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# The impact of comorbid conditions on outcomes of hip and knee replacement surgery: A systematic review and meta-analysis

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# ABSTRACT

**Objectives:** To systematically perform a meta-analysis of the association between different comorbid conditions on safety (short-term outcomes) and effectiveness (long-term outcomes) in patients undergoing hip and knee replacement surgery.

**Design:** Systematic Review and Meta-analysis

**Setting:** Various secondary care settings

**Participants:** A full range of adult patient populations undergoing elective hip and knee replacement surgery.

**Primary and secondary outcome measures:** We sought all studies that assessed the impact of 11 comorbid conditions on 10 outcomes (including surgical complications, readmissions, mortality, function, health-related quality of life, pain and revision surgery).

**Results:** Seventy studies were included with 16 (23%) reporting on at least 100,000 patients and 9 (13%) were of high quality. We found that comorbidities increased the short-term risk of hospital readmissions (8 of 11 conditions) and mortality (8 of 11 conditions). The impact on surgical complications was inconsistent across comorbid conditions. In the long-term, comorbid conditions increased the risk of revision surgery (6 of 11 conditions) and long-term mortality (7 of 11 conditions). The long-term impact on function, quality of life and pain varied across comorbid conditions.

**Conclusions:** This systematic review shows that comorbidities predominantly have an impact on the safety of hip and knee replacement surgery but little impact on its effectiveness. There is a need for high-quality studies also considering the severity of comorbid conditions.

## STRENGTH AND LIMITATIONS OF THIS STUDY

- This study went beyond published reviews by analysing the relative impact of individual comorbid conditions on multiple outcomes that relate not only to safety but also effectiveness of hip and knee replacement surgery.
- Further to previous studies, to allow for meta-analysis of all outcomes, continuous outcomes were converted to the corresponding odds ratio using the Hasselblad and Hedges approach.
- The search was limited to include specific comorbidities and outcomes so studies may have been missed.
- To enable a meta-analysis of the multiple conditions and outcomes, comorbid conditions and outcomes were grouped together and may have compromised the validity of the conclusions.

# INTRODUCTION

Hip and knee replacement surgery, the surgical replacement of a joint, is one of the most successful and cost effective interventions in medicine [1]. It offers considerable improvement in function and quality of life [2]. It is expected that the demand for hip and knee replacement will increase as the prevalence of hip and knee osteoarthritis rises due to increases in life expectancy [3].

There has been increasing interest in identifying the risk factors for poor outcomes of elective joint replacement to be able to optimise patients and improve outcomes. Previous research has reported variation in the use of hip and knee replacement according to socioeconomic status [4], sex [5], insurance status [6], ethnicity [7] and geography [8]. This variation may be explained in part by the lack of consensus amongst clinicians about the clinical indications for joint replacement surgery[9].

Comorbid conditions, conditions that are present in addition to the index condition but are unrelated to the latter, are on the rise around the world as more people are living with multiple morbidities. In a large US study using administrative data, 83.7% patients who had undergone hip or knee replacement had at least one comorbid condition [10]. This is higher than in the general population where in 2012 only 49.8% of US adults had at least one comorbid condition [11]. As the prevalence of people living with multiple morbidities increases with age it is expected that the number of patients undergoing elective hip and knee replacement with at least one comorbid condition will increase [12].

There have been a number of studies reporting the impact of comorbidity on outcomes after hip and knee replacement[13]. There is little evidence however, to which extent different individual comorbid conditions affect a variety of outcomes that relate not just to the safety

of the surgery but also long-term outcomes such as quality of life after hip and knee replacement surgery. Previous systematic reviews on comorbid conditions and outcomes of hip and knee replacement have typically focused on individual comorbidities [14], specific outcomes [15], process measures and cost[16], short-term outcomes following hip and knee replacement or the overall impact of composite comorbidity indices on outcomes [17].

This study provides evidence of the impact of different individual comorbid conditions on a wide range of surgical outcomes, including short-term outcomes related to the "safety" of the surgery and long-term outcomes related to the "effectiveness" of the surgery.

The aim of this systematic review and meta-analysis was to synthesise the literature on the impact of different individual comorbid conditions on short-term and long-term outcomes of hip and knee replacement surgery.

# METHODS

## Literature Search

A search of Medline, Embase, and CINAHL Plus, was conducted up to 31 May 2017 to identify studies written in English. Limitations were not placed on date. Search terms for hip and knee replacement were combined with search terms for health outcomes and search terms for 11 common comorbid conditions: heart disease, high blood pressure, stroke, leg pain due to poor circulation, lung disease, diabetes, kidney disease, diseases of the nervous system, liver disease, cancer and depression (see supplementary information 1). The conditions were selected because they are the comorbid conditions that are routinely captured in the national Patient Reported Outcome Measures programme for patients undergoing elective surgery in the English National Health Service and were considered relevant comorbidities in terms of outcome prediction[18]. Where possible MeSH or index terms were used. All the titles, selected abstracts and full text articles were reviewed for eligibility by two reviewers (BP, AA). Data extraction was conducted by BP and checked by AH. Any disagreements were resolved by two reviewers (JVM, AH). The reference lists of existing systematic reviews and included studies were also checked for additional eligible articles.

## Eligibility criteria and data extraction

We included published full text observational (either prospective or retrospective) studies in the English language that compared the outcomes of hip or knee replacement in patients with and without any of the 11 comorbid conditions. Studies including other joint replacements were only eligible if hip and/or knee replacement represented at least 90% of participants or if results were reported separately. Small studies, those with fewer than 100

participants, were excluded because hip and knee replacement are common procedures and the selected comorbid conditions are relatively common. Studies were ineligible if they failed to include at least one of the following outcomes: surgical complications, mortality, function, pain, health-related quality of life, hospital readmission, and revision surgery.

Information on the study design, population and measures of association was extracted for eligible studies. Data were extracted on the participants (type of surgery), source of study data, the specific condition and the definition of the outcome for each reported association between a comorbid condition and outcome in a study (see supplementary information 2). In addition, data were also extracted on the measure of association and its uncertainty and, for adjusted measures, the variables used in the adjusted analysis. Where possible, data on counts or means were used to calculate measures of association that had not been reported in the original study. Studies that indicated the statistical significance or otherwise of an association without reporting a quantitative metric were also recorded. Data were verified by a third reviewer (JVM).

Ten categories of outcome were defined. Five short term outcomes, those occurring closest to three months after surgery, were: surgical complications, occurrence of venous thromboembolism, surgical site infections, readmission to hospital, and mortality. Surgical complications were defined as the presence of any surgical complication as reported in a study. Two commonly reported surgical complications, venous thromboembolism and infection, were also examined separately. Five longer-term outcomes closest to one year postoperatively were: measures of hip or knee function, patient-reported quality of life, pain, revision surgery, and mortality. For function and quality of life, they were only eligible

for inclusion if analyses incorporated adjustment for pre-operative scores or if similarity of pre-operative scores was demonstrated.

## Quality Assessment

The internal and external validity of the studies was appraised using the Newcastle-Ottawa scale (NOS) [19] that was modified to meet the requirements of this study (see Table 1). Two reviewers (BP, AH) examined three items: patient selection, comparability of exposure and reference groups, and assessment of outcomes. For the comparability between the two groups, we focused on the following variables that previous studies have identified as predictors of various outcomes of hip and knee replacement surgery: age, sex, socioeconomic status, and ethnicity. We added an extra item to assess the comparability of the cohorts on the basis of whether the cohort of patients were drawn from multiple centres or a single centre and whether the data sources were from specialist arthroplasty databases. The total possible score was 13. A study with a score of 11 or greater was considered high quality (see supplementary information 3).

*Table 1 – Study quality appraisal using a modified Newcastle-Ottawa scale*

**Patient Selection**

1. Was the cohort of patients undergoing hip or knee replacement surgery with comorbid conditions representative?
2. Was the reference cohort for patients without comorbid conditions drawn from the same community?
3. Was the presence of comorbid conditions adequately verified? (Yes=secure record or structured interview/self-report)
4. Did the study demonstrate that the outcome of interest was not present at the start of the study?
5. Was the cohort or patients drawn from multiple communities?

**Comparability**

1. Did the study control for age and sex?
2. Did the study control for socioeconomic status and ethnicity?

**Outcome Assessment**

1. Was the outcome of interest clearly defined? (Yes=study-specific/self-report, joint registry, No=administrative data)
2. Was follow-up long enough for outcomes to occur? (Yes=short-term minimum 30 days, long-term minimum 6 months)
3. Was follow-up adequate? (Yes=completed follow up >90%)

**Studies were graded on an ordinal scoring scale with higher scores indicating studies of higher quality. A study could be awarded a maximum of one point for each numbered item except comparability items and the first item in outcome assessment, which could be awarded a maximum of two points for each numbered item.*

## Quantitative data synthesis and meta-analysis

An approach to data synthesis was chosen which allowed for a meta-analysis across multiple outcomes and conditions. This meta-synthesis approach has been used by other systematic reviews[20]. The first stage of data synthesis involved selecting each study's measures of association to be included in the meta-analyses for each of the possible combinations of comorbid condition and outcome. Individual studies might have multiple measures for different combinations, e.g., studies reporting multiple outcomes or different comorbid conditions. Studies might also have multiple measures for the same combination, e.g., unadjusted and adjusted measures, measures for controlled and uncontrolled diabetes, or measures for hip and knee replacement surgery. Separate measures for hip and knee replacement were included in a combination's meta-analysis because they comprised different groups of participants. For other multiple measures, a single measure was selected

for inclusion in a meta-analysis using the following criteria: adjusted over unadjusted measures, closer matching or more common categories of comorbid conditions for inexact mapping to the 11 selected conditions (see Table 2), and closer matching to the timing (3 or 12 months) and definition of outcomes.

*Table 2 - Mapping of comorbid conditions*

| Comorbid Condition | Number of studies | Included comorbid conditions |
|---|---|---|
| Cancer | 9 | All cancers but if reported separately cancer chosen in preference to metastasis. |
| Depression | 12 | All diagnoses of depression |
| Diabetes | 41 | Type 2 diabetes in preference to Type 1 diabetes. Controlled diabetes in preference to uncontrolled diabetes. Diabetes without complications in preference to diabetes with complications. |
| Diseases of the Nervous System | 6 | Alzheimer's disease, Parkinson's disease, Dementia |
| Heart Disease | 21 | Heart disease but if reported separately coronary heart disease, coronary artery disease or heart failure was chosen. |
| High blood pressure | 13 | High Blood Pressure |
| Kidney Disease | 19 | Renal disease but if reported separately chosen chronic kidney disease, chronic renal disease or renal failure |
| Liver disease | 7 | Liver disease but if reported separately cirrhosis chosen |
| Lung disease | 18 | Lung disease but if reported separately chronic obstructive pulmonary disorder chosen. |
| Poor circulation | 7 | Peripheral vascular disease |
| Stroke | 12 | Stroke or cerebrovascular disease |

Most of the studies reported outcomes as odds ratios or it was possible to derive an odds ratio. For studies reporting continuous outcomes the difference between means divided by the pooled standard deviation (standardised mean difference) was converted to the corresponding odds ratio (OR) using the Hasselblad and Hedges approach [21]. If higher scores represented a good outcome then reciprocal values were used to ensure that ORs greater than one represented higher odds of a poor outcome. Where zero events precluded the calculation of an odds ratio, each cell in the contingency table was inflated by adding 0.5[22] to allow calculation of an OR.

We estimated the pooled odds ratio for each combination of comorbid condition and outcome comprising two or more measures of association. Odds ratios were computed such that a result greater than one indicates a higher odds of a worse outcome in patients with a specified comorbid conditions compared to patients without. We used a random-effects model developed by DerSimonean and Laird [23]. Pooled odds ratios by condition were plotted for each outcome but no further pooling of results was undertaken. A sensitivity analysis was performed to assess the impact of the quality of the studies on the outcomes in which studies with a higher quality score were compared with studies of lower quality. The risk of publication bias in the included studies was assessed using the graphical assessment of the funnel plot[22] on outcomes which were reported on by a greater than 6 studies. All statistical analyses were carried out using STATA 14.

# RESULTS

## Selected studies

Full search results are represented in Figure 1. Of the 18,644 studies identified in the search, we included 70 studies [24-93], which produced 314 results for individual comorbid conditions and outcomes of hip and knee replacement surgery. The 70 studies had a range of patients sample sizes from 122 to 8,379,490. 16 (23%) studies had at least 100,000 patients. 26 (37%) studies reported combined hip and knee arthroplasties, 12 (17%) studies reported on hip arthroplasties only, 24 (34%) studies on knee arthroplasties and 9 (13%) studies reported hip and knee arthroplasties separately. 40 (70%) studies reported outcomes after primary hip or knee replacement. The 70 studies came from 13 different

countries with 37 (53%) coming from the USA. They were published between 1984 and 2017.

Overall, 43 (61%) studies only looked at single comorbid conditions and 35 (50%) only looked at single outcomes. 60 (86%) studies investigated the association between comorbid conditions and surgical complications (including VTE and surgical site infections), and only 5 (7%) quality of life. The comorbid condition that was most frequently studied was diabetes (41 studies), followed by heart disease (21 studies) and kidney disease (19 studies) (see Table 2). The least frequently studied comorbid condition was diseases of the nervous system (6 studies).

The median NOS score, the measure of study quality, was 10 (6 to 13). Of the 70, 9 (13%) studies met our predefined criteria for high quality of scores of greater than 11. The majority of studies had a representative cohort of patients with a specified comorbid condition (56 studies) and adjusted for potential confounders such as age and gender (41 studies).

## Short-term outcomes

### Surgical complications

In this meta-analysis, 15 studies reported an odds ratio for surgical complications in patients with comorbid conditions (see Figure 2). The risk of surgical complications was significantly higher in patients with cancer (pooled OR 1.33, 95% CI 1.09 to 1.62), diabetes (pooled OR 1.12, 95% CI 1.01 to 1.25), kidney disease (pooled OR 1.97, 95% CI 1.84 to 2.10) and stroke (pooled OR 1.40, 95% CI 1.03 to 1.90). No studies reported surgical complications in patients with nervous system diseases or poor circulation.

## Surgical site infections

Twenty-seven studies reported on surgical site infections after surgery. Overall, surgical site infections tended to occur more frequently in patients with comorbid conditions but the likelihood was only significantly higher in patients with diabetes (pooled OR 1.90, 95% CI: 1.32, 2.74) and liver disease (pooled OR 2.46, 95% CI 1.46 to 4.12) (see Figure 2). No studies reported the likelihood of surgical site infections in patients with high blood pressure, poor circulation or stroke.

## Venous thromboembolism (VTE)

Eighteen studies reported the risk of venous thromboembolism (VTE) postoperatively. Venous thromboembolism was more likely in patients with cancer (pooled OR 2.30, 95% CI: 1.35 to 3.92), depression (pooled OR 1.15, 95% CI: 1.02 to 1.30) and lung disease (pooled OR 1.29, 95% CI: 1.08 to 1.55). No studies reported the risk of VTE in patients with nervous system diseases, liver disease or poor circulation.

## Readmissions to hospital

Sixteen studies looked at the presence of comorbid conditions and being readmitted to hospital within 90 days after surgery. Overall, the likelihood of readmissions to hospital were significantly higher for patients with comorbid conditions (8 out of 11) with the highest likelihood in patients with liver disease (pooled OR 1.79, 95% CI 1.36 to 2.35) (see Figure 2). No studies reported the likelihood of readmissions in patients with nervous system diseases or depression.

## Short-term mortality

Thirteen studies looked at mortality within 90 days after surgery. Overall, the likelihood of short-term mortality tended to be significantly higher in patients with comorbid conditions

(8 out of 11) with the highest likelihood in patients with heart disease (pooled OR 2.96, 95% CI 1.95 to 4.48) (see Figure 2). In contrast, one study reported a significant lower likelihood of short-term mortality in patients with depression (pooled OR 0.53, 95% CI 0.32 to 0.88).

## Long-term outcomes

### Hip and knee function

Ten studies look at the impact of comorbid conditions on postoperative hip or knee function (see Figure 3). Knee or hip function measures included: The Knee Society Knee score [71 77], WOMAC score [27 28 73], Oxford Knee score [34], and Activities of Daily Living limitation [82 86 94]. The most frequently used measure was the WOMAC score. Overall, the impact of comorbid conditions on function was variable. Patients with depression (pooled OR 1.69, 95% CI 1.26 to 2.28), heart disease (pooled OR 1.24, 95% CI 1.01 to 1.52) and stroke (pooled OR 1.32, 95% CI 1.02 to 1.71) had worse function after surgery. Postoperative function in patients with heart disease [34] and stroke [86] were each only reported on by one study. No studies investigated the postoperative function in cancer patients.

### Health-related quality of life

Five studies compared the improvement in quality of life one year after surgery in patients with comorbid conditions with those patients without comorbidities. Measures of quality of life included the SF-12 [34], SF-36 [28 73 95] and the Health Utilities Index [27]. Overall, across comorbid conditions there was no consistent pattern. Quality of life was significantly worse for patients with heart disease (pooled OR 1.49, 95% CI 1.24 to 1.78) and lung disease (pooled OR 1.26, 95% CI 1.02 to 1.57). For patients with liver disease quality of life was significantly better after surgery (pooled OR 0.36, 95% CI 0.20 to 0.65) [34]. Postoperative quality of life in patients with heart disease and liver disease were each only reported by

one study. No studies investigated the postoperative quality of life in cancer or stroke patients.

### Pain

Ten studies reported on the association between comorbid conditions and pain. 5 (50%) studies looked at the outcome moderate-severe pain at 2-years and were studied by the same author [83 84]. Other measures of pain included the WOMAC pain score [27] and the Knee Society pain score [67 71]. Overall, pain tended to be worse for patients with comorbid conditions but was not statistically significant. No studies investigated the postoperative pain in patients with cancer, nervous system diseases, liver disease or high blood pressure.

### Revision surgery

Twelve studies reported on the likelihood of revision surgery in patients with comorbid conditions. Overall, revision surgery tended to be more likely in patients with comorbid conditions (6 out of 11) but the evidence remains weak. The pooled OR ranged from 1.11 (95% CI 1.02 to 1.21) for patients with high blood pressure to 1.96 (95% CI 1.16 to 3.30) for patients with liver disease. No studies reported the risk of revision surgery in patients with poor circulation or stroke.

### Long-term mortality

Twelve studies reported the association between comorbid conditions and long-term mortality. Overall, the risk of long-term mortality tended to be higher for patients with comorbid conditions (7 out of 11). The pooled OR ranged from 1.38 (95% CI 1.05 to 1.80) for lung disease to 3.40 (95% CI 1.17 to 9.86) for liver disease (see Figure 3). No studies investigated the risks of long-term mortality in patients with depression and poor circulation.

## Impact of comorbid conditions

There is a lack of consistency across short-term and long-term outcomes by different comorbid conditions. In the short-term, comorbidities had the most impact on readmissions to hospital and short-term mortality but the impact on surgical complications was variable with most results not statistically significant. In the long-term, comorbid conditions had the most impact on risk of revision surgery and long-term mortality. The impact on function and quality of life was inconsistent across comorbid conditions. The evidence for the impact of comorbid conditions on long-term outcomes was weaker than for short-term outcomes. Heart disease of all the included comorbid conditions had the most impact on both short-term and long-term outcomes with an increased likelihood of readmissions, short-term mortality, worse function, worse quality of life, revision surgery and long-term mortality.

## Publication Bias

We explored the possible impact of publication bias on outcomes: surgical complications, venous thromboembolism, surgical site infections, readmissions, pain, and mortality which had greater than six studies. This included studies in diabetic patients (see Figure 4) and kidney patients (see Figure 5). The studies were not evenly distributed across both sides of the funnel plot. This asymmetry suggests that studies publishing negative effects may be missing. The impact of comorbidities on outcomes of hip and knee replacement may therefore be overestimated.

## Sensitivity Analysis

We performed a sensitivity analysis to estimate the robustness of the results by evaluating the effects of study quality. Overall high-quality studies pointed in the same direction as the lower-quality studies, although the latter generally reported larger effects. Higher-quality studies did not include studies reporting on the outcomes function, quality of life and pain, which suggest the evidence on long-term outcomes is poor compared to the evidence of the impact of comorbid condition on short-term outcomes. This may be largely because of the smaller sample size of these studies, the lack of adjustment for confounders and the lack of patient-reported outcomes in joint registries which focus primarily on surgical complications, mortality and revision rates.

# DISCUSSION

**Main findings**

Overall, this meta-analysis demonstrates that patients with comorbid conditions are more likely to have a readmission and a higher short-term mortality in the early follow-up but there is little evidence that patients benefit significantly less in terms of health-related quality of life, function and pain compared to patients with no comorbid conditions. In the short-term, the impact on surgical complications was variable and mostly statistically insignificant. Patients with comorbid conditions tended to have a higher risk of revisions and long-term mortality but the available evidence was weak. There is some evidence of publication bias which may indicate an overestimation of the impact of comorbid conditions on outcomes. Given this, there is a need for high-quality studies in order to get a better understanding of the true impact of comorbidities on both short-term and long-term outcomes of hip and knee replacement.

Our study has implications for future research on clinical indication for joint replacement surgery. Clinicians should take into account prognostic factors that affect treatment effectiveness in their decision-making to refer or select patients for hip or knee replacement[96] but due to the lack of clarity on clinical indication for hip and knee replacement they are not able to do so effectively [97]. Further research, specifically focusing on the long-term outcomes such as function, quality of life and pain, and that stratify individual comorbidities according to severity are needed to provide clinicians with more evidence to guide their decision-making and management of patients with comorbid conditions and to minimise the variation and quality of care provided for this patient group.

**Quality of evidence**

Only 13% of the studies were graded as being of high quality. Poorer quality studies were typically less clear about the inclusion criteria for study patients and did not adjust for potential confounders such as age and gender. They were also based on either small single-site studies or large administrative data-based studies that use data sources that were not from specialist arthroplasty databases. Large administrative data-based studies greatly influenced the meta-analysis and thereby the limitations of these studies will therefore have a considerable influence on the validity of this meta-analysis. The higher quality studies primarily used joint registries and did not focus on patient-reported outcomes such as quality of life, function and pain.

Our sensitivity analysis showed that lower quality studies seem to overestimate the risk of short-term outcomes after hip and knee replacement in patients with comorbid conditions. Similarly, the evidence of publication bias towards reporting positive findings may indicate an overestimation of the impact of comorbid conditions on outcomes of hip and knee replacement surgery.

It is important to consider however, that patients included in the reported studies may represent a healthier population. Several studies have shown that patients are not accessing hip and knee replacement because clinicians are excluding complex and severe patients who are deemed too high-risk for surgery [98]. This may introduce selection bias which may lead to an underestimation of the true effect on the impact of comorbid conditions on outcomes of hip, and knee replacement surgery.

**Relation to prior reviews**

Our study provides evidence that comorbid conditions have an impact on safety of the surgery but little impact on the effectiveness of the surgery in terms of quality of life, function and pain after hip and knee replacement surgery. There have been a number of earlier systematic reviews reporting the impact of comorbid conditions on outcomes after hip and knee replacement surgery. One systematic review and meta-analysis following elective total hip replacement in diabetes patients found diabetes to be associated with a 2-fold increase risk of surgical site infections in line with our findings[14]. Another one looking at the impact of comorbidity and length of stay and costs found limited evidence that comorbidities increase length of stay and costs compared to patients with no or fewer comorbidities[16]. One systematic review looking at health-related quality of life in total hip and knee replacement reported that comorbid conditions was given as a reason for modest improvements in outcomes [15]. This finding was only based on two studies both using composite comorbidity measures. Another systematic review looking at all preoperative predictors for outcomes for hip and knee replacement however, demonstrated the inconsistency in study findings with seven studies reported a significant worse association between comorbid conditions and outcomes but six studies reported no significant association [17].

**Limitations**

For some combinations of outcomes and comorbid conditions there were no studies of impact or impact was only based on a single study. Only six studies focused on patients with diseases of the nervous system whereas over half of the studies we reviewed investigated outcomes in diabetic patients. Similarly, short-term outcomes, particularly surgical

complications, were commonly investigated but only five studies [27 28 34 73 95] reported on quality of life outcomes and the results on pain were from two publications[83 84]. This highlights that evidence on short-term outcomes is stronger than evidence on long-term outcomes. Half of the studies were analyses of data collected in population-based administrative datasets. This may account for the relative scarcity of studies reporting on long-term outcomes such as quality of life or function that need patient reported results.

The scope of this review required the grouping of heterogeneous studies. Across all studies, there were differences in study populations, definitions of comorbid conditions and their severity and definitions of outcomes and the timing of their measurement. To make the results comparable and to be able to conduct any form of meta-analysis, some comorbid conditions were grouped together, outcomes were categorised as short and long-term, and continuous outcomes were converted to odds ratio using the Hasselblad and Hedges approach. In addition, it was not possible to evaluate hip and knee replacement separately as 27 (38%) studies reported on combined hip and knee arthroplasties.

In addition to variation in definitions of comorbid conditions, few included studies graded comorbid conditions according to severity which would have allowed a better understanding of their impact. For the few studies that reported results according to the severity of a comorbid condition, we included the most common severity subgroup, therefore excluding the most severe patients.

## CONCLUSION

Clinicians should be aware of the short-term risks relating to the safety of the surgery in their management of patients with comorbid conditions. There is little evidence that patients with comorbid conditions benefit significantly less from hip and knee replacement in terms of quality of life, function and pain after surgery than patients without comorbid conditions. As a result comorbid conditions have an impact on safety but little impact on effectiveness of hip and knee replacement surgery. Future research should however, consider the severity of comorbid conditions to better understand the impact of comorbid conditions on outcomes.

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# REFERENCES

1. Liang MH, Cullen KE, Larson MG, et al. Cost-effectiveness of total joint arthroplasty in osteoarthritis. *Arthritis and rheumatism* 1986;29(8):937-43. doi: http://dx.doi.org/10.1002/art.1780290801 [published Online First: 1986/08/01]
2. Aamodt A, Nordsletten L, Havelin LI, et al. Documentation of hip prostheses used in Norway: a critical review of the literature from 1996--2000. *Acta orthopaedica Scandinavica* 2004;75(6):663-76. doi: http://dx.doi.org/10.1080/759369226 [published Online First: 2005/03/15]
3. Kurtz S, Ong K, Lau E, et al. Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. *The Journal of bone and joint surgery American volume* 2007;89(4):780-5. doi: 10.2106/jbjs.f.00222 [published Online First: 2007/04/04]
4. Neuburger J, Hutchings A, Black N, et al. Socioeconomic differences in patient-reported outcomes after a hip or knee replacement in the English National Health Service. *Journal of public health (Oxford, England)* 2013;35(1):115-24. doi: 10.1093/pubmed/fds048 [published Online First: 2012/06/26]
5. Juni P, Low N, Reichenbach S, et al. Gender inequity in the provision of care for hip disease: population-based cross-sectional study. *Osteoarthritis Cartilage* 2010;18(5):640-5. doi: http://dx.doi.org/10.1016/j.joca.2009.12.010
6. Schwarzkopf R, Phan DL, Hoang M, et al. Do patients with income-based insurance have access to total joint arthroplasty? *The Journal of arthroplasty* 2014;29(6):1083-6.e1. doi: 10.1016/j.arth.2013.11.022 [published Online First: 2014/01/11]
7. Singh JA, Lu X, Rosenthal GE, et al. Racial disparities in knee and hip total joint arthroplasty: an 18-year analysis of national Medicare data. *Annals of the rheumatic diseases* 2014;73(12):2107-15. doi: 10.1136/annrheumdis-2013-203494
8. Judge A, Welton NJ, Sandhu J, et al. Equity in access to total joint replacement of the hip and knee in England: cross sectional study. *Bmj* 2010;341:c4092. doi: http://dx.doi.org/10.1136/bmj.c4092
9. Cobos R, Latorre A, Aizpuru F, et al. Variability of indication criteria in knee and hip replacement: an observational study. *Bmc Musculoskeletal Disorders* 2010;11 doi: 10.1186/1471-2474-11-249
10. Hustedt JW, Goltzer O, Bohl DD, et al. Calculating the Cost and Risk of Comorbidities in Total Joint Arthroplasty in the United States. *Journal of Arthroplasty* 2017;32(2):355-61.e1. doi: http://dx.doi.org/10.1016/j.arth.2016.07.025
11. Ward BW, Schiller JS, Goodman RA. Multiple Chronic Conditions Among US Adults: A 2012 Update. *Preventing Chronic Disease* 2014;11:E62. doi: 10.5888/pcd11.130389
12. Singh JA, Lewallen DG. Increasing obesity and comorbidity in patients undergoing primary total hip arthroplasty in the U.S.: a 13-year study of time trends. *BMC Musculoskelet Disord* 2014;15:441. doi: 10.1186/1471-2474-15-441 [published Online First: 2014/12/19]
13. Sturmer T, Dreinhofer K, Grober-Gratz D, et al. Differences in the views of orthopaedic surgeons and referring practitioners on the determinants of outcome after total hip replacement. *Journal of Bone and Joint Surgery-British Volume* 2005;87B(10):1416-19. doi: 10.1302/0301-620x.87b10.16702
14. Tsang ST, Gaston P. Adverse peri-operative outcomes following elective total hip replacement in diabetes mellitus: a systematic review and meta-analysis of cohort studies. *The bone & joint journal* 2013;95-b(11):1474-9. doi: 10.1302/0301-620x.95b11.31716 [published Online First: 2013/10/24]
15. Ethgen O, Bruyere O, Richy F, et al. Health-related quality of life in total hip and total knee arthroplasty. A qualitative and systematic review of the literature. *The Journal of bone and joint surgery American volume* 2004;86-a(5):963-74. [published Online First: 2004/05/01]

16. Olthof M, Stevens M, Bulstra SK, et al. The association between comorbidity and length of hospital stay and costs in total hip arthroplasty patients: a systematic review. *J Arthroplasty* 2014;29(5):1009-14. doi: 10.1016/j.arth.2013.10.008 [published Online First: 2013/11/30]
17. Hofstede SN, Gademan MGJ, Vliet Vlieland TPM, et al. Preoperative predictors for outcomes after total hip replacement in patients with osteoarthritis: a systematic review. *BMC Musculoskeletal Disorders* 2016;17:212. doi: 10.1186/s12891-016-1070-3
18. Digital N. Patient Reported Outcome Measures in England: Data Dictionary, 2016.
19. Wells G, Shea B. Newcastle-Ottawa quality assessment scale cohort studies 2011 [Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
20. Linde K, Clausius N, Ramirez G, et al. Are the clinical effects of homeopathy placebo effects? A meta-analysis of placebo-controlled trials. *Lancet* 1997;350(9081):834-43. [published Online First: 1997/10/06]
21. Hasselblad V, Hedges LV. Meta-analysis of screening and diagnostic tests. *Psychological bulletin* 1995;117(1):167-78. doi: http://dx.doi.org/10.1037/0033-2909.117.1.167 [published Online First: 1995/01/01]
22. Egger M, Davey-Smith G, Altman D. Systematic Reviews in Health Care: Meta-Analysis in Context: John Wiley & Sons 2013.
23. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled clinical trials* 1986;7(3):177-88. doi: http://dx.doi.org/10.1016/0197-2456(86)90046-2 [published Online First: 1986/09/01]
24. Ackland GL, Moran N, Cone S, et al. Chronic kidney disease and postoperative morbidity after elective orthopedic surgery. *Anesth Analg* 2011;112(6):1375-81. doi: http://dx.doi.org/10.1213/ANE.0b013e3181ee8456
25. Adams AL, Paxton EW, Wang JQ, et al. Surgical outcomes of total knee replacement according to diabetes status and glycemic control, 2001 to 2009. *Journal of Bone & Joint Surgery, American Volume* 2013;95-A(6):481-87 7p. doi: 10.2106/JBJS.L.00109
26. Aggarwal VK, Tischler EH, Post ZD, et al. Patients with atrial fibrillation undergoing total joint arthroplasty increase hospital burden. *Journal of Bone & Joint Surgery - American Volume* 2013;95(17):1606-11. doi: http://dx.doi.org/10.2106/JBJS.L.00882
27. Amusat N, Beaupre L, Jhangri GS, et al. Diabetes that impacts on routine activities predicts slower recovery after total knee arthroplasty: an observational study. *J Physiother* 2014;60(4):217-23. doi: http://dx.doi.org/10.1016/j.jphys.2014.09.006
28. Ayers DC, Franklin PD, Ploutz-Snyder R, et al. Total knee replacement outcome and coexisting physical and emotional illness. *Clinical Orthopaedics & Related Research* 2005;440(1):157-61 5p. doi: http://dx.doi.org/10.1097/01.blo.0000185447.43622.93
29. Belmont PJ, Goodman GP, Rodriguez M, et al. Predictors of hospital readmission following revision total knee arthroplasty. *Knee surgery, sports traumatology, arthroscopy : official journal of the ESSKA* 2016;24(10):3329-38. doi: http://dx.doi.org/10.1007/s00167-015-3782-6
30. Bolognesi MP, Marchant Jr MH, Viens NA, et al. The Impact of Diabetes on Perioperative Patient Outcomes After Total Hip and Total Knee Arthroplasty in the United States. *Journal of Arthroplasty* 2008;23(6 SUPPL.):92-98. doi: http://dx.doi.org/10.1016/j.arth.2008.05.012
31. Browne JA, Sandberg BF, D'Apuzzo MR, et al. Depression is associated with early postoperative outcomes following total joint arthroplasty: a nationwide database study. *Journal of Arthroplasty* 2014;29(3):481-3. doi: http://dx.doi.org/10.1016/j.arth.2013.08.025
32. Buller LT, Best MJ, Klika AK, et al. The influence of psychiatric comorbidity on perioperative outcomes following primary total hip and knee arthroplasty; A 17-year analysis of the national hospital discharge survey database. *Journal of Arthroplasty* 2015;30(2):165-70. doi: http://dx.doi.org/10.1016/j.arth.2014.08.034
33. Chan PKH, Brenkel IJ, Aderinto J. The outcome of total hip arthroplasty in diabetes mellitus. *British Journal of Diabetes and Vascular Disease* 2005;5(3):146-49. doi: http://dx.doi.org/10.1177/14746514050050030601

34. Clement ND, MacDonald D, Burnett R, et al. Diabetes does not influence the early outcome of total knee replacement: a prospective study assessing the Oxford knee score, short form 12, and patient satisfaction. *Knee* 2013;20(6):437-41. doi: http://dx.doi.org/10.1016/j.knee.2013.07.009
35. Cohen SM, Te HS, Levitsky J. Operative risk of total hip and knee arthroplasty in cirrhotic patients. *Journal of Arthroplasty* 2005;20(4):460-6. doi: http://dx.doi.org/10.1016/j.arth.2004.05.004
36. Courtney PM, Boniello AJ, Berger RA. Complications Following Outpatient Total Joint Arthroplasty: An Analysis of a National Database. *Journal of Arthroplasty* 2017;32(5):1426-30. doi: http://dx.doi.org/10.1016/j.arth.2016.11.055
37. Deegan BF, Richard RD, Bowen TR, et al. Impact of chronic kidney disease stage on lower-extremity arthroplasty. *Orthopedics* 2014;37(7):e613-e18. doi: http://dx.doi.org/10.3928/01477447-20140626-51
38. Deleuran T, Vilstrup H, Overgaard S, et al. Cirrhosis patients have increased risk of complications after hip or knee arthroplasty. *Acta Orthop* 2015;86(1):108-13 6p. doi: 10.3109/17453674.2014.961397
39. Dowsey MM, Choong PF. Obese Diabetic Patients are at Substantial Risk for Deep Infection after Primary TKA. *Clinical Orthopaedics & Related Research* 2009;467(6):1577-81 5p. doi: 10.1007/s11999-008-0551-6
40. Erkocak OF, Yoo JY, Restrepo C, et al. Incidence of Infection and Inhospital Mortality in Patients With Chronic Renal Failure After Total Joint Arthroplasty. *The Journal of arthroplasty* 2016;31(11):2437-41. doi: https://doi.org/10.1016/j.arth.2016.04.031
41. Gandhi R, Razak F, Tso P, et al. Metabolic syndrome and the incidence of symptomatic deep vein thrombosis following total knee arthroplasty. *The Journal of rheumatology* 2009;36(10):2298-301. doi: 10.3899/jrheum.090282
42. Gaston MS, Amin AK, Clayton RAE, et al. Does a history of cardiac disease or hypertension increase mortality following primary elective total hip arthroplasty? *Surgeon* 2007;5(5):260-65. doi: http://dx.doi.org/10.1016/S1479-666X(07)80021-7
43. Huddleston JI, Maloney WJ, Wang Y, et al. Adverse events after total knee arthroplasty: a national Medicare study. *The Journal of arthroplasty* 2009;24(6 Suppl):95-100. doi: 10.1016/j.arth.2009.05.001 [published Online First: 2009/07/07]
44. Hunt LP, Ben-Shlomo Y, Clark EM, et al. 45-day mortality after 467 779 knee replacements for osteoarthritis from the National Joint Registry for England and Wales: an observational study. *The Lancet* 2014;384(9952):1429-36. doi: https://doi.org/10.1016/S0140-6736(14)60540-7
45. Hunt LP, Ben-Shlomo Y, Clark EM, et al. 90-day mortality after 409 096 total hip replacements for osteoarthritis, from the National Joint Registry for England and Wales: a retrospective analysis. *The Lancet* 2013;382(9898):1097-104. doi: https://doi.org/10.1016/S0140-6736(13)61749-3
46. Iorio R, Williams KM, Marcantonio AJ, et al. Diabetes mellitus, hemoglobin A1C, and the incidence of total joint arthroplasty infection. *Journal of Arthroplasty* 2012;27(5):726-9.e1. doi: http://dx.doi.org/10.1016/j.arth.2011.09.013
47. Inacio MCS, Pratt NL, Roughead EE, et al. Evaluation of three co-morbidity measures to predict mortality in patients undergoing total joint arthroplasty. *Osteoarthritis and Cartilage* 2016;24(10):1718-26. doi: https://doi.org/10.1016/j.joca.2016.05.006
48. Jain NB, Guller U, Pietrobon R, et al. Comorbidities increase complication rates in patients having arthroplasty. *Clinical Orthopaedics and Related Research* 2005(435):232-38. doi: http://dx.doi.org/10.1097/01.blo.0000156479.97488.a2
49. Jämsen E, Peltola M, Eskelinen A, et al. Comorbid diseases as predictors of survival of primary total hip and knee replacements: a nationwide register-based study of 96 754 operations on

patients with primary osteoarthritis. *Annals of the Rheumatic Diseases* 2013;72(12):1975-82 8p. doi: 10.1136/annrheumdis-2012-202064

50. Jämsen E, Peltola M, Puolakka T, et al. Surgical outcomes of hip and knee arthroplasties for primary osteoarthritis in patients with Alzheimer's disease: a nationwide registry-based case-controlled study. *Bone & Joint Journal* 2015;97-B(5):654-61 8p. doi: 10.1302/0301-620X.97B5.34382
51. Jämsen E, Puolakka T, Peltola M, et al. Surgical outcomes of primary hip and knee replacements in patients with Parkinson's disease: a nationwide registry-based case-controlled study. *Bone & Joint Journal* 2014;96-B(4):486-91 6p. doi: 10.1302/0301-620X.96B4.33422
52. Jorgensen CC, Knop J, Nordentoft M, et al. Psychiatric disorders and psychopharmacologic treatment as risk factors in elective fast-track total hip and knee arthroplasty. *Anesthesiology* 2015;123(6):1281-91. doi: http://dx.doi.org/10.1097/ALN.0000000000000632
53. Jorgensen CC, Madsbad S, Kehlet H. Postoperative morbidity and mortality in type-2 diabetics after fast-track primary total hip and knee arthroplasty. *Anesthesia and Analgesia* 2015;120(1):230-38. doi: http://dx.doi.org/10.1213/ANE.0000000000000451
54. Judge A, Javaid MK, Arden NK, et al. Clinical tool to identify patients who are most likely to achieve long-term improvement in physical function after total hip arthroplasty. *Arthritis Care & Research* 2012;64(6):881-89. doi: 10.1002/acr.21594
55. Kapoor A, Chew P, Silliman RA, et al. Venous thromboembolism after joint replacement in older male veterans with comorbidity. *Journal of the American Geriatrics Society* 2013;61(4):590-601. doi: http://dx.doi.org/10.1111/jgs.12161
56. Kapoor A, Labonte AJ, Winter MR, et al. Risk of venous thromboembolism after total hip and knee replacement in older adults with comorbidity and co-occurring comorbidities in the Nationwide Inpatient Sample (2003-2006). *BMC geriatrics* 2010;10:63. doi: http://dx.doi.org/10.1186/1471-2318-10-63
57. Karam JA, Huang RC, Abraham JA, et al. Total joint arthroplasty in cancer patients. *Journal of Arthroplasty* 2015;30(5):758-61. doi: http://dx.doi.org/10.1016/j.arth.2014.12.017
58. Keswani A, Lovy AJ, Robinson J, et al. Risk Factors Predict Increased Length of Stay and Readmission Rates in Revision Joint Arthroplasty. *Journal of Arthroplasty* 2016;31(3):603-8. doi: https://dx.doi.org/10.1016/j.arth.2015.09.050
59. Kildow BJ, Agaba P, Moore BF, et al. Postoperative Impact of Diabetes, Chronic Kidney Disease, Hemodialysis, and Renal Transplant After Total Hip Arthroplasty. *Journal of Arthroplasty* 2017;15 doi: http://dx.doi.org/10.1016/j.arth.2017.01.018
60. Kuo FC, Lin PC, Lu YD, et al. Chronic Kidney Disease Is an Independent Risk Factor for Transfusion, Cardiovascular Complication, and Thirty-Day Readmission in Minimally Invasive Total Knee Arthroplasty. *Journal of Arthroplasty* 2017;32(5):1630-34. doi: http://dx.doi.org/10.1016/j.arth.2016.12.006
61. Lee SW, Kumar GK, Kim TK. Unplanned readmissions after primary total knee arthroplasty in Korean patients: Rate, causes, and risk factors. *Knee* 2016;11 doi: http://dx.doi.org/10.1016/j.knee.2016.05.011
62. Liao KM, Lu HY. A national analysis of complications following total hip replacement in patients with chronic obstructive pulmonary disease. *Medicine (United States)* 2016;95 (12) (no pagination)(e3182) doi: http://dx.doi.org/10.1097/MD.0000000000003182
63. Marchant MH, Jr., Viens NA, Cook C, et al. The impact of glycemic control and diabetes mellitus on perioperative outcomes after total joint arthroplasty. *Journal of Bone & Joint Surgery - American Volume* 2009;91(7):1621-9. doi: http://dx.doi.org/10.2106/JBJS.H.00116
64. Martinez-Huedo MA, Villanueva M, De Andres AL, et al. Trends 2001 to 2008 in incidence and immediate postoperative outcomes for major joint replacement among Spanish adults suffering diabetes. *European Journal of Orthopaedic Surgery and Traumatology* 2013;23(1):53-59. doi: http://dx.doi.org/10.1007/s00590-011-0915-6

65. Mazoch M, Barnes CL, Cooper K. Complications in diabetic patients undergoing revision total joint arthroplasty. *Current Orthopaedic Practice* 2016;27(3):296-302 7p. doi: http://dx.doi.org/10.1097/BCO.0000000000000360
66. McCleery MA, Leach WJ, Norwood T. Rates of infection and revision in patients with renal disease undergoing total knee replacement in Scotland. *Journal of Bone & Joint Surgery, British Volume* 2010;92(11):1535-39 5p. doi: 10.1302/0301-620X.92B11.23870
67. Meding JB, Reddleman K, Keating ME, et al. Total knee replacement in patients with diabetes mellitus. *Clin Orthop Relat Res* 2003(416):208-16. doi: 10.1097/01.blo.0000093002.90435.56
68. Menendez ME, Park KJ, Barnes CL. Early Postoperative Outcomes After Total Joint Arthroplasty in Patients With Multiple Myeloma. *Journal of Arthroplasty* 2016;31(8):1645-48. doi: http://dx.doi.org/10.1016/j.arth.2016.01.029
69. Miric A, Inacio MC, Namba RS. The effect of chronic kidney disease on total hip arthroplasty. *Journal of Arthroplasty* 2014;29(6):1225-30. doi: http://dx.doi.org/10.1016/j.arth.2013.12.031
70. Miric A, Inacio MC, Namba RS. Can total knee arthroplasty be safely performed in patients with chronic renal disease? *Acta Orthop* 2014;85(1):71-8. doi: http://dx.doi.org/10.3109/17453674.2013.878829
71. Moon HK, Han CD, Yang IH, et al. Factors affecting outcome after total knee arthroplasty in patients with diabetes mellitus. *Yonsei Med J* 2008;49(1):129-37. doi: http://dx.doi.org/10.3349/ymj.2008.49.1.129
72. Pedersen AB, Mehnert F, Johnsen SP, et al. Risk of revision of a total hip replacement in patients with diabetes mellitus: A population-based follow up study. *Journal of Bone and Joint Surgery - Series B* 2010;92(7):929-34. doi: http://dx.doi.org/10.1302/0301-620X.92B7.24461
73. Perez-Prieto D, Gil-Gonzalez S, Pelfort X, et al. Influence of depression on total knee arthroplasty outcomes. *Journal of Arthroplasty* 2014;29(1):44-47. doi: http://dx.doi.org/10.1016/j.arth.2013.04.030
74. Radtke K, Tetzlaff T, Vaske B, et al. Arthroplasty-center related retrospective analysis of risk factors for Periprosthetic Joint Infection after primary and after revision Total Hip Arthroplasty. *Technology and Health Care* 2016;24(5):721-28. doi: http://dx.doi.org/10.3233/THC-161158
75. Rajamaki TJ, Jamsen E, Puolakka PA, et al. Diabetes is associated with persistent pain after hip and knee replacement. *Acta Orthop* 2015;86(5):586-93. doi: http://dx.doi.org/10.3109/17453674.2015.1044389
76. Rasouli MR, Menendez ME, Sayadipour A, et al. Direct Cost and Complications Associated With Total Joint Arthroplasty in Patients With Preoperative Anxiety and Depression. *The Journal of arthroplasty* 2016;31(2):533-6. doi: 10.1016/j.arth.2015.09.015 [published Online First: 2015/10/21]
77. Robertson F, Geddes J, Ridley D, et al. Patients with Type 2 diabetes mellitus have a worse functional outcome post knee arthroplasty: a matched cohort study. *Knee* 2012;19(4):286-9. doi: http://dx.doi.org/10.1016/j.knee.2011.06.001
78. Sanders RD, Bottle A, Jameson SS, et al. Independent preoperative predictors of outcomes in orthopedic and vascular surgery: the influence of time interval between an acute coronary syndrome or stroke and the operation. *Ann Surg* 2012;255(5):901-7. doi: http://dx.doi.org/10.1097/SLA.0b013e31824c438d
79. Seol YJ, Yoon TR, Lee DH, et al. Outcome analysis of hip or knee arthroplasty in patients with cirrhotic liver disease. *Journal of Orthopaedics* 2017;14(1):171-75. doi: http://dx.doi.org/10.1016/j.jor.2016.12.011
80. Sikora-Klak J, Zarling B, Bergum C, et al. The Effect of Comorbidities on Discharge Disposition and Readmission for Total Joint Arthroplasty Patients. *Journal of Arthroplasty* 2017;32(5):1414-17. doi: http://dx.doi.org/10.1016/j.arth.2016.11.035

81. Singh JA. Effect of comorbidity on quality of life of male veterans with prevalent primary total knee arthroplasty. *Clinical Rheumatology* 2009;28(9):1083-9. doi: http://dx.doi.org/10.1007/s10067-009-1195-y
82. Singh JA, Lewallen DG. Diabetes: A risk factor for poor functional outcome after total knee arthroplasty. *PLoS ONE* 2013;8 (11) (no pagination)(e78991) doi: http://dx.doi.org/10.1371/journal.pone.0078991
83. Singh JA, Lewallen DG. Medical comorbidity is associated with persistent index hip pain after total hip arthroplasty. *Pain medicine (Malden, Mass)* 2013;14(8):1222-29. doi: http://dx.doi.org/10.1111/pme.12153
84. Singh JA, Lewallen DG. Medical and psychological comorbidity predicts poor pain outcomes after total knee arthroplasty. *Rheumatology (Oxford, England)* 2013;52(5):916-23. doi: 10.1093/rheumatology/kes402
85. Singh JA, Lewallen DG. Underlying diagnosis predicts patient-reported outcomes after revision total knee arthroplasty. *Rheumatology (United Kingdom)* 2014;53(2):361-66. doi: http://dx.doi.org/10.1093/rheumatology/ket357
86. Singh JA, Lewallen DG. Cerebrovascular disease is associated with outcomes after total knee arthroplasty: a US total joint registry study. *Journal of Arthroplasty* 2014;29(1):40-3. doi: http://dx.doi.org/10.1016/j.arth.2013.04.003
87. Singh JA, Lewallen DG. Depression in primary TKA and higher medical comorbidities in revision TKA are associated with suboptimal subjective improvement in knee function. *BMC Musculoskelet Disord* 2014;15:127. doi: 10.1186/1471-2474-15-127 [published Online First: 2014/04/15]
88. Stundner O, Kirksey M, Chiu YL, et al. Demographics and Perioperative Outcome in Patients with Depression and Anxiety Undergoing Total Joint Arthroplasty: A Population-Based Study. *Psychosomatics* 2013;54(2):149-57. doi: http://dx.doi.org/10.1016/j.psym.2012.08.009
89. Tiberi JV, 3rd, Hansen V, El-Abbadi N, et al. Increased complication rates after hip and knee arthroplasty in patients with cirrhosis of the liver. *Clinical Orthopaedics & Related Research* 2014;472(9):2774-8. doi: http://dx.doi.org/10.1007/s11999-014-3681-z
90. Vannini P, Ciavarella A, Olmi R, et al. Diabetes as pro-infective risk factor in total hip replacement. *Acta Diabetol Lat* 1984;21(3):275-80.
91. Wang S, Zhao Y. Diabetes mellitus and the incidence of deep vein thrombosis after total knee arthroplasty: a retrospective study. *The Journal of arthroplasty* 2013;28(4):595-7. doi: 10.1016/j.arth.2012.07.023 [published Online First: 2012/11/17]
92. Warth LC, Pugely AJ, Martin CT, et al. Total Joint Arthroplasty in Patients with Chronic Renal Disease: Is It Worth the Risk? *Journal of Arthroplasty* 2015;30(9 Suppl):51-4. doi: http://dx.doi.org/10.1016/j.arth.2014.12.037
93. Zhao Z, Wang S, Ma W, et al. Diabetes mellitus increases the incidence of deep vein thrombosis after total knee arthroplasty. *Archives of Orthopaedic and Trauma Surgery* 2014;134(1):79-83. doi: 10.1007/s00402-013-1894-3
94. Singh JA, Lewallen D. Age, gender, obesity, and depression are associated with patient-related pain and function outcome after revision total hip arthroplasty. *Clinical Rheumatology* 2009;28(12):1419-30. doi: http://dx.doi.org/10.1007/s10067-009-1267-z
95. Judge A, Arden NK, Batra RN, et al. The association of patient characteristics and surgical variables on symptoms of pain and function over 5 years following primary hip-replacement surgery: a prospective cohort study. *BMJ Open* 2013;3(3):e002453. doi: 10.1136/bmjopen-2012-002453
96. Santaguida PL, Hawker GA, Hudak PL, et al. Patient characteristics affecting the prognosis of total hip and knee joint arthroplasty: a systematic review. *Canadian Journal of Surgery* 2008;51(6):428-36.

97. Wright JG, Hawker GA, Bombardier C, et al. Physician enthusiasm as an explanation for area variation in the utilization of knee replacement surgery. *Med Care* 1999;37(9):946-56. doi: http://dx.doi.org/10.1097/00005650-199909000-00010 [published Online First: 1999/09/24]

98. Dieppe PA. Inequalities in the Provision of Surgical Interventions: Whose Responsibility? *Journal of Rheumatology* 2011;38(3):401-02. doi: 10.3899/jrheum.101209

# FIGURE LEGEND

Figure 1 – Flow chart

Figure 2 – Forest plots of short-term outcomes

Figure 3 – Forest plots of long-term outcomes

Figure 4 – Funnel plot showing 95% confidence limits for any surgical complications, surgical site infections, venous thromboembolism, readmissions to hospital and pain in diabetic patients

Figure 5 – Funnel plot showing 95% confidence limits for any surgical site infections, readmissions to hospital, short-term mortality and long-term mortality in kidney disease patients

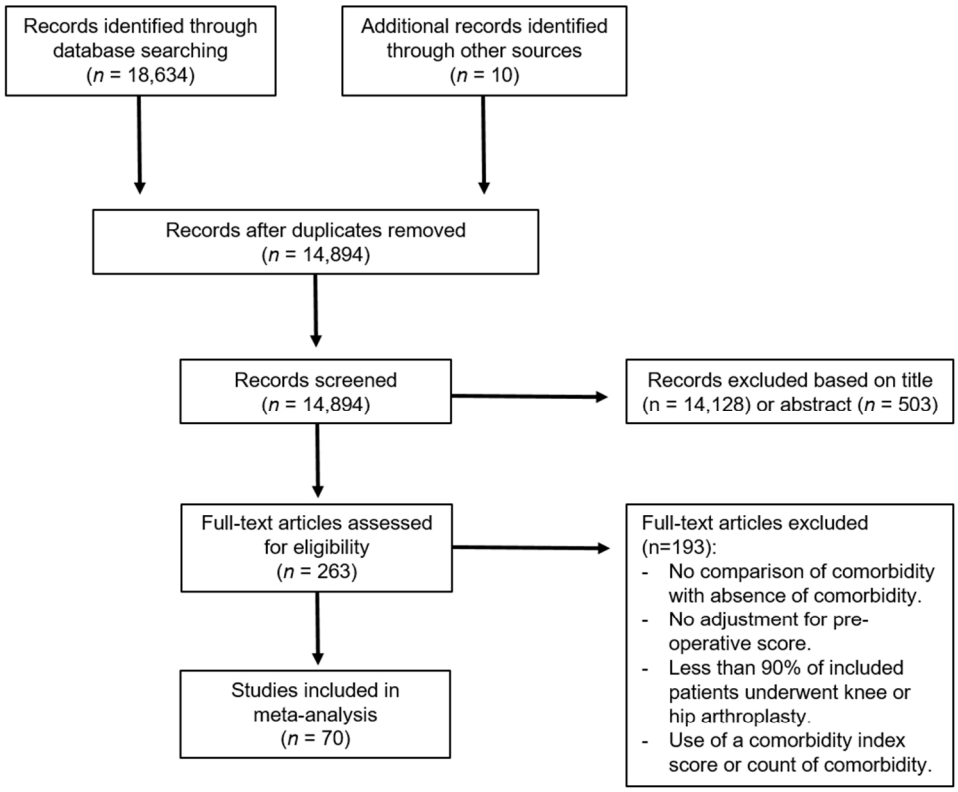


Figure 1 – Flow chart

87x72mm (300 x 300 DPI)

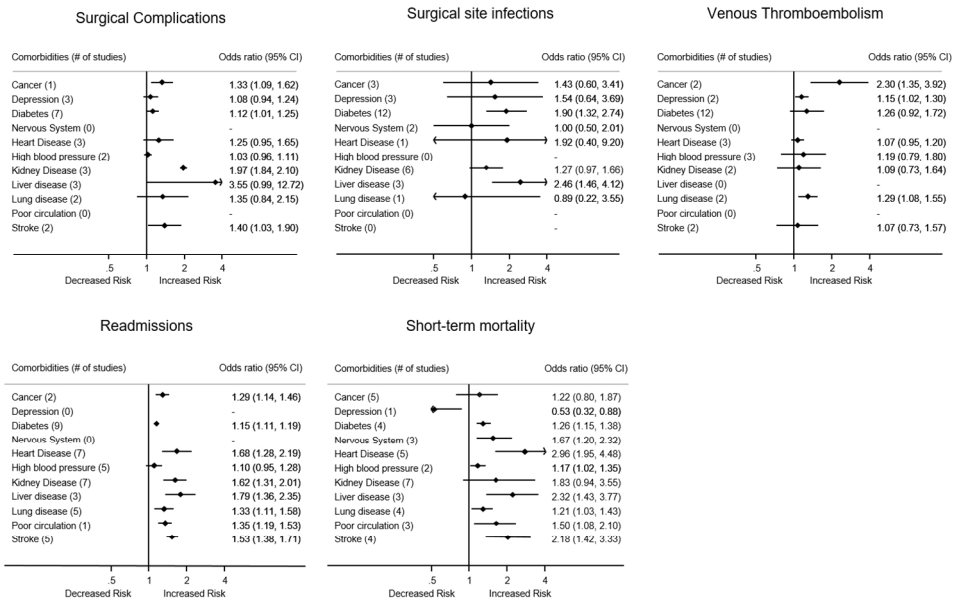


Figure 2 – Forest plots of short-term outcomes

131x86mm (300 x 300 DPI)

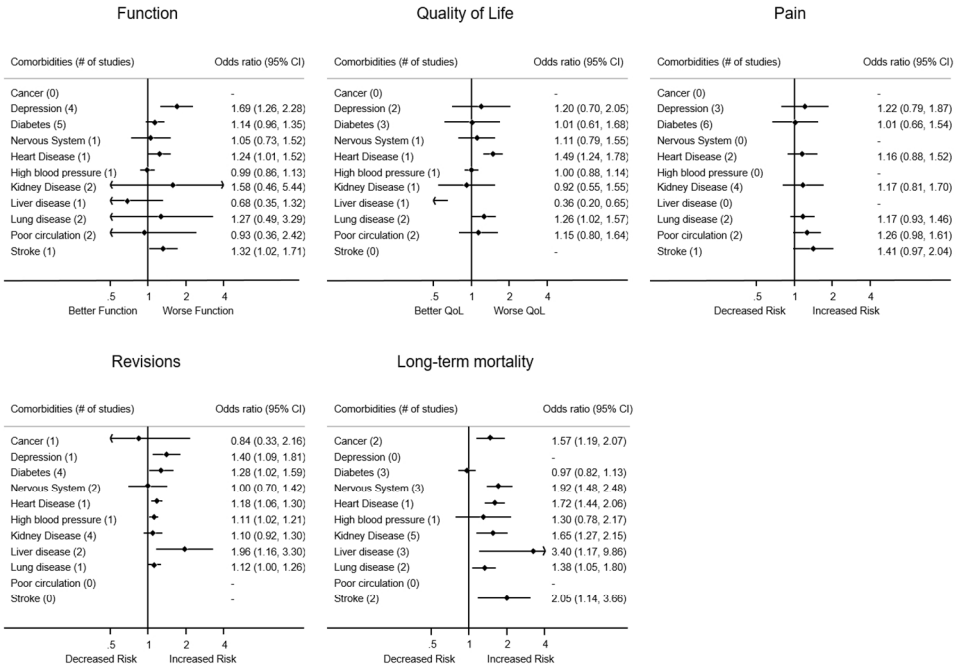


Figure 3 – Forest plots of long-term outcomes

122x88mm (300 x 300 DPI)

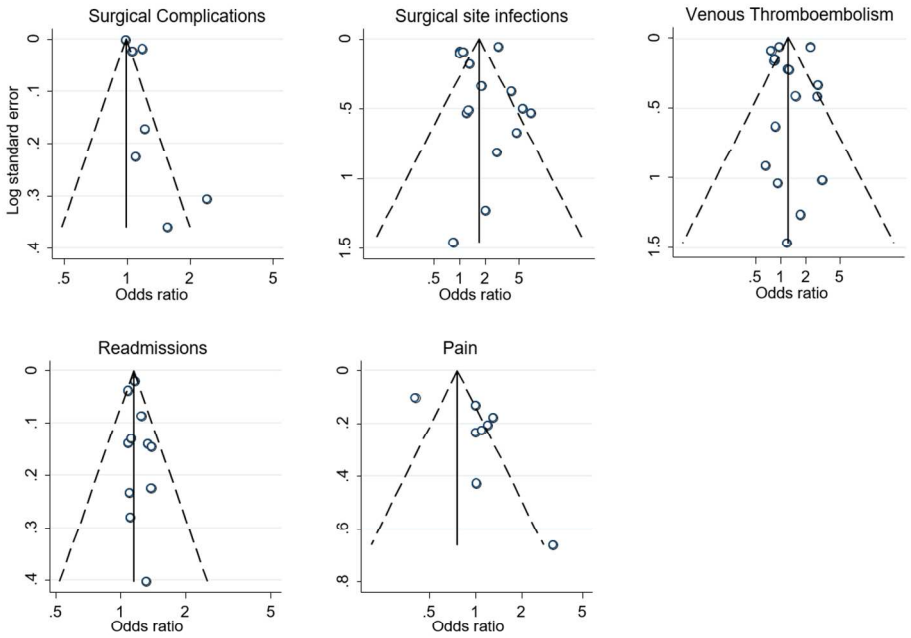


Figure 4 – Funnel plot showing 95% confidence limits for any surgical complications, surgical site infections, venous thromboembolism, readmissions to hospital and pain in diabetic patients

111x84mm (300 x 300 DPI)

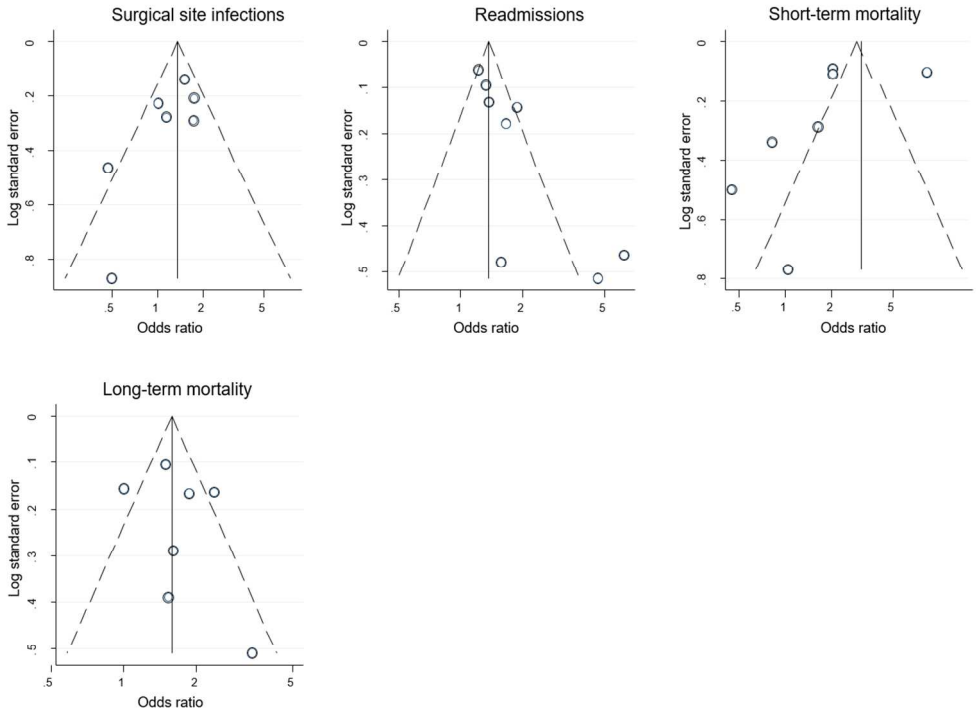


Figure 5 – Funnel plot showing 95% confidence limits for any surgical site infections, readmissions to hospital, short-term mortality and long-term mortality in kidney disease patients

111x84mm (300 x 300 DPI)

*Supplementary Information 1 – Search string*

| | |
|---|---|
| 1 | knee replacement.mp. or exp knee arthroplasty/ |
| 2 | hip replacement.mp. or exp hip arthroplasty/ |
| 3 | knee arthroplasty.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] |
| 4 | hip arthroplasty.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] |
| 5 | exp Arthroplasty, replacement/ |
| 6 | exp hip surgery/ or hip surgery.mp. |
| 7 | exp knee surgery/ or knee surgery.mp. |
| 8 | 1 or 3 or 7 |
| 9 | 2 or 4 or 6 |
| 10 | 8 and 9 |
| 11 | 8 or 9 or 10 |
| 12 | 11 or 5 |
| 13 | Humans/ |
| 14 | exp Comorbidity/ |
| 15 | charlson comorbidity index.mp. |
| 16 | elixhauser comorbidity index.mp. |
| 17 | exp Cardiovascular Diseases/ |
| 18 | exp Hypertension/ |
| 19 | exp Stroke/ |
| 20 | exp Peripheral Vascular Diseases/ |
| 21 | exp Lung Diseases/ |
| 22 | exp Diabetes Mellitus/ |
| 23 | exp Kidney Diseases/ |
| 24 | exp Nervous System Diseases/ |
| 25 | exp Liver Diseases/ |
| 26 | exp Neoplasms/ |
| 27 | exp Depression/ |
| 28 | exp Diabetes Complications/ |
| 31 | underlying diagnosis.mp. |
| 32 | comorbidit*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] |
| 33 | 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 |
| 34 | exp Postoperative Complications/ |
| 35 | exp Treatment Outcome/ |
| 36 | exp "Quality of Life"/ |

37 exp Mortality/
38 exp Infection/
39 exp Patient Readmission/
40 exp Reoperation/
41 exp Health Status/
42 outcomes.mp.
43 mortality.mp.
44 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43
45 12 and 13 and 33 and 44

*Supplementary Information 2 – Description of selected studies (n = 70)*

| Study | Data | | | Patient Sample | | | Comorbid Conditions | Outcomes |
|---|---|---|---|---|---|---|---|---|
| | Country | Years of data | Data source | Type of surgery | Primary or Revision surgery | Sample Size | | |
| Ackland (2011) | UK | 2004-2005 | Single-site | THA and TKA | Primary & Revision | 526 | Chronic Kidney disease | Infection, Pain, Postoperative morbidity |
| Adams (2013) | USA | 2001-2009 | Joint registry | TKA | Primary | 40,491 | Controlled diabetes | All-cause rehospitalizations, Deep Infection, Deep vein thrombosis, Revisions |
| Aggarwal (2013) | USA | 2007-2011 | Single-site | THA and TKA | Primary & Revision | 323 | Atrial Fibrillation | Readmission rate |
| Amusat (2014) | Canada | NS | Multi-site | TKA | Primary | 405 | Diabetes without impact on routine activities, Kidney Disease | Overall health (HUI3) -6m post-operative, WOMAC function, WOMAC pain |
| Ayers (2005) | USA | NS | Single-site | TKA | Primary | 165 | Lower extremity (PVD, venous insufficiency) | Mean change in Physical Function (SF-36) 12mths post surgery, Mean change in Physical Function (WOMAC) 12mths post surgery |
| Belmont (2016) | USA | 2011-2012 | Multi-site | TKA | Revision | 1754 | Cardiac disease, COPD, CVA/Stroke, Diabetes, Hypertension | Readmissions within 30 days |
| Bolognesi (2008) | USA | 1988-2003 | Administrative data | THA and TKA | Primary & Revision | 2,249,427 | Diabetes | DVT, Died, Infection |
| Browne (2014) | USA | 2006-2008 | Administrative data | THA and TKA | Primary | 497,222 | Depression | Infection, Pulmonary embolism |
| Buller (2015) | USA | 1990-2007 | Administrative data | THA and TKA | Primary | 8,379,490 | Chronic pulmonary disease, CAD, Depression, Diabetes, Hypertension | Adverse Events (wound complication , postoperative shock, postoperative bleeding, acute postoperative infection, acute postoperative anemia, acute renal failure, acute myocardial infarction, pulmonary embolism, induced mental disorder, pneumonia, pulmonary insufficiency, DVT, intubation and transfusion of blood) |
| Chan (2005) | UK | 2000-2003 | Single-site | THA | NS | 1,297 | Diabetes | Deep Infection, Deep vein thrombosis |
| Clement (2013) | UK | NS | Single-site | TKA | Primary | 2,389 | Depression, Diabetes, Heart disease, High blood pressure, | Post-operative OKS at 12mths, post-operative SF-12 at 12mths |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Kidney disease, Lung disease, Neurological diseases, Vascular disease | |
| Cohen (2005) | USA | 1986-2002 | Single-site | THA and TKA | Primary | 122 | Liver cirrhosis | Death, Major complications |
| Courtney (2017) | USA | 2011-2014 | Multi-site | THA and TKA | Primary | 169,406 | Cardiac disease, Diabetes, History of stroke, Preoperative creatinine >1.5mg/dL | 30 day complications (SSI, pneumonia, respiratory, pulmonary embolism, DVT, stroke, cardiac arrest, renal failure, UTI, sepsis, septic shock), 30 day readmissions |
| Deegan (2014) | USA | 2004-2011 | Single-site | THA and TKA | NS | 779 | Chronic Kidney Disease | Death, Infections, Revisions |
| Deleuran (2015) | Denmark | 1995-2001 | Administrative data | THA and TKA | Primary | 109,522 | Liver cirrhosis | Deep prosthetic infection, Intraoperative complications, Mortality within 30 days Readmission within 30 days, Revision in one year |
| Dowsey (2009) | Australia | 1998-2005 | Single-site | TKA | Primary | 1,214 | Cardiovascular disease, Diabetes, Respiratory diseases | Deep Infection |
| Erkocak (2016) | USA | 2000-2012 | Single-site | THA and TKA | NS | 1077 | Chronic Renal failure | Surgical site infections, In-hospital mortality |
| Gandhi (2009) | Canada | 1998-2006 | Single-site | TKA | NS | 1,460 | Diabetes, Hypertension | DVT within 3 months |
| Gaston (2007) | UK | 1998-2006 | Single-site | THA | Primary | 1,744 | Cerebrovascular disease, CHF, COPD, Diabetes | Mortality within 3mths after admission |
| Huddleston (2009) | USA | 2002-2004 | Multi-site | TKA | NS | 2,033 | Diabetes | Adverse events (deep infections, necrosis, nerve injury, dislocation, cardiovascular complication, periprosthetic fracture, Revision, UTI, DVT, Pneumonia, Death) |
| Hunt (2013) | UK | 2003-2011 | Joint registry | THA | NS | 409,096 | CHF, PVD, CVD, Chronic Pulmonary disease, Diabetes without complications, Renal disease, Cancer, Dementia | 90-day mortality |
| Hunt (2014) | UK | 2003-2011 | Joint registry | TKA | NS | 467,779 | CHF, PVD, CVD, Chronic Pulmonary disease, Diabetes without complications, Renal disease, Cancer, Dementia | 45-day mortality |
| Inacio (2016) | Australia | 2001-2012 | Administrative data | THA | NS | 30820 | Liver disease, CHF, Renal disease, Parkinson's disease, Dementia, | 90-day mortality, 1-year mortality |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Chronic airway disease, Solid tumour without metastasis | |
| Iorio (2012) | USA | 2004-2009 | Single-site | THA and TKA | Primary | 1,529 | Diabetes | Infection |
| Jain (2005) | USA | 1988-2000 | Administrative data | THA and TKA and shoulder arthroplasty | Primary | 959,839 | Diabetes, Hypertension | Complications (infections, wound infections, pulmonary embolism, thromophlebitis, vascular complications, other) |
| Jamsen (2013) | Finland | 1998-2008 | Joint registry | THA and TKA | Primary | 96,754 | Cancer, CHD, Depression, Diabetes, Hypertension (without CVD), Pulmonary disease | Risk of Revision surgery |
| Jamsen (2014) | Finland | 1998-2009 | Administrative data + Joint registry | THA and TKA | Primary | 3,428 | Parkinson's disease | Infection at 1 year, Mortality > 1 year Revisions in 0-2 years postoperative |
| Jamsen (2015) | Finland | 1998-2009 | Administrative data + Joint registry | THA and TKA | Primary | 4,526 | Alzheimer's disease | Mortality after 10 years, Rate of surgical site infection, Risk of Revision |
| Jorgensen (2015a) | Denmark | 2010-2012 | Multi-site | THA and TKA | Primary | 8,757 | Cardiovascular disease, Pulmonary disease | 90-day readmission |
| Jorgensen (2015b) | Denmark | 2010-2012 | Multi-site | THA and TKA | Primary | 8,055 | Diabetes Type II | "Diabetes-related morbidity" (cardiac arrhythmias, acute congestive heart failure, MI, prosthetic or wound infections, renal insufficiency, cerebral attacks, pneumonia, UTI>4days, dysregulated blood glucose, other infections), 90-day readmission |
| Judge (2012) | UK | 1993-1995 | Multisite | THA | NS | 282 | Diabetes | SF-36 Physical functioning |
| Kapoor (2010) | USA | 2003-2006 | Administrative data | THA and TKA | Primary | 316,671 | COPD, CAD, Cerebrovascular disease, Diabetes | Venous Thromboembolism |
| Kapoor (2013) | USA | 2002-2009 | Administrative data | THA and TKA | Primary & Revision | 24,051 | COPD, CAD, Cerebrovascular disease, Diabetes | Venous Thromboembolism |
| Karam (2015) | USA | 2000-2011 | Single-site | THA and TKA | Primary & Revision | 26,415 | Cancer | Deep vein thrombosis, Mortality Overall in-hospital complications, Periprosthetic joint infection |
| Keswani (2016) | USA | 2011-2013 | Multi-site | THA and TKA | Revision | 10,112 | Disseminated cancer, Cardiac disease, Diabetes, Renal disease, Stroke, Hypertension, Pulmonary disease | 30-day readmissions |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Kildow (2017) | USA | 2005-2012 | Multi-site | THA | NS | 61,778 | Diabetes | DVT- 30 days, Prosthetic Joint infection - 90 days, THA Revision - 2-years |
| Kuo (2017) | Taiwan | 2009-2012 | Single-site | TKA | Primary | 615 | Chronic Kidney Disease | 30-day readmissions |
| Lee (2017) | Korea | 2004-2013 | Single-site | TKA | Primary | 3,049 | Diabetes, Hypertension | 90-day readmission |
| Liao (2016) | Taiwan | 2004-2008 | Administrative data | THA | NS | 2,426 | Cardiovascular disease, CVA, Chronic Kidney disease, COPD, Hypertension | 1-year mortality, 30-day readmissions |
| Marchant (2009) | USA | 1988-2005 | Administrative data | THA and TKA | Primary & Revision | 1,030,013 | Controlled diabetes | DVT, Died, Infection |
| Martinez (2013) | Spain | 2001-2008 | Administrative data | THA and TKA | Primary | 373,131 | Diabetes | In-hospital mortality |
| Mazoch (2009) | USA | 2004-2012 | Single-site | THA and TKA | Revision | 130 | Diabetes | All complications, Infection |
| McCleery (2010) | UK | 1985-2008 | Joint registry | TKA | NS | 59,288 | Renal failure | Early infection (<90 days), Late Revision |
| Meding (2003) | USA | 1987-1999 | Single-site | TKA | Primary | 5,220 | Diabetes | Deep Infection, DVT, Knee Society Pain score - 1yr |
| Menendez (2016) | USA | 2002-2011 | Multi-site | THA and TKA | Primary | 6,054,344 | Multiple Myeloma | In-hospital mortality, SSI, Thromboembolic events |
| Miric (2014a) | USA | 2005-2010 | Joint registry | TKA | Primary | 41,852 | Chronic Renal Disease | DVT, Mortality (anytime), Mortality within 90 days, Readmission within 90 days, Revision, SSI deep |
| Miric (2014b) | USA | 2006-2010 | Joint registry | THA | Primary | 20,720 | Chronic Kidney Disease | DVT, Mortality (anytime), Mortality within 90 days, Readmission within 90 days, Revision (any), SSI (any) |
| Moon (2008) | Korea | 1995-2004 | Single-site | TKA | Primary | 1,581 | Diabetes | Deep joint infection, DVT, Knee Society Score – function, Knee Society Score – Pain, Overall complications |
| Pedersen (2010) | Denmark | 1996-2005 | Joint registry | THA | Primary | 57,575 | Diabetes | Overall Revisions |
| Perez (2014) | Spain | NS | Single-site | TKA | NS | 736 | Depression | SF-36 Physical component scores, WOMAC score |
| Radkte (2016) | Germany | 2011-2012 | Single-site | THA | Primary | 498 | Cancer, Depression, Diabetes | Periprosthetic joint infection |
| Rajamaki (2015) | Finland | 2009-2011 | Single-site | THA and TKA | Primary | 134 | Glucose metabolism abnormalities | Persistent Pain |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Rasouli (2016) | USA | 2009-2009 | Single-site | THA and TKA | Primary & Revision | 1,969 | Depression | Surgical complications |
| Robertson (2012) | UK | 1989-2002 | Single-site | TKA | NS | 734 | Diabetes | Knee Society knee score year 1 |
| Sanders (2012) | UK | 2006-2010 | Administrative data | THA and TKA | Primary | 414,985 | Cancer, Diabetes, Heart Failure, Hypertension, Liver disease, PVD, Renal failure, Respiratory disease, Stroke | In-hospital mortality, Readmission |
| Seol (2017) | South Korea | 2007-2015 | Multi-site | THA and TKA | Primary | 143 | Liver Cirrhosis | Infections, Medical complications |
| Sikora-Klak (2017) | USA | 2012-2014 | Single-site | THA and TKA | Primary | 2,914 | Diabetes | 90-day readmission |
| Singh (2014a) | USA | 1993-2005 | Joint registry | TKA | Primary and Revision | 8,672 | Depression | Knee status: much better 2- years |
| Singh (2009) | USA | 1993-2005 | Joint registry | THA | Revision | 2,687 | Depression | Moderate-Severe ADL limitation - 2 years<br>Moderate-severe pain - 2 years |
| Singh (2014b) | USA | 1993-2005 | Joint registry | TKA | Primary & Revision | 7,139 | Cerebrovascular disease | Moderate-Severe ADL limitation - 2 years<br>Moderate-severe pain - 2 years |
| Singh (2013a) | USA | 1993-2005 | Joint registry | THA | Primary & Revision | 8,394 | COPD, Diabetes, Heart disease, PVD, Renal disease | Moderate-severe pain at 2 years |
| Singh (2013b) | USA | 1993-2005 | Joint registry | TKA | Primary | 7,139 | Diabetes without complications | Moderate-severe ADL limitation 2 -years |
| Singh (2013c) | USA | 1993-2005 | Joint registry | TKA | Primary | 8,672 | COPD, Depression, Diabetes, Heart disease, PVD, Renal disease | Moderate-severe pain at 2 years |
| Singh (2014) | USA | 1993-2005 | Joint registry | TKA | Revision | 1,533 | Depression | Moderate-severe pain at 2 years |
| Stundner (2013) | USA | 2000-2008 | Administrative data | THA and TKA | Primary | 1,212,493 | Depression | In-hospital mortality, Major complications, Sepsis, Venous Thromboembolism |
| Tiberi (2014) | USA | 2000-2012 | Single-site | THA and TKA | NS | 230 | Liver cirrhosis | Infections within 90 days, Mortality most recent follow-up, Mortality within 90 days, Readmissions 90 days, Revision surgery during follow up |
| Vannini (1984) | Italy | 1969-1979 | Single-site | THA | NS | 1,227 | Diabetes | Post-surgery infections |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Wang (2013) | China | 2003-2011 | Single-site | TKA | NS | 245 | CHD, Diabetes, Hypertension | DVT |
| Warth (2015) | USA | 2006-2012 | Administrative data | THA and TKA | Primary | 74,300 | Chronic Renal disease | Overall complications |
| Zhao (2014) | China | 2011-2013 | Single-site | TKA | NS | 358 | Diabetes, Hypertension | DVT within 14 days |

*Note.* NS = not stated; THA = Total Hip Arthroplasty; TKA = Total Knee Arthroplasty; PVD = Peripheral Vascular Disease; COPD = Chronic Obstructive Pulmonary Disorder; CAD = Coronary Artery Disease ; CHD = Coronary Heart Disease ; CHF = Coronary Heart Failure; CVA/CVD = Cerebrovascular Accident/Disease; SF-36= Short-form 36; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; OKS = Oxford Knee Score; SF-12 = Short-form 12; SSI = Surgical Site Infection; DVT = Deep Vein Thrombosis; UTI = Uterine Infection; MI = Myocardial Infarction.

*Supplementary Information 3 - Quality appraisal of included 70 studies*

| Study | Patient Selection | | | | | Comparability | | Outcome Assessment | | | Overall quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Cohort Representative? | Patients drawn from same community? | Presence of comorbidities verified? | Outcome not present at the start? | Cohort drawn from multiple communities? | Controlled for age and sex? | Controlled for SES and Ethnicity? | Outcome of interest clearly defined? | Follow-up long enough? | Follow-up adequate? | |
| Ackland (2011) | Yes | Yes | Yes | Yes | No | No | No | Yes | NS | No | Low quality |
| Adams (2013) | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | High quality |
| Aggarwal (2013) | Yes | Yes | Yes | Yes | No | Yes | No | Yes | NS | No | Low quality |
| Amusat (2014) | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | No | Low quality |
| Ayers (2005) | No | Yes | Yes | Yes | No | Yes | No | Yes | Yes | No | Low quality |
| Belmont (2016) | Yes | Yes | Yes | Yes | Yes | Yes | No | No | Yes | Yes | Low quality |
| Bolognesi (2008) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | NS | No | Low quality |
| Browne (2014) | Yes | Yes | Yes | Yes | Yes | Yes | Yes (ethnicity) | No | NS | No | Low quality |
| Bulle (2015) | Yes | Yes | Yes | Yes | Yes | Yes | No | No | NS | No | Low quality |
| Chan (2004) | Yes | Yes | Yes | Yes | No | Yes | No | Yes | Yes | Yes | Low quality |
| Clement (2013) | Yes | Yes | Yes | Yes | No | No | No | Yes | Yes | Yes | Low quality |
| Cohen (2005) | Yes | Yes | Yes | Yes | No | No | No | Yes | Yes | No | Low quality |
| Courtney (2017) | Yes | Yes | Yes | Yes | Yes | Yes | Yes (ethnicity) | No | Yes | Yes | Low quality |
| Deegan (2014) | Yes | Yes | Yes | Yes | No | Yes | No | Yes | Yes | Yes | Low quality |
| Deleuran (2015) | Yes | Yes | Yes | Yes | Yes | Yes | No | No | Yes | Yes | Low quality |
| Dowsey (2009) | Yes | Yes | Yes | Yes | No | Yes | No | Yes | Yes | Yes | Low quality |
| Ekocak (2016) | Yes | Yes | Yes | Yes | No | No | No | No | Yes | Yes | Low quality |
| Gandhi (2009) | Yes | Yes | Yes | Yes | No | Yes | No | Yes | Yes | No | Low quality |
| Gaston (2007) | Yes | Yes | Yes | Yes | No | Yes | No | Yes | Yes | Yes | Low quality |
| Huddleston (2009) | Yes | Yes | Yes | Yes | Yes | Yes | Yes (ethnicity) | No | Yes | Yes | Low quality |
| Hunt (2013) | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | High quality |
| Hunt (2014) | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | High quality |
| Inacio (2016) | No | Yes | Yes | Yes | Yes | Yes | No | No | Yes | Yes | Low quality |
| Iorio (2012) | Yes | Yes | Yes | Yes | No | No | No | Yes | NS | No | Low quality |
| Jain (2005) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | NS | No | Low quality |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Jamsen (2013) | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | High quality |
| Jamsen (2014) | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | High quality |
| Jamsen (2015) | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | High quality |
| Jorgensen (2015a) | Yes | Yes | Yes | Yes | Yes | No | No | Yes | Yes | Yes | Low quality |
| Jorgensen (2015b) | Yes | Yes | Yes | Yes | Yes | No | No | Yes | Yes | Yes | Low quality |
| Judge (2012) | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | No | Low quality |
| Kapoor (2010) | No | Yes | Yes | Yes | Yes | Yes | No | No | NS | Yes | Low quality |
| Kapoor (2013) | No | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Low quality |
| Karam (2015) | Yes | Yes | Yes | Yes | No | No | No | Yes | Yes | Yes | Low quality |
| Keswani (2016) | Yes | Yes | Yes | Yes | Yes | Yes | No | No | Yes | Yes | Low quality |
| Kildow (2017) | No | Yes | Yes | Yes | Yes | No | No | No | Yes | Yes | Low quality |
| Kuo (2017) | No | Yes | Yes | Yes | No | Yes | No | Yes | Yes | Yes | Low quality |
| Lee (2017) | No | Yes | Yes | Yes | No | Yes | No | Yes | Yes | Yes | Low quality |
| Liao (2016) | No | Yes | Yes | Yes | Yes | Yes | No | No | Yes | Yes | Low quality |
| Marchant (2009) | No | Yes | Yes | Yes | Yes | Yes | Yes (SES) | No | Yes | Yes | Low quality |
| Martinez (2013) | No | Yes | Yes | Yes | Yes | Yes | No | No | Yes | Yes | Low quality |
| Mazoch (2009) | Yes | Yes | Yes | Yes | No | 1 | No | Yes | NS | Yes | Low quality |
| McCleery (2010) | Yes | Yes | Yes | Yes | Yes | Yes | No | No | Yes | Yes | Low quality |
| Meding (2003) | Yes | Yes | Yes | Yes | No | No | No | Yes | Yes | No | Low quality |
| Menendez (2016) | Yes | Yes | Yes | Yes | Yes | Yes | Yes (ethnicity) | No | Yes | Yes | Low quality |
| Miric (2014a) | Yes | Yes | Yes | Yes | Yes | Yes | Yes (ethnicity) | Yes | Yes | Yes | High quality |
| Miric (2014b) | Yes | Yes | Yes | Yes | Yes | Yes | Yes (ethnicity) | Yes | Yes | Yes | High quality |
| Moon (2008) | Yes | Yes | Yes | Yes | No | No | No | Yes | Yes | Yes | Low quality |
| Pedersen (2010) | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | High quality |
| Perez (2014) | Yes | Yes | Yes | Yes | No | No | No | Yes | Yes | Yes | Low quality |
| Radkte (2016) | No | Yes | Yes | Yes | No | No | No | Yes | Yes | Yes | Low quality |
| Rajamaki (2015) | Yes | Yes | Yes | Yes | No | Yes | No | Yes | Yes | No | Low quality |
| Rasouli (2016) | Yes | Yes | Yes | Yes | No | Yes | No | Yes | Yes | Yes | Low quality |
| Robertson (2012) | Yes | Yes | Yes | Yes | No | Yes | No | Yes | Yes | Yes | Low quality |
| Sanders (2012) | Yes | Yes | Yes | Yes | Yes | Yes | Yes (SES) | No | Yes | Yes | Low quality |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Seol (2017) | Yes | Yes | Yes | Yes | Yes | No | No | Yes | NS | Yes | Low quality |
| Sikora-Klak (2017) | No | Yes | Yes | Yes | No | No | No | Yes | Yes | No | Low quality |
| Singh (2014a) | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | No | Low quality |
| Singh (2009) | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | No | Low quality |
| Singh (2014b) | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | No | Low quality |
| Singh (2013a) | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | No | Low quality |
| Singh (2013b) | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | No | Low quality |
| Singh (2013c) | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | No | Low quality |
| Singh (2014) | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | No | Low quality |
| Stundner (2013) | Yes | Yes | Yes | Yes | Yes | Yes | Yes (ethnicity) | No | Yes | Yes | Low quality |
| Tiberi (2014) | Yes | Yes | Yes | Yes | No | No | No | Yes | Yes | Yes | Low quality |
| Vannini (1984) | Yes | Yes | Yes | Yes | No | No | No | Yes | Yes | Yes | Low quality |
| Wang (2013) | No | Yes | Yes | Yes | No | Yes | No | Yes | No | Yes | Low quality |
| Warth (2015) | Yes | Yes | Yes | Yes | Yes | No | No | No | Yes | Yes | Low quality |
| Zhao (2014) | No | Yes | Yes | Yes | No | Yes | No | Yes | No | Yes | Low quality |

*Note.* SES = Socioeconomic Status

BMJ Open

# The impact of comorbid conditions on outcomes of hip and knee replacement surgery: A systematic review and meta-analysis



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| | |

# The impact of comorbid conditions on outcomes of hip and knee replacement surgery: A systematic review and meta-analysis

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*Keywords:* Hip replacement, Knee replacement, outcomes, comorbidity, systematic review

Word Count: 4,881

# ABSTRACT

**Objective:** To systematically perform a meta-analysis of the association between different comorbid conditions on safety (short-term outcomes) and effectiveness (long-term outcomes) in patients undergoing hip and knee replacement surgery.

**Design:** Systematic Review and Meta-analysis

**Methods:** Medline, Embase and CINAHL Plus were searched up to May 2017.We included all studies that reported data to allow the calculation of a pooled odds ratio (OR) for the impact of 11 comorbid conditions on 10 outcomes (including surgical complications, readmissions, mortality, function, health-related quality of life, pain and revision surgery). The quality of included studies were assessed using a modified Newcastle-Ottawa scale. Continuous outcomes were converted to ORs using the Hasselblad and Hedges approach. Results were combined using a random effects meta-analysis.

**Outcomes:** The primary outcome was the adjusted OR for the impact of each 11 comorbid condition on each of the 10 outcomes compared to patients without the comorbid condition. Where the adjusted OR was not available the secondary outcome was the crude OR.

**Results:** Seventy studies were included with 16 (23%) reporting on at least 100,000 patients and 9 (13%) were of high quality. We found that comorbidities increased the short-term risk of hospital readmissions (8 of 11 conditions) and mortality (8 of 11 conditions). The impact on surgical complications was inconsistent across comorbid conditions. In the long-term, comorbid conditions increased the risk of revision surgery (6 of 11 conditions) and long-

term mortality (7 of 11 conditions). The long-term impact on function, quality of life and pain varied across comorbid conditions.

**Conclusions:** This systematic review shows that comorbidities predominantly have an impact on the safety of hip and knee replacement surgery but little impact on its effectiveness. There is a need for high-quality studies also considering the severity of comorbid conditions.

## STRENGTH AND LIMITATIONS OF THIS STUDY

- This study went beyond published reviews by analysing the relative impact of individual comorbid conditions on multiple outcomes that relate not only to safety but also effectiveness of hip and knee replacement surgery.
- Further to previous studies, to allow for meta-analysis of all outcomes, continuous outcomes were converted to the corresponding odds ratio using the Hasselblad and Hedges approach.
- The search was limited to include specific comorbidities and outcomes so studies may have been missed.
- To enable a meta-analysis of the multiple conditions and outcomes, comorbid conditions and outcomes were grouped together and may have compromised the validity of the conclusions.

# INTRODUCTION

Hip and knee replacement surgery, the surgical replacement of a joint, is one of the most successful and cost effective interventions in medicine [1]. It offers considerable improvement in function and quality of life [2]. It is expected that the demand for hip and knee replacement will increase as the prevalence of hip and knee osteoarthritis rises due to increases in life expectancy [3].

There has been increasing interest in identifying the risk factors for poor outcomes of elective joint replacement to be able to optimise patients and improve outcomes. Previous research has reported variation in the use of hip and knee replacement according to socioeconomic status [4], sex [5], insurance status [6], ethnicity [7] and geography [8]. This variation may be explained in part by the lack of consensus amongst clinicians about the clinical indications for joint replacement surgery[9].

Comorbid conditions, conditions that are present in addition to the index condition but are unrelated to the latter, are on the rise around the world as more people are living with multiple morbidities. In a large US study using administrative data, 83.7% patients who had undergone hip or knee replacement had at least one comorbid condition [10]. This is higher than in the general population where in 2012 only 49.8% of US adults had at least one comorbid condition [11]. As the prevalence of people living with multiple morbidities increases with age it is expected that the number of patients undergoing elective hip and knee replacement with at least one comorbid condition will increase [12].

There have been a number of studies reporting the impact of comorbidity on outcomes after hip and knee replacement[13-15]. There is little evidence however, to which extent different individual comorbid conditions affect a variety of outcomes that relate not just to

the safety of the surgery but also long-term outcomes such as quality of life after hip and knee replacement surgery. Previous systematic reviews on comorbid conditions and outcomes of hip and knee replacement have typically focused on individual comorbidities [16], specific outcomes [17], process measures and cost[18], short-term outcomes following hip and knee replacement or the overall impact of composite comorbidity indices on outcomes [14].

This study provides evidence of the impact of different individual comorbid conditions on a wide range of surgical outcomes, including short-term outcomes related to the "safety" of the surgery and long-term outcomes related to the "effectiveness" of the surgery.

The aim of this systematic review and meta-analysis was to synthesise the literature on the impact of different individual comorbid conditions on short-term and long-term outcomes of hip and knee replacement surgery.

# METHODS

## Patient and Public Involvement

This systematic review forms part of a wider piece of work investigating the access to and outcomes of hip and knee replacement surgery for patients with comorbidities. The protocol, including the systematic review, was reviewed by patient representatives on the NIHR CLAHRC North Thames Patient and Public Involvement committee. Their comments and feedback were incorporated in the protocol.

## Literature Search

A search of Medline, Embase, and CINAHL Plus, was conducted up to 31 May 2017 to identify studies written in English. Limitations were not placed on date. Search terms for hip and knee replacement were combined with search terms for health outcomes and search terms for 11 common comorbid conditions: heart disease, high blood pressure, stroke, leg pain due to poor circulation, lung disease, diabetes, kidney disease, diseases of the nervous system, liver disease, cancer and depression (see supplementary information 1). The conditions were selected because they are the comorbid conditions that are routinely captured in the national Patient Reported Outcome Measures programme for patients undergoing elective surgery in the English National Health Service and were considered relevant comorbidities in terms of outcome prediction[19]. Where possible MeSH or index terms were used. All the titles, selected abstracts and full text articles were reviewed for eligibility by two reviewers (BP, AA). Data extraction was conducted by BP and checked by AH. Any disagreements were resolved by two reviewers (JVM, AH). The reference lists of

existing systematic reviews and included studies were also checked for additional eligible articles.

## Eligibility criteria and data extraction

We included published full text observational (either prospective or retrospective) studies in the English language that compared the outcomes of hip or knee replacement in patients with and without any of the 11 comorbid conditions. Studies were ineligible if they used a summary comorbidity index (e.g. Charlson Comorbidity Index) or a single count of comorbidities because the aim of our study was to understand the impact of individual comorbid conditions. Studies including other joint replacements were only eligible if hip and/or knee replacement represented at least 90% of participants or if results were reported separately. Small studies, those with fewer than 100 participants, were excluded because hip and knee replacement are common procedures and the selected comorbid conditions are relatively common. Studies were ineligible if they failed to include at least one of the following outcomes: surgical complications, mortality, function, pain, health-related quality of life, hospital readmission, and revision surgery.

Information on the study design, population and measures of association was extracted for eligible studies. Data were extracted on the participants (type of surgery), source of study data, the specific condition and the definition of the outcome for each reported association between a comorbid condition and outcome in a study (see supplementary information 2). In addition, data were also extracted on the measure of association and its uncertainty and, for adjusted measures, the variables used in the adjusted analysis. Where possible, data on counts or means were used to calculate measures of association that had not been reported in the original study. Studies that indicated the statistical significance or otherwise of an

association without reporting a quantitative metric were also recorded. Data were verified by a third reviewer (JVM).

Ten categories of outcome were defined. Five short term outcomes, those occurring closest to three months after surgery, were: surgical complications, occurrence of venous thromboembolism, surgical site infections, readmission to hospital, and mortality. Surgical complications were defined as the presence of any surgical complication as reported in a study. Two commonly reported surgical complications, venous thromboembolism and infection, were also examined separately. Five longer-term outcomes closest to one year postoperatively were: measures of hip or knee function, patient-reported quality of life, pain, revision surgery, and mortality. We defined short-term outcomes as maximum three months and long-term outcomes as closest to one year after surgery because this reflected the definitions of outcomes used in the included studies and our judgement of events that reflect safety and effectiveness. For function and quality of life, they were only eligible for inclusion if analyses incorporated adjustment for pre-operative scores or if similarity of pre-operative scores was demonstrated. This was to ensure that the outcome captures the impact of surgery rather than any pre-operative difference in score.

## Quality Assessment

The internal and external validity of the studies was appraised using the Newcastle-Ottawa scale (NOS) [20] that was modified to meet the requirements of this study (see Table 1). Two reviewers (BP, AH) examined three items: patient selection, comparability of exposure and reference groups, and assessment of outcomes. For the comparability between the two groups, we focused on the following variables that previous studies have identified as

predictors of various outcomes of hip and knee replacement surgery: age, sex, socioeconomic status, and ethnicity. We added an extra item to assess the comparability of the cohorts on the basis of whether the cohort of patients were drawn from multiple centres or a single centre and whether the data sources were from specialist arthroplasty databases. The total possible score was 13. A study with a score of 11 or greater was considered high quality (see supplementary information 3). This was to ensure we only included the highest quality studies and excluded those where there were concerns with cohort selection, confounding and outcome assessment.

*Table 1 – Study quality appraisal using a modified Newcastle-Ottawa scale*

**Patient Selection**

1. Was the cohort of patients undergoing hip or knee replacement surgery with comorbid conditions representative?
2. Was the reference cohort for patients without comorbid conditions drawn from the same community?
3. Was the presence of comorbid conditions adequately verified? (Yes=secure record or structured interview/self-report)
4. Did the study demonstrate that the outcome of interest was not present at the start of the study?
5. Was the cohort or patients drawn from multiple communities?

**Comparability**

1. Did the study control for age and sex?
2. Did the study control for socioeconomic status and ethnicity?

**Outcome Assessment**

1. Was the outcome of interest clearly defined? (Yes=study-specific/self-report, joint registry, No=administrative data)
2. Was follow-up long enough for outcomes to occur? (Yes=short-term minimum 30 days, long-term minimum 6 months)
3. Was follow-up adequate? (Yes=completed follow up >90%)

**Studies were graded on an ordinal scoring scale with higher scores indicating studies of higher quality. A study could be awarded a maximum of one point for each numbered item except comparability items and the first item in outcome assessment, which could be awarded a maximum of two points for each numbered item.*

## Quantitative data synthesis and meta-analysis

An approach to data synthesis was chosen which allowed for a meta-analysis across multiple outcomes and conditions. This meta-synthesis approach has been used by a previous systematic review[21]. The first stage of data synthesis involved selecting each study's measures of association to be included in the meta-analyses for each of the possible combinations of comorbid condition and outcome. Individual studies might have multiple measures for different combinations, e.g., studies reporting multiple outcomes or different comorbid conditions. Studies might also have multiple measures for the same combination, e.g., unadjusted and adjusted measures, measures for controlled and uncontrolled diabetes, or measures for hip and knee replacement surgery. Separate measures for hip and knee replacement were included in a combination's meta-analysis because they comprised different groups of participants. For other multiple measures, a single measure was selected

for inclusion in a meta-analysis using the following criteria: adjusted over unadjusted measures, closer matching or more common subcategories of comorbid conditions for inexact mapping to the 11 selected conditions (see Table 2), and closer matching to the timing (3 or 12 months) and definition of outcomes.

*Table 2 - Mapping of comorbid conditions*

| Comorbid Condition | Number of studies | Included comorbid conditions |
|---|---|---|
| Cancer | 9 | All cancers but if reported separately cancer chosen in preference to metastasis. |
| Depression | 12 | All diagnoses of depression |
| Diabetes | 41 | Type 2 diabetes in preference to Type 1 diabetes. Controlled diabetes in preference to uncontrolled diabetes. Diabetes without complications in preference to diabetes with complications. |
| Diseases of the Nervous System | 6 | Alzheimer's disease, Parkinson's disease, Dementia |
| Heart Disease | 21 | Heart disease but if reported separately coronary heart disease, coronary artery disease or heart failure was chosen. |
| High blood pressure | 13 | High Blood Pressure |
| Kidney Disease | 19 | Renal disease but if reported separately chosen chronic kidney disease, chronic renal disease or renal failure |
| Liver disease | 7 | Liver disease but if reported separately cirrhosis chosen |
| Lung disease | 18 | Lung disease but if reported separately chronic obstructive pulmonary disorder chosen. |
| Poor circulation | 7 | Peripheral vascular disease |
| Stroke | 12 | Stroke or cerebrovascular disease |

Most of the studies reported outcomes as odds ratios or it was possible to derive an odds ratio. For studies reporting continuous outcomes the difference between means divided by the pooled standard deviation (standardised mean difference) was converted to the corresponding odds ratio (OR) using the Hasselblad and Hedges approach [22]. If higher scores represented a good outcome then reciprocal values were used to ensure that ORs greater than one represented higher odds of a poor outcome. Where zero events precluded the calculation of an odds ratio, each cell in the contingency table was inflated by adding 0.5[23] to allow calculation of an OR.

We estimated the pooled odds ratio for each combination of comorbid condition and outcome comprising two or more measures of association. Odds ratios were computed such that a result greater than one indicates a higher odds of a worse outcome in patients with a specified comorbid conditions compared to patients without. We used a random-effects model as results were drawn from different populations[24]. Pooled odds ratios by condition were plotted for each outcome. A sensitivity analysis was performed to assess the impact of the quality of the studies on the outcomes by comparing higher quality studies with studies of lower quality. The risk of publication bias was assessed using the graphical assessment of the funnel plot[23] on outcomes which were reported on by a greater than 6 studies. All statistical analyses were carried out using STATA 14.

# RESULTS

## Selected studies

Full search results are represented in Figure 1. Of the 18,644 studies identified in the search, we included 70 studies [25-94], which produced 314 results for individual comorbid conditions and outcomes of hip and knee replacement surgery. The 70 studies had a range of patients sample sizes from 122 to 8,379,490. 16 (23%) studies had at least 100,000 patients. 26 (37%) studies reported combined hip and knee arthroplasties, 12 (17%) studies reported on hip arthroplasties only, 24 (34%) studies on knee arthroplasties and 9 (13%) studies reported hip and knee arthroplasties separately. 40 (70%) studies reported outcomes after primary hip or knee replacement. The 70 studies came from 13 different countries with 37 (53%) coming from the USA. They were published between 1984 and 2017.

Overall, 43 (61%) studies only looked at single comorbid conditions and 35 (50%) only looked at single outcomes. 60 (86%) studies investigated the association between comorbid conditions and surgical complications (including VTE and surgical site infections), and only 5 (7%) quality of life. The comorbid condition that was most frequently studied was diabetes (41 studies), followed by heart disease (21 studies) and kidney disease (19 studies) (see Table 2). The least frequently studied comorbid condition was diseases of the nervous system (6 studies).

The median NOS score, the measure of study quality, was 10 (6 to 13). Of the 70, 9 (13%) studies met our predefined criteria for high quality of scores of greater than 11. The majority of studies had a representative cohort of patients with a specified comorbid condition (56 studies) and adjusted for potential confounders such as age and gender (41 studies).

## Short-term outcomes

### Surgical complications

In this meta-analysis, 15 studies reported an odds ratio for surgical complications in patients with comorbid conditions (see Figure 2). The risk of surgical complications was significantly higher in patients with cancer (pooled OR 1.33, 95% CI 1.09 to 1.62), diabetes (pooled OR 1.12, 95% CI 1.01 to 1.25), kidney disease (pooled OR 1.97, 95% CI 1.84 to 2.10) and stroke (pooled OR 1.40, 95% CI 1.03 to 1.90). No studies reported surgical complications in patients with nervous system diseases or poor circulation.

### Surgical site infections

Twenty-seven studies reported on surgical site infections after surgery. Overall, surgical site infections tended to occur more frequently in patients with comorbid conditions but the

likelihood was only significantly higher in patients with diabetes (pooled OR 1.90, 95% CI: 1.32, 2.74) and liver disease (pooled OR 2.46, 95% CI 1.46 to 4.12) (see Figure 2). No studies reported the likelihood of surgical site infections in patients with high blood pressure, poor circulation or stroke.

### Venous thromboembolism (VTE)

Eighteen studies reported the risk of venous thromboembolism (VTE) postoperatively. Venous thromboembolism was more likely in patients with cancer (pooled OR 2.30, 95% CI: 1.35 to 3.92), depression (pooled OR 1.15, 95% CI: 1.02 to 1.30) and lung disease (pooled OR 1.29, 95% CI: 1.08 to 1.55). No studies reported the risk of VTE in patients with nervous system diseases, liver disease or poor circulation.

### Readmissions to hospital

Sixteen studies looked at the presence of comorbid conditions and being readmitted to hospital within 90 days after surgery. Overall, the likelihood of readmissions to hospital were significantly higher for patients with comorbid conditions (8 out of 11) with the highest likelihood in patients with liver disease (pooled OR 1.79, 95% CI 1.36 to 2.35) (see Figure 2). No studies reported the likelihood of readmissions in patients with nervous system diseases or depression.

### Short-term mortality

Thirteen studies looked at mortality within 90 days after surgery. Overall, the likelihood of short-term mortality tended to be significantly higher in patients with comorbid conditions (8 out of 11) with the highest likelihood in patients with heart disease (pooled OR 2.96, 95% CI 1.95 to 4.48) (see Figure 2). In contrast, one study reported a significant lower likelihood of short-term mortality in patients with depression (pooled OR 0.53, 95% CI 0.32 to 0.88).

## Long-term outcomes

### Hip and knee function

Ten studies look at the impact of comorbid conditions on postoperative hip or knee function (see Figure 3). Knee or hip function measures included: The Knee Society Knee score [72 78], WOMAC score [28 29 74], Oxford Knee score [35], and Activities of Daily Living limitation [83 87 95]. The most frequently used measure was the WOMAC score. Overall, the impact of comorbid conditions on function was variable. Patients with depression (pooled OR 1.69, 95% CI 1.26 to 2.28), heart disease (pooled OR 1.24, 95% CI 1.01 to 1.52) and stroke (pooled OR 1.32, 95% CI 1.02 to 1.71) had worse function after surgery. Postoperative function in patients with heart disease [35] and stroke [87] were each only reported on by one study. No studies investigated the postoperative function in cancer patients.

### Health-related quality of life

Five studies compared the improvement in quality of life one year after surgery in patients with comorbid conditions with those patients without comorbidities. Measures of quality of life included the SF-12 [35], SF-36 [29 74 96] and the Health Utilities Index [28]. Overall, across comorbid conditions there was no consistent pattern. Quality of life was significantly worse for patients with heart disease (pooled OR 1.49, 95% CI 1.24 to 1.78) and lung disease (pooled OR 1.26, 95% CI 1.02 to 1.57). For patients with liver disease quality of life was significantly better after surgery (pooled OR 0.36, 95% CI 0.20 to 0.65) [35]. Postoperative quality of life in patients with heart disease and liver disease were each only reported by one study. No studies investigated the postoperative quality of life in cancer or stroke patients.

## Pain

Ten studies reported on the association between comorbid conditions and pain. 5 (50%) studies looked at the outcome moderate-severe pain at 2-years and were studied by the same author [84 85]. Other measures of pain included the WOMAC pain score [28] and the Knee Society pain score [68 72]. Overall, pain tended to be worse for patients with comorbid conditions but was not statistically significant. No studies investigated the postoperative pain in patients with cancer, nervous system diseases, liver disease or high blood pressure.

## Revision surgery

Twelve studies reported on the likelihood of revision surgery in patients with comorbid conditions. Overall, revision surgery tended to be more likely in patients with comorbid conditions (6 out of 11) but the evidence remains weak. The pooled OR ranged from 1.11 (95% CI 1.02 to 1.21) for patients with high blood pressure to 1.96 (95% CI 1.16 to 3.30) for patients with liver disease. No studies reported the risk of revision surgery in patients with poor circulation or stroke.

## Long-term mortality

Twelve studies reported the association between comorbid conditions and long-term mortality. Overall, the risk of long-term mortality tended to be higher for patients with comorbid conditions (7 out of 11). The pooled OR ranged from 1.38 (95% CI 1.05 to 1.80) for lung disease to 3.40 (95% CI 1.17 to 9.86) for liver disease (see Figure 3). No studies investigated the risks of long-term mortality in patients with depression and poor circulation.

## Impact of comorbid conditions

There is a lack of consistency across short-term and long-term outcomes by different comorbid conditions. In the short-term, comorbidities had the most impact on readmissions to hospital and short-term mortality but the impact on surgical complications was variable with most results not statistically significant. In the long-term, comorbid conditions had the most impact on risk of revision surgery and long-term mortality. The impact on function and quality of life was inconsistent across comorbid conditions. The evidence for the impact of comorbid conditions on long-term outcomes was weaker than for short-term outcomes. Heart disease of all the included comorbid conditions had the most impact on both short-term and long-term outcomes with an increased likelihood of readmissions, short-term mortality, worse function, worse quality of life, revision surgery and long-term mortality.

## Publication Bias

We explored the possible impact of publication bias on outcomes: surgical complications, venous thromboembolism, surgical site infections, readmissions, pain, and mortality which had greater than six studies. This included studies in diabetic patients (see Figure 4) and kidney patients (see Figure 5). The studies were not evenly distributed across both sides of the funnel plot. This asymmetry suggests that studies publishing negative effects may be missing. The impact of comorbidities on outcomes of hip and knee replacement may therefore be overestimated.

## Sensitivity Analysis

We performed a sensitivity analysis to estimate the robustness of the results by evaluating the effects of study quality (see supplementary information 4). Overall high-quality studies pointed in the same direction as the lower-quality studies, although the latter generally reported larger effects. Higher-quality studies did not include studies reporting on the outcomes function, quality of life and pain, which suggest the evidence on long-term outcomes is poor compared to the evidence of the impact of comorbid condition on short-term outcomes. This may be largely because of the smaller sample size of these studies, the lack of adjustment for confounders and the lack of patient-reported outcomes in joint registries which focus primarily on surgical complications, mortality and revision rates.

# DISCUSSION

**Main findings**

Overall, this meta-analysis demonstrates that patients with comorbid conditions are more likely to have a readmission and a higher short-term mortality in the early follow-up but there is little evidence that patients benefit significantly less in terms of health-related quality of life, function and pain compared to patients with no comorbid conditions. In the short-term, the impact on surgical complications was variable and mostly statistically insignificant. Patients with comorbid conditions tended to have a higher risk of revisions and long-term mortality but the available evidence was weak. There is some evidence of publication bias which may indicate an overestimation of the impact of comorbid conditions on outcomes. Given this, there is a need for high-quality studies in order to get a better understanding of the true impact of comorbidities on both short-term and long-term outcomes of hip and knee replacement.

Our study has implications for future research on clinical indication for joint replacement surgery. Clinicians should take into account prognostic factors that affect treatment effectiveness in their decision-making to refer or select patients for hip or knee replacement[97] but due to the lack of clarity on clinical indication for hip and knee replacement they are not able to do so effectively [98]. Further research, specifically focusing on the long-term outcomes such as function, quality of life and pain, and that stratify individual comorbidities according to severity are needed to provide clinicians with more evidence to guide their decision-making and management of patients with comorbid conditions and to minimise the variation and quality of care provided for this patient group.

**Quality of evidence**

Only 13% of the studies were graded as being of high quality. Poorer quality studies were typically less clear about the inclusion criteria for study patients and did not adjust for potential confounders such as age and gender. They were also based on either small single-site studies or large administrative data-based studies that use data sources that were not from specialist arthroplasty databases. Large administrative data-based studies greatly influenced the meta-analysis and thereby the limitations of these studies will therefore have a considerable influence on the validity of this meta-analysis. The higher quality studies primarily used joint registries and did not focus on patient-reported outcomes such as quality of life, function and pain.

Our sensitivity analysis showed that lower quality studies seem to overestimate the risk of short-term outcomes after hip and knee replacement in patients with comorbid conditions. Similarly, the evidence of reporting bias towards reporting positive findings may indicate an overestimation of the impact of comorbid conditions on outcomes of hip and knee replacement surgery. Due to the relatively small number of studies exploring the impact of each comorbid condition, it was not possible to fully explore the impact of publication bias and other factors that might cause heterogeneity.

It is important to consider, that patients included in the reported studies may represent a healthier population. Several studies have shown that patients are not accessing hip and knee replacement because clinicians are excluding complex and severe patients who are deemed too high-risk for surgery [99]. This may introduce selection bias which may lead to an underestimation of the true effect on the impact of comorbid conditions on outcomes of hip, and knee replacement surgery.

**Relation to prior reviews**

Our study provides evidence that comorbid conditions have an impact on safety of the surgery but little impact on the effectiveness of the surgery in terms of quality of life, function and pain after hip and knee replacement surgery. There have been a number of earlier systematic reviews reporting the impact of comorbid conditions on outcomes after hip and knee replacement surgery. One systematic review and meta-analysis following elective total hip replacement in diabetes patients found diabetes to be associated with a 2-fold increase risk of surgical site infections in line with our findings[16]. Another one looking at the impact of comorbidity and length of stay and costs found limited evidence that comorbidities increase length of stay and costs compared to patients with no or fewer comorbidities[18]. One systematic review looking at health-related quality of life in total hip and knee replacement reported that comorbid conditions was given as a reason for modest improvements in outcomes [17]. This finding was only based on two studies both using composite comorbidity measures. Another systematic review looking at all preoperative predictors for outcomes for hip and knee replacement however, demonstrated the inconsistency in study findings with seven studies reported a significant worse association between comorbid conditions and outcomes but six studies reported no significant association [14].

**Limitations**

For some combinations of outcomes and comorbid conditions there were no studies of impact or impact was only based on a single study. Only six studies focused on patients with diseases of the nervous system whereas over half of the studies we reviewed investigated outcomes in diabetic patients. Similarly, short-term outcomes, particularly surgical

complications, were commonly investigated but only five studies [28 29 35 74 96] reported on quality of life outcomes and the results on pain were from two publications[84 85]. This highlights that evidence on short-term outcomes is stronger than evidence on long-term outcomes. Half of the studies were analyses of data collected in population-based administrative datasets. This may account for the relative scarcity of studies reporting on long-term outcomes such as quality of life or function that need patient reported results.

We limited our review to studies with at least 100 patients and patients with the 11 comorbid conditions. Comorbid conditions that did not fit into the 11 categories that are captured in the Patient Reported Outcome Measures (PROMs) programme for patients undergoing elective surgery in the English National Health Service were not included in this review. In addition, specific outcomes and patient-reported measures were not specified in the literature search so this may have resulted in the omission of some studies that met the inclusion criteria. We performed manual searches of relevant journals however and checked the references lists of all included studies and other systematic reviews, so we believe that any missed studies would not affect our conclusions significantly.

The scope of this review required the grouping of heterogeneous studies. Across all studies, there were differences in study populations, definitions of comorbid conditions and their severity and definitions of outcomes and the constructs they are measuring and the timing of their measurement. To make the results comparable and to be able to conduct any form of meta-analysis, some comorbid conditions were grouped together, outcomes were categorised as short and long-term, and continuous outcomes were converted to odds ratio using the Hasselblad and Hedges approach. In addition, it was not possible to evaluate hip

and knee replacement separately as 27 (38%) studies reported on combined hip and knee arthroplasties.

In addition to variation in definitions of comorbid conditions, few included studies graded comorbid conditions according to severity which would have allowed a better understanding of their impact. For the few studies that reported results according to the severity of a comorbid condition, we included the most common severity subgroup, therefore excluding the most severe patients.

## CONCLUSION

Clinicians should be aware of the short-term risks relating to the safety of the surgery in their management of patients with comorbid conditions. There is little evidence that patients with comorbid conditions benefit significantly less from hip and knee replacement in terms of quality of life, function and pain after surgery than patients without comorbid conditions. As a result comorbid conditions have an impact on safety but little impact on effectiveness of hip and knee replacement surgery. Future research should however, consider the severity of comorbid conditions to better understand the impact of comorbid conditions on outcomes.

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# REFERENCES

1. Liang MH, Cullen KE, Larson MG, et al. Cost-effectiveness of total joint arthroplasty in osteoarthritis. *Arthritis and rheumatism* 1986;29(8):937-43. doi: http://dx.doi.org/10.1002/art.1780290801 [published Online First: 1986/08/01]
2. Aamodt A, Nordsletten L, Havelin LI, et al. Documentation of hip prostheses used in Norway: a critical review of the literature from 1996--2000. *Acta orthopaedica Scandinavica* 2004;75(6):663-76. doi: http://dx.doi.org/10.1080/759369226 [published Online First: 2005/03/15]
3. Kurtz S, Ong K, Lau E, et al. Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. *The Journal of bone and joint surgery American volume* 2007;89(4):780-5. doi: 10.2106/jbjs.f.00222 [published Online First: 2007/04/04]
4. Neuburger J, Hutchings A, Black N, et al. Socioeconomic differences in patient-reported outcomes after a hip or knee replacement in the English National Health Service. *Journal of public health (Oxford, England)* 2013;35(1):115-24. doi: 10.1093/pubmed/fds048 [published Online First: 2012/06/26]
5. Juni P, Low N, Reichenbach S, et al. Gender inequity in the provision of care for hip disease: population-based cross-sectional study. *Osteoarthritis Cartilage* 2010;18(5):640-5. doi: http://dx.doi.org/10.1016/j.joca.2009.12.010
6. Schwarzkopf R, Phan DL, Hoang M, et al. Do patients with income-based insurance have access to total joint arthroplasty? *The Journal of arthroplasty* 2014;29(6):1083-6.e1. doi: 10.1016/j.arth.2013.11.022 [published Online First: 2014/01/11]
7. Singh JA, Lu X, Rosenthal GE, et al. Racial disparities in knee and hip total joint arthroplasty: an 18-year analysis of national Medicare data. *Annals of the rheumatic diseases* 2014;73(12):2107-15. doi: 10.1136/annrheumdis-2013-203494
8. Judge A, Welton NJ, Sandhu J, et al. Equity in access to total joint replacement of the hip and knee in England: cross sectional study. *Bmj* 2010;341:c4092. doi: http://dx.doi.org/10.1136/bmj.c4092
9. Cobos R, Latorre A, Aizpuru F, et al. Variability of indication criteria in knee and hip replacement: an observational study. *Bmc Musculoskeletal Disorders* 2010;11 doi: 10.1186/1471-2474-11-249
10. Hustedt JW, Goltzer O, Bohl DD, et al. Calculating the Cost and Risk of Comorbidities in Total Joint Arthroplasty in the United States. *Journal of Arthroplasty* 2017;32(2):355-61.e1. doi: http://dx.doi.org/10.1016/j.arth.2016.07.025
11. Ward BW, Schiller JS, Goodman RA. Multiple Chronic Conditions Among US Adults: A 2012 Update. *Preventing Chronic Disease* 2014;11:E62. doi: 10.5888/pcd11.130389
12. Singh JA, Lewallen DG. Increasing obesity and comorbidity in patients undergoing primary total hip arthroplasty in the U.S.: a 13-year study of time trends. *BMC Musculoskelet Disord* 2014;15:441. doi: 10.1186/1471-2474-15-441 [published Online First: 2014/12/19]
13. Sturmer T, Dreinhofer K, Grober-Gratz D, et al. Differences in the views of orthopaedic surgeons and referring practitioners on the determinants of outcome after total hip replacement. *Journal of Bone and Joint Surgery-British Volume* 2005;87B(10):1416-19. doi: 10.1302/0301-620x.87b10.16702
14. Hofstede SN, Gademan MGJ, Vliet Vlieland TPM, et al. Preoperative predictors for outcomes after total hip replacement in patients with osteoarthritis: a systematic review. *BMC Musculoskeletal Disorders* 2016;17:212. doi: 10.1186/s12891-016-1070-3
15. Hilton ME, Gioe T, Noorbaloochi S, et al. Increasing comorbidity is associated with worsening physical function and pain after primary total knee arthroplasty. *BMC Musculoskelet Disord* 2016;17(1):421. doi: 10.1186/s12891-016-1261-y [published Online First: 2016/10/09]
16. Tsang ST, Gaston P. Adverse peri-operative outcomes following elective total hip replacement in diabetes mellitus: a systematic review and meta-analysis of cohort studies. *The bone & joint*

*journal* 2013;95-b(11):1474-9. doi: 10.1302/0301-620x.95b11.31716 [published Online First: 2013/10/24]
17. Ethgen O, Bruyere O, Richy F, et al. Health-related quality of life in total hip and total knee arthroplasty. A qualitative and systematic review of the literature. *The Journal of bone and joint surgery American volume* 2004;86-a(5):963-74. [published Online First: 2004/05/01]
18. Olthof M, Stevens M, Bulstra SK, et al. The association between comorbidity and length of hospital stay and costs in total hip arthroplasty patients: a systematic review. *J Arthroplasty* 2014;29(5):1009-14. doi: 10.1016/j.arth.2013.10.008 [published Online First: 2013/11/30]
19. Digital N. Patient Reported Outcome Measures in England: Data Dictionary, 2016.
20. Wells G, Shea B. Newcastle-Ottawa quality assessment scale cohort studies 2011 [Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
21. Linde K, Clausius N, Ramirez G, et al. Are the clinical effects of homeopathy placebo effects? A meta-analysis of placebo-controlled trials. *Lancet* 1997;350(9081):834-43. [published Online First: 1997/10/06]
22. Hasselblad V, Hedges LV. Meta-analysis of screening and diagnostic tests. *Psychological bulletin* 1995;117(1):167-78. doi: http://dx.doi.org/10.1037/0033-2909.117.1.167 [published Online First: 1995/01/01]
23. Egger M, Davey-Smith G, Altman D. Systematic Reviews in Health Care: Meta-Analysis in Context: John Wiley & Sons 2013.
24. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled clinical trials* 1986;7(3):177-88. doi: http://dx.doi.org/10.1016/0197-2456(86)90046-2 [published Online First: 1986/09/01]
25. Ackland GL, Moran N, Cone S, et al. Chronic kidney disease and postoperative morbidity after elective orthopedic surgery. *Anesth Analg* 2011;112(6):1375-81. doi: http://dx.doi.org/10.1213/ANE.0b013e3181ee8456
26. Adams AL, Paxton EW, Wang JQ, et al. Surgical outcomes of total knee replacement according to diabetes status and glycemic control, 2001 to 2009. *Journal of Bone & Joint Surgery, American Volume* 2013;95-A(6):481-87 7p. doi: 10.2106/JBJS.L.00109
27. Aggarwal VK, Tischler EH, Post ZD, et al. Patients with atrial fibrillation undergoing total joint arthroplasty increase hospital burden. *Journal of Bone & Joint Surgery - American Volume* 2013;95(17):1606-11. doi: http://dx.doi.org/10.2106/JBJS.L.00882
28. Amusat N, Beaupre L, Jhangri GS, et al. Diabetes that impacts on routine activities predicts slower recovery after total knee arthroplasty: an observational study. *J Physiother* 2014;60(4):217-23. doi: http://dx.doi.org/10.1016/j.jphys.2014.09.006
29. Ayers DC, Franklin PD, Ploutz-Snyder R, et al. Total knee replacement outcome and coexisting physical and emotional illness. *Clinical Orthopaedics & Related Research* 2005;440(1):157-61 5p. doi: http://dx.doi.org/10.1097/01.blo.0000185447.43622.93
30. Belmont PJ, Goodman GP, Rodriguez M, et al. Predictors of hospital readmission following revision total knee arthroplasty. *Knee surgery, sports traumatology, arthroscopy : official journal of the ESSKA* 2016;24(10):3329-38. doi: http://dx.doi.org/10.1007/s00167-015-3782-6
31. Bolognesi MP, Marchant Jr MH, Viens NA, et al. The Impact of Diabetes on Perioperative Patient Outcomes After Total Hip and Total Knee Arthroplasty in the United States. *Journal of Arthroplasty* 2008;23(6 SUPPL.):92-98. doi: http://dx.doi.org/10.1016/j.arth.2008.05.012
32. Browne JA, Sandberg BF, D'Apuzzo MR, et al. Depression is associated with early postoperative outcomes following total joint arthroplasty: a nationwide database study. *Journal of Arthroplasty* 2014;29(3):481-3. doi: http://dx.doi.org/10.1016/j.arth.2013.08.025
33. Buller LT, Best MJ, Klika AK, et al. The influence of psychiatric comorbidity on perioperative outcomes following primary total hip and knee arthroplasty; A 17-year analysis of the national hospital discharge survey database. *Journal of Arthroplasty* 2015;30(2):165-70. doi: http://dx.doi.org/10.1016/j.arth.2014.08.034

34. Chan PKH, Brenkel IJ, Aderinto J. The outcome of total hip arthroplasty in diabetes mellitus. *British Journal of Diabetes and Vascular Disease* 2005;5(3):146-49. doi: http://dx.doi.org/10.1177/14746514050050030601
35. Clement ND, MacDonald D, Burnett R, et al. Diabetes does not influence the early outcome of total knee replacement: a prospective study assessing the Oxford knee score, short form 12, and patient satisfaction. *Knee* 2013;20(6):437-41. doi: http://dx.doi.org/10.1016/j.knee.2013.07.009
36. Cohen SM, Te HS, Levitsky J. Operative risk of total hip and knee arthroplasty in cirrhotic patients. *Journal of Arthroplasty* 2005;20(4):460-6. doi: http://dx.doi.org/10.1016/j.arth.2004.05.004
37. Courtney PM, Boniello AJ, Berger RA. Complications Following Outpatient Total Joint Arthroplasty: An Analysis of a National Database. *Journal of Arthroplasty* 2017;32(5):1426-30. doi: http://dx.doi.org/10.1016/j.arth.2016.11.055
38. Deegan BF, Richard RD, Bowen TR, et al. Impact of chronic kidney disease stage on lower-extremity arthroplasty. *Orthopedics* 2014;37(7):e613-e18. doi: http://dx.doi.org/10.3928/01477447-20140626-51
39. Deleuran T, Vilstrup H, Overgaard S, et al. Cirrhosis patients have increased risk of complications after hip or knee arthroplasty. *Acta Orthop* 2015;86(1):108-13 6p. doi: 10.3109/17453674.2014.961397
40. Dowsey MM, Choong PF. Obese Diabetic Patients are at Substantial Risk for Deep Infection after Primary TKA. *Clinical Orthopaedics & Related Research* 2009;467(6):1577-81 5p. doi: 10.1007/s11999-008-0551-6
41. Erkocak OF, Yoo JY, Restrepo C, et al. Incidence of Infection and Inhospital Mortality in Patients With Chronic Renal Failure After Total Joint Arthroplasty. *The Journal of arthroplasty* 2016;31(11):2437-41. doi: https://doi.org/10.1016/j.arth.2016.04.031
42. Gandhi R, Razak F, Tso P, et al. Metabolic syndrome and the incidence of symptomatic deep vein thrombosis following total knee arthroplasty. *The Journal of rheumatology* 2009;36(10):2298-301. doi: 10.3899/jrheum.090282
43. Gaston MS, Amin AK, Clayton RAE, et al. Does a history of cardiac disease or hypertension increase mortality following primary elective total hip arthroplasty? *Surgeon* 2007;5(5):260-65. doi: http://dx.doi.org/10.1016/S1479-666X(07)80021-7
44. Huddleston JI, Maloney WJ, Wang Y, et al. Adverse events after total knee arthroplasty: a national Medicare study. *The Journal of arthroplasty* 2009;24(6 Suppl):95-100. doi: 10.1016/j.arth.2009.05.001 [published Online First: 2009/07/07]
45. Hunt LP, Ben-Shlomo Y, Clark EM, et al. 45-day mortality after 467 779 knee replacements for osteoarthritis from the National Joint Registry for England and Wales: an observational study. *The Lancet* 2014;384(9952):1429-36. doi: https://doi.org/10.1016/S0140-6736(14)60540-7
46. Hunt LP, Ben-Shlomo Y, Clark EM, et al. 90-day mortality after 409 096 total hip replacements for osteoarthritis, from the National Joint Registry for England and Wales: a retrospective analysis. *The Lancet* 2013;382(9898):1097-104. doi: https://doi.org/10.1016/S0140-6736(13)61749-3
47. Iorio R, Williams KM, Marcantonio AJ, et al. Diabetes mellitus, hemoglobin A1C, and the incidence of total joint arthroplasty infection. *Journal of Arthroplasty* 2012;27(5):726-9.e1. doi: http://dx.doi.org/10.1016/j.arth.2011.09.013
48. Inacio MCS, Pratt NL, Roughead EE, et al. Evaluation of three co-morbidity measures to predict mortality in patients undergoing total joint arthroplasty. *Osteoarthritis and Cartilage* 2016;24(10):1718-26. doi: https://doi.org/10.1016/j.joca.2016.05.006
49. Jain NB, Guller U, Pietrobon R, et al. Comorbidities increase complication rates in patients having arthroplasty. *Clinical Orthopaedics and Related Research* 2005(435):232-38. doi: http://dx.doi.org/10.1097/01.blo.0000156479.97488.a2

50. Jämsen E, Peltola M, Eskelinen A, et al. Comorbid diseases as predictors of survival of primary total hip and knee replacements: a nationwide register-based study of 96 754 operations on patients with primary osteoarthritis. *Annals of the Rheumatic Diseases* 2013;72(12):1975-82 8p. doi: 10.1136/annrheumdis-2012-202064
51. Jämsen E, Peltola M, Puolakka T, et al. Surgical outcomes of hip and knee arthroplasties for primary osteoarthritis in patients with Alzheimer's disease: a nationwide registry-based case-controlled study. *Bone & Joint Journal* 2015;97-B(5):654-61 8p. doi: 10.1302/0301-620X.97B5.34382
52. Jämsen E, Puolakka T, Peltola M, et al. Surgical outcomes of primary hip and knee replacements in patients with Parkinson's disease: a nationwide registry-based case-controlled study. *Bone & Joint Journal* 2014;96-B(4):486-91 6p. doi: 10.1302/0301-620X.96B4.33422
53. Jorgensen CC, Knop J, Nordentoft M, et al. Psychiatric disorders and psychopharmacologic treatment as risk factors in elective fast-track total hip and knee arthroplasty. *Anesthesiology* 2015;123(6):1281-91. doi: http://dx.doi.org/10.1097/ALN.0000000000000632
54. Jorgensen CC, Madsbad S, Kehlet H. Postoperative morbidity and mortality in type-2 diabetics after fast-track primary total hip and knee arthroplasty. *Anesthesia and Analgesia* 2015;120(1):230-38. doi: http://dx.doi.org/10.1213/ANE.0000000000000451
55. Judge A, Javaid MK, Arden NK, et al. Clinical tool to identify patients who are most likely to achieve long-term improvement in physical function after total hip arthroplasty. *Arthritis Care & Research* 2012;64(6):881-89. doi: 10.1002/acr.21594
56. Kapoor A, Chew P, Silliman RA, et al. Venous thromboembolism after joint replacement in older male veterans with comorbidity. *Journal of the American Geriatrics Society* 2013;61(4):590-601. doi: http://dx.doi.org/10.1111/jgs.12161
57. Kapoor A, Labonte AJ, Winter MR, et al. Risk of venous thromboembolism after total hip and knee replacement in older adults with comorbidity and co-occurring comorbidities in the Nationwide Inpatient Sample (2003-2006). *BMC geriatrics* 2010;10:63. doi: http://dx.doi.org/10.1186/1471-2318-10-63
58. Karam JA, Huang RC, Abraham JA, et al. Total joint arthroplasty in cancer patients. *Journal of Arthroplasty* 2015;30(5):758-61. doi: http://dx.doi.org/10.1016/j.arth.2014.12.017
59. Keswani A, Lovy AJ, Robinson J, et al. Risk Factors Predict Increased Length of Stay and Readmission Rates in Revision Joint Arthroplasty. *Journal of Arthroplasty* 2016;31(3):603-8. doi: https://dx.doi.org/10.1016/j.arth.2015.09.050
60. Kildow BJ, Agaba P, Moore BF, et al. Postoperative Impact of Diabetes, Chronic Kidney Disease, Hemodialysis, and Renal Transplant After Total Hip Arthroplasty. *Journal of Arthroplasty* 2017;15 doi: http://dx.doi.org/10.1016/j.arth.2017.01.018
61. Kuo FC, Lin PC, Lu YD, et al. Chronic Kidney Disease Is an Independent Risk Factor for Transfusion, Cardiovascular Complication, and Thirty-Day Readmission in Minimally Invasive Total Knee Arthroplasty. *Journal of Arthroplasty* 2017;32(5):1630-34. doi: http://dx.doi.org/10.1016/j.arth.2016.12.006
62. Lee SW, Kumar GK, Kim TK. Unplanned readmissions after primary total knee arthroplasty in Korean patients: Rate, causes, and risk factors. *Knee* 2016;11 doi: http://dx.doi.org/10.1016/j.knee.2016.05.011
63. Liao KM, Lu HY. A national analysis of complications following total hip replacement in patients with chronic obstructive pulmonary disease. *Medicine (United States)* 2016;95 (12) (no pagination)(e3182) doi: http://dx.doi.org/10.1097/MD.0000000000003182
64. Marchant MH, Jr., Viens NA, Cook C, et al. The impact of glycemic control and diabetes mellitus on perioperative outcomes after total joint arthroplasty. *Journal of Bone & Joint Surgery - American Volume* 2009;91(7):1621-9. doi: http://dx.doi.org/10.2106/JBJS.H.00116
65. Martinez-Huedo MA, Villanueva M, De Andres AL, et al. Trends 2001 to 2008 in incidence and immediate postoperative outcomes for major joint replacement among Spanish adults

suffering diabetes. *European Journal of Orthopaedic Surgery and Traumatology* 2013;23(1):53-59. doi: http://dx.doi.org/10.1007/s00590-011-0915-6

66. Mazoch M, Barnes CL, Cooper K. Complications in diabetic patients undergoing revision total joint arthroplasty. *Current Orthopaedic Practice* 2016;27(3):296-302 7p. doi: http://dx.doi.org/10.1097/BCO.0000000000000360
67. McCleery MA, Leach WJ, Norwood T. Rates of infection and revision in patients with renal disease undergoing total knee replacement in Scotland. *Journal of Bone & Joint Surgery, British Volume* 2010;92(11):1535-39 5p. doi: 10.1302/0301-620X.92B11.23870
68. Meding JB, Reddleman K, Keating ME, et al. Total knee replacement in patients with diabetes mellitus. *Clin Orthop Relat Res* 2003(416):208-16. doi: 10.1097/01.blo.0000093002.90435.56
69. Menendez ME, Park KJ, Barnes CL. Early Postoperative Outcomes After Total Joint Arthroplasty in Patients With Multiple Myeloma. *Journal of Arthroplasty* 2016;31(8):1645-48. doi: http://dx.doi.org/10.1016/j.arth.2016.01.029
70. Miric A, Inacio MC, Namba RS. The effect of chronic kidney disease on total hip arthroplasty. *Journal of Arthroplasty* 2014;29(6):1225-30. doi: http://dx.doi.org/10.1016/j.arth.2013.12.031
71. Miric A, Inacio MC, Namba RS. Can total knee arthroplasty be safely performed in patients with chronic renal disease? *Acta Orthop* 2014;85(1):71-8. doi: http://dx.doi.org/10.3109/17453674.2013.878829
72. Moon HK, Han CD, Yang IH, et al. Factors affecting outcome after total knee arthroplasty in patients with diabetes mellitus. *Yonsei Med J* 2008;49(1):129-37. doi: http://dx.doi.org/10.3349/ymj.2008.49.1.129
73. Pedersen AB, Mehnert F, Johnsen SP, et al. Risk of revision of a total hip replacement in patients with diabetes mellitus: A population-based follow up study. *Journal of Bone and Joint Surgery - Series B* 2010;92(7):929-34. doi: http://dx.doi.org/10.1302/0301-620X.92B7.24461
74. Perez-Prieto D, Gil-Gonzalez S, Pelfort X, et al. Influence of depression on total knee arthroplasty outcomes. *Journal of Arthroplasty* 2014;29(1):44-47. doi: http://dx.doi.org/10.1016/j.arth.2013.04.030
75. Radtke K, Tetzlaff T, Vaske B, et al. Arthroplasty-center related retrospective analysis of risk factors for Periprosthetic Joint Infection after primary and after revision Total Hip Arthroplasty. *Technology and Health Care* 2016;24(5):721-28. doi: http://dx.doi.org/10.3233/THC-161158
76. Rajamaki TJ, Jamsen E, Puolakka PA, et al. Diabetes is associated with persistent pain after hip and knee replacement. *Acta Orthop* 2015;86(5):586-93. doi: http://dx.doi.org/10.3109/17453674.2015.1044389
77. Rasouli MR, Menendez ME, Sayadipour A, et al. Direct Cost and Complications Associated With Total Joint Arthroplasty in Patients With Preoperative Anxiety and Depression. *The Journal of arthroplasty* 2016;31(2):533-6. doi: 10.1016/j.arth.2015.09.015 [published Online First: 2015/10/21]
78. Robertson F, Geddes J, Ridley D, et al. Patients with Type 2 diabetes mellitus have a worse functional outcome post knee arthroplasty: a matched cohort study. *Knee* 2012;19(4):286-9. doi: http://dx.doi.org/10.1016/j.knee.2011.06.001
79. Sanders RD, Bottle A, Jameson SS, et al. Independent preoperative predictors of outcomes in orthopedic and vascular surgery: the influence of time interval between an acute coronary syndrome or stroke and the operation. *Ann Surg* 2012;255(5):901-7. doi: http://dx.doi.org/10.1097/SLA.0b013e31824c438d
80. Seol YJ, Yoon TR, Lee DH, et al. Outcome analysis of hip or knee arthroplasty in patients with cirrhotic liver disease. *Journal of Orthopaedics* 2017;14(1):171-75. doi: http://dx.doi.org/10.1016/j.jor.2016.12.011

81. Sikora-Klak J, Zarling B, Bergum C, et al. The Effect of Comorbidities on Discharge Disposition and Readmission for Total Joint Arthroplasty Patients. *Journal of Arthroplasty* 2017;32(5):1414-17. doi: http://dx.doi.org/10.1016/j.arth.2016.11.035
82. Singh JA. Effect of comorbidity on quality of life of male veterans with prevalent primary total knee arthroplasty. *Clinical Rheumatology* 2009;28(9):1083-9. doi: http://dx.doi.org/10.1007/s10067-009-1195-y
83. Singh JA, Lewallen DG. Diabetes: A risk factor for poor functional outcome after total knee arthroplasty. *PLoS ONE* 2013;8 (11) (no pagination)(e78991) doi: http://dx.doi.org/10.1371/journal.pone.0078991
84. Singh JA, Lewallen DG. Medical comorbidity is associated with persistent index hip pain after total hip arthroplasty. *Pain medicine (Malden, Mass)* 2013;14(8):1222-29. doi: http://dx.doi.org/10.1111/pme.12153
85. Singh JA, Lewallen DG. Medical and psychological comorbidity predicts poor pain outcomes after total knee arthroplasty. *Rheumatology (Oxford, England)* 2013;52(5):916-23. doi: 10.1093/rheumatology/kes402
86. Singh JA, Lewallen DG. Underlying diagnosis predicts patient-reported outcomes after revision total knee arthroplasty. *Rheumatology (United Kingdom)* 2014;53(2):361-66. doi: http://dx.doi.org/10.1093/rheumatology/ket357
87. Singh JA, Lewallen DG. Cerebrovascular disease is associated with outcomes after total knee arthroplasty: a US total joint registry study. *Journal of Arthroplasty* 2014;29(1):40-3. doi: http://dx.doi.org/10.1016/j.arth.2013.04.003
88. Singh JA, Lewallen DG. Depression in primary TKA and higher medical comorbidities in revision TKA are associated with suboptimal subjective improvement in knee function. *BMC Musculoskelet Disord* 2014;15:127. doi: 10.1186/1471-2474-15-127 [published Online First: 2014/04/15]
89. Stundner O, Kirksey M, Chiu YL, et al. Demographics and Perioperative Outcome in Patients with Depression and Anxiety Undergoing Total Joint Arthroplasty: A Population-Based Study. *Psychosomatics* 2013;54(2):149-57. doi: http://dx.doi.org/10.1016/j.psym.2012.08.009
90. Tiberi JV, 3rd, Hansen V, El-Abbadi N, et al. Increased complication rates after hip and knee arthroplasty in patients with cirrhosis of the liver. *Clinical Orthopaedics & Related Research* 2014;472(9):2774-8. doi: http://dx.doi.org/10.1007/s11999-014-3681-z
91. Vannini P, Ciavarella A, Olmi R, et al. Diabetes as pro-infective risk factor in total hip replacement. *Acta Diabetol Lat* 1984;21(3):275-80.
92. Wang S, Zhao Y. Diabetes mellitus and the incidence of deep vein thrombosis after total knee arthroplasty: a retrospective study. *The Journal of arthroplasty* 2013;28(4):595-7. doi: 10.1016/j.arth.2012.07.023 [published Online First: 2012/11/17]
93. Warth LC, Pugely AJ, Martin CT, et al. Total Joint Arthroplasty in Patients with Chronic Renal Disease: Is It Worth the Risk? *Journal of Arthroplasty* 2015;30(9 Suppl):51-4. doi: http://dx.doi.org/10.1016/j.arth.2014.12.037
94. Zhao Z, Wang S, Ma W, et al. Diabetes mellitus increases the incidence of deep vein thrombosis after total knee arthroplasty. *Archives of Orthopaedic and Trauma Surgery* 2014;134(1):79-83. doi: 10.1007/s00402-013-1894-3
95. Singh JA, Lewallen D. Age, gender, obesity, and depression are associated with patient-related pain and function outcome after revision total hip arthroplasty. *Clinical Rheumatology* 2009;28(12):1419-30. doi: http://dx.doi.org/10.1007/s10067-009-1267-z
96. Judge A, Arden NK, Batra RN, et al. The association of patient characteristics and surgical variables on symptoms of pain and function over 5 years following primary hip-replacement surgery: a prospective cohort study. *BMJ Open* 2013;3(3):e002453. doi: 10.1136/bmjopen-2012-002453

97. Santaguida PL, Hawker GA, Hudak PL, et al. Patient characteristics affecting the prognosis of total hip and knee joint arthroplasty: a systematic review. *Canadian Journal of Surgery* 2008;51(6):428-36.
98. Wright JG, Hawker GA, Bombardier C, et al. Physician enthusiasm as an explanation for area variation in the utilization of knee replacement surgery. *Med Care* 1999;37(9):946-56. doi: http://dx.doi.org/10.1097/00005650-199909000-00010 [published Online First: 1999/09/24]
99. Dieppe PA. Inequalities in the Provision of Surgical Interventions: Whose Responsibility? *Journal of Rheumatology* 2011;38(3):401-02. doi: 10.3899/jrheum.101209

# FIGURE LEGEND

Figure 1 – Flow chart

Figure 2 – Forest plots of short-term outcomes

Figure 3 – Forest plots of long-term outcomes

Figure 4 – Funnel plot showing 95% confidence limits for any surgical complications, surgical site infections, venous thromboembolism, readmissions to hospital and pain in diabetic patients

Figure 5 – Funnel plot showing 95% confidence limits for any surgical site infections, readmissions to hospital, short-term mortality and long-term mortality in kidney disease patients

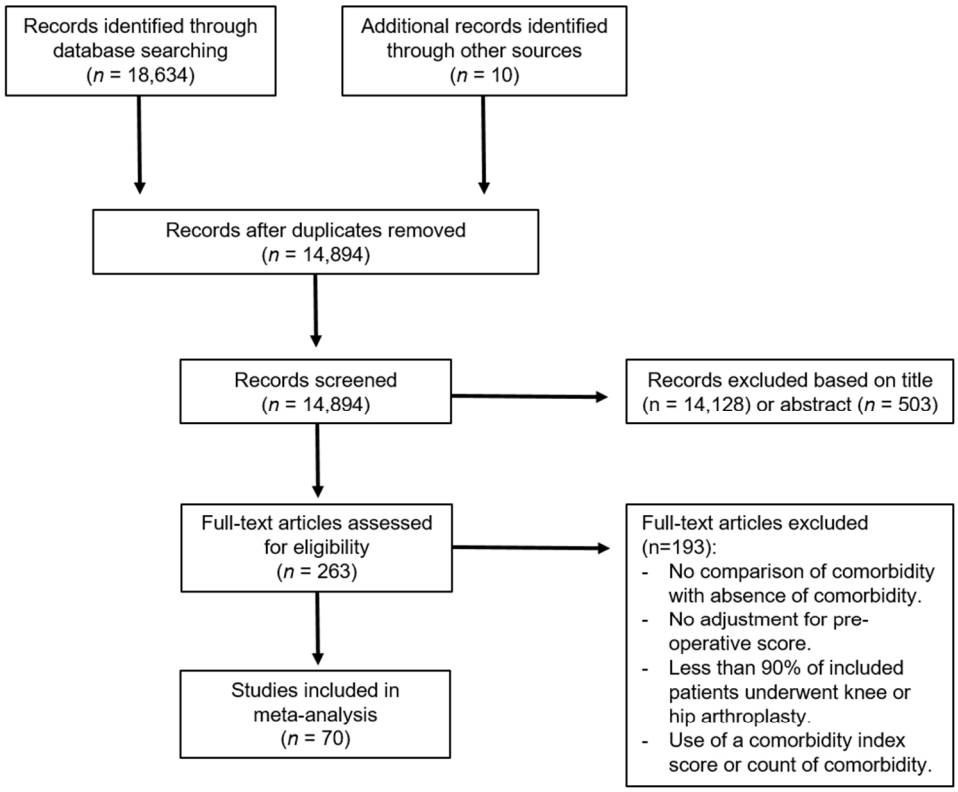


Figure 1 – Flow chart

87x72mm (300 x 300 DPI)

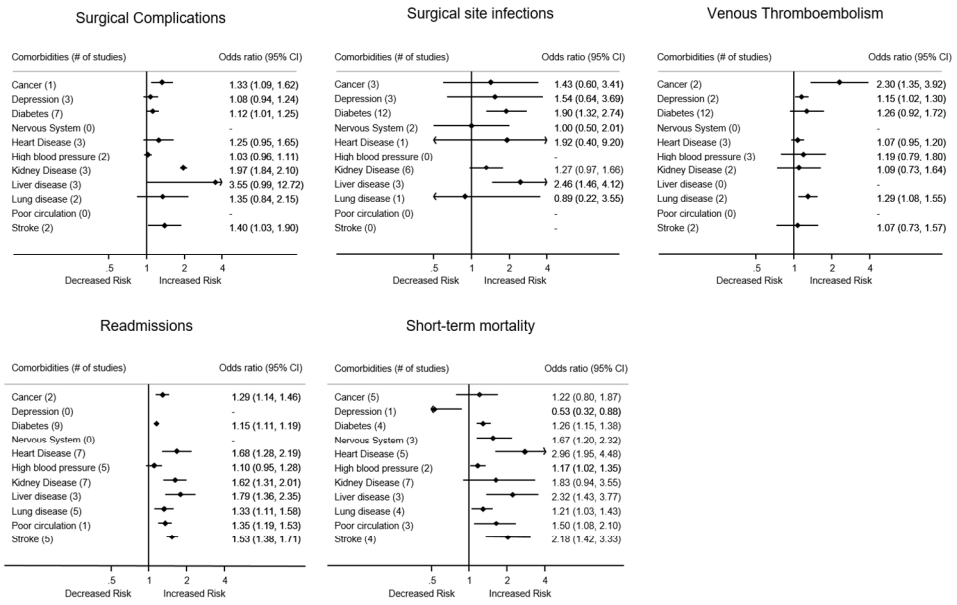


Figure 2 – Forest plots of short-term outcomes

131x86mm (300 x 300 DPI)

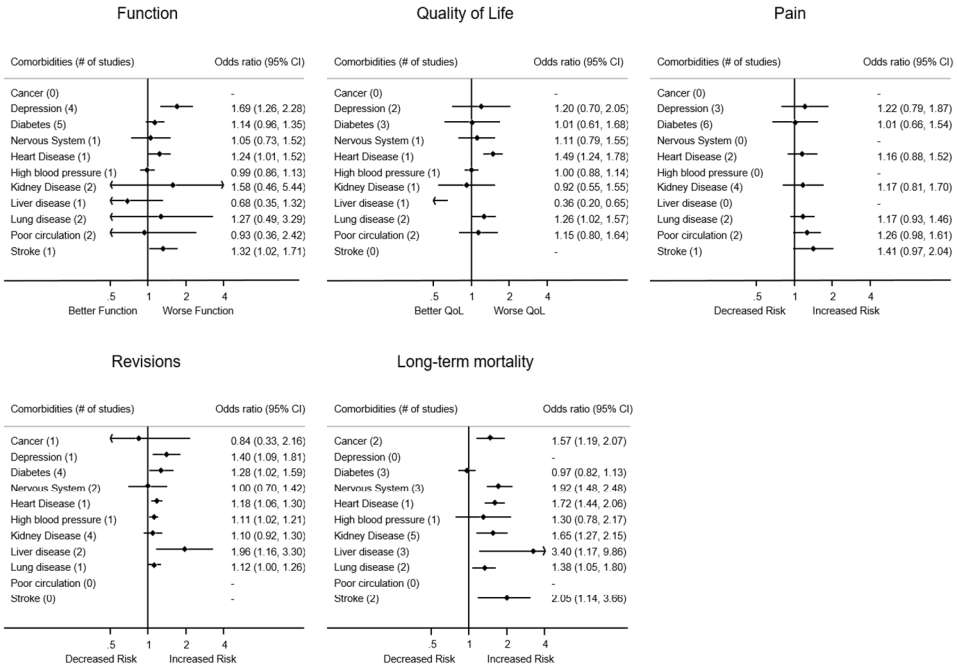


Figure 3 – Forest plots of long-term outcomes

122x88mm (300 x 300 DPI)

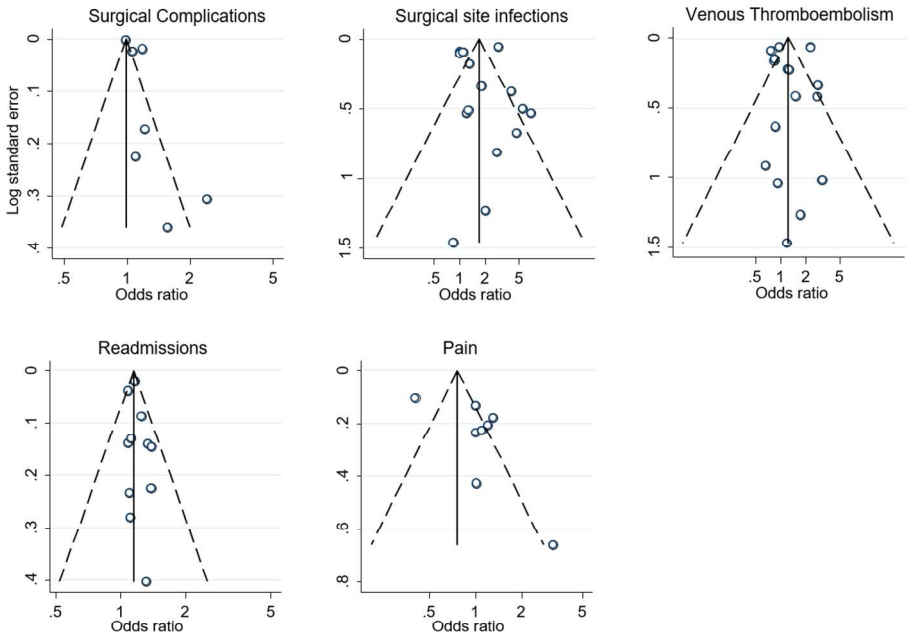


Figure 4 – Funnel plot showing 95% confidence limits for any surgical complications, surgical site infections, venous thromboembolism, readmissions to hospital and pain in diabetic patients

111x84mm (300 x 300 DPI)

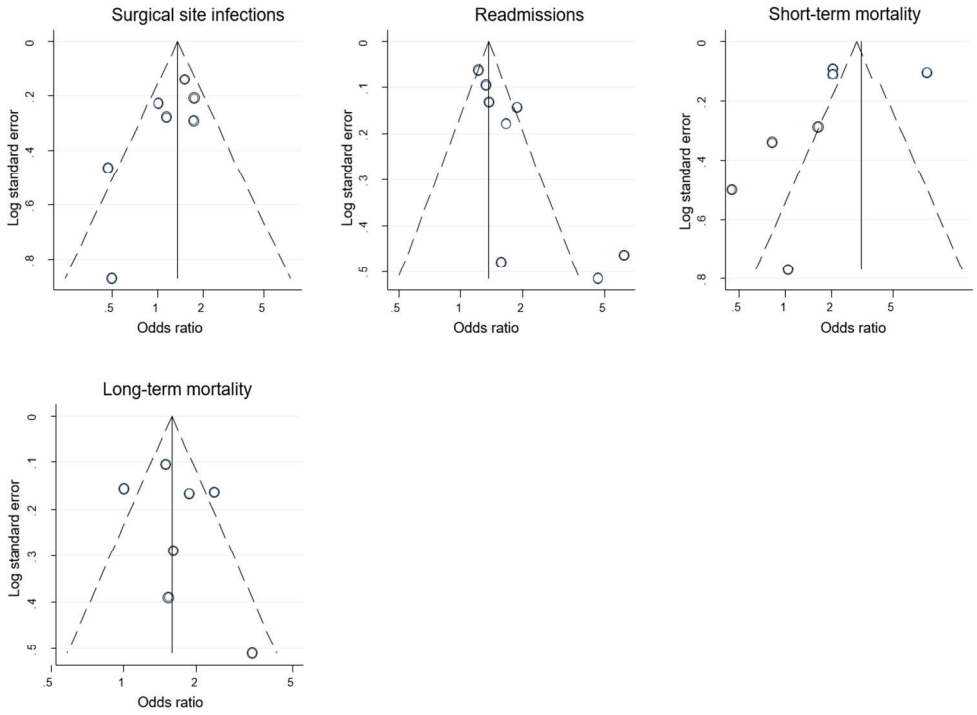


Figure 5 – Funnel plot showing 95% confidence limits for any surgical site infections, readmissions to hospital, short-term mortality and long-term mortality in kidney disease patients

111x84mm (300 x 300 DPI)

*Supplementary Information 1 – Search string*

| | |
|---|---|
| 1 | knee replacement.mp. or exp knee arthroplasty/ |
| 2 | hip replacement.mp. or exp hip arthroplasty/ |
| 3 | knee arthroplasty.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] |
| 4 | hip arthroplasty.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] |
| 5 | exp Arthroplasty, replacement/ |
| 6 | exp hip surgery/ or hip surgery.mp. |
| 7 | exp knee surgery/ or knee surgery.mp. |
| 8 | 1 or 3 or 7 |
| 9 | 2 or 4 or 6 |
| 10 | 8 and 9 |
| 11 | 8 or 9 or 10 |
| 12 | 11 or 5 |
| 13 | Humans/ |
| 14 | exp Comorbidity/ |
| 15 | charlson comorbidity index.mp. |
| 16 | elixhauser comorbidity index.mp. |
| 17 | exp Cardiovascular Diseases/ |
| 18 | exp Hypertension/ |
| 19 | exp Stroke/ |
| 20 | exp Peripheral Vascular Diseases/ |
| 21 | exp Lung Diseases/ |
| 22 | exp Diabetes Mellitus/ |
| 23 | exp Kidney Diseases/ |
| 24 | exp Nervous System Diseases/ |
| 25 | exp Liver Diseases/ |
| 26 | exp Neoplasms/ |
| 27 | exp Depression/ |
| 28 | exp Diabetes Complications/ |
| 31 | underlying diagnosis.mp. |
| 32 | comorbidit*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] |
| 33 | 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 |
| 34 | exp Postoperative Complications/ |
| 35 | exp Treatment Outcome/ |
| 36 | exp "Quality of Life"/ |

37 exp Mortality/
38 exp Infection/
39 exp Patient Readmission/
40 exp Reoperation/
41 exp Health Status/
42 outcomes.mp.
43 mortality.mp.
44 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43
45 12 and 13 and 33 and 44

*Supplementary Information 2 – Description of selected studies (n = 70)*

| Study | Data | | | Patient Sample | | | Comorbid Conditions | Outcomes |
|---|---|---|---|---|---|---|---|---|
| | Country | Years of data | Data source | Type of surgery | Primary or Revision surgery | Sample Size | | |
| Ackland (2011) | UK | 2004-2005 | Single-site | THA and TKA | Primary & Revision | 526 | Chronic Kidney disease | Infection, Pain, Postoperative morbidity |
| Adams (2013) | USA | 2001-2009 | Joint registry | TKA | Primary | 40,491 | Controlled diabetes | All-cause rehospitalizations, Deep Infection, Deep vein thrombosis, Revisions |
| Aggarwal (2013) | USA | 2007-2011 | Single-site | THA and TKA | Primary & Revision | 323 | Atrial Fibrillation | Readmission rate |
| Amusat (2014) | Canada | NS | Multi-site | TKA | Primary | 405 | Diabetes without impact on routine activities, Kidney Disease | Overall health (HUI3) -6m post-operative, WOMAC function, WOMAC pain |
| Ayers (2005) | USA | NS | Single-site | TKA | Primary | 165 | Lower extremity (PVD, venous insufficiency) | Mean change in Physical Function (SF-36) 12mths post surgery, Mean change in Physical Function (WOMAC) 12mths post surgery |
| Belmont (2016) | USA | 2011-2012 | Multi-site | TKA | Revision | 1754 | Cardiac disease, COPD, CVA/Stroke, Diabetes, Hypertension | Readmissions within 30 days |
| Bolognesi (2008) | USA | 1988-2003 | Administrative data | THA and TKA | Primary & Revision | 2,249,427 | Diabetes | DVT, Died, Infection |
| Browne (2014) | USA | 2006-2008 | Administrative data | THA and TKA | Primary | 497,222 | Depression | Infection, Pulmonary embolism |
| Buller (2015) | USA | 1990-2007 | Administrative data | THA and TKA | Primary | 8,379,490 | Chronic pulmonary disease, CAD, Depression, Diabetes, Hypertension | Adverse Events (wound complication , postoperative shock, postoperative bleeding, acute postoperative infection, acute postoperative anemia, acute renal failure, acute myocardial infarction, pulmonary embolism, induced mental disorder, pneumonia, pulmonary insufficiency, DVT, intubation and transfusion of blood) |
| Chan (2005) | UK | 2000-2003 | Single-site | THA | NS | 1,297 | Diabetes | Deep Infection, Deep vein thrombosis |
| Clement (2013) | UK | NS | Single-site | TKA | Primary | 2,389 | Depression, Diabetes, Heart disease, High blood pressure, | Post-operative OKS at 12mths, post-operative SF-12 at 12mths |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Kidney disease, Lung disease, Neurological diseases, Vascular disease | |
| Cohen (2005) | USA | 1986-2002 | Single-site | THA and TKA | Primary | 122 | Liver cirrhosis | Death, Major complications |
| Courtney (2017) | USA | 2011-2014 | Multi-site | THA and TKA | Primary | 169,406 | Cardiac disease, Diabetes, History of stroke, Preoperative creatinine >1.5mg/dL | 30 day complications (SSI, pneumonia, respiratory, pulmonary embolism, DVT, stroke, cardiac arrest, renal failure, UTI, sepsis, septic shock), 30 day readmissions |
| Deegan (2014) | USA | 2004-2011 | Single-site | THA and TKA | NS | 779 | Chronic Kidney Disease | Death, Infections, Revisions |
| Deleuran (2015) | Denmark | 1995-2001 | Administrative data | THA and TKA | Primary | 109,522 | Liver cirrhosis | Deep prosthetic infection, Intraoperative complications, Mortality within 30 days Readmission within 30 days, Revision in one year |
| Dowsey (2009) | Australia | 1998-2005 | Single-site | TKA | Primary | 1,214 | Cardiovascular disease, Diabetes, Respiratory diseases | Deep Infection |
| Erkocak (2016) | USA | 2000-2012 | Single-site | THA and TKA | NS | 1077 | Chronic Renal failure | Surgical site infections, In-hospital mortality |
| Gandhi (2009) | Canada | 1998-2006 | Single-site | TKA | NS | 1,460 | Diabetes, Hypertension | DVT within 3 months |
| Gaston (2007) | UK | 1998-2006 | Single-site | THA | Primary | 1,744 | Cerebrovascular disease, CHF, COPD, Diabetes | Mortality within 3mths after admission |
| Huddleston (2009) | USA | 2002-2004 | Multi-site | TKA | NS | 2,033 | Diabetes | Adverse events (deep infections, necrosis, nerve injury, dislocation, cardiovascular complication, periprosthetic fracture, Revision, UTI, DVT, Pneumonia, Death) |
| Hunt (2013) | UK | 2003-2011 | Joint registry | THA | NS | 409,096 | CHF, PVD, CVD, Chronic Pulmonary disease, Diabetes without complications, Renal disease, Cancer, Dementia | 90-day mortality |
| Hunt (2014) | UK | 2003-2011 | Joint registry | TKA | NS | 467,779 | CHF, PVD, CVD, Chronic Pulmonary disease, Diabetes without complications, Renal disease, Cancer, Dementia | 45-day mortality |
| Inacio (2016) | Australia | 2001-2012 | Administrative data | THA | NS | 30820 | Liver disease, CHF, Renal disease, Parkinson's disease, Dementia, | 90-day mortality, 1-year mortality |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Chronic airway disease, Solid tumour without metastasis | |
| Iorio (2012) | USA | 2004-2009 | Single-site | THA and TKA | Primary | 1,529 | Diabetes | Infection |
| Jain (2005) | USA | 1988-2000 | Administrative data | THA and TKA and shoulder arthroplasty | Primary | 959,839 | Diabetes, Hypertension | Complications (infections, wound infections, pulmonary embolism, thromophlebitis, vascular complications, other) |
| Jamsen (2013) | Finland | 1998-2008 | Joint registry | THA and TKA | Primary | 96,754 | Cancer, CHD, Depression, Diabetes, Hypertension (without CVD), Pulmonary disease | Risk of Revision surgery |
| Jamsen (2014) | Finland | 1998-2009 | Administrative data + Joint registry | THA and TKA | Primary | 3,428 | Parkinson's disease | Infection at 1 year, Mortality > 1 year Revisions in 0-2 years postoperative |
| Jamsen (2015) | Finland | 1998-2009 | Administrative data + Joint registry | THA and TKA | Primary | 4,526 | Alzheimer's disease | Mortality after 10 years, Rate of surgical site infection, Risk of Revision |
| Jorgensen (2015a) | Denmark | 2010-2012 | Multi-site | THA and TKA | Primary | 8,757 | Cardiovascular disease, Pulmonary disease | 90-day readmission |
| Jorgensen (2015b) | Denmark | 2010-2012 | Multi-site | THA and TKA | Primary | 8,055 | Diabetes Type II | "Diabetes-related morbidity" (cardiac arrhythmias, acute congestive heart failure, MI, prosthetic or wound infections, renal insufficiency, cerebral attacks, pneumonia, UTI>4days, dysregulated blood glucose, other infections), 90-day readmission |
| Judge (2012) | UK | 1993-1995 | Multisite | THA | NS | 282 | Diabetes | SF-36 Physical functioning |
| Kapoor (2010) | USA | 2003-2006 | Administrative data | THA and TKA | Primary | 316,671 | COPD, CAD, Cerebrovascular disease, Diabetes | Venous Thromboembolism |
| Kapoor (2013) | USA | 2002-2009 | Administrative data | THA and TKA | Primary & Revision | 24,051 | COPD, CAD, Cerebrovascular disease, Diabetes | Venous Thromboembolism |
| Karam (2015) | USA | 2000-2011 | Single-site | THA and TKA | Primary & Revision | 26,415 | Cancer | Deep vein thrombosis, Mortality Overall in-hospital complications, Periprosthetic joint infection |
| Keswani (2016) | USA | 2011-2013 | Multi-site | THA and TKA | Revision | 10,112 | Disseminated cancer, Cardiac disease, Diabetes, Renal disease, Stroke, Hypertension, Pulmonary disease | 30-day readmissions |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Kildow (2017) | USA | 2005-2012 | Multi-site | THA | NS | 61,778 | Diabetes | DVT- 30 days, Prosthetic Joint infection - 90 days, THA Revision - 2-years |
| Kuo (2017) | Taiwan | 2009-2012 | Single-site | TKA | Primary | 615 | Chronic Kidney Disease | 30-day readmissions |
| Lee (2017) | Korea | 2004-2013 | Single-site | TKA | Primary | 3,049 | Diabetes, Hypertension | 90-day readmission |
| Liao (2016) | Taiwan | 2004-2008 | Administrative data | THA | NS | 2,426 | Cardiovascular disease, CVA, Chronic Kidney disease, COPD, Hypertension | 1-year mortality, 30-day readmissions |
| Marchant (2009) | USA | 1988-2005 | Administrative data | THA and TKA | Primary & Revision | 1,030,013 | Controlled diabetes | DVT, Died, Infection |
| Martinez (2013) | Spain | 2001-2008 | Administrative data | THA and TKA | Primary | 373,131 | Diabetes | In-hospital mortality |
| Mazoch (2009) | USA | 2004-2012 | Single-site | THA and TKA | Revision | 130 | Diabetes | All complications, Infection |
| McCleery (2010) | UK | 1985-2008 | Joint registry | TKA | NS | 59,288 | Renal failure | Early infection (<90 days), Late Revision |
| Meding (2003) | USA | 1987-1999 | Single-site | TKA | Primary | 5,220 | Diabetes | Deep Infection, DVT, Knee Society Pain score - 1yr |
| Menendez (2016) | USA | 2002-2011 | Multi-site | THA and TKA | Primary | 6,054,344 | Multiple Myeloma | In-hospital mortality, SSI, Thromboembolic events |
| Miric (2014a) | USA | 2005-2010 | Joint registry | TKA | Primary | 41,852 | Chronic Renal Disease | DVT, Mortality (anytime), Mortality within 90 days, Readmission within 90 days, Revision, SSI deep |
| Miric (2014b) | USA | 2006-2010 | Joint registry | THA | Primary | 20,720 | Chronic Kidney Disease | DVT, Mortality (anytime), Mortality within 90 days, Readmission within 90 days, Revision (any), SSI (any) |
| Moon (2008) | Korea | 1995-2004 | Single-site | TKA | Primary | 1,581 | Diabetes | Deep joint infection, DVT, Knee Society Score – function, Knee Society Score – Pain, Overall complications |
| Pedersen (2010) | Denmark | 1996-2005 | Joint registry | THA | Primary | 57,575 | Diabetes | Overall Revisions |
| Perez (2014) | Spain | NS | Single-site | TKA | NS | 736 | Depression | SF-36 Physical component scores, WOMAC score |
| Radkte (2016) | Germany | 2011-2012 | Single-site | THA | Primary | 498 | Cancer, Depression, Diabetes | Periprosthetic joint infection |
| Rajamaki (2015) | Finland | 2009-2011 | Single-site | THA and TKA | Primary | 134 | Glucose metabolism abnormalities | Persistent Pain |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Rasouli (2016) | USA | 2009-2009 | Single-site | THA and TKA | Primary & Revision | 1,969 | Depression | Surgical complications |
| Robertson (2012) | UK | 1989-2002 | Single-site | TKA | NS | 734 | Diabetes | Knee Society knee score year 1 |
| Sanders (2012) | UK | 2006-2010 | Administrative data | THA and TKA | Primary | 414,985 | Cancer, Diabetes, Heart Failure, Hypertension, Liver disease, PVD, Renal failure, Respiratory disease, Stroke | In-hospital mortality, Readmission |
| Seol (2017) | South Korea | 2007-2015 | Multi-site | THA and TKA | Primary | 143 | Liver Cirrhosis | Infections, Medical complications |
| Sikora-Klak (2017) | USA | 2012-2014 | Single-site | THA and TKA | Primary | 2,914 | Diabetes | 90-day readmission |
| Singh (2014a) | USA | 1993-2005 | Joint registry | TKA | Primary and Revision | 8,672 | Depression | Knee status: much better 2- years |
| Singh (2009) | USA | 1993-2005 | Joint registry | THA | Revision | 2,687 | Depression | Moderate-Severe ADL limitation - 2 years<br>Moderate-severe pain - 2 years |
| Singh (2014b) | USA | 1993-2005 | Joint registry | TKA | Primary & Revision | 7,139 | Cerebrovascular disease | Moderate-Severe ADL limitation - 2 years<br>Moderate-severe pain - 2 years |
| Singh (2013a) | USA | 1993-2005 | Joint registry | THA | Primary & Revision | 8,394 | COPD, Diabetes, Heart disease, PVD, Renal disease | Moderate-severe pain at 2 years |
| Singh (2013b) | USA | 1993-2005 | Joint registry | TKA | Primary | 7,139 | Diabetes without complications | Moderate-severe ADL limitation 2 -years |
| Singh (2013c) | USA | 1993-2005 | Joint registry | TKA | Primary | 8,672 | COPD, Depression, Diabetes, Heart disease, PVD, Renal disease | Moderate-severe pain at 2 years |
| Singh (2014) | USA | 1993-2005 | Joint registry | TKA | Revision | 1,533 | Depression | Moderate-severe pain at 2 years |
| Stundner (2013) | USA | 2000-2008 | Administrative data | THA and TKA | Primary | 1,212,493 | Depression | In-hospital mortality, Major complications, Sepsis, Venous Thromboembolism |
| Tiberi (2014) | USA | 2000-2012 | Single-site | THA and TKA | NS | 230 | Liver cirrhosis | Infections within 90 days, Mortality most recent follow-up, Mortality within 90 days, Readmissions 90 days, Revision surgery during follow up |
| Vannini (1984) | Italy | 1969-1979 | Single-site | THA | NS | 1,227 | Diabetes | Post-surgery infections |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Wang (2013) | China | 2003-2011 | Single-site | TKA | NS | 245 | CHD, Diabetes, Hypertension | DVT |
| Warth (2015) | USA | 2006-2012 | Administrative data | THA and TKA | Primary | 74,300 | Chronic Renal disease | Overall complications |
| Zhao (2014) | China | 2011-2013 | Single-site | TKA | NS | 358 | Diabetes, Hypertension | DVT within 14 days |

*Note.* NS = not stated; THA = Total Hip Arthroplasty; TKA = Total Knee Arthroplasty; PVD = Peripheral Vascular Disease; COPD = Chronic Obstructive Pulmonary Disorder; CAD = Coronary Artery Disease ; CHD = Coronary Heart Disease ; CHF = Coronary Heart Failure; CVA/CVD = Cerebrovascular Accident/Disease; SF-36= Short-form 36; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; OKS = Oxford Knee Score; SF-12 = Short-form 12; SSI = Surgical Site Infection; DVT = Deep Vein Thrombosis; UTI = Uterine Infection; MI = Myocardial Infarction.

*Supplementary Information 3 - Quality appraisal of included 70 studies*

| Study | Patient Selection | | | | | Comparability | | Outcome Assessment | | | Overall quality score |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Cohort Representative? | Patients drawn from same community? | Presence of comorbidities verified? | Outcome not present at the start? | Cohort drawn from multiple communities? | Controlled for age and sex? | Controlled for SES and Ethnicity? | Outcome of interest clearly defined? | Follow-up long enough? | Follow-up adequate? | |
| Ackland (2011) | Yes | Yes | Yes | Yes | No | No | No | Yes | NS | No | 6 |
| Adams (2013) | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | 11 |
| Aggarwal (2013) | Yes | Yes | Yes | Yes | No | Yes | No | Yes | NS | No | 8 |
| Amusat (2014) | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | No | 10 |
| Ayers (2005) | No | Yes | Yes | Yes | No | Yes | No | Yes | Yes | No | 8 |
| Belmont (2016) | Yes | Yes | Yes | Yes | Yes | Yes | No | No | Yes | Yes | 9 |
| Bolognesi (2008) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | NS | No | 9 |
| Browne (2014) | Yes | Yes | Yes | Yes | Yes | Yes | Yes (ethnicity) | No | NS | No | 8 |
| Bulle (2015) | Yes | Yes | Yes | Yes | Yes | Yes | No | No | NS | No | 7 |
| Chan (2004) | Yes | Yes | Yes | Yes | No | Yes | No | Yes | Yes | Yes | 10 |
| Clement (2013) | Yes | Yes | Yes | Yes | No | No | No | Yes | Yes | Yes | 8 |
| Cohen (2005) | Yes | Yes | Yes | Yes | No | No | No | Yes | Yes | No | 7 |
| Courtney (2017) | Yes | Yes | Yes | Yes | Yes | Yes | Yes (ethnicity) | No | Yes | Yes | 10 |
| Deegan (2014) | Yes | Yes | Yes | Yes | No | Yes | No | Yes | Yes | Yes | 10 |
| Deleuran (2015) | Yes | Yes | Yes | Yes | Yes | Yes | No | No | Yes | Yes | 9 |
| Dowsey (2009) | Yes | Yes | Yes | Yes | No | Yes | No | Yes | Yes | Yes | 10 |
| Ekocak (2016) | Yes | Yes | Yes | Yes | No | No | No | No | Yes | Yes | 6 |
| Gandhi (2009) | Yes | Yes | Yes | Yes | No | Yes | No | Yes | Yes | No | 9 |
| Gaston (2007) | Yes | Yes | Yes | Yes | No | Yes | No | Yes | Yes | Yes | 10 |
| Huddleston (2009) | Yes | Yes | Yes | Yes | Yes | Yes | Yes (ethnicity) | No | Yes | Yes | 10 |
| Hunt (2013) | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | 11 |
| Hunt (2014) | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | 11 |
| Inacio (2016) | No | Yes | Yes | Yes | Yes | Yes | No | No | Yes | Yes | 8 |
| Iorio (2012) | Yes | Yes | Yes | Yes | No | No | No | Yes | NS | No | 6 |
| Jain (2005) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | NS | No | 9 |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Jamsen (2013) | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | 11 |
| Jamsen (2014) | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | 11 |
| Jamsen (2015) | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | 11 |
| Jorgensen (2015a) | Yes | Yes | Yes | Yes | Yes | No | No | Yes | Yes | Yes | 9 |
| Jorgensen (2015b) | Yes | Yes | Yes | Yes | Yes | No | No | Yes | Yes | Yes | 9 |
| Judge (2012) | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | No | 10 |
| Kapoor (2010) | No | Yes | Yes | Yes | Yes | Yes | No | No | NS | Yes | 7 |
| Kapoor (2013) | No | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | 10 |
| Karam (2015) | Yes | Yes | Yes | Yes | No | No | No | Yes | Yes | Yes | 8 |
| Keswani (2016) | Yes | Yes | Yes | Yes | Yes | Yes | No | No | Yes | Yes | 9 |
| Kildow (2017) | No | Yes | Yes | Yes | Yes | No | No | No | Yes | Yes | 6 |
| Kuo (2017) | No | Yes | Yes | Yes | No | Yes | No | Yes | Yes | Yes | 9 |
| Lee (2017) | No | Yes | Yes | Yes | No | Yes | No | Yes | Yes | Yes | 9 |
| Liao (2016) | No | Yes | Yes | Yes | Yes | Yes | No | No | Yes | Yes | 8 |
| Marchant (2009) | No | Yes | Yes | Yes | Yes | Yes | Yes (SES) | No | Yes | Yes | 9 |
| Martinez (2013) | No | Yes | Yes | Yes | Yes | Yes | No | No | Yes | Yes | 8 |
| Mazoch (2009) | Yes | Yes | Yes | Yes | No | 1 | No | Yes | NS | Yes | 8 |
| McCleery (2010) | Yes | Yes | Yes | Yes | Yes | Yes | No | No | Yes | Yes | 9 |
| Meding (2003) | Yes | Yes | Yes | Yes | No | No | No | Yes | Yes | No | 7 |
| Menendez (2016) | Yes | Yes | Yes | Yes | Yes | Yes | Yes (ethnicity) | No | Yes | Yes | 10 |
| Miric (2014a) | Yes | Yes | Yes | Yes | Yes | Yes | Yes (ethnicity) | Yes | Yes | Yes | 12 |
| Miric (2014b) | Yes | Yes | Yes | Yes | Yes | Yes | Yes (ethnicity) | Yes | Yes | Yes | 12 |
| Moon (2008) | Yes | Yes | Yes | Yes | No | No | No | Yes | Yes | Yes | 8 |
| Pedersen (2010) | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | 11 |
| Perez (2014) | Yes | Yes | Yes | Yes | No | No | No | Yes | Yes | Yes | 8 |
| Radkte (2016) | No | Yes | Yes | Yes | No | No | No | Yes | Yes | Yes | 7 |
| Rajamaki (2015) | Yes | Yes | Yes | Yes | No | Yes | No | Yes | Yes | No | 9 |
| Rasouli (2016) | Yes | Yes | Yes | Yes | No | Yes | No | Yes | Yes | Yes | 10 |
| Robertson (2012) | Yes | Yes | Yes | Yes | No | Yes | No | Yes | Yes | Yes | 10 |
| Sanders (2012) | Yes | Yes | Yes | Yes | Yes | Yes | Yes (SES) | No | Yes | Yes | 10 |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Seol (2017) | Yes | Yes | Yes | Yes | Yes | No | No | Yes | NS | Yes | 8 |
| Sikora-Klak (2017) | No | Yes | Yes | Yes | No | No | No | Yes | Yes | No | 6 |
| Singh (2014a) | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | No | 10 |
| Singh (2009) | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | No | 10 |
| Singh (2014b) | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | No | 10 |
| Singh (2013a) | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | No | 10 |
| Singh (2013b) | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | No | 10 |
| Singh (2013c) | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | No | 10 |
| Singh (2014) | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | No | 10 |
| Stundner (2013) | Yes | Yes | Yes | Yes | Yes | Yes | Yes (ethnicity) | No | Yes | Yes | 10 |
| Tiberi (2014) | Yes | Yes | Yes | Yes | No | No | No | Yes | Yes | Yes | 8 |
| Vannini (1984) | Yes | Yes | Yes | Yes | No | No | No | Yes | Yes | Yes | 8 |
| Wang (2013) | No | Yes | Yes | Yes | No | Yes | No | Yes | No | Yes | 8 |
| Warth (2015) | Yes | Yes | Yes | Yes | Yes | No | No | No | Yes | Yes | 7 |
| Zhao (2014) | No | Yes | Yes | Yes | No | Yes | No | Yes | No | Yes | 8 |

Note: SES = Socioeconomic Status

*Supplementary Information 4 – Sensitivity Analysis*

| Comorbidities | All Studies | | | | | High Quality Studies (Quality score ≥11) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | # of studies | # of patients | OR | 95% lower CI | 95% upper CI | # of studies | # of patients | OR | 95% lower CI | 95% upper CI |
| **Surgical Complications** | | | | | | | | | | |
| Cancer | 1 | <100,000 | 1.33 | 1.09 | 1.62 | 0 | | | | |
| Depression | 3 | >1M | 1.08 | 0.94 | 1.24 | 0 | | | | |
| Diabetes | 7 | >1M | 1.12 | 1.01 | 1.25 | 0 | | | | |
| Diseases of the Nervous System | 0 | | | | | 0 | | | | |
| Heart Disease | 3 | >1M | 1.25 | 0.95 | 1.65 | 0 | | | | |
| High blood pressure | 2 | >1M | 1.03 | 0.96 | 1.11 | 0 | | | | |
| Kidney Disease | 3 | <1M | 1.97 | 1.84 | 2.10 | 0 | | | | |
| Liver disease | 3 | <1M | 3.55 | 0.99 | 12.72 | 0 | | | | |
| Lung disease | 2 | >1M | 1.35 | 0.84 | 2.15 | 0 | | | | |
| Poor circulation | 0 | | | | | 0 | | | | |
| Stroke | 2 | <1M | 1.40 | 1.03 | 1.90 | 0 | | | | |
| **Venous Thromboembolism** | | | | | | | | | | |
| Cancer | 2 | >1M | 2.30 | 1.35 | 3.92 | 0 | | | | |
| Depression | 2 | >1M | 1.15 | 1.02 | 1.30 | 0 | | | | |
| Diabetes | 12 | >1M | 1.26 | 0.92 | 1.72 | 1 | <100,000 | 0.84 | 0.60 | 1.17 |
| Diseases of the Nervous System | 0 | | | | | 0 | | | | |
| Heart Disease | 3 | <1M | 1.07 | 0.95 | 1.20 | 0 | | | | |
| High blood pressure | 3 | <10,000 | 1.19 | 0.79 | 1.80 | 0 | | | | |
| Kidney Disease | 2 | <100,000 | 1.09 | 0.73 | 1.64 | 2 | <100,000 | 1.09 | 0.73 | 1.64 |
| Liver disease | 0 | | | | | 0 | | | | |
| Lung disease | 2 | <1M | 1.29 | 1.08 | 1.55 | 0 | | | | |
| Poor circulation | 0 | | | | | 0 | | | | |
| Stroke | 2 | <1M | 1.07 | 0.73 | 1.57 | 0 | | | | |
| **Surgical site infections** | | | | | | | | | | |
| Cancer | 3 | >1M | 1.43 | 0.60 | 3.41 | 0 | | | | |
| Depression | 3 | >1M | 1.54 | 0.64 | 3.69 | 0 | | | | |
| Diabetes | 12 | >1M | 1.90 | 1.32 | 2.74 | 1 | <100,000 | 1.31 | 0.92 | 1.86 |
| Diseases of the Nervous System | 2 | <10,000 | 1.00 | 0.50 | 2.01 | 2 | <10,000 | 1.00 | 0.50 | 2.01 |
| Heart Disease | 1 | <10,000 | 1.92 | 0.40 | 9.20 | 0 | | | | |
| High blood pressure | 0 | | | | | 0 | | | | |
| Kidney Disease | 6 | <1M | 1.27 | 0.97 | 1.66 | 2 | <100,000 | 1.06 | 0.75 | 1.50 |
| Liver disease | 3 | <1M | 2.46 | 1.46 | 4.12 | 0 | | | | |
| Lung disease | 1 | <10,000 | 0.89 | 0.22 | 3.55 | 0 | | | | |
| Poor circulation | 0 | | | | | 0 | | | | |
| Stroke | 0 | | | | | 0 | | | | |
| **Readmissions** | | | | | | | | | | |
| Cancer | 2 | <1M | 1.29 | 1.14 | 1.46 | 0 | | | | |
| Depression | 0 | | | | | 0 | | | | |
| Diabetes | 9 | <1M | 1.15 | 1.11 | 1.19 | 1 | <100,000 | 1.08 | 1.00 | 1.16 |
| Diseases of the Nervous System | 0 | | | | | 0 | | | | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Heart Disease | 7 | <1M | 1.68 | 1.28 | 2.19 | 0 | | | | |
| High blood pressure | 5 | <1M | 1.10 | 0.95 | 1.28 | 0 | | | | |
| Kidney Disease | 7 | <1M | 1.62 | 1.31 | 2.01 | 2 | <100,000 | 1.34 | 1.16 | 1.56 |
| Liver disease | 3 | <1M | 1.79 | 1.36 | 2.35 | 0 | | | | |
| Lung disease | 5 | <1M | 1.33 | 1.11 | 1.58 | 0 | | | | |
| Poor circulation | 1 | <1M | 1.35 | 1.19 | 1.53 | 0 | | | | |
| Stroke | 5 | <1M | 1.53 | 1.38 | 1.71 | 0 | | | | |
| **Short-term mortality** | | | | | | | | | | |
| Cancer | 5 | >1M | 1.22 | 0.80 | 1.87 | 0 | | | | |
| Depression | 1 | >1M | 0.53 | 0.32 | 0.88 | 0 | | | | |
| Diabetes | 4 | >1M | 1.26 | 1.15 | 1.38 | 0 | | | | |
| Diseases of the Nervous System | 3 | <1M | 1.67 | 1.20 | 2.32 | 0 | | | | |
| Heart Disease | 5 | >1M | 2.96 | 1.95 | 4.48 | 0 | | | | |
| High blood pressure | 2 | <1M | 1.17 | 1.02 | 1.35 | 0 | | | | |
| Kidney Disease | 7 | >1M | 1.83 | 0.94 | 3.55 | 2 | <100,000 | 0.73 | 0.42 | 1.26 |
| Liver disease | 3 | <1M | 2.32 | 1.43 | 3.77 | 0 | | | | |
| Lung disease | 4 | >1M | 1.21 | 1.03 | 1.43 | 0 | | | | |
| Poor circulation | 3 | >1M | 1.50 | 1.08 | 2.10 | 0 | | | | |
| Stroke | 4 | >1M | 2.18 | 1.42 | 3.33 | 0 | | | | |
| **Function** | | | | | | | | | | |
| Cancer | 0 | | | | | 0 | | | | |
| Depression | 4 | <100,000 | 1.69 | 1.26 | 2.28 | 0 | | | | |
| Diabetes | 5 | <100,000 | 1.14 | 0.96 | 1.35 | 0 | | | | |
| Diseases of the Nervous System | 1 | <10,000 | 1.05 | 0.73 | 1.52 | 0 | | | | |
| Heart Disease | 1 | <10,000 | 1.24 | 1.01 | 1.52 | 0 | | | | |
| High blood pressure | 1 | <10,000 | 0.99 | 0.86 | 1.13 | 0 | | | | |
| Kidney Disease | 2 | <10,001 | 1.58 | 0.46 | 5.44 | 0 | | | | |
| Liver disease | 1 | <10,000 | 0.68 | 0.35 | 1.32 | 0 | | | | |
| Lung disease | 2 | <10,000 | 1.27 | 0.49 | 3.29 | 0 | | | | |
| Poor circulation | 2 | <10,000 | 0.93 | 0.36 | 2.42 | 0 | | | | |
| Stroke | 1 | <10,000 | 1.32 | 1.02 | 1.71 | 0 | | | | |
| **Quality of Life** | | | | | | | | | | |
| Cancer | 0 | | | | | 0 | | | | |
| Depression | 2 | <10,000 | 1.20 | 0.70 | 2.05 | 0 | | | | |
| Diabetes | 3 | <10,000 | 1.01 | 0.61 | 1.68 | 0 | | | | |
| Diseases of the Nervous System | 1 | <10,000 | 1.11 | 0.79 | 1.55 | 0 | | | | |
| Heart Disease | 1 | <10,000 | 1.49 | 1.24 | 1.78 | 0 | | | | |
| High blood pressure | 1 | <10,000 | 1.00 | 0.88 | 1.14 | 0 | | | | |
| Kidney Disease | 1 | <10,000 | 0.92 | 0.55 | 1.55 | 0 | | | | |
| Liver disease | 1 | <10,000 | 0.36 | 0.20 | 0.65 | 0 | | | | |
| Lung disease | 2 | <10,000 | 1.26 | 1.02 | 1.57 | 0 | | | | |
| Poor circulation | 2 | <10,000 | 1.15 | 0.80 | 1.64 | 0 | | | | |
| Stroke | 0 | | | | | 0 | | | | |
| **Pain** | | | | | | | | | | |
| Cancer | 0 | | | | | 0 | | | | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Depression | 3 | <100,000 | 1.22 | 0.79 | 1.87 | 0 | | | | |
| Diabetes | 6 | <100,000 | 1.01 | 0.66 | 1.54 | 0 | | | | |
| Diseases of the Nervous System | 0 | | | | | 0 | | | | |
| Heart Disease | 2 | <100,000 | 1.16 | 0.88 | 1.52 | 0 | | | | |
| High blood pressure | 0 | | | | | 0 | | | | |
| Kidney Disease | 4 | <100,000 | 1.17 | 0.81 | 1.70 | 0 | | | | |
| Liver disease | 0 | | | | | 0 | | | | |
| Lung disease | 2 | <100,000 | 1.17 | 0.93 | 1.46 | 0 | | | | |
| Poor circulation | 2 | <100,000 | 1.26 | 0.98 | 1.61 | 0 | | | | |
| Stroke | 1 | <10,000 | 1.41 | 0.97 | 2.04 | 0 | | | | |
| **Revisions** | | | | | | | | | | |
| Cancer | 1 | <100,000 | 0.84 | 0.33 | 2.16 | 1 | <100,000 | 0.84 | 0.33 | 2.16 |
| Depression | 1 | <100,000 | 1.40 | 1.09 | 1.81 | 1 | <100,000 | 1.40 | 1.09 | 1.81 |
| Diabetes | 4 | >1M | 1.28 | 1.02 | 1.59 | 3 | <1M | 1.17 | 1.06 | 1.30 |
| Diseases of the Nervous System | 2 | <100,000 | 1.00 | 0.70 | 1.42 | 2 | <100,000 | 1.00 | 0.70 | 1.42 |
| Heart Disease | 1 | <100,000 | 1.18 | 1.06 | 1.30 | 1 | <100,000 | 1.18 | 1.06 | 1.30 |
| High blood pressure | 1 | <100,000 | 1.11 | 1.02 | 1.21 | 1 | <100,000 | 1.11 | 1.02 | 1.21 |
| Kidney Disease | 4 | <1M | 1.10 | 0.92 | 1.30 | 2 | <100,000 | 0.99 | 0.77 | 1.28 |
| Liver disease | 2 | <1M | 1.96 | 1.16 | 3.30 | 0 | | | | |
| Lung disease | 1 | <100,000 | 1.12 | 1.00 | 1.26 | 2 | <100,000 | 1.12 | 1.00 | 1.26 |
| Poor circulation | 0 | | | | | 0 | | | | |
| Stroke | 0 | | | | | 0 | | | | |
| **Long-term mortality** | | | | | | | | | | |
| Cancer | 2 | <100,000 | 1.57 | 1.19 | 2.07 | 0 | | | | |
| Depression | 0 | | | | | 0 | | | | |
| Diabetes | 3 | >1M | 0.97 | 0.82 | 1.13 | 0 | | | | |
| Diseases of the Nervous System | 3 | <100,000 | 1.92 | 1.48 | 2.48 | 2 | <10,000 | 1.67 | 1.24 | 2.25 |
| Heart Disease | 1 | <100,000 | 1.72 | 1.44 | 2.06 | 0 | | | | |
| High blood pressure | 1 | <10,000 | 1.30 | 0.78 | 2.17 | 0 | | | | |
| Kidney Disease | 5 | <100,000 | 1.65 | 1.27 | 2.15 | 2 | <100,000 | 1.24 | 0.84 | 1.83 |
| Liver disease | 3 | <100,000 | 3.40 | 1.17 | 9.86 | 0 | | | | |
| Lung disease | 2 | <10,000 | 1.38 | 1.05 | 1.80 | 0 | | | | |
| Poor circulation | 0 | | | | | 0 | | | | |
| Stroke | 2 | <100,000 | 2.05 | 1.14 | 3.66 | 0 | | | | |

# PRISMA 2009 Checklist

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 2 |
| **ABSTRACT** | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 2 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 4/5 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 5 |
| **METHODS** | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | N/A |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 6 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 6 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | Supplementary Information 1 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 11 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 7 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 7 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 8 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 11 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | 10 |

# PRISMA 2009 Checklist

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 8 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 11 |
| **RESULTS** | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 11 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOD, follow-up period) and provide the citations. | Supplementary Information 2 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | Supplementary Information 3 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 12/14 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | 12/14 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | 16/17 |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | 17 (Supplementary Information 4) |
| **DISCUSSION** | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 18 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 19/21 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 22 |
| **FUNDING** | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 23 |

*From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097