sum_{i=1}^{N} c_i'\Sigma^{-1}Z_{ci},\ C_2 = \sum_{i=1}^{N} c_i'\Sigma^{-1}Z_{ei}$$

$$a_i' = Y_i' - \left(\sum_{i=1}^{N} Y_i'\Sigma^{-1}X_i\right)\left(\sum_{i=1}^{N} X_i'\Sigma^{-1}X_i\right)^{-1} X_i'$$

$$b_i' = Z_{ci}' - \left(\sum_{i=1}^{N} Z_{ci}'\Sigma^{-1}X_i\right)\left(\sum_{i=1}^{N} X_i'\Sigma^{-1}X_i\right)^{-1} X_i'$$

$$c_i' = Z_{ei}' - \left(\sum_{i=1}^{N} Z_{ei}'\Sigma^{-1}X_i\right)\left(\sum_{i=1}^{N} X_i'\Sigma^{-1}X_i\right)^{-1} X_i'$$

Confidence Interval Estimation

Equations (17), (18), and (19) give point estimates of r, β, γ. To assess the robustness of these estimators, confidence intervals for each point estimate must be derived. Equation (15) is rearranged as follows:

$$PU_i = Y_i - (r\beta PZ_{ci} + \beta PZ_{ei} + PX_i\gamma)$$
$$F = (PU_1', PU_2', \ldots, PU_N')' \qquad (20)$$

Defining $\hat{\phi} = (\hat{r}, \hat{\beta}, \hat{\gamma})$, its distribution is derived according to statistical theory [24,25]:

$$\sqrt{N}\,(\hat{\phi} - \phi) \xrightarrow{d} N(0, \Omega)$$
$$\Omega = \{\lim_{N\to\infty} \frac{1}{N}(\frac{\partial F}{\partial \phi})'(\frac{\partial F}{\partial \phi})\}^{-1} \qquad (21)$$

In the case of a finite sample, the asymptotic matrix can be estimated by:

$$\Omega \approx \left(\frac{1}{N}(\frac{\partial F}{\partial \phi})'(\frac{\partial F}{\partial \phi})\Big|_{\phi=\hat{\phi}}\right)^{-1} \qquad (22)$$

Thus, the distribution of $\hat{\phi} = (\hat{r}, \hat{\beta}, \hat{\gamma})$ can be written as:

$$\hat{\phi} \xrightarrow{d} N\left\{\phi, \left((\frac{\partial F}{\partial \phi})'(\frac{\partial F}{\partial \phi})\Big|_{\phi=\hat{\phi}}\right)^{-1}\right\} \qquad (23)$$

Denoting w_{11} as the [1,1] element of

$$W = \left((\frac{\partial F}{\partial \phi})'(\frac{\partial F}{\partial \phi})\Big|_{\phi=\hat{\phi}}\right)^{-1},$$

the variance-covariance matrix of $\hat{\phi}$, it follows that an asymptotic 100(1-α)% confidence interval for C/E ratio $\hat{r}$ can be obtained by:

$$(\hat{r} - Z_{\alpha/2}\sqrt{w_{11}},\ \hat{r} + Z_{\alpha/2}\sqrt{w_{11}}) \qquad (24)$$

where $Z_{\alpha/2}$ is the critical value of a standardized normal distribution. Apparently, confidence intervals for $\hat{\beta}$, $\hat{\gamma}$ can also be computed similarly as equation (24).

A Feasible Two-Step Estimation Method

While equation (24) provides a conceptual framework for the confidence interval estimation of C/E ratio $\hat{r}$, it is estimable only upon a known variance-covariance matrix Σ of the error terms in the model system. In practice, however, Σ is usually not known. To accomplish this task, a feasible two-step method can be employed:

Step I. Applying OLS separately to equations (1) and (2), consistent estimates can be obtained for the residuals $\hat{u_{ci}}$, $\hat{u_{ei}}$ for $i = 1,2, \ldots, N$:

$$\hat{\sigma}_c^2 = \frac{1}{N}\sum \hat{u}_{ci}^2;\ \hat{\sigma}_e^2 = \frac{1}{N}\sum \hat{u}_{ei}^2;\ \hat{\sigma}_{ce} = \hat{\sigma}_{ec} = \frac{1}{N}\sum \hat{u}_{ci}\hat{u}_{ei} \qquad (25)$$

$$\hat{\Sigma} = \begin{pmatrix} \hat{\sigma}_c^2 & \hat{\sigma}_{ce} \\ \hat{\sigma}_{ec} & \hat{\sigma}_e^2 \end{pmatrix}$$

Step II. Substituting the above estimated variance-covariance matrix $\hat{\Sigma}$ into equations (17) (18) and (19), a feasible estimate of $\hat{\hat{\phi}} = (\hat{\hat{r}}, \hat{\hat{\beta}}, \hat{\hat{\gamma}})$ can be obtained. Similarly, the confidence interval for C/E ratio $\hat{\hat{r}}$ can be obtained from equation (24) with the substitution of $\hat{\Sigma}$, yielding a feasible estimate of $(\hat{\hat{r}} \pm Z_{\alpha/2}\sqrt{\hat{w}_{11}})$, in which the estimated variance-covariance matrix $\hat{w}$ has the following form:

$$\hat{w} = \begin{pmatrix} a_{11} & a_{12} & a_{13} \\ a_{21} & a_{22} & a_{23} \\ a_{31} & a_{32} & a_{33} \end{pmatrix}^{-1} \qquad (26)$$

where

$$a_{11} = \hat{\hat{\beta}}^2 \sum_{i=1}^{N} Z_{ci}'\hat{\Sigma}^{-1}Z_{ci};\ a_{12} = a_{21}$$
$$= \hat{\hat{\beta}}^2(\hat{\hat{r}}\sum_{i=1}^{N} Z_{ci}'\hat{\Sigma}^{-1}Z_{ci} + \sum_{i=1}^{N} Z_{ci}'\hat{\Sigma}^{-1}Z_{ei})$$

$$a_{13} = a_{31} = \hat{\hat{\beta}} \sum_{i=1}^{N} Z_{ci}'\hat{\Sigma}^{-1} X_i \,;\, a_{23} = a_{32}$$

$$= \hat{\hat{r}} \sum_{i=1}^{N} Z_{ci}'\hat{\Sigma}^{-1} X_i + \sum_{i=1}^{N} Z_{ei}'\hat{\Sigma}^{-1} X_i$$

$$a_{22} = \hat{\hat{r}} \sum_{i=1}^{N} Z_{ci}'\hat{\Sigma}^{-1} Z_{ci} + 2\hat{\hat{r}} \sum_{i=1}^{N} Z_{ci}'\hat{\Sigma}^{-1} Z_{ei} + \sum_{i=1}^{N} Z_{ei}'\hat{\Sigma}^{-1} Z_{ei} \,;$$

$$a_{33} = \sum_{i=1}^{N} X_i'\hat{\Sigma}^{-1} X_i$$

Simulation

Following the theoretical discussions on the simultaneous marginal-effect model versus the average-effect model, a simulation assessment of the two models is now provided using hypothetical data to show their relative performances in predicting a given set of population parameters.

Experimental Design

For the purpose of clarification, the model specification was simplified to include only four determinants: treatment effect, income effect, sex effect, and a stochastic disturbance term that measures the effects of unobserved factors. More formally, the data generating process (DGP) for the simulation was based upon the following model:

$$C_i = r\beta T_i + \gamma_1 X_{1i} + \gamma_2 X_{2i} + u_{ci} \qquad (27)$$

$$E_i = \beta T_i + \gamma_3 X_{1i} + \gamma_4 X_{2i} + u_{eI} \qquad (28)$$

where:

C_i = continuous variable for total cost;
E_i = continuous variable for outcomes (e.g., QALY);
X_{1i} = dummy variable being 1 for male, and 0 for female;
X_{2i} = continuous variable for individual annual income, assumed to range from \$5,000 to \$100,000, i.e., $X_{2i} \in$ (\$5,000, \$100,000);
T_i = dummy variable being 1 for treatment group, and 0 for control group;
β = treatment effect on the effectiveness function, assumed to be 0.5;
r = incremental cost-effectiveness ratio, assumed to be 10,000/QALY;
γ_1, γ_3 = sex effects on the cost and effectiveness functions, assumed to be 0.5 in both functions;
γ_2, γ_4 = income effects on the cost and effectiveness functions, assumed to be 0.1 and 0.0001 respectively;
u_{ci}, u_{ei} = unobserved terms, assumed to follow a joint normal distribution with a variance-covariance matrix as:

$$\Sigma = \begin{pmatrix} \sigma_c^2 & \sigma_{ce} \\ \sigma_{ec} & \sigma_e^2 \end{pmatrix} = \begin{pmatrix} 2 & 2 \\ 2 & 4 \end{pmatrix}$$

Simulation Results

Based on the assumed model specifications, 11 sets of cost and outcomes data were randomly generated by varying the sample size N from 25 through 20,000. The mean C/E ratios were then estimated using the conventional average-effect model and simultaneous model (Table 1). For average-effect C/E ratio measures, upper and lower bounds were computed using the Taylor Series method, a popular approach for average interval estimates [10]. As expected, measured against the true population C/E ratio, r = 10,000/QALY, the mean bias of the average-effect C/E ratio estimate is substantial as a result of failing to control for the effects of the confounding variables (income and sex). To be more specific, the simulated mean C/E ratio is systematically biased downward from its true value and such a bias is particularly significant when the sample size is relatively small. Moreover, the estimation bias always persists, while becoming smaller, even as sample size increases (Figure 1).

In contrast, the estimates of C/E ratios using the simultaneous model with the same data series were simulated. Upper and lower bounds for the mean C/E ratio using the suggested feasible two-stage method were computed. The simulation re-

Table 1 Simulation results for the marginal-effect model versus the average-effect model (true C/E ratio r = \$10,000/QALY)

	Average-effect Approach			Marginal-effect Approach		
N	$\hat{r}$	L Bound	U Bound	$\hat{r}$	L Bound	U Bound
25	8335	3044	13626	10522	6083	14960
50	8568	5379	11756	10279	7391	13166
75	8255	5673	10837	10191	7863	12518
100	8336	6146	10526	10105	8144	12066
150	8279	6449	10109	10030	8449	11611
200	8288	6642	9934	10068	8683	11454
500	8209	6996	9422	9998	9136	10861
1000	8209	7162	9256	10006	9395	10618
2000	8206	7335	9078	10009	9816	10202
10000	8195	7326	9065	9998	9805	10191
20000	8200	7340	9059	9998	9861	10134

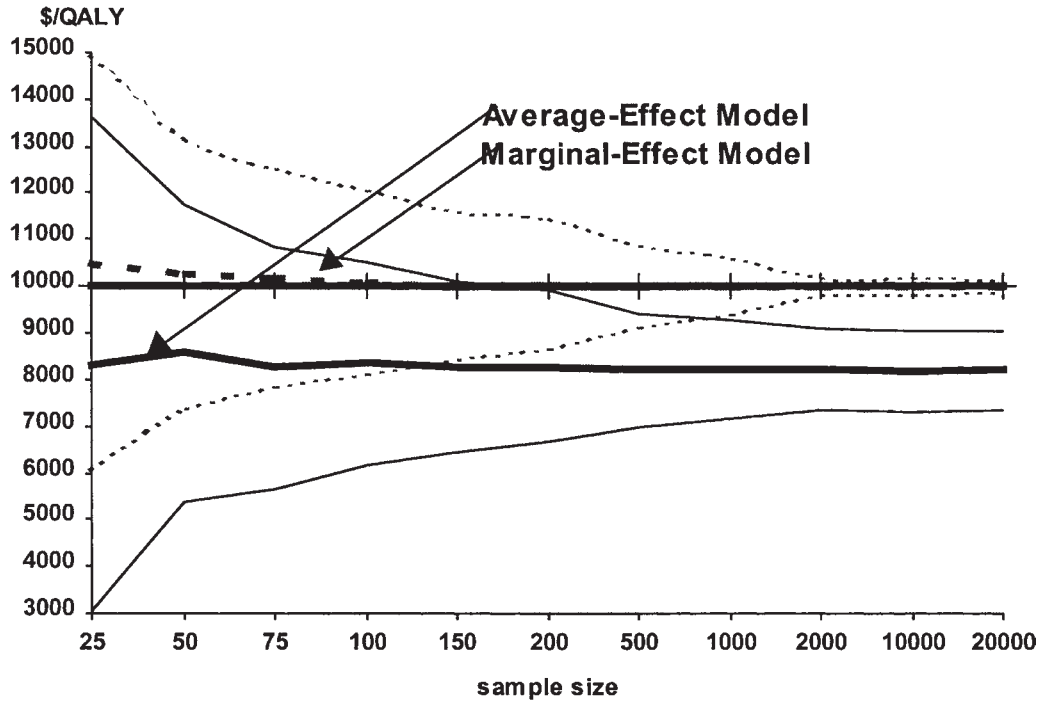

Figure 1 Simulated estimates of C/E Ratio (true C/E ratio = $10,000/QALY).

sults show that the simultaneous model performs superior to the average-effect model in capturing the true C/E ratio. First, the estimated C/E ratios from the simultaneous model are statistically consistent. That is, the estimated C/E ratios quickly converge onto the true C/E ratio. Second, the simultaneous model estimates are more efficient than the average-effect results in terms of estimation variance. It has been shown that the simultaneous model gives more precise confidence interval at any sample size than that of the average-effect model.

Conclusion

This study raises two fundamental questions concerning the validity (degree of bias) and efficiency of the incremental C/E ratio estimates. It has been shown in the study that the widely used average-effect approach is likely to give biased and inefficient C/E ratio estimates by failing to control for significant confounding factors when present. Alternatively, the simultaneous modeling approach suggests that a marginal-effect C/E ratio can be obtained by controlling for observed confounding factors and the simultaneity of cost and outcomes functions. A feasible two-step method was discussed to obtain consistent confidence interval estimates of C/E ratios from the simultaneous model. Following the demonstration of the two approaches on theoretical grounds, simulation work was shown using a series of hypothetical data that gave strong empirical evidence in support of the simultaneous model. In summary, the simulation results suggest that the simultaneous model is highly superior over the average-effect model in terms of lack of bias and efficiency of the estimated C/E ratio measures in relation to the assumed true C/E ratio.

It must be noted, however, that our discussions on the simultaneous model and its advantages over the average-effect model have some limitations. First, the advantages of the simultaneous model can be realized only in studies that analyze retrospective data or randomized controlled data that were confounded by some nonrandom disturbance such as patient self-selection effects in program participation or dropouts. In the cases where nontreatment effects are not significant, the simultaneous model and average-effect model should give statistically similar results.

Second, the estimation of the simultaneous model requires individual data at patient level so that any across-group differences due to observed patient characteristics can be explicitly controlled for in the model. However, aggregate data by patient group or region, for example, may not allow the model to be estimated.

Third, while observed confounding factors can be well controlled for in the simultaneous model, it is not by any means immune from estimation bias due to possible unobserved factors. For example, variables of patient health status, health behavior, or clinician's diagnostic and treatment behavior are usually not observable. These hard-to-measure variables often influence both patient treatment selection and health outcomes measures. As a result, failing to control for such unobserved factors could lead to biased estimates, and these problems are particularly significant in most nonexperimental studies. Recent development in methodology suggests that the instrumental-variables method appears to be a promising approach to dealing with selection bias issues when appropriate instruments can be identified [26–29].

Fourth, a simulation analysis of the two approaches was conducted using hypothetical data that were generated from a set of assumed parameters and distributions of the variables and model specifications. While varying these assumed parameters and distributions was not expected to alter the basic findings as ensured by our theoretical discussions, future simulation studies are necessary to further test the performance of the two approaches by employing more justified parameters and distributions from real data. It is suggested that conducting such a simulation analysis using disease-specific data with distribution parameters obtained from previous empirical studies would be a good exercise to test this model.

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