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ESTIMATING HSUVs FOR COMORBIDITIES

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Abstract

A comorbidity is defined as the presence of at least one additional health condition co-occurring with a primary health condition. Decision analytic models in healthcare depict the typical clinical pathway of patients in general clinical practice and frequently include health states defined to represent comorbidities such as sequelae or adverse events. Health state utility values (HSUV) are often not available for these and analysts generally estimate these. This article provides a summary of the methodological literature on estimating methods frequently used together with worked examples.

The three main methods used (minimum, multiplicative and additive) can produce a wide range in the values estimated. In general, the minimum method overestimates observed HSUVs and the magnitude of error tends to increase as the observed values decrease. Conversely, the additive and multiplicative methods generally underestimate observed values and the magnitude of the errors is generally greater for the additive method. HSUVs estimated using the multiplicative method tend to decrease for lower HSUVs and the largest errors are in observed HSUVs greater than 0.6.

Differences in estimated values can produce substantial differences in the resulting incremental cost effectiveness ratio. Based on the current evidence, the multiplicative method is advocated but additional research is required to determine appropriate methods when estimating values for additional comorbidities.

Key points for decision makers

- Ideally all HSUVs should be obtained directly from people with the conditions of interest and should only be estimated when the required evidence is not available.
- HSUVs for comorbidities should be estimated using the multiplicative method and the required multipliers should be obtained used age-adjusted condition-specific evidence where possible.
- It is recommended that a range of sensitivity analyses are performed to determine if results from the decision analytic model are robust to changes in HSUVs, preferably using a threshold analysis.

1. Introduction

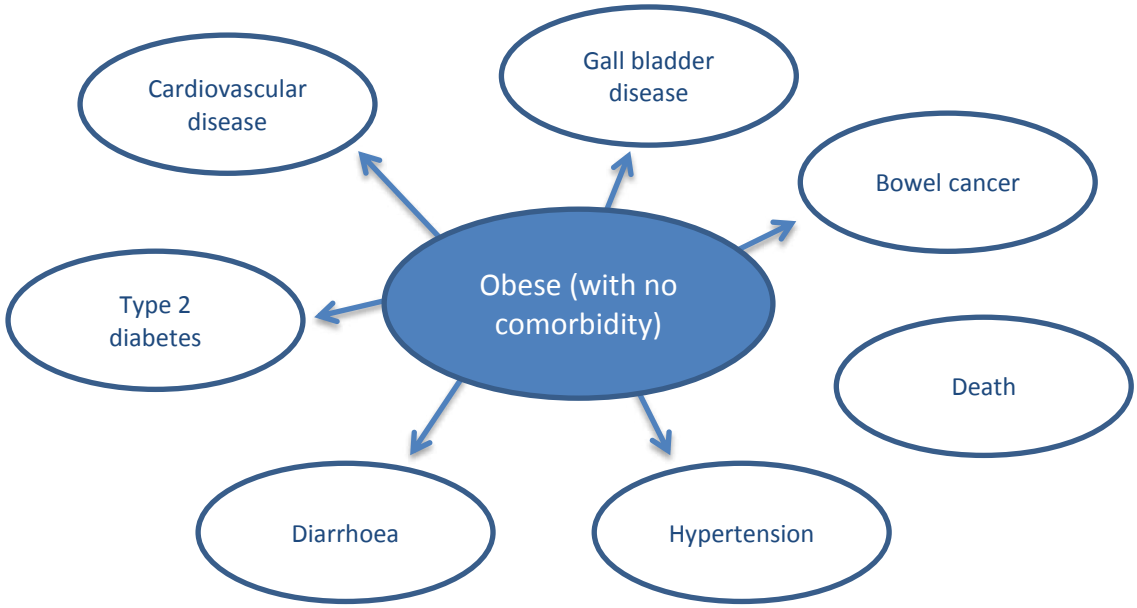
Decision analytic models in health care are designed to represent the typical clinical pathway followed by patients in general clinical practice. They can range from simple decision trees involving just two health states (e.g. alive and dead) to more complex models with numerous discrete health states representing the primary condition of interest, and additional health states representing associated clinical events or sequelea, prevalent comorbidities, and treatment related adverse events.

One example where multiple health states may be required is when exploring the potential benefits of weight loss interventions in obese populations. Obesity is associated with an increased risk of cardiovascular disease, type 2 diabetes, respiratory conditions, gallstones and some cancers. Pharmaceutical interventions prescribed for weight loss can produce adverse side effects such as diarrhoea or an increase in blood pressure levels, while surgical interventions such as gastric bypass are associated with infections, internal bleeding, and deep vein thrombosis. A decision analytic model assessing the benefits of a pharmaceutical intervention would potentially include at least some of these comorbidities. While the probability of the simultaneous presence of all the comorbidities presented in **Figure 1** is extremely small, it is reasonable to expect that an obese subject with diabetes may experience a heart attack or be diagnosed with obstructive sleep apnea at some point.

In addition to the independent decrement on HSUVs associated with changes in body mass index, to model the full effects of weight changes, analysts constructing such a model would require the HSUVs for health states representing combinations of the health conditions. While clinical studies provide evidence on the short-term health related quality of life (HRQoL) benefits of weight-loss, due to relatively low incidence rates for comorbidities, they may not provide the corresponding evidence from, for example, patients who have diabetes and experience a stroke.

This article provides a synopsis of the literature describing methodological research on methods used to estimate health state utility values (HSUVs) for comorbidities. A comorbidity is defined as the presence of at least one additional health condition co-occurring with a primary health condition. Recommendations and worked examples are provided where possible.

Figure 1 Health states in a decision analytic model assessing the potential benefits of a pharmaceutical intervention for weight loss



2. Preferred methods used to estimate HSUVs for comorbidities

Ideally HSUVs are obtained directly from people with the particular combination of conditions of interest. While there is now a substantial volume of evidence providing HSUVs for people with single health conditions, the evidence base for cohorts with comorbidities is more limited. In theory it is possible to design a study that would include every possible combination and permutation of health conditions. In reality, the associated resource implications are prohibitive, and analysts frequently need to utilise more limited evidence.

When HSUVs from individuals with comorbidities are not available, analysts may make use of mean HSUVs obtained from subgroups with individual conditions to estimate a mean HSUV for the comorbidity. For example, considering the obesity model, estimating a HSUV for diabetes and the comorbidity heart attack, analysts would use evidence obtained from people with diabetes (but no history of a heart attack) and evidence obtained from people with a history of a heart attack (but no history of diabetes) to estimate the required evidence. These data could be sourced from clinical studies that exclude patients with a history of specific conditions, or those taking non study drugs, although care should be taken to ensure check the exact exclusion criteria used to eliminate the risk of double counting. The technical question is how to use the evidence that is known from the subgroups with the single conditions, to estimate the potential effect on utility when the two conditions occur simultaneously.

Traditional estimation techniques include: the minimum method (assumes no additional decrement associated with comorbidity) [1,2,3,4] and the additive (applies the combined absolute disutility from the two single conditions on the baseline [1,2,3,4,5], thus has a constant effect) and multiplicative method (multiplies the two utilities from the single conditions, thus has a relative effect) [1,2,3,4,5,6]. There is evidence providing a statistical linear regression model that can be used to predict mean HSUVs (UK, EQ-5D-3L) for two comorbidities using mean HSUVs from subgroups with single conditions [2,3]. The research used EQ-5D evidence collected in the Health Survey for England and the function was obtained by regressing the mean EQ-5D from subgroups with just one particular health condition onto the mean EQ-5D from subgroups (n = 96) with two corresponding comorbidities (i.e. evidence from the subgroup who had condition A (but not condition B), and evidence from the subgroup who had condition B (but not condition A) were used to predict the EQ-5D score for the subgroup who had both condition A and condition B) [3]. While the results are promising, as the model has not been validated in external data, it cannot currently be recommended and details are provided in **Table 1** for completeness only. A worked example comparing results using the alternative methods is provided below.

Worked example

Using EQ-5D data and self-reported responses of history of particular health conditions collected in the Health Survey for England, evidence from a subgroup with diabetes (but no history of a heart attack) and evidence from a subgroup with a history of a heart attack (but no history of diabetes) are used to estimate a mean HSUV for the comorbidity diabetes and heart attack [7]. The observed mean EQ-5D score for the combined comorbidity diabetes and heart attack is 0.5188 whilst the mean scores for diabetes and heart attack are 0.7304 and 0.6492 respectively. The corresponding mean score for people who do not have these conditions (i.e. the condition specific baseline evidence) is 0.9864 for the absence of both conditions, 0.9361 for the absence of diabetes and 0.9378 for the absence of heart attack).

Using the alternative methods to estimate values for the health state diabetes and heart attack produces HSUVs ranging from 0.4921 when using the additive method, to 0.6492 when using the minimum method (see **Table 2** for calculations). The multiplicative method and statistical regression model produce estimates closer to the observed value (0.5188) at 0.5328 and 0.5310 respectively.

Table 1 Methods used to estimate HSUVs for comorbidities

Method	Function	
Additive	$U_{AB}^{Add} = U_{nA,nB} - ((U_{nA} - U_A) + (U_{nb} - U_B))$	Assumes a constant absolute decrement (relative to the baseline)
Minimum	$U_{AB}^{Min} = \min(U_{nAnB}, U_A, U_B)$	Assumes no additional decement over that observed for the condition with the lowest HSUV
Multiplicative	$U_{AB}^{Mult} = U_{nA,nB} \cdot \left(\frac{U_A}{U_{nA}}\right) \cdot \left(\frac{U_B}{U_{nB}}\right)$	Assumes a constant relative decrement (relative to the baseline)
Statistical regression model [3]	$U_{AB}^{LM} = \alpha + \beta_1 \cdot \min((U_{nA} - U_A), (U_{nB} - U_B)) + \beta_2 \cdot \max((U_{nA} - U_A), (U_{nB} - U_B)) + \beta_3 \cdot \min(U_{nA} U_{nB}) \frac{U_A}{U_{nA}} \cdot \frac{U_B}{U_{nB}} + \varepsilon$ α = -0.1007821; β_1 = 0.0439155; β_2 = 0.1545328; β_3 = 1.143514[##]	Incorporates terms representing the additive, multiplicative and minimum methods

[##] The coefficients provided in this table are suitable for UK EQ-5D 3L evidence only. **Key**: U – utility; superscripts – Add, Min, Mult, LM, represent the methods used (Add – additive; Min – minimum; Mult – multiplicative; LM – linear model); subscripts – A, B, AB, nA, nB, nAnB, represent the presence (or absence) of conditions (A – condition A (but not condtion B); B – condition B (but not condtion A); AB – both condition A and condition B; nA – not condition A; nB – not condition B; nAnB – neither condition A nor condition B). **NB**. These methods are only appropriate when combining evidence obtained using the same preference-based measure.

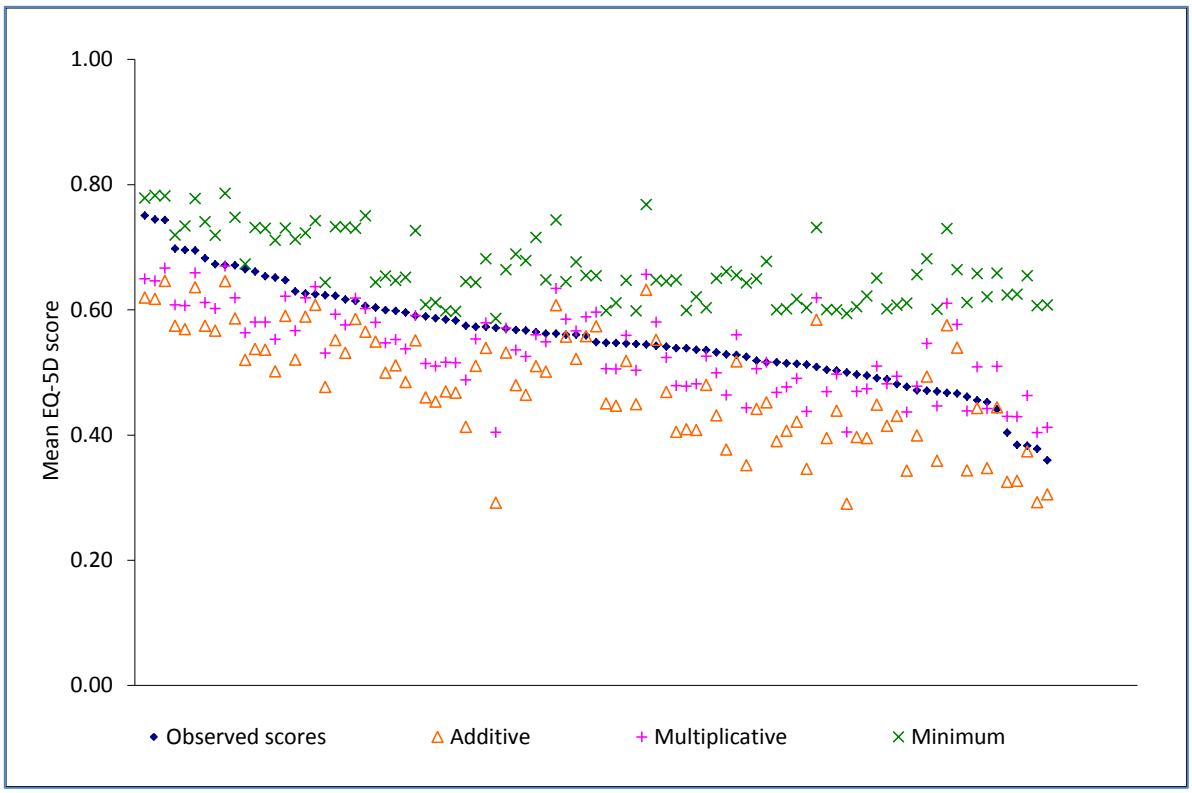
Table 2 Observed and estimated mean HSUVs for the comorbidity diabetes and heart attack

Condition	Observed mean HSUV	Age-matched mean HSUV from people without the condition(s) of interest[#]
Diabetes & heart attack	0.5188	No history of diabetes or heart attack = 0.9864
Just diabetes	0.7304	No history of diabetes = 0.9361
Just heart attack	0.6492	No history of heart attack = 0.9378
Method used	**Estimated mean HSUV**	**Calculations**
Additive	0.4921	$= 0.9864 - \big((0.9361 - 0.7304) + (0.9378 - 0.6492)\big)$
Minimum	0.6492	$= \min(0.9864, 0.7304, 0.6492)$
Multiplicative	0.5328	$= 0.9864 \times (0.7304 \div 0.9361) \times (0.6492 \div 0.9378)$
Statistical regression model	0.5310	$= -0.1007821 + 0.0439155 \times \min\big((0.9361 - 0.7304), (0.9378 - 0.6492)\big) + 0.1545328 \times \max\big((0.9361 - 0.7304), (0.9378 - 0.6492)\big) + 1.143514 \times \min(0.9361, 0.9378) \times (0.7304 \div 0.9361) \times (0.6492 \div 0.9378)$

[#] If condition specific age-matched evidence is not available, evidence from the general population may be used

The three traditional techniques can often produce substantially different scores and the estimated HSUVs may be noticeably different from the observed HSUVs. Using data from the Health Survey for England, **Figure 2** provides the observed and corresponding estimated EQ-5D scores for a variety of comorbidities [3]. The observed HSUVs are ordered by decreasing score and plotted with the corresponding calculated value. It can be seen that the minimum method overestimates all the observed scores and the magnitude of error in the estimated scores tends to increase as the observed scores decrease. Conversely, the additive and multiplicative methods generally underestimate the observed scores and the magnitude of error in the estimated scores is generally greater for the additive method [8]. There is a tendency for errors in the estimated values to decrease for lower HSUVs when using the multiplicative method (largest errors in values > 0.6).

Figure 2 Observed and estimated mean EQ-5D HSUVs for cohorts with two comorbidities



Source: adapted from Ara & Brazier, 2012[3]

3. Literature describing methods used to estimate HSUVs for comorbidities

A literature review conducted to inform a NICE Technical Support Document (searches: 1950 to February 2012) identified just 11 articles exploring the accuracy of methods used to estimate HSUVs for comorbidities [9]. As the existing empirical evidence provided conflicting results and conclusions, the main objective of the paper was to gain an understanding of potential reasons for differences in reported results and conclusions.

The authors reported the results and conclusions in the studies were influenced by the methods compared (the majority of studies compared just two methods), the range of HSUVs estimated (the observed mean HSUVs for the comorbidities in the majority of studies covered a truncated range at the higher end of the index), and the evidence used within the calculations (the accuracy of the methods increased when age- and condition-adjusted data were used to estimate the multipliers and decrements). In addition, summary statistics such as mean errors in the estimated HSUVs were often used to assess the performance of the methods. These statistics can conceal systematic errors as is seen in the HSUVs estimated using the minimum method in **Figure 2**.

While the authors of the review identified plausible explanations for the contradictory results and conclusions reported in the literature, they recommended that additional methodological research was required in this area. Based on the evidence reviewed, they concluded that when assessed across the full preference-based indices, the multiplicative method appeared to estimate the most accurate HSUVs. They recommended the multiplicative method using age and condition specific evidence to estimate the multipliers when possible. However, this recommendation was informed by research exploring the methods when used to estimate HSUVs for just two concurrent health conditions.

4. Uncertainty in HSUVs for comorbidities

When using estimated HSUVs in decision analytic models, it is particularly important to demonstrate the potential effect on the incremental cost-effectiveness ratio (ICER) when using alternative values. One approach might be to present ICERs generated using the alternative estimation methods as sensitivity analyses (retaining the multiplicative method in the base case). An alternative might be to present results using arbitrary adjustments to the estimated mean values (e.g. plus or minus 20%). However, the most appropriate approach would be to perform a threshold analysis, whereby the ICER threshold is used to determine the range of possible values the estimated HSUV would have to be within for the results to be considered cost-effective.

5. Issues and areas for future research

5.1 Estimating HSUVs for more than two concurrent comorbidities

The vast majority of published research on this topic presents results comparing the accuracy of methods when used to estimate HSUVs for just two concurrent health conditions. In practice, many people, and particularly the elderly, have more than two comorbidities. It is not possible to use the published regression models for more than two concurrent conditions as there is no term for additional comorbidities. Of the three traditional techniques, the minimum method has been shown to underestimate the effects on HSUVs when used for two concurrent comorbidities and it is reasonable to assume that it may produce larger errors if used to estimate a HSUV for three or more concurrent comorbidities. It is not known which of the additive and multiplicative methods would produce the most accurate estimates for more than two concurrent comorbidities. When adding the effects of additional comorbidities, the additive method will quickly produce HSUVs below the bottom range of the index while the multiplicative method will quickly tend towards zero. Given the findings from the research on two comorbidities, it seems likely that the multiplicative method might be the preferred method, but this is an area where additional research is justified.

5.2 Health dimensions affected by the condition(s)

The methods referenced above utilise the effect observed on the overall preference-based index irrespective of the characteristics of the health condition. It is possible that the combined effect of two conditions which both affect physical dimensions such as pain and self-care (e.g. rheumatoid arthritis and cancer) may differ substantially from the combined effect of two conditions which both affect mental health dimensions (e.g. schizophrenia and depression). This notion could be explored by using the proportions of responses to the health dimensions for the individual conditions to predict the proportion of responses to the health dimensions for the comorbidity, rather than the mean HSUVs.

5.3 Negative health state utility values

Although rare, there are occasions when the mean cohort HSUV is below zero. This can be problematic when using individual level data in a discrete event simulation but can also generate implausible values when estimating HSUVs for comorbidities. For example, when using the multiplicative method, combining an even number of negative HSUVs will produce a positive HSUV. Similarly, combining three of more large decrements using the additive method could produce a HSUV below the bottom limit of the preference-based index. It is unclear which of the methods are best suited to estimating HSUVs in these cases.

6. Summary

The differences in estimated HSUVs obtained using the alternative methods could potentially bias results generated from decision analytic models and thus have implications for policy decisions informed by these analyses. If policy makers are not empowered to gauge the magnitude or direction of potential differences in ICERs generated using the alternative methods this may undermine their confidence in results if the ICER is sensitive to changes in HSUVs. This is an area where more work is needed as all of the methods currently used have limitations, particularly at the individual level. Whichever method is used there is a risk of double-counting the decrements on health if the evidence used for the single health conditions includes patients with comorbidities. Consequently it is important to review the inclusion and exclusion criteria used in the original studies and to adhere to transparent reporting standards when describing the evidence used.

The current recommendation is to estimate HSUVs using the multiplicative method, with the caveat that caution is needed when estimating HSUVs for more than two concurrent comorbidities, or when at least one HSUV is below zero. A range of sensitivity analyses should be performed (e.g. threshold analysis) to explore the effect on the ICER when varying the HSUVs used within the model.

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Author contributions

RA reviewed the literature, wrote the first draft of the manuscript and made edits on the final draft. JEB made significant edits to the first and final draft of the manuscript. IAZ made significant edits to the first and final draft of the manuscript.

Compliance with Ethical Standards

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