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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.

Contributor ship statement: BP contributed to the study conception and design, literature screening, data extraction, analysis and interpretation of data, drafting of the manuscript and revision based on the comments of the co-author. AH contributed to the study conception and design, literature screening, data extraction, analysis and interpretation of data and drafting of the manuscript. JVM contributed to the study conception and design, literature screening, analysis and interpretation of data and critical revision of the manuscript. AA contributed to literature screening and the critical revision of the manuscript. SK contributed to the interpretation of data and the critical revision of the manuscript.

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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

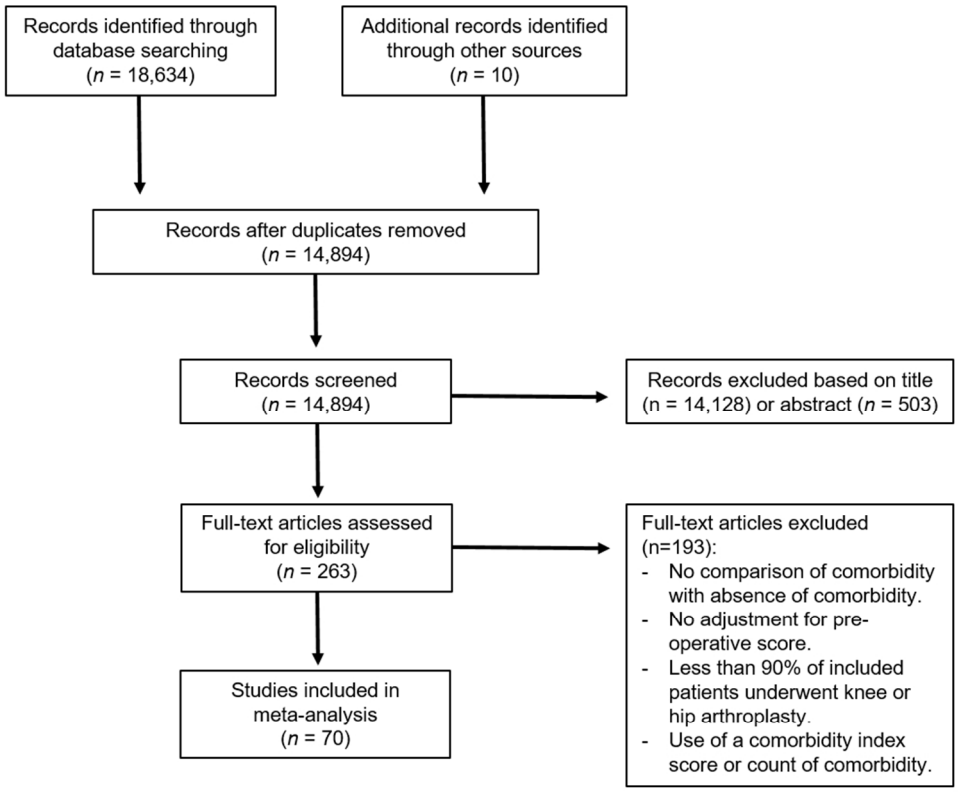

Figure 1 – Flow chart

87x72mm (300 x 300 DPI)

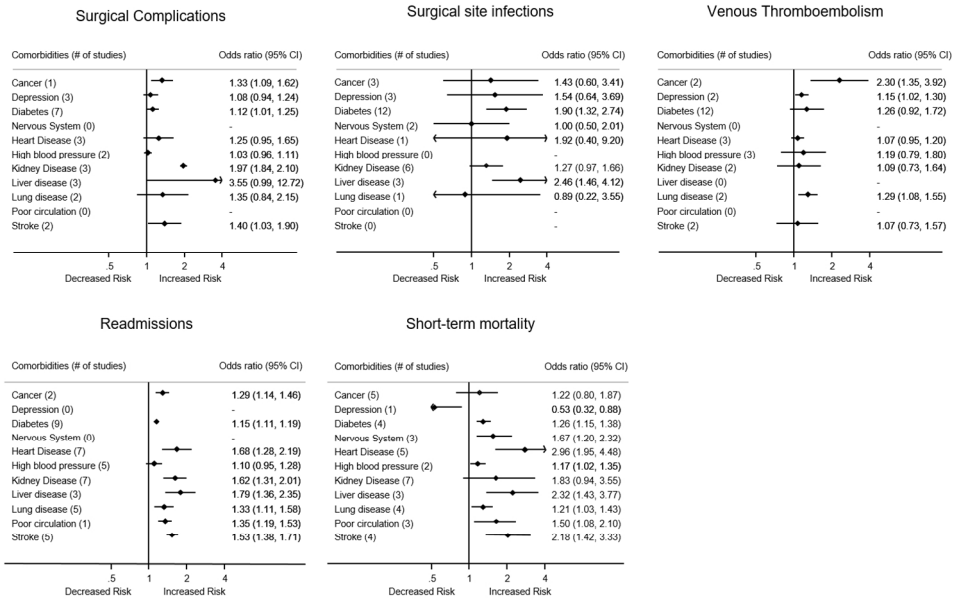

Figure 2 – Forest plots of short-term outcomes

131x86mm (300 x 300 DPI)

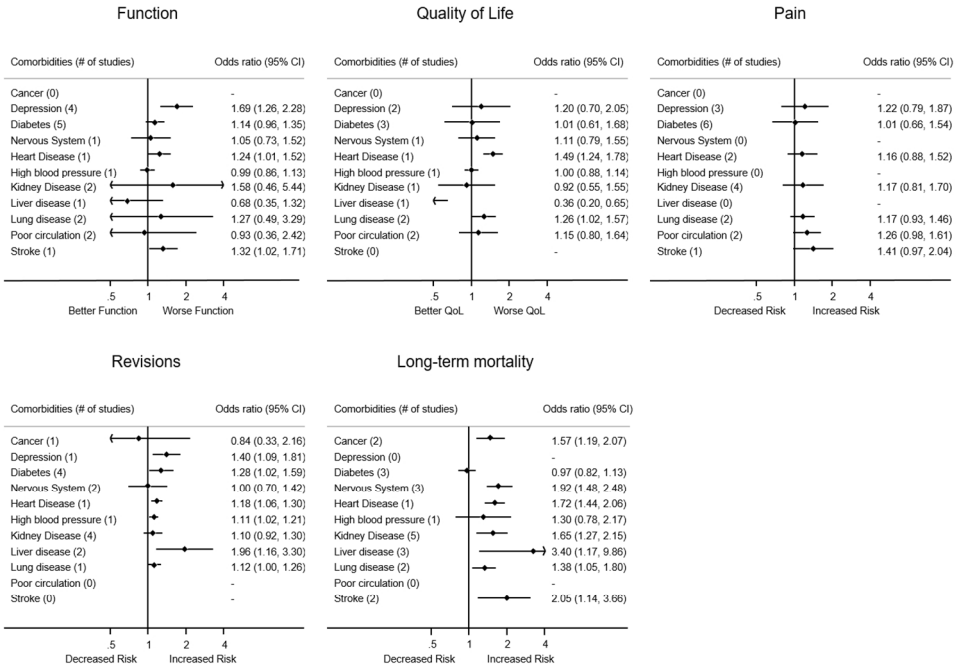

Figure 3 – Forest plots of long-term outcomes

122x88mm (300 x 300 DPI)

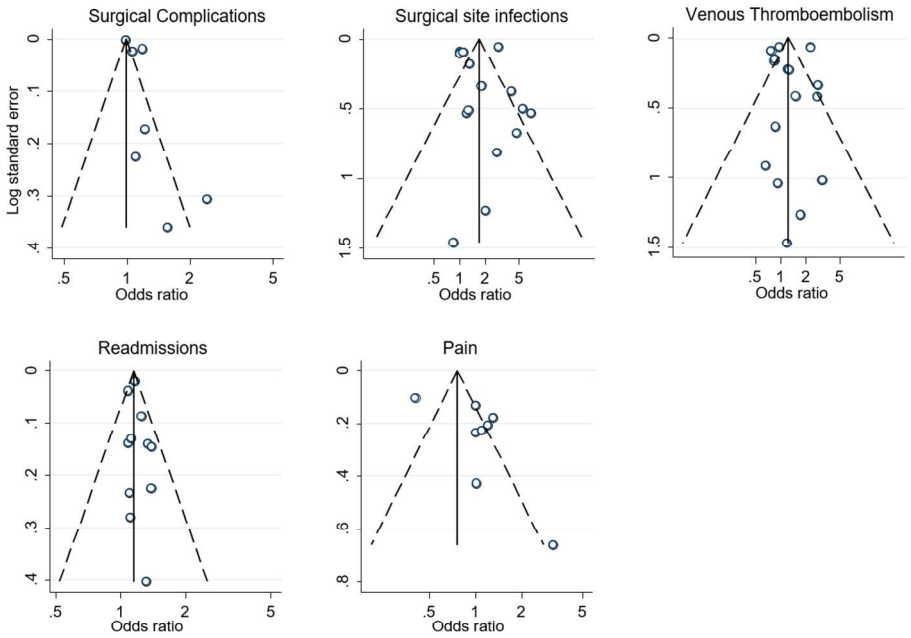

Figure 4 – Funnel plot showing 95% confidence limits for any surgical complications, surgical site infections, venous thromboembolism, readmissions to hospital and pain in diabetic patients

111x84mm (300 x 300 DPI)

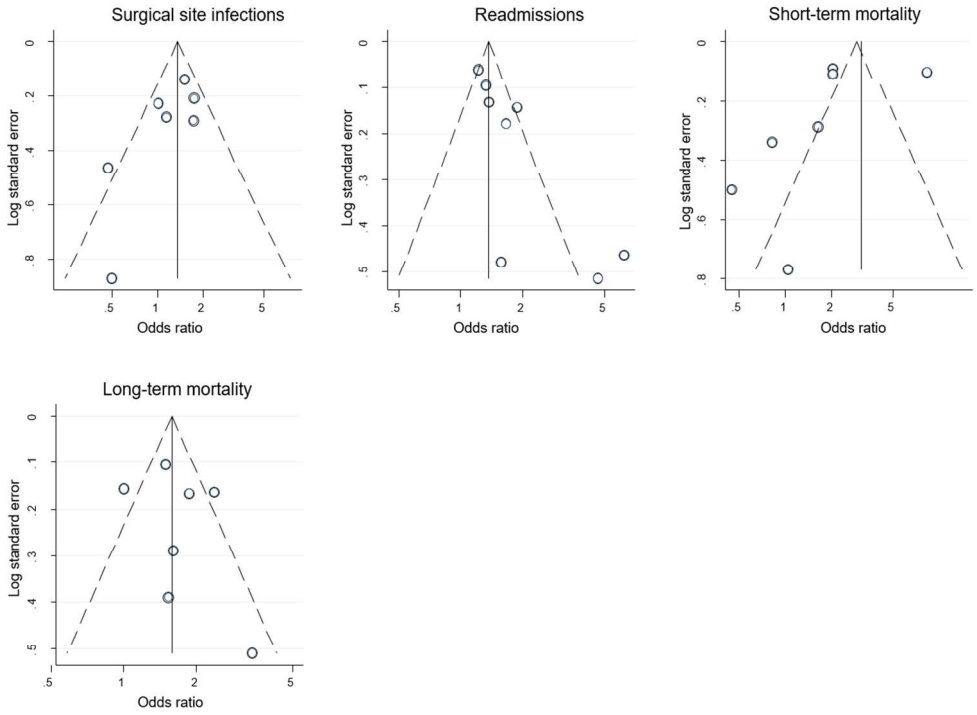

Figure 5 – Funnel plot showing 95% confidence limits for any surgical site infections, readmissions to hospital, short-term mortality and long-term mortality in kidney disease patients

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.
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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 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 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

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

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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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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

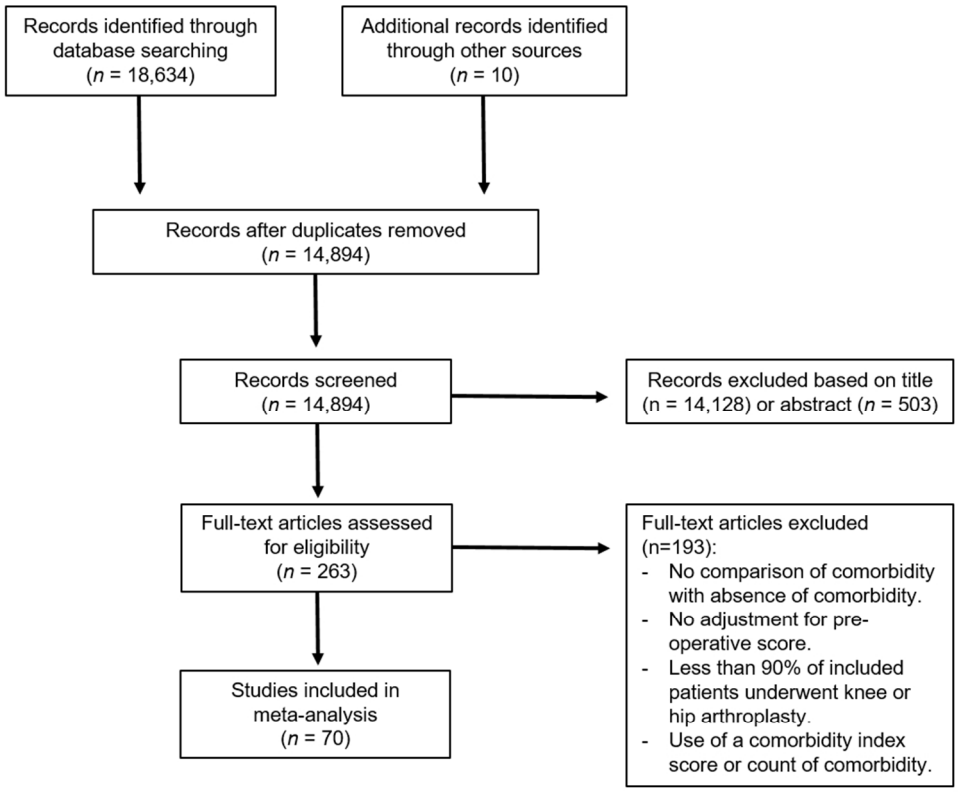

Figure 1 – Flow chart

87x72mm (300 x 300 DPI)

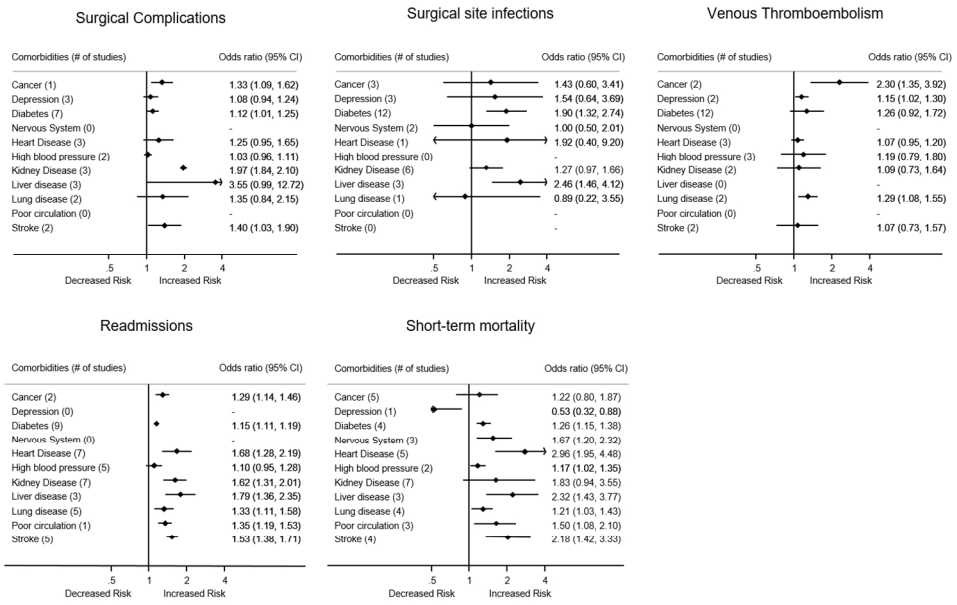

Figure 2 – Forest plots of short-term outcomes

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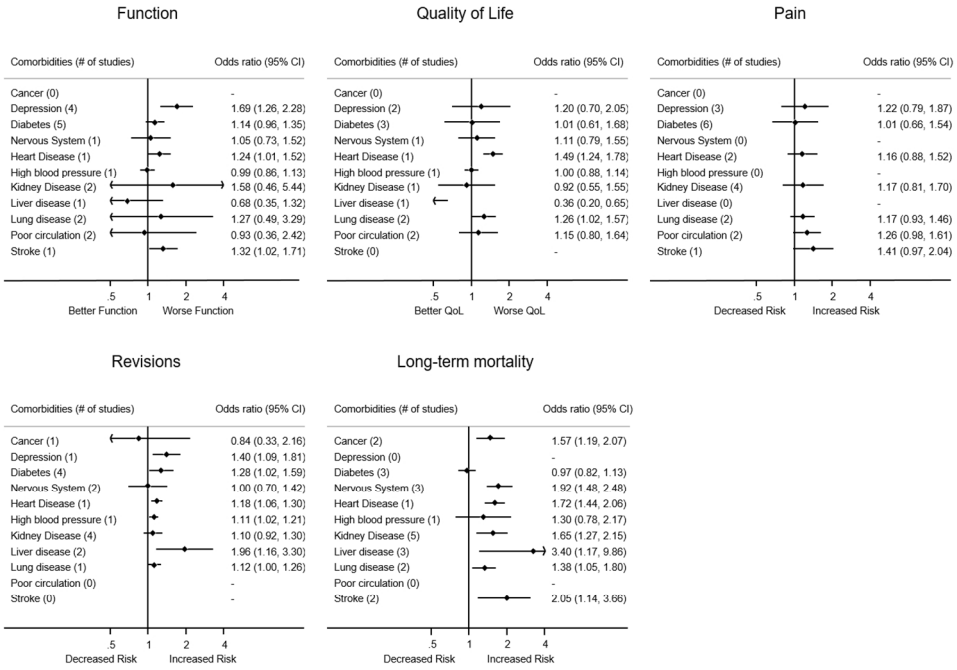

Figure 3 – Forest plots of long-term outcomes

122x88mm (300 x 300 DPI)

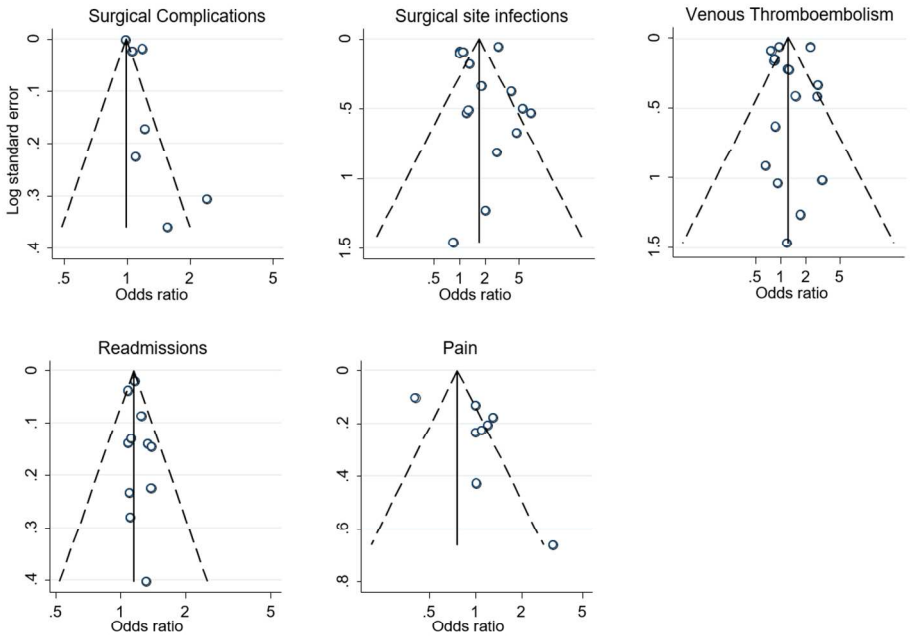

Figure 4 – Funnel plot showing 95% confidence limits for any surgical complications, surgical site infections, venous thromboembolism, readmissions to hospital and pain in diabetic patients

111x84mm (300 x 300 DPI)

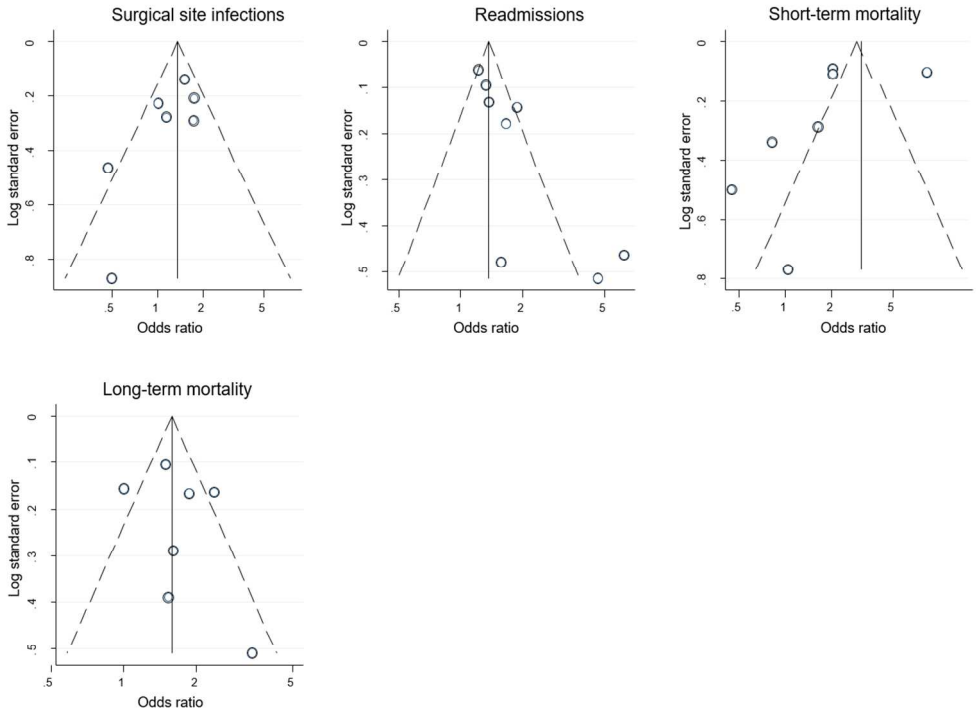

Figure 5 – Funnel plot showing 95% confidence limits for any surgical site infections, readmissions to hospital, short-term mortality and long-term mortality in kidney disease patients

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/
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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/
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31	underlying diagnosis.mp.
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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 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 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, PICOS, 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

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