Correlation between body mass index and two-stage revision failure of periprosthetic joint infection following total joint arthroplasty: A systematic review and meta-analysis

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Abstract
Background: Although the correlation between body mass index (BMI) and two-stage revision failure of periprosthetic joint infection (PJI) following total joint arthroplasty (TJA) have been frequently reported, the results remain controversial. Therefore, the correlation between them was systematically evaluated and meta-classified in this study.

Methods: Literature on the correlation between BMI and two-stage revision failure of PJI following TJA was retrieved in PubMed, Embase and Cochrane Library due May 2020. Stata 13.0 software and Cochrane Collaboration Review Manager software (RevMan version 5.3) were applied to data synthesis, subgroup analysis, analyses of publication bias, and sensitivity.

Results: A total of 15 observational studies included 1267 patients, of which 15 studies were included in systematic review and 11 studies in meta-analysis. Eight studies found a correlation between BMI and two-stage revision failure of PJI following TJA, but seven other studies found no correlation. Meta-analysis found that the risk of two-stage revision failure of PJI following TJA significantly boosted by 3.53 times in patients with BMI ≥ 30 kg/m² (OR = 3.53; 95% CI = 1.63–7.64 for the BMI ≥ 30 kg/m² vs. BMI < 30 kg/m²) and the risk of two-stage revision failure of PJI following TJA significantly increased by 2.92 times in patients with BMI ≥ 40 kg/m² (OR = 2.92; 95% CI = 1.06–8.03 for the BMI ≥ 40 kg/m² vs. BMI < 30 kg/m²). The subgroup analysis showed that significant association was observed among the studies performed in TKA (OR = 3.63; 95% CI = 2.27–5.82), but not among those conducted in THA (OR = 3.06; 95% CI = 0.42–22.19). A significant association remained consistent, as indicated by sensitivity analyses. Because there are too few studies that can be combined in the included studies, Egger’s and Begg’s tests were not performed.

Conclusion: Meta-analysis suggests that the risk of two-stage revision failure of PJI following TJA significantly boosted in obese patients. However, because there may be publication bias of this study, combined overall systematically evaluated and meta-analysis results, we cannot yet conclude that BMI is associated with two-stage revision failure of PJI following TJA.

Keywords
body mass index, periprosthetic joint infection, two-stage revision, systematic review, meta-analysis

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Introduction

Total joint arthroplasty is one of the most important surgical operations in the 21st century, it is widely used in advanced arthritis. Periprosthetic joint infection is one of the most severe complications that occur in patients who undergo total joint arthroplasty. At present, the two-stage revision is the main way to treat the periprosthetic joint infection following total joint arthroplasty, but there is still a risk of failure after the two-stage revision, reinfection rates reported in the literature range from 4 to 50%.1-4

More than 500 million people are obese worldwide, including one-third of men and women in the United States.5,6 Obesity increases the risk of osteoarthritis, and it is a key component in the sustained rise in the number of patients undergoing TJ A. Obesity (BMI [body mass index], ≥ 30 kg/m²) is a well-established risk factor for PJI.7-11 However, the role of obesity or BMI in two-stage revision failure of PJI following TJA is unclear.

The correlation between BMI and two-stage revision failure of PJI following TJA have been reported by many lately, but the results of studies are divergent and even controversial. In this study, we retrieved the published literature on two-stage revision failure of PJI following TJA from the inception of the PubMed database as an example, the literature search strategy is shown in Table 1.

Study selection criteria

Two independent investigators analyzed the initially selected articles to verify their relevance with the topic of the correlation between BMI and two-stage revision failure of PJI following TJA. Studies had to fulfill the following criteria for inclusion: outcome was two-stage revision failure of PJI following TJA; study design included case-control, retrospective and prospective cohorts, and cross-sectional studies; participants were selected without limitations to regions, ages, or social status. Trials were excluded according to following identifications: duplicate or overlapping data, animal experiments, conference abstracts, letters, and review articles. In case of any disagreement the results were discussed and unified by senior authors.

Data extraction

Data from the included studies were extracted and independently categorized by two of the authors in a predefined data extraction form. All disagreements were resolved by discussion. Design information, baseline population characteristics (mean age, sample size, and country), surgical approach, risk factors from all included studies were stratified into a standardized evidence table. All the data were rechecked to ensure accuracy. Study selections were shown in a PRISMA flow diagram.

Methodological quality assessment

The methodological quality of the included studies was evaluated by two independent reviewers based on the items of modified Newcastle-Ottawa Scale (NOS),14 comprising patient selection, study group comparability, and outcome assessment. The observational studies scored 0 to 9. Disparate opinions were discussed among the authors.

Statistical analysis

The meta-analysis and statistical analysis were performed using stata 13.0 software (Stata Corp, USA) and Cochrane Collaboration Review Manager software (RevMan version 5.3, Nordic Cochrane center, Copenhagen, Denmark). The
OR and 95% CIs were calculated. The I-square ($I^2$) test was adopted to evaluate the influence of heterogeneity on the output of the meta-analysis. $I^2$ values of 0%, 25%, 50%, and 75% represented no, low, medium, and high heterogeneity, respectively. Heterogeneity was tested using Cochran’s Q statistic and the $I^2$ metric: a $I^2 > 25\%$ was the cutoff of significant heterogeneity, and a fixed-effect model was used when a $I^2 < 25\%$; otherwise, a random effect model was preferred.\textsuperscript{15} A $p$ value of less than 0.05 was accepted as statistically significant. A sensitivity analysis\textsuperscript{16} was conducted by excluding one study at a time to evaluate the quality and consistency of the results. Egger’s and Begg’s

**Table 1. The Pubmed database literature search strategy.**

| #1 | “Prosthesis-related Infections” (Mesh) |
| #2 | Prosthesis-related infections |
| #3 | Prosthesis related infections |
| #4 | Infections, prosthesis-related |
| #5 | Prosthesis-related infection |
| #6 | Periprosthetic joint infection |
| #7 | Prosthetic joint infections |
| #8 | Periprosthetic infections |
| #9 | Infection of joint |
| #10 | Joint infection |
| #11 | PJI |
| #12 | #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 |
| #13 | “Reoperation” (Mesh) |
| #14 | Reoperation |
| #15 | Surgical revision |
| #16 | Surgery, repeat |
| #17 | Revision, surgical |
| #18 | Revision surgery |
| #19 | Surgery, revision |
| #20 | Repeat surgery |
| #21 | Revision, joint |
| #22 | Joint revision |
| #23 | Two-stage exchange |
| #24 | Two stage exchange |
| #25 | 2 stage exchange |
| #26 | Two-stage revision |
| #27 | Two stage revision |
| #28 | Two stage revision |
| #29 | second stage revision |
| #30 | TSR |
| #31 | #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 |
| #32 | “Body Mass Index” (Mesh) |
| #33 | Body mass index |
| #34 | Index, body mass |
| #35 | Quetelet index |
| #36 | Index, quetelet |
| #37 | Quetelet’s index |
| #38 | Quetelets index |
| #39 | BMI |
| #40 | Obesity |
| #41 | Fat |
| #42 | Obese |
| #43 | #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 |
| #44 | #12 AND #31 AND #43 |

OR and 95% CIs were calculated. The I-square ($I^2$) test was adopted to evaluate the influence of heterogeneity on the output of the meta-analysis. $I^2$ values of 0%, 25%, 50%, and 75% represented no, low, medium, and high heterogeneity, respectively. Heterogeneity was tested using Cochran’s Q statistic and the $I^2$ metric: a $I^2 > 25\%$ was the cutoff of
linear regression tests for publication bias were carried out. Subgroup analyses were performed according to different countries, operation methods, and effect type.

Results

Study selection process

As a result, 1231 references were initially retrieved, 539 were left after eliminating duplicate literature; and then 499 without high-relevant to our topic were discarded by reading titles and abstracts, and 40 studies remained. Finally, 25 full-text articles were abandoned because of the following reasons: 15 studies on irrelevant topics; five studies without full-text materials; three studies without sufficient data for extraction; one study was poster abstracts; one study was letters to the editor. Therefore, 15 observational studies with 1267 patients were included, of which 15 studies were included in systematic review and 11 studies in meta-analysis. The flow chart describing the selection process of the study was shown in Figure 1.

Study characteristics and methodological quality

15 observational studies about the correlation between BMI and two-stage revision failure of PJI following TJA were included in this study. The 15 included references encompassed retrospective cohort and retrospective case-control, with the publication years differing from 2013 to 2020. Four were conducted in Germany, five in the USA, four in China, Taiwan, and one in Italy, Canada, respectively. In the selected clinical trials, the sample size varied between 16 and 245. Eight studies found a correlation between BMI and two-stage revision failure of PJI following TJA, but seven other studies found no correlation. The failure rate of two-stage revision ranged from 6.8% to 42.86%. The basic characteristics of these studies are summarized in Table 2 and Table 3. In addition, all studies were evaluated as high methodological quality in accordance with the NOS scores.

Overall meta-analysis

$\text{BMI} \geq 30 \, \text{kg/m}^2 \text{ vs. } \text{BMI} < 30 \, \text{kg/m}^2$. Data from six studies\cite{17,20,21,23,25,27} on BMI $\geq 30 \, \text{kg/m}^2$ vs. BMI < 30 kg/m$^2$ were available for the meta-analysis by the random effect model due to a significant statistical heterogeneity ($I^2 = 83.4\%, p = 0.000$). It was found that the risk of two-stage revision failure of PJI following TJA significantly boosted by 3.53 times in patients with BMI $\geq 30 \, \text{kg/m}^2$ (OR = 3.53; 95% CI = 1.63–7.64), with high heterogeneity ($I^2 = 83.4\%, p = 0.000$; Figure 2). Thus,
Table 2. Characteristics of the included studies.

| Included studies | Study design     | Country     | Study characteristics | Study period | Adjustment factors                                                                 | Operation type | Conclusion by author |
|------------------|------------------|-------------|-----------------------|--------------|-----------------------------------------------------------------------------------|----------------|----------------------|
| Hoell S 2016     | Retrospective    | Germany     | 32 males, 73 ± 9.7 years | 2004–2008    | Sinus present, diabetes, smoking, BMI, Periprosthetic fracture, wound healing        | TKA            | Significant          |
|                  | cohort study     |             |                       |              | problems, corticosteroids, immune suppression, postoperative hematoma, blood         |                |                      |
| Watts CD 2014    | Retrospective    | USA         | 33 males, 60 ± 9 years (the morbidly obese group); 62 ± 8 years (the non-obese group.) | 1987–2007    | No be adjusted                                                                    | TKA            | Significant          |
|                  | cohort study     |             |                       |              |                                                                                  |                |                      |
| Houdek TM 2015   | Case-control     | USA         | 42 males, 63 ± 10 years | 1987–2007    | Alcoholism, smoking, BMI, primary bacteremia, other primary focus of infection,     | THA            | Significant          |
|                  | study            |             |                       |              | rheumatoid arthritis, gout, diabetes, malignancy, immune deficiency, congestive heart|                |                      |
|                  |                  |             |                       |              | failure, renal failure, liver cirrhosis, corticosteroids, chemotherapy, IV drug      |                |                      |
|                  |                  |             |                       |              | abuse                                                            |                |                      |
| Ahmad SS 2015    | Case-control     | Germany     | 69 males, 66 ± 12 years | 1999–2012    | No be adjusted                                                                    | THA            | Significant          |
|                  | study            |             |                       |              |                                                                                  |                |                      |
| Ma CY 2018       | Retrospective    | China       | 29 males, 70.1 ± 8.4 years | 2005–2015    | No be adjusted                                                                    | TKA            | Significant          |
|                  | cohort study     | Taiwan      |                       |              |                                                                                  |                |                      |
| Logroscino G 2019| Retrospective    | Italy       | 9 males, 69.4 ± 11.63 years | 2012–2016    | No be adjusted                                                                    | THA            | Significant          |
|                  | cohort study     |             |                       |              |                                                                                  |                |                      |
| Jhan SW 2017     | Retrospective    | China       | 43 males, 57 ± 14 years | 2005–2012    | Age, sex, age-adjusted CCI(1), BMI, ASA, previous revision surgery, McPherson       | TKA            | Significant          |
|                  | cohort study     | Taiwan      |                       |              | extremity grade, McPherson infection type, McPherson host grade, retained            |                |                      |
|                  |                  |             |                       |              | hardware (plates, screws, nails), additional re-debridment prior to reimplantation,  |                |                      |
|                  |                  |             |                       |              | dose of antibiotics in spacer, antibiotic cement used for reimplantation, use of   |                |                      |
|                  |                  |             |                       |              | antibiotic suppression after reimplantation, use of antibiotic suppression after     |                |                      |
|                  |                  |             |                       |              | reimplantation, adjusted using propensity score, staphylococcus species             |                |                      |
| Su YJ 2017       | Case-control     | China       | 18 males, Mean 47.3 (22–67) years | 2001–2012    | No be adjusted                                                                    | THA            | No significant       |
|                  | study            | Taiwan      |                       |              |                                                                                  |                |                      |
| Chen MJW 2020    | Retrospective    | China       | 30 males, Mean 69.5 (38–92) years | 2003–2013    | No be adjusted                                                                    | TKA            | No significant       |
|                  | cohort study     | Taiwan      |                       |              | Obesity, pre-operative CRP levels, cirrhosis, virulent pathogens, anaerobic          |                |                      |
|                  |                  |             |                       |              | pathogenesis, polymicrobial infection                                              |                |                      |
| Spiegel U 2013   | Retrospective    | Germany     | Unclear, Mean 61.7 (22–90) years | 2006–2008    | No be adjusted                                                                    | THA            | Significant          |
|                  | cohort study     |             |                       |              |                                                                                  |                |                      |
| Mortazavi SMJ    | Retrospective    | USA         | 62 males, Mean 67.5 (37–88) years | 1997–2007    | No be adjusted                                                                    | TKA            | No significant       |
|                  | cohort study     |             |                       |              |                                                                                  |                |                      |
| Claassen L 2015  | Retrospective    | Germany     | 21 males, 65.4 ± 10.6 years | 2011–2012    | No be adjusted                                                                    | TKA            | No significant       |
|                  | cohort study     |             |                       |              |                                                                                  |                |                      |
| Drexler M 2015   | Case-control     | Canada      | 43 males, Mean 68 (39–87) years | 2006–2012    | No be adjusted                                                                    | TKA            | No significant       |

THA = total hip arthroplasty, TKA = total knee arthroplasty, ASA = the American Society of Anesthesiologists, BMI = body mass index, TJA = total joint arthroplasty. CCI = Charlson Comorbidity Index.
Table 3. Characteristics of the included studies.

| Included studies | Treatment protocols                                                                 | The interval between the first and second stage | Replantation to reinfection time | Follow-up time |
|------------------|-------------------------------------------------------------------------------------|-----------------------------------------------|--------------------------------|----------------|
| Hoell S 2016¹⁷   | The protocol consisted of explantation of the prosthesis with implantation of a fixed antibiotic-loaded bone–cement spacer (1 g gentamicin and 1 g clindamycin/40 g cement) and at least 14 days of intravenous antibiotic administration, followed by at least 4 weeks of antibiotics orally. If necessary, additional antibiotics were mixed into the spacer, depending on the microbiological results, as an off-label application. After an interval of 14 days without antibiotics, C-reactive protein (CRP) was measured in serum. The second-stage procedure was performed 9–12 weeks after explantation. | 9–12 weeks                               | Mean 2.3 (0.6–3.7) years             | Mean 4.1 ± 2.7 years |
| Watts CD 2014¹⁸  | All patients placement of a high-dose antibiotic-impregnated spacer, organism-specific intravenous antibiotic therapy, and delayed reimplantation using antibiotic-impregnated cement. For all resections and reimplantations, vancomycin and/or an aminoglycoside were added to Simplex P bone cement (stryker orthopaedics, Mahwah, New Jersey) at the time of surgery. Antibiotic spacers contained a median of 3 g/batch of vancomycin (range, 0–4 g/batch) and 3.6 g/batch (range, 0–4.8 g/batch) of aminoglycoside for both the morbidly obese and non-obese groups. Reimplantations were performed using cement containing a median of 1 g/batch (range, 0–2 g/batch) of vancomycin and a median of 1.2 g/batch (range, 0–2.4 g/batch) of aminoglycoside for both the morbidly obese and non-obese groups. | Unclear                                  | 52 ± 29 months (the morbidly obese group); 48 ± 65 months (the non-obese group). | Mean 6.9 (5.1–10.8, the morbidly obese group); Mean 7.9 (5.0–11.1, the non-obese group). |
| Houdek TM 2015¹⁹ | All patients placement of a high-dose antibiotic-impregnated spacer, organism-specific intravenous antibiotic therapy, and delayed reimplantation. For all resections and reimplantations, vancomycin and/or an aminoglycoside (tobramycin or gentamicin) were added to Simplex cement (stryker, Mahwah, New Jersey) used in the surgery. The antibiotic spacers used in both the morbidly obese and non-obese groups contained a median of 3 g/batch (range, 0–4 g/batch) of vancomycin and 3.6 g/batch (range, 0–4.8 g/batch) of aminoglycoside. The reimplantations in both the morbidly obese and non-obese groups were performed with use of cement containing a median of 1 g/batch (range, 0–2 g/batch) of vancomycin and a median of 1.2 g/batch (range, 0–2.4 g/batch) of aminoglycoside. | Mean 34.3 (6–292) weeks; Mean 20.9 (6–208) weeks | 51 ± 47 months; 107 months               | Mean 8.1 (5.1–15.2); Mean 10.3 (5.1–20.8) |

(continued)
| Included studies | Treatment protocols | The interval between the first and second stage | Replantation to reinfection time | Follow-up time |
|------------------|---------------------|-----------------------------------------------|---------------------------------|----------------|
| Ahmad SS 2019<sup>20</sup> | With or without implantation of a gentamicin-impregnated cement spacer as a first-stage procedure (n = 9 [9%] temporary Girdlestone situation). All patients underwent 2 weeks of intravenous antibiotics followed by 10 weeks of oral antibiotics. After a 2-week interval without antibiotic treatment, a diagnostic joint aspiration was performed. Upon negative microbiology, the second-stage procedure was performed, which involved the removal of the cement spacer and the implantation of a revision implant. | Unclear | Unclear | Mean 60 (24–170) months |
| Ma CY 2018<sup>21</sup> | During the first stage, necrotic tissue was thoroughly debrided following removal of all implanted components. Antibiotic-loaded cement beads or a spacer, comprised of 40 g bone cement with 2–4 gm of vancomycin and 2–4 gm of piperacillin or ceftazidime, was inserted. After the first stage, intravenous organism-specific antibiotics were administered for at least 4 weeks followed by oral antibiotics for 2 weeks. | All reimplantations were performed after a minimum 2-week antibiotic holiday | 22 ± 19 months | 5.6 ± 2.3 (2–10) months |
| Logroscino G 2019<sup>22</sup> | The spacer’s implant (It’s not clear exactly) | 127.6 ± 90.1 days (in healed patients); 72.5 ± 33.6 days (in the failure ones) | Unclear | 23.8 ± 16.05 months |
| Jhan SW 2017<sup>23</sup> | Implantation of antibiotic-loaded cement beads. The regimen of antibiotics in the bone cement was determined according to the culture results: pre-operative joint aspiration or previous culture report. If the infecting microorganism could not be known at the time of resection arthroplasty, empirical combination of 2–4 g vancomycin and 2–4 g piperacillin per 40 g package of bone cement was used. Further debridement or exchange to sensitive antibiotic-loaded cement beads may be needed if the infection could not be controlled during the interim stage. Culture-specific parenteral antibiotics were given postoperatively for 4 weeks, followed by oral antibiotics for 2 weeks. | 20 ± 15.8 weeks | Unclear | 5.7 ± 2.4 years |
| Kurd MF 2010<sup>24</sup> | Two-stage exchange arthroplasty consisted of removal of total knee implants, as well as bone cement, irrigation, and debridement of the joint, and insertion of a static antibiotic-laden cement spacer block for at least 6 weeks (mean time to reimplantation 15 weeks; range, 6–62 weeks). The cement was impregnated with 4.0 g vancomycin and 3.6 g tobramycin for each 40 g Palacos I bone cement | Mean 15 (6–62) weeks | Unclear | Mean 35 (24–90) months |

(continued)
| Included studies | Treatment protocols | The interval between the first and second stage | Replantation to reinfection time | Follow-up time |
|------------------|---------------------|-----------------------------------------------|---------------------------------|----------------|
| Petis SM 2019<sup>15</sup> | Insertion of an antibiotic polymethylmethacrylate spacer, cement dowels were inserted into the femoral and tibial medullary canals for all spacers. All cement was Simplex P with combinations of vancomycin in 216 cases (mean, 2.7 g [range, 1–7 g] per batch) and tobramycin in 85 cases (mean, 2.8 g [range, 1.2–4.8 g] per batch) or gentamicin in 97 cases (mean, 3.4 g [range, 1.2–4.8 g] per batch). The mean duration of intravenous (IV) antibiotic therapy was 6 weeks (range, 4–26 weeks). | Mean 11 (5–54) weeks | Mean 47 (1–247) months | Mean 14 (2–25) years |
| Su YJ 2017<sup>26</sup> | Placement of an antibiotic-containing cement spacer. The spacer was static and mixed with 2.5 g vancomycin and 4 g meropenem per 40 g of cement. Intravenous antibiotic therapy for 6 weeks followed the resection. If the clinical physical examination and serology showed eradication of infection after 3 months without antibiotics treatment, reimplantation was performed. In the RHA, the prosthesis was fixed without cement after adequate debridement. The intraoperative pathology was arranged to confirm the eradication of infection before prosthesis implantation. | >3 months | 174 (42–270) days; 230 (90–300) days | 3(2–11) years |
| Chen MJW 2020<sup>27</sup> | Antibiotic-loaded bone cement mobile spacer implantation. Antibiotic-loaded bone cement was hand-mixed intraoperatively using four g of vancomycin powder with four g of ceftazidime powder per 40-g pack of polymethylmethacrylate (PMMA) polymer. Articulating mobile spacers were routinely used, except for cases when spacer dislocation was a major concern due to massive bone loss or lack of soft tissue integrity [13]. Pre-made silicone mold templates were utilized to construct mobile spacers. Culture-specific parenteral antibiotics were given postoperatively for 4 weeks, followed by 2 weeks of oral antibiotics. With a minimum interim period of 3 months and antibiotic holiday of 2 weeks. | >3 months | 13.1 ± 12.6 months | 65.1 (25–139) months |

(continued)
| Included studies | Treatment protocols                                                                 | The interval between the first and second stage | Replantation to reinfection time | Follow-up time       |
|------------------|--------------------------------------------------------------------------------------|-----------------------------------------------|---------------------------------|----------------------|
| Spiegel U 2013²⁸ | Implantation of an antibiotic-loaded cement spacer and a vacuum-assisted closure. For the most parts, the cement was loaded with gentamicin. In cases of bacterial resistance, vancomycin was used, according to the resistogram. Revision surgeries including changing of vacuum sealing, removing tissue specimens, and if necessary local debridement in cases of conspicuous tissue situation were continued until intraoperative biopsies showed no signs of bacterial growth. Subsequently, the antibiotic therapy was stopped. A surgical exploration followed after 4–7 days including sampling of bacterial biopsies, exchange of the spacer, secondary wound closure, and postoperative reuptake of antibiotic therapy for another 6 weeks. Another operative exploration was performed after an interval of 10–12 weeks. In cases of negative bacterial biopsies, the reimplantation of the prosthesis was performed with accompanying antibiotic prophylaxis for 6 weeks | 10–12 weeks                                  | Unclear                                        | 32 ± 8 months        |
| Mortazavi SMJ 2011²⁹ | Placement of an antibiotic-loaded cement spacer. The spacer was static versus dynamic at the discretion of the treating surgeon. It is standard at this institution to use 3 g vancomycin and 3.6 g tobramycin per 40 g of cement. After resection, the patient was treated with 6 weeks of intravenous antibiotics with a subsequent antibiotic holiday (2–6 weeks). Reimplantation was performed when deemed appropriate by the treating surgeon. At the time of reimplantation, antibiotic-loaded cement (1.2 g tobramycin and 1 g vancomycin per 40 g of cement) was used for fixation of the prosthesis | >6 weeks                                    | Unclear                                        | Mean 3.8 (2–9.4) years |

(continued)
| Included studies | Treatment protocols | The interval between the first and second stage | Replantation to reinfection time | Follow-up time |
|----------------|---------------------|-----------------------------------------------|--------------------------------|---------------|
| Claassen L 2015 | Placement of an antibiotic-loaded cement spacer. After the first stage the patient was started on vancomycin and clindamycin antibiotics until cultures returned with sensitivities. Then culture-directed antibiotics were administered intravenously for 2 weeks followed by antibiotic treatment per os for a total of 6 weeks of treatment. Eight weeks after first-stage procedure, with at least a 2-week antibiotic-free interval, a diagnostic aspiration was performed. When the final results of the aspiration were negative and there were no other signs of ongoing infection the second-stage procedure was performed. If signs or symptoms of infection persisted, we performed a second look operation with spacer exchange and re-debridement. A second course of antibiotic therapy was initiated based on the intraoperative and culture results for at least another 6 weeks. | 11.3 ± 5.6 weeks | Unclear | >12 months |
| Drexler M 2015 | An appropriately sized new femoral component and thin polyethylene liner were implanted (Nexgen LPS, Zimmer, Warsaw, IN), using three bags of Palacos cement (Heraeus, Wehrheim, Germany) that were mixed with 12 g of powdered vancomycin and 12 g powdered ceftazidime (4 g of each antibiotic per bag). The implants were then cemented into place with as much cement as possible packed between the bone surfaces and the implants allowing a 0–90 range of motion. The wound was closed in a standard fashion. Drains were not utilized to avoid unwarranted loss of antibiotic-loaded fluid. Antibiotics were administered intravenously for 6 weeks through a peripherally inserted central catheter (PICC line). | Mean 4.9 (1.5–18) months | Unclear | 36.2 (24–85) months |
subgroup analyses were conducted to investigate the potential factors that could substantially affect the between-study heterogeneity.

**BMI ≥ 40 kg/m² vs. BMI < 30 kg/m².** Data from two studies\(^{18,19}\) on BMI ≥ 40 kg/m² vs. BMI < 30 kg/m² were available for the meta-analysis by the random effect model due to a significant statistical heterogeneity ($I^2 = 71.3\%$, $p = 0.062$). It was found that the risk of two-stage revision failure of PJI following TJA significantly increased by 2.92 times in patients with BMI ≥ 40 kg/m² ($OR = 2.92; 95\% CI = 1.06–8.03$; Figure 3).

**Other body mass index comparisons.** Data from three studies\(^{22,24,28}\) on BMI (continuous variable) were available for the meta-analysis by the random effect model due to a significant statistical heterogeneity ($I^2 = 56\%, p = 0.10$). The results show that there were nonsignificant differences in

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**Figure 2.** The meta-analysis of the correlation between BMI (BMI ≥30 kg/m² vs. BMI <30 kg/m²) and two-stage revision failure of PJI following TJA.

**Figure 3.** The meta-analysis of the correlation between BMI (BMI ≥40 kg/m² vs. BMI <30 kg/m²) and two-stage revision failure of PJI following TJA.
BMI between the failure group and the success group (SMD = −0.48; 95% CI = −1.20–0.23; Figure 4).

**Subgroup analyses (BMI ≥ 30 kg/m² vs. BMI < 30 kg/m²)**

**Subgroup analysis of different effect type.** Subgroup analyses of different effect type were conducted. The subgroup analysis showed that significant correlations were basically consistent, significant association were observed among the studies performed in odds ratio (OR = 1.22; 95% CI = 1.07–1.40) and hazard ratio (OR = 4.10; 95% CI = 2.64–6.36). When original studies used hazard ratio as the effect type, there was no heterogeneity (I² = 0.00%, p = 0.467; Figure 5).

**Subgroup analysis of different countries.** Subgroup analyses of different countries were conducted. The subgroup analysis showed that significant association were observed among the studies performed in China, Taiwan (OR = 5.41; 95% CI = 2.51–11.68) and USA (OR = 3.10; 95% CI = 1.61–5.95), but not among those conducted in Germany (OR = 2.191; 95% CI = 0.57–8.44). And the heterogeneity was low when studies performed in China, Taiwan (I² = 12.3%, p = 0.320; Figure 6).

**Subgroup analysis of different operation method.** Subgroup analyses of different operation method were conducted. The subgroup analysis showed that significant association were observed among the studies performed in TKA (OR = 3.63; 95% CI = 2.27–5.82), but not among those conducted in THA (OR = 3.06; 95% CI = 0.42–22.19). And the heterogeneity was no when studies performed in TKA (I² = 0.0%, p = 0.653; Figure 7).

**Sensitivity analyses (BMI ≥ 30 kg/m² vs. BMI < 30 kg/m²)**

The sensitivity analysis was performed to assess whether individual studies would affect the overall results. We evaluated the effect of each study on the methodological quality through the sequential exclusion of single studies. The results showed that there was a nonsignificant
difference in the stability of the results (Figure 8), which validated the rationality and reliability of our analysis.

**Evaluation of publication bias**

Due to the insufficient number of included studies in the meta-analysis, evaluation of publication bias was not conducted (Including visual inspection of funnel plots, Egger and Begg tests).

**Discussion**

In this study, we conducted 15 observational studies which included 1267 patients, of which 15 studies were included in
Among the studies performed in TKA, analysis showed that significantly boosted in obese patients. The subgroup analysis showed that significant association were observed among the studies performed in TKA (OR = 3.63; 95% CI = 2.27–5.82), but not among those conducted in THA (OR = 3.06; 95% CI = 0.42–22.19). A significant association remained consistent, as indicated by sensitivity analyses. The two-stage revision is the gold standard for the treatment of periprosthetic joint infection following total joint arthroplasty, but there was still a 6.8%–42.86% failure rate. Previous meta-analysis showed that obesity was closely related to periprosthetic joint infection following total joint arthroplasty, however, the association between BMI and two-stage revision failure of PJI following TJA remains unclear. Though the correlation between BMI and two-stage revision failure of PJI following TJA has been rapidly reported, their results still remain divergent and even controversial.\(^{17–31}\) Our meta-analysis found that the risk of two-stage revision failure of PJI following TJA significantly boosted by 3.53 times in patients with BMI \(\geq 30\) kg/m\(^2\) (BMI \(\geq 30\) kg/m\(^2\) vs. BMI < 30 kg/m\(^2\)) and 2.92 times in patients with BMI \(\geq 40\) kg/m\(^2\) (BMI \(\geq 40\) kg/m\(^2\) vs. BMI < 30 kg/m\(^2\)). This shows a significant increase in the failure rate of two-stage revision in obese patients. When subgroup analysis was performed in different surgical methods, in the THA group, there was no statistically significant difference in failure rates between obese and non-obese patients, this may attribute to the insufficient inclusion of eligible studies. Systematic review found that nearly half of the original studies concluded that BMI was not associated with two-stage revision failure, therefore, we cannot yet conclude that BMI is associated with two-stage revision failure of PJI following TJA.

As the passages have exposed, two significant advantages of our study are clear. Firstly, as the correlation between BMI and two-stage revision failure of PJI following TJA were controversial, this meta-analysis assessed the potential correlation between BMI and two-stage revision failure of PJI following TJA through a thorough systematic study with rigorous analytical methods. Secondly, the rationality and reliability of our meta-analysis have been prudently and significantly improved in that the overall comprehensive estimation is based on a large sample size. In addition, sufficient sensitivity analysis has been carried out to ensure the reliability of this study.

The current systematically evaluated and meta-analysis has the following limitations and must be considered before our results are accepted. First, the selected studies in the systematically evaluated and meta-analysis were published between 2013 and 2020, the outcome evaluation indexes of the included studies were not completely consistent, and most of them did not adjust for confounding factors, meta-analysis evaluation data is insufficient. Second, the research included in this analysis is insufficient, and potential publication bias still exists. Third, this study only includes references in English. Therefore, we may have lost data from those in other languages.

**Conclusion**

In summary, our meta-analysis suggests that the risk of two-stage revision failure of PJI following TJA significantly boosted in obese patients. However, because there may be publication bias of this study, combined overall systematic review and meta-analysis results, we cannot yet conclude that BMI is associated with two-stage revision failure of PJI following TJA. This conclusion needs to be verified by more prospective studies.

**Author contributions**

(I) Conception and design: X Deng; (II) Administrative support: H Wang; (III) Provision of study materials or patients: J Guo, S Wu, W Chen; (IV) Collection and assembly of data: J Guo, H Wang; (V) Data analysis and interpretation: J Guo, S Wu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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