

# Enhanced recovery after surgery in children undergoing abdominal surgery: meta-analysis

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## Abstract

**Background:** Enhanced recovery after surgery (ERAS) is a multimodal approach that streamlines patient processes before, during, and after surgery. The goal is to reduce surgical stress responses and improve outcomes; however, the impact of ERAS programmes in paediatric abdominal surgery remains unclear. The authors aimed to review the effectiveness of ERAS on clinical outcomes in children undergoing abdominal surgery.

**Method:** CINAHL, CENTRAL, Embase, ProQuest, PubMed, and Scopus were searched for relevant studies published from inception until January 2021. The length of hospital stay (LOS), time to oral intake, time to stool, complication rates, and 30-day readmissions were measured. Meta-analyses and subgroup analyses were conducted using RevMan 5.4 with a random-effects model.

**Results:** Among 2371 records from the initial search, 111 articles were retrieved for full-text screening and 12 were included for analyses. The pooled mean difference (MD) demonstrated reduced LOS (MD  $-1.96$ ; 95 per cent c.i.  $-2.75$  to  $-1.17$ ), time to oral intake (MD  $-3.37$ ; 95 per cent c.i.  $-4.84$  to  $-1.89$ ), and time to stool (MD  $-4.19$ ; 95 per cent c.i.  $-6.37$  to  $-2.02$ ). ERAS reduced postoperative complications by half and 30-day readmission by 36 per cent. Subgroup analyses for continuous outcomes suggested that ERAS was more effective in children than adolescents.

**Conclusion:** ERAS was effective in improving clinical outcomes for paediatric patients undergoing abdominal surgery.

## Introduction

Nearly half of paediatric inpatient operations performed are abdominal<sup>1</sup>; however, no single measure has been found to reduce morbidity and hospital stay. Enhanced recovery after surgery (ERAS) was introduced by Kehlet<sup>2</sup> (1997) as a multimodal perioperative care pathway that streamlines patient processes before, during, and after surgery<sup>3</sup>, by preventing surgical stress and endocrine-metabolic responses<sup>2</sup>. ERAS has since been developed and implemented in various surgical specialties<sup>4</sup>, but rarely in the paediatric population, possibly due to the physiological differences between children and adults. Some of the interventions might be deemed inappropriate or more challenging to implement in paediatric populations<sup>5</sup>. Most current studies employ different combinations of ERAS principles, and the best practices for applying adult ERAS principles to children have yet to be determined<sup>5</sup>. There are no current recommendations regarding the modification of ERAS principles for paediatric populations<sup>5</sup>. Non-adherence to the

ERAS protocols is associated with an increased rate of medical errors and adverse events<sup>6,7</sup>.

In adults, ERAS protocols reduce the length of hospital stay (LOS), postoperative complications, time of return to gastrointestinal function, and total cost of hospital stay<sup>8</sup>. In children, Shinnick *et al.*<sup>9</sup> could not demonstrate a reduction in hospital stay as a result of ERAS, which was possibly due to the increased use of minimally invasive surgery. A meta-analysis of ERAS protocols in paediatric populations undergoing gastrointestinal surgery found no significant difference in the incidence of complications or 30-day readmission<sup>10</sup>; however, it decreases the LOS, improves the recovery of gastrointestinal function, and reduces the need for perioperative infusion, postoperative opioid administration, and costs. The review was limited by using only three databases and there were insufficient trials to determine whether there was significant heterogeneity among the studies or publication bias. Funnel plot asymmetry tests should only be conducted if the meta-analysis includes at least 10 studies<sup>11</sup>. To address this issue,

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the authors aimed to synthesize the available evidence of the effectiveness of ERAS in reducing the LOS, time to oral intake, time to stool, rates of complications, and 30-day readmissions in children undergoing abdominal surgery, comparing it with traditional outcomes.

## Methods

This systematic review followed the PRISMA guidelines<sup>12</sup>. The review protocol, which was strictly followed in this review, was submitted to the author's institution before the commencement of database searches but was not registered.

### Eligibility criteria

Patients aged between 4 weeks and 18 years who underwent abdominal surgery with the implementation of at least three elements of ERAS distinctive from traditional care were included (Table 1). Abdominal surgery refers to the surgical procedures performed to diagnose or treat a medical condition in the abdomen, including the stomach, small intestine, spleen, appendix, colon, and rectum. Studies that included a mixture of operations or a mixture in the population were included if the participants were within the age range, and data for those undergoing abdominal surgery could be analysed separately. Studies comparing ERAS with traditional perioperative care were included. The primary outcome was the LOS, and the secondary outcomes were time to oral intake, time to stool, rates of postoperative complications, and 30-day readmission. Studies adopting all English-language quantitative study designs (for example RCTs, quasi-experimental designs, cohort studies, or case-control studies) were included. Studies with ERAS compared with another intervention or used as a co-intervention were excluded. Conference abstracts, editorials, and letters were excluded. No time limit was applied.

### Information sources, search strategy, and selection process

The PubMed Clinical Queries, Cochrane Database of Systematic Reviews (SRs), and PROSPERO databases were searched to prevent duplication of SRs. Following consultation with the

library team, an extensive three-step search strategy was developed based on the Cochrane Handbook for Systematic Review. The authors searched published and unpublished studies through six databases, including PubMed, CENTRAL, Embase, CINAHL, Scopus, and ProQuest Dissertations and Theses Global. Based on different syntax rules of each database, index and key terms were explored and truncated (Table S1). Ongoing and unpublished trials were searched via a clinical trial registry (ClinicalTrials.gov). Hand-searching was performed in related articles and similar articles of relevant databases and the reference lists of selected studies and relevant SRs. All searches were conducted from inception until January 2021. Two independent reviewers (H.B.A. and S.B.D.) undertook screening and extraction of selected studies as well as the quality appraisal. Disagreements were resolved by the discussion with a third reviewer (H.G.H.).

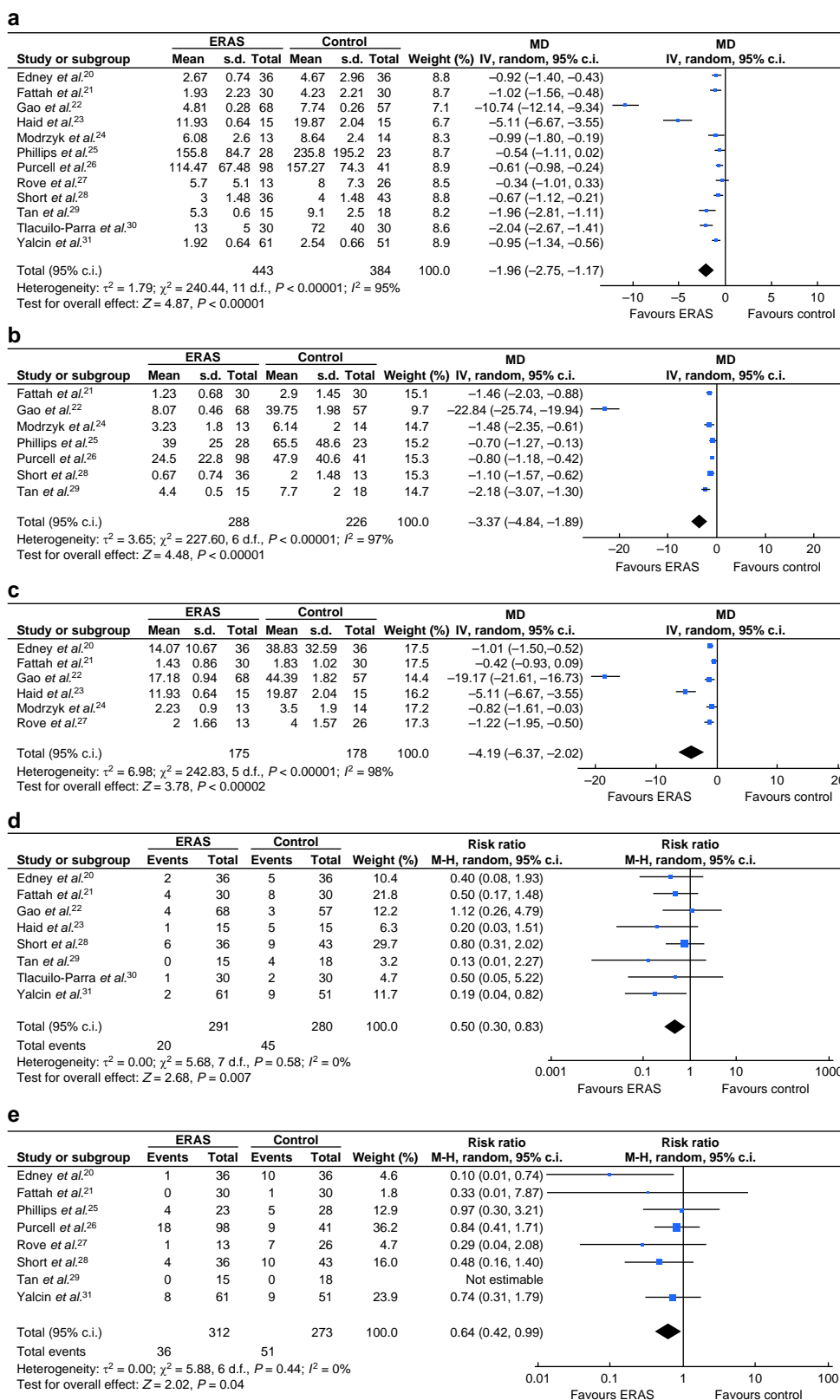
### Data extraction, methodological quality appraisal, and data analysis

Data extracted included authors, year, setting, country, design, sample size, intervention, outcomes, measures, attrition rate, intention-to-treat, protocol, trial registration, ERAS elements used, and funding. In the event of missing or incomplete data, authors were contacted for more information; if there was no response from the author, the study was excluded from the meta-analysis for the particular outcome. The studies were appraised using the Joanna Briggs Institute (JBI) critical appraisal instrument for RCTs<sup>13</sup> and cohort studies<sup>14</sup>. RevMan 5.4 Software was used for meta-analyses. Dichotomous data were analysed using the Mantel-Haenszel (M-H) method, calculating the risk ratio (RR) with a 95 per cent confidence interval (c.i.). Continuous data were analysed using the inverse variance (IV) method, calculating the mean (s.d.). Studies measuring the same outcome with a different measurement were combined using standardized mean difference (MD). Z-statistics was used to evaluate the overall combined effect of the intervention. Effect size, measuring the magnitude of ERAS effect, was expressed as Cohen *d* where *d* (0.1) = very small, *d* (0.2) = small, *d* (0.5) = medium, *d* (0.8) = large, *d* (1.2) = very large, and *d* (2.0) = huge (Sawilwsky, 2009). *I*<sup>2</sup> statistics were used to assess heterogeneity. When

**Table 1** Enhanced recovery after surgery protocol parameters

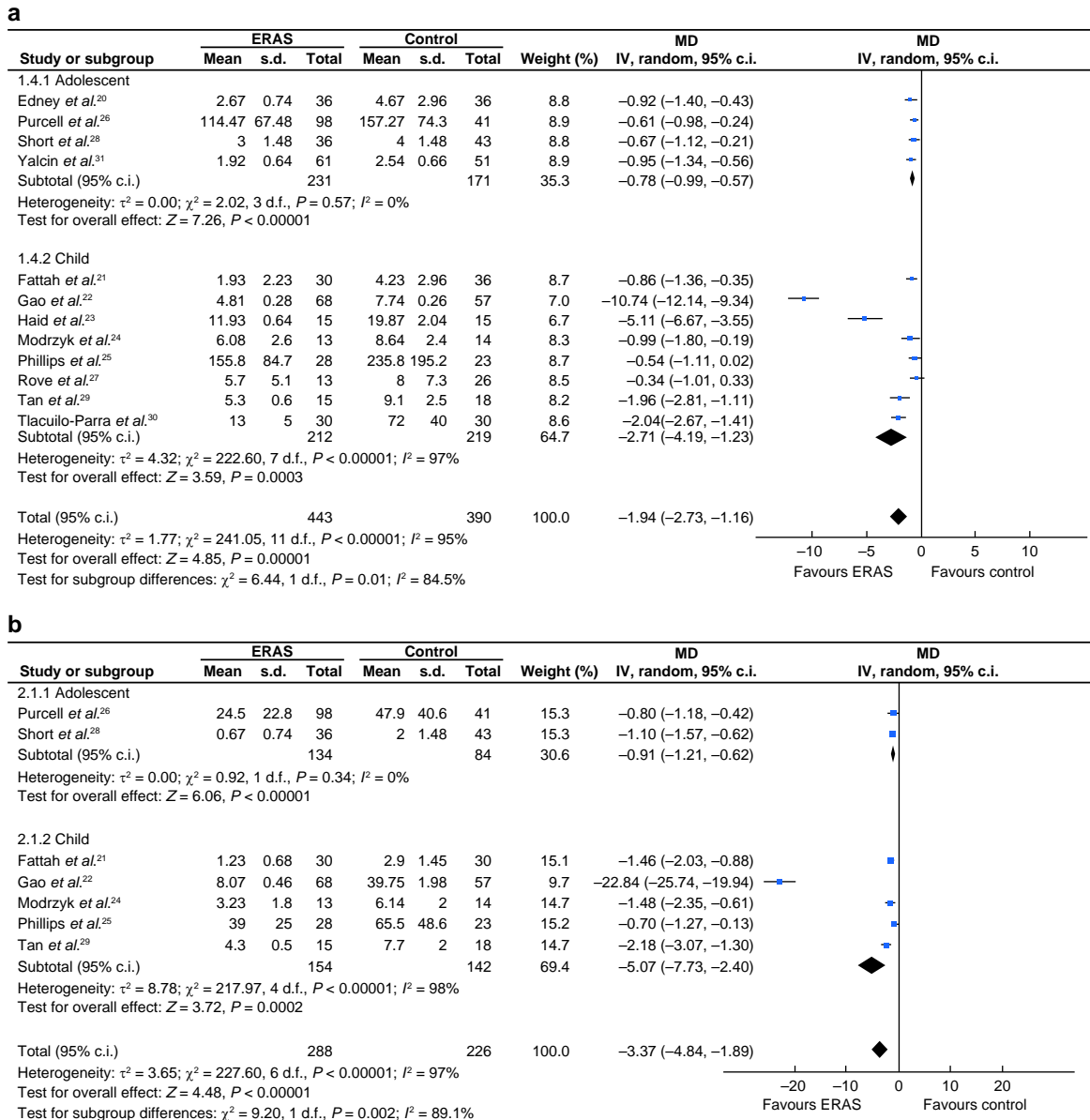
Phases of surgery	Key aspects	ERAS protocol for paediatrics
Preoperative	Preoperative counselling	Included
	Preoperative bowel preparation	Antibiotic and mechanical
	Nutritional assessment and treatment	Included
	Preoperative fasting (oral)	Fasting from breast milk for 4 h, formula for 6 h. Drinking 10% glucose solution
Intraoperative	Use of sedative preanaesthetic	Included with internal anaesthesia/surgical consensus
	Preoperative antibiotics	Within 60 min before incision
	Anaesthesia	Combination of caudal and general anaesthesia, opioid-sparing, or opioid-free
	Surgery	Minimally invasive surgery is preferred
Postoperative	Intraoperative fluid management	Included with internal anaesthesia/surgical consensus
	Maintenance of normothermia	Included
	Abdominal drainage tubes	Omitted (unless excessive exudates)
	Nasogastric tube	Included (but removed as soon as possible)
	Urethral catheters	Early removal POD 1–2
	Nausea and vomiting prophylaxis treatment	Included
	Early removal of i.v. fluids	Included
	Postoperative fasting	Early feeding
Routine postoperative mobilization care	Mobilization on POD 1	
Pain assessment and analgesia	Included (scheduled opioid-free analgesia)	

ERAS, enhanced recovery after surgery; i.v. intravenous; POD, postoperative day.



**Fig. 1** Forest plots: effectiveness of ERAS on all outcomes

**a** Length of hospital stay. **b** Time to oral intake. **c** Time to stool. **d** Rate of postoperative complications. **e** Rate of 30-day readmission. ERAS, enhanced recovery after surgery; MD, mean difference.



**Fig. 2 Forest plots: subgroup analyses findings**

**a** Length of hospital stay based on age group. **b** Time to oral intake based on age group. **c** Time to stool based on age group. **d** Time to stool based on surgery type. ERAS, enhanced recovery after surgery; MD, mean difference.

heterogeneity was present, a random-effects model was adopted. There were various methods used to explore the sources of heterogeneity. First, sensitivity analysis was used to maintain the pooled trials homogeneous by identifying and excluding the heterogeneous trials<sup>15</sup>. Second, subgroup analysis was carried out using predefined covariates<sup>15</sup> age group (children or adolescent population) and type of surgery (urology, colorectal, or gastrointestinal). Publication bias was assessed using Begg and Mazumdar's test for rank correlation<sup>16</sup> (Begg's test) and Egger's regression test<sup>17</sup> (Egger's test) and visually inspected using a funnel plot (plotting inversed standard error against MD). A  $P$  value  $\geq 0.05$  for Begg's test and Egger's test for a regression indicated that there was no publication bias<sup>18</sup>. In addition, the Cook's distance was used to identify potential outliers by monitoring for patterns that consider both the leverage and residual of each trial<sup>19</sup>.

## Results

The initial search generated 2371 records. A total of 277 duplicates were removed. Subsequently, 111 articles were retrieved for full-text review, of which 12 studies were included in this review. The PRISMA flowchart can be found in Fig. S1.

### Study characteristics

A total of 827 patients were involved in the 12 studies<sup>20-31</sup>, including two RCTs and 10 cohort studies, with sample sizes ranging from 30<sup>23</sup> to 139<sup>26</sup>. Table S2 shows the characteristics of all included studies. Ages ranged from 0.9 to 17 years. The specialties in the 12 included studies were colorectal ( $n=7$ ), gastrointestinal ( $n=3$ ), and urology ( $n=2$ ). The number of ERAS elements implemented in each protocol ranged from 3 to 16

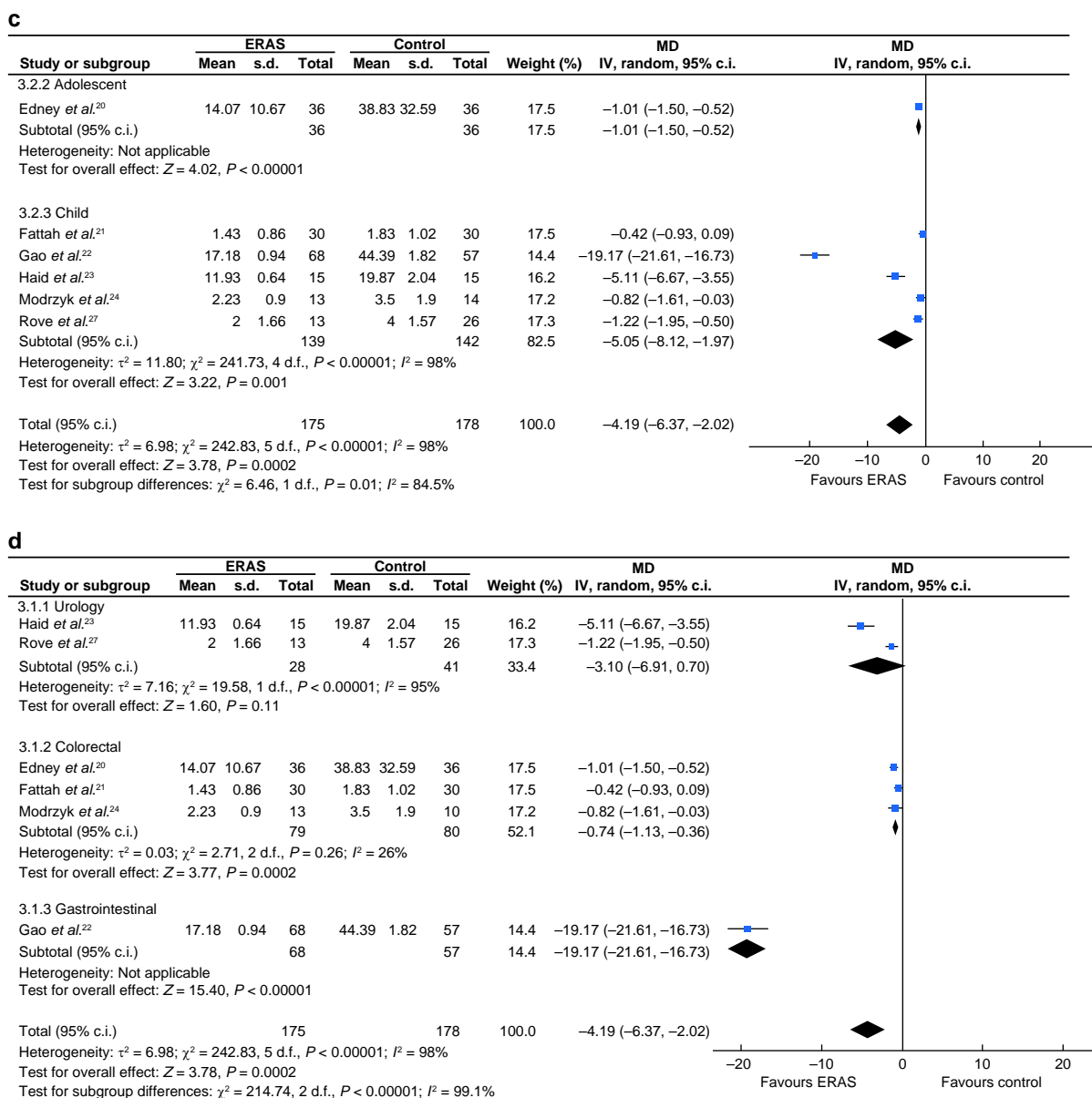


Fig. 2 Continued

elements, with the most common being postoperative early oral intake and mobilization.

### Methodological quality assessment

Critical appraisal of included studies is presented in Table S3. For the included RCTs, the nature of randomization and blinding was unclear. It was also unclear whether follow-up was completed in one study<sup>21</sup>. Among the cohort studies included, three<sup>23,24,29</sup> did not identify confounding factors, and five<sup>23–25,28,29</sup> did not address confounding factors. Question 8 was not applicable as outcomes appeared immediately after the intervention. Only two studies<sup>26,27</sup> reported on follow-ups and explained the loss to follow-up.

### LOS

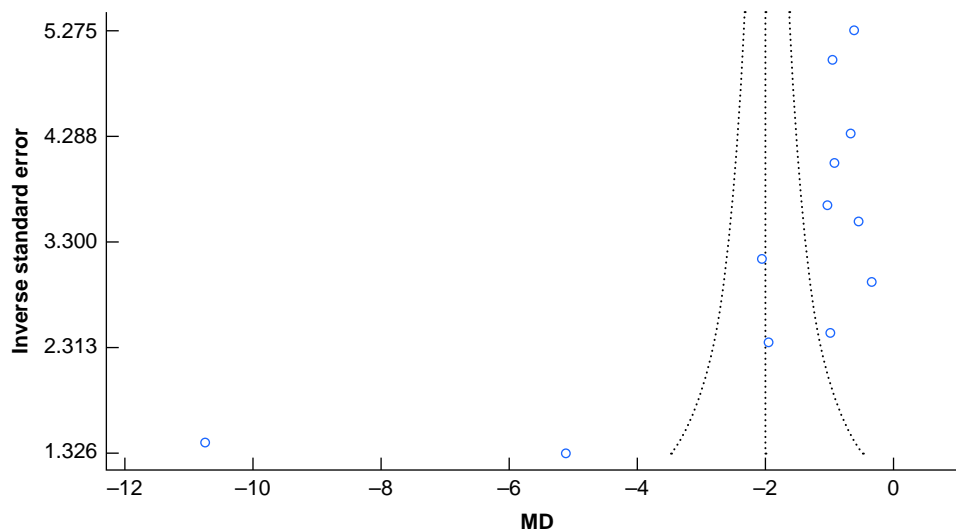
All included studies reported LOS (Fig. 1a). Meta-analysis showed a considerable reduction in the LOS (MD -1.96; 95 per cent c.i. -2.75 to -1.17;  $Z = 4.8$ ,  $P < 0.001$ ), and considerable heterogeneity

( $I^2 = 95$  per cent). Sensitivity analysis was performed (Fig. S2a) and identified three heterogeneous studies<sup>22,23,30</sup>, with  $I^2$  decreased to 37 per cent and reporting a large effect size of -0.83 (95 per cent c.i. -1.05 to -0.60). The findings of Tlacuillo-Parra *et al.*<sup>30</sup> may be heterogeneous due to having only three ERAS elements as compared with the other studies that averaged 16 elements.

Subgroup analyses showed a statistically significant subgroup difference between different age groups (chi-squared 6.44,  $P = 0.010$ ) (Fig. 2a), and that ERAS was effective in reducing LOS in adolescents with moderate effect (MD -0.78; 95 per cent c.i. -0.99 to -0.57;  $Z = 7.26$ ,  $P \leq 0.001$ ). ERAS was more effective in children (2 to 12 years of age) in reducing LOS (MD -2.71; 95 per cent c.i. -4.19 to -1.23;  $Z = 3.59$ ,  $P < 0.001$ ). Subgroup differences among different types of surgery were statistically insignificant (Fig. S3a).

### Time to oral intake

Eight studies involving 112 participants reported time to oral intake (Fig. 1b). One study was excluded from meta-analysis as



**Fig. 3** Funnel plot: length of hospital stay

MD, mean difference.

they reported oral intake dichotomously<sup>31</sup>. Four studies<sup>21,24,28,29</sup> reported time to oral intake in days, whereas three<sup>22,25,26</sup> reported in hours. ERAS considerably reduces time to oral intake with a large effect size (MD  $-3.37$ ; 95 per cent c.i.  $-4.84$  to  $-1.89$ ;  $Z = 4.48$ ,  $P < 0.001$ ).

Sensitivity analysis (Fig. S2b) was undertaken and one outlier<sup>22</sup> was found. This study reported a 52 per cent increase in patients resuming oral intake on postoperative day 1 with the implementation of ERAS. Subgroup analyses of age groups and types of surgery were performed. Statistically significant subgroup difference (chi-squared 9.20,  $P = 0.002$ ) was found between age groups (Fig. 2b). Adolescents seem to experience smaller effect (MD  $-0.91$ ; 95 per cent c.i.  $-1.21$  to  $-0.62$ ;  $Z = 6.06$ ,  $P < 0.001$ ) as compared with younger children (MD  $-5.07$ ; 95 per cent c.i.  $-7.73$  to  $-2.40$ ;  $P < 0.001$ ). Subgroup differences for types of surgery was statistically insignificant (Fig. S3b).

### Time to stool

Six studies involving 353 patients assessed the time to stool. Four<sup>21,23,24,27</sup> reported time to stool in days and two<sup>20,22</sup> reported it in hours. Meta-analyses revealed a considerable reduction in time to stool with a large effect size (MD  $-4.19$ ; 95 per cent c.i.  $-6.37$  to  $-2.02$ ;  $Z = 3.78$ ,  $P < 0.001$ ) (Fig. 1c).

Sensitivity analysis detected one outlier<sup>22</sup> (Fig. S2c). Subgroup analysis revealed significant differences (chi-squared 6.46,  $P = 0.01$ ) within age groups (Fig. 2c). In adolescents, ERAS implementation decreases time to stool with a large effect (MD  $-1.01$ ; 95 per cent c.i.  $-1.50$  to  $-0.52$ ;  $Z = 4.02$ ,  $P < 0.001$ ) and an even larger effect was observed in children (MD  $-5.05$ ; 95 per cent c.i.  $-8.12$  to  $-1.97$ ;  $Z = 3.22$ ,  $P = 0.001$ ). For types of surgery (Fig. 2d), subgroup analysis revealed significant differences in the reduction in time to stool and the three types of surgery (chi-squared 214.74,  $P < 0.001$ ). The effect of ERAS was statistically significant for colorectal and gastrointestinal surgery, with a moderate effect (MD  $-0.74$ ; 95 per cent c.i.  $-1.13$  to  $-0.36$ ;  $Z = 3.77$ ,  $P < 0.001$ ) and large effect (MD  $-19.17$ ; 95 per cent c.i.  $-21.61$  to  $-16.73$ ;  $Z = 15.40$ ,  $P < 0.001$ ) respectively.

### Rate of postoperative complications

Eight studies involving 571 patients were included in the meta-analysis of the rate of postoperative complications

(Fig. 1d). ERAS implementation resulted in a statistically significant (RR 0.50; 95 per cent c.i. 0.30 to 0.83;  $Z = 2.68$ ,  $P = 0.007$ ) reduction in the rate of postoperative complications by 50 per cent; with no heterogeneity. Subgroup analyses did not reveal any significant differences (Fig. S3c,d).

### 30-Day readmissions

Seven studies reported 30-day readmissions (Fig. 1e). ERAS resulted in statistically significant (RR 0.64; 95 per cent c.i. 0.42 to 0.99;  $Z = 2.02$ ,  $P = 0.040$ ) reduction in 30-day readmission by 36 per cent; with no heterogeneity. Subgroup analyses did not reveal any significant differences (Fig. S3e).

### Publication bias

Publication bias was assessed for LOS using a funnel plot (Fig. 3). Examination of studentized residuals revealed that the study by Gao et al.<sup>22</sup> was an outlier and overly influential according to Cook's distance, asserting the need for removal from the analysis. Both rank correlation ( $Z = -0.58$ ,  $P = 0.009$ ) and the regression test ( $Z = -4.59$ ,  $P = 0.001$ ) indicated potential funnel asymmetry, reinforcing the presence of publication bias.

## Discussion

This systematic review and meta-analysis presented evidence of the effectiveness of ERAS in children undergoing abdominal surgery. It demonstrated a reduction in LOS of paediatric patients with a large effect, consistent with previous studies<sup>9,10</sup> findings; however, the range of LOS reduction in this review (0.62–7.94 days) was less than other studies (1.3–13 days)<sup>9</sup>. The difference might be due to the types of surgical procedures performed, as the other review<sup>9</sup> encompassed all types of paediatric surgery. Furthermore, most studies employed minimally invasive surgery such as laparoscopy, further reducing the LOS difference between ERAS and the control group. A reduction in LOS under ERAS implementation may further reduce hospitalization costs and allow better bed utilization<sup>32</sup>. The impact of ERAS in reducing LOS in younger children compared with adolescents may be related to the significant effects of ERAS in improving time to oral feeding and time to stool. Other underlying factors could be the inherent

physiological differences between adolescents and children, with adolescent physiology being similar to young adults<sup>33</sup>.

The large effects observed with time to oral intake and time to stool may be associated with certain ERAS elements, which is consistent with findings from Arena et al.<sup>10</sup>. For example, early oral intake may reduce the risk of infection and anastomotic dehiscence<sup>34</sup>. Furthermore, time to oral intake and stool are the most common discharge criteria for abdominal surgery<sup>35</sup>. Similar to LOS findings, subgroup analyses saw a greater effect in children compared with adolescents for the time to oral intake, and time to stool; however, only time to stool revealed a significant difference following an analysis of the subgroup based on different types of surgery.

For other secondary outcomes, in contrast to that reported by Arena et al.<sup>10</sup>, this review demonstrated a 50 per cent reduction in the rate of postoperative complications and a 36 per cent reduction in the rate of 30-day readmission. Neither outcome showed significant subgroup differences based on age group and type of surgery. This could be due to a smaller number of studies and sample sizes included in the meta-analysis by Arena et al.<sup>10</sup> which could result in a small study effect, thereby underestimating the true effect.

Larger sample size studies are needed in the future to determine the true effect of the ERAS protocol on the rate of postoperative complications and the rate of 30-day readmission; however, as most of the ERAS elements are already implemented in conventional care<sup>36</sup>, it may be challenging to evaluate the effectiveness of ERAS protocols in paediatric settings as part of a quality improvement project.

In this review, the number of ERAS elements implemented in paediatric surgical settings has increased from 10<sup>9</sup> to 16. ERAS guidelines/protocols were implemented as a bundle instead of single ERAS elements. In contrast, the comparator of three studies<sup>23,24,31</sup> included single ERAS elements in conventional perioperative care; however, in the control group, there was low adherence to the implementation of these single elements. With the implementation of bundled ERAS protocols, there was an increase in adherence to these single ERAS elements. Implementing the ERAS protocol as a bundle could create a positive multiplicative effect on the clinical outcomes of LOS, time to oral intake, time to stool, postoperative complication rate, and 30-day readmission rate.

The results of this meta-analysis confirm the findings reported in past reviews about reducing LOS and improving other postoperative outcomes. Additionally, findings demonstrated that adherence to the implementation of ERAS elements as a bundle leads to improved postoperative outcomes. Institutions should provide structured guidelines and education to relevant staff members regarding the ERAS protocols to implement or promote adherence to the intervention.

Due to the high risk of bias in included studies, more robust evidence from well structured multicentre RCTs, or more rigorous observational studies, preferably with large sample sizes from multiple centres, is needed to further support and increase the generalisability of our review findings. Additionally, future research should explore the effects of ERAS on different paediatric surgical operations other than paediatric abdominal surgery. The authors propose that high-standard paediatric ERAS programme studies should provide well defined patient populations with specific eligibility criteria, ERAS protocol and assessment, an exclusive control group, clinically relevant outcomes, and measures of postoperative complications. In addition, strict adherence to the ERAS protocol and completeness of follow-up should be ensured.

This study has limitations. First, the included studies had a small sample size, were mostly conducted in a single centre, and were mainly developed in the USA, thereby restricting the generalization of findings to other healthcare systems. Second, the broad age range and types of surgery might have caused substantial heterogeneity in our meta-analyses. Third, while intraoperative fluid management is a component of ERAS, the authors did not synthesize the results in this review as only the most commonly reported outcomes were selected. Last, all 10 cohort studies were of low quality with a high risk of bias due to their study design, which may have impacted the internal and external validity of this review.

The two RCTs were at high risk of selection and allocation bias because there was insufficient information provided to determine the randomization techniques and whether the blinding technique was carried out for participants and researchers. Ideally, the authors should have used the Cochrane risk of bias tool to assess the risk of bias of included trials; however, their team chose to use a common instrument (JBI critical appraisal instrument) that can cover all types of quantitative study designs. The JBI has developed many critical appraisal checklists involving the feasibility, appropriateness, meaningfulness, and effectiveness of healthcare interventions<sup>37</sup>.

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## Disclosure

The authors declare no conflict of interest.

## Supplementary material

[Supplementary material](#) is available at *BJS Open* online.

## Data availability

Template data collection forms; data extracted from included studies; data used for all analyses; analytic code; and any other materials used in the review are available on request from the corresponding author.

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