Technical Appendix

Cemented, cementless and hybrid prostheses for total hip replacement: a cost-effectiveness analysis.

Contents

Overview

This technical appendix provides methodological details to support the main paper.

Section 1 gives details on the data sources and data linkage required to estimate the main input parameters to the cost-effectiveness model, namely health-related quality of life (QOL), prosthesis cost and revision rates.

Section 2 explains the exclusion criteria applied to each dataset and how prosthesis type was defined.

Section 3 provides details on the Markov model.

Section 4 details the approach we took for handling missing data in the estimation of QOL following total hip replacement (THR).

Section 5 explains how we calculated the costs of the initial THR procedure.

In section 6 we report the statistical methods for handling potential confounding, including Genetic Matching (GenMatch), when estimating the effect of prosthesis type on QOL. This section also elaborates on how we extrapolated QOL over the lifetime, and how we estimated QOL after the THR was revised.

Section 7 then presents an alternative approach for the analysis of the HRQoL data, solely based on ordinary least squares (OLS), as a sensitivity analysis.

Sections 8, 9 and 10 elaborates on how the rates of revision and re-revision were calculated. We provide further information on the data sources used, and the approaches taken to estimating and then extrapolating these rates over time. We explain how we calculated the proportion of revisions after infection, and how re-revision rates were derived.

Section 11 shows how we estimated mortality rates following THR.

Sections 12 and 13 provide details of how the probabilistic and structural sensitivity analyses were conducted.

Section 1: Data sources and linkage

Data sources

Three data sources provided individual patient data which informed each of the transition probabilities and QOL tariffs applied to health states in the model : Patient Reported Outcome Measures (PROMs); National Joint Register (NJR) and Hospital Episode Statistics (HES). Patient records were linked across the data sources to generate two linked patient data sets. Records in PROMs were linked to the corresponding patient record in both HES and NJR creating a PROMs-HES-NJR dataset which extended back to 2008 and supplied data for the analysis of QOL in each health state and length of stay (LOS) after primary THR surgery. Records in the NJR were linked to the corresponding patient record in HES creating a NJR-HES linked data set extending back to 2003 from which revision rates in the first five years were estimated. Data from HES alone, extending back to 1997, informed our analysis of revision rates beyond five years from surgery, re-revision rates and operative mortality.

The Patient Reported Outcome Measures programme (PROMs) has collected outcome data on all NHS funded patients in England since April 2009 for total hip replacement (THR); total knee replacement; groin hernia surgery; and varicose vein removal.(1) Both primary and revision THR surgery is included. A post-operative questionnaire is sent six months after surgery to patients returning a pre-operative questionnaire. Response rates for the pre-operative questionnaire for THR are 80%, and of these 81% complete a post-operative questionnaire within 12 months (data for April 2009 to February 2011). We accessed data on 85 528 THR patients who underwent THR between Aug 2008 and Dec 2010, including 9831 respondents to the pilot survey(2) undertaken as part of the development of the PROMs programme. Of these 60% had returned a post-operation questionnaire by the end of June 2011. Of these, 73 666 patients were aged 55 to 84 inclusive at the time of the operation.

The National Joint Registry (NJR) has collected data on joint replacement operations in England and Wales since 2003.(3) We accessed all of the NJR data on THR, including components implanted, up to the end of 2009 (n = 289 785). In addition, we had access to the NJR records beyond 2009 for patients returning a PROMs questionnaire, but this did not include data on the brand of prosthesis fitted.

The NHS has collected data on all inpatient hospital stays since 1987.(4) Data in Hospital Episode Statistics (HES) includes length of stay (LOS); Index of Multiple Deprivation (a measure of socio-economic status);(5) International Classification of disease (diagnosis) codes(6) and Office of Population, Censuses and Surveys (OPCS) (procedure) codes.(7) The data is linked to death records held by the Office of National Statistics allowing identification of the date of death, where appropriate. We accessed HES data from April 1997 to December 2009, and identified 583 130 primary THRs and 98 710 revision procedures using OPCS codes.

Linkage of data sets

Three quarters of all records on THR in the NJR (from 2003 to Dec 2009) were successfully linked to the corresponding entry in HES by the NHS Information Centre using an algorithm that included personal demographic data and NHS number (unique number assigned to all NHS patients). The linked NJR-HES data contained 216 693 records. The NHS information centre was able to link 55% of PROMs records to the procedure entry in both the NJR and HES creating a PROMs-NJR-HES dataset containing 46 798 patients, of which 39 734 were aged 55 to 84 inclusive.

Section 2: Exclusions and assignment of THR type

NJR-HES linked data

Data in the NJR component table on the brand of prosthesis implanted allowed assignment of THR type for the NJR-HES linked data. Of the 289 785 patients in the NJR data, 216 693 were linked to a record in HES. Primary, unilateral THR patients aged between 55 and 84; with a sole diagnosis of osteoarthritis; receiving a cemented, cementless or hybrid prostheses; without bone grafts or minimally invasive surgery; and funded by the NHS were included (n=144 661)).

HES only data

Assignment of THR type in HES only data relied on OPCS codes. These codes allow identification of primary and revision THRs and distinguished cemented and cementless THRs. Hybrid and reverse hybrid THRs were identifiable from 2006 with the introduction of version 4·3 of the OPCS classification system. Of the 583 130 patients identified as receiving a primary THR, 398 153 remained after applying exclusions for age and diagnosis, of which 358 039 were classified as cemented or cementless THRs. Of these, 201 655 patients had an operation prior to 24th December 2004 providing at least five years follow-up.

PROMs-NJR-HES data

The characteristics of the 73 666 patients in the PROMs dataset aged 55 to 84, before linkage to NJR are summarised in the first row of table 1. Linkage with the NJR was required to assign the type of THR and to apply patient exclusions. After linkage with the NJR and HES we had 39 734 records. The characteristics of this sample are reported in the second row of table 1, and are similar to the overall PROMs sample. We then excluded patients who were not in the target population- those without an exclusive diagnosis of osteoarthritis; patients receiving minimally invasive or computer guided surgery; bilateral procedures; bone grafts and privately funded patients, as outcomes for these patients might be expected to differ. We also excluded patients without a post-operative PROMs questionnaire because they had died as this is a separate state in the Markov model. This left a sample of 34 233 patients relevant for the estimation of prosthesis type on QOL and LOS. The characteristics of this dataset are reported in the third row of table 1.

Component data were available in the linked NJR record for 29% of PROMs-NJR-HES linked records. For the remaining records, THR type was assigned using an algorithm based on OPCS codes in HES and the NJR. The algorithm assigned: a cemented THR if the NJR OPCS code indicated a cemented THR and the HES OPCS codes indicated either a cemented THR or was missing/ambiguous; a cementless THR if the NJR OPCS code indicated a cementless THR and the HES OPCS codes indicated a cementless THR or was missing/ambiguous; a hybrid THR if the HES OPCS codes indicated a hybrid THR and the NJR OPCS code indicated a hybrid THR or was missing/ambiguous. Cross-checking records where both brand type and OPCS codes were available suggested that the algorithm correctly assigned 93% of cementless THRs, 95% of cemented THRs and 98% of hybrid THRs. After categorisation of the THR procedure we excluded 124 revisions, 255 resurfacing procedures, 562 reverse hybrids and 3089 procedures with ambiguous codes (Figure 1) After exclusions we had

30 203 records pertaining to primary THR which were used to estimate QOL and LOS after primary THR. The characteristics of this sample are shown in the fourth row of Table 1, and were similar to the original sample.

	Number	Mean age	Women (%)	More than one comorbidity (%)	Pre-operative QOL EQ5D	
					EQ5D	OHS
Before linking	73 666	69.9	58.9	23.5	0.343	18.05
After linking	39 734	69.9	60.1	23.5	0.342	17.97
After exclusions for diagnosis/surgical procedure	34 233	69.9	60.1	23.2	0.348	18.05
After exclusions for type of THR	30 203	69.9	60.0	23.4	0.348	18.03

Table 1 Characteristics of patients in the PROMs data before and after linkage to the NJR

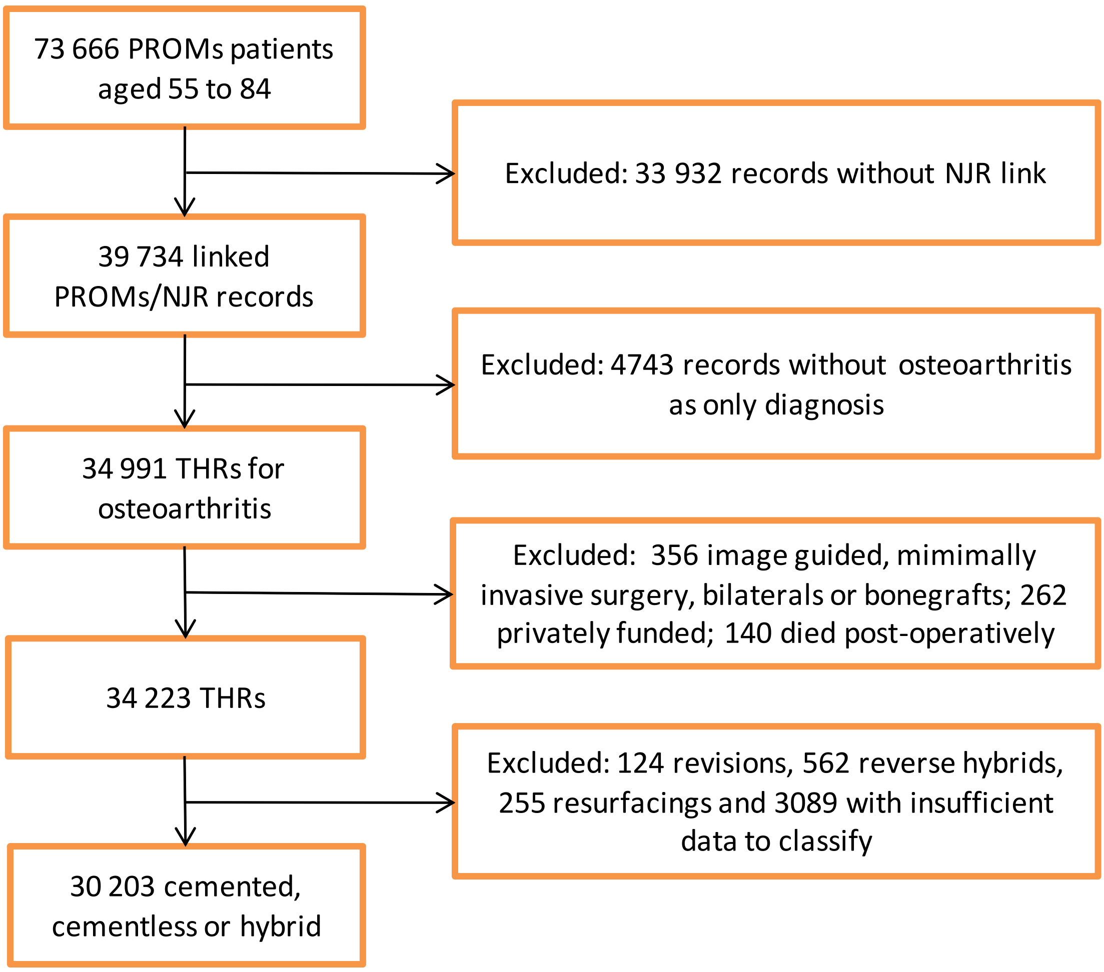


Figure 1 Flowchart illustrating exclusions prior to analysis of the PROMs data for QOL and LOS after primary THR

Section 3: Model parameters and structure

The Markov model used a time cycle of one year and did not apply a half cycle correction. Transitions were assumed to occur at the beginning of each time cycle. The model was run for 45 cycles. All parameters with the exception of costs were functions of age and sex, with additional covariate adjustment where appropriate. In the probabilistic model, each parameter was sampled from an appropriate distribution with the variance estimated from the regression model used in the parameter estimation. The correlation of error terms in the regression models was accommodated using the Cholesky decomposition of the covariance-correlation matrix. The parameters are tabulated below along with the source and the distribution assumed. Correlation-covariance matrices are available from the authors on request.

Parameter	Value*	Source	Distribution in PSA
QOL in Primary THR state	Initial values tabulated in Table 2 (main text) Value decreased by 0.0033 each cycle	PROMs-HES-NJR	Normal
QOL in one stage revision state	0.58996 + 0.07450**Male* – 0.00362**Age*	PROMs-HES-NJR	Normal
QOL in two stage revision state	0.50729 + 0.07450**Male* – 0.00362**Age*	PROMs-HES-NJR	Normal
QOL in revised THR state	1.06536 + 0.03526**Male* – 0.00572**Age*	PROMs-HES-NJR	Normal
Revision of primary THR	First 15 years tabulated in section 7 of appendix	NJR-HES HES (after year 5)	Lognormal
Probability of two stage revision	ExpΠ/(1+expΠ) where Π = -1.15309 + .58651**Male* + 0.26778**Time* – 0.06742*$Time^2$ – 0.94961**Cementless* – 0.67018**Hybrid*	NJR	Lognormal
Failure of revision procedure	1-exp(-365*expρ)) where ρ = -12.39242 + 0.16893**Male* + 0.10609**Age* – 0.00109*Age^2	HES	Lognormal
Revision of revised THR	1-exp(-365*expρ)) where ρ = -12.68287 + 0.16893**Male* + 0.13564**Age* – 0.00109*Age^2	HES	Lognormal
Death in year of THR surgery	1/(1+expα) where α = -12.2731 + 0.29175**Male* + 0.12018**Age*	HES	Lognormal
Death in other years	ONS value multiplied by 1.22026 – 0.50714**Male* – 0.00927**Age* + 0.00704**Male***Age* + 0.09299**Time* -0.00589*$Time^2$ Multiplier constrained to max 1 and min previous cycle's value	ONS data and HES data	Normal for multiplication factor. ONS data not parameterised
Cost of Primary THR	£5113(cemented)/£5900(cementless)/£5659(hybrd) + £225*LOS LOS tabulated in Table 2 (main text)	Lemon et al.(9) and LOS from PROMs-HES-NJR	LOS parameterised (Normal)
Cost of one-stage revision	£9,242	Klouche et al.(13)	Gamma
Cost of two-stage revision	£24,108	Klouche et al.(13)	Gamma

**Age* is patient age, *Male* is 1 for male, 0 for female, *Time* is time in years after surgery, LOS is length of stay in days, *Cementless* indicates a cementless prosthesis, *Hybrid* indicates a hybrid prosthesis.

Table 2 Markov model parameters

Section 4: Multiple imputation of missing data

Multiple Imputation using Chained Equations(8) (ICE command in Stata) was undertaken to account for missing data in the PROMs-NJR-HES linked records. The variables used in the imputation are tabulated below (Table 3). In addition, interaction variables used in the estimation of models of LOS or QOL following surgery were also included in the imputation model. Missing data from pre-operative PROMs questionnaires arose from items not completed. The majority of missing data from post-operative PROMs questionnaires arose from a missing questionnaire.

The pre-op questionnaire included a 'tick box' format to indicate the presence of 12 comorbidities (Stroke, heart disease, liver disease, kidney disease, arthritis, depression, cancer, problems of the nervous system, high blood pressure, circulation problems, lung disease and diabetes). We had to assume that an absence of a response indicated no problem rather than a missing entry. We included the presence of each comorbidity (except arthritis) as a dichotomous variable in the imputation model. Oxford hip scores were imputed as continuous variables using predicted mean matching to allow for the truncation of the distribution and skewness. Index of Multiple Deprivation scores and EQ-5D visual analogue scale responses were divided into five quintiles and imputed using ordered logistic regression. The distribution of Patient weight and BMI exhibited a small right tail in each case and both variables were treated as normally distributed variables. More highly skewed data, such as post-operative LOS were log transformed. Missing responses to each of the five dimensions of the EQ-5D-3L both pre-operative and post-operative were imputed using ordered logistic regression prior to calculating a QOL tariff. Five imputations were undertaken.

We chose to impute missing dimensions of the EQ-5D questionnaire rather than impute the resulting tariff for three reasons. Firstly, the distribution of EQ5-D tariff values deviates strongly from normal. The distribution is 'spikey' and truncated at the upper end. Secondly, we had some responses which were missing some but not all of the dimensions of the questionnaire. Finally we had patient reported data on comorbidities that was likely to be particularly relevant to some dimensions of the EQ-5D, such as whether the patient reported being depressed.

The impact of imputation on key QOL and LOS data is illustrated in Table 4 below. The impact on LOS was negligible due to the small proportion of observations with missing data. The post-operative EQ-5D-3L index score was lower after imputation across all three THR types. The impact on post-operative OHS scores was smaller.

Variable	Imputation form	Missing Data	Source
Weight	Normally distributed	65%	NJR
BMI	Normally distributed	36%	NJR
Pre-operative Oxford Hip	Normally distributed	<1%	pre-op PROMs
Assistance completing pre-op PROMs	Dichotomous	5%	pre-op PROMs
Duration of symptoms pre-op	Ordered categorical	<1%	pre-op PROMs
Previous hip surgery reported	Dichotomous	<1%	pre-op PROMs
Comorbidity (each of 11 comorbidities entered separately)	Dichotomous	None*	pre-op PROMs
Overall health – pre-op	Ordered categorical	4%	pre-op PROMs
Disability – pre-op	Dichotomous	15%	pre-op PROMs
EQ-5D-3L pre-op - mobility	Ordered categorical	2%	pre-op PROMs
EQ-5D-3L pre-op – self care	Ordered categorical	2%	pre-op PROMs
EQ-5D-3L pre-op – activity	Ordered categorical	2%	pre-op PROMs
EQ-5D-3L pre-op – pain	Ordered categorical	2%	pre-op PROMs
EQ-5D-3L pre-op – depression/anxiety	Ordered categorical	2%	pre-op PROMs
EQ-5D pre-op - VAS	Quintiles	11%	pre-op PROMs
Post-operative Oxford Hip	Normally distributed	34%	post-op PROMs
Satisfied with surgery	Ordered categorical	35%	post-op PROMs
Consider surgery successful	Ordered categorical	35%	post-op PROMs
Overall health post-op	Ordered categorical	35%	post-op PROMs
Disability – post-op	Dichotomous	45%	post-op PROMs
EQ-5D-3L post-op - mobility	Ordered categorical	35%	post-op PROMs
EQ-5D-3L post-op – self care	Ordered categorical	35%	post-op PROMs
EQ-5D-3L post-op – activity	Ordered categorical	35%	post-op PROMs
EQ-5D-3L post-op – pain	Ordered categorical	36%	post-op PROMs
EQ-5D-3L post-op – depression/anxiety	Ordered categorical	36%	post-op PROMs
EQ-5D post-op - VAS	Quintiles	38%	post-op PROMs
Treated at Treatment Centre	Dichotomous	None	NJR
Sex	Dichotomous	None	all three databases
Age	Continuous	None	all three databases
White/non-white	Dichotomous	9%	HES
Post-op length of stay	Log normally distributed	2%	HES
Number of diagnosis codes in HES	Log normally distributed	None	HES
IMD	Quintiles	1%	HES
ASA grade 1	Dichotomous	None	NJR
ASA grade 2	Dichotomous	None	NJR
ASA grade 3	Dichotomous	None	NJR
Operation by Consultant	Dichotomous	None	NJR
cementless prosthesis	Dichotomous	None	NJR and HES
Hybrid prosthesis	Dichotomous	None	NJR and HES
Operation in Supine position	Dichotomous	None	NJR
Living alone	Dichotomous	2%	HES

*Non-response indicates absence of the comorbidity.

Table 3 Variables used in the imputation of missing data and percentage of missing data from the PROMs-HES-NJR data used to estimate QOL after primary THR and LOS after primary THR

THR type	Post-op EQ-5D-3L index		Post-op OHS score		LOS	
	Complete data	Mean of 5 imputations	Complete case	Mean of 5 imputations	Complete case	Mean of 5 imputations
Cemented	0·765	0·759	37·80	37·73	5·52	5·52
Cementless	0·785	0·779	39·09	38·96	5·04	5·04
Hybrid	0·786	0·780	39·10	38·90	5·56	5·56

Table 4 Key outcome variables by THR type before and after imputation

Section 5: Initial procedure costs

The distribution of LOS following surgery was moderately right skewed with a long right tail. Regression using ordinary least squares (OLS) was used to estimate differences in LOS by THR procedure after adjusting for ASA grade, BMI, home environment, disability, type of hospital, comorbidities, IMD, EQ-5D-3L pre-score, OHS pre-score, age and sex. After adjustment for patient and provider characteristics LOS was significantly longer for hybrid THRs (0.29 days, $p = 0.001$) and cementless THRs (0.24 days, $p = 0.001$) compared to cemented THRs. Generalised Linear Modelling assuming a gamma distribution gave very similar results. The OLS model was used to predict LOS for the six subgroups (men and women aged 60, 70 and 80) assuming in turn that the relevant sub-population with an ASA grade 2 and a BMI below 30 received a cemented, a cementless or a hybrid THR. Sub-populations included patients a year older and a year younger than those in the subgroup to smooth out chance variation in baseline characteristics such as EQ-5D-3L tariff score.

We took a health services perspective to the cost analysis and ignored any impact on productivity changes. Theatre costs following primary THR were based on a publication by Lemon et al.(9) which estimated the total cost of cemented and cementless THR from data on 1118 THR patients at a large treatment centre in South-West London. The paper reported costs by prosthesis type including and excluding prosthesis costs and also reported average LOS by prosthesis type. We inflated the costs excluding prostheses to 2010 values using the HCHS inflation index(10) and then subtracted the estimated costs of LOS reported in the study based on a value of £225 per day.(11) After inflation and excluding prosthesis and LOS costs, cemented THRs cost £4374 and cementless THRs cost £4203. Costs of LOS were then added back into the estimate based on our analysis of HES data by age, gender and prosthesis type. Typical prices paid by a mid-size orthopaedic centre for the ten most common brands of prosthesis were obtained.(12) Prosthesis costs were estimated as the weighted mean of the three most common brands for cemented and cementless THRs and the two most common brands for hybrid THRs. Weights were determined according to the market share of each brand.(3) We assumed that theatre costs for hybrid THR were the same as for cemented THR as both procedures require cement preparation.

For the purposes of estimating revision costs we estimated the typical cost of a primary procedure at £6697 as the mean of the prosthesis and theatre costs for cemented and cementless THRs and LOS costs based on a mean of 5.29 days for the entire population aged 55-84. This figure was then multiplied by 1.4 to estimate the cost of a one-stage revision and 3.6 to estimate the cost of a two-stage revision.(13)

Section 6: Analysis of QOL after primary THR and before and after revision THR

GenMatch was undertaken in R(14) after multiple imputation using the R code GenMatch.(15) The following variables were included in the matching algorithm: BMI; ASA grade; IMD; number of comorbidities; presence of a consultant at surgery; surgery at a treatment centre; EQ-5D-3L tariff pre-score; OHS pre-score; age; sex; and self reported disabled status. The number of comorbidities reported by the patient was summed (excluding osteoarthritis) yielding a score from zero to 11. Dummy variables were created for patients with a BMI between 30 and 35 and for those with a BMI above 35. Patients were assigned to a quintile for IMD data. Three categories were created for ASA grade: one, two and three or higher. The NJR held data on the status of the lead and first assistant surgeon for the THR. A dummy variable was used to indicate the presence of a consultant in either position. A dummy variable was used to indicate treatment at a treatment centre (NHS or independent). For each of the six subgroups and for each imputation a matched outcome under cementless THR was found for each patient undergoing cemented THR and hybrid THR. The procedure was repeated to match cemented THRs to cementless and hybrid THRs, and hybrid THRs to cemented and cementless THRs. Hence a data set containing outcomes under cemented, cementless and hybrid THR was created for each patient subgroup and for each imputation (two corresponding matches to each observation).

Table 5 below provides Kolmorogorov-Smirnov tests of equivalence of distribution for continuous variables before and after matching for the two key subgroups: men and women aged 65-74. A low p value indicates a significant difference in the distribution of the variable between the matched population with the highlighted prostheses type and the population with the remaining two types. For example, the first five entries in the first column of table 3 show the p values for Kolmogorov-Smirnov tests of equality in the distribution of age in the population of 65-74 year olds with a cemented prosthesis compared to the population with a cementless or hybrid prosthesis. Each of the five rows reports the test for one of the five multiply imputed datasets. The values are all zero indicating that the distribution of age is significantly different. This is not surprising as cemented THR is more commonly undertaken on older patients and we would expect the distribution of 65-74 year olds to be more heavily populated at the upper end. The five entries in the second row report the Kolmogorov-Smirnov test comparing age in the population of 65-74 year olds with a cementless and hybrid prostheses against the matched set drawn from the population of 65-74 year olds with a cemented prosthesis. After matching the p-values are all higher indicating a similar distribution of age across the two samples. Differences in the distribution of the four continuous variables across the two subgroups are considerably reduced after matching.

Post-matching regression using OLS was then undertaken on each subgroup adjusting for each of the variables used in matching and including quadratic terms for age and quadratic and cubic terms for EQ-5D-3L pre-scores. Clustering on individual identification was used to adjust variance estimates for multiple selection of patients. Parameter estimates and variances were combined across the five imputed data sets using Rubin's rules.(16) Post-matching regression models were used to predict EQ-5D-3L scores for the six subgroups (men and women aged 60, 70 and 80) assuming in turn that the relevant sub-population with an ASA grade two and a BMI below 30 received a cemented, a cementless or a hybrid THR. Sub-populations included patients a year older and a year younger than those in the subgroup to smooth out chance variation in baseline characteristics such as EQ-5D-3L tariff score.

	Men aged 65-74						**Women aged 65-74**					
	Cemented		**Cementless**		**Hybrid**		**Cemented**		**Cementless**		**Hybrid**	
	before	after	before	After	before	after	before	after	before	after	before	after
Age												
Imputation 1	0·000	0·702	0·000	0·844	0·540	0·270	0·000	0·586	0·002	0·346	0·774	0·102
Imputation 2	0·000	0·832	0·000	0·720	0·550	0·152	0·000	0·962	0·000	0·726	0·790	0·100
Imputation 3	0·000	0·924	0·000	0·904	0·576	0·414	0·000	0·810	0·000	1·000	0·810	0·386
Imputation 4	0·000	0·596	0·000	0·938	0·562	0·218	0·000	0·686	0·002	0·880	0·794	0·214
Imputation 5	0·000	0·186	0·000	0·960	0·542	0·188	0·000	0·712	0·002	0·998	0·818	0·464
OHS												
Imputation 1	0·456	0·756	0·562	0·858	0·806	0·346	0·100	0·552	0·640	0·842	0·684	0·426
Imputation 2	0·458	0·302	0·540	0·924	0·862	0·148	0·074	0·774	0·534	0·878	0·572	0·062
Imputation 3	0·448	0·982	0·578	0·964	0·860	0·332	0·078	0·426	0·552	0·638	0·714	0·314
Imputation 4	0·424	0·714	0·542	0·910	0·850	0·214	0·058	0·794	0·516	0·860	0·638	0·320
Imputation 5	0·382	0·642	0·476	0·730	0·852	0·070	0·106	0·498	0·504	0·956	0·556	0·200
EQ-5D-3L												
Imputation 1	0·636	0·356	0·682	0·834	0·900	0·212	0·116	0·434	0·210	0·868	0·674	0·118
Imputation 2	0·666	0·406	0·640	0·742	0·858	0·168	0·086	0·178	0·296	0·878	0·566	0·100
Imputation 3	0·644	0·552	0·608	0·836	0·866	0·244	0·116	0·350	0·252	0·920	0·720	0·066
Imputation 4	0·730	0·192	0·650	0·658	0·888	0·276	0·106	0·218	0·270	0·782	0·668	0·182
Imputation 5	0·682	0·274	0·688	0·514	0·886	0·354	0·118	0·358	0·266	0·854	0·606	0·046
Comorbidities												
Imputation 1	0·196	0·912	0·278	0·934	0·798	0·062	0·154	0·800	0·640	1·000	0·418	0·548
Imputation 2	0·206	0·936	0·288	0·692	0·816	0·398	0·176	0·272	0·648	0·952	0·400	0·282
Imputation 3	0·214	0·118	0·288	0·726	0·796	0·080	0·118	0·696	0·670	0·656	0·436	0·026
Imputation 4	0·220	0·250	0·300	0·860	0·818	0·000	0·130	0·038	0·638	1·000	0·414	0·026
Imputation 5	0·192	0·992	0·284	0·856	0·812	0·824	0·120	0·128	0·656	0·998	0·406	0·008

Table 5 p values for Kolomogorov-Smirnov tests of equality of distributions for continuous matched variables for males and females aged 65-74

Extrapolation of QOL gains

There is strong evidence for a decline in health related QOL with age.(17, 18) We examined mean EQ-5D-3L scores by sex and ten year age groups for men and women aged 50 to 90 from the Medical Expenditure Panel Survey.(18) A linear function of age and sex provided the best fit to the data and generated a slope of minus 0·0033. The health state tariffs for the primary THR state in the model were reduced by 0·0033 QALYs at the end of each cycle to represent the impact of ageing on general health related QOL.

Health State tariffs during and after revision

The PROMs data included 3331 patients undergoing a revision THR. Since we could not determine if these patients had undergone their original, primary THR for osteoarthritis we restricted analysis to patients aged 65 to 90 (n = 2105) as younger patients were more likely to have received a primary THR for diagnoses other than osteoarthritis. Of these patients 1283 had post-operative EQ-5D-3L data. Pre-operative EQ-5D-3L scores (n = 2105) were modelled using OLS regression adjusting for age (linear), sex and whether the revision was one or two stage. We explored higher powers for age but concluded that the linear model provided adequate fit. The linear model was used to parameterise the one-stage and two-stage revision health states. This implicitly assumes that the burden on QOL imposed by revision is equivalent to spending a year in the health states reported pre-operatively by patients. The health state tariff for the revised THR state was parameterised as a linear function of age and sex using a model derived from OLS regression of post-operative EQ-5D-3L tariff scores (n = 1283). Table 6, below, presents illustrative estimates of QOL for men and women at different ages. As QOL in each revision state falls with age we did not undertake further adjustment for the effects of aging.

Sex and age at surgery	**QOL tariff before revision**		**QOL tariff**
	Aseptic revision	**Septic Revision**	**after revision**
Men aged 60	0·447	0·364	0·758
Men aged 70	0·411	0·328	0·700
Men aged 80	0·375	0·292	0·643
Men aged 90	0·338	0·256	0·586
Women aged 60	0·373	0·290	0·722
Women aged 70	0·336	0·254	0·665
Women aged 80	0·300	0·217	0·608
Women aged 90	0·264	0·181	0·551

Table 6 QOL tariffs before and after revision

Section 7: Sensitivity analysis of QOL after primary THR using OLS

In order to examine the robustness of the analysis of QOL after primary THR using GenMatch and OLS regression we conducted a sensitivity analysis in which the adjustment for covariate imbalance was undertaken with OLS regression only. The same covariates were included: BMI; ASA grade; IMD; number of comorbidities; presence of a consultant at surgery; surgery at a treatment centre; EQ-5D-3L tariff pre-score; OHS pre-score; age; sex; and self reported disabled status. Model fit, as judged by AIC, was optimised using a quadratic model for age.

Inspection of a plot of residual vs fitted values showed no evidence of heteroskedasticity. Plots of residual values against age and EQ-5D-3L pre-operative score also showed no evidence of heteroskedasticity. Consequently, we considered the estimation of robust standard errors unnecessary.

The OLS model generated a gain of 0·015 (p = 0·001) QALYs and 0·83 OHS points (p<0·001) for hybrid THRs compared to cemented THRs after adjusting for patient and provider characteristics. Cementless THRs provided a smaller increase in QOL compared to cemented THRs (0·007 (p = 0·04) QALYs and 0·47 (p = 0·002) OHS points). These findings proved robust to alternative specifications of the OLS model, and to the use of Tobit regression on log transformed EQ-5D-3L tariffs or Generalised Linear Modelling with a Gamma function. Interactions between age and THR type and sex and THR type were added to allow prediction of QOL by subgroup for the six subgroups (men and women aged 60, 70 and 80); likelihood ratio tests indicated that adding the interactions did not achieve a significant improvement in the model. QOL after primary THR with cemented, cementless and hybrid prostheses was then predicted for men and women aged 60, 70 and 80 with an ASA grade two and a BMI below 30 receiving a cemented, a cementless or a hybrid THR. The resulting values were used to parameterise the Primary THR health state in the sensitivity analysis.

Section 8: analysis of primary revision rates

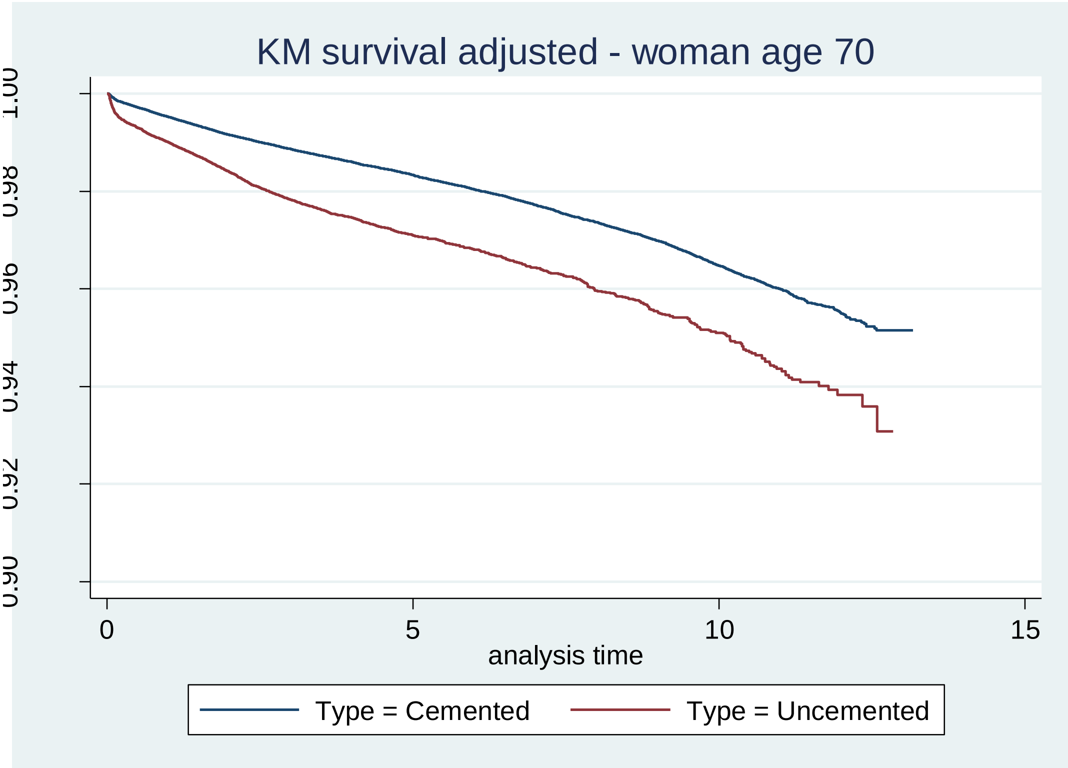
Revisions in the first few years following THR are primarily caused by infection, dislocation or poor surgical technique. The incidence of these causes of revision falls with time since surgery. Over the longer term, the incidence of revision due to aseptic loosening of the implant increases. The resulting overall hazard function is U-shaped with a minimum around five years after surgery. Consequently at least ten years of data are required to extrapolate long term revision rates with confidence. The Kaplan-Meier survival curves adjusted for age and sex for cemented and cementless THRs from the HES only data are presented in figure 2 below. Revision rates were estimated separately for years 1 to 5 after THR and years 6+ to allow for the U-shaped hazard function. This allowed us to fit a standard parametric function to revision data for the period five years or more from primary THR during which the hazard is rising, and then make a plausible extrapolation from this function. Data in the linked NJR-HES were used to estimate revision rates in the first five years. NJR data is limited beyond five years, and so HES only data were used to estimate revision rates beyond five years after THR. We treated death as a censoring event in all survival modelling of revisions.

Analysis of the NJR-HES linked data rejected an assumption of proportional hazards by THR type in the first five years, and this is clearly evident in the figure. The behaviour of hazards after five years does not follow the same pattern as hazards in the first five years. Analysis of data in HES from five years after THR indicated hazards after five years are proportional.

Since hazards are not proportional in the first five years, revision rates were estimated using three separate Piece-wise Constant (PWC) survival models for cemented, cementless and hybrid THRs.(19) Each was adjusted for age, gender, BMI and ASA grade. Yearly intervals for the piece-wise segments were applied, consistent with the time cycle of the Markov model. The PWC function assumes a constant hazard with the piece-wise intervals but allows the hazard to vary between intervals. This provides increased flexibility to model the change in hazard over time, compared to a standard parametric model which requires parameterisation of the relationship between the hazard and time. Analysis of the impact of BMI on revision rates indicated that the majority of patients with missing BMI data had a BMI below 30. Dummy variables were created for BMI between 30 and 35 and BMI over 35, and patients missing BMI data were assumed to have a BMI below 30. Two categories were used for ASA grade, one or two and three or higher, after initial analysis indicated little difference in revision rates for patients with ASA grade one or two.

Extrapolation of revision rates requires parameterisation of the relationship of the hazard with time. The dangers of extrapolating less than ten years of survival data have been recently highlighted.(20) Consequently, revision rates beyond five years were estimated using a single parametric model from HES only data which extended to 12 years. Data for cemented and cementless THRs was modelled assuming that observation commenced at five years after surgery. This maximised the fit of monotonic functions to the portion of the data in which hazards were rising. Weibull and Gompertz functions were compared as these functions support hazard rates which increase with time. Models were adjusted for age, gender and THR type. Adjustment for age in the ancillary parameter for both Weibull and Gompertz models improved the AIC and led to superior fit when compared to age stratified PWC functions over the range of observed data as judged by eye. Both Weibull and Gompertz models gave very similar AIC values. However, the Weibull function better matched the PWC function, as judged by eye. We applied the Gompertz function in a sensitivity analysis.

The linkage of HES and NJR data allowed capture of revisions that would have been missed when using HES alone. A weighting factor of 1.15 was estimated by comparing 5 year survival for patients in the NJR-HES linked data with survival estimates for the same patients generated from HES alone. Revision probabilities after five years generated from HES only data were multiplied by this weighting factor to allow for the slightly lower data capture in the non-linked data set. Table 7, below, gives the estimated annual revision probability by type of THR and year after primary THR for each of the six patient subgroups (15 years data



shown).

Figure 2 Kaplan-Meier survival curves for cemented and cementless THRs from HES only data adjusted for age and gender

	Annual revision probability								
	Age 60 at primary THR			Age 70 at primary THR			Age 80 at primary THR		
	Cem	**C-less**	**Hybrid**	**Cem**	**C-less**	**Hybrid**	**Cem**	**C-less**	**Hybrid**
Year after THR				**Men**					
1	0.74	1.20	0.89	0.62	1.14	0.83	0.56	1.28	1.17
2	0.49	0.57	0.37	0.41	0.54	0.34	0.37	0.60	0.49
3	0.43	0.56	0.41	0.36	0.53	0.38	0.32	0.60	0.54
4	0.34	0.37	0.37	0.28	0.35	0.34	0.25	0.40	0.48
5	0.41	0.41	0.49	0.35	0.39	0.46	0.31	0.43	0.64
6	0.63	0.53	0.63	0.47	0.40	0.47	0.28	0.23	0.28
7	0.77	0.64	0.77	0.52	0.44	0.52	0.29	0.24	0.29
8	0.90	0.76	0.90	0.57	0.48	0.57	0.30	0.25	0.30
9	1.05	0.88	1.05	0.62	0.52	0.62	0.30	0.25	0.30
10	1.19	1.00	1.19	0.66	0.55	0.66	0.31	0.26	0.31
11	1.34	1.12	1.34	0.71	0.59	0.71	0.32	0.27	0.32
12	1.49	1.25	1.49	0.75	0.62	0.75	0.32	0.27	0.32
13	1.65	1.37	1.65	0.79	0.66	0.79	0.33	0.27	0.33
14	1.80	1.50	1.80	0.82	0.69	0.82	0.33	0.28	0.33
15	1.96	1.64	1.96	0.86	0.72	0.86	0.34	0.28	0.34
				Women					
1	0.57	1.14	0.75	0.47	1.08	0.69	0.43	1.21	0.98
2	0.38	0.54	0.31	0.31	0.51	0.29	0.28	0.57	0.41
3	0.33	0.53	0.34	0.27	0.51	0.32	0.25	0.57	0.45
4	0.26	0.35	0.31	0.21	0.34	0.28	0.19	0.38	0.40
5	0.32	0.39	0.41	0.26	0.37	0.38	0.24	0.41	0.54
6	0.46	0.39	0.46	0.35	0.29	0.35	0.20	0.17	0.20
7	0.56	0.47	0.56	0.39	0.32	0.39	0.21	0.18	0.21
8	0.66	0.55	0.66	0.42	0.35	0.42	0.22	0.18	0.22
9	0.77	0.64	0.77	0.45	0.38	0.45	0.22	0.19	0.22
10	0.88	0.73	0.88	0.49	0.41	0.49	0.23	0.19	0.23
11	0.99	0.82	0.99	0.52	0.43	0.52	0.23	0.19	0.23
12	1.10	0.92	1.10	0.55	0.46	0.55	0.24	0.20	0.24
13	1.21	1.01	1.21	0.58	0.48	0.58	0.24	0.20	0.24
14	1.32	1.11	1.32	0.60	0.50	0.60	0.25	0.20	0.25
15	1.44	1.20	1.44	0.63	0.53	0.63	0.25	0.21	0.25

Cem: Cemented C-less: Cementless

Table 7 Yearly revision probabilities predicted for men and women aged 60, 70 and 80 with ASA grade 2 and BMI below 30 in the first 15 years

Section 9: Estimate of the proportion of two-stage revisions

Revisions due to infection usually occur in the first few years after surgery and are generally undertaken in two stages with a period of healing prior to insertion of the replacement prosthesis. We assumed that two stage revisions identified in the NJR were undertaken for infection. The proportion of revisions that are two stage peaks in the second year after surgery and then falls over time, and this proportion is higher for cemented THRs. The latter observation reflects similar likelihood of two stage revisions for cemented THRs compared to cementless and hybrid THRs, but a lower likelihood of single stage revisions. Analysis of the proportion of two-stage revisions was based on 273 two stage (155 cemented, 78 cementless, 40 hybrid) and 914 single stage (331 cemented, 417 cementless, 166 hybrid) revisions identified in the NJR for patients in the NJR-HES linked data included in the study (age 55-84, diagnosis of osteoarthritis, not receiving minimally invasive/computer guided surgery or bone grafts). The revisions analysed were all identified in data from the NJR which categorises revisions into one or two stage. Revisions for patients in the NJR-HES data identified only in HES were excluded as we could not reliably determine if they had been undertaken in two stages. The probability of a revision requiring two stages was modelled as a function of sex, time after surgery and primary THR procedure using logistic regression. The impact of age was insignificant but sex was significant. Hence values were predicted for men and women and applied to the subgroups as appropriate. The resulting values for the first eight years for a woman are tabulated below (Table 8). Values for men followed the same pattern.

Year after primary THR	Proportion of revisions requiring two stages (%)		
	Cemented	Cementless	Hybrid
1	27·8	13·0	16·5
2	29·2	13·7	17·4
3	27·8	12·9	16·4
4	23·9	10·8	13·8
5	18·2	7·9	10·2
6	12·2	5·1	6·6
7	7·0	2·8	3·7
8	3·5	1·4	1·8

Table 8 Estimated probability that revision requires two stages by THR type and year after primary surgery

Section 10: Estimate of re-revision rates

Using OPCS codes we were able to identify 98 710 patients in the HES only data undergoing a revision between 1st March 1997 and 31st December 2009. Analysis was restricted to patients aged 65 to 90 (n = 70 351) as patients under 65 were less likely to have undergone their primary THR for osteoarthritis. A further 5954 patients with no data on laterality were excluded. Revisions identified in HES occurring on the same hip were linked with the earliest procedure treated as the first revision and the next procedure as a *re-revision*. The resulting data had 54 134 patients and 5625 *re-revisions* with a mean follow-up time of 1587 days. Initial analysis showed a falling *re-revision* rate that reached a plateau around five years after the revision surgery. The Markov model allowed a higher *re-revision* rate for the first year after revision surgery (transitions from the one stage or two stage revision state) compared to subsequent years (transitions from the revised THR state). A piece-wise constant hazard function was fitted to the data adjusting for age and sex with a single boundary at one year. The model imposed a constant hazard with respect to time after the first year but allowed *re-revision* rates to vary with patient age. *Re-revision* risks were raised in the first year and were higher for younger patients. As *re-revision* risks are a function of age, the risk of *re-revision* for a patient in the revised THR state fell each year as the patient aged. Probabilities over a range of ages are tabulated below (table 9). Probability of *re-revision* in the first year was applied to patients in both the one-stage and two-stage revision states and resulted in patients transiting to the one-stage revision state (undergoing another revision). Probability of *re-revision* in subsequent years was applied to patients in the revised THR state and resulted in transition to the one-stage revision state.

	Probability of failure of revised prosthesis (%)			
	Men		**Women**	
Age	**First year Post surgery**	**Years 2+ Post surgery**	**First year Post surgery**	**Years 2+ Post surgery**
60	8·81	2·47	7·49	2·09
65	8·81	2·17	7·49	1·83
70	8·36	1·80	7·11	1·52
75	7·53	1·42	6·40	1·20
80	6·43	1·05	5·46	0·89
85	5·21	0·74	4·42	0·63
90	4·00	0·50	3·39	0·42

Table 9 Re-revision risks in the first and subsequent years after revision surgery

Section 11: Analysis of mortality following THR

There is strong evidence that patients receiving a THR for osteoarthritis have lower mortality rates than age and sex matched cohorts.(21-23) Notably, the same is not true for THR undertaken for other diagnoses such as rheumatoid arthritis.(24) Mortality rates in years two to ten after surgery were determined for patients undergoing primary THR from 1st March 1997 to 9th November 2008, aged 65 to 90, with a primary diagnosis of osteoarthritis in the HES only data (n = 280 962). Comparison with rates for age and sex matched cohorts from UK life tables, confirmed the observation that patients undergoing primary THR for osteoarthritis have lower mortality rates (see figure 3 below). Patients under the age of 65, where the potential for erroneously including non-osteoarthritis patients was higher, were excluded. Analysis suggested that the protective effect of selection for THR declined over time but did not decline to zero in the older age groups.

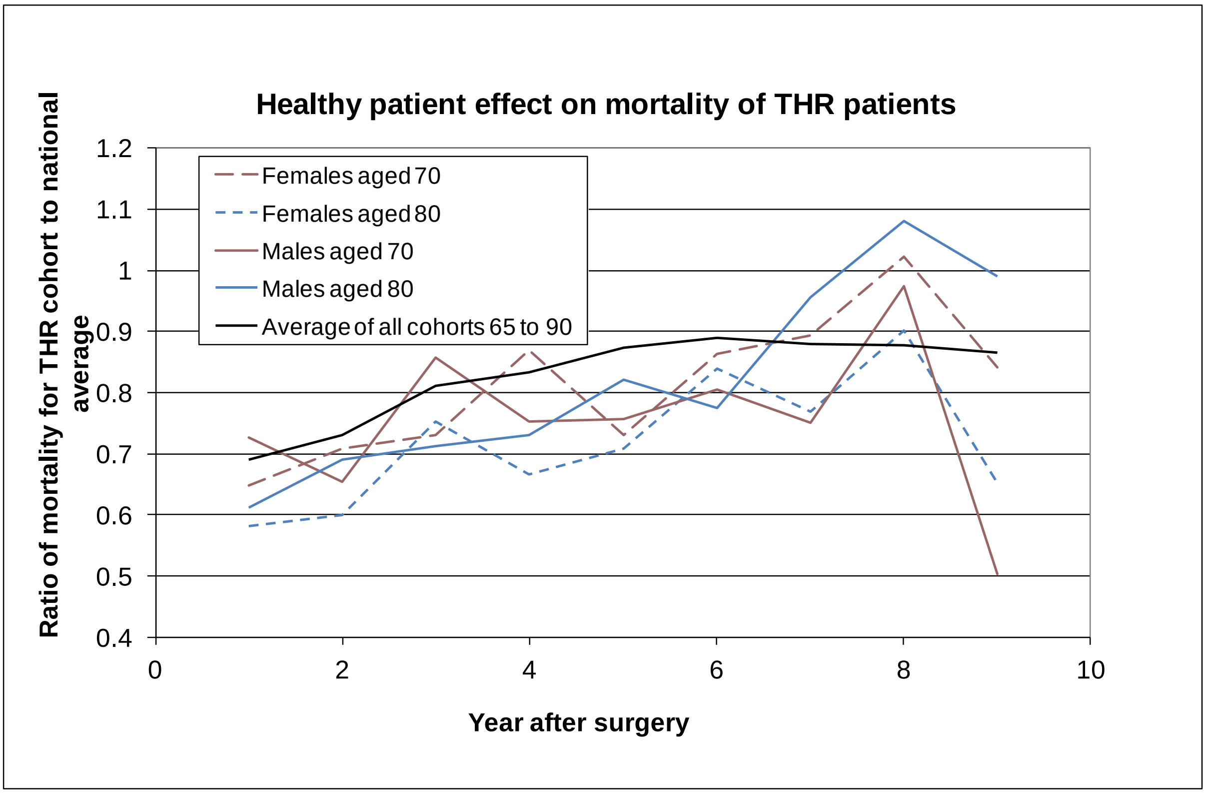


Figure 3 Ratio of mortality probabilities observed in HES for cohorts of patients undergoing primary THR for osteoarthritis compared with age and sex matched cohorts from UK life tables

Annual probabilities of dying in years two to ten following primary THR for the 52 cohorts of men and women aged 65 to 90 were derived from life table analysis of HES. These probabilities were paired with the probability for the UK cohort matched on age and sex and the ratio calculated. Ordinary Least Squares regression was used to fit a function of age, sex and years after primary surgery to this ratio. Annual probabilities of dying obtained from ONS were multiplied by the mortality ratio estimated from the function before applying them to the cohorts in the model. The mortality ratio predicted by the function rose with successive model cycles (years after primary THR) but did not reach a value of 1 for older patients. The inclusion of a quadratic term for time after surgery allowed a better fit to the observed data but the resulting ratio reached a maximum eight years after surgery and then began to decrease. Consequently, when parameterising mortality in the model, the ratio was capped at a maximum of one, and a minimum of the previous cycle's ratio. This ensured that once the maximum ratio was reached after 8 cycles this ratio was maintained for subsequent cycles. Values estimated by the function and applied in the model are tabulated for each patient subgroup in Table 10.

Data from the HES only dataset was also used to estimate the probability of dying within one year of revision surgery (effectively the sum of operative mortality and all cause mortality). Again, we excluded patients under the age of 65 who may be more likely to have undergone a primary THR for a diagnosis other than osteoarthritis. A logit model was estimated on patients between the age of 65 and 90 undergoing a revision with at least one year of follow-up (up to 9th Nov 2008, 62 984 patients) adjusting for age and sex. Probabilities over a range of ages are tabulated below (Table 11). Note that probabilities for patients aged under 65 represent out of sample predictions. We applied the same probabilities for mortality after primary THR. Where predicted values exceeded all cause mortality by 10% or more (between 88 and 92 depending on sex and age at primary THR), the model parameters were capped at 10% plus all cause mortality.

Year after primary THR	**Mortality ratio**					
	Men			**Women**		
	Age 60	**Age 70**	**Age 80**	**Age 60**	**Age 70**	**Age 80**
2	0.742	0.720	0.697	0.827	0.734	0.641
3	0.805	0.783	0.761	0.890	0.798	0.705
4	0.857	0.835	0.813	0.942	0.849	0.757
5	0.897	0.875	0.853	0.982	0.889	0.797
6	0.925	0.903	0.881	1.000	0.917	0.825
7	0.942	0.920	0.897	1.000	0.934	0.841
8	0.946	0.924	0.902	1.000	0.939	0.846
9	0.946	0.924	0.902	1.000	0.939	0.846
10	0.946	0.924	0.902	1.000	0.939	0.846

Table 10 Mortality ratio (multiplier) applied to ONS mortality data to adjust for the 'healthy patient' effect

Probability of dying in the year following revision surgery (%)		
Age	**Men**	**Women**
60	0·84	0·63
65	1·52	1·14
70	2·74	2·06
75	4·89	3·70
80	8·57	6·54
85	14·60	11·32
90	23·77	18·89

Table 11 Probability of dying in the year following revision

Section 12: Parameterisation of sampling uncertainty

The Markov model was fully probabilistic, incorporating sampling uncertainty around each of the parameters. Means and variances for the distributions around each parameter were derived from the regression models used in their estimation. The Cholesky decomposition of the covariance-correlation matrix was used to correlate the uncertainty around coefficient estimates in each regression model, effectively assuming a multivariate normal distribution for the errors on the regression coefficients. The distributions assumed for each parameter are given in table 2 of the appendix. Standard errors for QOL tariffs and LOS estimates were small compared to the distance between the parameter mean and the feasible bounded range of the parameters (0 for LOS, 1 for EQ-5D-3L tariff) effectively negating the possibility of estimating values outside these bounds. We considered sampling uncertainty in the mortality rates derived from UK life tables to be small enough to ignore. Parameters for Gamma distributions applied to revision costs were derived from the standard errors reported alongside the revision cost estimates.

Section 13: Details on sensitivity analyses and resulting CEACs

Figures 4 to 8 illustrate the CEACs obtained after running the following sensitivity analyses: assuming differences in QOL by THR type are maintained for two years; analysis of QOL after primary THR using OLS regression; extrapolating revision rates using a Gompertz model; modifying the Markov model to include a failed hip state; excluding patients with a metal-on-metal prosthesis. Further details of the methods for the latter three sensitivity analyses are provided below.

Extrapolating revision rates using a Gompertz model

Model fit and visual inspection suggested both the Gompertz and Weibull models provided a good fit to revisions observed after five years for cemented and cementless prostheses in the HES only data. Extrapolations of the data with the two models gradually diverge with time, with the Gompertz model predicting higher revision rates. We applied the Weibull model in the base case and examined the Gompertz model in a sensitivity analysis. At very extended time points the Gompertz model predicted extremely high revision rates and we had to cap rates at 100% to prevent the model predicting revision rates over 100% after 40 years for 60 year olds. At this point, effectively, all prostheses are deemed to have failed.

Modifying the model to include a failed hip state

In the base case model predicted mortality rates in the year following revision surgery exceed all cause mortality by more than 10% as age approaches 90. This is in accordance with the observed data in HES. However, surgeons may be unwilling to perform revisions on very old patients with elevated operative and post-operative mortality risks. The model was modified to include a state representing patients with a failed hip deemed ineligible for surgery. Patients transited to this state if their primary or revision prosthesis failed, and mortality for the year of the revision would have been in excess of 10% above their predicted mortality in the absence of a revision operation. Patients stayed in this state until they died and received the same QOL as patients in the revision operation state (based on pre-operative EQ-5D-3L data modelled as a function of age and gender). In practice these patients may well require additional social support costs but we had no estimates on this so we assumed that additional costs were zero.

Excluding patients with metal-on-metal bearings

Recent evidence has highlighted the poor performance of prostheses in which the articulating surfaces are both metal (‘metal-on-metal’ prostheses).(26) We undertook a sensitivity analysis in which we excluded all patients identified as receiving a metal-on-metal prosthesis and re-estimated the model parameters: QOL after primary THR; LOS after primary THR; and revision rates after primary THR after. We excluded all patients with a metal-on-metal prostheses from the GenMatch samples prior to post-matching OLS regression, to adjust for any remaining imbalances between observed and matched samples. We then predicted QOL following primary THR for the six age and sex subgroups as previously described. Likewise, patients identified as having a metal-on-metal prosthesis were excluded from the NJR-HES linked data and revision rates in the first five years after primary THR were re-estimated using three separate piece-wise constant survival models for the data on cemented, cementless and hybrid prostheses as previously described.

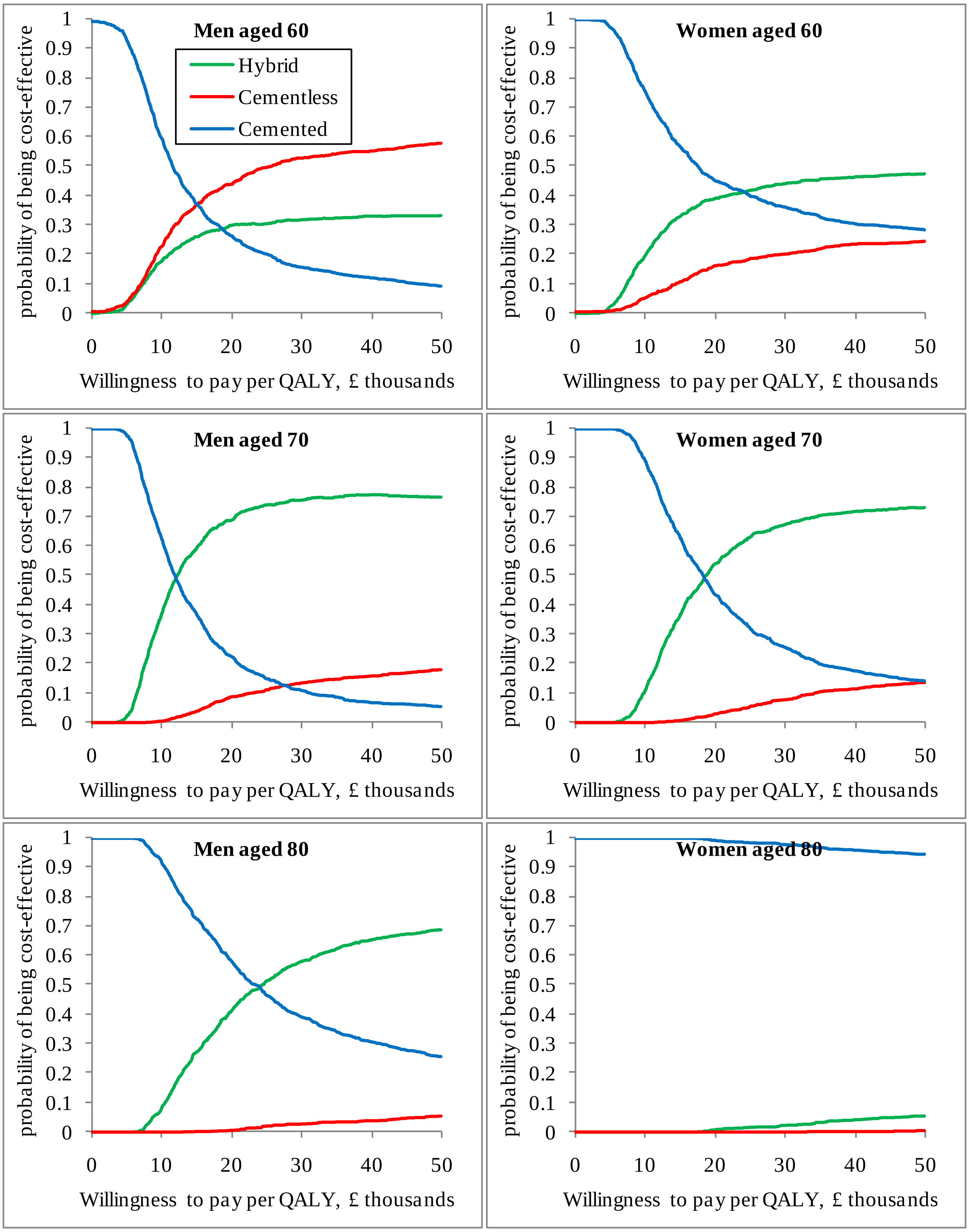


Figure 4 Cost-effectiveness Acceptability Curves by subgroup assuming differences in QOL by THR type are maintained for 2 years post surgery

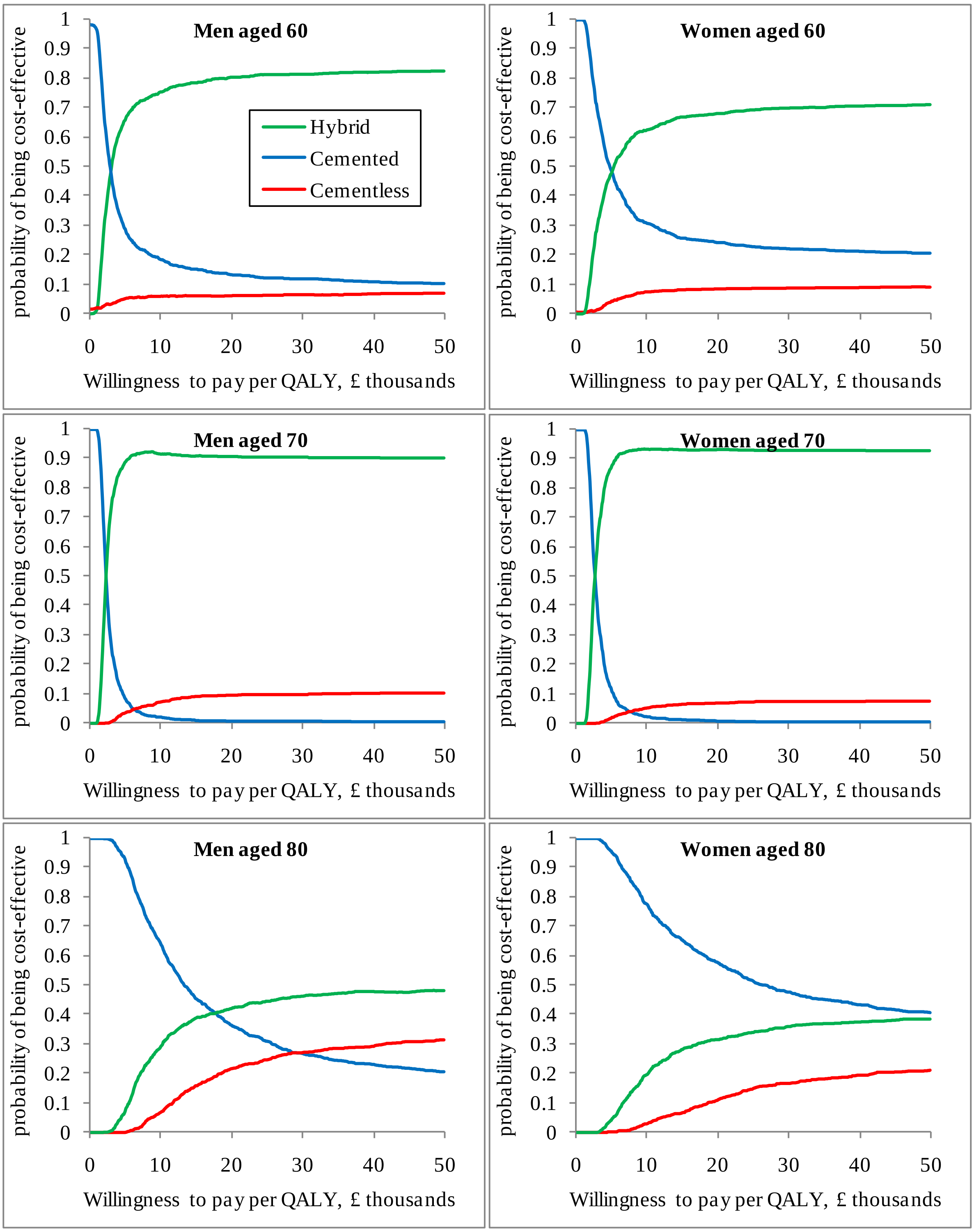


Figure 5 Cost-effectiveness Acceptability Curves by subgroup after estimating QOL after primary THR by THR type using OLS regression

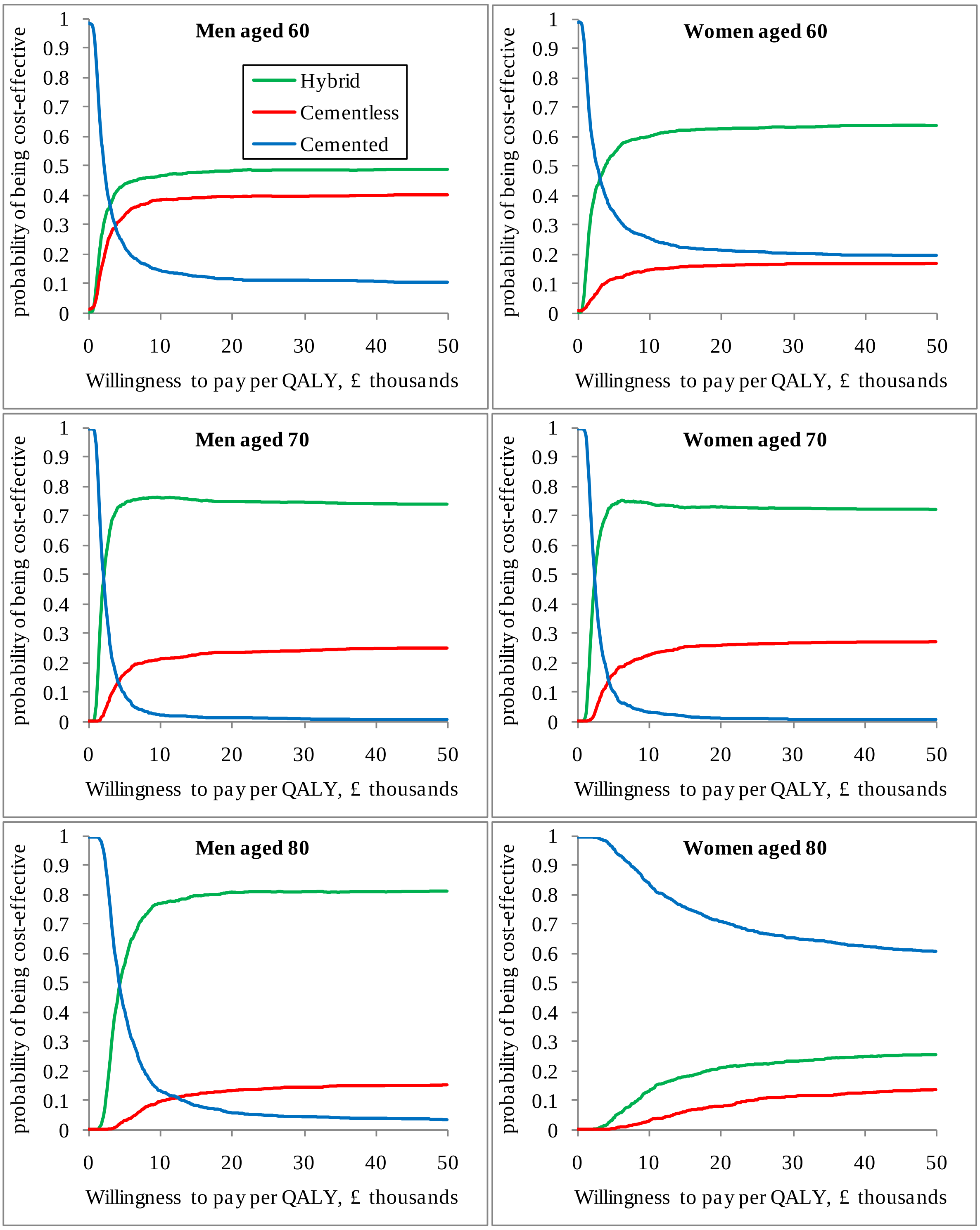


Figure 6 Cost-effectiveness Acceptability Curves by subgroup after extrapolation of revision rates using a Gompertz survival model

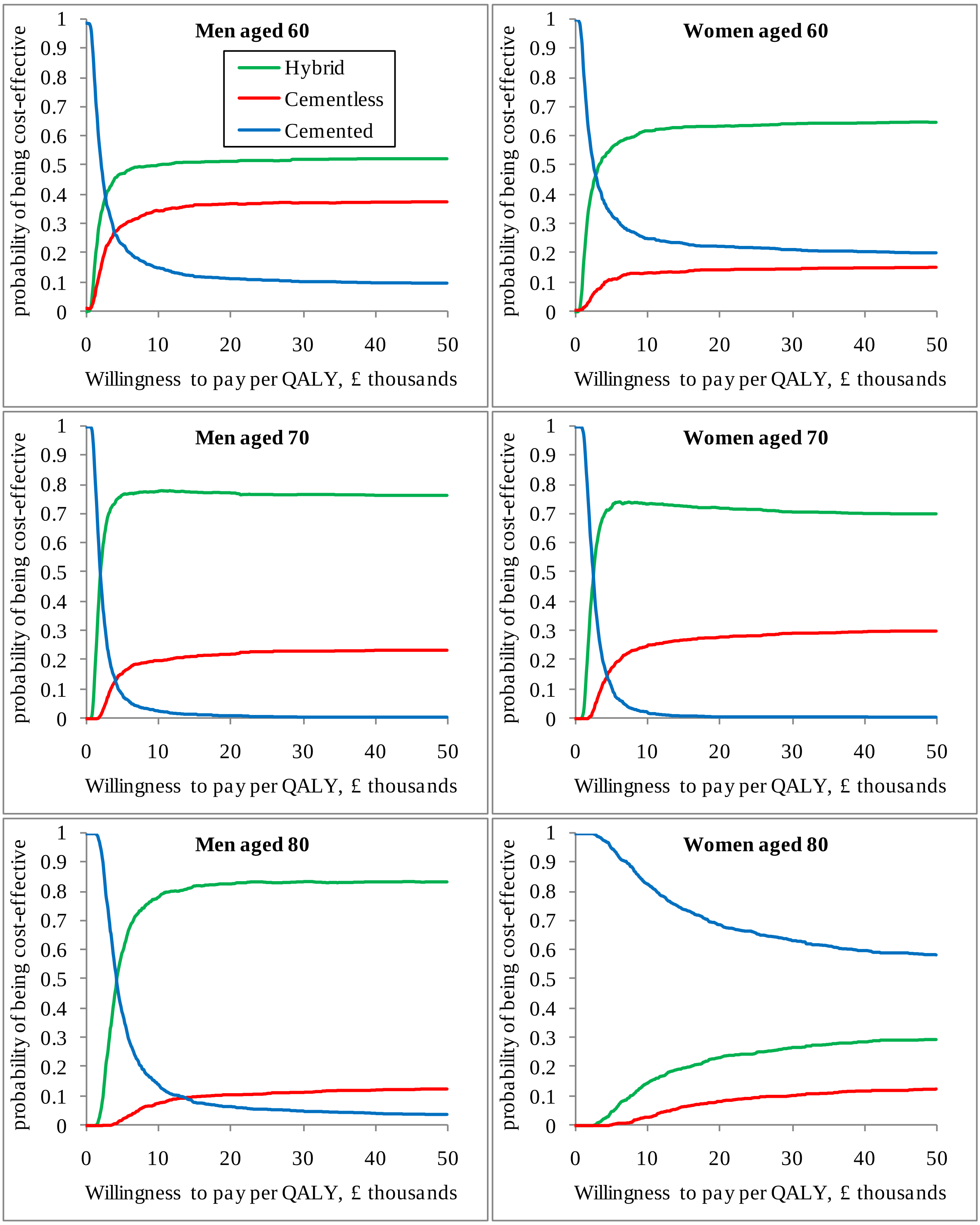


Figure 7 Cost-effectiveness Acceptability Curves by subgroup assuming patients with a predicted operative mortality greater than 10% do not undergo revision

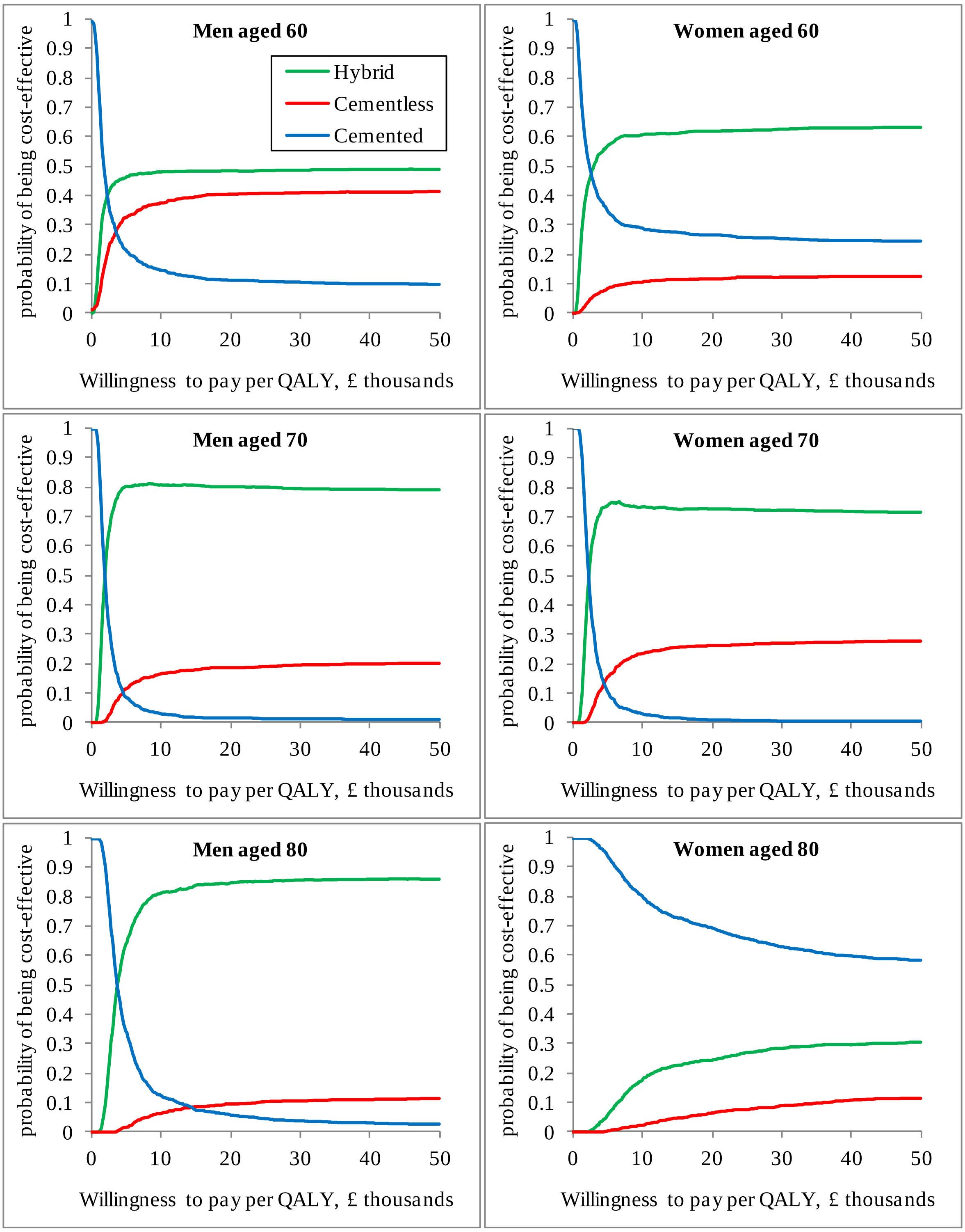


Figure 8 Cost-effectiveness Acceptability Curves by subgroup after exclusion of patients with metal-on-metal joint articulation

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