Main cause of death following primary total hip and knee replacement for osteoarthritis; A cohort study of 26,766 deaths following 332,734 hip replacements and 29,802 deaths following 384,291 knee replacements performed from 2003 to 2012 using data from the National Joint Registry for England and Wales.

Hunt L, School of Clinical Sciences, University of Bristol; Ben-Shlomo Y, School of Social & Community Medicine, University of Bristol; Whitehouse M, School of Clinical Sciences, University of Bristol; Porter M, Wrightington Hospital, Wrightington, Lancashire; Blom A, School of Clinical Sciences, University of Bristol.

Abstract

Background

Patients undergoing joint replacement are selected for surgery and thus have a lower mortality rate than age and sex matched individuals other than a transient post-operative increased rate. Understanding the causes of death following joint replacement would allow targeted strategies to reduce the risk of death and optimize outcome. We aimed to determine the rates and causes of mortality for patients undergoing joint replacement compared with the age and sex matched general population.

Methods

We compared causes and rates of mortality with the age and sex matched general population for a linked cohort (National Joint Registry, Hospital Episodes Statistics and Office for National Statistics) of 332,734 and 384,291 patients undergoing primary hip and knee replacement (26,766 and 29,802 deaths respectively from 2003 to 2012).
Results

The main causes of death were malignancy (hips: 9,037 cases, 33·8%; knees: 9,917, 33·3%), circulatory (hips: 8,784, 32·8%; knees: 9,932, 33·3%), respiratory (hips: 2,928, 10·9%; knees: 2,932, 9·8%) and digestive diseases (hips: 1,465, 5·5%; knees: 1,572, 5·3%). There was a relative reduction in mortality (39%) compared to the general population that resolved by 7 years for hips (overall SMR 0·61, 95%CI 0·60-0·62) and knees (43%), which partially attenuated by 7 years (overall SMR 0·57, 95% CI 0·56-0·57).

Ischaemic heart disease was the commonest cause of death within 90 days (hips: 431 deaths; 29%; knees: 436 deaths; 31%). There was an elevated risk of death for circulatory, respiratory and most markedly for digestive causes for this period compared to 90 days to 1 year.

Conclusions

Ischaemic heart disease is the leading cause of death and there is an increase in post-operative digestive disease mortality following joint replacement. Interventions targeted at reducing these may have the biggest effect on mortality.

Level of evidence: Level II
**Introduction**

Patients undergoing hip and knee replacement are selected by their capacity to undergo major surgery with the highest risk patients excluded leading to a lower than expected risk of death than the general age and sex matched population.\textsuperscript{1-3} However, undergoing surgery causes a short-term increase in the risk of death that returns to baseline between 30 and 90-days post-operation.\textsuperscript{2-4}

Older patients and males have higher mortality rates.\textsuperscript{4,5} Cardiac disease and thromboembolic complications are major causes of short-term mortality.\textsuperscript{5,6}

We wished to examine what were the major causes of short, medium and long-term mortality in this population compared to the age and sex matched population. We chose to look separately at hip and knee replacements to determine if results were similar for both procedures, presumably reflecting increased risk associated with anaesthesia and post-operative care rather than the nature of the intervention. These findings may be helpful to identify those at greatest risk of mortality, to suggest potential preventative interventions and to enable clinicians and patients to consider the trade-off between the short-term increased peri-operative risks versus longer-term benefits.

**Materials and Methods**

**Patients and Data Sources**

We started with 539,372 linkable primary hip and 589,028 linkable primary knee replacements carried out from April 2003 to December 2012 inclusive, reported in the National Joint Registry’s (NJR) 10\textsuperscript{th} Annual report.\textsuperscript{7} Exclusions included those with an untraceable NHS number, withdrawn consent or uncertain age and/or gender (261 hips; 243 knees) and those undergoing simultaneous
bilateral operations (6,182 hips; 15,142 knees). From the remainder, we identified 479,191 unilateral hip replacements and 550,787 knee replacements where osteoarthritis (OA) was the only stated surgical indication. Only the first of sequential joint replacements of the same type at different times were included leaving 424,156 hips and 469,989 knees, of whom 33,759 and 36,002 respectively died on or before the censoring date (31/12/2012).

The ‘main’ causes of death (ICD 10) for the deaths were obtained from the Office for National Statistics (ONS) with NJR linkage via the patient’s Hospital Episode Statistics (HES) identifier. Patients with a record in the NJR but no HES record for inpatient stays for joint replacement procedures up to the end of November 2012 were excluded. HES records did not exist for patients without an NHS-funded procedure recorded in the NJR, or only with procedures in Wales and hence were excluded. 332,734 of the patients undergoing hip replacement (26,766 deaths) and 384,291 of the patients undergoing knee replacement (29,802 deaths) could be linked.

Of the 91,422 patients who underwent hip replacement and the 85,698 who underwent knee replacement with no associated HES identifier, 67,700 (74%) and 57,924 (68%) respectively had their operation performed in an independent hospital/treatment centre and 19,697 (22%) and 23,426 (27%) had their replacements performed in Wales. Amongst the remaining 4,025 (4%) and 4,348 (5%), 1,664 and 1,870, respectively, had their operation in December 2012 and the rest are unknown.

We subdivided the main causes of death into five groups, according to the first letter of the ICD code: malignant neoplasms (‘C’), circulatory system (‘I’), respiratory system (‘J’), digestive system (‘K’), and all others. Further, ‘a priori’ subdivision, was made of the circulatory system deaths into ischaemic heart disease (ICD10 codes I20-I25 inclusive), pulmonary heart disease/diseases of the pulmonary circulation (I26-I28), and cerebrovascular disease (I60-I69).
Statistics

Patients were divided into four age groups: <60, 60-69, 70-79, and 80+ years at operation and Kaplan-Meier curves were used to describe the cumulative mortality for men and women up to a maximum of 9.75 years from operation. Cumulative incidence function curves (CIF) were constructed for the defined ‘competing’ causes of death; these CIFs properly sum to total cumulative mortality. Cause of death was not known (NK) for 380 of the 26,766 hip replacement deaths and for 484 of the 29,802 knee replacement deaths; whilst the likely impact is small, arbitrarily they have been grouped separately.

Observed (O) and expected numbers of deaths (E) were compared for the grouped causes of death above. Expected numbers of deaths were calculated by obtaining age and gender specific mid-year populations and numbers of deaths for each cause for England and Wales from the ONS for 2003-2012. These were used to calculate age-gender and cause-specific annual mortality rates. For each patient we calculated the total times at risk within each age-band within each calendar year and calculated the patients expected mortality by multiplying these by the appropriate rates and then summing them and then summing across patients. The Standardized Mortality Ratios (SMR) were calculated by dividing observed by expected number of deaths with 95% Confidence Intervals. We further partitioned follow-up periods into intervals of time following the primary operation, using cut-points of 90-days and 1, 3, 5 and 7-years and calculated SMRs for these intervals. Statistical analysis used Stata v13.1 (StataCorp LP, TX, USA).

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**Results**

**Hip Replacement**

33,759 patients of 424,156 patients died in the study period. 332,734 cases (26,766 deaths) had a HES identifier enabling cause of death to be determined. The proportion of males in this final cohort was lower than in the remainder (40.4% compared to 42.8%; Appendix Table 1), the patients were older (median 70 (IQR:62-76) years vs. 69 (61-76)) and they had slightly greater all-cause cumulative mortality (5-years Kaplan-Meier estimated cumulative percentage mortality 9.5% (95%CI:9.4-9.7) vs. 8.0% (95%CI:7.8-8.2). Finally, all-cause SMR (Table 1) was slightly higher in the 332,734 than in the whole cohort of 424,156 (0.61 (95%CI:0.60-0.62) vs. 0.59 (0.58-0.60)).

Malignant disease was the main cause of death in 9,037 cases (33.8%), circulatory in 8,784 (32.8%), respiratory in 2,928 (10.9%) and digestive in 1,465 (5.5%). 4,172 patients died of other causes and the cause was unknown in 380 (Appendix Table 2).

Figures 1a-1d show the cumulative incidences of competing risk of death by age and gender. In patients under the age of 60 (Figure 1a), males have a slightly higher cumulative risk of mortality driven by a higher rate of death due to circulatory diseases. With increasing age (Figures 1b-1d),
the relative risk of death for males increased markedly compared to women with cancer, respiratory disease, and circulatory disease.

The cohort showed a marked selection effect with a 39% relative reduction in mortality (SMR 0.61, 95%CI:0.60-0.62), based on 26,766 observed and 43,976 expected deaths (Table 1). This was seen for all five categories of cause of death but had disappeared (“waning effect”) by 7 years for neoplasms, circulatory, and digestive system related deaths. Respiratory deaths and the “other” group of deaths showed a persistent relative reduction in mortality even at 7-10 years. For most causes, the SMR was time dependent. It was lowest in the period from 90-days to 1-year post surgery then slowly rising; the overall SMR was 0.89 (95%CI:0.86-0.93) at 7-10 years.

Deaths within 90-days post-operation showed elevated risks compared to the 90-day to 1-year period in circulatory, respiratory, digestive, and other causes. The digestive group showed a 30% relative increased mortality (SMR 1.30, 95%CI:1.09-1.53) compared to the general population. The ICD codes where most deaths occurred were duodenal ulcer (K26), vascular disorders of intestine (K55), paralytic ileus and intestinal obstruction (K56), and diverticular disease (K57), with the first three categories almost certainly reflecting post-operative complications (Appendix Table 3). Malignancy had an SMR of 0.19 (95%CI:0.16-0.23) that rose to 0.52 (95%CI:0.49-0.55) from 90-days to 1-year.

A more detailed examination of circulatory diseases (Table 2) showed markedly elevated risks within 90-days for ischaemic heart disease (I20-I25) with 431 deaths (SMR 1.21 95%CI:1.10-1.33). Pulmonary heart disease, including pulmonary embolism (I26-I28), was very rare with only 20 deaths within 90-days (SMR 1.27 95%CI:0.78-1.97). There was no evidence of acute increased risk of death due to cerebrovascular disease (I60-I69) whose SMR (0.38, 95%CI:0.30-0>47) did not differ within 90-days as compared to the 90-day to 1-year period.
Knee Replacement

36,002 patients out of 469,989 patients died. 384,291 had HES identifiers enabling the cause of death to be determined in 29,802 deaths. The proportion of males in the final 384,291 was lower than the remainder (42.9% vs. 44.8%) and they were slightly older (median 70 (IQR:63-76) years vs. 69 (62-76); Appendix Table 1). The all-cause SMR (Table 3) was slightly higher in the 384,291 than in the 469,989 (0.57 (95%CI:0.56-0.57) vs. 0.56 (0.55-0.56)).

The major causes of death were malignant disease in 9,917 cases (33.3%), circulatory in 9,932 (33.3%), respiratory in 2,932 (9.8%), and digestive in 1,572 (5.3%). 4,965 patients died of other causes and the cause was unknown in 484 (Appendix Table 2).

The cumulative mortality risk for men and women by age groups (Figures 2a-2d) were similar with men having greater mortality in all age groups. There was evidence of relative excess of male mortality from malignant disease even in the youngest age group.

The selection effect of patients receiving knee replacement was even stronger with an overall 43% relative reduction in mortality (SMR 0.57, 95%CI:0.56-0.57; Table 3). There was a residual reduction in SMRs for all five categories of causes of death, except deaths due to digestive system diseases, even at 7-10 years’ follow-up, though a similar waning effect was seen. Excess mortality in the immediate post-operative period was seen for circulatory, respiratory, digestive, and other causes of death compared to the 90-day to 1-year period. There was a paucity of malignant deaths (SMR 0.10, 95%CI:0.08-0.12) in this period. The specific ICD codes with the highest number of deaths for the digestive group were the same as for hip replacements (Appendix Table 3). Examination of circulatory deaths (Table 2) again found excess mortality from IHD and pulmonary diseases in the immediate post-operative period compared to the 90-day to 1-year period. Deaths due to pulmonary diseases including pulmonary embolus within 90-
days of surgery (I26-I28) was higher than expected than in the general population (SMR 1.55, 95%CI:1.03-2.25).

**Discussion**

We have observed a marked selection effect for mortality amongst patients receiving hip or knee replacement. This is due to the confounding effect of health status which determines the likelihood of undergoing elective surgical intervention and subsequent mortality. This pattern is seen in non-surgical examples such as occupational cohorts where the mortality risk of workers selected in certain jobs is lower than the general population\(^\text{10}\) and migrant studies, where migrants in general show lower mortality than the population of origin either because of better health or higher socio-economic status facilitating the ability to migrate\(^\text{11,12}\) The clearest example of this marked selection is the low post-operative mortality for cancer related deaths as advanced cancer would usually be a contra-indication for joint replacement for OA.

The waning effect is also recognised in the occupational literature, though its interpretation is more complex as a toxic work-related exposure may have long-term harms that negate beneficial selection. Assuming joint replacement does not increase mortality risk, for example increased mobility following intervention leading to greater falls-related mortality, then the most likely explanation for this pattern is that the ageing cohort may develop co-morbidity that would now prohibit them from having a joint replacement and hence lose their selection advantage. In addition the ageing control population will include a greater proportion of “healthy survivors” as those with premature mortality die.\(^\text{13}\)

We observed a greater selection bias for patients undergoing knee replacement and though the waning effect appeared slower, this probably reflects an improved baseline so it merely takes
more time before the knee cohort reach the same mortality as the general population. This
difference in selection is unlikely to be explained by differences in age or gender,¹⁴ neither can it
be explained by differences in co-morbidity profile or severity as these are very similar between
the hip and knee cohorts (Appendix Table 4). A comparison of the social gradients of those
receiving either knee or hip replacements found a stronger inverse social gradient for hips than
knees, so that rates fell with higher area deprivation.¹⁵ This would suggest, paradoxically, more
social selection for hip than knee replacement, but this study did not examine provision in
relation to need for surgery. Another possibility is that patients and/or surgeons are more
conservative in their desire for knee surgery so that given the same level of pre-operative risk,
patients with knee pain are less likely to undergo surgery.

The pattern of causes of death by age and gender are what one might expect from the general
population mortality trends; men have a greater mortality risk than women in relation to
cardiovascular disease but at younger ages cancer mortality is important.

We expected to see an excess in IHD and thromboembolic mortality in the immediate post-
operative period, however the elevated risk of digestive system deaths was unexpected. We
suspect that a proportion of these deaths are attributable to post-operative complications, given
the similarity of patterns for both procedures and may be preventable through more assiduous
patient selection or improved peri-operative care. Clinicians should be aware of this and
anticipate problems such as perforations, obstructions and gastrointestinal bleeds. The routine
use of preventative strategies such as antacids, proton pump inhibitors¹⁶ and preoperative
carbohydrate drinks may reduce this increased risk of mortality secondary to digestive
disorders.¹⁷ The common use of non-steroidal anti-inflammatory drugs in patients with
osteoarthritis may lead to an increased risk of cardiac and digestive system deaths in this population.\textsuperscript{18}

Measures to decrease death from pulmonary embolus are now used routinely and there is evidence that using both mechanical and chemical thromboprophylaxis is associated with decreased post-operative mortality.\textsuperscript{2,3} Despite small numbers, we still found evidence of a modest elevated risk. This may reflect some degree of under-management or patients where an explicit decision was made not to use thromboprophylaxis because of contra-indications. The only way to resolve this question would be to undertake a confidential enquiry and perform root cause analysis.

IHD is the greatest single cause of mortality for either procedure. Clinicians should focus their attention on preventing these deaths, thereby maximising the added value of the surgical procedure. Joint replacement itself may be cardioprotective and this may be due to increased capacity for physical activity and its beneficial effects on risk factors common for circulatory system related deaths.\textsuperscript{18} Strategies such as the routine use of low dose aspirin in older males may be sensible\textsuperscript{19-22} as well as maximizing tertiary prevention strategies in those patients with established cardiac risk. It is hard to know what proportion of the almost 3,500 deaths that occurs in the first year post-operatively could have been delayed given better medical care or preoperative screening.

It is well established that patients have a short-term elevation in risk of mortality after hip and knee replacement. Lie and colleagues have compared this elevated risk to the general population and have identified an excess mortality of 0·12% lasting for 26-days.\textsuperscript{4} We have previously compared mortality in the post-operative period with those on the waiting list for surgery in order to minimize the selection effect, showing an excess mortality of 0·26% at 30-days\textsuperscript{23} for hip
replacement and 0.31% at 30-days\textsuperscript{24} for knee replacement. The selection effect of decreased mortality in the longer term post-arthroplasty has been described,\textsuperscript{1} but the duration was not previously established.

Berstock et al. noted that six out of seven studies reporting mortality after hip and knee arthroplasty reported higher mortality after hip replacement, but the difference was not statistically significant (p=0.3 for both 30 and 90-day mortality).\textsuperscript{5} Furthermore, eight out of nine studies reporting cause of death identified cardiovascular causes as the major cause of death. The marked increase in death from gastrointestinal causes was not shown, probably because previous studies were under-powered to identify this.

A major strength of this analysis is the large size of the cohorts, allowing us to look at cause of death in greater detail over a prolonged follow-up time and make comparisons between the interventions. We were not able to link all NJR records and there is some evidence that those that were not linked had lower mortality, which is consistent with the observation that a large proportion of these subjects were treated in the independent sector and were presumably of higher socioeconomic status and lower mortality risk. We are reliant on the accuracy of death certification which may have errors although this will apply to both cohorts as well as the general population control group. It is likely that deaths in the immediate post-operative period are better ascertained due to the need for a coroner’s post-mortem. We cannot tell whether some of these events were potentially preventable as this would require detailed note extraction.

Patients with the potential for post-operative complications relating to the digestive system should be identified pre-operatively and may require more rigorous post-operative monitoring and management including the use of prophylactic antacids, proton pump inhibitors and preoperative carbohydrate drinks to avoid some of the increased post-operative mortality risk.
due to digestive disorders. However, as IHD remains the main cause of death after joint replacement, preventative strategies should target those patients whose cardiovascular risk could be improved. This will not only increase life expectancy but enhance the cost-effectiveness of joint replacement.
References


23. ***Blinded by JBJS***.

24. ***Blinded by JBJS***.
Figure Legends

Figure 1: Cumulative all-cause mortality shown separately for men and women up to 9.75 years after primary hip replacement (THR), together with cumulative incidence rates for competing risk of death malignancy, circulatory, respiratory and digestive disorders and deaths from other causes

(a) Age<60 years at primary operation
   (i) Cumulative all-cause mortality
   (ii) Cumulative incidences for competing causes of death

(b) Age 60-69 years at primary operation
   (i) Cumulative all-cause mortality
   (ii) Cumulative incidences for competing causes of death

(c) Age 70-79 years at primary operation
   (i) Cumulative all-cause mortality
   (ii) Cumulative incidences for competing causes of death

(d) Age 80+ years at primary operation
   (i) Cumulative all-cause mortality
   (ii) Cumulative incidences for competing causes of death

Figure 2: Cumulative all-cause mortality shown separately for men and women up to 9.75 years after primary knee replacement (TKR), together with cumulative incidence rates for
competing risk of death malignancy, circulatory, respiratory and digestive disorders and deaths from other causes

(a) Age<60 years at primary operation
(i) Cumulative all-cause mortality
(ii) Cumulative incidences for competing causes of death

(b) Age 60-69 years at primary operation
(i) Cumulative all-cause mortality
(ii) Cumulative incidences for competing causes of death

(c) Age 70-79 years at primary operation
(i) Cumulative all-cause mortality
(ii) Cumulative incidences for competing causes of death

(d) Age 80+ years at primary operation
(i) Cumulative all-cause mortality
(ii) Cumulative incidences for competing causes of death