Barrett, M. C., Wilkinson, F. O., Blom, A. W., Whitehouse, M. R., & Kunutsor, S. K. (2021). Incidence, temporal trends and potential risk factors for aseptic loosening following primary unicompartmental knee arthroplasty: a meta-analysis of 96,294 knees. *The Knee*, *31*, 28-38. https://doi.org/10.1016/j.knee.2021.04.005

Supplementary Material

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Supplementary Material 1. PRISMA checklist

Section/topic	Item No	Checklist item	Reported on page No
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable, background, objectives, data sources, study eligibility criteria, participants, interventions, study appraisal and synthesis methods, results, limitations, conclusions and implications of key findings, systematic review registration number	2
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known	Introduction
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS)	Introduction
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (such as web address), and, if available, provide registration information including registration number	Methods
Eligibility criteria	6	Specify study characteristics (such as PICOS, length of follow-up) and report characteristics (such as years considered, language, publication status) used as criteria for eligibility, giving rationale	Methods
Information sources	7	Describe all information sources (such as databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched	Methods
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	Supplementary Material 3
Study selection	9	State the process for selecting studies (that is, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis)	Methods
Data collection process	10	Describe method of data extraction from reports (such as piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators	Methods
Data items	11	List and define all variables for which data were sought (such as PICOS, funding sources) and any assumptions and simplifications made	Methods
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis	Methods
Summary measures	13	State the principal summary measures (such as risk ratio, difference in means).	Methods
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (such as I^2 statistic) for each meta-analysis	Methods
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (such as publication bias, selective reporting within studies)	Methods
Additional analyses	16	Describe methods of additional analyses (such as sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified	Methods
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram	Results, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (such as study size, PICOS, follow-up period) and provide the citations	Results, Table 1, Table 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see item 12).	Results, Table 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present for each study (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot	Results, Figures 2-4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency	Results, Figures 2-4; Supplementary Materials 5-7
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15)	Not applicable
Additional analysis	23	Give results of additional analyses, if done (such as sensitivity or subgroup analyses, meta-regression) (see item 16)	Results
Discussion			
Summary of evidence	24	Summarise the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (such as health care providers, users, and policy makers)	Discussion
Limitations	25	Discuss limitations at study and outcome level (such as risk of bias), and at review level (such as incomplete retrieval of identified research, reporting bias)	Discussion
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research	Discussion
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (such as supply of data) and role of funders for the systematic review	12

Supplementary Material 2. MOOSE checklist

Incidence, temporal trends and potential risk factors for aseptic loosening following primary unicompartmental knee arthroplasty: a meta-analysis of 96,294 knees

Criteria		Brief description of how the criteria were handled in the review
Reporting of background		
√	Problem definition	Data on incidence rates of aseptic loosening (AL) following primary unicompartmental arthroplasty (UKA) is variable. The nature and magnitude of the risk factors that increase the risk of AL in this population is uncertain. We conducted a systematic meta-analysis to evaluate the incidence and its temporal trends as well as potential risk factors for AL following primary UKA.
√	Hypothesis statement	Several patient-, surgery-, implant-, and hospital-related factors influence the risk of AL following primary UKA
√	Description of study outcomes	Incidence, temporal trends and risk factors for aseptic loosening
√	Type of exposure	Patient-, surgery-, implant-, and hospital-related factors
√	Type of study designs used	Longitudinal studies (prospective or retrospective case control, prospective cohort, retrospective cohort, case-cohort, nested-case control, or clinical trials)
√	Study population	Patients followed for aseptic loosening following primary UKA
Reporting of search strategy should include		
√	Qualifications of searchers	
√	Search strategy, including time period included in the synthesis and keywords	Time period: from inception to 6th April 2020 The detailed search strategy can be found in Supplementary Material 3
√	Databases and registries searched	MEDLINE, EMBASE, Web of Science and Cochrane databases
√	Search software used, name and version, including special features	OvidSP was used to search EMBASE and MEDLINE EndNote used to manage references
√	Use of hand searching	We searched bibliographies of retrieved papers
√	List of citations located and those excluded, including justifications	Details of the literature search process are outlined in the flow chart. The citation list for excluded studies are available on request.
√	Method of addressing articles published in languages other than English	Not applicable
√	Method of handling abstracts and unpublished studies	Abstracts with no full text publications were not included.
√	Description of any contact with authors	We contacted authors of studies that did not provide adequate data in their studies
Reporting of methods should include		
√	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Detailed inclusion and exclusion criteria are described in the Methods section.
√	Rationale for the selection and coding of data	Data extracted from each of the studies were relevant to the population characteristics, study design, exposure, and outcome.
√	Assessment of confounding	We assessed confounding by ranking individual studies on the basis of different adjustment levels and performed sub-group analyses to evaluate differences in the overall estimates according to levels of adjustment.
√	Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	Study quality was assessed based on the nine-star Newcastle–Ottawa Scale using pre-defined criteria namely: population representativeness, comparability (adjustment of confounders), ascertainment of outcome.
√	Assessment of heterogeneity	Heterogeneity of the studies was quantified with I^2 statistic that provides the relative amount of variance of the summary effect due to the between-study heterogeneity and explored using meta-regression and stratified analyses
√	Description of statistical methods in sufficient detail to be replicated	Description of methods of meta-analyses, sensitivity analyses, and meta-regression are detailed in the methods. We performed random effects meta-analysis with Stata 15.
√	Provision of appropriate tables and graphics	Table 1; Figures 1-4; Supplementary Materials 1-7
Reporting of results should include		

√	Graph summarizing individual study estimates and overall estimate	Figures 2-4; Supplementary Materials 5-7
√	Table giving descriptive information for each study included	Table 2
√	Results of sensitivity testing	Not applicable
√	Indication of statistical uncertainty of findings	95% confidence intervals were presented with all summary estimates.
Reporting of discussion should include		
√	Quantitative assessment of bias	Sensitivity analyses indicate heterogeneity in strengths of the association due to most common biases in observational studies. The systematic review is limited in scope, as it involves published data. Individual participant data is needed. Limitations have been discussed.
√	Justification for exclusion	All studies were excluded based on the pre-defined inclusion criteria in methods section.
√	Assessment of quality of included studies	Brief discussion included in 'Methods' section & Table 2
Reporting of conclusions should include		
√	Consideration of alternative explanations for observed results	Discussion
√	Generalization of the conclusions	Discussed in the context of the results.
√	Guidelines for future research	We recommend analyses of individual participant data
√	Disclosure of funding source	In "Acknowledgement" section

Supplementary Material 3. Literature search strategy

Relevant studies, published from inception to 6th April 2020 were identified through electronic searches limited to the English language using MEDLINE, Embase, Web of Science, and Cochrane databases. Electronic searches were supplemented by scanning reference lists of articles identified for all relevant studies (including review articles), by hand searching of relevant journals and by correspondence with study investigators.

1 exp Arthroplasty, Replacement, Shoulder/ (22113)
2 Partial knee replacement.mp. (35)
3 Partial knee arthroplasty.mp. (41)
4 Unicondylar knee replacement.mp. (64)
5 Unicondylar knee arthroplasty.mp. (185)
6 Unicompartmental knee arthroplasty.mp. (980)
7 Unicompartmental knee replacement.mp. (271)
8 Aseptic loosening.mp. (4304)
9 wear.mp. (25516)
10 exp Osteolysis/ (6976)
11 1 or 2 or 3 or 4 or 5 or 6 or 7 (22260)
12 8 or 9 or 10 (34461)
13 11 and 12 (1785)

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Each part was specifically translated for searching the other databases (EMBASE, Web of Science, and Cochrane databases)

Supplementary Material 4. Reference list of included articles

1. Lo Presti M, Costa GG, Cialdella S, Agrò G, Grassi A, Caravelli S, et al. Return to Sports after Unicompartmental Knee Arthroplasty: Reality or Utopia? A 48-Month Follow-Up Prospective Study. J Knee Surg. 2019;32(2):186-91.
2. Kleeblad LJ, Borus TA, Coon TM, Dounchis J, Nguyen JT, Pearle AD. Midterm Survivorship and Patient Satisfaction of Robotic-Arm-Assisted Medial Unicompartmental Knee Arthroplasty: A Multicenter Study. J Arthroplasty. 2018;33(6):1719-26.
3. Campi S, Pandit H, Hooper G, Snell D, Jenkins C, Dodd CAF, et al. Ten-year survival and seven-year functional results of cementless Oxford unicompartmental knee replacement: A prospective consecutive series of our first 1000 cases. Knee. 2018;25(6):1231-7.
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6. Greco NJ, Lombardi AV, Price AJ, Berend ME, Berend KR. Medial Mobile-Bearing Unicompartmental Knee Arthroplasty in Young Patients Aged Less Than or Equal to 50 Years. J Arthroplasty. 2018;33(8):2435-9.
7. Baur J, Zwicky L, Hirschmann MT, Ilchmann T, Clauss M. Metal backed fixed-bearing unicondylar knee arthroplasties using minimal invasive surgery: a promising outcome analysis of 132 cases. BMC Musculoskelet Disord. 2015;16:177.
8. Chalmers BP, Mehrotra KG, Sierra RJ, Pagnano MW, Taunton MJ, Abdel MP. Reliable outcomes and survivorship of unicompartmental knee arthroplasty for isolated compartment osteonecrosis. Bone Joint J. 2018;100-B(4):450-4.
9. White SH, Roberts S, Kuiper JH. The twin peg Oxford knee - Medium term survivorship and surgical principles. Knee. 2018;25(2):314-22.
10. Choy WS, Lee KW, Kim HY, Kim KJ, Chun YS, Yang DS. Mobile bearing medial unicompartmental knee arthroplasty in patients whose lifestyles involve high degrees of knee flexion: A 10-14year follow-up study. Knee. 2017;24(4):829-36.
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12. Dyrhovden GS, Lygre SHL, Badawy M, Gøthesen Ø, Furnes O. Have the Causes of Revision for Total and Unicompartmental Knee Arthroplasties Changed During the Past Two Decades? Clin Orthop Relat Res. 2017;475(7):1874-86.
13. Xu T, Lao Y, Wang J, Liu F, Xiao L, Tong P. Mid-term results of Oxford phase-3 medial unicompartmental knee arthroplasty for medial arthritis in Chinese patients. ANZ J Surg. 2017;87(4):287-90.
14. Streit MR, Streit J, Walker T, Bruckner T, Philippe Kretzer J, Ewerbeck V, et al. Minimally invasive Oxford medial unicompartmental knee arthroplasty in young patients. Knee Surg Sports Traumatol Arthrosc. 2017;25(3):660-8.
15. Bruni D, Gagliardi M, Akkawi I, Raspugli GF, Bignozzi S, Marko T, et al. Good survivorship of all-polyethylene tibial component UKA at long-term follow-up. Knee Surg Sports Traumatol Arthrosc. 2016;24(1):182-7.
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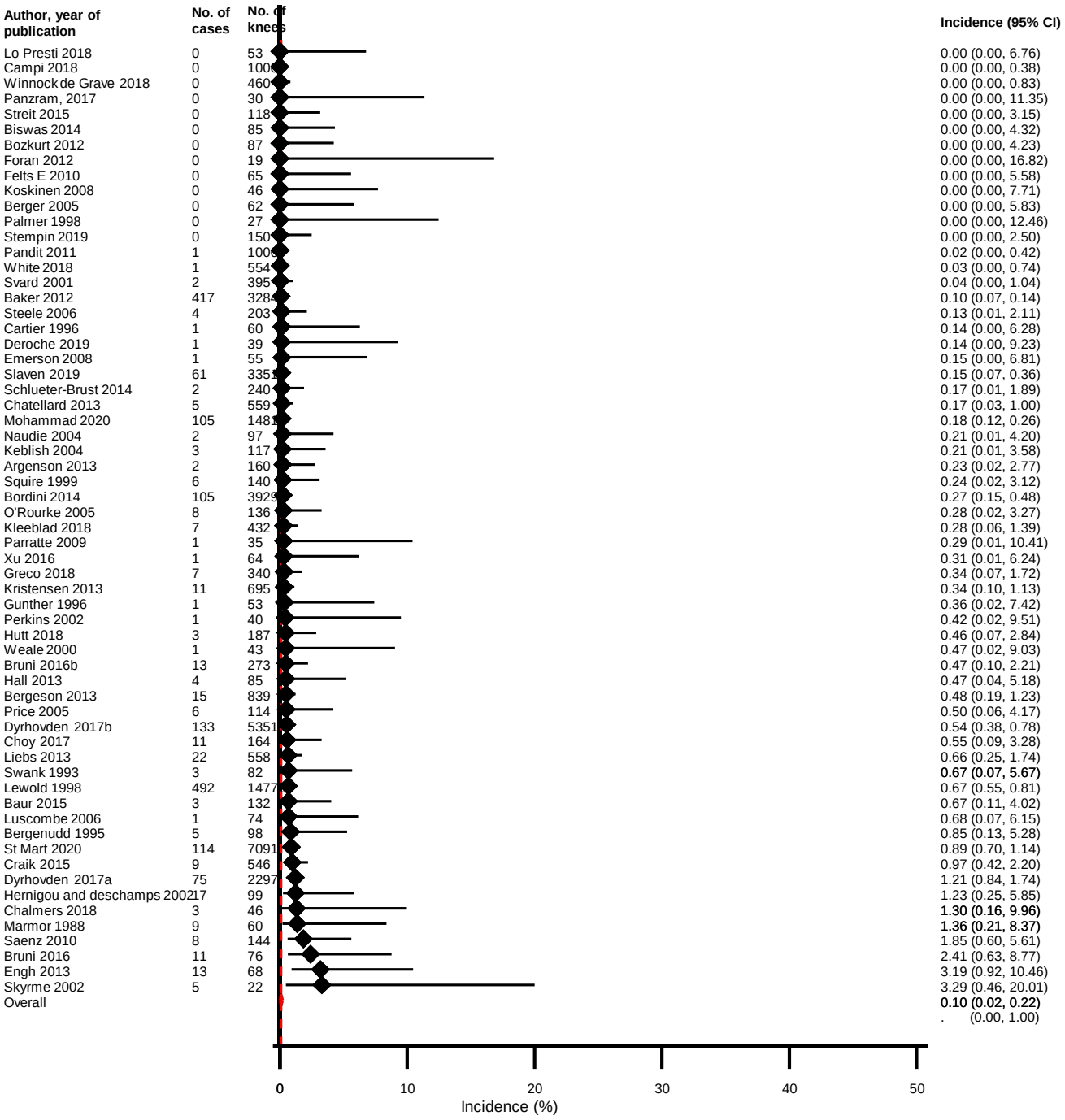
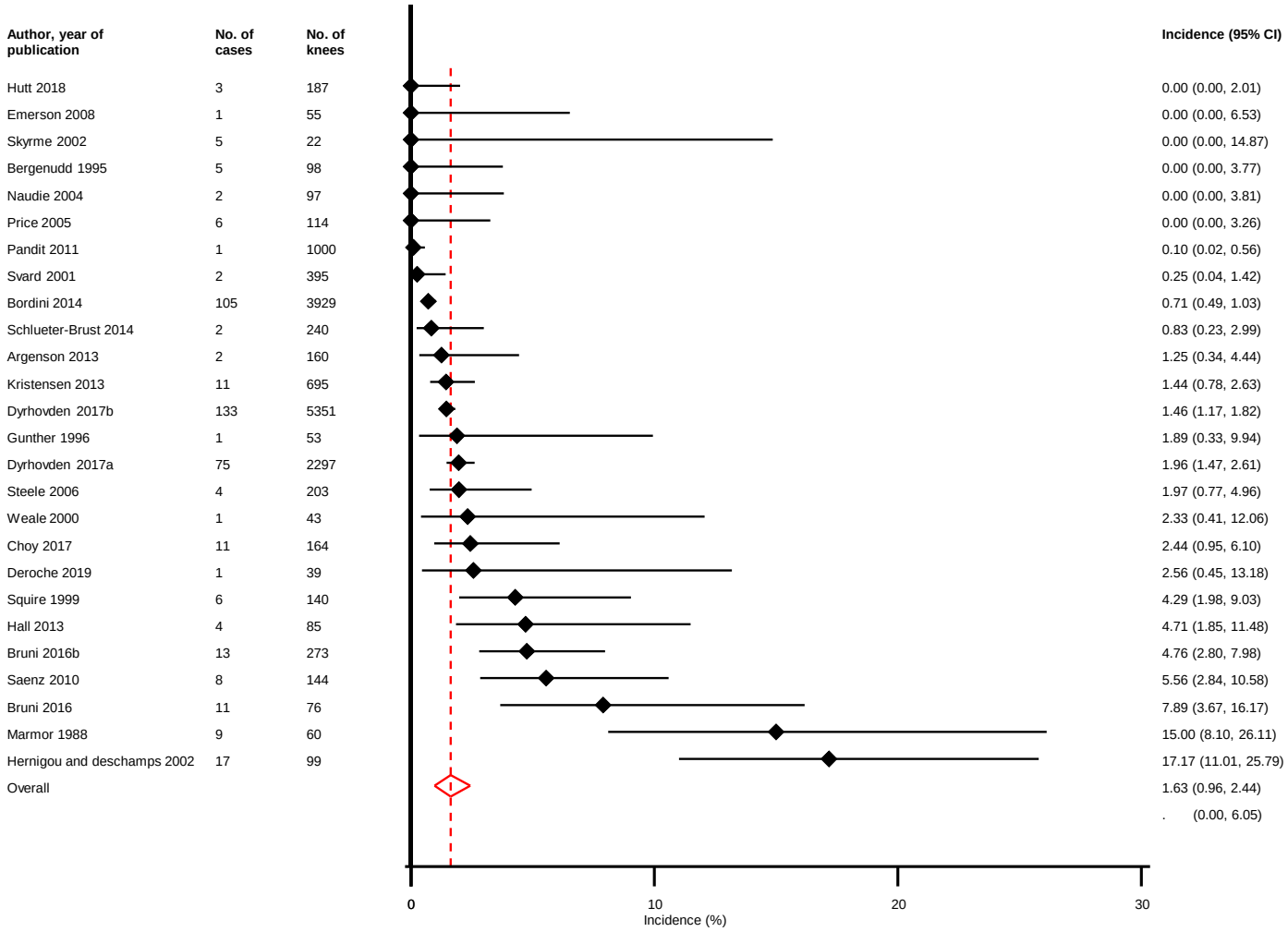
Supplementary Material 5. Annual revision rate of aseptic loosening

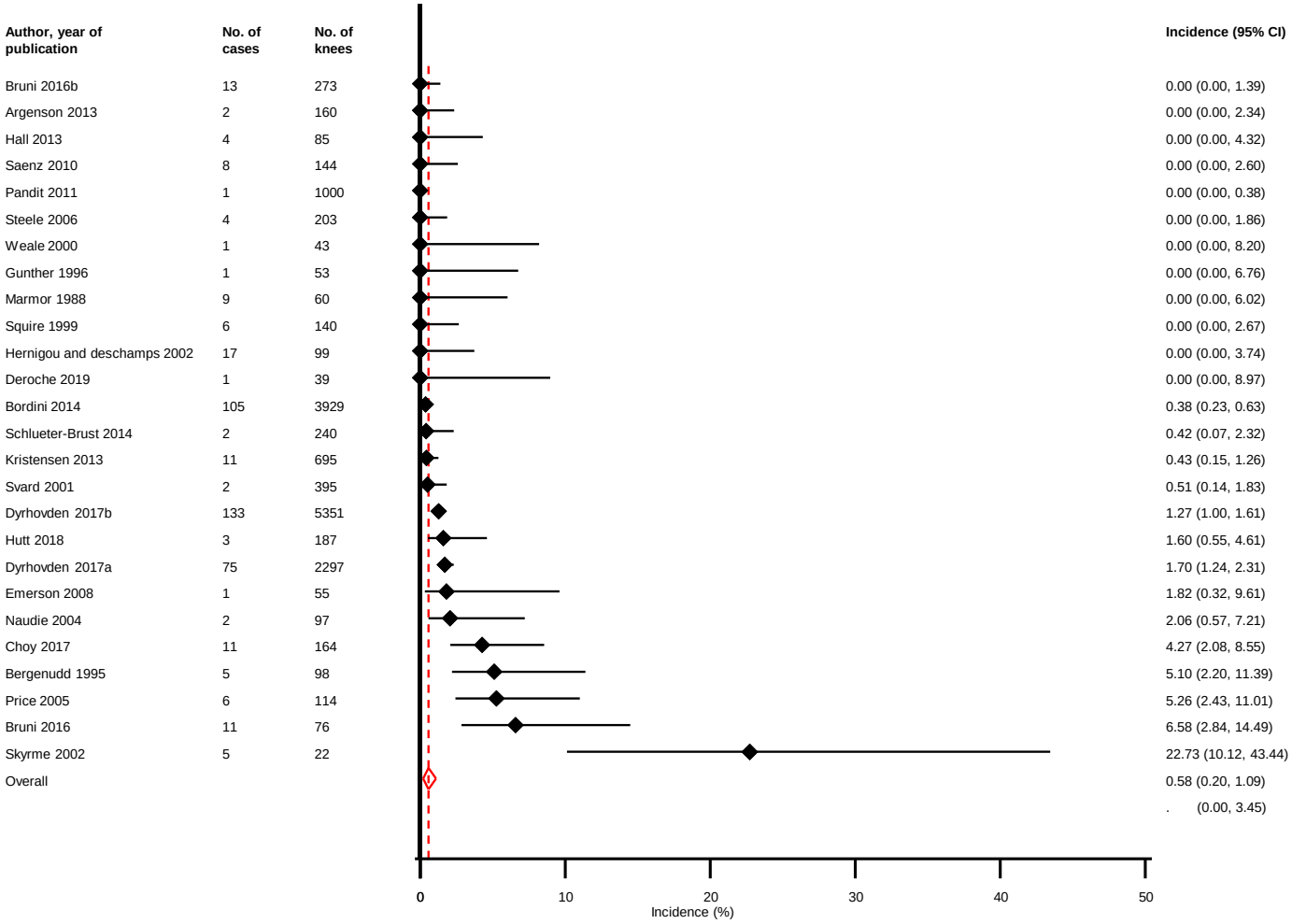


Supplementary Material 6. Incidence of tibial loosening



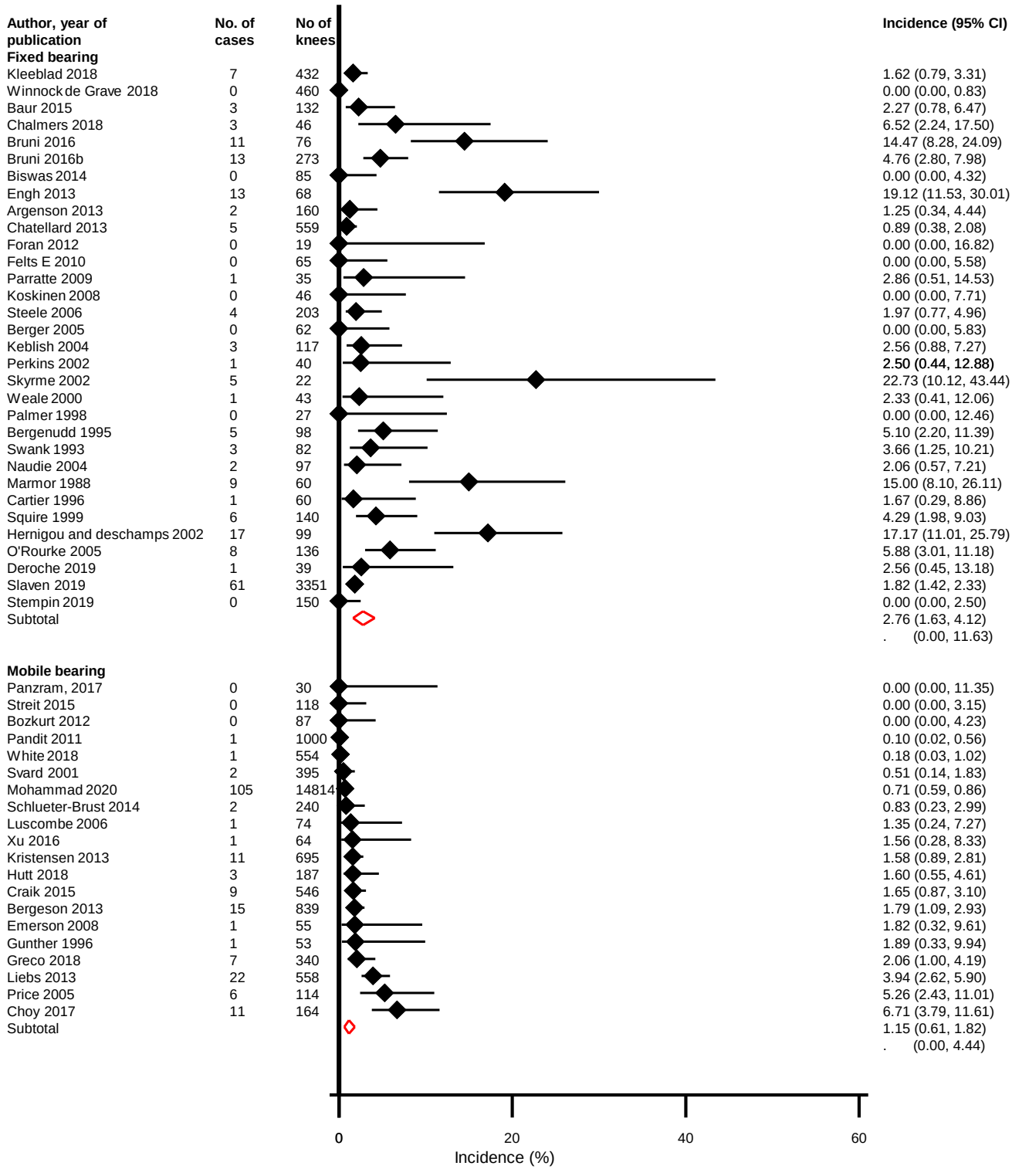
CI, confidence interval

Supplementary Material 7. Incidence of femoral loosening

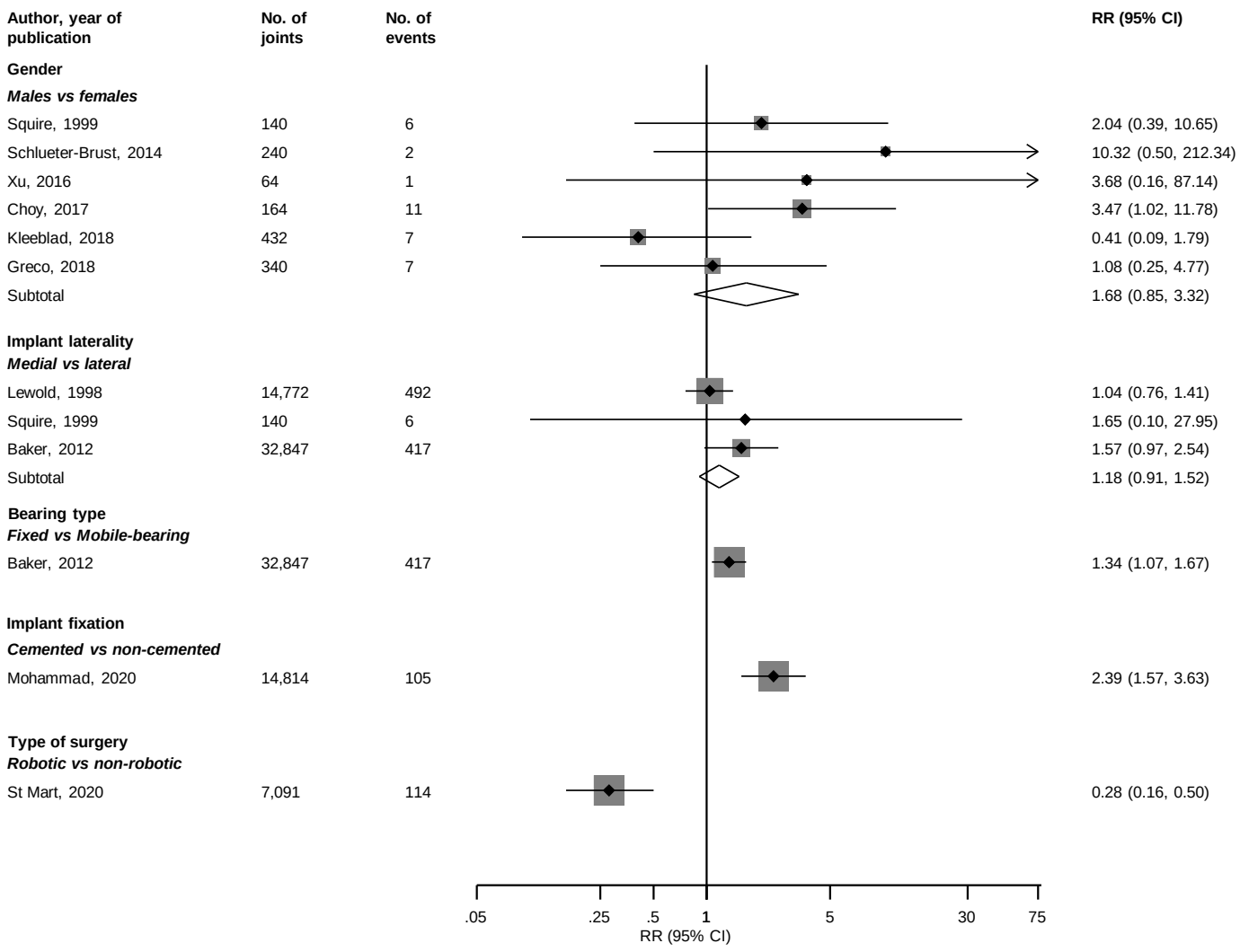


CI, confidence interval

Supplementary Material 8. Incidence of aseptic loosening for fixed and mobile bearings



Supplementary Material 9. Associations of potential risk factors for aseptic loosening following unicompartmental knee arthroplasty



CI, confidence; RR, relative risk

Table 1. Summary characteristics of the 63 unique studies

Characteristics	Numbers
Population	**N**
Procedures	96,294
Aseptic loosening	1,752
Tibial loosening	26 studies; 241 cases
Femoral loosening	26 studies; 162 cases
Study characteristics	
Location	N studies (N Procedures)
Europe	40 (82,387)
North America	18 (3,198)
Asia	2 (228)
Pacific	2 (7,130)
Africa	1 (3,351)
Study design	N studies (N Procedures)
Retrospective cohorts	32 (86,684)
Prospective cohorts	31 (9,610)
Weighted mean follow-up (min-max), years	7.7 (4.2; 1.2-21.0)
Median (IQR) study quality score for observational studies	7 (7-7)
Study level participant characteristics	
Weighted mean age (SD; min-max), years	66.0 (2.9; 46.0-73.6)
Median (IQR) % males	46.4 (34.5-52.6)

IQR=interquartile range; N, number; SD, standard deviation

Table 2. Characteristics of studies included in review

Author, year of publication	Year of study	Country	Average age (yrs)	Study Design	% Male	Mean/median follow-up duration	No. of knees	No. of AL cases	Study Quality*
Lo Presti 2018	2010-2015	Italy	59.7	Prospective cohort	35	4.0	53	0	6
Kleeblad 2018	2009-2011	USA	67.3	Prospective cohort	58	5.7	432	7	6
Campi 2018	2004-2011	United Kingdom	65.9	Prospective cohort	55	7.0	1000	0	7
Hutt 2018	2005-2013	United Kingdom	64.2	Prospective cohort	49.2	3.5	187	3	7
Winnock de Grave 2018	2005-2013	Belgium	66.0	Retrospective cohort	52	5.5	460	0	8
Greco 2018	2003-2014	USA	46.5	Retrospective cohort	41	6.1	340	7	6
Baur 2015	2006-2010	Switzernald	69.0	Retrospective cohort	50	3.4	132	3	8
Chalmers 2018	2002-2014	USA	66.0	Retrospective cohort	56	5.0	46	3	5
White 2018	2003-2013	UK	67.0	Retrospective cohort	51	6.6	554	1	8
Choy 2017	2002-2005	Korea	64.2	Retrospective cohort	20.6	12.1	164	11	6
Panzram, 2017	2007-2009	Germany	62.4	Retrospective cohort	50	5.0	30	0	7
Dyrhovden 2017a	1994-2004	Norway	65.5	Retrospective cohort	38	2.7	2297	75	8
Dyrhovden 2017b	2005-2015	Norway	64.5	Retrospective cohort	48	4.6	5351	133	8
Xu 2016	2004-2010	China	59.0	Prospective cohort	20.1	5.0	64	1	6
Streit 2015	2001-2007	Germany	57.0	Prospective cohort	50	5.0	118	0	7
Bruni 2016	2006-2009	Italy	62.0	Prospective cohort	47.4	6.0	76	11	7
Bruni 2016b	2000-2007	Italy	67.9	Retrospective cohort	36.6	10.2	273	13	8
Craik 2015	2006-2011	UK	66.0	Retrospective cohort	53	1.7	546	9	6
Bordini 2014	2000-2011	Italy	67.3	Retrospective cohort	29	10.0	3929	105	8
Schlueter-Brust 2014	1991-1999	Germany	69.0	Retrospective cohort	32.5	5.0	240	2	7
Biswas 2014	2000-2009	USA	49.0	Prospective cohort	56	4.0	85	0	6
Engh 2013	2000-2008	USA	65.0	Prospective cohort	51.2	6.0	68	13	7
Kristensen 2013	2002-2011	Denmark	NR	Prospective cohort	53.4	4.6	695	11	7
Argenson 2013	1989-1997	France	66.0	Prospective cohort	NR	5.5	160	2	7
Chatellard 2013	1988-2010	France	69.5	Retrospective cohort	37.8	5.2	559	5	7
Liebs 2013	2002-2009	Germany	73.6	Retrospective cohort	33	6.0	558	22	8
Bergeson 2013	2004-2008	USA	62.8	Prospective cohort	43.7	3.7	839	15	6
Bozkurt 2012	2008-2011	Turkey	57.0	Prospective cohort	9.5	1.2	87	0	7
Hall 2013	1997-2002	UK	65.0	Retrospective cohort	57	10.0	85	4	7
Foran 2013	1998-2005	USA	58.0	Prospective cohort	33.3	15.0	19	0	7
Baker 2012	2003-2010	United Kingdom	64.5	Retrospective cohort	52.2	12.5	32847	417	9
Felts 2010	1989-2006	France	54.7	Retrospective cohort	46.8	11.2	65	0	7
Saenz 2010	2002-2005	USA	72.0	Prospective cohort	46	3.0	144	8	7
Parratte 2009	1989-2001	France	46.0	Retrospective cohort	32.3	9.7	35	1	7
Koskinen 2008	1992-2001	Finland	66.3	Prospective cohort	33.3	7.0	46	0	7
Emerson 2008	1989-1994	USA	64.0	Prosepctive cohort	41.8	11.8	55	1	7
Luscombe 2006	1998-2001	United Kingdom	63.4	Prosepctive cohort	55	2.0	74	1	6
Pandit 2011	1998-2009	United Kingdom	66.0	Prosepctive cohort	48	5.6	1000	1	7
Steele 2006	1974-1994	United Kingdom	67.1	Prosepctive cohort	36.7	14.8	203	4	7
Berger 2005	1987-1993	USA	68.0	Prosepctive cohort	34	12.0	62	0	7
Keblish 2004	1981-1996	USA	68.0	Prosepctive cohort	30	12.0	117	3	6
Gioe 2003	1991-NR	USA	67.3	Retrospective cohort	44.7	NR	516	10	6
Perkins 2002	1990-1997	USA	65.5	Retrospective cohort	55	6.0	40	1	9
Skyrme 2002	1990-1994	United Kingdom	68.0	Retrospective cohort	58.8	6.9	22	5	7
Weale 2000	1989-1992	United Kingdom	69.6	Retrospective cohort	37.8	5.0	43	1	7
Palmer 1998	1986-1990	United Kingdom	70.3	Prospective cohort	74.2	7.8	27	0	7
Bergenudd 1995	1984-1990	Sweden	72.0	Retrospective cohort	24.5	6.0	98	5	7
Swank 1993	1983-1987	USA	69.0	Retrospective cohort	45.8	5.5	82	3	9
Svard 2001	1983-1999	Sweden	69.6	Retrospective cohort	47.6	12.5	395	2	7

Gunther 1996	NR	United Kingdom	68.0	Retrospective cohort	7.8	5.2	53	1	7
Lewold1998	1975-1995	Sweden	71.0	Retrospective cohort	36	5.0	14772	492	6
Naudie 2004	1989-2000	Canada	68.0	Retrospective cohort	53.6	10.0	97	2	7
Marmor 1988	1972-1976	USA	63.0	Prospective cohort	35.3	11.0	60	9	6
Cartier 1996	1974-1984	USA	65.0	Prospective cohort	64.8	12.0	60	1	6
Squire 1999	1975-1982	United Kingdom	70.9	Prospective cohort	50	18.0	140	6	7
Hernigou and Deschamps 2002	1978-1988	France	70.0	Prospective cohort	NR	14.0	99	17	7
Price 2005	1983-2000	United Kingdom	69.9	Prospective cohort	40	10.5	114	6	7
O'Rourke 2005	1975-1982	USA	70.9	Prospective cohort	49.5	21.0	136	8	7
Deroche 2019	1998-2003	Australia	65.4	Prosepctive cohort	15.4	17.9	39	1	7
Mohammad 2020	2005-2016	United Kingdom	65.0	Retrospective cohort	58	4.0	14814	105	9
Slaven 2019	2000-2018	Egypt	NR	Prospective cohort	NR	11.8	3351	61	7
Stempin 2019	2009-2014	Poland	70.5	Retrospective cohort	26.7	5.0	150	0	7
St Mart 2020	2015-2018	Australia	65.0	Retrospective cohort	56	1.8	7091	124	9

NR, not reported; *assessed using 9-point Newcastle-Ottawa Scale

Figure legends

Figure 1. PRISMA flow diagram

Figure 2. Incidence of aseptic loosening following primary UKR across eligible studies

The summary incidence rate estimate presented was calculated using random effects models; CI, confidence interval (bars)

Figure 3. Incidence of aseptic loosening at specific follow-up times

Figure 4. Temporal trends in the incidence of aseptic loosening following primary UKR

A, Incidence by median year of data collection; B, Meta-regression bubble plot of incidence against median year of study data collection

Table Legends:

Table 1. Summary characteristics of the 63 unique studies

IQR=interquartile range; N, number; SD, standard deviation

Table 2. Characteristics of studies included in review

NR, not reported; *assessed using 9-point Newcastle-Ottawa Scale

Review Protocol 150836

1. Title
Incidence of and risk factors for aseptic loosening following primary unicondylar knee replacement.

2. Proposed authors
Matthew C. Barrett, Setor K Kunutsor, Michael R Whitehouse, Ashley W Blom

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4. Timeline
September-December 2019

5. Background and Rationale
Not applicable

6. Research Hypothesis
(i) There is variability in the incidence ~~rates~~ of aseptic loosening following primary unicondylar knee replacement

(ii) A range of patient-, surgery-, and hospital-related factors influence the risk of aseptic loosening following unicondylar knee replacement.

7. Objectives
1. To assess and summarise incidence rates of aseptic loosening following unicondylar knee replacement.
2. To quantify the nature and magnitude of potential longitudinal associations of several patient-, surgery-, and hospital-related factors with the risk of aseptic loosening following unicondylar knee replacement
3. To assess these associations by study and individual level characteristics such as geographical location, sex differences, average duration of follow-up, number of outcomes, study design, aseptic loosening definition and study quality.
4. We also seek to identify any gaps in the existing evidence.

8. Data searches
We will systematically search for longitudinal studies (prospective or retrospective ~~case-control, prospective~~ cohort~~, retrospective cohort~~, case-cohort, nested-case control, or clinical trials) reporting on the associations of any patient-, surgery-, or hospital-related factor with aseptic loosening following primary unicondylar knee replacement in MEDLINE, Embase, Web of Science, and Cochrane databases from inception to date. The computer-based searches will combine free and MeSH search terms and combination of key words related to the population (e.g., "unicondylar knee arthroplasty") and outcome (e.g., "aseptic loosening"). There will be no restrictions on language. Reference lists of retrieved articles will be manually scanned for all relevant additional studies and review articles.

9. Type of studies to be included
Longitudinal studies (prospective or retrospective ~~case control, prospective cohort, retrospective~~ cohort, case-cohort, nested-case control, or clinical trials)

10. Condition or domain being studied
Aseptic loosening following unicondylar knee replacement

11. Participants/ population
Studies will be included if they recruited patients who have undergone primary unicondylar knee replacement and reported on aseptic loosening outcomes or on the associations of any patient-, surgery-, or hospital-related factors with risk of aseptic loosening after follow-up.

12. Exclusions
(i) Studies comprising revision unicondylar knee replacement or a mixture of primary and revision joint replacements from which data could not be extracted on primary joint replacements
(ii) Studies restricted to patients with prevalent diseases (e.g. diabetes, osteoarthritis, rheumatoid arthritis, etc.) or selected populations which had no comparison or control groups.
(iii) Studies that assessed exposures (conditions) that developed after the joint replacement
(iv) Studies that exclusively focused on any other surgical approach apart from elective unicondylar knee replacement such as in the setting of trauma, non-union, fracture, bilateral arthroplasty, or arthroscopy.

13. Intervention(s) / exposure(s)
Patient-related factors
(i) Sociodemographic factors: age, sex, ethnicity, body mass index, socioeconomic status, smoking status, tobacco use, alcohol consumption
(ii) Previous medical and surgical history: indication for index surgery, history of diabetes, history of hypertension, malignancy, cardiovascular disease, and other comorbidities.
(iii) Laterality of affected condyle.

Surgery-related factors
(i) Surgical approach
(ii) Position of patient
(iii) Length of surgery
(iv) Use of bone cement
(v) Type of implant/bearing surface

Hospital-related factors
(i) Hospital surgical volume
(ii) Surgeon experience

14. Comparators/control
Non-exposed control groups of the various exposures being evaluated as listed above

15. Outcome(s)
Primary outcomes
Aseptic loosening

Secondary outcomes
Not applicable

16. Data extraction, (selection and coding)
The data extraction will be conducted by two independent reviewers. A standardized predesigned data collection form will be used for data extraction. Data will be abstracted, where available, on study, publication date, geographical location, mean age, percentage of males, duration of follow-up, sample size, type of exposures (risk factors), number of aseptic loosening outcomes, risk estimates (risk ratios

for cohort studies and odds ratios for case-control) and degree of adjustment for potential confounders. Each article will be assessed using the inclusion criteria and any disagreement regarding eligibility of an article will be discussed, and agreement reached by consensus with a third reviewer. Authors of eligible studies will be contacted to provide additional information where necessary. Additionally, in the case of multiple publications, the study with the most up-to-date or comprehensive information will be included.

17. Risk of bias (quality) assessment

Methodological quality will be assessed based on the nine-star Newcastle–Ottawa Scale (NOS),[1] a validated tool for assessing the quality of non-randomised studies, including cohort and case-control studies. It uses three pre-defined domains namely: selection of participants (population representativeness), comparability (adjustment for confounders), and ascertainment of outcomes of interest. The NOS assigns a maximum of four points for selection, two points for comparability, and three points for outcome. Nine points on the NOS reflects the highest study quality.

18. Strategy for data synthesis

Risk estimates (risk ratios for cohort studies and odds ratios for case-control) will be used as the common measure of association across studies. Risk estimates will be calculated for studies that report raw counts. When reported risk estimates cannot be calculated, we will obtain the relevant estimates through correspondence with the study authors. Random-effects models will be used to combine summary measures to minimise the effect of between-study heterogeneity. [2] Heterogeneity will be assessed using the Cochrane χ^2 statistic and the I^2 statistic.[3]

19. Analysis of subgroups or subsets

Study-level characteristics including geographical location, study design, sex differences, average duration of follow-up, number of outcomes, study design, aseptic loosening definition, and study quality will be pre-specified as characteristics for assessment of heterogeneity, which will be conducted using stratified analysis and random effects meta-regression.

20. Dissemination plans

Conference presentation
Presentation to the wider NHS community
Publication in a relevant journal

21. References

1. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2011. www.ohri.ca/programs/clinical_epidemiology/oxford.asp.; http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp Accessed 20 August.

2. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials.* 1986;7(3):177-188.

3. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ.* 2003;327(7414):557-560.