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Increased early mortality after total knee arthroplasty using conventional instrumentation compared to technology-assisted surgery: an analysis of linked national registry data.

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3 **1 Title**
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6 2 Increased early mortality after total knee arthroplasty using conventional instrumentation
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8 3 compared to technology-assisted surgery: an analysis of linked national registry data.
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15 26 **ABSTRACT**

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18 27 **Objectives**

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22 28 This study aims to compare early mortality after total knee arthroplasty (TKA) using
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24 29 conventional intramedullary instrumentation to TKA performed using technology-assisted
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26 30 (non-intramedullary) instrumentation.

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29 31 **Design**

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32 32 Comparative observational study. Using data from a large national registry from 2003 to 2019
33
34 33 inclusive, the 30-day mortality after unilateral TKA performed for osteoarthritis was compared
35
36 34 between procedures using conventional instrumentation and those using technology-assisted
37
38 35 instrumentation. Firth logistic regression was used to calculate odds ratios, adjusting for age,
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40 36 sex, use of cement and procedure year for the whole period, and additionally adjusting for
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42 37 American Society of Anesthesiologists (ASA) physical status classification system class and
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44 38 body mass index (BMI) for the period 2015 to 2019. The analyses were repeated for 90-day
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46 39 mortality.

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51 52 **Setting**

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54 55 National arthroplasty registry.

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57 58 **Participants**

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3 43 People undergoing unilateral, elective TKR for osteoarthritis from 2003 to 2019 inclusive.
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6 44 **Interventions**
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9 45 TKA performed using conventional intramedullary instrumentation and TKR performed using
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11 46 technology-assisted instrumentation.
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15 47 **Main outcome measures**
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18 48 30- and 90-day mortality.
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21 49 **Results**
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24 50 A total of 581,818 unilateral TKA procedures performed for osteoarthritis were included, of
25
26 51 which 602 (0.10%) and 1,159 (0.20%) died within 30 and 90 days of surgery, respectively. The
27
28 52 odds ratio of death within 30 days following TKA performed with conventional
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30 53 instrumentation compared to technology-assisted instrumentation, adjusted for age, sex,
31
32 54 cement use, procedure year, ASA and BMI was 1.72 (95% CI, 1.23 to 2.41, p=0.001). The
33
34 55 corresponding odds ratios for 90-day mortality was 1.35 (95% CI, 1.07 to 1.69, p=0.010).
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39 56 **Conclusions**
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42 57 The use of conventional instrumentation during TKA is associated with higher odds of early
43
44 58 post-operative death than when technology-assisted instrumentation is used. This difference
45
46 59 may be explained by complications related to fat embolism secondary to the use of
47
48 60 intramedullary rods used in conventional instrumentation. Given the high number of TKA
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50 61 performed annually worldwide, increasing the use of technology-assisted instrumentation may
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52 62 reduce early post-operative mortality.
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58 64 **Strengths and limitations of this study**
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- 65 • Use of national linked data
- 66 • Large sample size
- 67 • Adjustment for known likely confounders
- 68 • Observational study design (possible unmeasured confounders)

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69 INTRODUCTION

70 Total knee arthroplasty (TKA) is a common procedure for severe osteoarthritis of the knee,
71 with an average annual rate of 135 per 100,000 population in contributing OECD countries and
72 226 per 100,000 in Australia.^{1,2} Conventional instrumentation for TKA surgery requires the
73 insertion of a long intramedullary rod into the femur (and sometimes the tibia) which is then
74 used as a reference for alignment of the cutting blocks applied to the bone for prosthesis
75 preparation. This insertion creates fat and bone marrow embolization, as shown by
76 transesophageal echocardiography and analysed by biopsy.³ The embolic material may
77 produce fat embolism syndrome, which includes respiratory, cardiac, haematological, and
78 neurological complications and sudden death.⁴⁻⁶ Over the last two decades, three new
79 techniques have been introduced that allow alignment to be referenced without intramedullary
80 instrumentation. These technology-assisted instrumentation techniques are computer
81 navigation, image-derived instrumentation and robotic assistance. Although these techniques
82 were developed to improve post-operative alignment, evidence for this is variable. Computer
83 navigation has demonstrated improved alignment compared to standard instruments, however,
84 there is mixed evidence that revision rates or patient reported outcomes are superior using this
85 technique.⁷⁻¹³ However, trials comparing any of these newer techniques to conventional
86 instrumentation were underpowered to detect early mortality post-operatively, which has been
87 decreasing over time and is currently approximately 0.1% at 30 days.^{14,15}

88 This study aims to compare the 30-day all-cause mortality after TKA between procedures
89 performed using conventional intramedullary instrumentation to those performed using
90 technology-assisted instrumentation using data from a large national registry.

91 METHODS

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3 92 The Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR) is
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5 93 a national registry with near complete (over 98%) coverage of TKA procedures performed in
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7 94 Australia since 2003.² AOANJRR data from January 2003 to December 2019 for patients
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9 95 undergoing unilateral TKA for osteoarthritis were used. Patients undergoing bilateral same-
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11 96 day primary TKA or any primary TKA within 90 days of a contralateral primary TKA were
12
13 97 excluded. AOANJRR data include patient-identified data and surgical variables, which
14
15 98 includes the use of assistive technology, and these data are linked to the National Death Index
16
17 99 twice yearly to record fact and date of death. The AOANJRR has collected data on American
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19 100 Society of Anesthesiologists (ASA) class¹⁶ (a measure of comorbidity and mortality risk) since
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21 101 2012 and body mass index (BMI) since 2015.

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27 102 The increased mortality associated with TKA is maximal within 30 days but may extend to 90
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29 103 days post surgery.^{17,18} Therefore, 30-day mortality was chosen as the primary outcome and 90-
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31 104 day mortality was chosen as a secondary outcome. Age, sex, use of bone cement, ASA class
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33 105 and BMI were chosen as potential confounders due to their known association with mortality.
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35 106 Procedure year was added as a covariate due to the increase in the proportion of cases using
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37 107 technology-assisted instrumentation over time and, because 30-day mortality has been
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39 108 decreasing over time.¹⁴

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44 109 Technology-assisted surgery was defined as any procedure using computer navigation, image
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46 110 derived instrumentation (IDI) or robotic assistance. Computer navigation involves the use of a
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48 111 tracking device, most commonly an infrared camera, and a computer. Rigid reference arrays
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50 112 are attached to the patient and a registration process enables the software to determine the
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52 113 patient's anatomy and accurately track instruments to assist surgery. The surgeon then makes
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54 114 the appropriate bone cuts and monitors the alignment of the knee. Robotic assistance uses
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56 115 similar principles, but a robotic arm guides the cutting tools to facilitate the surgery. Both these
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58 116 techniques allow intra operative verification of the component position. IDI is the use of

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3 117 individualised custom-made 3D printed guides or cutting blocks derived from pre-operative
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5 118 CT or MRI scans of the patient's knee. These guides or blocks are used to perform the required
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8 119 bone cuts and are specific to each patient's anatomy. Conventional instrumentation was defined
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10 120 as any procedure not using any of the technology-assisted methods. Cause of death was not
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12 121 used, as multiple causes are often reported, it may be inconsistently reported,¹⁹ and it is less
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14 122 relevant than overall mortality.

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16
17 123 Between-group differences in mortality were expressed as odds ratios, calculated by logistic
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19 124 regression adjusting for age, sex and procedure year. Due to low numbers of deaths, Firth
20
21 125 logistic regression (which uses penalized likelihood) was used to avoid the small sample bias
22
23 126 inherent in regression using conventional maximum likelihood estimation.²⁰ Adjusted
24
25 127 mortality was obtained after direct standardisation of the crude cumulative mortality data, by
26
27 128 5-year age intervals and sex, to the Estimated Resident Population Status, based on the 2001
28
29 129 census. Interaction terms were tested for each covariate against instrumentation type.

30
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32 130 A secondary analysis of mortality adjusted for age, sex, procedure year, bone cement use, ASA
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34 131 and BMI was performed in the subset of procedures performed since 2015 (when ASA and
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36 132 BMI data were available). Both analyses were repeated using 90-day mortality as the outcome
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38 133 measure.

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41 134 A sensitivity analysis was performed by restricting the population to patients who had only one
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43 135 primary TKA recorded in the AOANJRR, which excluded all patients with contralateral TKA.

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46 136 As it was unlikely that patients died in another country within 30 or 90 days of surgery without
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48 137 registration of their death, an assumption of no missing data was made.

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51 138 Patients or the public were not involved in the design, or conduct, or reporting, or dissemination
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53 139 plans of our research.
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3 **140 RESULTS**
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6 **141** A total of 581,818 unilateral TKA procedures were included from 1 January 2003 to 31
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8 **142** December 2019. The increasing use of technology-assisted instrumentation over time is shown
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11 **143** in Figure 1, and descriptive data of patient demographics and the use of technology-assisted
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13 **144** surgery is provided in Table 1. Procedures using technology-assisted surgery comprised
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15 **145** 129,179 computer navigation, 34,898 image-derived instrumentation, 7,288 robotic assisted
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18 **146** and 869 using a combination of technologies.
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21 **147**

22
23 **148** Table 1. Demographic data and use of technology-assisted surgery in patients undergoing
24
25 **149** unilateral TKA.
26

	Technology- assisted surgery	Not technology- assisted surgery	Total
Mean age (SD) in years	68.5 (9.0)	69.1 (9.2)	69.0 (9.1)
Sex (proportion male)	43.3%	42.0%	42.4%
ASA Class (proportion)			
1	5.6%	5.2%	5.4%
2	53.8%	54.5%	54.2%
3	39.4%	39.1%	39.3%
4	1.2%	1.2%	1.2%
5	0.0%	0.0%	0.0%
Mean BMI (SD)	32.0 (14.2)	32.3 (17.1)	32.2 (15.8)
Procedures	170,496	411,322	581,818

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54 **151** The distribution of deaths between groups for 30-day and 90-day post-surgical periods are
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56 **152** provided in Tables 2 and 3, respectively. The odds ratio of death within 30 days for TKA
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59 **153** performed with conventional instrumentation compared to technology-assisted
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154 instrumentation, adjusted for age, sex, cement use and procedure year was 1.48 (95% CI, 1.19
 155 to 1.85, $p < 0.001$). For the subset of 212,937 procedures where ASA and BMI data were
 156 available, the odds ratio adjusted for age, sex, procedure year, cement use, ASA and BMI was
 157 1.72 (95% CI, 1.23 to 2.41, $p = 0.001$). The corresponding odds ratios for 90-day mortality were
 158 1.27 (95% CI, 1.09 to 1.47, $p = 0.002$) and 1.35 (95% CI, 1.07 to 1.69, $p = 0.010$). The models
 159 for the fully adjusted analyses are shown in Table 4. Two-way interaction terms between age,
 160 sex, BMI, ASA class, cement use and procedure year, and use of technology-assisted
 161 instrumentation were tested and found to be not significant for both 30- and 90-day mortality.
 162 The sensitivity analysis restricted to patients who had only one unilateral TKA recorded
 163 showed similar significant differences between technology assisted and conventional
 164 instrumentation, although the overall (and standardised) mortality was higher in this group
 165 (analyses not shown).

166
 167 Table 2. 30-day mortality following unilateral TKA for osteoarthritis.

	Patients (n)	Deaths (n)	Deaths (%)	Standardised mortality
Conventional instrumentation	411,322	495	0.120	0.036
Technology-assisted instrumentation	170,496	107	0.063	0.018
Total	581,818	602	0.103	0.031

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 169 Table 3. 90-day mortality following unilateral TKA for osteoarthritis.

	Patients (n)	Deaths (n)	Deaths (%)	Standardised mortality
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Conventional instrumentation	411,322	919	0.233	0.074
Technology-assisted instrumentation	170,496	240	0.141	0.043
Total	581,818	1,159	0.199	0.065

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171 Table 4. Full regression model for 30-day mortality using data from 2015 to 2019, inclusive.

Variable	30-day mortality		90-day mortality	
	OR (95% CI)	P value	OR (95% CI)	P value
Technology assisted (vs conventional)	1.72 (1.23, 2.43)	0.001	1.35 (1.07, 1.69)	0.01
ASA class (ref = 1)				
2	2.14 (0.43, 10.66),	<0.001	1.52 (0.59, 3.91)	0.001
3	4.68 (0.94, 23.25)	0.07	3.33 (1.30, 8.53)	0.08
4	16.62 (3.04, 90.78)	0.19	12.07 (4.37, 33.38)	0.07
5	419.4 (11.78, 14934)	0.003	141.8 (5.11, 3935)	0.02
Age (per year)	1.08 (1.06, 1.10)	<0.001	1.08 (1.07, 1.10)	0.01
BMI (ref = normal)				
Underweight	0.96 (0.56, 1.64)	0.80	5.87 (2.38, 14.51)	<0.001
Overweight	0.95 (0.51, 1.77)	0.79	0.99 (0.69, 1.42)	0.02
Obese class 1	1.25 (0.63, 2.48)	0.55	0.88 (0.61, 1.29)	0.002
Obese class 2	0.93 (0.55, 1.56)	0.70	0.89 (0.57, 1.38)	0.01
Obese class 3	1.12 (0.07, 18.12)	0.94	1.06 (0.65, 1.75)	0.26
Procedure year (per year)	1.06 (0.94, 1.18)	0.35	1.02 (0.95, 1.11)	0.57
Female (vs male)	0.63 (0.46, 0.87)	0.004	0.62 (0.50, 0.78)	<0.001
No cement (vs cement)	1.89 (1.15, 3.09)	<0.001	1.35 (0.91, 2.00)	0.14

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173 **DISCUSSION**

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3 174 *Statement of principal findings*
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6 175 The use of conventional instrumentation during unilateral TKA was associated with a
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8 176 significantly higher 30-day mortality when compared to technology-assisted instrumentation,
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10 177 allowing for differences in age, sex, cement use, ASA class, BMI and year of procedure.
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14 178 *Strengths and weaknesses of the study*
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17 179 A strength of this study is the use of national data and the large sample size. Furthermore,
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19 180 adjusting for patient-level factors and procedure year, has accounted for differences in patient
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21 181 selection, improvements in perioperative management and the increasing use of technology-
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23 182 assisted instrumentation over time.
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27 183 This study is limited by the possibility that the associations may be subject to residual
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29 184 confounding from unknown variables. Randomised trials to answer this question may not be
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31 185 feasible due to the very large sample size required due to the small event rate. Surgical times
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33 186 are reported to be slightly longer when technology-assisted methods are used,³⁵ but this would
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35 187 not be expected to be associated with a reduction in mortality.
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39 188 *Strengths and weaknesses in relation to other studies*
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42 189 The relative mortality of conventional and technology assisted instrumentation in TKA has not
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44 190 been previously reported.
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48 191 *Meaning of the study: possible explanations and implications for clinicians and policymakers*
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51 192 This difference in mortality has not been previously reported and may be related to the insertion
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53 193 of an intramedullary rod into the femur (and in some cases, the tibia) during conventional
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55 194 instrumentation and the resulting fat embolism. Initial studies using non-invasive intra-
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57 195 operative ultrasound have demonstrated that there are less emboli with computer navigation
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3 196 compared to conventional instrumentation, although these studies were small.^{21,22} However,
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5 197 later studies with larger study populations have shown that while avoiding intramedullary
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7 198 instrumentation does not significantly reduce the incidence of fat embolization during
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10 199 TKA,^{23,24} it may reduce the embolic load.²⁵ Cerebral fat embolism has also been reported after
11
12 200 standard TKA^{4,26} but there is a lack of studies comparing technology assisted and standard
13
14 201 instrumented TKA. Alternatively, fat emboli may arise from other parts of the surgery such as
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16 202 impaction of the femoral and tibial implants, but this is unlikely to differ between technology
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19 203 assisted and conventionally instrumented TKA.²³⁻²⁵

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22 204 The higher 30-day mortality associated with cementless fixation may also be related to fat
23
24 205 emboli due to potential higher impaction forces used in cementless fixation. This association
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26 206 has not previously been reported, however a recent study from the Dutch arthroplasty register
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28 207 showed that the odds ratio for 30-day mortality in cementless fixation compared to cemented
29
30 208 fixation was 1.46 (95% CI 0.74 to 2.90). This difference was not statistically significant but
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32 209 used a smaller sample than that used in the current study.²⁷

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37 210 Stein et al examined over 900 million patients using data from the US National Hospital
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39 211 Discharge Survey from 1979 to 2005 and reported 41,000 patients (0.004%) with fat embolism
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41 212 syndrome.²⁸ They stated that the incidence of fat embolism with lower limb joint replacement
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43 213 was too low to calculate accurately. However, it is possible that cases of sudden death
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45 214 associated with surgery were not diagnosed as fat embolism syndrome.^{4,29}

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49 215 Another possible cause for the observed difference in mortality is perioperative blood loss.
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51 216 Although blood loss was not measured in this study, previous research has shown surgical
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53 217 blood loss is lower with technology-assisted knee surgery.^{30,31} This factor may also affect
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55 218 mortality directly or by reducing the need for blood transfusion.
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3 219 Although the odds ratios for the associations were lower for 90-day mortality, the 90-day
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5 220 mortality is higher, such that the difference likely relates to a similar risk difference. The higher
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8 221 odds ratio for 30-day mortality compared to 90-day mortality suggests that the largest
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10 222 difference in mortality occurs in the early post-operative period. Mortality after TKA has fallen
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12 223 over the last few decades and the current 30-day mortality after TKA is approximately
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14 224 0.1%.^{14,15} Given the low event rate for death post-TKA, the odds ratios found in this analysis
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16 225 can be approximated as risk ratios. This suggests that the use of conventional instrumentation
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18 226 is associated with a 72% increase in 30-day mortality after TKA when compared to assistive
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20 227 technology use. It is estimated that approximately one million TKA are performed in the US
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22 228 annually with that rate expected to rise significantly up to 2050.^{32,33} Globally, assuming over
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24 229 two million cases are performed annually,³⁴ if the difference in mortality is due to the use of
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26 230 conventional instrumentation, the use of technology assisted instrumentation would result in
27
28 231 approximately one thousand fewer deaths per year, depending on the current rate of technology
29
30 232 assisted instrumentation.

36 233 *Unanswered questions and future research*

39 234 This study should be replicated using large datasets and joint registries from other regions that
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41 235 collect data on technology assisted TKA. If verified, this finding has a major implication for
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43 236 the conduct of TKA surgery worldwide. While there is little clinical disadvantage to using
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45 237 technology-assisted surgery, there is an increased cost. Future research may determine the cost
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47 238 effectiveness of using technology assisted instrumentation.

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3 241 **Ethics approval statement**
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6 242 The project was approved by the following ethics committees: University of South Australia
7
8 243 HREC (200890), Sydney Local Health District Ethics Review Committee (RPAH Zone,
9
10 244 HREC/18/RPAH/90), Calvary Health Care Adelaide HREC (18-CHREC-F004), Mater
11
12 245 Misericordiae Ltd HREC (HREC/18/MHS/45), St Vincent's Health and Aged Care HREC
13
14 246 (HREC 18/14), University of Tasmania HREC (H0017292), Calvary Health Care Tasmania
15
16 247 HREC (010418), St John of God HREC (1408), Calvary Health Care (ACT)(25-2018).
17
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21 248 **Figure legend**
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23

24 249 Figure 1: The use of technology assisted instrumentation over time for primary unilateral TKA.
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26

27 250 **Contributorship statement**
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29

30 251 IAH and DK conceived the study. All authors contributed to the methods. YP performed the
31
32 252 statistical analysis. IAH drafted the manuscript. All authors contributed to the literature review
33
34 253 and manuscript preparation. IAH is guarantor for the study.
35
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37

38 254 **Competing interests**
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40

41 255 There are no competing interests for any author.
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43

44 256 **Funding statement**
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46

47 257 No funding was received for the conduct of this study.
48
49

50 258 **Data sharing statement**
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52

53 259 Data are held by the Australian Orthopaedic Association National Joint Replacement Registry
54
55 260 and are available on request subject to conditions. External access to and use of de-identified
56
57 261 AOANJRR data must be in accordance with AOANJRR policies (Ref No POL.S3.3, S3.4,
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3 262 S3.5) available on the registry website: <https://aoanjrr.sahmri.com/policies>. Requests for data
4
5 263 use can be made by contacting the AOANJRR Manager:

6
7
8 264 Cindy Turner, Manager AOANJRR

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10
11 265 Telephone: +618 8128 4284

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14 266 Email: cturner@aoanjrr.org.au

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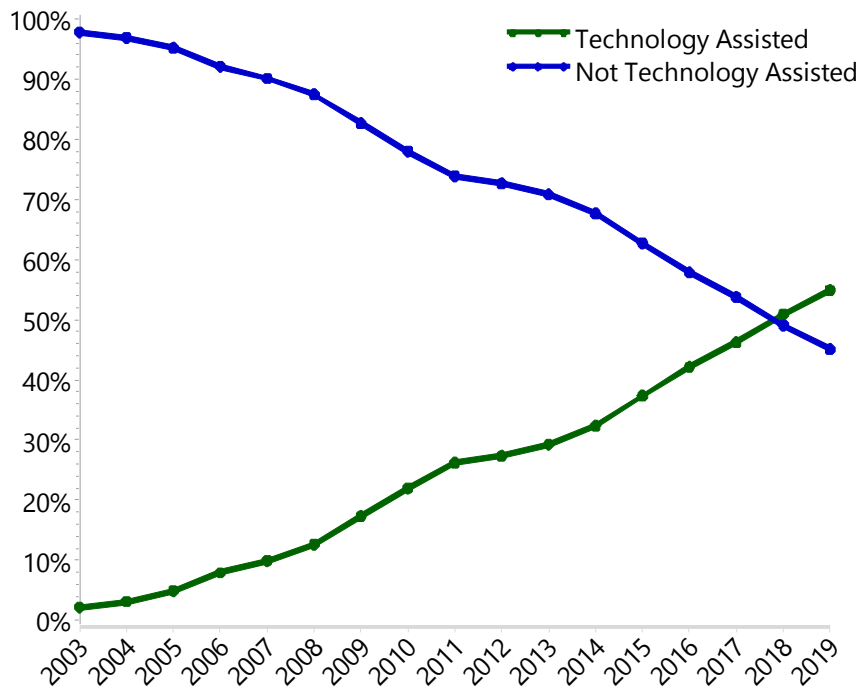
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STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Location
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	Line 2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	Line 26
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Line 70
Objectives	3	State specific objectives, including any prespecified hypotheses	Line 88
Methods			
Study design	4	Present key elements of study design early in the paper	Lines 92-137
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Lines 92-101
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Lines 92-101
		(b) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Lines 102-122
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	Lines 102-129
Bias	9	Describe any efforts to address potential sources of bias	Lines 123-137
Study size	10	Explain how the study size was arrived at	Convenience sample. Lines 95-95
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Lines 123-129
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	Lines 123-137
		(b) Describe any methods used to examine subgroups and interactions	Lines 130-137
		(c) Explain how missing data were addressed	Lines 136-137
		(d) If applicable, explain how loss to follow-up was addressed	Lines 136-137
		(e) Describe any sensitivity analyses	Lines 134-135
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	Lines 141-146

		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	Not necessary
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1, Line 148
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	Lines 151-152
Outcome data	15*	Report numbers of outcome events or summary measures over time	Tables 2, 3. Lines 167, 169
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	Table 4, Line 171
		(b) Report category boundaries when continuous variables were categorized	NA
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Lines 160-163
Discussion			
Key results	18	Summarise key results with reference to study objectives	Lines 174-177
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	Lines 178-187
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Lines 191-232
Generalisability	21	Discuss the generalisability (external validity) of the study results	Lines 234-235
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	Line 22

*Give information separately for exposed and unexposed groups.

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 <http://www.strobe-statement.org>.

BMJ Open

Increased early mortality after total knee arthroplasty using conventional instrumentation compared to technology-assisted surgery: an analysis of linked national registry data.

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Primary Subject Heading:	Surgery
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Keywords:	Knee < ORTHOPAEDIC & TRAUMA SURGERY, RHEUMATOLOGY, EPIDEMIOLOGY

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3 **1 Title**
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6 2 Increased early mortality after total knee arthroplasty using conventional instrumentation
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8 3 compared to technology-assisted surgery: an analysis of linked national registry data.
9

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12 **4 Authors**
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15 26 **ABSTRACT**

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18 27 **Objectives**

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22 28 This study aims to compare early mortality after total knee arthroplasty (TKA) using
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24 29 conventional intramedullary instrumentation to TKA performed using technology-assisted
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26 30 (non-intramedullary) instrumentation.

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29 31 **Design**

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32 32 Comparative observational study. Using data from a large national registry, the 30-day
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34 33 mortality after unilateral TKA performed for osteoarthritis was compared between procedures
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36 34 using conventional instrumentation and those using technology-assisted instrumentation. Firth
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38 35 logistic regression was used to calculate odds ratios, adjusting for age, sex, use of cement and
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40 36 procedure year for the whole period, and additionally adjusting for American Society of
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42 37 Anesthesiologists (ASA) physical status classification system class and body mass index
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44 38 (BMI) for the period 2015 to 2019. This analysis was repeated for 7-day and 90-day mortality.

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47 39 **Setting**

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50 40 National arthroplasty registry.

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53 41 **Participants**

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56 42 People undergoing unilateral, elective TKR for osteoarthritis from 2003 to 2019 inclusive.
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43 **Interventions**

44 TKA performed using conventional intramedullary instrumentation or technology-assisted
45 instrumentation.

46 **Main outcome measures**

47 30-day mortality (primary), and 7-day and 90-day mortality.

48 **Results**

49 A total of 581,818 unilateral TKA procedures performed for osteoarthritis were included, of
50 which 602 (0.10%) died within 30 days of surgery. The odds ratio of death within 30 days
51 following TKA performed with conventional instrumentation compared to technology-assisted
52 instrumentation, adjusted for age, sex, cement use, procedure year, ASA and BMI was 1.72
53 (95% CI, 1.23 to 2.41, p=0.001). The corresponding odds ratios for 7-day and 90-day mortality
54 were 2.21 (96% CI, 1.34 to 3.66, p=0.002) and 1.35 (95% CI, 1.07 to 1.69, p=0.010),
55 respectively.

56 **Conclusions**

57 The use of conventional instrumentation during TKA is associated with higher odds of early
58 post-operative death than when technology-assisted instrumentation is used. This difference
59 may be explained by complications related to fat embolism secondary to intramedullary rods
60 used in conventional instrumentation. Given the high number of TKA performed annually
61 worldwide, increasing the use of technology-assisted instrumentation may reduce early post-
62 operative mortality.

63 **Strengths and limitations of this study**

- 64 • Use of national linked data

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- 65 • Large sample size
- 66 • Adjustment for known likely confounders
- 67 • Observational study design (possible unmeasured confounders)

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68 INTRODUCTION

69 Total knee arthroplasty (TKA) is a common procedure for severe osteoarthritis of the knee,
70 with an average annual rate of 135 per 100,000 population in contributing OECD countries and
71 226 per 100,000 in Australia.^{1,2} Conventional instrumentation for TKA surgery requires the
72 insertion of a long intramedullary rod into the femur (and sometimes the tibia) which is then
73 used as a reference for alignment of the cutting blocks applied to the bone for prosthesis
74 preparation. This insertion creates fat and bone marrow embolization, as shown by
75 transesophageal echocardiography and analysed by biopsy.³ The embolic material may
76 produce fat embolism syndrome, which includes respiratory, cardiac, haematological, and
77 neurological complications and sudden death.⁴⁻⁶ Over the last two decades, three new
78 techniques have been introduced that allow alignment to be referenced without intramedullary
79 instrumentation. These technology-assisted instrumentation techniques are computer
80 navigation, image-derived instrumentation and robotic assistance. Although these techniques
81 were developed to improve post-operative alignment, evidence for this is variable. Computer
82 navigation has demonstrated improved alignment compared to standard instruments, however,
83 there is mixed evidence that revision rates or patient reported outcomes are superior using this
84 technique.⁷⁻¹³ However, trials comparing any of these newer techniques to conventional
85 instrumentation were underpowered to detect early mortality post-operatively, which has been
86 decreasing over time (possibly due to improvements in operative and peri-operative
87 management) and is currently approximately 0.1% at 30 days.^{14,15}

88 This study aims to compare the 30-day all-cause mortality after TKA between procedures
89 performed using conventional intramedullary instrumentation to those performed using
90 technology-assisted instrumentation using data from a large national registry.

91 METHODS

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3 92 The Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR) is
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5 93 a national registry with near complete (over 98%) coverage of TKA procedures performed in
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7 94 Australia since 2003.² AOANJRR data from January 2003 to December 2019 for patients
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9 95 undergoing unilateral TKA for osteoarthritis were used. Patients undergoing bilateral same-
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11 96 day primary TKA or any primary TKA within 90 days of a contralateral primary TKA were
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13 97 excluded. AOANJRR data include patient-identified data and surgical variables, which
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15 98 includes the use of assistive technology, and these data are linked to the National Death Index
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17 99 twice yearly to record fact and date of death. All data used in the analysis were available in the
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19 100 AOANJRR from inception except the American Society of Anesthesiologists (ASA) class¹⁶ (a
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21 101 measure of comorbidity and mortality risk, available since 2012) and body mass index (BMI,
22
23 102 available since 2015).

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29 103 The increased mortality associated with TKA is maximal within 30 days but may extend to 90
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31 104 days post surgery.^{17,18} Therefore, 30-day mortality was chosen as the primary outcome; 7-day
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33 105 and 90-day mortality were chosen as secondary outcomes. Age, sex, use of bone cement, ASA
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35 106 class and BMI were chosen as potential confounders due to their known association with
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37 107 mortality. Procedure year was added as a covariate due to the increase in the proportion of
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39 108 cases using technology-assisted instrumentation over time and, because 30-day mortality has
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41 109 been decreasing over time.¹⁴

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46 110 Technology-assisted surgery was defined as any procedure using computer navigation, image
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48 111 derived instrumentation (IDI) or robotic assistance. Computer navigation involves the use of a
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50 112 tracking device, most commonly an infrared camera, and a computer. Rigid reference arrays
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52 113 are attached to the patient and a registration process enables the software to determine the
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54 114 patient's anatomy and accurately track instruments to assist surgery. The surgeon then makes
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56 115 the appropriate bone cuts and monitors the alignment of the knee. Robotic assistance uses
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58 116 similar principles, but a robotic arm guides the cutting tools to facilitate the surgery. Both these

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3 117 techniques allow intra operative verification of the component position. IDI is the use of
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5 118 individualised custom-made 3D printed guides or cutting blocks derived from pre-operative
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8 119 CT or MRI scans of the patient's knee. These guides or blocks are used to perform the required
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10 120 bone cuts and are specific to each patient's anatomy. Conventional instrumentation was defined
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12 121 as any procedure not using any of the technology-assisted methods. Cause of death was not
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14 122 used, as multiple causes are often reported, it may be inconsistently reported,¹⁹ and it is less
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16 123 relevant than overall mortality.

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20 124 Between-group differences in mortality were expressed as odds ratios, calculated by logistic
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22 125 regression adjusting for age, sex and procedure year. Due to low numbers of deaths, Firth
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24 126 logistic regression (which uses penalized likelihood) was used to avoid the small sample bias
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26 127 inherent in regression using conventional maximum likelihood estimation.²⁰ Adjusted
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28 128 mortality was obtained after direct standardisation of the crude cumulative mortality data, by
29
30 129 5-year age intervals and sex, to the Estimated Resident Population Status, based on the 2001
31
32 130 census. Interaction terms were tested for each covariate against instrumentation type.

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37 131 A secondary analysis of mortality adjusted for age, sex, procedure year, bone cement use, ASA
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39 132 and BMI was performed in the subset of procedures performed since 2015 (when ASA and
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41 133 BMI data were available). Fully adjusted analyses were repeated using 7-day and 90-day
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43 134 mortality as the outcome measures.

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47 135 A sensitivity analysis was performed by restricting the population to patients who had only one
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49 136 primary TKA recorded in the AOANJRR, which excluded all patients with contralateral TKA.

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52 137 As it was unlikely that patients died in another country within 30 or 90 days of surgery without
53
54 138 registration of their death, an assumption of no missing data was made.

55 56 57 58 139 **Patient and public involvement**

140 Patients or the public were not involved in the design, or conduct, or reporting, or dissemination
 141 plans of our research.

142 RESULTS

143 A total of 581,818 unilateral TKA procedures were included from 1 January 2003 to 31
 144 December 2019. The increasing use of technology-assisted instrumentation over time is shown
 145 in Figure 1, and descriptive data of patient demographics and the use of technology-assisted
 146 surgery is provided in Table 1. Procedures using technology-assisted surgery comprised
 147 129,179 computer navigation, 34,898 image-derived instrumentation, 7,288 robotic assisted
 148 and 869 using a combination of technologies.

149 Table 1. Demographic data and use of technology-assisted surgery in patients undergoing
 150 unilateral TKA.

	Technology- assisted surgery	Conventional surgery	Total
Mean age (SD) in years	68.5 (9.0)	69.1 (9.2)	69.0 (9.1)
Sex (proportion male)	43.3%	42.0%	42.4%
ASA Class* (proportion)			
1	5.6%	5.2%	5.4%
2	53.8%	54.5%	54.2%
3	39.4%	39.1%	39.3%
4	1.2%	1.2%	1.2%
5	0.0%	0.0%	0.0%
Mean BMI** (SD)	32.0 (14.2)	32.3 (17.1)	32.2 (15.8)
Procedures	170,496	411,322	581,818

151 * ASA Class was available for 293,624 procedures

152 ** BMI was available for 213,259 procedures

153 The distribution of deaths between groups for 30-day, and 7- and 90-day post-surgical periods
 154 are provided in Tables 2 and 3, respectively. The odds ratio of death within 30 days for TKA
 155 performed with conventional instrumentation compared to technology-assisted
 156 instrumentation, adjusted for age, sex, cement use and procedure year was 1.48 (95% CI, 1.19
 157 to 1.85, $p < 0.001$). For the subset of 212,937 procedures where ASA and BMI data were
 158 available, the odds ratio adjusted for age, sex, procedure year, cement use, ASA and BMI was
 159 1.72 (95% CI, 1.23 to 2.41, $p = 0.001$). The corresponding (fully adjusted) odds ratios for 7-day
 160 and 90-day mortality were 2.27 (95%CI, 1.33 to 8.74, $p = 0.002$) and 1.35 (95% CI, 1.07 to
 161 1.69, $p = 0.010$), respectively. The models for the fully adjusted analyses are shown in Table 4.
 162 Two-way interaction terms between age, sex, BMI, ASA class, cement use and procedure year,
 163 and use of technology-assisted instrumentation were tested and found to be not significant.

164 The sensitivity analysis restricted to patients who had only one unilateral TKA recorded
 165 showed similar significant differences between technology assisted and conventional
 166 instrumentation, although the overall (and standardised) mortality was higher in this group
 167 (analyses not shown).

168 Table 2. 30-day mortality following unilateral TKA for osteoarthritis.

Group	Patients (n)	Deaths (n)	Deaths (%)	Standardised mortality
Conventional instrumentation	411,322	495	0.120	0.036
Technology-assisted instrumentation	170,496	107	0.063	0.018
Total	581,818	602	0.103	0.031

169

170 Table 3. 7-day and 90-day mortality following unilateral TKA for osteoarthritis.

Group	Patients (n)	7-day mortality			90-day mortality		
		Deaths (n)	Deaths (%)	Standardised mortality	Deaths (n)	Deaths (%)	Standardised mortality
Conventional instrumentation	411,322	214	0.052	0.005	919	0.233	0.074
Technology- assisted instrumentation	170,496	38	0.022	0.015	240	0.141	0.043
Total	581,818	252	0.043	0.012	1,159	0.199	0.065

171

172 Table 4. Full regression model for mortality using data from 2015 to 2019, inclusive.

Variable	30-day mortality		7-day mortality		90-day mortality	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Conventional vs technology assisted	1.72 (1.23, 2.43)	0.001	2.21 (1.34, 3.66)	0.002	1.35 (1.07, 1.69)	0.01
ASA class (ref = 1)						
2	2.14 (0.43, 10.66)	<0.001	1.10 (0.22, 5.47)	0.91	1.52 (0.59, 3.91)	0.001
3	4.68 (0.94, 23.25)	0.07	1.89 (0.38, 9.38)	0.44	3.33 (1.30, 8.53)	0.08
4	16.62 (3.04, 90.78)	0.19	4.23 (0.64, 27.99)	0.07	12.07 (4.37, 33.38)	0.07
5	419.4 (11.78, 14934)	0.003	451.5 (13.69, 14894)	<0.001	141.8 (5.11, 3935)	0.02
Age (per year)	1.08 (1.06, 1.10)	<0.001	1.08 (1.05, 1.17)	0.01	1.08 (1.07, 1.10)	0.01
BMI (ref = normal)						
Underweight	0.96 (0.56, 1.64)	0.80	3.25 (0.20, 53.22)	0.09	5.87 (2.38, 14.51)	<0.001
Overweight	0.95 (0.51, 1.77)	0.79	1.06 (0.47, 2.37)	0.89	0.99 (0.69, 1.42)	0.02
Obese class 1	1.25 (0.63, 2.48)	0.55	1.23 (0.54, 2.81)	0.62	0.88 (0.61, 1.29)	0.002
Obese class 2	0.93 (0.55, 1.56)	0.70	1.25 (0.49, 3.19)	0.65	0.89 (0.57, 1.38)	0.01
Obese class 3	1.12 (0.07, 18.12)	0.94	2.50 (0.95, 6.57)	0.06	1.06 (0.65, 1.75)	0.26
Procedure year (per year)	1.06 (0.94, 1.18)	0.35	0.97 (0.83, 1.14)	0.73	1.02 (0.95, 1.11)	0.57
Female (vs male)	0.63 (0.46, 0.87)	0.004	0.52 (0.33, 0.83)	0.005	0.62 (0.50, 0.78)	<0.001
No cement (vs cement)	1.89 (1.15, 3.09)	<0.001	1.84 (0.92, 3.67)	0.09	1.35 (0.91, 2.00)	0.14

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3 174 **DISCUSSION**
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6 175 *Statement of principal findings*
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9 176 The use of conventional instrumentation during unilateral TKA was associated with a
10
11 177 significantly higher 30-day mortality when compared to technology-assisted instrumentation,
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13 178 allowing for differences in age, sex, cement use, ASA class, BMI and year of procedure.
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17 179 *Strengths and weaknesses of the study*
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20 180 A strength of this study is the use of national data and the large sample size. Furthermore,
21
22 181 adjusting for patient-level factors and procedure year, has accounted for differences in patient
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24 182 selection, improvements in perioperative management and the increasing use of technology-
25
26 183 assisted instrumentation over time.
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29
30 184 This study is limited by the possibility that the associations may be subject to residual
31
32 185 confounding from unknown variables. Randomised trials to answer this question may not be
33
34 186 feasible due to the very large sample size required due to the small event rate. Surgical times
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36 187 are reported to be slightly longer when technology-assisted methods are used,²¹ but this would
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38 188 not be expected to be associated with a reduction in mortality.
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42 189 *Strengths and weaknesses in relation to other studies*
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46 190 The relative mortality of conventional and technology assisted instrumentation in TKA has not
47
48 191 been previously reported.
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51 192 *Meaning of the study: possible explanations and implications for clinicians and policymakers*
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54 193 This difference in mortality has been recently reported (with stronger effect) for bilateral
55
56 194 TKA²² and may be related to the insertion of an intramedullary rod into the femur (and in some
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58 195 cases, the tibia) during conventional instrumentation and the resulting fat embolism. Initial
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3 196 studies using non-invasive intra-operative ultrasound have demonstrated that there are less
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5 197 emboli with computer navigation compared to conventional instrumentation, although these
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8 198 studies were small.^{23,24} However, later studies with larger study populations have shown that
9
10 199 while avoiding intramedullary instrumentation does not significantly reduce the incidence of
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12 200 fat embolization during TKA,^{25,26} it may reduce the embolic load.²⁷ Cerebral fat embolism has
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14 201 also been reported after standard TKA^{4,28} but there is a lack of studies comparing technology
15
16 202 assisted and standard instrumented TKA. Alternatively, fat emboli may arise from other parts
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18 203 of the surgery such as impaction of the femoral and tibial implants, but this is unlikely to differ
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20 204 between technology assisted and conventionally instrumented TKA.²⁵⁻²⁷

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23
24 205 The higher 30-day mortality associated with cementless fixation may also be related to fat
25
26 206 emboli due to potential higher impaction forces used in cementless fixation. This association
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28 207 has not previously been reported, however a recent study from the Dutch arthroplasty register
29
30 208 showed that the odds ratio for 30-day mortality in cementless fixation compared to cemented
31
32 209 fixation was 1.46 (95% CI 0.74 to 2.90). This difference was not statistically significant but
33
34 210 used a smaller sample than that used in the current study.²⁹

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39 211 Stein et al examined over 900 million patients using data from the US National Hospital
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41 212 Discharge Survey from 1979 to 2005 and reported 41,000 patients (0.004%) with fat embolism
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43 213 syndrome.³⁰ They stated that the incidence of fat embolism with lower limb joint replacement
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45 214 was too low to calculate accurately. However, it is possible that cases of sudden death
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47 215 associated with surgery were not diagnosed as fat embolism syndrome.^{4,31}

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51 216 Another possible cause for the observed difference in mortality is perioperative blood loss.
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53 217 Although blood loss was not measured in this study, previous research has shown surgical
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55 218 blood loss is lower with technology-assisted knee surgery.^{32,33} This factor may also affect
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57 219 mortality directly or by reducing the need for blood transfusion.
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3 220 Although the odds ratios for the associations were lower for 90-day mortality, the 90-day
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5 221 mortality is higher, such that the difference likely relates to a similar risk difference. The higher
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7 222 odds ratio for 7-day compared to 30-day mortality, and 30-day compared to 90-day mortality
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9 223 suggests that the largest difference in mortality occurs in the early post-operative period.
10
11 224 Mortality after TKA has fallen over the last few decades and the current 30-day mortality after
12
13 225 TKA is approximately 0.1%.^{14,15} Given the low event rate for death post-TKA, the odds ratios
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15 226 found in this analysis can be approximated as risk ratios. This suggests that the use of
16
17 227 conventional instrumentation is associated with a 72% increase in 30-day mortality after TKA
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19 228 when compared to assistive technology use. It is estimated that approximately one million TKA
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21 229 are performed in the US annually with that rate expected to rise significantly up to 2050.^{34,35}
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23 230 Globally, assuming over two million cases are performed annually,³⁶ if the difference in
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25 231 mortality is due to the use of conventional instrumentation, the use of technology assisted
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27 232 instrumentation would result in approximately one thousand fewer deaths per year, depending
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29 233 on the current rate of technology assisted instrumentation.
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36 234 *Unanswered questions and future research*

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39 235 This study should be replicated using large datasets and joint registries from other regions that
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41 236 collect data on technology assisted TKA. If verified, this finding has a major implication for
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43 237 the conduct of TKA surgery worldwide. While there is little clinical disadvantage to using
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45 238 technology-assisted surgery, there is an increased cost. Future research may determine the cost
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47 239 effectiveness of using technology assisted instrumentation.
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3 240 **Ethics approval statement**
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6 241 The AOANJRR is approved by the Commonwealth of Australia as a federal quality assurance
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8 242 activity (QAA 3/2017) under Part VC of the Health Insurance Act, 1973. All AOANJRR
9
10 243 studies are conducted in accordance with ethical principles of research (the Helsinki
11
12 244 Declaration II).
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16 245 **Figure legend**
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19 246 Figure 1: The use of technology assisted instrumentation over time for primary unilateral TKA.
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23 247 **Contributorship statement**
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26 248 IAH contributed to study concept, design, analysis, interpretation and drafted the manuscript.
27
28 249 IAH has approved the final version of the manuscript and agrees to be accountable for the
29
30 250 work. IAH has approved the final version of the manuscript and agrees to be accountable for
31
32 251 the work. DK contributed to concept, interpretation and revising the manuscript. DK has
33
34 252 approved the final version of the manuscript and agrees to be accountable for the work. YP
35
36 253 conducted the statistical analysis and revised the manuscript. YP has approved the final version
37
38 254 of the manuscript and agrees to be accountable for the work. PL contributed to study design,
39
40 255 interpretation and manuscript revision. PL has approved the final version of the manuscript and
41
42 256 agrees to be accountable for the work. RdS contributed to study design, interpretation and
43
44 257 manuscript revision. RdS has approved the final version of the manuscript and agrees to be
45
46 258 accountable for the work. SEG contributed to study design, interpretation and manuscript
47
48 259 revision. SEG has approved the final version of the manuscript and agrees to be accountable
49
50 260 for the work.
51
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55
56 261 **Competing interests**
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58

59 262 There are no competing interests for any author.
60

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3 263 **Funding statement**
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6 264 No funding was received for the conduct of this study.
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9 265 **Data sharing statement**
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12 266 Data are held by the Australian Orthopaedic Association National Joint Replacement Registry
13
14 267 and are available on request subject to conditions. External access to and use of de-identified
15
16 268 AOANJRR data must be in accordance with AOANJRR policies (Ref No POL.S3.3, S3.4,
17
18 269 S3.5) available on the registry website: <https://aoanjrr.sahmri.com/policies>. Requests for data
19
20
21 270 use can be made by contacting the AOANJRR Manager:

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25 271 Manager AOANJRR

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28 272 Telephone: +618 8128 4284
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31 273 Email: cturner@aoanjrr.org.au
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34 274 **REFERENCES**
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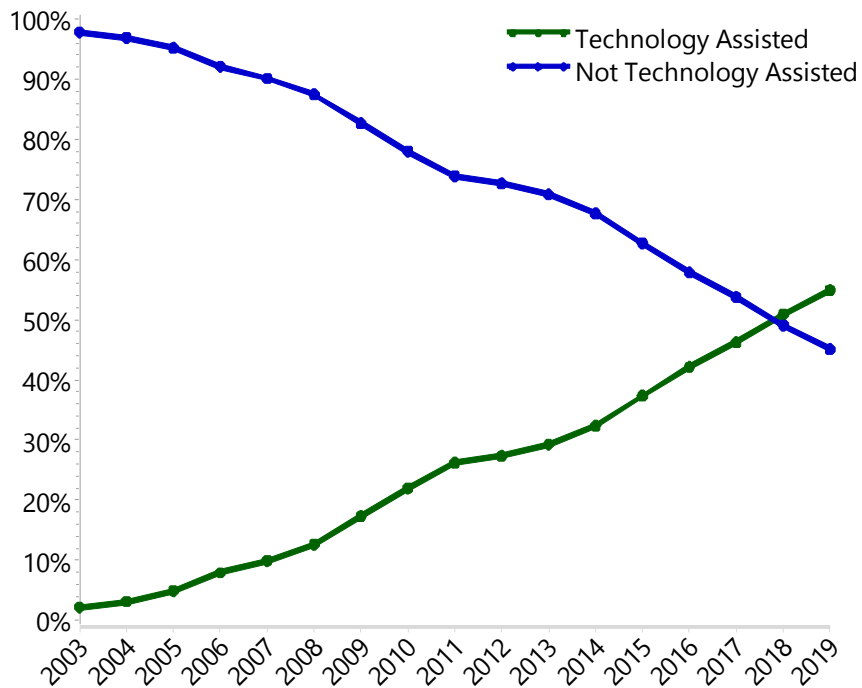
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Peer review only

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Location
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	Line 2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	Lines 26-64
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Lines 74-92
Objectives	3	State specific objectives, including any prespecified hypotheses	Lines 93-95
Methods			
Study design	4	Present key elements of study design early in the paper	Lines 98-150
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Lines 98-108
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Lines 100-103
		(b) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Lines 103-142
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	Lines 103-133
Bias	9	Describe any efforts to address potential sources of bias	Lines 137-150
Study size	10	Explain how the study size was arrived at	Convenience sample. Lines 100-103
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Lines 136-142
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	Lines 136-150
		(b) Describe any methods used to examine subgroups and interactions	Lines 142-148
		(c) Explain how missing data were addressed	Lines 149-150
		(d) If applicable, explain how loss to follow-up was addressed	Lines 149-150
		(e) Describe any sensitivity analyses	Lines 147-148
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	Lines 156-161

		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	Not necessary
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1, Line 162
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	Lines 168-169
Outcome data	15*	Report numbers of outcome events or summary measures over time	Tables 2, 3. Lines 183, 185
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	Table 4, Line 202
		(b) Report category boundaries when continuous variables were categorized	NA
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Tables 2 and 3 contain absolute risks
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Lines 174-182
Discussion			
Key results	18	Summarise key results with reference to study objectives	Lines 207-209
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	Lines 215-219
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Lines 224-280
Generalisability	21	Discuss the generalisability (external validity) of the study results	Line 282
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	Line 306

*Give information separately for exposed and unexposed groups.

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 <http://www.strobe-statement.org>.