

Age, sex, race and ethnicity representativeness of randomised controlled trials in peri-operative medicine

W.A. Lindsay^{1,2}, M.M. Murphy^{1,3}, D.S. Almghairbi⁴, I.K. Moppett⁵

1 Health Service Research Centre Fellow, 4 PhD Student, 5 Professor, Division of Clinical Neuroscience, University of Nottingham, Queen's Medical Centre, Nottingham, UK

2 Specialist Registrar, Department of Anaesthesia, Sheffield Teaching Hospitals, Sheffield, UK

3 Specialist Registrar, Department of Anaesthesia, Nottingham University Hospitals, Nottingham, UK

Correspondence to: I.K. Moppett.

Email: iain.moppett@nottingham.ac.uk

Accepted: 2 December 2019

Short title: Representativeness of trials in peri-operative medicine

Key words: peri-operative; trial; age; ethnicity; sex.

Twitter: @IainMoppett

Summary

The applicability of the results of any clinical trial will depend to a large extent on whether the study population is representative of the population seen in clinical practice. The growing older surgical population presents challenges for peri-operative researchers to ensure there is adequate representation of patients in terms of their age, sex, race and ethnicity in clinical trials. A review of purposively sampled published randomised controlled trials was performed to establish the age, sex, race and ethnicity of study participants. These data were compared to national registry data for the relevant surgical populations. We included 224 peri-operative trials that had been cited in 469 retrieved meta-analyses. Of these, 50 (22.3%) had an upper age limit to recruitment. The median (range [IQR]) difference in study population age from the registry population age was -2.4 (-6.2 to 1.0 [-34.7 to 14.5]) years for all the randomised controlled trials identified, -6.2 (-9.4 to -2.8 [-18.6 to 4.6]) years for randomised controlled trials investigating patients undergoing hip arthroplasty and -3.4 (-9.6 to -1.1 [-34.7 to 2.9]) years for trials involving patients undergoing surgery for fractured neck of femur. In 92 (41.1%) randomised controlled trials, the proportion of each sex in the study population was more than 25% different from the proportion in the registry population. Only 5 (2.2%) published data on the race or ethnicity of participants. We conclude that peri-operative randomised controlled trials are unlikely to be representative of the age and sex of clinically treated surgical populations. Researchers must endeavour to ensure representative study populations are recruited to future clinical trials.

Introduction

The applicability of the results of any clinical trial depends to a large extent on whether the study population is representative of the population of patients treated in clinical practice. Ideally, this would at least include representation of: age; sex; race; and ethnicity. The global population is ageing, and it is predicted that by 2050, the number of people aged > 60 y will more than double to 2.1 billion [1]. Fowler et al. have shown that the population of patients having surgery in England are ageing faster than the population as a whole, and estimate that by 2030, one-fifth of those aged > 75 y will undergo surgery each year [2].

Under-representation of older patients in clinical trials [3–5] has resulted in numerous agencies producing guidance on the inclusion of older patients to improve adequate representation and hence the applicability of any findings [6,7]. Historically, there has been an under-recruitment of females to clinical trials [8]. This has been in part attributed to the discouragement of females of child-bearing age from participation, particularly following the thalidomide scandal of the 1960s [9]. Reporting on this issue together with publication of guidance on clinical trial sex-representation appears to have resulted in improved representation [9,10]. Despite this, female under-representation in clinical research continues to be reported [11,12].

The expanding and increasingly older surgical population presents challenges for peri-operative trialists to ensure there is adequate patient representation in clinical trials. We aimed to assess the adequacy of representation of: age; sex; race; and ethnicity of peri-operative research trials compared with contemporaneous national surgical populations.

Methods

We conducted a review of randomised controlled trials (RCTs) in peri-operative medicine. A purposive sampling approach was used, and we aimed to extract data on clinical trials likely to have been of greatest impact. Studies were selected that: aimed to answer a clinical question relevant to a high-volume major surgical population; examined core peri-operative domains; and were included in recent meta-analyses.

We used English surgical registry data to identify major surgical procedures frequently performed on older people [13]. Seven different surgical subgroups were chosen: colorectal resection; elective hip arthroplasty; elective knee arthroplasty; operative management of fractured neck of femur; transurethral resection of prostate and transurethral resection of bladder tumour; nephrectomy; and lung resection. Selection criteria for surgical subgroups can be found in Supplementary Appendix S1. In England, these seven operative categories account for 125,000 operations per year in patients aged > 75 y and 228,000 operations in all patients (see Supplementary Appendix S2 for frequency of each operation stratified by age). The most common procedure in older adults is cataract surgery (221,000 procedures per year in patients aged > 75 y). Trials in these patients were excluded, as it is a minor procedure and peri-operative research in this area is sparse.

Based on investigator discussions and following an initial scoping review of the literature, five domains of peri-operative interventions were chosen. These were: enhanced recovery after surgery; goal directed therapy; patient blood management; pain management; and pre-operative optimisation. Selection criteria for peri-operative domains can be found in Supplementary Appendix S1. We employed a purposive sampling strategy to identify peri-operative RCTs that have been included in meta-analyses, and are therefore likely to impact clinical practice. An initial search was performed to identify meta-analyses of the different peri-operative interventions in the specified surgical subgroups. Randomised controlled trials were then selected from these meta-analyses to be

used in our analysis. Literature searches were conducted using the electronic databases Ovid MEDLINE, Embase and the Cochrane Central Register of Controlled Trials.

We performed 35 searches across seven surgical categories and five research domains. Results were restricted to systematic reviews published during 2009 or later. A full list of the search terms used can be found in Supplementary Appendix S3. The search was conducted on 28 December 2018. The titles and abstracts of the search results were screened independently by two investigators. Any disagreement was resolved by a third investigator. Meta-analyses investigating the specified peri-operative intervention in the specified surgical subgroup were selected. Studies looking specifically at paediatric populations were excluded.

Full texts of meta-analyses identified by our literature search were reviewed to ensure they met the inclusion criteria. Randomised controlled trials cited in the retrieved meta-analyses were selected. If there were 20 or more RCTs identified for any of the 35 search categories, the 10 most recent and then the 10 most cited of the remaining RCTs were used in our analysis. The full text of each of the identified RCTs was reviewed independently by two investigators. Any disagreement was resolved by a third investigator. The following data were extracted: the year of start and end of study recruitment; the country of treatment of the primary study population; the number of participants; the proportion of females; central values (mean or median) and spread (standard deviation or interquartile range); whether an age subgroup analysis was performed; whether participant race or ethnicity was reported (as defined by the primary study authors); the presence of any study population inclusion or exclusion criteria which the reviewer felt would exclude or bias against older people or a particular sex. The midpoints of the trial recruitment were used to represent the study year when making comparisons with registry data.

We extracted information regarding surgical subgroup population age and sex from the published data of three national registries: Hospital Episodes Statistics (England) [13], Federal Statistics Office of Germany [14] and Australian Institute of Health and Welfare [15]. Age data from the National Hip Fracture Database [16] were used in the analysis of RCTs involving patients undergoing surgical management of a fractured neck of femur. The procedure codes used to identify each of the surgical subpopulations in each of the registries are included in Supplementary Appendix S4. Where not available, total mean age and standard deviations were calculated from the age group data provided by the registries. Where registry data was reported for financial years, the start year was used in the analysis. Where registry data was not available for certain years, data from the nearest year with data recorded was used in the analysis.

To report age representation, the mean registry age for the nearest year with available data was subtracted from the central value of the study age (mean or median). Values less than zero represent studies with average ages less than the corresponding registry population. Due to the asymmetrical sex balance in some populations (notably hip fracture), the sex representation was reported as the ratio of the proportion of male participants in the study compared to the proportion in the registry population. Values less than one represent under-representation of males, and greater than one, over-representation. Due to the lack of reported data on race and ethnicity, these data are reported narratively.

Data analysis was performed with Stata version 15 (Stata Corp, College Station, TX, USA). Data are presented descriptively. There is no inferential statistical analysis as this was felt to be inappropriate given the nature of our non-random sample.

Results

We identified 469 meta-analyses from which we screened 1158 RCTs and included 366 (31.6%). Of these, 224 (61.2%) met the eligibility criteria and were included in the final analysis (Fig. 1). A definitive list of included studies is provided in Supplementary Appendix S5. Of the 224 RCTs: 63 (28.1%) studied patients undergoing colorectal resection; 46 (20.5%) studied patients undergoing elective knee arthroplasty; 39 (17.4%) studied patients undergoing elective hip arthroplasty; 41 (18.3%) studied patients undergoing surgical management of a fractured neck of femur; 4 (1.8%) investigated patients undergoing transurethral resection of prostate or transurethral resection of bladder tumour; 1 (0.4%) studied patients undergoing nephrectomy; and 34 (15.2%) investigated patients undergoing lung resection. Given the limited number of RCTs identified studying nephrectomy, transurethral resection of prostate and transurethral resection of bladder tumour populations, we did not perform individual analyses of these data.

There was a total of 22,404 participants in all included RCTs. The median (IQR [range]) number of participants was 66 (45–110 [15–2016]). Of the 224 analysed RCTs, 114 (50.9%) were conducted in Europe, 34 (15.2%) in North America, 11 (4.9%) in Australasia, 64 (28.6%) in Asia, and 1 (0.4%) in South America. Registry data were qualitatively similar between all the included national registries. Data are therefore presented using the Hospital Episodes Statistics (England) database unless otherwise specified. For data on the age of patients undergoing operative management of fractured neck of femur, we used the National Hip Fracture Database. Additional analyses using German and Australian data are included in Supplementary Appendix S6.

The median (IQR [range]) difference between the study population age (mean or median) and the registry population age (mean) was: -2.4 (-6.2 to 1.0 [-34.7 to 14.5]) years for all RCTs identified; 0.3 (-4.3 to 3.0 [-28.2 to 9.8]) years for colorectal resection RCTs; -6.2 (-9.4 to -2.8 [-18.6 to 4.6]) years for elective hip arthroplasty RCTs; -1.7 (-3.2 to 0.3 [-8.8 to 6.2]) years for elective knee arthroplasty RCTs; -3.4 (-9.5 to -1.1 [-34.7 to 2.9]) years for surgery for fractured neck of femur RCTs; and -0.6 (-6.6 to 3 [-23.5 to 14.5]) years for lung resection RCTs (Fig. 2).

We made a judgement that 77 (34.4%) RCTs had exclusion criteria which might have unnecessarily excluded or biased against the inclusion of older people. Of these, 50 (22.3%) RCTs had an upper age limit to recruitment and 18 (7.4%) excluded patients with specified comorbidities, even though these participants were appropriate candidates for the study intervention. Eleven (4.5%) RCTs excluded patients based on ASA grade, despite this not being a clinical contra-indication to the study intervention. Thirteen (5.3%) RCTs excluded patients with cognitive impairment rather than on a formal assessment of capacity.

Regarding the 41 RCTs on patients undergoing surgery for fractured neck of femur: 7 (17.1%) had exclusion criteria felt to unnecessarily exclude older patients; 5 (12.2%) had upper age limits to recruitment; 15 (36.6%) had a lower age limit to recruitment; and two (4.9%) published an age subgroup analysis.

In 92 (41.1%) RCTs, the proportion of each sex in the study population was more than 25% different from the proportion in registry population. In 32 (14.3%) RCTs, the proportion of each sex in the study population was more than 50% different from the proportion in registry population (Fig. 3).

Five (2.2%) RCTs published data on the race or ethnicity of participants.

Discussion

We found that our sample of peri-operative RCTs were insufficiently representative of the age of surgical populations treated in clinical practice. While there was often misrepresentation of sex in individual RCTs, we did not find evidence of a systematic misrepresentation of one sex over another.

Race and ethnicity of RCT participants are rarely reported. We found that 25% of RCTs we identified had a population that was younger than the surgical population of England by 6.2 years or more, with individual RCTs under-representing the national surgical age by up to 33 years. Under-representation of older people was most consistently seen in RCTs investigating patients undergoing hip arthroplasty or surgical management of a fractured neck of femur. The proportion of males and females in 41% of the RCTs in our sample was at least 25% higher or lower than in the overall surgical population of England. While historically there has been under recruitment of females to clinical trials [8], we found no convincing evidence of a consistent sex recruitment bias in our sample.

Lack of representation is likely multi-factorial. Individual RCTs are, in theory, a random sample from the whole population, so some variation is to be expected, more so with smaller studies. Indeed, if such variation was not present, questions might be raised about data integrity [17]. Our study reports data from a non-random, purposively sampled range of studies. It is possible, though we suggest unlikely, that our selection of studies was biased. We nevertheless found clear evidence that study inclusion and exclusion criteria systematically biased against the involvement of older people. We did not observe any evidence of criteria that bias for or against males or females.

Older people are often more likely to trigger exclusion criteria regardless of the appropriateness of the intervention under investigation. We found evidence of this with 34% of the sample RCTs having selection criteria felt to unnecessarily exclude older people and 22% having an upper age limit to recruitment. Several other barriers to the recruitment of older people, which could result in a selection bias, have been identified [18–20]. Older people may be less likely to consent due to: sensory and cognitive limitations; frailty; a reluctance to take on something onerous; or reluctance of a family member or caregiver to support an older person in a research project [18]. Investigators may be less likely to recruit older people due to apprehension about the impact of enrolling patients with multiple comorbidities on dropout rates and adverse events, and logistical concerns regarding the inclusion of frailer, older patients [19].

Fewer RCTs involving patients undergoing surgical management of a fractured neck of femur had recruitment age limits or other potentially age discriminatory exclusion criteria, and many had a lower age limit to recruitment. This likely represents a deliberate effort by researchers to increase recruitment of older people. Despite this, the mean or median age of the population in over 75% of these RCTs remains below the registry population mean age, highlighting the difficulty in achieving age representative recruitment. The extent to which sampling error or selection bias contribute to a difference in age between an RCT population and the treated surgical population may not matter in terms of the generalisability of any findings. Whether a study is non-representative of the treated surgical population by chance, or by design, it still creates a problem with interpretation.

Race or ethnicity of RCT participants was only reported in five RCTs. The relationship between race, ethnicity and health outcomes is complex. It has been argued that race and ethnicity serve as proxies for a mix of genetic, disease, social, behavioural, or clinical characteristics, that should be considered individually rather than under the umbrella of a racial or ethnic group [21]. While it may not be appropriate to stratify research by race or ethnicity, awareness of the race and ethnicities of research participants is clearly important if researchers are going to consider their potential implications and ensure equal opportunities are provided for participation in clinical research.

This analysis has a number of strengths. The purposive sampling strategy resulted in the identification of RCTs that were likely to have impacted on clinical practice, and it is therefore of importance that their study populations were representative. We sampled 224 RCTs for analysis. Randomised controlled trials were only selected if they investigated specific surgical populations for

which registry data were available, allowing reliable comparisons to be made between the study and registry populations. The availability of annualised English registry data from 1998 to 2017 for all the surgical categories, except the surgical management of a fractured neck of femur, allowed these RCT populations to be matched by year for comparisons with registry data.

There are several limitations to our analysis. Limited registry data were available for patients undergoing surgery for fractured neck of femur. Data on age from the National Hip Fracture Database from 2017 and English registry data on sex from 2012 to 2017 were used in the analysis, and these RCT populations were, therefore, not matched by year to registry data. Due to a lack of openly available international surgical registry data, we were unable to compare RCT population age and sex to geographically matched registry populations. Age and sex differences between RCT and registry populations will influence the generalisability of RCT findings to the surgical population of the country of the registry, but will not necessarily reflect age and sex differences in other countries due to geographical variation in the surgical population. We were unable to include RCTs studying the effect of a peri-operative intervention on more than one surgical group, as we would have been unable to compare the study population age to specific registry data. This resulted in a number of potentially influential peri-operative RCTs being excluded from our analysis.

A key issue facing clinical research is an understanding of the impact of ageing, multi-morbidity and frailty on outcomes following medical and surgical interventions. This is amplified in the 'old-old', however this is defined. Neither the RCTs nor the registries provide consistent data on this population (e.g. aged > 80 y or identified as being frail) which leaves a clear gap in our understanding of this high-risk population. Advances in peri-operative care and a changing national and global demographic mean that surgery is being offered to an increasingly diverse population. The evidence of non-representative RCT populations in this analysis highlights the importance of endeavouring to recruit representative research populations if findings are to be reliably generalised to the overall population. Although there is some variation, sex representativeness seems to be adequate. A better understanding and awareness of barriers to recruitment of older people when planning clinical trials may improve representative recruitment and help ensure research is following patient need. Unnecessary age discriminatory exclusion criteria including age limits should clearly be avoided.

Acknowledgements

Protocol was registered in PROSPERO (CRD42019121045). IM is a member of the NICE topic expert group for Quality Standards for hip fracture and is Deputy Director of the Health Service Research Centre of the National Institute of Academic Anaesthesia (NIAA). No external funding and no other conflicts of interests declared.

References

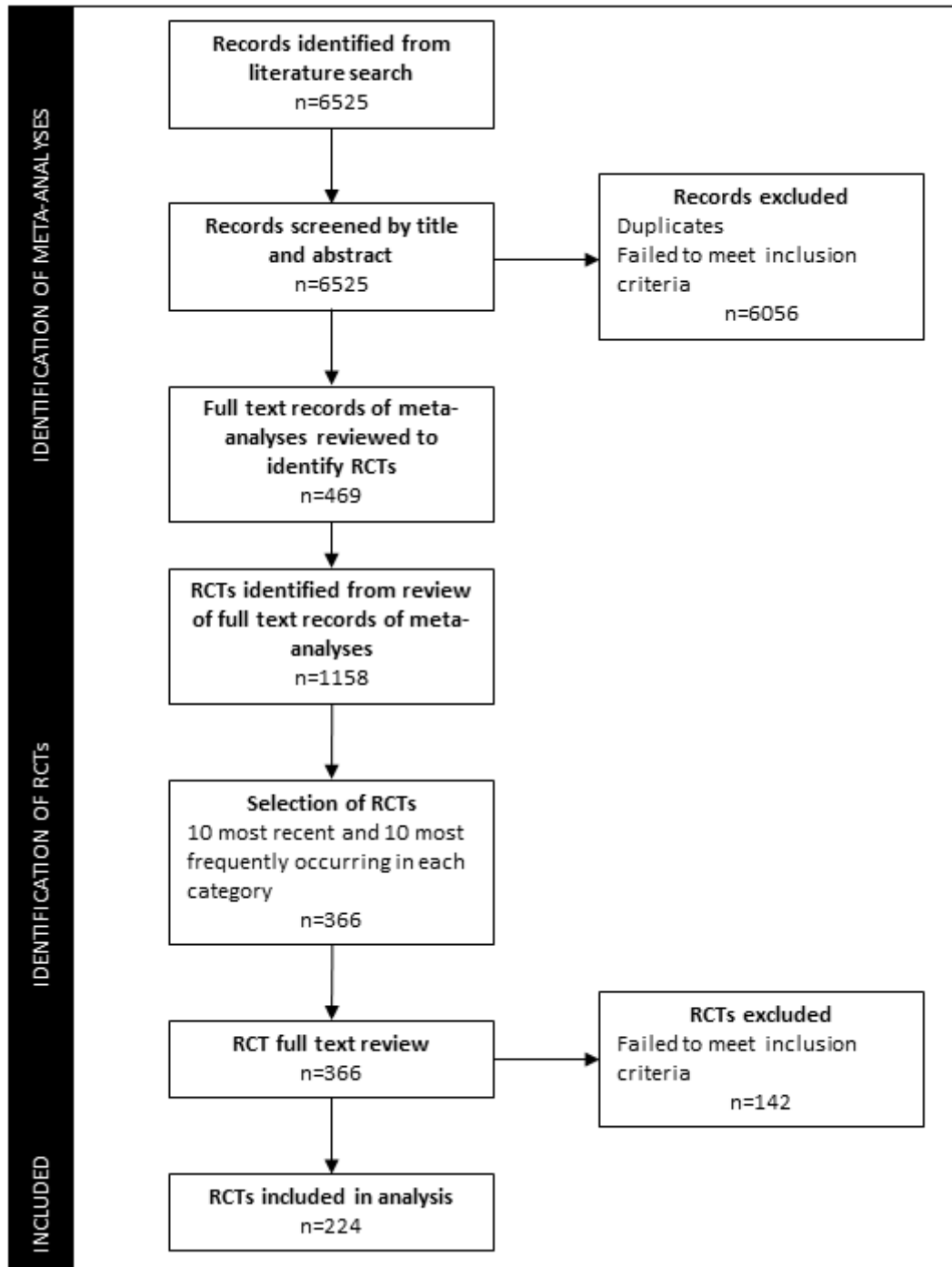
1. United Nations. World Population Ageing 2017. <https://www.un.org/en/development/desa/population/theme/ageing/WPA2017.asp> (accessed 27/06/19).
2. Fowler AJ, Abbott TEF, Prowle J, Pearse RM. Age of patients undergoing surgery. *British Journal of Surgery* 2019; **106**: 1012-8.
3. Gurwitz JH, Col NF, Avorn J. The exclusion of the elderly and women from clinical trials in acute myocardial infarction. *Journal of the American Medical Association* 1992; **268**: 1417.
4. Lee PY, Alexander KP and Hammill BG, et al. Representation of elderly persons and women in published randomized trials of acute coronary syndromes. *Journal of the American Medical Association* 2001; **286**: 708–13.
5. Hutchins LF, Unger JM, and Crowley JJ, et al. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. *New England Journal of Medicine* 1999; **341**: 2061–7.
6. FDA. US Government Accountability Office. Prescription drugs: FDA guidance and regulations related to data on elderly persons in clinical drug trials. 2007.
7. NIHR. Equity in Clinical Research: Inclusion of older participants. [https://www.nihr.ac.uk/nihr-in-your-area/ageing/documents/Ageing equity statement WEB.pdf](https://www.nihr.ac.uk/nihr-in-your-area/ageing/documents/Ageing%20equity%20statement%20WEB.pdf) (accessed 27/06/19).
8. Pilote L, Raparelli V. Participation of women in clinical trials. *Journal of the American College of Cardiology* 2018; **71**: 1970–2.
9. Liu KA, Mager NAD. Women’s involvement in clinical trials: historical perspective and future implications. *Pharmacy Practice* 2016; **14**: 708.
10. Labots G, Jones A, and de Visser SJ, et al. Gender differences in clinical registration trials: is there a real problem? *British Journal of Clinical Pharmacology* 2018; **84**: 700–7.
11. Hoel AW, Kayssi A and Brahmanandam S. Under-representation of women and ethnic minorities in vascular surgery randomized controlled trials. *Journal of Vascular Surgery* 2009; **50**: 349–54.
12. Jagsi R, Motomura AR and Amarnath S, et al. Under-representation of women in high-impact published clinical cancer research. *Cancer* 2009; **115**: 3293–301.
13. Hospital Episode Statistics (HES) - NHS Digital. <https://digital.nhs.uk/data-and-information/data-tools-and-services/data-services/hospital-episode-statistics> (accessed June 27/06/19).
14. Statistisches Bundesamt. https://www.destatis.de/EN/Home/_node.html (accessed 27/06/19).
15. Australian Institute of Health and Welfare. <https://www.aihw.gov.au/> (accessed 27/06/19).
16. The National Hip Fracture Database. <https://www.nhfd.co.uk/> (accessed 27/06/19).
17. Carlisle JB. The analysis of 168 randomised controlled trials to test data integrity. *Anaesthesia* 2012; **67**: 521–37.
18. McHenry JC, Insel KC, and Einstein GO, et al. Recruitment of older adults: success may be in the details. *The Gerontologist* 2015; **55**: 845–53.
19. McMurdo MET, Roberts H and Parker S, et al. Improving recruitment of older people to research through good practice. *Age and Ageing* 2011; **40**: 659–65.
20. Fudge N, Wolfe CDA, McKeivitt C. Involving older people in health research. *Age and Ageing* 2007; **36**: 492–500.
21. Rathore SS, Krumholz HM. Race, ethnic group, and clinical research. *British Medical Journal* 2003; **327**: 763–4.

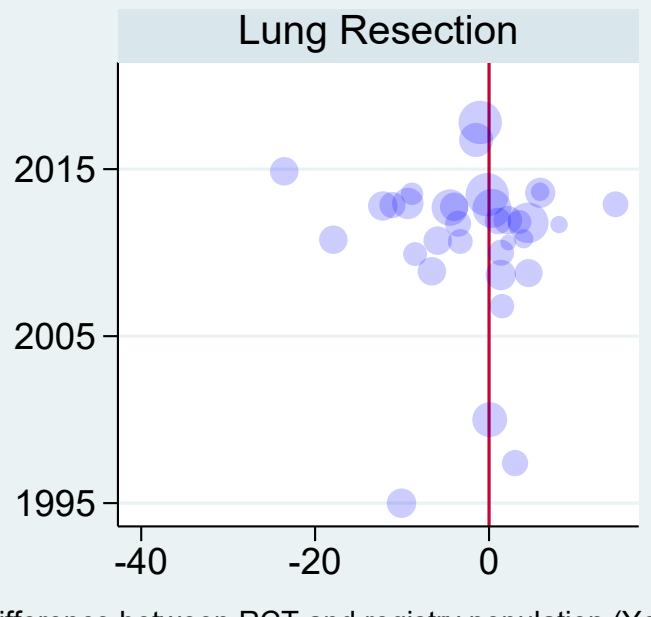
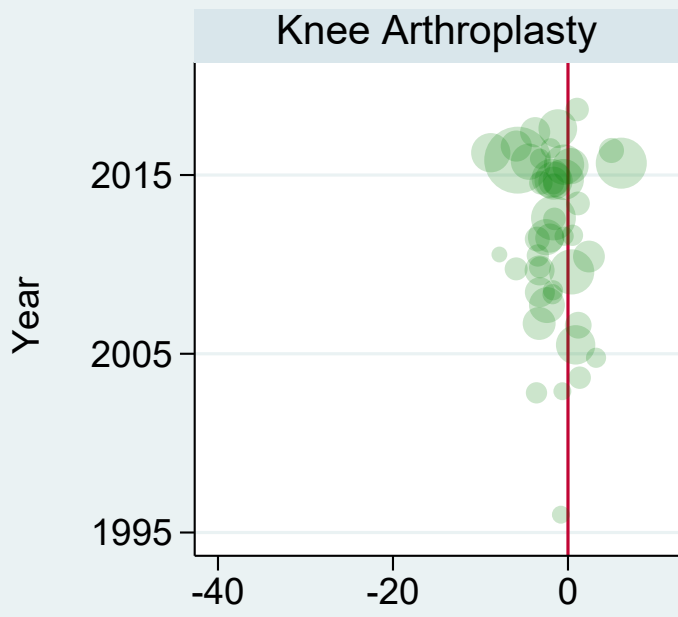
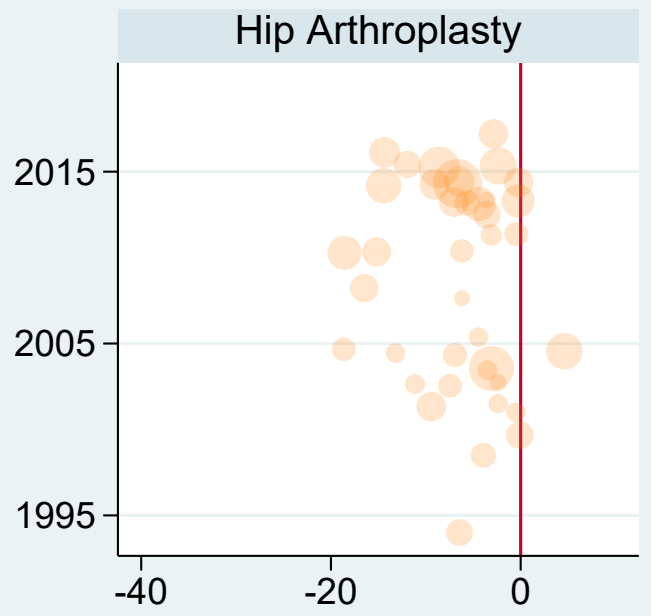
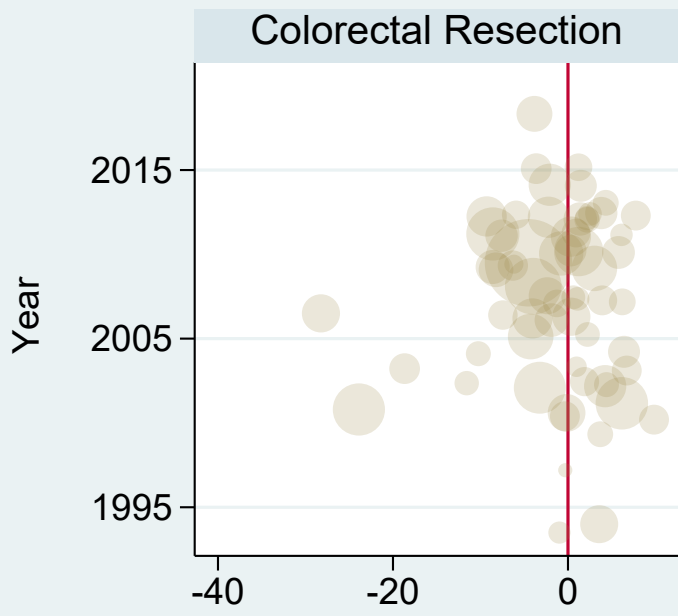
Legends for figures

Figure 1 – Randomised controlled trial selection flowchart.

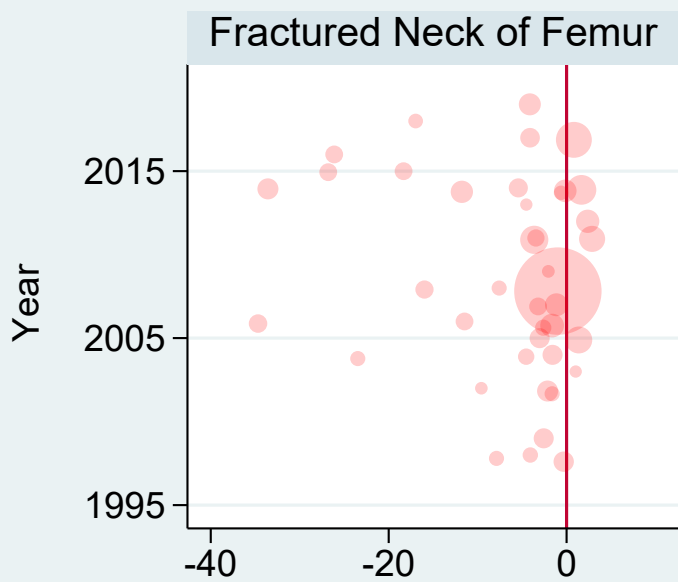
Figure 2 – Bubble plots for each surgical category showing the difference between the mean or median age of the randomised controlled studies and the mean age of the equivalent populations in the English hospital registry according to the middle year of study recruitment. Marker radius is proportional to the number of study participants.

Figure 3 – Bubble plots for each surgical category showing the ratio of the proportion of male participants in the randomised controlled studies compared with the proportion in the English hospital registry according to the middle year of study recruitment. Values less than one represent under-representation of males, and greater than one, over-representation. Marker radius is proportional to the number of study participants.

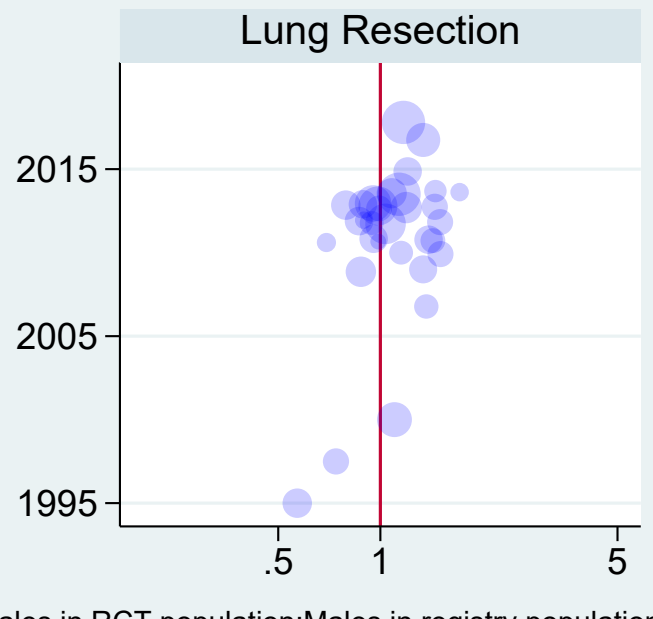
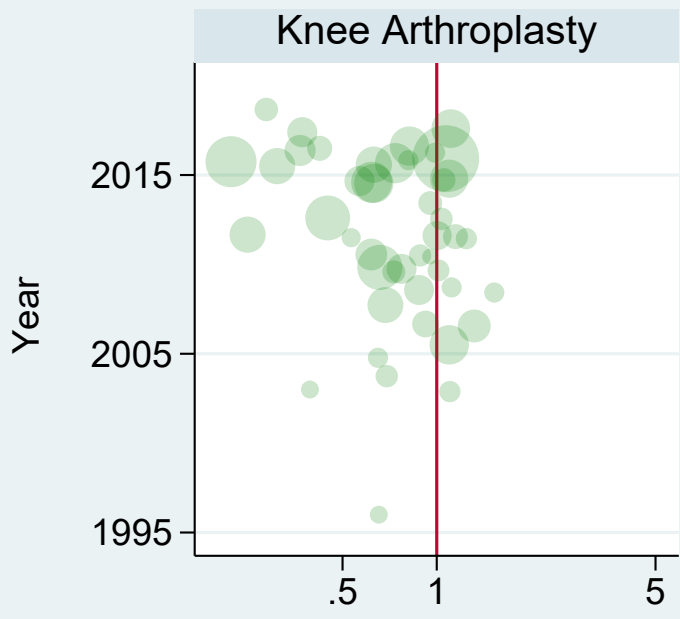
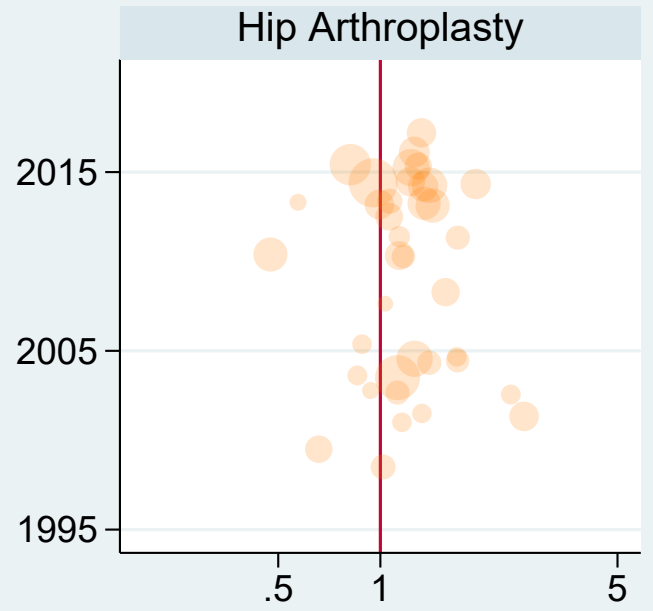
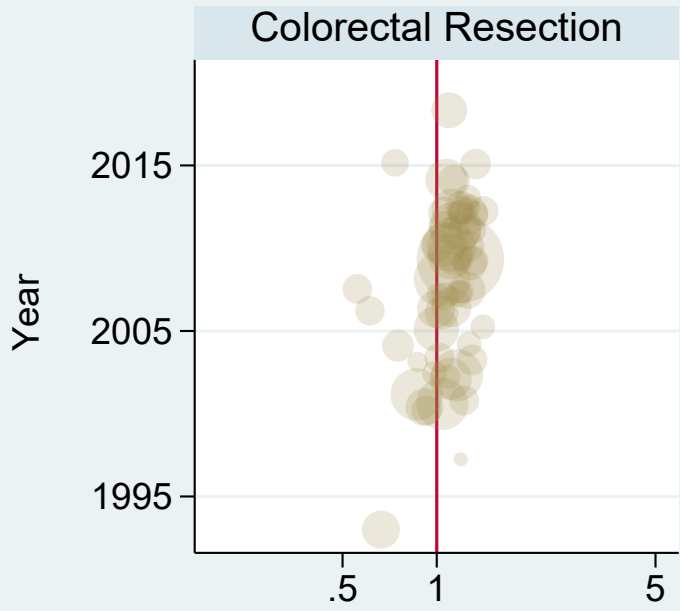




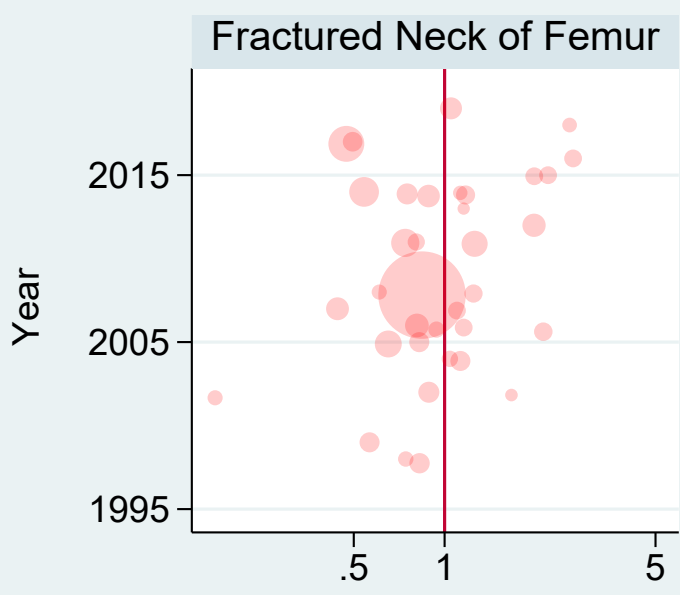
Age difference between RCT and registry population (Years)



Age difference between RCT and registry population (Years)



Males in RCT population:Males in registry population



Males in RCT population:Males in registry population

S1 - Inclusion/Exclusion Criteria

META-ANALYSIS SELECTION CRITERIA

- Meta-analysis
- Not solely studying a paediatric population
- Published since 2008
- Review includes but not necessarily limited to the defined surgical population
- English language

-Surgical subgroups

-Colorectal

Colorectal resection
Open or laparoscopic

-Elective Arthroplasty

Elective patients
Hip arthroplasty
Knee arthroplasty
Primary

-#NOF

Hip fracture patients undergoing operative management

-TURP/TURBT

TURP
TURBT

-Nephrectomy

Nephrectomy – total or partial
Open or laparoscopic

-Lung resection

Pneumonectomy/lobectomy/segmentectomy

VATS or thoracotomy

-Research subgroups

-ERAS

Study assessing ERAS pathway:

Not study of isolated components of ERAS

-GDT

Study related to perioperative goal directed fluid therapy

Effect of GDT

-Perioperative blood management

Study related to perioperative blood management:

iron (oral/IV)

EPO

transfusion

cell salvage

transfusion thresholds

tranexamic acid

-Pain

Study related to perioperative pain management:

Medications

Regional techniques

-Pre-operative optimisation

CPET

Prehabilitation

STUDY SELECTION CRITERIA

- RCT
- Study specific to the defined surgical population
- Surgical and research categories as defined above
- English language

S2 – Frequency of procedure stratified by age using 2016-2017 HES data

Procedure	No. of HES Primary Procedures 2016-2017					
	Age >65 years	Age >70 years	Age >75 years	Age >80 years	Age >85 years	Age >90 years
TURBT	31879	26349	19292	12068	5622	1539
TURP	3379	2546	1615	839	276	50
Nephrectomy	3601	2480	1466	621	145	17
Colorectal resection	19784	15021	9894	5540	1978	342
Primary hip	65760	49824	32668	17165	6515	1554
Primary Knee	64533	46792	28145	13154	4018	564
Hip Fracture	34591	33000	30231	25551	17736	8352
Lung	5735	3896	2086	799	148	9
Cataract	336787	288660	220909	137896	60599	14933

S3 – Search Terms for Surgical Categories and Perioperative Domains

-TURP and TURBT

MEDLINE (Ovid interface)

1. Transurethral Resection of Prostate/
2. Transurethral resection of prostate.mp. or TURP.mp.
3. Transurethral resection of bladder tumour.mp. or TURBT.mp.
4. Transurethral resection.mp.
5. Urinary Bladder Neoplasms/ or Prostate/
6. 4 and 5
7. 1 or 2 or 3 or 6

EMBASE (Ovid interface)

1. Transurethral resection of prostate.mp. or TURP.mp.
2. Transurethral resection of bladder tumour.mp. or TURBT.mp.
3. transurethral resection/
4. 1 or 2 or 3

CENTRAL (Wiley Online Library)

1. MeSH descriptor: [Transurethral Resection of Prostate] explode all trees
2. Transurethral resection
3. TURP
4. TURBT
5. #1 or #2 or #3 or #4

-NEPHRECTOMY

MEDLINE (Ovid interface)

1. NEPHRECTOMY/ or nephrectom*.mp.
2. renal resection.mp or kidney resection.mp.
3. 1 or 2

EMBASE (Ovid interface)

1. Nephrectomy/ or radical nephrectomy/ or bilateral nephrectomy/ or partial nephrectomy/ or nephrectom*.mp.
2. renal resection.mp or kidney resection.mp.
3. 1 or 2

CENTRAL (Wiley Online Library)

1. MeSH descriptor: [Nephrectomy] explode all trees
2. Nephrectomy
3. Renal resection or kidney resection
4. #1 or #2 or #3

-COLORECTAL

MEDLINE (Ovid interface)

1. Colorectal Surgery/
2. ((colorectal or rect* or colon or sigmoid) and (surgery or surgical or procedure or resection)).mp.
3. 1 or 2

EMBASE (Ovid interface)

1. colorectal surgery/
2. ((colorectal or rect\$ or colon or sigmoid) and (surgery or surgical or procedure or resection)).mp.
3. 1 or 2

CENTRAL (Wiley Online Library)

1. MeSH descriptor:[Colorectal Surgery] explode all trees
2. ((colorectal or rect* or colon or sigmoid) and (surgery or surgical or procedure or resection))
3. #1 or #2

-ELECTIVE LOWER LIMB ARTHROPLASTY

MEDLINE (Ovid interface)

1. Arthroplasty, Replacement, Hip/
2. (hip* adj5 (replac* or operat* or surg* or arthroplast*)).mp.
3. Arthroplasty, Replacement, Knee/
4. (knee* adj5 (replac* or operat* or surg* or arthroplasty*)).mp.
5. 1 or 2 or 3 or 4

EMBASE (Ovid interface)

1. hip arthroplasty/
2. (hip\$ adj5 (replac\$ or operat\$ or surg\$ or arthroplast\$)).mp.
3. Knee arthroplasty/
4. (knee\$ adj5 (replac\$ or operat\$ or surg\$ or arthroplasty\$))
5. 1 or 2 or 3 or 4

CENTRAL (Wiley Online Library)

1. MeSH descriptor: [Arthroplasty, Replacement, Hip] explode all trees
2. (hip* NEAR (replac* or operat* or surg* or arthroplast*))
3. MeSH descriptor: [Arthroplasty, Replacement, Knee] explode all trees
4. (knee* NEAR (replac* or operat* or surg* or arthroplasty*))
5. #1 or #2 or #3 or #4

-#NOF

MEDLINE (Ovid interface)

1. Hip Fractures/
2. ((hip* or femur* or femoral* or trochant* or pertrochant* or subtrochant* or extracapsular*) adj5 fracture*).mp.

3. 1 or 2

EMBASE (Ovid interface)

1. hip fracture/
2. ((hip\$ or femur\$ or femoral\$ or trochant\$ or pertrochant\$ or subtrochant\$ or extracapsular\$) adj5 fracture\$).mp.
3. 1 or 2

CENTRAL (Wiley Online Library)

1. MeSH descriptor: [Hip Fractures] explode all trees
2. ((hip* or femur* or femoral* or trochant* or pertrochant* or subtrochant* or extracapsular*) NEAR fracture*)
3. #1 or #2

-LUNG RESECTION

MEDLINE (Ovid interface)

1. PNEUMONECTOMY/ or pneumonectomy.mp.
2. Thoracic Surgery/ or Thoracotomy/ or thoracic surgery.mp. or thoracotomy.mp.
3. (pulmonary or lung) and (resection or lobectomy or excision).mp.
4. 1 or 2 or 3

EMBASE (Ovid interface)

1. Lung resection/
2. Pneumonectomy.mp.
3. thoracic surgery.mp or thoracotomy.mp. or thorax surgery/ or thoracotomy/
4. ((pulmonary or lung) and (resection or lobectomy or excision).mp.
5. 1 or 2 or 3 or 4

CENTRAL (Wiley Online Library)

1. MeSH descriptor: [Pneumonectomy] explode all trees
2. MeSH descriptor: [Thoracotomy] explode all trees
3. MeSH descriptor: [Thoracic Surgery] explode all trees
4. (pulmonary or lung) and (resection or lobectomy or excision)
5. #1 or #2 or #3 or #4

-ERAS

MEDLINE (Ovid interface)

1. ((enhanced or early) and (rehabilitation* or recovery* or convalesce*)).mp.
2. Fast track.mp.
3. ERAS.mp.
4. 1 or 2 or 3

EMBASE (Ovid interface)

1. ((enhanced or early) and (rehabilitation\$ or recovery\$ or convalesce\$)).mp.
2. Fast track.mp.
3. ERAS.mp.
4. 1 or 2 or 3

CENTRAL (Wiley Online Library)

1. ((enhanced or early) and (rehabilitation* or recovery* or convalesce*))
2. Fast track
3. ERAS
4. #1 or #2 or #3

-GDT

MEDLINE (Ovid interface)

1. (goal directed or goal orientated or goal target* or goal-directed).mp.
2. Cardiac Volume/ or (cardiac output or cardiac index or cardiac volume).mp.
3. Stroke Volume/ or stroke volume.mp.
4. (oxygen delivery or oxygen consumption).mp.
5. Fluid Therapy/ or (fluid therapy or fluid loading or fluid administration).mp.
6. (pulse pressure variation or pleth index variation or systolic pressure variation).mp.
7. (optimisation or optimization).mp.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7

EMBASE (Ovid interface)

1. (goal directed or goal orientated or goal target\$ or goal-directed).mp.
2. heart volume/
3. (cardiac output or cardiac index or cardiac volume).mp.
4. fluid therapy/ or (fluid therapy or fluid loading or fluid administration).mp.
5. heart stroke volume/ or stroke volume.mp.
6. (pulse pressure variation or pleth index variation or systolic pressure variation).mp.
7. (oxygen delivery or oxygen consumption).mp.
8. (optimisation or optimization).mp.

CENTRAL (Wiley Online Library)

1. MeSH descriptor: [Fluid Therapy] explode all trees
2. MeSH descriptor: [Stroke Volume] explode all trees
3. MeSH descriptor: [Cardiac Output] explode all trees
4. goal directed or goal orientated or goal target* or goal-directed
5. cardiac output or cardiac index or cardiac volume
6. oxygen delivery or oxygen consumption
7. fluid therapy or fluid loading or fluid administration
8. pulse pressure variation or pleth index variation or systolic pressure variation
9. optimisation or optimization
10. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9

-PERI-OPERATIVE BLOOD MANAGEMENT

MEDLINE (Ovid interface)

1. IRON/ or iron.mp.
2. (Ferric compounds/ or FERROUS COMPOUNDS/) or ((ferric or ferrous) adj5 compound*)
3. (Blood Transfusion/ or Erythrocyte Transfusion/)

4. ((transfus* or red cell* or red blood cell* or RBC* or PRBC*) adj5 (trigger* or threshold* or target* or restrict* or liberal* or aggressive* or conservative* or prophylactic* or limit* or protocol* or policy or policies or practic* or indicat* or strateg* or regimen* or criteri* or standard* or management or program*)).mp.
5. ((h*emoglobin or h*ematocrit or HB or HCT) adj5 (polic* or practic* or protocol* or trigger* or threshold* or maintain* or indicator* or strateg* or criteri* or standard*)).mp.
6. (transfu* or posttransfus* or retransfus* or hypertansfus* or h*emotranfus* or red cell* or red blood cell* or RBC* or erythrocyte*).mp.
7. ((allogen*ic adj2 blood) or (blood adj2 exposure) or (unit* adj2 blood) or (blood adj3 management) or (blood adj product*) or (blood adj component*) or (donor* adj2 blood) or (donat* adj2 blood)).mp.
8. (blood sparing or cell salvage or cell saver* or (blood adj2 salvag*) or blood support or (blood adj2 requir*) or (blood adj2 replac*) or autotransfus*).mp.
9. Tranexamic Acid/
10. (tranexamic acid or amchafibrin or anvitoff or cyklokapron or Sepercil or exacyl or lysteda or spotof or t*amcha or tranhexamic acid or transamin or Transcam or ugurol).mp.
11. Perioperative Period/
12. Perioperative Care/
13. (Preoperative or perioperative or postoperative).mp.
14. ((prior or before or post or after) adj3 (surg* or operat*)).mp.
15. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
16. 11 or 12 or 13 or 14
17. 15 and 16

EMBASE (Ovid interface)

1. Iron/ or iron.mp.
2. ((ferrous or ferric) adj5 compound\$).mp.
3. (Blood Transfusion/ or Erythrocyte Transfusion/)
4. ((transfus\$ or red cell\$ or red blood cell\$ or RBC\$ or PRBC\$) adj5 (trigger\$ or threshold\$ or target\$ or restrict\$ or liberal\$ or aggressive\$ or conservative\$ or prophylactic\$ or limit\$ or protocol\$ or policy or policies or practic\$ or indicat\$ or strateg\$ or regimen\$ or criteri\$ or standard\$ or management or program\$)).mp.
5. ((h?emoglobin or h?ematocrit or HB or HCT) adj5 (polic\$ or practic\$ or protocol\$ or trigger\$ or threshold\$ or maintain\$ or indicator\$ or strateg\$ or criteri\$ or standard\$)).mp.
6. (transfu\$ or posttransfus\$ or retransfus\$ or hypertansfus\$ or h?emotranfus\$ or red cell\$ or red blood cell\$ or RBC\$ or erythrocyte\$).mp.
7. ((allogen?ic adj2 blood) or (blood adj2 exposure) or (unit\$ adj2 blood) or (blood adj3 management) or (blood adj product\$) or (blood adj component\$) or (donor\$ adj2 blood) or (donat\$ adj2 blood)).mp.
8. (blood sparing or cell salvage or cell saver\$ or (blood adj2 salvag\$) or blood support or (blood adj2 requir\$) or (blood adj2 replac\$) or autotransfus\$).mp.
9. tranexamic acid/
10. (tranexamic acid or amchafibrin or anvitoff or cyklokapron or Sepercil or exacyl or lysteda or spotof or t?amcha or tranhexamic acid or transamin or Transcam or ugurol).mp.
11. preoperative care/ or preoperative treatment/ or preoperative period/ or perioperative period/
12. (Preoperative or perioperative or postoperative).mp.

13. ((prior or before or post or after) adj3 (surg\$ or operat\$)).mp.
14. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
15. 9 or 10 or 11 or 12 or 13
16. 14 and 15

CENTRAL (Wiley Online Library)

1. MeSH descriptor: [Iron] in all MeSH products
2. MeSH descriptor: [Ferric Compounds] explode all trees
3. ((ferric or ferrous) near compound*)
4. MeSH descriptor [Blood Transfusion] explode all trees
5. MeSH descriptor [Erythrocyte Transfusion] explode all trees
6. ((transfus* or red cell* or red blood cell* or RBC* or PRBC*) near (trigger* or threshold* or target* or restrict* or liberal* or aggressive* or conservative* or prophylactic* or limit* or protocol* or policy or policies or practic* or indicat* or strateg* or regimen* or criteri* or standard* or management or program*))
7. ((h*emoglobin or h*ematocrit or HB or HCT) near (polic* or practic* or protocol* or trigger* or threshold* or maintain* or indicator* or strateg* or criteri* or standard*))
8. (transfu* or posttransfus* or retransfus* or hypertansfus* or h*emotranfus* or red cell* or red blood cell* or RBC* or erythrocyte*)
9. ((allogen*ic near blood) or (blood near exposure) or (unit* near blood) or (blood near management) or (blood near product*) or (blood near component*) or (donor* near blood) or (donat* near blood))
10. (blood sparing or cell salvage or cell saver* or (blood near salvag*) or blood support or (blood near requir*) or (blood near replac*) or autotransfus*)
11. MeSH descriptor: [Tranexamic Acid] explode all trees
12. (tranexamic acid or amchafibrin or anvitoff or cyklokapron or Sepercil or exacyl or lysteda or spotof or t*amcha or tranhexamic acid or transamin or Transcam or ugurol)
13. MeSH descriptor: [Preoperative Care] explode all trees
14. MeSH descriptor: [Preoperative Period] explode all trees
15. MeSH descriptor: [Perioperative Period] explode all trees
16. (Preoperative or perioperative or postoperative)
17. ((prior or before or post or after) near (surg* or operat*))
18. #1 or #2 or #3 or #4 or # or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12
19. #13 or #14 or #15 or #16 or #17
20. #18 and #19

-PAIN

MEDLINE (Ovid interface)

1. postoperative pain/
2. (pain* and (postoperative or post operative or surg*)).mp.
3. 1 or 2

EMBASE (Ovid interface)

1. postoperative pain/
2. (pain\$ and (postoperative or post operative or surg\$)).mp.
3. 1 or 2

CENTRAL (Wiley Online Library)

1. MeSH descriptor: [Pain, Postoperative] explode all trees
2. (pain* and (postoperative or post operative or surg*)).mp.
3. 1 or 2

-PRE-OP OPTIMISATION

MEDLINE (Ovid interface)

1. Exercise Test/ or (exercise test or exercise capacity or cardiopulmonary exercise or cardiopulmonary reserve).mp.
2. Anaerobic Threshold/ or (anaerobic threshold, aerobic capacity or aerobic fitness).mp.
3. Oxygen Consumption/ or (oxygen consumption or peak oxygen).mp.
4. (CPET or CPEX or VO2).mp.
5. PREOPERATIVE PERIOD/ or PREOPERATIVE CARE/
6. (preoperative or pre-operative or pre-surgery).mp.
7. 1 or 2 or 3 or 4 or 5
8. 5 or 6
9. 7 and 8
10. (prehab* or (preoperative and (rehabilitation or exercise or training or physiotherapy or physical therapy or exercise training))).mp.
11. EXERCISE/ and 8
12. 9 or 10 or 11

EMBASE (Ovid interface)

1. exercise test/ or (exercise test or exercise capacity or cardiopulmonary exercise or cardiopulmonary reserve).mp.
2. (anaerobic threshold, aerobic capacity or aerobic fitness).mp.
3. oxygen consumption/ or (oxygen consumption or peak oxygen).mp.
4. (CPET or CPEX or VO2).mp.
5. Preoperative care/ or preoperative period/
6. (preoperative or pre-operative or pre-surgery).mp.
7. 1 or 2 or 3 or 4 or 5
8. 5 or 6
9. 7 or 8
10. (prehab\$ or (preoperative and (rehabilitation or exercise or training or physiotherapy or physical therapy or exercise training))).mp.
11. exercise/ and 8
12. 9 or 10 or 11

CENTRAL (Wiley Online Library)

1. MeSH descriptor: [Exercise Test] explode all trees
2. MeSH descriptor: [Anaerobic Threshold] explode all trees
3. MeSH descriptor: [Oxygen Consumption] explode all trees
4. exercise test or exercise capacity or cardiopulmonary exercise or cardiopulmonary reserve
5. anaerobic threshold, aerobic capacity or aerobic fitness
6. oxygen consumption or peak oxygen
7. CPET or CPEX or VO2
8. MeSH descriptor: [Preoperative Care] explode all trees

9. MeSH descriptor: [Preoperative Period] explode all trees
10. Preoperative or pre-operative or pre-surgery
11. #1 or #2 or #3 or #4 or #5 or #6 or #7
12. #8 or #9 or #10
13. #11 and #12
14. prehab* or (preoperative and (rehabilitation or exercise or training or physiotherapy or physical therapy or exercise training))
15. MeSH descriptor: [Exercise] explode all trees
16. #15 and #12
17. #13 or #14 or #16

SEARCHES

1. TURP and TURBT **AND** ERAS
2. TURP and TURBT **AND** GDT
3. TURP and TURBT **AND** PERIOPERATIVE BLOOD MANAGEMENT
4. TURP and TURBT **AND** PAIN
5. TURP and TURBT **AND** PRE-OP OPTIMISATION
6. NEPHRECTOMY **AND** ERAS
7. NEPHRECTOMY **AND** GDT
8. NEPHRECTOMY **AND** PERIOPERATIVE BLOOD MANAGEMENT
9. NEPHRECTOMY **AND** PAIN
10. NEPHRECTOMY **AND** PRE-OP OPTIMISATION
11. COLORECTAL **AND** ERAS
12. COLORECTAL **AND** GDT
13. COLORECTAL **AND** PERIOPERATIVE BLOOD MANAGEMENT
14. COLORECTAL **AND** PAIN
15. COLORECTAL **AND** PRE-OP OPTIMISATION
16. ELECTIVE LOWER LIMB ARTHROPLASTY **AND** ERAS
17. ELECTIVE LOWER LIMB ARTHROPLASTY **AND** GDT
18. ELECTIVE LOWER LIMB ARTHROPLASTY **AND** PERIOPERATIVE BLOOD MANAGEMENT
19. ELECTIVE LOWER LIMB ARTHROPLASTY **AND** PAIN
20. ELECTIVE LOWER LIMB ARTHROPLASTY **AND** PRE-OP OPTIMISATION
21. #NOF **AND** ERAS
22. #NOF **AND** GDT
23. #NOF **AND** PERIOPERATIVE BLOOD MANAGEMENT
24. #NOF **AND** PAIN
25. #NOF **AND** PRE-OP OPTIMISATION
26. LUNG RESECTION **AND** ERAS
27. LUNG RESECTION **AND** GDT
28. LUNG RESECTION **AND** PERIOPERATIVE BLOOD MANAGEMENT
29. LUNG RESECTION **AND** PAIN
30. LUNG RESECTION **AND** PRE-OP OPTIMISATION

S4 - Procedure Codes**Destatis/GBE**

TURP/TURBT

5573

5601

Nephrectomy

5553

5554

Colorectal resection

5452

5455

5456

Primary Hip

5820

Primary Knee

5822

Lung resection

5322

5323

5324

5325

5327

5328

AIHW

TURP/TURBT

1100

1165

Nephrectomy

1048

1049

Colorectal resection

913

Primary Hip

1489

Primary Knee

1518

Lung resection

553

552

551

HES

TURP/TURBT

M42

M65

Nephrectomy

M02

M03

Colorectal resection

H04

H05

H06

H07

H08

H09

H10

H11

H29

H33

Primary Hip

W37

W38

W39

W93

W94

W95

Primary Knee

W40

W41

W42

Lung resection

E54

NOF

W19.1

W24.1

W46.1

W47.1

S5 – RCT References

Colorectal

Ahn E, Kang H, Choi GJ, et al. Intravenous lidocaine for effective pain relief after a laparoscopic colectomy: a prospective, randomized, double-blind, placebo-controlled study. *Int Surg* 2015; **100**: 394-401

Anderson AD, McNaught CE, MacFie J, Tring I, Barker P, Mitchell CJ. Randomized clinical trial of multimodal optimization and standard perioperative surgical care. *Br J Surg* 2003; **90**: 1497-504

Basse L, Jakobsen DH, Bardram L, et al. Functional recovery after open versus laparoscopic colonic resection: a randomized, blinded study. *Ann Surg* 2005; **241**: 416-23

Boulind CE, Ewings P, Bulley SH, et al. Feasibility study of analgesia via epidural versus continuous wound infusion after laparoscopic colorectal resection. *Br J Surg* 2013; **100**: 395-402

Braga M, Gianotti L, Vignali A, Carlo VD. Preoperative oral arginine and n-3 fatty acid supplementation improves the immunometabolic host response and outcome after colorectal resection for cancer. *Surgery* 2002; **132**: 805-14

Brandstrup B, Svendsen PE, Rasmussen M, et al. Which goal for fluid therapy during colorectal surgery is followed by the best outcome: near-maximal stroke volume or zero fluid balance? *Br J Anaesth* 2012; **109**: 191-9

Burden ST, Hill J, Shaffer JL, Campbell M, Todd C. An unblinded randomised controlled trial of preoperative oral supplements in colorectal cancer patients. *J Hum Nutr Diet* 2011; **24**: 441-8

Carli F, Charlebois P, Stein B, et al. Randomized clinical trial of prehabilitation in colorectal surgery. *Br J Surg* 2010; **97**: 1187-97

Challand C, Struthers R, Sneyd JR, et al. Randomized controlled trial of intraoperative goal-directed fluid therapy in aerobically fit and unfit patients having major colorectal surgery. *Br J Anaesth* 2012; **108**: 53-62

Chen WK, Ren L, Wei Y, Zhu DX, Miao CH, Xu JM. General anesthesia combined with epidural anesthesia ameliorates the effect of fast-track surgery by mitigating immunosuppression and facilitating intestinal functional recovery in colon cancer patients. *Int J Colorectal Dis* 2015; **30**: 475-81

Christodoulakis M, Tsiftsis DD. Preoperative epoetin alfa in colorectal surgery: a randomized, controlled study. *Ann Surg Oncol* 2005; **12**: 718-25

Conway DH, Mayall R, Abdul-Latif MS, Gilligan S, Tackaberry C. Randomised controlled trial investigating the influence of intravenous fluid titration using oesophageal Doppler monitoring during bowel surgery. *Anaesthesia* 2002; **57**: 845-9

Delaney CP, Zutshi M, Senagore AJ, Remzi FH, Hammel J, Fazio VW. Prospective, randomized, controlled trial between a pathway of controlled rehabilitation with early

ambulation and diet and traditional postoperative care after laparotomy and intestinal resection. *Dis Colon Rectum* 2003; **46**: 851-9

Edwards TJ, Noble EJ, Durran A, Mellor N, Hosie KB. Randomized clinical trial of preoperative intravenous iron sucrose to reduce blood transfusion in anaemic patients after colorectal cancer surgery. *Br J Surg* 2009; **96**: 1122-8

Feng F, Li XH, Shi H, et al. Fast-track surgery combined with laparoscopy could improve postoperative recovery of low-risk rectal cancer patients: a randomized controlled clinical trial. *J Dig Dis* 2014; **15**: 306-13

Gatt M, Anderson AD, Reddy BS, Hayward-Sampson P, Tring IC, MacFie J. Randomized clinical trial of multimodal optimization of surgical care in patients undergoing major colonic resection. *Br J Surg* 2005; **92**: 1354-62

Gillis C, Li C, Lee L, et al. Prehabilitation versus rehabilitation: a randomized control trial in patients undergoing colorectal resection for cancer. *Anesthesiology* 2014; **121**: 937-47

Gillis C, Loiselle SE, Fiore JF, Jr., et al. Prehabilitation with Whey Protein Supplementation on Perioperative Functional Exercise Capacity in Patients Undergoing Colorectal Resection for Cancer: A Pilot Double-Blinded Randomized Placebo-Controlled Trial. *J Acad Nutr Diet* 2016; **116**: 802-12

Gomez-Izquierdo JC, Trainito A, Mirzakandov D, et al. Goal-directed Fluid Therapy Does Not Reduce Primary Postoperative Ileus after Elective Laparoscopic Colorectal Surgery: A Randomized Controlled Trial. *Anesthesiology* 2017; **127**: 36-49

Haase O, Schwenk W, Hermann C, Muller JM. Guided imagery and relaxation in conventional colorectal resections: a randomized, controlled, partially blinded trial. *Dis Colon Rectum* 2005; **48**: 1955-63

Heiss MM, Tarabichi A, Delanoff C, et al. Perisurgical erythropoietin application in anemic patients with colorectal cancer: A double-blind randomized study. *Surgery* 1996; **119**: 523-7

Henriksen MG, Jensen MB, Hansen HV, Jespersen TW, Hesselov I. Enforced mobilization, early oral feeding, and balanced analgesia improve convalescence after colorectal surgery. *Nutrition* 2002; **18**: 147-52

Hubner M, Blanc C, Roulin D, Winiker M, Gander S, Demartines N. Randomized clinical trial on epidural versus patient-controlled analgesia for laparoscopic colorectal surgery within an enhanced recovery pathway. *Ann Surg* 2015; **261**: 648-53

Ionescu D, Iancu C, Ion D, et al. Implementing fast-track protocol for colorectal surgery: a prospective randomized clinical trial. *World J Surg* 2009; **33**: 2433-8

Jammer I, Ulvik A, Erichsen C, Lodemel O, Ostgaard G. Does central venous oxygen saturation-directed fluid therapy affect postoperative morbidity after colorectal surgery? A randomized assessor-blinded controlled trial. *Anesthesiology* 2010; **113**: 1072-80

Kaba A, Laurent SR, Detroz BJ, et al. Intravenous lidocaine infusion facilitates acute rehabilitation after laparoscopic colectomy. *Anesthesiology* 2007; **106**: 11-8; discussion 5-6

Kettelhack C, Hones C, Messinger D, Schlag PM. Randomized multicentre trial of the influence of recombinant human erythropoietin on intraoperative and postoperative transfusion need in anaemic patients undergoing right hemicolectomy for carcinoma. *Br J Surg* 1998; **85**: 63-7

Khoo CK, Vickery CJ, Forsyth N, Vinall NS, Eyre-Brook IA. A prospective randomized controlled trial of multimodal perioperative management protocol in patients undergoing elective colorectal resection for cancer. *Ann Surg* 2007; **245**: 867-72

Kim DJ, Mayo NE, Carli F, Montgomery DL, Zavorsky GS. Responsive measures to prehabilitation in patients undergoing bowel resection surgery. *Tohoku J Exp Med* 2009; **217**: 109-15

King PM, Blazeby JM, Ewings P, et al. Randomized clinical trial comparing laparoscopic and open surgery for colorectal cancer within an enhanced recovery programme. *Br J Surg* 2006; **93**: 300-8

Lidder PG, Sanders G, Whitehead E, et al. Pre-operative oral iron supplementation reduces blood transfusion in colorectal surgery - a prospective, randomised, controlled trial. *Ann R Coll Surg Engl* 2007; **89**: 418-21

MacFie J, Woodcock NP, Palmer MD, Walker A, Townsend S, Mitchell CJ. Oral dietary supplements in pre- and postoperative surgical patients: a prospective and randomized clinical trial. *Nutrition* 2000; **16**: 723-8

Mouawad NJ, Leichtle SW, Kaoutzani C, et al. Pain control with continuous infusion preperitoneal wound catheters versus continuous epidural analgesia in colon and rectal surgery: A randomized controlled trial. *Am J Surg* 2018; **215**: 570-6

Muller S, Zalunardo MP, Hubner M, Clavien PA, Demartines N. A fast-track program reduces complications and length of hospital stay after open colonic surgery. *Gastroenterology* 2009; **136**: 842-7

Neudecker J, Schwenk W, Junghans T, Pietsch S, Bohm B, Muller JM. Randomized controlled trial to examine the influence of thoracic epidural analgesia on postoperative ileus after laparoscopic sigmoid resection. *Br J Surg* 1999; **86**: 1292-5

Niraj G, Kelkar A, Hart E, et al. Comparison of analgesic efficacy of four-quadrant transversus abdominis plane (TAP) block and continuous posterior TAP analgesia with epidural analgesia in patients undergoing laparoscopic colorectal surgery: an open-label, randomised, non-inferiority trial. *Anaesthesia* 2014; **69**: 348-55

Noblett SE, Snowden CP, Shenton BK, Horgan AF. Randomized clinical trial assessing the effect of Doppler-optimized fluid management on outcome after elective colorectal resection. *Br J Surg* 2006; **93**: 1069-76

Oh TK, Yim J, Kim J, et al. Effects of preoperative ultrasound-guided transversus abdominis plane block on pain after laparoscopic surgery for colorectal cancer: a double-blind randomized controlled trial. *Surg Endosc* 2017; **31**: 127-34

Qvist N, Boesby S, Wolff B, Hansen CP. Recombinant human erythropoietin and hemoglobin concentration at operation and during the postoperative period: reduced need for blood

transfusions in patients undergoing colorectal surgery--prospective double-blind placebo-controlled study. *World J Surg* 1999; **23**: 30-5

Rashid A, Gorissen KJ, Ris F, et al. No benefit of ultrasound-guided transversus abdominis plane blocks over wound infiltration with local anaesthetic in elective laparoscopic colonic surgery: results of a double-blind randomized controlled trial. *Colorectal Dis* 2017; **19**: 681-9

Ren L, Zhu D, Wei Y, et al. Enhanced Recovery After Surgery (ERAS) program attenuates stress and accelerates recovery in patients after radical resection for colorectal cancer: a prospective randomized controlled trial. *World J Surg* 2012; **36**: 407-14

Senagore AJ, Delaney CP, Mekhail N, Dugan A, Fazio VW. Randomized clinical trial comparing epidural anaesthesia and patient-controlled analgesia after laparoscopic segmental colectomy. *Br J Surg* 2003; **90**: 1195-9

Serclova Z, Dytrych P, Marvan J, et al. Fast-track in open intestinal surgery: prospective randomized study (Clinical Trials Gov Identifier no. NCT00123456). *Clin Nutr* 2009; **28**: 618-24

Smedley F, Bowling T, James M, et al. Randomized clinical trial of the effects of preoperative and postoperative oral nutritional supplements on clinical course and cost of care. *Br J Surg* 2004; **91**: 983-90

Smith SR, Draganic B, Pockney P, et al. Transversus abdominis plane blockade in laparoscopic colorectal surgery: a double-blind randomized clinical trial. *Int J Colorectal Dis* 2015; **30**: 1237-45

Srinivasa S, Taylor MH, Singh PP, Yu TC, Soop M, Hill AG. Randomized clinical trial of goal-directed fluid therapy within an enhanced recovery protocol for elective colectomy. *Br J Surg* 2013; **100**: 66-74

Staikou C, Avramidou A, Ayiomamitis GD, Vrakas S, Argyra E. Effects of intravenous versus epidural lidocaine infusion on pain intensity and bowel function after major large bowel surgery: a double-blind randomized controlled trial. *J Gastrointest Surg* 2014; **18**: 2155-62

Taqi A, Hong X, Mistraletti G, Stein B, Charlebois P, Carli F. Thoracic epidural analgesia facilitates the restoration of bowel function and dietary intake in patients undergoing laparoscopic colon resection using a traditional, nonaccelerated, perioperative care program. *Surg Endosc* 2007; **21**: 247-52

Tikuisis R, Miliauskas P, Lukoseviciene V, et al. Transversus abdominis plane block for postoperative pain relief after hand-assisted laparoscopic colon surgery: a randomized, placebo-controlled clinical trial. *Tech Coloproctol* 2016; **20**: 835-44

Turunen P, Carpelan-Holmstrom M, Kairaluoma P, et al. Epidural analgesia diminished pain but did not otherwise improve enhanced recovery after laparoscopic sigmoidectomy: a prospective randomized study. *Surg Endosc* 2009; **23**: 31-7

van Bree SH, Vlug MS, Bemelman WA, et al. Faster recovery of gastrointestinal transit after laparoscopy and fast-track care in patients undergoing colonic surgery. *Gastroenterology* 2011; **141**: 872-80.e1-4

van Bree SH, Vlug MS, Bemelman WA, et al. Faster recovery of gastrointestinal transit after laparoscopy and fast-track care in patients undergoing colonic surgery. *Gastroenterology* 2011; **141**: 872-80.e1-4

Veenhof AA, Vlug MS, van der Pas MH, et al. Surgical stress response and postoperative immune function after laparoscopy or open surgery with fast track or standard perioperative care: a randomized trial. *Ann Surg* 2012; **255**: 216-21

Veenhof AA, Vlug MS, van der Pas MH, et al. Surgical stress response and postoperative immune function after laparoscopy or open surgery with fast track or standard perioperative care: a randomized trial. *Ann Surg* 2012; **255**: 216-21

Wakeling HG, McFall MR, Jenkins CS, et al. Intraoperative oesophageal Doppler guided fluid management shortens postoperative hospital stay after major bowel surgery. *Br J Anaesth* 2005; **95**: 634-42

Walter CJ, Maxwell-Armstrong C, Pinkney TD, et al. A randomised controlled trial of the efficacy of ultrasound-guided transversus abdominis plane (TAP) block in laparoscopic colorectal surgery. *Surg Endosc* 2013; **27**: 2366-72

Wang G, Jiang Z, Zhao K, et al. Immunologic response after laparoscopic colon cancer operation within an enhanced recovery program. *J Gastrointest Surg* 2012; **16**: 1379-88

Wang G, Jiang Z, Zhao K, et al. Immunologic response after laparoscopic colon cancer operation within an enhanced recovery program. *J Gastrointest Surg* 2012; **16**: 1379-88

Wang G, Jiang ZW, Xu J, et al. Fast-track rehabilitation program vs conventional care after colorectal resection: a randomized clinical trial. *World J Gastroenterol* 2011; **17**: 671-6

West MA, Loughney L, Lythgoe D, et al. Effect of prehabilitation on objectively measured physical fitness after neoadjuvant treatment in preoperative rectal cancer patients: a blinded interventional pilot study. *Br J Anaesth* 2015; **114**: 244-51

Yang D, He W, Zhang S, Chen H, Zhang C, He Y. Fast-track surgery improves postoperative clinical recovery and immunity after elective surgery for colorectal carcinoma: randomized controlled clinical trial. *World J Surg* 2012; **36**: 1874-80

Zakhaleva J, Tam J, Denoya PI, Bishawi M, Bergamaschi R. The impact of intravenous fluid administration on complication rates in bowel surgery within an enhanced recovery protocol: a randomized controlled trial. *Colorectal Dis* 2013; **15**: 892-9

Zingg U, Miskovic D, Hamel CT, Erni L, Oertli D, Metzger U. Influence of thoracic epidural analgesia on postoperative pain relief and ileus after laparoscopic colorectal resection : Benefit with epidural analgesia. *Surg Endosc* 2009; **23**: 276-82

Elective knee arthroplasty

Affas F, Nygard EB, Stiller CO, Wretenberg P, Olofsson C. Pain control after total knee arthroplasty: a randomized trial comparing local infiltration anesthesia and continuous femoral block. *Acta Orthop* 2011; **82**: 441-7

Andersen KV, Bak M, Christensen BV, Harazuk J, Pedersen NA, Soballe K. A randomized, controlled trial comparing local infiltration analgesia with epidural infusion for total knee arthroplasty. *Acta Orthop* 2010; **81**: 606-10

Calatayud J, Casana J, Ezzatvar Y, Jakobsen MD, Sundstrup E, Andersen LL. High-intensity preoperative training improves physical and functional recovery in the early post-operative periods after total knee arthroplasty: a randomized controlled trial. *Knee Surg Sports Traumatol Arthrosc* 2017; **25**: 2864-72

Cankaya D, Dasar U, Satilmis AB, Basaran SH, Akkaya M, Bozkurt M. The combined use of oral and topical tranexamic acid is a safe, efficient and low-cost method in reducing blood loss and transfusion rates in total knee arthroplasty. *J Orthop Surg (Hong Kong)* 2017; **25**: 2309499016684725

den Hertog A, Gliesche K, Timm J, Muhlbauer B, Zebrowski S. Pathway-controlled fast-track rehabilitation after total knee arthroplasty: a randomized prospective clinical study evaluating the recovery pattern, drug consumption, and length of stay. *Arch Orthop Trauma Surg* 2012; **132**: 1153-63

D'Lima DD, Colwell CW, Jr., Morris BA, Hardwick ME, Kozin F. The effect of preoperative exercise on total knee replacement outcomes. *Clin Orthop Relat Res* 1996: 174-82

Gao F, Sun W, Guo W, Li Z, Wang W, Cheng L. Topical Administration of Tranexamic Acid Plus Diluted-Epinephrine in Primary Total Knee Arthroplasty: A Randomized Double-Blinded Controlled Trial. *J Arthroplasty* 2015; **30**: 1354-8

Good L, Peterson E, Lisander B. Tranexamic acid decreases external blood loss but not hidden blood loss in total knee replacement. *Br J Anaesth* 2003; **90**: 596-9

Goyal N, Chen DB, Harris IA, Rowden NJ, Kirsh G, MacDessi SJ. Intravenous vs Intra-Articular Tranexamic Acid in Total Knee Arthroplasty: A Randomized, Double-Blind Trial. *J Arthroplasty* 2017; **32**: 28-32

Gstoettner M, Raschner C, Dirnberger E, Leimser H, Krismer M. Preoperative proprioceptive training in patients with total knee arthroplasty. *Knee* 2011; **18**: 265-70

Huang SW, Chen PH, Chou YH. Effects of a preoperative simplified home rehabilitation education program on length of stay of total knee arthroplasty patients. *Orthop Traumatol Surg Res* 2012; **98**: 259-64

Huber EO, Roos EM, Meichtry A, de Bie RA, Bischoff-Ferrari HA. Effect of preoperative neuromuscular training (NEMEX-TJR) on functional outcome after total knee replacement: an assessor-blinded randomized controlled trial. *BMC Musculoskelet Disord* 2015; **16**: 101

Kampitak W, Tanavalee A, Ngarmukos S, Amarase C, Songthamwat B, Boonshua A. Comparison of Adductor Canal Block Versus Local Infiltration Analgesia on Postoperative Pain and Functional Outcome after Total Knee Arthroplasty: A Randomized Controlled Trial. *Malays Orthop J* 2018; **12**: 7-14

Kim DH, Lin Y, Goytizolo EA, et al. Adductor canal block versus femoral nerve block for total knee arthroplasty: a prospective, randomized, controlled trial. *Anesthesiology* 2014; **120**: 540-50

Lee QJ, Ching WY, Wong YC. Blood Sparing Efficacy of Oral Tranexamic Acid in Primary Total Knee Arthroplasty: A Randomized Controlled Trial. *Knee Surg Relat Res* 2017; **29**: 57-62

Lee SY, Chong S, Balasubramanian D, Na YG, Kim TK. What is the Ideal Route of Administration of Tranexamic Acid in TKA? A Randomized Controlled Trial. *Clin Orthop Relat Res* 2017; **475**: 1987-96

Liao CD, Liou TH, Huang YY, Huang YC. Effects of balance training on functional outcome after total knee replacement in patients with knee osteoarthritis: a randomized controlled trial. *Clin Rehabil* 2013; **27**: 697-709

Luna IE, Kehlet H, Jensen CM, et al. The Effect of Preoperative Intra-Articular Methylprednisolone on Pain After TKA: A Randomized Double-Blinded Placebo Controlled Trial in Patients With High-Pain Knee Osteoarthritis and Sensitization. *J Pain* 2017; **18**: 1476-87

Lunn TH, Kristensen BB, Andersen LO, et al. Effect of high-dose preoperative methylprednisolone on pain and recovery after total knee arthroplasty: a randomized, placebo-controlled trial. *Br J Anaesth* 2011; **106**: 230-8

Mahadevan D, Walter RP, Minto G, Gale TC, McAllen CJ, Oldman M. Combined femoral and sciatic nerve block vs combined femoral and periarticular infiltration in total knee arthroplasty: a randomized controlled trial. *J Arthroplasty* 2012; **27**: 1806-11

Maniar RN, Kumar G, Singhi T, Nayak RM, Maniar PR. Most effective regimen of tranexamic acid in knee arthroplasty: a prospective randomized controlled study in 240 patients. *Clin Orthop Relat Res* 2012; **470**: 2605-12

Matassi F, Duerinckx J, Vandenneucker H, Bellemans J. Range of motion after total knee arthroplasty: the effect of a preoperative home exercise program. *Knee Surg Sports Traumatol Arthrosc* 2014; **22**: 703-9

McKay C, Prapavessis H, Doherty T. The effect of a prehabilitation exercise program on quadriceps strength for patients undergoing total knee arthroplasty: a randomized controlled pilot study. *Pm r* 2012; **4**: 647-56

Moghtadaei M, Farahini H, Faiz SH, Mokarami F, Safari S. Pain Management for Total Knee Arthroplasty: Single-Injection Femoral Nerve Block versus Local Infiltration Analgesia. *Iran Red Crescent Med J* 2014; **16**: e13247

Murata-Ooiwa M, Tsukada S, Wakui M. Intravenous Acetaminophen in Multimodal Pain Management for Patients Undergoing Total Knee Arthroplasty: A Randomized, Double-Blind, Placebo-Controlled Trial. *J Arthroplasty* 2017; **32**: 3024-8

O'Neal JB, Freiberg AA, Yelle MD, et al. Intravenous vs Oral Acetaminophen as an Adjunct to Multimodal Analgesia After Total Knee Arthroplasty: A Prospective, Randomized, Double-Blind Clinical Trial. *J Arthroplasty* 2017; **32**: 3029-33

Rooks DS, Huang J, Bierbaum BE, et al. Effect of preoperative exercise on measures of functional status in men and women undergoing total hip and knee arthroplasty. *Arthritis Rheum* 2006; **55**: 700-8

Roy SP, Tanki UF, Dutta A, Jain SK, Nagi ON. Efficacy of intra-articular tranexamic acid in blood loss reduction following primary unilateral total knee arthroplasty. *Knee Surg Sports Traumatol Arthrosc* 2012; **20**: 2494-501

Seo JG, Moon YW, Park SH, Kim SM, Ko KR. The comparative efficacies of intra-articular and IV tranexamic acid for reducing blood loss during total knee arthroplasty. *Knee Surg Sports Traumatol Arthrosc* 2013; **21**: 1869-74

Skofter B, Maribo T, Mechlenburg I, Hansen PM, Soballe K, Dalgas U. Efficacy of Preoperative Progressive Resistance Training on Postoperative Outcomes in Patients Undergoing Total Knee Arthroplasty. *Arthritis Care Res (Hoboken)* 2016; **68**: 1239-51

Song EK, Seon JK, Prakash J, Seol YJ, Park YJ, Jin C. Combined Administration of IV and Topical Tranexamic Acid is Not Superior to Either Individually in Primary Navigated TKA. *J Arthroplasty* 2017; **32**: 37-42

Spreng UJ, Dahl V, Hjal A, Fagerland MW, Raeder J. High-volume local infiltration analgesia combined with intravenous or local ketorolac+morphine compared with epidural analgesia after total knee arthroplasty. *Br J Anaesth* 2010; **105**: 675-82

Sun Q, Yu X, Wu J, Ge W, Cai M, Li S. Efficacy of a Single Dose and an Additional Dose of Tranexamic Acid in Reduction of Blood Loss in Total Knee Arthroplasty. *J Arthroplasty* 2017; **32**: 2108-12

Toftdahl K, Nikolajsen L, Haraldsted V, Madsen F, Tonnesen EK, Soballe K. Comparison of peri- and intraarticular analgesia with femoral nerve block after total knee arthroplasty: a randomized clinical trial. *Acta Orthop* 2007; **78**: 172-9

Tong QJ, Lim YC, Tham HM. Comparing adductor canal block with local infiltration analgesia in total knee arthroplasty: A prospective, blinded and randomized clinical trial. *J Clin Anesth* 2018; **46**: 39-43

Topp R, Swank AM, Quesada PM, Nyland J, Malkani A. The effect of prehabilitation exercise on strength and functioning after total knee arthroplasty. *Pm r* 2009; **1**: 729-35

Veien M, Sorensen JV, Madsen F, Juelsgaard P. Tranexamic acid given intraoperatively reduces blood loss after total knee replacement: a randomized, controlled study. *Acta Anaesthesiol Scand* 2002; **46**: 1206-11

Villadsen A, Overgaard S, Holsgaard-Larsen A, Christensen R, Roos EM. Postoperative effects of neuromuscular exercise prior to hip or knee arthroplasty: a randomised controlled trial. *Ann Rheum Dis* 2014; **73**: 1130-7

Wang JW, Chen B, Lin PC, Yen SH, Huang CC, Kuo FC. The Efficacy of Combined Use of Rivaroxaban and Tranexamic Acid on Blood Conservation in Minimally Invasive Total Knee Arthroplasty a Double-Blind Randomized, Controlled Trial. *J Arthroplasty* 2017; **32**: 801-6

Williamson L, Wyatt MR, Yein K, Melton JT. Severe knee osteoarthritis: a randomized controlled trial of acupuncture, physiotherapy (supervised exercise) and standard management for patients awaiting knee replacement. *Rheumatology (Oxford)* 2007; **46**: 1445-9

Wong J, Abrishami A, El Beheiry H, et al. Topical application of tranexamic acid reduces postoperative blood loss in total knee arthroplasty: a randomized, controlled trial. *J Bone Joint Surg Am* 2010; **92**: 2503-13

Xie J, Ma J, Yao H, Yue C, Pei F. Multiple Boluses of Intravenous Tranexamic Acid to Reduce Hidden Blood Loss After Primary Total Knee Arthroplasty Without Tourniquet: A Randomized Clinical Trial. *J Arthroplasty* 2016; **31**: 2458-64

Xu B, Ma J, Huang Q, Huang ZY, Zhang SY, Pei FX. Two doses of low-dose perioperative dexamethasone improve the clinical outcome after total knee arthroplasty: a randomized controlled study. *Knee Surg Sports Traumatol Arthrosc* 2018; **26**: 1549-56

Yuan X, Li B, Wang Q, Zhang X. Comparison of 3 Routes of Administration of Tranexamic Acid on Primary Unilateral Total Knee Arthroplasty: A Prospective, Randomized, Controlled Study. *J Arthroplasty* 2017; **32**: 2738-43

Zeng WN, Liu JL, Wang FY, Chen C, Zhou Q, Yang L. Low-Dose Epinephrine Plus Tranexamic Acid Reduces Early Postoperative Blood Loss and Inflammatory Response: A Randomized Controlled Trial. *J Bone Joint Surg Am* 2018; **100**: 295-304

Zohar E, Ellis M, Ifrach N, Stern A, Sapir O, Fredman B. The postoperative blood-sparing efficacy of oral versus intravenous tranexamic acid after total knee replacement. *Anesth Analg* 2004; **99**: 1679-83, table of contents

Elective hip arthroplasty

Ferrara PE, Rabini A, Maggi L, et al. Effect of pre-operative physiotherapy in patients with end-stage osteoarthritis undergoing hip arthroplasty. *Clin Rehabil* 2008; **22**: 977-86

Gao F, Sun W, Guo W, Li Z, Wang W, Cheng L. Topical Application of Tranexamic Acid Plus Diluted Epinephrine Reduces Postoperative Hidden Blood Loss in Total Hip Arthroplasty. *J Arthroplasty* 2015; **30**: 2196-200

Gilbey HJ, Ackland TR, Wang AW, Morton AR, Troughet T, Tapper J. Exercise improves early functional recovery after total hip arthroplasty. *Clin Orthop Relat Res* 2003: 193-200

Gocen Z, Sen A, Unver B, Karatosun V, Gunal I. The effect of preoperative physiotherapy and education on the outcome of total hip replacement: a prospective randomized controlled trial. *Clin Rehabil* 2004; **18**: 353-8

Harley BJ, Beaupre LA, Jones CA, Cinats JG, Guenther CR. The effect of epsilon aminocaproic acid on blood loss in patients who undergo primary total hip replacement: a pilot study. *Can J Surg* 2002; **45**: 185-90

Husted H, Blond L, Sonne-Holm S, Holm G, Jacobsen TW, Gebuhr P. Tranexamic acid reduces blood loss and blood transfusions in primary total hip arthroplasty: a prospective randomized double-blind study in 40 patients. *Acta Orthop Scand* 2003; **74**: 665-9

Imai N, Dohmae Y, Suda K, Miyasaka D, Ito T, Endo N. Tranexamic acid for reduction of blood loss during total hip arthroplasty. *J Arthroplasty* 2012; **27**: 1838-43

Kayupov E, Fillingham YA, Okroj K, et al. Oral and Intravenous Tranexamic Acid Are Equivalent at Reducing Blood Loss Following Total Hip Arthroplasty: A Randomized Controlled Trial. *J Bone Joint Surg Am* 2017; **99**: 373-8

Lei YT, Xu B, Xie XW, Xie JW, Huang Q, Pei FX. The efficacy and safety of two low-dose perioperative dexamethasone on pain and recovery following total hip arthroplasty: a randomized controlled trial. *Int Orthop* 2018; **42**: 499-505

Lemay E, Guay J, Cote C, Roy A. Tranexamic acid reduces the need for allogenic red blood cell transfusions in patients undergoing total hip replacement. *Can J Anaesth* 2004; **51**: 31-7

Lunn TH, Kristensen BB, Andersen LO, et al. Effect of high-dose preoperative methylprednisolone on pain and recovery after total knee arthroplasty: a randomized, placebo-controlled trial. *Br J Anaesth* 2011; **106**: 230-8

Martinez V, Cymerman A, Ben Ammar S, et al. The analgesic efficiency of combined pregabalin and ketamine for total hip arthroplasty: a randomised, double-blind, controlled study. *Anaesthesia* 2014; **69**: 46-52

Mawatari M, Higo T, Tsutsumi Y, Shigematsu M, Hotokebuchi T. Effectiveness of autologous fibrin tissue adhesive in reducing postoperative blood loss during total hip arthroplasty: a prospective randomised study of 100 cases. *J Orthop Surg (Hong Kong)* 2006; **14**: 117-21

Niskanen RO, Korkala OL. Tranexamic acid reduces blood loss in cemented hip arthroplasty: a randomized, double-blind study of 39 patients with osteoarthritis. *Acta Orthop* 2005; **76**: 829-32

North WT, Mehran N, Davis JJ, Silverton CD, Weir RM, Laker MW. Topical vs Intravenous Tranexamic Acid in Primary Total Hip Arthroplasty: A Double-Blind, Randomized Controlled Trial. *J Arthroplasty* 2016; **31**: 1022-6

Randelli F, Banci L, Ragone V, Pavesi M, Randelli G. Effectiveness of fibrin sealant after cementless total hip replacement: a double-blind randomized controlled trial. *Int J Immunopathol Pharmacol* 2013; **26**: 189-97

Rikalainen-Salmi R, Forster JG, Makela K, et al. Local infiltration analgesia with levobupivacaine compared with intrathecal morphine in total hip arthroplasty patients. *Acta Anaesthesiol Scand* 2012; **56**: 695-705

Rooks DS, Huang J, Bierbaum BE, et al. Effect of preoperative exercise on measures of functional status in men and women undergoing total hip and knee arthroplasty. *Arthritis Rheum* 2006; **55**: 700-8

Sculco PK, McLawhorn AS, Desai N, Su EP, Padgett DE, Jules-Elysee K. The Effect of Perioperative Corticosteroids in Total Hip Arthroplasty: A Prospective Double-Blind Placebo Controlled Pilot Study. *J Arthroplasty* 2016; **31**: 1208-12

Smith LK, Williams DH, Langkamer VG. Post-operative blood salvage with autologous retransfusion in primary total hip replacement. *J Bone Joint Surg Br* 2007; **89**: 1092-7

Thybo KH, Schmidt H, Hagi-Pedersen D. Effect of lateral femoral cutaneous nerve-block on pain after total hip arthroplasty: a randomised, blinded, placebo-controlled trial. *BMC Anesthesiol* 2016; **16**: 21

Villadsen A, Overgaard S, Holsgaard-Larsen A, Christensen R, Roos EM. Postoperative effects of neuromuscular exercise prior to hip or knee arthroplasty: a randomised controlled trial. *Ann Rheum Dis* 2014; **73**: 1130-7

Wang AW, Gilbey HJ, Ackland TR. Perioperative exercise programs improve early return of ambulatory function after total hip arthroplasty: a randomized, controlled trial. *Am J Phys Med Rehabil* 2002; **81**: 801-6

Wei W, Wei B. Comparison of topical and intravenous tranexamic acid on blood loss and transfusion rates in total hip arthroplasty. *J Arthroplasty* 2014; **29**: 2113-6

Xie J, Ma J, Yue C, Kang P, Pei F. Combined use of intravenous and topical tranexamic acid following cementless total hip arthroplasty: a randomised clinical trial. *Hip Int* 2016; **26**: 36-42

Yamasaki S, Masuhara K, Fuji T. Tranexamic acid reduces blood loss after cementless total hip arthroplasty-prospective randomized study in 40 cases. *Int Orthop* 2004; **28**: 69-73

Yi Z, Bin S, Jing Y, Zongke Z, Pengde K, Fuxing P. Tranexamic Acid Administration in Primary Total Hip Arthroplasty: A Randomized Controlled Trial of Intravenous Combined with Topical Versus Single-Dose Intravenous Administration. *J Bone Joint Surg Am* 2016; **98**: 983-91

Yue C, Kang P, Yang P, Xie J, Pei F. Topical application of tranexamic acid in primary total hip arthroplasty: a randomized double-blind controlled trial. *J Arthroplasty* 2014; **29**: 2452-6

Zufferey PJ, Lanoiselee J, Chapelle C, et al. Intravenous Tranexamic Acid Bolus plus Infusion Is Not More Effective than a Single Bolus in Primary Hip Arthroplasty: A Randomized Controlled Trial. *Anesthesiology* 2017; **127**: 413-22

Surgical management of a fractured neck of femur

Bartha E, Arfwedson C, Imnell A, Fernlund ME, Andersson LE, Kalman S. Randomized controlled trial of goal-directed haemodynamic treatment in patients with proximal femoral fracture. *Br J Anaesth* 2013; **110**: 545-53

Baruah RK, Borah PJ, Haque R. Use of tranexamic acid in dynamic hip screw plate fixation for trochanteric fractures. *J Orthop Surg (Hong Kong)* 2016; **24**: 379-82

Beaudoin FL, Haran JP, Liebmann O. A comparison of ultrasound-guided three-in-one femoral nerve block versus parenteral opioids alone for analgesia in emergency department patients with hip fractures: a randomized controlled trial. *Acad Emerg Med* 2013; **20**: 584-91

Bernabeu-Wittel M, Romero M, Ollero-Baturone M, et al. Ferric carboxymaltose with or without erythropoietin in anemic patients with hip fracture: a randomized clinical trial. *Transfusion (Paris)* 2016; **56**: 2199-211

Binder EF, Brown M, Sinacore DR, Steger-May K, Yarasheski KE, Schechtman KB. Effects of extended outpatient rehabilitation after hip fracture: a randomized controlled trial. *JAMA* 2004; **292**: 837-46

Braid V, Barber M, Mitchell SL, Martin BJ, Granat M, Stott DJ. Randomised controlled trial of electrical stimulation of the quadriceps after proximal femoral fracture. *Aging Clin Exp Res* 2008; **20**: 62-6

Carson JL, Terrin ML, Barton FB, et al. A pilot randomized trial comparing symptomatic vs. hemoglobin-level-driven red blood cell transfusions following hip fracture. *Transfusion (Paris)* 1998; **38**: 522-9

Carson JL, Terrin ML, Noveck H, et al. Liberal or restrictive transfusion in high-risk patients after hip surgery. *N Engl J Med* 2011; **365**: 2453-62

Emara WM, Moez KK, Elkhoully AH. Topical versus intravenous tranexamic acid as a blood conservation intervention for reduction of post-operative bleeding in hemiarthroplasty. *Anesth Essays Res* 2014; **8**: 48-53

Fletcher AK, Rigby AS, Heyes FL. Three-in-one femoral nerve block as analgesia for fractured neck of femur in the emergency department: a randomized, controlled trial. *Ann Emerg Med* 2003; **41**: 227-33

Foss NB, Kristensen BB, Bundgaard M, et al. Fascia iliaca compartment blockade for acute pain control in hip fracture patients: a randomized, placebo-controlled trial. *Anesthesiology* 2007; **106**: 773-8

Foss NB, Kristensen MT, Jensen PS, Palm H, Krasheninnikoff M, Kehlet H. The effects of liberal versus restrictive transfusion thresholds on ambulation after hip fracture surgery. *Transfusion (Paris)* 2009; **49**: 227-34

Fujihara Y, Fukunishi S, Nishio S, Miura J, Koyanagi S, Yoshiya S. Fascia iliaca compartment block: its efficacy in pain control for patients with proximal femoral fracture. *J Orthop Sci* 2013; **18**: 793-7

Gorodetskyi IG, Gorodnichenko AI, Tursin PS, Reshetnyak VK, Uskov ON. Non-invasive interactive neurostimulation in the post-operative recovery of patients with a trochanteric fracture of the femur. A randomised, controlled trial. *J Bone Joint Surg Br* 2007; **89**: 1488-94

Graham C, Baird K, McGuffie A. A Pilot Randomised Clinical Trial of 3-In-1 Femoral Nerve Block and Intravenous Morphine as Primary Analgesia for Patients Presenting to the Emergency Department with Fractured Hip. *Hong Kong Journal of Emergency Medicine* 2008; **15**: 205-11

Haghighi M, Ettehad H, Mardani-Kivi M, et al. Does Tranexamic Acid Reduce Bleeding during Femoral Fracture Operation? *Arch Bone Jt Surg* 2017; **5**: 103-8

Iamaroon A, Raksakietisak M, Halilamien P, Hongsawad J, Boonsararuksapong K. Femoral nerve block versus fentanyl: Analgesia for positioning patients with fractured femur. *Local Reg Anesth* 2010; **3**: 21-6

- Jadon A, Kedia SK, Dixit S, Chakraborty S. Comparative evaluation of femoral nerve block and intravenous fentanyl for positioning during spinal anaesthesia in surgery of femur fracture. *Indian J Anaesth* 2014; **58**: 705-8
- Lamb SE, Oldham JA, Morse RE, Evans JG. Neuromuscular stimulation of the quadriceps muscle after hip fracture: a randomized controlled trial. *Arch Phys Med Rehabil* 2002; **83**: 1087-92
- Lei J, Zhang B, Cong Y, et al. Tranexamic acid reduces hidden blood loss in the treatment of intertrochanteric fractures with PFNA: a single-center randomized controlled trial. *J Orthop Surg Res* 2017; **12**: 124
- Mitchell SL, Stott DJ, Martin BJ, Grant SJ. Randomized controlled trial of quadriceps training after proximal femoral fracture. *Clin Rehabil* 2001; **15**: 282-90
- Moppett IK, Rowlands M, Mannings A, Moran CG, Wiles MD. LiDCO-based fluid management in patients undergoing hip fracture surgery under spinal anaesthesia: a randomized trial and systematic review. *Br J Anaesth* 2015; **114**: 444-59
- Moseley AM, Sherrington C, Lord SR, Barraclough E, St George RJ, Cameron ID. Mobility training after hip fracture: a randomised controlled trial. *Age Ageing* 2009; **38**: 74-80
- Newman B, McCarthy L, Thomas PW, May P, Layzell M, Horn K. A comparison of pre-operative nerve stimulator-guided femoral nerve block and fascia iliaca compartment block in patients with a femoral neck fracture. *Anaesthesia* 2013; **68**: 899-903
- Nie H, Yang YX, Wang Y, Liu Y, Zhao B, Luan B. Effects of continuous fascia iliaca compartment blocks for postoperative analgesia in patients with hip fracture. *Pain Res Manag* 2015; **20**: 210-2
- Oldmeadow LB, Edwards ER, Kimmel LA, Kipen E, Robertson VJ, Bailey MJ. No rest for the wounded: early ambulation after hip surgery accelerates recovery. *ANZ J Surg* 2006; **76**: 607-11
- Parker MJ. Randomised trial of blood transfusion versus a restrictive transfusion policy after hip fracture surgery. *Injury* 2013; **44**: 1916-8
- Reavley P, Montgomery AA, Smith JE, et al. Randomised trial of the fascia iliaca block versus the '3-in-1' block for femoral neck fractures in the emergency department. *Emerg Med J* 2015; **32**: 685-9
- Sadeghi M, Mehr-Aein A. *Does a single bolus dose of tranexamic acid reduce blood loss and transfusion requirements during hip fracture surgery? A prospective randomized double blind study in 67 patients.* 2007
- Sherrington C, Lord SR. Home exercise to improve strength and walking velocity after hip fracture: a randomized controlled trial. *Arch Phys Med Rehabil* 1997; **78**: 208-12
- Sherrington C, Lord SR, Herbert RD. A randomised trial of weight-bearing versus non-weight-bearing exercise for improving physical ability in inpatients after hip fracture. *Aust J Physiother* 2003; **49**: 15-22

Sherrington C, Lord SR, Herbert RD. A randomized controlled trial of weight-bearing versus non-weight-bearing exercise for improving physical ability after usual care for hip fracture. *Arch Phys Med Rehabil* 2004; **85**: 710-6

Sinclair S, James S, Singer M. Intraoperative intravascular volume optimisation and length of hospital stay after repair of proximal femoral fracture: randomised controlled trial. *BMJ* 1997; **315**: 909-12

Szucs S, Iohom G, O'Donnell B, et al. Analgesic efficacy of continuous femoral nerve block commenced prior to operative fixation of fractured neck of femur. *Perioper Med (Lond)* 2012; **1**: 4

Tengberg PT, Foss NB, Palm H, Kallemose T, Troelsen A. Tranexamic acid reduces blood loss in patients with extracapsular fractures of the hip: results of a randomised controlled trial. *Bone Joint J* 2016; **98-b**: 747-53

Tian S, Shen Z, Liu Y, Zhang Y, Peng A. The effect of tranexamic acid on hidden bleeding in older intertrochanteric fracture patients treated with PFNA. *Injury* 2018; **49**: 680-4

Tsauo JY, Leu WS, Chen YT, Yang RS. Effects on function and quality of life of postoperative home-based physical therapy for patients with hip fracture. *Arch Phys Med Rehabil* 2005; **86**: 1953-7

Tuncer S, Sert OA, Yosunkaya A, Mutlu M, Celki J, Okesli S. Patient-controlled femoral nerve analgesia versus patient-controlled intravenous analgesia for postoperative analgesia after trochanteric fracture repair. *Acute Pain* 2003; **4**: 105-8

Vijay BS, Bedi V, Mitra S, Das B. Role of tranexamic acid in reducing postoperative blood loss and transfusion requirement in patients undergoing hip and femoral surgeries. *Saudi J Anaesth* 2013; **7**: 29-32

Yun MJ, Kim YH, Han MK, Kim JH, Hwang JW, Do SH. Analgesia before a spinal block for femoral neck fracture: fascia iliaca compartment block. *Acta Anaesthesiol Scand* 2009; **53**: 1282-7

Zufferey PJ, Miquet M, Quenet S, et al. Tranexamic acid in hip fracture surgery: a randomized controlled trial. *Br J Anaesth* 2010; **104**: 23-30

TURP/TURBT

Bala I, Bharti N, Chaubey VK, Mandal AK. Efficacy of gabapentin for prevention of postoperative catheter-related bladder discomfort in patients undergoing transurethral resection of bladder tumor. *Urology* 2012; **79**: 853-7

Kumsar S, Dirim A, Toksoz S, Saglam HS, Adsan O. Tranexamic acid decreases blood loss during transurethral resection of the prostate (TUR -P). *Cent European J Urol* 2011; **64**: 156-8

Rannikko A, Petas A, Taari K. Tranexamic acid in control of primary hemorrhage during transurethral prostatectomy. *Urology* 2004; **64**: 955-8

Zhang Z, Cao Z, Xu C, et al. Solifenacin is able to improve the irritative symptoms after transurethral resection of bladder tumors. *Urology* 2014; **84**: 117-21

Nephrectomy

Baik JS, Oh AY, Cho CW, Shin HJ, Han SH, Ryu JH. Thoracic paravertebral block for nephrectomy: a randomized, controlled, observer-blinded study. *Pain Med* 2014; **15**: 850-6

Lung Resection

Arbane G, Douiri A, Hart N, et al. Effect of postoperative physical training on activity after curative surgery for non-small cell lung cancer: a multicentre randomised controlled trial. *Physiotherapy* 2014; **100**: 100-7

Arbane G, Tropman D, Jackson D, Garrod R. Evaluation of an early exercise intervention after thoracotomy for non-small cell lung cancer (NSCLC), effects on quality of life, muscle strength and exercise tolerance: randomised controlled trial. *Lung Cancer* 2011; **71**: 229-34

Asida SM, Youssef IA, Mohamad AK, Abdelrazik AN. Post-thoracotomy pain relief: Thoracic paravertebral block compared with systemic opioids. *Egyptian Journal of Anaesthesia* 2012; **28**: 55-60

Benzo R, Wigle D, Novotny P, et al. Preoperative pulmonary rehabilitation before lung cancer resection: results from two randomized studies. *Lung Cancer* 2011; **74**: 441-5

Bimston DN, McGee JP, Liptay MJ, Fry WA. Continuous paravertebral extrapleural infusion or post-thoracotomy pain management. *Surgery* 1999; **126**: 650-6; discussion 6-7

Brocki BC, Andreasen JJ, Langer D, Souza DS, Westerdahl E. Postoperative inspiratory muscle training in addition to breathing exercises and early mobilization improves oxygenation in high-risk patients after lung cancer surgery: a randomized controlled trial. *Eur J Cardiothorac Surg* 2016; **49**: 1483-91

Casati A, Alessandrini P, Nuzzi M, et al. A prospective, randomized, blinded comparison between continuous thoracic paravertebral and epidural infusion of 0.2% ropivacaine after lung resection surgery. *Eur J Anaesthesiol* 2006; **23**: 999-1004

Dong Q, Zhang K, Cao S, Cui J. Fast-track surgery versus conventional perioperative management of lung cancer-associated pneumonectomy: a randomized controlled clinical trial. *World J Surg Oncol* 2017; **15**: 20

Edvardsen E, Skjonsberg OH, Holme I, Nordsletten L, Borchsenius F, Anderssen SA. High-intensity training following lung cancer surgery: a randomised controlled trial. *Thorax* 2015; **70**: 244-50

Esme H, Apiliogullari B, Duran FM, Yoldas B, Bekci TT. Comparison between intermittent intravenous analgesia and intermittent paravertebral subpleural analgesia for pain relief after thoracotomy. *Eur J Cardiothorac Surg* 2012; **41**: 10-3

Fang Y, Zhao Q, Huang D, Shufang G, Lv J. Effects of exercise training on surgery tolerability in lung cancer patients with impaired pulmonary function. *Life Science Journal* 2013; **10**: 1943-8

Fawzi H, El-Tohamy S. Effect of perioperative oral pregabalin on the incidence of post-thoracotomy pain syndrome. *Ain-Shams Journal of Anaesthesiology* 2014; **7**: 143-7

Granger CL, Chao C, McDonald CF, Berney S, Denehy L. Safety and feasibility of an exercise intervention for patients following lung resection: a pilot randomized controlled trial. *Integr Cancer Ther* 2013; **12**: 213-24

Grider JS, Mullet TW, Saha SP, Harned ME, Sloan PA. A randomized, double-blind trial comparing continuous thoracic epidural bupivacaine with and without opioid in contrast to a continuous paravertebral infusion of bupivacaine for post-thoracotomy pain. *J Cardiothorac Vasc Anesth* 2012; **26**: 83-9

Grosen K, Drewes AM, Hojsgaard A, Pfeiffer-Jensen M, Hjortdal VE, Pilegaard HK. Perioperative gabapentin for the prevention of persistent pain after thoracotomy: a randomized controlled trial. *Eur J Cardiothorac Surg* 2014; **46**: 76-85

Hotta K, Endo T, Taira K, et al. Comparison of the analgesic effects of continuous extrapleural block and continuous epidural block after video-assisted thoracoscopic surgery. *J Cardiothorac Vasc Anesth* 2011; **25**: 1009-13

Huang J, Lai Y, Zhou X, et al. Short-term high-intensity rehabilitation in radically treated lung cancer: a three-armed randomized controlled trial. *J Thorac Dis* 2017; **9**: 1919-29

Joseph C, Gaillat F, Duponq R, et al. Is there any benefit to adding intravenous ketamine to patient-controlled epidural analgesia after thoracic surgery? A randomized double-blind study. *Eur J Cardiothorac Surg* 2012; **42**: e58-65

Kaya FN, Turker G, Mogol EB, Bayraktar S. Thoracic paravertebral block for video-assisted thoracoscopic surgery: single injection versus multiple injections. *J Cardiothorac Vasc Anesth* 2012; **26**: 90-4

Kinney MA, Mantilla CB, Carns PE, et al. Preoperative gabapentin for acute post-thoracotomy analgesia: a randomized, double-blinded, active placebo-controlled study. *Pain Pract* 2012; **12**: 175-83

Kobayashi R, Mori S, Wakai K, et al. Paravertebral block via the surgical field versus epidural block for patients undergoing thoracotomy: a randomized clinical trial. *Surg Today* 2013; **43**: 963-9

Lee JH, Jeon Y, Bahk JH, et al. Pulse pressure variation as a predictor of fluid responsiveness during one-lung ventilation for lung surgery using thoracotomy: randomised controlled study. *Eur J Anaesthesiol* 2011; **28**: 39-44

Licker M, Karenovics W, Diaper J, et al. Short-Term Preoperative High-Intensity Interval Training in Patients Awaiting Lung Cancer Surgery: A Randomized Controlled Trial. *J Thorac Oncol* 2017; **12**: 323-33

Licker M, Karenovics W, Diaper J, et al. Short-Term Preoperative High-Intensity Interval Training in Patients Awaiting Lung Cancer Surgery: A Randomized Controlled Trial. *J Thorac Oncol* 2017; **12**: 323-33

Morano MT, Mesquita R, Da Silva GP, et al. Comparison of the effects of pulmonary rehabilitation with chest physical therapy on the levels of fibrinogen and albumin in patients with lung cancer awaiting lung resection: a randomized clinical trial. *BMC Pulm Med* 2014; **14**: 121

Muehling BM, Halter GL, Schelzig H, et al. Reduction of postoperative pulmonary complications after lung surgery using a fast track clinical pathway. *Eur J Cardiothorac Surg* 2008; **34**: 174-80

Pehlivan E, Turna A, Gurses A, Gurses HN. The effects of preoperative short-term intense physical therapy in lung cancer patients: a randomized controlled trial. *Ann Thorac Cardiovasc Surg* 2011; **17**: 461-8

Perttunen K, Nilsson E, Heinonen J, Hirvisalo EL, Salo JA, Kalso E. Extradural, paravertebral and intercostal nerve blocks for post-thoracotomy pain. *Br J Anaesth* 1995; **75**: 541-7

Raveglia F, Rizzi A, Leporati A, Di Mauro P, Cioffi U, Baisi A. Analgesia in patients undergoing thoracotomy: epidural versus paravertebral technique. A randomized, double-blind, prospective study. *J Thorac Cardiovasc Surg* 2014; **147**: 469-73

Richardson J, Sabanathan S, Jones J, Shah RD, Cheema S, Mearns AJ. A prospective, randomized comparison of preoperative and continuous balanced epidural or paravertebral bupivacaine on post-thoracotomy pain, pulmonary function and stress responses. *Br J Anaesth* 1999; **83**: 387-92

Sebio Garcia R, Yanez-Brage MI, Gimenez Moolhuyzen E, Salorio Riobo M, Lista Paz A, Borro Mate JM. Preoperative exercise training prevents functional decline after lung resection surgery: a randomized, single-blind controlled trial. *Clin Rehabil* 2017; **31**: 1057-67

Sokouti M, Aghdam BA, Golzari SE, Moghadaszadeh M. A comparative study of postoperative pulmonary complications using fast track regimen and conservative analgesic treatment: a randomized clinical trial. *Tanaffos* 2011; **10**: 12-9

Stigt JA, Uil SM, van Riesen SJ, et al. A randomized controlled trial of postthoracotomy pulmonary rehabilitation in patients with resectable lung cancer. *J Thorac Oncol* 2013; **8**: 214-21

Yazigi A, Abou-Zeid H, Srouji T, Madi-Jebara S, Haddad F, Jabbour K. The effect of low-dose intravenous ketamine on continuous intercostal analgesia following thoracotomy. *Ann Card Anaesth* 2012; **15**: 32-8

S6 – Analyses using HES, GBE, AIHW and NHFD data

Summary measures of RCT/Registry age difference for each registry

Procedure	Registry	Min	q25	Median	q75	Max
All	HES(NHFD)	-34.6809	-6.1901	-2.35629	0.981484	14.545
	HES	-33.0917	-6.17563	-1.90461	1.096123	14.545
	GBE	-31.7238	-7.55545	-3.07469	0.048821	17.61159
	AIHW	-28.5167	-4.70708	-0.80977	2.398872	18.27774
Colorectal	HES	-28.2257	-4.26041	0.304695	3.023033	9.832649
	GBE	-31.7238	-8.40224	-3.31587	0.868568	7.269524
	AIHW	-28.5167	-4.46523	0.364212	2.826591	10.59104
Hip	HES	-18.6405	-9.42756	-6.1901	-2.86228	4.609863
	GBE	-20.9987	-11.9552	-8.33936	-5.18903	3.198608
	AIHW	-18.7561	-10.0581	-6.08201	-3.00547	4.698059
Knee	HES	-8.82103	-3.24651	-1.68695	0.288216	6.094757
	GBE	-8.46256	-3.20728	-1.71823	0.429756	6.343826
	AIHW	-7.33189	-1.73556	-0.39561	1.741684	7.548225
NOF	HES	-33.0917	-7.98681	-1.85581	0.451012	4.465836
	NHFD	-34.6809	-9.576	-3.44501	-1.13818	2.87664
Lung	HES	-23.5458	-6.57	-0.05827	3	14.545
	GBE	-20.5185	-5.33481	2.617842	5.738934	17.61159
	AIHW	-19.4637	-3.85254	4.073856	6.741352	18.27774

Summary measures of the ratio of the proportion of male participants in the study compared to the proportion in the registry for each registry

Procedure	Registry	Min	q25	Median	q75	Max
All	HES	0.173505	0.826214	1.067265	1.243704	2.666358
	GBE	0.254528	0.871969	1.094538	1.232728	2.81669
	AIHW	0.166955	0.78645	1.046821	1.240336	2.483572
Colorectal	HES	0.557685	1.020133	1.119786	1.224439	1.411036
	GBE	0.54967	1.023178	1.111122	1.220935	1.422793
	AIHW	0.584254	1.064218	1.199177	1.300191	1.511076
Hip	HES	0.474404	1.019272	1.198132	1.393673	2.652365
	GBE	0.48771	1.073242	1.240116	1.434457	2.81669
	AIHW	0.422475	0.911814	1.083268	1.252788	2.400206
Knee	HES	0.220187	0.617954	0.772217	1.034822	1.527217
	GBE	0.254528	0.71221	0.940175	1.232892	1.942955
	AIHW	0.213959	0.591925	0.769482	1.016522	1.516606
NOF	HES	0.173505	0.7422	0.913311	1.210451	2.666358
Lung	HES	0.569181	0.91801	1.090541	1.352014	1.712668
	GBE	0.528709	0.758334	0.918951	1.147904	1.42055
	AIHW	0.566154	0.839987	1.023957	1.279466	1.586719