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ORIGINAL ARTICLE

Risk factors for periprosthetic joint infection following primary total hip or knee arthroplasty: a meta-analysis

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Key words
Meta-analysis; Periprosthetic joint infection; Risk factor; Systematic review; Total joint arthroplasty

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Abstract

To identify risk factors for periprosthetic joint infection following primary total joint arthroplasty, a systematic search was performed in Pubmed, Embase and Cochrane library databases. Pooled odds ratios (ORs) or standardised mean differences (SMDs) with 95% confidence intervals (CIs) were calculated. Patient characteristics, surgical-related factors and comorbidities, as potential risk factors, were investigated. The main factors associated with infection after total joint arthroplasty (TJA) were male gender (OR, 1·48; 95% CI, 1.19–1.85), age (SMD, −0·10; 95% CI, −0.17–−0.03), obesity (OR, 1·54; 95% CI, 1·25–1·90), alcohol abuse (OR, 1·88; 95% CI, 1·32–2·68), American Society of Anesthesiologists (ASA) scale > 2 (OR, 2·06; 95% CI, 1·77–2·39), operative time (SMD, 0·49; 95% CI, 0·19–0·78), drain usage (OR, 0·36; 95% CI, 0·18–0·74), diabetes mellitus (OR, 1·58; 95% CI, 1·37–1·81), urinary tract infection (OR, 1·53; 95% CI, 1.09–2.16) and rheumatoid arthritis (OR, 1·57; 95% CI, 1·30–1·88). Among these risk factors, ASA score > 2 was a high risk factor, and drain usage was a protective factor. There was positive evidence for some factors that could be used to prevent the onset of infection after TJA.

Introduction

Total hip arthroplasty (THA) and total knee arthroplasty (TKA) have been proven to be highly successful procedures for improving quality of life and reducing pain in patients with severe joint diseases. However, despite the widely reported success of the procedures, prosthetic joint infection (PJI), as an infrequent but well-recognised complication, affects some patients after joint arthroplasty (1). As reported by previous studies, PJI is associated with extremely poor postoperative outcomes and high incidence of mortality (2,3). Several investigators have shown that the management of PJI is extremely costly, and it has placed a large economic burden on the health care system (4,5). Thus, identifying potential risk factors is of great importance.

A number of risk factors for PJI after total joint arthroplasty (TJA) have been described, including obesity (6,7), rheumatoid arthritis (8), operating time (6), urinary tract infection (9), blood transfusion (10) and diabetes mellitus (7). However, the results of clinical trials were various and markedly disagree. Meta-analysis, by the method of pooling the results of high-quality studies, could increase the statistical power of the association analysis and obtain more precise estimates of effect. Thus, we collected all relevant studies and made a comprehensive review. The purpose of this meta-analysis was to identify risk factors, including intrinsic patient characteristics, surgical-related factors and comorbid conditions, and quantify the magnitude of the risk in the patients undergoing TJA surgery.

Key Messages

- periprosthetic joint infection is a severe complication following total joint arthroplasty
- a meta-analysis of published literature was conducted to identify risk factors that are associated with periprosthetic joint infection
- male gender, age, obesity, alcohol abuse, ASA score > 2, operative time, drain usage, diabetes mellitus, urinary tract infection and rheumatoid arthritis are significant risk factors for periprosthetic joint infection

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Materials and methods

Literature search

We performed this meta-analysis in accordance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) statement (11). Retrieval online was conducted in the following databases: PubMed, Embase and Cochrane library databases. The data of search was from the earliest available records in 1966 to 25 December 2015. The following search terms and Boolean operators were used to identify potential studies: ('knee' or 'hip' or 'joint') and ('infection') and ('risk' or 'predictor' or 'factor'). The search was restricted to human subjects and those written in English. We also retrieved the references of all publications to identify additional studies for potential inclusion.

Inclusion and exclusion criteria

Two authors conducted the literature screening independently according to inclusion and excluding criteria. The following inclusive selection criteria were used (1): the study design was an observational study, including both cohort and case–control studies (2); patients underwent primary THA or TKA (3); PJI was investigated (4); possible risk factors for infection were explored; and (5) sufficient data were present to estimate the odds ratios (ORs) or standardised mean differences (SMDs) with 95% confidence intervals (CIs).

According to the Centres for Disease Control criteria (12), surgical site infections were classified into superficial incisional infection, deep incisional infection and space infection. For the joint, it is difficult to make a distinction between deep incisional infection and space infection. Thus, both types of infection were deemed to be PJI. Besides, during follow-up, patients who underwent revised surgery because of infection were also considered PJI.

To decrease the heterogeneity, studies were excluded if they included patients with superficial surgical site infection or involved revised joint arthroplasty.

Data extraction and outcome measures

The following general characteristics were extracted from included studies: first author, publication year, country, period of investigation, number of patients in case and control group, infection ratio and identified significant risk factors. When the same population was reported in several publications, we retained only the most informative article or complete study to avoid duplication of information. Data were extracted independently by two authors, and any disagreements concerning paper eligibility were resolved by discussion and consensus.

Briefly, we investigated risk factors involving three aspects: patient-related factors, surgical-related factors and comorbid conditions. There were a total of 16 risk factors, including male gender, age, obesity, smoking, alcohol abuse, steroid usage, American Society of Anesthesiologists (ASA) scale, operative time, bilateral surgery, transfusion, drain usage, cementation, diabetes mellitus, urinary tract infection, hypertension and rheumatoid arthritis. In this study, obesity was defined as the body mass index ≥ 30 kg/m (2); ASA score greater than three was interpreted as significant system disease in decompensated state, and we tried to figure out whether greater ASA > 2 was a risk factor.

The methodological quality of studies was assessed independently by two reviewers using the Newcastle–Ottawa Scale (NOS) for observational studies (13). The scores ranged from 0 to 9, and a study with an NOS score ≥ 6 was considered high quality.

Statistical analysis

We used Stata 11·0 (Stata Corporation, College Station, TX) to conduct all statistical analyses. From every study, we extracted the data to calculate ORs for dichotomous outcomes and SMDs for continuous outcomes. If the exact number of patients with risk factors were not available, the ORs with 95% CI from univariate analysis were used. The associations between every potential factor and the risk of PJI were assessed, with $P < 0{\cdot}05$ indicating a significant difference. Heterogeneity amongst the studies was qualitatively evaluated by Q-test statistics, with the significance set at $P < 0{\cdot}10$, and quantitatively tested by I^2 statistics, with $I^2 > 50\%$ indicating large inconsistency. A random-effects model was used in the case of significant heterogeneity ($P < 0{\cdot}10$ or $I^2 > 50\%$); otherwise, a fixed-effects model was used. Besides, we used OR value as a criteria to better illustrate the associations. If a significant difference exists, it was considered a high risk factor if OR ≥ 2, a moderate risk factor if $1 <$ OR < 2 and a protective factor if OR < 1.

As both THA and TKA were investigated, subgroup analyses were performed according to the position of surgery. Publication bias was assessed by the Begg test when the number of involved studies ≥ 10.

Results

Search results and study characteristics

As shown in Figure 1, the literature search yielded 254 titles of potentially relevant articles. Of these, 89 articles were excluded because of duplication. After title and abstract review, 129 records were excluded, and 36 full articles retained for further assessment. After full text review, 12 articles were excluded. Finally, 24 unique studies were included in the meta-analysis (9,14–36).

The basic characteristics of the included studies are summarised in Table 1. The publication year of the 24 studies ranged from 1998 to 2016. According to the NOS score, 9 studies scored 8 (9,17,19,22,23,25,27,32,34), 11 studies scored 7 (15,16,18,24,26,28–30,33,35,36) and 4 studies scored 6 (14,20,21,31). All studies were of high quality.

Main results of meta-analysis

Of the 24 studies, 16 reported the incidence of PJI (9,14,16,18,19,21–25,27,29,31,32,34,35). Based on the results of 16 studies, the infection rate ranged from 0·51% to 3·35%, and the cumulated infection rate was 1·17%. Significant heterogeneity was observed among the studies when evaluating the following potential risk factors: obesity, operative time,

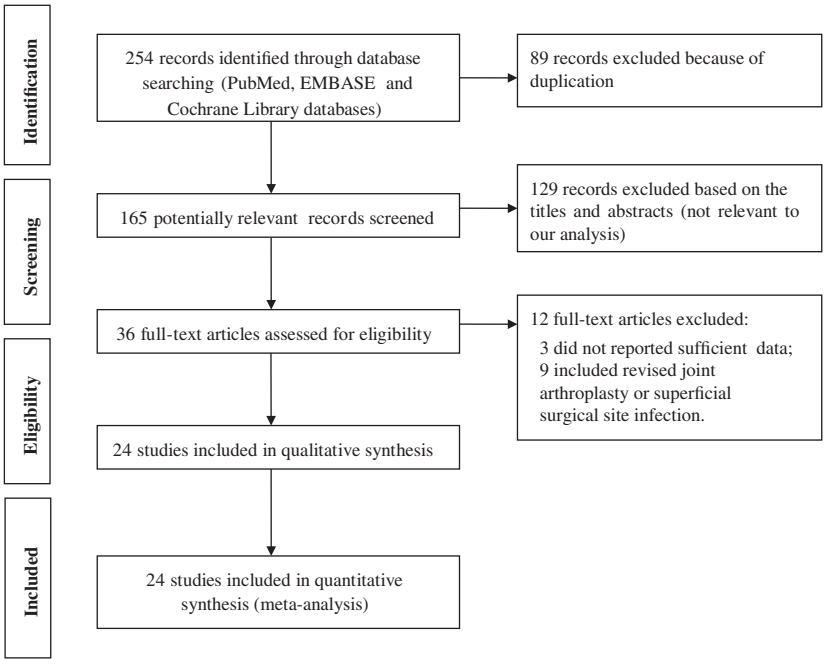

Figure 1 Flow diagram of literature search.

bilateral surgery, transfusion, cementation, diabetes mellitus, urinary tract infection, hypertension and rheumatoid arthritis. Based on the combined ORs or SMDs, we identified the following risk factors: male gender (OR, 1·48; 95% CI, 1·19–1·85), age (SMD, −0·10; 95% CI, −0.17–−0·03), obesity (OR, 1·54; 95% CI, 1·25–1.90), alcohol abuse (OR, 1·88; 95% CI, 1·32–2·68), ASA score > 2 (OR, 2·06; 95% CI, 1·77–2·39), operative time (SMD, 0·49; 95% CI, 0·19–0·78), drain usage (OR, 0·36; 95% CI, 0·18–0·74), diabetes mellitus (OR, 1·58; 95% CI, 1·37–1·81), urinary tract infection (OR, 1·53; 95% CI, 1·09–2·16) and rheumatoid arthritis (OR, 1·57; 95% CI, 1·30–1·88). Among the significant risk factors, ASA score > 2 was a high risk factor, and drain usage was a protective factor. Other factors were not identified as significant risk factors for infection following TJA ($P > 0.05$).

We further conducted subgroup analyses according to the position of surgery. In the THA subgroup, male gender was not a significant risk factor (OR, 1·21; 95% CI, 0·95–1·55); however, it was considered to be a significant risk factor in TKA subgroup (OR, 2·39; 95% CI, 1·69–3·39). Besides, in the THA subgroup, there was no significant difference in age between case and control groups (SMD, −0·04; 95% CI, −0·19–0·11), but the age was significantly younger in case group than control group in the TKA subgroup (SMD, −0·10; 95% CI, −0·19–−0·01). The main results of this meta-analysis are listed in Table 2, and analysis for male gender, obesity, diabetes mellitus and rheumatoid arthritis as significant risk factors is presented by forest plots in Figure 2.

Publication bias

The Begg test showed that no significant publication bias was found among the studies investigating infection and risk factors for male gender ($P = 0.49$), obesity ($P = 0.84$), diabetes mellitus ($P = 0.84$) or rheumatoid arthritis ($P = 0.73$).

Discussion

Our meta-analysis comprehensively and systematically reviewed the current available literature and found that (a) the accumulated incidence of PJI after TJA was 1·17%; (b) multiple risk factors were identified to be associated with PJI, including male gender, age, obesity, alcohol abuse, ASA score > 2, operative time, drain usage, diabetes mellitus, urinary tract infection and rheumatoid arthritis; (c) smoking, steroid use, bilateral surgery, transfusion, cementation or hypertension has not been proven to be risk factors and (d) younger age and male gender may have had an effect on infection after TKA but may not be associated with infection after THA.

In the clinical practice, obese patients are more likely to undergo TJA (37). Our results showed that the risk of PJI in obese patients is 1·9-fold higher than non-obese patients. Obese patients may be at an increased risk of PJI because of prolonged operative time or the presence of other medical comorbidities. Besides, this patient population is also at an increased risk of wound complications such as haematoma formation and wound dehiscence. ASA score was a physical status score of preoperative risk as documented in an anaesthetist's preoperative assessment chart. A score greater than three was interpreted as significant system disease in decompensated state. In our study, we found that ASA ≥ 2 was another patient-related risk factor of infection after TJA, and this result is in accordance with several previous studies (6,38).

PJI developed in THA and TKA had many similarities, but there are still some differences that deserve a discussion. In the subgroup analysis, younger age and male gender was proven to be associated with PJI after TKA, but the difference between groups was not seen in the THA subgroup. The underlying mechanism causing this difference has yet to be defined. We assumed that younger and male patients are generally more active than older and female patients and thus may potentially cycle their implant in greater numbers, leading to a higher

Table 1 The basic characteristics of the 24 included studies

First author	Publication year	Country	Period	Position	Case	Control	Infection ratio	NOS score	Identified significant risk factors
Berbari (36)	1998	United states	1969–1991	Hip, knee	462	462	–	7	Rheumatoid arthritis steroid therapy, diabetes mellitus
Dowsey (35)	2008	Australia	1998–2005	Hip	22	1185	22/1207	7	Obesity
Pulido (9)	2008	United states	2001–2006	Hip, knee	63	9182	63/9245	8	ASA score > 2, allogenic blood transfusion, urinary tract infection
Dowsey (34)	2009	Australia	1998–2005	Knee	18	1196	18/1214	8	Male gender, drain usage
Jamsen (33)	2009	Finland	1997–2004	Knee	–	–	-/40135	7	Rheumatoid arthritis, male gender
Malinzak (32)	2009	United states	1991–2004	Hip, knee	43	6065	43/6108	8	Diabetes mellitus, obesity, younger age
Asensio (31)	2010	Spain	2005–2006	Knee	44	106	50/5496	6	Diabetes mellitus
Cordero-Ampuero (30)	2010	Spain	1997–2007	Hip	24	100	–	7	Longer operative time, urinary tract infection
Pedersen (29)	2010	Denmark	1995–2008	Hip	597	80159	597/80756	7	Male gender
Peel (28)	2011	Australia	2000–2007	Hip, knee	63	126	–	7	Blood transfusion
Suzuki (27)	2011	Japan	1995–2006	Knee	17	2005	17/2022	8	Male gender, smoking
Bozic (26)	2012	United states	1998–2007	Knee	–	–	-/83011	7	Diabetes mellitus, obesity, rheumatoid arthritis
Bozic (25)	2012	United states	1998–2007	Hip	1371	39548	1371/40919	8	Rheumatoid arthritis, obesity, diabetes mellitus
Jamsen (24)	2012	Finland	2002–2008	Hip, knee	52	7129	52/7181	7	Obesity, diabetes mellitus
Namba (23)	2012	United states	2001–2009	Hip	155	30336	155/30491	8	Diabetes mellitus, obesity, ASA score >2, bilateral surgery, longer operating time
Namba (22)	2013	United states	2001–2009	Knee	404	55812	404/56216	8	Male gender, bilateral surgery
Somayaji (21)	2013	Canada	2000–2010	Hip, knee	5	254	5/259	6	–
Bozic (20)	2014	United states	1990–2011	Hip	89	499	–	6	Obesity, female gender
Gomez-Lesmes (19)	2014	Spain	2007–2009	Knee	32	1299	32/1331	8	Male gender, diabetes mellitus, ASA score >2, blood transfusion
Sousa (18)	2014	United Kingdom, Portugal, and Spain	2010–2011	Hip, knee	43	2454	43/2497	7	ASA score >2
Wu (17)	2014	China	2000–2012	Hip, knee	45	252	–	8	Old age, obesity, alcohol abuse
Crowe (16)	2015	United states	2009–2011	Knee	26	3393	26/3419	7	Male gender, smoking
Gupta (15)	2015	United states	2001–2006	Hip, knee	339	339	–	7	Obesity, diabetes mellitus
Amin (14)	2016	United states	2008–2012	Knee	16	1612	16/1628	6	–

ASA, American Society of Anesthesiologists; NOS, Newcastle–Ottawa Scale.

Table 2 The main outcomes of meta-analysis and subgroup analysis

Risk factors	No. of studies	OR or SMD	LL 95%CI	UL 95%CI	*P* value	*Q*-test (*P*)	I^2 (%)
Male gender	15	1·48*	1·19	1·85	<0·01‡	<0·01	74·2
THA subgroup	5	1·21*	0·95	1·55	0·85‡	<0·01	74·7
TKA subgroup	6	2·39*	1·69	3·39	<0·01‡	<0·01	68·2
Age	8	−0·10†	−0·17	−0·03	<0·01§	0·55	0·0
THA subgroup	2	−0·04†	−0·19	0·11	0·63§	0·47	0·0
TKA subgroup	4	−0·10†	−0·19	−0·01	0·03§	0·91	0·0
Obesity (BMI ≥ 30)	12	1·54*	1·25	1·90	<0·01‡	0·01	58·8
THA subgroup	4	2·04*	1·71	2·44	<0·01§	0·97	0·0
TKA subgroup	4	1·39*	1·21	1·60	<0·01§	0·69	0·0
Smoking	5	1·48*	0·83	2·64	0·18§	0·55	0·0
THA subgroup	1	0·32*	0·04	2·37	0·26§	–	–
TKA subgroup	3	1·84*	0·93	3·63	0·08§	0·85	0·0
Alcohol abuse	3	1·88*	1·32	2·68	<0·01§	0·42	0·0
THA subgroup	1	2·09*	1·25	3·50	<0·01§	–	–
TKA subgroup	1	1·45*	0·83	2·53	0·19§	–	–
Steroid usage	2	0·85*	0·34	2·11	0·73§	0·84	0·0
THA subgroup	2	0·85*	0·34	2·11	0·73§	0·84	0·0
TKA subgroup	0	–	–	–	–	–	–
ASA score >2	6	2·06*	1·77	2·39	<0·01§	0·62	0·0
THA subgroup	1	2·37*	1·71	3·27	<0·01§	–	–
TKA subgroup	3	1·89*	1·57	2·28	0·01§	0·62	0·0
Operative time	4	0·49†	0·19	0·78	<0·01‡	<0·01	87·5
THA subgroup	2	0·32†	0·17	0·47	<0·01‡	<0·01	95·8
TKA subgroup	2	0·31†	0·22	0·40	<0·01§	0·78	0·0
Bilateral surgery	2	0·80*	0·53	1·21	0·30‡	<0·01	94·6
THA subgroup	1	3·80*	1·67	8·66	<0·01‡	–	–
TKA subgroup	1	0·47*	0·29	0·76	<0·01‡	–	–
Transfusion	8	1·44*	0·87	2·39	0·16‡	<0·01	76·9
THA subgroup	2	0·57*	0·06	5·73	0·63‡	<0·01	92·4
TKA subgroup	3	1·95*	0·79	4·83	0·15‡	0·04	68·2
Drain usage	4	0·36*	0·18	0·74	<0·01§	0·18	38·0
THA subgroup	1	1·36*	0·32	5·89	0·68§	–	–
TKA subgroup	1	0·24*	0·06	0·96	0·04§	–	–
Cementation	2	0·95*	0·34	2·65	0·91‡	0·14	55·1
THA subgroup	1	2·10*	0·49	9·07	0·32‡	–	–
TKA subgroup	0	–	–	–	–	–	–
Diabetes mellitus	15	1·58*	1·37	1·81	<0·01‡	0·05	41·9
THA subgroup	5	1·51*	1·33	1·71	<0·01§	0·47	0·0
TKA subgroup	7	1·66*	1·25	2·19	<0·01‡	0·01	63·1
Urinary tract infection	5	1·53*	1·09	2·16	0·01‡	<0·01	81·7
THA subgroup	2	4·80*	0·25	92·9	0·30‡	<0·01	92·4
TKA subgroup	1	1·14*	1·03	1·27	0·01‡	–	–
Hypertension	7	1·09*	0·92	1·28	0·32‡	0·10	43·3
THA subgroup	2	1·07*	0·68	1·69	0·78‡	0·14	54·0
TKA subgroup	3	1·07*	0·98	1·17	0·15§	0·15	47·7
Rheumatoid arthritis	12	1·57*	1·30	1·88	0·03‡	0·06	41·8
THA subgroup	4	1·75*	1·49	2·06	<0·01§	0·30	18·7
TKA subgroup	5	1·34*	1·18	1·52	<0·01§	0·17	37·9

ASA, American Society of Anesthesiologists; BMI, body mass index; LL, lower limit; OR, odds ratios; SMD, standardised mean differences; THA, total hip arthroplasty; TKA, total knee arthroplasty; UL, upper limit.

*OR.

†SMD.

‡Random-effects model was performed.

§Fixed-effects model was performed.

chance of infection. It is possible that this effect is more obvious in knee joint prostheses than hip joint prostheses. However, we cannot draw a definite conclusion yet without further studies.

Operative time and drain usage were two surgical-related factors that were proven to be associated with joint infection following TJA. A previous study conducted by Namba *et al.* observed an increased risk of infection per every additional 15 minutes of operative time (22). In the study conducted by Kurtz *et al.*, the authors found that a TKA operative time of longer than 210 minutes, compared with less than 120 minutes,

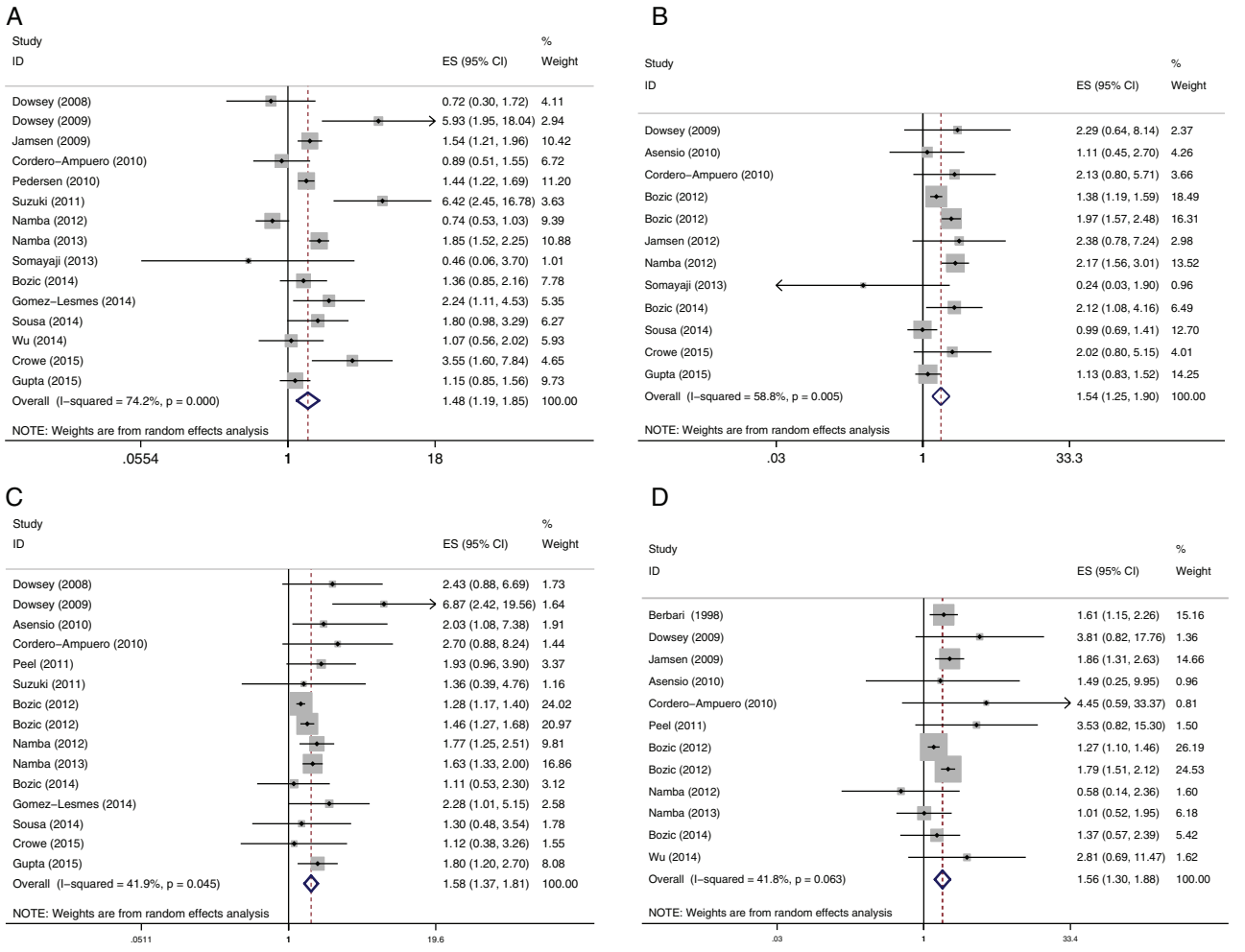

Figure 2 Forest plots of the meta-analysis of (A) male gender, (B) obesity, (C) diabetes mellitus and (D) rheumatoid arthritis as significant risk factors for periprosthetic joint infection after total joint arthroplasty.

was associated with an increased risk of infection (39). Their conclusions were in accordance with our findings. Drain usage was found to have a protective effect against PJI. There is a chance that drain usage decreases the incidence of haematoma formation and subsequently decreased the risk of infection.

Among the comorbid conditions, diabetes mellitus and rheumatoid arthritis were proven to be associated with PJI after TJA. Several studies have suggested that diabetes increase the risk of postoperative infection in TJA patients (7,24). Diabetic patients are known to be susceptible to infection because of their impaired defences against bacteria. What is more, diabetes mellitus could impair wound healing because microangiopathic changes could reduce the tissue concentrations of antibiotics and lead to local tissue ischaemia (40). Previous epidemiological studies have identified that rheumatoid arthritis predisposes patients to PJI because of immunosuppressive conditions. However, a challenge is to differentiate whether the increased risk is because of the underlying condition or the immunomodulatory therapy (41–43). Rheumatoid arthritis may also be associated with poor nutritional status, which could also lead to an increased risk of postoperative PJI.

This meta-analysis was conducted in a strict and comprehensive process, but there are still some limitations that should be noticed. First, nearly all of the included studies were observational and retrospective. This could result in considerable bias and had potential impacts on our final results. Second, the original diseases, the race of patients and duration of follow-up were varied among these studies, which definitely resulted in considerable heterogeneity and affected our results. Third, because of the limited numbers of studies, it was impossible to estimate the effects of every possible risk factor. Further studies should pay more attention to other factors.

In summary, the present analysis demonstrates that male gender, age, obesity, alcohol abuse, ASA score > 2, operative time, drain usage, diabetes mellitus, urinary tract infection and rheumatoid arthritis are significant risk factors for PJI after TJA surgery. Awareness of these risk factors will help surgeons optimise the patient's preoperative condition and surgical procedure and help decrease the incidence of postoperative infection. However, there was still a need for further high-quality research to strengthen the evidence.

Author contribution

LK and JC conducted the literatures screening; WD and YS extracted data; and LK and YZ assessed the methodological quality of studies. LK and YS wrote the manuscript. JC and YS reviewed the manuscript. All persons designated as authors are qualified for authorship.

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