Multiplicative with Linear Transformation (MLT): An Improvement on the Multiplicative Method for Age and Sex Adjustment of Utilities?

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Poster MSR7

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Introduction

- The 2022 National Institute for Health and Care Excellence (NICE) methods guide update explicitly recommends adjusting utility values for age over long time horizons to reflect decreases in quality of life for the general population, with a preference for the multiplicative method over the additive method.[1]
- Adjusting utilities for age is also recommended by a recent International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force good practices report.[2]
- Age adjustment of health state utility values (HSUV) in NICE appraisals appears to have become more routine over time, with two-thirds of NICE appraisals including it between November 2018 and 2019 compared with just 8.5% of appraisals between 2005 and 2008.[3,4]
- However, current guidance provides limited discussion around practical implementation, as well as the limitations of the multiplicative method, when conducting age adjustment of utilities.
- Furthermore, while perhaps less important to account for than age differences, utilities can also be adjusted for differences in sex characteristics between modelled and reference populations.

Objectives

- Describe and highlight limitations of the multiplicative method
- Propose a potential improvement on the multiplicative method using linear transformation to address limitations and improve generalisability across utility measures

Methods

- For any HSUV *"u"*, we can describe it in terms of the health state it represents (*"h"*), as well as the age (*"x"*) and sex characteristics (*"y"*) associated with the HSUV, as follows:

$$u^{h}_{x,y}$$

- When applying the multiplicative method, we assume that the proportional difference between our HSUV for a given population and the age-/sex-matched baseline utility value is preserved for all ages and sex characteristics. For a health state h_i derived from a population with mean age x_r and percentage male y_r, we can then calculate a utility multiplier m_i as:

$$\mathrm{m_i} = \frac{u^{h_i}_{x_r,y_r}}{u^{b}_{x_r,y_r}}$$

- Therefore, for any chosen age value *"x"* and sex characteristic *"y"* in our model, we can calculate an adjusted the HSUV $u^{h_i}_{x,y}$ as follows:
  - **Multiplicative method:**

$$u^{h_i}_{x,y} = u^{b}_{x,y} * \mathrm{m_i} = u^{b}_{x,y} * \frac{u^{h_i}_{x_r,y_r}}{u^{b}_{x_r,y_r}} \quad (1)$$

- Consider a series of worked examples using United Kingdom (UK) tariff EQ-5D-3L utility values as described in **Table 1**, for four hypothetical health states of "mild," "moderate," "severe," and "very severe." For the sake of simplicity and comparability across health states, we assume that all utility values were derived from all male populations with the same mean reference age of 45 years.

Table 1. Hypothetical health state utility values (HSUVs)

Health state	UK EQ-5D-3L utility value	Mean reference age	Reference % male
Mild disease	0.75	45.0 years	100%
Moderate disease	0.40		
Severe disease	0.05		
Very severe disease	-0.45		

- Using the recent NICE Decision Support Unit (DSU) report Adjusted Limited Dependent Variable Mixture General Population Utility Model as a baseline, and (for simplicity) assuming we are interested in modelling a male population, **Figures 1A-1D** show our HSUV curves adjusted for age for each of the HSUVs described in **Table 1**, including the unadjusted original utility values and reference age line at 45 years.[5]
- While the multiplicative method produces potentially plausible utility curves where the original utility values are ≥0, it is worth noting that this method prevents extrapolations from going below 0 even for small utility values (as shown in **Figure 1C**). However, we see that for more extreme negative utility values (**Figure 1D**), that the multiplicative method produces increasing utility values with age if applied as described (which is likely implausible).
- If using a utility measure where the lowest attainable utility value for individuals remaining alive is above 0 (such as the Short-Form Six-Dimension [SF-6D] or the Child Health Utility 9D [CHU-9D]), the multiplicative method could also generate values outside the bounds of the utility measure for lower utility scores when extrapolating to higher age values.

Figure 1A. Hypothetical "mild disease" health state utility curves by age

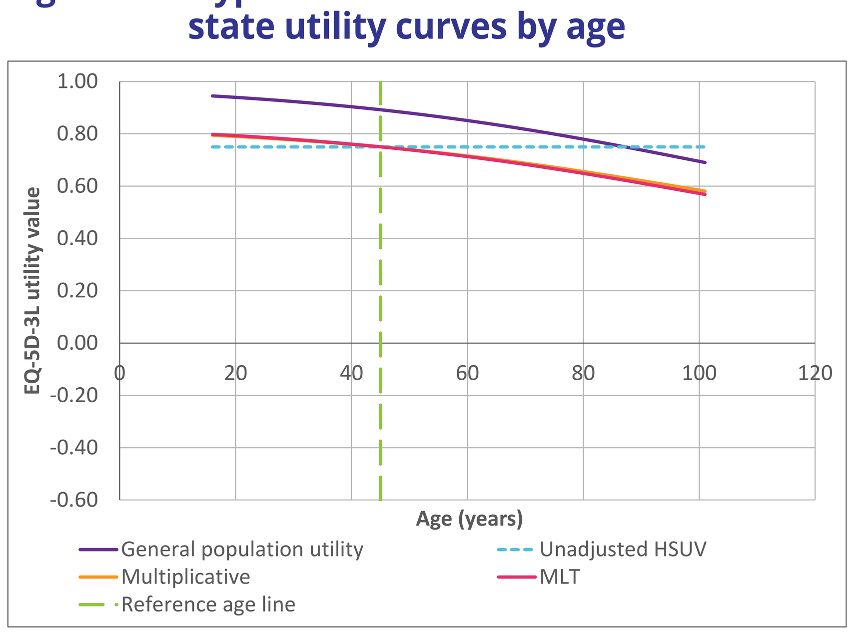
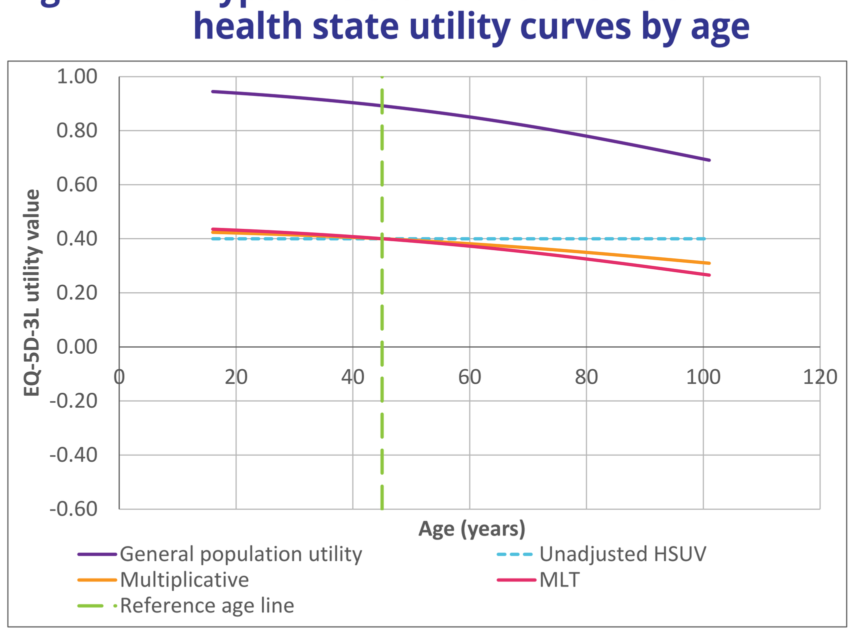


Figure 1B. Hypothetical "moderate disease" health state utility curves by age



HSUV, health state utility values; MLT, Multiplicative with linear transformation

Methods (Cont'd)

Figure 1C. Hypothetical "severe disease" health state utility curves by age

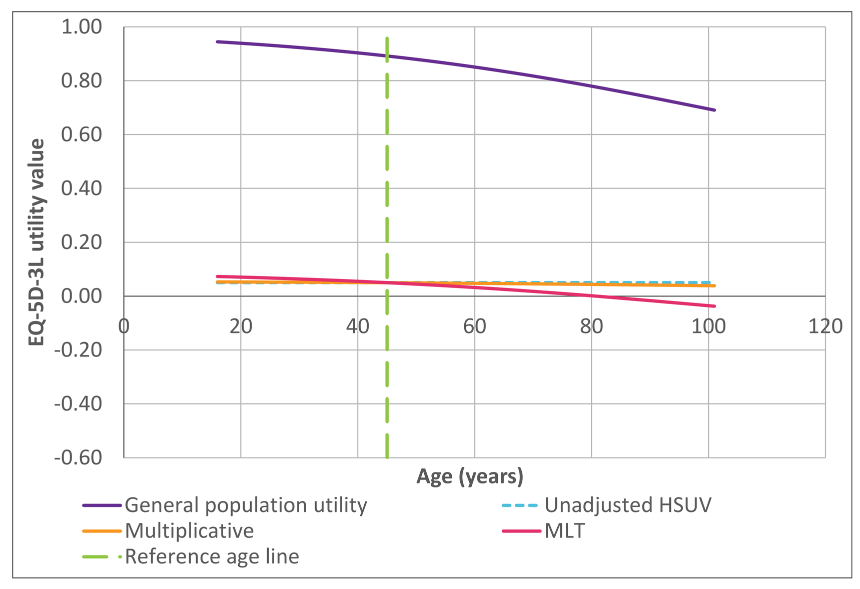
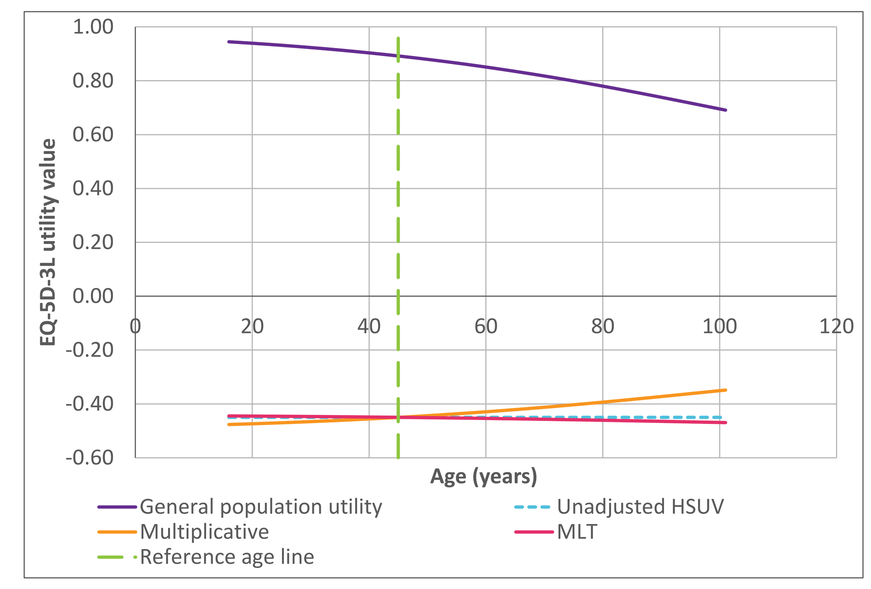


Figure 1D. Hypothetical "very severe disease" health state utility curves by age



HSUV, health state utility values; MLT, Multiplicative with linear transformation

- To address these methodological limitations, we can impose simple "corrections" to the methods as follows, where u^{lower_a} indicates the lowest attainable utility value for the chosen measure for individuals remaining alive:
  - **Multiplicative method (with lower bound and negative utility corrections):**

$$u^{h_i}_{x,y} = \begin{cases} Max(u^{h_i}_{x_r,y_r}, u^{lower\_a}),\ if\ u^{h_i}_{x_r,y_r} < 0 \\ Max(u^{b}_{x,y} * \frac{u^{h_i}_{x_r,y_r}}{u^{b}_{x_r,y_r}}, u^{lower\_a}),\ if\ u^{h_i}_{x_r,y_r} \geq 0 \end{cases} \quad (2)$$

- However, these provide relatively crude fixes to the observed limitations of these methods. We propose another potential solution to the bounding issues observed with the multiplicative method, by performing linear transformations onto a 0–1 scale when calculating and applying the utility multiplier (m_i).
- To achieve this, we use u^{lower_a} to perform the following linear transformations of both our original HSUV and our age- and sex-matched baseline utility value (assuming that all utility measures have an upper bound of 1):
  - Linear transformation of health state utility for reference population to a 0–1 scale:

$$\frac{u^{h_i}_{x_r,y_r} - u^{lower\_a}}{1 - u^{lower\_a}}$$

  - Linear transformation of baseline utility for reference population:

$$\frac{u^{b}_{x_r,y_r} - u^{lower\_a}}{1 - u^{lower\_a}}$$

- Then, our utility multiplier m_i can be calculated by dividing the linearly transformed health state utility by the linearly transformed baseline utility as follows:

$$\mathrm{m_i} = \frac{\frac{u^{h_i}_{x_r,y_r} - u^{lower\_a}}{1 - u^{lower\_a}}}{\frac{u^{b}_{x_r,y_r} - u^{lower\_a}}{1 - u^{lower\_a}}} = \frac{u^{h_i}_{x_r,y_r} - u^{lower\_a}}{u^{b}_{x_r,y_r} - u^{lower\_a}}$$

- To apply our transformed utility multiplier, we also need to transform the baseline utility for our chosen modelled age *"x"* and sex characteristics *"y"* to a 0–1 scale:
  - Linear transformation of baseline utility for chosen model population to 0–1 scale (for any age *"x"* and sex characteristics *"y"*):

$$\frac{u^{b}_{x,y} - u^{lower\_a}}{1 - u^{lower\_a}}$$

  - Application of the multiplier on the 0–1 scale:

$$\frac{u^{b}_{x,y} - u^{lower\_a}}{1 - u^{lower\_a}} * \mathrm{m_i} = \frac{u^{b}_{x,y} - u^{lower\_a}}{1 - u^{lower\_a}} * \frac{u^{h_i}_{x_r,y_r} - u^{lower\_a}}{u^{b}_{x_r,y_r} - u^{lower\_a}} \quad (3)$$

- To return back to our original utility scale, we need to reverse the linear transformation process, by multiplying by $1-u^{lower\_a}$ and then adding u^{lower_a} on to the result. However, we observe that multiplying by $1-u^{lower\_a}$ cancels out the denominator of the first fraction in Equation (3), and the resulting formula for our multiplicative with linear transformation approach becomes:
  - **Multiplicative with linear transformation (MLT) method:**

$$u^{h_i}_{x,y} = \left(u^{b}_{x,y} - u^{lower\_a}\right) * \frac{u^{h_i}_{x_r,y_r} - u^{lower\_a}}{u^{b}_{x_r,y_r} - u^{lower\_a}} + u^{lower\_a} \quad (4)$$

- Despite requiring several linear transformations, we see that the resulting Equation (4) represents a relatively simple extension to our original multiplicative method in Equation (1), as several "$1-u^{lower\_a}$" terms are cancelled out throughout the process, and is generalisable across different utility measures.
- This method also avoids the need for additional crude fixes as per Equation (2) to handle negative utility values or prevent values below u^{lower_a}.
- The MLT method is also extendable to conducting age and sex adjustment of disutility values, and for combining utilities for multiple HSUVs.
- As shown in **Figures 1A–1D**, regardless of the method applied, we see that our HSUV curves meet at the original utility value and reference age line. Below the reference age, the MLT method produces slightly higher utility values than the multiplicative method in each case, with lower utility values for ages above the reference age.

Conclusions

- The MLT method addresses some of the bounding and scaling issues of the multiplicative approach, without much additional complexity.
- Similar to the multiplicative method, the MLT approach is also extendable to adjusting disutility values as well as combining HSUVs for multiple comorbidities.
- While the MLT method requires further validation, it represents a more generalisable approach that could be considered in addition to the multiplicative method when performing age and sex adjustment of HSUVs.

References

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