Patients' risk factors for periprosthetic joint infection in total hip arthroplasty: A systematic review and meta-analysis of 34 studies

Chao Tu
Department of orthopedics, Second xiangya hospital. Hunan key laboratory of tumor models and individualized medicine.
Xiaolei Ren
Hunan key laboratory of tumor models and individualized medicine. Second xiangya hospital, Department of orthopedics.
Chenghao Zhang
Second xiangya hospital, Hunan key laboratory of tumor models and individualized medicine.
Lin Qi
Department of orthopedics, Second xiangya hospital.
Wanchun Wang
Department of orthopedics, Second xiangya hospital.
Qiong Lu
Department of pharmacy, Second xiangya hospital
Zhihong Li (lizhihong@csu.edu.cn)
Second Xiangya Hospital https://orcid.org/0000-0002-1944-9671

Research

Keywords: periprosthetic joint infection, PJI, total hip arthroplasty, THA, risk factors

Posted Date: July 21st, 2020

DOI: https://doi.org/10.21203/rs.3.rs-43619/v1

Title: Patients' risk factors for periprosthetic joint infection in total hip arthroplasty: A systematic review and meta-analysis of 34 studies

Short running title: Patients' Risk Factors for Periprosthetic Joint Infection in THA

Highlights:

1. High BMI and several medical chracteristics are correlated with increased PJI risk following THA.
2. Protective factors for PJI after THA include dysplasia/ dislocation and OA.
3. Female gender is protective for PJI only after long follow-up (≥3years).

ABSTRACT

Background: Periprosthetic joint infection (PJI) is a catastrophic complication following total hip arthroplasty (THA). This meta-analysis aimed to identify the individual-related risk factors that predispose patients to PJI undergoing THA.

Methods: We performed extensive literature retrieval from related databases from inception to October 20, 2019. Patient-related risk factors were compared and grouped according to modifiable factors (BMI, smoke and alcohol abuse), non- modifiable factors (gender, age), and medical history characteristics, such as diabetes mellitus (DM), avascular necrosis (AVN) of femoral head, femoral neck fracture, rheumatoid arthritis (RA), cardiovascular disease (CVD), and osteoarthritis (OA) etc. Meta-analysis was performed using risk ratios with 95% corresponding intervals. Sensitivity analysis and publication bias were performed to assess the credibility of the results.

Results: Overall, 34 studies with 2,141,960 hips were included. By implementing cumulative meta-analysis, we found that higher BMI significantly increased the rate of PJI after THA. Meanwhile, medical characteristics comprising DM, AVN, femoral neck fracture, RA, CVD, chronic pulmonary disease and neurological disease, were also markedly associated with higher PJI risk. Conversely, dysplasia or dislocation, and OA were protective factors. Notably, female gender was protective for PJI only after longer follow-up. Besides, age, smoking, alcohol abuse, previous joint surgery, renal disease, hypertension, cancer and steroid use were not correlated with risk of PJI.

Conclusion: Our finding indicates that the main risk factors for PJI are high BMI, DM, AVN, femoral neck fracture, RA, CVD, chronic pulmonary disease, and neurological disease. Protective factors are female gender, dysplasia/ dislocation and OA.

Keywords: periprosthetic joint infection, PJI, total hip arthroplasty, THA, risk factors.

Introduction

Total hip arthroplasty (THA) has served as a successful elective surgical procedure that provides pain relief, restores joint function, and consequently enhances overall quality-of-life for millions of patients worldwide [1-3]. Although most patients benefit significantly from this advanced technique, there is still a minority of patients may suffer with device failure and thus need multiple additional operations [4, 5].

Periprosthetic joint infection (PJI) is defined as infection involving the joint prosthesis and adjacent tissue. The incidence for PJI has been reported to range from 0.25% to 2.0% [6]. It is a rare but devastating morbidity since it may jeopardize the results of the procedure, and even increase mortality [1, 7]. Tremendous efforts have been invested and improvements in prosthesis material and surgical technique have been achieved in THA in recent years [8]. However, the incidence of PJI is still increasing across the globe alongside the increasing prevalence of revision surgery, morbid obesity epidemic, and other comorbidities. Treatment for PJI usually consists of prolonged systemic use of antibiotics, debridement and surgery, which may pose substantial burden of compromised function and impaired quality of life to patients [1, 6]. Moreover, patients with PJI are associated with higher financial burden and greater medical resource utilization on the current health care system [9, 4, 10]. Therefore, identification of potential risk factors and the magnitude of its effects are of great value for early detection and reduction of the incidence of PJI.

Nowadays, attention has been directed toward a plausible link between PJI and patients' individual risk factors in addition to the surgical- and hospital-related factors. More recently, emerging evidences have been reported concerning the potential patient-related risk factors for PJI, such as obesity [11-13, 4, 14], diabetes mellitus (DM) [15, 14, 16, 17], male gender [18], rheumatoid arthritis (RA) [19, 20], and pulmonary diseases [6, 21]. However, the power of these studies may be impaired due to a limited number of recruited patients, discrepancy results and range of potential risk factor studies. Besides, many of these risk factors were updated and even revised in recent years, which may consolidate or oppose against the previous evidences. Moreover, optimization of modifiable risk factor for PJI should be attempted and put in emphasis in clinical practice, while only limited studies have separated the modifiable and non-modifiable risk factors to PJI. Given the limitations and remained controversies abovementioned, we took into account all the available literature and performed this updated meta-analysis, aiming to identify the potential individual risk

121 factors for PJI undergoing THA.

122

123 **Materials and Methods**

124 **Literature Search Strategy**

125 The MOOSE (Meta-analysis of Observational Studies in Epidemiology) and PRISMA (Preferred
126 Reporting Items for Systematic reviews and Meta-Analysis) guidelines were followed for the
127 completion of this study [22, 23].

128 A computer-aided systematic literature retrieval was performed without restriction of language.
129 Databases including Pubmed, Web of Science, and the Cochrane Library were searched from
130 inception to October 20th, 2019, with search terms in variably combinations listed as follows: ("PJI"
131 OR "periprosthetic joint infection" OR "prosthetic joint infection" or "deep infection" OR "deep
132 surgical site infection") AND ("surgical" OR "surgical approach" OR "surgical incision" OR
133 "incision") AND ("THA" OR "THR" OR "total hip arthroplasty" OR "total hip replacement").
134 Specially, only primary THAs were included in this meta-analysis.

135 Additionally, cross-references checking of each enrolled study were manually performed to
136 identify possible additional articles.

137 Articles with potentially relevant titles and abstracts were screened and scored firstly by two
138 independent investigators (CT and XLR). A third investigator (LQ) was consulted in the event of
139 discrepancies between the two reviewers. Afterwards, the full manuscripts may be read if the studies
140 could meet the inclusion criteria and the relevant information will be extracted.

141 **Study Selection**

142 Included studies met the following criteria: 1) Quantitative observational studies including
143 prospective cohorts or retrospective case-control trials; 2) Studies reported odds ratio (ORs) or risk
144 ratio (RRs) for dichotomous risk factors and mean difference for continuous factors, or allowed
145 calculation of ORs/ RRs from sufficient raw data; and 3) Risk factors must be demographic, comorbid,
146 behavioral, infectious, native joint disease, other patient-related risk factors.

147 Exclusion criteria were as follows: 1) Insufficient data to estimate a pooled RR; 2) Duplicated
148 data from the same authors, excluding the earlier and small studies; 3) Not focused on risk factors of
149 PJI; 4) Documents without original raw data, such as correspondences, editorial materials, and
150 reviews; 5) Not related to THA; and 6) Superficial infection.

151

152 **Data Extraction and Methodological Quality Assessment**

153 Two investigators carefully reviewed and screened the titles and abstracts independently to
154 identify eligible studies as per the inclusion and exclusion criteria. The full text was read if necessary.
155 Information items extracted from enrolled trials included as follows: first author, year of publication,
156 location and investigation year of the study, study design, duration of follow-up (years), number of
157 participants involved, confounders adjusted, age, and gender. Demographic risk factors, including
158 behavioral risk factors, comorbid conditions, native joint disease, and other patient-related risk factors
159 were searched for PJI.

160 Quality assessment was performed by using the Newcastle-Ottawa Scale (NOS) as previously
161 described [24].

162 **Sensitivity Analysis**

163 Sensitivity analysis was used to assess the robustness of the results and was planned based on the
164 risk of bias assessment. A sensitivity analysis was performed for all the risk factors with substantial
165 heterogeneity. Meta-regression was done for gender and DM.

166 **Statistical analysis**

167 This meta-analysis was conducted by using the STATA software (Stata 12.0) and Review
168 Manager (RevMan 5.3). Due to variability in the populations and risk factors of included studies,
169 random-effects models were adopted for meta-analysis. Data were categorized and analyzed by
170 groups of risk factors.

171 The heterogeneity across the eligible studies was quantified using I^2 statistic. Meta-regression
172 was done to explore heterogeneity and determine the causes of heterogeneity.

173

174 ## Results

175 **Search Results and Study Identification**

176 A total of 3,899 articles were collected by search strategy from PubMed, Web of science, and the
177 Cochrane library. After assessment according to the inclusion eligibility criteria, 34 studies
178 comprising 2,141,960 hips in total were finally recruited in this meta-analysis (Figure 1). Articles
179 with irrelevant topics like those without risk factors, reviews, meeting abstracts and papers with
180 duplicate reports or unavailable data were excluded. Particularly, 75 studies which investigated risk

factors of PJI both in total knee arthroplasty (TKA) and THA were excluded because the data of only THA could not be extracted. Among the included articles, eight were published in Asia-Pacific region, including Australia, Korea and Malaysia. Besides, ten studies were performed in the USA and sixteen in Europe including UK, Finland, Spain, Italy, Netherlands, Switzerland, Belgium and Portugal. All studies were published between 2001 and 2018 except two performed by Surin [25] and Vannini [15], which were published in 1983 and 1984, respectively. The investigation years ranged from 1969 to 2016. Study design included prospective case-control, prospective cohort, retrospective case-control and retrospective cohort studies. The mean ± standard deviation of follow-up time was 3.32± 2.95 years. The methodological quality was evaluated by NOS scores and calculated total quality scores ranged from 5 to 8 (Table S1). All the characteristics details of included studies were demonstrated in Table 1.

Effect of modifiable Individual Factors on the Incidence of PJI

Modifiable individual risk factors among studies were compared in terms of BMI (body mass index), smoke and alcohol abuse. Eighteen studies were included in the BMI comparison. Subgroup analyses were further adopted according to different cut-off values, in which the patients were stratified by 30, 35 and 40 kg/m^2 cut-off value group. All the pooled RRs and 95% CI were shown in Table 2. In all the subgroups based on BMI cut-off value, the results indicated that higher BMI was associated with higher incidence of PJI (Figure 2A). The pooled RR (95% CI) of smoke and alcohol comparisons were 1.24 (0.85-1.82) (Figure 2B) and 2.84 (0.81-10.02) (Figure 2C), respectively, which suggested that smoke and alcohol abuse were not risk factors relating to PJI.

The heterogeneity in BMI and smoke analysis groups were not significant (I^2<50%, P>0.05). Although results exhibited significant heterogeneity (I^2=66.7%, P=0.083), the few number of the included studies were not enough to analyze the source of heterogeneity.

Effect of Non-modifiable Individual Factors on the Incidence of PJI

Gender and age were analyzed as non-modifiable individual factors to explore their effects on the incidence of PJI. Meta-analysis of gender factor included data from 18 studies. The forest plot of overall pooled RRs (Figure 3A) showed no significant difference in the prevalence of PJI between the male and female groups (RR=1.15, 95% CI: 1.00-1.32) under a random-effects model. Since obvious heterogeneity was observed (I^2=84.8%, p<0.001), subgroup analyses were further performed to identify the possible varieties, in which the patients were stratified by location, follow-up duration

(years), study design and confounders adjustment (Table 3). Univariate meta-regressions showed significant relevance between the incidence of PJI and study design (p=0.022). Seven studies from prospective studies group revealed that male had higher risk suffering from PJI than female (1.39 1.13-1.72). Whereas, retrospective study group still had no significant difference (0.997, 0.81-1.23) (Figure 3C). Besides, long-term follow-up duration (≥3years) also showed that female gender was a protective risk factor (1.35, 1.13-1.62) of PJI after THA, as shown in Figure 3B.

Seven studies reported data regarding relevance between different age stages and the incidence of PJI. The overall pooled RR and 95% CI (0.85, 0.71-1.01) were calculated using a random model and results exhibited heterogeneity (I^2=59.0%, P=0.023) in some degree (Figure 3D). It indicates that more evidence is needed to confirm age as a risk factor of PJI.

Effect of Medical History Characteristics on the Incidence of PJI

Fourteen medical history characteristics reported in studies were associated with PJI, and details were presented in Table 4. Fifteen studies exhibited the effect of diabetes mellitus (DM) on the incidence of PJI (Figure 4A). The overall pooled RR and corresponding 95% CI (1.75, 1.32-2.32) was calculated using a random model and results showed obvious heterogeneity (I^2=87.4%, p<0.001). Similarly, subgroup analyses were performed to find potentially explicable variety (Figure S1). Furthermore, meta-analysis results indicated that avascular necrosis (AVN) of femoral head (Figure 4B), femoral neck fracture (Figure 4C), rheumatoid arthritis (RA) (Figure 4D), cardiac vascular disease (CVD) (Figure 4E), chronic pulmonary disease (Figure 4F), neurological diseases including dementia and Parkinson's disease (Figure 4G) were significant risk factors of the incidence of PJI after THA. While the comparisons about osteoarthritis (OA) vs. non-OA, and dysplasia or dislocation vs. non groups showed the opposite effects on PJI, implicating that OA and dysplasia/dislocation could be served as protective factors for PJI (Figure 5). Additionally, there was not enough evidence to prove the previous joint surgery, renal disease, hypertension, cancer, and steroid use history associating with PJI (Figure S2). The details of the above pooled RRs, 95% CI and heterogeneity analysis were revealed in Table 4.

Sensitivity Analysis

Sensitivity analysis was performed to assess whether the pooled results were credible. In BMI comparison, sensitivity analysis illustrated that excluding the study by Lenguerrand *et al*. [26] changed the original results and the modified pooled RR (95%CI) was 2.44 (2.07-2.86) after

241 excluding this study (Figure 6A). However, the significance of BMI in predicting PJI risk was not
242 altered, indicating that high BMI was still positively correlated with increased PJI risk.

243 **Publication Bias**

244 Funnel plots, Egger's and Begg's tests were performed to evaluate the publication bias of the
245 included studies, visually and statistically. BMI comparison had publication bias (P=0.009 with
246 Egger's test). RR and 95% CI (2.028, 1.852-2.22) were modified with trimming and filled method
247 (Figure 6B, 6C). In addition, DM comparison also had publication bias (P=0.029 with Begg's test).
248 Trimming and filled method was further applied to modify RR with corresponding 95% CI (1.714,
249 1.293-2.271) (Figure S1E, S1F).

250

251 **Discussion**

252 Our systematic review focus on the patient-related factors associated with PJI, other than
253 surgical- or hospital-related factors. The main finding of this meta-analysis was that the high BMI was
254 the main risk factor for PJI. Additionally, DM and other comorbidities, such as AVN, RA, CVD,
255 chronic pulmonary disease, and neurological disease were also pivotal risk factors for PJI. On the
256 contrary, dysplasia or dislocation, OA were protective factors. Besides, female gender was protective
257 after long follow-up duration (≥3 years). Moreover, age, smoking, alcohol abuse and other medical
258 history such as previous joint surgery, renal disease, hypertension, cancer and steroid use were not
259 correlated with risk of PJI.

260 Obesity poses a major health challenge worldwide [1]. Consistent with previous finding [27, 18],
261 our data showed that patients with a BMI greater than 40, 35, or 30 had a 3.64, 2.46, or 2.02–fold
262 higher risk of PJI compared with those counterparts with less BMI, respectively. Obese patients are
263 more prone to increased risk of PJI in the peri-operative setting, which may be attributed to prolonged
264 operative and anesthetic time, higher risk of colonization for *C. avidum* in the groin [11], longer
265 hospital stay and high readmission rates within 30 days [9]. Besides, being obese is usually correlated
266 with higher presence of other commodities including metabolic syndrome, wound dehiscence, and
267 heart disease [1]. Notably, we found that the PJI risk increased exponentially along with BMI value.
268 Similarly, Xu C *et al*. demonstrated that each one-unit increase in BMI was correlated with an 8%
269 higher risk of PJI [4], thus the morbidly obese patients (BMI >40 kg/m^2) may have the highest
270 likelihood of complications [13]. Another study also confirmed that all-cause revision rater after

primary TJA doubled in patients with BMI ≥35 kg/m^2, and even tripled in morbidly obese patients when compared with the controls [28, 7]. Accordingly, the increased risk of obesity should be weighed against the benefits of THA [7].

The relationship between DM and PJI has been well-established with a projected increase for years [29, 27, 18]. Our study showed that, comparing with non-DM patients, those undergoing THA with DM carried 1.75-fold greater risk of PJI (1.75, 1.32-2.32). Further stratified analyses, such as location, study design or analyses method, did not alter the unfavorable predictive value of DM on PJI risk. Epidemiological studies have identified that DM predisposes patients to PJI, probably due to increased infection rate of bacteria, impaired immune response, and postoperative hyperglycemia [30]. HbA1c is a widely used biomarker for diagnosis and monitoring of type 2 DM [17]. Recently, Cancienne JM *et al*. reviewed 7,736 patients who underwent THA, and identified that HbA1c of 7.5 mg/dl could serve as a threshold for prediction of PJI after THA [10].

Both two studies reported the association between AVN or femoral neck fracture and PJI, and the pooled results indicated a 1.65 or 1.75-times increased risk of PJI than non-group, respectively. In contrast, four studies demonstrated the relationship between OA and PJI risk, and the calculated RR with corresponding CI was 0.70 (0.62-079), suggesting a protective role of OA in PJI. It is generally accepted that patients underwent THA for AVN are more likely to have readmission and surgical complications including bleeding transfusion [31]. Meanwhile, patients with femoral neck fracture undergoing THA also confer to higher rate of dislocation, infection and reoperation [32], which may be accountable for the increased potential of PJI [33]. OA refers to a common degenerative joint disease, and contribute to a majority cause for THA. However, compared with other commodities, patients with OA seem to have decreased occurrence of PJI after surgery. Another meta-analysis consisting of 37 studies reached a similar conclusion, showing that OA was protective factor in predicting PJI after THA/TKA [18]. Besides, Mayers W *et al*. searched the patients' profiles with primary THA in US from 2001-2010, and found that patient underwent THA for OA have lesser medical complications and lower incidence for myocardial infarction than those with AVN [34].

RA and CVD have been reported as independent risk factors for PJI [3, 35]. Consistently, our results showed that PJI incidence were 1.41 or 1.52 times higher in patients reporting a history of RA or CVD, respectively. Patients with RA are more susceptible to PJI thought to be secondary to immune-suppressive therapies and poor nutritional conditions [18, 20]. Meanwhile, patient with CVD

are recommended to receive aggressive anticoagulation therapy, such as aspirin or warfarin, may markedly increases risk of bleeding and wound hematoma after THA [1, 35], and thereby increase PJI rate [18].

Moreover, our study showed that patients with chronic pulmonary had 1.22–fold higher risk of PJI, and neurological disease may even double the risk of PJI (1.93, 1.03-3.60) when compared with non-group, which is in accordance with the published literature [18, 3, 35]. A meta-analysis conducted by Resende VAC *et al*. [18] showed that chronic lung disease significantly increased the risk for PJI after TJA. In addition to THA/TKA, another large multi-institutional retrospective study comprising 6,977 patients also revealed a significant positive association between chronic lung disease and total ankle arthroplasties (TAA) [36]. More recently, a meta-analysis with eight studies enrolled further confirmed that increased risk of PJI following TAA for patients with lung disease [37].

Gender shows conflicting results among the selected studies. A number of studies have demonstrated that male patients are more vulnerable to PJI compared to women [18, 33]. Whereas other studies have refuted this, claiming women had an elevated risk of deep infection than men [38, 39]. Our results showed that gender was not markedly correlated with PJI risk (1.15, 1.00-1.32). However, subgroup analyses showed that male patients had a higher risk of PJI after longer follow-up years (1.35, 1.13-1.62) or in prospective studies (1.39, 1.13-1.72). It is worth noting that male patients seem to coincide with higher incidence of unfavorable behavioral factors, which may result in increased risk of PJI. Therefore, more studies are needed to claim the association between gender and PJI.

The impact of age has been controversial among the enrolled studies. In general, older patients are more prone to postoperative infection caused by less competent immunity [5], malnutrition status [30] and complex medical comorbidities [8]. On the contrary, a multi-center analysis of 623,253 joint replacements claimed that younger age was closely correlated with elevated PJI [26], which may be attributed to active use cycles of implants, higher possibility of infection and revision surgery [30]. Besides, another meta-analysis with 2,470,827 patients also demonstrated older age was a protective factor in TJA [18]. Interestingly, we found that age had not direct influence on risk rate of PJI (0.85, 0.71-1.01), which was consistent with the results concluded by Kunutsor SK *et al* [40]. Recently, a single-center retrospective study comprising 23,966 patients also demonstrated that age alone was not a risk factor for PJI after adjusting for confounding variables [8], indicating that other covariates

should be taken into account for assessing the relationship between age and PJI. Future studies are needed to further address these findings by adequately controlling the confounders.

Previous meta-analyses have demonstrated that smoking and alcohol abuse may result in increased risk PJI. Therefore, it is of great importance to encourage smoking and alcohol cessation during peri-operation period, and some reports suggested a 4-6 week cessation prior to surgery may be effective [1]. Specifically, excessive smoking was documented as to increase incidence of infection, mainly due to impaired wound-healing capacity, disrupted immune response, as well as nicotine or carbon monoxide-mediated vasoconstriction, soft-tissue hypo-perfusion, hypoxia, and thrombi formation [1]. While alcohol could affect the immune system and contribute to impaired phagocytic function [30]. In addition, alcohol abuse is a deleterious factor for developing cirrhosis, which may in turn increase risk of infection [30]. Intriguing, our pooled results showed that smoking and alcohol abuse were not correlated with PJI following THA. However, it should be noted that smoking may contribute to synergistic effect on elevated risk of PJI (3.54-fold) for patients with obesity [41, 4]. Accordingly, caution is still warranted when considering a THA in tobacco and alcohol users. More trials are still needed to extensively elucidate the underlying mechanism between smoking/ alcohol abuse and PJI.

It is imperative that both the surgeons and patients understand and identify the modifiable risk factors prior to THA so that they could make prudent decisions in the perioperative management, mitigate the risk of PJI, and therefore decrease the enormous financial and social burden of PJI [1, 9]. The findings in this meta-analysis, along with advanced diagnostic and treatment approaches, will allow the development of prevention strategies and increase the adherence to the clinical practice. Taken together, these results may offer a help in developing guidelines on prevention of PJI after THA, and eventually establishing strategies to control it.

However, it should be noted that some limitations remain to be addressed. First, most of the studies were retrospective, giving rise to a comparative low quality of evidence as per the NOS score. In addition, high proportion of retrospective studies would lead to inherent bias inevitably [42]. Second, number of included hips among the selected studies ranged from 33 to 1,158,742, the inclusion of these studies may lead to bias and confounding within our results. Third, the RRs were not adjusted to include more participants. Fourth, the follow-up time was heterogeneous among studies with a range from 0.25 to 10 years, and did not differentiate time of onset of infection after

primary arthroplasty. Fifth, the races vary among the selected studies, which may lead to discrepancies between various studies [30]. Lastly, another relevant issue and potential confounder of the results was the different diagnostic tools for PJI used in the original studies and the lack of a risk factor definition in the eligible studies, except for obesity was defined as BMI.

Conclusion

Taken together, this meta-analysis identified significant risk factors for PJI associated with THA are high BMI, DM, AVN, femoral neck fracture, RA, CVD, chronic pulmonary disease, and neurological disease, while protective factors include female gender, OA and dysplasia/ dislocation. We therefore suggest optimization of modifiable risk factors such as BMI for reducing the risk of PJI in clinical practice.

Abbreviations

AVN: avascular necrosis
CIs: corresponding intervals
CVD: cardiovascular disease
DM: diabetes mellitus
MOOSE: Meta-analysis of Observational Studies in Epidemiology
NOS: Newcastle-Ottawa Scale
OA: osteoarthritis
ORs: odds ratio
PJI: periprosthetic joint infection
PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analysis
RA: rheumatoid arthritis
RRs: risk ratios
TAA: total ankle arthroplasty
TKA: total knee arthroplasty
THA: total hip arthroplasty
THR: total hip replacement

Author contributions

C Tu and XL Ren worked for the study equally. C Tu designed the methodology of the study and performed the literature retrieval, data analysis and interpretation. XL Ren contributed to the study methodology, performed the literature retrieval and data analysis. CH Zhang and L Qi participated in the data analysis. WC Wang critically reviewed and revised the manuscript. ZH Li and Q Lu worked for the study equally. They conceptualized the study, participated in the study design, data interpretation, and manuscript revision. All authors read and approved the final manuscript as submitted.

Competing interest statement

We declare that we have no conflict of interest.

Funding statement

This work was supported by the National Natural Science Foundation of China [grant number 81902745]; the Natural Science Foundation of Hunan Province, China [grant number 2018JJ3716].

References

1. Eka A, Chen AF. Patient-related medical risk factors for periprosthetic joint infection of the hip and knee. Ann Transl Med 2015; 3(16): 233. https://doi.org/10.3978/j.issn.2305-5839.2015.09.26.

2. Papalia R, Vespasiani-Gentilucci U, Longo UG, Esposito C, Zampogna B, Antonelli Incalzi R et al. Advances in management of periprosthetic joint infections: an historical prospective study. Eur Rev Med Pharmacol Sci 2019;23(2 Suppl):129-38. https://doi.org/10.26355/eurrev_201904_17482.

3. Bozic KJ, Ong K, Lau E, Berry DJ, Vail TP, Kurtz SM et al. Estimating risk in Medicare patients with THA: an electronic risk calculator for periprosthetic joint infection and mortality. Clin Orthop Relat Res 2013;471(2):574-83. https://doi.org/10.1007/s11999-012-2605-z.

4. Xu C, Guo H, Wang Q, Qu P, Bell K, Chen J. Interaction of obesity with smoking and inflammatory arthropathies increases the risk of periprosthetic joint infection: a propensity score matched study in a Chinese Han population. J Hosp Infect 2019;101(2):222-8. https://doi.org/10.1016/j.jhin.2018.06.017.

5. Tu C, He J, Wang W, Li Z. Revision for PJI after total hip replacement: more exploration is needed. Lancet Infect Dis 2018;18(11):1182. https://doi.org/10.1016/S1473-3099(18)30570-X.

6. Lee QJ, Mak WP, Wong YC. Risk factors for periprosthetic joint infection in total knee arthroplasty. J Orthop Surg (Hong Kong) 2015;23(3):282-6. https://doi.org/10.1177/230949901502300303.

7. Shohat N, Fleischman A, Tarabichi M, Tan TL, Parvizi J. Weighing in on Body Mass Index and Infection After Total Joint Arthroplasty: Is There Evidence for a Body Mass Index Threshold? Clin Orthop Relat Res 2018;476(10):1964-9. https://doi.org/10.1007/s11999.0000000000000141.

8. Inoue D, Xu C, Yazdi H, Parvizi J. Age alone is not a risk factor for periprosthetic joint infection. J Hosp Infect 2019;103(1):64-8. https://doi.org/10.1016/j.jhin.2019.04.005.

9. Girardi FM, Liu J, Guo Z, Valle AGD, MacLean C, Memtsoudis SG. The impact of obesity on resource utilization among patients undergoing total joint arthroplasty. Int Orthop 2019;43(2):269-74. https://doi.org/10.1007/s00264-018-4059-8.

10. Cancienne JM, Werner BC, Browne JA. Is There a Threshold Value of Hemoglobin A1c That Predicts Risk of Infection Following Primary Total Hip Arthroplasty? J Arthroplasty 2017;32(9S):S236-S40. https://doi.org/10.1016/j.arth.2017.01.022.

11. Boni L, Kuster SP, Bartik B, Zbinden R, Zingg PO, Achermann Y. Association of Cutibacterium avidum Colonization in the Groin With Obesity: A Potential Risk Factor for Hip Periprosthetic Joint Infection. Clin Infect Dis 2018;67(12):1878-82. https://doi.org/10.1093/cid/ciy379.

12. Dowsey MM, Choong PF. Obesity is a major risk factor for prosthetic infection after primary hip arthroplasty. Clin Orthop Relat Res 2008;466(1):153-8. https://doi.org/10.1007/s11999-007-0016-3.

13. Tu C, Wang W, Li Z. Letter to the Editor concerning the paper "Long-term outcome of total knee arthroplasty in morbid obesity patients". Int Orthop 2020;44(1):105-106. https://doi.org/10.1007/s00264-019-04410-1.

14. Jamsen E, Nevalainen P, Eskelinen A, Huotari K, Kalliovalkama J, Moilanen T. Obesity, diabetes, and preoperative hyperglycemia as predictors of periprosthetic joint infection: a single-center analysis of 7181 primary hip and knee replacements for osteoarthritis. J Bone Joint Surg Am 2012;94(14):e101. https://doi.org/10.2106/JBJS.J.01935.

15. Vannini P, Ciavarella A, Olmi R, Flammini M, Moroni A, Galuppi V et al. Diabetes as pro-infective risk factor in total hip replacement. Acta Diabetol Lat 1984;21(3):275-80.

16. Kildow BJ, Agaba P, Moore BF, Hallows RK, Bolognesi MP, Seyler TM. Postoperative Impact of Diabetes, Chronic Kidney Disease, Hemodialysis, and Renal Transplant After Total Hip Arthroplasty. J Arthroplasty 2017;32(9s):S135-S40.e1. https://doi.org/10.1016/j.arth.2017.01.018.
17. Kwon SS, Kwon JY, Park YW, Kim YH, Lim JB. HbA1c for diagnosis and prognosis of gestational diabetes mellitus. Diabetes Res Clin Pract 2015;110(1):38-43. https://doi.org/10.1016/j.diabres.2015.07.014.
18. Resende VAC, Neto AC, Nunes C, Andrade R, Espregueira-Mendes J, Lopes S. Higher age, female gender, osteoarthritis and blood transfusion protect against periprosthetic joint infection in total hip or knee arthroplasties: a systematic review and meta-analysis. Knee Surg Sports Traumatol Arthrosc 2018. Nov 9. https://doi.org/10.1007/s00167-018-5231-9.
19. Burn E, Edwards CJ, Murray DW, Silman A, Cooper C, Arden NK et al. The impact of rheumatoid arthritis on the risk of adverse events following joint replacement: a real-world cohort study. Clin Epidemiol 2018;10:697-704. https://doi.org/10.2147/clep.s160347.
20. Ravi B, Escott B, Shah PS, Jenkinson R, Chahal J, Bogoch E et al. A systematic review and meta-analysis comparing complications following total joint arthroplasty for rheumatoid arthritis versus for osteoarthritis. Arthritis Rheum 2012;64(12):3839-49. https://doi.org/10.1002/art.37690.
21. Hanson CG, Barner KL, Rose-Reneau Z, Kortz M. The Impact of Chronic Obstructive Pulmonary Disease and Hospital Teaching Status on Mortality, Cost, and Length of Stay in Elective Total Hip Arthroplasty Patients. Cureus 2019;11(4):e4443. https://doi.org/10.7759/cureus.4443.
22. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D et al. Meta-analysis of observational studies in epidemiology - A proposal for reporting. Jama-J Am Med Assoc 2000;283(15):2008-12. https://doi.org/DOI 10.1001/jama.283.15.2008.
23. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. Bmj 2015;350:g7647. https://doi.org/10.1136/bmj.g7647.
24. Zhang C, Ren X, He J, Wang W, Tu C, Li Z. The prognostic value of long noncoding RNA SNHG16 on clinical outcomes in human cancers: a systematic review and meta-analysis. Cancer cell international. 2019;19:261. https://doi.org/10.1186/s12935-019-0971-2.
25. Surin VV, Sundholm K, Backman L. Infection after total hip replacement. With special reference to a discharge from the wound. J Bone Joint Surg Br 1983;65(4):412-8.
26. Lenguerrand E, Whitehouse MR, Beswick AD, Kunutsor SK, Burston B, Porter M et al. Risk factors associated with revision for prosthetic joint infection after hip replacement: a prospective observational cohort study. Lancet Infect Dis 2018;18(9):1004-14. https://doi.org/10.1016/S1473-3099(18)30345-1.
27. Malinzak RA, Ritter MA, Berend ME, Meding JB, Olberding EM, Davis KE. Morbidly obese, diabetic, younger, and unilateral joint arthroplasty patients have elevated total joint arthroplasty infection rates. J Arthroplasty 2009;24:84-8. https://doi.org/10.1016/j.arth.2009.05.016.
28. Zingg M, Miozzari HH, Fritschy D, Hoffmeyer P, Lubbeke A. Influence of body mass index on revision rates after primary total knee arthroplasty. Int Orthop 2016;40(4):723-9. https://doi.org/10.1007/s00264-015-3031-0.
29. Everhart JS, Altneu E, Calhoun JH. Medical comorbidities are independent preoperative risk factors for surgical infection after total joint arthroplasty. Clin Orthop Relat Res 2013;471(10):3112-9. https://doi.org/10.1007/s11999-013-2923-9.
30. Wu C, Qu X, Liu F, Li H, Mao Y, Zhu Z. Risk factors for periprosthetic joint infection after total

hip arthroplasty and total knee arthroplasty in Chinese patients. PloS one 2014;9(4):e95300. https://doi.org/10.1371/journal.pone.0095300.
31. Lovecchio FC, Manalo JP, Demzik A, Sahota S, Beal M, Manning D. Avascular Necrosis Is Associated With Increased Transfusions and Readmission Following Primary Total Hip Arthroplasty. Orthopedic 2017;40(3):171-6. https://doi.org/10.3928/01477447-20170117-03.
32. Eskildsen SM, Kamath GV, Del Gaizo DJ. Age matters when comparing hemiarthroplasty and total hip arthroplasty for femoral neck fractures in Medicare patients. Hip Int 2019;29(6):674-9. https://doi.org/10.1177/1120700018816924.
33. Pedersen AB, Svendsson JE, Johnsen SP, Riis A, Overgaard S. Risk factors for revision due to infection after primary total hip arthroplasty. A population-based study of 80,756 primary procedures in the Danish Hip Arthroplasty Registry. Acta Orthop 2010;81(5):542-7. https://doi.org/10.3109/17453674.2010.519908.
34. Mayers W, Schwartz B, Schwartz A, Moretti V, Goldstein W, Shah R. National trends and in hospital outcomes for total hip arthroplasty in avascular necrosis in the United States. Int Orthop 2016;40(9):1787-92. https://doi.org/10.1007/s00264-015-3089-8.
35. Bozic KJ, Lau E, Kurtz S, Ong K, Rubash H, Vail TP et al. Patient-related risk factors for periprosthetic joint infection and postoperative mortality following total hip arthroplasty in Medicare patients. J Bone Joint Surg Am 2012;94(9):794-800. https://doi.org/10.2106/JBJS.K.00072.
36. Althoff A, Cancienne JM, Cooper MT, Werner BC. Patient-Related Risk Factors for Periprosthetic Ankle Joint Infection: An Analysis of 6977 Total Ankle Arthroplasties. J Foot Ankle Surg 2018;57(2):269-72. https://doi.org/10.1053/j.jfas.2017.09.006.
37. Smyth NA, Kennedy JG, Parvizi J, Schon LC, Aiyer AA. Risk factors for periprosthetic joint infection following total ankle replacement. Foot Ankle Surg 2019. Aug 7. https://doi.org/10.1016/j.fas.2019.07.015.
38. Namba RS, Inacio MC, Paxton EW. Risk factors associated with surgical site infection in 30,491 primary total hip replacements. J Bone Joint Surg Br 2012;94(10):1330-8. https://doi.org/10.1302/0301-620X.94B10.29184.
39. Ridgeway S, Wilson J, Charlet A, Kafatos G, Pearson A, Coello R. Infection of the surgical site after arthroplasty of the hip. J Bone Joint Surg Br 2005;87(6):844-50. https://doi.org/10.1302/0301-620X.87B6.15121.
40. Kunutsor SK, Whitehouse MR, Blom AW, Beswick AD, Team I. Patient-Related Risk Factors for Periprosthetic Joint Infection after Total Joint Arthroplasty: A Systematic Review and Meta-Analysis. PloS one 2016;11(3):e0150866. https://doi.org/10.1371/journal.pone.0150866.
41. Crowe B, Payne A, Evangelista PJ, Stachel A, Phillips MS, Slover JD et al. Risk Factors for Infection Following Total Knee Arthroplasty: A Series of 3836 Cases from One Institution. J Arthroplasty 2015;30(12):2275-8. https://doi.org/10.1016/j.arth.2015.06.058.
42. Guo W, Lu X, Liu Q, Zhang T, Li P, Qiao W et al. Prognostic value of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio for breast cancer patients: An updated meta-analysis of 17079 individuals. Cancer medicine 2019;8(9):4135-48. https://doi.org/10.1002/cam4.2281.
43. Bozic KJ, Ward DT, Lau EC, Chan V, Wetters NG, Naziri Q et al. Risk factors for periprosthetic joint infection following primary total hip arthroplasty: a case control study. J Arthroplasty 2014;29(1):154-6. https://doi.org/10.1016/j.arth.2013.04.015.
44. Chee YH, Teoh KH, Sabnis BM, Ballantyne JA, Brenkel IJ. Total hip replacement in morbidly obese patients with osteoarthritis RESULTS OF A PROSPECTIVELY MATCHED STUDY. J Bone

Joint Surg Br 2010;92b(8):1066-71. https://doi.org/10.1302/0301-620x.92b8.22764.
45. Choong PFM, Dowsey MM, Carr D, Daffy J, Stanley P. Risk factors associated with acute hip prosthetic joint infections and outcome of treatment with a rifampin-based regimen. Acta Orthop 2007;78(6):755-65. https://doi.org/10.1080/17453670710014527.
46. Cordero-Ampuero J, de Dios M. What are the risk factors for infection in hemiarthroplasties and total hip arthroplasties? Clin Orthop Relat Res 2010;468(12):3268-77. https://doi.org/10.1007/s11999-010-1411-8.
47. Dale H, Skramm I, Lower HL, Eriksen HM, Espehaug B, Furnes O et al. Infection after primary hip arthroplasty A comparison of 3 Norwegian health registers. Acta Orthop 2011;82(6):646-54. https://doi.org/10.3109/17453674.2011.636671.
48. Davis AM, Wood AM, Keenan ACM, Brenkel IJ, Ballantyne JA. Does body mass index affect clinical outcome post-operatively and at five years after primary unilateral total hip replacement performed for osteoarthritis? A MULTIVARIATE ANALYSIS OF PROSPECTIVE DATA. J Bone Joint Surg Br 2011;93b(9):1178-82. https://doi.org/10.1302/0301-620x.93b9.26873.
49. de Boer AS, Geubbels EL, Wille J, Mintjes-de Groot AJ. Risk assessment for surgical site infections following total hip and total knee prostheses. J Chemother 2001;13:42-7. https://doi.org/10.1179/joc.2001.13.Supplement-2.42.
50. Gittings DJ, Courtney PM, Ashley BS, Hesketh PJ, Donegan DJ, Sheth NP. Diagnosing Infection in Patients Undergoing Conversion of Prior Internal Fixation to Total Hip Arthroplasty. J Arthroplasty 2017;32(1):241-5. https://doi.org/10.1016/j.arth.2016.06.047.
51. Gonzalez AI, Luime JJ, Uckay I, Hannouche D, Hoffmeyer P, Lubbeke A. Is There an Association Between Smoking Status and Prosthetic Joint Infection After Primary Total Joint Arthroplasty? J Arthroplasty 2018;33(7):2218-24. https://doi.org/10.1016/j.arth.2018.02.069.
52. Huotari K, Lyytikainen O, Seitsalo S, Hospital Infection Surveillance T. Patient outcomes after simultaneous bilateral total hip and knee joint replacements. J Hosp Infect 2007;65(3):219-25. https://doi.org/10.1016/j.jhin.2006.10.018.
53. Jung P, Morris AJ, Zhu M, Roberts SA, Frampton C, Young SW. BMI is a key risk factor for early periprosthetic joint infection following total hip and knee arthroplasty. N Z Med J 2017;130(1461):24-34.
54. Kurtz SM, Lau EC, Son MS, Chang ET, Zimmerli W, Parvizi J. Are We Winning or Losing the Battle With Periprosthetic Joint Infection: Trends in Periprosthetic Joint Infection and Mortality Risk for the Medicare Population. J Arthroplasty 2018;33(10):3238-45. https://doi.org/10.1016/j.arth.2018.05.042.
55. Lubbeke A, Stern R, Garavaglia G, Zurcher L, Hoffmeyer P. Differences in outcomes of obese women and men undergoing primary total hip arthroplasty. Arthrit Rheum-Arthr 2007;57(2):327-34. https://doi.org/10.1002/art.22542.
56. Maoz G, Phillips M, Bosco J, Slover J, Stachel A, Inneh I et al. The Otto Aufranc Award: Modifiable versus Nonmodifiable Risk Factors for Infection After Hip Arthroplasty. Clin Orthop Relat R 2015;473(2):453-9. https://doi.org/10.1007/s11999-014-3780-x.
57. van Kasteren ME, Manniën J, Ott A, Kullberg BJ, de Boer AS, Gyssens IC. Antibiotic prophylaxis and the risk of surgical site infections following total hip arthroplasty: timely administration is the most important factor. Clin Infect Dis 2007;44(7):921-7. https://doi.org/10.1086/512192
58. McIntosh AL HA, Wenger DE, Osmon DR. Recent intraarticular steroid injection may increase infection rates in primary THA. Clin Orthop Relat Res 2006;451:50-4. https://doi.org/

10.1097/01.blo.0000229318.51254.79
59. Meermans G, Corten K, Simon JP. Is the Infection Rate in Primary THA Increased After Steroid Injection? Clin Orthop Relat R 2012;470(11):3213-9. https://doi.org/10.1007/s11999-012-2390-8.
60. Muilwijk J, Walenkamp GH, Voss A, Wille JC, van den Hof S. Random effect modelling of patient-related risk factors in orthopaedic procedures: results from the Dutch nosocomial infection surveillance network 'PREZIES'. J Hosp Infect 2006;62(3):319-26. https://doi.org/10.1016/j.jhin.2005.08.006.
61. Ong KL, Kurtz SM, Lau E, Bozic KJ, Berry DJ, Parvizi J. Prosthetic Joint Infection Risk After Total Hip Arthroplasty in the Medicare Population. J Arthroplasty 2009;24(6):105-9. https://doi.org/10.1016/j.arth.2009.04.027.
62. Peel TN, Dowsey MM, Daffy JR, Stanley PA, Choong PF, Buising KL. Risk factors for prosthetic hip and knee infections according to arthroplasty site. J Hosp Infect 2011;79(2):129-33. https://doi.org/10.1016/j.jhin.2011.06.001.
63. Rondon AJ, Tan TL, Schlitt PK, Greenky MR, Phillips JL, Purtill JJ. Total Joint Arthroplasty in Patients With Parkinson's Disease: Survivorship, Outcomes, and Reasons for Failure. J Arthroplasty 2018;33(4):1028-32. https://doi.org/10.1016/j.arth.2017.11.017.
64. Smith JO, Frampton CMA, Hooper GJ, Young SW. The Impact of Patient and Surgical Factors on the Rate of Postoperative Infection After Total Hip Arthroplasty-A New Zealand Joint Registry Study. J Arthroplasty 2018;33(6):1884-90. https://doi.org/10.1016/j.arth.2018.01.021.
65. Song KH, Kim ES, Kim YK, Jin HY, Jeong SY, Kwak YG et al. Differences in the risk factors for surgical site infection between total hip arthroplasty and total knee arthroplasty in the Korean Nosocomial Infections Surveillance System (KONIS). Infect Control Hosp Epidemiol 2012;33(11):1086-93. https://doi.org/10.1086/668020.
66. Tai SM, Imbuldeniya AM, Munir S, Walter WL, Walter WK, Zicat BA. The Effect of Obesity on the Clinical, Functional and Radiological Outcome of Cementless Total Hip Replacement: A Case-Matched Study With a Minimum 10-Year Follow-Up. J Arthroplasty 2014;29(9):1758-62. https://doi.org/10.1016/j.arth.2014.04.033.
67. Triantafyllopoulos GK, Soranoglou VG, Memtsoudis SG, Sculco TP, Poultsides LA. Rate and Risk Factors for Periprosthetic Joint Infection Among 36,494 Primary Total Hip Arthroplasties. J Arthroplasty 2018;33(4):1166-70. https://doi.org/10.1016/j.arth.2017.11.040.
68. Yong KS, Kareem BA, Ruslan GN, Harwant S. Risk factors for infection in total hip replacement surgery at Hospital Kuala Lumpur. Med J Malaysia 2001;56 Suppl C:57-60.

FIGURE LEGENDS

Figure 1. PRISMA Flow diagram showing the study selection process.

Figure 2. Forest plots of the meta-analysis of modifiable risk factors, including BMI (A), smoking (B), and alcohol abuse (C) as risk factors for periprosthetic joint infection following total hip arthroplasty. The diamond squares represent the pooled risk ratios (RRs) and corresponding 95% confidence intervals (CIs), while the squares and horizontal lines demonstrate the proportional weight and 95% CI of each included study, respectively.

Figure 3. Forest plots of the meta-analysis of non-modifiable risk factors, including gender (A) and age (D) as risk factors for periprosthetic joint infection (PJI) following total hip arthroplasty. Subgroup analysis for gender with different follow-up duration (B) or study design (C) were further shown to identify the possible association between gender with PJI.

Figure 4. Forest plots of the meta-analysis of medical history characteristics, including diabetes mellitus (A), avascular necrosis (B), femoral neck fracture (C), rheumatoid arthritis (D), cardiac vascular disease (E), chronic pulmonary disease (F), and neurological diseases (G) as risk factors for periprosthetic joint infection following total hip arthroplasty.

Figure 5. Forest plots of the meta-analysis of medical history characteristics, including dysplasia or dislocation (A), and osteoarthritis (B) as risk factors for periprosthetic joint infection following total hip arthroplasty.

Figure 6. Sensitivity analysis (A), and Begg's funnel plot (B) of the outcome: BMI. Funnel plot after modified with trimmed and filled method (C) of the outcome: BMI.

Figure S1. Subgroup analysis for diabetes mellitus (DM) with different location (A), Follow-up years (B), study design (C) or confounders adjusted (D) were shown to identify the possible association between DM with PJI after total hip arthroplasty (THA). Begg's funnel plot (E) and funnel plot after modified using trimmed and filled method (F) of the outcome: DM.

Figure S2. Forest plots of the meta-analysis of medical history characteristics, including previous joint surgery (A), renal disease (B), hypertension (C), cancer (D), and steroid use (E) as risk factors for periprosthetic joint infection following total hip arthroplasty.

Figures

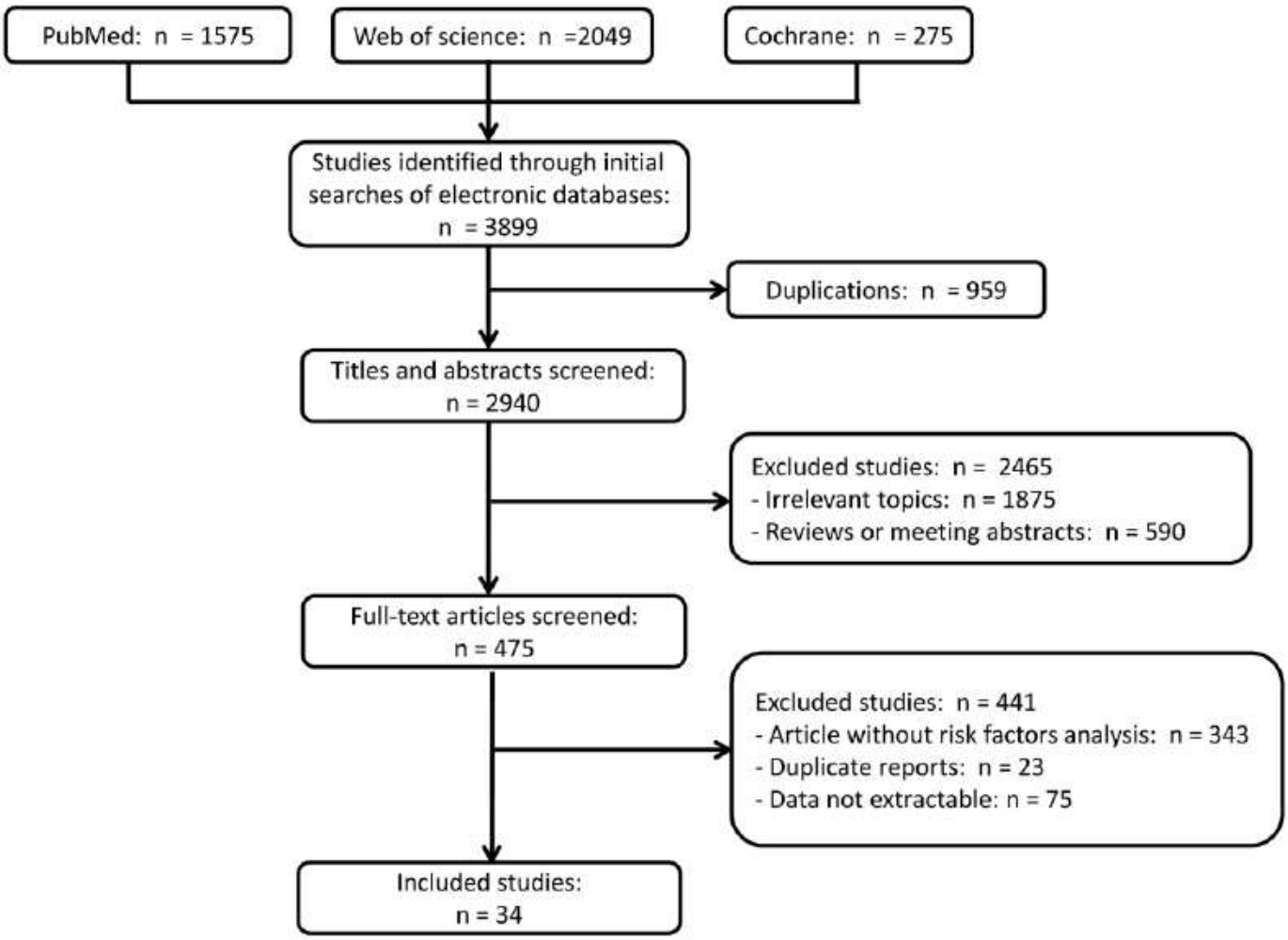

Figure 1

PRISMA Flow diagram showing the study selection process.

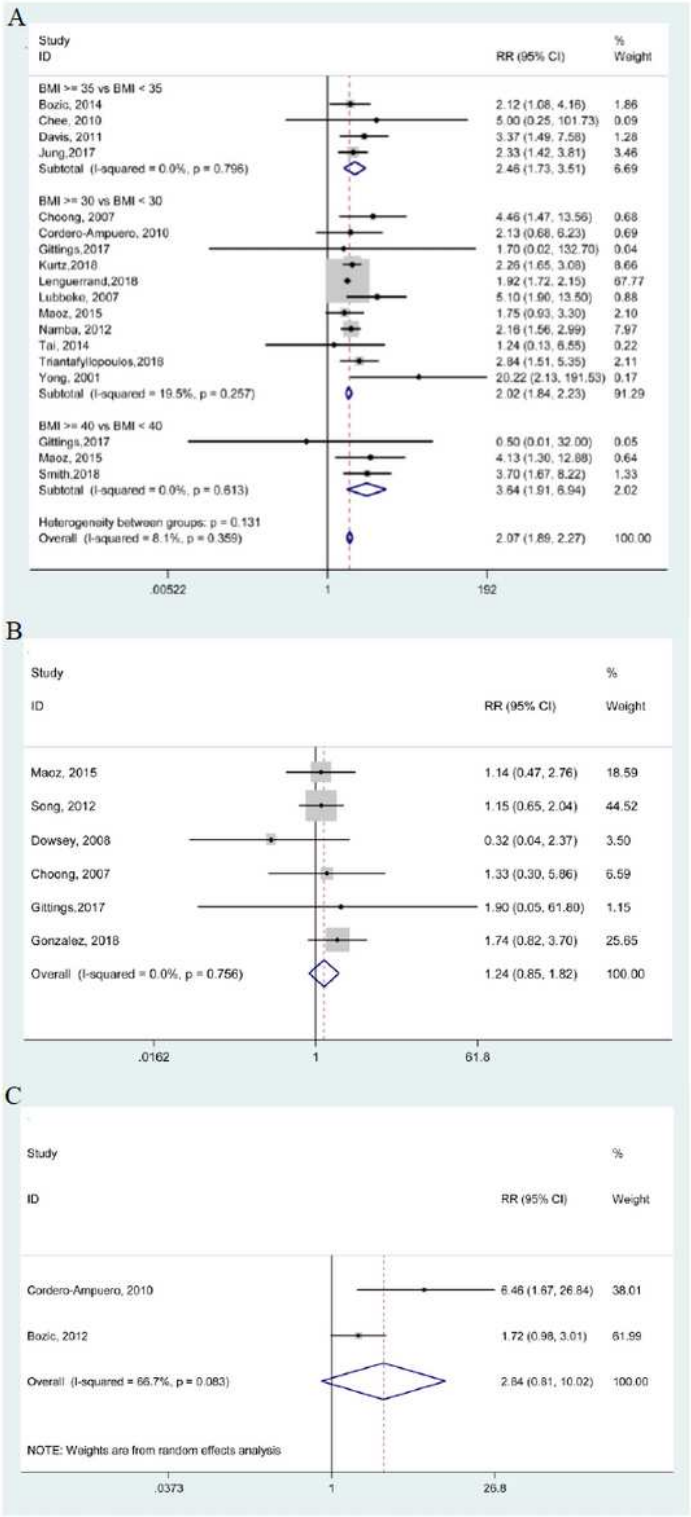

Figure 2

Forest plots of the meta analysis of modifiable risk factors, including BMI (A), smoking (B), and alcohol abuse (C) as risk factors for periprosthetic joint infection following total hip arthroplasty. The diamond squares represent the pooled risk ratios (RRs) and corresponding 95% confidence intervals (CIs), while the squares and horizontal lines demonstrate the proportional weight and 95% CI of each included study, respectively.

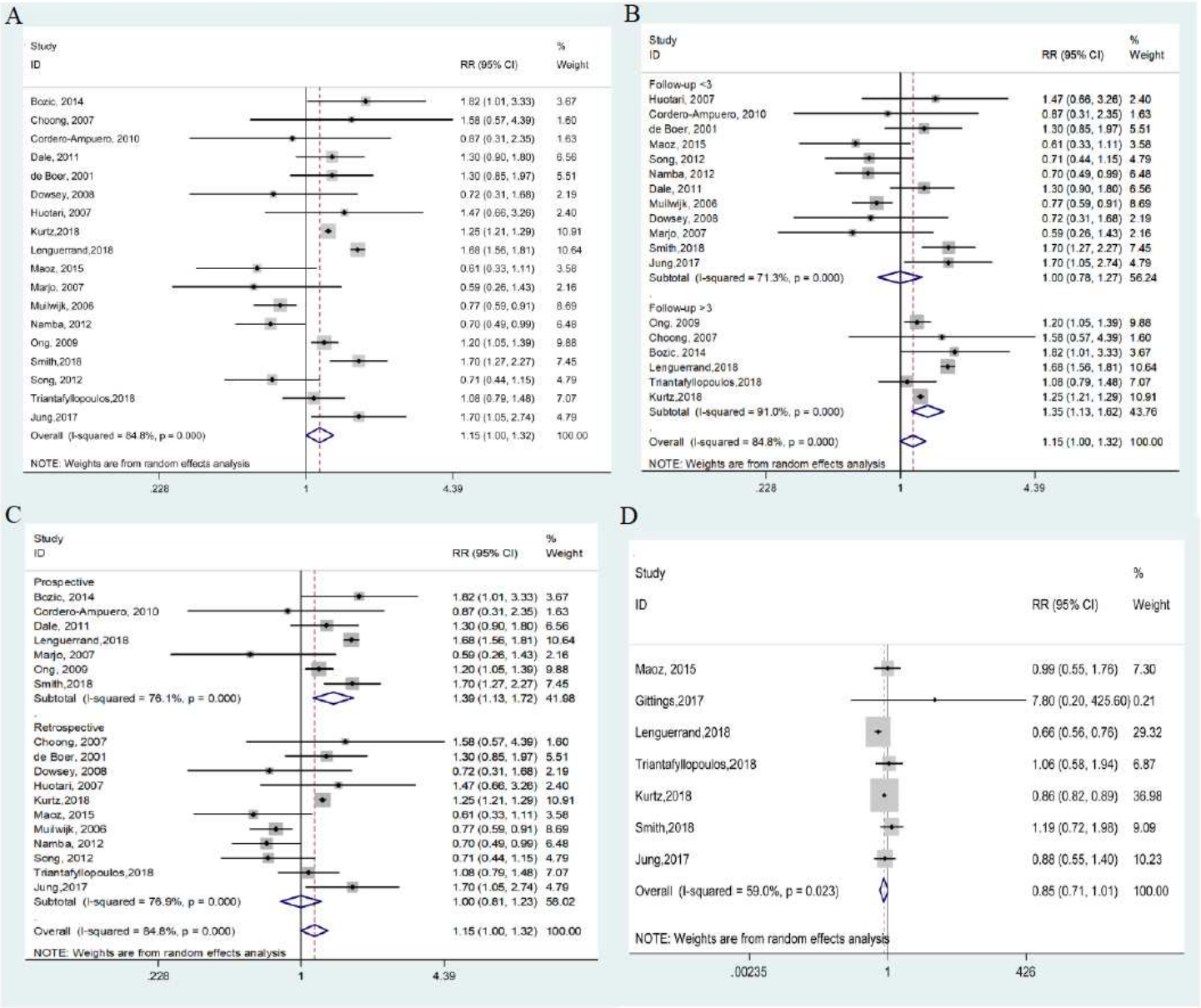

Figure 3

Forest plots of the meta analysis of non modifiable risk factors, including gender (A) and age (D) as risk factors for periprosthetic joint infection (PJI) following total hip arthroplasty. Subgroup analysis for gender with different follow up duration (B) or study design (C) were further shown to identify the possible association between gender with PJI.

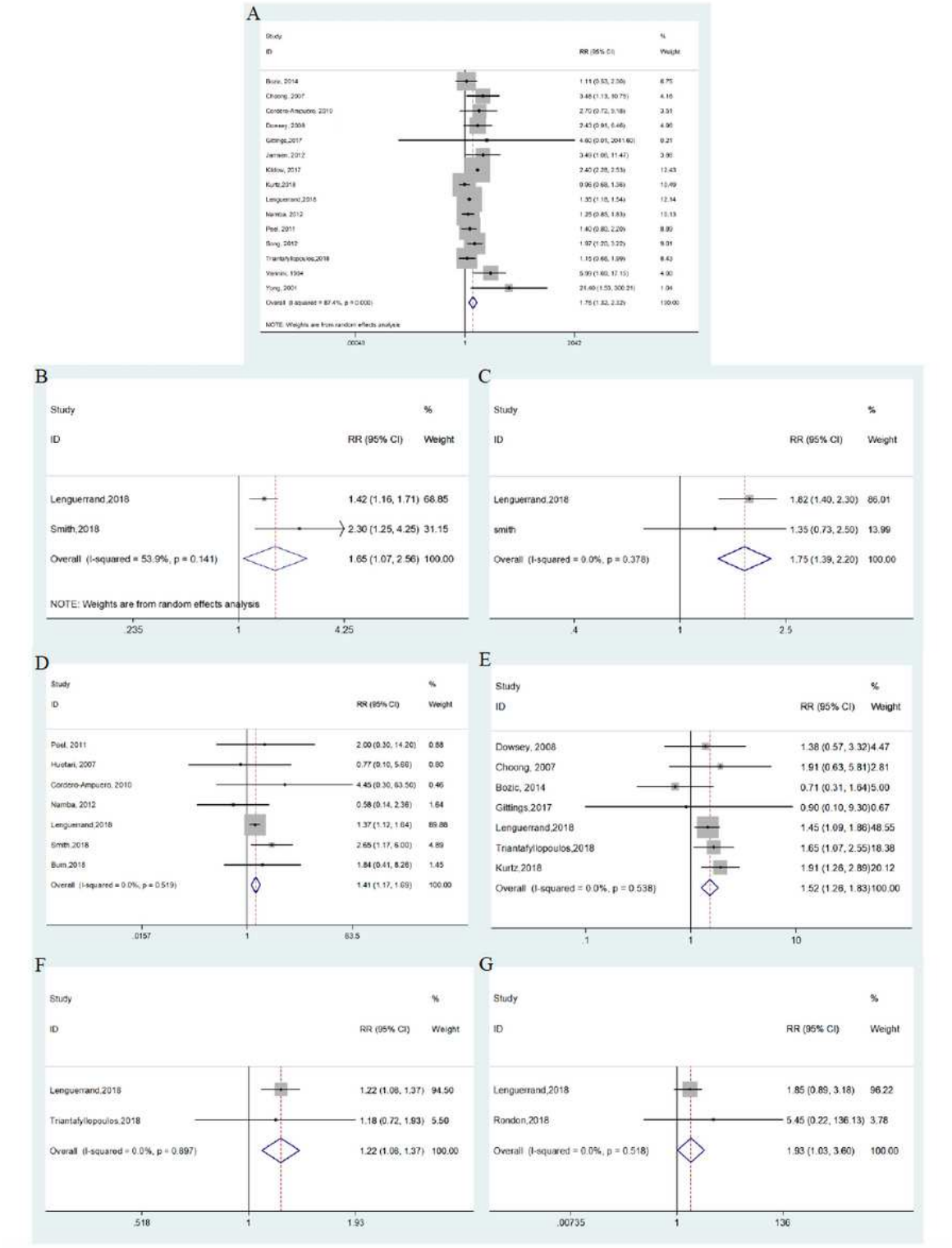

Figure 4

Forest plots of the meta analysis of medical history characteristics, including diabetes mellitus (A), avascular necrosis (B), femoral neck fracture (C), rheumatoid arthritis (D), cardiac vascular disease (E), chronic pulmonary disease (F), and neurological diseases (G) as risk factors for periprosthetic joint infection following total hip arthroplasty.

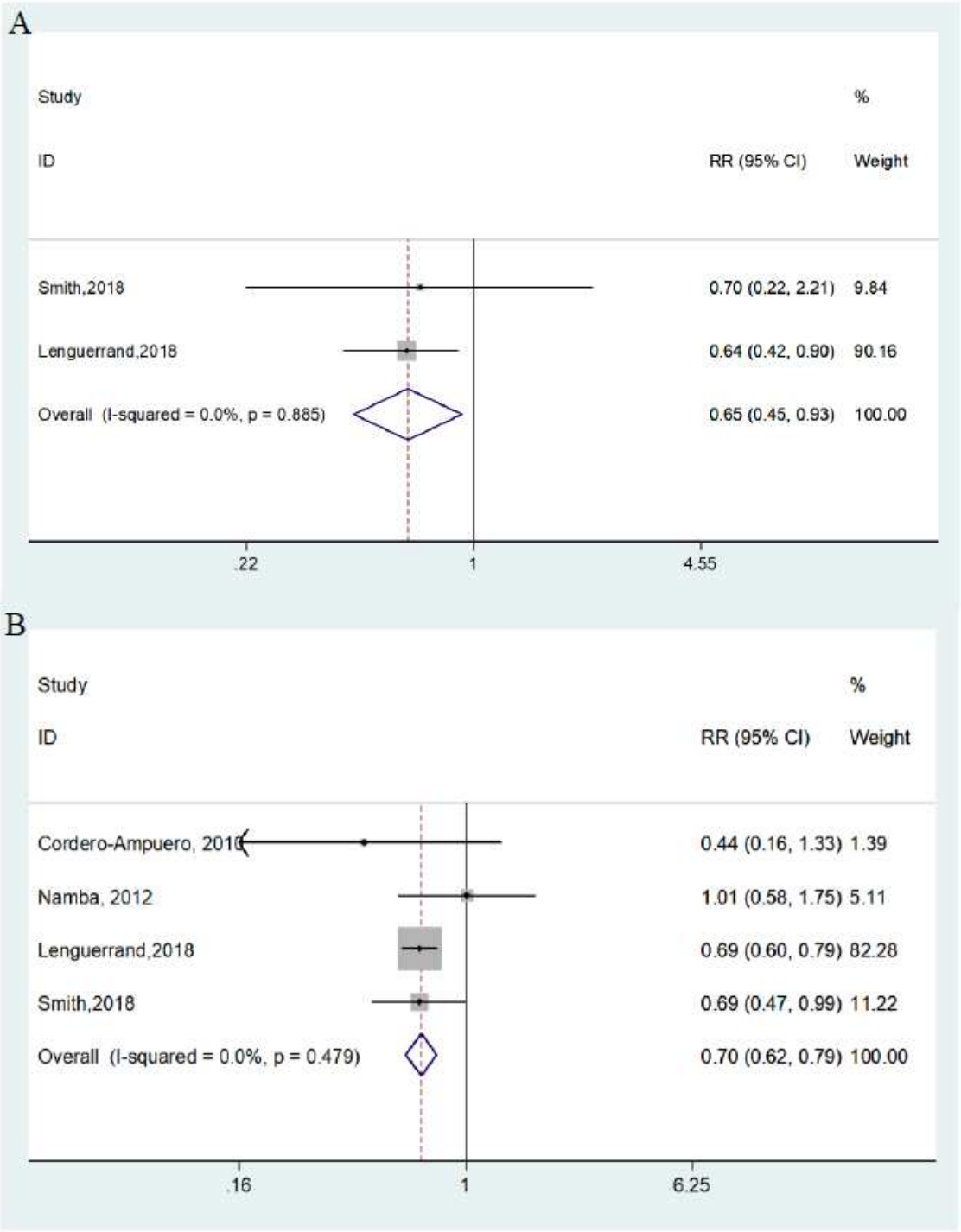

Figure 5

Forest plots of the meta analysis of medical history characteristics, including dysplasia or dislocation (A), and osteoarthritis (B) as risk factors for periprosthetic joint infection following total hip arthroplasty.

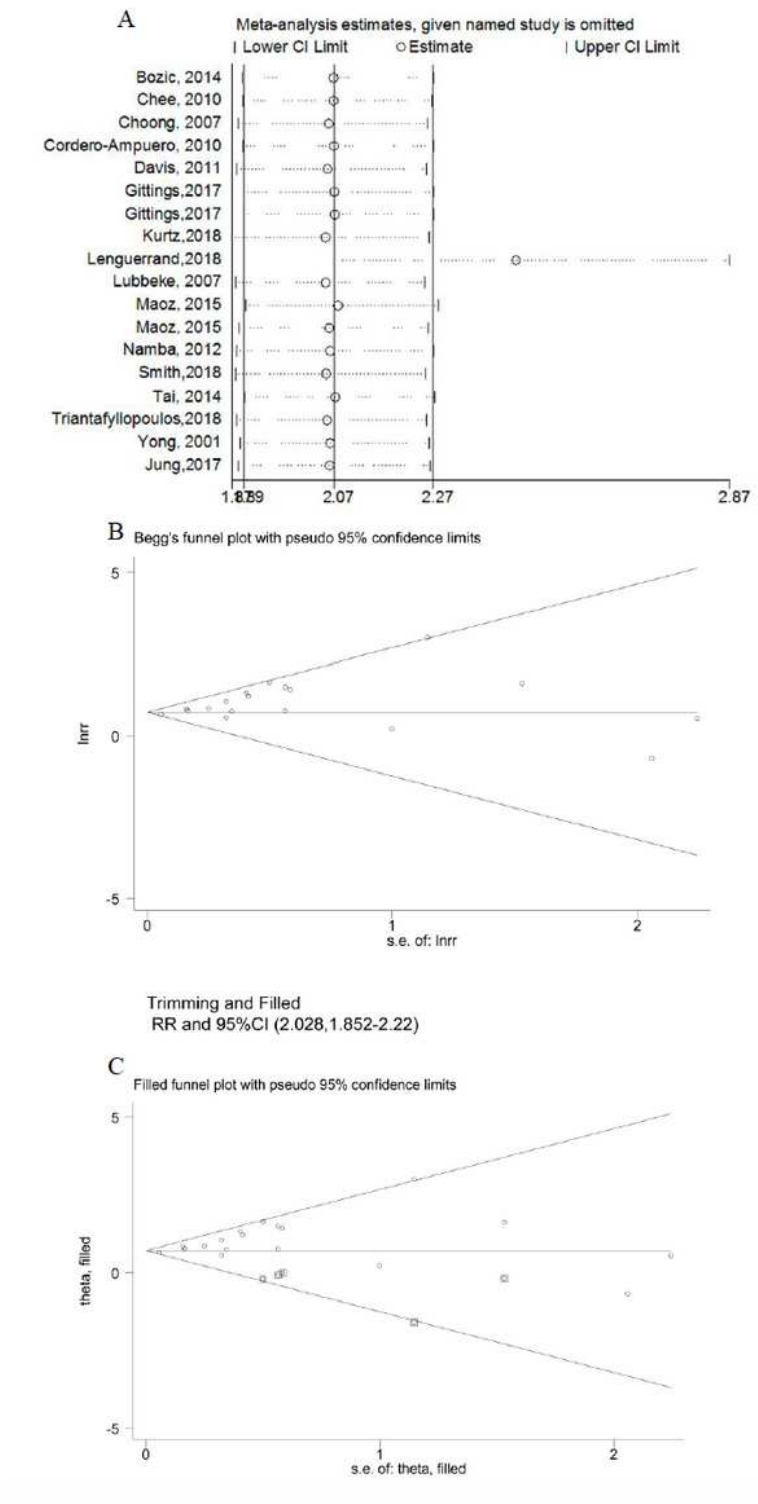

Figure 6

Sensitivity analysis (A), and Begg's funnel plot (B) of the outcome: BMI. Funnel plot after modified with trimmed and filled method (C) of the outcome: BMI.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Tables.pdf
- Supplementarytableandfigures.pdf