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**EDITORIAL**

- 101 Mitochondrial dysfunction in type 2 diabetes: A neglected path to skeletal muscle atrophy  
*Wu JJ, Xian HM, Yang DW, Yang F*
- 105 Deep learning automation of radiographic patterns for hallux valgus diagnosis  
*Hussain A, Lee C, Hu E, Amirouche F*

**MINIREVIEWS**

- 110 Review and update on the management of triangular fibrocartilage complex injuries in professional athletes  
*Pace V, Bronzini F, Novello G, Mosillo G, Braghiroli L*

**ORIGINAL ARTICLE****Retrospective Study**

- 118 Mid-term outcomes of a kinematically designed cruciate retaining total knee arthroplasty  
*Katzman JL, Habibi AA, Haider MA, Cardillo C, Fernandez-Madrid I, Mefiah M, Schwarzkopf R*
- 129 Academic productivity correlates with industry earnings in foot and ankle fellowship programs in the United States: A retrospective analysis  
*Anastasio AT, Baumann AN, Walley KC, Hitchman KJ, O'Neill C, Kaplan J, Adams SB*
- 139 Burden of routine orthopedic implant removal a single center retrospective study  
*AlOmran AK, Alosaimi N, Alshaikhi AA, Bakhurji OM, Alzahrani KJ, Salloom BZ, Alabduladhem TO, AlMulhim AI, Alumran A*

**Observational Study**

- 147 Limb Lengthening and Reconstruction Society orthopedic surgeons in the United States: An analysis of geographical distribution, academic, leadership, and demographic characteristics  
*Hoveidaei AH, Niakan R, Hosseini-Asl SH, Annasamudram A, Conway JD*

**Prospective Study**

- 156 High rate of clinically relevant improvement following anatomical total shoulder arthroplasty for glenohumeral osteoarthritis  
*Nyring MRK, Olsen BS, Amundsen A, Rasmussen JV*
- 163 Effect of ankle versus thigh tourniquets on post-operative pain in foot and ankle surgery  
*Mishra A, Barakat A, Mangwani J, Kazda J, Tiwatane S, Shaikh SMA, Houchen-Wolloff L, Kaushik V*
- 170 Assessment of the effectiveness of weight-adjusted antibiotic administration, for reduced duration, in surgical prophylaxis of primary hip and knee arthroplasty  
*Okoro T, Wan M, Mukabeta TD, Malev E, Gross M, Williams C, Manjra M, Kuiper JH, Murnaghan J*

**META-ANALYSIS**

- 180** Meta-analysis of factors influencing anterior knee pain after total knee arthroplasty  
*Feng H, Feng ML, Cheng JB, Zhang X, Tao HC*

**LETTER TO THE EDITOR**

- 192** Adenylate cyclase activates the cAMP signalling pathway to enhance platelet-rich plasma-treated Achilles tendon disease, a theoretical bioinformatics-based study  
*Sun JY, Li C, Du FY*

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# Meta-analysis of factors influencing anterior knee pain after total knee arthroplasty

Hui Feng, Ming-Li Feng, Jing-Bo Cheng, Xiang Zhang, Hai-Cheng Tao

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## Abstract

### BACKGROUND

Total knee arthroplasty (TKA) is a mature procedure recommended for correcting knee osteoarthritis deformity, relieving pain, and restoring normal biomechanics. Although TKA is a successful and cost-effective procedure, patient dissatisfaction is as high as 50%. Knee pain after TKA is a significant cause of patient dissatisfaction; the most common location for residual pain is the anterior region. Between 4% and 40% of patients have anterior knee pain (AKP).

### AIM

To investigate the effect of various TKA procedures on postoperative AKP.

### METHODS

We searched PubMed, EMBASE, and Cochrane from January 2000 to September 2022. Randomized controlled trials with one intervention in the experimental group and no corresponding intervention (or other interventions) in the control group were collected. Two researchers independently read the title and abstract of the studies, preliminarily screened the articles, and read the full text in detail according to the selection criteria. Conflicts were resolved by consultation with a third researcher. And relevant data from the included studies were extracted and analyzed using Review Manager 5.4 software.

### RESULTS

There were 25 randomized controlled trials; 13 were comparative studies with or without patellar resurfacing. The meta-analysis showed no significant difference between the experimental and control groups ( $P = 0.61$ ). Six studies were comparative studies of circumpatellar denervation *vs* non-denervation, divided into three subgroups for meta-analysis. The two-subgroup meta-analysis showed no significant difference between the experimental and the control groups ( $P = 0.31$ ,  $P = 0.50$ ). One subgroup meta-analysis showed a significant difference between the experimental and control groups ( $P = 0.001$ ). Two studies compared fixed-bearing TKA and mobile-bearing TKA; the results meta-analysis showed no

significant difference between the experimental and control groups ( $P = 0.630$ ). Two studies compared lateral retinacular release *vs* non-release; the meta-analysis showed a significant difference between the experimental and control groups ( $P = 0.002$ ); two other studies compared other factors.

## CONCLUSION

Patellar resurfacing, mobile-bearing TKA, and fixed-bearing TKA do not reduce the incidence of AKP. Lateral retinacular release can reduce AKP; however, whether circumpatellar denervation can reduce AKP is controversial.

**Key Words:** Total knee arthroplasty; Anterior knee pain; Knee osteoarthritis; Interventions; Meta-analysis

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**Core Tip:** In our meta-analysis, we searched PubMed, EMBASE, and Cochrane from January 2000 to September 2022, and we included only high level randomized controlled trials in order to get more accurate results. We discussed the influence of multiple factors on anterior knee pain after total knee arthroplasty, with different results from previous studies.

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## INTRODUCTION

Knee osteoarthritis is a chronic joint disease characterized by articular cartilage degeneration and secondary hyperosteoarthritis[1]. The primary symptom is pain during knee joint weight-bearing and activity, severely affecting the quality of life. In the early stage, conservative treatment with medication is effective; however, in the middle and late stages (especially in the end stage), knee pain is severe, and the effective treatment is knee replacement[2,3]. Total knee arthroplasty (TKA) is a mature procedure recommended for correcting knee osteoarthritis deformity, relieving pain, and restoring normal biomechanics[4]. The patients enjoy excellent long-term survival[5-8]. Although TKA is a successful and cost-effective procedure, patient dissatisfaction is as high as 50%. Knee pain after TKA is a significant cause of patient dissatisfaction; the most common location for residual pain is the anterior region[9]. Between 4% and 40% of patients have anterior knee pain (AKP)[10-12]. In this review, we searched PubMed, EMBASE, and the Cochrane database for randomized controlled trials related to AKP after TKA to explore the effects of various TKA approaches on AKP.

## MATERIALS AND METHODS

### Eligibility criteria and outcome definitions

Studies were selected based on the following inclusion criteria: (1) Type of studies: A randomized controlled trial; (2) subjects: Patients undergoing TKA for the first time; (3) intervention: Not limited; (4) control group: Intervention different from the experimental group or no intervention; and (5) evaluation indicators: Occurrence of AKP (incidence and pain degree). The exclusion criteria were as follows: Patellar surgery, fracture history, high tibial osteotomy, no AKP, review or expert reports, cadaveric studies, model studies, and case reports.

### Information sources and search strategy

PubMed, EMBASE, and the Cochrane Library were searched from January 2000 to September 2022. The keywords were "Total Knee Arthroplasty", "Anterior Knee Pain", and other related Medline search heading terms or expressions.

### Study selection and data extraction

Two researchers independently read the title and abstract of the studies, preliminarily screened the articles, and read the full text in detail according to the selection criteria. Conflicts were resolved by consultation with a third researcher. We retrieved 294 articles from three databases. After reading the title and abstract, 67 articles were identified. After reading the full text, articles without AKP were excluded, and the controversies were resolved. Finally, 25 articles were included in this review. A flowchart of the studies considered for inclusion is shown in [Figure 1](#).

### Quality assessment

According to the Cochrane Risk of Bias tool, the risk of bias of each randomized controlled trial was graded as low, high, or unclear based on: (1) Random sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessment; (5) incomplete outcome data; (6) selective reporting, and (7) other bias.

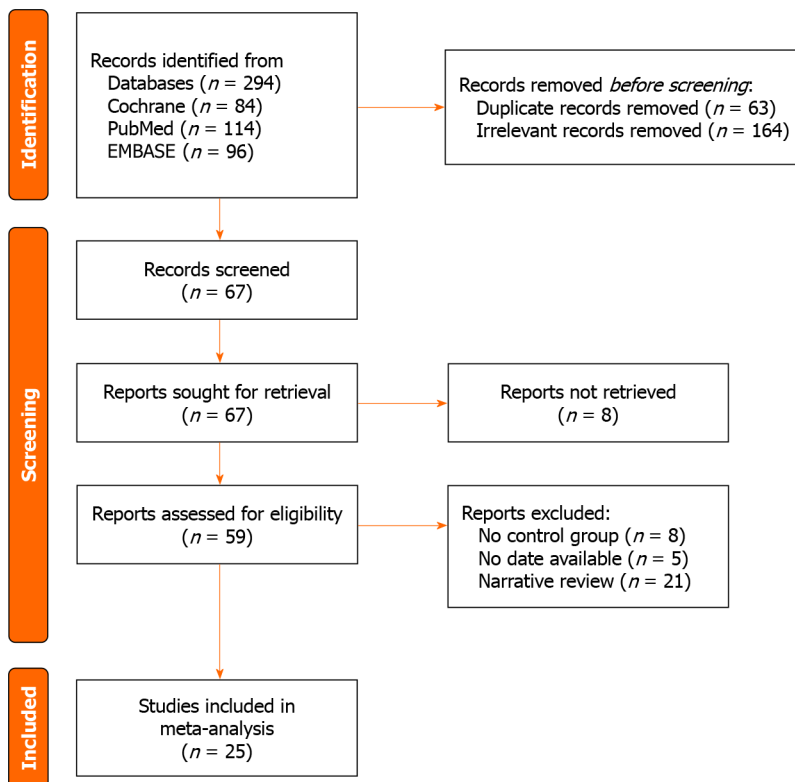


Figure 1 Flowchart of included studies.

The risk of bias assessments is shown in Figures 2 and 3.

### Data synthesis and analysis

Data on study design, study population, interventions, and outcomes were extracted from the included articles' text, figures, and tables. Dichotomous outcomes were expressed as risk ratios with 95% confidence intervals (95% CIs), while continuous outcomes were expressed as mean or standard mean differences with 95% CI. Heterogeneity was expressed as  $P$  and  $I^2$ . This value of  $I^2$  ranges from 0% (complete consistency) to 100% (complete inconsistency). If the  $P$  value of the heterogeneity test was  $< 0.1$  or  $I^2 > 50\%$ , a random-effects model was used in place of the fixed modality.

Publication bias was tested using funnel plots. Forest plots were used to graphically present the results of individual studies and the respective pooled effect size estimate. All statistical analyses were performed using Review Manager version 5.4.

## RESULTS

### Effect of patellar resurfacing on AKP

We included 13 studies on the effect of patellar replacement on AKP after TKA[4,13-24]. Ten reported the number of patients with AKP in each group, and the remaining three evaluated AKP using a visual analog scale (VAS) and hospital for special surgeries patellar score. These three studies did not conduct meta-analyses. There were 1197 TKA patients in these ten studies, including 586 TKA patients with patellar resurfacing (121 AKP) and 611 TKA patients without patellar resurfacing (100 AKP). The basic information of the ten studies (Table 1) and the forest plot (Figure 4) and funnel plot (Figure 5) of the meta-analysis are as follows ( $I^2 = 0\%$ , using the fixed modality,  $P = 0.13$ , suggesting that there was no significant difference between the two groups. The funnel plot was symmetrical, suggesting no publication bias).

### Effect of circumpatellar denervation on AKP

Six studies[25-30] compared circumpatellar denervation with non-denervation in TKA. The patellofemoral Feller score (PFS) was used to evaluate postoperative AKP in two studies, VAS was used in two studies, and the remaining two reported the number of cases of AKP in each group; therefore, they were divided into three subgroups for meta-analysis. The basic information of the six articles is presented in Tables 2 and 3.

### PFS score subgroup

There were two studies[25,26] with 138 cases in the denervation group and 131 in the non-denervation group. The meta-analysis forest plot is shown in Figure 6A ( $I^2 = 66\%$ , using the random-effects model,  $P = 0.31$ , suggesting no significant difference between the groups).

**Table 1 Basic information (e.g., patellar resurfacing vs no patellar resurfacing)**

Ref.	Follow-up time	Patients included (resurfacing/non-resurfacing)	Resurfacing		Non-resurfacing	
			Patients with AKP	Patients available	Patients with AKP	Patients available
Koh <i>et al</i> [16], 2019	5 yr	49/49	29	49	30	49
Thiengwittayaporn <i>et al</i> [15], 2019	1 yr	42/42	0	41	2	39
Ha <i>et al</i> [17], 2019	5 yr	66/66	1	60	1	60
Deroche <i>et al</i> [13], 2022	18.0 months (mean)	123/123	14	116	15	105
Agarwala <i>et al</i> [4], 2018	19.0 months	60/60	7	60	9	60
Zou <i>et al</i> [19], 2011	16.5 months (mean)	64/64	7	64	9	64
Burnett <i>et al</i> [22], 2004	10 yr	50/50	7	19	5	20
Burnett <i>et al</i> [20], 2009	10 yr	59/59	8	38	6	40
Barrack <i>et al</i> [24], 2001	70.5 months	59/59	9	47	8	46
Wood <i>et al</i> [23], 2002	48.0 months (mean)	110/110	15	91	39	127

AKP: Anterior knee pain.

**Table 2 The basic information of the studies (with or without circumpatellar denervation)**

Ref.	Follow-up time	Patients included (denervation/non-denervation)	Denervation		Non-denervation	
			Patients with AKP	Patients available	Patients with AKP	Patients available
Jonbergen <i>et al</i> [29], 2011	1 yr	150/150	25	131	42	131
Pulavarti <i>et al</i> [28], 2014	2 yr	63/63	53	61	51	58

AKP: Anterior knee pain.

**Table 3 The basic information of the studies (with or without circumpatellar denervation)**

Ref.	Follow-up time	Patients available (denervation/non-denervation)	Score	Denervation		Non-denervation	
				Mean	SD	Mean	SD
Kwon <i>et al</i> [26], 2015	5 yr	50/50	PFS	14.10	1.00	14.20	1.20
Goicoechea <i>et al</i> [25], 2021	1 yr	88/81	PFS	12.60	3.50	13.60	2.70
Altay <i>et al</i> [27], 2012	3 yr	35/35	VAS	2.20	1.10	2.82	1.20
Deekshith <i>et al</i> [30], 2020	2 yr	50/49	VAS	1.34	0.47	1.60	0.53

VAS: Visual analog scale; PFS: Patellofemoral Feller score.

**VAS score subgroup**

There were two studies with 85 patients in the denervation group and 84 in the non-denervation group[27,30]. The meta-analysis forest plot is shown in **Figure 6B** ( $I^2 = 34\%$ , using the fixed modality,  $P = 0.001$ , suggesting that the difference between the groups was statistically significant).



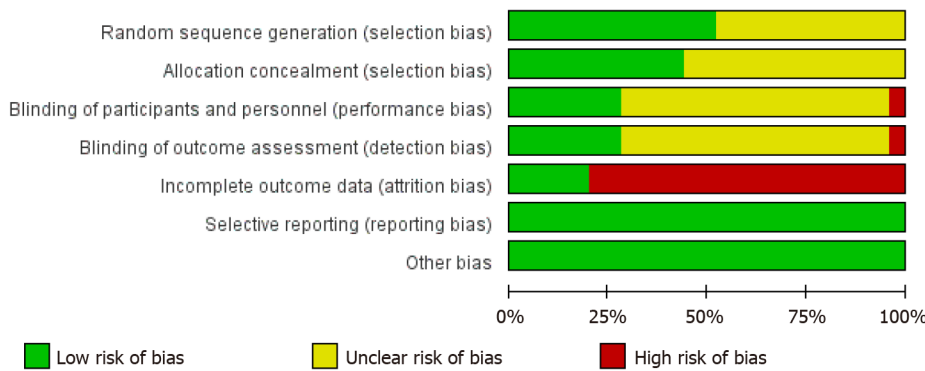


Figure 2 Proportions in the methodological quality assessment.

### Subgroup of the number of patients with AKP

There were two studies with 213 patients in the denervation group and 213 in the non-denervation group[28,29]. The meta-analysis forest plot is shown in Figure 6C ( $I^2 = 90\%$ , using the random-effects model,  $P = 0.50$ , suggesting no significant difference between the groups).

### Effects of using fixed or mobile-bearing TKA on AKP

There were two studies comparing mobile-bearing and fixed-bearing designs. There were 88 cases of fixed-bearing and 71 of mobile-bearing[31,32]. The basic information of the studies (Table 4) and the forest plot of meta-analysis (Figure 6D) are as follows ( $I^2 = 12\%$ , using the fixed modality,  $P = 0.63$ , suggesting that there was no significant difference between the two groups).

### Effect of lateral retinacular release on AKP

We included two comparative studies of lateral retinacular release and non-release, with 135 cases in the release group and 130 in the non-release group[33,34]. The basic information of the two studies (Table 5) and the forest plot of meta-analysis (Figure 6E) are as follows ( $I^2 = 0\%$ , using the fixed modality,  $P = 0.002$ , suggesting that the difference between the two groups was statistically significant).

### Effect of other factors on AKP

Yuan *et al*[35] reported differences in patellofemoral function, clinical outcomes, and radiographic parameters between the freehand and cutting guide patellar resection techniques in patients undergoing TKA. The authors randomly assigned 100 patients to the freehand technique group and the cutting guide technique group, with 50 patients in each group. Finally, 42 patients in the cutting guide technique group and 44 patients in the freehand technique group were available for analysis. AKP occurred in 7.14% of the patients in the cutting guide technique group and 9.09% in the freehand technique group. There was no significant difference between the two groups. Fahmy *et al*[36] randomized into an experimental group, including patients with complete excision of the infrapatellar pad of fat (IPFP) and the control group with IPFP preservation. The authors randomly assigned 90 patients to the experimental and the control groups. At 6 months follow-up, 10 knees and 14 knees had AKP in IPFP preservation and excision group patients, respectively. The pain decreased during the follow-up period until the number of cases was almost equal at the final visit. There was no significant difference in AKP between the groups. Each group’s mean VAS pain scores were comparable throughout the recorded follow-up period.

## DISCUSSION

### Effect of patellar resurfacing on AKP

Patellar resurfacing in TKA has long been controversial; some authors believe that patellar resurfacing can improve patient satisfaction, reduce postoperative AKP, and reduce the revision rate[37-40], while others hold the opposite view [41,42]. We analyzed 13 randomized controlled trials of patellar resurfacing and non-resurfacing. Of these, 12 showed no significant difference in postoperative AKP between the groups. Wood *et al*[23] showed that postoperative AKP was lower in the patellar resurfacing group than in the non-resurfacing group. In that study, surgery was performed by one of six experienced surgeons or their trainees under their supervision, and the follow-up time varied substantially (36-79 months, mean 48 months). Different surgeons have different surgical preferences, and the postoperative results also show substantial differences. The patients were followed up for a minimum of 36 months and a maximum of 79 months. The incidence of AKP and the severity of pain after TKA decreased with time. Therefore, comparing results at 36 and 79 months is not appropriate. These reasons may explain the different results between Wood *et al*[23] and other studies

Our meta-analysis showed no significant difference in the incidence of postoperative AKP between the patellar resurfacing group and the non-resurfacing group. Patellar resurfacing increases the operative time and blood loss.

**Table 4** The basic information of the studies (effects of using fixed or mobile-bearing total knee arthroplasty)

Ref.	Follow-up time	Fixed		Mobile	
		Patients with AKP	Patients available	Patients with AKP	Patients available
Feczko <i>et al</i> [31], 2017	5.0 yr	11	48	6	42
Breugem <i>et al</i> [32], 2014	7.9 yr	5	40	5	29

AKP: Anterior knee pain.

**Table 5** The basic information of the studies (lateral retinacular release vs non-release)

Ref.	Follow-up time	Lateral retinacular release		Non-release	
		Patients with AKP	Patients available	Patients with AKP	Patients available
Zhu <i>et al</i> [33], 2017	5 years	4	64	12	62
Zha <i>et al</i> [34], 2014	7.9 years	4	71	14	68

AKP: Anterior knee pain.

Furthermore, the patella in Asians is generally thin, leading to an increased risk of postoperative patellar fracture[41,42]. Therefore, we do not recommend patellar resurfacing in TKA.

#### **Effect of circumpatellar denervation on AKP**

The peripatellar soft tissue and retropatellar fat pad have been reported to be the source of AKP[43,44]. Immunohistochemical studies of nerve distribution in this area have shown the presence of substance-p nociceptive fibers in the peripatellar soft tissue[45]. Electrocautery disables these pain receptors and achieves desensitization or denervation of the anterior knee region. Thus, postoperative AKP can be reduced[46,47]. In our review, six studies compared circumpatellar denervation and non-denervation in TKA. Due to the inconsistency of the indicators to evaluate postoperative AKP, the meta-analysis was divided into three subgroups.

The results of the PFS score subgroup with AKP showed no significant difference between the denervation and non-denervation groups, while the VAS score subgroup showed that denervation was superior to non-denervation. Due to the large incision of TKA, peripatellar soft tissue and retropatellar fat pad are injured to a greater extent; therefore, achieving the surgical goal by performing only circumpatellar denervation is challenging. The heterogeneity among the six studies was considerable. The sample size was small, and the power of meta-analysis was weak; therefore, more studies are needed.

#### **Effects of fixed or mobile-bearing TKA on AKP**

The theoretical advantage of the mobile-bearing TKA is the ability to self-align and accommodate minor mismatches[32]. The design of the mobile-bearing TKA could lead to a better range of motion during knee flexion activities[48]. Breugem *et al*[12] found that over a one-year follow-up, the incidence of postoperative AKP of mobile-bearing TKA was lower than that of fixed-bearing TKA. However, postoperative AKP tended to be the same over time[32]. This result is similar to other studies[49,50]. This review included two studies comparing fixed-bearing TKA and mobile-bearing TKA, with follow-up times of 5.0 and 7.9 years, respectively. The meta-analysis showed no difference in the incidence of AKP between the groups. Therefore, the advantage of mobile-bearing TKA might decrease over time.

#### **Effect of lateral retinacular release on AKP**

Theoretically, proper lateral retinacular release improves patellar tracking and reduces patellofemoral contact pressure. These factors have been reported to be closely related to AKP[51,52]. In a prospective cohort study of 271 patients, Lee *et al*[51] found that patients who underwent patellar decompression had less AKP than those who did not. Wilson *et al*[52] found that patients with AKP had abnormal patellar tracking compared with patients without AKP. This review included two studies comparing lateral retinacular release and non-release in TKA. The meta-analysis showed that lateral retinacular release reduced AKP. No studies reported that lateral retinacular release produces adverse postoperative complications. Proper lateral retinacular release increases the intraoperative field of vision, which is conducive to successful outcomes.

#### **Effect of other factors on AKP**

In patellar resections when conducting TKA, a number of principles should be considered including restoring patellar height, performing a symmetric resection, avoiding under-resection, and minimizing over-stuffing of the patellofemoral joint[53]. Reasonable patellar excision is more beneficial to the installation of patellar components. At the same time, reasonable excision can reduce AKP, patellar fracture and patellar injury[54,55]. This review included one study

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Chengzhi Ha 2019	+	+	+	+	-	+	+
DAVID J. WOOD 2002	?	?	?	?	-	+	+
Etienne Deroche 2022	?	?	?	?	-	+	+
Fuzhen Yuan 2019	+	+	+	+	-	+	+
Guo-Chun Zha 2014	+	+	?	?	-	+	+
H. P. W. van Jonbergen 2011	+	+	+	+	-	+	+
In Jun Koh 2019	+	+	+	+	+	+	+
Lokesh Chawla 2018	+	+	-	-	+	+	+
M.A. Altay 2012	+	+	?	?	-	+	+
Mahmoud Fahmy 2022	+	+	+	+	+	+	+
Nerea Goicoechea 2021	?	?	?	?	-	+	+
P.Z.Feczko 2017	?	?	?	?	-	+	+
R. S. J. Burnett 2007	+	+	+	+	-	+	+
R. Stephen Burnett 2004	?	?	?	?	-	+	+
R. Stephen J. Burnett 2009	?	?	?	?	-	+	+
Ramnadh S. Pulavarti 2014	?	?	?	?	-	+	+
ROBERT L. BARRACK 2001	?	?	?	?	-	+	+
S.R. K. Deekshith 2020	+	+	?	?	-	+	+
Sae Kwang Kwon 2015	+	?	?	?	-	+	+
Sanjay Agarwala 2018	?	?	?	?	+	+	+
Satit Thiengwittayaporn 2019	?	?	?	?	-	+	+
Stefan J. M. Breugem 2014	?	?	?	?	-	+	+
Tom M. van Raaij 2021	+	+	+	+	-	+	+
Yonggen Zou 2011	?	?	?	?	+	+	+
Yongliang Zhu 2017	+	?	?	?	-	+	+

Figure 3 Methodological quality.

comparing freehand and cutting guide patellar resection techniques in TKA. In their prospective randomized controlled trial, no statistically significant difference was observed in the incidence of AKP between the two groups. Therefore, better knee function may be more related to basic principles, including excellent lower limb alignment, proper prosthetic placement, intact ligaments, and greater lower limb strength[35].

The IPFP is a piece of fat tissue located between the patellar ligament, the inferior patellar end, and the proximal tibia. Anatomically, it is considered to be an intraarticular extrasynovial compartment that may support effective joint

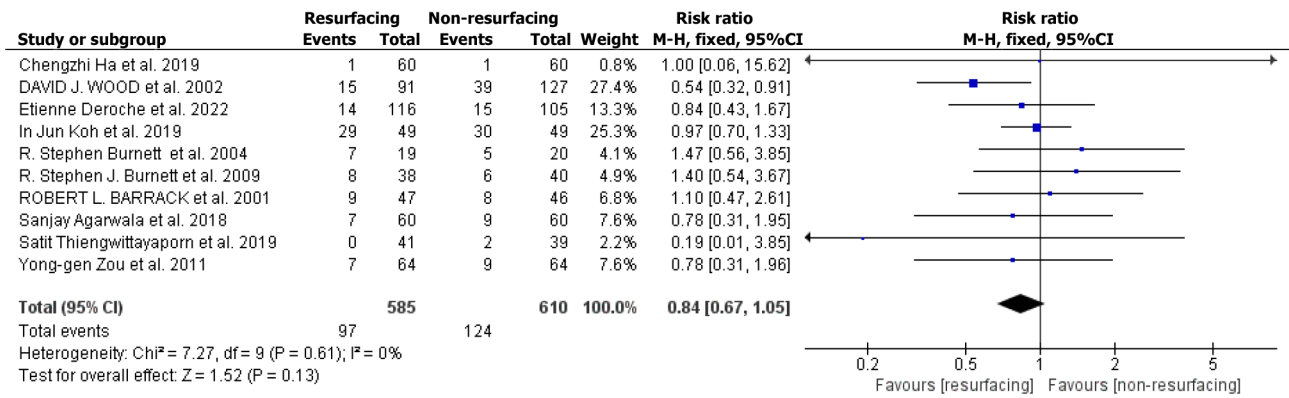


Figure 4 Forest plot for patellar resurfacing vs no resurfacing. 95%CI: 95% confidence interval.

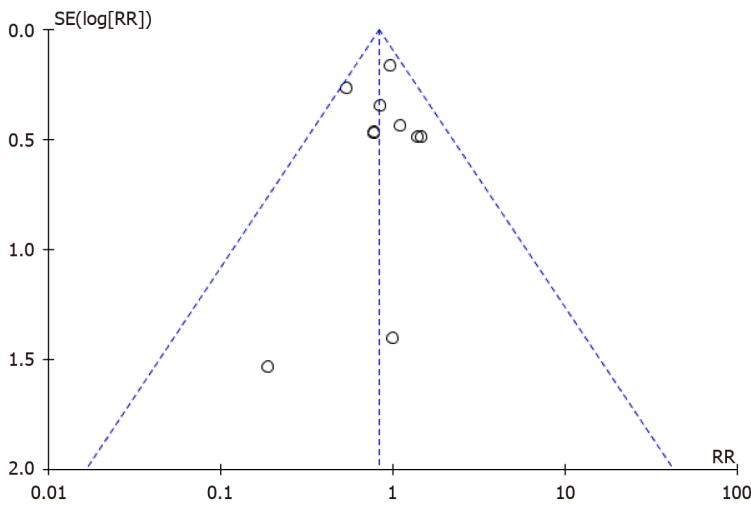
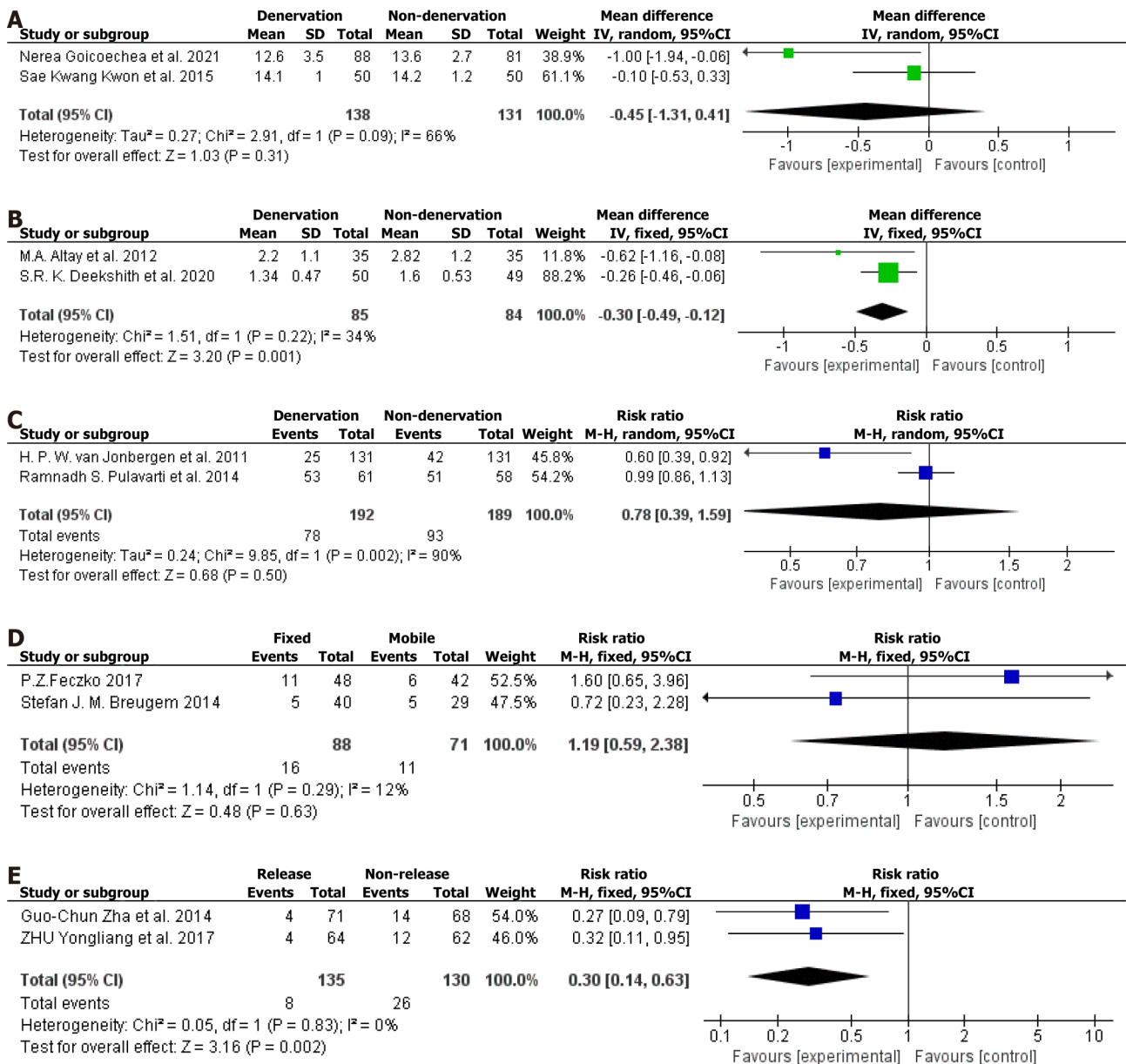


Figure 5 Funnel plot for patellar resurfacing vs no resurfacing.

lubrication[56]. The sufficient surgical exposure often prompts many surgeons to remove it during surgery, as there is debate about the effectiveness of its removal, but there is not complete agreement. In the study of Fahmy *et al*[36], the difference of the postoperative AKP, range of motion, oxford knee score and the clinical outcomes whether infrapatellar fat pad was excised or not were statistically insignificant. Therefore, surgeons had better to save the IPFP if conventional exposure can be reached; otherwise, resection is preferred to improve exposure.

The exact pathogenesis of AKP may be multifactorial. Laubach *et al*[57] concluded that quadriceps muscle strength, inlay thickness, and the patella position might be of particular relevance in avoiding postsurgical AKP. The results of another study suggest that the successful repair of the medial patellofemoral ligament after using a medial parapatellar approach in TKA could reduce the high rate of postoperative AKP[58]. There are many other factors that may be related to AKP after TKA[59-61]. Due to the lack of randomized controlled trials in the exploration of these factors, they were not included in the meta-analysis of this study.

Our meta-analysis had several strengths. First, it resulted in a different conclusion from the 2 reached in earlier meta-analyses[62,63]. In the study by Duan *et al*[62], the results showed that patellar resurfacing had a significant protective effect on AKP with low heterogeneity and robust results. In our analysis, the incidence of AKP was not statistically significant with or without patellar replacement in TKA. A meta-analysis conducted by Xie *et al*[63]. concluded that patellar denervation could significantly relieve AKP during follow-up up to 12 months, but not beyond 12 months. We found that the results of different assessment methods for AKP were different. Second, only randomized controlled trials were included in our study, and the results obtained were more accurate. Third, the studies we included were screened independently by two researchers according to inclusion and exclusion criteria, we used Cochrane Risk of Bias tool to assess publication bias, and these results indicated that publication bias was well controlled. This meta-analysis also had limitations. First, only a small number of trials was analyzed since we only included randomized controlled trials. Second, there is no single definition of AKP, and distinguishing patellofemoral pain syndrome is difficult. Third, the studies included in the meta-analysis applied different techniques and diagnostic criteria to AKP, which could lead to performance bias. Given these limitations, more high-level research is still needed in the future.



**Figure 6 Forest plot.** A: Forest plot for patellofemoral Feller score subgroups; B: Forest plot for the visual analog scale score subgroup; C: Forest plot for the subgroup of patients with anterior knee pain; D: Forest plot for using fixed or mobile-bearing total knee arthroplasty; E: Forest plot for lateral retinacular release vs non-release. 95%CI: 95% confidence interval.

## CONCLUSION

This meta-analysis of currently available evidence indicates that patellar resurfacing, mobile-bearing TKA, and fixed-bearing TKA can't relieve AKP postoperatively after TKA. We do not recommend patellar replacement in TKA unless patellar replacement is necessary. In evaluating the effect of patellar denervation on TKA, the results of different assessment methods for AKP were different. Therefore, future high-level research is warranted for validation. Besides, lateral retinacular release in TKA is recommended because it is safe and result in good clinical outcomes in controlling AKP.

## ARTICLE HIGHLIGHTS

### Research background

Knee osteoarthritis seriously affects the quality of life of the elderly. Total knee arthroplasty (TKA) is an effective treatment for end-stage osteoarthritis. Anterior knee pain (AKP) after TKA is the main cause of dissatisfaction in the elderly. The management of AKP after total knee replacement is very important.

**Research motivation**

Although total knee replacement is very successful, postoperative AKP is common and a major cause of patient dissatisfaction. By studying the influencing factors of AKP after TKA, we can improve the quality of life of patients and improve the surgical methods.

**Research objectives**

To study the influencing factors of AKP after TKA. We identified certain intraoperative factors that may improve the occurrence of postoperative AKP. It provides some help for the management of AKP after TKA.

**Research methods**

This study is a meta-analysis. We combined some previous randomized controlled trials to get new conclusions. We analyzed the influence of several different factors on AKP after TKA.

**Research results**

There are few randomized controlled trials for many factors, and more high-quality studies are needed to further explore.

**Research conclusions**

We found that patellar replacement or not did not affect the incidence of postoperative AKP. We found that different assessment methods for AKP may produce different results.

**Research perspectives**

More randomized controlled trials are needed for further validation in the future.

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**FOOTNOTES**

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**Author contributions:** Feng H contributed to conceptualization, methodology, investigation, formal analysis, writing-original draft; Feng ML contributed to conceptualization, funding acquisition, resources, supervision, writing-review, and editing; Cheng JB contributed to data curation and writing-original draft; Tao HC contributed to visualization and investigation; Zhang X contributed to visualization and investigation.

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