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Association of malnutrition with periprosthetic joint and surgical site infections after total joint arthroplasty: a systematic review and meta-analysis

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SUMMARY

Background: A growing body of evidence associates malnutrition with several adverse outcomes.
Aim: To investigate the link between malnutrition with surgical site and periprosthetic joint infections (SSIs and PJIs) following total knee and hip arthroplasty (TKA and THA) through a comprehensive meta-analysis of observational studies.
Methods: A systematic search was conducted on PubMed and Scopus databases through December 2018, and recent proceedings of major orthopaedic meetings. Data from eligible studies were extracted and synthesized; pooled odds ratios (ORs) with 95% confidence intervals (CIs) were estimated.
Findings: Seven publications were included, reporting eight independent cohort studies with >250,000 subjects. SSIs and PJIs were more likely to develop in malnourished patients (OR: 2.49; 95% CI: 2.13–2.90; and 3.62; 2.33–5.64, respectively). The association of SSI with malnutrition was evident both after TKA (2.42; 1.94–3.02) and after THA (2.66; 1.64–4.30). Similarly, PJI was associated with malnutrition after TKA (2.55; 1.10–5.91) and after THA (3.10; 1.84–5.25). Finally, PJI correlated with malnutrition both after primary arthroplasty (3.58; 1.82–7.03) and revision arthroplasty (3.96; 2.47–6.33). The subgroup analysis by study setting confirmed the relationship between PJI and malnutrition in hospital (6.02; 3.07–11.81) and population-based (2.80; 1.76–4.44) studies.

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Conclusion: Malnutrition is associated with PJIs and SSIs after total joint arthroplasty. Further high-quality research is warranted to confirm or refute these findings.

Introduction

Periprosthetic joint infection (PJI) after total joint arthroplasty (TJA) is one of the leading causes of failure for knee and hip replacements. Concern about this complication has increased over the years, as the annual number of performed arthroplasties is constantly rising. The current incidence of PJI is estimated to be 0.2–2.0%, and there are predictions for 38,000–270,000 PJIs annually in the USA by 2030 [1–4]. During the last decade, a great effort was made to develop guidelines for PJI diagnosis and treatment, with international consensus meetings held for this purpose reflecting the importance of the issue [5]. These meetings have highlighted potential risk factors for PJI, including malnutrition.

The effects of malnutrition on postoperative outcomes following orthopaedic surgeries have been widely studied. There is a growing body of literature linking malnutrition with various complications including wound healing problems, persistent wound drainage, and susceptibility to infections [6–9]. The mechanism by which malnutrition may result in increased rates of complications involves impairment of the immune system to fight infections due to reduced number of lymphocytes, and impairment of wound healing due to reduced collagen synthesis [10]. Since clinical signs and symptoms of malnutrition are not easy to detect (except from severe cases), several methods to detect malnutrition have been developed including anthropometric tests, laboratory values, and scoring systems [10–12]. Among them, the most widely used laboratory parameters for evaluation of malnutrition include albumin, transferrin, and total lymphocyte count [5].

Because of the association of malnutrition with adverse outcomes following joint arthroplasties, preoperative screening is recommended in patients suspected for malnutrition. The optimal method for nutritional status improvement is not clear. Strategies include administration of high-protein supplements, vitamin and mineral supplementation, and increased consumption of calories [5].

Although several studies have been conducted to evaluate the association of malnutrition with postoperative complications, the relationship between suboptimal nutritional status and SSI or PJI following total knee and hip arthroplasty (TKA and THA) has not yet been clearly determined. This study aimed to evaluate this association through a comprehensive meta-analysis of epidemiological studies.

Methods

Our study protocol is registered with the International Prospective Register of Systematic Reviews (PROSPERO: http://www.crd.york.ac.uk/prospero) [13]. The current work was performed in accordance with the Cochrane Handbook, and with the MOOSE and PRISMA guidelines [14–16].

Data sources and searches

We systematically searched PubMed and Scopus databases from inception to December 31st 2018. Our search strategy combined terms related to the type of surgery ('knee arthroplasty', 'hip arthroplasty', or 'joint replacement') with those related to exposure ('malnutrition', 'hypoalbuminemia', or 'albumin') and outcomes ('infection', or 'complication'). The search was restricted to articles published in English. Two authors (A.G.T. and D.V.P.) independently examined titles and abstracts of the studies identified in the search, excluding those that were clearly irrelevant. The full text of the selected articles was carefully studied to determine whether it contained information on the topic of interest. Their reference lists were carefully scanned to identify any eligible studies missed by the electronic database search. Finally, the Cochrane Library was searched, as well as recent international conference proceedings (Annual Congress of the European Federation of National Associations of Orthopaedics, and Annual Meeting of the American Academy of Orthopedic Surgeons; 2015–2018), for additional eligible studies.

Selection criteria

We considered observational epidemiological studies (retrospective or prospective) investigating the association of malnutrition with SSI and PJI in patients having undergone total joint arthroplasty. Studies were eligible if they included patients with total knee or hip arthroplasty, evaluated malnutrition as a risk factor for SSI and/or PJI, and reported (or provided sufficient data to determine) an effect estimate with its confidence interval (CI). All articles were considered irrespective of publication type; thus, we did not exclude articles published as short reports or conference abstracts, even though critical appraisal of such publications may be limited.

Because of the well-known variation in the definition of PJI, outcomes were categorized as PJI when: (i) revision arthroplasty was required for elimination of the infection, (ii) they were organ space infections according to the Centers for Disease Control and Prevention classification for surgical site infections, or (iii) they met the criteria of the Musculoskeletal Infection Society for PJI [17–19]. On the other hand, malnutrition was defined based on laboratory values: albumin <3.5 g/dL, or transferrin <200 mg/dL, or total lymphocyte count (TLC) <1500 mm^3 [20].

For multiple studies involving the same population, data from the most up-to-date or comprehensive one (higher number of cases/complete data) were included.

Data extraction and quality assessment

Two authors (A.G.T. and D.V.P.) independently abstracted the following information from each study in a standardized data abstraction form: first author's last name, publication year, geographical setting, study design and setting

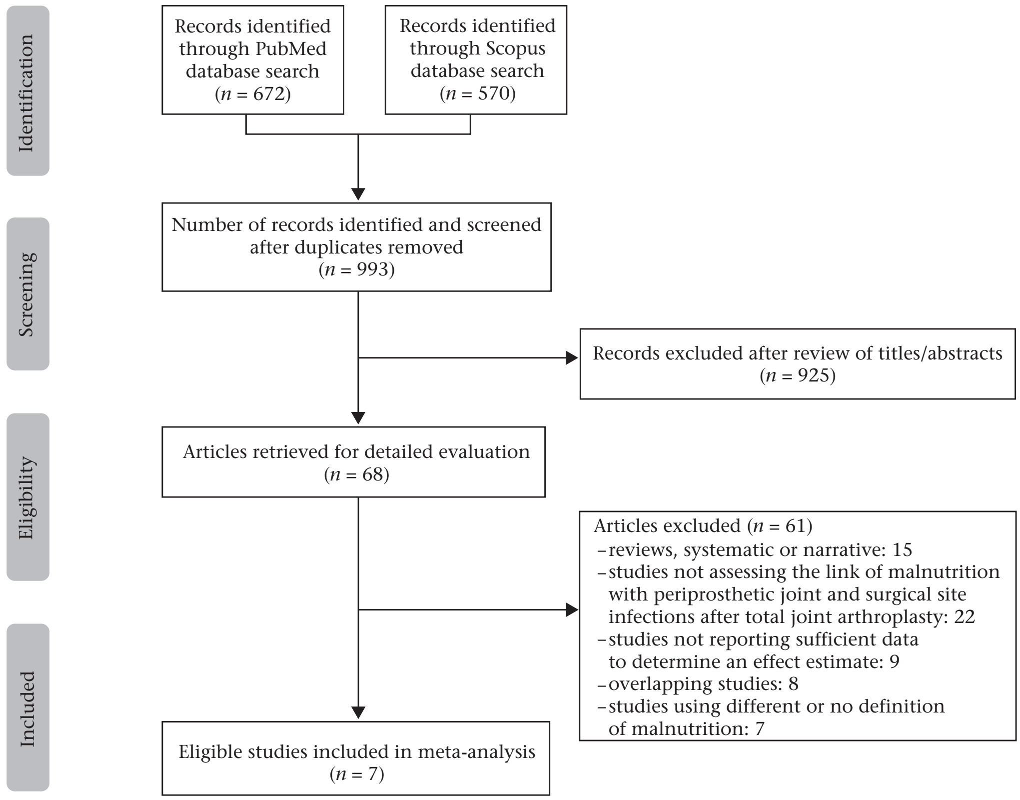

Figure 1. Summary of the evidence search and selection process.

(population- or hospital-based), duration of follow-up, number of subjects, population characteristics (age, sex), operated joint (knee, hip), type of surgery (primary or revision arthroplasty), definition of malnutrition (albumin, transferrin or TLC), reported outcomes (SSI, PJI), and the estimated effect size with its 95% CI. In studies reporting more than one estimate of effect, the 'most adjusted' estimate was extracted, i.e. the estimate that reflected the greatest degree of control for potential confounders. Any discrepancies in data extraction were settled by consensus, referring back to the original article.

The risk of bias in included studies was examined using the Newcastle–Ottawa Scale, a validated tool that incorporates information on three predefined domains: selection of the study groups; comparability of the groups; and ascertainment of either the exposure or outcome of interest for case–control or cohort studies, respectively [21]. Studies could be awarded a total of four stars for selection, two for comparability, and three for assessment of the outcome or exposure, for a total of nine stars per study. Studies scoring at least six stars were considered as having low risk of bias (i.e. high quality).

Quantitative data synthesis

Pooled effect estimates and 95% CIs were calculated under the assumption of a random-effects model (DerSimonian–Laird approach) [22]. Publication bias was evaluated using the Begg's and Egger's tests, as well as the funnel plot [23,24]. To examine whether the results of the studies were homogeneous, Cochran's *Q*-test was used, with $P \leq 0.10$ considered significant [25]. We also calculated the I^2-statistic, which quantifies the proportion of total variation across studies that is due to heterogeneity rather than chance; cut-offs of <30%, 30–59%, 60–75% and >75% were used to suggest low, moderate, substantial, and considerable heterogeneity, respectively [26,27].

To examine the stability of results and explore heterogeneity, the studies were grouped on the basis of study setting (population-based registries or databases vs hospital-based studies), operated joint, type of arthroplasty (primary vs revision), and separate analyses were conducted. Pooled effect estimates derived from subgroup analyses were compared with tests of interaction [28].

For statistical analysis, R software (version 3.5.2) was used [29]. For all the tests (except for heterogeneity), $P < 0.05$ indicates statistical significance. All *P*-values are two-tailed.

Results

Search results

After removal of duplicate publications, our search yielded 993 citations (Figure 1). Studies that were clearly irrelevant to the topic of interest were excluded and detailed evaluation through full text reviews was subsequently performed in 68 studies. The reference lists of these studies were also scanned for any relevant studies. Finally, seven publications met eligibility criteria and were included [30–36]. One publication reported two studies; its analysis regarding malnutrition and surgical infections was performed in two different populations (with TKA and THA, respectively) [31]. Eight studies were not included because they had evaluated the association of

Table I
Studies included in the meta-analysis

Study	Country	Time period	Design	Setting	Surgery	Exposure	Outcomes	No. of subjects	'Infection' cases	OR	(95% CI)	Control for potential confounding factors[a]
Ryan *et al.* (hip) [31]	USA	2005–2015	Cohort	Database	THA	Malnutrition	SSI	48,751	605	2.47	(1.88–3.24)	Unadjusted for SSI, adjusted
							PJI		126	3.10	(1.84–5.25)	for PJI: 1–4
Ryan *et al.* (knee) [31]	USA	2005–2015	Cohort	Database	TKA	Malnutrition	SSI	79,661	678	1.92	(1.44–2.55)	Unadjusted for SSI, adjusted
							PJI		122	1.60	(0.81–3.18)	for PJI: 1–4
Haro-Gómez *et al.* [30]	Mexico	2012–2014	Cohort	Hospital	THA	Malnutrition	SSI	75	9	6.12	(1.17–31.87)	Unadjusted
Roche *et al.* [32]	USA	2007–2015	Cohort	Database	TKA	Malnutrition	SSI	114,379	14,422	2.72	(2.60–2.84)	Unadjusted
Blevins *et al.* [33]	USA	2000–2016	Cohort	Hospital	TJA	Malnutrition	PJI	8796	112	4.69	(2.42–9.08)	Adjusted, NR
Kamath *et al.* [34]	USA	2006–2014	Cohort	Database	Revision TKA	Malnutrition	SSI	4551	153	2.48	(1.74–3.53)	Unadjusted for SSI, adjusted
							PJI		77	3.79	(2.31–6.21)	for PJI: 1, 4–8
Yi *et al.* [35]	USA	2002–2010	Cohort	Hospital	Revision TJA	Malnutrition	PJI	375	12	5.85	(1.31–26.05)	1, 2, 5, 6, 7, 9
Courtney *et al.* [36]	USA	2013	Cohort	Hospital	TJA	Malnutrition	PJI	670	7	18.75	(3.57–98.29)	Unadjusted

CI, confidence interval; NR, not reported; OR, odds ratio; PJI, periprosthetic joint infection; SSI, surgical site infection; THA, total hip arthroplasty; TJA, total joint arthroplasty; TKA, total knee arthroplasty.
[a] 1, sex; 2, BMI; 3, smoking status; 4, American Society of Anesthesiologists (ASA) classification; 5, age; 6, Charlson Comorbidity Index (CCI) score; 7, race; 8, year of surgery; 9, insurance type.

interest on same populations with included studies [37–44]. There was full agreement between the two independent reviewers regarding study selection.

The eight included studies evaluated malnutrition as a risk factor for the development of SSI or PJI after total knee or hip arthroplasty, and they reported (or provided sufficient data to determine) an effect estimate along with its 95% CI. All studies were retrospective cohort studies, with three being population-based [31,32,34] and the remaining four being hospital-based [30,33,35,36] studies. The number of SSI cases ranged from seven to 14,422 with a total number of 16,000 cases, and the number of PJI cases ranged from seven to 126 with a total number of 456. The mean age of patients ranged from 60.8 to 67.0 years. Five out of the six studies assessing risk for PJI were adjusted for confounding factors [31,33–35], whereas none of the five studies assessing the risk for SSI was controlled for any confounder [30–32,34]. Only one study was conducted outside of the USA (Mexico) [30]. Publication dates ranged from 2015 to 2018. Study characteristics are presented in Table I.

Risk of bias assessment using the Newcastle–Ottawa scale

A total number of seven stars was accredited to five studies [31,33–35]; one study scored six [32], one study scored five [36], and one study scored four stars [30]. Overall, six out of eight studies had a total score of six or more and were classified as high-quality studies according to the Newcastle–Ottawa scale (Supplementary Table S1).

Results of meta-analyses

Association of malnutrition with PJI and SSI

Six studies reported specific data on PJI [31,33–36], whereas five studies investigated the impact of malnutrition on SSI [30–32,34]. Development of PJI after joint arthroplasty was 3.6 times more likely to occur in malnourished patients (OR: 3.62; 95% CI: 2.33–5.64) (Figure 2). Likewise, development of SSI after joint arthroplasty was significantly associated with presence of preoperative malnutrition (OR: 2.49; 95% CI: 2.13–2.90) (Figure 3). The estimated *P*-values for the Begg's and Egger's tests were 0.45 and 0.99 for PJI, 0.99 and 0.59 for SSI, suggesting a low probability of publication bias. The funnel plots for PJI and SSI did not indicate any asymmetry (Supplementary Figures S1 and S2). The I^2-values were 52% and 44% for PJI and SSI, respectively, indicating moderate heterogeneity among the included studies for both outcomes (Table II).

Analysis by operated joint (TKA vs THA)

Specific data on SSI in patients with THA were reported in two studies [30,31], whereas three studies reported specific data on SSI in patients with TKA [31,32,34]. Only one study specifically investigated PJI in patients with THA [31], and two studies analysed PJI in patients with TKA [31,34]. Regarding SSI, a significant association with malnutrition was identified after both TKA (OR: 2.42; 95% CI: 1.94–3.02) and THA (OR: 2.66; 95% CI: 1.64–4.30) (Figure 4). PJI after TKA was 2.5 times more likely to occur in malnourished patients (OR: 2.55; 95% CI: 1.10–5.91) (Figure 5). A similar association was identified in

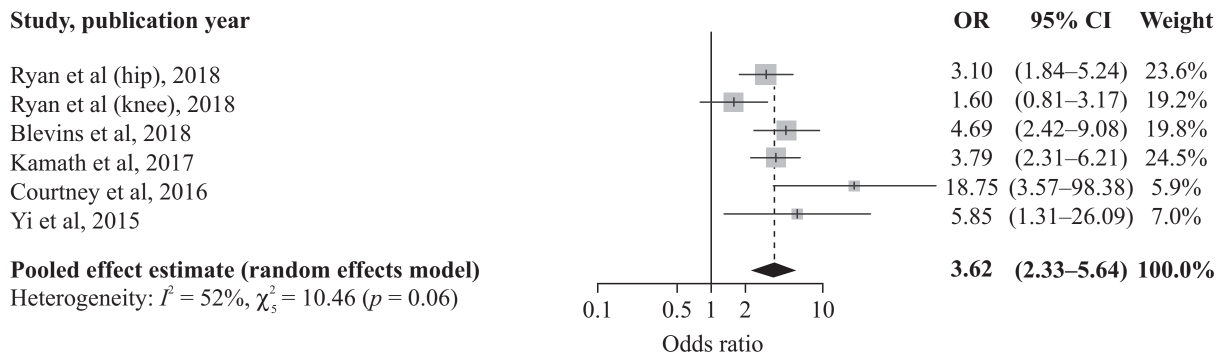

Figure 2. Forest plot for periprosthetic joint infections. OR, odds ratio; CI, confidence interval.

one study specifically analysing PJI in 48,751 THA patients (OR: 3.10; 95% CI: 1.84–5.25) [31].

Analysis by type of surgery (primary vs revision)

The association of malnutrition with PJI after primary arthroplasty was examined in four studies [31,33,36], whereas two studies reported data on PJI after revision (for aseptic reasons) arthroplasty [34,34]. There was a strong association between PJI and malnutrition after primary arthroplasty (OR: 3.58; 95% CI: 1.82–7.03) (Figure 6). A similar association was seen for revision arthroplasty (OR: 3.96; 95% CI: 2.47–6.33) (Figure 6). The test of interaction did not reveal any significant difference (primary vs revision arthroplasty, $P = 0.81$).

Analysis by setting (hospital-based vs population-based)

The subgroup analysis by study setting showed malnutrition to be strongly associated with PJI in both hospital-based (OR: 6.02; 95% CI: 3.07–11.81) and population-based studies (OR: 2.80; 95% CI: 1.76–4.44 (Figure 7). Though population-based studies are of higher quality compared to hospital-based studies (being less susceptible to bias), the two pooled effect-estimates were not significantly different (test of interaction for hospital-based vs population-based studies, $P = 0.06$).

Discussion

Our systematic review and meta-analysis assessed the relationship between malnutrition and postoperative surgical infection following total knee and hip arthroplasty. Seven publications reporting eight independent cohort studies (with >250,000 subjects) were analysed, and a strong association between malnutrition and postoperative surgical infections was identified. The association of SSI and PJI with malnutrition was evident both after TKA and THA. Interestingly, PJI correlated with malnutrition both after primary and revision arthroplasty, while the analysis by study setting confirmed the relationship of malnutrition with PJI in both hospital- and population-based studies.

To the best of our knowledge, this is the most comprehensive meta-analysis evaluating the association of malnutrition with surgical infections (including SSI and PJI) after total hip and knee arthroplasty. Recently, a systematic review and meta-analysis examined the association of malnutrition with wound complications and infections following TJA; however, this study analysed data regarding wound complications, but did not assess the association of malnutrition with surgical infections [45]. Wound complication is a vague term, which substantially differs from surgical infection; it includes different adverse events such as delayed healing, wound dehiscence or persistent wound drainage. Another meta-analysis by Zhu *et al.* assessed the impact of several factors including malnutrition on the development of periprosthetic joint infections following TJA [46]. Data solely from two studies on malnutrition were synthesized (OR: 2.94; 95% CI: 1.97–5.53). In comparison with these studies, our meta-analysis included a substantially higher number of studies, and infection cases, since five out of seven studies included were published in 2018 (Gu *et al.* [45] searched the literature up to December 2017, and Zhu *et al.* [46] searched the literature up to March 2014).

Our study has strengths. This is the first meta-analysis examining the association of malnutrition with PJI, and the

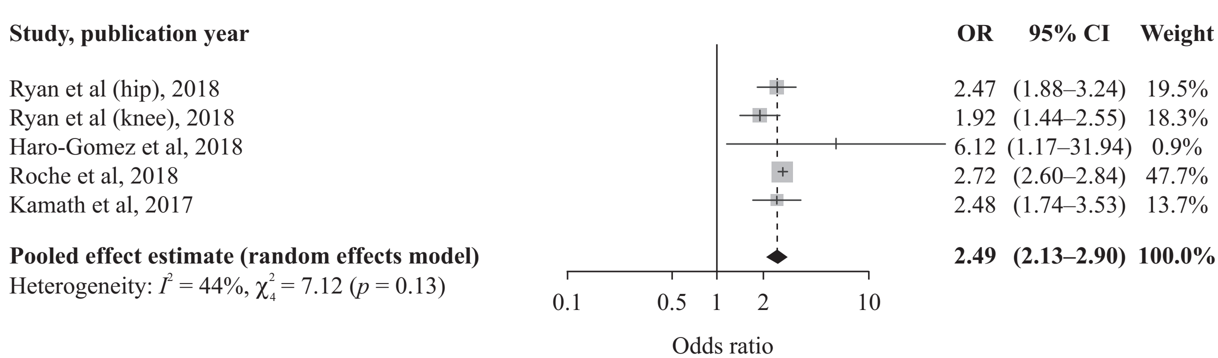

Figure 3. Forest plot for surgical site infections. OR, odds ratio; CI, confidence interval.

Table II
Meta-analysis results

Infections	No. of studies	Random-effects model		Tests of homogeneity			Tests of publication bias	
		OR	(95% CI)	*Q*-value (d.f.)	*P*-value	I^2	Begg's *P*-value	Egger's *P*-value
Surgical site infections								
All studies	5	2.49	(2.13–2.90)	7.12 (4)	0.13	44%	0.99	0.49
Total knee arthroplasty	3	2.42	(1.94–3.02)	5.79 (2)	0.06	65%	0.99	0.38
Total hip arthroplasty	2	2.66	(1.64–4.30)	1.13 (1)	0.29	11%	–	–
Periprosthetic joint infections								
All studies	6	3.62	(2.33–5.64)	10.46 (5)	0.06	52%	0.45	0.31
Total knee arthroplasty	2	2.55	(1.10–5.91)	4.01 (1)	0.05	75%	–	–
Total hip arthroplasty	1	3.10	(1.84–5.25)	–	–	–	–	–
Primary arthroplasty	4	3.58	(1.82–7.03)	9.61 (3)	0.02	69%	0.73	0.40
Revision arthroplasty	2	3.96	(2.47–6.33)	0.29 (1)	0.59	0	–	–
Hospital setting	3	6.02	(3.07–11.81)	2.32 (2)	0.31	14%	0.30	0.40
Database setting	3	2.80	(1.76–4.44)	4.09 (2)	0.13	51%	0.30	0.06

OR, odds ratio; CI, confidence interval; d.f., degrees of freedom.

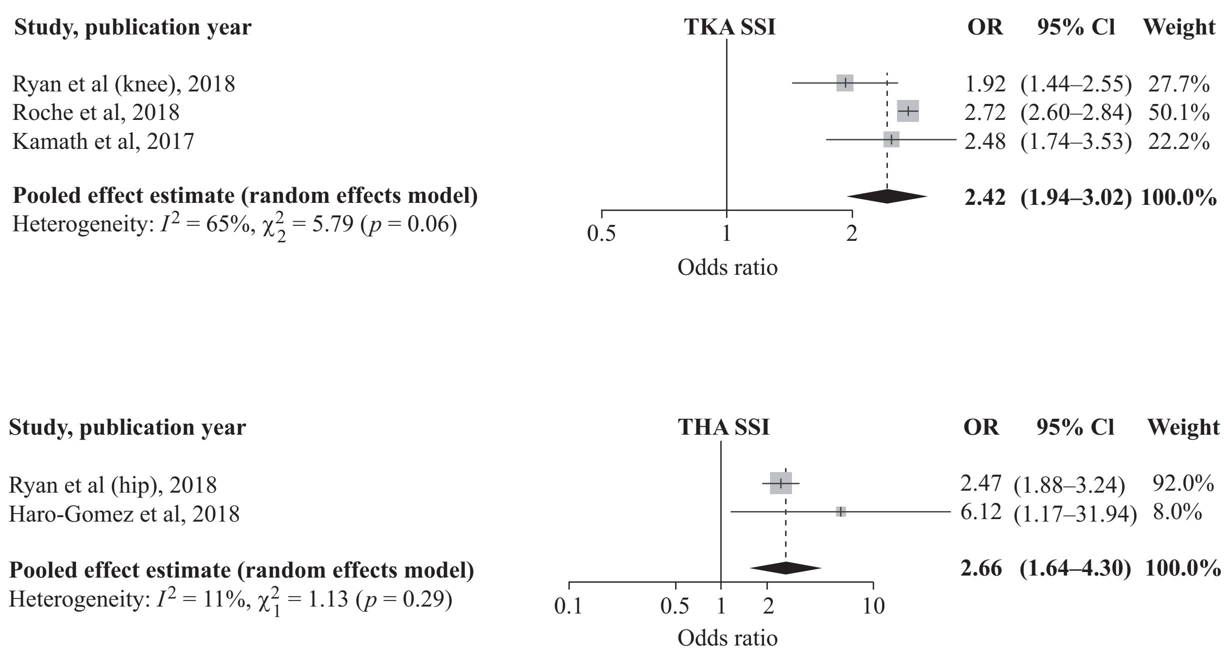

Figure 4. Forest plot for surgical site infections after TKA and THA. TKA, total knee arthroplasty; THA, total hip arthroplasty; SSI, surgical site infection.

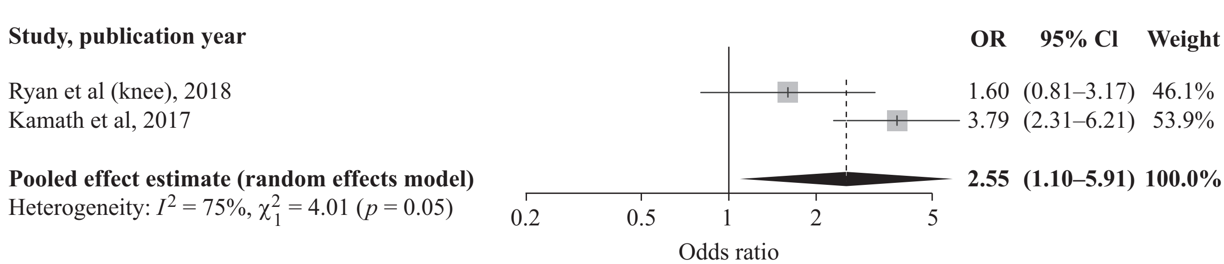

Figure 5. Forest plot for periprosthetic joint infections after total knee arthroplasty. OR, odds ratio; CI, confidence interval.

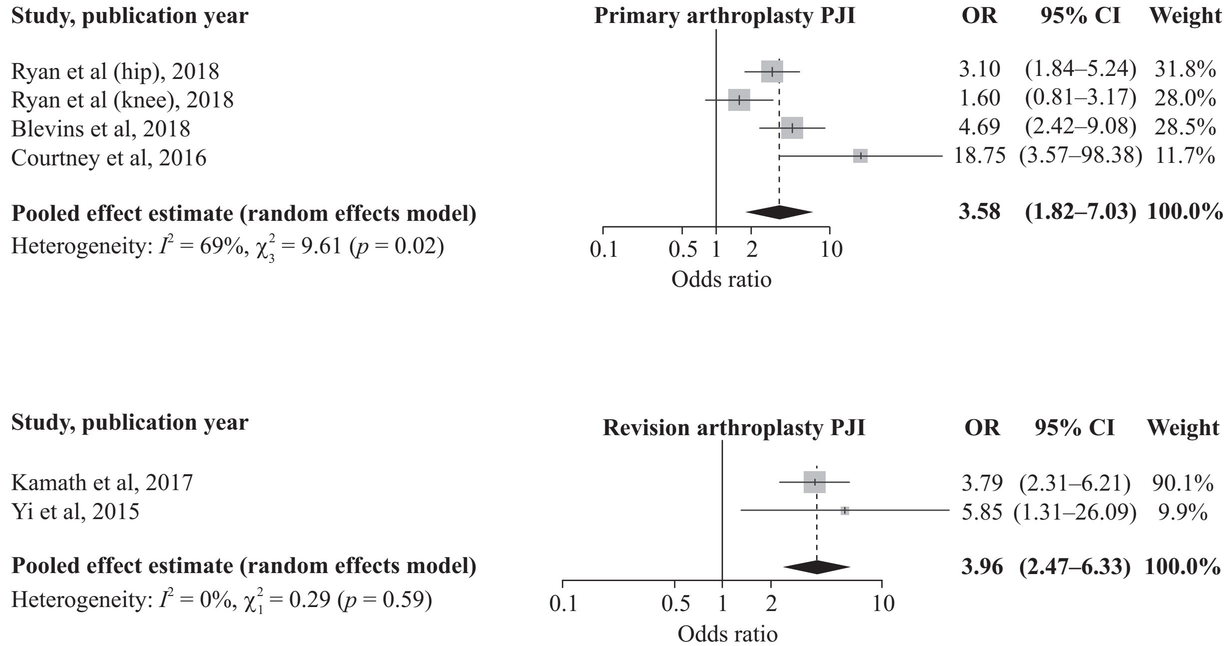

Figure 6. Forest plot for periprosthetic joint infections after primary and revision arthroplasty. OR, odds ratio; CI, confidence interval; PJI, periprosthetic joint infection.

most comprehensive one regarding SSI. The robust criteria used for the definition of PJI further enhance the reliability of our findings, ensuring that the assessed outcomes indeed represented these devastating complications. Finally, the fact that the pooled effect estimate for PJI was based solely on data from studies that controlled for potential confounders further adds to the reliability of our findings.

Nevertheless, our study has several limitations. First, most of the primary studies had a short follow-up duration (about 30–90 days), thus cases of chronic PJI and SSI may have been missed. Therefore, this meta-analysis mostly evaluates acute PJI and SSI. Second, a moderate between-studies heterogeneity was seen (I^2: 44% for SSI and 52% for PJI). This may be partially explained by differences in study designs and settings

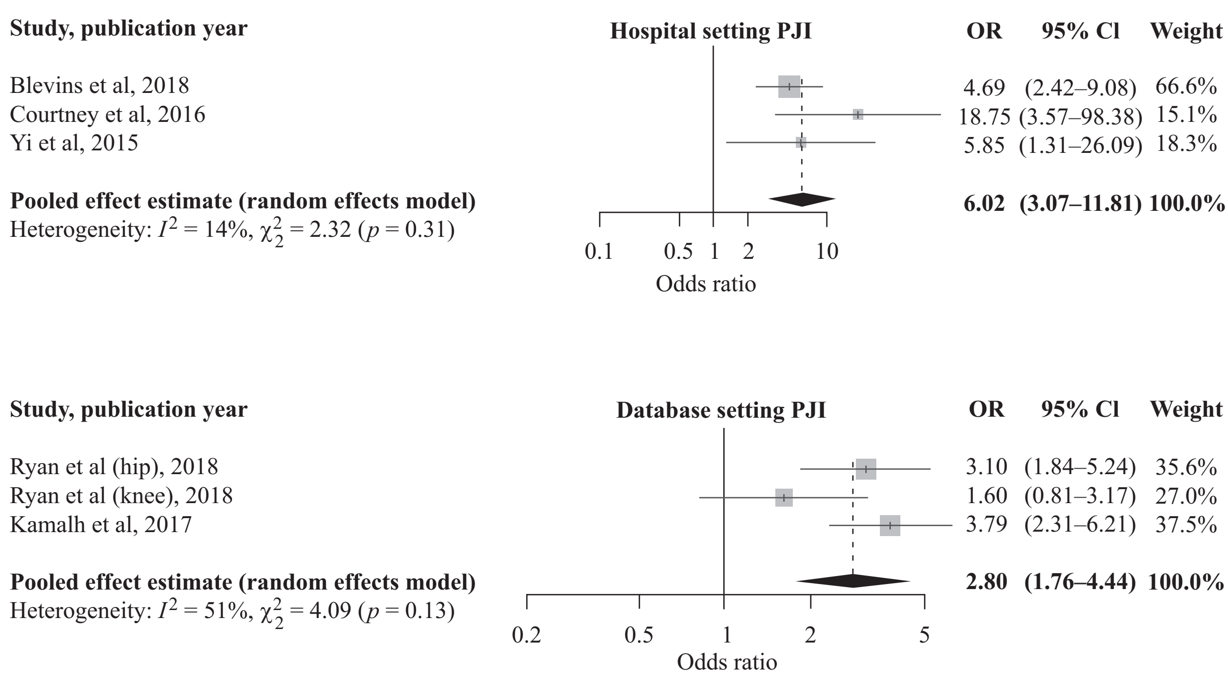

Figure 7. Forest plot for periprosthetic joint infections in hospital and population-based studies. OR, odds ratio; CI, confidence interval; PJI, periprosthetic joint infections.

(even though not statistically significant, a tendency towards different results between hospital vs population-based studies was noted). Third, whereas adjustment for confounding factors was performed in almost all studies of PJI, there were slight differences among the factors controlled for. Moreover, there was no such control in the studies of SSI. Finally, the definition of exposure (malnutrition) was based solely on serologic markers, which may raise concerns about whether robust diagnosis of malnutrition was achieved. However, there is no gold standard for detection of malnutrition, and laboratory assessment of nutritional status is well accepted in the literature. Given the above limitations, there is a clear need for further studies to better understand the impact of preoperative malnutrition on the incidence of PJI and SSI after total arthroplasties.

Our findings on the association between malnutrition and postoperative surgical infections are in agreement with current knowledge on the pathophysiology of infection, and are thus biologically plausible. A sound immune system relies on competent lymphocytes for eradication or prevention of infections; since malnutrition results in decreased lymphocyte count, these patients are more prone to infections [10,20]. Moreover, malnutrition affects collagen synthesis and fibroblast proliferation due to deficient protein reserves. Decreased albumin levels also lead to tissue oedema and a decrease in oxygen tension [31,47]. Due to these detrimental effects, wound healing is impaired. Skin has a major protective role against pathogen colonization of underlying tissue; thus prolonged exposure of underlying subcutaneous tissue to pathogens due to impaired wound healing further predisposes patients to surgical infections [45].

Besides surgical infections, malnutrition is also an important risk factor for several other adverse events after joint arthroplasties. It correlates with prolonged length of hospital stay, and increased rates of readmission [41,48]. There is a large amount of evidence linking malnutrition with wound complications including delayed wound healing, wound dehiscence, procrastination of wound drainage, and haematoma formation [7,8,11,44,49]. Malnourished patients are also at increased risk for renal, cardiovascular, pulmonary, and neurovascular complications after joint arthroplasty. Additionally, a recent study showed that 30-day mortality is higher in these patients [41,44,49].

Preoperative identification and management of all the modifiable risk factors for surgical infections, such as malnutrition, are of paramount importance. Laboratory assessment of nutritional status is recommended in all patients undergoing joint arthroplasty, and certain strategies for patient optimization in cases of malnutrition before surgery should be implemented. Common strategies include consumption of protein-enhanced supplemental beverages and increase of caloric intake in the preoperative period, and in certain cases consultation with a nutritionist is recommended [5,45]. However, it should be noted that although malnutrition is a well-recognized risk factor for SSI and PJI, there is a lack of direct evidence on the effectiveness of correcting malnutrition in reducing the incidence of these complications; this is an area for future clinical research.

In conclusion, the accumulated evidence clearly demonstrates that PJI and SSI after hip and knee arthroplasties are more likely to develop when preoperative malnutrition is present. Nutritional status should always be assessed and addressed prior to these elective procedures.

Conflict of interest statement
None declared.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jhin.2019.04.020.

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