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SURVEY

What Host Factors Affect Aseptic Loosening After THA and TKA?

Jeffrey J. Cherian DO, Julio J. Jauregui MD, Samik Banerjee MD, Todd Pierce MD, Michael A. Mont MD

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Abstract

Background Aseptic loosening is the most common cause for revisions after lower-extremity total joint arthroplasties, however studies differ regarding the degree to which host factors influence loosening.

Questions/purpose We performed a systematic review to determine which host factors play a role in the development of clinical and/or radiographic failure from aseptic loosening after (1) THA and (2) TKA.

Methods Two searches on THA and TKA, respectively, using four electronic databases (EMBASE, CINAHL Plus, PubMed, and Scopus) were conducted. We identified a total of 209 reports that encompassed nine potential host factors affecting aseptic loosening. Inclusion criteria for consideration of scientific clinical reports were that 20 or more patients were involved, with more than 1-year followup, with at least three studies pertaining to each factor, and at least six of the Methodological Index for Non-randomized Studies criteria met, and with raw data for odds ratio (OR) calculations. Twenty-one studies (16 THA studies with 45,779 hips and five TKA studies with 288 knees, respectively) were used to calculate weighted OR and CIs (using the random effects theory) and study heterogeneity for four different host factors in THAs (male sex, high activity level, obesity defined as BMI $\geq$ 30 kg/m^2, and current or former tobacco use) and one factor in TKA (BMI $\geq$ 30 kg/m^2), which were placed in a forest plot.

Results For THA, male sex (OR, 1.39; 95% CI, 1.22–1.58; $p = 0.001$) and high activity level (University of California Los Angeles [UCLA] activity score $\geq$ 8 points; OR, 4.24; 95% CI, 2.46–7.31; $p = 0.001$) were associated with aseptic loosening. However, obesity (OR, 1.01; 95% CI, 0.73–1.40; $p = 0.96$), and tobacco use (OR, 1.96; 95% CI, 0.43–8.97; $p = 0.39$) were not associated with an increased risk of aseptic loosening after THA with the numbers available. For TKA, we found no host factors associated with loosening. In particular, obesity (BMI $\geq$ 30 kg/m^2) was not associated with aseptic loosening with the numbers available (OR, 2.28; 95% CI, 0.60–8.62; $p = 0.22$).

Conclusions Patients undergoing a lower-extremity total joint arthroplasty who engage in impact sports should be counseled regarding their potential increased risk of aseptic loosening; however, given the weak evidence available, we believe that higher-level studies are necessary to clearly define the risk factors, particularly with newer-generation constructs.

Level of Evidence Level IV, therapeutic study.

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J. J. Cherian, J. J. Jauregui, S. Banerjee, T. Pierce,
M. A. Mont (✉)
Rubin Institute for Advanced Orthopedics, Center for Joint Preservation and Replacement, Sinai Hospital of Baltimore, 2401 West Belvedere Avenue, Baltimore, MD 21215, USA
e-mail: mmont@lifebridgehealth.org

Introduction

A lower-extremity total joint arthroplasty has been one of the most successful orthopaedic procedures with multiple reports describing greater than 90% survivorship at 15 to

20 years [1, 26, 40]. Despite the clinical success of the arthroplasties, aseptic loosening is one of the major causes of failure [29, 45]. Aseptic loosening has been reported to be one of the most common causes for revisions, accounting for almost 55% of hip [47] and 31% of knee [49] revisions. As such, it is imperative to optimize primary outcomes in total joint arthroplasties and to avoid the difficulties and complication rates that can be found with revisions.

Various theories have been proposed for the cause of aseptic loosening which have been based predominantly on empiric observations, experimental and clinical studies, and anecdotal reports [18, 33, 34]. One of the most commonly proposed theories is that the development of excess-wear particles produces a proinflammatory state [18], which leads to increased osteoclast differentiation and macrophage production. This ultimately leads to local osteolysis and aseptic loosening around the prosthesis [34]. The final pathways to progressive particle wear leading to aseptic loosening and construct failure are driven by the inflammatory-mediated osteolysis. Additionally, several other factors can affect patient susceptibility to aseptic loosening after lower-extremity total joint arthroplasty. The factors generally can be divided into host-, genetic-, surgical-, and prosthesis-related factors; however, there is no consensus regarding the degree to which host factors influence aseptic loosening.

Therefore, we performed a systematic review to identify various host factors that have been reported to be associated with aseptic implant loosening, thereby decreasing duration of implant survival. Specifically, we asked: What host factors have been consistently reported to be associated with the development of clinical and/or radiographic failure owing to aseptic loosening in patients who underwent (1) THA and (2) TKA?

Methods

Two of the coauthors (JJC, SB) performed a thorough literature search using the EMBASE, CINAHL Plus, PubMed, and Scopus electronic libraries. All studies published from January 1976 to September 2013 were evaluated using a combination of the Boolean search strings Wear*, Aseptic*, Loosening*, Revision*, Risk*, Osteolysis*, Knee*, and Hip* to identify host factors associated with aseptic loosening in THA and TKA. Using our search criteria, 715 reports were identified. The collected reports identified nine host factors associated with increased rates of aseptic loosening, including patient age, sex, BMI, activity levels, social habits (consuming alcohol and tobacco use), preoperative diagnoses (diabetes, rheumatoid arthritis, osteonecrosis), and bone geometry and quality.

We performed a secondary structured search of the same databases between January 1976 and September 2013 to identify reports that focused on each host factor associated with aseptic loosening. We used a combination of the Boolean search strings knee[title], hip[title], arthroplast*[title], tobacco[title], smok*[title], replace*[title], alcohol*[title], cigarette[title], bone[title], loose*[title], BMI[title], obes*[title], age[title], sex[title], gender[title], geometry[title], activi*[title], aseptic[title], loosening [title], wear[title], diabet*[title], quality[title], type A [title], type B[title], type C[title], Singh index[title], Dorr[title], rheum*[title], and osteonecrosis[title] to identify all reports on the factors related to aseptic loosening.

We considered for inclusion: (1) scientific clinical reports describing the effect of various host factors for aseptic loosening; (2) studies with outcomes for 20 or more patients; (3) clinical studies that had three or more reports on specific host factors for knees and hips; and (4) studies with more than a 1-year minimum followup. We excluded: (1) case reports; (2) review reports; (3) clinical studies reporting outcomes for less than 20 patients; (4) less than a 1-year minimum followup; (5) basic science studies; (6) reports focusing on preoperative diagnoses (diabetes, rheumatoid arthritis, osteonecrosis,) resulting from previous systematic reviews published on these topics, in that we considered the current literature too extensive to include such in a single report; (7) reports not written or translated into English; and (8) reports on arthroplasties using metal-on-metal implants. Additionally, we excluded studies that evaluated: (1) surgical factors; (2) medication use; (3) implant factors; (4) genetic polymorphisms; (4) instability; and (5) endotoxins in the role of excess aseptic loosening. The initial search resulted in 3405 reports for evaluation. Through a title and abstract review, using the additional exclusion criteria, we disqualified 3196 studies, resulting in 209 reports that were found potentially relevant. The 209 reports were recovered in full and examined in detail by two authors (SB, JJC) independently, and studies included in our final analysis were selected by a consensus decision. The content of each article was critically analyzed to avoid including multiple reports with the same patient population published by the same author. When such a situation was encountered, the study with the larger group of patients and/or the longer followup was included in the analysis. A third author's (JJJ) opinion was sought when a consensus decision could not be reached, which resulted in 63 studies for further analysis, and bibliographies for these reports were individually searched to extract additional studies for the final analysis. This resulted in an additional 21 studies leading to a total of 84 reports.

Additionally, each manuscript was assessed using the Methodological Index for Non-randomized Studies

(MINORS) criteria [50]. The MINORS criteria scoring was modified to an all-or-nothing scale where studies that adequately reported an index of the MINORS criteria received 1 point [50]. This approach has been used and validated [55]. Studies that did not report or inadequately reported one of the criterion received no points, and all studies that had less than 6 points were excluded. A modified MINORS then was used because of the inherit difficulty in applying the traditional MINORS scoring scale with the loss to followup for our included studies. For example, we found several studies with substantial patient loss to followup, and the standard MINORS scoring system would assign 1 point to the study for reporting it. Because there were a large number of studies with a loss to followup—markedly greater than 5%—using an all-or-nothing scoring system allowed for more appropriate evaluation of all relevant studies. Furthermore, we did not include studies that had a loss to followup greater than 25%. After assessing each report for MINORS criteria, a total of 60 studies had at least 6 points, thereby qualifying for inclusion in our review.

All studies were analyzed by three of the authors (SB, JJC, JJJ) for study type, publication year, mean age (range), mean followup (range), aseptic loosening rate, odds ratio (OR) for aseptic loosening, and level of evidence. Of the studies that met our modified MINORS criteria, 21 contained the raw data that allowed us to calculate a weighted OR of aseptic loosening after total joint arthroplasty. For THA, the OR of four separate host factors, which included male sex (three studies on 40,615 hips) [4, 16, 37], high activity level (University of California Los Angeles [UCLA] activity score $\geq$ 8 points) (three studies on 178 hips) [14, 30, 42], tobacco use (three studies in 2040 hips) [20, 21, 35], and obesity (seven studies in 2946 hips) [2, 15, 28, 31, 34, 37, 51] were calculated (Fig. 1). For TKA, we were able to calculate a weighted OR of aseptic loosening in patients with a BMI of 30 kg/m^2 or greater (five studies in 288 knees) [11, 13, 27, 36, 39] (Fig. 1).

All outcome metrics and raw data were tabulated in an Excel spreadsheet (Excel 2011; Microsoft Corporation, Redmond, WA, USA). In studies reporting raw data for each cohort, MedCalc® (MedCalc® Software, Osteen, Belgium) was used to calculate a weighted OR, 95% CIs, and p values. Additionally, MedCalc® was used to create multiple forest plots and to calculate the total random effects, which assumed variety in the effects of the selected studies and thereby addresses study heterogeneity. As such, wider CIs were allowed because studies with more statistical power carried more weight in determining the weighted OR with their CIs. Furthermore, this allowed for an accurate depiction of the power of this study. A p value less than 0.05 was used to determine statistical significance.

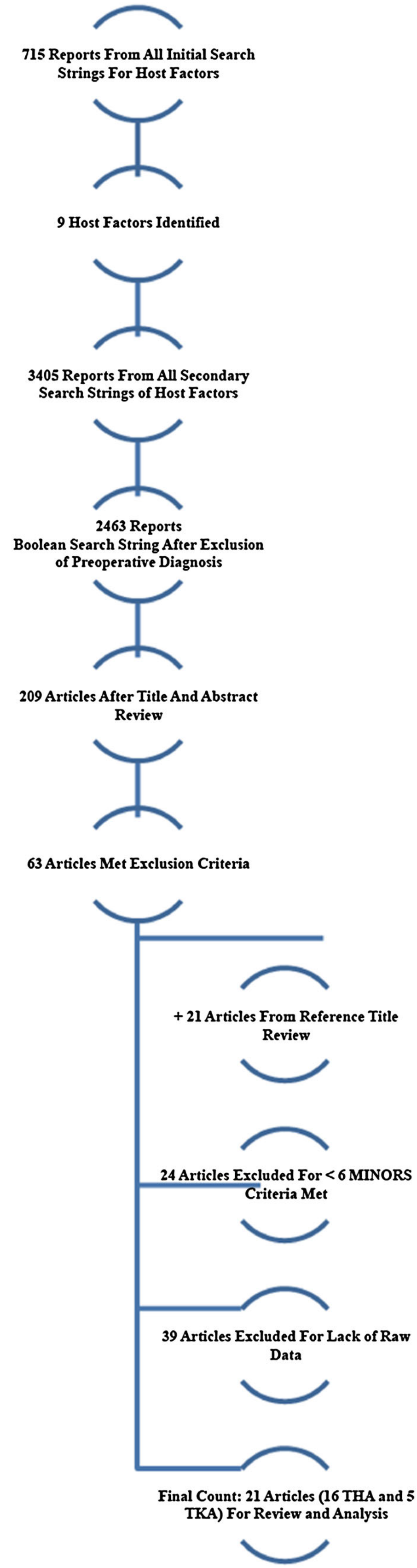

Fig. 1 Our literature search showed a total of 21 reports for analysis (MINORS = Methodological Index for Non-randomized Studies).

Table 1. THA sex studies

Study	LOE	MINORS	Number of hips	Mean age, years (range)	Mean followup, years (range)	Revision because of wear (%)	Overall aseptic loosening rate	Outcomes
Inacio et al. [16]	III	9	35,140	67 (20–90)	3 (1.3–5.1)	3.4	10.6	Women had a 29% higher risk of implant failure than men
Munger et al. [37]	III	7	725	65 (NR)	NR	NR	NR	Women had significantly lower risk of aseptic loosening (OR, 0.4; $p < 0.001$)
Bordini et al. [4]	IV	6	4750	NR	NR	2.8	NR	Stem survivorship negatively affected by male sex ($p = 0.02$)

MINORS = Methodological Index for Non-randomized Studies; OR = odds ratio; LOE = level of evidence; NR = not reported.

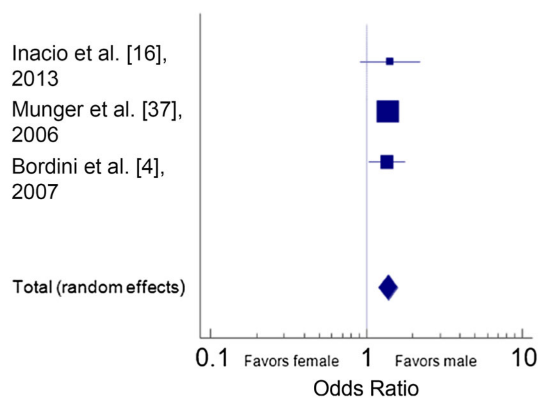

Fig. 2 The forest plot shows the odd ratios (OR) for aseptic loosening for male sex after THA (OR, 1.39; 95% CI, 1.22–1.58; $p = 0.001$).

Results

Host factors analyzed in THA were male sex, increased activity level, increased BMI, and tobacco use. Men were more likely to have a diagnosis of loosening than women (OR, 1.39; 95% CI, 1.22–1.58; $p = 0.001$) (Table 1; Fig. 2). In addition, patients with high activity levels were more likely to experience loosening compared with patients with medium or low activity levels, (OR, 4.24; 95% CI, 2.46–7.31; $p = 0.001$) (Table 2; Fig. 3). However, patients who had a BMI of 30 kg/m^2 or greater showed no difference with the numbers available in the risk of aseptic loosening compared with patients with a BMI less than 30 kg/m^2 (OR, 1.01; 95% CI, 0.73–1.40; $p = 0.96$) (Table 3; Fig. 4). Similarly, tobacco use (current and former) was not associated with aseptic loosening of the prosthesis with the numbers available (OR, 1.96; 95% CI, 0.43–8.97; $p = 0.39$) (Table 4; Fig. 5).

For patients with a BMI of 30 kg/m^2 or greater and who underwent a TKA, there was no difference with the numbers available in their risk of aseptic loosening compared with patients with a BMI less than 30 kg/m^2 (OR, 2.28; 95% CI, 0.60–8.62; $p = 0.22$) (Table 5; Fig. 6).

Discussion

Lower-extremity arthroplasty is efficacious and generally results in excellent long-term survivorship; however, aseptic loosening remains a concern. Various host factors have been associated with the development of aseptic loosening, but studies have differed regarding the degree to which host factors influence loosening. Thus, the aim of our systematic review was to identify the host factors associated with aseptic loosening. We found that high activity level and male sex were associated with an increase in aseptic loosening rates after THA, but we found no host factors associated with loosening after TKA.

There were several limitations to our review. Unfortunately, there is a paucity of prospective studies [14, 30]

Table 2. Activity level studies

Study	LOE	MINORS	Number of hips	Mean age, years (range)	Mean followup years (range)	Revision because of wear (%)	Wear (mm)	Overall aseptic loosening rate	Outcomes
Ollivier et al. [42]	III	7	70	58 (NR)	11 (10–15)	20/6*	0.145	20	Practicing high-impact sport increased wear rate ($p < 0.001$), and decreased survivorship ($p < 0.001$); OR, 3.64
Gschwend et al. [14]	III	6	50	65 (47–84)	10 (9–12)	NR	NR	6.6	Significantly higher wear in very active patients ($p < 0.05$)
Lübbeke et al. [30]	IV	8	58	68 (30–91)	8 (4–12)	0.8	NR	24	Compared with low (5.8%) and moderate (7.5%) activity, patients with high activity had higher rates of osteolysis (OR, 3.9)

MINORS = Methodological Index for Non-randomized Studies; LOE = level of evidence; OR = odds ratio; NR = not reported.

* Revision rate difference between high-activity (20%) and low-activity cohorts (6%).

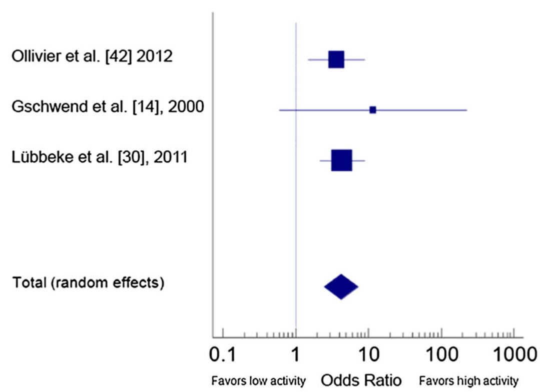

Fig. 3 The forest plot shows the odd ratios (OR) for aseptic loosening for patients with a high activity level after THA (OR, 4.24; 95% CI, 2.46–7.31; p = 0.001).

regarding risk factors associated with loosening thereby decreasing the strength of our conclusions. However, because our study evaluated prognostic factors, we believe that the use of retrospective studies is acceptable in performing our analysis and formulating our conclusions. Additionally, many of the studies considered did not include the raw data, so the OR of some host factors that may be associated with aseptic loosening could not be calculated. However, we think that by implementing our MINORS criteria and excluding studies that had greater than 25% loss to followup provides a basic level of evidence that allows the results of our study to be plausible. In addition, owing to the volume of the databases and the number of years spanned in many of the studies evaluated, analysis of the many changes in polyethylene processing, sterilization, implant design (especially cemented versus cementless constructs in THA), and surgical technique (which also can affect loosening rates) was not performed. A much more accurate way to analyze these factors would be to identify a large population of patients with one implant design, surgical technique, specific type of polyethylene, and sterilization technique. Unfortunately, this is not likely to be possible; most studies by this stratification are heterogeneous and therefore, one must appreciate this as a critical limitation that should be addressed in future studies of the same factors.

In addition, aseptic loosening results from multifactorial causes, and our study did not address surgical, implant, genetic, pharmacologic, and endotoxin factors that may play a role. We focused specifically on host-related factors which can be assessed preoperatively, thus allowing surgeons to be aware of and to discuss the risks with their patients before surgery. Another important set of limitations relates to the host factors analyzed. For example, when analyzing tobacco use, we were unable to separate current from former tobacco use, thereby making it difficult

Table 3. BMI studies

Study	LOE	MINORS	Number of hips	Mean age, years (range)	Mean followup, years (range)	Revision because of wear (%)#	Overall aseptic loosening rate	Outcomes
Lubbeke et al. [30]	III	7	589	NR	5 (NR)	0.8/0.9	NR	No association between obese BMI and risk of revision
Munger et al. [37]	III	7	725	65 (NR)	NR	NR	NR	Increased the risk of stem loosening per additional unit of BMI (OR, 1.03; $p < 0.02$)
Andrew et al. [2]	IV	9	1059	NR (21–94)	NR (3–5)	1.5/1.3/0	NR	Obese patients had no significant radiologic changes ($p > 0.05$)
McLaughlin et al. [34]	IV	8	209	54 (20–77)	15 (10–19)	60/67.9	8.3	No statistically significant difference was identified between the obese and nonobese patients regarding clinical and radiologic outcomes or complications
Lehman et al. [28]	IV	7	60	50 (17–67)	2 (NR)	6.7/9.2	NR	No statistically significant association between increased BMI and need for revision. (6.7% revision rate obese vs. 9.2% nonobese)
Ibrahim et al. [15]	IV	6	179	66.4 (33–86)	NR	3.6/3.2	NR	No association between BMI and need for revision surgery (total obese: 3.6%; nonobese: 3.2%)
Søballe et al. [51]	IV	6	125	70 (28–89)	5 (NR)	2.1	2.4	Similar outcomes obese versus nonobese (radiographic signs of loosening equally common between obese vs. nonobese)

MINORS = Methodological Index for Non-randomized Studies; LOE = level of evidence; OR = odds ratio; NR = not reported.

Revision rates of obese and nonobese cohorts.

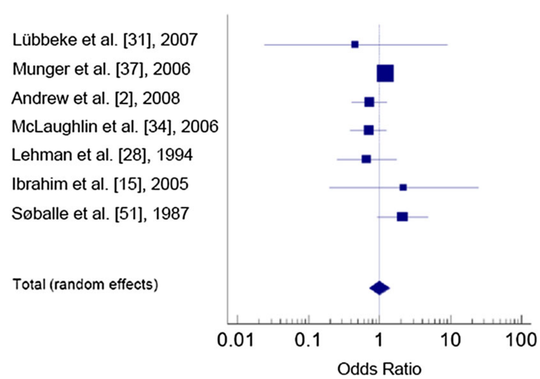

Fig. 4 The forest plot shows the odd ratios (OR) for aseptic loosening for BMI of 30 kg/m^2 or greater after THA (OR, 1.01; 95% CI, 0.73–1.40; $p = 0.96$).

to infer whether smoking cessation can reduce the risk of aseptic loosening. Furthermore, although many studies [2, 9, 10, 34, 37, 38, 43, 46, 48, 51, 52] examined the role of obesity, there were not enough raw data to stratify results based on morbid obesity in THA (n = 26 hips) (BMI $\geq$ 40 kg/m^2) and there was only one study [40] that specifically examined outcomes of super obesity in TKA (n = 101 knees) (BMI $\geq$ 50 kg/m^2). Therefore, we were unable to examine an association between morbid obesity and aseptic loosening after THA or TKA.

Among modifiable risk factors, multiple factors such as high activity level [3, 14, 17, 30, 43, 44, 48], obesity [2, 9, 10, 34, 37, 38, 43, 46, 48, 51, 52], and smoking [10, 12, 16, 17, 19, 32, 35, 41] may be associated with an increase in the risk of aseptic loosening after THA.

Among nonmodifiable risk factors, male sex [4, 5, 16, 37, 38, 42, 46, 48, 52] and younger patient age (< 65 years) [1, 4–7, 12, 17, 22–25, 37, 38, 43, 46, 52, 53] have been studied for their potential association with aseptic loosening. Even though we found an association

Table 4. Tobacco use (current and former)

Study	LOE	MINORS	Number of hips	Mean age, years (range)	Mean followup, years (range)	Revision because of wear (%)	Overall aseptic loosening rate	Outcomes
Kapadia et al. [19]	III	6	110	55 (35–84)	4 (2–6)	5/1⁺	1	Nonsmoker group was 99% (1% revision rate), survivorship which was significantly higher than 92% (5% revision rate survivorship among the smokers (p = 0.0011)
Khan et al. [21]	IV	7	1767	69 (NR)	NR (5 to NR)	0.8/1.5/ 1.3*	NR	No significant difference in the revision rates between nonsmokers (0.8%), current smokers (1.5%), and exsmokers (1.3%) (p = 0.67)
Meldrum et al. [35]	IV	6	165	61 (21–83)	NR (5 to NR)	11.8/1.9⁺	NR	Revision rate 11.8% smokers vs. 1.9% nonsmokers; p = 0.0012

MINORS = Methodological Index for Non-randomized Studies; LOE = level of evidence; NR = not reported.

⁺ Revision rates of smokers and nonsmokers; *revision rates for nonsmokers, smokers, and exsmokers.

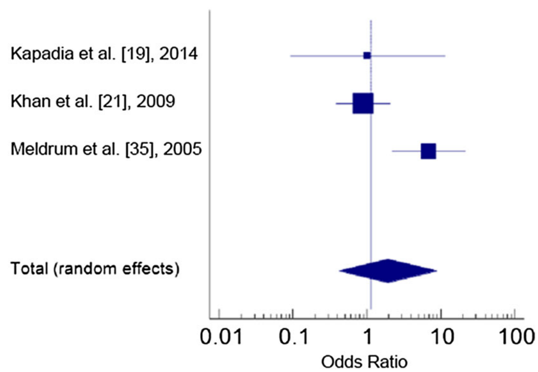

Fig. 5 The forest plot shows the odd ratios (OR) for aseptic loosening for tobacco use after THA (OR, 1.96; 95% CI, 0.43–8.97; p = 0.39).

with male sex, we were unable to determine an association with age owing to the lack of available raw data. Furthermore, although there was no association between the risk of aseptic loosening and BMI of 30 kg/m^2 or greater, this finding may have been attributable to the small number of studies available to calculate the OR and CIs. Although we found no association between tobacco use (current and former) and loosening, we still believe surgeons should encourage weight loss and smoking cessation among their patients because of the well-known potential advantages to overall health.

Similar to THA, a high BMI has been associated with increased aseptic loosening rates after TKA [49]. Although we did not find an association between obesity and aseptic loosening, this may be attributable to the small cohorts in each study chosen. Therefore, any future studies regarding this potential association should have larger cohort sizes. Moreover, there are studies linking increased rates of aseptic loosening to an increased BMI [8, 11, 39, 44, 54, 56]. Conversely, there are multiple studies that have shown no association between patient obesity (BMI $\geq$ 30 kg/m^2) and aseptic loosening rates [13, 27, 36, 39, 57]. Although our study was unable to analyze other host factors, previous studies have associated younger age [4, 6, 15, 21, 24, 36, 41, 45, 53], increased activity level [11, 16, 44, 52], and tobacco use [20] with increased rates of aseptic loosening. To appropriately analyze whether these host factors have an association with aseptic loosening, future studies should report their raw data regarding the incidence of aseptic loosening with each of these various factors. Moreover, it will be important to examine the role of morbid obesity and super obesity (BMI $\geq$ 50 kg/m^2) and see if these two subclassifications of obesity negatively affect implant survivorship.

It is possible that multiple interrelated factors are associated with an increased frequency of aseptic loosening.

Table 5. TKA with obese BMI studies

Study	LOE	MINORS	Number of knees	Mean age, years (range)	Mean followup, years (range)	Revision because of wear (%)	Outcomes
Naziri et al. [39]	III	9	99	60 (43–74)	5 (3–7)	6/2*	No significant difference in implant survivorship in patients > 50 kg/m^2 compared with < 30 kg/m^2 (6% superobese revision rate vs. 2% nonobese revision rate)
Foran et al. [11]	III	8	27	62 (36–78)	15 (7–18)	7.4	Obese patients had 3 times higher revision rates (p > 0.05)
Griffin et al. [13]	III	7	73	68 (46–82)	11 (10–12)	7.3	Similar overall rates of loosening and wear between obese and nonobese patients (all revisions were in nonobese group)
Mont et al. [36]	III	7	50	61 (30–74)	7 (2–11)	8/4*	Weight as an independent factor should not compromise the results of TKA. (8% obese vs. 4% control)
Krushell & Fingeroth [27]	IV	7	39	67 (4–81)	NR (5 to NR)	5.1	No statistically significant difference was identified between the obese and nonobese patients regarding radiolucencies

MINORS = Methodological Index for Non-randomized Studies; LOE = level of evidence; NR = not reported.

* Revision rates for patients with a BMI > 50 kg/m^2 (6%) compared with < 30 kg/m^2 (2%).

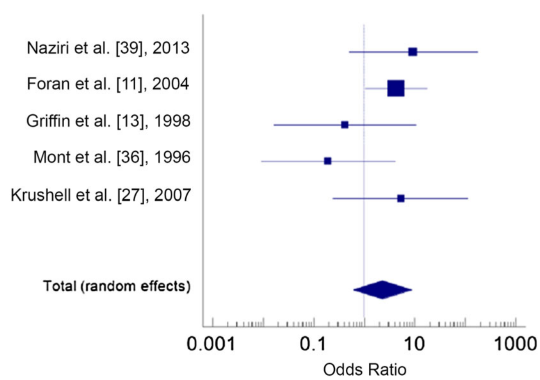

Fig. 6 The forest plot shows the odds ratios (OR) for aseptic loosening for obese BMI ≥ 30 kg/m^2 after TKA (OR, 2.28; 95% CI, 0.60–8.62; p = 0.22).

However, the only risk factors that we found that were associated with aseptic loosening after THA were male sex and high activity level. Therefore, we believe that patients undergoing THA who regularly engage in impact sports should be informed of their increased risk for aseptic loosening and should be counseled to avoid impact sports after THA. We cannot make any recommendations regarding patients after TKA as we were unable to find any risk factors associated with loosening. Given the paucity of high-quality evidence available on this subject, we believe there is need for further studies on these factors associated with aseptic loosening with the use of newer implant designs. Furthermore, future studies should focus on whether the correction of other studied modifiable risk factors, such as tobacco use and obesity, leads to a tangible reduction in the incidence of aseptic loosening after THA or TKA.

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