Risk factors associated with revision for prosthetic joint infection after hip replacement: a prospective observational cohort study

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Summary
Background The risk of prosthetic joint infection (PJI) is influenced by patient, surgical, and health-care factors. Existing evidence is based on short-term follow-up. It does not differentiate between factors associated with early onset caused by the primary intervention from those associated with later onset more likely to result from haematogenous spread. We aimed to assess the overall and time-specific associations of these factors with the risk of revision due to PJI after primary total hip replacement.

Methods We did a prospective observational cohort study analysing 623 253 primary hip procedures performed between April 1, 2003, and Dec 31, 2013, in England and Wales and recorded the number of procedures revised because of PJI. We investigated the associations between risk factors and risk of revision for PJI across the overall follow-up period using Poisson multilevel models. We reinvestigated the associations by post-operative time periods (0–3 months, 3–6 months, 6–12 months, 12–24 months, >24 months) using piece-wise exponential multilevel models with period-specific effects. Data were obtained from the National Joint Registry linked to the Hospital Episode Statistics data.

Findings 2705 primary procedures were subsequently revised for an indication of PJI between 2003 and 2014, after a median (IQR) follow up of 4–6 years (2–6–7–0). Among the factors associated with an increased revision due to PJI there were male sex (1462 [1·2–2·0%] of 1 237 170 male-years vs 1243 [0·7–7·0%] of 1849 691 female-years; rate ratio [RR] 1·7 [95% CI 1·6–1·8]), younger age (739 [1·1%] of 68 808 person-years <60 years vs 242 [0·6–6·0–8·8%] of 387 049 person-years ≥80 years; 0·7 [0·6–0·8]), elevated body-mass index (BMI; 941 [1·8%] of 517 278 person-years with a BMI ≥30 kg/m² vs 272 [0·9%] of 297 686 person-years with a BMI <25 kg/m²; 1·9 [1·7–2·2]), diabetes (245 [1·4%] of 178 381 person-years with diabetes vs 2120 [1·0%] of 2 043 507 person-years without diabetes; 1·4 [1·2–1·5]), dementia (5 [10·1‰] of 497 person-years with dementia at 3 months vs 311 [2·6‰] of 120 850 person-years without dementia; 3·8 [2·7–2·8]), previous septic arthritis (22 [7·2‰] of 305 565 person-years with previous infection vs 2683 [0·9‰] of 3 083 806 person-years without previous infection; 6·7 [4·2–9·8]), fractured neck of femur (66 [1·5%] of 43 378 person-years operated for a fractured neck of femur vs 2639 [0·9‰] of 3 043 483 person-years without a fractured neck of femur; 1·8 [1·4–2·3]); and use of the lateral surgical approach (1 334 [1·0‰] of 1 399 287 person-years for lateral vs 1242 [0·8‰] of 1 565 913 person-years for posterior; 1·3 [1·2–1·4]). Use of ceramic rather than metal bearings was associated with a decreased risk of revision for PJI (94 [0·4%] of 239 512 person-years with ceramic-on-ceramic bearings vs 602 [0·5‰] of 1 114 239 person-years with metal-on-polyethylene bearings at ≥24 months; RR 0·6 [0·4–0·7]; and 82 [0·4‰] of 190 884 person-years with ceramic-on-polyethylene bearings vs metal-on-polyethylene bearings at ≥24 months; 0·7 [0·5–0·9]). Most of these factors had time-specific effects. The risk of revision for PJI was marginally or not influenced by the grade of the operating surgeon, the absence of a consultant surgeon during surgery, and the volume of procedures performed by hospital or surgeon.

Interpretation Several modifiable and non-modifiable factors are associated with the risk of revision for PJI after primary hip replacement. Identification of modifiable factors, use of targeted interventions, and beneficial modulation of some of these factors could be effective in reducing the incidence of PJI. It is important for clinicians to consider non-modifiable factors and factors that exhibit time-specific effects on the risk of PJI to counsel patients appropriately preoperatively.

Funding National Institute for Health Research.

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Introduction Hip replacement is a successful and cost-effective elective surgical intervention that is widely used to treat disabling joint pain, mainly caused by osteoarthritis. Some patients experience complications and one of the most severe is prosthetic joint infection (PJI), which is most commonly caused by coagulase-negative staphylococcus or Staphylococcus aureus. Although uncommon, PJI is devastating and leads to severe pain, poor function, reduced quality of life, and even death. The treatment...
Evidence before this study
Prosthetic joint infection (PJI) is a devastating complication after hip replacement. In a systematic review published in 2016, we searched MEDLINE, Embase, Web of Science, and The Cochrane Library databases from inception up to Sept 1, 2015, using a registered protocol (PROSPERO: CRD42015023485) to identify the role of patient characteristics on the risk of developing PJI. Our search strategy combined terms related to exposures (eg, “risk factor”, “body mass index”, “comorbidity”) with those related to outcomes (eg, “perioperative joint infection”, “prosthetic joint infection”, “deep prosthetic infection”, “deep infection”, “deep surgical site infection”). Longitudinal studies that reported on the associations of any patient factors with PJI after primary or revision total arthroplasty, who had at least 12 months of follow-up and who had a Newcastle-Ottawa Scale score of more than 5 were eligible. 412 508 hip replacements were pooled and showed that male sex, high body-mass index (BMI), steroid use, diabetes, rheumatoid arthritis, congestive heart failure, depression, and smoking and alcohol intake are each associated with an increased risk of PJI. The published literature was limited by short-term postoperative follow-up, variably adjusted data which did not enhance consistent comparison, substantial heterogeneity between contributing studies, and by not disentangling factors associated with early onset of PJI caused by the primary intervention from factors associated with later onset resulting from haematogenous spread. Older reviews had investigated the role of surgical intervention and health-care setting factors on the risk of revision for PJI but were also limited by the size of the studied samples, infected cases, short postoperative follow-up (≤12 months), and between study heterogeneity. Repeating the search on March 19, 2018, we identified two registry studies and a meta-analysis published since our previous review. Registry studies from Denmark and New Zealand observed increased risk of PJI in men, older patients, those with a high BMI, and those with rheumatoid arthritis. The meta-analysis showed weak evidence of reduced risk of PJI for non-metallic bearing surfaces. The authors highlighted the need for larger studies with adjustment for confounders.

Added value of this study
This study investigated the overall and postoperative period-specific effects of patient, surgical, and health system factors on the risk of revision for PJI, with a single dataset of 623 053 primary hip replacements in which patients were followed up for up to 11 years. Considering patient characteristics, this work corroborates the previous findings of our review and identifies other factors such as younger age, chronic pulmonary disease, liver disease, and dementia that are associated with an increased risk of PJI. Surgical factors, including indication for the primary surgery, surgery type, the lateral surgical approach, and non-ceramic bearing surfaces, were associated with an increased risk of PJI. We identified no effects or only small effects for surgeon and hospital volume or surgeon grade. More importantly, we identified that these factors have a different effect according to the postoperative period considered, with comorbidities such as dementia influencing early revision for PJI and liver diseases influencing long-term revision. The effect of bearing surfaces also varied according to the period considered but factors, such as age or BMI, increased the risk during all postoperative periods.

Implications of all the available evidence
The risk of revision for PJI after primary hip replacement is multifactorial, mainly driven by patient and surgical level factors with time-varying effects. The modifiable factors identified in this study should be considered by clinicians in their practice to develop targeted interventions and propose beneficial modulation of some of these factors. Of equal importance is for clinicians to consider the non-modifiable factors and the factors that exhibit time-specific effects on the risk of PJI, to counsel patients appropriately preoperatively.

burden is high for patients and health-care systems. Revision surgery is usually required and is complex, protracted, and associated with further complications. A large rise in the number of primary hip replacements is predicted and a proportionate rise in the number of patients requiring revision for PJI is expected. In England and Wales alone, over 1000 revision procedures are performed annually because of PJI of the hip.

Identification of individuals at high risk of PJI helps to inform the development of preventive strategies and optimise the detection of PJI. The risk of developing PJI is influenced by non-modifiable and modifiable patient, surgical, and health-care characteristics. In our systematic review of patient risk factors for PJI, we identified male sex, smoking, increasing body-mass index (BMI), steroid use, previous joint surgery, and comorbidities, such as diabetes, rheumatoid arthritis, and depression. Limitations of this review included short-term follow-up, pooled estimates based on variably adjusted data, and evidence of substantial heterogeneity between study settings. These limitations are also applicable to other systematic reviews of surgical and health-care system factors associated with revision for PJI.

Given these limitations, large-scale cohort studies are needed with adequate power to provide evidence on the nature and magnitude of the associations of potential risk factors for PJI. It is important to disentangle factors associated with early onset of PJI, which are likely to be the consequence of the primary intervention, from factors associated with later onset, which are more likely to result from haematogenous spread. We aimed to assess the overall and postoperative period-specific associations of patient, surgical, and
health-care setting factors with the risk of revision due to PJI in prospectively collected observational data of 623,253 primary total hip replacements performed in England and Wales.

**Methods**

**Study design and participants**

In this observational cohort study, we report analyses of data for England and Wales from the National Joint Registry (NJR) for England, Wales, Northern Ireland, and the Isle of Man between April 1, 2003, and Dec 31, 2014. NJR data were linked to Hospital Episode Statistics and Patient Episode Database for Wales to obtain data on inpatient and day case admissions. Data from the Office for National Statistics were linked to obtain the date of death.

We included all patients who had a primary hip replacement between April 1, 2003, and Dec 31, 2013, in the study. Patient consent was obtained for data collection and linkage by the NJR. According to the National Health Service Health Research Authority, separate consent and ethical approval were not required for this study.

**Procedures**

We analysed primary hip replacements performed between April 1, 2003, and Dec 31, 2013, and revision procedures due to PJI that occurred after the primary replacement between April 1, 2003, and Dec 31, 2014. The reason for revision was recorded by clinicians at the time of the revision procedure and reflected a clinical judgment sufficient to lead the surgeon to perform an invasive procedure tailored to tackle a PJI. The diagnosis and treatment strategy for PJI was at the discretion of the surgeon and treating unit and was reflective of contemporary practice over the study period, with raised inflammatory markers, joint specific symptoms, sinuses, and positive microbiological cultures being common diagnostic features over that period.

Each patient who had a primary hip replacement was followed up for a minimum of 12 months until the end of the observation period (Dec 31, 2014) or until the date of revision for PJI, revision for another indication, or death. Revisions for PJI included debridement and implant retention with modular exchange, a single or a two-stage revision procedure.14

We considered the patient characteristics age, sex, ethnicity, BMI, American Society of Anaesthesiologists (ASA) grade, and comorbidities. We obtained data for ethnicity and comorbidities from the Hospital Episode Statistics records. We used ICD-10 codes to classify comorbidities for which patients had been admitted to hospital in the 5 years preceding their primary operation (appendix).15

We considered surgical factors such as indication for surgery, anaesthesia type, thromboprophylaxis regime, surgical approach, hip replacement type, bearing surface, use of bone graft, and occurrence of intraoperative complications.

We considered health system factors such as hospital type, funding stream, country, operating surgeon grade, consultant involvement, and volume of hip surgeries (categorised into quartiles) performed by the hospital, operating surgeon and surgeon in charge of the procedure in the preceding 12 months.

**Statistical methods**

We first investigated the associations between the risk factors and risk of revision for PJI across the overall follow-up period. We used Poisson multilevel models accounting for clustering at unit level (random intercept). Clustering at surgeon level was negligible and therefore ignored.

PJI management varies according to the time since the primary procedure and onset of infection. Early onset of PJI within 24 months of primary procedure is generally considered to result from the primary intervention. Later onset of PJI is more likely to be due to haematogenous spread. For patients with early postoperative or acute haematogenous PJI and a short duration of symptoms, debridement, modular exchange, and implant retention rather than full revision are appropriate.6 Therefore, we reinvestigated the associations over several at-risk postoperative periods: 0–3 months, 3–6 months, 6–12 months, 12–24 months, and more than 24 months. We split each patient’s at-risk period (time elapsed between their primary procedure and endpoint) according to the time spent in each of these periods and we assigned the revision for PJI status (revised for PJI or not) to the relevant period. We used a piece-wise exponential multilevel model with period-specific effects to assess these associations—ie, their rate ratios (RR) and 95% CIs across these time-periods.16,17 We did analyses by running MLwiN from Stata 14.1 (StataCorp LP, TX, USA) using Markov Chain Monte Carlo methods.18 To account for test multiplicity, we derived adjusted p values using Simes’ false discovery rate testing controlling procedure.19,20 To be confident that 95% of the effects tested were not due to chance, we only discussed evidence of association for adjusted p value of 0.05 or lower.

We did the analyses on the overall sample for all exposures except for ethnicity and comorbidities, which we investigated in the 495,456 patients operated on in England with a record of hospital admission in HES but not in PEDW, and no evidence of residency outside England (appendix). We adjusted the regressions for age, sex, ASA grade, and BMI. BMI is an important risk factor for PJI but has substantial missing data in the NJR (47%), partly because it was not included as a variable in the early data collection forms. We used a multiple imputation strategy to impute BMI, assuming that data were missing at random, using a Gaussian normal regression imputation model with the factors age, sex, and ASA used as covariates, and the log of the observed event or censoring time and revision for PJI status. Due to the computational time required by each multilevel piece-wise model, we computed only five imputations.
and combined regression estimates by Rubin’s rules. Unadjusted and adjusted models without BMI are available on request. To avoid overadjustment, we did not adjust models investigating the effect of comorbidities for ASA grade, a proxy indicator of comorbid profile.

Role of the funding source
The National Institute for Health Research had no role in study design, data collection analysis, interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
623,253 primary hip procedures were done in 460 different surgical units with a median (IQR) of 1050 (460–1940) per unit. Baseline study sample characteristics are presented in figure 1 and the table. 2705 primary procedures were subsequently revised for an indication of PJI after a median (IQR) follow-up of 4·6 years (2·6–7·0); 14% (n=372) of these within 3 months, 8% (n=204) in 3–6 months, 14% (n=374) in 6–12 months, 23% (n=612) in 12–24 months, and 42% (n=1143) beyond 24 months from the primary procedure. The mean patient age was 68 years (SD 11). The sample is presented by time periods in the appendix.

Men were at higher risk of revision for PJI in all time periods than women (figure 2). Over the entire follow-up, the risk was lower for patients older than 60 years. However, this reduced risk was only observed after the first 6 months (appendix). BMI of 30 kg/m² or higher was associated with an increased risk compared with BMI of less than 25 kg/m². Patients with an ASA grade of 2 or higher were at greater risk than healthy patients (table). This was particularly evident during the first 6 months (appendix).

Operations done via a posterior surgical approach had the lowest risk of revision for PJI compared with other surgical approaches (figure 2). The surgical approach did not influence the early risk of revision for PJI (figure 3), but from 3 months onwards patients who had undergone a lateral approach were at higher risk (appendix).

Patients who had a primary hip resurfacing were at lower risk of revision for PJI (figure 2), but this lower risk was not evident in the first 3 postoperative months (figure 3). In the early postoperative period, patients who
| Patients, n | Person-years | Cases, n | Incidence per 1000 person-years (95% CI) |
|------------|--------------|---------|----------------------------------------|
| Sex        |              |         |                                        |
| Female     | 372256       | 1849691 | 1243 0.67 (0.64–0.71)                  |
| Male       | 250957       | 123710  | 1462 1.18 (1.12–1.24)                  |
| Age, years |              |         |                                        |
| <60        | 131803       | 688000  | 739 1.07 (1.00–1.15)                   |
| 60–69      | 191128       | 979663  | 942 0.96 (0.90–1.03)                   |
| 70–79      | 210387       | 1033850 | 782 0.76 (0.70–0.81)                   |
| ≥80        | 89935        | 387049  | 242 0.63 (0.55–0.71)                   |
| Ethnicity  |              |         |                                        |
| White      | 469129       | 2256675 | 2308 1.02 (0.98–1.07)                  |
| Black African origin | 2855 | 13152  | 12 0.91 (0.47–1.59)                   |
| South Asian| 1605         | 7223    | 6 0.83 (0.30–1.81)                     |
| Other and mixed | 3235 | 14405  | 14 0.97 (0.53–1.63)                   |
| Unclear    | 18636        | 95431   | 25 0.26 (0.17–0.38)                    |
| Unavailable* | 127797 | 698972  | 340 0.49 (0.44–0.54)                   |
| Body mass index, kg/m² |          |         |                                        |
| <25        | 71584        | 297686  | 272 0.91 (0.83–1.01)                   |
| 25–29.9    | 122047       | 532826  | 580 1.04 (0.96–1.12)                   |
| ≥30        | 125856       | 512728  | 941 1.82 (1.70–1.94)                   |
| Missing    | 292776       | 1174072 | 912 0.53 (0.50–0.57)                   |
| American Society of Anaesthesiologists grade |  |         |                                        |
| 1          | 114367       | 657059  | 482 0.73 (0.67–0.80)                   |
| 2          | 418335       | 2050622 | 1722 0.87 (0.83–0.91)                  |
| 3–5        | 90551        | 393780  | 451 1.15 (1.04–1.26)                   |
| Chronic pulmonary disease |  |         |                                        |
| No         | 433003       | 2127270 | 2064 0.97 (0.93–1.01)                  |
| Yes        | 62453        | 260618  | 301 1.15 (1.03–1.29)                   |
| Unavailable* | 127797 | 698972  | 340 0.49 (0.44–0.54)                   |
| Diabetes   |              |         |                                        |
| No         | 453057       | 2209507 | 2120 0.96 (0.92–1.00)                  |
| Yes        | 42399        | 178381  | 245 1.13 (1.21–1.56)                   |
| Unavailable* | 127797 | 698972  | 340 0.49 (0.44–0.54)                   |
| Dementia   |              |         |                                        |
| No         | 493382       | 2381198 | 2355 0.99 (0.95–1.03)                  |
| Yes        | 2074         | 6690    | 10 1.49 (0.72–2.75)                    |
| Unavailable* | 127797 | 698972  | 340 0.49 (0.44–0.54)                   |
| Liver disease |          |         |                                        |
| No         | 491430       | 2327883 | 2327 0.98 (0.94–1.02)                  |
| Yes        | 40256        | 15005   | 38 2.53 (1.79–3.48)                    |
| Unavailable* | 127797 | 698972  | 340 0.49 (0.44–0.54)                   |
| Congestive heart failure |  |         |                                        |
| No         | 484748       | 2346960 | 2307 0.98 (0.94–1.02)                  |
| Yes        | 10708        | 40928   | 58 1.42 (1.08–1.83)                    |
| Unavailable* | 127797 | 698972  | 340 0.49 (0.44–0.54)                   |
| Connective tissue and rheumatic disease |  |         |                                        |
| No         | 473594       | 2292733 | 2251 0.98 (0.94–1.02)                  |
| Yes        | 21862        | 95156   | 114 1.20 (0.99–1.44)                   |
| Unavailable* | 127797 | 698972  | 340 0.49 (0.44–0.54)                   |

(Table continues in next column)
had undergone an uncremented, hybrid, or reverse hybrid total hip replacement (THR other, figure 3B) were at higher risk than those with cemented implants but from 3 to 24 months, they were at lower or similar risk (appendix). Further analysis showed a higher early risk of revision in patients with hybrid implant THRrs (RR<sub>early-1-7</sub>, 95% CI 1-2–2-3) than in those with reverse hybrid implants (0-9, 0-4–2-0).

Table: Sample description and incidence rates

| Patients, n | Person-years | Cases, n | Incidence per 1000 person-years (95% CI) |
|-------------|--------------|---------|---------------------------------------|

### Inflammatory arthropathy

| Type of bearing | | |
|-----------------|----------------|---------|---------------------------------------|
| Metal-on- | 367 226 | 1 805 843 | 1 505 | 0 83 (0-79–0-88) |
| Metal-on- | 68 761 | 447 609 | 526 | 1 18 (1-08–1-28) |
| Ceramic-on- | 73 607 | 328 183 | 525 | 0 77 (0-68–0-87) |
| Ceramic-on- | 99 651 | 428 600 | 342 | 0 80 (0-72–0-89) |
| Ceramic-on- | 2 263 | 10 553 | 20 | 1 90 (1-16–2-93) |
| Other | 11 745 | 66 073 | 60 | 0 91 (0-69–1-17) |

### General anaesthesia

| Type of anaesthesia | | |
|------------------|----------------|---------|---------------------------------------|
| No | 322 710 | 532 700 | 1 317 | 0 86 (0-81–0-91) |
| Yes | 299 543 | 1 554 661 | 1 388 | 0 89 (0-85–0-94) |

### Electrical or non-invasive stimulation

| Type of technique | | |
|------------------|----------------|---------|---------------------------------------|
| No | 568 425 | 2 752 938 | 2 415 | 0 88 (0-84–0-91) |
| Yes | 54 828 | 3 33 932 | 290 | 0 87 (0-77–0-97) |

### Other bone grafts

| Type of bone graft | | |
|-------------------|----------------|---------|---------------------------------------|
| No | 597 493 | 2 958 905 | 2 588 | 0 87 (0-84–0-91) |
| Yes | 25 760 | 127 956 | 117 | 0 91 (0-76–1-10) |

(Continued from previous column)
The risk of revision for PJI was also influenced by the type of bearing surfaces and this varied according to the time period. In the early postoperative period, no differences were observed (figure 3). Between 3 and 24 months, metal-on-metal THRs had a lower or similar risk than did metal-on-polyethylene THRs; beyond 24 months, the risk was higher for metal-on-metal (appendix). When the model was further adjusted for the type of surgery (resurfacing and THR cemented or not) the higher revision risk for PJI in the metal-on-metal group was identified earlier, from 12 months postoperation onwards (RR12–24mth 1·8, 95% CI 1·3–2·3; RR >24mth 2·2, 1·8–2·6). Ceramic-on-ceramic and ceramic-on-polyethylene surfaces were associated with a lower risk of long-term revision (from 12 months for ceramic-on-ceramic and 24 months for ceramic-on-polyethylene postoperation onwards) than metal-on-polyethylene bearings, which
also had a higher risk of long-term revision for PJI (appendix).

Little or no difference in the risk of revision for PJI was found for the choice of anaesthetic technique, thromboprophylaxis regime, use of acetabular bone graft, or experience of intraoperative complication (figures 2, 3; appendix). Patients who received a femoral bone graft during the primary procedure were at higher risk of PJI with no evidence of a postoperative period-specific effect (figure 3; appendix).

The risk of revision for PJI was not different between Wales and England nor between the funding sources of the primary procedure (figure 2).

Revision for PJI was not influenced by the grade of the operating surgeon and the presence or absence of a consultant surgeon during surgery (figure 2). Operating surgeons who had performed over 63 procedures in the 12 months preceding the primary surgery were weakly associated with a lower risk of
discussion

At the patient level, men, younger patients, and those with high BMI or high ASA grades had an increased risk of revision for PJI. Comorbidities that increased the risk of revision for PJI included chronic pulmonary disease, diabetes, dementia, liver disease, congestive heart failure, and connective tissue or rheumatic diseases. These comorbidities and elevated BMI can potentially be optimised before surgery. A targeted preoperative intervention for male patients with high BMI and specific comorbidities seems particularly relevant.

At the surgical level, patients undergoing THR for fractured neck of femur or avascular necrosis were at higher risk of revision for PJI. Patients with a fracture are different to those who have conditions such as osteoarthritis, generally being older with a higher risk of mortality. Conditions that cause avascular necrosis, such as steroid use or irradiation, cause immunosuppression and also predispose towards PJI. The markedly higher risk in those with historical infection of the hip is novel, though unsurprising, and might be due to quiescent bacteria or other immune conditions that predispose to PJI. Lateral surgical approach and use of femoral bone graft also increased the risk. The increased risk with the lateral surgical approach is a novel finding that we postulate is due to increased tissue damage and bleeding caused by violating the abductor mechanism. Previous studies have suggested that the lateral approach is associated with more bleeding, worse patient related outcomes, and higher mortality. Approximately one third of hip replacements undertaken in England and Wales in 2016, still utilised this approach—although its use is declining. Early revision for PJI was higher in those receiving uncemented than cemented implants independent of bearing surface. At later time points, the risk was lower for uncemented THRs and resurfacings. This might reflect an initial protective effect of antibiotic impregnated bone cement. Long-term risk was higher in metal-on-metal bearings, possibly due to the soft tissue destruction associated with these implants, and was lower in bearings that included ceramic heads, which is concordant with a report from the Medicare population in the USA. In this Medicare population, ceramic bearings were used in younger and healthier patients. Our study adjusted for age and health status, which should mitigate the effects of any selection bias. A meta-analysis also showed weak evidence of reduced risk of PJI for ceramic bearing surfaces.

Factors at the health-care system level appear to be less important with no marked sustained associations across the time periods studied.

Consistent with previous studies, we observed higher risk in men and patients with high BMI. Contrary to previous findings, younger patients were at higher risk, which could reflect the increased follow up in our study. Older patients could be at lower risk due to a propensity to non-operative management of PJI in this group. Smoking has previously been identified as a risk factor and although we did not have information on smoking habit, the surrogate comorbidity of chronic pulmonary disease was associated with increased risk. Evidence of an association between alcohol intake and increased risk has been inconsistent. We observed higher risk in patients with liver disease, but this might represent several pathologies. Our study corroborates the previous findings of increased risk in patients with diabetes, rheumatoid arthritis, and congestive heart failure. We have shown for the first time that dementia is associated with an increased risk of early revision for PJI, which might reflect the high prevalence of other comorbidities in these patients.

The current study has several strengths. To our knowledge, this is the largest and most comprehensive investigation of several patient, surgical, and health-care related factors and their risk for revision for PJI of the hip. We used a large-scale cohort design comprising more participants (n=623 253) than those of the most up-to-date review on the topic (n=512 508 hip and knee replacements). Other strengths include the longer term follow-up of the cohort (median 4·6 years) and cutting-edge statistical analyses, which include the assessment of the effects of these potential risk factors at time-specific periods.

Our study has some limitations. Although prospectively collected, our data is observational and we can only draw inferences on the nature and magnitude of the associations but cannot establish causation. In the UK, no national gold standards have been agreed upon that are available to orthopaedic surgeons to diagnose PJI. As such, the reported indication of PJI in the NJR might vary between units but is reflective of contemporary practice with raised inflammatory markers, joint specific symptoms, sinuses, and positive microbiological cultures being used to diagnose PJI. The PJI diagnosis reflects a clinical judgment sufficient to lead the surgeon to conduct a very severe and invasive procedure tailored to tackle a PJI. Issues relating to under-reporting of revision for PJI, and thus potentially lower incidence estimates, are acknowledged. Linkage of the NJR data to microbiology data could reduce any misdiagnoses of PJI.
but has proven to be of limited generalisability with 12% NJR linkage achievable."

The associations we have identified might vary with different causative pathogens, but unfortunately we do not have the data to explore this. Our findings should be considered as conservative estimates of the risk factors with the strongest effects. The investigations of the effect of comorbidities were limited to a subset of NJR patients linked to HES. This subset had higher ASA grades and therefore higher rate of revision for PJI than those excluded from these investigations, but they did not differ in terms of age, sex, BMI, or surgical characteristics, suggesting little evidence of differential selection bias. All other factors were investigated on the entire sample.

We have done appropriate modelling to adjust for known relevant confounders but residual confounding is still possible. We had no specific data on confounders, such as smoking and alcohol consumption, but have surrogate markers, such as chronic pulmonary disease and liver disease. BMI was not collected in the early years of the registry necessitating imputation of the data as with a previous study on this dataset. Competing risk due to revision for another cause or death, which in combination affected 55% of the primary hip replacements in the dataset during the period of observation, could not be accounted for in the modelling strategy. This was a pragmatic decision because we chose a strategy focusing on time-specific effects while accounting for the clustering nature of the data to disentangle the effect associated with surgical factors (likely to be more marked in the short-term to mid-term follow-up period) from those associated with health-risk behaviour (likely to be more marked in the mid-term to long-term follow-up period). This strategy was optimal because evidence supports non-proportional hazard rates. Finally, it was not possible to investigate any ethnic disparities in terms of revision for PJI due to the insufficient number of ethnic minority patients reviewed for PJI.

Preventive strategies for PJI largely focus on hygiene, use of protective equipment, management of care equipment and occupational exposure, and safe care of linen, the environment, and waste. Combinations of systemic antibiotics, antibiotic-impregnated cement, and linen, the environment, and waste. Combinations of equipment and occupational exposure, and safe care of use of protective equipment, management of care for PJI.

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