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Systematic review

Systematic Review and Meta-Analysis of Tobacco Use as a Risk Factor for Prosthetic Joint Infection After Total Hip Replacement

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ABSTRACT

Background: A prosthetic joint infection (PJI) is one of the possible complications after total hip arthroplasty (THA). Several studies, but not all, have reported smoking as a risk factor of PJIs in orthopaedic surgery. This study summarizes the most recent evidence using a systematic review of whether tobacco use (not only tobacco smoking) is a risk factor in developing PJIs, specifically after THA.
Methods: Ovid Medline, EMBASE, Scopus, Web of Science, and Cochrane databases were searched from inception to July 2019 to identify case-control studies that examined the PJI risk in tobacco users and tobacco nonusers undergoing THA. Publication bias was also assessed through funnel plots.
Results: Searches identified 2689 articles, and 10 of these, involving a total of 20,640 patients, met the inclusion criteria. The overall odds ratio (pooled odds ratio) to develop either a superficial infection, a deep infection, or an infection requiring revision surgery for tobacco users vs nonusers was 1.54 (95% confidence interval: 1.25-1.91) when a fixed-effect model was used and 1.56 (95% confidence interval: 1.10-2.21) when a random-effect model was used. No publication bias was observed among the identified studies.
Conclusions: The findings of the study indicated that tobacco use is associated with a higher risk of PJIs in patients undergoing THA.

Introduction and background

Prosthetic joint infection (PJI) is recognized as an infection that involves the joint prosthesis and adjacent tissue [1]. Despite both surgical and antimicrobial therapies being used for the management and prevention, one to 2 percent of patients undergoing primary total hip arthroplasty (THA) develop a PJI [2]. These infections can occur at any point in time after a primary or a revision surgery, although about a third of PJIs occurs in the first days and weeks after arthroplasty [3]. PJIs are of great concern for both patients and health providers as they are associated to repeated or longer hospital admission, severe pain, functional deficit, and poor health outcomes and result in a significant economic burden and deterioration of patients' quality of life [4]. According to the National Health Services, the cost associated to elective revision surgery due to PJI was £12,214 [5]. As PJI management remains challenging and costly, the most commonly used approach is prevention of such infections by minimizing risk factors. In addition, identifying potential PJI risk factors is of great clinical significance as it could assist orthopaedic surgeons in the decision-making process and elaborate interventions to optimize the patient's benefits from hip replacement surgery as well. Numerous risk factors have been identified for PJI after total joint arthroplasty; these include being of male gender [6-8], obesity [7,9-11], diabetes [7,9,11,12], rheumatoid arthritis [13,14], alcohol abuse [7,11], and long operating time [3,6,8].

Tobacco use is another modifiable risk factor that has been considered for postoperatory complications [15] or PJI after either hip or knee joint replacement [16]. Components of cigarette smoke such as nicotine, carbon monoxide, and hydrogen cyanide have been found to negatively impact the wound healing process [17,18]. The mechanisms of action of these chemicals are different; for example, nicotine is a recognized vasoconstrictor, and thus, it reduces the blood flow to the skin, reducing the mass transport of nutrients with the possibility of tissue ischemia hindering the healing process of injured tissues [18]; carbon monoxide decreases the transport of oxygen, while hydrogen cyanide inhibits the activity of the enzymes involved in the oxidative metabolism and oxygen transport at cellular level [18]. Another possible contribution of tobacco usage to the risk of PJI is the reduction in blood flow

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and oxygenation in tissues, resulting in low levels of glycose and acidosis [19-21]. Recently, smoking has also been proven to be related to impairment of the immune system [22].

The hip and knee represent different anatomical locations of the body, but, despite the relative similar incidence of joint replacement surgery, the risk of PJI is greater after knee arthroplasty than after hip arthroplasty [10,23,24]. Because of these differences, our study considers exclusively hip arthroplasty instead of aggregating both joints [16] or even THA, total knee arthroplasty, total shoulder arthroplasty, total elbow arthroplasty, and total ankle arthroplasty [10]. This aggregation results in a weighted risk of PJI based on the relative abundance of each joint in the study cohort. Information specifically describing hip replacement was not reported; therefore, our objective was to address this clear evidence gap. A recent study, very comprehensively eliciting risk factors associated to PJI specifically after hip arthroplasty, did not consider the smoking/tobacco use status of the patients undergoing arthroplasty [25]; moreover, a previous attempt to synthesize the available knowledge through meta-analysis could only include studies published before 2015 [26], and thus, the reported conclusions may not be fully up to date. Our purpose was to address this clear knowledge gap assessing the role of tobacco use on the risk of developing PJI after hip replacement through a systematic literature review and meta-analysis to provide a contemporary synthesis of the available evidence to educate clinical advice.

Material and methods

Systematic literature review

Data source and search strategy

This review was conducted in line with the Preferred Reporting Items for Systematic reviews and Meta-analyses guidelines [27]. A systematic search through Ovid Medline, EMBASE, Scopus, Web of Science, and Cochrane databases was carried out in July 2019. A multistring search strategy was conducted by combining keywords related to the intervention, outcomes, and type of arthroplasty. The searches were restricted to studies published in the English language. The full research strategy and the number of hits for each of the databases searched are presented in Appendix.

Bibliographies of eligible articles and clinical guidelines [28,29] were also searched to identify additional studies of interest to the review.

Eligibility criteria

Two authors independently first evaluated the titles and abstracts to identify possibly relevant studies; after that, full text of the chosen studies was obtained, and inclusion criteria were applied; the reason for exclusion was also recorded. Table 1 shows the eligibility criteria of the included studies in this research. In case of disagreement between the reviewers, final determination was obtained through consensus.

Studies addressing total joint arthroplasty in general, without specifying the joint replacement site, were included if data reported THA separately. Similarly, studies that explored various risk factors for PJIs were included only if they presented sufficient data for calculating the odds ratio (OR) with 95% confidence interval (CI) for tobacco users vs nonusers.

Data extraction

The following data were extracted from each study that was included: fist author, publication year, country of origin, study design, minimum duration of follow-up, sample size, number of cases and control, case definitions, and confounders controlled. Outcomes of interest were the number of observed superficial infections (defined as an infections involving “only skin or subcutaneous tissue of the incision”), deep infections (defined as infections involving the “deep soft tissues” [eg, fascial and muscle layers]), or revision surgeries (regardless of the number of stages) resulting from PJIs observed in the cohort over a follow-up period of at least 30 days; shorter follow-up was not considered because of the possibility of missing infections developing at later stages. Revision surgeries not resulting from infections (ie, aseptic loosening) were not included; similarly, reports of generic “surgical intervention” after the initial THA were excluded unless a specification that all interventions were revisions due to infections.

Quality assessment of studies included

Data quality of the included studies was evaluated based on the Newcastle-Ottawa Scale (NOS) [30]. In case-control studies, the NOS evaluates a series of quality parameters (selection, confounder, and exposure) in each study. Eight questions with multiple answers related to the quality parameters are answered with a possible score of one point or zero for each. Therefore, the final NOS score ranges from 0 to 8; the final assessment of the data quality of the studies is defined as follows: 7-8 points indicate very good studies, 5-6 points indicate good studies, 4 points define studies as satisfactory, while studies with 0-3 points are considered unsatisfactory.

Statistical analysis

ORs and 95% CIs of PJIs for tobacco users vs nonusers in each study were calculated. Meta-analysis of the OR to assess the association between the tobacco use and risk of PJIs was carried out

Table 1
Research eligibility criteria (PICOS format).

Criteria	Inclusion criteria	Exclusion criteria
Population	• Adult patients including both males and females who were undergoing elective primary (unilateral and bilateral or simultaneous) and revision total hip arthroplasties. • Cemented or uncemented.	• Patients diagnosed with bone cancer disorders. • Patients undergoing hemiarthroplasty. • Nonhuman population.
Intervention	Not available	
Comparators	Tobacco users vs nonusers	Any other categorization of patient population.
Outcomes	• The number of patients developing periprosthetic joint infection (deep and/or superficial infections). • The number of patients developing peri-prosthetic joint infection requiring revision surgery. • Minimum follow-up period of 1 month.	Any other outcome not of interest or with follow-up period <1 month.
Study type	Longitudinal (prospective and retrospective) studies.	• Case reports. • Commentary. • Letters to editor.
Language restrictions	Only English language.	Any language other than English.

using the Mantel-Haenszel method for fixed- and random-effect models; the DerSimonian-Laird estimator for τ^2 was used, and a statistically significant level of $P < .05$ was applied. Potential publication bias was presented graphically by the funnel plot and quantitatively assessed using the Egger's test.

Sensitivity analysis considering specific subgroups (specific end point reported, geographical location of the studies, study design, overall number of infections reported, and minimum follow-up duration) was also conducted.

The possible relation between the minimum follow-up duration of the studies and the reported OR of risk of an infectious outcome after THA was analyzed by meta-regression.

All analyses were performed in R (version 3.6.1, R Foundation for Statistical Computing, Vienna, Austria) [31] using the "rmeta" [32] and "metafor" [33] packages.

Results

Search results

The literature search strategies (Tables A1-A5) identified 3536 potentially relevant articles from Ovid Medline, EMBASE, Scopus, Web of Science, and Cochrane databases, in addition to 13 articles from reference chaining that represented articles with titles suggesting possible relevance and not identified in the searches. After removing the duplications, 2689 articles remained and then 61 articles were initially selected based on title and abstract screening for further evaluation. After a detailed evaluation, which included full-text review, 10 studies met the inclusion criteria and were included in the meta-analysis [34-43].

The most common reasons for exclusion was population (n = 12); the remaining studies were excluded because of the following reasons: not suitable outcome (n = 8) reported, not meeting the intervention (n = 5) or study type (n = 10) criteria, or for other reasons (n = 16) such as not been published in English or the lack of data for the group of interest. All 10 included studies were identified in the searches and did not originate from other sources. The Preferred Reporting Items for Systematic reviews and Meta-analyses flow diagram (Fig. 1) illustrates the literature search and selection strategy with the number of studies considered at each stage of the process.

Cohort characteristics and quality assessment of included studies

The characteristics of the 10 studies included in this review are summarized in Table 2. These cohort studies were conducted in the United States (n = 5), Switzerland (n = 2), Australia (n = 2), and the United Kingdom (n = 1). Studies were predominantly retrospective (n = 6), and the remaining studies were prospective (n = 4); only one study used propensity score adjustment for covariates. The sample size of either tobacco users or control (nonuser arm) varied from 31 to 7929; the sample size of the meta-analysis was 20,640 participants that involved 5328 tobacco users and 15,312 nonusers. The follow-up period ranged from 1 month to 5 years. The definition of the end points reported varied among the included studies; only deep infections were considered in some studies (n = 3), whereas others considered only infections resulting in revision surgery (n = 3). The occurrence of both superficial and deep infections was reported in 4 studies. Overall, the number of observed superficial infections was reported in 4 studies, the number of deep infections was reported in 7 studies, and the number of revision surgeries due to infections was reported in 5 studies.

Two of 10 studies stated the definition of tobacco nonuser (control) cohort, whereas the rest did not fully declare the control group inclusion criteria (ie, never used tobacco or quit tobacco at least a certain period of time before THA). There was variation in the tobacco user definition among studies, and in 4 studies, the clarification criteria were not reported. Moreover, the data quality assessment by the NOS demonstrated that all 10 studies had reasonable quality for meta-analysis. Five studies scored 7 points, 2 studies scored 6 points, and 3 studies scored 4 points, which is interpreted, respectively, as very good, good, and satisfactory quality (Table A6).

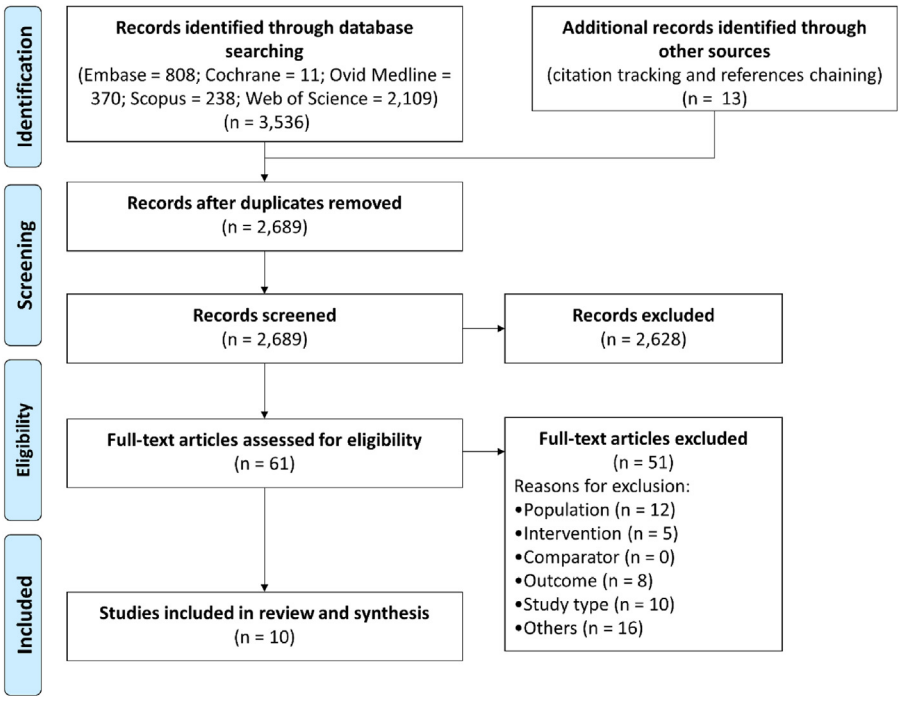

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flowchart [27].

Table 2
Results of cohort characteristics included in meta-analysis.

Author (publication year)	Country	Study design	Minimum follow up-period (months)	Confounding controlled	Number of tobacco nonusers (infection type/end point)	Number of tobacco users (infection type/ end point)	Definition of tobacco users (case)	Definition of nonusers (control)
Bedard et al. (2018) [34]	USA	Retrospective	30 days	Gender, BMI, diabetes, dialysis, operating time	7029 (superficial 63; deep 1350)	1208 (superficial 7; deep 39)	Patients reported smoking cigarettes in the year before their admission for surgery.	NR
Choong et al. (2004) [35]	Australia	Prospective	16	Age, gender, diabetes, cardiovascular, operating time, implant type	728 (deep 12)	91 (deep 2)	NR	NR
Dowsey et al. (2008) [36]	Australia	Retrospective	12	Age, gender, diabetes, cardiovascular, operating time, implant type	1051 (deep 21)	156 (deep 1)	NR	NR
Gonzalez et al. (2018) [38]	Switzerland	Prospective	6	NR	3152 (deep 30)	2046 (deep 38)	Definition of smoking was not reported, except they include former and current smokers under the case group.	NR
Kapadia et al. (2014) [37]	USA	Retrospective	24	Gender, age, BMI	220 (superficial 0, deep 0, revision 0)	110 (superficial 3, deep 1, revision 5)	"Current" smokers; smoked a minimum of 100 cigarettes (or nicotine equivalent in their lifetime and one cigarette within 30 days of the operative date).	NR
Khan et al. (2009) [39]	UK	Prospective	6	ASA score, Harris hip score, cardiovascular disease, diabetes	917 (superficial 46, deep 3, revision 12)	268 (superficial 13, deep 3, revision 2)	Smokers: smoking daily in the 30 days before admission to hospital and never smoked: patients who had never smoked regularly at any time in their lifetime.	Never smoked: patients who had never smoked regularly at any time in their lifetime.
Lombardi Jr et al. (2013) [40]	USA	Retrospective	1	Age, BMI, diabetes, implant type, procedure	271 (revision 4)	86 (revision 7)	Current smokers had an average 35, SD 22.8 pack-years (range 4-105 pack/years)	NR
Lubbeke et al. (2014)	Switzerland	Retrospective	21.6	Age and BMI	1230 (revision 9)	734 (revision 7)	NR	NR
Meldrum et al. (2005) [42]	USA	Retrospective	60	BMI	116 (revision 5)	31 (revision 2)	Smokers consumed an average 1.2 packs of cigarettes per day (range, 0.25 to 2 packs per day, or smoked cigars or pipes, and chewed tobacco).	NR
Sahota et al. (2018) [43]	USA	Retrospective	30 days	Age, gender, BMI, diabetes, cardiovascular disease, operating time	598 (superficial 7, deep 1)	598 (superficial 5, deep 8)	Current smokers: regularly smoked cigarettes in the past year before surgery.	Patients who had not smoked cigarettes in the past year before surgery.

ASA, American Society of Anesthesiologists; NR, not reported; SD, standard deviation; BMI, body mass index.
Superficial infection, an infection involving "only skin or subcutaneous tissue of the incision"; deep infection, an infection involving the "deep soft tissues (eg, fascial and muscle layers) of the incision" or "any part of the anatomy other than the incision".

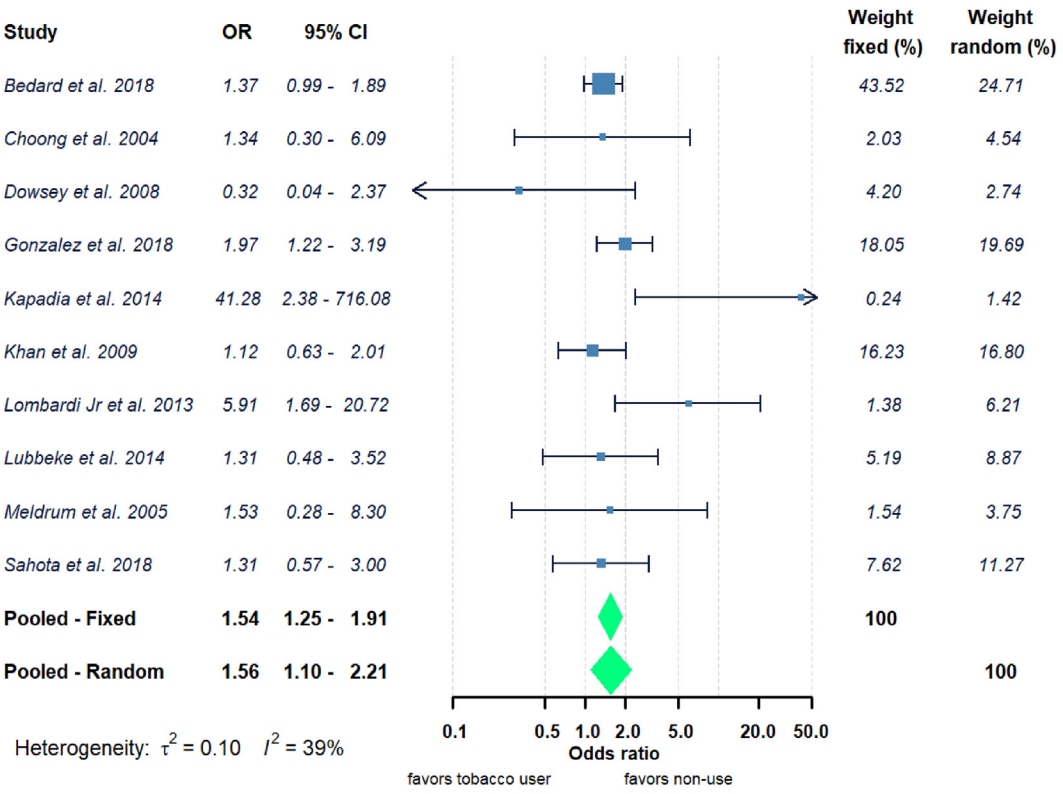

Figure 2. Forest plot of risk (reporting odds ratio (OR) and 95% confidence interval (CI)) of cumulative infection outcomes considered (superficial or deep infection and revision surgery) after hip replacement between tobacco users and nonusers.

Association between tobacco use and PJIs

The OR of an infection outcome (superficial infection, deep infection, or revision surgery) of tobacco users compared with tobacco nonusers for each of the analyzed studies varied from 0.32 to 41.28. The overall OR (pooled OR) for the 10 studies was 1.54 (95% CI = 1.25-1.91) when a fixed-effect model was used and 1.56 (95% CI = 1.10-2.21) when a random-effect model was used. The pooled OR was statistically significant for both models ($P < .0001$ and $P = .0005$ for fixed- and random-effect models, respectively); consequently, using tobacco increased the risk of the possible infection end points considered in patients undergoing THA when compared with the control group (tobacco nonusers) (Fig. 2). The test of heterogeneity of the included studies returned a $\tau^2 = 0.010$ and $I^2 = 39\%$.

When specific outcomes were considered (Fig. 3), the impact of tobacco use was still statistically significant when deep infections (7 studies) or revision surgeries (5 studies) were individually considered with pooled OR of 1.81 (95% CI = 1.39-2.36) and 2.02 (95% CI = 1.16-3.52), respectively. The meta-analysis of the 4 studies reporting the incidence of superficial infections after THA revealed that tobacco use was not a statistically significant factor (OR = 0.89 [95% CI = 0.58-1.37]) The heterogeneity of the subgroups reporting superficial or deep infections was lower than in all the 10 studies ($\tau^2 = 0.10$ and $I^2 = 29\%$ for superficial infections and $\tau^2 = 0.014$ and $I^2 = 6.4\%$ for deep infections). The heterogeneity of the subgroup reporting revision surgeries after infections was higher than in all the 10 studies ($\tau^2 = 0.71$ and $I^2 = 56\%$).

Publication bias

Under visual examination, the funnel plot of the included studies in this meta-analysis of infections after THA in tobacco users vs nonusers exhibited symmetry (Fig. 4). Furthermore, the Egger's test determined a *P* value of 0.27 demonstrating that there was no potential publication bias among the included studies.

Sensitivity analysis

The risk associated with tobacco use was not different comparing prospective or retrospective studies; moreover, studies with minimum follow-up longer than 1-year return pooled OR for tobacco use were not statistically different from studies with follow-up shorter than 1 year. Similarly, the study size, assessed through the overall number of infections reported, did not impact the tobacco use association with infection risk after THA when the threshold of 50 total PJIs reported in the study was used. Studies conducted in Europe or the United States did not statistically differ in the risk of reaching the specific end points of this review; the 2 studies conducted in Australia had much larger CIs, and the pool OR did not reveal an increased risk of infection for tobacco users (Fig. 5).

Metaregression

The possible impact of the minimum follow-up duration on the pooled OR was assessed by metaregression (Fig. 6). The linear regression between individual studies reported the OR and minimum follow-up had an intercept of 1.49 ($P < .05$) and a slope of 0.0037 ($P > .05$); therefore, the minimum follow-up time was not statistically affecting the pooled ORs.

Discussion

The rationale of this study was to summarize the most recent available results and determine the impact of using tobacco (smoking cigarette, cigars or pipes, chewing tobacco) on the development of PJIs after THA. There has been a contrast in the

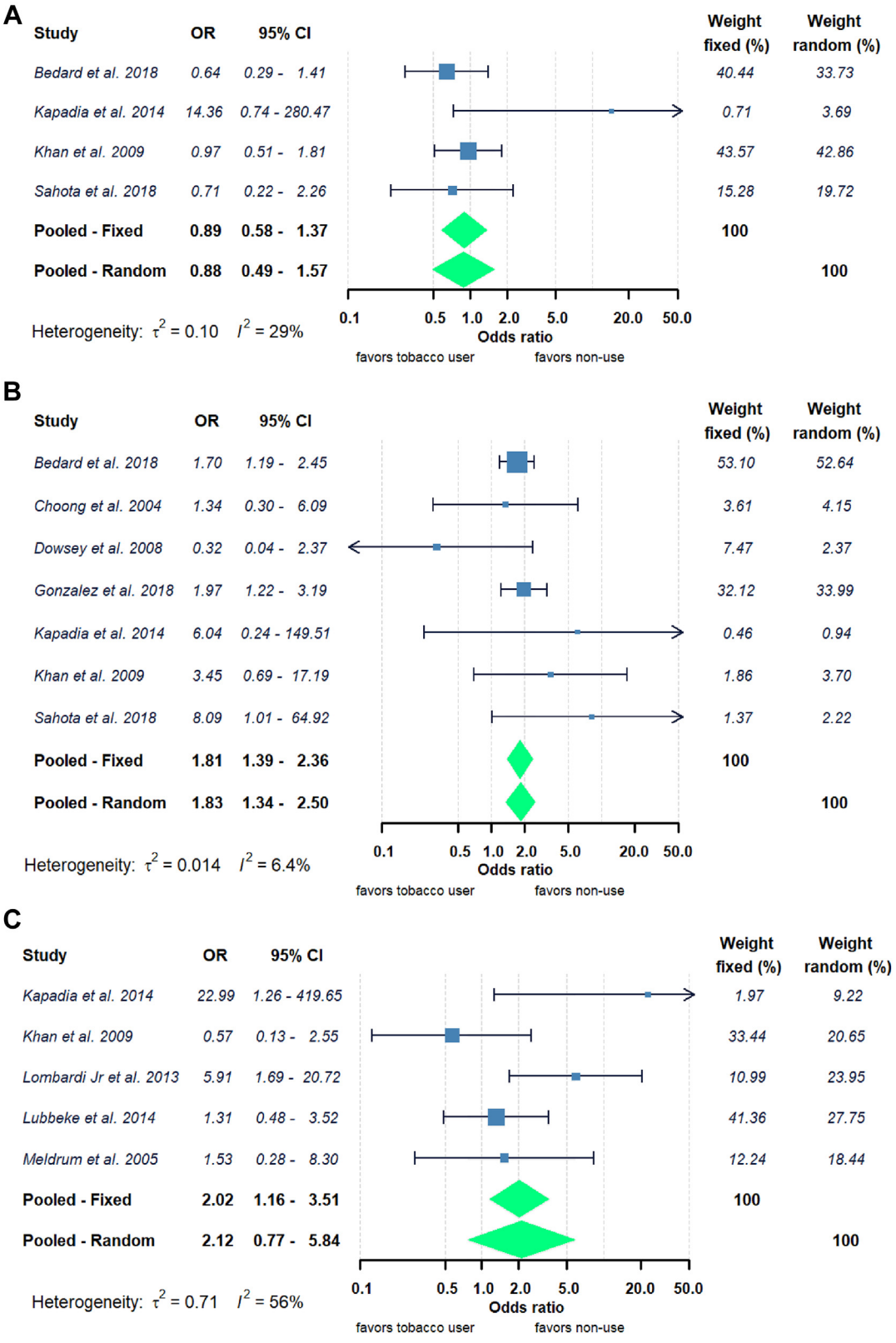

Figure 3. Forest plot of risk (reporting odds ratio [OR] and 95% confidence interval [CI]) of superficial infection (A), deep infection (B), and revision surgery as a consequence of the infection (C) after hip replacement between tobacco users and nonusers.

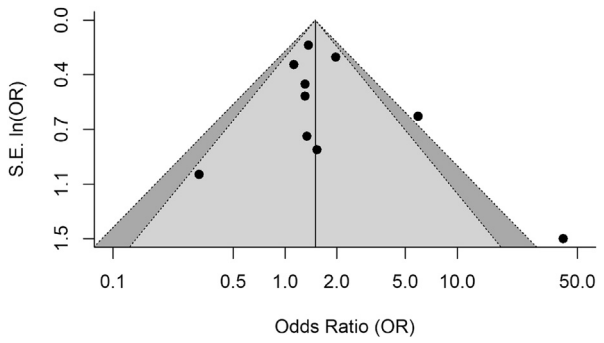

Figure 4. Funnel plot of included studies in the meta-analysis. Light gray area represents the 90% confidence interval and the dark gray area represents the 95% confidence area. SE, standard error).

conclusions of studies examining the association between tobacco use and the risk of PJIs possibly because of small sample sizes or unidentified confounders. For instance, the association of smoking with PJIs was proven in some studies [34,37,44-46], whereas other publications did not show such relation [39,42,47-49]. Previous reviews have partially addressed this question, but this systematic review and meta-analysis endeavored to provide a more contemporary assessment of tobacco use on the risk of PJIs specifically after THA. As surgical techniques and antimicrobial agents/processes evolve while, at the same time, microbial resistance rise, it is important to consider the most recent evidence as the situation may have been changed from previous studies. The historical timeline of the OR for developing PJIs after hip replacement did not reach statistical power until around 2013, while the most recent studies contributed to the reduction of the level of uncertainty (Fig. 7); furthermore, the 3 most recent studies were not included in any of

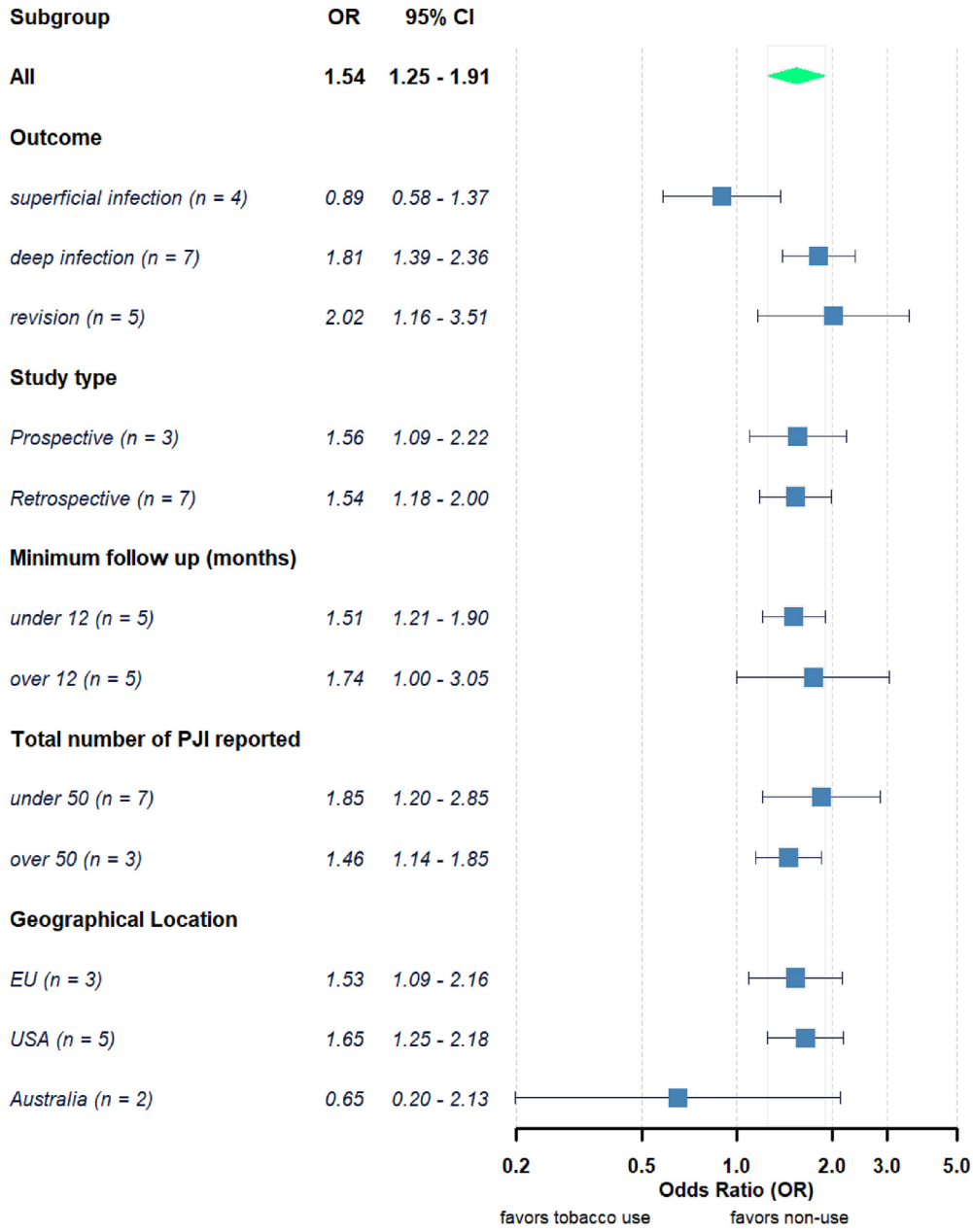

Figure 5. Pooled odds ratios (ORs) and 95% confidence interval (CIs) of developing PJIs after total hip replacement comparing tobacco users to nonusers grouped according to several study characteristics.

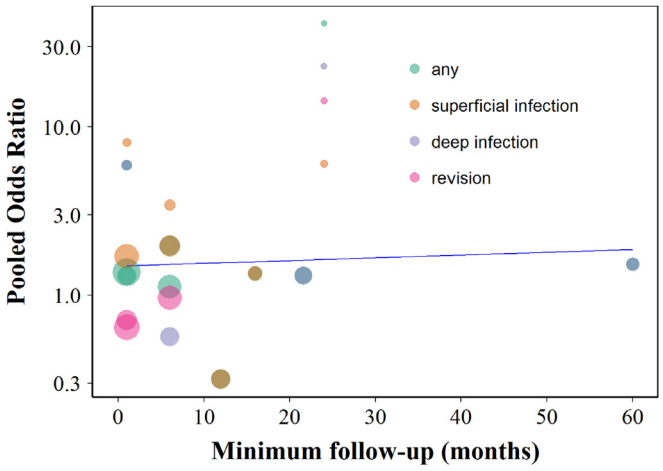

Figure 6. Correlation between pooled odds ratios (ORs) of developing PJIs after total hip replacement comparing tobacco users to nonusers grouped according to reported outcomes. Blue line represents meta-regression. The bubble size represents 1/(95% CI) of the study OR.

the previous systematic reviews. The pooled OR of developing PJIs for never vs ever tobacco users was previously reported to be 1.67 (95% CI = 1.25-2.20) [10,16]; thus, the impact of using tobacco on the risk of PJIs after hip replacement observed in this work is in agreement with findings on similar studies. Only one systematic review and meta-analysis of studies looked at the relation between smoking and deep infection specifically after THA [26]. The overall risk ratio for smoking impact on deep infection was 3.71 (95% CI = 1.86-7.41); these results reveal an increased deep infection risk in patients who smoked but are based on only 4 cohort studies with a limited sample size and do not represent the most recent clinical evidence because of the time elapsed since its publication.

The research findings presented here reflect the recommendation of tobacco use cessation before THA; however, the present study did not attempt to identify the optimal time of abstinence from tobacco use that could improve hip arthroplasty outcome and reduce the rate of PJIs; moreover, the heterogeneous definition of tobacco nonusers in the identified study did not allow for this type of subgroup analysis. Nevertheless, 6-8 weeks of abstinence from smoking before orthopaedic surgery have been identified as able to reduce the infection rate significantly [50].

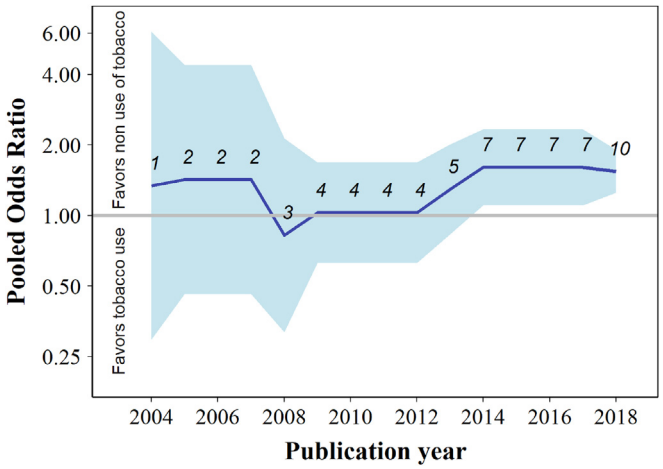

Figure 7. Timeline of the progression of pooled odds ratio of PJIs after THA in tobacco users vs nonusers (blue line) and 95% confidence interval (light blue area). Numbers represent the number of studies included in the meta-analysis.

Our results clearly demonstrate that tobacco use has a detrimental impact on the probability of adverse infectious events such as deep infections or revision surgery after hip replacement surgery; however, the role of tobacco use on the likelihood of superficial infections is still not so clear (Fig. 3). These results also suggest that smoking increases the chances of developing PJIs and that the extent of the infection is influenced by the tobacco use status of the patient as tobacco use is a significant factor in developing deep infection but not superficial infections. This could be the consequence of tobacco use impacting more the organism's ability to fight deeper and more extent infections than infections localized on the outer skin layers. It is also possible that the number of studies addressing specifically the impact of tobacco smoking/use on the surgical superficial infection as outcome has not reached a sufficient sample size and further investigation is needed.

The overall number of patients represented in this review constitutes a strength of the study along with the geographical spread of the populations considered. Furthermore, despite the general negative perception of tobacco as a risk factor, no publication bias has been observed among the included studies; this and the general high score in the study quality assessment are additional strengths of this work. Nevertheless, some weaknesses are also affecting this review and should be considered when interpreting the results of this investigation. For instance, the retrospective design of most of the included studies could lead to lack of randomization and to poorly defined confounding factors, and thus, it could jeopardize the validity of the results [51]. Despite the possible negative impact of a retrospective design, the sensitivity analysis did not reveal significant differences between the outcomes of prospective and retrospective studies.

Besides our effort to incorporate all studies reporting infections as primary end point or infections causing revision to produce more representative data, we found variability in infection reporting and the duration of follow-up in the included studies that ranged between 1 month and 5 years. It could be hypothesized that short follow-up periods may underestimate the risk of PJI occurrence as PJIs can develop months and years after the initial surgery; however, the sensitivity analysis revealed that the pooled OR of studies with follow-up longer than 1 year was not different than that of studies with follow-up up to 1 year; moreover, the results of the metaregression (Fig. 6) revealed no statistically significant role of the study with minimum follow-up duration on the pooled OR. This demonstrates the impact of tobacco on PJIs does not vary with the time from surgery; such observation was also reported by the study by Kunutsor [10] that used a similar threshold value. In addition, we observed heterogeneity between the analyzed studies in terms of tobacco amount consumed and the definition of nonusers as patients who never consumed tobacco or stopped at a certain period of time; moreover, we were unable to account for the different covariates used in individual studies for estimating ORs. Most of the studies controlled for some confounding between control and case population; age, gender, body mass index, diabetes, cardiovascular disease, and operating time were the most likely factors to be equal; however, no single factor was controlled in all studies.

Conclusions

The findings of this study provide a contemporary synthesis of the available evidence related to tobacco use as a risk factor for PJIs in patients undergoing THA. Patients who consume tobacco are at a significant greater risk of developing PJIs, particularly deep infection or infection requiring revision surgery, than patients who do not consume tobacco; thus, additional preventive measurements

are advisable when tobacco users undergo THA to reduce the likelihood of PJIs.

Conflict of interest

The authors declare there are no conflicts of interest.

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References

[1] Tande AJ, Patel R. Prosthetic joint infection. Clin Microbiol Rev 2014;27(2):302–45.
[2] Osmon DR, Berbari EF, Berendt AR, et al. Diagnosis and management of prosthetic joint infection: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis 2013;56(1):e1–25.
[3] 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 Suppl):105–9.
[4] Adeli B, Parvizi J. Strategies for the prevention of periprosthetic joint infection. J Bone Joint Surg Br 2012;94(11 Suppl A):42–6.
[5] Vanhegan IS, Malik AK, Jayakumar P, Islam UI, Haddad FS. A financial analysis of revision hip arthroplasty: the economic burden in relation to the national tariff. J Bone Joint Surg Br 2012;94(5):619–23.
[6] Hinarejos P, Guirro P, Leal J, et al. The use of erythromycin and colistin-loaded cement in total knee arthroplasty does not reduce the incidence of infection: a prospective randomized study in 3000 knees. J Bone Joint Surg Am 2013;95(9):769–74.
[7] Lenguerrand E, Whitehouse MR, Beswick AD, et al. Risk factors associated with revision for prosthetic joint infection following knee replacement: an observational cohort study from England and Wales. Lancet Infect Dis 2019;19(6):589–600.
[8] Kurtz SM, Ong KL, Lau E, Bozic KJ, Berry D, Parvizi J. Prosthetic joint infection risk after TKA in the Medicare population. Clin Orthop Relat Res 2010;468(1):52–6.
[9] Jamsen E, Nevalainen P, Eskelinen A, Huotari K, 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.
[10] Kunutsor SK, Whitehouse MR, Blom AW, Beswick AD, INFORM team. Patient-related risk factors for periprosthetic joint infection after total joint arthroplasty: a systematic review and meta-analysis. PLoS One 2016;11(3):e0150866.
[11] 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.
[12] Golden SH, Peart-Vigilance C, Kao WH, Brancati FL. Perioperative glycemic control and the risk of infectious complications in a cohort of adults with diabetes. Diabetes Care 1999;22(9):1408–14.
[13] Ravi B, Croxford R, Hollands S, et al. Increased risk of complications following total joint arthroplasty in patients with rheumatoid arthritis. Arthritis Rheumatol 2014;66(2):254–63.
[14] Ravi B, Escott B, Shah PS, 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.
[15] Netscher DT, Clamon J. Smoking: adverse effects on outcomes for plastic surgical patients. Plast Surg Nurs 1994;14(4):205–10.
[16] Bedard NA, DeMik DE, Owens JM, Glass NA, DeBerg J, Callaghan JJ. Tobacco use and risk of wound complications and periprosthetic joint infection: a systematic review and meta-analysis of primary total joint arthroplasty procedures. J Arthroplasty 2019;34(2):385–96.
[17] Whiteford L. Nicotine, CO and HCN: the detrimental effects of smoking on wound healing. Br J Community Nurs 2003;8(12):S22–6.
[18] Silverstein P. Smoking and wound healing. Am J Med 1992;93(1a):S22–4.
[19] Jensen JA, Goodson WH, Hopf HW, Hunt TK. Cigarette smoking decreases tissue oxygen. Arch Surg 1991;126(9):1131–4.
[20] Morecraft R, Blair WF, Brown TD, Gable RH. Acute effects of smoking on digital artery blood flow in humans. J Hand Surg Am 1994;19(1):1–7.
[21] Sørensen LT, Jørgensen S, Petersen LJ, Hemmingsen U, Bülow J, Loft S, et al. Acute effects of nicotine and smoking on blood flow, tissue oxygen, and aerobe metabolism of the skin and subcutis. J Surg Res 2009;152(2):224–30.
[22] Valiathan R, Miguez MJ, Patel B, Arheart KL, Asthana D. Tobacco smoking increases immune activation and impairs T-cell function in HIV infected patients on antiretrovirals: a cross-sectional pilot study. PLOS ONE 2014;9(5):e97698.
[23] Beam E, Osmon D. Prosthetic joint infection update. Infect Dis Clin North Am 2018;32(4):843–59.
[24] Koh CK, Zeng I, Ravi S, Zhu M, Vince KG, Young SW. Periprosthetic joint infection is the main cause of failure for modern knee arthroplasty: an analysis of 11,134 knees. Clin Orthop Relat Res 2017;475(9):2194–201.
[25] Lenguerrand E, Whitehouse MR, Beswick AD, 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.
[26] Teng S, Yi C, Krettek C, Jagodzinski M. Smoking and risk of prosthesis-related complications after total hip arthroplasty: a meta-analysis of cohort studies. PLoS One 2015;10(4):e0125294.
[27] Moher D, Liberati A, Tetzlaff J, Altman DG, Prisma Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6(7):e1000097.
[28] NICE. Total hip replacement and resurfacing arthroplasty for end-stage arthritis of the hip [TA304]. National Institute for Health and Care Excellence 2014. https://www.nice.org.uk/guidance/ta304/resources/total-hip-replacement-and-resurfacing-arthroplasty-for-endstage-arthritis-of-the-hip-pdf-82602365977285. [Accessed 26 February 2014].
[29] Workgroup Convened by the Musculoskeletal Infection Society. New definition for periprosthetic joint infection. J Arthroplasty 2011;26(8):1136–8.
[30] Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010;25(9):603–5.
[31] R Core Team, R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2013.
[32] Schwarzer G. meta: an R package for meta-analysis. R News 2007;7:40–5.
[33] Viechtbauer W. Conducting meta-analyses in R with the metafor package. J Stat Softw 2010;36(3):1–48.
[34] Bedard NA, Dowdle SB, Owens JM, Duchman KR, Gao Y, Callaghan JJ. What is the impact of smoking on revision total hip arthroplasty? J Arthroplasty 2018;33(7s):S182–5.
[35] Choong PF, Dowsey MM, Carr D, Daffy J, Stanley P. Risk factors associated with acute hip prosthetic joint infections and outcome of treatment with a rifampinbased regimen. Acta Orthop 2007;78(6):755–65.
[36] Dowsey MM, Choong PFM. Obesity is a major risk factor for prosthetic infection after primary hip arthroplasty. Clin Orthop Relat Res 2008;466(1):153–8.
[37] Kapadia BH, Issa K, Pivec R, Bonutti PM, Mont MA. Tobacco use may be associated with increased revision and complication rates following total hip arthroplasty. J Arthroplasty 2014;29(4):777–80.
[38] Gonzalez AI, Luime JJ, Uçkay I, Hannouche D, Hoffmeyer P, Lübbeke A. Is there an association between smoking status and prosthetic joint infection after primary total joint arthroplasty? J Arthroplasty 2018;33(7):2218–24.
[39] Khan LA, Cowie JG, Ballantyne JA, Brenkel IJ. The complication rate and medium-term functional outcome after total hip replacement in smokers. Hip Int 2009;19(1):47–51.
[40] Lombardi Jr AV, Berend KR, Adams JB, Jefferson RC, Sneller MA. Smoking may be a harbinger of early failure with ultraporous metal acetabular reconstruction. Clin Orthop Relat Res 2013;471(2):486–97.
[41] Lübbeke A, Rothman KJ, Garavaglia G, et al. Strong association between smoking and the risk of revision in a cohort study of patients with metal-on-metal total hip arthroplasty. J Orthop Res 2014;32(6):762–8.
[42] Meldrum RD, Wurtz LD, Feinberg JR, Capello WN. Does smoking affect implant survivorship in total hip arthroplasty? A preliminary retrospective case series. Iowa Orthop J 2005;25:17.
[43] Sahota S, Lovecchio F, Harold RE, Beal MD, Manning DW. The effect of smoking on thirty-day postoperative complications after total joint arthroplasty: a propensity score-matched analysis. J Arthroplasty 2018;33(1):30–5.
[44] Møller AM, Pedersen T, Villebro N, Munksgaard A. Effect of smoking on early complications after elective orthopaedic surgery. J Bone Joint Surg Br 2003;85(2):178–81.
[45] Sadr Azodi O, Bellocco R, Eriksson K, Adami J. The impact of tobacco use and body mass index on the length of stay in hospital and the risk of post-operative complications among patients undergoing total hip replacement. J Bone Joint Surg Br 2006;88(10):1316–20.
[46] Maoz G, Phillips M, Bosco J, et al. The Otto Aufranc Award: modifiable versus nonmodifiable risk factors for infection after hip arthroplasty. Clin Orthop Relat Res 2015;473(2):453–9.
[47] Havelin LI, Engesaæter LB, Langeland N, Vollset SE. Patient-related risk factors for early revision of total hip replacements. A population register-based case-control study of 674 revised hips. Acta Orthop Scand 1997;68(3):207–15.
[48] Bischoff-Ferrari HA, Lingard EA, Losina E, et al. Psychosocial and geriatric correlates of functional status after total hip replacement. Arthritis Care Res: Off J Am Col Rheum 2004;51(5):829–35.
[49] Malinzak RA, Ritter MA. Postoperative wound infection: 35 years of experience. Orthopedics 2006;29(9):797–8.
[50] Møller AM, Villebro N, Pedersen T, Tønnesen H. Effect of preoperative smoking intervention on postoperative complications: a randomised clinical trial. The Lancet 2002;359(9301):114–7.
[51] Deeks JJ, Higgins JP, Altman DG, Cochrane Statistical Methods Group. Analysing data and undertaking meta-analyses. In: Cochrane Handbook for Systematic Reviews of Interventions. Wiley Online Library; 2008. p. 241–84.

Table A1
Ovid MEDLINE® search strategy.

#	Searches	Results
1	Exp Arthroplasty, Replacement/	50,550
2	Total Joint Replacement.mp.	1783
3	Total Joint replacement.mp.	1783
4	Exp Arthroplasty, Replacement, Hip/ or exp Hip Prosthesis/	37,920
5	hip replacements.mp.	2309
6	hip arthroplasty.tw.	19,806
7	hip arthroplasty.mp.	20,597
8	hip replacement.tw.	10,324
9	exp Hip Prosthesis/	22,199
10	THA.mp	9652
11	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10	73,816
12	exp Smoking/ or smok*.mp.	310,072
13	exp Cigarette Smoking/ or exp Cigar Smoking/ or exp Smoking/	141,087
14	exp Tobacco/	29,660
15	exp Nicotine/	24,655
16	#12 or #13 or #14 or #15	342,792
17	#11 and #16	370

Table A2
EMBASE search strategy.

#	Search	Results
1	exp Arthroplasty, Replacement/	16,342
2	Total Joint Replacement.mp.	2572
3	Total Joint replacement.mp.	2572
4	exp Arthroplasty, Replacement, Hip/ or exp Hip Prosthesis/	46,799
5	hip replacements.mp.	3070
6	hip arthroplasty.tw.	24,733
7	hip arthroplasty.mp.	36,336
8	hip replacement.tw.	14,253
9	exp Hip Prosthesis/	44,641
10	THA.mp.	13,452
11	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10	79,495
12	exp Smoking/ or smok*.mp.	507,291
13	exp Cigarette Smoking/ or exp Cigar Smoking/ or exp Smoking/	376,834
14	exp Tobacco/	47,576
15	exp Nicotine/	47,701
16	#12 or #13 or #14 or #15	558,084
17	#11 and #16	808

Table A3
Cochrane library search strategy.

#	Search	Results
1	("arthroplasty"):ti,ab,kw OR ("replacement arthroplasties"):ti,ab,kw OR (Joint Prosthesis Implantation):ti,ab,kw OR (Joint Replacement):ti,ab,kw OR (Total Joint Replacement):ti,ab,kw	11,412
2	("hip-joint"):ti,ab,kw OR (hip prosthesis):ti,ab,kw OR ("total hip arthroplasties"):ti,ab,kw OR ("hip replacement arthroplasty"):ti,ab,kw	4061
3	#1 and #2	2306
4	(SMOK*):ti,ab,kw	33,603
5	#3 and #4	11

Table A4
Scopus search strategy.

#	Search	Results
1	TITLE-ABS-KEY (hip AND replacement*)	43,850
2	TITLE-ABS-KEY (hip AND arthroplasty)	47,505
3	TITLE-ABS-KEY (hip AND prosthesis)	52,635
4	TITLE-ABS-KEY (joint AND replacement*)	25,027
5	TITLE-ABS-KEY (joint AND arthroplasty*)	52,409
6	(TITLE-ABS KEY (hip AND replacement*)) OR (TITLE-ABS-KEY (hip AND arthroplasty)) OR (TITLE-ABS-KEY (hip AND prosthesis)) OR (TITLE-ABS-KEY (joint AND replacement*)) OR (TITLE-ABS-KEY (joint AND arthroplasty*))	117,421
7	(TITLE-ABS-KEY (joint AND infection*) OR TITLE-ABS-KEY (periprosthetic AND joint AND infection) OR TITLE-ABS-KEY (surgical AND site AND infection*) OR TITLE-ABS-KEY (wound AND infection*) OR TITLE-ABS-KEY (deep AND infection*) OR TITLE-ABS-KEY (superficial AND infection) OR TITLE-ABS-KEY (infection*) OR TITLE-ABS-KEY (peri-prosthetic AND joint AND infection) OR TITLE-ABS-KEY (peri AND prosthetic AND joint AND infection))	2,472,938
8	((TITLE-ABS-KEY (hip AND replacement*)) OR (TITLE-ABS-KEY (hip AND arthroplasty)) OR (TITLE-ABS-KEY (hip AND prosthesis)) OR (TITLE-ABS-KEY (joint AND replacement*)) OR (TITLE-ABS-KEY (joint AND arthroplasty*))) AND ((TITLE-ABS-KEY (joint AND infection*) OR TITLE-ABS-KEY (periprosthetic AND joint AND infection) OR TITLE-ABS-KEY (surgical AND site AND infection*) OR TITLE-ABS-KEY (wound AND infection*) OR TITLE-ABS-KEY (deep AND infection*) OR TITLE-ABS-KEY (superficial AND infection) OR TITLE-ABS-KEY (infection*) OR TITLE-ABS-KEY (peri-prosthetic AND joint AND infection) OR TITLE-ABS-KEY (peri AND prosthetic AND joint AND infection)))	18,622
9	((TITLE-ABS-KEY (hip AND replacement*)) OR (TITLE-ABS-KEY (hip AND arthroplasty)) OR (TITLE-ABS-KEY (hip AND prosthesis)) OR (TITLE-ABS-KEY (joint AND replacement*)) OR (TITLE-ABS-KEY (joint AND arthroplasty*))) AND ((TITLE-ABS-KEY (joint AND infection*) OR TITLE-ABS-KEY (periprosthetic AND joint AND infection) OR TITLE-ABS-KEY (surgical AND site AND infection*) OR TITLE-ABS-KEY (wound AND infection*) OR TITLE-ABS-KEY (deep AND infection*) OR TITLE-ABS-KEY (superficial AND infection) OR TITLE-ABS-KEY (infection*) OR TITLE-ABS-KEY (peri-prosthetic AND joint AND infection) OR TITLE-ABS-KEY (peri AND prosthetic AND joint AND infection))) AND (LIMIT-TO (LANGUAGE , "English"))	16,195
10	((TITLE-ABS-KEY (hip AND replacement*)) OR (TITLE-ABS-KEY (hip AND arthroplasty)) OR (TITLE-ABS-KEY (hip AND prosthesis)) OR (TITLE-ABS-KEY (joint AND replacement*)) OR (TITLE-ABS-KEY (joint AND arthroplasty*))) AND ((TITLE-ABS-KEY (joint AND infection*) OR TITLE-ABS-KEY (periprosthetic AND joint AND infection) OR TITLE-ABS-KEY (surgical AND site AND infection*) OR TITLE-ABS-KEY (wound AND infection*) OR TITLE-ABS-KEY (deep AND infection*) OR TITLE-ABS-KEY (superficial AND infection) OR TITLE-ABS-KEY (infection*) OR TITLE-ABS-KEY (peri-prosthetic AND joint AND infection) OR TITLE-ABS-KEY (peri AND prosthetic AND joint AND infection)))) AND (TITLE-ABS-KEY (risk AND factor*)) AND (LIMIT-TO (LANGUAGE , "English"))	2746
11	((((TITLE-ABS-KEY (hip AND replacement*)) OR (TITLE-ABS-KEY (hip AND arthroplasty)) OR (TITLE-ABS-KEY (hip AND prosthesis)) OR (TITLE-ABS-KEY (joint AND replacement*)) OR (TITLE-ABS-KEY (joint AND arthroplasty*))) AND ((TITLE-ABS-KEY (joint AND infection*) OR TITLE-ABS-KEY (periprosthetic AND joint AND infection) OR TITLE-ABS-KEY (surgical AND site AND infection*) OR TITLE-ABS-KEY (wound AND infection*) OR TITLE-ABS-KEY (deep AND infection*) OR TITLE-ABS-KEY (superficial AND infection) OR TITLE-ABS-KEY (infection*) OR TITLE-ABS-KEY (peri-prosthetic AND joint AND infection) OR TITLE-ABS-KEY (peri AND prosthetic AND joint AND infection)))) AND (TITLE-ABS-KEY (risk AND factor*))) AND (ALL (smoking)) AND (LIMIT-TO (LANGUAGE , "English"))	238

Table A5
Web of science search strategy.

#	Search	Results
1	TOPIC: (hip arthroplasty) OR TOPIC: (hip replacement) OR TOPIC: (hip prosthesis) Indexes = SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan = All years	58,044
2	TOPIC: (infect*) OR TOPIC: (periprosthetic joint infection) OR TOPIC: (deep infection) OR TOPIC:(superficial infection) OR TOPIC: (readmission) OR TOPIC: (revision surgery) Indexes = SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan = All years	1,813,702
3	#2 AND #1 Indexes = SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan = All years	12,242
4	ALL FIELDS: (risk factor*) Indexes = SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan = All years	1,092,892
5	#4 AND #3 Indexes = SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan = All years	2109

Table A6
Quality appraisal (case-control studies) for the 7 studies included in the meta-analysis.

Criteria	Bedard et al. (2018) [34]	Choong et al. (2004) [35]	Dowsey et al. (2008) [36]	Gonzalez et al. (2018) [38]	Kapadia et al. (2014) [37]	Khan et al. (2009) [39]	Lombardi et al. (2013) [40]	Lubbeke et al. (2014) [41]	Meldrum et al. (2005) [42]	Sahota et al. (2018) [43]
Selection										
Is the case definition adequate? a) Yes, with independent validation b) Yes, eg, record linkage or based on self-reports c) No description	a (+1)	a (+1)	a (+1)	a (+1)	a (+1)	a (+1)	a (+1)	a (+1)	b (0)	a (+1)
Representativeness of the cases a) Consecutive or obviously representative series of cases b) Potential for selection biases or not stated	a (+1)	a (+1)	a (+1)	a (+1)	a (+1)	a (+1)	a (+1)	a (+1)	a (+1)	a (+1)
Selection of controls a) Community controls b) Hospital controls c) No description	a (+1)	a (+1)	a (+1)	a (+1)	a (+1)	a (+1)	a (+1)	a (+1)	a (+1)	a (+1)
Definition of controls a) No history of disease (end point) b) No description of source	b (0)	b (0)	b (0)	a (+1)	a (+1)	a (+1)	a (+1)	a (+1)	a (+1)	a (+1)
Confounder										
Comparability of cases and controls on the basis of the design or analysis a) Study controls for age and education b) Study controls for any additional factor	b (+1)	b (+1)	b (+1)	b (+1)	a (+1)	b (+1)	b (+1)	b (+1)	b (+1)	a (+1)
Exposure										
Ascertainment of exposure a) Secure record (eg, surgical records) b) Structured interviews were blind to case/control status c) Interview not blinded to case/control status d) Written self-report or medical record only e) No description	e (0)	e (0)	e (0)	d (0)	d (0)	e (0)	d (0)	d (0)	d (0)	d (0)
The same method of ascertainment for cases and controls a) Yes b) No	b (0)	b (0)	b (0)	a (+1)	a (+1)	a (+1)	a (+1)	a (+1)	a (+1)	a (+1)
Nonresponse rate a) The same rate for both groups b) Nonrespondents described c) Different rate and no designation	b (0)	b (0)	b (0)	a (+1)	a (+1)	b (0)	a (+1)	a (+1)	a (+1)	a (+1)
Overall score: Very good studies: 7 to 8 points Good studies: 5 to 6 points satisfactory: 4 points Unsatisfactory studies: 0 to 3 points	4 Satisfactory	4 Satisfactory	4 Satisfactory	7 Very good	7 Very good	6 Very good	7 Very good	7 Very good	6 Very good	7 Very good