Rationing of total knee replacement: A cost-effectiveness analysis on a large trial dataset

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Abstract

Objectives: Many UK primary care trusts (PCTs) have recently introduced eligibility criteria restricting total knee replacement (TKR) to patients with low pre-operative Oxford Knee Scores (OKS) to cut expenditure. We evaluate these criteria by assessing the cost-effectiveness of TKR compared with no knee replacement for patients with different baseline characteristics from an NHS perspective.

Design: The cost-effectiveness of TKR in different patient subgroups was assessed using regression analyses of patient-level data from the Knee Arthroplasty Trial (KAT), a large pragmatic randomised controlled trial comparing different knee prostheses. Costs and quality-adjusted life-years (QALYs) observed in the KAT trial over a five-year time horizon following TKR were compared with conservative assumptions about the costs and outcomes that would have been accrued had TKR not been performed.

Results: On average, primary TKR and five years of subsequent care cost £7,458 per patient (standard deviation, SD: £4,058), and patients gained an average of 1.33 (SD: 1.43) QALYs. As result, TKR cost £5,623 per QALY gained. Although costs and health outcomes varied with age and sex, TKR cost less than £20,000 per QALY gained for patients of ASA grade 1 or 2 who had baseline OKS of 39 or below, and for ASA grade 3 patients with OKS of 34 or below, even with highly conservative assumptions about costs and outcomes without TKR. Body mass index (BMI) had no significant effect on costs or outcomes. Restricting TKR to patients with pre-operative OKS of 26 or less would inappropriately deny a highly cost-effective treatment to more than 10,000 patients annually.

Conclusions: TKR is highly cost-effective for most current patients if the NHS is willing to pay £20,000-£30,000 per QALY gained. At least 97% of TKR patients in England have more severe symptoms than the thresholds we have identified, suggesting further rationing by OKS is probably unjustified.

Article summary

Article focus

- We assess the cost-effectiveness of total knee replacement (TKR) compared with no knee replacement for patients with different baseline characteristics from a National Health Service (NHS) perspective.
- In particular, we assess the appropriateness of eligibility criteria recently introduced by many UK primary care trusts (PCTs), which restrict TKR to patients with low pre-operative Oxford Knee Scores (OKS) to cut expenditure.

Key messages

- We find TKR to be highly cost-effective, costing £5,623 per quality-adjusted life-year (QALY) gained for the average patient.
- TKR costs less than £20,000 per QALY gained for healthy patients with OKS of ≤39, or ≤34 for patients who have other conditions restricting their daily activities.
- We find no evidence to support the criteria for restricting access to TKR that have been proposed by some PCTs and calculate that restricting TKR to those patients with pre-operative OKS of 26 or less would deny a highly cost-effective treatment to more than 10,000 patients per year.

Strengths and limitations of this study

- This is the first study assessing how the cost-effectiveness of TKR varies with OKS and the first assessing the clinical/economic implications of the newly-introduced rationing criteria.
- Analyses are based on patient-level data from a large pragmatic trial with detailed, prospective collection of utilities, baseline characteristics and all major knee-related NHS resource use.
- Our study makes several highly conservative assumptions: in particular, assuming that patients would have accrued no knee-related costs and remained at baseline utility without TKR. Furthermore, the KAT sample included only 37 patients with pre-operative OKS >35. As result, TKR may be also cost-effective for some patients with OKS above 39.

Introduction

Total knee replacement (TKR) is a highly effective treatment for patients with bone-on-bone osteoarthritis and significant knee symptoms, producing substantial reductions in symptoms (particularly pain)[1] and lasting for at least 15 years in 83-94% of cases.[2] However, about 18% of patients consider the outcomes of their surgery to be only fair or poor,[1] and a small proportion experience complications.[3-5] Previous economic evaluations have found TKR to be highly cost-effective, with a cost-effectiveness ratio between €1,276 and $18,300 per quality-adjusted life-year (QALY) gained for the average patient[6-10]: well below the £20,000-£30,000 per QALY range that the National Institute for Health and Clinical Excellence (NICE) considers cost-effective.[11] However, studies suggest that the costs and benefits of TKR vary between patient subgroups, with TKR being more cost-effective in younger patients,[9] those attending high-volume centres[7] and those deemed low-risk based on age, comorbidities, and poverty criteria.[7] There is also evidence that older patients have higher medical costs,[12] although other studies suggest that knee replacement is also cost-effective in nonagenarians[13] and draw conflicting conclusions on how benefits vary with body mass index (BMI).[14-16]

In the current economic environment there is great pressure to reduce NHS expenditure and numerous Primary Care Trusts (PCTs) have proposed cutting costs by limiting access to joint replacement[17-24] or classifying these procedures as being of limited value.[23-25] Since around 60,000 primary TKR procedures are conducted in England and Wales each year,[26] savings could be made with little loss of patient welfare *if* it were possible to reliably predict which patients obtain little/no benefit from TKR based on explicit, evidence-based criteria. Although the widely-used Oxford Knee Score (OKS) was developed to assess outcomes of knee replacement in trial populations,[27] several PCTs have set maximum OKS thresholds (ranging from 18 to 32), above which patients are ineligible for TKR.[17-23] However, we are not aware of any clinical or cost-effectiveness justification for these thresholds. Furthermore, many patients with higher OKS have significant symptoms or limitations to daily activities that could be improved by surgery. If rationing policies are to be adopted, cost-effectiveness analysis offers the only fair basis for designing them, since it ensures that NHS resources are allocated to maximise the health gained from available resources. As treatments are generally considered cost-effective if they cost less than £20,000-£30,000 per quality-adjusted life-year (QALY) gained,[11] restricting TKR to those patients for whom the procedure

costs less than £20,000-£30,000 per QALY gained would be a reasonable approach, potentially realising savings that could be invested in other treatments giving greater health gains. However, we are aware of no published evidence assessing how the cost-effectiveness of TKR varies with OKS.

We therefore use data from the Knee Arthroplasty Trial (KAT)[28, 29] to assess the appropriateness of rationing knee replacement by OKS, age, BMI, and clinical characteristics, by calculating the cost-effectiveness of TKR in different patient subgroups. In contrast to previous studies evaluating the cost-effectiveness of TKR that relied upon data from small cohorts with short follow-up,[6-10, 13] the KAT trial dataset provides detailed, prospective individual patient data on baseline characteristics, treatments, complications, costs, and quality of life, and now has more than five years' follow-up on 2352 patients.

Methods

We assessed the cost-effectiveness of primary TKR compared with no knee replacement for patients with different baseline characteristics. Our analysis took a National Health Service (NHS) perspective and excluded personal and social services from the analysis, although TKR is likely to delay admission to residential care,[13] reduce personal care costs and help recipients to continue paid employment. A cost-utility analysis was conducted, which assessed cost-effectiveness in terms of cost per quality-adjusted life-year (QALY) gained to capture the quality of life gains associated with TKR.

Data on costs and quality of life following TKR were taken from the KAT trial (ISRCTN 45837371): a pragmatic, partial-factorial, unblinded randomised controlled trial (RCT) in which 2352 participants attending 34 UK centres were randomly allocated to undergo TKR with/without a metal-backed tibial component, with/without patellar resurfacing, and/or with/without a mobile bearing.[28, 29] Five-year trial results demonstrated that patients experience substantial improvements in quality of life and functional status following knee replacement that are maintained out to five years[29]; further follow-up is ongoing. Our analysis took a five-year time horizon in line with the results published to date[29]; costs and health benefits occurring more than five years after primary TKR were conservatively excluded.

KAT participants completed the Oxford Knee Score (OKS) and EQ-5D questionnaires immediately before and three months after TKR and annually thereafter. The OKS is a validated 12-item questionnaire to assess health status and outcomes in relation to knee replacement,[27] while the EQ-5D is a generic health state preference measure.[30] Health state preference values ("utilities") for EQ-5D profiles were based on time-trade-off valuations by members of the UK general public.[30] The number of QALYs that each patient accrued following TKR was calculated as the area under the utility curve, with linear interpolation between utility measurements; those patients who died were assumed to remain at the last observed utility until death.

Healthcare resource use data (including knee-related outpatient, general practice and physiotherapy consultations, and theatre time, hospital days, complications and knee components used during the primary admission for TKR and during any knee-related readmissions) were collected prospectively for all KAT participants and valued at 2007-08 prices, as described previously.[29] Costs incurred after Year 1 were discounted at 3.5% per year based on current UK recommendations.[31]

The number of QALYs gained from TKR was calculated as the number of QALYs observed minus the number of QALYs expected without TKR. Since all KAT participants underwent TKR, assumptions were needed to estimate the costs and QALYs that would have been accrued if no TKR procedures had occurred in the five-year time horizon. We assumed that:

- Without TKR, patients would have remained at their baseline EQ-5D utility for five years or until death (if sooner). In practice, patients' symptoms and quality of life are likely to deteriorate due to worsening arthritis[16, 32] and increasing age.[33]
- The seven KAT participants who died before hospital discharge would have survived for five years at baseline utility without TKR but that TKR had no effect on the date of death for other patients. This assumption is highly conservative since those patients who die soon after joint replacement tend to be older[5, 34] and have comorbidities that could have led to death without TKR.[5]
- Patients would not have used any healthcare resources due to their knee problems if they had not undergone TKR. This assumption is highly conservative since osteoarthritis patients will receive medical management without TKR and a recent Canadian case-control study suggested that TKR recipients accrued lower costs 6-18 months after the procedure than matched controls who had arthritis but no TKR.[32]

Since these assumptions are likely to underestimate the benefits and overestimate the additional costs of TKR, we evaluated the effect of relaxing these assumptions in sensitivity analyses.

The 7% of data on baseline characteristics, resource use and quality of life that were missing were imputed by multiple imputation using the ice command[35-37] (version 1.3.0) within Stata Version 11.0 (College Station, TX), thereby avoiding the bias and inefficiency associated with complete case analysis.[37-39] Treatment indicators and the covariates included in subsequent regression analyses were included in the imputation model to avoid bias.[37] Fifty imputed datasets were generated and results combined.

Regression models were used to estimate how the costs and QALYs gained from TKR vary with baseline characteristics and to predict outcomes for different patient groups without subdividing the trial population into small patient subgroups. Since costs and QALYs were highly skewed, generalised linear models (GLM) with gamma family distributions were used to predict total costs and the QALYs accrued with or without TKR; prior to regression, the number of QALYs accrued was subtracted from the maximum number of QALYs that could have been accrued over the five-year trial period to ensure that all QALY data were positive. We evaluated the effect of six baseline characteristics on costs and QALYs with/without TKR:

- Female sex;
- Age at time of operation;
- Baseline OKS (using the new, 0-48, scoring system[40]);
- American Society of Anesthesiologists (ASA) grade 3 (symptomatic illness with minimal restriction on daily life) rather than grades 1 (fit & healthy) or 2 (asymptomatic illness with no restriction on daily life);
- BMI (kg/m^2);
- Presence of arthritis in one knee rather than in both knees or generally.

Since the introduction of biologic therapies has changed management of rheumatoid arthritis and as rheumatoid arthritis patients and those with severe comorbidities are likely have very different costs and outcomes from most patients, 108 rheumatoid patients and 13 patients of ASA grade 4 were excluded from the analysis.

All regression analyses were conducted in Stata Version 11. Bootstrapping was used to capture uncertainty around cost-effectiveness ratios and correlations between costs and QALYs with/without TKR; the regression models for costs and outcomes were run for each of 125 bootstrap samples drawn from each imputed KAT dataset and results combined using Rubin's rule.[38] Predicted costs and the predicted number of QALYs accrued with and without TKR in different patient groups were calculated from regression coefficients and used to estimate incremental cost-effectiveness ratios (ICERs). Bootstrap results were used to calculate cost-effectiveness acceptability curves (CEACs),[41] which plot the probability of treatment being cost-effective against the ceiling ratio (i.e. the maximum that society is willing or able to pay per QALY gained).

We also calculated number of patients in England and Wales eligible for TKR under different rationing policies based on 61,651 patients undergoing primary TKR each year.[26] The proportion of patients eligible for TKR under different rationing criteria was based on analysis of an extract of patient-level Patient Reported Outcome Measures[1] (PROMs) data on admissions for knee replacement up to 31st December 2010, supplemented where necessary by the baseline characteristics from the KAT sample.

Results

Of the 2131 KAT participants who had osteoarthritis, were ASA grades 1-3 and underwent TKR as part of the trial, the mean baseline OKS was 18 (standard deviation, SD: 7.5), mean age 71 (SD: 8.0), mean BMI 30 (SD: 5.5), and 45% (956/2131) were female (Figure 1); further baseline characteristics of the trial population have been reported previously.[28]

Mean EQ-5D utility rose substantially within three months of TKR from 0.39 at baseline to 0.71 at one year, and declined gradually thereafter (Figure 1, Table 1). However, baseline utility and the quality of life gains associated with TKR varied between patient subgroups. In particular, women and patients with low OKS (i.e. poor knee function), higher ASA grade or morbid obesity at baseline tended to have lower quality of life at all timepoints (Figure 1), although those in the lowest OKS quintile experienced significantly greater health gains from TKR than the top quintile ($p<0.001$; calculated using linear regression combining imputed datasets using mim command).

Table 1: EQ-5D utility, costs and estimated QALYs for subgroups with different baseline OKS

OKS decile		**1 (worst)**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 (best)**	**All patients**
Baseline OKS range		**<9**	**9-11**	**12-13**	**14-15**	**16-17**	**18-19**	**20-21**	**22-24**	**25-27**	**>27**	**0-48**
No. KAT participants		204	213	186	232	193	224	195	256	194	234	**2131**
EQ-5D utility (SE)	Baseline	0.54 (0.007)	0.58 (0.006)	0.64 (0.006)	0.66 (0.005)	0.71 (0.005)	0.71 (0.005)	0.70 (0.004)	0.74 (0.004)	0.61 (0.004)	0.67 (0.003)	**0.39 (0.002)**
	3 mths	0.51 (0.007)	0.60 (0.007)	0.68 (0.006)	0.70 (0.006)	0.71 (0.006)	0.75 (0.005)	0.69 (0.006)	0.78 (0.004)	0.75 (0.005)	0.77 (0.004)	**0.68 (0.002)**
	1 year	0.49 (0.008)	0.54 (0.007)	0.66 (0.007)	0.67 (0.006)	0.68 (0.007)	0.73 (0.005)	0.66 (0.007)	0.76 (0.005)	0.79 (0.005)	0.84 (0.004)	**0.71 (0.002)**
	2 year	0.47 (0.008)	0.53 (0.007)	0.64 (0.007)	0.63 (0.006)	0.67 (0.007)	0.71 (0.006)	0.68 (0.007)	0.72 (0.005)	0.78 (0.005)	0.81 (0.005)	**0.68 (0.002)**
	3 year	0.43 (0.008)	0.49 (0.008)	0.61 (0.007)	0.62 (0.007)	0.65 (0.007)	0.68 (0.007)	0.64 (0.007)	0.70 (0.006)	0.76 (0.006)	0.79 (0.006)	**0.66 (0.002)**
	4 year	0.43 (0.008)	0.50 (0.008)	0.57 (0.008)	0.58 (0.007)	0.63 (0.007)	0.67 (0.007)	0.59 (0.007)	0.68 (0.006)	0.71 (0.007)	0.75 (0.006)	**0.63 (0.002)**
	5 year	0.47 (0.006)	0.58 (0.005)	0.65 (0.005)	0.65 (0.005)	0.67 (0.008)	0.73 (0.007)	0.47 (0.006)	0.58 (0.005)	0.65 (0.005)	0.65 (0.005)	**0.61 (0.002)**
Total cost (SE)*		£8657 (£157)	£7715 (£81)	£7495 (£73)	£7081 (£63)	£7185 (£69)	£7567 (£82)	£7619 (£102)	£7128 (£61)	£7399 (£94)	£6917 (£67)	**£7458 (£28)**
QALYs with TKR (SE)*		2.17 (0.029)	2.48 (0.027)	2.94 (0.024)	2.99 (0.022)	3.13 (0.025)	3.30 (0.022)	3.09 (0.025)	3.40 (0.019)	3.50 (0.020)	3.67 (0.020)	**3.08 (0.025)**
QALYs without TKR (SE)*		0.15 (0.02)	0.62 (0.022)	0.94 (0.026)	1.14 (0.026)	1.63 (0.029)	2.04 (0.026)	2.39 (0.026)	2.55 (0.021)	2.78 (0.02)	3.02 (0.02)	**1.75 (0.031)**
QALY gain from TKR (SE)*		2.02 (0.032)	1.86 (0.031)	2.00 (0.033)	1.85 (0.031)	1.51 (0.034)	1.26 (0.030)	0.69 (0.027)	0.85 (0.023)	0.73 (0.02)	0.65 (0.02)	**1.33 (0.01)**
ICER*		£4,295	£4,153	£3,747	£3,836	£4,770	£6,007	£10,971	£8,391	£10,167	£10,697	**£5,623**

* Discounted at 3.5% per annum

Abbreviations: ICER, incremental cost-effectiveness ratio; OKS, Oxford Knee Score (new scoring system running from zero [severe problems on all functions] to 48 [no problems])[40]; QALY, quality-adjusted life-year; SE, standard error around the mean; TKR, total knee replacement.

On average, each admission for primary TKR cost £6,363 (SD: £1,702). Readmissions, revision procedures and GP, outpatient, and physiotherapy consultations related to the study knee over the following five years cost a further £1,095 (SD: £3,579) per patient, giving a total cost of £7,458 (SD: £4,058) per patient. TKR was more costly in patients with low baseline OKS, but the greater QALY gains meant that TKR was better value for money in this patient group than in patients with moderate symptoms (Table 1). Subgroup analyses suggested that TKR cost less than £11,000/QALY gained across all OKS deciles: well below the £20,000-£30,000/QALY gained range that NICE currently consider good value for money.[11]

However, cost-effectiveness also varied substantially between patients within each OKS decile. We therefore used regression models to estimate the costs, QALY gains and cost-effectiveness of TKR in a wide range of patient subgroups while controlling for multiple baseline characteristics. Our results indicated that four factors have a significant effect on cost-effectiveness: age, sex, baseline OKS and ASA grade (Table 2). BMI and the presence of arthritis in other joints besides the study knee had no significant effect on either the costs or QALY gains associated with TKR (p>0.05).

Table 2: Results of the regression analysis

Baseline characteristic	Coefficient (SE)		
	QALY loss with TKR†	QALY loss without TKR†	Total costs with TKR
Female sex	0.056 (0.065)	-0.001 (0.054)	593 (181)*
Age at operation (years)	0.007 (0.003)*	0.002 (0.004)	-8 (12)
Pre-operative OKS	-0.040 (0.004)*	-0.087 (0.004)*	-52 (12)*
ASA grade 3	0.414 (0.067)*	0.227 (0.087)*	492 (208)*
Constant	1.712 (0.201)*	4.274 (0.325)*	8573 (881)*

* p<0.05
† QALY loss indicates the number of discounted QALYs that would have been accrued if patients had experienced an EQ-5D utility of 1 for five years (4.67 QALYs) minus the number of discounted QALYs that the patient actually experienced.
The incremental cost-effectiveness ratio (expressed as cost/QALY) for any given patient equals: (female x 593 - age x 8 - OKS x 52 + ASAgrade3or4 x 492 + 8573)/((female x -0.001 + age x 0.002 - OKS x 0.087 + ASAgrade3 x 0.227 + 4.274) - (female x 0.056 + age x 0.007 - OKS x 0.040 + ASAgrade3 x 0.414 + 1.712). Costs and QALYs were discounted at 3.5% per annum.
Abbreviations: ASA, American Society of Anesthesiologists classification (1=completely fit and healthy, 2=some illness but no effect on daily activity, 3=symptomatic illness with minimal restriction on life); OKS, Oxford Knee Score (new scoring system running from zero [severe problems on all functions] to 48 [no problems])[40]; QALY, quality-adjusted life-year; TKR, total knee replacement.

Figure 2 shows the cost-effectiveness of TKR for each multivariate group, using charts similar in design to widely-used cardiovascular risk tables.[42] The charts demonstrate that TKR is clearly cost-effective across a wide range of patient groups. For example, TKR costs less than £20,000/QALY gained for 71-year-old men with no symptomatic illness unless baseline OKS is above 40 (equivalent to having very minor problems on up to eight of the 12 activities mentioned in OKS or moderate-severe pain only on exertion). The maximum OKS at which TKR becomes cost-ineffective was lower for older patients, women, and those with symptomatic disease, but TKR remained cost-effective for all patients with OKS below 32 regardless of age, sex, or ASA grade. A simplified analysis controlling only for OKS and ASA grade suggested that TKR is cost-effective for all ASA grade 1 or 2 patients with baseline OKS of 39 or less, and all ASA grade 3 patients with OKS ≤34.

There was substantial uncertainty around the cost-effectiveness ratios for patients with very high baseline OKS, since only 37 trial participants had OKS above 35 at baseline. However, we estimate that there is a 99% probability that TKR is cost-effective (at a £20,000/QALY ceiling ratio) for the average ASA grade 1-2 patient with a baseline OKS of 35, and a 53% probability for ASA grade 3 (Figure 3).

Since each additional baseline characteristic increases the complexity of the eligibility criteria and may also raise ethical or equity concerns, we estimated the number of patients who would receive TKR under different eligibility criteria. This analysis suggested that restricting TKR to those patients for whom the operation was predicted to cost less than £20,000/QALY gained based on the simplified model (allowing only for ASA grade and OKS) would lead to 2000 fewer TKR procedures being conducted in England and Wales each year (3% fewer than the 61,651 procedures conducted in 2009/10[26]). If the decision rules were simplified further to provide TKR to all patients with baseline OKS ≤38, all but 1700 of the 61,651 patients currently receiving TKR in England and Wales in 2009/10[26] would be eligible. Allowing for other baseline characteristics had minimal effect on patient numbers or predicted costs or benefits, suggesting that decisions about suitability for TKR can be based on OKS alone.

Sensitivity analyses were conducted to assess the effect of extending the time horizon of our analysis up to 10 years, and of assuming that EQ-5D utility would have fallen by 0.5% per year without TKR,[33] that all knee-related ambulatory consultations would have occurred without TKR, and that the mean length of stay has fallen by 41% (5.9 days[26] vs 10.0) since the KAT operations took place in 1999-2003. Changing any of these assumptions produced lower ICERs than the base case analysis, confirming that the current analysis is highly conservative and suggesting that TKR may be cost-effective for ASA grade 1-2 patients with baseline

OKS as high as 43. Excluding patients with incomplete data had no effect on conclusions.

Discussion

We found TKR to cost £5,623 per QALY gained for the average patient (similar to estimates from previous studies[6-10]) and therefore represent very good value for money compared with the £20,000-£30,000/QALY threshold typically used in NHS decision-making.[11] Our study also confirms previous findings[7, 9, 16] that costs and benefits vary with age and comorbidity. We found pre-operative OKS to be the best predictor of post-operative costs, outcomes and cost-effectiveness.

Our analyses were based on patient-level data from a large pragmatic trial with detailed, prospective collection of costs, utilities and baseline characteristics that permit extensive subgroup analyses. Furthermore, unlike some previous economic evaluations, our study took full account of uncertainty and included all knee-related NHS costs accrued in the first five years after TKR. The main limitation of our analysis was the small number of patients with high OKS. Since KAT recruited only 37 patients with OKS >35, further studies are required to evaluate TKR in this patient subgroup. Analyses were also based on *post hoc* comparisons between outcomes before and after TKR, rather than between randomly-assigned treatment groups. As a result, our study does not provide unbiased estimates of the QALY gains from TKR, and regression towards the mean may have caused our study to overestimate the quality of life improvement attributable to TKR and/or the effect of pre-operative OKS on QALY gains.

We made several highly conservative assumptions: in particular, assuming that patients would have accrued no knee-related costs and would have remained at baseline utility without TKR, whereas previous studies have found that patients accrue substantial costs and show clinical worsening without TKR.[32] We also assumed that those patients who died before hospital discharge would have survived for five years if they had not had TKR; in reality, those patients dying soon after TKR tend to be older[5, 34] and frailer[5] pre-operatively and some studies suggest that patients undergoing hip replacement have higher long-term survival than the general population[43, 44] (although this may be due to patient selection[34, 43]). When these assumptions were relaxed, TKR was cost-effective for ASA grade 1-2 patients with baseline OKS ≤43. The costs and benefits of TKR are likely to vary between centres and over time due to variations in patient demographics, component prices, length of stay, and operation time; sensitivity analyses demonstrated that TKR may have become more cost-effective since the KAT procedures were conducted in 1999-2003 due to reductions in length of stay.

Our analyses show that if TKR were to be rationed based on cost-effectiveness, OKS would be a reasonable tool to use to set the threshold, although there may, of course, be practical difficulties with using a patient-reported measure to determine treatment eligibility: particularly if patients know how their questionnaire responses will be used or if test-retest reliability is low in this setting. Based on regression and subgroup analyses, we can be confident that TKR costs less than £20,000/QALY for all ASA grade 1-2 patients with baseline OKS ≤39 and for ASA grade 3 patients with OKS ≤34. Using these thresholds to determine who received treatment would avoid around 2000 TKR procedures per year in England and Wales, saving around £11.8 million per year. However, the higher thresholds suggested by sensitivity analyses using less conservative assumptions suggest that all TKR is cost-effective for all but 100 patients per year, which is unlikely to achieve sufficient savings to warrant rationing of TKR. Although the cost-effectiveness of knee replacement was also influenced by gender and age, taking account of these factors as well as OKS and ASA grade would increase the complexity of eligibility criteria, reduce equality of access to healthcare and have minimal effect on NHS budgets.

Our analysis shows that the thresholds proposed by some PCTs[17-23] are inappropriate and would deny a highly cost-effective treatment to thousands of patients with severe arthritis. The current situation also introduces a postcode lottery with different PCTs using different eligibility criteria. We estimate that limiting knee replacement to patients with OKS ≤26 would prevent more than 10,000 people from receiving TKR. This would be inequitable as TKR costs £10,697 per QALY gained for this group, whereas NICE routinely recommend treatments with ICERs in the region of £20,000-£30,000/QALY gained[11, 45, 46] and are willing to pay substantially more for end of life care.[47] Furthermore, the finding that TKR and subsequent monitoring is more costly for patients with low OKS suggests that delaying TKR until symptoms have deteriorated may be a false economy. Although some PCTs have considered restricting TKR further for obese patients,[17, 20, 24, 48] we found BMI to have no significant effect on costs (p=0.442), QALY gains (p=0.098) or the incidence of peri- or post-operative complications (p>0.26): even when ASA grade was omitted from regression analyses.

Eligibility criteria for rheumatoid arthritis patients and patients with ASA grade 4 remain unclear, although ASA grade 4 patients would normally be considered unfit for surgery, and the decision to operate on such patients would be based on a case-by-case consideration of whether the benefits outweigh the risks. While our study focused on the costs and benefits of TKR, patients with high baseline OKS often undergo unicompartmental knee replacement, which is cheaper than TKR due to lower component prices, fewer complications and shorter inpatient stay.[49-51] The OKS threshold for unicompartmental replacement may therefore be even higher than for TKR, since it produces marked quality of life improvements in patients with high baseline scores.[49] This remains an area for future research.

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Competing interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organisation for the submitted work with the exception of those declared in the funding statement. AG, RF and GM declare that they have no financial relationships with any organisations that might have an interest in the submitted work in the previous three years and no other relationships or activities that could appear to have influenced the submitted work. DM receives royalties paid to him by Biomet and HD has undertaken consultancy work for Pfizer on drugs for rheumatoid arthritis but both declare that they have no other financial relationships with any organisations that might have an interest in the submitted work in the previous three years and no other relationships or activities that could appear to have influenced the submitted work.

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Contributorship statement

HD, AG and DM conceived and developed the principles and methods underpinning the current analysis. GM was involved in primary data collection and database management, while HD conducted the analysis under AG's supervision and guidance from other authors. HD drafted the manuscript with input from all other authors; all authors have approved the final manuscript. The KAT trial was designed and run by the KAT trial group, which comprised Suzanne Breeman, Marion Campbell, HD, Jackie Ellington, Nick Fiddian, RF, Adrian Grant, AG, Linda Johnston, GM, Richard Morris and DM.

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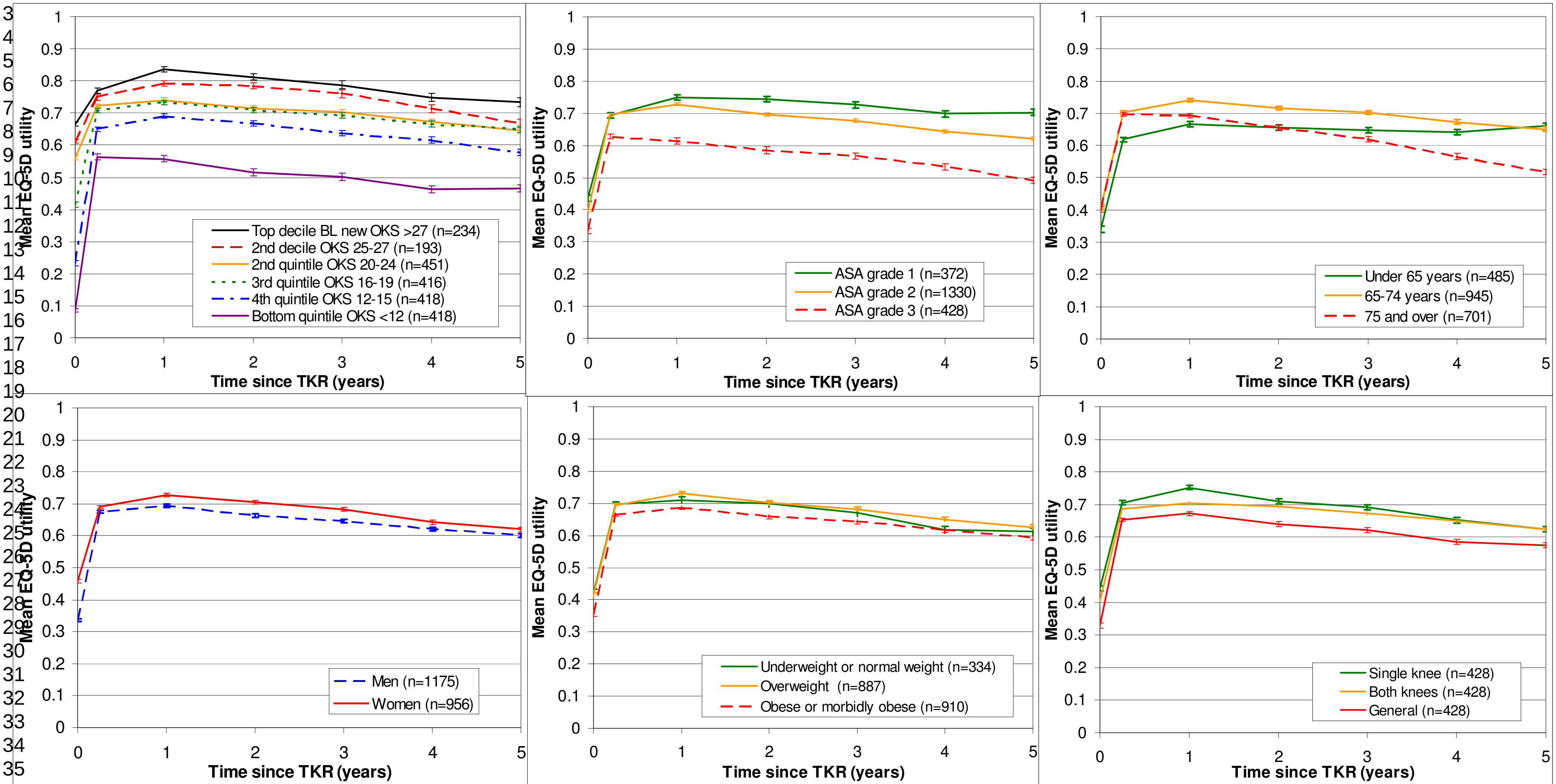
Figure 1: EQ-5D utility by subgroup

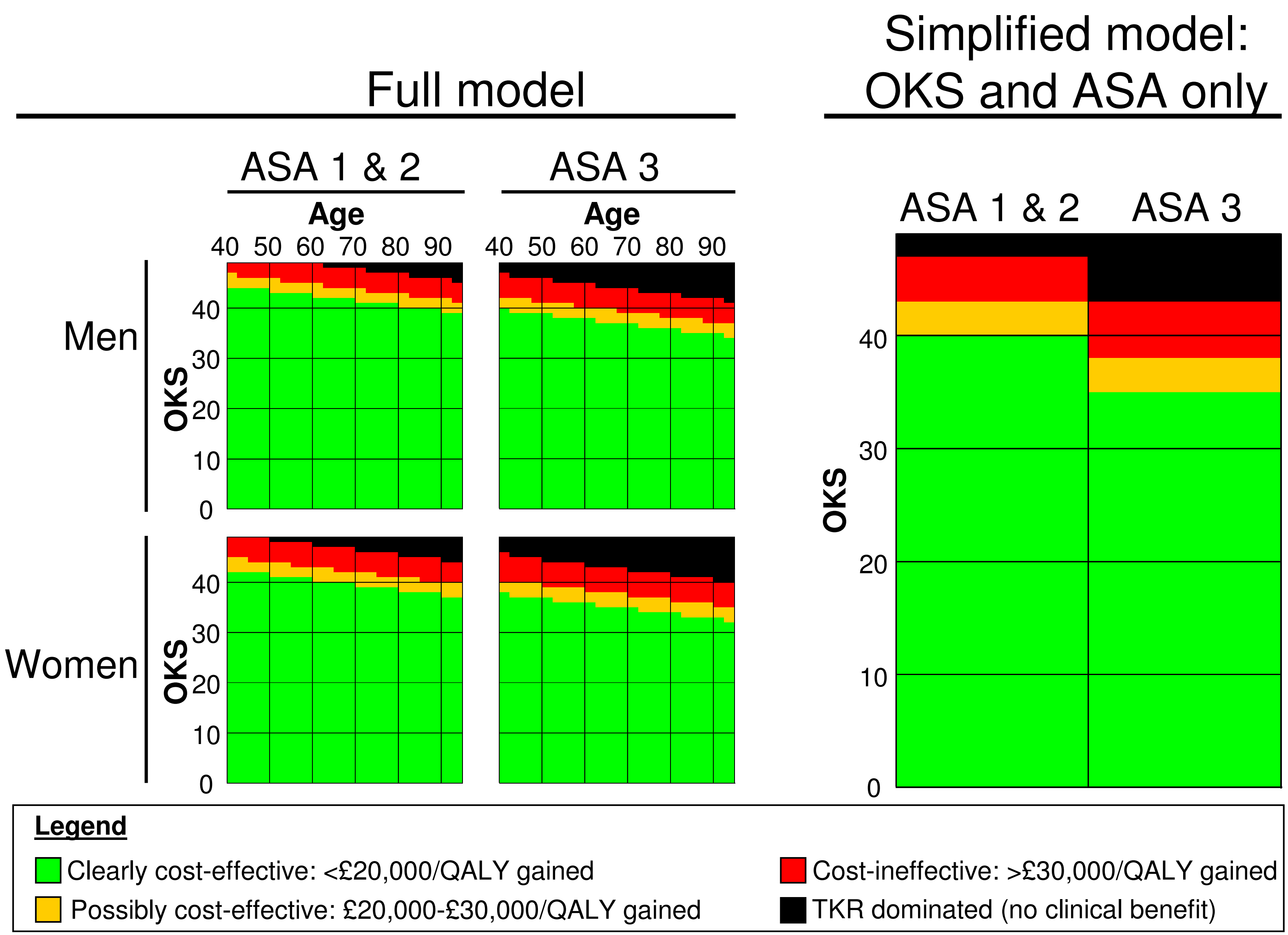
Abbreviations: ASA, American Society of Anesthesiologists classification (1=completely fit and healthy, 2=some illness but no effect on daily activity, 3=symptomatic illness with minimal restriction on life, 4=symptomatic illness with severe restriction on life); OKS, Oxford Knee Score (new scoring system running from zero [severe problems on all functions] to 48 [no problems])[40]; TKR, total knee replacement.
Error bars show 95% confidence intervals.

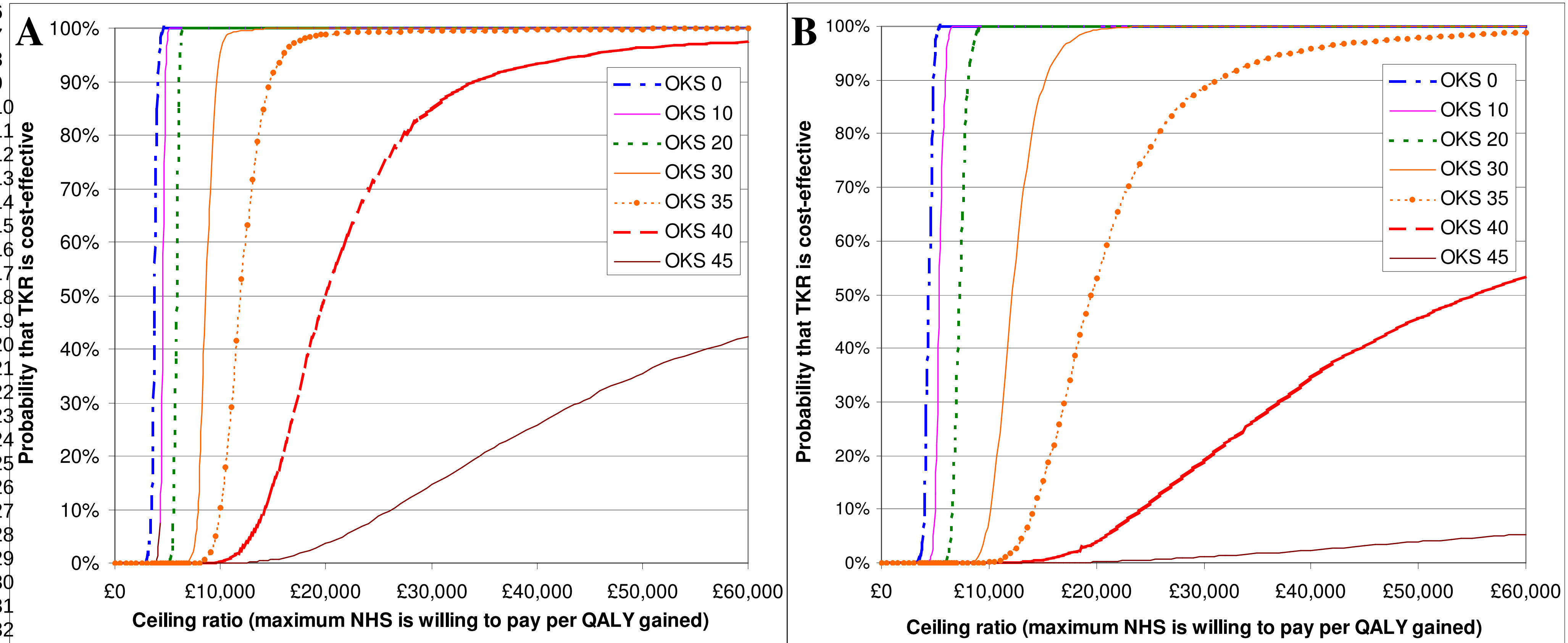
Figure 2: Cost-effectiveness prediction charts estimated based on predictions of regression models.

Abbreviations: ASA, American Society of Anesthesiologists classification (1=completely fit and healthy, 2=some illness but no effect on daily activity, 3=symptomatic illness with minimal restriction on life); OKS, Oxford Knee Score (new scoring system running from zero [severe problems on all functions] to 48 [no problems])[40]; QALY, quality-adjusted life-year; TKR, total knee replacement.

Figure 3: Cost-effectiveness acceptability curves for different patient subgroups at different baseline Oxford Knee Scores (OKS). A: American Society of Anesthesiologists (ASA) grade 1 and 2 patients. B: ASA grade 3 patients.


Mean EQ-5D utility
Time since TKR (years)
Top decile BL new OKS >27 (n=234)
2nd decile OKS 25-27 (n=193)
2nd quintile OKS 20-24 (n=451)
3rd quintile OKS 16-19 (n=416)
4th quintile OKS 12-15 (n=418)
Bottom quintile OKS <12 (n=418)
ASA grade 1 (n=372)
ASA grade 2 (n=1330)
ASA grade 3 (n=428)
Under 65 years (n=485)
65-74 years (n=945)
75 and over (n=701)
Men (n=1175)
Women (n=956)
Underweight or normal weight (n=334)
Overweight (n=887)
Obese or morbidly obese (n=910)
Single knee (n=428)
Both knees (n=428)
General (n=428)


Full model
Simplified model: OKS and ASA only
ASA 1 & 2
ASA 3
Age
40 50 60 70 80 90
Men
Women
OKS
0
10
20
30
40
Legend
Clearly cost-effective: <£20,000/QALY gained
Possibly cost-effective: £20,000-£30,000/QALY gained
Cost-ineffective: >£30,000/QALY gained
TKR dominated (no clinical benefit)


A
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Probability that TKR is cost-effective
£0
£10,000
£20,000
£30,000
£40,000
£50,000
£60,000
Ceiling ratio (maximum NHS is willing to pay per QALY gained)
OKS 0
OKS 10
OKS 20
OKS 30
OKS 35
OKS 40
OKS 45
B
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Probability that TKR is cost-effective
£0
£10,000
£20,000
£30,000
£40,000
£50,000
£60,000
Ceiling ratio (maximum NHS is willing to pay per QALY gained)
OKS 0
OKS 10
OKS 20
OKS 30
OKS 35
OKS 40
OKS 45

Health economic checklist for "Rationing of total knee replacement: A cost-effectiveness analysis on a large trial dataset"

Study design	**Page**
(1) The research question is stated	5, paragraphs 2 & 3
(2) The economic importance of the research question is stated	4-5
(3) The viewpoint(s) of the analysis are clearly stated and justified	5, paragraph 3
(4) The rationale for choosing the alternative programmes or interventions compared is stated	4-5
(5) The alternatives being compared are clearly described	5, paragraph 3
(6) The form of economic evaluation used is stated	5, paragraph 3
(7) The choice of form of economic evaluation is justified in relation to the questions addressed	5, paragraph 3
Data collection	
(8) The source(s) of effectiveness estimates used are stated	5, paragraph 4
(9) Details of the design and results of effectiveness study are given (if based on a single study)	5, paragraph 4
(10) Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	N/A
(11) The primary outcome measure(s) for the economic evaluation are clearly stated	5, paragraph 3
(12) Methods to value health states and other benefits are stated	6, paragraph 1
(13) Details of the subjects from whom valuations were obtained are given	6, paragraph 1
(14) Productivity changes (if included) are reported separately	N/A
(15) The relevance of productivity changes to the study question is discussed	5, paragraph 3
(16) Quantities of resources are reported separately from their unit costs	Given in reference 29
(17) Methods for the estimation of quantities and unit costs are described	
(18) Currency and price data are recorded	N/A
(19) Details of currency of price adjustments for inflation or currency conversion are given	Given in reference 29
(20) Details of any model used are given	N/A
(21) The choice of model used and the key parameters on which it is based are justified	N/A
Analysis and interpretation of results	
(22) Time horizon of costs and benefits is stated	5, paragraph 4
(23) The discount rate(s) is stated	6, paragraph 2
(24) The choice of rate(s) is justified	6, paragraph 2
(25) An explanation is given if costs or benefits are not discounted	N/A
(26) Details of statistical tests and confidence intervals are given for stochastic data	8, paragraph 1
(27) The approach to sensitivity analysis is given	11, paragraph 4
(28) The choice of variables for sensitivity analysis is justified	11, paragraph 4
(29) The ranges over which the variables are varied are stated	N/A
(30) Relevant alternatives are compared	5, paragraph 3
(31) Incremental analysis is reported	Tables 1 & 2
(32) Major outcomes are presented in a disaggregated as well as aggregated form	Tables 1 & 2
(33) The answer to the study question is given	12, paragraph 2 & page 13 paragraphs 2-3
(34) Conclusions follow from the data reported	5, 12-13
(35) Conclusions are accompanied by the appropriate caveats	12-13

Authors may enter N/A if an item on the checklist is not appropriate, but this is only acceptable for items 9,10, 12-15, 20, 21, 23-29, and 31.

Rationing of total knee replacement: A cost-effectiveness analysis on a large trial dataset

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Rationing of total knee replacement: A cost-effectiveness analysis on a large trial dataset

Running header:
Rationing of total knee replacement

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Data sharing statement: No additional data available.

Protocol: Available at http://www.hta.ac.uk/protocols/199500100001.pdf.

Abstract

Objectives: Many UK primary care trusts (PCTs) have recently introduced eligibility criteria restricting total knee replacement (TKR) to patients with low pre-operative Oxford Knee Scores (OKS) to cut expenditure. We evaluate these criteria by assessing the cost-effectiveness of TKR compared with no knee replacement for patients with different baseline characteristics from an NHS perspective.

Design: The cost-effectiveness of TKR in different patient subgroups was assessed using regression analyses of patient-level data from the Knee Arthroplasty Trial (KAT), a large, pragmatic, randomised trial comparing knee prostheses.

Setting: 34 UK hospitals.

Participants: 2131 osteoarthritis patients undergoing TKR.

Interventions and outcome measures: Costs and quality-adjusted life-years (QALYs) observed in the KAT trial within five years of TKR were compared with conservative assumptions about the costs and outcomes that would have been accrued had TKR not been performed.

Results: On average, primary TKR and five years of subsequent care cost £7,458 per patient (standard deviation, SD: £4,058), and patients gained an average of 1.33 (SD: 1.43) QALYs. As result, TKR cost £5,623 per QALY gained. Although costs and health outcomes varied with age and sex, TKR cost less than £20,000 per QALY gained for patients with ASA grade 1-2 who had baseline OKS <40, and for ASA grade 3 patients with OKS <35, even with highly conservative assumptions about costs and outcomes without TKR. Body mass index had no significant effect on costs or outcomes. Restricting TKR to patients with pre-operative OKS <27 would inappropriately deny a highly cost-effective treatment to >10,000 patients annually.

Conclusions: TKR is highly cost-effective for most current patients if the NHS is willing to pay £20,000-£30,000 per QALY gained. At least 97% of TKR patients in England have more severe symptoms than the thresholds we have identified, suggesting further rationing by OKS is probably unjustified.

Trial registration: ISRCTN 45837371

Article summary

Article focus

- We assess the cost-effectiveness of total knee replacement (TKR) compared with no knee replacement for patients with different baseline characteristics from a National Health Service (NHS) perspective.
- In particular, we assess the appropriateness of eligibility criteria recently introduced by many UK primary care trusts (PCTs), which restrict TKR to patients with low (i.e. poor) pre-operative Oxford Knee Scores (OKS) to cut expenditure.

Key messages

- We find TKR to be highly cost-effective, costing £5,623 per quality-adjusted life-year (QALY) gained for the average patient.
- TKR costs less than £20,000 per QALY gained for healthy patients with OKS of <40, or <35 for patients who have other conditions restricting their daily activities.
- We find no evidence to support the criteria for restricting access to TKR that have been proposed by some PCTs and calculate that restricting TKR to those patients with pre-operative OKS of 26 or less would deny a highly cost-effective treatment to more than 10,000 patients per year.

Strengths and limitations of this study

- This is the first study assessing how the cost-effectiveness of TKR varies with OKS and the first assessing the clinical/economic implications of the newly-introduced rationing criteria.
- Analyses are based on patient-level data from a large pragmatic trial with detailed, prospective collection of utilities, baseline characteristics and all major knee-related NHS resource use, including revisions and ambulatory care.
- Our study makes several highly conservative assumptions: in particular, assuming that patients would have accrued no knee-related costs and remained at baseline utility without TKR. Furthermore, the KAT sample included only 37 patients with pre-operative OKS >35. As result, TKR may be also cost-effective for some patients with OKS above 39.

Introduction

Total knee replacement (TKR) is a highly effective treatment for patients with bone-on-bone osteoarthritis and significant knee symptoms, producing substantial reductions in symptoms (particularly pain)[1] and lasting for at least 15 years in 83-94% of cases.[2] However, about 18% of patients consider the outcomes of their surgery to be only fair or poor,[1] and a small proportion experience complications.[3-5] Previous economic evaluations have found TKR to be highly cost-effective, with a cost-effectiveness ratio between €1,276 and $18,300 per quality-adjusted life-year (QALY) gained for the average patient[6-10]: well below the £20,000-£30,000 per QALY range that the National Institute for Health and Clinical Excellence (NICE) considers cost-effective.[11] However, studies suggest that the costs and benefits of TKR vary between patient subgroups, with TKR being more cost-effective in younger patients,[9] those attending high-volume centres[7] and those deemed low-risk based on age, comorbidities, and poverty criteria.[7] There is also evidence that older[12] and obese[13] patients have higher medical costs, although other studies suggest that knee replacement is also cost-effective in nonagenarians[14] and draw conflicting conclusions on how benefits vary with body mass index (BMI).[15-17]

In the current economic environment there is great pressure to reduce NHS expenditure and numerous Primary Care Trusts (PCTs) have proposed cutting costs by limiting access to joint replacement[18-25] or classifying these procedures as being of limited value.[24-26] Since around 60,000 primary TKR procedures are conducted in England and Wales each year,[27] savings could be made with little loss of patient welfare *if* it were possible to reliably predict which patients obtain little/no benefit from TKR based on explicit, evidence-based criteria. Although the widely-used Oxford Knee Score (OKS) was developed to assess outcomes of knee replacement in trial populations,[28] several PCTs have set maximum OKS thresholds (ranging from 18 to 32), above which patients are ineligible for TKR.[18-24] However, we are not aware of any clinical or cost-effectiveness justification for these thresholds. Furthermore, many patients with higher OKS have significant symptoms or limitations to daily activities that could be improved by surgery. If rationing policies are to be adopted, cost-effectiveness analysis offers the only fair basis for designing them, since it ensures that NHS resources are allocated to maximise the health gained from available resources. As treatments are generally considered cost-effective if they cost less than £20,000-£30,000 per quality-adjusted life-year (QALY) gained,[11] restricting TKR to those patients for whom the procedure

costs less than £20,000-£30,000 per QALY gained would be a reasonable approach, potentially realising savings that could be invested in other treatments giving greater health gains. However, we are aware of no published evidence assessing how the cost-effectiveness of TKR varies with OKS.

We therefore use data from the Knee Arthroplasty Trial (KAT)[29, 30] to assess the appropriateness of rationing knee replacement by OKS, age, BMI, and clinical characteristics, by calculating the cost-effectiveness of TKR in different patient subgroups. In contrast to previous studies evaluating the cost-effectiveness of TKR that relied upon data from small cohorts with short follow-up,[6-10, 14] the KAT trial dataset provides detailed, prospective individual patient data on baseline characteristics, treatments, complications, costs, and quality of life, and now has more than five years' follow-up on 2352 patients.

Methods

We assessed the cost-effectiveness of primary TKR compared with no knee replacement for patients with different baseline characteristics. Our analysis took a National Health Service (NHS) perspective and excluded personal and social services from the analysis, although TKR is likely to delay admission to residential care,[14] reduce personal care costs and help recipients to continue paid employment. A cost-utility analysis was conducted, which assessed cost-effectiveness in terms of cost per quality-adjusted life-year (QALY) gained to capture the quality of life gains associated with TKR.

Data on costs and quality of life following TKR were taken from the KAT trial (ISRCTN 45837371): a pragmatic, partial-factorial, unblinded randomised controlled trial (RCT) in which 2352 participants attending 34 UK centres were randomly allocated to undergo TKR with/without a metal-backed tibial component, with/without patellar resurfacing, and/or with/without a mobile bearing.[29, 30] Five-year trial results demonstrated that patients experience substantial improvements in quality of life and functional status following knee replacement that are maintained out to five years[30]; further follow-up is ongoing. Our analysis took a five-year time horizon in line with the results published to date[30]; costs and health benefits occurring more than five years after primary TKR were conservatively excluded.

KAT participants completed the Oxford Knee Score (OKS) and EQ-5D questionnaires immediately before and three months after TKR and annually thereafter. The OKS is a validated 12-item questionnaire for assessing health status and outcomes in relation to knee replacement that gives an unweighted total score ranging from 0 (severe problems on all items) to 48 (no problems on any item).[28] The EQ-5D is a generic health state preference measure[31]; health state preference values ("utilities") for EQ-5D profiles were based on time-trade-off valuations by members of the UK general public.[31] EQ-5D utilities range from -0.594 (extreme problems on all five domains) to 1 (perfect health) and indicate the value placed on different levels of health. The number of QALYs that each patient accrued following TKR was calculated as the area under the utility curve, with linear interpolation between utility measurements; those patients who died were assumed to remain at the last observed utility until death.

Healthcare resource use data (including knee-related outpatient, general practice and physiotherapy consultations, and theatre time, hospital days, complications and knee components used during the primary admission for TKR and during any knee-related readmissions or revisions) were collected prospectively for all KAT participants and valued at 2007-08 prices, as described previously.[30] Costs incurred after Year 1 were discounted at 3.5% per year based on current UK recommendations.[32]

The number of QALYs gained from TKR was calculated as the number of QALYs observed minus the number of QALYs expected without TKR. Since all KAT participants underwent TKR, assumptions were needed to estimate the costs and QALYs that would have been accrued if no TKR procedures had occurred in the five-year time horizon. We assumed that:

- Without TKR, patients would have remained at their baseline EQ-5D utility for five years or until death (if sooner). In practice, patients' symptoms and quality of life are likely to deteriorate due to worsening arthritis[17, 33] and increasing age.[34]
- The seven KAT participants who died before hospital discharge would have survived for five years at baseline utility without TKR but that TKR had no effect on the date of death for other patients. This assumption is highly conservative since those patients who die soon after joint replacement tend to be older[5, 35] and have comorbidities that could have led to death without TKR.[5]
- Patients would not have used any healthcare resources due to their knee problems if they had not undergone TKR. This assumption is highly conservative

since osteoarthritis patients will receive medical management without TKR and a recent Canadian case-control study suggested that TKR recipients accrued lower costs 6-18 months after the procedure than matched controls who had arthritis but no TKR.[33]

Since these assumptions are likely to underestimate the benefits and overestimate the additional costs of TKR, we evaluated the effect of relaxing these assumptions in sensitivity analyses.

The 7% of data on baseline characteristics, resource use and quality of life that were missing were imputed by multiple imputation using the ice command[36-38] (version 1.3.0) within Stata Version 11.0 (College Station, TX), thereby avoiding the bias and inefficiency associated with complete case analysis.[38-40] Treatment indicators and the covariates included in subsequent regression analyses were included in the imputation model to avoid bias.[38] Fifty imputed datasets were generated and results combined.

Regression models were used to estimate how the costs and QALYs gained from TKR vary with baseline characteristics and to predict outcomes for different patient groups without subdividing the trial population into small patient subgroups. Since costs and QALYs were highly skewed, generalised linear models (GLM) with gamma family distributions were used to predict total costs and the QALYs accrued with or without TKR; prior to regression, the number of QALYs accrued was subtracted from the maximum number of QALYs that could have been accrued over the five-year trial period to ensure that all QALY data were positive. We evaluated the effect of six baseline characteristics on costs and QALYs with/without TKR:

- Male sex;
- Age at time of operation;
- Baseline OKS (using the new, 0-48, scoring system[41]);
- American Society of Anesthesiologists (ASA) grade 3 (symptomatic illness with minimal restriction on daily life) rather than grades 1 (fit & healthy) or 2 (asymptomatic illness with no restriction on daily life);
- BMI (kg/m^2);
- Presence of arthritis in one knee rather than in both knees or generally.

Since the introduction of biologic therapies has changed management of rheumatoid arthritis and as rheumatoid arthritis patients and those with severe comorbidities are likely have very different costs and outcomes from most patients, 108 rheumatoid arthritis patients and 13 patients with ASA grade 4 were excluded from the analysis. One hundred 100 patients who were randomised to total vs unicompartmental knee replacement or died or withdrew from the trial before surgery were also excluded from the analysis, giving a final sample size of 2131.

All regression analyses were conducted in Stata Version 11. Bootstrapping was used to capture uncertainty around cost-effectiveness ratios and correlations between costs and QALYs with/without TKR; the regression models for costs and outcomes were run for each of 125 bootstrap samples drawn from each imputed KAT dataset and results combined using Rubin's rule.[39] Predicted costs and the predicted number of QALYs accrued with and without TKR in different patient groups were calculated from regression coefficients and used to estimate incremental cost-effectiveness ratios (ICERs). Bootstrap results were used to calculate cost-effectiveness acceptability curves (CEACs),[42] which plot the probability of treatment being cost-effective against the ceiling ratio (i.e. the maximum that society is willing or able to pay per QALY gained).

We also calculated the number of patients in England and Wales eligible for TKR under different rationing policies based on 61,651 patients undergoing primary TKR each year.[27] The proportion of patients eligible for TKR under different rationing criteria was based on analysis of an extract of patient-level Patient Reported Outcome Measures[1] (PROMs) data on admissions for knee replacement up to 31st December 2010, supplemented where necessary by the baseline characteristics from the KAT sample.

Results

Of the 2131 KAT participants who had osteoarthritis, were ASA grades 1-3 and underwent TKR as part of the trial, the mean baseline OKS was 18 (standard deviation, SD: 7.5), mean age 71 (SD: 8.0), mean BMI 30 (SD: 5.5), and 45% (956/2131) were male (Figure 1); further baseline characteristics of the trial population have been reported previously.[29]

Mean EQ-5D utility rose substantially within three months of TKR from 0.39 at baseline to 0.71 at one year, and declined gradually thereafter (Figure 1, Table 1). However, baseline utility and the quality of life gains associated with TKR varied between patient subgroups. In particular, women and patients with low OKS (i.e. poor knee function), higher ASA grade or obesity at baseline tended to have lower quality of life at all timepoints (Figure 1), although those in the lowest OKS quintile experienced significantly greater health gains from TKR than the top quintile ($p<0.001$; calculated using linear regression, combining imputed datasets using the mim command).

On average, each admission for primary TKR cost £6,363 (SD: £1,702). Readmissions, revision procedures and GP, outpatient, and physiotherapy consultations related to the study knee over the following five years cost a further £1,095 (SD: £3,579) per patient, giving a total cost of £7,458 (SD: £4,058) per patient. TKR was more costly in patients with low baseline OKS, but the greater QALY gains meant that TKR was better value for money in this patient group than in patients with moderate symptoms (Table 1). Subgroup analyses suggested that TKR cost less than £11,000/QALY gained across all OKS deciles: well below the £20,000-£30,000/QALY gained range that NICE currently consider good value for money.[11]

However, cost-effectiveness also varied substantially between patients within each OKS decile. We therefore used regression models to estimate the costs, QALY gains and cost-effectiveness of TKR in a wide range of patient subgroups while controlling for multiple baseline characteristics. Our results indicated that four factors have a significant effect on cost-effectiveness: age, sex, baseline OKS and ASA grade (Table 2). BMI and the presence of arthritis in other joints besides the study knee had no significant effect on either the costs or QALY gains associated with TKR ($p>0.05$).

Table 1: EQ-5D utility, costs and estimated QALYs for subgroups with different baseline OKS

OKS decile		**1 (worst)**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 (best)**	**All patients**
Baseline OKS range		**<9**	**9-11**	**12-13**	**14-15**	**16-17**	**18-19**	**20-21**	**22-24**	**25-27**	**>27**	**0-48**
No. KAT participants		204	213	186	232	193	224	195	256	194	234	**2131**
EQ-5D utility (SE)†	Baseline	0.03 (0.004)	0.14 (0.005)	0.21 (0.006)	0.25 (0.006)	0.36 (0.006)	0.46 (0.006)	0.55 (0.005)	0.57 (0.004)	0.61 (0.004)	0.67 (0.003)	**0.39 (0.002)**
	3 mths	0.54 (0.007)	0.58 (0.006)	0.64 (0.006)	0.66 (0.005)	0.71 (0.005)	0.71 (0.005)	0.70 (0.004)	0.74 (0.004)	0.75 (0.005)	0.77 (0.004)	**0.68 (0.002)**
	1 year	0.51 (0.007)	0.60 (0.007)	0.68 (0.006)	0.70 (0.006)	0.71 (0.006)	0.75 (0.005)	0.69 (0.006)	0.78 (0.004)	0.79 (0.005)	0.84 (0.004)	**0.71 (0.002)**
	2 year	0.49 (0.008)	0.54 (0.007)	0.66 (0.007)	0.67 (0.006)	0.68 (0.007)	0.73 (0.005)	0.66 (0.007)	0.76 (0.005)	0.78 (0.005)	0.81 (0.005)	**0.68 (0.002)**
	3 year	0.47 (0.008)	0.53 (0.007)	0.64 (0.007)	0.63 (0.006)	0.67 (0.007)	0.71 (0.006)	0.68 (0.007)	0.72 (0.005)	0.76 (0.006)	0.79 (0.006)	**0.66 (0.002)**
	4 year	0.43 (0.008)	0.49 (0.008)	0.61 (0.007)	0.62 (0.007)	0.65 (0.007)	0.68 (0.007)	0.64 (0.007)	0.70 (0.006)	0.71 (0.007)	0.75 (0.006)	**0.63 (0.002)**
	5 year	0.43 (0.008)	0.50 (0.008)	0.57 (0.008)	0.58 (0.007)	0.63 (0.007)	0.67 (0.007)	0.59 (0.007)	0.68 (0.006)	0.67 (0.008)	0.73 (0.007)	**0.61 (0.002)**
Total cost (SE)*		£8657 (£157)	£7715 (£81)	£7495 (£73)	£7081 (£63)	£7185 (£69)	£7567 (£82)	£7619 (£102)	£7128 (£61)	£7399 (£94)	£6917 (£67)	**£7458 (£28)**
QALYs with TKR (SE)*		2.17 (0.029)	2.48 (0.027)	2.94 (0.024)	2.99 (0.022)	3.13 (0.025)	3.30 (0.022)	3.09 (0.025)	3.40 (0.019)	3.50 (0.020)	3.67 (0.020)	**3.08 (0.025)**
QALYs without TKR (SE)*		0.15 (0.02)	0.62 (0.022)	0.94 (0.026)	1.14 (0.026)	1.63 (0.029)	2.04 (0.026)	2.39 (0.026)	2.55 (0.021)	2.78 (0.02)	3.02 (0.02)	**1.75 (0.031)**
QALY gain from TKR (SE)*		2.02 (0.032)	1.86 (0.031)	2.00 (0.033)	1.85 (0.031)	1.51 (0.034)	1.26 (0.030)	0.69 (0.027)	0.85 (0.023)	0.73 (0.02)	0.65 (0.02)	**1.33 (0.01)**
ICER*		£4,295	£4,153	£3,747	£3,836	£4,770	£6,007	£10,971	£8,391	£10,167	£10,697	**£5,623**

* Discounted at 3.5% per annum
† EQ-5D utility is measured on a scale from 1 (perfect health) to -0.594, where 0 is equivalent to death.
Abbreviations: ICER, incremental cost-effectiveness ratio; OKS, Oxford Knee Score (new scoring system running from zero [severe problems on all functions] to 48 [no problems])[41]; QALY, quality-adjusted life-year; SE, standard error around the mean; TKR, total knee replacement.

Table 2: Results of the regression analysis

Baseline characteristic	Coefficient (SE)		
	QALY loss with TKR†	QALY loss without TKR†	Total costs with TKR (£)
Male sex	0.056 (0.065)	-0.001 (0.054)	593 (181)*
Age at operation (years)	0.007 (0.003)*	0.002 (0.004)	-8 (12)
Pre-operative OKS	-0.040 (0.004)*	-0.087 (0.004)*	-52 (12)*
ASA grade 3	0.414 (0.067)*	0.227 (0.087)*	492 (208)*
Constant	1.712 (0.201)*	4.274 (0.325)*	8573 (881)*

* p<0.05
† QALY loss indicates the number of discounted QALYs that would have been accrued if patients had experienced an EQ-5D utility of 1 for five years (4.67 QALYs) minus the number of discounted QALYs that the patient actually experienced.
The incremental cost-effectiveness ratio (expressed as cost/QALY) for any given patient equals: (male x 593 - age x 8 - OKS x 52 + ASAgrade3 x 492 + 8573)/((male x -0.001 + age x 0.002 - OKS x 0.087 + ASAgrade3 x 0.227 + 4.274) - (male x 0.056 + age x 0.007 - OKS x 0.040 + ASAgrade3 x 0.414 + 1.712). Costs and QALYs were discounted at 3.5% per annum.
Abbreviations: ASA, American Society of Anesthesiologists classification (1=completely fit and healthy, 2=some illness but no effect on daily activity, 3=symptomatic illness with minimal restriction on life); OKS, Oxford Knee Score (new scoring system running from zero [severe problems on all functions] to 48 [no problems])[41]; QALY, quality-adjusted life-year; TKR, total knee replacement.

Figure 2 shows the cost-effectiveness of TKR for each multivariate group, using charts similar in design to widely-used cardiovascular risk tables.[43] The charts demonstrate that TKR is clearly cost-effective across a wide range of patient groups. For example, TKR costs less than £20,000/QALY gained for 71-year-old women with no symptomatic illness unless baseline OKS is above 40 (equivalent to having very minor problems on up to eight of the 12 activities mentioned in OKS or moderate-severe pain only on exertion). The threshold OKS at which TKR becomes cost-ineffective was lower for older patients, men, and those with symptomatic disease, but TKR remained cost-effective for all patients with OKS below 32 regardless of age, sex, or ASA grade. A simplified analysis controlling only for OKS and ASA grade suggested that TKR is cost-effective for all ASA grade 1 or 2 patients with baseline OKS <40, and all ASA grade 3 patients with OKS <35.

There was substantial uncertainty around the cost-effectiveness ratios for patients with very high baseline OKS, since only 37 trial participants had OKS above 35 at baseline. However, we estimate that there is a 99% probability that TKR is cost-effective (at a £20,000/QALY ceiling ratio) for the average ASA grade 1-2 patient with a baseline OKS of 35, and a 53% probability for ASA grade 3 (Figure 3).

Since each additional baseline characteristic increases the complexity of the eligibility criteria and may also raise ethical or equity concerns, we estimated the number of patients who would receive TKR under different eligibility criteria. This analysis suggested that restricting TKR to those patients for whom the operation was predicted to cost less than £20,000/QALY gained based on the simplified model (allowing only for ASA grade and OKS) would lead to 2000 fewer TKR procedures being conducted in England and Wales each year (3% fewer than the 61,651 procedures conducted in 2009/10[27]). If the decision rules were simplified further to provide TKR to all patients with baseline OKS <39, all but 1700 of the 61,651 patients currently receiving TKR in England and Wales in 2009/10[27] would be eligible. Allowing for other baseline characteristics had minimal effect on patient numbers or predicted costs or benefits, suggesting that decisions about suitability for TKR can be based on OKS alone.

Sensitivity analyses were conducted to assess the effect of extending the time horizon of our analysis up to 10 years, and of assuming that EQ-5D utility would have fallen by 0.5% per year without TKR,[34] that all knee-related ambulatory consultations would have occurred without TKR, and that the mean length of stay has fallen by 41% (5.9 days[27] vs 10.0) since the KAT operations took place in 1999-2003. Changing any of these assumptions produced lower ICERs than the base case analysis, confirming that the current analysis is highly conservative and suggesting that TKR may be cost-effective for ASA grade 1-2 patients with baseline OKS as high as 43. Excluding patients with incomplete data had no effect on conclusions. Although statistically significant, adding an age-squared term to the regression model had no effect on the conclusions, while a sensitivity analysis adding an OKS-squared term suggested that TKR may be cost-effective for all patients of ASA grade 1 or 2. Recoding BMI as a dummy variable indicating whether or not patients were obese (BMI ≥30) did not change the conclusions and obesity had no significant effect on costs or QALYs.

Discussion

We found TKR to cost £5,623 per QALY gained for the average patient (similar to estimates from previous studies[6-10]) and therefore represent very good value for money compared with the £20,000-£30,000/QALY threshold typically used in NHS decision-making.[11] Our study also confirms previous findings[7, 9, 17] that costs and benefits vary with age and comorbidity, but evaluates such characteristics, and pre-operative knee function, in multivariate analyses, which has not (to our knowledge) been done previously. We found pre-operative OKS to be the best predictor of post-operative costs, outcomes and cost-effectiveness.

Our analyses were based on patient-level data from a large trial with detailed, prospective collection of costs, utilities and baseline characteristics that permit extensive subgroup analyses. KAT used a pragmatic design, with broad inclusion criteria and no restrictions on peri- or post-operative care other than randomised aspects of component design[29, 30]; as result, the trial cohort is similar to the national PROMs cohort and costs and benefits are likely to be comparable to those in routine clinical practice. Furthermore, unlike some previous economic evaluations, our study took full account of uncertainty and included all knee-related NHS costs accrued in the first five years after TKR. The main limitation of our analysis was the small number of patients with high OKS. Since KAT recruited only 37 patients with OKS >35, further studies are required to evaluate TKR in this patient subgroup. Analyses were also based on *post hoc* comparisons between outcomes before and after TKR, rather than between randomly-assigned treatment groups. As a result, our study does not provide unbiased estimates of the QALY gains from TKR, and regression towards the mean may have caused our study to overestimate the quality of life improvement attributable to TKR and/or the effect of pre-operative OKS on QALY gains.

We made several highly conservative assumptions: in particular, assuming that patients would have accrued no knee-related costs and would have remained at baseline utility without TKR, whereas previous studies have found that patients accrue substantial costs and show clinical worsening without TKR.[33] We also assumed that those patients who died before hospital discharge would have survived for five years if they had not had TKR; in reality, those patients dying soon after TKR tend to be older[5, 35] and frailer[5] pre-operatively and some studies suggest that patients undergoing hip replacement have higher long-term survival than the general population[44, 45] (although this may be due to patient selection[35, 44]). When these assumptions were relaxed, TKR was cost-effective for ASA grade 1-2 patients with baseline OKS <44. The costs and benefits of TKR are likely to vary between centres and over time due to variations in patient demographics, component prices, length of stay, and operation time; sensitivity analyses demonstrated that TKR may have become more cost-effective since the KAT procedures were conducted in 1999-2003 due to reductions in length of stay.

Our analyses show that if TKR were to be rationed based on cost-effectiveness, OKS would be a reasonable tool to use to set the threshold, although there may, of course, be practical difficulties with using a patient-reported measure to determine treatment eligibility: particularly if patients know how their questionnaire responses will be used or if test-retest reliability is low in this setting. The decision to operate must also take into consideration other factors, such as radiographic findings and patient choice. Based on regression and subgroup analyses, we can be confident that TKR costs less than £20,000/QALY for all ASA grade 1-2 patients with baseline OKS <40 and for ASA grade 3 patients with OKS <35. Using these thresholds to determine who received treatment would avoid around 2000 TKR procedures per year in England and Wales, saving around £11.8 million per year. However, the higher thresholds suggested by sensitivity analyses using less conservative assumptions suggest that TKR is cost-effective for all but 100 patients per year, which is unlikely to achieve sufficient savings to warrant rationing of TKR. Although the cost-effectiveness of knee replacement was also influenced by gender and age, taking account of these factors as well as OKS and ASA grade would increase the complexity of eligibility criteria, reduce equality of access to healthcare and have minimal effect on NHS budgets.

The results also demonstrate that the thresholds proposed by some PCTs[18-24] are inappropriate and would deny a highly cost-effective treatment to thousands of patients with severe arthritis. The current situation also introduces a postcode lottery with different PCTs using different eligibility criteria. We estimate that limiting knee replacement to patients with OKS ≤26 would prevent more than 10,000 people from receiving TKR. This would be inequitable as TKR costs £10,697 per QALY gained for this group, whereas NICE routinely recommend treatments with ICERs in the region of £20,000-£30,000/QALY gained[11, 46, 47] and are willing to pay substantially more for end of life care.[48] Furthermore, the finding that TKR and subsequent monitoring is more costly for patients with low OKS suggests that delaying TKR until symptoms have deteriorated may be a false economy. Although some PCTs have considered restricting TKR further for obese patients,[18, 21, 25, 49] we found BMI to have no significant effect on costs (p=0.442), QALY gains (p=0.098) or the incidence of peri- or post-operative complications (p>0.26). Although BMI remained non-significant even when ASA grade was omitted from regression analyses, it is difficult to isolate the effect of obesity from other correlated variables (e.g. comorbidity); as result, further research on obesity may be warranted: particularly since a previous study observed a significant correlation between BMI and costs.[13]

Eligibility criteria for rheumatoid arthritis patients and patients with ASA grade 4 remain unclear, although ASA grade 4 patients would normally be considered unfit for surgery, and the decision to operate on such patients would be based on a case-by-case consideration of whether the benefits outweigh the risks. While our study focused on the costs and benefits of TKR, patients with high baseline OKS often undergo unicompartmental knee replacement; further research is needed to evaluate how the cost-effectiveness of unicompartmental replacement varies with OKS.

In conclusion, TKR is highly cost-effective for the vast majority of patients who currently undergo this procedure in the UK. Although costs and health benefits vary with baseline OKS, the rationing thresholds proposed by some PCTs[18-24] are not supported by evidence on health outcomes or cost-effectiveness.

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Competing interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organisation for the submitted work with the exception of those declared in the funding statement. AG, RF and GM declare that they have no financial relationships with any organisations that might have an interest in the submitted work in the previous three years and no other relationships or activities that could appear to have influenced the submitted work. DM receives royalties paid to him by Biomet and HD has undertaken consultancy work for Pfizer on drugs for rheumatoid arthritis but both declare that they have no other financial relationships with any organisations that might have an interest in the submitted work in the previous three years and no other relationships or activities that could appear to have influenced the submitted work.

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Contributorship statement

HD, AG and DM conceived and developed the principles and methods underpinning the current analysis. GM was involved in primary data collection and database management, while HD conducted the analysis under AG's supervision and guidance from DM, GM and RF. HD drafted the manuscript with input from all other authors; all authors have approved the final manuscript and were involved in the interpretation of results. The KAT trial was conceived, designed and run by the KAT trial group, which comprised Suzanne Breeman, Marion Campbell, HD, Jackie Ellington, Nick Fiddian, RF, Adrian Grant, AG, Linda Johnston, GM, Richard Morris and DM.

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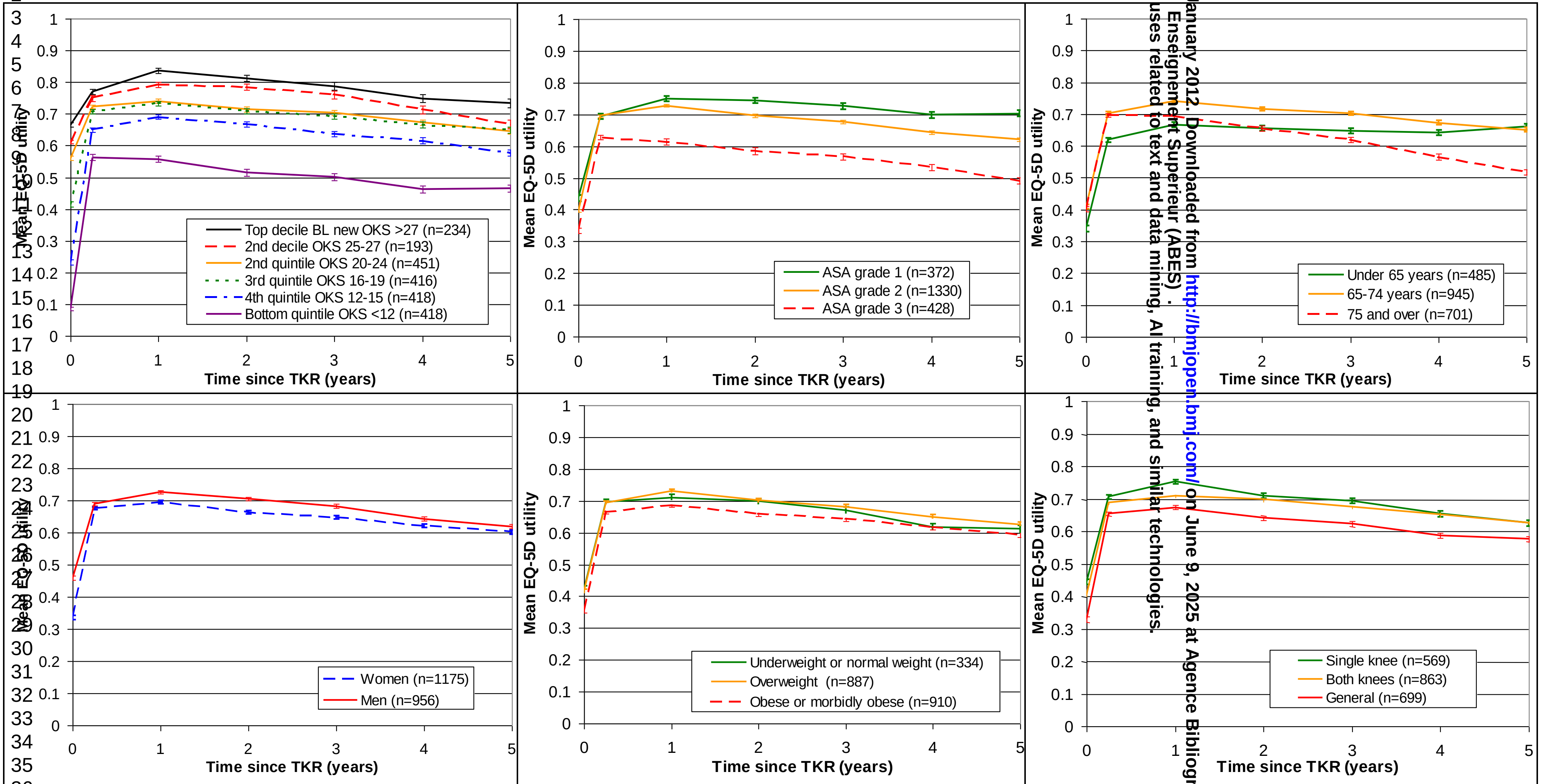
Figure 1: EQ-5D utility by subgroup

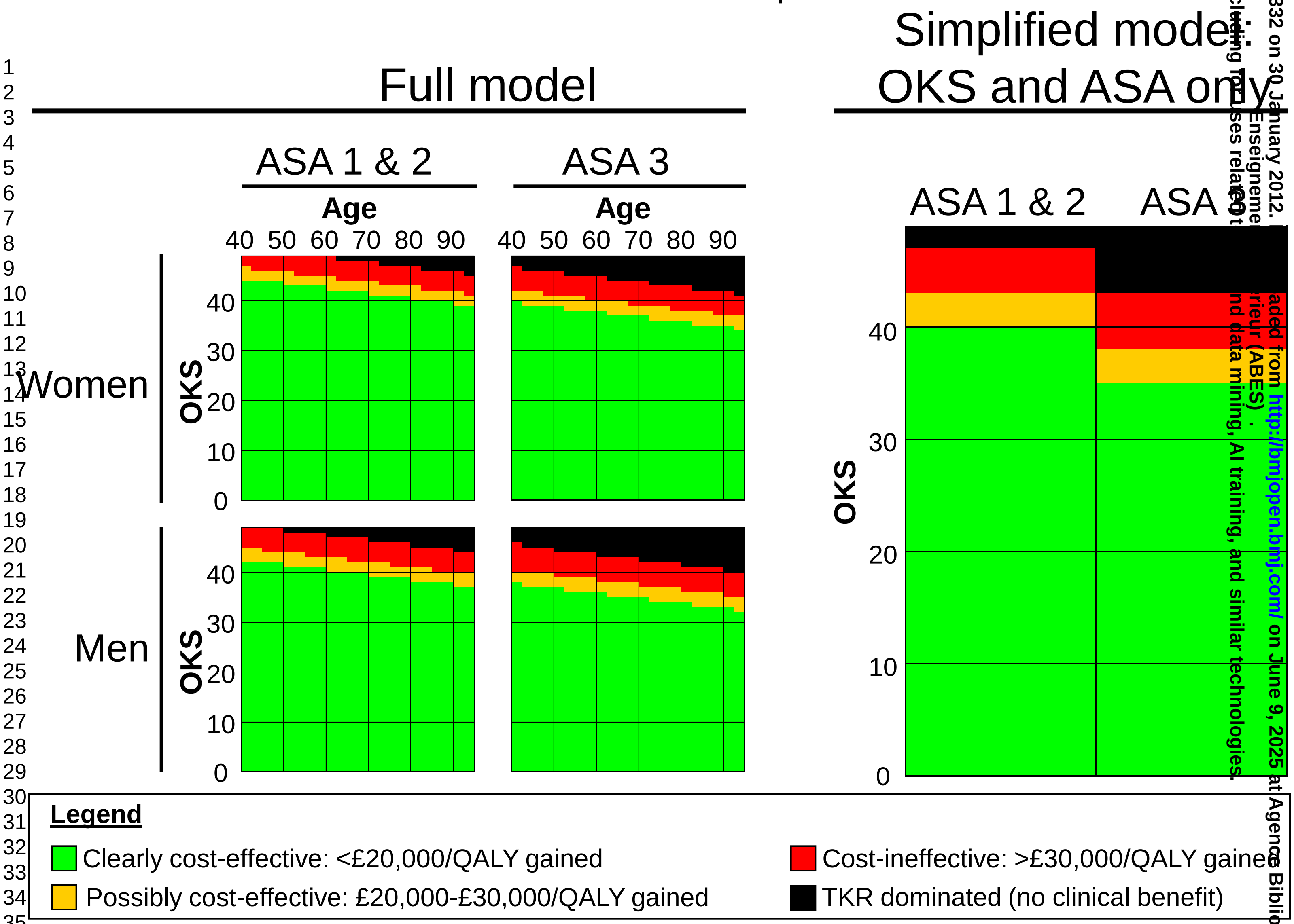
Abbreviations: ASA, American Society of Anesthesiologists classification (1=completely fit and healthy, 2=some illness but no effect on daily activity, 3=symptomatic illness with minimal restriction on life); OKS, Oxford Knee Score (new scoring system running from zero [severe problems on all functions] to 48 [no problems])[41]; TKR, total knee replacement.
Error bars show 95% confidence intervals. EQ-5D utility is measured on a scale from 1 (perfect health) to -0.594, where 0 is equivalent to death.

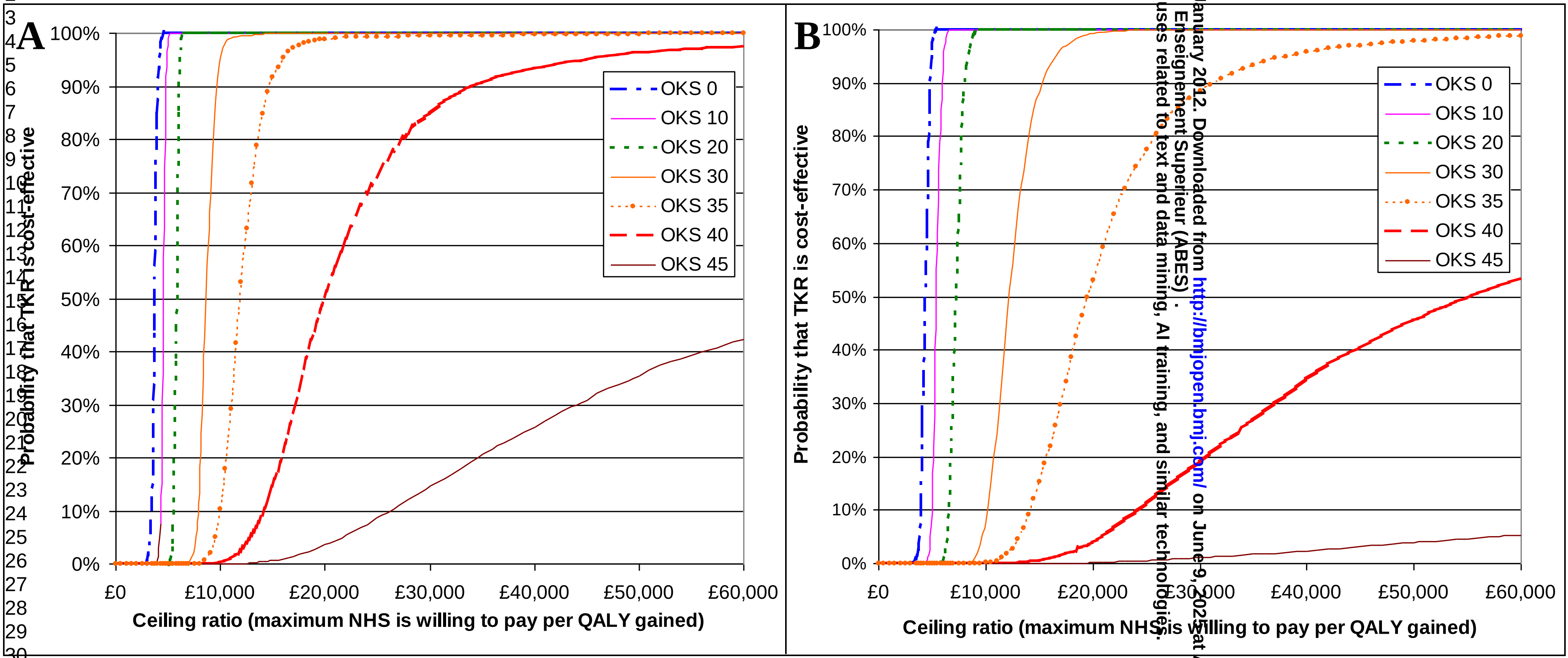
Figure 2: Cost-effectiveness prediction charts estimated based on predictions of regression models.

Abbreviations: ASA, American Society of Anesthesiologists classification (1=completely fit and healthy, 2=some illness but no effect on daily activity, 3=symptomatic illness with minimal restriction on life); OKS, Oxford Knee Score (new scoring system running from zero [severe problems on all functions] to 48 [no problems])[41]; QALY, quality-adjusted life-year; TKR, total knee replacement.

Figure 3: Cost-effectiveness acceptability curves for different patient subgroups at different baseline Oxford Knee Scores (OKS). A: American Society of Anesthesiologists (ASA) grade 1 and 2 patients. B: ASA grade 3 patients.


Mean EQ-5D utility
Top decile BL new OKS >27 (n=234)
2nd decile OKS 25-27 (n=193)
2nd quintile OKS 20-24 (n=451)
3rd quintile OKS 16-19 (n=416)
4th quintile OKS 12-15 (n=418)
Bottom quintile OKS <12 (n=418)
Time since TKR (years)
Mean EQ-5D utility
ASA grade 1 (n=372)
ASA grade 2 (n=1330)
ASA grade 3 (n=428)
Time since TKR (years)
Mean EQ-5D utility
Under 65 years (n=485)
65-74 years (n=945)
75 and over (n=701)
Time since TKR (years)
Mean EQ-5D utility
Women (n=1175)
Men (n=956)
Time since TKR (years)
Mean EQ-5D utility
Underweight or normal weight (n=334)
Overweight (n=887)
Obese or morbidly obese (n=910)
Time since TKR (years)
Mean EQ-5D utility
Single knee (n=569)
Both knees (n=863)
General (n=699)
Time since TKR (years)


Full model
Simplified model: OKS and ASA only
ASA 1 & 2
ASA 3
Age
40 50 60 70 80 90
OKS
0
10
20
30
40
Women
Men
ASA 1 & 2
ASA 3
Legend
Clearly cost-effective: <£20,000/QALY gained
Possibly cost-effective: £20,000-£30,000/QALY gained
Cost-ineffective: >£30,000/QALY gained
TKR dominated (no clinical benefit)


A
B
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Probability that TKR is cost-effective
£0
£10,000
£20,000
£30,000
£40,000
£50,000
£60,000
Ceiling ratio (maximum NHS is willing to pay per QALY gained)
OKS 0
OKS 10
OKS 20
OKS 30
OKS 35
OKS 40
OKS 45

Rationing of total knee replacement: A cost-effectiveness analysis on a large trial dataset

Running header:
Rationing of total knee replacement

Key words:
Economic evaluation; total knee replacement; heterogeneity; subgroup analysis; randomised controlled trial.

Authors:
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Collaborator: The KAT Trial Group

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Word count: 3,691 (main text of introduction, methods, results and discussion)
Number of figures: 3
Number of tables: 2

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Ethics: The KAT trial was approved by the Multi Centre Research Ethics Committee for Scotland in November 1998 (research protocol MREC/98/0/100) and was approved by the Local Research Ethics Committees in each study centre recruiting trial participants. Further details are available on request.

Data sharing statement: No additional data available.

Protocol: Available at http://www.hta.ac.uk/protocols/199500100001.pdf.

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Abstract

Objectives: Many UK primary care trusts (PCTs) have recently introduced eligibility criteria restricting total knee replacement (TKR) to patients with low pre-operative Oxford Knee Scores (OKS) to cut expenditure. We evaluate these criteria by assessing the cost-effectiveness of TKR compared with no knee replacement for patients with different baseline characteristics from an NHS perspective.

Design: The cost-effectiveness of TKR in different patient subgroups was assessed using regression analyses of patient-level data from the Knee Arthroplasty Trial (KAT), a large, pragmatic, randomised trial comparing knee prostheses.

Setting: 34 UK hospitals.

Participants: 2131 osteoarthritis patients undergoing TKR.

Interventions and outcome measures: Costs and quality-adjusted life-years (QALYs) observed in the KAT trial within five years of TKR were compared with conservative assumptions about the costs and outcomes that would have been accrued had TKR not been performed.

Results: On average, primary TKR and five years of subsequent care cost £7,458 per patient (standard deviation, SD: £4,058), and patients gained an average of 1.33 (SD: 1.43) QALYs. As result, TKR cost £5,623 per QALY gained. Although costs and health outcomes varied with age and sex, TKR cost less than £20,000 per QALY gained for patients with ASA grade 1-2 who had baseline OKS <40, and for ASA grade 3 patients with OKS <35, even with highly conservative assumptions about costs and outcomes without TKR. Body mass index had no significant effect on costs or outcomes. Restricting TKR to patients with pre-operative OKS <27 would inappropriately deny a highly cost-effective treatment to >10,000 patients annually.

Conclusions: TKR is highly cost-effective for most current patients if the NHS is willing to pay £20,000-£30,000 per QALY gained. At least 97% of TKR patients in England have more severe symptoms than the thresholds we have identified, suggesting further rationing by OKS is probably unjustified.

Trial registration: ISRCTN 45837371

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Article summary

Article focus

- We assess the cost-effectiveness of total knee replacement (TKR) compared with no knee replacement for patients with different baseline characteristics from a National Health Service (NHS) perspective.
- In particular, we assess the appropriateness of eligibility criteria recently introduced by many UK primary care trusts (PCTs), which restrict TKR to patients with low (i.e. poor) pre-operative Oxford Knee Scores (OKS) to cut expenditure.

Key messages

- We find TKR to be highly cost-effective, costing £5,623 per quality-adjusted life-year (QALY) gained for the average patient.
- TKR costs less than £20,000 per QALY gained for healthy patients with OKS of <40, or <35 for patients who have other conditions restricting their daily activities.
- We find no evidence to support the criteria for restricting access to TKR that have been proposed by some PCTs and calculate that restricting TKR to those patients with pre-operative OKS of 26 or less would deny a highly cost-effective treatment to more than 10,000 patients per year.

Strengths and limitations of this study

- This is the first study assessing how the cost-effectiveness of TKR varies with OKS and the first assessing the clinical/economic implications of the newly-introduced rationing criteria.
- Analyses are based on patient-level data from a large pragmatic trial with detailed, prospective collection of utilities, baseline characteristics and all major knee-related NHS resource use, including revisions and ambulatory care.
- Our study makes several highly conservative assumptions: in particular, assuming that patients would have accrued no knee-related costs and remained at baseline utility without TKR. Furthermore, the KAT sample included only 37 patients with pre-operative OKS >35. As result, TKR may be also cost-effective for some patients with OKS above 39.

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Introduction

Total knee replacement (TKR) is a highly effective treatment for patients with bone-on-bone osteoarthritis and significant knee symptoms, producing substantial reductions in symptoms (particularly pain)[1] and lasting for at least 15 years in 83-94% of cases.[2] However, about 18% of patients consider the outcomes of their surgery to be only fair or poor,[1] and a small proportion experience complications.[3-5] Previous economic evaluations have found TKR to be highly cost-effective, with a cost-effectiveness ratio between €1,276 and $18,300 per quality-adjusted life-year (QALY) gained for the average patient[6-10]: well below the £20,000-£30,000 per QALY range that the National Institute for Health and Clinical Excellence (NICE) considers cost-effective.[11] However, studies suggest that the costs and benefits of TKR vary between patient subgroups, with TKR being more cost-effective in younger patients,[9] those attending high-volume centres[7] and those deemed low-risk based on age, comorbidities, and poverty criteria.[7] There is also evidence that older[12] and obese[13] patients have higher medical costs, although other studies suggest that knee replacement is also cost-effective in nonagenarians[14] and draw conflicting conclusions on how benefits vary with body mass index (BMI).[15-17]

In the current economic environment there is great pressure to reduce NHS expenditure and numerous Primary Care Trusts (PCTs) have proposed cutting costs by limiting access to joint replacement[18-25] or classifying these procedures as being of limited value.[24-26] Since around 60,000 primary TKR procedures are conducted in England and Wales each year,[27] savings could be made with little loss of patient welfare *if* it were possible to reliably predict which patients obtain little/no benefit from TKR based on explicit, evidence-based criteria. Although the widely-used Oxford Knee Score (OKS) was developed to assess outcomes of knee replacement in trial populations,[28] several PCTs have set maximum OKS thresholds (ranging from 18 to 32), above which patients are ineligible for TKR.[18-24] However, we are not aware of any clinical or cost-effectiveness justification for these thresholds. Furthermore, many patients with higher OKS have significant symptoms or limitations to daily activities that could be improved by surgery. If rationing policies are to be adopted, cost-effectiveness analysis offers the only fair basis for designing them, since it ensures that NHS resources are allocated to maximise the health gained from available resources. As treatments are generally considered cost-effective if they cost less than £20,000-£30,000 per quality-adjusted life-year (QALY) gained,[11] restricting TKR to those patients for whom the procedure

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costs less than £20,000-£30,000 per QALY gained would be a reasonable approach, potentially realising savings that could be invested in other treatments giving greater health gains. However, we are aware of no published evidence assessing how the cost-effectiveness of TKR varies with OKS.

We therefore use data from the Knee Arthroplasty Trial (KAT)[29, 30] to assess the appropriateness of rationing knee replacement by OKS, age, BMI, and clinical characteristics, by calculating the cost-effectiveness of TKR in different patient subgroups. In contrast to previous studies evaluating the cost-effectiveness of TKR that relied upon data from small cohorts with short follow-up,[6-10, 14] the KAT trial dataset provides detailed, prospective individual patient data on baseline characteristics, treatments, complications, costs, and quality of life, and now has more than five years' follow-up on 2352 patients.

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Methods

We assessed the cost-effectiveness of primary TKR compared with no knee replacement for patients with different baseline characteristics. Our analysis took a National Health Service (NHS) perspective and excluded personal and social services from the analysis, although TKR is likely to delay admission to residential care,[14] reduce personal care costs and help recipients to continue paid employment. A cost-utility analysis was conducted, which assessed cost-effectiveness in terms of cost per quality-adjusted life-year (QALY) gained to capture the quality of life gains associated with TKR.

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Data on costs and quality of life following TKR were taken from the KAT trial (ISRCTN 45837371): a pragmatic, partial-factorial, unblinded randomised controlled trial (RCT) in which 2352 participants attending 34 UK centres were randomly allocated to undergo TKR with/without a metal-backed tibial component, with/without patellar resurfacing, and/or with/without a mobile bearing.[29, 30] Five-year trial results demonstrated that patients experience substantial improvements in quality of life and functional status following knee replacement that are maintained out to five years[30]; further follow-up is ongoing. Our analysis took a five-year time horizon in line with the results published to date[30]; costs and health benefits occurring more than five years after primary TKR were conservatively excluded.

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KAT participants completed the Oxford Knee Score (OKS) and EQ-5D questionnaires immediately before and three months after TKR and annually thereafter. The OKS is a validated 12-item questionnaire for assessing health status and outcomes in relation to knee replacement that gives an unweighted total score ranging from 0 (severe problems on all items) to 48 (no problems on any item).[28] The EQ-5D is a generic health state preference measure[31]; health state preference values ("utilities") for EQ-5D profiles were based on time-trade-off valuations by members of the UK general public.[31] EQ-5D utilities range from -0.594 (extreme problems on all five domains) to 1 (perfect health) and indicate the value placed on different levels of health. The number of QALYs that each patient accrued following TKR was calculated as the area under the utility curve, with linear interpolation between utility measurements; those patients who died were assumed to remain at the last observed utility until death.

Healthcare resource use data (including knee-related outpatient, general practice and physiotherapy consultations, and theatre time, hospital days, complications and knee components used during the primary admission for TKR and during any knee-related readmissions or revisions) were collected prospectively for all KAT participants and valued at 2007-08 prices, as described previously.[30] Costs incurred after Year 1 were discounted at 3.5% per year based on current UK recommendations.[32]

The number of QALYs gained from TKR was calculated as the number of QALYs observed minus the number of QALYs expected without TKR. Since all KAT participants underwent TKR, assumptions were needed to estimate the costs and QALYs that would have been accrued if no TKR procedures had occurred in the five-year time horizon. We assumed that:

- Without TKR, patients would have remained at their baseline EQ-5D utility for five years or until death (if sooner). In practice, patients' symptoms and quality of life are likely to deteriorate due to worsening arthritis[17, 33] and increasing age.[34]
- The seven KAT participants who died before hospital discharge would have survived for five years at baseline utility without TKR but that TKR had no effect on the date of death for other patients. This assumption is highly conservative since those patients who die soon after joint replacement tend to be older[5, 35] and have comorbidities that could have led to death without TKR.[5]
- Patients would not have used any healthcare resources due to their knee problems if they had not undergone TKR. This assumption is highly conservative

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since osteoarthritis patients will receive medical management without TKR and a recent Canadian case-control study suggested that TKR recipients accrued lower costs 6-18 months after the procedure than matched controls who had arthritis but no TKR.[33]

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Since these assumptions are likely to underestimate the benefits and overestimate the additional costs of TKR, we evaluated the effect of relaxing these assumptions in sensitivity analyses.

The 7% of data on baseline characteristics, resource use and quality of life that were missing were imputed by multiple imputation using the ice command[36-38] (version 1.3.0) within Stata Version 11.0 (College Station, TX), thereby avoiding the bias and inefficiency associated with complete case analysis.[38-40] Treatment indicators and the covariates included in subsequent regression analyses were included in the imputation model to avoid bias.[38] Fifty imputed datasets were generated and results combined.

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Regression models were used to estimate how the costs and QALYs gained from TKR vary with baseline characteristics and to predict outcomes for different patient groups without subdividing the trial population into small patient subgroups. Since costs and QALYs were highly skewed, generalised linear models (GLM) with gamma family distributions were used to predict total costs and the QALYs accrued with or without TKR; prior to regression, the number of QALYs accrued was subtracted from the maximum number of QALYs that could have been accrued over the five-year trial period to ensure that all QALY data were positive. We evaluated the effect of six baseline characteristics on costs and QALYs with/without TKR:

- Male sex;
- Age at time of operation;
- Baseline OKS (using the new, 0-48, scoring system[41]);
- American Society of Anesthesiologists (ASA) grade 3 (symptomatic illness with minimal restriction on daily life) rather than grades 1 (fit & healthy) or 2 (asymptomatic illness with no restriction on daily life);
- BMI (kg/m^2);
- Presence of arthritis in one knee rather than in both knees or generally.

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Since the introduction of biologic therapies has changed management of rheumatoid arthritis and as rheumatoid arthritis patients and those with severe comorbidities are likely have very different costs and outcomes from most patients, 108 rheumatoid arthritis patients and 13 patients with ASA grade 4 were excluded from the analysis. One hundred 100 patients who were randomised to total vs unicompartmental knee replacement or died or withdrew from the trial before surgery were also excluded from the analysis, giving a final sample size of 2131.

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All regression analyses were conducted in Stata Version 11. Bootstrapping was used to capture uncertainty around cost-effectiveness ratios and correlations between costs and QALYs with/without TKR; the regression models for costs and outcomes were run for each of 125 bootstrap samples drawn from each imputed KAT dataset and results combined using Rubin's rule.[39] Predicted costs and the predicted number of QALYs accrued with and without TKR in different patient groups were calculated from regression coefficients and used to estimate incremental cost-effectiveness ratios (ICERs). Bootstrap results were used to calculate cost-effectiveness acceptability curves (CEACs),[42] which plot the probability of treatment being cost-effective against the ceiling ratio (i.e. the maximum that society is willing or able to pay per QALY gained).

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We also calculated the number of patients in England and Wales eligible for TKR under different rationing policies based on 61,651 patients undergoing primary TKR each year.[27] The proportion of patients eligible for TKR under different rationing criteria was based on analysis of an extract of patient-level Patient Reported Outcome Measures[1] (PROMs) data on admissions for knee replacement up to 31st December 2010, supplemented where necessary by the baseline characteristics from the KAT sample.

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Results

Of the 2131 KAT participants who had osteoarthritis, were ASA grades 1-3 and underwent TKR as part of the trial, the mean baseline OKS was 18 (standard deviation, SD: 7.5), mean age 71 (SD: 8.0), mean BMI 30 (SD: 5.5), and 45% (956/2131) were male (Figure 1); further baseline characteristics of the trial population have been reported previously.[29]

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Mean EQ-5D utility rose substantially within three months of TKR from 0.39 at baseline to 0.71 at one year, and declined gradually thereafter (Figure 1, Table 1). However, baseline utility and the quality of life gains associated with TKR varied between patient subgroups. In particular, women and patients with low OKS (i.e. poor knee function), higher ASA grade or obesity at baseline tended to have lower quality of life at all timepoints (Figure 1), although those in the lowest OKS quintile experienced significantly greater health gains from TKR than the top quintile ($p<0.001$; calculated using linear regression, combining imputed datasets using the mim command).

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On average, each admission for primary TKR cost £6,363 (SD: £1,702). Readmissions, revision procedures and GP, outpatient, and physiotherapy consultations related to the study knee over the following five years cost a further £1,095 (SD: £3,579) per patient, giving a total cost of £7,458 (SD: £4,058) per patient. TKR was more costly in patients with low baseline OKS, but the greater QALY gains meant that TKR was better value for money in this patient group than in patients with moderate symptoms (Table 1). Subgroup analyses suggested that TKR cost less than £11,000/QALY gained across all OKS deciles: well below the £20,000-£30,000/QALY gained range that NICE currently consider good value for money.[11]

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However, cost-effectiveness also varied substantially between patients within each OKS decile. We therefore used regression models to estimate the costs, QALY gains and cost-effectiveness of TKR in a wide range of patient subgroups while controlling for multiple baseline characteristics. Our results indicated that four factors have a significant effect on cost-effectiveness: age, sex, baseline OKS and ASA grade (Table 2). BMI and the presence of arthritis in other joints besides the study knee had no significant effect on either the costs or QALY gains associated with TKR ($p>0.05$).

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Table 1: EQ-5D utility, costs and estimated QALYs for subgroups with different baseline OKS

OKS decile		1 (worst)	2	3	4	5	6	7	8	9	10 (best)	All patients
Baseline OKS range		**<9**	**9-11**	**12-13**	**14-15**	**16-17**	**18-19**	**20-21**	**22-24**	**25-27**	**>27**	**0-48**
No. KAT participants		204	213	186	232	193	224	195	256	194	234	**2131**
EQ-5D utility (SE)†	Baseline	0.03 (0.004)	0.14 (0.005)	0.21 (0.006)	0.25 (0.006)	0.36 (0.006)	0.46 (0.006)	0.55 (0.005)	0.57 (0.004)	0.61 (0.004)	0.67 (0.003)	**0.39 (0.002)**
	3 mths	0.54 (0.007)	0.58 (0.006)	0.64 (0.006)	0.66 (0.005)	0.71 (0.005)	0.71 (0.005)	0.70 (0.004)	0.74 (0.004)	0.75 (0.005)	0.77 (0.004)	**0.68 (0.002)**
	1 year	0.51 (0.007)	0.60 (0.007)	0.68 (0.006)	0.70 (0.006)	0.71 (0.006)	0.75 (0.005)	0.69 (0.006)	0.78 (0.004)	0.79 (0.005)	0.84 (0.004)	**0.71 (0.002)**
	2 year	0.49 (0.008)	0.54 (0.007)	0.66 (0.007)	0.67 (0.006)	0.68 (0.007)	0.73 (0.005)	0.66 (0.007)	0.76 (0.005)	0.78 (0.005)	0.81 (0.005)	**0.68 (0.002)**
	3 year	0.47 (0.008)	0.53 (0.007)	0.64 (0.007)	0.63 (0.006)	0.67 (0.007)	0.71 (0.006)	0.68 (0.007)	0.72 (0.005)	0.76 (0.006)	0.79 (0.006)	**0.66 (0.002)**
	4 year	0.43 (0.008)	0.49 (0.008)	0.61 (0.007)	0.62 (0.007)	0.65 (0.007)	0.68 (0.007)	0.64 (0.007)	0.70 (0.006)	0.71 (0.007)	0.75 (0.006)	**0.63 (0.002)**
	5 year	0.43 (0.008)	0.50 (0.008)	0.57 (0.008)	0.58 (0.007)	0.63 (0.007)	0.67 (0.007)	0.59 (0.007)	0.68 (0.006)	0.67 (0.008)	0.73 (0.007)	**0.61 (0.002)**
Total cost (SE)*		£8657 (£157)	£7715 (£81)	£7495 (£73)	£7081 (£63)	£7185 (£69)	£7567 (£82)	£7619 (£102)	£7128 (£61)	£7399 (£94)	£6917 (£67)	**£7458 (£28)**
QALYs with TKR (SE)*		2.17 (0.029)	2.48 (0.027)	2.94 (0.024)	2.99 (0.022)	3.13 (0.025)	3.30 (0.022)	3.09 (0.025)	3.40 (0.019)	3.50 (0.020)	3.67 (0.020)	**3.08 (0.025)**
QALYs without TKR (SE)*		0.15 (0.02)	0.62 (0.022)	0.94 (0.026)	1.14 (0.026)	1.63 (0.029)	2.04 (0.026)	2.39 (0.026)	2.55 (0.021)	2.78 (0.02)	3.02 (0.02)	**1.75 (0.031)**
QALY gain from TKR (SE)*		2.02 (0.032)	1.86 (0.031)	2.00 (0.033)	1.85 (0.031)	1.51 (0.034)	1.26 (0.030)	0.69 (0.027)	0.85 (0.023)	0.73 (0.02)	0.65 (0.02)	**1.33 (0.01)**
ICER*		£4,295	£4,153	£3,747	£3,836	£4,770	£6,007	£10,971	£8,391	£10,167	£10,697	**£5,623**

* Discounted at 3.5% per annum
† EQ-5D utility is measured on a scale from 1 (perfect health) to -0.594, where 0 is equivalent to death.
Abbreviations: ICER, incremental cost-effectiveness ratio; OKS, Oxford Knee Score (new scoring system running from zero [severe problems on all functions] to 48 [no problems])[41]; QALY, quality-adjusted life-year; SE, standard error around the mean; TKR, total knee replacement.

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Table 2: Results of the regression analysis

Baseline characteristic	Coefficient (SE)		
	QALY loss with TKR†	QALY loss without TKR†	Total costs with TKR (£)
Male sex	0.056 (0.065)	-0.001 (0.054)	593 (181)*
Age at operation (years)	0.007 (0.003)*	0.002 (0.004)	-8 (12)
Pre-operative OKS	-0.040 (0.004)*	-0.087 (0.004)*	-52 (12)*
ASA grade 3	0.414 (0.067)*	0.227 (0.087)*	492 (208)*
Constant	1.712 (0.201)*	4.274 (0.325)*	8573 (881)*

* p<0.05
† QALY loss indicates the number of discounted QALYs that would have been accrued if patients had experienced an EQ-5D utility of 1 for five years (4.67 QALYs) minus the number of discounted QALYs that the patient actually experienced.
The incremental cost-effectiveness ratio (expressed as cost/QALY) for any given patient equals: (male x 593 - age x 8 - OKS x 52 + ASAgrade3 x 492 + 8573)/((male x -0.001 + age x 0.002 - OKS x 0.087 + ASAgrade3 x 0.227 + 4.274) - (male x 0.056 + age x 0.007 - OKS x 0.040 + ASAgrade3 x 0.414 + 1.712). Costs and QALYs were discounted at 3.5% per annum.
Abbreviations: ASA, American Society of Anesthesiologists classification (1=completely fit and healthy, 2=some illness but no effect on daily activity, 3=symptomatic illness with minimal restriction on life); OKS, Oxford Knee Score (new scoring system running from zero [severe problems on all functions] to 48 [no problems])[41]; QALY, quality-adjusted life-year; TKR, total knee replacement.

Figure 2 shows the cost-effectiveness of TKR for each multivariate group, using charts similar in design to widely-used cardiovascular risk tables.[43] The charts demonstrate that TKR is clearly cost-effective across a wide range of patient groups. For example, TKR costs less than £20,000/QALY gained for 71-year-old women with no symptomatic illness unless baseline OKS is above 40 (equivalent to having very minor problems on up to eight of the 12 activities mentioned in OKS or moderate-severe pain only on exertion). The threshold OKS at which TKR becomes cost-ineffective was lower for older patients, men, and those with symptomatic disease, but TKR remained cost-effective for all patients with OKS below 32 regardless of age, sex, or ASA grade. A simplified analysis controlling only for OKS and ASA grade suggested that TKR is cost-effective for all ASA grade 1 or 2 patients with baseline OKS ≤40, and all ASA grade 3 patients with OKS ≤35.

There was substantial uncertainty around the cost-effectiveness ratios for patients with very high baseline OKS, since only 37 trial participants had OKS above 35 at baseline. However, we estimate that there is a 99% probability that TKR is cost-effective (at a £20,000/QALY ceiling ratio) for the average ASA grade 1-2 patient with a baseline OKS of 35, and a 53% probability for ASA grade 3 (Figure 3).

Since each additional baseline characteristic increases the complexity of the eligibility criteria and may also raise ethical or equity concerns, we estimated the number of patients who would receive TKR under different eligibility criteria. This analysis suggested that restricting TKR to those patients for whom the operation was

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predicted to cost less than £20,000/QALY gained based on the simplified model (allowing only for ASA grade and OKS) would lead to 2000 fewer TKR procedures being conducted in England and Wales each year (3% fewer than the 61,651 procedures conducted in 2009/10[27]). If the decision rules were simplified further to provide TKR to all patients with baseline OKS <39, all but 1700 of the 61,651 patients currently receiving TKR in England and Wales in 2009/10[27] would be eligible. Allowing for other baseline characteristics had minimal effect on patient numbers or predicted costs or benefits, suggesting that decisions about suitability for TKR can be based on OKS alone.

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Sensitivity analyses were conducted to assess the effect of extending the time horizon of our analysis up to 10 years, and of assuming that EQ-5D utility would have fallen by 0.5% per year without TKR,[34] that all knee-related ambulatory consultations would have occurred without TKR, and that the mean length of stay has fallen by 41% (5.9 days[27] vs 10.0) since the KAT operations took place in 1999-2003. Changing any of these assumptions produced lower ICERs than the base case analysis, confirming that the current analysis is highly conservative and suggesting that TKR may be cost-effective for ASA grade 1-2 patients with baseline OKS as high as 43. Excluding patients with incomplete data had no effect on conclusions. Although statistically significant, adding an age-squared term to the regression model had no effect on the conclusions, while a sensitivity analysis adding an OKS-squared term suggested that TKR may be cost-effective for all patients of ASA grade 1 or 2. Recoding BMI as a dummy variable indicating whether or not patients were obese (BMI ≥30) did not change the conclusions and obesity had no significant effect on costs or QALYs.

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Discussion

We found TKR to cost £5,623 per QALY gained for the average patient (similar to estimates from previous studies[6-10]) and therefore represent very good value for money compared with the £20,000-£30,000/QALY threshold typically used in NHS decision-making.[11] Our study also confirms previous findings[7, 9, 17] that costs and benefits vary with age and comorbidity, but evaluates such characteristics, and pre-operative knee function, in multivariate analyses, which has not (to our knowledge) been done previously. We found pre-operative OKS to be the best predictor of post-operative costs, outcomes and cost-effectiveness.

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Our analyses were based on patient-level data from a large trial with detailed, prospective collection of costs, utilities and baseline characteristics that permit extensive subgroup analyses. KAT used a pragmatic design, with broad inclusion criteria and no restrictions on peri- or post-operative care other than randomised aspects of component design[29, 30]; as result, the trial cohort is similar to the national PROMs cohort and costs and benefits are likely to be comparable to those in routine clinical practice. Furthermore, unlike some previous economic evaluations, our study took full account of uncertainty and included all knee-related NHS costs accrued in the first five years after TKR. The main limitation of our analysis was the small number of patients with high OKS. Since KAT recruited only 37 patients with OKS >35, further studies are required to evaluate TKR in this patient subgroup. Analyses were also based on *post hoc* comparisons between outcomes before and after TKR, rather than between randomly-assigned treatment groups. As a result, our study does not provide unbiased estimates of the QALY gains from TKR, and regression towards the mean may have caused our study to overestimate the quality of life improvement attributable to TKR and/or the effect of pre-operative OKS on QALY gains.

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We made several highly conservative assumptions: in particular, assuming that patients would have accrued no knee-related costs and would have remained at baseline utility without TKR, whereas previous studies have found that patients accrue substantial costs and show clinical worsening without TKR.[33] We also assumed that those patients who died before hospital discharge would have survived for five years if they had not had TKR; in reality, those patients dying soon after TKR tend to be older[5, 35] and frailer[5] pre-operatively and some studies suggest that patients undergoing hip replacement have higher long-term survival than the general population[44, 45] (although this may be due to patient selection[35, 44]). When these assumptions were relaxed, TKR was cost-effective for ASA grade 1-2 patients with baseline OKS <44. The costs and benefits of TKR are likely to vary between centres and over time due to variations in patient demographics, component prices, length of stay, and operation time; sensitivity analyses demonstrated that TKR may have become more cost-effective since the KAT procedures were conducted in 1999-2003 due to reductions in length of stay.

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Our analyses show that if TKR were to be rationed based on cost-effectiveness, OKS would be a reasonable tool to use to set the threshold, although there may, of

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course, be practical difficulties with using a patient-reported measure to determine treatment eligibility: particularly if patients know how their questionnaire responses will be used or if test-retest reliability is low in this setting. The decision to operate must also take into consideration other factors, such as radiographic findings and patient choice. Based on regression and subgroup analyses, we can be confident that TKR costs less than £20,000/QALY for all ASA grade 1-2 patients with baseline OKS <40 and for ASA grade 3 patients with OKS <35. Using these thresholds to determine who received treatment would avoid around 2000 TKR procedures per year in England and Wales, saving around £11.8 million per year. However, the higher thresholds suggested by sensitivity analyses using less conservative assumptions suggest that TKR is cost-effective for all but 100 patients per year, which is unlikely to achieve sufficient savings to warrant rationing of TKR. Although the cost-effectiveness of knee replacement was also influenced by gender and age, taking account of these factors as well as OKS and ASA grade would increase the complexity of eligibility criteria, reduce equality of access to healthcare and have minimal effect on NHS budgets.

The results also demonstrate that the thresholds proposed by some PCTs[18-24] are inappropriate and would deny a highly cost-effective treatment to thousands of patients with severe arthritis. The current situation also introduces a postcode lottery with different PCTs using different eligibility criteria. We estimate that limiting knee replacement to patients with OKS ≤26 would prevent more than 10,000 people from receiving TKR. This would be inequitable as TKR costs £10,697 per QALY gained for this group, whereas NICE routinely recommend treatments with ICERs in the region of £20,000-£30,000/QALY gained[11, 46, 47] and are willing to pay substantially more for end of life care.[48] Furthermore, the finding that TKR and subsequent monitoring is more costly for patients with low OKS suggests that delaying TKR until symptoms have deteriorated may be a false economy. Although some PCTs have considered restricting TKR further for obese patients,[18, 21, 25, 49] we found BMI to have no significant effect on costs (p=0.442), QALY gains (p=0.098) or the incidence of peri- or post-operative complications (p>0.26). Although BMI remained non-significant even when ASA grade was omitted from regression analyses, it is difficult to isolate the effect of obesity from other correlated variables (e.g. comorbidity); as result, further research on obesity may be warranted: particularly since a previous study observed a significant correlation between BMI and costs.[13]

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Eligibility criteria for rheumatoid arthritis patients and patients with ASA grade 4 remain unclear, although ASA grade 4 patients would normally be considered unfit for surgery, and the decision to operate on such patients would be based on a case-by-case consideration of whether the benefits outweigh the risks. While our study focused on the costs and benefits of TKR, patients with high baseline OKS often undergo unicompartmental knee replacement; further research is needed to evaluate how the cost-effectiveness of unicompartmental replacement varies with OKS.

In conclusion, TKR is highly cost-effective for the vast majority of patients who currently undergo this procedure in the UK. Although costs and health benefits vary with baseline OKS, the rationing thresholds proposed by some PCTs[18-24] are not supported by evidence on health outcomes or cost-effectiveness.

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Competing interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organisation for the submitted work with the exception of those declared in the funding statement. AG, RF and GM declare that they have no financial relationships with any organisations that might have an interest in the submitted work in the previous three years and no other relationships or activities that could appear to have influenced the submitted work. DM receives royalties paid to him by Biomet and HD has undertaken consultancy work for Pfizer on drugs for rheumatoid arthritis but both declare that they have no other financial relationships with any organisations that might have an interest in the submitted work in the previous three years and no other relationships or activities that could appear to have influenced the submitted work.

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The authors conducted the research independently of all funding organisations. The funders had no role in the collection, analysis or interpretation of data, writing of the manuscript or the decision to publish. The authors had full access to all of the data (including statistical reports and tables) in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Contributorship statement

HD, AG and DM conceived and developed the principles and methods underpinning the current analysis. GM was involved in primary data collection and database management, while HD conducted the analysis under AG's supervision and guidance from DM, GM and RF. HD drafted the manuscript with input from all other authors; all authors have approved the final manuscript and were involved in the interpretation of results. The KAT trial was conceived, designed and run by the KAT trial group, which comprised Suzanne Breeman, Marion Campbell, HD, Jackie Ellington, Nick Fiddian, RF, Adrian Grant, AG, Linda Johnston, GM, Richard Morris and DM.

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Figure 1: EQ-5D utility by subgroup

Abbreviations: ASA, American Society of Anesthesiologists classification (1=completely fit and healthy, 2=some illness but no effect on daily activity, 3=symptomatic illness with minimal restriction on life); OKS, Oxford Knee Score (new scoring system running from zero [severe problems on all functions] to 48 [no problems])[41]; TKR, total knee replacement.

Error bars show 95% confidence intervals. EQ-5D utility is measured on a scale from 1 (perfect health) to -0.594, where 0 is equivalent to death.

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Figure 2: Cost-effectiveness prediction charts estimated based on predictions of regression models.

Abbreviations: ASA, American Society of Anesthesiologists classification (1=completely fit and healthy, 2=some illness but no effect on daily activity, 3=symptomatic illness with minimal restriction on life); OKS, Oxford Knee Score (new scoring system running from zero [severe problems on all functions] to 48 [no problems])[41]; QALY, quality-adjusted life-year; TKR, total knee replacement.

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Figure 3: Cost-effectiveness acceptability curves for different patient subgroups at different baseline Oxford Knee Scores (OKS). A: American Society of Anesthesiologists (ASA) grade 1 and 2 patients. B: ASA grade 3 patients.

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Health economic checklist for "Rationing of total knee replacement: A cost-effectiveness analysis on a large trial dataset"

Study design	**Page**
(1) The research question is stated	5, paragraphs 2 & 3
(2) The economic importance of the research question is stated	4-5
(3) The viewpoint(s) of the analysis are clearly stated and justified	5, paragraph 3
(4) The rationale for choosing the alternative programmes or interventions compared is stated	4-5
(5) The alternatives being compared are clearly described	5, paragraph 3
(6) The form of economic evaluation used is stated	5, paragraph 3
(7) The choice of form of economic evaluation is justified in relation to the questions addressed	5, paragraph 3
Data collection	
(8) The source(s) of effectiveness estimates used are stated	5, paragraph 4
(9) Details of the design and results of effectiveness study are given (if based on a single study)	5, paragraph 4
(10) Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	N/A
(11) The primary outcome measure(s) for the economic evaluation are clearly stated	5, paragraph 3
(12) Methods to value health states and other benefits are stated	6, paragraph 1
(13) Details of the subjects from whom valuations were obtained are given	6, paragraph 1
(14) Productivity changes (if included) are reported separately	N/A
(15) The relevance of productivity changes to the study question is discussed	5, paragraph 3
(16) Quantities of resources are reported separately from their unit costs	Given in reference 29
(17) Methods for the estimation of quantities and unit costs are described	
(18) Currency and price data are recorded	N/A
(19) Details of currency of price adjustments for inflation or currency conversion are given	Given in reference 29
(20) Details of any model used are given	N/A
(21) The choice of model used and the key parameters on which it is based are justified	N/A
Analysis and interpretation of results	
(22) Time horizon of costs and benefits is stated	5, paragraph 4
(23) The discount rate(s) is stated	6, paragraph 2
(24) The choice of rate(s) is justified	6, paragraph 2
(25) An explanation is given if costs or benefits are not discounted	N/A
(26) Details of statistical tests and confidence intervals are given for stochastic data	8, paragraph 1
(27) The approach to sensitivity analysis is given	11, paragraph 4
(28) The choice of variables for sensitivity analysis is justified	11, paragraph 4
(29) The ranges over which the variables are varied are stated	N/A
(30) Relevant alternatives are compared	5, paragraph 3
(31) Incremental analysis is reported	Tables 1 & 2
(32) Major outcomes are presented in a disaggregated as well as aggregated form	Tables 1 & 2
(33) The answer to the study question is given	12, paragraph 2 & page 13 paragraphs 2-3
(34) Conclusions follow from the data reported	5, 12-13
(35) Conclusions are accompanied by the appropriate caveats	12-13

Authors may enter N/A if an item on the checklist is not appropriate, but this is only acceptable for items 9,10, 12-15, 20, 21, 23-29, and 31.