



Abram, S. G. F., Judge, A., Beard, D. J., & Price, A. J. (2019). Rates of adverse outcomes and revision surgery following anterior cruciate ligament (ACL) reconstruction: a study of 104,255 procedures using the national hospital episodes database for England, UK. *American Journal of Sports Medicine*, 2533-2542. <https://doi.org/10.1177%2F0363546519861393>

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1 **Rates of adverse outcomes and revision surgery following anterior cruciate ligament (ACL)**  
2 **reconstruction: a study of 110,945 procedures using the national hospital episodes database for**  
3 **England, UK**

4

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6

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22

23 **ABSTRACT**

24

25 **BACKGROUND**

26 Following ACL injury, ACL reconstruction is an elective procedure and therefore an understanding of the  
27 attributable risk from undergoing ACL reconstruction is necessary for patients to make a fully informed  
28 treatment decision.

29 **PURPOSE**

30 To determine the absolute risk of adverse outcomes including reoperation following ACL reconstruction with  
31 comparison, where possible, to the rate of adverse events reported in the general population.

32 **STUDY DESIGN**

33 Cohort study

34 **METHODS**

35 National hospital data on all ACL reconstructions performed in England between April 1, 1997 and March 31,  
36 2017 were analysed. Revision cases, bilateral procedures within 6 months, and cases with concurrent cartilage  
37 or multiple ligament surgery were excluded. The primary outcome was the occurrence of at least one serious  
38 complication (myocardial infarction, stroke, pulmonary embolism, infection requiring surgery, fasciotomy,  
39 neurovascular injury, or death) within 90-days. Additionally, 5-year rates of revision ACL reconstruction,  
40 contralateral reconstruction, and meniscal surgery were investigated.

41 **RESULTS**

42 133,270 ACL reconstructions were performed of which 104,255 were eligible for analysis. Within 90 days,  
43 serious complications occurred in 675 (0.65%; 95% confidence interval [CI] 0.60-0.70), including 494  
44 reoperations for infection (0.47%; 95% CI 0.43-0.52) and 129 pulmonary embolisms (0.12%; 95% CI 0.10-  
45 0.15). Of 54,275 patients with at least 5 years follow-up, 1746 (3.22%; 95% CI 3.07-3.37) underwent revision  
46 ACL reconstruction in the same knee, 1553 contralateral ACL reconstruction (2.86%; 95% CI 2.72-3.01), and  
47 340 (0.63%; 0.56-0.70) subsequent meniscal surgery. The overall risk of serious complications fell over time  
48 (adjusted odds ratio [OR] 0.96 per year; 95% CI 0.95-0.98) however older patients (adjusted OR 1.11 per 5-  
49 years; 95% CI 1.07-1.16) and patients with a greater modified Charlson comorbidity index (adjusted OR 2.41  
50 per 10-units; 95% CI 1.65-3.51) were are higher risk. For every 850 (95% CI 720-1039) ACL reconstructions

51 done, one pulmonary embolism could be provoked. For every 213 (95% CI 195-233), one native knee joint  
52 infection could be provoked.

### 53 **CONCLUSION**

54 The overall risk of adverse events following ACL reconstruction is low, however some rare but serious  
55 complications, including infection or pulmonary embolism, may occur. Around 3% of patients undergo a  
56 further same side or opposite side ACL reconstruction within five years. These data will inform shared  
57 decision making between clinicians and patients considering their treatment options.

58

### 59 **What is known about this subject**

- 60 • Before this study, several systematic reviews have attempted to estimate the risk of adverse events  
61 after ACL reconstruction however the findings have been limited by small numbers of studies, small  
62 number of patients, non-representative data sources, and concerns about incomplete data capture.
- 63 • For infection rates, a systematic review of level 2 studies published in 2017 reported a 0.43% deep  
64 infection rate (58/13401; 95% CI 0.32 to 0.56). For pulmonary embolism, a systematic review of 47  
65 included studies published in 2016 reported a rate of 0.14% (1/704; 95% CI 0.00 to 0.79). A rate of  
66 revision ACL reconstruction of 3.59% (587/16336; 95% CI 3.31 to 3.89) was reported from a large  
67 military health database series in 2016. A systematic review published in 2015 previously estimated a  
68 12.5% (335/2682) risk of contralateral ACL injury.

69

### 70 **What this study adds to existing knowledge**

- 71 • ACL reconstruction was associated with a 0.65% risk of serious complications within 90 days  
72 (pulmonary embolism, infection requiring surgery, myocardial infarction, stroke, fasciotomy,  
73 neurovascular injury, death).
- 74 • Using comparative general population data, it was determined that for every 850 fewer ACL  
75 reconstructions performed, one pulmonary embolism and four native knee joint infections could be  
76 provoked.
- 77 • Within 5-years, 3.2% patients require revision ACL reconstruction in the same knee, 0.63% undergo  
78 meniscal surgery in the same knee, and 2.9% undergo ACL reconstruction in the opposite knee.

79 Women are at lower risk of revision surgery and meniscal surgery but not opposite side  
80 reconstruction, in comparison to men.

- 81 • Although the risk of adverse events after ACL reconstruction is greater than after arthroscopic partial  
82 meniscectomy, the overall risk from this type of surgery remains low.
- 83 • Nevertheless, as ACL reconstruction may be an avoidable intervention for many people following  
84 ACL injury, this new understanding of risk and reoperation rates is crucial for patients to be able to  
85 make an informed treatment decision.

86

DRAFT

87 **INTRODUCTION**

88

89 The incidence of anterior cruciate ligament (ACL) injury in the population is approximately 0.03%  
90 per year, rising to over 3% in studies of certain professional athletes.<sup>26</sup> Reconstruction of the ACL is  
91 frequently recommended due to functional impairment and concerns about the development of  
92 meniscal or articular cartilage damage from recurrent instability of the knee.<sup>15,35</sup> The population rate  
93 of ACL reconstruction ranges from approximately 8 to 52/100,000 people between countries;<sup>5,26</sup> in  
94 England, the intervention rate was 24/100,000 in 2016-17.<sup>2</sup>

95

96 In 2010, a clinical trial indicated that for many patients with an ACL injury, a strategy of  
97 rehabilitation with optional delayed ACL reconstruction may avoid the need for surgery.<sup>16</sup> Other  
98 groups, however, continue to advocate early reconstruction due the risks of cartilage and meniscal  
99 damage from recurrent knee instability.<sup>11,14,16,19,25</sup> As ACL reconstruction is an elective procedure,  
100 besides the anticipated benefits of undergoing the procedure, it is crucially important for patients and  
101 clinicians to have knowledge of the specific risks.<sup>6</sup> Before this study, several studies have attempted  
102 to estimate the risk of adverse events after ACL reconstruction.<sup>4,13,21,22,24,32-34</sup> The findings, however,  
103 have generally been limited by small numbers of studies, small number of patients, non-  
104 representative data sources, and concerns about incomplete data capture.

105

106 The purpose of this study was to determine the risks of adverse outcomes following anterior cruciate  
107 ligament reconstruction within 90-days of surgery, with comparison, where possible, to the rate of  
108 adverse events reported in the general population. The secondary aim was to examine the risk of  
109 subsequent ipsilateral and contralateral ACL reconstruction within 5-years.

110

111

## 112 **METHODS**

113

### 114 Data source

115 National Hospital Episode Statistics (HES) data was obtained from NHS Digital (application DARS-  
116 NIC-68703) and linked with the Office for National Statistics (ONS) mortality dataset. HES contains  
117 a record of all patient attendances at NHS hospitals in England, covering episodes of care delivered  
118 in treatment centres (including those in the independent sectors) funded by the NHS, episodes of care  
119 in England where patients are resident outside of England, and privately funded patients treated  
120 within NHS England hospitals.<sup>28</sup> The information recorded in the HES database includes patient  
121 demographic and residence data, primary and secondary diagnoses including comorbidities, and all  
122 procedures undertaken. The ONS mortality dataset contains national death certificate data,  
123 irrespective of whether the death occurred in hospital or in the community.

124

### 125 Procedures

126 All HES records between 1 April 1997 and 31 March 2017 were extracted for patients undergoing  
127 ACL reconstruction. Episodes were identified from the Classification of Surgical Operations and  
128 Procedures (OPCS-4) codes in the procedure fields within the HES data (W742 [excluding repair or  
129 synthetic graft procedures W841, W842, W723, W724]).<sup>29</sup> Simultaneous or staged (within 6 months)  
130 bilateral cases were excluded along with cases with concurrent articular cartilage or multiple  
131 ligament surgery. Per patient, per side, only the first (primary) ACL procedure was included as an  
132 index procedure. For each patient identified as undergoing an index ACL reconstruction, all the  
133 patient's prior and subsequent hospital episodes were identified for the entire data extraction period.  
134 Subsequent revision procedures in the same patient were not eligible for analysis as index procedures  
135 but were analysed as reoperation outcomes (see Outcomes, below). Cases missing essential data  
136 (age, sex, procedure date, procedure laterality) were excluded from the study. Cases missing non-  
137 essential data (index of multiple deprivation, ethnicity, rurality) were included except for analyses  
138 adjusting for these specific variables.

139

140 Outcomes

141 Complications were identified by a review of a combination of the twenty International Statistical  
142 Classification of Diseases and Related Health Problems (ICD-10) diagnosis fields per hospital  
143 episode and twenty-four OPCS operation fields per episode.<sup>29,39</sup> Complications identified from the  
144 ICD-10 diagnosis fields were as follows: pulmonary embolism (PE), myocardial infarction, stroke,  
145 lower respiratory tract infection, acute kidney injury, urinary tract infection, and neurovascular  
146 injury. Complications identified from the OPCS operation codes were confirmed to match with the  
147 laterality (left versus right) of the index procedure using the OPCS laterality codes. The procedure-  
148 based complications were as follows: joint infection, fasciotomy, general reoperation (any surgical  
149 procedure performed in the same knee within 90 days), revision ACL reconstruction, meniscal  
150 surgery, contralateral ACL reconstruction. Mortality data was extracted from the ONS mortality  
151 fields. The primary outcome was the occurrence of at least one serious complication within 90-days  
152 of an index ACL reconstruction. A serious complication was defined as either myocardial infarction,  
153 stroke, pulmonary embolism, infection requiring surgery (open or arthroscopic irrigation and lavage  
154 or debridement [excluding haemarthrosis]), fasciotomy, neurovascular injury, or death. The rate of  
155 each individual complication was then evaluated secondarily, with each complication counted  
156 whether in isolation of in combination with other adverse outcomes. The secondary outcomes were  
157 revision ACL reconstruction procedures, subsequent meniscal surgery procedures in the same knee,  
158 and contralateral knee ACL reconstruction procedures within 5-years.

159

160 Statistical analysis

161 Stata v15.1 (StataCorp, College Station, Texas, USA) was used to perform all analysis. Descriptive  
162 statistics were used to report demographic data. Complication rates were reported with confidence  
163 intervals corresponding to the proportion of the study sample. Logistic regression methods were used  
164 to first calculate the unadjusted odds of each complication occurring within 90-days by age, sex,  
165 index of multiple deprivation (quintile derived from regional factors in England including average



166 income, employment, education, housing, and crime; 1=least deprived area, 5=most deprived),<sup>30</sup>  
167 ethnicity, modified Charlson comorbidity index (Summary Hospital-level Mortality Indicator  
168 Specification; derived with a maximum 5-year ICD-10 diagnosis code lookback period),<sup>7,20,41</sup> year of  
169 treatment, ethnicity, and rurality. The odds ratios were then adjusted including all these variables in  
170 the same statistical model. Cox proportional hazards modelling, adjusted in the same manner, was  
171 used to identify associations with same side revision ACL reconstruction, contralateral ACL  
172 reconstruction, and same side meniscal surgery. Long-term rates of revision ACL reconstruction  
173 were also assessed using a mortality adjusted Kaplan-Meier survival analysis (not undergoing  
174 revision surgery).

175  
176 In order to guide patients and clinicians regarding the relative risk of undergoing the procedure, age-  
177 sex matched general population study data was reviewed where available in published data.  
178 Population and adverse event numbers were extracted from the ONS national mortality report and  
179 from publications reporting population rates of myocardial infarction, pulmonary embolus, stroke,  
180 and septic arthritis respectively.<sup>10,12,17,36,38</sup> Annualised rates were adjusted directly to estimate 90-day  
181 complication rates. The relative risk (risk ratio) of adverse events was calculated, where possible, by  
182 comparing the adverse event rate in an age-sex matched sample of patients in the general population.  
183 The number needed to harm (NNH) was calculated from the risk difference between the study cohort  
184 and the general population data (attributable risk).

185

#### 186 Role of the funding source

187 The sponsors of the study had no role in the design or conduct of the study. All authors take  
188 responsibility for the contents of the study and the decision to proceed to publication.

189 **RESULTS**

190

191 Between 1 April 1997 and 31 March 2017, 133 270 ACL reconstructions (124 489 patients) were  
192 identified of which 104 255 (102 309 patients) were included (Figure 1). The mean age of the case  
193 cohort was 29.2 years (SD 9.68) and 23 435 (22.5%) were performed in female patients (Table 1).  
194 The majority of patients had no record of comorbidities (modified Charlson index zero; 90.65%),  
195 were of white ethnicity (75.62%), and from urban regions (79.97%) (Table 1). For five-year follow-  
196 up ipsilateral ACL and meniscal surgery and contralateral ACL reconstruction, data was available  
197 for 54,275 procedures (Table 2).

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199 **Figure 1: Case selection**

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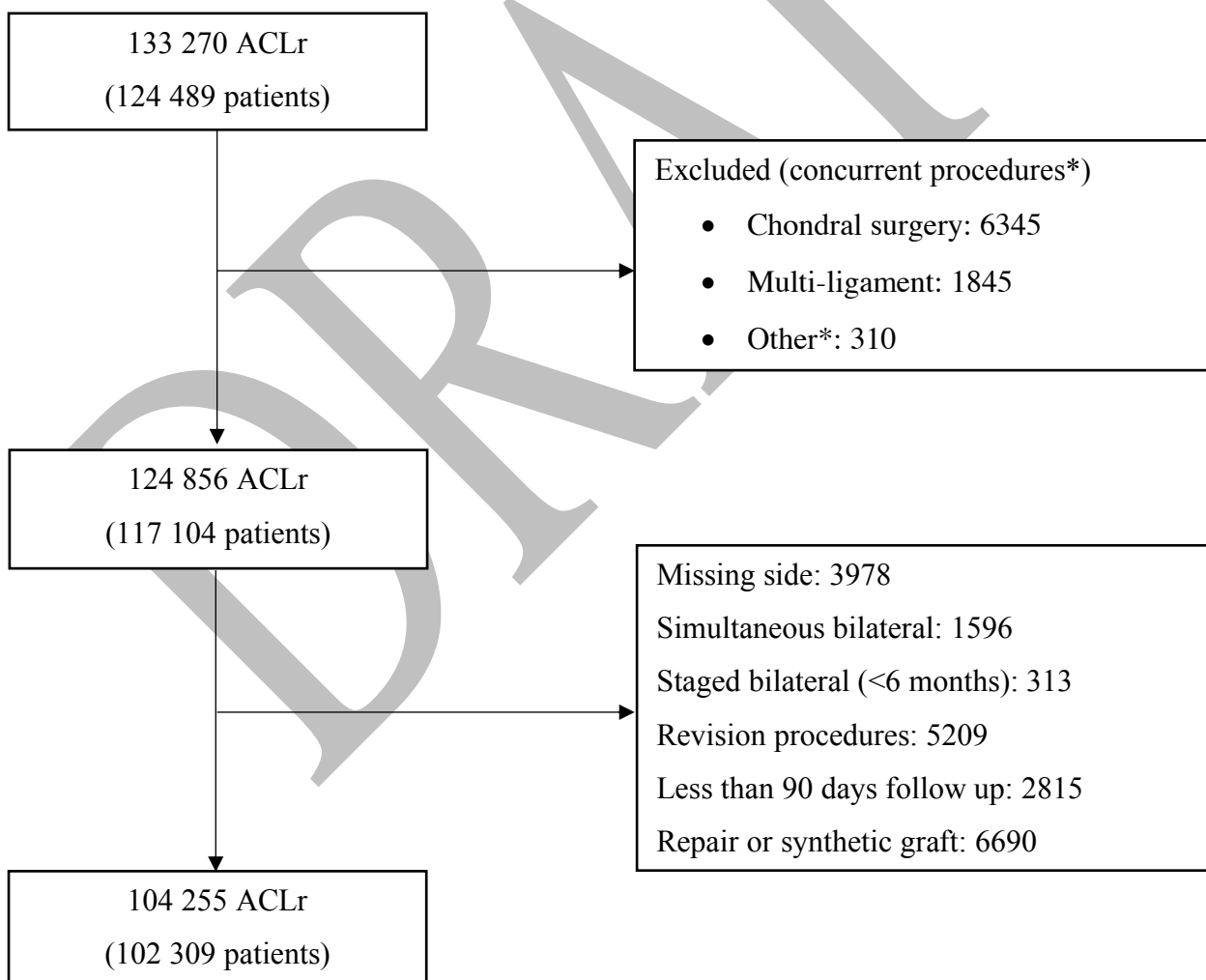
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215 \* Same side or contralateral surgical procedures (not mutually exclusive). Other procedures included knee arthroplasty, fusion,  
 216 interposition.

217

218 **TABLE 1: Demographics**

219

	n	%
<b>All procedures</b>		
Total	104 255	100%
<b>Sex</b>		
Male	80820	77.52% (77.27, 77.77)
Female	23435	22.48% (22.23, 22.73)
<b>Age group (years)</b>		
<20	15357	14.73% (14.52, 14.95)
20-39	72331	69.38% (69.10, 69.66)
40-59	16069	15.41% (15.19, 15.63)
60-79	475	0.46% (0.42, 0.50)
80+	23	0.02% (0.01, 0.03)
<b>Charlson index</b>		
0	94503	90.65% (90.47, 90.82)
1 - 15	9711	9.31% (9.14, 9.49)
16 - 30	39	0.04% (0.03, 0.05)
31 - 50	2	0.00% (0.00, 0.01)
<b>IMD</b>		
1	21761	20.87% (20.63, 21.12)
2	20853	20.00% (19.76, 20.25)
3	20902	20.05% (19.81, 20.29)
4	20173	19.35% (19.11, 19.59)
5	18860	18.09% (17.86, 18.33)
Missing	1706	
<b>Rurality</b>		
Urban	83376	79.97% (79.73, 80.22)
Rural	20064	19.25% (19.01, 19.49)
Missing	815	
<b>Ethnicity</b>		
White	78839	75.62% (75.36, 75.88)
Asian	4658	4.47% (4.34, 4.60)
Black	2025	1.94% (1.86, 2.03)
Mixed	1245	1.19% (1.13, 1.26)
Other	1821	1.75% (1.67, 1.83)
Missing	15667	

220

221 The rates of adverse medical and surgical outcomes within 90-days, and ligamentous or meniscal  
 222 reoperation within 5-years, are summarised in Table 2. Overall, 0.97% underwent any reoperation  
 223 with 90-days (1013/104255; 95% CI 0.91 to 1.03) and 0.65% developed a serious complication  
 224 (675/104255; 95% CI 0.60 to 0.70) including a rate of 0.47% reoperations for presumed deep  
 225 infection (494/104255; 95% CI 0.43 to 0.52). The rate of pulmonary embolism was 0.12%  
 226 (129/104255; 95% CI 0.10 to 0.15), of neurovascular injury was 0.02% (19/104255; 95% CI 0.01 to  
 227 0.03), and of fasciotomy was 0.02% (17/104255; 95% CI 0.01 to 0.03). Within 5-years, 3.22%  
 228 (1746/54275; 95% CI 3.07 to 3.37) underwent a revision ACL reconstruction in the same knee,  
 229 2.86% (1553/54275; 95% CI 2.72 to 3.01) underwent ACL reconstruction to the opposite knee, and  
 230 0.63% (340/54275; 95% CI 0.56 to 0.70) underwent subsequent meniscal surgery in the same knee.  
 231 The longer-term rates of revision ACL reconstruction are summarised in the mortality adjusted  
 232 Kaplan-Meier chart, Figure 2, estimating revision rates out to 15-years by age group. Younger  
 233 patients were at greater risk of revision as shown (Figure 2, Table 4).

234

235 **TABLE 2: Adverse outcomes within 90-days and reoperation rates within 5-years**

	n	% (95% CI)
<b>90-day adverse outcomes (n=104 255)</b>		
Any re-operation‡	1013	0.97% (0.91, 1.03)
Serious complication †	675	0.65% (0.60, 0.70)
Infection*	494	0.47% (0.43, 0.52)
Lower respiratory tract infection	102	0.10% (0.08, 0.12)
Urinary tract infection	44	0.04% (0.03, 0.06)
Pulmonary embolism	129	0.12% (0.10, 0.15)
Myocardial infarction	4	< 0.01% (0.00, 0.01)
Mortality	14	0.01% (0.01, 0.02)
Stroke	2	< 0.01% (0.00, 0.01)
Acute kidney injury	13	0.01% (0.01, 0.02)
Neurovascular injury	19	0.02% (0.01, 0.03)
Fasciotomy	17	0.02% (0.01, 0.03)
Fatal pulmonary embolus	0	0.00% (0.00, 0.00)

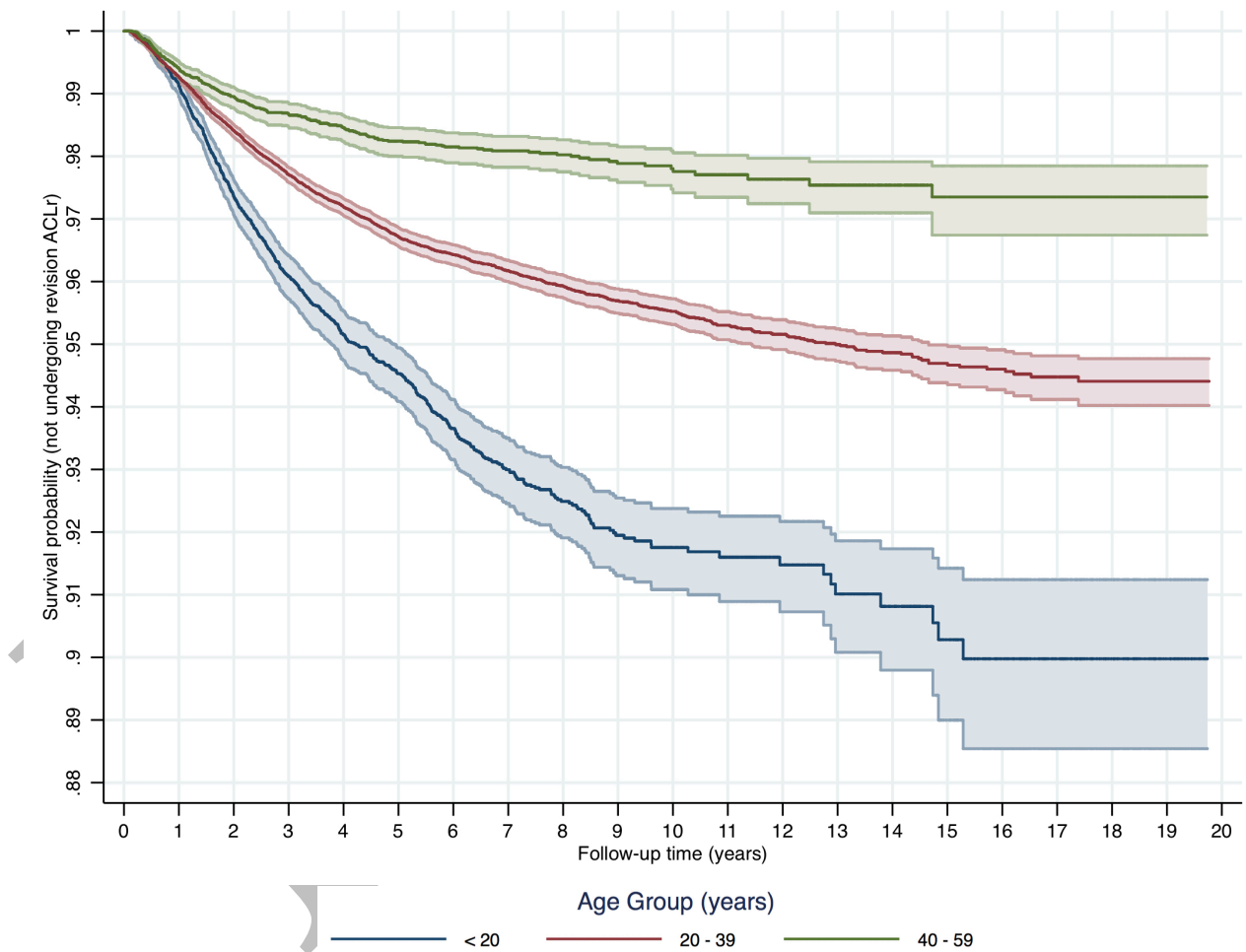
5-year reoperation (n = 54 275)		
Revision ACLr	1746	3.22% (3.07, 3.37)
Subsequent contralateral ACLr	1553	2.86% (2.72, 3.01)
Meniscal surgery	340	0.63% (0.56, 0.70)

236

237 † = At least one serious complication within 90 days, defined as either pulmonary embolism, myocardial infarction, stroke, infection  
 238 requiring surgery, fasciotomy, neurovascular injury, or death; \* = Infection requiring surgery (open or arthroscopic lavage and  
 239 irrigation or debridement of wound or joint); ‡ = Any procedure performed in the same knee (e.g. washout, meniscal repair, repeat  
 240 meniscectomy, chondroplasty, ligamentous surgery, fasciotomy); ACLr = ACL reconstruction

241

242 **Figure 2: Long-term survival curve (not undergoing subsequent revision ACL reconstruction)**



243

244 \* Age groups < 20 years and > 59 years suppressed due to small numbers

245

246 Patient factors associated with adverse outcomes within 90-days are summarised in Table 3. Female  
 247 patients were at lower odds of serious complications and infection; the overall odds of serious  
 248 complications and of infection fell slightly over time (Table 3). Older age groups (under 20-years vs.

249 20-39-years vs. 40-59-years) were at greater risk of serious complications and pulmonary embolism  
 250 as were patients with a greater modified Charlson comorbidity index (Table 3). Index of multiple  
 251 deprivation and rurality did not affect the odds of complications. Patients of black ethnicity were  
 252 found to be at greater odds of serious complications (adjusted OR 1.61; 95% CI 1.03 to 2.52) mainly  
 253 due to greater odds of infection in comparison to patients in White ethnicity groups (adjusted OR  
 254 1.88; 95% CI 1.16 to 3.05). The adjusted odds of serious complications by each patient factor  
 255 (including patient age) is shown graphically in the forest plot, Figure 3.

256

257 **TABLE 3: Unadjusted and adjusted odds<sup>‡</sup> of serious complication, pulmonary embolism, infection**

258

	Serious complication † (90 days)		Pulmonary embolism (90 days)		Infection* (90 days)	
	Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)
<b>Sex</b>						
Male	1.00	1.00	1.00	1.00	1.00	1.00
Female	0.63 (0.51, 0.77)	0.61 (0.49, 0.77)	0.96 (0.63, 1.45)	0.91 (0.58, 1.41)	0.49 (0.38, 0.64)	0.48 (0.36, 0.65)
<b>Age group</b>						
<20	0.61 (0.47, 0.79)	0.60 (0.45, 0.80)	0.35 (0.15, 0.81)	0.42 (0.18, 0.98)	0.65 (0.48, 0.87)	0.64 (0.47, 0.88)
20-39	1.00	1.00	1.00	1.00	1.00	1.00
40-59	1.20 (0.98, 1.46)	1.26 (1.02, 1.56)	2.25 (1.54, 3.30)	2.50 (1.66, 3.76)	0.88 (0.68, 1.13)	0.90 (0.68, 1.18)
60-79	2.25 (1.06, 4.77)	1.94 (0.84, 4.45)	5.74 (1.81, 18.24)	5.32 (1.58, 17.93)	0.82 (0.20, 3.32)	0.45 (0.06, 3.22)
80+	6.83 (0.92, 50.79)	7.63 (1.01, 57.56)	-	-	-	-
<b>Year</b>						
Per year	0.98 (0.96, 0.99)	0.96 (0.95, 0.98)	0.97 (0.94, 1.01)	0.97 (0.93, 1.01)	0.98 (0.96, 1.00)	0.97 (0.94, 0.99)
<b>Modified Charlson comorbidity index</b>						
Per unit	1.11 (1.07, 1.14)	1.10 (1.05, 1.14)	1.16 (1.10, 1.23)	1.11 (1.04, 1.19)	1.07 (1.02, 1.12)	1.08 (1.03, 1.14)
<b>Index of multiple deprivation (quintile)</b>						
1 = least	1.00	1.00	1.00	1.00	1.00	1.00
2	1.08 (0.86, 1.36)	1.05 (0.82, 1.34)	0.73 (0.43, 1.24)	0.62 (0.35, 1.09)	1.16 (0.88, 1.52)	1.18 (0.89, 1.58)
3	0.95 (0.75, 1.21)	0.95 (0.74, 1.22)	0.79 (0.47, 1.33)	0.66 (0.37, 1.15)	0.99 (0.74, 1.31)	1.02 (0.76, 1.37)
4	0.93 (0.73, 1.18)	0.83 (0.64, 1.09)	0.56 (0.31, 1.00)	0.48 (0.25, 0.90)	1.02 (0.77, 1.36)	0.91 (0.67, 1.24)
5 = most	1.02 (0.80, 1.29)	0.98 (0.75, 1.27)	1.05 (0.64, 1.72)	1.06 (0.62, 1.78)	1.05 (0.79, 1.40)	0.97 (0.71, 1.32)
<b>Rurality</b>						
Urban	1.00	1.00	1.00	1.00	1.00	1.00
Rural	1.08 (0.89, 1.30)	1.06 (0.86, 1.31)	0.90 (0.57, 1.42)	0.90 (0.54, 1.49)	1.08 (0.86, 1.34)	1.06 (0.83, 1.36)
<b>Ethnicity</b>						
White	1.00	1.00	1.00	1.00	1.00	1.00
Asian	1.11 (0.79, 1.56)	1.13 (0.80, 1.60)	1.15 (0.53, 2.48)	1.18 (0.54, 2.56)	1.13 (0.76, 1.69)	1.13 (0.75, 1.69)
Black	1.53 (0.99, 2.38)	1.61 (1.03, 2.52)	0.76 (0.19, 3.06)	0.75 (0.18, 3.09)	1.81 (1.13, 2.91)	1.88 (1.16, 3.05)

Mixed	0.35 (0.11, 1.10)	0.40 (0.13, 1.23)	-	-	0.49 (0.16, 1.52)	0.53 (0.17, 1.65)
Other	1.13 (0.67, 1.93)	1.19 (0.70, 2.03)	1.26 (0.40, 3.98)	1.31 (0.41, 4.15)	1.23 (0.67, 2.24)	1.27 (0.69, 2.32)

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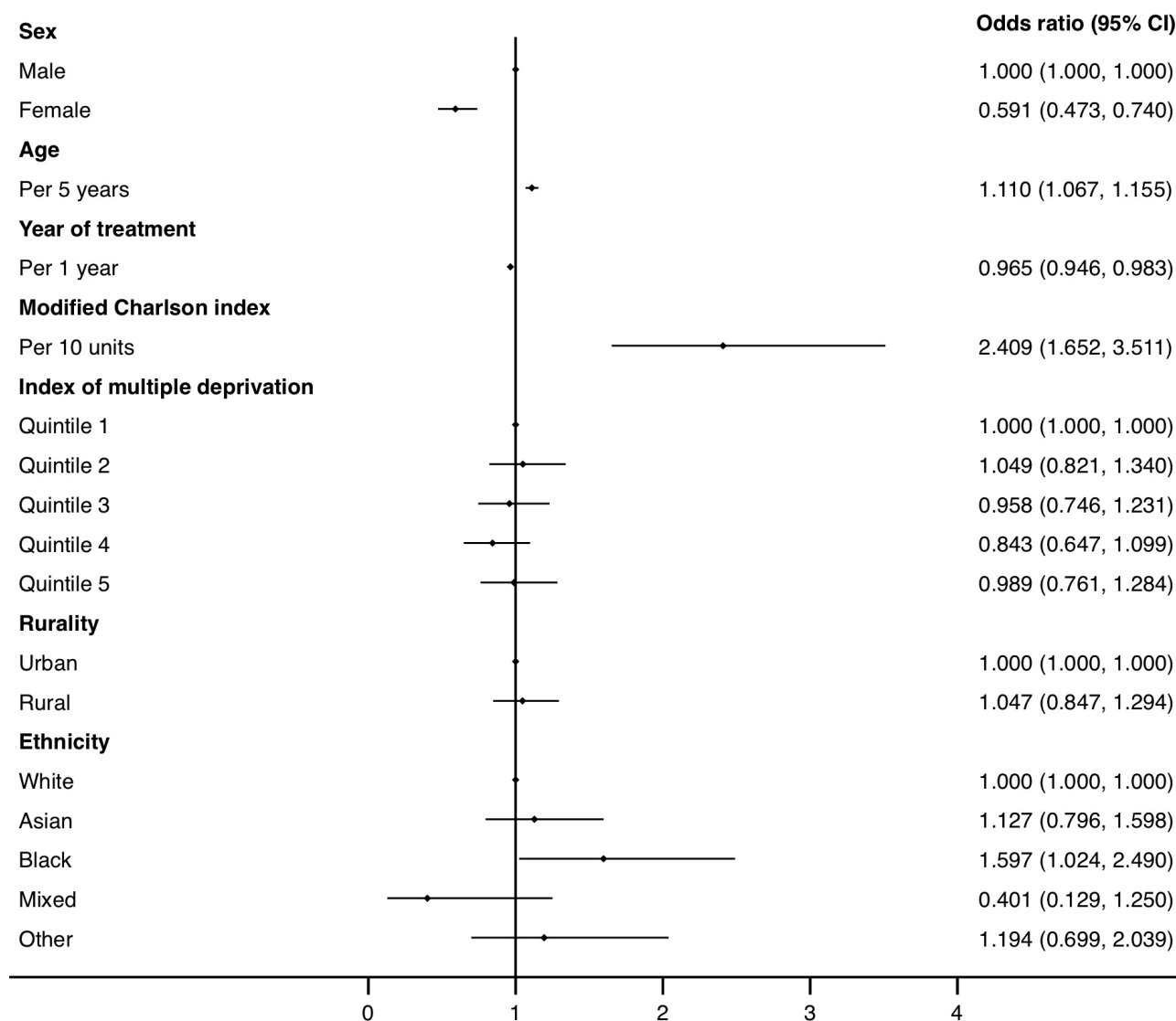
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‡ = procedure level multi-variable logistic regression model including sex, age group, year, Charlson co-morbidity index, index of multiple deprivation, rurality, and ethnicity; OR = odds ratio; CI = confidence interval; † = At least one serious complication within 90 days, defined as either pulmonary embolism, myocardial infarction, stroke, infection requiring surgery, fasciotomy, neurovascular injury, or death; \* = open or arthroscopic irrigation and lavage or debridement; - = suppressed.

DRAFT

264 **Figure 3: Forest plot of adjusted‡ odds of any serious complication within 90-days**



265

266 ‡ = procedure level multi-variable logistic regression model including sex, age group, year, modified Charlson  
 267 comorbidity index, index of multiple deprivation (quintile), rurality, and ethnicity

268

269 The patient factors associated with the risk of revision ACL reconstruction, contralateral ACL  
 270 reconstruction, and same side meniscal surgery is summarised in Table 4. Female patients were at  
 271 lower risk of revision ACL reconstruction (adjusted hazard ratio [HR] 0.81; 95% CI 0.74 to 0.89)  
 272 and subsequent meniscal surgery (adjusted HR 0.61; 95% CI 0.49 to 0.75), but not contralateral ACL  
 273 reconstruction (adjusted HR 1.06; 95% CI 0.95 to 1.18; Table 4). Older age groups (under 20-years  
 274 vs. 20-39-years vs. 40-59-years vs 60-79-years), patients from rural regions or greater deprivation,  
 275 and patients of Asian and Black ethnicity were less likely to undergo revision ACL reconstruction  
 276 (Table 4). Patients of Asian ethnicity were also of lower risk of meniscus surgery but increased risk



277 of contralateral ACL reconstruction (Table 4). All three outcomes were slightly more common over  
 278 the duration of the study by year of treatment. Patients with a greater modified Charlson comorbidity  
 279 index were slightly more likely to undergo revision ACL reconstruction (adjusted HR 1.03 per unit;  
 280 95% CI 1.01 to 1.06) but not meniscal surgery (adjusted HR 0.99; 95% CI 0.93 to 1.05) or  
 281 contralateral reconstruction (adjusted HR 0.99; 95% CI 0.96 to 1.03; Table 4).

282  
 283 The rate of mortality was lower in the ACL reconstruction cohort than reported in the general  
 284 population (risk ratio [RR] 0.09; 95% CI 0.05 to 0.14) (Table 5). For male patients (under the age of  
 285 80 years) undergoing ACL reconstruction, the risk of myocardial infarction was lower than in the  
 286 general population (RR 0.09; 95% CI 0.03 to 0.23). No myocardial infarction was identified for this  
 287 age-group in a female patient after ACL reconstruction. The rate of stroke (under the age of 75  
 288 years) was also lower in the ACL reconstruction cohort than the general population (RR 0.06; 95%  
 289 CI 0.01 to 0.23). In comparison, the risk of pulmonary embolism (RR 20.60; 95% CI 15.68 to 27.06)  
 290 and infection (RR 385.91; 95% CI 282.60 to 526.98) was elevated in comparison to general  
 291 population data. These data correspond to an estimated number needed to harm of 850 (95% CI 720-  
 292 1039) for one pulmonary embolism and 213 (95% CI 195-233) for one knee joint infection.

293  
 294 **TABLE 4: Unadjusted and adjusted hazard ratios for subsequent ipsilateral revision reconstruction,**  
 295 **contralateral ligament reconstruction, ipsilateral meniscal surgery**

296

	Revision ACLr		Subsequent Contralateral ACLr		Subsequent meniscal surgery	
	Crude HR (95% CI)	Adjusted HR (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)
<b>Sex</b>						
Male	1.00	1.00	1.00	1.00	1.00	1.00
Female	0.79 (0.73, 0.87)	0.81 (0.74, 0.89)	1.05 (0.95, 1.15)	1.06 (0.95, 1.18)	0.62 (0.50, 0.76)	0.61 (0.49, 0.75)
<b>Age group</b>						
<20	1.78 (1.64, 1.93)	1.75 (1.61, 1.91)	2.28 (2.08, 2.51)	2.12 (1.92, 2.35)	2.22 (1.88, 2.61)	2.11 (1.78, 2.50)
20-39	1.00	1.00	1.00	1.00	1.00	1.00
40-59	0.52 (0.46, 0.59)	0.51 (0.44, 0.58)	0.44 (0.37, 0.52)	0.42 (0.35, 0.51)	0.36 (0.26, 0.50)	0.34 (0.24, 0.48)
60-79	0.23 (0.07, 0.70)	0.15 (0.04, 0.61)	0.23 (0.06, 0.93)	0.13 (0.02, 0.89)	-	-

80+	-	-	-	-	-	-
<b>Year</b>						
Per year	1.03 (1.02, 1.04)	1.01 (1.00, 1.02)	1.07 (1.06, 1.09)	1.06 (1.04, 1.07)	1.14 (1.11, 1.17)	1.12 (1.09, 1.15)
<b>Modified Charlson comorbidity index</b>						
Per unit	1.03 (1.01, 1.05)	1.03 (1.01, 1.06)	1.00 (0.97, 1.04)	0.99 (0.96, 1.03)	1.01 (0.95, 1.07)	0.99 (0.93, 1.05)
<b>Index of multiple deprivation (quintile)</b>						
1 = least	1.00	1.00	1.00	1.00	1.00	1.00
2	0.87 (0.78, 0.96)	0.88 (0.79, 0.97)	0.93 (0.82, 1.06)	0.95 (0.82, 1.09)	0.98 (0.79, 1.20)	0.94 (0.75, 1.16)
3	0.79 (0.71, 0.88)	0.80 (0.72, 0.89)	1.01 (0.89, 1.15)	1.00 (0.87, 1.15)	0.82 (0.66, 1.03)	0.83 (0.66, 1.04)
4	0.78 (0.70, 0.87)	0.74 (0.66, 0.82)	0.99 (0.87, 1.13)	0.96 (0.83, 1.11)	0.79 (0.63, 0.99)	0.75 (0.60, 0.95)
5 = most	0.68 (0.61, 0.77)	0.64 (0.56, 0.72)	1.03 (0.91, 1.18)	0.96 (0.83, 1.11)	0.58 (0.45, 0.74)	0.52 (0.40, 0.69)
<b>Rurality</b>						
Urban	1.00	1.00	1.00	1.00	1.00	1.00
Rural	0.83 (0.75, 0.91)	0.76 (0.69, 0.84)	1.02 (0.92, 1.13)	0.98 (0.87, 1.11)	0.98 (0.81, 1.17)	0.89 (0.73, 1.08)
<b>Ethnicity</b>						
White	1.00	1.00	1.00	1.00	1.00	1.00
Asian	0.75 (0.62, 0.90)	0.73 (0.61, 0.89)	1.34 (1.11, 1.61)	1.31 (1.09, 1.59)	0.59 (0.37, 0.91)	0.58 (0.37, 0.91)
Black	0.72 (0.55, 0.95)	0.74 (0.56, 0.97)	1.05 (0.78, 1.42)	1.00 (0.74, 1.35)	0.69 (0.38, 1.25)	0.73 (0.40, 1.34)
Mixed	1.15 (0.85, 1.55)	1.09 (0.81, 1.46)	1.26 (0.87, 1.84)	1.09 (0.75, 1.59)	1.17 (0.63, 2.19)	1.05 (0.56, 1.97)
Other	0.48 (0.33, 0.69)	0.50 (0.34, 0.72)	1.04 (0.75, 1.45)	1.07 (0.77, 1.48)	0.46 (0.21, 1.03)	0.49 (0.22, 1.09)

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‡ = procedure level Cox proportional hazards model including sex, age group, year, Charlson co-morbidity index, index of multiple deprivation, rurality, and ethnicity. HR = hazard ratio; CI = confidence interval; ACLr = anterior cruciate ligament reconstruction; - = suppressed.

304 **TABLE 5: 90-day adverse event rates in study cohort versus age and/or sex matched general population**  
 305 **data**  
 306

	General population risk % (95% CI) [publication reference]	Study cohort risk % (95% CI)	Risk ratio (95% CI)
<b>Mortality</b>			
Overall:	0.158% (0.157, 0.159) <sup>10 *</sup>	0.013% (0.007, 0.023)	0.09 (0.05, 0.14)
Age < 20 years:	0.007% (0.007, 0.008) <sup>10 *</sup>	0.007% (0.000, 0.036)	0.89 (0.12, 6.30)
Age 20 - 39 years:	0.011% (0.011, 0.012) <sup>10 *</sup>	0.010% (0.004, 0.020)	0.84 (0.40, 1.77)
Age 40 - 59 years:	0.043% (0.042, 0.044) <sup>10 *</sup>	0.031% (0.010, 0.073)	0.73 (0.30, 1.75)
Age 60 - 79 years:	0.233% (0.230, 0.236) <sup>10 *</sup>	0.000% (0.000, 0.774)	-
Age 80 + years:	2.043% (2.026, 2.060) <sup>10 *</sup>	4.348% (0.110, 21.949)	2.08 (0.31, 14.18)
<b>Myocardial infarction</b>			
Men (age < 80):	0.058% (0.049, 0.067) <sup>38</sup>	0.005% (0.001, 0.013)	0.09 (0.03, 0.23)
Women (age < 80):	0.028% (0.022, 0.035) <sup>38</sup>	0.000% (0.000, 0.016)	-
<b>Pulmonary embolism</b>			
Overall:	0.006% (0.005, 0.007) <sup>36</sup>	0.124% (0.103, 0.147)	20.60 (15.68, 27.06)
<b>Stroke</b>			
Age < 75 years:	0.034% (0.030, 0.039) <sup>12</sup>	0.002% (0.000, 0.007)	0.06 (0.01, 0.23)
<b>Septic arthritis (native knee joint infection)</b>			
Overall:	0.001% (0.001, 0.002) <sup>17 ‡</sup>	0.474% (0.433, 0.517)	385.91 (282.60, 526.98)

307

308 - = suppressed;

309 \* = Office for National Statistics population level data for England (2016, excluding death due to cancer);

310 ‡ = excluding iatrogenic causes.

311

312 **DISCUSSION**

313

314 Principal findings

315 Our study of 104 255 procedures shows that serious adverse events occur rarely following ACL  
316 reconstruction and that the risk of serious complications has fallen slightly over time. Most medical  
317 adverse events occur less frequently following ACL reconstruction than in the general population  
318 which is likely a healthy-cohort observation, however there is an important attributable risk of a  
319 pulmonary embolism and infection. For every 850 ACL reconstructions performed, one pulmonary  
320 embolism and four knee infections could occur and be attributed to the procedure. Around 3.2% of  
321 patients undergo revision ACL reconstruction and 2.9% contralateral ACL reconstruction within  
322 five-years. These findings will be crucial to informing patients and clinicians when deciding whether  
323 to proceed with elective ACL reconstruction. The recognised benefits of the procedure can now be  
324 interpreted in the context of the associated potential risks.

325

326 Comparison with previous studies

327 Despite the number of ACL reconstruction procedures performed worldwide,<sup>2,5,26</sup> the adverse  
328 outcomes attributable to undergoing the procedure have previously been poorly defined. Several  
329 studies have reported adverse events following “knee arthroscopy” but few have reported data  
330 specifically for ACL reconstruction in comparison to more commonly performed purely  
331 arthroscopic, procedures such as arthroscopic partial meniscectomy.<sup>4,13,21,22,24,32–34,37</sup> In comparison,  
332 anterior cruciate ligament reconstruction is a more major intervention, associated with greater  
333 operative time and usually both open and arthroscopic incisions and techniques.<sup>31</sup>

334

335 In our study, only pulmonary embolism and infection were found to occur at a greater rate than  
336 observed in comparative general population data. These findings are similar to those reported  
337 recently for a cohort of 699 965 arthroscopic partial meniscectomy procedures.<sup>1</sup> In this  
338 meniscectomy cohort, serious complications occurred in 0.32% (95% CI 0.30 to 0.33) in comparison

339 to 0.65% (95% CI 0.60 to 0.70) following ACL reconstruction using the same definitions. This  
340 difference in the serious complication rate was driven in part by a higher reoperation rate for  
341 infection following ACL reconstruction at 0.47% (95% CI 0.43 to 0.52) in comparison to 0.14%  
342 (95% CI 0.13 to 0.14) following arthroscopic partial meniscectomy.<sup>1</sup> The infection rate identified in  
343 our study was similar but statistically more precise with an estimated deep infection rate of 0.43%  
344 (58/13401; 95% CI 0.32 to 0.56) ACL reconstruction cases reported in a systematic review of level 2  
345 studies in 2017.<sup>4</sup> It is, however, higher than a rate of 0.14% (7/4933; 95% CI 0.05 to 0.29) reported  
346 in a study of the American College of Surgeons National Surgical Quality Improvement Program  
347 (ACS NSQIP) database.<sup>9</sup> With comparison to general population data, the estimated number needed  
348 to harm for infection was 213 for our ACL reconstruction cohort versus 749 for the arthroscopic  
349 partial meniscectomy cohort.<sup>1</sup>

350  
351 The rate of pulmonary embolism within 90-days was greater in our ACL reconstruction cohort at  
352 0.12% (95% CI 0.10 to 0.15) in comparison to 0.08% (95% CI 0.07 to 0.09) in the recent  
353 arthroscopic partial meniscectomy cohort.<sup>1</sup> No cases of fatal pulmonary embolism were identified  
354 following ACL reconstruction. The pulmonary embolism rate was comparable but statistically much  
355 more precise than the estimated rate of pulmonary embolism reported in a systematic review of  
356 forty-seven ACL reconstruction studies published in 2016, which reported a mean pulmonary  
357 embolism rate of 0.14% but with wide confidence intervals (1/704; 95% CI 0.00 to 0.79).<sup>22</sup> The rate  
358 is also the same as another 2016 study of 4933 patients reporting a PE rate of 0.12% within 30-days  
359 (6/4933).<sup>9</sup> With comparison to general population data, the number needed to harm for pulmonary  
360 embolism was estimated to be 850 for ACL reconstruction in comparison to 1390 for arthroscopic  
361 partial meniscectomy.<sup>1</sup>

362  
363 Prescribing data is unavailable in this database and therefore the type and duration of any antibiotic  
364 or venous thromboembolic (VTE) prophylaxis given to the patients in this study is unknown and it is  
365 likely that local practice varied. Previous work suggested that while antibiotic prophylaxis is routine

366 in most countries, VTE prophylaxis rates vary from around 17% Norway, 51% in the United States,  
367 to 79% in Denmark.<sup>18,23</sup> The findings in this study may support further investigation and  
368 consideration of routine VTE prophylaxis in this population.

369

370 Other direct surgical complications such as neurovascular injury and fasciotomy could not be  
371 compared to general population data. Both neurovascular injury and fasciotomy procedures were  
372 identified rarely following ACL reconstruction, at 0.02% in both cases. It must be noted, however,  
373 that these rates are approximately 5-10 times greater than reported following arthroscopic partial  
374 meniscectomy.<sup>1</sup> The greater risk of these complications, infection, and pulmonary embolism,  
375 associated with ACL reconstruction in comparison to arthroscopic partial meniscectomy is  
376 unsurprising given the more invasive nature of ACL reconstruction, with additional surgical  
377 incisions and more prolonged operative time.<sup>31</sup>

378

379 Regarding reoperation rates, the largest previous study published in 2016 reported an ACL revision  
380 rate of 3.6% (587/16336; 95% CI 3.31 to 3.89), utilising US military health record data.<sup>32</sup> Our study  
381 reports a very similar rate of revision at 3.22% and adds importantly to these data, reporting  
382 contralateral ACL reconstruction in 2.86% and same side meniscal surgery in 0.63% within five-  
383 years. The risk of revision ACL reconstruction was considerably greater in younger age groups,  
384 although it unknown if this reflects differences in injury rates or differences in propensity to re-  
385 operate following injury.

386

387 It is interesting that the risk of revision ACL reconstruction in the same knee was similar to the risk  
388 of contralateral ACL reconstruction, which suggests that both the reconstructed ligament and the  
389 native opposite knee ligament are at comparable risk of rupture following an ACL reconstruction. A  
390 systematic review of nine studies and a smaller number of patients previously reported an ipsilateral  
391 graft re-rupture rate of 7.9% (211/2682) but a higher 12.5% (335/2682) risk of contralateral ACL  
392 injury.<sup>24</sup> Rates of subsequent meniscal surgery after ACL injury have rarely been reported. Frobell

393 et. al. reported a 9.7% (6/62; 95% CI 3.6 to 19.9) following ACL reconstruction and up to 49.2%  
394 (29/59; 95% CI 35.9 to 62.5) following a non-operative treatment strategy. A much lower rate of  
395 subsequent meniscal surgery was observed in our population at 0.63% (95% CI 0.56 to 0.70) which  
396 may reflect higher thresholds for subsequent intervention or lower symptomatic injury rates.

397

398 Our study found revision reconstruction rates to be lower in women. This finding is similar to a  
399 recent systematic review of smaller studies which reported lower rates of ipsilateral graft rupture in  
400 women.<sup>27</sup> This review also found women had a higher rate of contralateral knee injury however in  
401 our study we found no difference in contralateral knee reconstruction rates in women versus men.  
402 Subsequent meniscal surgery rates were also lower in women than men. Our study provides clear  
403 reference data for reconstruction rates in men and women and further investigation into the  
404 physiological, anatomical, and biomechanical factors that underlie these differences is warranted,  
405 with specific focus on preventative interventions. These findings will be crucial to the education of  
406 patients following ACL injury and reconstruction and inform collaboration between patients,  
407 physiotherapists, and clinicians in optimising current and future rehabilitation strategies.

408

#### 409 Strengths and limitations

410 Our study is strengthened by the inclusion of 104 255 ACL reconstruction cases over a twenty-year  
411 period, utilising data from the complete national health database for England, UK. To our  
412 knowledge, this is by far the largest reported series of ACL reconstruction cases and the largest to  
413 report adverse outcomes. Patients undergoing bilateral surgery (within 6 months), multiple ligament  
414 reconstruction, ACL repair, synthetic graft procedures, or articular cartilage surgery were excluded.  
415 Patients undergoing concurrent meniscal procedures were, however, included as these procedures  
416 were common (approximately 28%) and therefore including these cases makes the cohort more  
417 representative of normal practice. Our study is also the most comprehensive evaluation of adverse  
418 outcomes, including the broad range of surgical and medical complications that may occur and,  
419 where possible, risk has been compared to age-sex matched general population data. The comparison

420 to general population data is relative crude but together with adverse outcome data following  
421 arthroscopic partial meniscectomy extracted from the same database, provides for the first time an  
422 important estimate of the attributable risk associated with ACL reconstruction.

423

424 HES data includes diagnosis and intervention data from admitted hospital care episodes in the  
425 national health service, England, and is collected routinely for hospital reimbursement, audit and  
426 research purposes. Although HES comprehensively records diagnosis and procedural data for  
427 patients admitted to hospital, there are some limitations. Although our data included a patient-  
428 specific modified Charlson comorbidity index, there are some important patient specific factors such  
429 as body mass index and smoking status that are not recorded in HES and are likely to impact upon  
430 risk. Regarding the accuracy of data coding in the database, the Charlson comorbidity index as  
431 calculated from HES diagnosis fields and records of serious vascular complications have been  
432 validated against primary care data.<sup>8,40</sup> Some patient variables such as ethnicity, however, may be  
433 less reliably coded. It is also important to note that the OPCS-4 codes used to identify ACL  
434 reconstruction procedures for our patient cohort will have captured some posterior cruciate ligament  
435 reconstruction procedures. This is inevitable given the nature of the codes used for this procedure but  
436 the proportion of the posterior cruciate ligament reconstruction procedures performed is very small  
437 in comparison to ACL reconstruction and therefore we believe these procedures are unlikely to have  
438 materially altered our findings.<sup>3</sup> The first ACL reconstruction per patient, per knee, was considered  
439 the primary procedure and revision procedures identified as any subsequent ACL reconstruction.  
440 Any primary procedure undertaken prior to 1<sup>st</sup> April 1997, however, would not be identified and  
441 therefore it is possible a small number of revision procedures could have been included in our cohort  
442 as no “revision” code is available. From HES data we are also unable to determine the impact from  
443 operative factors, such as reconstruction technique and choice of graft on outcome as these operative  
444 techniques are not recorded.

445



446 Diagnoses from primary care or the outpatient department are not available in the HES inpatient  
447 dataset unless these diagnoses were associated with a later hospital admission for care or surgery.  
448 This means, for example, that the reported revision ACL reconstruction and contralateral ACL  
449 reconstruction rates in our study will be lower than the true ACL injury rates in the population.  
450 Similarly, soft tissue infections managed non-operatively will not have been recorded. Another  
451 limitation of the HES database is that laboratory and radiological data is not recorded. Therefore,  
452 whilst cases of knee open or arthroscopic irrigation and lavage or debridement with an associated  
453 'haemarthrosis' diagnosis code were not recorded as infections, from the remaining lavage and  
454 debridement procedures we cannot distinguish procedures performed for a laboratory confirmed  
455 infection from those with a suspected infection. The clinical implications in each case may be quite  
456 different and an important limitation of this observational HES data. It must also be considered that  
457 some patients may have undergone their primary ACL reconstruction in the national health service  
458 but subsequent care in the private health sector. This is unlikely to have affected the record of  
459 adverse events within 90-days, as patients are highly likely to have returned to a national health  
460 hospital in these cases. In the longer term, however, some patients may have chosen to have revision  
461 ACL reconstruction or contralateral ACL reconstruction in the private health sector and would not be  
462 captured and this must be considered when interpreting our long-term reoperation data. Minor  
463 adverse outcomes that may have been managed in primary care would also not be captured. Our  
464 findings are, however, by far the most comprehensive to date regarding the true risk of serious  
465 complications associated with undergoing ACL reconstruction and, we believe, should be broadly  
466 generalisable to ACL reconstruction practice in developed countries, worldwide.

467

468 Conclusion

469 Whilst the risk of adverse events following ACL reconstruction is greater than following  
470 arthroscopic partial meniscectomy, the overall risk is still low and most medical complications  
471 (myocardial infarction, stroke, death) occur less frequently following ACL reconstruction than in the  
472 general population. Nevertheless, rare but serious complications including pulmonary embolism,

473 infection, fasciotomy and neurovascular injury may be provoked by undergoing ACL reconstruction.  
474 Same side and contralateral knee ACL reconstruction was performed in 3.2% and 2.9% of cases  
475 within 5-years of primary ACL reconstruction respectively. Our findings will be crucial to informing  
476 patients considering the relative risks and benefits of undergoing early ACL reconstruction in  
477 comparison to the emerging treatment strategy of rehabilitation and optional delayed ACL  
478 reconstruction. Further work is required to optimise not only the primary treatment selection but also  
479 strategies to reduce reinjury rates.

480

DRAFT

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