Supplementary article data

Age- and health-related quality of life after total hip replacement
Decreasing gains in patients above 70 years of age

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Supplement

This supplement presents common alternative statistical techniques for the non-linear relationship between age and the two HRQoL measures. All of the methods have different skeletons that guide the fit to the data, thereby allowing different relationships. There is a common theme among many although the details may appear slightly different.

Statistical software

All analyses were performed using R (ver. 3.0.2), and packages rms (ver. 4.1-1) for restricted cubic splines, mfp (ver. 1.4.9) for multiple fractional polynomials and mgcv (ver. 1.7-28) for generalized additive modeling.

Comparison between alternative methods

As the histogram below indicates age is normally distributed with thin tales. We were therefore interested to find a non-linear methodology that is not only defined by the central portion.

To compare different models we used 10-fold cross-validation where we not only looked at the average root mean squared errors (RMSE) but also studied the central RMSE and the RMSE at the tails/periphery. The central age group was defined as the between the lower and upper quintile, 61 to 77.9, while the peripheral group where those outside this range. The only part that differed between the method’s models was the modeling of the age variable, all other parameters were modeled the same regardless of methodology for the age variable.

The overall method RMSE differed little from the cross-validated for most of the methods, see Table 1. Restricted cubic splines (RCS) and multiple fractional polynomial (MFP) models performed similarly, the former being slightly better. For selecting the method flexibility either the Bayesian information criterion (BIC) or the Akaike information criterion (AIC) was used for all but the MFP. The BIC and AIC variants were mostly similar although the polynomial fits seemed to benefit from the more restrictive BIC approach.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{age_distribution}
\caption{The age distribution between the sexes in the population.}
\end{figure}
Multiple fractional polynomials have been proposed as an alternative to splines. These use a defined set of exponential transformations of the variable, where it omits predictors according to their p-values.

Table 1. Method comparison by root mean square error (RMSE) for 10-fold cross validation. The higher values indicate poorer model generalizability. A large discrepancy between the overall RMSE and the cross-validated may indicate a problem with generalizability. The peripheral indicates the RMSE for those outside the lower and upper quintile, i.e. the extremes, while the central depicts the RMSE for those within the range.

<table>
<thead>
<tr>
<th>Method</th>
<th>Overall EQ-5D Index</th>
<th>Overall EQ VAS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Central</td>
<td>Peripheral</td>
</tr>
<tr>
<td>RCS</td>
<td>0.10032</td>
<td>0.10037</td>
</tr>
<tr>
<td>BIC (main)</td>
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<tr>
<td>AIC</td>
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<td>0.10042</td>
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<tr>
<td>Polynomials</td>
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<td>0.10036</td>
</tr>
<tr>
<td>Polynomial</td>
<td>0.10031</td>
<td>0.10338</td>
</tr>
<tr>
<td>Restricted cubic splines</td>
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<td>0.10345</td>
</tr>
<tr>
<td>MFP</td>
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<td>0.10041</td>
</tr>
<tr>
<td>GAM</td>
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<td>0.10034</td>
</tr>
<tr>
<td>Thin plate regression</td>
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<td>0.10034</td>
</tr>
<tr>
<td>Cubic regression</td>
<td>0.10027</td>
<td>0.10034</td>
</tr>
<tr>
<td>P-splines</td>
<td>0.10027</td>
<td>0.10034</td>
</tr>
</tbody>
</table>

Linear regression models

Linear regression is commonly applied and allows a multitude of different methods for modeling non-linear variables.

Restricted cubic splines

In the main article the BIC method was used to restrict the number of knots for the restricted cubic spline, also known as natural splines. It is a conservative approach that limits the spline flexibility and thus favors less complex models compared to the AIC. Below graph is generating after choosing number of knots through the AIC criterion where the EQ-5D index exhibits a more complex behavior.

MFG - multiple fractional polynomial

Multiple fractional polynomials have been proposed as an alternative to splines. These use a defined set of exponential transformations of the variable, where it omits predictors according to their p-values.

Polynomials

Polynomials can be of varying degrees and have often been argued as a simple approach to fitting a more flexible non-linear relationship. The simplest approach is to include the squared term and see if the p-value indicates significance, i.e. generating a second age variable that is age^2. Below we have two alternatives for polynomial fits, one where the degree of the polynomial is decided depending on the AIC and one where the BIC is used as restricting criteria.
As the majority of the patients are located around the mean age, 69.1 years, it is important to remember that these patients will have the strongest influence on the curve appearance. It is therefore possible that the tails are less reliable than the central portion.

**B-splines**

B-splines, alias Basis spline, are common alternatives to restricted cubic splines that also uses knots to control for flexibility. Just as with polynomials these have more flexible tails than restricted cubic splines.

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**BIC**

![Figure 4. Polynomials using BIC](image)

**AIC**

![Figure 5. Polynomials using AIC](image)

**BIC**

![Figure 6. B-splines using BIC](image)

**AIC**

![Figure 7. B-splines using AIC](image)
**Generalized additive models**

Generalized additive model (GAM) are an extension to generalized linear models and specializes in non-linear relationships. The models penalize the smoothness in different ways to avoid over-fitting.

**Thin plate regression splines**

This is generally the most common type of smoother in GAM models. The name refers to the physical analogy of bending a thin sheet of metal.

**Cubic regression splines**

The basis for the spline is cubic with evenly spread knots.

**P-splines**

P-splines are similar to B-splines in that they share basis with the main difference that P-splines enforce a penalty on the coefficients.

**Other methods**

**LOWESS**

The LOWESS stands for locally weighted scatter-plot smoothing. It uses localized subsets to fit models and then connects these subsets for the full sample. Note that the LOWESS graph is not adjusted for any covariates, including the preoperative HRQoL.