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**Which patient-related factors are linked to superficial surgical site infection and the progression into a periprosthetic joint infection after elective primary total joint arthroplasty?
A cross-sectional study on 1,291 patients**

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3 1 Which patient-related factors are linked to superficial surgical site
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5 2 infection and the progression into a periprosthetic joint infection after
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7 3 elective primary total joint arthroplasty?
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10 4 A cross-sectional study on 1,291 patients
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14 6 Running title: Which patient-related factors are linked to superficial surgical site infection and the
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16 7 progression in to a periprosthetic joint infection?
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27 13

28 14 **Declarations**

29
30 15 None of the authors have any conflict of interest to declare.

31 16 *Ethics approval*

32
33 17 The study design was reviewed and approved by the Human Research Ethics Committee in
34
35 18 Uppsala, Sweden, Nr: 2019-01425.
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2
3 27 **Abstract**

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6 29 **Objectives:** The incidence of superficial surgical site infection (SSSI) may increase the risk of
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9 30 periprosthetic joint infection (PJI). The objective of this study is to identify patient-related risk factors
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11 31 associated with SSSI and investigate their correlation with the progression of PJI. **Design:** 1,291
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13 32 primary elective hip and knee prostheses were included. Patients were interviewed ≥ 3 months after
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15
16 33 surgery to answer questions about the postoperative period, including any occurrences of SSSI. The
17
18 34 diagnosed PJI was determined by an orthopaedic surgeon and a specialist in infectious diseases. All
19
20 35 patients with PJI underwent revision surgery. **Setting:** This study was performed at Uppsala University
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23 36 Hospital, Uppsala.

24
25 37 **Participants:** 1,184 patients and 1,314 joints were included. Because of bilateral surgery during the
26
27 38 same operative session, 23 joints were excluded due to an increased risk of infection.

28
29 39 **Primary and secondary outcome measures:** Which of the patient-related risk factors; joint, age,
30
31 40 sex, the American Society of Anaesthesiologists classification (ASA), body mass index (BMI),
32
33 41 smoking, diabetes and rheumatic disease associated with 1) superficial surgical site infection and 2)
34
35 42 the progress in to a periprosthetic joint infection.

36
37 43 **Results:** 7.0% of the patients developed an SSSI and 26.7% of those progressed to a PJI. Factors
38
39 44 found with increased adjusted risk ratio (aRR) for SSSI were: knee surgery (1.9; 95% confidence
40
41 45 interval CI: 1.2 – 3.1), age ≥ 65 years (1.7; 95% CI: 1.1 – 2.8) and BMI ≥ 35 (2.3; 95% CI: 1.2 – 4.2).
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43 46 Male patients showed a significant risk of developing PJI after SSSI, with a RR of 3.3 (95% CI: 1.1
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45 47 – 10.5).

46
47 48 **Conclusions:** Patients developing SSSI have a great risk on progress to PJI. Older obese patients
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49 49 considered for elective primary total knee arthroplasty seem to have an increased risk of developing
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51 50 SSSI and male gender is the most significant risk factor to progress from SSSI into PJI.
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52 **Strengths and limitations of this study**

53 Strengths

- 54 - Large cohort size (n=1291)
- 55 - Meticulous follow-up of each patient
- 56 - Exclusively includes patients with primary elective joint surgery

57 Limitations

- 58 - Retrospective study design
- 59 - Small number of infections leading to the risk of a type II error.

60

61 **Keywords**

62 Periprosthetic joint infection (PJI), superficial surgical site infection (SSSI), total joint arthroplasty,
63 risk factors.

64 **Introduction**

65 Infection after TJA can be defined as either superficial involving skin or subcutaneous tissue only (a
66 superficial surgical site infection, SSSI) or deep (periprosthetic joint infection, PJI) with deep soft
67 tissue involvement (e.g., fascial and muscle layers) and the prosthesis. The incidence of SSSI after
68 TJA can vary from 1 to 10% (1, 2) and may increase the risk of PJI by up to 35 times (3). The
69 frequency of PJI ranges between 1 and 5% (4-7). Patient-related risk factors, such as obesity, RA,
70 smoking, male sex, age, alcohol abuse, American Society of Anaesthesiologists (ASA) classification
71 >2 and diabetes mellitus (DM) (8-16), have been described as risk factors for PJI. In clinical practice
72 priority should be to identify patients at high risk for SSSI and PJI, aiming for patient optimisation
73 and the opportunity to manage modifiable risk factors since it is essential to seize any opportunity to
74 optimise all prerequisites for the best achievable surgical outcome. Our primary objectives were to
75 1) determine which patient-related factors are linked to superficial surgical site infection (SSSI) and
76 2) investigate the progression in to a deep periprosthetic joint infection (PJI). Our study aims to (i)
77 identify patient-related risk factors associated with SSSI and (ii) investigate their correlation with the
78 progression of PJI.

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80 **Methods**

81 *Study design*

82 This cross-sectional study of primary elective prostheses in hip or knee joints included patients in a
83 national project designed to lower the incidence of hospital-related infections (17). Patients included
84 in this study were treated at Uppsala University hospital from November 2008 to December 2012, and
85 interviewed ≥ 3 months after surgery to answer questions about the postoperative period. The patients'
86 records were reviewed to determine whether there had been any documentation of difficulties with
87 wound-healing or whether antibiotics were prescribed to treat an infection related to arthroplasty
88 surgery.

89 In a retrospective review of patient records selected patients fulfilled the criteria for PJI (18), but
90 those criteria had not been used at diagnosis. Patient records were reviewed for patient-related risk
91 factors while a local arthroplasty register was used to obtain perioperative information about whether
92 revision surgery had been necessary due to persistent PJI. Follow-up was a minimum of 5 years.

93 This study was limited to patient-related risk factors associated with developing an SSSI and focused
94 on those factors that might be possible to avoid or optimise preoperatively.

95 Consent for publication was considered in the application to the Human Research Ethics

96 Committee. However, no consent, verbal or written was needed, due to the retrospective study

97 design. The study design was reviewed and approved by the Human Research Ethics Committee

98 (Dnr: 2019-01425).

99 *Patient and Public Involvement*

100 Patients or the public were not involved in the development of the research question, outcome

101 measures, the design, conduct, reporting, or dissemination plans of our research. The results of this

102 study will not be separately disseminated to study participants.

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2 106 *Study population*

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5 107 1,184 patients and 1,314 joints were included. Because of bilateral surgery during the same operative
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7 108 session, 23 joints were excluded due to an increased risk of infection. 1,291 surgeries (815 hips, 476
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9 109 knees) were included.

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12 110 Only cemented components were used in all knees. Hip prostheses were cemented, cementless or
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14 111 hybrids. In all cemented prostheses antibiotic-loaded cement with gentamycin was applied. All
15
16 112 patients received systemic pre- and perioperative antibiotic prophylaxis in accordance with national
17
18 113 guidelines (cloxacillin, and in the case of penicillin allergy, clindamycin).

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21 114 *Statistics*

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23 115 Descriptive statistics were used to summarise and report demographic characteristics.

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25 116 *Confounders*

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28 117 Such patient-related factors as joint, sex, age, BMI, RA, ASA classification, smoking and DM were
29
30 118 considered clinically relevant confounders in the correlation between arthroplasty surgery and SSSI
31
32 119 or PJI.

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35 120 These specific patient-related variables have previously been linked to exposure and outcome and are
36
37 121 not considered in the causal pathway between potential risk factors and outcome (Figure 1).

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39 122 Some of the relevant confounders were analysed as categorical variables: ASA classification: <3 or
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41 123 ≥ 3 , BMI: <35 or ≥ 35 and Age: <65 years or ≥ 65 years.

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44 124 Patients with DM included both type 1 and 2 (drug- or diet-treated). In an initial analysis logistic
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46 125 regression was performed, entering all covariates as singular variables. Crude risk ratios (RRs) for
47
48 126 SSSI and PJI were calculated for each variable with 95% confidence intervals (95% CIs). In the next
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51 127 step the covariates were entered in the regression model, with RRs mutually adjusted for all
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53 128 covariates. Adjusted RRs (aRRs) for each covariate were calculated for the occurrence of SSSI or PJI
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55 129 and any progression of SSSI in to PJI.

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58 130 All statistical analyses were performed using SPSS (version 26.0) and p-values ≤ 0.05 were
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60 131 considered statistically significant.

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60**Results**

The total number of surgeries for prosthetic hip or knee joints was 1,291. 90 knee joints (7.0%) developed an SSSI and 24 (1.9%) a PJI. Of the 90 joints with SSSI, 24 (26.7%) progressed to a PJI (Figure 2).

In the hip cohort (815) 41 joints (5.0%) developed an SSSI, and 9 (1.1%) a PJI. In the knee cohort (476), 49 joints ((10.0%) developed an SSSI and 15 (3.2%) a PJI (Table 1).

Table 1. Number of postoperative infections

Variable	SSSI	PJI
Total cohort (1291)	90 (7.0 %)	24 (1.9%)
Hip (815)	41 (5.0 %)	9 (1.1%)
Knee (476)	49 (10.3 %)	15 (3.2%)

SSSI (superficial surgical site infection), PJI (periprosthetic joint infection).

142 Demographic characteristics of the cohorts are outlined in Table 2.

Table 2. Demographic characteristics

Variable	Total cohort n = 1291	Hip cohort n = 815 (63%)	Knee cohort n = 476 (37%)	Range
Mean age (year)	63	61	65	18–96
Age				
<65	729 (56%)	479 (59%)	250 (53%)	
≥65	562 (44%)	336 (41%)	226 (47%)	
ASA-class^a				
≤2	1048 (82%)	679 (85%)	369 (79%)	
≥3	225 (18%)	125 (15%)	100 (21%)	
Mean Body mass index	28	27	29	14–51
BMI^b				
<35	1145 (90%)	743 (92%)	402 (86%)	
≥35	130 (10%)	63 (8%)	67 (14%)	
Gender				
Woman	731 (57%)	421 (52%)	310 (65%)	
Man	560 (43%)	394 (48%)	166 (35%)	
Smoking^c				
No	1141 (90%)	716 (90%)	425 (90%)	
Yes	129 (10%)	84 (10%)	45 (10%)	
Diabetes^a				
No	1145 (90%)	731 (91%)	414 (88%)	
Yes	128 (10%)	73 (9%)	55 (12%)	
Rheumatological disease^d				
No	1052 (88%)	689 (91%)	363 (83%)	
Yes	139 (12%)	67 (9%)	72 (17%)	

ASA (American Society of Anaesthesiologists), BMI (Body mass index).

^a missing data in 18 cases

^b missing data in 16 cases

^c missing data in 21 cases

^d missing data in 100 cases

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2 150 *Risk factors for SSSI*

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5 151 Risk factors with a significant crude RR for developing SSSI were knee surgery (2.2; 95% CI: 1.4 –
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7 152 3.3), age ≥ 65 years (1.7; 95% CI: 1.1 – 2.6), ASA classification ≥ 3 (2.3; 95% CI: 1.4 – 3.7), BMI ≥ 35
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9 153 (2.4; 95% CI: 1.4 – 4.2) and rheumatic disease (1.9; 95% CI: 1.1 – 3.4). Adjusting for all covariates,
10
11 154 factors with significant aRRs for SSSI were knee surgery (1.9; 95% CI 1.2 – 3.1), age ≥ 65 years (1.7;
12
13 95% CI: 1.1 – 2.8) and BMI ≥ 35 (2.3; 95% CI: 1.2 – 4.2) (Table 3).
14 155

16 **Table 3. Risk ratio (RR) for SSSI**

Variable	SSSI	Crude RR (95 % CI)	P-value	Adjusted RR (95 % CI)	P-value
No SSSI 1201 (93%)					
SSSI 90 (7%)					
Joint					
Hip	41 (45%)				
Knee	49 (55%)	2,2 (1,4 – 3,3)	0,000	1,9 (1,2 – 3,1)	0,005
Age					
<65	40 (44%)				
≥ 65	50 (56%)	1,7 (1,1 – 2,6)	0,018	1,7 (1,1 – 2,8)	0,024
ASA class^a					
≤ 2	61 (69%)				
≥ 3	28 (31%)	2,3 (1,4 – 3,7)	0,001	1,6 (0,9 – 2,7)	0,069
Body mass index					
<35	72 (80%)				
≥ 35	18 (20%)	2,4 (1,4 – 4,2)	0,002	2,3 (1,2 – 4,2)	0,010
Gender					
Woman	49 (54%)				
Men	41 (46%)	1,1 (0,7 – 1,7)	0,666	1,4 (0,9 – 2,2)	0,206
Smoking^a					
No	80 (90%)				
Yes	9 (10%)	1,0 (0,5 – 2,0)	0,988	1,1 (0,5 – 2,4)	0,836
Diabetes^a					
No	76 (85%)				
Yes	13 (15%)	1,6 (0,9 – 3,0)	0,142	1,2 (0,6 – 2,3)	0,606
Rheumatological disease^b					
No	68 (81%)				
Yes	16 (19%)	1,9 (1,1 – 3,4)	0,031	1,7 (0,9 – 3,2)	0,077

156 SSSI (superficial surgical site infection), ASA (American Society of Anaesthesiologists), CI (confidence interval)

157 ^a missing data in 1 case

158 ^b missing data in 6 cases

159

160 *Risk factors for PJI*

161 Risk factors with a significant crude RR for the development of PJI were knee surgery, ASA
162 classification ≥ 3 and BMI ≥ 35 . Factors with significant aRRs for PJI were knee surgery (2.6; 95%
CI: 1.4 – 4.2) and BMI ≥ 35 (2.3; 95% CI: 1.2 – 4.2) (Table 3).

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3 163 CI: 1.1 – 6.4), ASA classification ≥ 3 (3.2; 95% CI: 1.3 – 7.9), BMI ≥ 35 (3.0; 95% CI: 1.2 – 4.2) and
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5 164 male sex (3.0; 95% CI: 1.2 – 7.5) (Table 4).

6
7 **Table 4. Risk ratio (RR) for PJI**

Variable	PJI	Crude RR (95 % CI)	P-value	Adjusted RR (95 % CI)	P-value
No PJI	1267 (98,1%)				
PJI	24 (1,9%)				
Joint					
Hip	9 (38%)				
Knee	15 (63%)	2,9 (1,3 – 6,7)	0,012	2,6 (1,1 – 6,4)	0,033
Age					
<65	12 (50%)				
≥ 65	12 (50%)	1,3 (0,6 – 2,9)	0,520	1,0 (0,4 – 2,5)	0,941
ASA class					
≤ 2	12 (50%)				
≥ 3	12 (50%)	4,9 (2,2 – 11,0)	0,000	3,2 (1,3 – 7,9)	0,010
Body Mass Index					
<35	17 (71%)				
≥ 35	7 (29%)	3,8 (1,5 – 9,3)	0,004	3,0 (1,2 – 4,2)	0,032
Gender					
Woman	9 (38%)				
Men	15 (62%)	2,2 (0,9 – 5,1)	0,063	3,0 (1,2 – 7,5)	0,016
Smoking					
No	23 (96%)				
Yes	1 (4%)	0,4 (0,1 – 2,8)	0,345	2,2 (0,3 – 16,8)	0,448
Diabetes					
No	19 (79%)				
Yes	5 (21%)	2,4 (0,9 – 6,6)	0,086	1,4 (0,5 – 4,0)	0,544
Rheumatological disease					
No	19 (79%)				
Yes	5 (21%)	2,0 (0,7 – 5,5)	0,166	1,9 (0,6 – 5,5)	0,259

41 165 SSSI (superficial surgical site infection), PJI (periprosthetic joint infection), ASA (American Society of Anaesthesiologists)
42 166 CI (confidence interval)

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169 *Risk factors for PJI in patients with SSSI*

170 In the group of patients with SSSI the only significant risk factor for progression to PJI was male sex,
 171 with an aRR of 3.3 (95% CI: 1.1 – 10.5) (Table 5).

Table 5. Risk ratio (RR) for PJI in patients with SSSI

Variable	PJI	Crude RR (95 % CI)	P-value	Adjusted RR (95 % CI)	P-value
SSSI - no PJI 66 (73%)					
SSSI - PJI 24 (27%)					
Joint					
Hip	9 (37%)				
Knee	15 (63%)	1,6 (0,6 – 4,1)	0,357	1,5 (0,5 – 4,4)	0,462
Age					
<65	12 (50%)				
≥65	12 (50%)	1,4 (0,5 – 3,5)	0,523	1,6 (0,6 – 4,9)	0,376
ASA-class					
≤2	12 (50%)				
≥3	12 (50%)	3,0 (1,1 – 8,2)	0,025	3,1 (1,0 – 10,0)	0,051
Body Mass Index					
<35	17 (71%)				
≥35	7 (29%)	2,1 (0,7 – 6,1)	0,195	2,0 (0,5 – 8,1)	0,316
Gender					
Woman	9 (37%)				
Men	15 (63%)	2,6 (1,0 – 6,7)	0,055	3,3 (1,1 – 10,5)	0,041
Smoking					
No	23 (96%)				
Yes	1 (4%)	3,2 (0,4 – 27,0)	0,282	0,3 (0,4 – 39,5)	0,230
Diabetes					
No	19 (79%)				
Yes	5 (21%)	1,9 (0,6 – 6,4)	0,317	1,6 (0,3 – 7,5)	0,556
Rheumatological disease					
No	19 (79%)				
Yes	5 (21%)	0,9 (0,3 – 2,8)	0,792	1,2 (0,3 – 5,1)	0,780

SSSI (superficial surgical site infection), PJI (periprosthetic joint infection), ASA (American Society of Anaesthesiologists)
 CI (confidence interval)

Discussion

This study shows that knee surgery, age >65 years and obesity are independent risk factors for the development of SSSI. Superficial wound complications were associated with PJI in 24% of the cases, and male sex was a significant factor in the progression into PJI. A recent meta-analysis, showed that male sex was a risk factor for PJI development, especially after total knee arthroplasty (TKA) supports these results (19). The link between male sex and PJI may be attributed to some contributing behavioural factors, including smoking, diet, hygiene and alcohol consumption, but the reasons behind this are not clear. Sex-related differences in immune response due to bacteria (e.g., *Staphylococcus aureus* and *Pseudomonas aeruginosa*) have been reported. In addition, septicaemia and bacteraemia occur more frequently in males than females (20), but whether it will or will not this affect the development of SSSI or PJI has yet to be investigated.

Patients with knee prostheses have shown a higher rate of PJI and are known to be in greater need of revision surgery than patients with hip prostheses (6, 9, 12, 19). There is less soft tissue around the knee than around the hip, meaning a shorter distance between skin and joint. Blood circulation around the knee area is more exposed to impact than the hip area and the perfusion is easier to disturb.

Age was a significant risk factor for SSSI in our study, which is congruent with results from a large (n=1,000 patients) retrospective study (1). An elderly patient may have pre-existing medical conditions and fragile skin that can impair wound healing and cause SSSI.

A high ASA classification posed a significant risk factor for developing PJI and SSSI in the univariate analysis but not after adjusting for the other covariates. The correlation between a high ASA classification and infection after surgery may be explained because the ASA classification encapsulates several other known risk factors (e.g., smoking, DM and obesity). Each of these risk factors has been independently associated with a higher risk of surgical site infection resulting from tissue hypoperfusion and subsequent impaired immunological function (13, 21).

Excess weight/obesity is a known risk factor for osteoarthritis, TJA and PJI (22). Multiple medical comorbidities, including DM type II, hypertension and cardiovascular diseases, are usually associated

1
2 202 with obesity, affecting patients' BMI and ASA classification (23-25). In this study BMI \geq 35 was a
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5 203 risk factor for SSSI and PJI. The association between BMI and postoperative wound complications
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7 204 may be explained by prolonged or more complicated arthroplasty surgery (26) and protracted
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9 205 postoperative wound drainage (27). The present results are in line with large register-based studies.
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11 206 Sayed-Noor et al. observed that the risk of reoperation within 2 to 5 years increased in patients with
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14 207 higher BMI classification (I-III) (28). In another study with 19,000 patients by Shohat et al. noted
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16 208 that the BMI cut-off threshold was associated with an increased risk of PJI (29). No threshold for PJI
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18 209 was observed (29), although a higher BMI classification was linked to an increased risk of PJI.
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20
21 210 The rate of SSSI (7.0%) and PJI (1.9%) in this study is consistent with international studies showing
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23 211 levels of SSSI ranging from 1-10% (1, 30) and PJI ranging from 0.2-2.23% (5, 6, 8).
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25 212 Two major strengths of this study are cohort size (n=1291) and the meticulous follow-up of each
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27
28 213 patient. This thorough postoperative follow-up confirms that the number of recorded incidents of
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30 214 SSSI is accurate, and the follow-up time of 5 years is sufficient to reveal any potential cases of PJI.
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32 215 Similar studies have presented larger cohorts but only on registers (31, 32) or shorter follow-ups (1,
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34 216 2, 31). Our study exclusively includes patients with primary elective joint surgery to minimise the
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37 217 influence of other risk factors concatenated with the initial trauma (hip fractures) or extended impact
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39 218 on the tissue (revision surgery). This inclusion criterion is an additional strength of the study given
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42 219 that the rate of PJI is known to be higher after trauma and revision surgery (33).
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44 220 A potential limitation is the retrospective nature of the study design. Therefore, there may be
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46 221 inaccuracies or misinterpretations of information received from medical records. Another limitation
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48 222 is that SSSI is not culture-verified but determined by medical assessment, reflecting clinical reality.
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51 223 As in infection-related research in general in which a small number of infections is a major challenge,
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53 224 this study may have failed to detect a link between a potential risk factor and postoperative infection
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55 225 due to a type II error. A larger cohort would have been desirable.
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226 **Conclusion**

227 In conclusion, this study demonstrates that patients developing SSSI after primary elective hip or
228 knee arthroplasty have a great risk to progress into PJI. Older (≥ 65 years) obese patients seem to have
229 an increased risk of developing SSSI. Male gender is a significant patient-related risk factor to
230 progress from SSSI into PJI.

231 **Acknowledgement**

232 We thank Jakob Viklander for his valuable assistance during data compilation.

233 **Availability of data and materials**

234 The dataset generated and analysed during the current study are available from the corresponding
235 author on reasonable request.

236 **Competing interests**

237 The authors declare that they have no competing interests in this work.

238 **Funding**

239 This research received no specific grant from any funding agency in the public, commercial or not-
240 for-profit sectors.

241 **Authors' contributions**

242 Both authors (HE, SL) made substantial contributions to conception and design of the study
243 and in acquisition, analysis and interpretation of data. Both authors (HE, SL) have been
244 involved in drafting the manuscript and given final approval of the version to be published.

245 Both authors (HE, SL) have participated sufficiently in the work to take public responsibility
246 for appropriate portions of the content and agreed to be accountable for all aspects of the work
247 in ensuring that questions related to the accuracy or integrity of any part of the work are
248 appropriately investigated and resolved.

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2

3 **249 Abbreviations**

4 250 Superficial surgical site infection: SSSI; Periprosthetic joint infection: PJI; Total joint arthroplasty:

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6 251 TJA; Total hip arthroplasty: THA; Total knee arthroplasty: TKA; Body mass index: BMI; American

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8 252 Society of Anaesthesiologists classification: ASA classification; Rheumatologic disease: RA;

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10 253 Diabetes mellitus: DM; Adjusted RR: aRR.

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347 **Figure legends**

348 Figure 1. Directed acyclic graph for selecting confounders.

349 The circle with an arrow indicates the exposure; the circles with an (I) illustrate outcomes; and the circles
350 without text indicate confounders used in the statistical model.

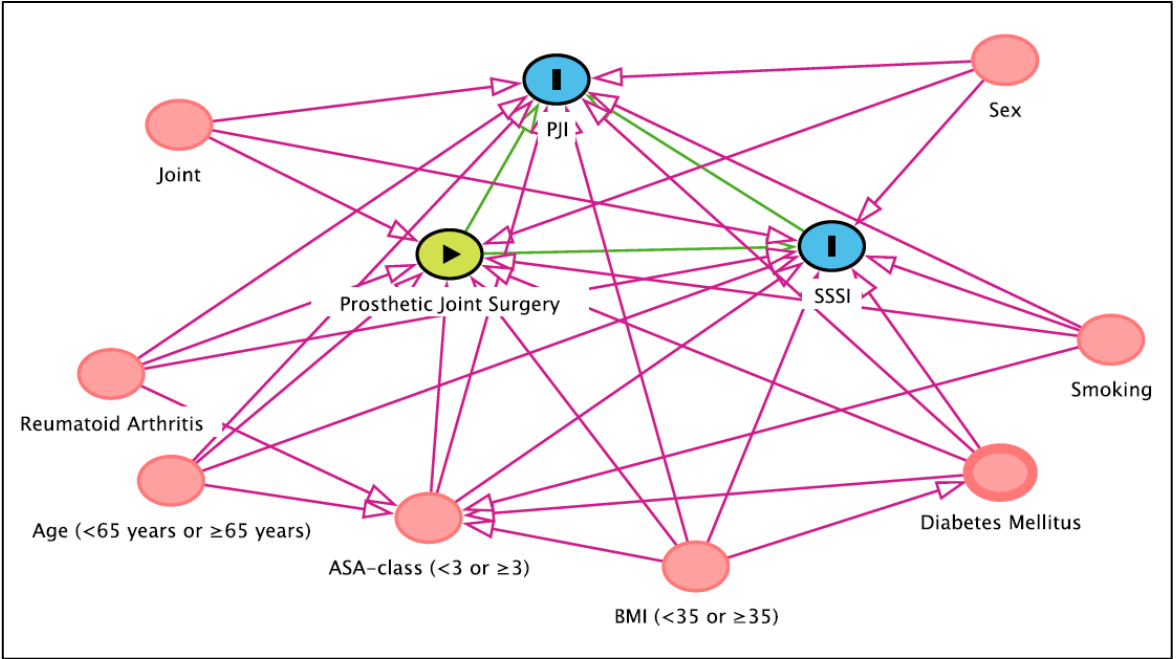
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352 Figure 2. Proportion of SSSI and PJI in the total cohort.

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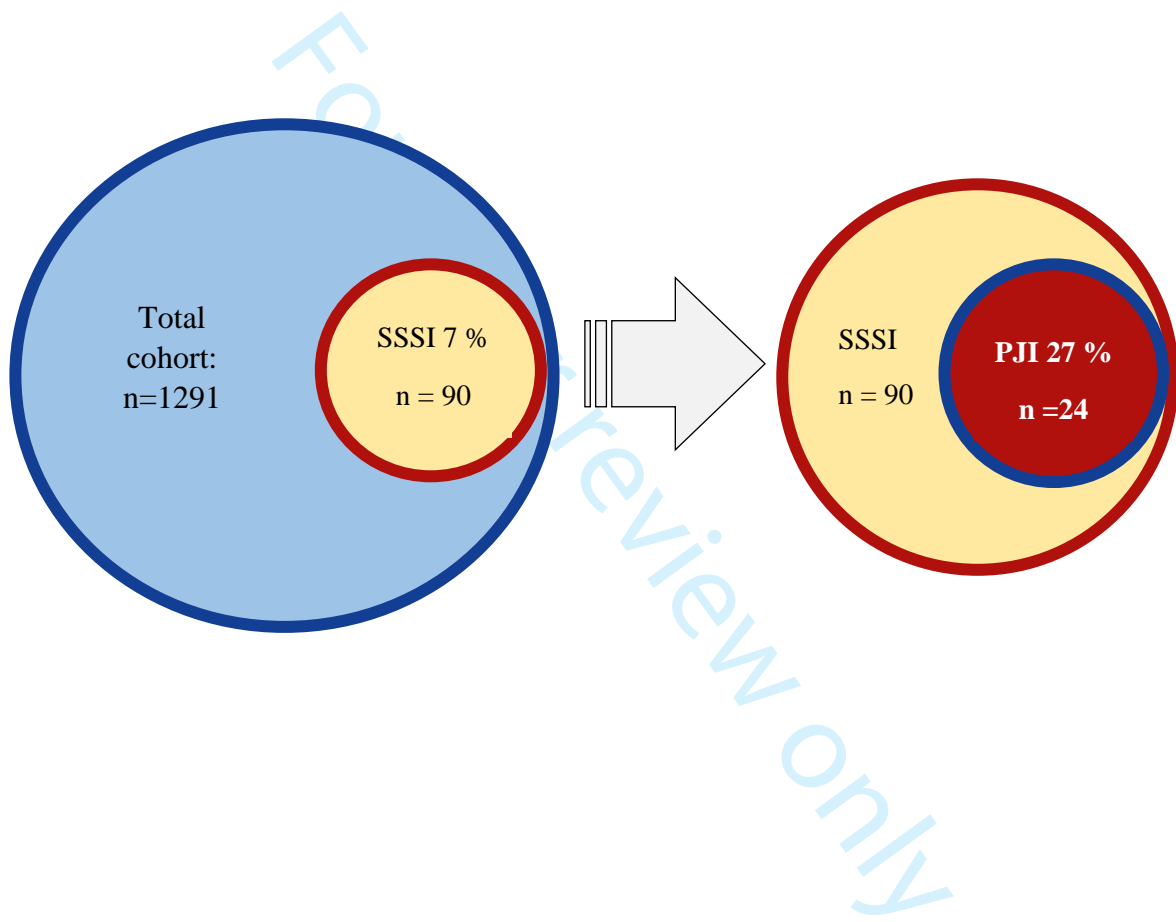
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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	na
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	na
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	5
		(b) Describe any methods used to examine subgroups and interactions	5
		(c) Explain how missing data were addressed	5
		(d) If applicable, describe analytical methods taking account of sampling strategy	na
		(e) Describe any sensitivity analyses	na
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	6
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest	6
Outcome data	15*	Report numbers of outcome events or summary measures	7
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	8 5 na
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Patient-related factors associated with superficial surgical site infection and the progression into a periprosthetic joint infection after elective primary total joint arthroplasty: a single-centre, retrospective study in Sweden

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Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Infectious diseases
Keywords:	Musculoskeletal disorders < ORTHOPAEDIC & TRAUMA SURGERY, Adult orthopaedics < ORTHOPAEDIC & TRAUMA SURGERY, Hip < ORTHOPAEDIC & TRAUMA SURGERY, Knee < ORTHOPAEDIC & TRAUMA SURGERY

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14 6 Running title: Patient-related factors associated with superficial surgical site infection and the
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16 7 progression into a periprosthetic joint infection after elective primary total joint arthroplasty
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28 14 **Declarations**

29
30 15 None of the authors have any conflict of interest to declare.

31 16 *Ethics approval*

32
33 17 The study design was reviewed and approved by the Human Research Ethics Committee in
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35 18 Uppsala, Sweden, Nr: 2019-01425.
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27 Abstract

28 **Objectives:** The incidence of superficial surgical site infection (SSSI) may increase the risk of
29 periprosthetic joint infection (PJI). The objective of this study is to identify patient-related risk factors
30 associated with SSSI and investigate their correlation with the progression of PJI. **Design:** In this
31 retrospective study 1,191 elective hip and knee prostheses were included. Patients were interviewed
32 ≥ 3 months after surgery to answer questions about the postoperative period. Patients' records were
33 reviewed to determine whether there had been any documentation of difficulties with wound-healing
34 or antibiotics were prescribed to treat an infection related to arthroplasty surgery. Diagnosed PJI was
35 determined by an orthopaedic surgeon in consultation with a consultant in infectious diseases.

36 **Setting:** This study was performed at Uppsala University Hospital.

37 **Participants:** 1,191 joints were included of which, 433 were knees and 758 hips. **Primary and
38 secondary outcome measures:** Which of the patient-related risk factors; joint, age, sex, the
39 American Society of Anaesthesiologists (ASA) classification body mass index (BMI), smoking,
40 diabetes and rheumatic disease associated with 1) superficial surgical site infection and 2) the
41 progress into periprosthetic joint infection.

42 **Results:** 84 (7%) of the total cohort developed an SSSI, of which 24 (29%) progressed to a PJI.
43 Factors found with increased adjusted risk ratio (aRR) for SSSI were: knee surgery (1.7; 95% CI: 1.1
44 – 2.7), age ≥ 65 years (1.7; 95% CI: 1.1 – 2.8), BMI ≥ 30 (1.9; 95% CI: 1.0 – 3.4) and ASA
45 classification ≥ 3 (1.7; 95% CI: 1.0 – 2.9). The factor with significant aRR for progression from SSSI
46 to PJI was ASA classification ≥ 3 (3.3; 95% CI: 1.0 – 10.3).

47 **Conclusions:** Patients developing SSSI have a great risk of progress into PJI. Older obese patients
48 with high ASA classification considered for elective total knee arthroplasty seem to have an increased
49 risk of developing SSSI. Patients with a high ASA classification have the highest risk of progressing
50 from SSSI into PJI.

51 **Strengths and limitations of this study**

- 52 • Strengths of this study are a large cohort size (n=1191)
- 53 • Meticulous follow-up of each patient and exclusive inclusion of patients with primary elective
54 arthroplasty surgery on hip or knee.
- 55 • Limitations of this study are the retrospective study design, small number of infections leading
56 to a potential risk of a type II error.

57 **Keywords**

58 Periprosthetic joint infection (PJI), superficial surgical site infection (SSSI), total joint arthroplasty
59 (TJA), risk factors.

60 **Introduction**

61 Infection after TJA can be defined as either superficial involving skin or subcutaneous tissue only (a
62 superficial surgical site infection, SSSI) or deep (periprosthetic joint infection, PJI) with deep soft
63 tissue involvement (e.g., fascial and muscle layers) and the prosthesis. The incidence of SSSI after
64 TJA can vary from 1 to 10% (1-3) and may increase the risk of subsequent PJI by up to 35 times (3).
65 The frequency of PJI ranges between 1 and 5% (4-7). Patient-related risk factors, such as obesity,
66 rheumatoid arthritis (RA), smoking, male sex, age, alcohol abuse, American Society of
67 Anaesthesiologists (ASA) classification >2 and diabetes mellitus (DM) (8-15), have been described
68 as risk factors for PJI but not confirmed as risk factors for SSSI. In clinical practice priority should
69 be to identify patients at high risk for SSSI and PJI, aiming for patient optimisation and the
70 opportunity to manage modifiable risk factors since it is essential to seize any opportunity to optimise
71 all prerequisites for the best achievable surgical outcome. Our primary objectives were to 1)
72 determine which patient-related factors are linked to SSSI and 2) investigate the progression into a
73 PJI.

74 **Methods**

75 *Study design*

76 This retrospective study of primary elective prostheses in hip or knee joints included patients in a
77 national project designed to lower the incidence of hospital-related infections (16). Patients included
78 in this study were treated at Uppsala University hospital from November 2008 to December 2012,
79 and interviewed ≥ 3 months after surgery to answer questions about the postoperative period. The
80 patients' records were reviewed to determine whether there had been any documentation of
81 difficulties with wound-healing or whether antibiotics were prescribed to treat an infection related to
82 arthroplasty surgery. An orthopedic consultant reviewed all information from the patients' records
83 (recorded from general practitioners or orthopedic consultants) including possible wound healing
84 problems or antibiotic prescription due to suspected postoperative infection. This information and the
85 results of the patient interview were taken under consideration in order to determine the occurrence
86 of SSSI. The diagnosed PJI was determined by a consultant orthopaedic surgeon in consultation with
87 a consultant in infectious diseases. In a retrospective review of patient records selected patients
88 fulfilled the criteria for PJI (17), but those criteria had not been used at diagnosis. Patient records
89 were reviewed for patient-related risk factors while a local arthroplasty register was used to obtain
90 perioperative information about whether revision surgery had been necessary due to persistent PJI.
91 Follow-up was a minimum of 5 years.

92 This study was limited to patient-related risk factors associated with developing an SSSI and focused
93 on those factors that might be possible to avoid or optimise preoperatively.

94 Consent for publication was considered in the application to the Human Research Ethics

95 Committee. However, no consent, verbal or written was needed, due to the retrospective study

96 design. The study design was reviewed and approved by the Human Research Ethics Committee
97 (Dnr: 2019-01425).

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2 100 *Patient and Public Involvement*

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5 101 Patients or the public were not involved in the development of the research question, outcome
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7 102 measures, the design, conduct, reporting, or dissemination plans of our research. The results of this
8
9 103 study will not be separately disseminated to study participants.

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11
12 104 *Study population*

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14 105 1,191 joints were included, of which 664 were men, 527 women, 433 were knees and 758 hips.

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16 106 Only cemented components were used in all knees. Hip prostheses were cemented, cementless or
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18 107 hybrids. In all cemented prostheses antibiotic-loaded cement with gentamycin was applied. All
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20 108 patients received systemic pre- and perioperative antibiotic prophylaxis in accordance with national
21
22 109 guidelines (cloxacillin, and in the case of penicillin allergy, clindamycin).

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25 110 *Confounders*

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28 111 Such patient-related factors as joint, sex, age, BMI, RA, ASA classification, smoking and DM were
29
30 112 considered clinically relevant confounders in the correlation between arthroplasty surgery and SSSI
31
32 113 or PJI. These specific patient-related variables have previously been linked to exposure and outcome
33
34 114 and are not considered in the causal pathway between potential risk factors and outcome (Figure 1).
35
36 115 Relevant confounders were analysed as categorical variables: ASA classification: <3 or ≥ 3 , for BMI
37
38 116 the WHO (World Health Organization)-classification was used and divided into the following groups:
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40 117 BMI <25 (under- and normal weight), $25 \leq \text{BMI} < 30$ (overweight) and BMI ≥ 30 (obesity class I-III),
41
42 118 and Age: <65 years or ≥ 65 years. Patients with DM included both type 1 and 2 (drug- or diet-treated).
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46 119 *Statistics*

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48 120 Descriptive statistics were used to summarise and report demographic characteristics.

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50 121 In an initial analysis logistic regression was performed, entering all covariates as singular variables.
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52 122 Crude risk ratios (RRs) for SSSI and PJI were calculated for each variable with 95% confidence
53
54 123 intervals (95% CIs). In the next step, the covariates were entered into the regression model, with RRs
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56 124 mutually adjusted for all covariates. Adjusted RRs (aRRs) for each covariate were calculated for the
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58 125 occurrence of SSSI or PJI and any progression of SSSI into PJI.
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126 All statistical analyses were performed using SPSS (version 26.0) and p-values ≤ 0.05 were
 127 considered statistically significant.

128 Results

129 The total number of surgeries for prosthetic hip or knee joints was 1,191. 84 joints (7%) developed
 130 an SSSI and 24 (2%) a PJI. Of the 84 joints with SSSI, 24 (29%) progressed to a PJI (Figure 2).

131 In the hip cohort (758) 40 joints (5%) developed an SSSI, and 11 (2%) a PJI. In the knee cohort (433),
 132 44 joints (10%) developed an SSSI and 13 (3%) a PJI (Table 1).

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Table 1. Number of postoperative infections

Variable	SSSI	PJI
Total cohort (1191)	84 (7.1%)	24 (2.0%)
Hip (758)	40 (5.3%)	11 (1.5%)
Knee (433)	44 (10.4%)	13 (3.1%)

SSSI (superficial surgical site infection), PJI (periprosthetic joint infection).

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Demographic characteristics of the cohorts are outlined in Table 2.

Table 2. Demographic characteristics

Variable	Total cohort	Hip	Knee	Range
	n = 1191	n = 758 (64%)	n = 433 (36%)	
Mean age (year)	63	61	65	18–96
Age				
<65	673 (56%)	447 (59%)	226 (52%)	
≥65	518 (44%)	331 (41%)	207 (48%)	
ASA-class^a				
≤2	964 (81%)	631 (84%)	333 (78%)	
≥3	210 (18%)	117 (16%)	93 (22%)	
Mean Body mass index	28	27	29	14–51
BMI				
BMI<25 ^b	356 (30%)	259 (34%)	97 (22%)	
25≤BMI<30	474 (40%)	307 (41%)	167 (39%)	
BMI≥30	361 (30%)	192 (25%)	169 (39%)	
Sex				
Woman	664 (56%)	387 (51%)	277 (64%)	
Man	527 (44%)	371 (49%)	156 (36%)	
Smoking^c				
No	1064 (90%)	673 (89%)	391 (90%)	
Yes	122 (10%)	81 (11%)	41 (10%)	
Diabetes				
No	1067 (90%)	686 (91%)	381 (88%)	
Yes	124 (10%)	72 (9%)	52 (12%)	
Rheumatological disease				
No	1052 (88%)	690 (91%)	362 (84%)	
Yes	139 (12%)	68 (9%)	71 (16%)	

ASA (American Society of Anaesthesiologists), BMI (Body mass index).

^a missing data in 17 cases

^b underweight 17 cases (BMI under 18.5)

^c missing data in 5 cases

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2 147 *Risk factors for SSSI*

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5 148 Risk factors with a significant crude RR for developing SSSI were knee surgery (2.0; 95% CI: 1.3 –
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7 149 3.2), age ≥ 65 years (1.8; 95% CI: 1.2 – 2.8), ASA classification ≥ 3 (2.4; 95% CI: 1.5 – 3.8) and
8
9 150 rheumatic disease (1.9; 95% CI: 1.1 – 3.3). Adjusting for all covariates, factors with significant aRRs
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11 151 for SSSI were knee surgery (1.7; 95% CI 1.1 – 2.7), age ≥ 65 years (1.7; 95% CI: 1.1 – 2.8), ASA
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13 classification ≥ 3 (1.7; 95% CI: 1.0 – 2.9) and BMI ≥ 30 (1.9; 95% CI: 1.0 – 3.4) (Table 3).
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16 **Table 3. Risk ratio (RR) for SSSI**

Variable	Crude RR (95 % CI)	P-value	Adjusted RR (95 % CI)	P-value
No SSSI	1107 (9%)			
SSSI	84 (7%)			
Joint				
Hip	ref		ref	
Knee	2.0 (1.3 - 3.2)	0.002	1.7 (1.1 - 2.7)	0.022
Age				
<65	ref		ref	
≥ 65	1.8 (1.2 - 2.8)	0.010	1.7 (1.1 - 2.8)	0.024
ASA class^a				
≤ 2	ref		ref	
≥ 3	2.4 (1.5 - 3.8)	0.001	1.7 (1.0 - 2.9)	0.038
Body mass index				
BMI < 25	ref		ref	
$25 \leq \text{BMI} < 30$	1.4 (0.8 - 2.2)	0.211	1.1 (0.6 - 2.0)	0.780
BMI ≥ 30	2.3 (0.9 - 5.5)	0.075	1.9 (1.0 - 3.4)	0.045
Sex				
Woman	ref		ref	
Men	1.1 (0.7 - 1.7)	0.677	1.1 (0.8 - 2.1)	0.298
Smoking^b				
No	ref		ref	
Yes	1.1 (0.5 - 2.3)	0.811	1.1 (0.5 - 2.3)	0.841
Diabetes				
No	ref		ref	
Yes	1.6 (0.9 - 3.1)	0.118	1.1 (0.6 - 2.2)	0.753
Rheumatological disease				
No	ref		ref	
Yes	1.9 (1.1 - 3.3)	0.031	1.7 (0.9 - 3.1)	0.089

153 ASA (American Society of Anaesthesiologists), BMI (Body mass index).

154 ^amissing data in 17 cases

155 ^bmissing data in 5 cases

156 *Risk factors for PJI*

157 The only risk factor with a significant crude RR for the development of PJI was ASA classification
158 ≥ 3 (4.8; 95% CI: 2.1 – 10.9). Factors with significant aRRs for PJI were ASA classification ≥ 3 (3.8;
159 95% CI: 1.6 – 9.1), and male sex (2.8; 95% CI: 1.2 – 6.9) (Supplementary table 1).

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2 160 *Risk factors for PJI in patients with SSSI*

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5 161 In the group of patients with SSSI, the only risk factor with a significant crude RR for the development
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7 162 of PJI was ASA classification ≥ 3 (3.0; 95% CI: 1.1 – 8.1). The adjusted relative risk shown for ASA
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9 163 classification was (3.3; 95% CI: 1.0 – 10.3) (Table 4).

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12 **Table 4. Risk ratio (RR) for PJI in patients with SSSI**

Variable	Crude RR (95 % CI)	P-value	Adjusted RR (95 % CI)	P-value
SSSI - no PJI 60 (71%)				
SSSI - PJI 24 (29%)				
Joint				
Hip	ref		ref	
Knee	1.1 (0.4 – 2.9)	0.836	1.3 (0.4 – 3.6)	0.663
Age				
<65	ref		ref	
≥ 65	1.5 (0.6 – 3.9)	0.404	2.0 (0.7 – 6.2)	0.212
ASA-class				
≤ 2	ref		ref	
≥ 3	3.0 (1.1 – 8.1)	0.030	3.3 (1.0 – 10.3)	0.044
Body Mass Index				
BMI<25	ref		ref	
25 \leq BMI<30	1.7 (0.6 – 5.0)	0.309	2.3 (0.5 – 9.6)	0.264
BMI ≥ 30	1.2 (0.5 – 3.1)	0.728	1.8 (0.5 – 7.1)	0.411
Sex				
Woman	ref		ref	
Men	2.5 (0.9 – 6.6)	0.065	2.8 (0.9 – 8.3)	0.064
Smoking				
No	ref		ref	
Yes	4.9 (0.5 – 51.1)	0.188	5.3 (0.5 – 54.4)	0.160
Diabetes				
No	ref		ref	
Yes	0.6 (0.2 – 2.0)	0.394	1.3 (0.3 – 5.7)	0.774
Rheumatological disease				
No	ref		ref	
Yes	1.2 (0.4 – 3.8)	0.792	1.1 (0.3 – 4.7)	0.883

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46 164 ASA (American Society of Anaesthesiologists), BMI (Body mass index).

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2 167 **Discussion**

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5 168 Identifying, mitigating, and optimising amenable risk factors for SSSI and PJI is a highly desirable
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7 169 approach for prevention of this devastating complication. The results of our study is relevant and
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10 170 offer new insight concerning the relationship between patient-related risk factors for SSSI and their
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12 171 correlation to the risk of PJI development. The risk and consequences of PJI after TJA is well
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14 172 described earlier (2, 5, 12). Further, the occurrence of SSSI is shown to increase the risk of
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16 173 subsequent PJI by up to 35 times (3). However, factors affecting the progression of SSSI into PJI
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19 174 have not been presented before. Identification and optimisation of risk factors for SSSI may decrease
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21 175 the risk of subsequent PJI.

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23 176 *Patient related risk factors for superficial surgical site infection*

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26 177 This study shows that knee surgery, age >65 years, a high ASA classification and obesity are
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28 178 independent risk factors for the development of SSSI after elective primary joint arthroplasty.

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30 179 Knee surgery seems to be a risk factor for developing SSSI after elective primary arthroplasty. Earlier
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32 180 studies have shown patients with knee prostheses to have a higher risk of PJI and to be in greater need
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35 181 of revision surgery than patients with hip prostheses (6, 8, 11, 18). Since there is less soft tissue
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37 182 around the knee than around the hip, meaning a shorter distance between skin and joint it is reasonable
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40 183 that the risk for superficial infection also is increased. The blood circulation around the knee area is
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42 184 more exposed to impact than the hip area and the perfusion is easier to disturb. Increased tourniquet
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44 185 time has been identified as an individual risk factor for deep infection and impaired wound healing
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46 186 and prolonged wound discharge after total knee arthroplasty (1), but this analysis is excluded from
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49 187 this study due to lack of this information.

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51 188 Age as a significant risk factor for SSSI shown in this study is congruent with results from a large
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53 189 (n=1,000) retrospective study (1) by Carroll et al. Elderly patients may have pre-existing medical
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55 190 conditions and fragile skin that can impair wound healing and cause SSSI.

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58 191 The correlation between a high ASA classification and infection after surgery may be explained due
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60 192 to that the ASA classification encapsulates several other known risk factors (e.g., smoking, DM and

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obesity). These risk factors have been independently associated with a higher risk of surgical site infection resulting from tissue hypoperfusion and subsequent impaired immunological function (12). In our study, obese patients have 1.9 times higher risk to develop SSSI after primary elective arthroplasty. Shohat et al. reported in a study including 19,000 patients that the risk for infection increases with higher BMI levels, though no threshold for PJI was observed (19). Our results are also in line with another large register-based study by Sayed-Noor et al. which observed that the risk of reoperation within 2 to 5 years increased in patients with higher BMI classification (obesity class I-III) (20). The association between BMI and postoperative wound complications may be explained by linked comorbidities such as DM type II (21), prolonged or more complicated arthroplasty surgery (22) and protracted postoperative wound drainage (23). Further, it has been proposed that although overweight and obese patients may not be calorie deficient, they may often be micronutrient and protein deficient (24-27). Thus can, malnutrition paradoxically be associated with increasing BMI. Patients with preoperative malnutrition are shown to have higher rates of comorbidities (congestive heart failure, previous cardiac surgery, hypertension, dyspnea, chronic obstructive pulmonary disease, renal disease requiring dialysis, stroke, diabetes, chronic corticosteroid use, bleeding disorders) (28). Higher rates of surgical site infection after total joint arthroplasty are shown in patients with hypoalbuminemia (29).

It has been described that RA is a risk factor on developing PJI after TJA. A systematic review by Kong et al. presented a significant odds ratio for PJI in RA patients with a THA of 1.75 (95% CI: 1.49 – 2.06) (11) and an odds ratio of 1.34 (95% CI: 1.18 – 1.52) in patients with a TKA. We found that RA had a significant crude RR for the development of SSSI after primary TJA. The risk was 1.7 times higher for RA patients than in patients without RA when adjusting for all covariates and was close to a statistically significance (Table 3). The significance of the association between RA and SSSI may be missed out in this analysis, due to the small number of infections and type II statistical error.

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2 219 *Patient related risk factors for development of deep surgical site infection*

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5 220 We found that superficial wound complications were associated with the development of PJI in 29%,
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7 221 and high ASA classification was the factor shown to be significant (3.3 times higher than patients
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9 222 with ASA<3) in the progression into PJI. ASA classification is a crude estimate of a patient's medical
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11 223 condition and has been associated with the risk of PJI in numerous previous reports (10, 11). Blanco
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14 224 et al. report a 15-fold odds ratio (95% CI: 6.54–35.80) for PJI in patients with ASA classification ≥ 3
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16 225 and another study by Panula et al. presented a hazard ratio of 3.2 (95% CI: 2.0–5.1) for the same ASA
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18 226 classification (30).

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21 227 In our analysis male sex was close to a significant risk factor for progression from SSSI into PJI both
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23 228 as singular variable and after adjustment for all covariates (2.8 times higher risk for men than women).

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26 229 A recent meta-analysis showed that male sex was a risk factor for PJI development, especially after
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28 230 total knee arthroplasty (TKA) (18). The link between male sex and PJI may be attributed to some
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30 231 contributing behavioural factors, including smoking, diet, hygiene and alcohol consumption, but the
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32 232 reasons behind this are not clear. Sex-related differences in immune response due to bacteria (e.g.,
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34 233 *Staphylococcus aureus* and *Pseudomonas aeruginosa*) have been reported. In addition, septicaemia
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37 234 and bacteraemia occur more frequently in males than females (21), but whether it will or will not
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39 235 affect the development of SSSI or PJI has yet to be investigated. The absence of statistically
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41 236 significance for male sex as a risk factor of developing PJI after SSSI can depend on the total number
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44 237 of infected patients including in our study.

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46 238 *Prevention of postoperative infection*

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48 239 The rate of SSSI (7%) and PJI (2%) in this study is consistent with international studies showing
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51 240 levels of SSSI ranging from 1-10% (1, 31) and PJI ranging from 0.2-2.23% (5-7). This work is
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53 241 focused on patient-related factors with a possible effect on the occurrence of SSSI or PJI after elective
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55 242 primary TJA. There are several other factors related to the surgery such as operation time,
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58 243 intraoperative blood loss, number of door openings, discipline in the operating room, antibiotic-
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60 244 prophylaxis used, surgeon's experience, that can affect the overall risk for postoperative infection, but

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3 245 those are not included in this current analysis. With the challenging complication of PJI and its major
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5 246 burden on patients (32) and health systems (33), prevention through the implementation of effective
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7 247 strategies is the first and best strategy and should be a priority. Identifying high-risk patients planning
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9 248 to undergo arthroplasty surgery and providing interventions, when possible, by modifying these risk
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11 249 factors, might form the basis of PJI prevention strategies in the future.

13 14 250 *Strengths*

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16 251 Two major strengths of this study are the large cohort size (n=1191) and the meticulous follow-up of
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18 252 each patient. This thorough postoperative follow-up confirms that the number of recorded incidents
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20 253 of SSSI is accurate, and the follow-up time of 5 years (mean 7.3; range: 5.1-9.2) years is sufficient to
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22 254 reveal any potential cases of PJI. Similar studies have presented larger cohorts but only on registers
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24 255 (32, 34) or shorter follow-ups (1, 2, 34).

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26 256 Additionally, our study exclusively includes patients with primary elective joint surgery to minimise
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28 257 the influence of other risk factors concatenated with the initial trauma (hip fractures) or extended
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30 258 impact on the tissue (revision surgery). This inclusion criterion is an additional strength of the study
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32 259 given that the rate of PJI is known to be higher after trauma and revision surgery (35). According to
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34 260 preoperative screening routines in our hospital patients with a history of excessive use of alcohol, IV
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36 261 drug use, poor oral hygiene or other medical conditions or medications that compromise immunity
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38 262 referred to our unit for primary arthroplasty are excluded from surgery or already rehabilitated before
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40 263 surgery.

41 42 264 *Limitations*

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44 265 A potential limitation is the retrospective nature of our study design. Therefore, there may be
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46 266 inaccuracies or misinterpretations of information received from medical records. However, all
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48 267 patients included in this study were interviewed in person to answer questions about the postoperative
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50 268 period and the information was in that way verified.

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52 269 Another limitation is that SSSI is not culture-verified but determined by a consultant orthopaedic
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54 270 surgeon which reflects the clinical reality. Cultures taken at a superficial infection can be misleading

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3 271 and classified as contamination, even if a possibility of a clinical significance of skin flora found in
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5 272 cultures recently has been raised (36).

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7 273 As in infection-related research in general in which a small number of infections is a major challenge,
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9 274 this study may have failed to detect a link between a potential risk factor and postoperative infection
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11 275 due to a type II error.

12 13 14 15 276 **Conclusion**

16
17 277 In conclusion, this study demonstrates that patients developing SSSI after primary elective hip or
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19 278 knee arthroplasty have a great risk to progress into PJI. Older obese patients with high ASA
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21 279 classification seem to have an increased risk of developing SSSI. A high ASA classification
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23 280 significantly affects the progression from SSSI into PJI.

24 25 26 27 281 **Acknowledgement**

28
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30 31 32 283 **Availability of data and materials**

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34 284 The dataset generated and analysed during the current study is available from the corresponding
35
36 285 author on reasonable request.

37 38 39 286 **Competing interests**

40
41 287 The authors declare that they have no competing interests in this work.

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47
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49 50 51 291 **Authors' contributions**

52
53 292 Both authors (HE, SL) made substantial contributions to conception and design of the study

54
55 293 and to acquisition, analysis and interpretation of data. Both authors (HE, SL) have been

56
57 294 involved in drafting the manuscript and given final approval of the version to be published.

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60 295 Both authors (HE, SL) have participated sufficiently in the work to take public responsibility

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3 296 for appropriate portions of the content and agreed to be accountable for all aspects of the work
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5 297 in ensuring that questions related to the accuracy or integrity of any part of the work are
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7 298 appropriately investigated and resolved.
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10 299 **Abbreviations**

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12 300 Superficial surgical site infection: SSSI; Periprosthetic joint infection: PJI; Total joint arthroplasty:
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14 301 TJA; Total hip arthroplasty: THA; Total knee arthroplasty: TKA; Body mass index: BMI; American
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16 302 Society of Anaesthesiologists classification: ASA classification; Rheumatologic disease: RA;
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19 303 Diabetes mellitus: DM; Adjusted RR: aRR.
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Figure legends

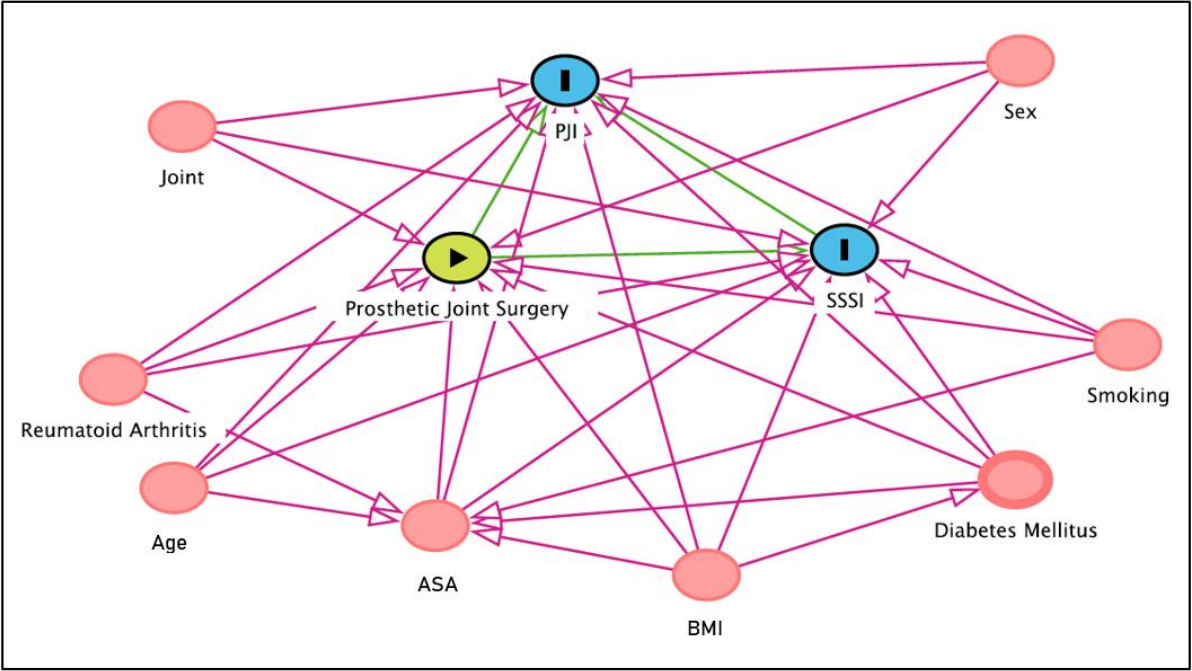
Figure 1. Directed acyclic graph for selecting confounders.

The circle with an arrow indicates the exposure; the circles with an (I) illustrate outcomes; and the circles without text indicate confounders used in the statistical model.

Figure 2. Proportion of SSSI and PJI in the total cohort

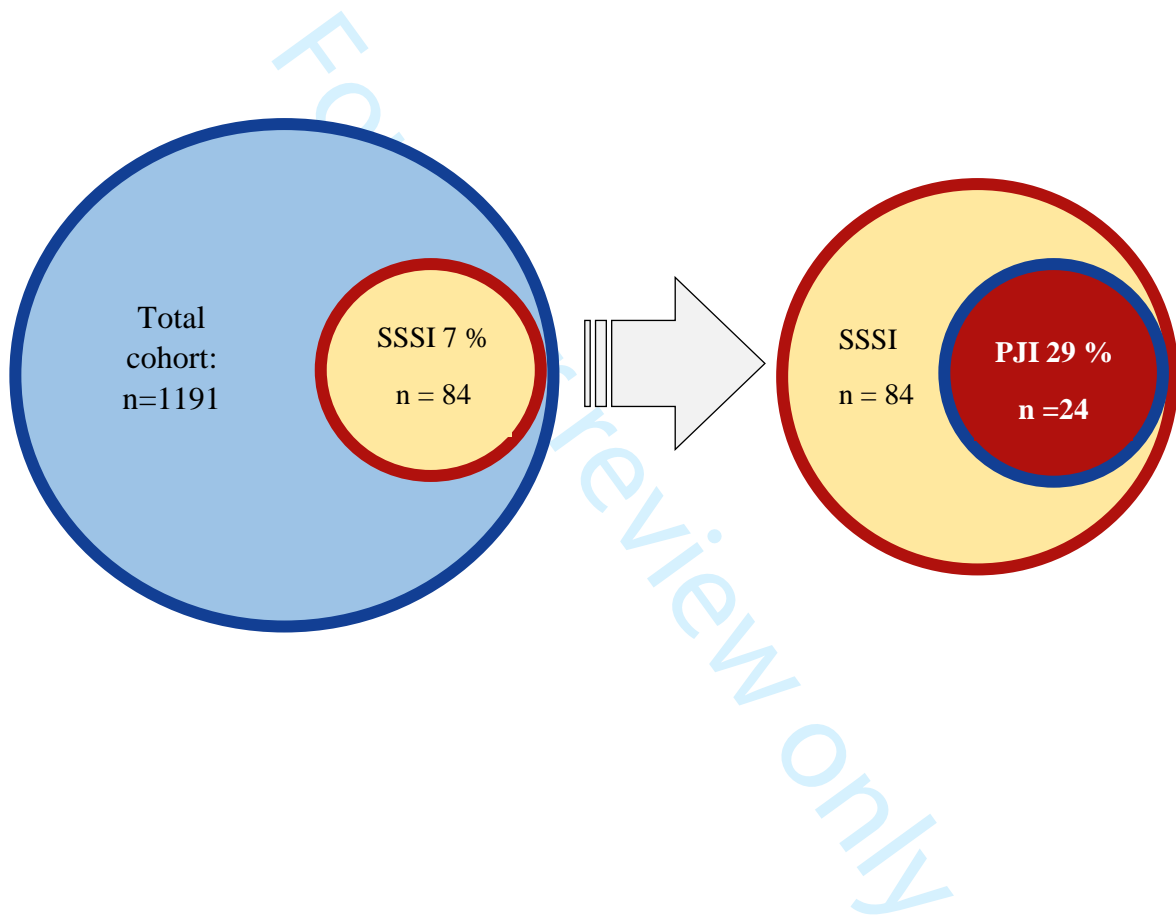
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Supplementary table 1. Risk ratio (RR) for PJI

SSSI - no PJI	1167 (98%)			
SSSI - PJI	24 (2%)			
Variable	Crude RR (95 % CI)	P-value	Adjusted RR (95 % CI)	P-value
Joint				
Hip	ref		ref	
Knee	2.1 (0.9 – 4.7)	0.073	2.0 (0.8 – 4.8)	0.112
Age				
<65	ref		ref	
≥65	1.3 (0.6 – 2.9)	0.517	1.1 (0.5 – 2.7)	0.781
ASA-class^a				
≤2	ref		ref	
≥3	4.8 (2.1 – 10.9)	0.000	3.8 (1.6 – 9.1)	0.003
Body Mass Index				
BMI<25	ref		ref	
25≤BMI<30	2.0 (0.8 – 5.1)	0.142	1.9 (0.6 – 5.9)	0.271
BMI≥30	1.9 (0.9 – 4.4)	0.110	1.2 (0.4 – 3.3)	0.772
Sex				
Woman	ref		ref	
Men	2.1 (0.9 – 4.9)	0.075	2.8 (1.2 – 6.9)	0.022
Smoking^b				
No	ref		ref	
Yes	2.7 (0.4 – 20.0)	0.338	2.5 (0.3 – 19.0)	0.379
Diabetes				
No	ref		ref	
Yes	2.3 (0.9 – 6.3)	0.101	1.4 (0.5 – 4.1)	0.543
Rheumatological disease				
No	ref		ref	
Yes	2.0 (0.8 -5.5)	0.166	1.8 (0.6 – 5.2)	0.294

ASA (American Society of Anaesthesiologists), BMI (Body mass index).

^amissing data in 17 cases

^bmissing data in 5 cases

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	na
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	na
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	5
		(b) Describe any methods used to examine subgroups and interactions	5
		(c) Explain how missing data were addressed	5
		(d) If applicable, describe analytical methods taking account of sampling strategy	na
		(e) Describe any sensitivity analyses	na
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	6
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest	6
Outcome data	15*	Report numbers of outcome events or summary measures	7
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	8 5 na
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Patient-related factors associated with superficial surgical site infection and progression to a periprosthetic joint infection after elective primary total joint arthroplasty: a single-centre, retrospective study in Sweden

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Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Infectious diseases
Keywords:	Musculoskeletal disorders < ORTHOPAEDIC & TRAUMA SURGERY, Adult orthopaedics < ORTHOPAEDIC & TRAUMA SURGERY, Hip < ORTHOPAEDIC & TRAUMA SURGERY, Knee < ORTHOPAEDIC & TRAUMA SURGERY

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3 1 **Patient-related factors associated with superficial surgical site**
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7 3 **elective primary total joint arthroplasty: a single-centre, retrospective**
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14 6 Running title: Patient-related factors associated with superficial surgical site infection and the
15 7 progression to a periprosthetic joint infection after elective primary total joint arthroplasty
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3 28 **Abstract**

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5 29 **Objectives:** Superficial surgical site infection (SSSI) may increase the risk of serious complications
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7 30 such as periprosthetic joint infection (PJI). This study aims to identify patient-related risk factors
8
9 31 associated with SSSI and investigate their correlation with the progression of PJI.

10 32 **Design:** In this retrospective study 1,191 elective hip and knee prostheses were included. Patients
11
12 33 were interviewed 3-5 months after surgery to answer questions about the postoperative period. Patient
13
14 34 records were reviewed to determine whether there had been any documentation of wound-healing
15
16 35 difficulties or whether antibiotics were prescribed to treat an infection related to arthroplasty surgery.

17 36 **Setting:** Uppsala University Hospital, patients treated between November 2008 to December 2012.

18 37 **Participants:** The study population comprised 433 knees and 758 hips.

19 38 **Outcome measures:** We studied patient-related risk factors (joint, age, sex, the American Society of
20
21 39 Anesthesiologists (ASA) classification, body mass index (BMI), smoking, diabetes and rheumatic
22
23 40 disease) to determine whether they were associated with 1) SSSI and 2) the progress from SSSI to
24
25 41 PJI.

26 42 **Results:** 84 (7%) patients of the total cohort developed SSSI. This infection progressed to a PJI in 24
27
28 43 (29%) of the patients. Factors with increased adjusted risk ratios (aRRs) for SSSIs were knee surgery
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30 44 (1.7; 95% confidence interval, CI: 1.1 – 2.7), age ≥ 65 years (1.7; 95% CI: 1.1 – 2.8), BMI ≥ 30 (1.9;
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32 45 95% CI: 1.0 – 3.4) and ASA classification ≥ 3 (1.7; 95% CI: 1.0 – 2.9). ASA classification ≥ 3 was the
33
34 46 only factor showing a significant progression from SSSI to PJI (aRR=3.3; 95% CI: 1.0 – 10.3).

35 47 **Conclusions:** The risk of progressing from a SSSI to a PJI is high. Older patients, patients with
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37 48 obesity, and those with a high ASA classification considered for elective total knee arthroplasty seem
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39 49 to have an increased risk of developing SSSI. Patients with a high ASA classification seem to have
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41 50 an increased risk of progressing from SSSI to PJI.

42 51

52 **Strengths and limitations of this study**

- 53 • Strengths of this study include the large cohort size (n=1,191) and careful follow-up of each
54 patient.
- 55 • Exclusive inclusion of patients with primary elective arthroplasty surgery on the hip or knee.
- 56 • Limitations of this study include the retrospective study design and the small number of
57 infections, leading to a potential risk of a type II error.

58 **Keywords**

59 Periprosthetic joint infection (PJI), superficial surgical site infection (SSSI), total joint arthroplasty
60 (TJA), risk factors.

61 **Introduction**

62 Infection after total joint arthroplasty (TJA) can be defined as either superficial involving skin or
63 subcutaneous tissue only (a superficial surgical site infection, SSSI) or deep (periprosthetic joint
64 infection, PJI) with deep soft tissue involvement (e.g., fascial and muscle layers) and the prosthesis.
65 The incidence of SSSI after TJA can vary from 1 to 10% (1, 2, 3) and may increase the risk of
66 subsequent PJI by 35-fold (3). The frequency of PJI ranges between 1 and 5% (4-7). Patient-related
67 risk factors, such as obesity, rheumatoid arthritis (RA), smoking, male sex, age, alcohol abuse,
68 American Society of Anesthesiologists (ASA) classification >2 and diabetes mellitus (DM) (8-16),
69 have been described as risk factors for PJI but not confirmed as risk factors for SSSI. In clinical
70 practice priority should be to identify high-risk patients for SSSI and PJI, aiming for optimal patient
71 outcomes and the opportunity to manage modifiable risk factors. It is essential to seize any possibility
72 to optimise all prerequisites for the best achievable surgical outcome. Thus, we sought to 1) determine
73 which patient-related factors are linked to SSSI and 2) investigate the progression from SSSI to PJI.

74 **Methods**

75 *Study design*

76 This retrospective study of primary elective prostheses in hip or knee joints included patients in a
77 national project designed to reduce the incidence of hospital-related infections (17). The study
78 patients were treated at Uppsala University Hospital from November 2008 to December 2012 and
79 interviewed 3-5 months after surgery to answer questions about the postoperative period. Patient
80 medical records were reviewed to determine whether there had been any documentation of difficulties
81 with wound healing or whether antibiotics were prescribed to treat an infection related to hip or knee
82 arthroplasty. An orthopaedic consultant reviewed all information from patient records (recorded from
83 general practitioners or orthopaedic consultants), including possible wound healing complications or
84 antibiotic prescriptions due to suspected postoperative infection. This information and the results of
85 the patient interview were used to determine the occurrence of SSSI. The diagnosis of PJI was made
86 by a consultant orthopaedic surgeon in consultation with a consultant in infectious diseases. In a
87 retrospective review of patient records selected patients met the criteria for PJI (18), but those criteria
88 were not used at the time of diagnosis. Patient records were reviewed for patient-related risk factors,
89 and a local arthroplasty register was used to obtain information about revision surgery that had been
90 necessary due to persistent PJI. This study was limited to patient-related risk factors associated with
91 the development of SSSI and focused on factors that may be avoidable or preoperatively optimised.
92 Consent for publication was considered in the application to the Human Research Ethics
93 Committee. Because this was a retrospective study, no consent (written or verbal) was needed for this
94 work. The study design was reviewed and approved by the Human Research Ethics Committee (Dnr:
95 2019-01425).

97 *Study population*

98 The study population comprised 664 men, 527 women and the study material included 1,191 joints
99 (433 knees, 758 hips). Hip prostheses were cemented, cementless or hybrids. Only cemented

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2 100 components were used in all knees. In all cemented prostheses antibiotic-loaded cement with
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5 101 gentamycin was applied. All patients received systemic pre- and perioperative antibiotic prophylaxis
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7 102 in accordance with national guidelines (cloxacillin, and in the case of penicillin allergy, clindamycin).
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9 103 *Confounders*

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11 104 Patient-related factors (e.g., joint, sex, age, body mass index (BMI), RA, ASA classification,
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14 105 smoking, DM) were considered clinically relevant for the association between arthroplasty and SSSI
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16 106 or PJI. These specific patient-related variables have previously been linked to exposure and outcome
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18 107 and are not considered in the causal pathway between potential risk factors and outcome (Figure 1).
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20
21 108 Relevant confounders were analysed as categorical variables: ASA classification (<3 or ≥3), age (<65
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23 109 years or ≥65 years) and DM (patients with DM included both type 1 and 2, drug- or diet-related). For
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25 110 BMI, the WHO (World Health Organisation) classification was used and divided into the following
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28 111 groups: BMI <25 (under and normal weight), 25 ≤BMI<30 (overweight) and BMI ≥30 (obesity class
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30 112 I-III).

31 32 113 *Statistics*

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35 114 Descriptive statistics were used to summarise and report demographic characteristics.

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37 115 In an initial analysis logistic regression was performed, entering covariates as single variables. Crude
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39 116 risk ratios (RRs) for SSSI and PJI were calculated for each variable with 95% confidence intervals
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42 117 (95% CIs). The covariates were entered into the regression model in the next step, with RRs mutually
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44 118 adjusted for all covariates. An adjusted RR (aRR) for each covariate was calculated for the occurrence
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46 119 of SSSI or PJI and any progression of SSSI to PJI.

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48 120 All statistical analyses were performed using SPSS (version 26.0) and p-values ≤0.05 were
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51 121 considered significant.

52 53 122 *Patient and public involvement*

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55 123 Patients or the public were not involved in developing the research questions, outcome measures, the
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58 124 design, conduct, reporting or dissemination plans of our research. The results of this study will not
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60 125 be distributed separately to study participants.

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Results

The number of surgeries for prosthetic hip or knee joints was 1,191. 84 joints (7%) developed an SSSI and 24 (2%) a PJI. Of the 84 joints with SSSI, 24 (29%) progressed to a PJI (Figure 2).

In the hip cohort (758) 40 joints (5%) developed an SSSI and 11 (2%) a PJI. In the knee cohort (433) 44 joints (10%) developed an SSSI and 13 (3%) a PJI (Table 1).

Table 1. Number of postoperative infections

Variable	SSSI	PJI
Total cohort (1,191)	84 (7.1%)	24 (2.0%)
Hip (758)	40 (5.3%)	11 (1.5%)
Knee (433)	44 (10.4%)	13 (3.1%)

SSSI (superficial surgical site infection), PJI (periprosthetic joint infection).

Demographic characteristics of the cohorts are outlined in Table 2.

Table 2. Cohort demographic characteristics

Variable	Total cohort n = 1,191	Hip n = 758 (64%)	Knee n = 433 (36%)	Range
Mean age (year)	63	61	65	18–96
Age				
<65	673 (56%)	447 (59%)	226 (52%)	
≥65	518 (44%)	331 (41%)	207 (48%)	
ASA-class				
≤2	964 (81%)	631 (84%)	333 (78%)	
≥3	210 (18%)	117 (16%)	93 (22%)	
Mean BMI	28	27	29	14–51
BMI				
BMI <25 ^b	356 (30%)	259 (34%)	97 (22%)	
25≤BMI<30	474 (40%)	307 (41%)	167 (39%)	
BMI ≥30	361 (30%)	192 (25%)	169 (39%)	
Sex				
Women	664 (56%)	387 (51%)	277 (64%)	
Men	527 (44%)	371 (49%)	156 (36%)	
Smoking^c				
No	1064 (90%)	673 (89%)	391 (90%)	
Yes	122 (10%)	81 (11%)	41 (10%)	
Diabetes				
No	1067 (90%)	686 (91%)	381 (88%)	
Yes	124 (10%)	72 (9%)	52 (12%)	
Rheumatological disease				
No	1052 (88%)	690 (91%)	362 (84%)	

Yes	139 (12%)	68 (9%)	71 (16%)
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ASA (American Society of Anesthesiologists), BMI (body mass index).

^a missing data in 17 cases

^b underweight 17 cases (BMI <18.5)

^c missing data in 5 cases

Risk factors for SSSI

Risk factors with a significant crude RR for developing SSSI were knee surgery (RR=2.0; 95% CI: 1.3 – 3.2), age ≥ 65 years (RR=1.8; 95% CI: 1.2 – 2.8), ASA classification ≥ 3 (RR=2.4; 95% CI: 1.5 – 3.8) and rheumatic disease (RR=1.9; 95% CI: 1.1 – 3.3). Adjusting for all covariates, factors with significant aRRs for SSSI were knee surgery (aRR=1.7; 95% CI 1.1 – 2.7), age ≥ 65 years (aRR=1.7; 95% CI: 1.1 – 2.8), ASA classification ≥ 3 (aRR=1.7; 95% CI: 1.0 – 2.9) and BMI ≥ 30 (aRR=1.9; 95% CI: 1.0 – 3.4) (Table 3).

Table 3. Risk ratio (RR) for SSSI

Variable	Crude RR (95 % CI)	P-value	Adjusted RR (95 % CI)	P-value
No SSSI 1107 (9%)				
SSSI 84 (7%)				
Joint				
Hip	ref		ref	
Knee	2.0 (1.3 – 3.2)	0.002	1.7 (1.1 – 2.7)	0.022
Age				
<65	ref		ref	
≥ 65	1.8 (1.2 – 2.8)	0.010	1.7 (1.1 – 2.8)	0.024
ASA class^a				
≤ 2	ref		ref	
≥ 3	2.4 (1.5 – 3.8)	0.001	1.7 (1.0 – 2.9)	0.038
BMI				
BMI <25	ref		ref	
25 \leq BMI <30	1.4 (0.8 – 2.2)	0.211	1.1 (0.6 – 2.0)	0.780
BMI ≥ 30	2.3 (0.9 – 5.5)	0.075	1.9 (1.0 – 3.4)	0.045
Sex				
Women	ref		ref	
Men	1.1 (0.7 – 1.7)	0.677	1.1 (0.8 – 2.1)	0.298
Smoking^b				
No	ref		ref	
Yes	1.1 (0.5 – 2.3)	0.811	1.1 (0.5 – 2.3)	0.841
Diabetes				
No	ref		ref	
Yes	1.6 (0.9 – 3.1)	0.118	1.1 (0.6 – 2.2)	0.753
Rheumatological disease				
No	ref		ref	
Yes	1.9 (1.1 – 3.3)	0.031	1.7 (0.9 – 3.1)	0.089

ASA (American Society of Anesthesiologists), BMI (body mass index).

^a missing data in 17 cases

^b missing data in 5 cases

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2 152 *Risk factors for PJI*

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5 153 The only risk factor with a significant crude RR for the development of PJI was ASA classification
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7 154 ≥ 3 (RR=4.8; 95% CI: 2.1 – 10.9). Factors with significant aRRs for PJI were ASA classification ≥ 3
8
9 155 (aRR=3.8; 95% CI: 1.6 – 9.1) and male sex (aRR=2.8; 95% CI: 1.2 – 6.9) (Supplementary Table 1).

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12 156 *Risk factors for PJI in patients with SSSI*

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14 157 The only risk factor with a significant crude RR for the development of PJI in the SSSI group was
15
16 158 ASA classification ≥ 3 (RR=3.0; 95% CI: 1.1 – 8.1). The aRR shown for ASA classification was 3.3
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18 159 (95% CI: 1.0 – 10.3) (Table 4).

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21 **Table 4. Risk ratio (RR) for PJI in patients with SSSI**

Variable	Crude RR (95 % CI)	P-value	Adjusted RR (95 % CI)	P-value
SSSI – no progression to PJI				
	60 (71%)			
SSSI – progression to PJI				
	24 (29%)			
Joint				
Hip	ref		ref	
Knee	1.1 (0.4 – 2.9)	0.836	1.3 (0.4 – 3.6)	0.663
Age				
<65	ref		ref	
≥ 65	1.5 (0.6 – 3.9)	0.404	2.0 (0.7 – 6.2)	0.212
ASA class				
≤ 2	ref		ref	
≥ 3	3.0 (1.1 – 8.1)	0.030	3.3 (1.0 – 10.3)	0.044
BMI				
BMI <25	ref		ref	
25 \leq BMI <30	1.7 (0.6 – 5.0)	0.309	2.3 (0.5 – 9.6)	0.264
BMI ≥ 30	1.2 (0.5 – 3.1)	0.728	1.8 (0.5 – 7.1)	0.411
Sex				
Women	ref		ref	
Men	2.5 (0.9 – 6.6)	0.065	2.8 (0.9 – 8.3)	0.064
Smoking				
No	ref		ref	
Yes	4.9 (0.5 – 51.1)	0.188	5.3 (0.5 – 54.4)	0.160
Diabetes				
No	ref		ref	
Yes	0.6 (0.2 – 2.0)	0.394	1.3 (0.3 – 5.7)	0.774
Rheumatological disease				
No	ref		ref	
Yes	1.2 (0.4 – 3.8)	0.792	1.1 (0.3 – 4.7)	0.883

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57 160 ASA (American Society of Anesthesiologists), BMI (body mass index).

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162 Discussion

163 Identifying, mitigating and optimising risk factors for SSSI and PJI is a desirable approach to prevent
164 this devastating complication. The results of our study are relevant and provide new insight into the
165 relationship between patient-related risk factors for SSSI and their association with the risk of PJI
166 development. The risk and consequences of PJI after TJA have been described elsewhere (2, 5, 12).
167 It has been reported that the occurrence of SSSI increases the risk of PJI by up to 35 times (3).
168 However, factors affecting the progression from SSSI to PJI have not been investigated. Identifying
169 and optimising risk factors for SSSI may decrease the risk of PJI.

170 *Patient-related risk factors for superficial surgical site infection*

171 This study shows that knee surgery, age >65 years, a high ASA classification (≥ 3) and obesity (BMI
172 >30) are independent risk factors for developing SSSI after elective primary joint arthroplasty.

173 Knee surgery seems to be a risk factor for developing SSSI after elective primary arthroplasty. Studies
174 have shown that patients with knee prostheses have a higher risk of PJI and are in greater need of
175 revision surgery than patients with hip prostheses (6, 9, 12, 19). Because there is less soft tissue
176 around the knee than around the hip, meaning a shorter distance between skin and joint, the risk of
177 superficial infection is also increased. Blood circulation around the knee area is more exposed to
178 impact than the hip area and perfusion is more easily disturbed. Increased tourniquet time has been
179 identified as an individual risk factor for deep infection, impaired wound healing and prolonged
180 wound discharge after total knee arthroplasty (TKA) (1). However, due to a lack of data, this analysis
181 could not be included in this study.

182 Our finding that age is a significant risk factor for SSSI is congruent with the results from a large
183 (n=1,000) retrospective study (1). Older patients (≥ 65 years) may have pre-existing medical
184 conditions and fragile skin that could impair wound healing, making them more susceptible to SSSI.

185 The correlation between a high ASA score and infection after surgery can be explained because the
186 ASA classification encapsulates several other known risk factors (e.g., smoking, DM, obesity). These

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2 187 risk factors have been independently associated with a higher risk of surgical site infection due to
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5 188 tissue hypoperfusion and subsequent impaired immunological function (13).

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7 189 Our obese patients have a 1.9 times higher risk of SSSI after primary elective arthroplasty. Shohat et

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9 190 al. reported in a study including 19,000 patients that the risk for infection increases with higher BMI

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11 191 levels, although no BMI threshold was observed (20). Our results align with another large register-

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14 192 based study that reported an increased risk of reoperation in patients with higher BMI classification

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16 193 (obesity class I-III) (21). The association between BMI and postoperative wound complications may

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18 194 be explained by linked comorbidities (e.g., DM type II) (22), prolonged or more complicated

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20 195 arthroplasty surgery (23) and protracted postoperative wound drainage (24). It has also been

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22 196 suggested that, although overweight and obese patients may not be calorie deficient, they are often

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24 197 micronutrient and protein deficient (25-28). Thus, malnutrition can be linked to increased BMI.

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26 198 Patients with preoperative malnutrition have higher rates of comorbidities (congestive heart failure,

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28 199 previous cardiac surgery, hypertension, dyspnoea, chronic obstructive pulmonary disease, renal

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30 200 disease requiring dialysis, stroke, diabetes, chronic corticosteroid use, bleeding disorders) (29).

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32 201 Higher rates of surgical site infection after TJA are shown in patients with hypoalbuminemia (30).

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34 202 It has been described that RA is a risk factor for developing PJI after TJA. A systematic review

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36 203 presented a significant odds ratio (OR) for PJI in RA patients with a THA of 1.75 (95% CI: 1.49 –

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38 204 2.06) (12) and an OR of 1.34 (95% CI: 1.18 – 1.52) in patients with a TKA. We found that RA had a

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40 205 significant crude RR for developing SSSI after primary TJA. The risk was 1.7 times higher for

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42 206 patients with RA than those without RA when adjusting for all covariates, although this risk

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44 207 difference was not statistically significant (Table 3). The significance of the association between RA

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46 208 and SSSI may have gone undetected in this analysis because of the small number of infections and

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48 209 type II statistical error.

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53 211 *Patient-related risk factors for the development of deep surgical site infection*

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2 212 We found that superficial wound complications were associated with developing PJI in 29% of our
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5 213 patients, with high ASA classification (3.3 times higher than patients with ASA <3) a determining
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7 214 factor in the progression from SSSI to PJI. ASA classification is a crude estimate of a patient's medical
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9 215 condition and a high score has been associated with the risk of PJI in numerous reports (11, 12). For
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11 216 instance, Blanco et al. reported a 15-fold OR (95% CI: 6.54–35.80) for PJI in patients with ASA
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13
14 217 classification ≥ 3 and Panula et al. presented an HR of 3.2 (95% CI: 2.0–5.1) for the same ASA
15
16 218 classification (31).

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18 219 A recent meta-analysis showed that male sex was a risk factor for PJI development, especially after
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21 220 TKA (19). In our analysis male sex was close to a significant risk factor for progression from SSSI
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23 221 into PJI, both as a single variable and after adjustment for all covariates (2.8 times higher risk for
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25 222 men than women). The link between male sex and PJI may be attributed to certain contributing
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28 223 behavioural factors, including smoking, diet, hygiene and alcohol consumption, but the underlying
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30 224 reasons for this are unclear. Sex-related differences in immune response due to bacteria (e.g.,
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32 225 *Staphylococcus aureus* and *Pseudomonas aeruginosa*) have been reported. In addition, septicaemia
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34 226 and bacteraemia occur more frequently in males than females (32), but whether they will affect the
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37 227 development of SSSI or PJI has yet to be determined. The absence of statistical significance for male
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39 228 sex as a risk factor of developing PJI after SSSI can depend on the total number of infected patients
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42 229 in our study.

43 44 230 *Prevention of postoperative infection*

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46 231 The rate of SSSI (7%) and PJI (2%) in this study is consistent with international studies showing
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48 232 levels of SSSI ranging from 1-10% (1, 33) and PJI ranging from 0.2-2.23% (5, 6, 8). The present
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51 233 work is focused on patient-related factors with a possible effect on the occurrence of SSSI or PJI after
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53 234 elective primary TJA. Several other factors related to the surgery (e.g., operation time, intraoperative
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55 235 blood loss, number of door openings, discipline in the operating room, antibiotic-prophylaxis used,
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58 236 surgeon's experience) may affect the risk of postoperative infection. However, those factors are not
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60 237 included in our analysis. With the challenging complexity of PJI and its heavy burden on patients

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2 238 (34) and healthcare systems (35), prevention through effective strategies is the first and best approach
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5 239 and should be prioritized. Identifying high-risk patients planning to undergo arthroplasty surgery and
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7 240 providing interventions when possible by modifying these risk factors might form the basis of PJI
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9 241 prevention strategies in the future.

11 242 *Strengths*

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14 243 Two major strengths of this study are the large sample size (n=1,191) and the meticulous follow-up
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16 244 of each patient. This thorough postoperative follow-up confirms that the number of recorded incidents
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18 245 of SSSI is accurate, and the follow-up time of 5 (mean 7.3; range 5.1-9.2) years is sufficient to reveal
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21 246 potential cases of PJI. Similar studies have presented larger cohorts but only on registers (36, 37) or
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23 247 shorter follow-ups (1, 2, 36).

25 248 Additionally, our study includes patients with primary elective joint surgery to minimise the influence
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28 249 of other risk factors connected to the initial trauma (hip fractures) or extended impact on the tissue
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30 250 (revision surgery). This inclusion criterion is an additional strength of the study given that the rate of
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32 251 PJI is known to be higher after trauma and revision surgery (38). According to preoperative screening
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35 252 routines in our hospital, patients with a history of excessive alcohol use, intravenous drug use, poor
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37 253 oral hygiene or other medical conditions or medications that compromise immunity are excluded
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39 254 from surgery or rehabilitated before surgery.

41 255 *Limitations*

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44 256 A potential limitation is the retrospective nature of our study design. Therefore, there may be
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46 257 inaccuracies or misinterpretations of information retrieved from medical records. All our patients,
47
48 258 however, were interviewed in person to answer questions about the postoperative period. Thus, the
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51 259 information from medical reports was verified.

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53 260 Another limitation is that SSSI is not culture-verified but determined by a consultant orthopaedic
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55 261 surgeon that reflects the clinical reality. Cultures of a superficial infection can be misleading, which
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58 262 can be classified as contamination, even if a possibility of a clinical significance of skin flora found
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60 263 in cultures has recently been reported (39).

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264 As in infection-related research in general, where a small number of infections are a major challenge,
265 this study may have failed to detect an association between a potential risk factor and postoperative
266 infection due to a type II error.

267 **Conclusion**

268 In conclusion, this study demonstrates that older obese patients with a high ASA classification may
269 have an increased risk of developing SSSI. Patients developing SSSI after primary elective hip or
270 knee arthroplasty have a high risk of progressing into PJI and a high ASA classification significantly
271 affects the progression from SSSI to PJI.

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6
7 290 **Ethics approval**

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10 291 The study design was reviewed and approved by the Human Research Ethics Committee in
11
12 292 Uppsala, Sweden, Nr: 2019-01425.

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14 293 **Data availability statement**

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17 294 The dataset generated and analysed during the current study is available from the corresponding
18
19 295 author on reasonable request.

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21
22 296 **Competing interests**

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24
25 297 The authors declare that they have no competing interests in this work.

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39
40 303 and acquisition, analysis and interpretation of data. Both authors (HE, SL) have been
41
42 304 involved in drafting the manuscript and given final approval of the version to be published.

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45 305 Both authors (HE, SL) have participated sufficiently in the work to take public responsibility
46
47 306 for appropriate portions of the content and agreed to be accountable for all aspects of the work
48
49 307 in ensuring that questions related to the accuracy or integrity of any part of the work are
50
51 308 appropriately investigated and resolved.

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53
54 309 **Abbreviations**

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56 310 Superficial surgical site infection: SSSI; Periprosthetic joint infection: PJI; Total joint arthroplasty:
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59 311 TJA; Total hip arthroplasty: THA; Total knee arthroplasty: TKA; Body mass index: BMI; American
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2 312 Society of Anesthesiologists classification: ASA classification; Rheumatologic disease: RA; Diabetes
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5 313 mellitus: DM; Risk ratios RR; Adjusted RR: aRR.
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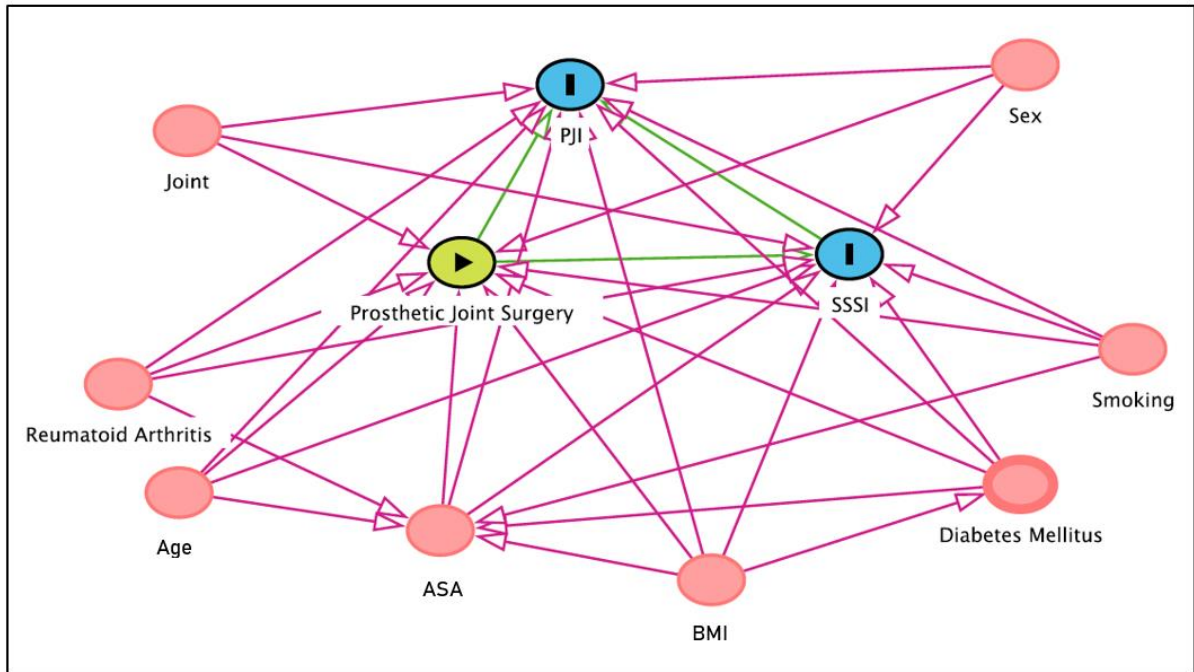
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Figure legends

Figure 1. Directed acyclic graph for the selection of confounders

The circle with an arrow indicates the exposure, the circles with an (I) illustrate outcomes and the circles without text indicate confounders used in the statistical model.

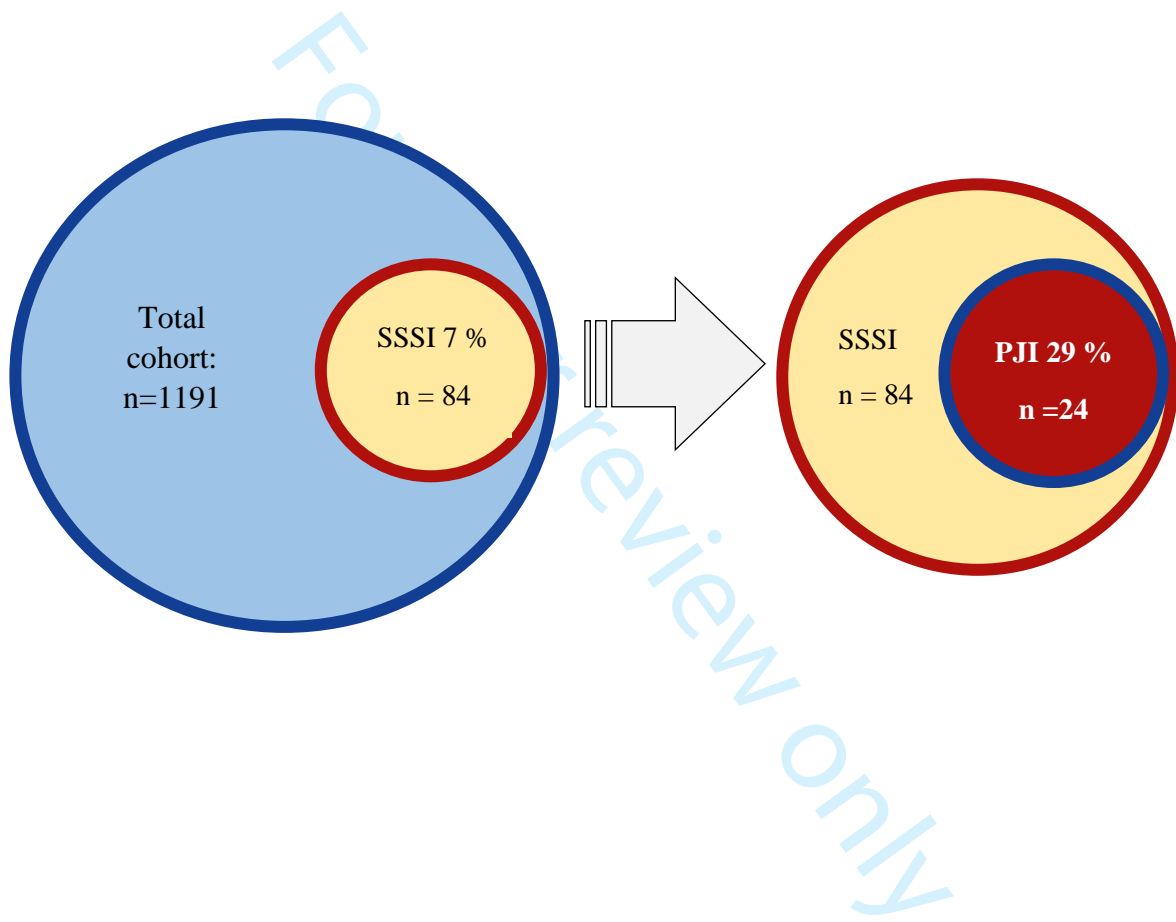
Figure 2. Proportion of SSSI and PJI in the total cohort



For review only

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Supplementary Table 1. Risk ratio (RR) for PJI

SSSI - no PJI	1167 (98%)			
SSSI - PJI	24 (2%)			
Variable	Crude RR (95 % CI)	P-value	Adjusted RR (95 % CI)	P-value
Joint				
Hip	ref		ref	
Knee	2.1 (0.9 – 4.7)	0.073	2.0 (0.8 – 4.8)	0.112
Age				
<65	ref		ref	
≥65	1.3 (0.6 – 2.9)	0.517	1.1 (0.5 – 2.7)	0.781
ASA-class^a				
≤2	ref		ref	
≥3	4.8 (2.1 – 10.9)	0.000	3.8 (1.6 – 9.1)	0.003
BMI				
BMI<25	ref		ref	
25≤BMI<30	2.0 (0.8 – 5.1)	0.142	1.9 (0.6 – 5.9)	0.271
BMI≥30	1.9 (0.9 – 4.4)	0.110	1.2 (0.4 – 3.3)	0.772
Sex				
Woman	ref		ref	
Men	2.1 (0.9 – 4.9)	0.075	2.8 (1.2 – 6.9)	0.022
Smoking^b				
No	ref		ref	
Yes	2.7 (0.4 – 20.0)	0.338	2.5 (0.3 – 19.0)	0.379
Diabetes				
No	ref		ref	
Yes	2.3 (0.9 – 6.3)	0.101	1.4 (0.5 – 4.1)	0.543
Rheumatological disease				
No	ref		ref	
Yes	2.0 (0.8 -5.5)	0.166	1.8 (0.6 – 5.2)	0.294

ASA (American Society of Anaesthesiologists), BMI (Body mass index).

^a missing data in 17 cases

^b missing data in 5 cases

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	na
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	na
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	5
		(b) Describe any methods used to examine subgroups and interactions	5
		(c) Explain how missing data were addressed	5
		(d) If applicable, describe analytical methods taking account of sampling strategy	na
		(e) Describe any sensitivity analyses	na
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	6
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest	6
Outcome data	15*	Report numbers of outcome events or summary measures	7
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	8 5 na
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.