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SYSTEMATIC REVIEWS

Impact of enhanced recovery pathways on safety and efficacy of hip and knee arthroplasty: A systematic review and meta-analysis

Marion JLF Heymans, Nanne P Kort, Barbara AM Snoeker, Martijn GM Schotanus

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Abstract

BACKGROUND

Over the past decades, clinical pathways (CPs) for hip and knee arthroplasty have been strongly and continuously evolved based on scientific evidence and innovation.

AIM

The present systematic review, including meta-analysis, aimed to compare the safety and efficacy of enhanced recovery pathways (ERP) with regular pathways for patients with hip and/or knee arthroplasty.

METHODS

A literature search in healthcare databases (Embase, PubMed, Cochrane Library, CINAHL, and Web of Science) was conducted from inception up to June 2018. Relevant randomized controlled trials as well as observational studies comparing ERP, based on novel evidence, with regular or standard pathways, prescribing care as usual for hip and/or knee arthroplasty, were included. The effect of both CPs was assessed for (serious) adverse events [(S)AEs], readmission rate, length of hospital stay (LoS), clinician-derived clinical outcomes, patient reported outcome measures (PROMs), and financial benefits. If possible, a meta-analysis was performed. In case of considerable heterogeneity among studies, a qualitative analysis was performed.

RESULTS

Forty studies were eligible for data extraction, 34 in meta-analysis and 40 in qualitative analysis. The total sample size consisted of more than 2 million patients undergoing hip or knee arthroplasty, with a mean age of 66 years and with 60% of females. The methodological quality of the included studies ranged from average to good. The ERP had lower (S)AEs [relative risk (RR): 0.9, 95% confidence interval (CI): 0.8-1] and readmission rates (RR: 0.8, 95%CI: 0.7-1), and reduced LoS [median days 6.5 (0.3-9.5)], and showed similar or improved outcomes for functional recovery and PROMs compared to regular pathways. The analyses for readmission presented a statistically significant difference in the enhanced recovery pathway in favor of knee arthroplasties (P = 0.01). ERP were reported to be cost effective, and the cost reduction varied largely between studies (€109 and $20573). The overall outcomes of all studies reported using Grading of Recommendation, Assessment, Development and Evaluation, presented moderate or high quality of evidence.

CONCLUSION

This study showed that implementation of ERP resulted in improved clinical and patient related outcomes compared to regular pathways in hip and knee arthroplasty, with a potential reduction of costs.

Key Words: Hip arthroplasty; Knee arthroplasty; Joint arthroplasty; Clinical pathway; Enhanced recovery pathway; Systematic review; Meta-analysis

Core Tip: Enhanced recovery pathways for hip and knee arthroplasty help the patient and the multidisciplinary team to achieve the best possible results. Based on the results presented, it may help health care providers to make informed decisions regarding the optimization of currently used regular pathways. We strongly recommend orthopedic surgeons worldwide to keep up-to-date with the latest literature and to optimize their regular pathway with the latest evidence. This study involves an extensive literature search for care pathways for hip and knee arthroplasty, and the effects on multiple outcomes have been analyzed in terms of (serious) adverse events, readmissions, length of hospital stay, functional recovery, patient reported outcome measures, and costs.

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INTRODUCTION

The numbers of hip and knee arthroplasties performed worldwide are growing as a result of the increased incidence of osteoarthritis[1-5]. With the increasing life expectancy, hip and knee osteoarthritis will become a significant health issue in the upcoming years[6] and thereby arthroplasty surgeries will increasingly be performed. Clinical pathways (CPs) have been introduced to improve the quality of hip and knee arthroplasty, by optimizing recovery, minimizing variation in care, and reducing costs[7,8]. Due to scientific advancement, innovation, and novel technologies, CPs for hip and knee arthroplasty are continuously being changed. The enhanced recovery pathways (ERP) are based on novel evidence, while regular pathways are not necessarily based on the latest evidence. Because the optimizations in CPs are accomplished with an increase in costs, time, and resources[9], but might also be able to reduce costs in the long term[10], it is essential to gain knowledge on the actual benefits of the ERP. Therefore, we included all ERP studies for hip and knee arthroplasty and investigated the impact of the optimization process. This study, as far as we know, is the most extensive systematic review (SR) and meta-analysis on CPs for hip and knee arthroplasty.

The purpose of this SR and meta-analysis was to investigate the effect of *enhanced recovery pathways* compared to *regular pathways* for total hip arthroplasty (THA), total knee arthroplasty (TKA), and/or unicompartmental knee arthroplasty (UKA) on (serious) adverse events [(S)AEs], readmission rate, length of hospital stay (LoS), clinician-derived clinical outcomes (*e.g.*, Knee- and Hip Society Scores), patient reported outcome measures (PROMs), and costs. This present SR and meta-analysis is complementary to previous reviews[1,11-18].

MATERIALS AND METHODS

A review protocol was developed according to the Preferred Items for Reporting Systematic Reviews and Meta-Analysis (PRISMA-P) statement[19] and registered in PROSPERO, the International Prospective Register of Systematic Reviews, in September 2016 (CRD42016040210).

Literature search

A systematic literature search in five key healthcare databases was conducted (MH). Embase.com, PubMed, Wiley/Cochrane Library, Clarivate Analytics/Web of Science, and Ebsco/CINAHL were searched from inception until June 10, 2018. Three trial registers were searched to identify ongoing unpublished trials, including the World Health Organization portal, ClinicalTrials.gov, and PROSPERO. The first terms used, including all synonyms, were ‘knee arthroplasty’ or ‘hip arthroplasty’ combined with ‘clinical pathways’ or ‘enhanced recovery’ or ‘ambulatory care’ or ‘outpatients’. There was no restriction on language or publication type or date.

Eligibility criteria

Randomized controlled trials (RCTs) and observational studies written in English, comparing within the studies ERP with the foregoing regular pathway, including patients 18 years or older undergoing THA, TKA, and/or UKA, were included. At least one of the following outcomes needed to be evaluated for inclusion for one of the arthroplasties: (S)AEs, readmission rate, LoS, functional recovery, PROMs, and costs. Descriptive articles (*e.g.*, historical articles) and studies investigating patients who underwent revision, fracture, or bilateral arthroplasty were excluded.

Study selection

The results of the literature search were collated and de-duplicated in RefWorks[20]. All articles were screened on title and abstract independently by two reviewers (MH and MS). After retrieving and examining the full text of all potentially relevant articles, both reviewers indicated independently if the study should be included. Disagreements regarding study inclusion were resolved by consensus between the two reviewers.

One reviewer (MH) extracted and added data into Review Manager (RevMan)[21] and the other (MS) verified the accuracy of the data; disagreements were resolved by discussion and if no agreement was reached, by the involvement of a third reviewer (BS).

Clinical pathways

We divided the CPs into ERP and regular pathways. It is challenging to get consensus on a definition for ERP[32], because of the different concepts of care under different health care systems. CPs with rapid or enhanced recovery, fast-track, day care, or outpatient surgery, including novel experimental evidence, are an updated version of the regular pathway and were defined as ERP. These pathways are continually evolving, aiming to improve the standard of care. Several factors may streamline these ERP, during the pre-, peri-, and/or post-operative stage. We used the definitions as stated by Galbraith *et al*[11] for the specific elements of ERP. The regular pathways, maintaining the standard or non-optimized program and containing the previous evidence, prescribe care as usual. The regular pathways were considered to be the initial procedures. A pragmatic approach was chosen to distinguish between regular and enhanced. Results between ERP and regular pathways were compared for (S)AEs, LoS, functional recovery, PROMs, and costs.

Outcomes

The following data were extracted systematically from the included papers by both reviewers (MH and MS): Author, publication year, study design, procedure, clinical pathways, number of participants, patients’ characteristics, country, and outcomes. We determined AEs as patient events and wound disorders, surgical and/or prosthesis related[3]. SAEs were reported as undesired medical events, not necessarily associated with the treatment[22]. Classification as AE or SAE was analyzed together as one outcome measure in (S)AE. Readmission rate was registered as the number of readmissions related to the hip or knee surgery. LoS was evaluated as time in days between hospital admission and discharge. Clinical outcomes were assessed in terms of functional recovery and with the use of PROMs. Costs included only intramural hospital costs and were reported in the monetary unit of the study.

Risk of bias

For all included studies, a risk-of-bias (RoB) table was used to identify potential sources of bias with the use of the Cochrane Collaboration tool[23] or the ROBINS-I tool[24] for RCTs and non-randomized studies, respectively. Two authors (MH and MS) independently assessed the RoB. The outcomes of all studies were reported using Grading of Recommendation, Assessment, Development and Evaluation (GRADE)[25].

Statistical analysis

Outcomes were summarized using RevMan 5.3[21]. We extracted all data used from the original studies. To quantify the statistical heterogeneity in the studies, the I^2 value was used. Only if studies were sufficiently clinically, methodologically, and statistically homogenous, the data were pooled in a meta-analysis. In case of considerable heterogeneity (> 75%), a qualitative analysis was performed[23] and outcomes between included studies were described. In the situation where one of the sensitivity analyses showed no considerable heterogeneity (< 75%), a meta-analysis was performed on this outcome. For the meta-analysis, we used a random effects model and report relative risk (RR) with 95% confidence interval (CI). We present the results within forest plots, subdivided for type of arthroplasty (THA, TKA, and/or UKA). If no distinction between the different arthroplasties was possible, analysis for the combined group were included as a subgroup (THA and/or TKA and/or UKA). In a sensitivity analysis, we also combined (S)AE with a follow-up time of 30 d or more and readmission rate as one combined outcome, as they are interrelated in clinical practice. Studies for (S)AE with a follow-up time of 30 d or more were analyzed because of their clinical relevance. P value ≤ 0.05 was considered statistically significant.

RESULTS

The full search strategies can be found in the Supplementary material (Databases and search strings). This systematic search identified 7901 references. The literature search and selection process are shown in Figure 1. After removal of duplicates, 4502 references remained for screening on title and abstract. Of these, 106 full-text articles were assessed for eligibility. No additional records were identified by checking reference lists. Eventually, 40 studies were included[3,7,26-63]. A summary of the characteristics of these studies is given in Table 1.

We included five RCTs[7,28,30,35,38], six prospective cohort studies[31,33,37,41,50,52], thirteen retrospective cohort studies[36,42-44,46,51,53,54,57-59,62,63], five observational cohort studies[27,34,45,47,60], four case control studies[3,48,49,56], four comparative studies with prospective[32,61] and retrospective designs for the standard CPs[39,55], and one each prospective pilot study[26], prospective follow-up study[29], and propensity score matched study[40]. Nine articles studied THA[26,29,38,41,50,52,54,60,63], nineteen studied TKA[3,7,30-33,36,37,39,42,44,48,49,51,55,58,59,61,62], six studied UKA[3,43,45,48,55,56], and eleven studied both hip and knee arthroplasty[27,28,34,35,40,43,46,47,53,56,57]. Of the included studies, which were published between 1999 and 2018, eighteen were conducted in the United States[26,30,31,36,38,40,42-46,51,53-55,59,60,63], five in the Netherlands[3,27,48,50,56], three each in the United Kingdom[34,37,41], Germany[7,32,33], and Canada[35,49,61], two in Spain[29,57], and one each in Australia[28], Malaysia[39], Italy[58], New Zealand[47], Denmark[52], and Finland[62]. The setting varied from a hospital[3,26,27,34,41,47,48,50,56,57,60-62] to a medical[36,40,42,43-46,53,54,59] or orthopedic center[7,35,37,38,51,52,55,58,63], a tertiary[28,30,49] or a university hospital[29,32,33,39], or a single institution[31].

The total sample size consisted of 2223534 patients undergoing hip or knee arthroplasty; 997765 patients were treated according to ERP compared with 1225769 patients with regular pathways (Table 1). Overall, more female patients were included (60.1%). Of 5095 (0.2%) patients, sex was not reported. The mean age was 65.1 years for patients with ERP and 66.5 years for those with regular pathways. The mean body mass index was similar for both CPs (30 kg/m^2). In ERP, 25 studies applied enhanced elements during the pre-operative phases, mostly for education[27,32-36,41,47,50,52,57,61,62], 19 applied during the peri-operative phase, *e.g.*, for pre-medication or neuraxial-regional anesthesia[3,26,34-37,41,47,50,57,58,60], and 35 during the postoperative phase, mostly for the rehabilitation program or early discharge home[3,7,26,27,29,31,32,35,36,38,40,42-49,51,54,55,57,59-61]. An overview of the pre-, peri-, and postoperative management during ERP is listed in Table 2.

Risk of bias

The methodological quality is presented in a RoB summary (Figures 2 and 4) and as percentages (Figures 3 and 5) for the RCTs and non-randomized studies, respectively. Blinding of participants and personnel was not possible because of the content of the CPs. Selection bias was unclear in three RCTs (60%) and blinding of outcome in two RCTs (40%). Five non-randomized studies were of high quality with a low RoB, whereas three were of low-quality with a serious RoB. All low-quality studies had bias due to confounding. A serious or critical bias in the selection of the reported results was found in the majority of studies (71%). In 31% of the studies, the outcome could have been influenced by knowledge of the applied CPs. Five studies reported missing data (14%), and four had bias due to selection of participants (11%). Overall, the methodological quality of the included studies ranged from average to

Table 1 Characteristics of the included studies, patient demographics, ERP versus regular pathways, and outcome

Author/year	Procedure	Study design	Country/setting	ERP/regular pathway	Number participants ERP/regular pathway	Participants characteristics ERP/regular pathway	Outcome
Arshi *et al*[42]; 2017	TKA	Retrospective cohort	United States; Humana subset of the pearl-diver patient record database	Outpatient/inpatient	*n* = 133.342; 4.391/128.951	Age: (70-74), modus 65-69; Men-women: (1.560-2.831)/(46.805-82.146)	LoS, (S)AE
Auyong *et al* [36]; 2015	TKA	Retrospective cohort	United States; Medical center	Updated ERAS/ERAS	*n* = 252; 126/126	Age: 66.02 (10.02)/68.44 (9.98); Men-women: (44-82)/(41-85); BMI: 31.88 (7.629)/31.3 (6.562)	LoS, (S)AE, functional recovery, PROMs, readmission
Basques *et al* [43]; 2017	THA; TKA	Retrospective matched cohort	United States; NSQIP database	Same day/inpatient	*n* = 177.818, 1.236/176.582; THA: *n* = 63.360, 368/368; TKA: *n* = 110.410, 608/608; UKA: *n* = 4.048, 260/260	Age: Most between 65-74; Men-women: (46.6%-53.4%)/(39.8%-60.2%); BMI: Most between 25-29.9	LoS, (S)AE, readmission
Bertin *et al*[26]; 2005	THA	Pilot study, retrospectively chosen control group	United States; Hospital	Outpatient/existing protocol	*n* = 20; 10/10	Age: 62/63; Men-women: (6-4)/(5-5); BMI: 30.024/29.64	LoS, (S)AE, costs
Bovonratwet *et al*[44]; 2017	TKA	Retrospective cohort	United States; NSQIP database	Outpatient/inpatient	*n* = 112.922; 642/112.280	Age: 64/67; Men-women: (265-377)/(41.821-70.459); BMI: 32/33	LoS, (S)AE, readmission
Bovonratwet *et al*[45]; 2017	UKA	Cohort	United States; NSQIP database	Outpatient/inpatient	*n* = 5880; 568/5312	Age: 62.9/63.7; Men-women: (284-284)/(2501-2811); BMI: 31.5/31.6	LoS, (S)AE, readmission
Brunenberg *et al* [27]; 2005	THA; TKA	Before-after trial	Netherlands; University hospital	Joint recovery programme/usual care	*n* = 160; THA: *n* = 98, 48/50; TKA: *n* = 62, 30/32	Age: 64.4 (28-87); THA: Age 63.38 (11.48)/ 65.4 (13.04), Men-women% (35.4-64.6)/(24-76); TKA: Age 64.9(9.43)/63.94 (12.6), Men-women % (33.3-66.7)/(31.3-68.7)	LoS, functional recovery; PROMs; costs
Castorina *et al* [58]; 2017	TKA	Retrospective observa-tional cohort study	Italy; Orthopedics traumatology and rehabil-itation unit	Fast track/traditional group	*n* = 132; 95/37	Age: 71.1 (7.77)/74.62 (± 6.42)	Functional recovery; (S)AE
Courtney *et al* [46]; 2017	THA; TKA	Retrospective cohort	United States; NSQIP database	Outpatient/inpatient	*n* = 169.406; 1220/168.186	Age: 63.1/65.9; Men-women: (539-681)/(67.687-100.499); BMI: 32.1/31.7	LoS, (S)AE, readmission
Courtney *et al* [59]; 2018	TKA	Retrospective cohort	United States; NSQIP database	Outpatient/short stay/LOS ≥ 2 d	*n* = 49.136; 365/3033/45.738		LoS, (S)AE, readmission
den Hertog *et al* [7]; 2012	TKA	Randomized prospective study	Germany; Hospital	Fast-track group/standard care re-habilitation	*n* = 147 (ITT), 74/73; *n* = 140 (PP), 71/69	Age: 66.58 (8.21)/68.25 (7.91); Men-women: (23-51)/(20-53); BMI: 31.17 (5.82)/30.38 (6.05)	LoS, (S)AE, functional recovery, PROMs
Dowsey *et al* [28]; 1999	THA; TKA	Prospective randomized controlled study	Australia; Tertiary hospital	Clinical pathway/control	*n* = 163; 92/71	Age: 64.2/68.2; Men-women: 56/107	LoS, (S)AE, functional recovery, readmission
Featherall *et al* [60]; 2018	THA	Cohort	United States; Clinic	Full protocol/transition cohort/Pre-protocol	*n* = 6090; 2081/2009/2000	Age: 63.77 (11.72)/64.09 (12.04)/64.03 (12.09); Men-women: (1033-1048)/(983-1026)/(960-1040); BMI: 30.13 (6.17)/ 29.93 (6.19)/ 30.09 (6.38)	LoS, (S)AE, cost

Gauthier-Kwan *et al*[61]; 2018	TKA	Prospective comparative cohort	Canada; Hospital	Outpatient/inpatient	*n* = 86; 43/43	Age: 62.5 (50.4-75), 62.5 (51.2-74); Men-women: (29-14)/(22-21); BMI: 28.6 (23.7-35.8)/30.4 (23.5-41.6)	LoS, (S)AE, readmission, functional outcome, PROMs
Gooch *et al*[35]; 2012	THA; TKA	RCT	Canada; Bone and Joint Health Institute	New clinical pathway/standard care	*n* = 1570, 1066 (THA: 615; TKA: 451)/504 (THA: 278; TKA: 226)	Age: 69 (11.1)/69 (10.4); Men-women%: (39.6-60.4)/(40.1-59.9); BMI: 29.5 (5.6)/29.4 (5.4)	(S)AE, functional recovery, PROMs
Goyal *et al*[38]; 2017	THA	Prospective randomized study	United States; Two reconstruction centres	Outpatient/inpatient	*n* = 220; 112/108	Age: 59.8 (8.5) (59.3) (27-74)/60.2 (8.9) (61) (34-74); Men-women: (59-53)/(58-50); BMI: 27.6 (4.1) (27.1) (18-38.4)/ 28.3 (4.7) (27.7) (18.4-39.9)	LoS, (S)AE, readmission, functional recovery, PROMs
Gwynne-Jones *et al*[47]; 2017	THA; TKA	Matched cohort study	New Zealand; Hospital	Post ERAS/pre ERAS	*n* = 1035, 528/507; THA: 318/314; TKA: 210/193	THA: Age 68.3 (11.8)/66.8 (11.8), Men-women (146-172)/(146-168); TKA: Age 70.4 (8.9)/69.8 (9.0), Men-women: 107-103/83-110	LoS, (S)AE, readmission, PROMs
Ho *et al*[30]; 2007	TKA	Randomized controlled trial; retrospective cost analysis	United States; Tertiary teaching hospital	Critical pathway/no uniform CP	*n* = 90; 3 cohorts: 30/30/30	Age: 66/67/68; Men-women: (14-16)/(14-16)/(14-16); Weight: 89/91/88	LoS, (S)AE, costs
Hoorntje *et al* [48]; 2017	UKA	Case control study	Netherlands; Hospital	Outpatient/fast-track	*n* = 40; 20/20	Age: 62.2 (5.5)/63.8 (7.5); Men-women: (10-10)/(7-13); BMI: 27.8 (3.7)/30.5 (7.0)	LoS, PROMs
Huang *et al*[49]; 2017	TKA	Prospective case control study	Canada; Tertiary academic medical centre	Same day discharge/inpatient	*n* = 40; 20/20	Age: 58.5 (5.6)/61.5 (5.9); Men-women: (14-6)/(14-6); BMI: 29.0 (3.7)/30.6 (5.3)	LoS, (S)AE, readmission, cost
Ismail A *et al* [39]; 2016	TKA	Non-randomized control trial	Malaysia; University hospital	CP/control	*n* = 152; 73/79	Age: 66.1/64.7	LoS, (S)AE, readmission
Jimenez Muñoz *et al*[29]; 2006	THA	Prospective follow-up study	Spain; University general hospital	After CP/prior CP	*n* = 487; 384/98; 309/75	Not present	LoS, (S)AE
Klapwijk *et al* [50]; 2017	THA	Prospective cohort	Netherlands; Hospital	Outpatient/inpatient	*n* = 94; 42/52	Age: 61 (41-78)/68 (48-82); Men-women: (17-25)/(21-31); BMI: 29 (20-35) /26 (18-39)	LoS, (S)AE, functional recovery, PROMs
Klingenstein *et al*[51]; 2017	TKA	Retrospective cohort	United States; Joint replacement centre	Short stay/traditional stay	*n* = 2287; 1502/785	Age: 71.7 (5.4)/73.3 (6.1); Men-women%: (39-61)/(25-75); BMI ≥ 30 (%): 50/57	LoS, (S)AE, readmission
Kolisek *et al*[31]; 2009	TKA	Prospective matched cohort	United States; Hospital	Outpatient/conventional inpatient stay	*n* = 128; 64/64	Age: 55 (42-64)/55 (42-63); Men-women: (40-24)/(40-24); BMI: 30.8 (24.3-38)/30.8(24.2-37.8)	LoS, (S)AE, functional recovery, PROMs, readmission
Kort *et al*[3]; 2017	UKA	Case control study	Netherlands; Hospital	Outpatient/rapid recovery	*n* = 40; 20/20	Age: 60.5 (5.65)/61.2 (5.15); Men-women: (13-7)/(11-9); BMI: 29.1 (3.85)/27.7 (3.27)	LoS, (S)AE, readmission, PROMs
Larsen *et al*[52]; 2017	THA	Observational cohort	Denmark; Orthopedic clinic	Day case (< 12 h)/standard 2-d	*n* = 56; 20/36	Age: 64.6; Men-women: 15-5; BMI: 28.8 (23.8-33.7)	LoS, (S)AE, readmission, PROMs
Lovecchio *et al* [40]; 2016	THA; TKA	Propensity score matched study	United States; NSQIP database	Outpatient/fast-track inpatients	*n* = 1968, 492/1476; THA/TKA: (183-585)/(309-891)	Age: Most between 60 to 69; Men-women: (217-275)/(664-812); BMI between 25-30	LoS, (S)AE, readmission
Maempel *et al*	THA	Prospective cohort	United Kingdom; Hospital	ERP/traditional rehabilitation	*n* = 1161; 550/611	Age: 64 (18-94)/66 (23-90); Men-women: (212-	LoS, (S)AE,

[41]; 2016						338)/(242-369); BMI: 30 (7)/29 (7)	functional recovery, PROMs
Maempel *et al* [37]; 2015	TKA	Non-randomized prospective cohort	United Kingdom; Arthroplasty clinic	ERP/traditional rehabilitation	*n* = 165; 84/81	Age: 69.8 (8.9)/70.1 (10.5); Men-women: (42-42)/(37-44); BMI: 32.4 (22.6-46.6)/31.8 (20.5-41.9)	LoS, (S)AE, functional recovery
Malviya *et al* [34]; 2011	THA; TKA	Observational study	United Kingdom; Hospital	ERP/traditional pathway	*n* = 4500; 1500 (THA: 630; TKA: 870)/3000 (THA: 1368; TKA: 1632)	Age: 68/69; Men-women: (711-789)/(1482-1518)	LoS, (S)AE, readmission
Nelson *et al*[54]; 2017	THA	Retrospective cohort, data prospectively collected	United States; NSQIP database	Outpatient/inpatient	*n* = 63.844; 420/63.424	Age: 62/65; Men-women: (222-198)/(28.587-34.833); BMI most between 25-30	LoS, (S)AE, readmission
Pamilo *et al*[62]; 2018	TKA	Retrospective cohort	Finland; Finnish Hospital Discharge Register	Fast-track CP/non-fast-track	*n* = 4256, 2310/1946; Hospital A: 624/437	Age and sex: No statistically significant difference between CP's	LoS, (S)AE, readmission
Renkawitz *et al* [32]; 2010	TKA	Prospective parallel group design	Germany; Orthopaedic university medical centre	Optimized accelerated CP/standard CP	*n* = 143; 67/76	Age: 67 (9)/68.1 (11.1); Men-women: (14-53)/(23-53); BMI: 31.4 (5.1)/30.7 (5.6)	LoS, (S)AE, readmission, functional recovery
Richter *et al*[55]; 2017	UKA	Retrospective chart review	United States; Surgical outpatient center	Outpatient/inpatient	*n* = 22; 12/10	Age: 67.2 (9.2)/64.5 (9.8); Men-women: (7-5)/(8-2); BMI: 28.7 (5.1)/25.8 (8.1)	LoS, (S)AE, readmission, cost
Schotanus *et al* [69]; 2017	TKA; UKA	Case control study	Netherlands; Hospital	Outpatient/ERP	*n* = 361; 94/267	Age: 63.4 (8.0)/68.4 (9.0); Men-women: (49-45)/(94-173); BMI: 28.25 (3.68)/29.49 (5.05)	LoS, PROMs
Toy *et al*[63]; 2018	THA	Retrospective cohort	United States; Ambulatory surgery centers	Later outpatient pathway/initial outpatient pathway	*n* = 145; 72/73	Age: 55 (27-70); Men-women: 76-49; BMI: 29.7 (19.6-43)	LoS, (S)AE, readmission
Wilche *et al*[57]; 2017	THA; TKA	Retrospective review	Spain; Hospital	Fast-track recovery/conventional recovery	*n* = 200; THA: 50/50; TKA: 50/50	Age: 69.24 (9.64)/73.07 (8.33); Men-women: (40-60)/(40-60)	LoS, (S)AE, readmission, cost

Age in years, mean ± SD (median) (range); Weight in kg. BMI: Body mass index; NSQIP: National Surgical Quality Improvement Program; THA: Total hip arthroplasty; TKA: Total knee arthroplasty; CP: Clinical pathway; UKA: Unicompartmental knee arthroplasty; Los: Length of hospital stay; (S)AE: (Serious) adverse events; PROMS: Patient reported outcome measures; ERP: Enhanced recovery pathways; ERAS: Enhanced Recovery After Orthopedic Surgery; RCT: Randomized controlled trial.

good.

Heterogeneity

The studies varied clinically (*e.g.*, patient characteristics and CPs) and methodologically. Different measurement tools were used, and outcome measures were reported in different ways across studies. Therefore, a meta-analysis was only feasible with studies that used the same measurement tools. For this study, data for the sensitivity analyses were pooled for (S)AEs and readmission rate. A qualitative analysis was performed for the results of LoS, functional recovery, PROMs, and costs.

(S)AEs and readmission rate

Thirty-five studies examined AEs, SAEs, or both[3,7,26,28-32,34-47,49-52,54,55,57-63] and twenty four examined readmission rate[3,28,31,32,34,36,38,39,40,43-47,49,51-52,54,55,57,59,61-63]. The follow-up time

Table 2 Pre-, peri-, and post-operative management during enhanced recovery pathways

Author	Year	ERP			Preoperative					Peri-operative							Post-operative				
		Pre-operative	Peri-operative	Post-operative	Education	Outpatient consultation	Discharge planning	Physiotherapy	Pre-assessment outpatient clinic	Day of surgery admission	Pre-medication	Optimal hydration	Neuraxial-regional anaesthesia	Multimodal blood loss reduction	+/- peri articular injection	Avoid surgical drains	Multimodal analgesia regimen	Day of surgery mobilisation	Venous thromboembolic prophylaxis	Rehabilitation programme	Early discharge home
Arshi *et al*[42]	2017			X																	X
Auyong *et al*[36]	2015	X	X	X	X						X		X				X	X			X
Basques *et al*[43]	2017			X																	X
Bertin *et al*[26]	2005	X	X	X				X			X		X							X	X
Bovonra-twet *et al*[44]	2017			X																	X
Bovonra-twet *et al*[45]	2017			X																	X
Brunen-berg *et al*[27]	2005	X		X	X				X											X	
Casto-rina *et al*[58]	2017	X	X	X									X				X				
Court-ney *et al*[46]	2017			X																	X
Court-ney *et al*[59]	2018			X																	X
den Hertog *et al*[7]	2012	X		X														X		X	X
Dowsey *et al*[28]	1999		X	X																	

Featherall *et al*[60]	2018	X	X	X					X						X		X			X	
Gauthier-Kwan *et al*[61]	2018	X	X	X	X						X		X				X			X	X
Gooch *et al*[35]	2012	X	X	X	X	X	X	X			X		X					X		X	
Goyal *et al*[38]	2017			X													X				X
Gwynne-Jones *et al*[47]	2017	X	X	X	X					X	X		X	X				X		X	
Ho *et al* [30]	2007	X	X																		
Hoorntje *et al*[48]	2017	X	X	X								X								X	X
Huang *et al*[49]	2017	X	X	X		X				X					X					X	
Ismail A *et al*[39]	2016																				
Jimenez Muñoz *et al*[29]	2006			X																X	X
Klapwijk *et al*[50]	2017	X	X	X	X						X		X			X		X			
Klingenstein *et al*[51]	2017			X																	X
Kolisek *et al*[31]	2009	X		X														X		X	X
Kort *et al*[3]	2017	X	X	X			X	X		X	X									X	X
Krummenauer *et al*[33]	2011	X		X	X	X														X	
Larsen *et al*[52]	2017	X		X	X													X			

Lovecchio *et al*[40]	2016			X																	X
Maempel *et al*[41]	2016	X	X	X	X	X	X	X					X					X			
Maempel *et al*[37]	2015	X	X	X		X				X			X					X			
Malviya *et al*[34]	2011	X	X	X	X				X		X		X					X			
Molloy *et al*[53]	2017																				
Nelson *et al*[54]	2017			X																	X
Pamilo *et al*[62]	2018	X			X	X															
Renkawitz *et al*[32]	2010	X	X	X	X	X			X									X		X	
Richter *et al*[55]	2017			X																	X
Schotanus *et al*[69]	2017	X	X	X			X			X								X			
Toy *et al* [63]	2018	X				X															
Wilches *et al*[57]	2017	X	X	X	X				X		X	X	X	X				X		X	

ERP: Enhanced recovery pathways.

varied from 8 d up to 24 mo postoperatively.

In the ERP, there were less (S)AEs (RR: 0.9; 95%CI: 0.8-1) and a lower readmission rate (RR: 0.8; 95%CI: 0.7-1) when compared to the regular pathways. The analyses for overall (S)AEs resulted in considerable heterogeneity (I^2 = 83%, P = 0.2). Studies of (S)AEs with a follow-up time of 30 d or more yielded a RR of 0.9 (95%CI: 0.8-1), with substantial heterogeneity (I^2 = 74%, P = 0.3) (Figures 6 and 7). Only the THA subgroup showed heterogeneity (I^2 = 89%, P = 0.7) while the TKA (I^2 = 21%, P = 0.2) and the combined groups (THA and TKA; I^2 = 47%, P = 0.1) were homogeneous.

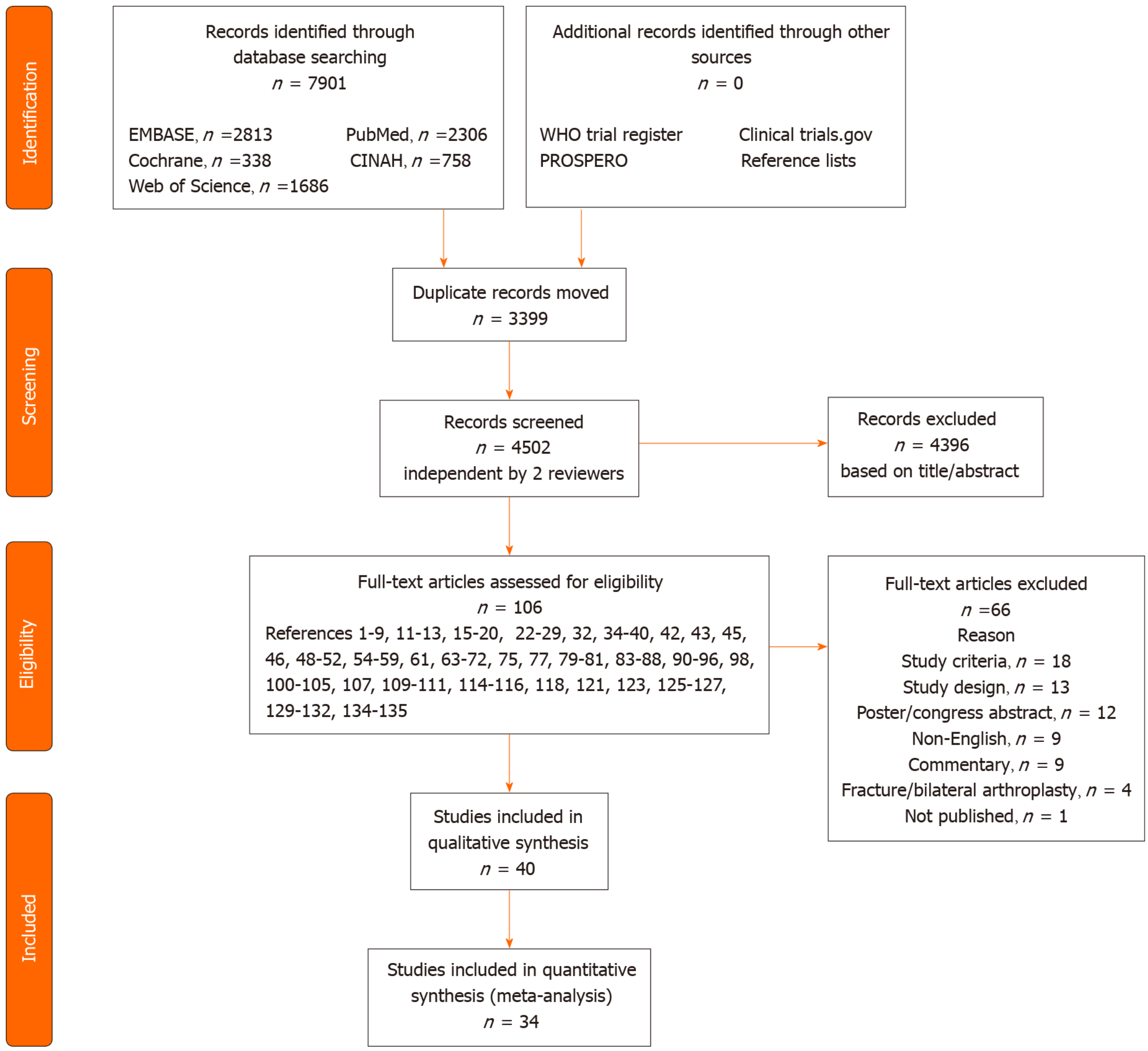

Figure 1 Flow diagram of the literature search and selection procedure. WHO: World Health Organization.

The analyses for readmission rate were homogenous (I^2 = 48%, P = 0.2). The readmission rate in ERP was statistically significant different in favor of the knee arthroplasties without heterogeneity (TKA: I^2 = 15%, P = 0.01; UKA: I^2 = 0%, P = 0.01). The plots for readmission rate for THA, TKA, UKA, and the combined subgroups (THA and TKA) are shown in Figures 8 and 9.

Sensitivity analyses of (S)AEs together with readmission rate resulted in a RR of 0.9 (95%CI: 0.7-1) with substantial heterogeneity (I^2 = 84%, P = 0.1). According to GRADE, there was moderate quality of evidence for (S)AE and readmission rate (Table 3).

Length of hospital stay

Thirty-eight studies described LoS[3,7,26-34,36-57,59-63]. A reduced LoS was found in all ERPs, of which 20 studies reported a statistically significant reduction ranging between 0.5-10.1, 3.2-10.0, 2.8-7.1, and 2.6 d for the THA[29,41,50,52,60,63], TKA[7,30,32,36,37,39,62], the combined outcome of THA and TKA[27,28,34,47,53,57], and UKA[3], respectively. The overall median LoS reduced up to 6.5 d. For regular pathways, the median values were between 0.5 and 16 d and the mean values were between 1.5 to 19.5 d. All the analyzed arthroplasties showed high heterogeneity for LoS (> I^2 = 98%). The GRADE table shows high evidence for LoS (Table 3).

Clinician-derived outcome and PROMs

Functional recovery was assessed in 13 studies for THA[38,41,50], TKA[7,31,32,36,37,58,61], and the combined subgroup THA and TKA[27,28,35], respectively. The Harris Hip Score, Range of Motion, and scores from the American Knee Society were mostly reported. Four articles studied THA[38,41,50,52], six studied TKA[7,31,33,36,56,61], and three each studied UKA[3,48,56] and both THA and TKA[27,35,47] regarding the PROMs, using similar measurement types. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) questionnaire, EuroQual, Oxford Knee Score, and pain scales were mostly used as PROMs.

Table 3 Grading of Recommendation, Assessment, Development and Evaluation evidence profile: Enhanced recovery pathways compared to regular pathways for hip and knee arthroplasty

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	(S)AE	Control	Relative (95%CI)	Absolute		
Functional recovery (follow-up 24 mo)												
12	Randomised trials	No serious risk of bias	Serious[1]	No serious indirectness	No serious imprecision	None	0/2289 (0%)	0/1802 (0%) 0%	Not pooled	Not pooled Not pooled	Moderate	Important
PROMs (follow-up 24 mo; Better indicated by lower values)												
15	Randomised trials	No serious risk of bias	Serious[2]	No serious indirectness	No serious imprecision	None	2966	2388	-	Not pooled	Moderate	Important
LoS (follow-up 24 mo; Better indicated by lower values)												
38	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	997447	1573895	-	MD 2.45 lower (3.42 to 1.48 lower)	High	Important
(S)AEs												
34	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[3]	No serious imprecision	None	2103/18344 (11.5%)	83989/540864 (15.5%) 11.7%	RR 0.91 (0.78 to 1.06)	14 fewer per 1000 (from 34 fewer to 9 more) 11 fewer per 1000 (from 26 fewer to 7 more)	Moderate	Important
Readmission (follow-up 24 mo)												
23	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[4]	None	273/9846 (2.8%)	8360/406167 (2.1%) 2.7%	RR 0.83 (0.65 to 1.07)	3 fewer per 1000 (from 7 fewer to 1 more) 5 fewer per 1000 (from 9 fewer to 2 more)	Moderate	Important

[1]Different outcomes for functional recovery: HHS [with/without range of motion (ROM), pain], American Knee Society Score, ROM.

[2]Different patient reported outcome measures: SF-36, WOMAC, KATZ.

[3]No clear distinction between adverse event (AE) and serious AE.

[4]Wide confidence interval.

(S)AE: (Serious) adverse event; CI: Confidence interval; PROMS: Patient reported outcome measures; LoS: Length of hospital stay; RR: Relative risk.

The follow-up time differed from the first postoperative day up to 24 mo postoperatively. In view of the clinician-derived outcomes and PROMs, the results in the ERP were similar or improved for THA [41,50,52], TKA[31-33,58,61], UKA[48], and the combined group THA and TKA[27], or were statistically significant better than those in the regular pathways for TKA[7,36,56], UKA[3], and the combined group THA and TKA[35,47]. Moderate quality for functional recovery and PROMs is presented in GRADE (Table 3).

Figure 2 Cochrane risk of bias summary of the randomized controlled trials. Review authors' judgements about each risk of bias item. Low RoB (green + symbol), high RoB (red - symbol), or unclear RoB (yellow - symbol) is shown.

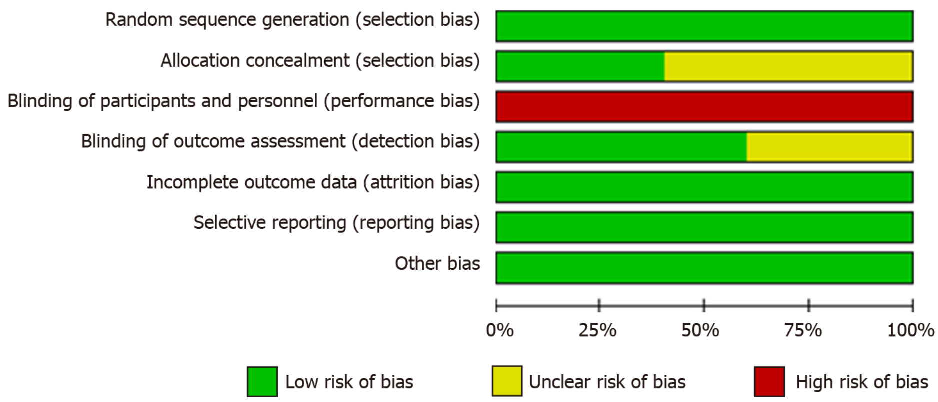

Figure 3 Cochrane RoB graph: Review authors' judgements about each risk of bias item presented as percentages across all included randomized studies.

Costs

Nine observational studies analyzed costs[26,27,30,33,49,53,55,57,60]. The reduction in LoS resulted in statistically significant cost savings for THA in an ERP compared to the regular pathways[26]. Preadmission, physical therapy, and home care charges resulted in a saving for the combined group (THA and TKA) per patient[27] and reduced hospital costs after TKA[30]. Hospital costs were reduced significantly in patients operated for knee arthroplasty in an ERP because of the reduction in room costs, fewer laboratory tests, used medications, physical therapy, and meal costs[30,49,55]. The cost reduction per patient for knee arthroplasty was in favor of the ERP[27,30,33,49,55,57], with a range between €109 and $20573. The cost savings per patient for hip arthroplasty was also higher for the ERP[26,27,57,60] with a range between €581 and $2500. The ERP resulted in a statistically significant economic saving for both knee and hip arthroplasty[49,55,57,60] without affecting complication rate[34], functional improvement, and satisfaction of the patient operated after THA or UKA[26,55]. The individual cost/benefit relation was inferior only in one TKA study[33].

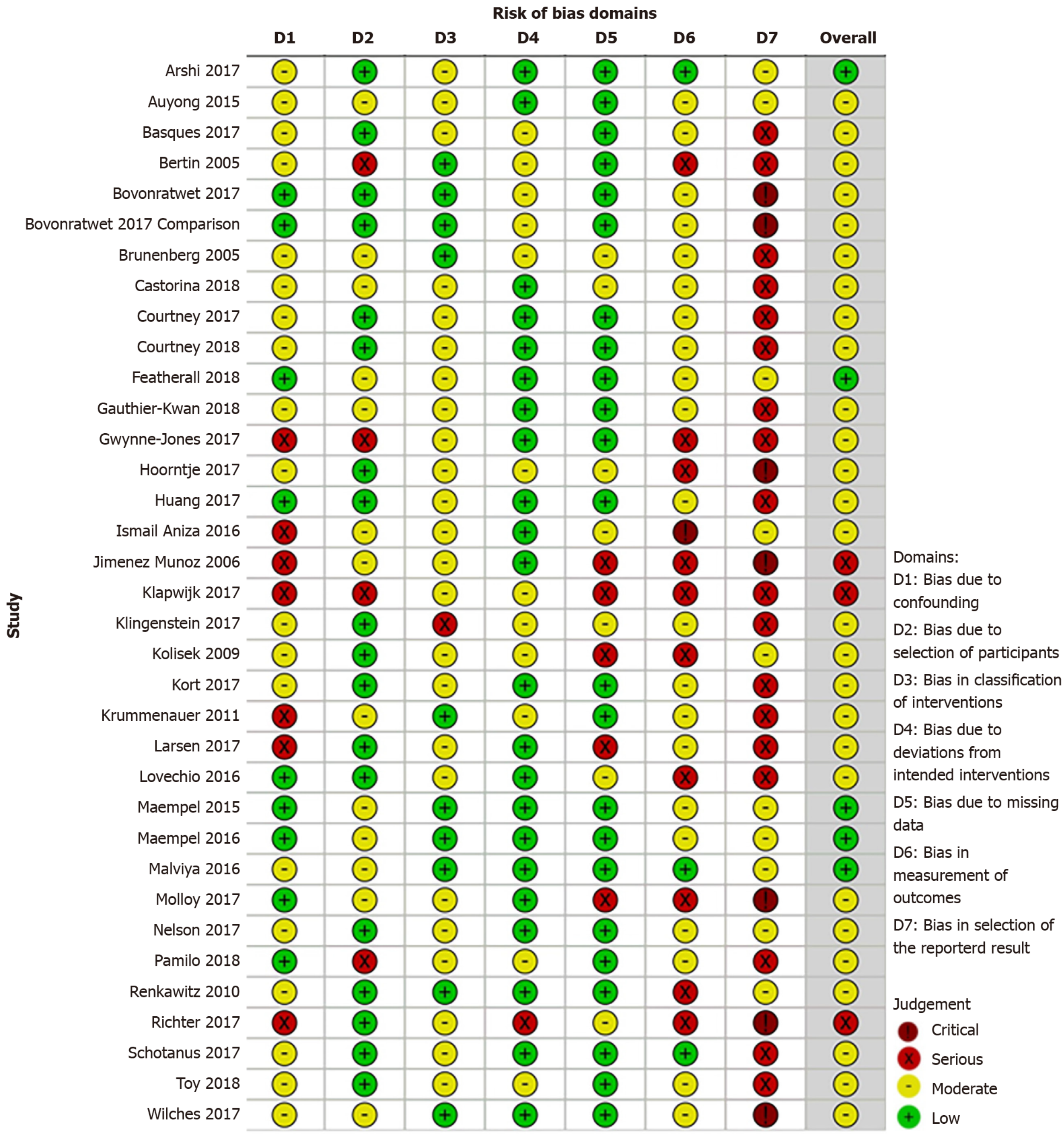

Figure 4 ROBINS-I bias assessment of the non-randomized studies. Review authors' judgements about each risk of bias domain.

DISCUSSION

The most important findings of the present SR and meta-analysis were that the use of ERP yielded similar or improved outcomes for patients with hip and/or knee arthroplasty. In the ERP, there were less (S)AEs and a lower readmission rate when compared to the regular pathways. The readmission rate in the ERP was statistically significant different in favor of the knee arthroplasties without heterogeneity. There were improved results for clinician-derived outcomes and PROMs, reduced LoS, and saved costs compared to regular pathways.

Multiple enhancements can be taken during the pre-, peri-, or post-operative program, to upgrade a regular pathway to enhanced, with respect to local situations. Continuously looking for improvements is important for successful hip and/or knee CPs.

Explanation of findings

The overall methodological quality varied due to the inclusion of five RCTs and 35 observational studies. The studies were heterogeneous regarding patient populations, hospital resources and procedures, multi-disciplinary teams, surgical and anesthetic techniques, practice variation, and follow-up times. Most of the heterogeneity was probably due to methodological differences between the

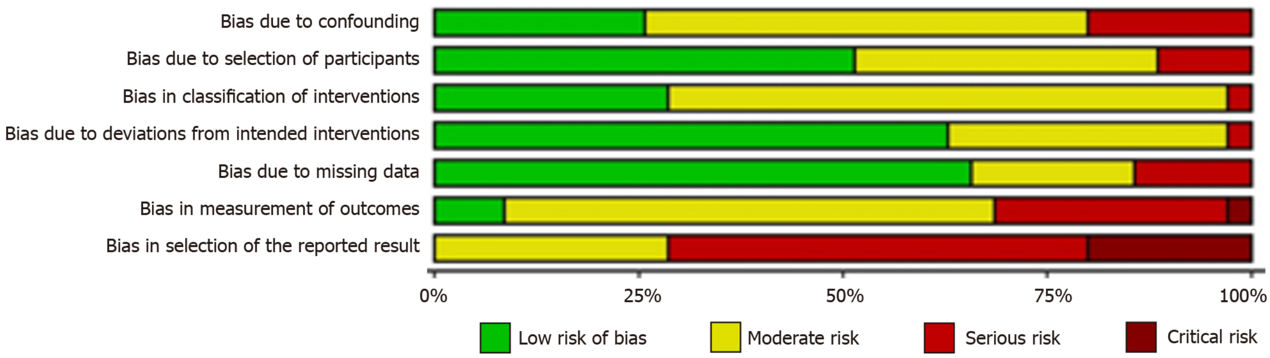

Figure 5 ROBINS-I weighted summary plot.

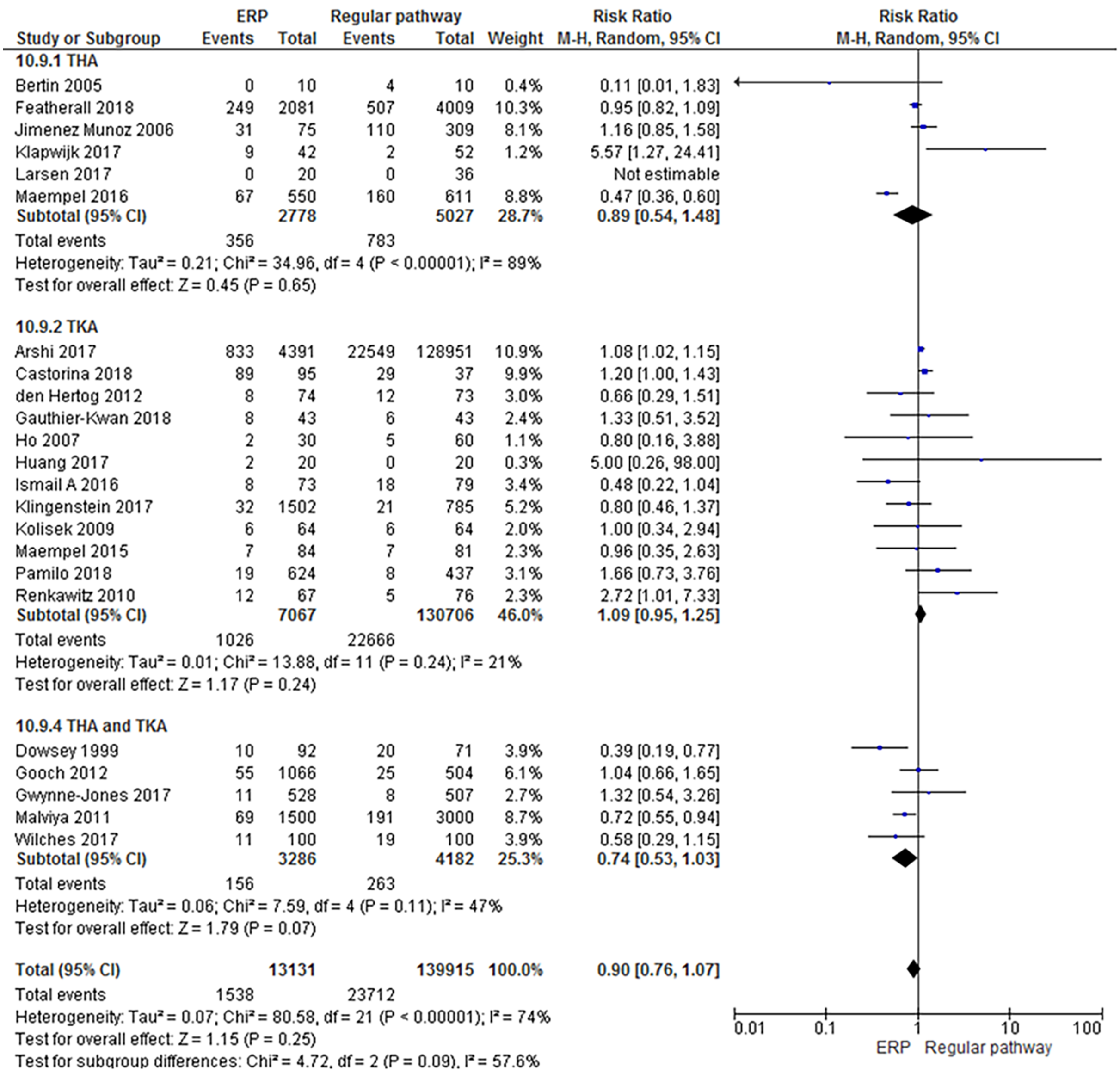

Figure 6 Forest plot with relative risk for each study and pooled relative risk with 95% confidence interval for (serious) adverse events with a follow-up time of 30 d or more for enhanced recovery pathways *vs* regular pathways for hip and knee arthroplasty. THA: Total hip arthroplasty; TKA: Total knee arthroplasty; CI: Confidence interval; ERP: Enhanced recovery pathways.

included studies. The included studies were published throughout the past 20 years, the view of hospital stays after an operation and discharge criteria have been changed over time. And, the obtained data came from different healthcare systems from different countries, from retrospective studies or from national registries. Nevertheless, even within all this practical and methodological variation, the

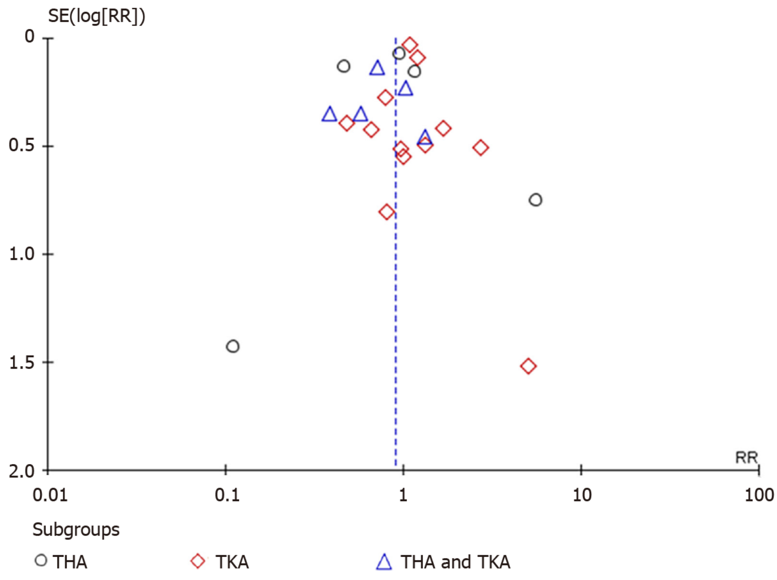

Figure 7 Funnel plot for the studies with described (serious) adverse events with a follow-up time of 30 d or more. THA: Total hip arthroplasty; TKA: Total knee arthroplasty; RR: Risk ratio.

outcomes indicated a positive effect in favor of ERP.

The results of the meta-analysis demonstrated less (S)AEs in patients following the ERP, with fewer readmissions compared to the regular pathways (P = 0.25). Substantial heterogeneity was present when AE and SAE were analyzed together and separately for the different arthroplasties (THA, TKA, and both combined). This heterogeneity was probably due to the lack of definition in primary studies. Also, not all studies made a distinction between AE and SAE. For further investigation, consensus on terminology is recommended. Compared to our findings, another study found statistically significant fewer complications for the ERP compared to the regular pathway[18]. Because of the relative high risk of postoperative complications, careful patient selection for outpatient joint arthroplasty is crucial to obtain successful outcomes[42,44-46,54,63].

All studies showed a reduction in LoS after implementing ERP. In half of these studies, this reduction was statistically significant, which is in line with previous SRs[13,17,18]. LoS can be influenced by preoperative patient education and patient expectations[11,27,28,31,36,37,41,48,57,62,64,65], training in home-based rehabilitation settings[3], and a positive influence from relatives[28,52,53]. The discharge also influenced LoS from the hospital to a rehabilitation center or a center with care facilities instead of discharge to the home environment[28,32,33,47,50]. The reduction of LoS allowed more joint replacements without additional bed capacity and could therefore have a potential positive economic effect[34].

Implementation of CPs for hip and knee arthroplasty were associated with similar or improved outcome for clinician-derived outcome and PROMs. These outcomes represent the best subjective measurement of clinical outcome[66]. However, there is no single best outcome measurement tool after arthroplasty. Besides the positive results of PROMs, various scores are not capturing changes due to a lack of power as averse to a lack of change, *e.g.*, floor and ceiling effects[67]. It could therefore be that further improvement in one of the CPs was not detected. In order to characterize the objective changes in physical activity after arthroplasty in detail, activity monitoring can be used to capture changes over time and to detect potential objective differences[68,69].

This study indicated that patients in the ERP had a substantial reduction in hospital costs, mainly explained by the shorter stay. With a hip arthroplasty incidence of 468000, national cost savings of CP implementation would amount to greater than $1.2 billion annually in costs from a payer perspective in the United States[60]. For joint arthroplasty, the mean hospital cost from 2002-2013 increased about 50%, as a result of rising total joint arthroplasties and prices of implants[53]. Long waiting lists and the contribution to health expenditure growth since joint replacement are expensive interventions, and the increasing economic burden on public healthcare providers should also be taken into account[1,70]. Besides, the improvement of CPs is accomplished with investment in training, knowledge, and adjustments to daily practice for the surgeon, nurse, and physiotherapist[3,58,71]. Establishing the real cost and saving obtained by a CP can be complicated. Savings also depend on charge systems and reimbursement[55,57].

Strengths and limitations

Some limitations should be noted. Due to methodological as well as statistical heterogeneity, a meta-analysis could not be performed for most outcomes. In most of these studies, a high RoB was present,

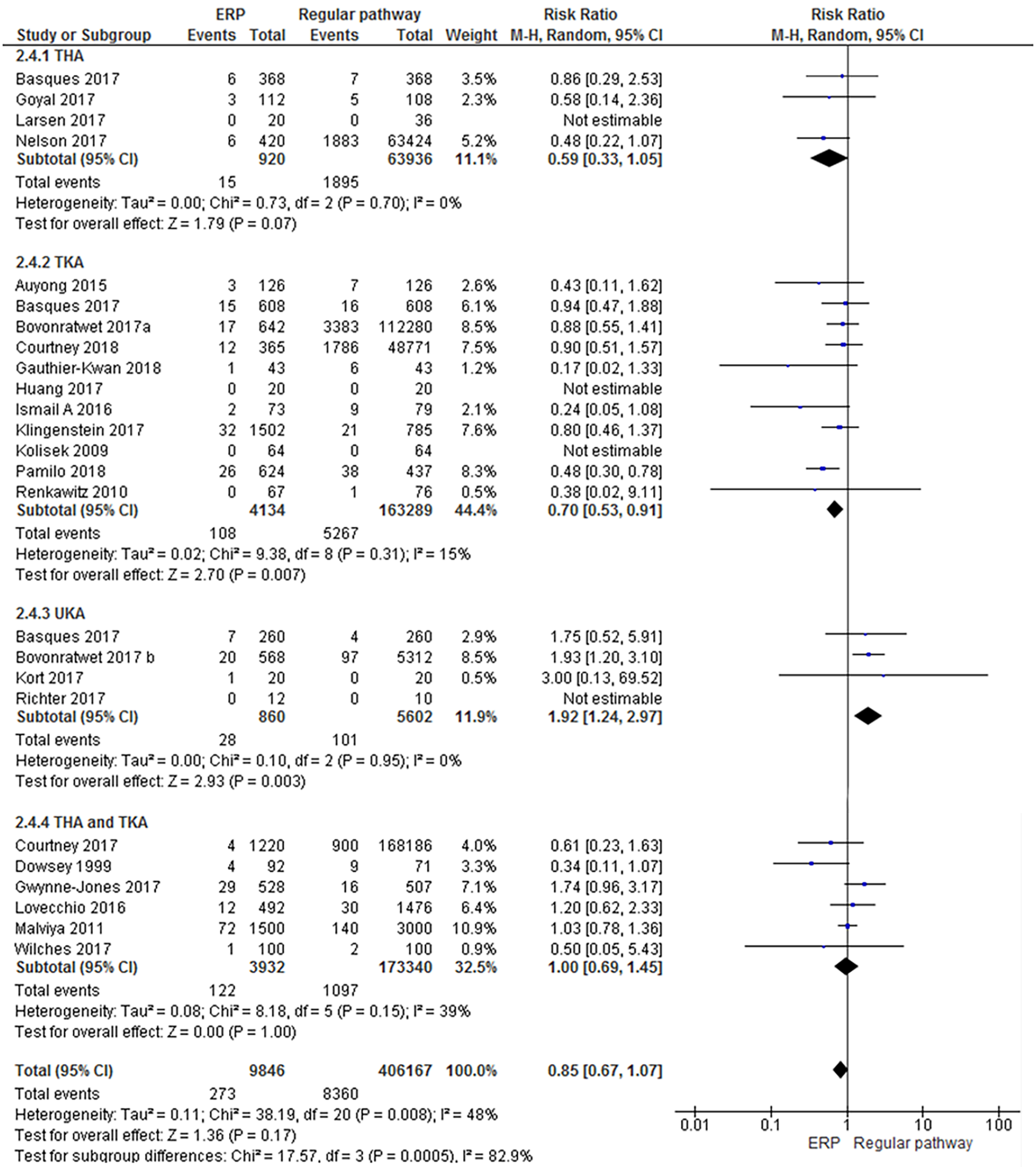

Figure 8 Forest plot with relative risk for each study and pooled relative risk with 95% confidence interval for readmission for enhanced recovery pathways *vs* regular pathways. THA: Total hip arthroplasty; TKA: Total knee arthroplasty; CI: Confidence interval; ERP: Enhanced recovery pathways.

which could have overestimated our results. Selection bias occurred due to the lack of randomization. Performance bias was present because the staff and patients were not blinded to the CP strategy. Clinical bias during data collection was possible because data from large databases were used. Reporting bias is a problem in primary studies because of the selective reporting of outcomes.

Due to the high heterogeneity, it was only possible to perform a meta-analysis for (S)AEs and readmission rate for the different arthroplasties. Although a cut-off I^2 value of 75% has been chosen beforehand, we also present results that exceed this limit, to indicate the trend, *e.g.*, (S)AEs with a follow-up of 30 d or more in the THA (I^2 = 89%, P = 0.7).

The lack of a clear definition for regular pathways and ERP makes it difficult to pool results and compare between large groups of studies. By pointing out the enhanced aspects, we tried to solve this limitation as much as possible.

The strengths of this review include an extensive literature strategy. All included studies compared outcomes from an enhanced recovery pathway with a regular pathway. Data from a large population of

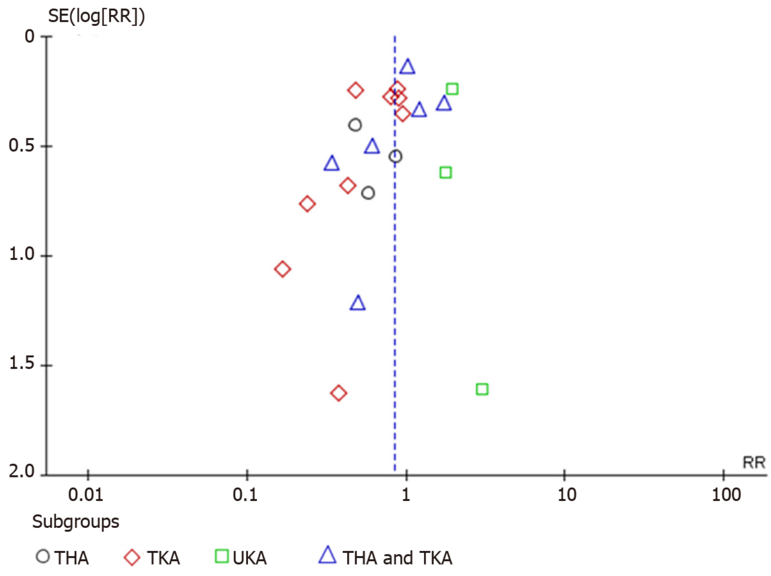

Figure 9 Funnel plot for the studies with described readmission. THA: Total hip arthroplasty; TKA: Total knee arthroplasty; UKA: Unicompartmental knee arthroplasty; RR: Risk ratio.

over 2 million patients were analyzed, including both hip and/or knee arthroplasty, with different follow-up times and outcome measures. Even, an update with the recent literature will provide comparable insights to continuously updating CPs to achieve the most optimal results for patients, professionals, and organizations.

CONCLUSION

Based on the present SR and meta-analysis, it can be concluded that ERPs for hip and/or knee arthroplasty can result in less SAEs with reduced readmission rate and length of stay, and similar or improved clinical outcomes and PROMs with financial benefits, when compared to regular pathways.

ARTICLE HIGHLIGHTS

Research background

Over the past 20 years, clinical pathways (CPs) for total knee and hip arthroplasty have been evolved and optimized. Based on novel evidence and new standards, at this moment we can safely discharge patients on the day of surgery. Whereas in the past, 2-wk bed rest was the standard.

Research motivation

A clinical pathway is a stochastic process that needs to be updated with the latest evidence so the hospital, orthopedic surgeon, and other staff involved in this multidisciplinary approach will be satisfied, with financial benefits for the hospital and improved outcome for the patients. Although, these days in modern medicine, orthopedic surgeons, nurses and hospital staff still needs to be convinced by these optimized CPs. For this reason, we did this systematic review and meta-analysis.

Research objectives

The aim of the present review was to compare the effect of enhanced recovery pathways with regular pathways for adult patients with elective hip and/or knee arthroplasty for (serious) adverse events [(S)AEs], readmission rate, length of hospital stay (LoS), clinician-derived clinical outcomes, patient reported outcome measures (PROMs), and costs.

Research methods

A systematic literature search was conducted in EMBASE, PubMed, Cochrane Library, Web of Science, and CINAHL. All relevant studies were considered for analysis based on the defined eligibility criteria. For the included studies, the risk of bias was assessed. Data for sensitivity analysis were pooled for (S)AE and readmission. A qualitative analysis was performed for the results of LoS, clinician-derived outcome, PROMs, and costs.

Research results

A total of 40 studies were included, 34 in meta-analysis and 40 in qualitative analysis, with data of more than 2 million patients. The meta-analysis presented less (S)AEs in patients following the enhanced recovery pathways (ERP), with fewer readmissions when compared to the regular pathways. The readmission rate was statistically different in favor for the knee arthroplasties without heterogeneity. A reduced LoS was found in all ERP, and in half of these studies, this reduction was statistically significant. The implementation of CPs for hip and knee arthroplasty was associated with similar or improved outcome for clinician-derived outcome and PROMs. ERP were reported to be cost effective. The overall outcomes of all studies reported using Grading of Recommendation, Assessment, Development and Evaluation, presented moderate or high quality of evidence.

Research conclusions

The implementation of ERP for hip and/or knee arthroplasty results in improved clinical and patient related outcomes with financial benefits, compared to regular pathways.

Research perspectives

Based on the results presented, we recommend orthopedic surgeons worldwide, to keep optimizing their standard pathway with the latest evidence. This paper highlights the importance that regular pathways for hip and knee arthroplasty continuously need to be updated according to the latest scientific evidence, which can result in improved clinical outcomes with satisfied patients and financial benefits for patients, healthcare organizations, and hospital management. In this context, high-quality care for hip and/or knee arthroplasty can be achieved.

FOOTNOTES

Author contributions: Heymans MJ designed the study, gathered and analyzed the data, wrote the initial draft of the manuscript, and managed the study; Kort NP is initiator of pathway optimization; Snoeker BA ensured the accuracy of the data; Schotanus MG conceived the study, analyzed the data, and wrote the manuscript; Kort NP, Snoeker BA, and Schotanus MG revised the manuscript; and all authors read and approved the final manuscript.

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