Advantages of the Net Benefit Regression Framework for Economic Evaluations of Interventions in the Workplace

A Case Study of the Cost-Effectiveness of a Collaborative Mental Health Care Program for People Receiving Short-Term Disability Benefits for Psychiatric Disorders

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Objective: Economic evaluations commonly accompany trials of new treatments or interventions; however, regression methods and their corresponding advantages for the analysis of cost-effectiveness data are not well known. **Methods:** To illustrate regression-based economic evaluation, we present a case study investigating the cost-effectiveness of a collaborative mental health care program for people receiving short-term disability benefits for psychiatric disorders. We implement net benefit regression to illustrate its strengths and limitations. **Results:** Net benefit regression offers a simple option for cost-effectiveness analyses of person-level data. By placing economic evaluation in a regression framework, regression-based techniques can facilitate the analysis and provide simple solutions to commonly encountered challenges. **Conclusions:** Economic evaluations of person-level data (eg, from a clinical trial) should use net benefit regression to facilitate analysis and enhance results.

Cost-effectiveness analysis (CEA) is a popular type of economic evaluation that frequently accompanies studies of new treatments and interventions. One of its main rationales is the high cost of health care. In many countries, CEA is required as "economic evidence" to inform health care funding decisions. The benefits of conducting economic evaluation to evaluate new interventions in the workplace are also becoming more recognized.[1,2] A recent review of the studies of comprehensive health promotion and disease management programs at the worksite concluded that "the most salient issue for managed care organizations and corporations to address is not whether worksite health promotion and disease management programs should be implemented to reduce risks and enhance productivity, but rather how such programs should be designed, implemented, and evaluated to achieve optimal clinical and cost-effectiveness."[3] Companies considering new occupational health interventions are very focused on both clinical and cost outcomes.[3] As such, cost-effectiveness is a key component of current knowledge transfer and dissemination strategies related to the adoption of new interventions in the workplace.

As the need has grown to study the cost-effectiveness of occupational health and safety (OHS) interventions, so has related research activity. For example, there is now a textbook devoted to the economic evaluation of interventions for OHS, with material about types of economic analyses and decision rules.[4] In addition, a recent systematic review of OHS interventions found 72 interventions studied with economic analysis.[5] As collaboration grows between workplaces and research partners to evaluate the cost-effectiveness of new interventions, it will be critical for researchers to be aware of the latest methods for person-level analysis of cost-effectiveness data. When evaluating workplace interventions, often basic methods are not an option. Simple randomized studies are not well-represented in the occupational literature, as workplaces often feature challenges such as short study timelines, small sample sizes, and other contextual factors that may preclude doing a randomized study.[5] Even randomized studies or matched samples have the potential for "new way" and "usual way" groups to differ (eg, if randomization or matching does not work perfectly). When these challenges arise, it is typical to control for potential confounders or effect modifiers by employing regression techniques.

This article illustrates regression-based methods for CEA. In particular, it focuses on net benefit regression, which has a variety of benefits that address shortcomings in conventional CEA methods. These benefits are illustrated using a case study of a collaborative mental health care (CMHC) program for people receiving short-term disability benefits for psychiatric disorders. Although the concepts of net benefit[6] and net benefit regression[7] have been referenced at least once before in the *Journal of Occupational and Environmental Medicine*, it is the goal of this article to clarify how to use and interpret the net benefit regression method, so that more authors and readers can appreciate what it offers.

METHODS

Net Benefit Regression Framework

Net benefit regression describes the activity of doing regression analysis on net benefit data. Net benefit regression has two main steps: (1) to calculate net benefit (for each person in the dataset); (2) to do regression (using each person's net benefit as the dependent variable). One of the most practical advantages of the net benefit regression approach is being able to use established statistical techniques to analyze cost-effectiveness data (eg, to adjust for imperfect randomization or to identify important patient subgroups). Placing economic evaluation in a regression framework also allows consideration of regression diagnostics not traditionally employed when comparing aggregate measures across the arms of a trial. The net benefit regression framework was proposed a decade ago to facilitate regression methods in CEA.[8] At that time, the conventional statistic reported in most cost-effectiveness studies was the incremental cost-effectiveness ratio (ICER).

Building From the ICER

Mathematically, the ICER estimate is defined as

$$\mathrm{ICER} = \frac{\Delta \mathrm{C}}{\Delta \mathrm{E}} = \frac{\mathrm{C}_{\mathrm{TX}} - \mathrm{C}_{\mathrm{UC}}}{\mathrm{E}_{\mathrm{TX}} - \mathrm{E}_{\mathrm{UC}}}$$

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where C_t and E_t are equal to the sample means for study participants receiving either the new intervention (t = TX) or usual care (t = UC). As a ratio, the ICER is troublesome to estimate; however, its parts—the numerator and denominator—can be estimated easily by regression. For example, if one defines an indicator variable TX = 1, if a study participant received the new intervention, and TX = 0, if a study participant received usual care, then one can use ordinary least squares (OLS) to estimate the simple linear regressions

$$C = \alpha_0 + \alpha_1 TX + \varepsilon_c \quad \text{and} \quad E = \xi_0 + \xi_1 TX + \varepsilon_E,$$

and regardless of the distribution of the error terms, the OLS estimates of α_1 and ξ_1 are the best linear unbiased estimates of ΔC and ΔE, respectively.[8]

This observation holds for multiple linear regression as well, when the analyst might want to control for a variety of confounders (eg, $X_2, \cdots, X_p$) in regressions such as

$$\begin{aligned} C &= \alpha_0 + \alpha_1 TX + \alpha_2 X_2 +, \cdots, + \alpha_p X_p + \varepsilon_c \quad \text{and} \\ E &= \xi_0 + \xi_1 TX + \xi_2 X_2 +, \cdots, + \xi_p X_p + \varepsilon_E. \end{aligned}$$

Lastly, by adding an interaction term (say, between X_p and TX), it is possible to explore hypothesis-generating questions about subgroups for whom the new intervention may be more (or less) cost-effective.

Importance of Willingness to Pay

Quite commonly, a new intervention costs more ($\Delta C > 0$) and is more effective ($\Delta E > 0$), yielding a positive ICER. The challenge then with using the ICER to make recommendations is that it needs to be compared with a willingness to pay (WTP) threshold. If the ICER < WTP, the new intervention is cost-effective when C and E > 0; if the ICER > WTP, the new intervention is not cost-effective. For example, a CEA may produce estimates of ΔC = \$150 and ΔE = 2 less disability days. The ICER estimate indicates that the new intervention will cost \$75 for an additional 1-day reduction in days lost from work (ie, ICER $\equiv \Delta C/\Delta E$ = \$150/2 less disability days = \$75/1 less disability day). Whether this represents good value for money is ultimately a question about how much the decision maker is willing to pay for 1 less disability day.

There are two general philosophies about the unknown WTP. The first is that the budget should inform the WTP (ie, how much a payer is willing to pay should be linked to how much a payer has available to spend). The second is that the WTP should inform the budget (ie, how much a payer buys will determine the payer's bill). The first approach is more aligned with traditional economic thinking, involving constrained optimization with a fixed budget.[9] The second approach is more evident in applied settings where context, and not budget, is seen as the top priority. However, given that external researchers are aware neither of the contexts nor of the budgets under which companies operate, the "correct" WTP to use is not commonly known to researchers. Consequently, methods that treat WTP as unknown are indicated (eg, varying WTP and exploring how a recommendation based on the estimated ICER will change). Net benefit regression makes use of the uncertainty about the "correct" WTP value in CEA by considering the incremental net benefit statistic.

Introducing Incremental Net Benefit

Two groups of researchers introduced the net benefit concept used in net benefit regression.[10,11] When net benefit (NB) is measured in monetary units (eg, dollars or euros), the incremental net benefit (INB) is the monetary difference between expected net benefit of the new intervention (NB_{TX}) and the expected net benefit of usual care (NB_{UC}). Mathematically, INB is defined in dollars as

$$\begin{aligned} INB &= WTP \times \Delta E - \Delta C = WTP \times (E_{TX} - E_{UC}) - (C_{TX} - C_{UC}) \\ &= (WTP \times E_{TX}) - C_{TX} - [(WTP \times E_{UC}) - C_{UC}] \\ &= NB_{TX} - NB_{UC}. \end{aligned}$$

The INB statistic can be written equivalently as either $WTP \times \Delta E - \Delta C$ or $NB_{TX} - NB_{UC}$, a difference in the group means where $NB_t = \Sigma nb_i/n_t$, where nb_i is an individual's net benefit (ie, $nb_i \equiv WTP \times e_i - c_i$) and n_t is the number of people receiving treatment t. Doing economic evaluation using the INB statistic allows both estimation and uncertainty to be conducted in a unified regression framework.

Regression of Individual Net Benefit on the Treatment Indicator Yields an Estimate of INB

By computing each person i's net benefit (nb_i) as $WTP \times e_i - c_i$ and using it for a dependent variable, one can run a simple or multiple linear regression of the form

$$\begin{aligned} nb_i &= \beta_0 + \beta_0 TX + \varepsilon_{nb\_s} \quad \text{or} \\ nb_i &= \beta_0 + \beta_1 TX + \beta_2 X_2 +, \cdots, + \beta_p X_p + \varepsilon_{nb\_m}, \text{ respectively.} \end{aligned}$$

If the estimate of $\beta_1 > 0$, the new intervention is cost-effective. This is because estimates of β_1 are estimates of $WTP \times \Delta E - \Delta C$, the INB (for the proof see the online Appendix to Hoch and Dewa[12]). The linearity of the dependent variable nb_i makes the estimate of $\beta_1 = WTP \times \xi_1 - \alpha_1$. Although the ratio of the estimates for α_1 and ξ_1 can be used as an estimate of the ICER, this procedure yields a biased estimate in the statistical sense since the expected value of the ICER estimate does not equal the true value of the ICER parameter (ie, the ICER is a ratio and the expected value of a fraction does not equal the expected value of the numerator over the expected value of the denominator, according to Jensen's inequality). In contrast, the OLS estimate of β_1 is a best linear unbiased estimate of INB.[8] In addition, the 95% confidence interval (CI) for the ICER cannot be made accurately from the separate CIs for the estimates of α_1 and ξ_1 because this process ignores the correlation between the cost and effect data.[13] In contrast, the CI for the estimate of β_1 is the CI for the INB.

Estimating the INB statistic in place of the ICER statistic embraces rather than solves the problem that WTP is unknown. By estimating net benefit regression equations with WTP values that are small, medium, and large, one can gauge how sensitive cost-effectiveness conclusions are to WTP assumptions. A natural starting value for the WTP is the ICER estimate as this yields an INB estimate of zero (INB $\equiv WTP \times \Delta E - \Delta C$ and if $WTP = \Delta C/\Delta E$ then INB = 0). When WTP = \$0, the INB reduces to estimating $-\Delta C$ or an estimate of $-\alpha_1$. When $WTP \rightarrow \infty$, the INB estimates $WTP \times \Delta E$, with an estimate of $WTP \times \xi_1$. Thus, creating nb_i for each study participant is like making a weighted combination of the value of worker outcome achieved, net of the cost to achieve it. The WTP value is the conversion factor allowing cost and effect data to be valued in the same units. The INB is the monetary amount by which the new intervention is expected to create more value than usual care, overall. Net benefit regression allows one to utilize regression techniques to produce better cost-effectiveness estimates (eg, the OLS estimate of β_1, the INB, is unbiased; the estimate of the ICER is not) as well as characterize uncertainty using CIs or *P* values to form the cost-effectiveness acceptability curve (CEAC).[14] We illustrate this next with a case study.

Case Study Description

Dewa and colleagues[15] recently conducted an economic evaluation of a CMHC pilot program for people on short-term disability leave for psychiatric disorders. They employed a quasi-experimental design, with two groups receiving short-term disability benefits for psychiatric disorders. One group ($n_{TX} = 73$) was treated in a CMHC program for their disability episode. The comparison group ($n_{UC} = 51$) received short-term disability benefits related to psychiatric disorders in the prior year, and did not receive CMHC. Both groups met screening criteria for the CMHC program. An economic evaluation was conducted from the employer's perspective; the CEA used "days lost from work" as the outcome of interest. The effectiveness variable was rescaled so that $\Delta E > 0$ would indicate a more effective program.

The analysis featured challenges that are easily addressed with net benefit regression. The first challenge was that the matching process to select a comparison group from the previous year that was comparable to the intervention group was not entirely successful. This failure to get "like" groups is not unusual and can happen even in randomized controlled trials.[8] However, in this case study, the variable that differed was age, a continuous variable (preventing easy stratification of the groups). The second challenge was that the new intervention seemed to save money (ie, $\Delta C < 0$) and be more effective at reducing days lost from work (ie, $\Delta E > 0$). As a result, the ICER estimate was negative. Despite seemingly good news, negative ICERs are difficult to analyze, but one benefit of the net benefit concept is that it makes it possible to characterize estimation and uncertainty for ICERs < 0.[10,11] The results from using net benefit regression to analyze these data are presented below.

RESULTS

Table 1 shows that although the two study groups were chosen to be similar, there are some differences. In particular, the difference in age is statistically significant according to the results of a *t* test ($P < 0.01$), a Wilcoxon ranked sum test ($P < 0.01$), and a nonparametric equality-of-medians test ($P < 0.05$). In contrast, the groups do not differ in terms of the percentage composition of females and employees with major depressive disorder as a primary diagnosis (responsible for their disability leave).

TABLE 1. Baseline Characteristics of the Study Population

	Intervention Group	Control Group
Baseline characteristics	All ($n = 73$)	All ($n = 51$)
Female, *n* (%)	66 (90.4)	42 (82.4)
Major depressive disorder, as primary diagnosis, *n* (%)	49 (67.1)	36 (70.6)
Age, mean (SD),* yrs	43.7 (8.7)	48.7 (8.2)

*Age differs between the two groups ($P < 0.05$).
SD, standard deviation.

Because age differs between the two groups, it is clearly a potential confounder. Because age is a continuous variable, it is more natural to include it as a continuous independent variable rather than stratify by it. Table 2 presents various regression estimates for simple and multiple linear regressions of cost, effect, and net benefit. Both groups have a very high percentage of females, and with the small sample sizes, we did not include a female indicator variable in the regression analyses. However, we did include an indicator variable for major depressive disorder as a primary diagnosis in our initial analyses. The inclusion of this variable did not affect our results, so we omitted it from our final models for the sake of parsimony. We present the results of our final models (having the independent variables age and a treatment indicator) in Table 2, with the regression equations specified in the column "Regression Equation."

The estimate of α_1 is negative (ie, $\Delta C < 0$) meaning the new intervention seems to save money, and it is more effective at reducing disability days (effectiveness has been scaled so that $\Delta E > 0$ indicates a more effective program). Inclusion of the age variable produces CIs consistent with the new intervention being statistically significantly cheaper and more effective. To illustrate the influence of these findings on the numerator and denominator of the ICER and their overall impact on cost-effectiveness, Fig. 1A illustrates 95% CIs for the estimation of ΔC (α_1) and ΔE (ξ_1).

It is clear that adjusting for age moves the estimate and the 95% CI to a more economically attractive location (ie, in a south-east direction so that the new intervention appears more cost saving and more effective). Figure 1B illustrates the uncertainty surrounding the probability that the new intervention is cost-effective as a function of the unknown WTP. The x's and o's in Fig. 1B correspond to one-sided *P* values from net benefit regression at various WTP values.[14] Lastly, Fig. 2 graphs the INB (vertical axis) by WTP (horizontal axis), illustrating the ΔNB (or INB) and 95% CI portions of Table 2. The estimated INB line has a positive slope and a negative x-intercept. The 95% CIs both have x-intercepts at values where WTP < 0.

DISCUSSION

The INB by the WTP graph shown in Fig. 2 illustrates the results from net benefit regression and facilitates an efficient presentation of comprehensive information. In this single figure, one can "see" estimates of ΔE and ΔC, estimates of the ICER and the

TABLE 2. Regression Estimates of ΔC, ΔE, and ΔNB* on the Basis of $n = 124$*

Dependent Variable	Regression Equation	Estimate (95% Confidence Interval)
Cost, ΔC (in Canadian dollars)	$C = \alpha_0 + \alpha_{1TX}$	− \$355 (−\$834 to \$124)
	$C = \alpha_0 + \alpha_{1TX} + \alpha_{2age}$	− \$503 (−\$996 to −\$11)
Effect, ΔE (disability days avoided)	$E = \xi_0 + \xi_{1TX}$	15 d (1 to 28 d)
	$E = \xi_0 + \xi_{1TX} + \xi_{2age}$	16 d (2 to 30 d)
WTP value used to create net benefit, ΔNB (in Canadian dollars)		
WTP = −\$185	$nb = \beta_0 + \beta_{1TX} + \beta_{2age}$	− \$2,410 (−\$4821 to \$0)
WTP = −\$32 (WTP = ICER)	$nb = \beta_0 + \beta_{1TX} + \beta_{2age}$	\$0 (−\$508 to \$508)
WTP = −\$1	$nb = \beta_0 + \beta_{1TX} + \beta_{2age}$	\$487 (\$0 to \$974)
WTP = \$0	$nb = \beta_0 + \beta_{1TX} + \beta_{2age}$	\$503 (\$11 to \$966)
WTP = \$10	$nb = \beta_0 + \beta_{1TX} + \beta_{2age}$	\$661 (\$96 to \$1225)
WTP = \$50	$nb = \beta_0 + \beta_{1TX} + \beta_{2age}$	\$1290 (\$285 to \$2296)

*Incremental net benefit (INB) can be abbreviated as ΔNB to emphasize that it is made from incremental cost (ΔC) and incremental effect (ΔE) as $\Delta NB = WTP \times \Delta E - \Delta C$.
ICER, incremental cost-effectiveness ratio; WTP, willingness to pay.

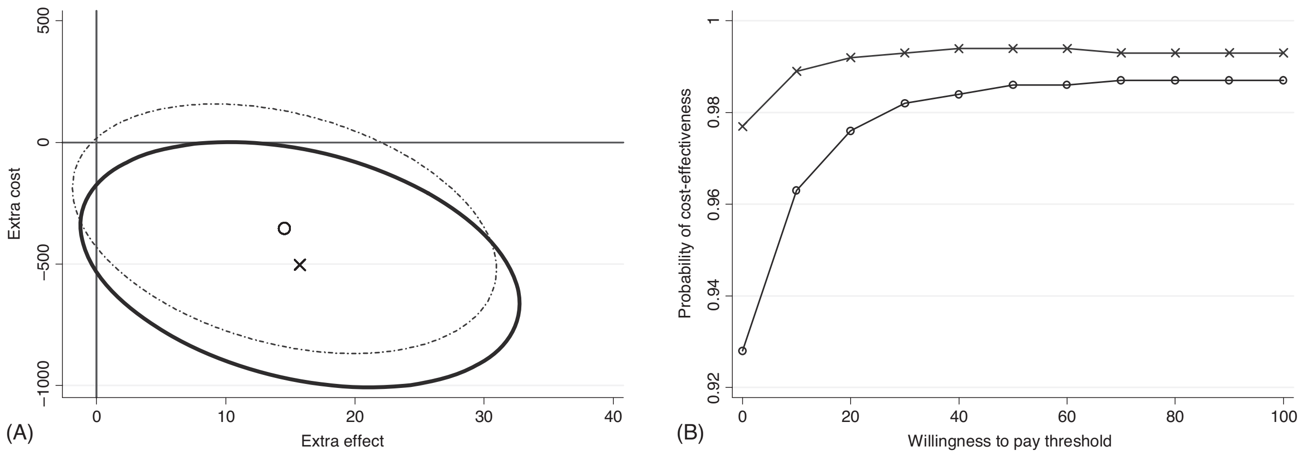

FIGURE 1. (A) The 95% confidence ellipse for the age-adjusted analysis (confidence interval indicated by a solid ellipse; estimate indicated by an "x") covers a more economically attractive area than the 95% confidence ellipse for the unadjusted analysis (confidence interval indicated by a dashed ellipse; estimate indicated by an "o"). (B) The cost-effectiveness acceptability curve characterizes the uncertainty about the new intervention being cost-effective as a function of willingness to pay. The curve for the age-adjusted analysis (plotted with "x's") seems more economically attractive than the curve for the unadjusted analysis (plotted with "o's").

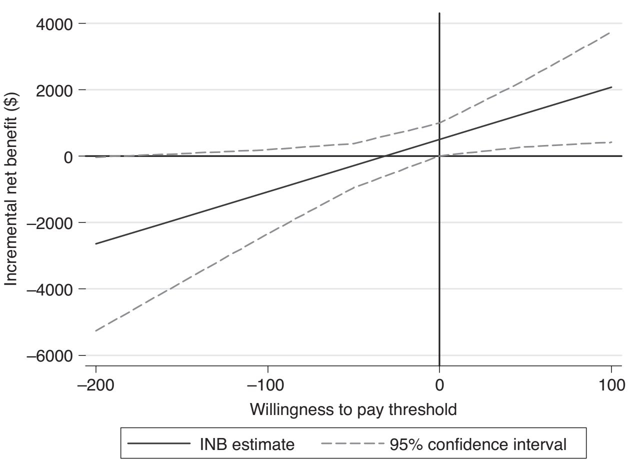

FIGURE 2. Incremental net benefit by willingness to pay: estimate and statistical uncertainty.

INB, and measures associated with their uncertainty. The equation of the solid line in Fig. 2 is the estimate of INB; that is, WTP $\times$ ΔE $-$ ΔC. As WTP is along the horizontal axis, the positive slope indicates $\Delta E > 0$, meaning the new intervention is more effective. When WTP = \$0, the equation for the INB line is $-\Delta$C. Because the y-intercept in Fig. 2 is positive, this means $-\Delta C > 0$ or alternatively $\Delta C < 0$, indicating the new intervention is less costly. As noted in the Methods section, when WTP is set equal to the ICER estimate, the INB = 0. In Fig. 2, the x-intercept at −\$32 conveys that the ICER = −32. This indicates that the ICER < 0 and suggests that activities related to estimation and uncertainty should involve the INB statistic.[10,11] The value for the INB estimate can be read from the solid line, highlighting that it is a function of WTP. In Fig. 2, the INB estimate is always positive (ie, the line in Fig. 2 is always above 0 for WTP > 0), and this means the new intervention is estimated to be cost-effective, regardless of a company's WTP (assuming, of course, that WTP $\geq$ 0). The same observation holds for both the upper and lower 95% CIs (the dashed lines) for the INB estimate. This is akin to the new intervention being statistically significantly cost-effective, as the INB estimate is statistically significantly different from zero (both 95% CI lines are above 0 for WTP $\geq$ 0). The upper and lower 95% CIs for the INB intersect the x-axis at −\$185 and −\$1, and this is the Fieller 95% CI for the ICER.[16]

In short, Fig. 2 shows that after adjusting for the imbalance in age, the new intervention seems to be (1) more effective than usual care ($\Delta E > 0$); (2) less costly than usual care ($\Delta C < 0$); (3) cost-effective regardless of what WTP a company endorses; and (4) characterized by a negative ICER estimate and a negative 95% CI, suggesting the presentation of a positive INB and its positive 95% CI.

Experts have argued that the focus of CEA should be on producing estimates of cost-effectiveness and characterizing their uncertainty.[17] In terms of creating cost-effectiveness estimates, analysts can choose from either the ICER or the INB (or both). In situations where the ICER estimate is negative or uncertainty spans more than one quadrant (eg, a situation depicted in Fig. 1A), there are difficulties with interpreting the estimate and characterizing the uncertainty.[10,11] For example, an ICER of −\$500 (derived from $\Delta C/\Delta E = -\$50/0.1$) is neither the same as an ICER of −\$500 (derived from $\Delta C/\Delta E = -\$50{,}000/100$) nor is it the same as an ICER of −\$500 (derived from $\Delta C/\Delta E = \$50/-10$). In some situations, authors organize estimates and uncertainty by where it occurs on a graph like Fig. 1A. Recent articles in the *Journal of Occupational and Environmental Medicine* provide published examples of this,[6,7,18] and we have presented results this way as well.[19] However, this method of presentation takes the ICER, a continuous concept, and reduces it into a four-category variable. This is an intuitive way of conveying variability, but other methods can convey more exactly how the estimate's uncertainty affects the probability that the new treatment is cost-effective. The CEAC illustrated in Fig. 1B does this. However, the CEAC has been criticized for only characterizing uncertainty (and not showing if the INB > 0).[20,21] An INB by WTP graph, illustrated in Fig. 2, addresses this limitation by showing both the INB estimate and characterizing uncertainty. Net benefit regression allows one to create an INB by WTP graph while adjusting for whatever covariates are deemed relevant. In this case, the results graphed in Fig. 2 are adjusted for age. When there are concerns about whether parametric assumptions hold (eg, in situations with skewed data and/or small sample size), one can always use bootstrap resampling techniques. However, it has been our experience that there is usually not much quantitative difference (and even less qualitative difference) when a CEAC is made from parametric *P* values versus nonparametric bootstrapping techniques.[14]

Another advantage of net benefit regression is that it helps the analyst produce results that are congruent with health economic principles. Statisticians and health economists have debated whether reporting average cost-effectiveness ratios (ACERs = C/E) vis-à-vis ICERs (ICERs = $\Delta C/\Delta E$) is acceptable for the results of an economic evaluation.[22] It is not difficult to find examples of applied research reporting economic results using ACERs. For example, the *Journal of Occupational and Environmental Medicine* recently published an economic evaluation reporting ACERs,[23] and we have presented results this way as well.[24] The use of the INB clarifies why ACERs are incorrect.[25] Using net benefit regression obviates the need to remember whether it is C/E or $\Delta C/\Delta E$ that is of interest. The coefficient on the treatment indicator variable in a net benefit regression is the INB, and the value of WTP that yields a coefficient estimate of zero is the ICER. In the rare circumstance where the ACER truly does make sense to report (eg, when costs and effects of usual care are both 0), the coefficient on the treatment indicator variable is the average net benefit of the new intervention (NB_{TX}), and the value of WTP that yields a coefficient estimate of zero is the ACER.

CONCLUSIONS

This article illustrates the net benefit regression framework, a method for CEA, when person-level data are available.[8] The framework allows incremental cost and incremental effect to be estimated either separately (eg, using seemingly unrelated regression equations) or together (ie, using net benefit as a dependent variable). The former option can be useful in situations where the analyst wishes to employ different strategies to estimate incremental cost and incremental effect (eg, if a covariate X_p is known to affect employees' outcomes but not their costs), whereas the latter option is more common and can be as straightforward as simple linear regression using OLS. However, net benefit regression can accommodate more ambitious analytical strategies with more advanced regression techniques (eg, using regression diagnostics to explore model assumptions, employing interaction terms to generate hypotheses about employees for whom an intervention is especially cost-(in)effective and/or using propensity scores when data are observational). In the case study presented in this article, we were able to adjust our CEA for covariates using multiple linear regression. Plotting our results on an incremental net benefit by WTP curve illustrated our estimate of cost-effectiveness and the associated uncertainty. The graph allows the results to be customized to a variety of settings because the results reflect the unknown WTP's impact on conclusions about cost-effectiveness. Authors of economic evaluations are encouraged to consider analyzing their data and presenting the results using the techniques illustrated in this case study.

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