When does quality-adjusting life-years matter in cost-effectiveness analysis?

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Summary

Purpose: This paper investigates the impact of quality-of-life adjustment on cost-effectiveness analyses, by comparing ratios from published studies that have reported both incremental costs per (unadjusted) life-year and per quality-adjusted life-year for the same intervention.

Methods: A systematic literature search identified 228 original cost–utility analyses published prior to 1998. Sixty-three of these analyses (173 ratio pairs) reported both cost/LY and cost/QALY ratios for the same intervention, from which we calculated medians and means, the difference between ratios (cost/LY minus cost/QALY) and between reciprocals of the ratios, and cost/LY as a percentage of the corresponding cost/QALY ratio. We also compared the ratios using rank-order correlation, and assessed the frequency with which quality-adjustment resulted in a ratio crossing the widely used cost-effectiveness thresholds of $20 000, $50 000, and $100 000/QALY or LY.

Results: The mean ratios were $69 100/LY and $103 100/QALY, with corresponding medians of $24 600/LY and $20 400/QALY. The mean difference between ratios was approximately $34 300 (median difference: $1300), with 60% of ratio pairs differing by $10 000/year or less. Mean difference between reciprocals was 59 (QA)LYs per million dollars (median: 2.1). The Spearman rank-order correlation between ratio types was 0.86 (p < 0.001). Quality-adjustment led to a ratio moving either above or below $50 000/LY (or QALY) in 8% of ratio pairs, and across $100 000 in 6% of cases.

Conclusions: In a sizable fraction of cost–utility analyses, quality adjusting did not substantially alter the estimated cost-effectiveness of an intervention, suggesting that sensitivity analyses using ad hoc adjustments or ‘off-the-shelf’ utility weights may be sufficient for many analyses. The collection of preference weight data should be subjected to the same scrutiny as other data inputs to cost-effectiveness analyses, and should only be undertaken if the value of this information is likely to be greater than the cost of obtaining it. Copyright © 2004 John Wiley & Sons, Ltd.

Keywords quality-adjusted life-years; preference weights; utilities; cost–utility analysis; cost-effectiveness analysis
Introduction and Objectives

Cost–utility analyses (CUAs) that measure cost-effectiveness in costs per quality-adjusted life-year (QALY) have increasingly become the standard in cost-effectiveness analysis (CEA) [1]. The US Public Health Service’s Panel on Cost-Effectiveness in Health and Medicine (USPHS Panel) has recommended that, for analyses intended to inform resource allocation, a reference case should be included that measures cost-effectiveness as incremental costs/QALY (here abbreviated $dC/dQALY$) [2 (p. 122)]. However, many investigators still estimate and report cost-effectiveness ratios as incremental costs/life-year ($dC/dLY$), rather than as $dC/dQALY$ [3,4]. In addition, the collection of utility data to quality-adjust years of life can be expensive and resource-intensive. If quality-adjusted and unadjusted analyses are expected to produce similar results (that is, the addition of quality-adjustment would not change decisions), analysts might reasonably forego performing complete reference case CEAs to save time and money.

Analysts are, therefore, faced with the dilemma of how to perform CUAs within reasonable cost and time constraints. Without some ‘methodological triage,’ analysts run the risk of producing theoretically elegant analyses that have little chance to influence decisions because they take so long to complete, or of never performing them to begin with because they are too expensive. The USPHS Panel explicitly recognized this dilemma in their formulation of the ‘rule of reason’ [2 (p. 71)]. This rule states that, in designing CEA models, analysts should consider the importance of each cost and effect component in deciding whether to include an element in the actual analysis.

While some authors have discussed the issue of whether or not quality adjustment is always necessary when conducting a CEA, mainly from a theoretical standpoint [5–7], there have been few attempts to use empiric data to answer this question [8]. Our main objective in this study was to explore how often decisions might differ if made based on $dC/dLY$ rather than $dC/dQALY$, using published CEAs that present ratios as both $dC/dQALY$ and $dC/dLY$ for the same intervention. That is, how often did the extra effort of collecting and using quality-adjustments pay off by substantially affecting the results of CEAs? Comparisons of these paired ratios were used to:

1. quantify the absolute and relative differences between the cost-effectiveness of the same intervention as measured by $dC/dQALY$ and $dC/dLY$;
2. explore how the differences between measures might affect resource allocation decisions made using commonly used thresholds; and,
3. identify the factors causing $dC/dQALY$ to be substantially higher than $dC/dLY$ (and vice versa), and the factors associated with larger differences.

Methods

Data sources

We explored the differences between $dC/dLY$ and $dC/dQALY$ ratios using the Cost Utility Analysis Database developed at the Harvard Center for Risk Analysis [1,9], a comprehensive database of published studies that is based on a systematic literature search of relevant computerized databases. The database contains 228 original CUAs that present 645 $dC/dQALY$ ratios published prior to 1998. Details about the database have been published previously [1,9,10] and are also available on our Web site [11].

Of the 228 articles in the CUA database, 63 reported both $dC/dQALY$ and $dC/dLY$ for the same intervention, either as baseline comparisons or through sensitivity analyses on preference weights (by setting health-related quality of life adjustments to zero). The 63 studies reporting both estimates contained 173 $dC/dLY$ and $dC/dQALY$ ratio pairs. (Because cost-effectiveness analyses often compare several possible programs or intensity levels, a single article could contribute several ratio pairs, ranging from 1 to 18 here.) To allow cross-study comparisons on a common scale, we converted all ratios into 1998 United States dollars, using the appropriate foreign exchange factors and the general Consumer Price Index [9]. All statistical analyses were performed using SPSS for Windows, ver. 10.0.7 (SPSS, Inc., Chicago, IL).

Analytic plan

Quantifying the differences between $dC/dQALY$ and $dC/dLY$. To quantify the absolute differences
between cost-effectiveness as measured by \( \text{dC}/\text{dQALY} \) and \( \text{dC}/\text{dLY} \) for the same intervention, the quality-adjusted and unadjusted ratios were tabulated in two ways, as the *ratio differences* (calculated as \( \text{dC}/\text{dLY} \) minus \( \text{dC}/\text{dQALY} \) estimates for the same interventions), and as *reciprocal differences* (calculated as \( \text{dQALY}/\text{dC} \) minus \( \text{dLY}/\text{dC} \) and expressed as QALYs or LYs per million dollars). The ratio differences provide a measure of the change in estimated cost-effectiveness brought about by quality-adjustment. We also determined the number of times the differences between ratios were positive and the number of times negative. Because the incremental costs (\( \text{dC} \)) are identical in both ratios in each pair, the differences between the ratios are driven by differences between the reciprocals of the effectiveness measures (\( \text{dLY} \) and \( \text{dQALY} \)), rather than by differences between the effect sizes themselves. Therefore, we also calculated an alternative measure that is proportional to the effectiveness difference, namely, the differences between the reciprocals of the ratios, expressed as \( \text{dLY} \) or \( \text{dQALY} \) per million dollars. These 'effectiveness-cost ratios' emphasize the incremental health gains per resources spent, a concept that may be more intuitive and ethically satisfying to those who are unfamiliar with economic evaluation than is the cost per LY or per QALY [12]. We also compared the *relative sizes* of the ratios, calculating \( \text{dC}/\text{dLY} \) as a percentage of the corresponding \( \text{dC}/\text{dQALY} \) ratio (\( \text{dQALY}/\text{dLY} \)).

To compare the numerical \( \text{dC}/\text{dLY} \) and \( \text{dC}/\text{dQALY} \) ratios and their reciprocals, as well as these measures of difference between them, we calculated descriptive statistics, including medians and arithmetic means. We compared the rankings of interventions based on each ratio type by calculating the Spearman rank-order correlation between \( \text{dC}/\text{dQALY} \) and \( \text{dC}/\text{dLY} \). Spearman correlations were used rather than Pearson because the ratio distributions were heavily skewed. We also took the log of each ratio to produce more normal distributions, and calculated Pearson correlations. Correlations near +1 indicate that the rank ordering of the quality-adjusted \( C/E \) ratios closely matched the order of the unadjusted ratios, while those near 0 indicate that there was little relation between the two sets of rankings.

**Threshold analysis.** To explore how the differences between \( \text{dC}/\text{dLY} \) and \( \text{dC}/\text{dQALY} \) ratios might affect resource allocation decisions made using each type of ratio, we determined the numbers of cases where analyzed interventions crossed one of several commonly used ‘decision thresholds’ [14] when \( \text{dC}/\text{dQALY} \) is used rather than \( \text{dC}/\text{dLY} \) and vice versa. Specifically, we examined how often the use of quality-adjustment caused an estimated ratio to move across key thresholds used in the literature (such as \( \$50,000 \) or \( \$100,000/LY \) or QALY), or to the intervention being dominated (that is, gaining fewer QALYs or LYs at higher cost that the alternative). This allowed some quantification of how often quality-adjustment might ‘make a difference’ in actual resource allocation decisions.

*Identifying factors associated with differences.* To identify which aspects of a given intervention were associated with differences across ratio pairs, we used variables related to the natural history of the conditions and interventions, all of which could be specified prior to the conduct of a CEA. Three investigators (RHC, SG, MB) classified each condition and intervention in the data set into the appropriate categories. (For example, is the condition acute or chronic, or is the intervention preventive, curative, or palliative?) Discrepancies among responses were resolved by using the majority response. For each variable, we recorded the value which we hypothesized would be associated with larger differences between the quality-adjusted and unadjusted ratios. For example, we hypothesized that interventions for chronic conditions would be associated with larger differences than those for acute diseases, because any QoL effects would more likely be long-term rather than short-term.

We then performed two regression analyses: one that attempted to determine which factors were associated with positive or negative ratio differences (logistic regression), and one for factors associated with larger differences (linear regression). Binary logistic regressions were performed with the sign of the ratio difference as the dependent variable and the factors discussed above as independent variables. This regression indicates the types of conditions or interventions for which quality adjustment was most likely to make the estimated QALYs either higher (if the sign of the ratio difference is positive) or lower (if negative) than the corresponding estimate of unadjusted life-years. We also performed multivariate regression analyses with the reciprocal difference \( \text{dQALY}/\text{dC}−\text{dLY}/\text{dC} \) as the
dependent variable. We hypothesized that the reciprocal differences variable would perform better in the regression analyses because its distribution was more normal than the distribution of the ratio difference \( (dC/dLY - dC/dQALY) \) variable, which was highly skewed. While transformation of the dependent variable makes the interpretation of regression results somewhat more difficult, the use of reciprocals to normalize the dependent variable’s distribution should lead to more efficient regression estimates. We also checked for autocorrelation of errors using the Durbin–Watson statistic, because we were analyzing at the ratio level and many studies reported several ratios.

### Results

#### Quantifying the differences between \( dC/dQALY \) and \( dC/dLY \)

The 173 \( dC/dLY \) and \( dC/dQALY \) ratio pairs from the 63 published CUAs are listed on our Web site [12], along with the differences between ratio types, the reciprocals of each ratio type and their differences, and \( dQALY/dLY \). In 33 of these 173 ratio pairs, the incremental cost/life-year or incremental cost/QALY (or both) was estimated to be cost-saving or dominated. Because no specific cost per QALY could be associated with cost-saving or dominated ratios, these ratio pairs were not used in the quantitative analyses that follow, leaving us with 140 valid numerical ratio pairs.

The \( dC/dLY - dC/dQALY \) differences were positive in 85 cases (61%) and negative in 51 cases (36%), with four ratio pairs showing no difference (Table 1). That is, \( dC/dLY \) ratios were greater than their paired \( dC/dQALY \) ratios more often than the other way around. The median \( dC/dLY \) and \( dC/dQALY \) ratios for the sample of identical interventions were approximately $24 600/LY and $20 400/QALY (Table 2), while the means, approximately $69 100/LY and $103 000/QALY (Table 2), were much higher than their respective medians. This contrast reflects the fact that the distributions of \( dC/dLY \) and \( dC/dQALY \) ratios were highly positively skewed, with the highest ratios being approximately $2 400 000/LY and $8 900 000/QALY (for the same intervention). With this outlier removed, the mean \( dC/dQALY \) equals approximately $35 000/QALY and mean \( dC/dLY \), approximately $44 000/LY.

The Spearman rank-order correlation was 0.86 \( (p < 0.001, \text{Table 2}) \). After log transformation, the Pearson correlation between the two ratio types was 0.84 \( (p < 0.001, \text{Figure 1}) \). The mean difference between ratios \( (dC/dLY - dC/dQALY) \) was approximately −$34 300, with a median difference of approximately $1300 (Table 2). As expected, the distribution of the ratio differences was also heavily skewed (Table 2, Figure 2). The difference between the maximum ratios mentioned-

<table>
<thead>
<tr>
<th>Sign of ratio difference</th>
<th>( N )</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive ( (dC/dLY &gt; dC/dQALY) )</td>
<td>85</td>
<td>60.7</td>
</tr>
<tr>
<td>Zero ( (dC/dLY \approx dC/dQALY) )</td>
<td>4</td>
<td>2.9</td>
</tr>
<tr>
<td>Negative ( (dC/dLY &lt; dC/dQALY) )</td>
<td>51</td>
<td>36.4</td>
</tr>
<tr>
<td>Total</td>
<td>140</td>
<td>100.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Statistic</th>
<th>( dC/dQALY ) ( (n = 145) )</th>
<th>( dC/dLY ) ( (n = 142) )</th>
<th>Ratio difference ( (n = 140) )</th>
<th>( dQALY/dC \times 10^6 ) ( (n = 145) )</th>
<th>( dLY/dC \times 10^6 ) ( (n = 142) )</th>
<th>Reciprocal difference ( (\times 10^6) ) ( (n = 140) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>20 366</td>
<td>24 600</td>
<td>1276</td>
<td>49</td>
<td>41</td>
<td>2.1</td>
</tr>
<tr>
<td>Mean</td>
<td>103 075</td>
<td>69 104</td>
<td>−34 306</td>
<td>136</td>
<td>141</td>
<td>59</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>734 693</td>
<td>215 308</td>
<td>549 855</td>
<td>280</td>
<td>650</td>
<td>238</td>
</tr>
<tr>
<td>Skewness</td>
<td>11.89</td>
<td>9.48</td>
<td>−11.52</td>
<td>4.45</td>
<td>11.08</td>
<td>4.54</td>
</tr>
<tr>
<td>Spearman’s rho</td>
<td>( 0.86^* )</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\* \( p < 0.001 \).

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**Table 2. Summary descriptive statistics \( (n = 63 \text{ studies}) \)**

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above leads to a negative outlier difference of \(-$6\,400\,000\). When this outlier is excluded, the mean ratio difference is approximately \(+$1\,800\) (standard deviation = 72 800). Sixty percent of the ratio pairs \(n = 84\) differed from each other by \(+$10\,000/\text{year}\) or less in absolute terms (Figure 2).

The means of the reciprocals of the ratios were similar in value (at 141 LYs per million dollars and 136 QALYs per million dollars), as were the medians (Table 2). The distributions of the reciprocals of the ratios were less skewed than those for the ratios themselves, as was that of the reciprocal differences (Table 2). The mean reciprocal difference was 59 (QA)LYs per million dollars, with a median difference of only 2.1 (Table 2). When \(dC/d\text{LY}\) was expressed as a percentage of the corresponding \(dC/d\text{QALY}\) ratio, 22% of the \(dC/d\text{LY}\) ratios were within 10% of the corresponding \(dC/d\text{QALY}\) ratio, while 19% were greater than 1.5 times the paired \(dC/d\text{QALY}\) ratio (data not shown).

Threshold analysis

Quality-adjustment led to a previously unadjusted ratio moving either above or below \$50\,000 in 14 of the 173 ratio pairs (8.1%; Table 3). Quality-adjustment caused a ratio pair to cross \$100\,000 in 11 cases (6.4%; Table 3). Five interventions were no longer dominated when \(dC/d\text{QALY}\) was used rather than \(dC/d\text{LY}\), while two cases that reported positive \(dC/d\text{LY}\) ratios were dominated for \(dC/d\text{QALY}\) (total = 7 or 4.0%). Overall, the number of interventions for which the use of quality adjustment would lead to the estimated ratio crossing any of these thresholds is 32, or approximately 18% of the 173 cases.

Identifying factors associated with differences

We performed a logistic regression analysis with the sign of the ratio difference (positive or negative) as the dependent variable, using the condition- and intervention-level independent variables in Table 4. Significant explanatory variables in the final logistic regression model were whether the condition is chronic and whether negative long-term sequelae (defined as interventions associated with negative side effects or
Table 4. Independent variables used in the multivariate analyses, and results of (A) the final logistic regression model for the sign of the ratio difference (positive or negative) \((n = 136)\) and (B) the final multivariate linear regression model with reciprocal differences \(({d\text{QALY} - d\text{LY}}/dC \times 10^6)\) as the dependent variable (adjusted \(R^2 = 0.13)\)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Categories</th>
<th>(A) Logistic regression</th>
<th>(B) Linear regression</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Explanatory, condition level</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Term</td>
<td>Acute, chronic&lt;sup&gt;a&lt;/sup&gt;</td>
<td>+1.44 (0.44)</td>
<td>0.001</td>
</tr>
<tr>
<td>Symptomatic?</td>
<td>Y/N</td>
<td>NS&lt;sup&gt;b&lt;/sup&gt;</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Explanatory, intervention level</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Term</td>
<td>Acute, chronic&lt;sup&gt;a&lt;/sup&gt;, intermittent</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Purpose</td>
<td>Preventive, curative, palliative</td>
<td>NS</td>
<td>187.73 (46.36) [palliative] &lt;0.001</td>
</tr>
<tr>
<td>Negative sequelae?</td>
<td>No, short-, long-term</td>
<td>−1.17 (0.45)</td>
<td>0.009</td>
</tr>
</tbody>
</table>

<sup>a</sup> Value of variable for which we hypothesized that differences between ratios would be greater.
<sup>b</sup> NS = not significant.

unintended outcomes that last longer than 2 years) are associated with the intervention (Table 4). If a condition was chronic, it was associated with an increase in the likelihood of a positive ratio difference \((dC/d\text{LY} > dC/d\text{QALY})\), while the presence of long-term negative sequelae was associated with negative ratio differences.

For the linear regression model with reciprocal differences as the dependent variable (Table 4), we found that chronic conditions and palliative interventions were significantly associated with positive increases in the reciprocal difference. The presence of long-term negative sequelae were associated with decreases in the reciprocal difference. However, this model explained only about 13% of the variation in the reciprocal differences (adjusted \(R^2 = 0.13)\). Attempts to account for more of the observed variance, through transformations of the dependent variable and the inclusion of additional explanatory variables, were not successful. Examination of the Durbin–Watson statistic (1.54) reveals no definitive indication that autocorrelation of errors within studies is a problem in this model, even though we are analyzing at the ratio rather than study level.

**Discussion**

Cost-effectiveness analysis is one tool to help inform resource allocation decisions and the prioritization of medical interventions [14,15]. We identified 63 studies that reported both quality-adjusted and unadjusted cost-effectiveness ratios estimated for the same intervention, which provided us with a unique opportunity to explore systematically the relation between quality-adjusted and unadjusted ratios. The two ratio types were highly correlated, and differences between them appeared relatively small in over two-thirds of the cases. Although quality-adjusting life-years is now widely advocated for cost-effectiveness analyses, we found that in most cases quality adjustment had relatively little effect on the final estimated cost-effectiveness ratio. This suggests that in many studies, quality adjustment with minimal data collection (for example, ad hoc adjustments or previously published utility weights for health states) may be adequate to obtain a reasonable estimate of the cost-effectiveness of a given intervention.

However, we also found that quality adjustment had a sizeable impact in a small but non-trivial fraction of cases. Quality adjustment led to a ratio moving across potential ‘cost-effective thresholds’ (such as $50 000/LY or QALY) in almost one-fifth of the cases in this data set. This suggests that some form of sensitivity analysis or value of information analysis on the importance of quality adjustment should be undertaken before deciding how much effort to put into the collection of QoL or preference weight data. For example, if a value of information analysis indicated that the expected value of the optimal choice with QoL
information minus the expected value without that information is smaller than the expected cost of obtaining that information, then the analyst should not undertake the collection of QoL data. If other variables are likely to have a greater effect on the final estimate of cost-effectiveness, analysts might focus their attention on obtaining better estimates of those inputs rather than on the collection of health utilities for quality adjustment. This information may be useful because the accelerating pipeline of new technology has the potential to overwhelm the resources available to evaluate their cost-effectiveness. Of course, analysts may wish to include quality adjustment even in studies where it is not expected to make much difference, so that a reference case exists for comparison with other studies [2].

To decide a priori whether quality-adjustment is important to a given analysis, it would be helpful to know which types of conditions and interventions are most likely to be associated with substantial differences between quality-adjusted and unadjusted ratios. In our regression analyses, quality-adjustment seemed to be most important when the condition being studied was chronic, when the intervention was palliative, and when the intervention included long-term negative sequelae. Interventions that are provided for chronic conditions were associated with larger positive reciprocal differences, indicating that these interventions are more likely to increase the incremental QALYs gained than are those for acute conditions. This finding confirms our prior belief that quality-adjustment would be more important for chronic conditions than for acute ones, because these would be more likely to have long-term effects on QoL. Using cost-per-QALY as the measure of cost-effectiveness, rather than cost-per-LY, may therefore make interventions for chronic conditions appear relatively more cost-effective than those for acute conditions, on average. Palliative interventions, where the main purpose is to improve QoL rather than to extend life, were also associated with larger positive reciprocal differences. Interventions with long-term negative sequelae are associated with large negative reciprocal differences. The presence of long-term side effects from an intervention would be expected to cause a decrease in the incremental QALYs relative to the LYs gained from that intervention. It should be emphasized, however, that these results are only a rough guide, and should not be taken to indicate that the absence of these factors means that quality-adjustment is not important in a given analysis (or that their presence implies that it will necessarily be important).

There are several limitations to these analyses. While our literature search included several computerized databases, we were not able to identify analyses that were either in unlisted publications or not published at all. Thus, any publication bias in cost–utility analyses would be reflected in our database. A bias might exist, for example, if investigators are more likely to perform a cost-per-QALY study if they anticipate important differences from cost-per-LY. In addition, because our search algorithm was focused on finding CUAs, we may have missed some studies that estimated both costs per QALY and costs per life-year. Also, this group of CEAs provides only an incomplete snapshot of the field, and may not be generalizable to other settings (because of differences in disease prevalence, medical practice or costs). Finally, the above analyses assume that studies performed the QoL adjustments correctly. To be complete, we would need to assess whether all relevant effects (e.g. non-fatal side effects and non-fatal disease effects) were included and valued correctly.

In summary, we found that in many individual cost–utility analyses published before 1998, quality adjusting has not substantially affected results, while in others it had substantial effects. If the intervention or condition being studied is not expected to have much impact on QoL relative to mortality effects, and if time and resources are especially constrained, analysts may choose to forgo quality-adjustment altogether, allowing them to concentrate efforts on data inputs for which the value of information is higher. Further research should confirm the factors that determine when quality adjustment will be most important.

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