Annals of Internal Medicine ORIGINAL RESEARCH

The Value of Total Knee Replacement in Patients With Knee Osteoarthritis and a Body Mass Index of 40 kg/m^2 or Greater

A Cost-Effectiveness Analysis

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Background: Total knee replacement (TKR) is an effective and cost-effective strategy for treating end-stage knee osteoarthritis. Greater risk for complications among TKR recipients with a body mass index (BMI) of 40 kg/m^2 or greater has raised concerns about the value of TKR in this population.

Objective: To assess the value of TKR in recipients with a BMI of 40 kg/m^2 or greater using a cost-effectiveness analysis.

Design: Osteoarthritis Policy Model to assess long-term clinical benefits, costs, and cost-effectiveness of TKR in patients with a BMI of 40 kg/m^2 or greater.

Data Sources: Total knee replacement parameters from longitudinal studies and published literature, and costs from Medicare Physician Fee Schedules, the Healthcare Cost and Utilization Project, and published data.

Target Population: Recipients of TKR with a BMI of 40 kg/m^2 or greater in the United States.

Time Horizon: Lifetime.

Perspective: Health care sector.

Intervention: Total knee replacement.

Outcome Measures: Cost, quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratios (ICERs), discounted at 3% annually.

Results of Base-Case Analysis: Total knee replacement increased QALYs by 0.71 year and lifetime medical costs by $25 200 among patients aged 50 to 65 years with a BMI of 40 kg/m^2 or greater, resulting in an ICER of $35 200. Total knee replacement in patients older than 65 years with a BMI of 40 kg/m^2 or greater increased QALYs by 0.39 year and costs by $21 100, resulting in an ICER of $54 100.

Results of Sensitivity Analysis: In TKR recipients with a BMI of 40 kg/m^2 or greater and diabetes and cardiovascular disease, ICERs were below $75 000 per QALY. Results were most sensitive to complication rates and preoperative pain levels. In the probabilistic sensitivity analysis, at a $55 000-per-QALY willingness-to-pay threshold, TKR had a 100% and 90% likelihood of being a cost-effective strategy for patients aged 50 to 65 years and patients older than 65 years, respectively.

Limitation: Data are derived from several sources.

Conclusion: From a cost-effectiveness perspective, TKR offers good value in patients with a BMI of 40 kg/m^2 or greater, including those with multiple comorbidities.

Primary Funding Source: National Institute of Arthritis and Musculoskeletal and Skin Diseases of the National Institutes of Health.

Ann Intern Med. 2021;174:xxx-xxx. doi:10.7326/M20-4722 **Annals.org**
For author, article, and disclosure information, see end of text.
This article was published at Annals.org on 23 March 2021.

Obesity is a major risk factor for knee osteoarthritis (1), which affects more than 14 million adults in the United States (2). Because no structure-modifying treatments exist, adults with advanced knee osteoarthritis often consider total knee replacement (TKR). In the United States, more than 680 000 TKRs were done in 2014, and the number continues to increase (3–5). A growing proportion of patients receiving TKR are obese (body mass index [BMI] ≥30 kg/m^2) (6–8). In fact, 45.5% of TKR recipients in 2006 to 2010 had a BMI between 30 and less than 40 kg/m^2, and 14.8% had a BMI of 40 kg/m^2 or greater (9).

Yet, many surgeons remain hesitant to operate on patients with morbid obesity (BMI ≥40 kg/m^2), which is associated with increased risks for perioperative deep tissue infection, poor wound healing, venous thromboembolism, and implant failure (10–13). In 2013, the American Association of Hip and Knee Surgeons reported that "the morbidly obese (BMI >40 kg/m^2) and the super obese (BMI >50 kg/m^2) have complication profiles that may outweigh the functional benefits of TKR" (14). Despite these increased risks, prior studies suggest that patient-reported outcomes of TKR are similar between patients who are nonobese and patients with a BMI of 40 kg/m^2 or greater (15, 16). Thus, although patients with a BMI of 40 kg/m^2 or greater have greater perioperative risks than those with lower BMIs, they may also experience substantial pain reduction and large quality-of-life gains after TKR.

Total knee replacement has been shown to be cost-effective in a general population of patients with knee osteoarthritis (17–21). In the only prior study of the cost-effectiveness of TKR in recipients with a BMI greater than 30 kg/m^2, Ponnusamy and colleagues (22) provided evidence suggesting that TKR is cost-effective in persons with a BMI of 40 to 50 kg/m^2 and greater than 50 kg/m^2.

See also:

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Supplement

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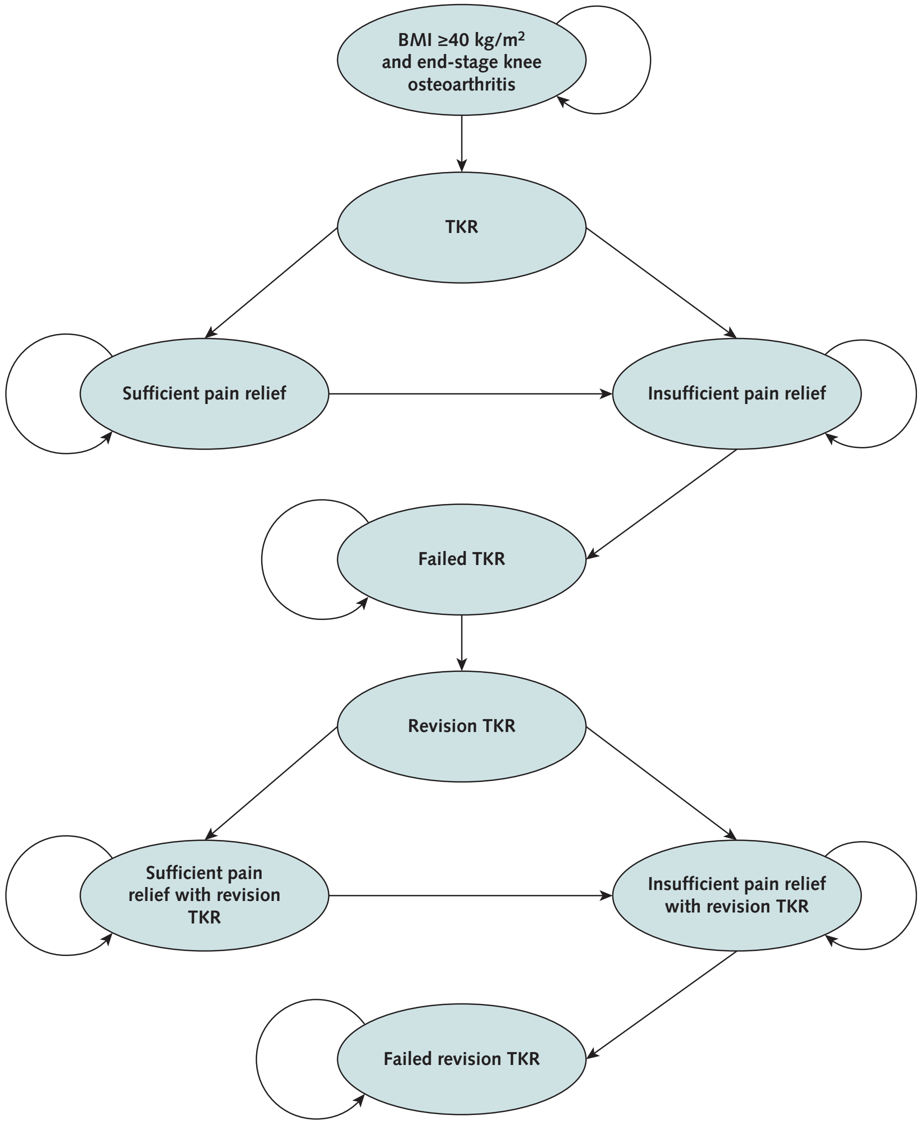
Figure 1. Health states and treatment sequence in the OAPol Model among TKR recipients.



Patients may spend several cycles in the same state or transition to another health state. The arrows specify transitions between health states, defined as probabilities in the input parameters of the OAPol Model. "Sufficient" pain relief refers to a post-TKR health state associated with quality-of-life improvement. Death may occur from every health state. BMI = body mass index; OAPol = Osteoarthritis Policy; TKR = total knee replacement.

However, their work did not consider differences in perioperative primary TKR mortality or other surgery-associated adverse events by obesity level. We aimed to evaluate the cost-effectiveness of TKR in patients with a BMI of 40 kg/m^2 or greater, accounting for increased complication rates and mortality among these patients.

METHODS

Analytic Overview

In 2 patient populations (aged 50 to 65 years and aged >65 years) with BMI of 40 kg/m^2 or greater, end-stage symptomatic knee osteoarthritis, and the prevalence and incidence of 5 prognostically important groups of comorbidities (see section 2.4 of the **Supplement**, available at Annals.org, for more detail), we used the Osteoarthritis Policy (OAPol) Model to evaluate the incremental cost-effectiveness ratio (ICER) of TKR. We calculated the ICER as the ratio of the difference in costs (lifetime medical costs in 2018 U.S. dollars with and without TKR) to the corresponding difference in quality-adjusted life-years (QALYs), discounting both outcomes at 3% annually (23). We conducted analyses from the health care sector's perspective because cost-effectiveness considerations may inform TKR recommendations made by hospitals and health systems.

The OAPol Model

A widely published, validated microsimulation of knee osteoarthritis (20, 24–27) (**Figure 1**), the OAPol

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Model simulates the natural history and treatment of 1 million persons one at a time, with each person assigned demographic (age, sex, and race/ethnicity) and clinical characteristics (BMI; preoperative pain; and presence of cardiovascular disease [CVD], diabetes mellitus [DM], cancer, chronic obstructive pulmonary disease, or non-osteoarthritis musculoskeletal diseases) based on user-defined distributions. Over 6-month model cycles, patients pass through health states and accumulate osteoarthritis-related and non–osteoarthritis-related QALYs and medical costs. Quality of life (QOL) is expressed as a utility—with values of 0.0 assigned to death and 1.0 assigned to perfect health—stratified by obesity, knee pain, age, number of comorbidities, and treatment-related complications. Pain relief from TKR leads to higher QOL, and TKR-related complications reduce QOL and increase cost. Centers for Disease Control and Prevention Life Tables, modified by comorbidities, determine the risk for death (28–30). Documentation for the OAPol Model, version 4.1.0, is available on request.

Treatment Strategies

Our model examined 2 strategies: all patients accepted and had TKR, and all patients did not have TKR.

Model Inputs

The OAPol Model inputs are stratified by 3 domains: population characteristics, TKR-related treatment characteristics, and treatment methods in the absence of TKR. Table 1 lists key input parameters (see other parameters in the Supplement).

Population Characteristics

A total of 75% of patients were women, and 88% were White (34). Mean age was 59 years (SD, 5) and 72 years (SD, 5) in the cohorts aged 50 to 65 years and older than 65 years, respectively (31–33), with BMI distributions stratified by age, sex, and race/ethnicity (Table 1). On the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain scale (0 = best and 100 = worst; severe pain is >40), patients aged 50 to 65 years had an average preoperative pain score of 54 (SD, 15), and patients older than 65 years had an average preoperative pain score of 48 (SD, 12) (Table 1). Each patient with a BMI of 40 kg/m^2 or greater received an additional QOL utility decrement of 0.07 (section 2.3.2 of the Supplement).

TKR Treatment

Benefits. We derived average improvements in WOMAC pain after primary TKR from previously reported studies (31–33) (Table 1; section 3.3.1 of the Supplement). We

Table 1. Key Model Inputs for Patients With End-Stage Knee Osteoarthritis and a BMI ≥40 kg/m^2

Input Parameter	Age Group		Reference
	50-65 Years	>65 Years	
Population characteristics			
Mean age (SD), *y*	58.8 (4.5)	72.0 (5.3)	31–33
Female, %	75.0	75.0	34
Race/ethnicity, %			
White	88.0	88.0	34
Black	4.5	4.5	34
Hispanic	3.0	3.0	34
Mean BMI (SD), *kg/m^2*			
White, male	45.0 (5.2)	43.1 (1.8)	35
White, female	43.0 (4.9)	44.8 (4.7)	35
Black, male	45.1 (4.9)	44.5 (3.3)	35
Black, female	44.3 (5.2)	46.3 (6.7)	35
Hispanic, male	42.9 (2.6)	42.9 (1.9)	35
Hispanic, female	46.5 (5.2)	42.8 (2.8)	35
Mean preoperative pain score (SD)*	54.2 (15.3)	47.5 (12.0)	31–33
	Both Age Groups		
TKR characteristics			
Primary TKR			
Mean pain decrement (SD) among patients with moderate preoperative pain†	16.5 (16.4)		31–33
Mean pain decrement (SD) among patients with severe preoperative pain‡	38.1 (18.0)		31–33
Revision TKR			
Mean pain decrement (SD) among patients with moderate preoperative pain	13.1 (16.4)		31–33
Mean pain decrement (SD) among patients with severe preoperative pain	30.2 (18.0)		31–33
Costs§			
TKR cost, $	18 955		36–38
Revision TKR cost, $	26 687		36–38
Additional medical costs due to obesity and not related to osteoarthritis of the knee (per year), $	3573		39

BMI = body mass index; TKR = total knee replacement; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.
* Preoperative pain according to the WOMAC pain scale (0 = best and 100 = worst). Among patients aged 50 to 65 years with a BMI ≥40 kg/m^2, 17% had moderate preoperative pain, and 82% had severe preoperative pain. Among patients older than 65 years with a BMI ≥40 kg/m^2, 26% had moderate preoperative pain, and 73% had severe pain.
† Moderate pain: WOMAC pain scale score of 15 to 40.
‡ Severe pain: WOMAC pain scale score greater than 40.
§ All costs are in 2018 U.S. dollars.

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used published data on failure probabilities, stratified by BMI, to estimate the probability of implant survival in the first 6 months after TKR (40–42) (section 3.2.1 of the Supplement).

Harms. We derived probabilities of the following TKR complications: pulmonary embolism, pneumonia, readmission, renal failure, deep venous thrombosis, wound dehiscence, and periprosthetic joint infection (40) (section 3.1.1 of the Supplement). All complications increased costs and decreased QOL (sections 3.1.2 and 3.1.3 of the Supplement); periprosthetic joint infection always led to revision TKR. After the first 6 months, TKR had a 0.48% annual probability of failure to provide pain relief (section 3.3.1 of the Supplement). In the event of a surgical failure, we modeled an increase in WOMAC pain on the basis of pain scores for primary and revision TKR (section 3.3.2 of the Supplement) (43). Furthermore, recipients of revision TKR had worse pain outcomes and more surgical complications than recipients of primary TKR (43, 44) (sections 3.1.1, 3.2.2, and 3.3.3 of the Supplement).

Costs. Body mass index greater than 40 kg/m^2 has been shown to be associated with an increase in TKR procedure costs (36), reflecting greater resource consumption, such as longer operative times, greater anesthesia costs, and longer length of stay. We used data from several sources to determine a one-time primary TKR cost of $18 955 for patients with a BMI of 40 kg/m^2 or greater (36–38); the cost of revision TKR for patients with a BMI of 40 kg/m^2 or greater was $7732 more than primary TKR (Table 1; section 3.4.1 of the Supplement). Patients had a 28% likelihood of visiting a physician's office every 6 months after TKR at $169 per visit, sustained for the duration of their life (section 3.4.2 of the Supplement) (5, 18), and each complication was associated with an additional cost (section 3.1.3 of the Supplement). To account for the effects of obesity on nonosteoarthritis medical costs and QOL, patients incurred medical costs that were not related to osteoarthritis and a decrement in QOL annually (39) (section 2.3 of the Supplement).

Treatment Methods in the Absence of TKR

We assumed that in the absence of TKR, patients with knee osteoarthritis and a BMI of 40 kg/m^2 or greater exhausted all available conservative treatment regimens and resorted to occasional analgesic pain management, which incurred costs but did not provide sustained pain relief.

Sensitivity Analyses

Varying Cohort Characteristics

Comorbidities. Because TKR outcomes have been shown to be worse for patients with comorbidities such as DM and CVD (45, 46), we examined how these comorbidities affect TKR cost-effectiveness among persons with a BMI of 40 kg/m^2 or greater. In addition to our base-case analysis for the overall population of TKR recipients with a BMI of 40 kg/m^2 or greater, we did 4 analyses stratified by presence or absence of DM or CVD: no DM or CVD, DM only, CVD only, and both DM and CVD. Comorbidities decreased QOL and increased background medical costs and patients' risk for incurring TKR complications (section 3.1.4 of the Supplement) (37, 47–50).

Cohorts With BMI Less Than 40 kg/m^2. For comparison, we examined populations with BMI less than 30 kg/m^2 and BMI of 30 to less than 40 kg/m^2. Parameters that varied by BMI included pre-TKR pain, nonosteoarthritis medical costs, and TKR complication probabilities. Input values for these cohorts are provided in section 4.1 of the Supplement.

One-Way Deterministic Sensitivity Analyses

We varied pre-TKR pain levels, TKR treatment efficacy, pain failure probabilities, and complication probabilities in one-way deterministic sensitivity analyses. We increased and decreased pre-TKR pain by 50% in 10% increments (from 150% to 50% of base-case pain). We varied TKR treatment efficacy similarly, from 50% (worst case) to 150% of base-case efficacy. Annual late pain failure probabilities were tested at 0.25%, 1.0%, 2.0%, and 3.0% (base-case probability was 0.48%). Complication rates ranged from 50% of base-case probabilities to 700%.

Probabilistic Sensitivity Analyses

Probabilistic sensitivity analysis assigns a distribution to multiple parameters simultaneously where point estimates carry substantial uncertainty (51). We did a probabilistic sensitivity analysis focused on the effectiveness of TKR in each age group by simultaneously varying the QOL utility decrement due to obesity, late pain failure probabilities, TKR implant survival probabilities (primary and revision), and complication probabilities (primary and revision). We focused on parameters depicting TKR effectiveness because these are the TKR-related parameters that carry sizable uncertainty in this population. We used a normal distribution for the utility decrement and a β distribution for the remaining parameters (Supple-ment Tables 25 and 26). We created 1000 scenarios with parameters repeatedly drawn from each distribution. Each unique set of inputs produces a unique set of model outputs. We aggregated these results in a cost-effectiveness acceptability curve, which shows the percentage of simulations for which TKR was cost-effective across a range of willingness-to-pay (WTP) thresholds.

Role of the Funding Source

This project was supported by National Institute of Arthritis and Musculoskeletal and Skin Diseases grants R01AR074290, K24AR057827, K24AR070892, P30AR 072571, and P30AR072577. The funding source played no role in the design, conduct, or reporting of the study.

RESULTS

Base-Case Analysis

Table 2 presents discounted quality-adjusted life expectancies (QALEs), discounted lifetime costs, and ICERs of the base-case analysis. Total knee replacement

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in patients aged 50 to 65 years with a BMI of 40 kg/m^2 or greater resulted in an estimated discounted QALE of 10.1 years, compared with 9.3 years for patients without TKR. Patients with TKR accrued an additional $25 200 in costs over age-matched patients without TKR (ICER = $35 200 per QALY). Of this younger cohort, 0.45% had a periprosthetic joint infection.

Patients older than 65 years with TKR had a QALE of 6.7 years versus 6.3 years for age-matched patients without TKR; TKR increased costs by $21 100, resulting in an ICER of $54 100 per QALY. Of this older cohort, 0.61% had a periprosthetic joint infection.

In addition, TKR improved patient pain (**Supplement Figures 1** to **3**). More than 50% of patients older than 65 years with a BMI of 40 kg/m^2 or greater had WOMAC pain scores of 15 or below during the first 5 years after surgery, compared with fewer than 1% of patients who did not have TKR (**Supplement Figure 3**). On average, these patients' pain decreased 34.4 WOMAC points after TKR; those without TKR those without TKR did not experience meaningful changes in pain over time.

Sensitivity Analyses

Varying Cohort Characteristics

Stratified Analysis by Presence of DM or CVD. **Table 2** also shows results for patients with knee osteoarthritis and no comorbidities, DM, CVD, or both DM and CVD. In the absence of DM or CVD, we estimated the ICER for TKR at $34 500 per QALY for those aged 50 to 65 years, and $46 900 per QALY for those older than 65 years. The ICERs were higher than in the base case for the comorbidity cohorts; for patients older than 65 years, ICERs for the DM, CVD, and both DM and CVD groups were $63 000 per QALY, $64 400 per QALY, and $71 100 per QALY, respectively.

Cohorts With BMI Less Than 30 kg/m^2 and BMI of 30 to Less Than 40 kg/m^2. The ICERs for the cohort with BMIs less than 30 kg/m^2 were $27 500 per QALY for those aged 50 to 65 years and $34 400 per QALY for those older than 65 years. Corresponding ICERs for the cohort with BMIs of 30 to less than 40 kg/m^2 were $37 200 per QALY and $49 400 per QALY. Compared with lifetime medical costs of $249 300 for patients aged 50 to 65 years with TKR and a BMI of 40 kg/m^2 or greater, the lifetime costs of patients of the same age were $199 800 in those with a BMI of 30 to less than 40 kg/m^2 and $156 300 in those with a BMI less than 30 kg/m^2. We present detailed results in section 5 of the **Supplement**.

One-Way Sensitivity Analyses

Figure 2 depicts results of the one-way sensitivity analyses discussed below.

Table 2. Results of Cost-Effectiveness Analysis for Patients With a BMI ≥40 kg/m^2 and End-Stage Knee Osteoarthritis

Age Group	TKR	PJI, %*	QALYs	Cost, $†	ICER per QALY, $
Base case					
50–65 y	No	–	9.34	224 100	35 200
	Yes	0.45	10.05	249 300	
>65 y	No	–	6.32	176 400	54 100
	Yes	0.61	6.71	197 500	
No prevalent comorbidities					
50–65 y	No	–	9.55	192 600	34 500
	Yes	0.44	10.29	217 900	
>65 y	No	–	6.40	153 000	46 900
	Yes	0.60	6.85	174 100	
DM prevalent					
50–65 y	No	–	9.26	235 500	39 000
	Yes	0.77	9.96	263 100	
>65 y	No	–	6.30	181 000	63 000
	Yes	0.87	6.67	204 100	
CVD prevalent					
50–65 y	No	–	9.21	238 100	39 000
	Yes	0.52	9.94	266 500	
>65 y	No	–	6.31	181 400	64 400
	Yes	0.68	6.68	205 400	
Both DM and CVD prevalent					
50–65 y	No	–	9.16	247 000	41 200
	Yes	0.77	9.89	277 300	
>65 y	No	–	6.30	185 100	71 100
	Yes	0.87	6.66	210 500	

CVD = cardiovascular disease; DM = diabetes mellitus; ICER = incremental cost-effectiveness ratio; PJI = periprosthetic joint infection; QALY = quality-adjusted life-year; TKR = total knee replacement.
* Percentage of cohort that had a periprosthetic joint infection.
† All costs are in 2018 U.S. dollars.

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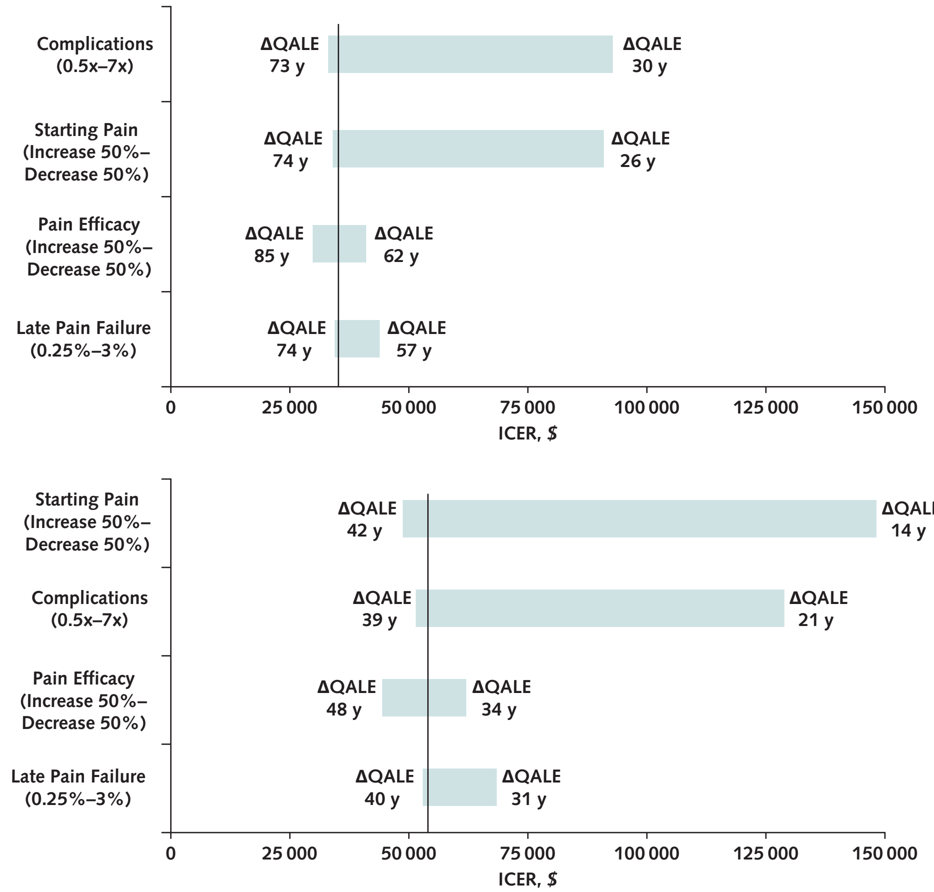
Figure 2. Deterministic sensitivity analysis results.



This figure shows the effect of varying input parameters on the cost-effectiveness of TKR in patients with a body mass index of 40 kg/m^2 or greater in 2 age groups: 50 to 65 years (*top*) and >65 years (*bottom*). The *x*-axis reports the ICER, calculated as the ratio of the difference in costs (total medical costs with and without TKR) to the corresponding difference in QALE. In each analysis, all parameters were held at base-case values except for the parameters shown on the *y*-axis, which were varied according to the range of values listed. The leftmost end of each bar represents the ICER when the parameter of interest is set to the most favorable value; the rightmost side represents the ICER at the parameter's least favorable value. The exception for this is starting pain; because of the U-shaped relationship between starting pain and outcomes of knee replacement, the minimum ICER for the group aged 50 to 65 y corresponds to a 10% increase in starting pain, and the minimum ICER for the group aged >65 y corresponds to a 20% increase in starting pain. For all parameters, the ΔQALE at the left and right of each bar indicates the respective QALE benefit per 100 persons. The black vertical line shows the base-case ICER, as reported in Table 2. Costs are reported in 2018 U.S. dollars. ICER = incremental cost-effectiveness ratio; QALE = quality-adjusted life expectancy; TKR = total knee replacement.

Varying Pre-TKR Pain Levels

Recipients of TKR with higher preoperative pain had a greater pain improvement after TKR. For example, in patients aged 50 to 65 years with a BMI of 40 kg/m^2 or greater and preoperative WOMAC pain set to 27 (50% below the base case of 54 and no longer severe), the average post-TKR decrease in WOMAC pain score was 19 points in contrast to a 48-point decrease in those starting with pain set to 81 (50% above the base case). Costs remained approximately constant. Average lifetime medical costs were $247 900 with 50% less pain and $249 500 with 50% more pain. The ICERs for these 2 groups were $90 700 per QALY and $42 800 per QALY, respectively. Similar results were seen in the older than 65 years age group, with decreasing pre-TKR pain leading to a higher ICER of $148 000 per QALY, and increasing pre-TKR pain leading to a lower ICER of $57 800 per QALY.

TKR Pain Efficacy

Among patients older than 65 years with a BMI of 40 kg/m^2 or greater, neither decreasing TKR effectiveness by 50% nor increasing effectiveness by 50% substantially affected lifetime medical costs ($197 500 vs. $197 600). However, increasing effectiveness by 50% increased the incremental QALYs gained after TKR to 0.48 year (ICER, $44 600 per QALY), whereas decreasing effectiveness by 50% decreased the incremental QALYs gained to 0.34 year (ICER, $62 000 per QALY). Similarly, among patients aged 50 to 65 years, decreasing TKR pain efficacy by 50% led to a higher ICER of $41 100 per QALY, whereas increasing it resulted in a lower ICER.

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TKR Late Pain Failure

In patients older than 65 years with a BMI of 40 kg/m^2 or greater, increasing the probability of annual late pain failure from 0.48% to 3.0% decreased QALYs gained after TKR to 0.31 year (0.39 year in the base case), but across all pain failure levels considered, ICERs never exceeded $70 000 per QALY.

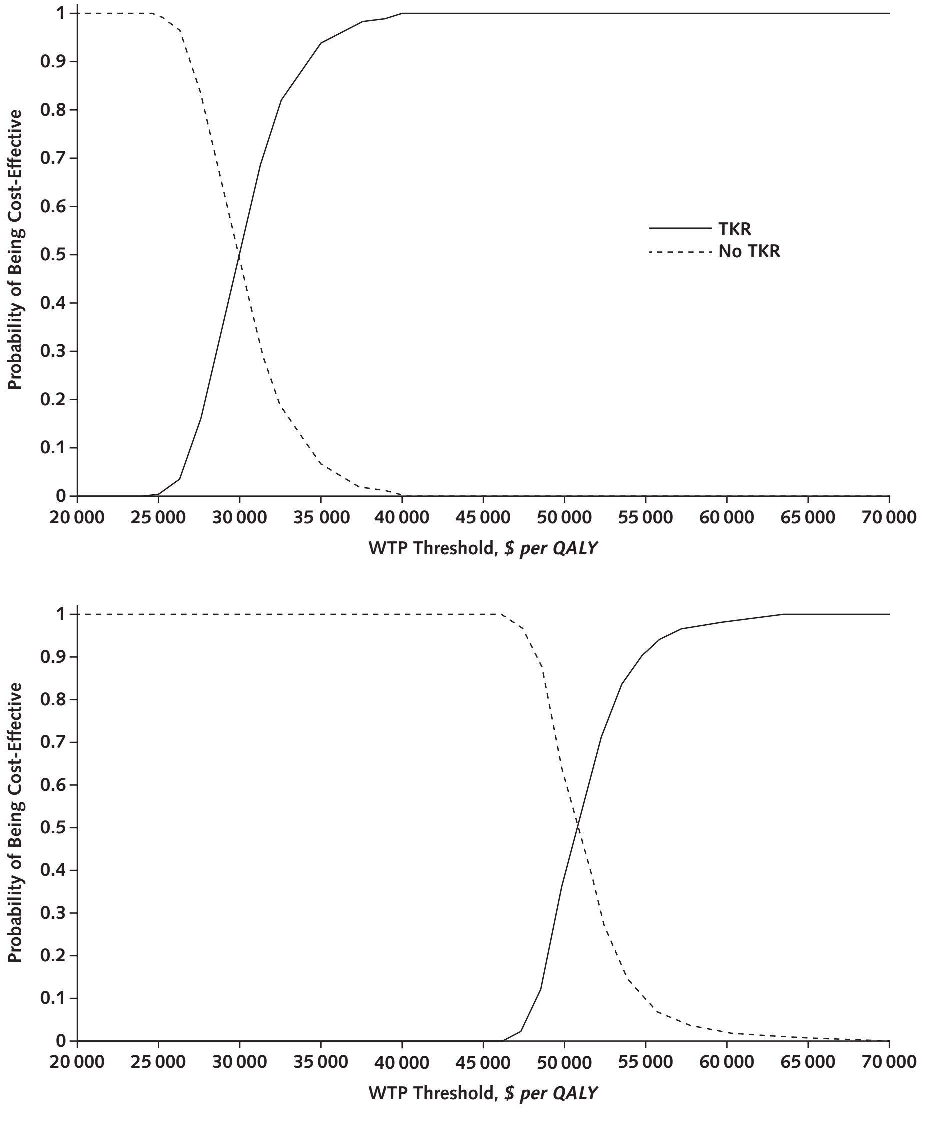
Complications

The ICERs remained below the $100 000-per-QALY WTP threshold for all patients aged 50 to 65 years with a BMI of 40 kg/m^2 or greater, even with a 7-fold increase in all complication probabilities ($92 700 per QALY). Furthermore, ICERs remained below $71 000 per QALY with a 3-fold increase in complications ($45 500 per QALY for ages 50 to 65 years; $70 300 per QALY for ages >65 years). For patients older than 65 years, all ICERs remained below the $100 000-per-QALY WTP threshold except when complication probabilities increased 7-fold (ICER, $128 800 per QALY).

Probabilistic Sensitivity Analysis (Focused on Effectiveness of TKR)

Figure 3 displays cost-effectiveness acceptability curves for patients aged 50 to 65 years and patients older than 65 years with a BMI of 40 kg/m^2 or greater and presents the proportion of model simulations for which each strategy was cost-effective at a given WTP

Figure 3. Probabilistic sensitivity analysis results for patients with a body mass index of 40 kg/m^2 or greater and aged 50 to 65 years (*top*) or older than 65 years (*bottom*).



The curves show the proportion of simulations (out of 1000) for which TKR was cost-effective at a given WTP threshold. The WTP thresholds, measured in 2018 U.S. dollars per QALY, are listed along the *x*-axis. Each of the 1000 analyses are independently sampled model input parameters from the distributions specified in **Supplement Tables 25** and **26**. QALY = quality-adjusted life-year; TKR = total knee replacement; WTP = willingness-to-pay.

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threshold. Across 1000 runs, the QALE was 10.06 years (95% CI, 9.01 to 11.11 years) for patients aged 50 to 65 years with TKR, and 9.28 years (CI, 8.23 to 10.33 years) for those not receiving TKR in the same age range. Corresponding costs were $247 437 (CI, $245 384 to $249 489) and $224 040 (CI, $223 836 to $224 243), respectively. For patients older than 65 years, the QALEs for cohorts with and without TKR were 6.72 years (CI, 6.04 to 7.40 years) and 6.31 years (CI, 5.63 to 7.00 years). Corresponding costs for this age group were $197 087 (CI, $196 376 to $197 799) and $176 256 (CI, $176 057 to $176 454). The probability that TKR is cost-effective is 90% for a WTP threshold of $55 000 per QALY in patients older than 65 years and 100% in those aged 50 to 65 years.

Discussion

We used the OAPol Model to quantify the tradeoffs in cost and QOL of TKR versus no TKR for patients with a BMI of 40 kg/m^2 or greater across 2 age strata. Our base-case results suggest that TKR is cost-effective for patients aged 50 to 65 years with a BMI of 40 kg/m^2 or greater for any WTP threshold greater than $35 200 per QALY and for patients older than 65 years at all WTP thresholds above $54 100 per QALY. In higher-risk cohorts of TKR recipients with BMIs of 40 kg/m^2 or greater and DM, CVD, or both DM and CVD, the ICERs for patients older than 65 years were $63 000 per QALY, $64 400 per QALY, and $71 100 per QALY, respectively.

In this cost-effectiveness analysis of TKR, we incorporated higher pain levels and increased complication and mortality rates in TKR recipients with a BMI of 40 kg/m^2 or greater to reflect the association between perioperative risk and BMI. We also varied these parameters by age. Although there is no widely accepted WTP threshold, the ICER of $35 200 is substantially lower than ICERs for many generally accepted medical interventions (52, 53). Assuming a conservative WTP threshold of $50 000 per QALY, even a 40% increase in TKR costs for the younger age group would lead to ICERs below $50 000 per QALY. Total knee replacement also offers a good value in patients aged 65 years or older with a BMI of 40 kg/m^2 or greater, with an ICER of $54 100 per QALY. That said, fewer patients with TKR and a BMI of 40 kg/m^2 or greater fall into the older demographic; of 585 127 patients with primary TKR analyzed by Meller and colleagues (34), 32 994 (5.64%) were older than 65 years with a BMI of 40 kg/m^2 or greater.

Our results should be interpreted in the context of certain limitations. We assumed that sex and race/ethnicity distributions did not differ across age groups and derived these data from a sample of TKR recipients who were older than 65 years (34). We also assumed that patients who are considering TKR have similar demographic and clinical characteristics as those who had TKR, but we recognize that selection bias may occur in clinical practice. We derived pre- and post-TKR pain data from longitudinal cohort studies (31–33), but only 9% of patients in those studies had a BMI of 40 kg/m^2 or greater (54). To address this limitation, we did extensive sensitivity analyses to examine the effects of uncertainty in our input parameters related to effectiveness of TKR in this population, which showed that our cost-effectiveness conclusions remained robust despite the wide variability in these parameters. In addition, despite large variability, we drew pain decrements from a normal distribution because of limited options for distribution choice in the OAPol Model.

We based rates of complications on published data, which limited our ability to stratify by age. This uncertainty was examined with a sensitivity analysis; increasing complication rates 3-fold for patients older than 65 years yielded an ICER below $71 000 per QALY. There are few estimates of TKR outcomes in patients with CVD, so we estimated complication rates for the CVD cohort using data from an article that focused on patients with congestive heart failure (49). We assumed no additional mortality attributable to TKR for those with CVD, DM, and both CVD and DM. In the model, we account for excess mortality due to comorbidities in 2 ways: increased risk for "chronic" death due to comorbidities and increased risk for major postoperative complications with accompanying risk for death. We believe that these 2 sources of increased mortality due to comorbidity capture additional risk for death during the 6 months after TKR not related to postoperative complications.

Although we compared TKR to nonsurgical management, including intermittent pain management with analgesics, we did not examine physical activity or health modification programs, which have been shown to be efficacious in short-term studies (55). We assumed that all patients eligible and willing to have TKR completed prior rounds of physical therapy and lifestyle modification without receiving meaningful benefits. Although TKR leads to substantial pain relief in patients with and without morbid obesity, it does not lead to appreciable weight loss or changes in physical activity levels (56). Additional interventions focused on weight loss after TKR could further improve the value of TKR.

We acknowledge that clinicians may have practical concerns that we did not factor into our analysis. High BMI creates additional surgical difficulty, and operating room and surgical equipment is not always designed to accommodate patients with a BMI of 40 kg/m^2 or greater (57). In deciding whether to operate, patients and physicians should be fully informed and should carefully weigh the potential improvements in the patient's QOL against possible surgical risks. Patient safety concerns should take precedence over our cost-effectiveness findings because the cost-effectiveness of a procedure does not imply reduced risk for perioperative complications.

This study has important clinical care, policy, and research implications. Currently, instead of doing TKR on patients with a BMI of 40 kg/m^2 or greater, many surgeons recommend weight-loss interventions, such as exercise or bariatric surgery (58). However, published data indicate that fewer than 15% of patients lose 5% or more of their body weight before TKR (59). In addition, bundled payment models that reward positive outcomes and efficiency may further dissuade surgeons from

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operating on patients with a BMI of 40 kg/m^2 or greater who are perceived to be at higher risk. Our analysis suggests that withholding TKR from persons with a BMI of 40 kg/m^2 or greater may not be justified from an effectiveness or a cost-effectiveness perspective. Even under unfavorable conditions (such as multiple comorbidities, TKR efficacy decreased by 50%, or complication probabilities increased 7-fold), the procedure remained quality-adjusted life prolonging, on average, and had a cost-effectiveness ratio that never exceeded $148 000 per QALY. Total knee replacement in patients with a BMI of 40 kg/m^2 or greater seems to be a valuable treatment strategy.

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Note: This study was approved by the Partners Institutional Review Board, protocol 2006P001290.

Acknowledgment: The authors thank Ms. Aleksandra Kostic for assistance with the final rounds of analysis.

Grant Support: By grants R01 AR074290, K24 AR057827, K24 AR070892, P30 AR072571, and P30 AR072577 from the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the National Institutes of Health.

Disclosures: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M20-4722.

Reproducible Research Statement: *Study protocol:* Not applicable; OAPol model overview and strategies are described in the main body of the manuscript. *Statistical code:* We encourage collaborations on special request to Dr. Losina (e-mail, elosina@bwh.harvard.edu). *Data set:* Most of the input data used in the analysis are reported in the main body of the manuscript or in the Supplement (available at Annals.org).

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References

1. King LK, March L, Anandacoomarasamy A. Obesity & osteoarthritis. Indian J Med Res. 2013;138:185-93. [PMID: 24056594]
2. Deshpande BR, Katz JN, Solomon DH, et al. Number of persons with symptomatic knee osteoarthritis in the US: impact of race and ethnicity, age, sex, and obesity. Arthritis Care Res (Hoboken). 2016;68:1743-1750. [PMID: 27014966] doi:10.1002/acr.22897
3. Inacio MCS, Paxton EW, Graves SE, et al. Projected increase in total knee arthroplasty in the United States–an alternative projection model. Osteoarthritis Cartilage. 2017;25:1797-1803. [PMID: 28801208] doi:10.1016/j.joca.2017.07.022
4. Losina E, Thornhill TS, Rome BN, et al. The dramatic increase in total knee replacement utilization rates in the United States cannot be fully explained by growth in population size and the obesity epidemic. J Bone Joint Surg Am. 2012;94:201-7. [PMID: 22298051] doi:10.2106/JBJS.J.01958
5. Agency for Healthcare Research and Quality. Healthcare Cost and Utilization Project. Accessed at https://hcupnet.ahrq.gov/#setup on 4 January 2021.
6. Fehring TK, Odum SM, Griffin WL, et al. The obesity epidemic: its effect on total joint arthroplasty. J Arthroplasty. 2007;22:71-6. [PMID: 17823020]
7. Odum SM, Springer BD, Dennos AC, et al. National obesity trends in total knee arthroplasty. J Arthroplasty. 2013;28:148-51. [PMID: 23953395] doi:10.1016/j.arth.2013.02.036
8. Woon CY, Piponov H, Schwartz BE, et al. Total knee arthroplasty in obesity: in-hospital outcomes and national trends. J Arthroplasty. 2016;31:2408-2414. [PMID: 27259393] doi:10.1016/j.arth.2016.04.028
9. Belmont PJ Jr, Goodman GP, Waterman BR, et al. Thirty-day postoperative complications and mortality following total knee arthroplasty: incidence and risk factors among a national sample of 15,321 patients. J Bone Joint Surg Am. 2014;96:20-6. [PMID: 24382720] doi:10.2106/JBJS.M.00018
10. Amin AK, Clayton RA, Patton JT, et al. Total knee replacement in morbidly obese patients: results of a prospective, matched study. J Bone Joint Surg Br. 2006;88:1321-6. [PMID: 17012421]
11. Issa K, McElroy MJ, Pourtaheri S, et al. Outcomes of primary total knee arthroplasty in the morbidly obese patients. J Long Term Eff Med Implants. 2013;23:301-7. [PMID: 24579897]
12. Martin JR, Jennings JM, Dennis DA. Morbid obesity and total knee arthroplasty: a growing problem. J Am Acad Orthop Surg. 2017;25:188-194. [PMID: 28146438] doi:10.5435/JAAOS-D-15-00684
13. Järvenpää J, Kettunen J, Kröger H, et al. Obesity may impair the early outcome of total knee arthroplasty. Scand J Surg. 2010;99:45-9. [PMID: 20501358]
14. Workgroup of the American Association of Hip and Knee Surgeons Evidence Based Committee. Obesity and total joint arthroplasty: a literature based review. J Arthroplasty. 2013;28:714-21. [PMID: 23518425] doi:10.1016/j.arth.2013.02.011
15. Li W, Ayers DC, Lewis CG, et al. Functional gain and pain relief after total joint replacement according to obesity status. J Bone Joint Surg Am. 2017;99:1183-1189. [PMID: 28719557] doi:10.2106/JBJS.16.00960
16. Turki AS, Dakhil YA, Turki AA, et al. Total knee arthroplasty: effect of obesity and other patients' characteristics on operative duration and outcome. World J Orthop. 2015;6:284-9. [PMID: 25793169] doi:10.5312/wjo.v6.i2.284
17. Dakin H, Gray A, Fitzpatrick R, et al; KAT Trial Group. Rationing of total knee replacement: a cost-effectiveness analysis on a large trial data set. BMJ Open. 2012;2:e000332. [PMID: 22290396] doi:10.1136/bmjopen-2011-000332

Downloaded from https://annals.org by Univ of Penn Library on 03/22/2021.

18. **Jüni P, Reichenbach S, Dieppe P.** Osteoarthritis: rational approach to treating the individual. Best Pract Res Clin Rheumatol. 2006;20:721-40. [PMID: 16979535]

19. **Kamaruzaman H, Kinghorn P, Oppong R.** Cost-effectiveness of surgical interventions for the management of osteoarthritis: a systematic review of the literature. BMC Musculoskelet Disord. 2017;18:183. [PMID: 28486957] doi:10.1186/s12891-017-1540-2

20. **Losina E, Walensky RP, Kessler CL, et al.** Cost-effectiveness of total knee arthroplasty in the United States: patient risk and hospital volume. Arch Intern Med. 2009;169:1113-21; discussion 1121-2. [PMID: 19546411] doi:10.1001/archinternmed.2009.136

21. **Waimann CA, Fernandez-Mazarambroz RJ, Cantor SB, et al.** Cost-effectiveness of total knee replacement: a prospective cohort study. Arthritis Care Res (Hoboken). 2014;66:592-9. [PMID: 24124052] doi:10.1002/acr.22186

22. **Ponnusamy KE, Vasarhelyi EM, Somerville L, et al.** Cost-effectiveness of total knee arthroplasty vs nonoperative management in normal, overweight, obese, severely obese, morbidly obese, and super-obese patients: a Markov model. J Arthroplasty. 2018;33:S32-S38. [PMID: 29550168] doi:10.1016/j.arth.2018.02.031

23. **Neumann PJ, Sanders GD, Russell LB, et al.** Cost-Effectiveness in Health and Medicine. 2nd ed. Oxford Univ Pr; 2016.

24. **Katz JN, Smith SR, Collins JE, et al.** Cost-effectiveness of nonsteroidal anti-inflammatory drugs and opioids in the treatment of knee osteoarthritis in older patients with multiple comorbidities. Osteoarthritis Cartilage. 2016;24:409-18. [PMID: 26525846] doi:10.1016/j.joca.2015.10.006

25. **Losina E, Paltiel AD, Weinstein AM, et al.** Lifetime medical costs of knee osteoarthritis management in the United States: impact of extending indications for total knee arthroplasty. Arthritis Care Res (Hoboken). 2015;67:203-15. [PMID: 25048053] doi:10.1002/acr.22412

26. **Smith SR, Katz JN, Collins JE, et al.** Cost-effectiveness of tramadol and oxycodone in the treatment of knee osteoarthritis. Arthritis Care Res (Hoboken). 2017;69:234-242. [PMID: 27111538] doi:10.1002/acr.22916

27. **Weinstein AM, Rome BN, Reichmann WM, et al.** Estimating the burden of total knee replacement in the United States. J Bone Joint Surg Am. 2013;95:385-92. [PMID: 23344005] doi:10.2106/JBJS.L.00206

28. **Arias E, Heron M, Xu J.** United States life tables, 2014. Natl Vital Stat Rep. 2017;66:1-64. [PMID: 29155687]

29. **Global BMI Mortality Collaboration, Di Angelantonio E, Bhupathiraju S, et al.** Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents. Lancet. 2016;388:776-86. [PMID: 27423262] doi:10.1016/S0140-6736(16)30175-1

30. **Centers for Disease Control and Prevention, National Center for Health Statistics.** National Vital Statistics Survey 2014-2016. Accessed at www.cdc.gov/nchs/products/nvsr.htm on 4 January 2021.

31. **Dave AJ, Selzer F, Losina E, et al.** Is there an association between whole-body pain with osteoarthritis-related knee pain, pain catastrophizing, and mental health. Clin Orthop Relat Res. 2015;473:3894-902. [PMID: 26443774] doi:10.1007/s11999-015-4575-4

32. **Losina E, Collins JE, Daigle ME, et al.** The AViKA (Adding Value in Knee Arthroplasty) postoperative care navigation trial: rationale and design features. BMC Musculoskelet Disord. 2013;14:290. [PMID: 24119081] doi:10.1186/1471-2474-14-290

33. **Losina E, Collins JE, Wright J, et al.** Postoperative care navigation for total knee arthroplasty patients: a randomized controlled trial. Arthritis Care Res (Hoboken). 2016;68:1252-9. [PMID: 26714179] doi:10.1002/acr.22829

34. **Meller MM, Toossi N, Johanson NA, et al.** Risk and cost of 90-day complications in morbidly and superobese patients after total knee arthroplasty. J Arthroplasty. 2016;31:2091-8. [PMID: 27062354] doi:10.1016/j.arth.2016.02.062

35. **Centers for Disease Control and Prevention.** National Health and Nutrition Examination Survey data. Accessed at https://www.cdc.gov/nchs/nhanes/index.htm on 4 January 2021.

36. **Kim SH.** Morbid obesity and excessive hospital resource consumption for unilateral primary hip and knee arthroplasty. J Arthroplasty. 2010;25:1258-66. [PMID: 19879721] doi:10.1016/j.arth.2009.09.005

37. **Bozic KJ, Lau E, Kurtz S, et al.** Patient-related risk factors for postoperative mortality and periprosthetic joint infection in Medicare patients undergoing TKA. Clin Orthop Relat Res. 2012;470:130-7. [PMID: 21874391] doi:10.1007/s11999-011-2043-3

38. **Centers for Medicare & Medicaid Services.** Physician fee schedule. Accessed at www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/PhysicianFeeSched on 4 January 2021.

39. **Tsai AG, Williamson DF, Glick HA.** Direct medical cost of overweight and obesity in the USA: a quantitative systematic review. Obes Rev. 2011;12:50-61. [PMID: 20059703] doi:10.1111/j.1467-789X.2009.00708.x

40. **George J, Piuzzi NS, Ng M, et al.** Association between body mass index and thirty-day complications after total knee arthroplasty. J Arthroplasty. 2018;33:865-871. [PMID: 29107493] doi:10.1016/j.arth.2017.09.038

41. **Bordini B, Stea S, Cremonini S, et al.** Relationship between obesity and early failure of total knee prostheses. BMC Musculoskelet Disord. 2009;10:29. [PMID: 19265522] doi:10.1186/1471-2474-10-29

42. **Paxton EW, Namba RS, Maletis GB, et al.** A prospective study of 80,000 total joint and 5000 anterior cruciate ligament reconstruction procedures in a community-based registry in the United States. J Bone Joint Surg Am. 2010;92 Suppl 2:117-32. [PMID: 21123596] doi:10.2106/JBJS.J.00807

43. **Greidanus NV, Peterson RC, Masri BA, et al.** Quality of life outcomes in revision versus primary total knee arthroplasty. J Arthroplasty. 2011;26:615-20. [PMID: 20541360] doi:10.1016/j.arth.2010.04.026

44. **Liang H, Bae JK, Park CH, et al.** Comparison of mode of failure between primary and revision total knee arthroplasties. Orthop Traumatol Surg Res. 2018;104:171-176. [PMID: 29032308] doi:10.1016/j.otsr.2017.10.003

45. **Meding JB, Reddleman K, Keating ME, et al.** Total knee replacement in patients with diabetes mellitus. Clin Orthop Relat Res. 2003:208-16. [PMID: 14646763]

46. **Podmore B, Hutchings A, van der Meulen J, et al.** Impact of comorbid conditions on outcomes of hip and knee replacement surgery: a systematic review and meta-analysis. BMJ Open. 2018;8:e021784. [PMID: 29997141] doi:10.1136/bmjopen-2018-021784

47. **Bozic KJ, Lau E, Ong K, et al.** Risk factors for early revision after primary TKA in Medicare patients. Clin Orthop Relat Res. 2014;472:232-7. [PMID: 23661301] doi:10.1007/s11999-013-3045-0

48. **Chen J, Cui Y, Li X, et al.** Risk factors for deep infection after total knee arthroplasty: a meta-analysis. Arch Orthop Trauma Surg. 2013;133:675-87. [PMID: 23558519] doi:10.1007/s00402-013-1723-8

49. **Curtis GL, Newman JM, George J, et al.** Perioperative outcomes and complications in patients with heart failure following total knee arthroplasty. J Arthroplasty. 2018;33:36-40. [PMID: 28844769] doi:10.1016/j.arth.2017.07.043

50. **Webb ML, Golinvaux NS, Ibe IK, et al.** Comparison of perioperative adverse event rates after total knee arthroplasty in patients with diabetes: insulin dependence makes a difference. J Arthroplasty. 2017;32:2947-2951. [PMID: 28559194] doi:10.1016/j.arth.2017.04.032

51. **Briggs A, Sculpher M, Claxton K.** Decision Modelling for Health Economic Evaluation. Oxford Univ Pr; 2006.

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52. **Howell M, Walker RC, Howard K.** Cost effectiveness of dialysis modalities: a systematic review of economic evaluations [Letter]. Appl Health Econ Health Policy. 2019;17:315-330. [PMID: 30714086] doi:10.1007/s40258-018-00455-2
53. **McCarthy I, O'Brien M, Ames C, et al; International Spine Study Group.** Incremental cost-effectiveness of adult spinal deformity surgery: observed quality-adjusted life years with surgery compared with predicted quality-adjusted life years without surgery. Neuro-surg Focus. 2014;36:E3. [PMID: 24785485] doi:10.3171/2014.3.FOCUS1415
54. **Collins JE, Donnell-Fink LA, Yang HY, et al.** Effect of obesity on pain and functional recovery following total knee arthroplasty. J Bone Joint Surg Am. 2017;99:1812-1818. [PMID: 29088035] doi:10.2106/JBJS.17.00022
55. **Skou ST, Roos EM, Laursen MB, et al.** A randomized, controlled trial of total knee replacement. N Engl J Med. 2015;373:1597-606. [PMID: 26488691] doi:10.1056/NEJMoa1505467
56. **Dowsey MM, Liew D, Stoney JD, et al.** The impact of preoperative obesity on weight change and outcome in total knee replacement: a prospective study of 529 consecutive patients. J Bone Joint Surg Br. 2010;92:513-20. [PMID: 20357327] doi:10.1302/0301-620X.92B4.23174
57. **Hammond KL.** Practical issues in the surgical care of the obese patient. Ochsner J. 2013;13:224-7. [PMID: 23789009]
58. **Pellegrini CA, Ledford G, Hoffman SA, et al.** Preferences and motivation for weight loss among knee replacement patients: implications for a patient-centered weight loss intervention. BMC Musculoskelet Disord. 2017;18:327. [PMID: 28764783] doi:10.1186/s12891-017-1687-x
59. **Inacio MC, Kritz-Silverstein D, Raman R, et al.** The impact of pre-operative weight loss on incidence of surgical site infection and readmission rates after total joint arthroplasty. J Arthroplasty. 2014;29:458-64.e1. [PMID: 24018161] doi:10.1016/j.arth.2013.07.030

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