Abstract

Background: Prosthetic joint infection (PJI) is one of the possible complications following total hip arthroplasty (THA). Several studies, but not all, have reported smoking as a risk factor of PJI in orthopedic 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 PJI, 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 PJI risk in tobacco users and tobacco non-user undergoing THA. Publication bias was also assessed through funnel plots.

Results: Searches identified 2,689 articles, 10 of these, involving a total of 20,640 patients, met the inclusion criteria. The overall odds ratio (pooled OR) to develop either a superficial infection, a deep infection or an infection requiring revision surgery for tobacco users vs. non-users 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 employed. No publication bias was observed among the identified studies.

Conclusions: The findings of the study indicated that tobacco use is associated with higher risk of PJI in patients undergoing THA.

KEYWORDS: hip replacement, smoking, tobacco, PJI, infections, risk factors

1 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 employed for the management and prevention, one to two percent of patients undergoing primary total hip arthroplasty (THA) develop a PJI [2]. These infections can occur at any point in time following a primary or a revision surgery; even though 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 (NHS), the cost associated to elective revision surgery due to PJI was £12,214 [5]. As PJI management remains challenging and costly, the most commonly employed approach is prevention of such infections through minimizing risk factors. Also, identifying potential PJI risk factors is of great clinical significance as it could assist orthopedics 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 post operatory 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 is different, for example nicotine is a recognized vasoconstrictor 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 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].

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 hip [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 were 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 following hip replacement through a systematic literature review and meta-analysis to provide a contemporary synthesis of the available evidence to educate clinical advice.

2 Material and methods

2.1 Systematic literature review

2.1.1 Data source and search strategy

This review was conducted in line with the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) guidelines [27]. A systematic search through Ovid Medline, EMBASE, Scopus, Web of Science and Cochrane databases was carried in July 2019. A multi-string 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 is presented in appendix.

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

2.1.2 Eligibility Criteria

Two authors independently first evaluated the titles and abstracts to identify possibly relevant studies, after that, full-text of chosen studies was obtained and inclusion criteria applied; reason for exclusion were 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 total hip arthroplasty separately. Similarly, studies that explored various risk factor for PJI were included only if presented sufficient data for calculating the OR with 95% confidence interval for tobacco users vs. non-users.

2.1.3 Data extraction

The following data were extracted from each study that were included: Fist author, publication year, country of origin, study design, minimum duration of follow up, sample size, number of cases and control, case definitions, 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" (e.g., fascial and muscle layers)) or revision surgeries (regardless of the number of stages) resulting from PJI observed in the cohort over a follow-up period of at least 30 days; shorter follow-up were not considered because of the possibility of missing infections developing at later stages. Revision surgeries not resulting from infections (i.e. aseptic loosening) were not included; similarly reports of generic "surgical intervention" following the initial THA were excluded unless a specification that all interventions were revisions due to infections.

2.1.4 Quality assessment of studies included

Data quality of the included studies was evaluated according to the Newcastle Ottawa Scale (NOS) [30]. In case-control studies, 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 studies data quality 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 .

2.2 Statistical analysis

Odds ratios (OR) and 95% confidence interval (95% CI) of PJI for tobacco users vs. non-users in each study were calculated. Meta-analysis of OR to assess the association between

tobacco use and risk of PJI was carried out using the Mantel-Haenszel method for fixed and random effect models; the DerSimonian-Laird estimator for τ^2 was employed and a statistically significance level $p < 0.05$ was applied. Potential publication bias was presented graphically by the funnel plot and quantitatively assesses through the Egger's test.

Sensitivity analysis considering specific subgroups (specific endpoint 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 through meta-regression.

All analyses were performed in R (version 3.6.1) [31] using the "rmeta" [32] and "metafor" [33] packages.

3 Results

3.1 Search results

The literature search strategies (Table A 1 - Table A 5) identified 3,536 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, 2,689 papers remained, then 61 articles were initially selected based on titles and abstracts screening for further evaluation. Following 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: 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 ten included studies were identified in the searches and did not originate from other sources. The PRISMA flow diagram (Figure 1) illustrates the literature search and selection strategy with the number of studies considered at each stage of the process.

3.2 Cohort characteristics and quality assessment of included studies

The characteristics of the ten 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 (non-users arm) varied from 31 to 7,929; the sample size of the meta-analysis was 20,640 participants that involved 5,328 tobacco users and 15,312 non-users. The follow-up period ranged from one month to five years. The definition of the end points reported varied among the included studies, only deep infections were considered in some studies (n=3), while other 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 out of ten studies stated the definition of tobacco non-user (control) cohort while the rest did not fully declare the control group inclusion criteria (i.e. never used tobacco or quit tobacco at least a certain period of time prior to THA). There was variation in the tobacco

users definition among studies and in four studies the clarification criteria were not reported. Moreover, the data quality assessment by NOS scale demonstrated that all ten studies had reasonable quality for meta-analysis. Five studies scored 7 points, two studies scored 6 points, and three studies scored 4 points that is interpreted respectively as very good, good, and satisfactory quality (Table A 6).

3.3 Association between tobacco use and PJI

OR of an infection outcome (superficial infection, deep infection or revision surgery) of tobacco users compared tobacco non-users for each of the analyzed studies varied from 0.32 to 41.28. The overall odds ratio (pooled OR) for the ten 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 employed. The pooled OR was statistically significant for both models ($p < 0.0001$ and $p = 0.0005$ for fixed and random effect model respectively); consequently, using tobacco increased the risk of the possible infection endpoints considered in patients undergoing THA when compared to the control group (tobacco non-user) (Figure 2). The test of heterogeneity of the included studies returned a $\tau^2 = 0.010$ and $I^2 = 39\%$.

When specific outcomes were considered (Figure 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 = 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 the all ten for the 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 ten studies (τ^2 = 0.71 and I^2 = 56%).

3.4 Publication bias

Under visual examination, the funnel plot of the included studies in this meta-analysis of infections following THA in tobacco users vs. non-users exhibited symmetry (Figure 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.

3.5 Sensitivity analysis

The risk associated to 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 not statistically different from studies with follow-up shorter than one year. Similarly, the study size, assessed through the overall number of infections reported, did not impact the tobacco use association with infection risk following THA when the threshold of 50 total PJI reported in the study was used. Studies conducted in Europe or USA did not statistically differ in the risk of reaching the specific end-points of this review; the two studies conducted in Australia had much larger confidence intervals and the pool OR did not reveal an increased risk of infection for tobacco users (Figure 5).

3.6 Meta-regression

The possible impact of the minimum follow-up duration on the pooled OR was assessed through meta-regression (Figure 6). The linear regression between individual study reported OR and minimum follow-up had an intercept of 1.49 ($p < .05$) and a slope of 0.0037 ($p > 0.05$); therefore the minimum follow-up time was not statistically affecting the pooled ORs.

4 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 PJI after THA. There has been a contrast in the conclusions of studies examining the association between tobacco use and risk of PJI possibly because of small sample sizes or unidentified confounders. For instance, the association of smoking with PJI was proven in some study [34, 37, 44-46], while 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 PJI 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 odds ratio for developing PJI 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 (Figure 7); furthermore the three most recent studies were not included in any of the previous systematic reviews. The pooled odds ratio of developing PJI for never versus ever tobacco user was previously reported to be 1.67 (95% CI 1.25 - 2.20) [16][10], thus the impact of using tobacco on the risk of PJI following 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 four 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 PJI, moreover the heterogeneous definition of tobacco non-user in the identified study did not allow for this type of subgroup analysis. Nevertheless, 6-8 weeks of abstinence from smoking before orthopedic surgery have been identified as able to reduce the infection rate significantly [50].

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 is still not so clear (Figure 3). These results also suggests that smoking increase the chances of developing PJI 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 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 have not reach a sufficient sample size and further investigation is needed.

The overall number of patients represented in this review constitute 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.

Beside our effort to incorporate all studies reporting infections as primary endpoint or infections causing revision to produce more representative data, we found variability in infection reporting as well as the duration of follow-up in the included studies that ranged between one month and 5 years. It could be hypothesized that short follow-up periods may underestimate the risk of PJI occurrence as PJI 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 one year was not different than that of studies with follow-up up to 1 year; moreover the results of the meta-regression (Figure 6) revealed that not statistically significant role of the study minimum follow-up duration on the pooled OR This demonstrate the impact of tobacco on PJI does not varies with the time from surgery; such observation was also reported by Kunutsor, Whitehouse [10] that used a similar threshold value. Also, we observed heterogeneity between the analyzed studies in terms of tobacco amount consumed and definition of non-user 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, BMI, diabetes, cardiovascular, operating time where the most likely factors to be equal, however no single factor was controlled in all studies.

5 Conclusions

The findings of this study provide a contemporary synthesis of the available evidence related tobacco use as risk factor for PJI in patients undergoing THA. Patients who consume tobacco are at a significant greater risk of developing PJI, 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 in order to reduce the likelihood of PJI.

6 Acknowledgements

The authors would like to thank Ministry of Education of Saudi Arabia for providing a PhD scholarship to Bsmah Bojan. The funder had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

7 References

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Tables

Table 1. Research eligibility criteria (PICOS format)

	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 hemi-arthroplasty. • Non-human population.
Intervention	Not available	
Comparators	tobacco users vs non-user	Any other categorization of patient population
Outcomes	• Number of patients developing peri-prosthetic joint infection (deep and/or superficial infections). • Number of patients developing peri-prosthetic joint infection requiring revision surgery • Minimum follow-up period of one 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 not English

Table 2. Cohort characteristics results included in meta-analysis

Author (publication year)	Country	Study design	Minimum follow up-period (months)	Confounding controlled	Number of non-tobacco users (infection type/end-point)	Number of tobacco users (infection type/end-point)	Definition of tobacco user (case)	Definition of non-user (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 report except they include former and current smoker 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 cigarette (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, hip Harris score, cardiovascular diabetes	917 (superficial 46, deep 3, revision 12)	268 (superficial 13, deep 3, revision 2)	Smokers; smoking daily in the 30 days prior to 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, 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 two 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, 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

NR: not reported; SD: standard deviation; superficial infection: an infection involving “only skin or subcutaneous tissue of the incision”; deep infection: an infection involving the “deep soft tissues (e.g. fascial and muscle layers) of the incision” or “any part of the anatomy other than the incision”.

Figures

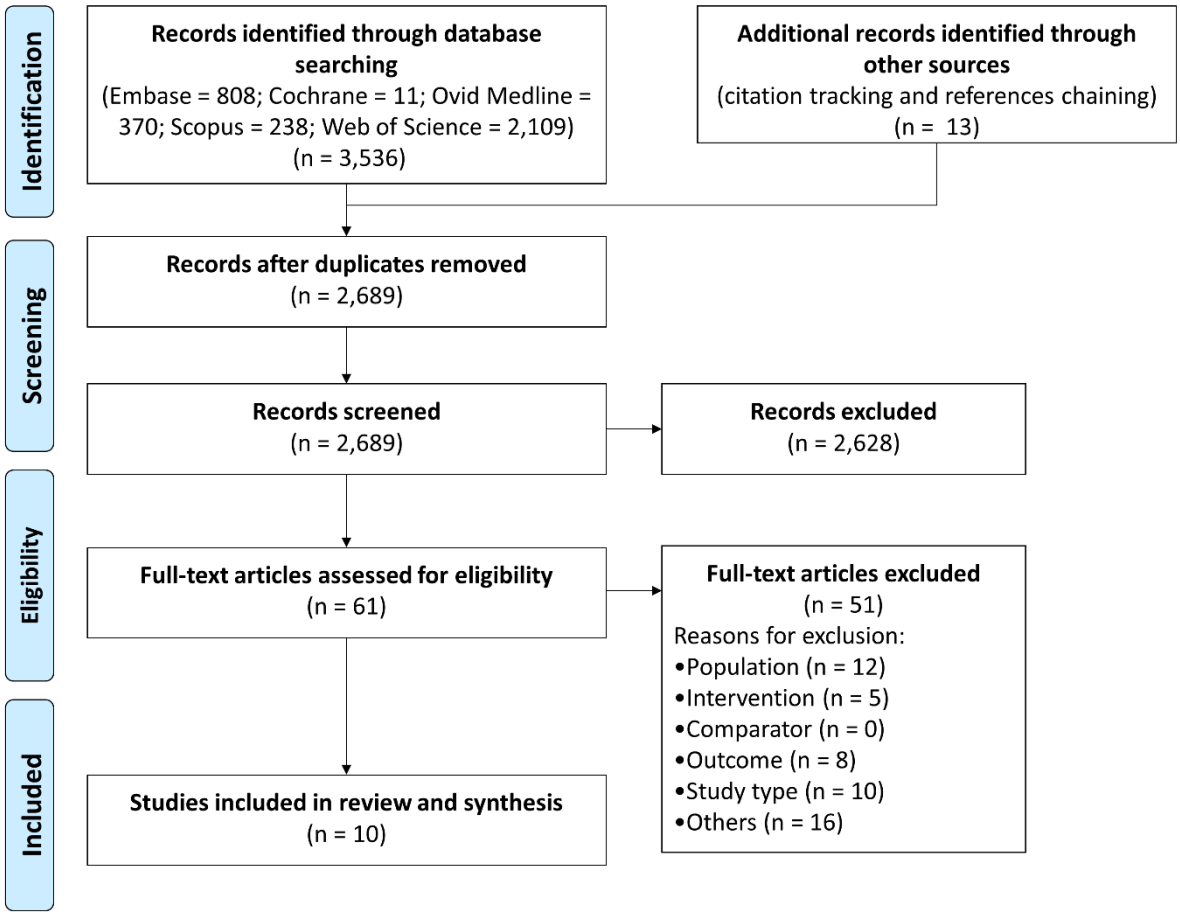

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flowchart [27].

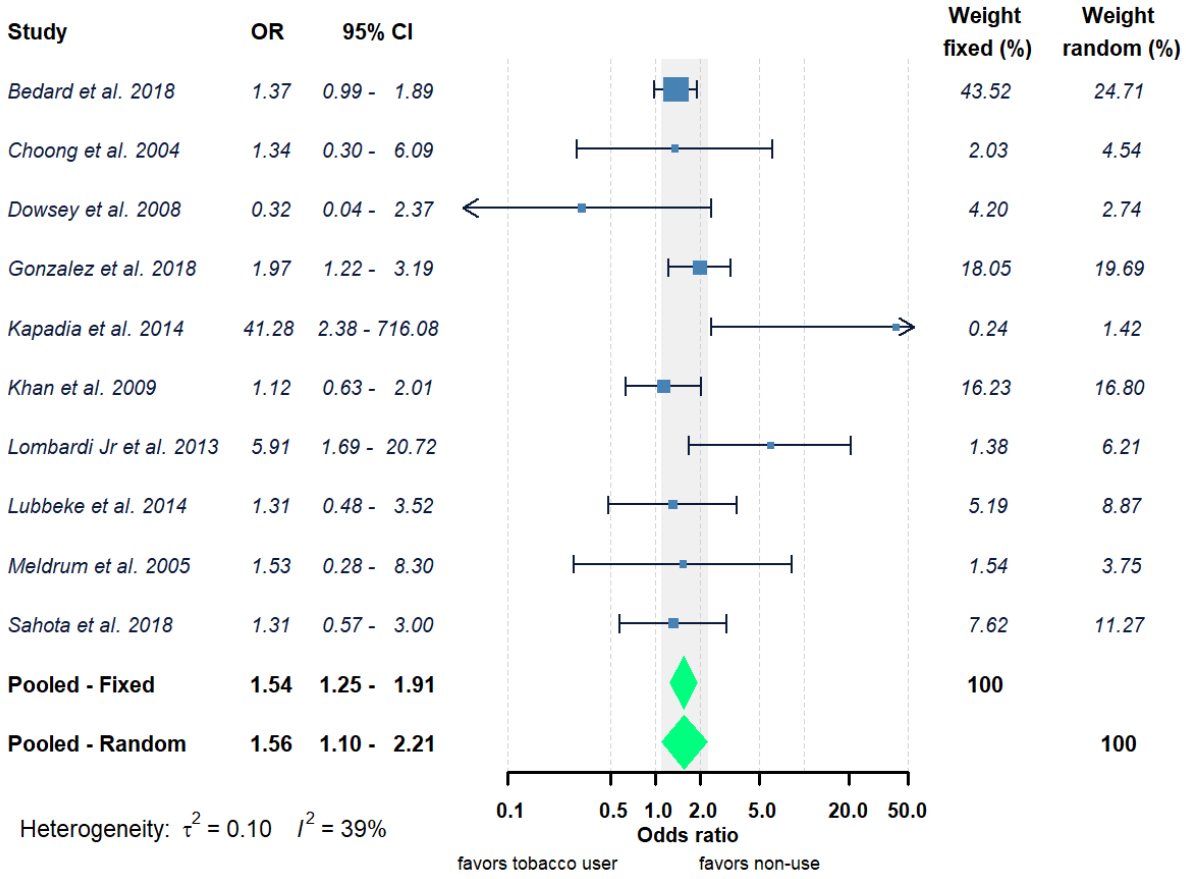

Figure 2. Forest plot of risk (reporting odds ratio (OR) and 95% confidence interval (CI)) of cumulative infection outcomes considered (superficial or deep infection and revision surgery) after hip replacement between tobacco users and non-users.

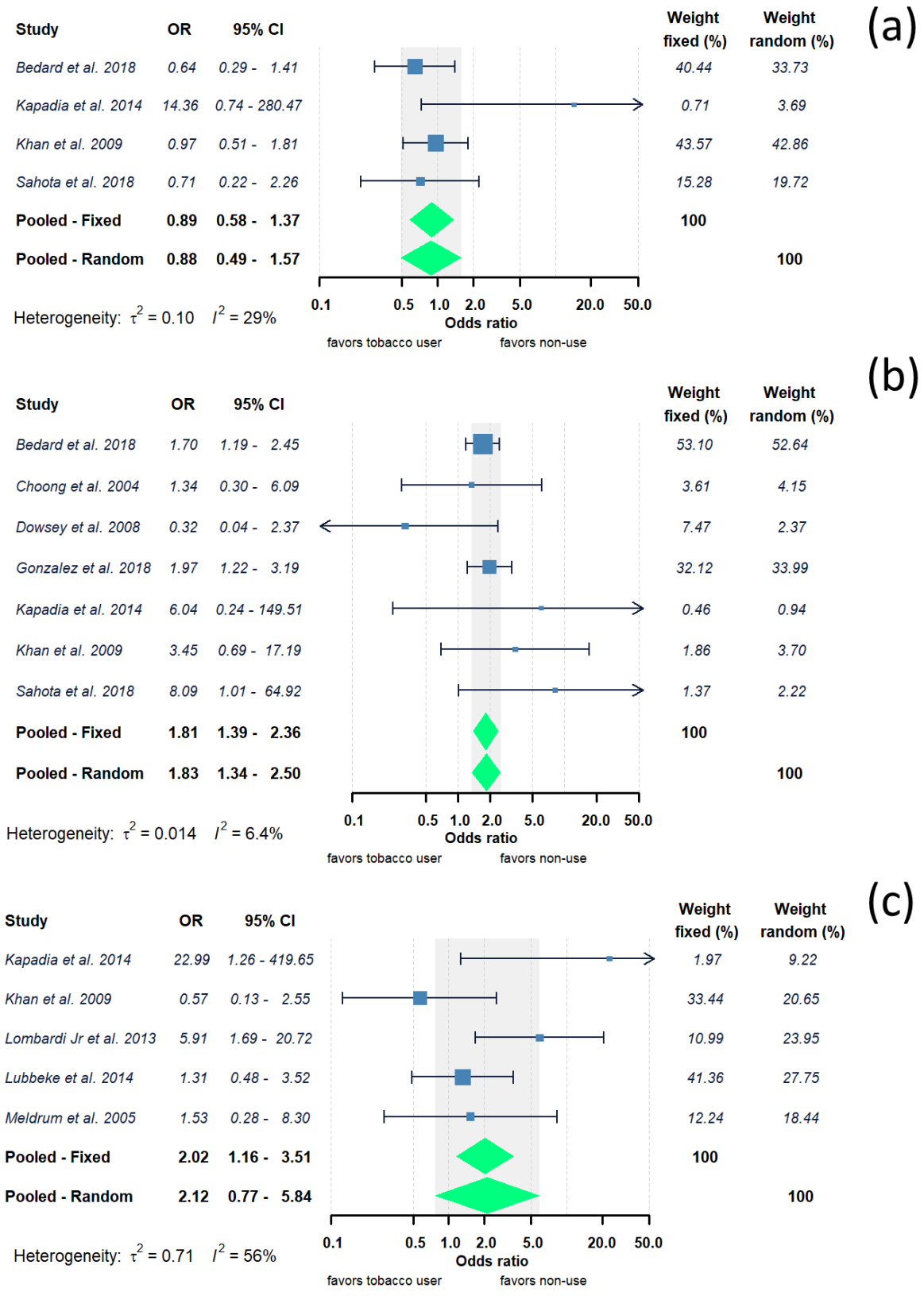

Figure 3. Forest plot of risk (reporting odds ratio (OR) and 95% confidence interval (CI)) of

superficial infection (a), deep infection (b) and revision surgery as consequence of infection (c) after hip replacement between tobacco users and non-users.

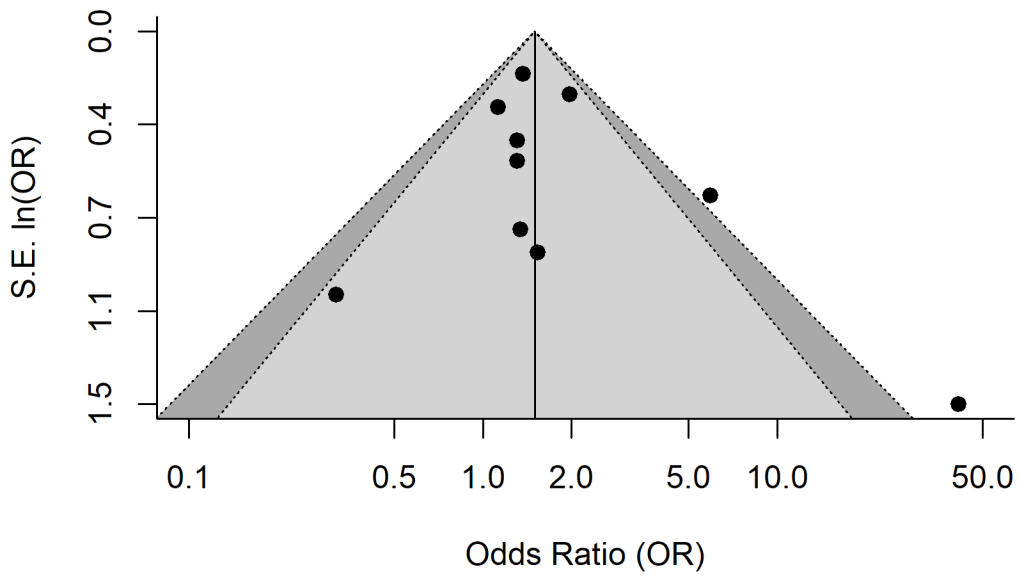

Figure 4. Funnel plot of included studies in the meta-analysis. Light gray area represent 90% confidence interval and dark gray area represent the 95% confidence area. (S.E.: standard error)

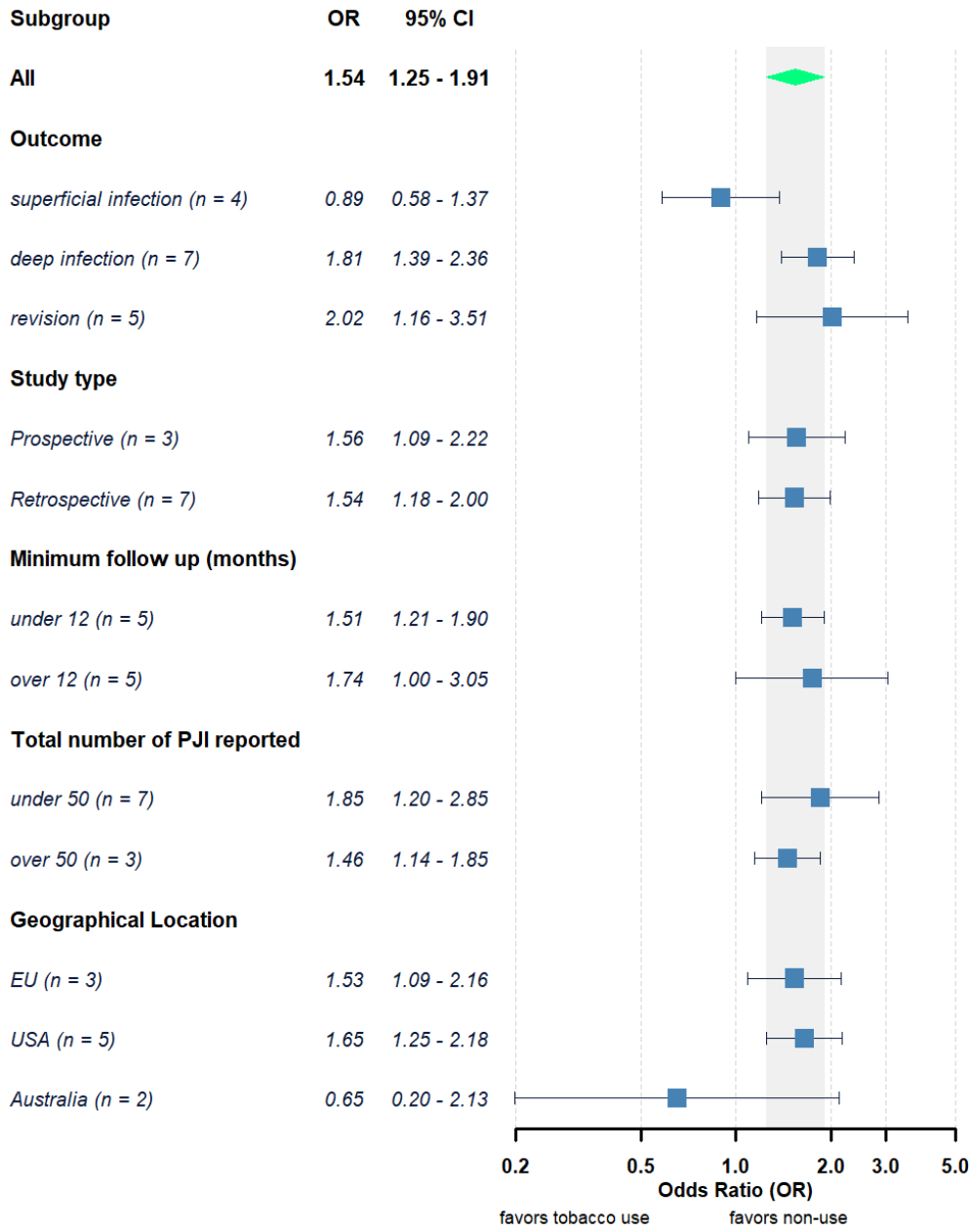

Figure 5. Pooled odds ratios (OR) and 95% confidence interval (CI) of developing PJI after total hip replacement comparing tobacco users to non-users grouped according to several study characteristics.

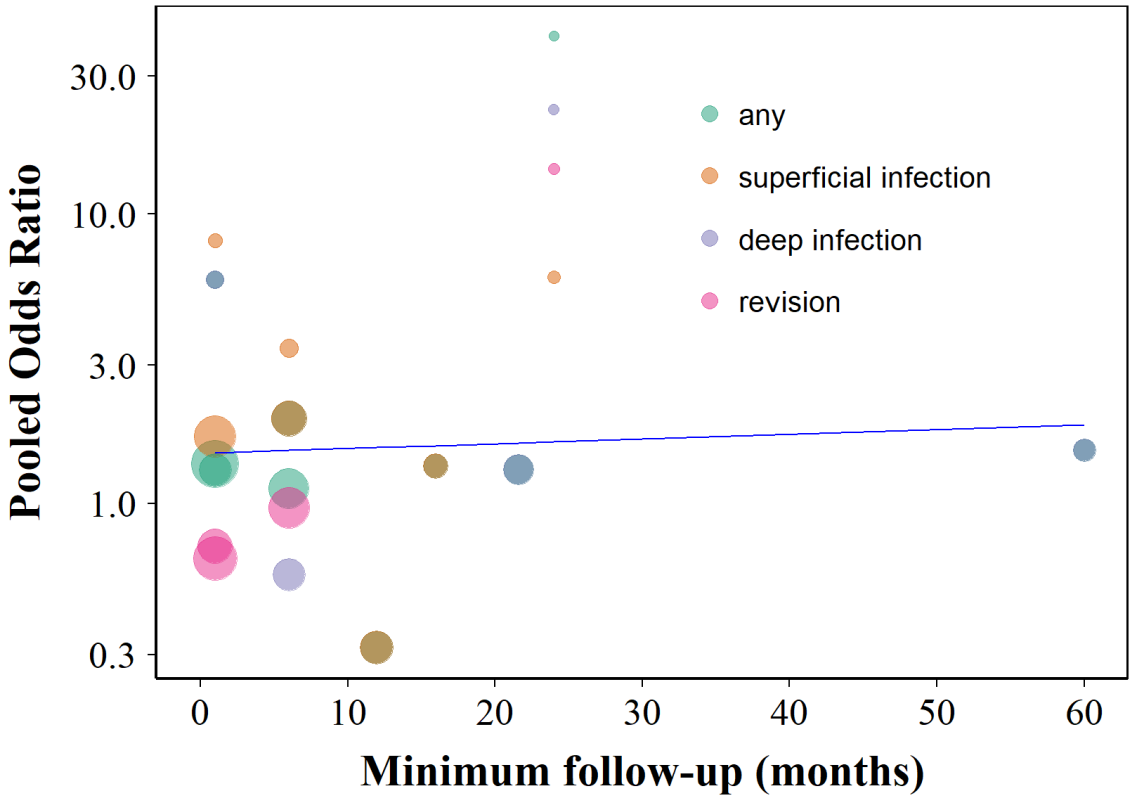

Figure 6. Correlation between pooled odds ratios (OR) of developing PJI after total hip replacement comparing tobacco users to non-users grouped according to reported outcomes. Blue line represent meta-regression. Bubble size represent 1/(95% CI) of the study OR.

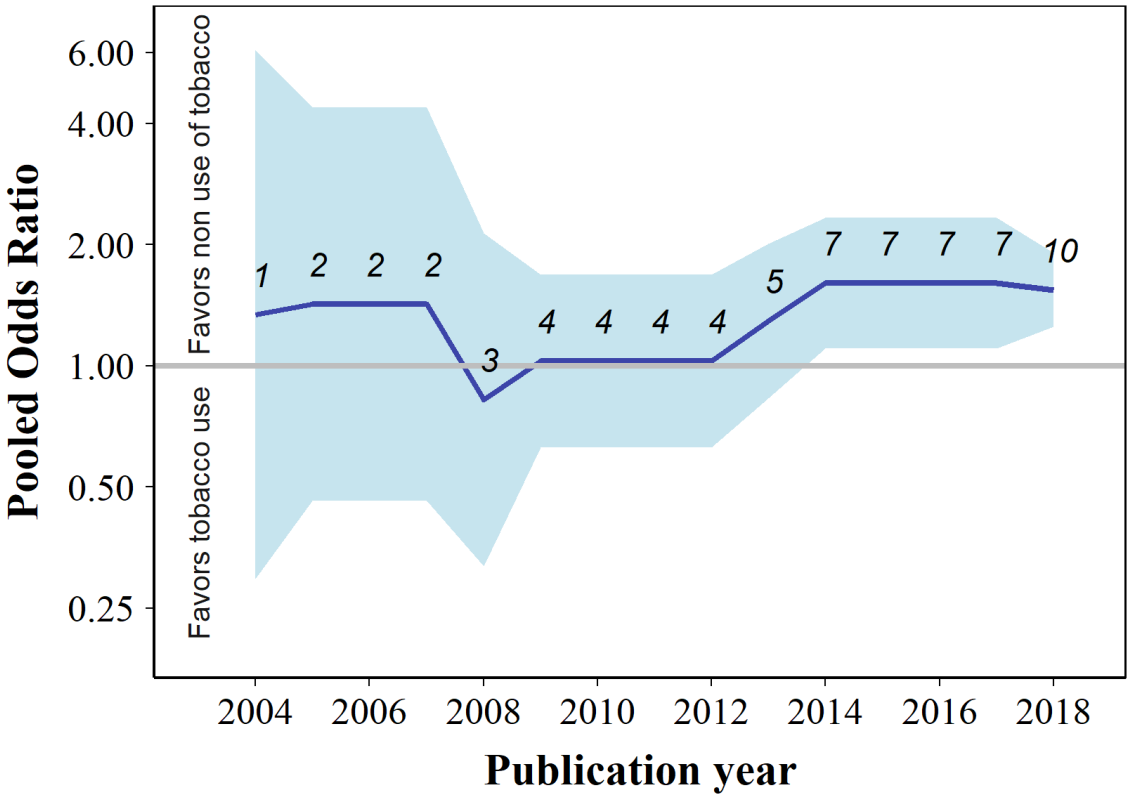

Figure 7. Timeline of the progression of pooled odds ratio of PJI following THA in tobacco users versus non-users (blue line) and 95% confidence interval (light blue area). Numbers represent number of studies included in the meta analysis.

Systematic review and meta-analysis of tobacco use as a risk factor for prosthetic joint infection following total hip replacement

- Appendix

By

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Search Strategy

Search strategy and number of hits for the identification of studies reporting periprosthetic joint infection after primary total hip arthroplasty in Ovid MEDLINE database (**Table A 1**).

Table A 1. Ovid MEDLINE® Search strategy.

#	**Searches**	**Results**
1	Exp Arthroplasty, Replacement/	50,550
2	Total Joint Replacement.mp.	1,783
3	Total Joint replacement.mp.	1,783
4	Exp Arthroplasty, Replacement, Hip/ or exp Hip Prosthesis/	37,920
5	hip replacements.mp.	2,309
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	9,652
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

Search strategy and number of hits for the identification of studies reporting peri-prosthetic joint infection after primary total hip arthroplasty in EMBASE database (**Table A 2**).

Table A 2. EMBASE Search strategy.

#	**Search**	**Results**
1	exp Arthroplasty, Replacement/	16,342
2	Total Joint Replacement.mp.	2,572

3	Total Joint replacement.mp.	2,572
4	exp Arthroplasty, Replacement, Hip/ or exp Hip Prosthesis/	46,799
5	hip replacements.mp.	3,070
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

Search strategy and number of hits for the identification of studies reporting smoking with periprosthetic joint infection after primary total hip arthroplasty in Cochrane library database (**Table A 3**).

Table A 3. 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	4,061
3	#1 and #2	2,306
4	(SMOK*):ti,ab,kw	33,603
5	#3 and #4	11

Search strategy and number of hits for the identification of studies reporting smoking with periprosthetic joint infection after primary total hip arthroplasty in Scopus database (**Table A 4**).

Table A 4. 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-	16,195

	KEY (deep AND infection*) OR TITLE-ABS-KEY (superficial AND infection) OR TITLE-ABS-KEY (infection*) OR TITLE-ABS-KEY (periprosthetic AND joint AND infection) OR TITLE-ABS-KEY (peri AND prosthetic AND joint AND infection))) AND (LIMIT-TO (LANGUAGE , "English"))	
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 (periprosthetic 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"))	2,746
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 (periprosthetic 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

Search strategy and number of hits for the identification of studies reporting periprosthetic joint infection after primary total hip arthroplasty in Web of Science database (**Table A 5**).

Table A 5. 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	2,109

Critical appraisal results

Table A 6. Quality appraisal (case-control studies) for the seven studies included in the meta-analysis

	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, e.g. 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 (endpoint) 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 (e.g. surgical records) b) structured interview where 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)
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)
Non-Response rate a) same rate for both groups b) non respondents described c) rate different 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	4 Satisfactory	4 Satisfactory	4 Satisfactory	7 Very Good	7 Very Good	6 Good	7 Very Good	7 Very Good	6 Good	7 Very Good

Unsatisfactory Studies: 0 to 3 points										