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

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

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

Word Count: 4,553

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 longterm 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.

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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 surgery⁹.

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 replacement¹³. 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 cost¹⁶, 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.

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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 prediction¹⁸. 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

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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). BMJ Open: first published as 10.1136/bmjopen-2018-021784 on 11 July 2018. Downloaded from http://bmjopen.bmj.com/ on April 23, 2024 by guest. Protected by copyright

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.

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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 reviews²⁰. 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

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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.

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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 plot²² 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% Cl 1.09 to 1.62), diabetes (pooled OR 1.12, 95% Cl 1.01 to 1.25), kidney disease (pooled OR 1.97, 95% Cl 1.84 to 2.10) and stroke (pooled OR 1.40, 95% Cl 1.03 to 1.90). No studies reported surgical complications in patients with nervous system diseases or poor circulation.

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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. BMJ Open: first published as 10.1136/bmjopen-2018-021784 on 11 July 2018. Downloaded from http://bmjopen.bmj.com/ on April 23, 2024 by guest. Protected by copyright

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% Cl 1.26 to 2.28), heart disease (pooled OR 1.24, 95% Cl 1.01 to 1.52) and stroke (pooled OR 1.32, 95% Cl 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

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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.

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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 shortterm 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.

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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 replacement⁹⁶ 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.

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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 singlesite 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 2fold increase risk of surgical site infections in line with our findings¹⁴. 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 comorbidities¹⁶. 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

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2 3	complications, were commonly investigated but only five studies ^{27 28 34 73 95} reported on
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5	quality of life outcomes and the results on pain were from two publications ^{83 84} . This
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7	highlights that evidence on short-term outcomes is stronger than evidence on long-term
8 9	
9 10	outcomes. Half of the studies were analyses of data collected in population-based
11	,
12	administrative datasets. This may account for the relative scarcity of studies reporting on
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14	long-term outcomes such as quality of life or function that need patient reported results.
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18	The scope of this review required the grouping of heterogeneous studies. Across all studies,
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20	there were differences in study populations, definitions of comorbid conditions and their
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22 23	severity and definitions of outcomes and the timing of their measurement. To make the
25 24	was the comparable and to be able to conduct on the set of mate and wis come and wid
25	results comparable and to be able to conduct any form of meta-analysis, some comorbid
26	conditions were grouped together, outcomes were estagatized as short and long torm, and
27	conditions were grouped together, outcomes were categorised as short and long-term, and
28	continuous outcomes were converted to odds ratio using the Hasselblad and Hedges
29 30	continuous outcomes were converted to ouds ratio using the masseiblad and nedges
31	approach. In addition, it was not possible to evaluate hip and knee replacement separately
32	approach. In addition, it was not possible to evaluate hip and knee replacement separately
33	as 27 (38%) studies reported on combined hip and knee arthroplasties.
34	us 27 (50%) studies reported on combined nip und knee drimoplastics.
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36 37	In addition to variation in definitions of comorbid conditions, few included studies graded
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39	comorbid conditions according to severity which would have allowed a better
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41	understanding of their impact. For the few studies that reported results according to the
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43	severity of a comorbid condition, we included the most common severity subgroup,
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46	therefore excluding the most severe patients.
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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

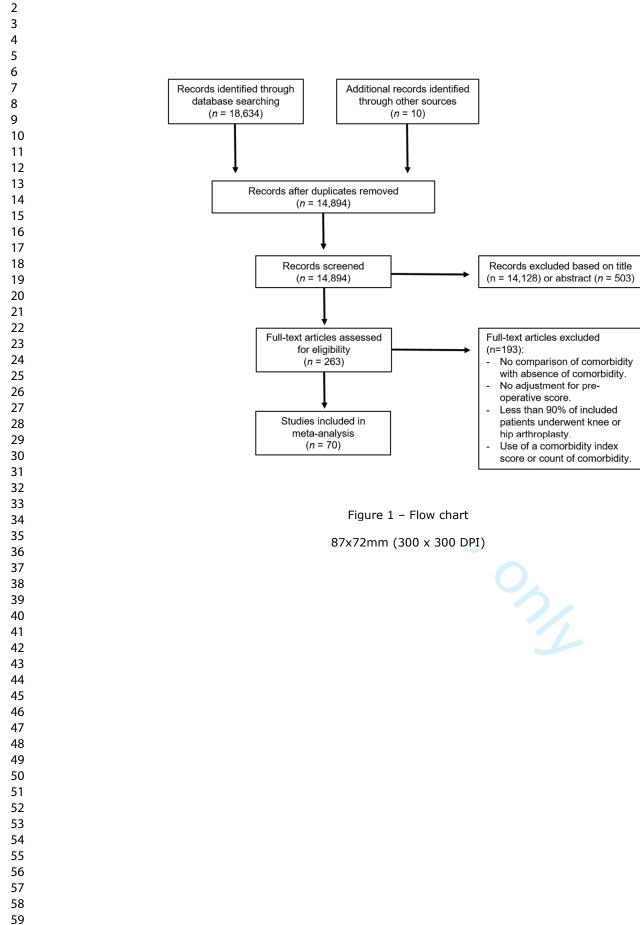
patients

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

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patients



1 2 3 4 5 6 7 Surgical site infections Venous Thromboembolism Surgical Complications 8 Comorbidities (# of studies) Odds ratio (95% CI) Comorbidities (# of studies) Odds ratio (95% CI) Comorbidities (# of studies) Odds ratio (95% CI) 9 Concentratives (# 01 studi Cancer (1) Diabetes (7) Nervous System (0) Heart Disease (3) High blood pressure (2) Kidney Disease (3) Liver disease (3) Liver disease (2) Poor circulation (0) Stroke (2) Cancer (3) Depression (3) Diabetes (12) Heart Disease (1) High blood pressure (1) High blood pressure (1) Liver disease (3) Lung disease (1) Poor circulation (0) Stroke (0) Cancer (2) Depression (2) Diabetes (12) Nervous System (0) Heart Disease (3) High blood pressure Kidney Disease (2) Liver disease (0) Lung disease (2) Poor circulation (0) Stroke (2) 1.43 (0.60, 3.41) 1.54 (0.64, 3.69) 1.90 (1.32, 2.74) 1.00 (0.50, 2.01) 1.92 (0.40, 9.20) 1.33 (1.09, 1.62) 1.08 (0.94, 1.24) 1.12 (1.01, 1.25) 2.30 (1.35, 3.92) 1.15 (1.02, 1.30) 1.26 (0.92, 1.72) 10 11 -1.25 (0.95, 1.65) 1.03 (0.96, 1.11) 1.97 (1.84, 2.10) 3.55 (0.99, 12.72) 1.35 (0.84, 2.15) 1.07 (0.95, 1.20) 12 1.19 (0.79, 1.80) 1.09 (0.73, 1.64) -1.27 (0.97, 1.66) 2.46 (1.46, 4.12) 0.89 (0.22, 3.55) 13 1.29 (1.08, 1.55) 14 -1.40 (1.03, 1.90) -1.07 (0.73, 1.57) 15 .5 Decreased Risk 2 Increased Risk .5 Decreased Risk Inco ed Risl Decrea ed Risk 16 17 Readmissions Short-term mortality 18 Comorbidities (# of studies Odds ratio (95% CI) Comorbidities (# of studies) Odds ratio (95% CI) 19 1.22 (0.80, 1.87) 0.53 (0.32, 0.88) 1.26 (1.15, 1.38) Cancer (2) 1.29 (1.14, 1.46) Cancer (5) Depression (0) Diabetes (9) 20 Depression (1) Diabetes (4) 1.15 (1.11, 1.19) Nervous System (0) Heart Disease (7) High blood pressure (5) Nervous System (3) Heart Disease (5) High blood pressure (2) Kidney Disease (7) 1.67 (1.20, 2.32) 2.96 (1.95, 4.48) 1.17 (1.02, 1.35) 21 -1.68 (1.28, 2.19) 1.10 (0.95, 1.28) 1.62 (1.31, 2.01) 1.79 (1.36, 2.35) 22 Kidney Disease (7) Liver disease (3) 1.83 (0.94, 3.55) --++ +++ 2.32 (1.43, 3.77) Liver disease (3) 23 1.33 (1.11, 1.58) Lung disease (5) Lung disease (4) 1.21 (1.03, 1.43) Poor circulation (1) 1.35 (1.19, 1.53) 1.53 (1.38, 1.71) Poor circulat Stroke (4) ion (3) 1.50 (1.08, 2.10) 2.18 (1.42, 3.33) 24 Stroke (5) 25 2 eased Risk .5 d Risk Decre ed Risk Ind 26 27

Figure 2 – Forest plots of short-term outcomes

131x86mm (300 x 300 DPI)

59 60

28

29 30

Quality of Life

Odds ratio (95% CI)

1 20 (0 70 2 05)

1.01 (0.61, 1.68) 1.11 (0.79, 1.55)

1.49 (1.24, 1.78)

1.00 (0.88, 1.14) 0.92 (0.55, 1.55) 0.36 (0.20, 0.65)

1.26 (1.02, 1.57)

1.15 (0.80, 1.64)

Odds ratio (95% CI)

1.57 (1.19, 2.07)

-0.97 (0.82, 1.13)

1 92 (1 48 2 48)

1.72 (1.44, 2.06) 1.30 (0.78, 2.17)

1.65 (1.27, 2.15)

3.40 (1.17, 9.86)

.38 (1.05, 1.80)

2.05 (1.14, 3.66)

Comorbidities (# of studies)

ion (2)

Nervous System (1)

Heart Disease (1)

High blood pressure Kidney Disease (1) Liver disease (1)

Lung disease (2)

Poor circulation (2) Stroke (0)

Comorbidities (# of studies)

Cancer (2)

Diabetes (3)

Depression (0)

Nervous System (3)

Kidney Disease (5)

Liver disease (3) Lung disease (2) Poor circulation (0) Stroke (2)

De

.5

Figure 3 - Forest plots of long-term outcomes

122x88mm (300 x 300 DPI)

Liver disease (3)

High blood pressure (1)

Heart Disease (1)

Better Qol

Long-term mortality

+

2 4

Worse QoL

Cancer (0)

Depression (3) Diabetes (3)

Pain

Odds ratio (95% CI)

1.22 (0.79, 1.87) 1.01 (0.66, 1.54)

1.16 (0.88, 1.52)

1.17 (0.81, 1.70) 1.17 (0.93, 1.46)

1.26 (0.98, 1.61) 1.41 (0.97, 2.04)

2

Comorbidities (# of studies)

on (3)

Nervous System (0)

Heart Disease (2)

High blood pressure Kidney Disease (4) Liver disease (0) ure (0

Lung disease (2)

Poor circulation (2) Stroke (1)

Dec ed Risk Ince d Risk

Cancer (0)

Depression (3 Diabetes (6)

Function

Odds ratio (95% CI)

1 69 (1 26 2 28)

1.14 (0.96, 1.35) 1.05 (0.73, 1.52)

1.24 (1.01, 1.52)

0.99 (0.86, 1.13) 1.58 (0.46, 5.44) 0.68 (0.35, 1.32)

1.27 (0.49, 3.29)

0.93 (0.36, 2.42)

1.32 (1.02, 1.71)

Odds ratio (95% CI)

0.84 (0.33, 2.16)

1.40 (1.09, 1.81) 1.28 (1.02, 1.59)

1 00 (0 70 1 42)

1.18 (1.06, 1.30) 1.11 (1.02, 1.21)

1.10 (0.92, 1.30)

1.96 (1.16. 3.30)

1.12 (1.00, 1.26)

Worse Function

Comorbidities (# of studies)

Cancer (0)

Depression (4) Diabetes (5)

Nervous System (1)

High blood pressure Kidney Disease (2) Liver disease (1)

Lung disease (2)

Stroke (1)

Cancer (1)

Depression (1)

Nervous System (2)

Kidney Disease (4)

Lung disease (1) Poor circulation (0)

Dec

Liver disease (2)

Stroke (0)

Heart Disease (1) High blood pressure (1)

Diabetes (4)

Poor circulation (2)

Better Function

Comorbidities (# of studies)

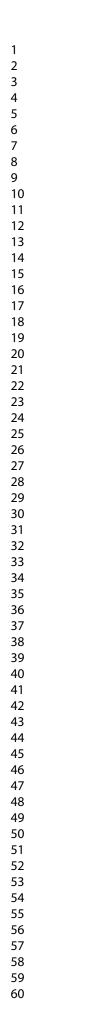
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Heart Disease (1)

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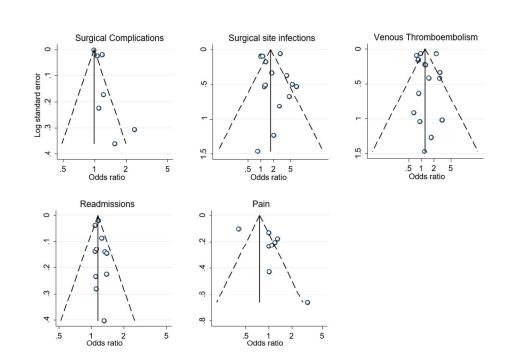
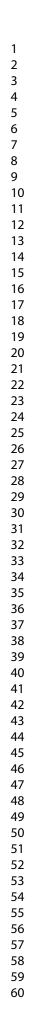


Figure 4 – Funnel plot showing 95% confidence limits for any surgical complications, surgical site infections, venous thromboembolism, readmissions to hospital and pain in diabetic patients

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111x84mm (300 x 300 DPI)

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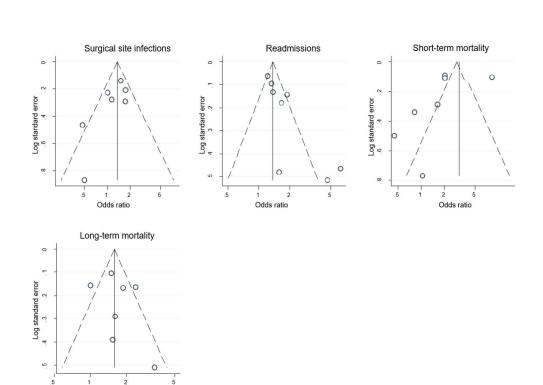


Figure 5 – Funnel plot showing 95% confidence limits for any surgical site infections, readmissions to hospital, short-term mortality and long-term mortality in kidney disease patients

Odds ratio

111x84mm (300 x 300 DPI)

 Supplementary information 1 - Search string 1 knee replacement.mp. or exp knee arthroplasty/ 2 hip replacement.mp. or exp kip arthroplasty/ knee arthroplasty.mp. Imp-title, abstract, original title, name of substance word, 3 subject heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] hip arthroplasty.mp. Imp-title, abstract, original title, name of substance word, a subject heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] e exp Arthroplasty, replacement/ e exp Comorbidity index.mp. e exp Cardiovascular Diseases/ e exp Everpheral Vascular Diseases/ e exp Nervous System Dise	1		
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Supplementary Information	on 2 – Description of selected studies (n = 70)
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upplementary	Information	2 – Description	of selected studies	(n = 70)	BMJ (Jpen	Comorbid Conditions	3 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5
Study		Data		Pat	tient 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	
Adams (2013)	USA	2001-2009	Joint registry	ТКА	Primary	40,491	Controlled diabetes	
Aggarwal (2013)	USA	2007-2011	Single-site	THA and TKA	Primary & Revision	323	Atrial Fibrillation	Readmission rate
Amusat (2014)	Canada	NS	Multi-site	ТКА	Primary	405	Diabetes without impact on routine activities, Kidney Disease	3 operative, WOMAC function, WOMAC
Ayers (2005)	USA	NS	Single-site	ТКА	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	ТКА	Revision	1754	Cardiac disease, COPD, CVA/Stroke, Diabetes, Hypertension Diabetes	
Bolognesi (2008)	USA	1988-2003	Administrative data	THA and TKA	Primary & Revision	2,249,427	<u> </u>	
Browne (2014)	USA	2006-2008	Administrative data	THA and TKA	Primary	497,222	Depression	
Buller (2015)	USA	1990-2007	Administrative data	THA and TKA	Primary	8,379,490	Chronic pulmonary disease, CAD Depression, Diabetes, Hypertension	postoperative shock, postoperative bleeding, acute postoperative infection acute postoperative anemia, acute rena failure, acute myocardial infarction, pulmonary embolism, induced mental disorder, pneumonia, pulmonary
Chan (2005)	UK	2000-2003	Single-site	THA	NS	1,297		
Clement (2013)	UK	NS	Single-site	ТКА	Primary	2,389	Depression, Diabetes, Heart disease, High blood pressure,	Post-operative OKS at 12mths, post- operative SF-12 at 12mths

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							Kidney disease, Lung disease, 21	
							Neurological diseases, Vascular	
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, Histor of stroke, Preoperative creatinin >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	from ht	Deep prosthetic infection, Intraoperativ complications, Mortality within 30 days Readmission within 30 days, Revision in one year
Dowsey (2009)	Australia	1998-2005	Single-site	ТКА	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	ТКА	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	ТКА	NS	2,033	Diabetes on April 23, 2	DVT, Pneumonia, Death)
Hunt (2013)	UK	2003-2011	Joint registry	THA	NS	409,096	CHF, PVD, CVD, Chronic Pulmona disease, Diabetes without complications, Renal disease, Cancer, Dementia	
Hunt (2014)	UK	2003-2011	Joint registry	ТКА	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, opyright	90-day mortality, 1-year mortality

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USA USA Finland Finland	2004-2009 1988-2000 1998-2008 1998-2009	Single-site Administrative data Joint registry Administrative data + Joint	THA and TKA THA and TKA and shoulder arthroplasty THA and TKA	Primary Primary Primary	1,529 959,839 96,754	Chronic airway disease, Solid tumour without metastasis Diabetes Diabetes, Hypertension Cancer, CHD, Depression, Diabetes, Hypertension (without	018-02178 0 Infection 1 Complications (infections, wound infections, pulmonary embolism, thromophlebitis, vascular complicatio other) Risk of Revision surgery
USA Finland Finland	1988-2000 1998-2008	Administrative data Joint registry Administrative	THA and TKA and shoulder arthroplasty THA and TKA	Primary	959,839	tumour without metastasis Diabetes Diabetes, Hypertension Cancer, CHD, Depression,	 Infection Complications (infections, wound infections, pulmonary embolism, thromophlebitis, vascular complicatio other) Risk of Revision surgery
USA Finland Finland	1988-2000 1998-2008	Administrative data Joint registry Administrative	THA and TKA and shoulder arthroplasty THA and TKA	Primary	959,839	Diabetes Diabetes, Hypertension Cancer, CHD, Depression,	 Infection Complications (infections, wound infections, pulmonary embolism, thromophlebitis, vascular complicatio other) Risk of Revision surgery
Finland Finland	1998-2008	data Joint registry Administrative	and shoulder arthroplasty THA and TKA		,	Diabetes, Hypertension Cancer, CHD, Depression,	 Complications (infections, wound infections, pulmonary embolism, thromophlebitis, vascular complicatio other) Risk of Revision surgery
Finland		Administrative		Primary	96,754	Cancer, CHD, Depression,	Risk of Revision surgery
	1998-2009		THA and TKA			Diabetes, Hypertension (without CVD), Pulmonary disease	Downl
Finland		registry		Primary	3,428	Parkinson's disease	 Infection at 1 year, Mortality > 1 year Revisions in 0-2 years postoperative Mortality after 10 years, Rate of surgi
	1998-2009	Administrative data + Joint registry	THA and TKA	Primary	4,526	Alzheimer's disease	Mortality after 10 years, Rate of surgi site infection, Risk of Revision
Denmark	2010-2012	Multi-site	THA and TKA	Primary	8,757		3 .
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, cerebra attacks, pneumonia, UTI>4days, dysregulated blood glucose, other infections), 90-day readmission SF-36 Physical functioning
UK	1993-1995	Multisite	THA	NS	282		프 SF-36 Physical functioning 않
USA	2003-2006	Administrative data	THA and TKA	Primary	316,671		Venous Thromboembolism
USA	2002-2009	Administrative data	THA and TKA	Primary & Revision	24,051		တ္ Venous Thromboembolism ထ
USA	2000-2011	Single-site	THA and TKA	Primary & Revision	26,415	Cancer	Deep vein thrombosis, Mortality Overall in-hospital complications, Periprosthetic joint infection
USA	2011-2013	Multi-site	THA and TKA	Revision	10,112	Disseminated cancer, Cardiac disease, Diabetes, Renal disease, Stroke, Hypertension, Pulmonary disease	te cte by copyright.
	Denmark UK USA USA	Denmark 2010-2012 UK 1993-1995 USA 2003-2006 USA 2002-2009 USA 2000-2011	Denmark 2010-2012 Multi-site Denmark 2010-2012 Multi-site UK 1993-1995 Multisite USA 2003-2006 Administrative data USA 2002-2009 Administrative data USA 2000-2011 Single-site	Denmark2010-2012Multi-siteTHA and TKADenmark2010-2012Multi-siteTHA and TKAUK1993-1995MultisiteTHAUSA2003-2006Administrative dataTHA and TKA dataUSA2002-2009Administrative dataTHA and TKA dataUSA2000-2011Single-siteTHA and TKA	Denmark2010-2012Multi-siteTHA and TKAPrimaryDenmark2010-2012Multi-siteTHA and TKAPrimaryUK1993-1995MultisiteTHANSUSA2003-2006Administrative dataTHA and TKAPrimaryUSA2002-2009Administrative dataTHA and TKAPrimary & RevisionUSA2000-2011Single-siteTHA and TKAPrimary & Revision	Denmark2010-2012Multi-siteTHA and TKAPrimary8,757Denmark2010-2012Multi-siteTHA and TKAPrimary8,055UK1993-1995MultisiteTHANS282USA2003-2006Administrative dataTHA and TKAPrimary316,671USA2002-2009Administrative dataTHA and TKAPrimary & Revision24,051 RevisionUSA2000-2011Single-siteTHA and TKAPrimary & Revision26,415 Revision	Denmark 2010-2012 Multi-site THA and TKA Primary 8,757 Cardiovascular disease, Pulmona disease Denmark 2010-2012 Multi-site THA and TKA Primary 8,055 Diabetes Type II UK 1993-1995 Multisite THA NS 282 Diabetes USA 2003-2006 Administrative THA and TKA Primary 316,671 COPD, CAD, Cerebrovascular disease, Diabetes USA 2002-2009 Administrative THA and TKA Primary & 24,051 COPD, CAD, Cerebrovascular disease, Diabetes USA 2000-2011 Single-site THA and TKA Primary & 26,415 Cancer USA 2011-2013 Multi-site THA and TKA Primary & 26,415 Cancer USA 2011-2013 Multi-site THA and TKA Revision 10,112 Disseminated cancer, Cardiac disease, Stroke, Hypertension, Pulmonary disease

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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	ТКА	Primary	615	Chronic Kidney Disease	30-day readmissions
Lee (2017)	Korea	2004-2013	Single-site	ТКА	Primary	3,049	Diabetes, Hypertension	90-day readmission
Liao (2016)	Taiwan	2004-2008	Administrative data	THA	NS	2,426	Hypertension	90-day readmission 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		All complications, Infection
McCleery (2010)	UK	1985-2008	Joint registry	ТКА	NS	59,288	Renal failure	Early infection (<90 days), Late Revision
Meding (2003)	USA	1987-1999	Single-site	ТКА	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	ТКА	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	ТКА	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	ТКА	NS	736	Depression	SF-36 Physical component scores,
Radkte (2016)	Germany	2011-2012	Single-site	THA	Primary	498	Cancer, Depression, Diabetes	WOMAC score Periprosthetic joint infection
Rajamaki (2015)	Finland	2009-2011	Single-site	THA and TKA	Primary	134	Glucose metabolism abnormalitie	e Persistent Pain

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(2016) Robertson (2012)	USA	2000 2000						pe
(2016) Robertson (2012)	USA	2000 2000						6/bmjopen-2018
Robertson (2012)		2009-2009	Single-site	THA and TKA	Primary & Revision	1,969	Depression	O Surgical complications
Sanders	UK	1989-2002	Single-site	ТКА	NS	734	Diabetes	Knee Society knee score year 1
(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
	South Korea	2007-2015	Multi-site	THA and TKA	Primary	143		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	ТКА	Primary and Revision	8,672		Knee status: much better 2- years
Singh (2009)	USA	1993-2005	Joint registry	THA C	Revision	2,687	Depression .	Moderate-Severe ADL limitation - 2 years Moderate-severe pain - 2 years
Singh (2014b)	USA	1993-2005	Joint registry	ТКА	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	ТКА	Primary	7,139	Diabetes without complications	Moderate-severe ADL limitation 2 - S>
Singh (2013c)	USA	1993-2005	Joint registry	ТКА	Primary	8,672	COPD, Depression, Diabetes, Head disease, PVD, Renal disease	전 편 Moderate-severe pain at 2 years C
	USA	1993-2005	Joint registry	ТКА	Revision	1,533	Democratica	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 recent follow-up, Mortality within 9 days, Readmissions 90 days, Revisic surgery during follow up Post-surgery infections
Vannini (1984)	Italy	1969-1979	Single-site	THA	NS	1,227	Diabetes	Post-surgery infections

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Wang	China	2003-2011	Single-site	ТКА	NS	245	CHD, Diabetes, Hypertension	121	DVT
(2013)								78 7	
Warth	USA	2006-2012	Administrative	THA and TKA	Primary	74,300	Chronic Renal disease	4 0	Overall complications
(2015)			data					Э Ц	
Zhao	China	2011-2013	Single-site	ТКА	NS	358	Diabetes, Hypertension	1	DVT within 14 days
(2014)								Jul	

...throplasty; PVD = Peri, ...rF = Coronary Heart Failure; CV. ..arction. Note. NS = not stated; THA = Total Hip Arthroplasty; TKA = Total Knee Arthroplasty; PVD = Peripheral Vascular Disease; COPD = Chyonic 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; SSE- Surgical Site Infection; DVT = Deep Vein Thrombosis; UTI = Uterine Infection; MI = Myocardial Infarction. ided from http://bmjopen.bmj.com/ on April 23, 2024 by guest. Protected by copyright

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upplementary Infor	mation 3 - Quality	appraisal of includ	led 70 studies					6/bmjopen-2018-021784 o			
Study			Patient Selection			Comparability		20 4 0 Outro	Overall		
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The impact of comorbid conditions on outcomes of hip and knee replacement surgery: A systematic review and metaanalysis

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

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

Word Count: 4,881

ABSTRACT

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

Design: Systematic Review and Meta-analysis

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

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

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

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

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

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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.

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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 surgery⁹.

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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 replacement¹³⁻¹⁵. There is little evidence however, to which extent different individual comorbid conditions affect a variety of outcomes that relate not just to

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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 cost¹⁸, 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.

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 prediction¹⁹. 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

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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, healthrelated 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

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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

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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 Jundin_b . 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 review²¹. 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

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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 populations²⁴. 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 plot²³ 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.

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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 P.C. 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

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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. BMJ Open: first published as 10.1136/bmjopen-2018-021784 on 11 July 2018. Downloaded from http://bmjopen.bmj.com/ on April 23, 2024 by guest. Protected by copyright

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).

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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.

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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 ⁶⁸⁷². 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.

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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% Cl 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.

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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 shortterm 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.

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 shortterm 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.

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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 replacement⁹⁷ 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.

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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 singlesite 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.

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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 2fold increase risk of surgical site infections in line with our findings¹⁶. 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 comorbidities¹⁸. 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

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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.

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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.

Contributorship 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. The NIHR CLAHRC North Thames Patient and Public Involvement committee reviewed the protocol.

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Data sharing statement: No additional data are available.

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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

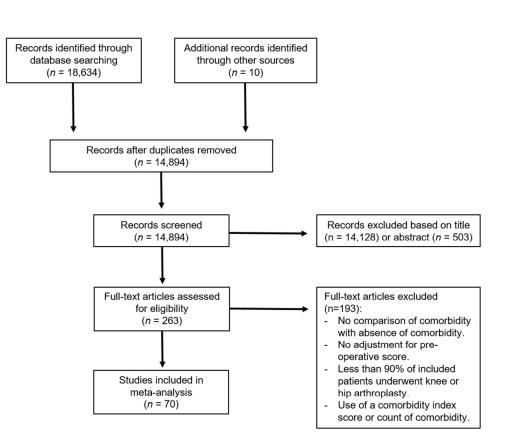
site infections, venous thromboembolism, readmissions to hospital and pain in diabetic

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

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87x72mm (300 x 300 DPI)

Venous Thromboembolism



Cancer (1)		1.33 (1.09, 1.62)
Depression (3)	+	1.08 (0.94, 1.24)
Diabetes (7)	+	1.12 (1.01, 1.25)
Nervous System (0)		-
Heart Disease (3)	+-	1.25 (0.95, 1.65)
High blood pressure (2)	+	1.03 (0.96, 1.11)
Kidney Disease (3)	+	1.97 (1.84, 2.10)
Liver disease (3)		3.55 (0.99, 12.72
Lung disease (2)	+•	1.35 (0.84, 2.15)
Poor circulation (0)		-
Stroke (2)	—	1.40 (1.03, 1.90)
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Decreased Risk	Increased Ris	sk

(3) 2) rstem (2) ase (1) pressure (0) ease (6) se (3) se (1) ation (0)			1.43 (0.60, 3.41) 1.54 (0.64, 3.69) 1.90 (1.32, 2.74) 1.00 (0.50, 2.01) 1.92 (0.40, 9.20) - 1.27 (0.97, 1.66) 2.46 (1.46, 4.12) 0.89 (0.22, 3.55) - -
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Decrease	d Risk	Increased Risk	

Short-term mortality

Odds ratio (95% CI)

Odds ratio (95% CI)

Surgical site infections

		-						-
Cancer (2)				+	_	2.30 (1.35, 3.	92
Depression (2)		+				1.15 (1.02, 1.	30
Diabetes (12)		++	_			1.26 (0.92, 1.	72
Nervous System (0)						-		
Heart Disease (3)		+				1.07 (0.95, 1.	20
High blood pressure (3)	_	+	_			1.19 (0.79, 1.	80
Kidney Disease (2)	_	+	_			1.09 (0.73, 1.	64
Liver disease (0)						-		
Lung disease (2)		-+	-			1.29 (1.08, 1.	55
Poor circulation (0)						-		
Stroke (2)	_	•	-			1.07 (0.73, 1.	57
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Comorbidities (# of studies



Comorbidities (# of studies)

Cancer (3)

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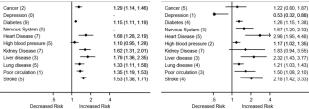
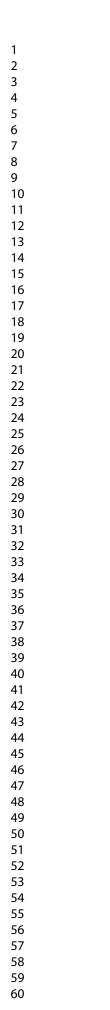


Figure 2 – Forest plots of short-term outcomes

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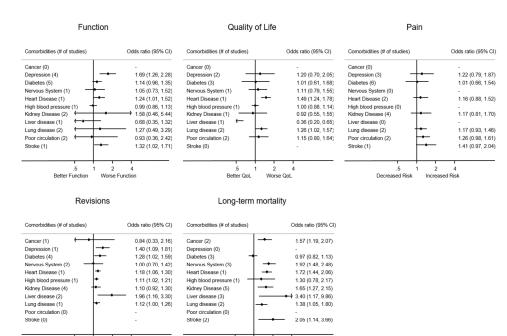


Figure 3 - Forest plots of long-term outcomes

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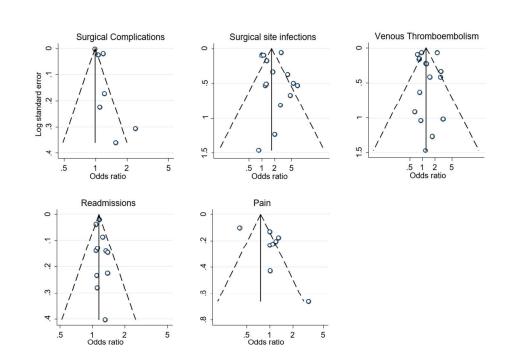
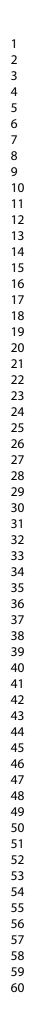


Figure 4 – Funnel plot showing 95% confidence limits for any surgical complications, surgical site infections, venous thromboembolism, readmissions to hospital and pain in diabetic patients

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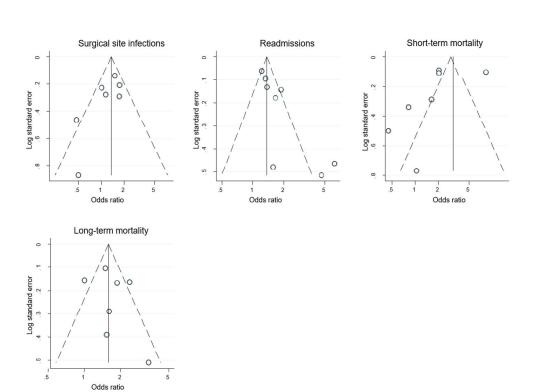


Figure 5 – Funnel plot showing 95% confidence limits for any surgical site infections, readmissions to hospital, short-term mortality and long-term mortality in kidney disease patients

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Study

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Patient Sample

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	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	ТКА	Primary	40,491	Controlled diabetes	
Aggarwal (2013)	USA	2007-2011	Single-site	THA and TKA	Primary & Revision	323	Atrial Fibrillation	Readmission rate
Amusat (2014)	Canada	NS	Multi-site	ТКА	Primary	405	Diabetes without impact on to routine activities, Kidney Disease	operative, WOMAC function, WOMAC pain
Ayers (2005)	USA	NS	Single-site	ТКА	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	ТКА	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	g	,,
Browne (2014)	USA	2006-2008	Administrative data	THA and TKA	Primary	497,222	Depression	
Buller (2015)	USA	1990-2007	Administrative data	THA and TKA	Primary	8,379,490	Chronic pulmonary disease, CAD	postoperative shock, postoperative bleeding, acute postoperative infection, acute postoperative anemia, acute renal failure, acute myocardial infarction, pulmonary embolism, induced mental disorder, pneumonia, pulmonary
Chan (2005)	UK	2000-2003	Single-site	THA	NS	1,297		
Clement (2013)	UK	NS	Single-site	ТКА	Primary	2,389	Depression, Diabetes, Heart Co disease, High blood pressure, py	Post-operative OKS at 12mths, post- operative SF-12 at 12mths
							2.	

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

Data

					BM.	J Open	6(bm.jopen- 2018-02 8-02 Kidney disease, Lung disease, 21	
							Neurological diseases, Vascular	
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, Histor of stroke, Preoperative creatinin >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	Chronic Kidney Disease	Deep prosthetic infection, Intraoperativ complications, Mortality within 30 days Readmission within 30 days, Revision in one year
Dowsey (2009)	Australia	1998-2005	Single-site	ТКА	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	ТКА	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	ТКА	NS	2,033	Diabetes on April 23, 2	DVT, Pneumonia, Death)
Hunt (2013)	UK	2003-2011	Joint registry	ТНА	NS	409,096	CHF, PVD, CVD, Chronic Pulmona disease, Diabetes without by complications, Renal disease, co Cancer, Dementia	90-day mortality
Hunt (2014)	UK	2003-2011	Joint registry	ТКА	NS	467,779	CHF, PVD, CVD, Chronic Pulmonary disease, Diabetes without complications, Renal disease, Cancer, Dementia	
	Australia	2001-2012	Administrative	THA	NS	30820	Liver disease, CHF, Renal disease	90-day mortality, 1-year mortality

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2004-200 1988-200 1998-200 1998-200 1998-200 1998-200	 Administrative data Joint registry Administrative data + Joint registry Administrative data + Joint registry Administrative data + Joint registry 	THA and TKA THA and TKA and shoulder arthroplasty THA and TKA THA and TKA	Primary Primary Primary Primary Primary	1,529 959,839 96,754 3,428 4,526	Diabetes, Hypertension Cancer, CHD, Depression, Diabetes, Hypertension (without CVD), Pulmonary disease Parkinson's disease Alzheimer's disease	Mortality after 10 years, Rate of surgi
1988-200 1998-200 1998-200 1998-200	 Administrative data Joint registry Administrative data + Joint registry Administrative data + Joint registry Administrative data + Joint registry 	THA and TKA and shoulder arthroplasty THA and TKA THA and TKA THA and TKA	Primary Primary Primary	959,839 96,754 3,428	Diabetes, Hypertension Cancer, CHD, Depression, Diabetes, Hypertension (without CVD), Pulmonary disease Parkinson's disease Alzheimer's disease	Complications (infections, wound infections, pulmonary embolism, thromophlebitis, vascular complicatio other) Risk of Revision surgery Infection at 1 year, Mortality > 1 year Revisions in 0-2 years postoperative Mortality after 10 years, Rate of surgi
1988-200 1998-200 1998-200 1998-200	 Administrative data Joint registry Administrative data + Joint registry Administrative data + Joint registry Administrative data + Joint registry 	THA and TKA and shoulder arthroplasty THA and TKA THA and TKA THA and TKA	Primary Primary Primary	959,839 96,754 3,428	Diabetes, Hypertension Cancer, CHD, Depression, Diabetes, Hypertension (without CVD), Pulmonary disease Parkinson's disease Alzheimer's disease	Complications (infections, wound infections, pulmonary embolism, thromophlebitis, vascular complicatio other) Risk of Revision surgery Infection at 1 year, Mortality > 1 year Revisions in 0-2 years postoperative Mortality after 10 years, Rate of surgi
1998-200 1998-200 1998-200	data 08 Joint registry 09 Administrative data + Joint registry 09 Administrative data + Joint registry	and shoulder arthroplasty THA and TKA THA and TKA THA and TKA	Primary Primary	96,754 3,428	Alzheimer's disease	Mortality after 10 years, Rate of surgi
1998-200 1998-200	09 Administrative data + Joint registry 09 Administrative data + Joint registry	THA and TKA THA and TKA	Primary	3,428	Alzheimer's disease	Mortality after 10 years, Rate of surgi
1998-200	data + Joint registry 09 Administrative data + Joint registry	THA and TKA	•		Alzheimer's disease	Mortality after 10 years, Rate of surgi
	data + Joint registry		Primary	4,526	Alzheimer's disease	Mortality after 10 years, Rate of surgi
2010-201	12 Multi-site	TUA and TVA				site infection, Risk of Revision
		THA and TKA	Primary	8,757	Cardiovascular disease, Pulmona disease	d
2010-201	12 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, cerebra attacks, pneumonia, UTI>4days, dysregulated blood glucose, other infections), 90-day readmission
1993-199	95 Multisite	THA	NS	282	Diabetes	▶ infections), 90-day readmission 금: SF-36 Physical functioning 않
2003-200	06 Administrative data	THA and TKA	Primary	316,671		Venous Thromboembolism
2002-200	09 Administrative data	THA and TKA	Primary & Revision	24,051		Venous Thromboembolism
2000-201	5	THA and TKA	Primary & Revision	26,415	Cancer	Deep vein thrombosis, Mortality Overall in-hospital complications, Periprosthetic joint infection 30-day readmissions
2011-201	13 Multi-site	THA and TKA	Revision	10,112	disease, Diabetes, Renal disease, Stroke, Hypertension, Pulmonar disease	te 30-day readmissions cred by copyright.
	2011-20	2011-2013 Multi-site	2011-2013 Multi-site THA and TKA			2011-2013 Multi-site THA and TKA Revision 10,112 Disseminated cancer, Cardiac disease, Diabetes, Renal disease Stroke, Hypertension, Pulmonar disease

					BMJ	Open		2
							Diabetes Chronic Kidney Disease	2 2 2 2
Kildow (2017)	USA	2005-2012	Multi-site	THA	NS	61,778	Diabetes	DVT- 30 days, Prosthetic Joint infec 90 days, THA Revision - 2-years
Kuo (2017)	Taiwan	2009-2012	Single-site	ТКА	Primary	615	_	۸.
Lee (2017)	Korea	2004-2013	Single-site	ТКА	Primary	3,049	Diabetes, Hypertension	90-day readmission
Liao (2016)	Taiwan	2004-2008	Administrative data	THA	NS	2,426	Chronic Kidney disease, COPD,	5 1-year mortality, 30-day readmissio 2 0
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 a	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	ТКА	NS	59,288	Renal failure	Early infection (<90 days), Late Revi
Meding (2003)	USA	1987-1999	Single-site	ТКА	Primary	5,220	Diabetes	Deep Infection, DVT, Knee Society F 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	ТКА	Primary	41,852	Chronic Renal Disease	 DVT, Mortality (anytime), Mortality within 90 days, Readmission within 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 days, Revision (any), SSI (any)
Moon (2008)	Korea	1995-2004	Single-site	ТКА	Primary	1,581	Diabetes	Deep joint infection, DVT, Knee Soc Score – function, Knee Society Score
Pedersen (2010)	Denmark	1996-2005	Joint registry	THA	Primary	57,575	Diabetes c	
Perez (2014)	Spain	NS	Single-site	ТКА	NS	736	Depression	⁺ SF-36 Physical component scores,
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 abnormalitie	😠 Persistent Pain

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Rasouli (2016)	USA	2009-2009	Single-site	THA and TKA	Primary & Revision	1,969	Depression	-0 21 Surgical complications 8
Robertson (2012)	UK	1989-2002	Single-site	ТКА	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, PVI Renal failure, Respiratory diseas 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	ТКА	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	ТКА	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	ТКА	Primary	7,139	Diabetes without complications	Moderate-severe ADL limitation 2 -y
Singh (2013c)	USA	1993-2005	Joint registry	ТКА	Primary	8,672	COPD, Depression, Diabetes, He disease, PVD, Renal disease	Moderate-severe pain at 2 years
Singh (2014)	USA	1993-2005	Joint registry	ТКА	Revision	1,533	Depression	Noderate-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 recent follow-up, Mortality within 90 days, Readmissions 90 days, Revision surgery during follow up Post-surgery infections
Vannini (1984)	Italy	1969-1979	Single-site	THA	NS	1,227	Diabetes	Post-surgery infections

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Wang	China	2003-2011	Single-site	ТКА	NS	245	CHD, Diabetes, Hypertension	121	DVT
(2013)								78 7	
Warth	USA	2006-2012	Administrative	THA and TKA	Primary	74,300	Chronic Renal disease	4 0	Overall complications
(2015)			data					Э Ц	
Zhao	China	2011-2013	Single-site	ТКА	NS	358	Diabetes, Hypertension	1	DVT within 14 days
(2014)								Jul	

...rthroplasty; PVD = Peri, ...HF = Coronary Heart Failure; CVA, ...arthritis Index; OKS = Oxford Knee Score, ...arction. Note. NS = not stated; THA = Total Hip Arthroplasty; TKA = Total Knee Arthroplasty; PVD = Peripheral Vascular Disease; COPD = Chyonic 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; SSE- Surgical Site Infection; DVT = Deep Vein Thrombosis; UTI = Uterine Infection; MI = Myocardial Infarction. ided from http://bmjopen.bmj.com/ on April 23, 2024 by guest. Protected by copyright

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Supplementary Information 3 - Quality appraisal of included 70 studies
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pplementary Infor	mation 3 - Quality	appraisal of incluc	led 70 studies					6/bmjopen-2018-021784			
Study			Patient Selection			Comr	arability	0 Outco	me Assessmen	t	Overall
	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?	Qutcome of interest clearly Edefined?	Follow-up long enough?	Follow-up adequate?	quality score
Ackland (2011)	Yes	Yes	Yes	Yes	No	No	No	018 Yes	NS	No	6
Adams (2013)	Yes	Yes	Yes	Yes	Yes	Yes	No	-	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	Downloaded Yes	Yes	No	10
Ayers (2005)	No	Yes	Yes	Yes	No	Yes	No	d Yes	Yes	No	8
Belmont (2016)	Yes	Yes	Yes	Yes	Yes	Yes	No	from No	Yes	Yes	9
olognesi (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
ulle (2015)	Yes	Yes	Yes	Yes	Yes	Yes	No	No No No Yes Yes Yes No	NS	No	7
Chan (2004)	Yes	Yes	Yes	Yes	No	Yes	No	Pres Yes	Yes	Yes	10
Clement (2013)	Yes	Yes	Yes	Yes	No	No	No	D Yes	Yes	Yes	8
Cohen (2005)	Yes	Yes	Yes	Yes	No	No	No	J. Yes	Yes	No	7
Courtney (2017)	Yes	Yes	Yes	Yes	Yes	Yes	Yes (ethnicity)	No No	Yes	Yes	10
Deegan (2014)	Yes	Yes	Yes	Yes	No	Yes	No	9 Yes	Yes	Yes	10
Deleuran (2015)	Yes	Yes	Yes	Yes	Yes	Yes	No	April	Yes	Yes	9
Dowsey (2009)	Yes	Yes	Yes	Yes	No	Yes	No	iii 23 Yes 33	Yes	Yes	10
kocak (2016)	Yes	Yes	Yes	Yes	No	No	No		Yes	Yes	6
andhi (2009)	Yes	Yes	Yes	Yes	No	Yes	No	20 No 2024 Yes	Yes	No	9
iaston (2007)	Yes	Yes	Yes	Yes	No	Yes	No	by Yes	Yes	Yes	10
luddleston (2009)	Yes	Yes	Yes	Yes	Yes	Yes	Yes (ethnicity)	gues.	Yes	Yes	10
lunt (2013)	Yes	Yes	Yes	Yes	Yes	Yes	No	Ves	Yes	Yes	11
lunt (2014)	Yes	Yes	Yes	Yes	Yes	Yes	No	Tote Yes	Yes	Yes	11
nacio (2016)	No	Yes	Yes	Yes	Yes	Yes	No	octe No	Yes	Yes	8
orio (2012)	Yes	Yes	Yes	Yes	No	No	No	t. Protected by capyright.	NS	No	6
ain (2005)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	S No	NS	No	9

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Jamsen (2013)	Yes	Yes	Yes	Yes	Yes	Yes	No	0217 Yes	Yes	Yes	11
Jamsen (2014)	Yes	Yes	Yes	Yes	Yes	Yes	No	784 Yes	Yes	Yes	11
Jamsen (2015)	Yes	Yes	Yes	Yes	Yes	Yes	No	9 Yes	Yes	Yes	11
Jorgensen (2015a)	Yes	Yes	Yes	Yes	Yes	No	No	<u>ک</u> Yes	Yes	Yes	9
Jorgensen (2015b)	Yes	Yes	Yes	Yes	Yes	No	No	uly Yes	Yes	Yes	9
Judge (2012)	Yes	Yes	Yes	Yes	Yes	Yes	No	N Yes	Yes	No	10
Kapoor (2010)	No	Yes	Yes	Yes	Yes	Yes	No		NS	Yes	7
Kapoor (2013)	No	Yes	Yes	Yes	Yes	Yes	Yes	Downloaded	Yes	Yes	10
Karam (2015)	Yes	Yes	Yes	Yes	No	No	No		Yes	Yes	8
Keswani (2016)	Yes	Yes	Yes	Yes	Yes	Yes	No	Q P No	Yes	Yes	9
Kildow (2017)	No	Yes	Yes	Yes	Yes	No	No	fro No	Yes	Yes	6
Kuo (2017)	No	Yes	Yes	Yes	No	Yes	No	B Yes	Yes	Yes	9
Lee (2017)	No	Yes	Yes	Yes	No	Yes	No	No yes yes No No yes No Yes Yes No No Yes Yes No Yes Yes No Yes	Yes	Yes	9
Liao (2016)	No	Yes	Yes	Yes	Yes	Yes	No	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	n.b No	Yes	Yes	8
Mazoch (2009)	Yes	Yes	Yes	Yes	No	1	No	J. Yes	NS	Yes	8
McCleery (2010)	Yes	Yes	Yes	Yes	Yes	Yes	No	No No	Yes	Yes	9
Meding (2003)	Yes	Yes	Yes	Yes	No	No	No	g Yes	Yes	No	7
Menendez (2016)	Yes	Yes	Yes	Yes	Yes	Yes	Yes (ethnicity)	Apr No	Yes	Yes	10
Miric (2014a)	Yes	Yes	Yes	Yes	Yes	Yes	Yes (ethnicity)	No Yes Yor	Yes	Yes	12
Miric (2014b)	Yes	Yes	Yes	Yes	Yes	Yes	Yes (ethnicity)	N Yes	Yes	Yes	12
Moon (2008)	Yes	Yes	Yes	Yes	No	No	No	2024 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	gues	Yes	Yes	8
Radkte (2016)	No	Yes	Yes	Yes	No	No	No	t Yes	Yes	Yes	7
Rajamaki (2015)	Yes	Yes	Yes	Yes	No	Yes	No	Tote Yes	Yes	No	9
Rasouli (2016)	Yes	Yes	Yes	Yes	No	Yes	No	t. Yes Yes Yes Yes No No	Yes	Yes	10
Robertson (2012)	Yes	Yes	Yes	Yes	No	Yes	No	Ö Yes	Yes	Yes	10
Sanders (2012)	Yes	Yes	Yes	Yes	Yes	Yes	Yes (SES)	<u> </u>	Yes	Yes	10

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Seol (2017)	Yes	Yes	Yes	Yes	Yes	No	No	217 Yes 4 Yes	NS	Yes	8
Sikora-Klak (2017)	No	Yes	Yes	Yes	No	No	No	4 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	on 11 July 2018.	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	Of Yes	Yes	No	10
Singh (2013b)	Yes	Yes	Yes	Yes	Yes	Yes	No		Yes	No	10
Singh (2013c)	Yes	Yes	Yes	Yes	Yes	Yes	No	O Yes	Yes	No	10
Singh (2014)	Yes	Yes	Yes	Yes	Yes	Yes	No	loa Yes	Yes	No	10
Stundner (2013)	Yes (ethnicity)	Downloaded No	Yes	Yes	10						
Tiberi (2014)	Yes	Yes	Yes	Yes	No	No	No	fo Yes	Yes	Yes	8
Vannini (1984)	Yes	Yes	Yes	Yes	No	No	No	from http://bmjop Yes	Yes	Yes	8
Wang (2013)	No	Yes	Yes	Yes	No	Yes	No	fe Yes	No	Yes	8
Warth (2015)	Yes	Yes	Yes	Yes	Yes	No	No	bm No	Yes	Yes	7
Zhao (2014)	No	Yes	Yes	Yes	No	Yes	No	S Yes	No	Yes	8
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Supplementary Information 4 – Sensitivity Analysis

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upplementary Information 4 – S	ensitivity Analysi	S						21.		
								<u>0</u>		
Comorbidities	# of studies	# of notionts	All Studies OR	95% lower Cl	05%	# of studies	High Qual # of patients	ity Studies (☐ OR	Quality score ≥11) 95% lower Cl	95% upp
Surgical Complications	# of studies	# of patients	OR	95% lower Cl	95% upper Cl	# of studies	# of patients	13 OR	95% lower Cl	95% upp
Cancer	1	<100,000	1.33	1.09	1.62	0				
Depression	3	<100,000 >1M	1.08	0.94	1.02	0		July 2018.		
Diabetes	7	>1M >1M	1.08	1.01	1.24	0		2		
Diseases of the Nervous System	0	>1141	1.12	1.01	1.25	0		01		
Heart Disease	3	>1M	1.25	0.95	1.65	0				
High blood pressure	2	>1M	1.03	0.96	1.11	0		D		
Kidney Disease	3	<1M	1.97	1.84	2.10	0		WI		
Liver disease	3	<1M	3.55	0.99	12.72	0		olc		
Lung disease	2	>1M	1.35	0.84	2.15	0		ăd		
Poor circulation	0			0101	2.20	0		ed		
Stroke	2	<1M	1.40	1.03	1.90	0		Downloaded frc		
Venous Thromboembolism							1	В.		
Cancer	2	>1M	2.30	1.35	3.92	0		http://bmjopen.bmj.com/ or		
Depression	2	>1M	1.15	1.02	1.30	0		t d		
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		<u> </u>		
Heart Disease	3	<1M	1.07	0.95	1.20	0		e B		
High blood pressure	3	<10,000	1.19	0.79	1.80	0		en		
Kidney Disease	2	<100,000	1.09	0.73	1.64	2	<100,000	2 1.09	0.73	1.64
Liver disease	0					0		.		
Lung disease	2	<1M	1.29	1.08	1.55	0		8		
Poor circulation	0					0		7		
Stroke	2	<1M	1.07	0.73	1.57	0		9		
Surgical site infections	-	•						≥	-	
Cancer	3	>1M	1.43	0.60	3.41	0		April		
Depression	3	>1M	1.54	0.64	3.69	0		μ ₂ β ⁻ 1.31		
Diabetes	12	>1M	1.90	1.32	2.74	1	<100,000	³⁰ 1.31	0.92	1.86
Diseases of the Nervous System	2	<10,000	1.00	0.50	2.01	2	<10,000	201.00 2024	0.50	2.01
Heart Disease	1	<10,000	1.92	0.40	9.20	0		24		
High blood pressure	0					0		by		
Kidney Disease	6	<1M	1.27	0.97	1.66	2	<100,000	<u>و</u> 1.06	0.75	1.50
Liver disease	3	<1M	2.46	1.46	4.12	0		gues:		
Lung disease	1	<10,000	0.89	0.22	3.55	0				
Poor circulation	0					0		Pro		
Stroke	0					0		Protect		
Readmissions	-		4.55			-	1	Ö	1	
Cancer	2	<1M	1.29	1.14	1.46	0		led		
Depression	0					0	100.000	by		
Diabetes	9	<1M	1.15	1.11	1.19	1	<100,000	d by copyright.	1.00	1.16
Diseases of the Nervous System	0	1	1		1	0		ы	1	1

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								6/bmjopen-2018-021784		
Heart Disease	7	<1M	1.69	1.29	2.10	0		18-02		1
			1.68	1.28	2.19	0		217		
High blood pressure Kidney Disease	5 7	<1M <1M	1.10 1.62	0.95 1.31	1.28 2.01	0 2	<100,000	8	1.16	
Liver disease	3	<1M	1.62	1.31	2.01	0	<100,000	P 1.34 O	1.10	
Lung disease	5	<1M	1.79	1.30	1.58	0				
Poor circulation	1	<1M	1.35	1.11	1.58	0		1		
Stroke	5	<1M	1.53	1.38	1.55	0		lur		
Short-term mortality	5		1.55	1.56	1./1	0				
Cancer	5	>1M	1.22	0.80	1.87	0		2018.		
Depression	1	>1M	0.53	0.32	0.88	0		8.		
Diabetes	4	>1M	1.26	1.15	1.38	0		Downloaded 0.73		
Diseases of the Nervous System	3	<1M	1.67	1.20	2.32	0		WC WC		
Heart Disease	5	>1M	2.96	1.95	4.48	0		nlo		
High blood pressure	2	<1M	1.17	1.02	1.35	0		bac		
Kidney Disease	7	>1M	1.83	0.94	3.55	2	<100,000	0.73	0.42	
Liver disease	3	<1M	2.32	1.43	3.77	0		l fr		
Lung disease	4	>1M	1.21	1.03	1.43	0		from		
Poor circulation	3	>1M	1.50	1.08	2.10	0		h h		
Stroke	4	>1M	2.18	1.42	3.33	0		http:		
Function								//tmjopen.bmj.com/ on April 2		
Cancer	0					0		<u>.</u>		
Depression	4	<100,000	1.69	1.26	2.28	0		р		
Diabetes	5	<100,000	1.14	0.96	1.35	0		en		
Diseases of the Nervous System	1	<10,000	1.05	0.73	1.52	0		.br		
Heart Disease	1	<10,000	1.24	1.01	1.52	0		nj.		
High blood pressure	1	<10,000	0.99	0.86	1.13	0		ğ		
Kidney Disease	2	<10,001	1.58	0.46	5.44	0		n/		
Liver disease	1	<10,000	0.68	0.35	1.32	0		on		
Lung disease	2	<10,000	1.27	0.49	3.29	0		Ą		
Poor circulation Stroke	2	<10,000 <10,000	0.93 1.32	0.36 1.02	2.42 1.71	0		orii		
Quality of Life	L	<10,000	1.32	1.02	1./1	0		N W		
Cancer	0					0				
Depression	2	<10,000	1.20	0.70	2.05	0		2024		
Diabetes	3	<10,000	1.20	0.61	1.68	0		4		
Diseases of the Nervous System	1	<10,000	1.01	0.79	1.55	0		by gues		
Heart Disease	1	<10,000	1.49	1.24	1.78	0		gu		
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		ro		
Lung disease	2	<10,000	1.26	1.02	1.57	0		tec		
Poor circulation	2	<10,000	1.15	0.80	1.64	0		te		
Stroke	0	,	_		-	0		t. Protected by		
Pain							•	¥		•
Cancer	0					0		copyright.		
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								8-C		
Depression	3	<100,000	1.22	0.79	1.87	0		21		
Diabetes	6	<100,000	1.01	0.66	1.54	0		78		
Diseases of the Nervous System	0					0		4		
Heart Disease	2	<100,000	1.16	0.88	1.52	0		on		
High blood pressure	0					0		1		
Kidney Disease	4	<100,000	1.17	0.81	1.70	0		_ _		
Liver disease	0					0		ul)		
Lung disease	2	<100,000	1.17	0.93	1.46	0		2		
Poor circulation	2	<100,000	1.26	0.98	1.61	0		July 2018.		
Stroke	1	<10,000	1.41	0.97	2.04	0				
Revisions							•	Do		
Cancer	1	<100,000	0.84	0.33	2.16	1	<100,000	0.84 0 1.40 0 1.17 0 1.00	0.33	2.1
Depression	1	<100,000	1.40	1.09	1.81	1	<100,000	o 1.40	1.09	1.8
Diabetes	4	>1M	1.28	1.02	1.59	3	<1M	a 1.17	1.06	1.3
Diseases of the Nervous System	2	<100,000	1.00	0.70	1.42	2	<100,000	8 1.00	0.70	1.4
Heart Disease	1	<100,000	1.18	1.06	1.30	1	<100,000	∃ 1.18	1.06	1.3
High blood pressure	1	<100,000	1.11	1.02	1.21	1	<100,000	Tron 1.18	1.02	1.2
Kidney Disease	4	<1M	1.10	0.92	1.30	2	<100,000	<u>-</u> 0.99	0.77	1.2
Liver disease	2	<1M	1.96	1.16	3.30	0		Ŧ		
Lung disease	1	<100,000	1.12	1.00	1.26	2	<100,000	1.12	1.00	1.2
Poor circulation	0					0		Ĕ		
Stroke	0					0		B		
Long-term mortality								h 0.99 http://1.12 popen		
Cancer	2	<100,000	1.57	1.19	2.07	0		r.bmj.com/ 1.67		
Depression	0					0		. 그.		
Diabetes	3	>1M	0.97	0.82	1.13	0		8		
Diseases of the Nervous System	3	<100,000	1.92	1.48	2.48	2	<10,000	2 1.67	1.24	2.2
Heart Disease	1	<100,000	1.72	1.44	2.06	0		on		
High blood pressure	1	<10,000	1.30	0.78	2.17	0		ר ק ר		
Kidney Disease	5	<100,000	1.65	1.27	2.15	2	<100,000	₽ ₽ 1.24	0.84	1.8
Liver disease	3	<100,000	3.40	1.17	9.86	0		i ≕i		
Lung disease	2	<10,000	1.38	1.05	1.80	0		23,		
Poor circulation	0					0		20		
Stroke	2	<100,000	2.05	1.14	3.66	0		2024		
•								4 by gu		

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BRISMA 1

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PRISMA 2009 Checklist

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	2009	Checklist	
³ ⁴ 5 Section/topic	#	Checklist item	Reported on page #
⁶ 7 TITLE		or Or	
8 Title	1	Identify the report as a systematic review, meta-analysis, or both.	2
	<u> </u>		
1 Structured summary 12 13	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
		nloa	
16 Rationale	3	Describe the rationale for the review in the context of what is already known.	4/5
¹⁷ Objectives 18	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
20 METHODS		p://b	
Protocol and registration 22 23	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
24 Eligibility criteria 25	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
²⁶ 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
26 29 Search 30	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary Information 1
3 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
34 Data collection process 35	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
³⁶ Data items 37	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
38 39 Risk of bias in individual 40 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
4 Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	11
42 43 Synthesis of results 44	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
45 46		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	



PRISMA 2009 Checklist

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PRISMA 2	009	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, PICO, 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 summar 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 to role of funders for the systematic review.	23

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