

Efficacy of bowel preparation regimens for colon capsule endoscopy: a systematic review and meta-analysis



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ABSTRACT

Background and study aims Colon capsule endoscopy (CCE) is an alternative to conventional colonoscopy (CC) in specific clinical settings. High completion rates (CRs) and adequate cleanliness rates (ACRs) are fundamental quality parameters if CCE is to be widely implemented as a CC equivalent diagnostic modality. We conducted a systematic review and meta-analysis to investigate the efficacy of different bowel preparations regimens on CR and ACR in CCE.

Patients and methods We performed a systematic literature search in PubMed, Embase, CINAHL, Web of Science, and the Cochrane Library. Data were independently extracted per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The primary outcome measures (CR, ACR) were retrieved from the individual studies and pooled event rates were calculated.

Results Thirty-four observational (OBS) studies (n=3,789) and 12 randomized clinical trials (RCTs) (n=1,214) comprising a total 5,003 patients were included. The overall CR was 0.798 (95% CI, 0.764–0.828); the highest CRs were observed with sodium phosphate (NaP) + gastrografin booster (n=2, CR=0.931, 95% CI, 0.820–0.976). The overall ACR was 0.768 (95% CI, 0.735–0.797); the highest ACRs were observed with polyethylene glycol (PEG) + magnesium citrate (n=4, ER=0.953, 95% CI, 0.896–0.979).

Conclusions In the largest meta-analysis on CCE bowel preparation regimens, we found that both CRs and ACRs are suboptimal compared to the minimum recommended standards for CC. PEG laxative and NaP booster were the most commonly used but were not associated with higher CRs or ACRs. Well-designed studies on CCE should be performed to find the optimal preparation regimen.

Introduction

Colon capsule endoscopy (CCE) was introduced in 2006 as a novel diagnostic modality for colorectal examination [1]. In contrast to conventional colonoscopy (CC), CCE does not have capabilities for biopsy, polypectomy or lens cleansing and provides a lower-quality image (especially when compared to the newer generation colonoscopes); however, it offers a comfortable, minimally invasive, diagnostic procedure with a favorable safety profile and no need for sedation [2]. A recent systematic review showed that CCE has high sensitivity and specificity for per-patient polyp detection, compared to CC [3]. Nevertheless, improvements in colon cleanliness and the rate of complete examinations (to mitigate the limitations mentioned above) are needed before wider implementation in screening populations is considered. Studies have consistently shown that improvement in bowel cleanliness increases the sensitivity and specificity of CCE for detecting polyps >6 mm [4]. Preparation in CCE is of utmost importance as it allows the detection and better characterization of polypoid findings and other mucosa pathology as well, which otherwise would not have been visible. However, the field of clinical practice in terms of procedural preparation (laxatives, boosters and/or prokinetics) is diverse, and the endoscopic community is keen for guidance based on a critical review of existing literature.

We conducted a comprehensive systematic literature review and meta-analysis to assess the bowel preparation regimens for CCE with specific regard to completion rates (CRs) and adequate cleanliness rates (ACRs). The primary aims were to present pooled estimates for CRs and ACRs stratified by type of laxative, type of booster, and prokinetic. The secondary aimed was to perform a meta-regression analysis for CR, ACR and colon transit times (CTT) with the following explanatory variables: 1) age (mean); 2) sex (% of males); 3) total number of patients; 4) type of booster; 5) laxative volume with/without a booster; and 6) type of prokinetics.

Patients and methods

Data sources, search strategy and inclusion/exclusion criteria

Two independent authors (TBM and IL) searched PubMed, Embase, CINAHL, Web Of Science and the Cochrane library from database inception June 20, 2020 for observational studies (OBS) and randomized controlled trials (RCTs) published in English and reporting CRs, ACRs, and CTTs. The separate arms of RCTs were treated as observational ones, thus included in the pooled estimation, with the indication though of the study design in synthesis plots.

The following search terms were used in PubMed/Embase/ Cochrane Library: ((Colon capsule OR colon capsule endoscopy OR CCE OR pan-enteric capsule OR capsule colonoscopy OR Pill-Cam) AND (bowel preparation OR laxative OR bowel cleansing OR PEG)). The electronic search was supplemented by a manual review of reference lists from eligible publications and relevant reviews.

Inclusion criteria were: (1) peer-reviewed human studies of observational and clinical types; and (2) reporting data on completeness and quality of cleanliness.

We excluded reviews, opinions papers, case reports and conference papers.

Outcomes

Primary outcomes were CRs and ACRs. The secondary outcome was CTT. We evaluated these outcomes regarding the usage of different types of boosters and prokinetics and different types of laxatives administration. For this analysis, a 4-point scale by Leighton-Rex was modified into 2-point assessment as follows: Adequate = excellent, good; Inadequate = fair, poor [5].

Data abstraction

Data on study design and aim, risk of bias (ROB), patient data (e.g., age, sex) and intervention characteristics, (e.g., laxative type, type of laxative administration, type of booster, type of prokinetics) from each study were independently extracted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standard by four investigators (TB-M, IS, IL, PC) [6].

The extraction list was split in two, and each of them allocated to a pair of investigators who extracted data in duplicates. Whenever data were missing for the review, corresponding authors were contacted for additional information via emails. Disagreements between investigators (TB-M, IS, IL, PC) were resolved through consensus, with the final decision made by two of the senior authors (AK and ET).

Risk of bias in individual studies

The risk of bias was evaluated by using the STROBE assessment for OBS [7]. Each item from the tool was evaluated and, if fulfilled within the study, 1 point was added. Therefore, the rating was the sum of points received for each item of STROBE. The highest number of points to be achieved was 32.

The bias for each included RCT was assessed per guidelines of the Cochrane Collaboration's tool [8]. Within each bias category (selection, performance, detection, attrition and reporting) of the assessment tool the level of bias was rated as "low risk", "high risk," or "unclear risk."

Overall, the risk of bias was evaluated based on the assumption that higher number of points in STROBE evaluation in case of OBS and the higher number of low risk-of-bias assessments in RCTs, / the greater quality of a study.

Risk of bias across studies

To explore the existence of publication or other types of bias, when detected by the inconsistency index (I^2) measuring the proportion of unexplained variation across studies, a funnel plot of standard error by diagnostic yield (DY) was produced.

Data synthesis and statistical analysis

We conducted a random-effects meta-analysis of outcomes for which ≥ 2 studies contributed data, using Comprehensive Meta-Analysis V3.3.070 (<http://www.meta-analysis.com>). The I^2 index was applied to measure heterogeneity together with the

χ^2 test of homogeneity, with $P < 0.05$ indicating statistically significant heterogeneity. All analyses tests were two-sided and the significance level was set to 0.05.

For continuous outcomes, we analyzed the pooled means for endpoint scores using observed cases data. Categorical outcomes were analyzed by calculating the pooled event rates. We conducted subgroup and exploratory maximum likelihood random-effects meta-regression analyses of all outcomes. Finally, we inspected funnel plots and used Egger's regression test to quantify whether publication bias could have influenced the results [9].

Meta-regression variables included: 1) age (mean); 2) sex (% of males); 3) total number of patients; 4) type of booster; 5) laxative volume with/without a booster; and 6) type of prokinetics. Finally, we inspected funnel plots and used Egger's regression test and the Duval and Tweedie's trim and fill method if necessary, to quantify whether publication bias could have influenced the results [10]. Z test of the null hypothesis was run. The assumption of homogeneity in effects was tested using the Q statistic with a k-1 degree of freedom (k—the number of studies). In addition, we used the index of heterogeneity – Higgins' I^2 – and assumed that heterogeneity is considered high if $I^2 > 75\%$. To confirm the robustness of the results, we performed a sensitivity analysis, i.e. a leave-one-out approach.

Results

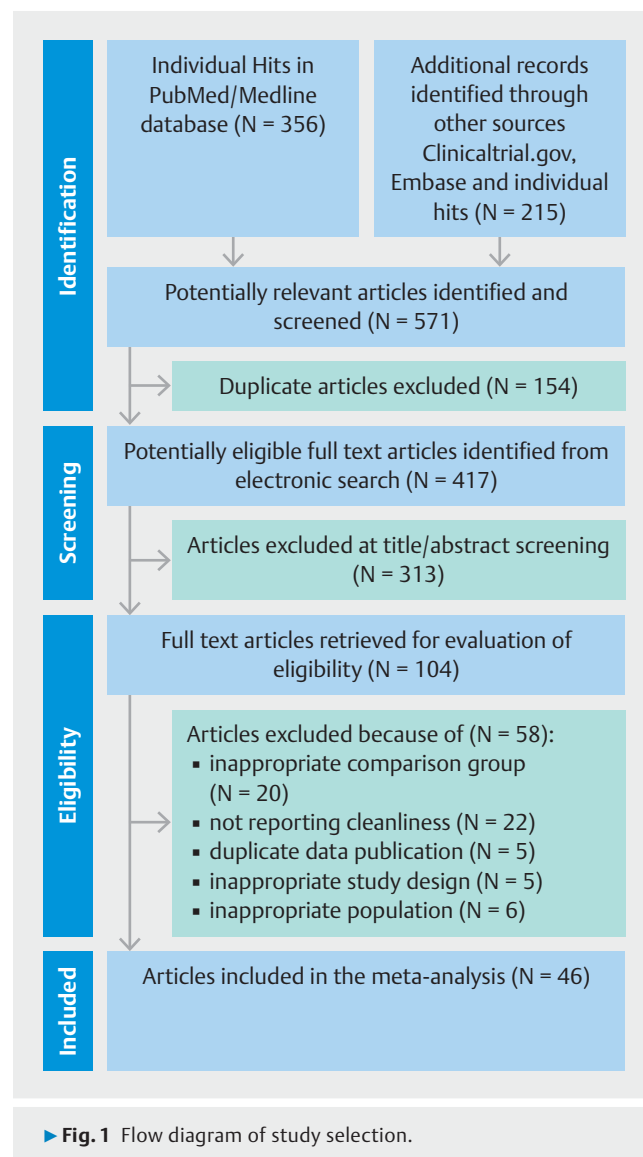
Search results

The initial search yielded 571 hits. A total of 154 studies were excluded for being duplicates and further 313 studies were omitted after evaluation on the title/abstract level. In the second stage, we subjected 104 full-text articles to review. Of those, 58 articles were excluded, yielding 46 studies that were included in the meta-analysis. A flow diagram of the process of this meta-analysis is shown in ► Fig. 1.

Study, patient and regimen characteristics

Altogether, 62 study arms with different preparation regimens in 34 OBS studies (n = 3,789) and 12 (RCTs) (n = 1,214) with a total of 5,003 patients conducted in 15 countries were included in the present meta-analysis. The percentage of men in both study groups was comparable (OBS: 49.46% vs. RCT: 51.41%). The mean age of study participants was 56.39 years (7.66) (OBS: 53.35 [8.77] vs. RCT: 56.45 years [6.22] years). The most commonly used bowel preparation was polyethylene glycol (PEG) (37 studies)/PEG plus ascorbic acid (PEGAA) (22 studies) administered in a split-dosing regimen (50 studies). The predominantly used boosters were sodium phosphate (NaP) (24 studies) and PEGAA (10 studies). However, regarding NaP usage, most studies utilized non-NaP-based boosters (34 studies).

Prokinetics administered on demand have been added to the protocol for bowel preparation for CCE in all, except five studies, to stimulate the progression of the capsule in the stomach. The most common prokinetics used were domperidone (DOM) (31 studies) and metoclopramide (MET) (11 studies). Patients in all studies included in this analysis received dietary recom-



mendations before the CCE procedure. Bisacodyl suppositories as a stimulant laxative have been uniformly used on-demand across most studies for stimulating the expulsion of the capsule. The CCE models were either PillCam CCE1 (18 studies) or PillCam CCE2 (44 studies). A pan-enteric Crohn's Capsule (PCC) was used in only one study.

Detailed characteristics of the included studies in this meta-analysis are presented in ► Table 1 [11–56].

Risk of bias

For OBS studies, the mean number of points in STROBE assessment tool was 25.65(5.02) points (median 28, min = 17, max = 32) (Supplementary Table 1). The mean number of low risk-of-bias assessments for the RCT studies included in the meta-analysis was 5.83(1.64) points (median = 6, min = 3, max = 7) (Supplementary Table 2). There was one OBS study with the highest number of points (32 points) and 2 RCTs with a maximum number of low ROB assessments (8 points). None of the includ-

► **Table 1** Study characteristics.

| Study | Year | Country | Design | CCE type | N | Laxative | Booster | Prokinetic(s) |
|--------------------------|------|-----------------------------------|--------|-------------|-----|------------------------------|----------------------|---------------|
| Schoofs [11] | 2006 | Belgium | OBS | CCE1 | 41 | PEG | NaP | DOM |
| van Gossum [12] | 2009 | France | OBS | CCE1 | 332 | PEG | NaP | DOM |
| Eliakim [13] | 2009 | Israel | OBS | CCE2 | 98 | PEG | NaP | DOM |
| Gay [14] | 2010 | France | OBS | CCE1 | 128 | PEG | NaP | DOM |
| Spada [15] | 2011 | Italy | OBS | CCE2 | 117 | PEG | NaP | DOM |
| Herrerías-Gutiérrez [16] | 2011 | Spain | OBS | CCE1 | 144 | PEG | NaP | DOM |
| Spada [17] | 2011 | Italy | OBS | CCE2 | 47 | PEG | NaP | DOM |
| Rondonotti [18] | 2014 | Italy | OBS | CCE2 | 50 | PEGAA | NaP | MET |
| Hagel [19] | 2014 | Germany | OBS | CCE2 | 24 | PEG | NaP | NA |
| Triantafyllou [20] | 2014 | Greece | OBS | CCE1 | 50 | PEG | NaP | DOM |
| Saito [21] | 2015 | Japan | OBS | CCE2 | 72 | PEG | PEG + MgCit + MOS | MET/MOS |
| Rex [22] | 2015 | USA, France, China, Spain, Israel | OBS | CCE2 | 792 | PEG | Suprep | MET |
| Spada [23] | 2015 | Italy | OBS | CCE2 | 100 | PEG | NaP + GG | DOM |
| Togashi [24] | 2015 | Japan | OBS | CCE2 | 29 | PEGAA | PEG + GG + MOS | DOM |
| Boal Carvalho [25] | 2015 | Portugal | OBS | CCE2 | 12 | PEG | NaP | DOM |
| Romero-Vazquez [26] | 2016 | Spain | OBS | CCE1 / CCE2 | 165 | PEG | NaP | MET |
| Ota [27] | 2017 | Japan | OBS | CCE2 | 20 | PEG | PEG + MgCit | NA |
| Zhou [28] | 2017 | China | OBS | CCE2 | 31 | PEG | PEG + MOS | NA |
| Nogales [29] | 2017 | Spain | OBS | CCE2 | 96 | PEG | NaP | MET |
| Igawa [30] | 2017 | Japan | OBS | CCE2 | 30 | PEG | PEG + MgCit + MOS | MET |
| Sato [31] | 2017 | Japan | OBS | CCE2 | 70 | PEG + MgCit | PEG + MgCit + MOS | MET |
| Pioche [32] | 2018 | France | OBS | CCE2 | 20 | PEG | NaP | DOM |
| Takano [33] | 2018 | Japan | OBS | CCE2 | 30 | MgCit + Sen-noside | PEGAA + MgCit | MOS |
| Kobaek-Larsen [34] | 2018 | Denmark | OBS | CCE2 | 253 | PEGAA | PEGAA | DOM |
| Okabayashi [35] | 2018 | Japan | OBS | CCE2 | 39 | PEG | PEG + CO | MET |
| Eliakim [36] | 2018 | Israel, Italy, Spain | OBS | PCCE | 41 | PEG | Suprep | MET |
| Parodi [37] | 2018 | Italy, France | OBS | CCE2 | 177 | PEG | NaP | DOM |
| Baltes [38] | 2018 | Germany | OBS | CCE2 | 36 | PEGAA | PEGAA + NaP | DOM |
| Voska [39] | 2019 | Czech Republic | OBS | CCE2 | 236 | PEG | NaP | MET |
| Yamada [40] | 2019 | Japan | OBS | CCE2 | 53 | PEG | PEG + CO + NaP + MOS | NA |
| González-Suárez [41] | 2020 | Spain | OBS | CCE2 | 147 | PEGAA | PEGAA + GG | MET |
| Otani [42] | 2020 | Japan | OBS | CCE2 | 60 | PEG | PEG + MgCit + MOS | NA |
| Pecere [43] | 2020 | Italy | OBS | CCE2 | 222 | PEG | NaP + GG | DOM |
| Utano [44] | 2020 | Japan | OBS | CCE2 | 27 | PEGAA + So-dium picosul-fate | MgCit + GG | DOM |

► **Table 1** (Continuation)

| Study | Year | Country | Design | CCE type | N | Laxative | Booster | Prokinetic(s) |
|------------------------|------|-------------|--------|----------|-----|----------|------------------------|--------------------|
| Eliakim [45] a | 2006 | Israel | RCT | CCE1 | 44 | PEG | NaP | Tegaserod |
| Eliakim b | 2006 | | RCT | CCE1 | 46 | PEG | NaP | Tegaserod |
| Spada [46] a | 2011 | Italy | RCT | CCE2 | 20 | PEG | PEG | DOM |
| Spada b | | | RCT | CCE2 | 20 | PEG | NaP | DOM |
| Hartmann [47] a | 2012 | Germany | RCT | CCE2 | 26 | PEGAA | PEGAA | DOM |
| Hartmann b | | | RCT | CCE2 | 24 | PEGAA | PEGAA | DOM |
| Kakugawa [48] a | 2012 | Japan | RCT | CCE1 | 33 | PEG | MgCit | MOS |
| Kakugawa b | | | RCT | CCE1 | 31 | PEG | MgCit | MOS |
| Argüelles-Arias [49] a | 2014 | Spain | RCT | CCE2 | 28 | PEGAA | NaP | DOM |
| Argüelles-Arias b | | | RCT | CCE2 | 30 | PEG | NaP | DOM |
| Ramos50 a | 2014 | Spain | RCT | CCE1 | 20 | PEG | NaP | DOM |
| Ramos b | | | RCT | CCE1 | 20 | PEG | NaP | DOM |
| Brechmann51 a | 2016 | Germany | RCT | CCE1 | 20 | PEGAA | PEGAA | ERY |
| Brechmann b | | | RCT | CCE1 | 6 | PEGAA | PEGAA | ERY |
| Brechmann c | | | RCT | CCE1 | 12 | PEGAA | PEGAA | ERY |
| Brechmann d | | | RCT | CCE1 | 12 | PEGAA | PEGAA + senna tea | ERY |
| Kastenberg [52] a | 2017 | USA, Cyprus | RCT | CCE2 | 55 | PEG | Suprep + GG | MET/ERY |
| Kastenberg b | | | RCT | CCE2 | 52 | PEG | Suprep | MET/ERY |
| Alvarez-Urturi [53] a | 2017 | Spain | RCT | CCE1 | 27 | PEGAA | PEGAA | MET |
| Alvarez-Urturi b | | | RCT | CCE1 | 24 | PEGAA | NaP | MET |
| Buijs [54] a | 2018 | Denmark | RCT | CCE2 | 57 | PEGAA | PEGAA + chewing gum | DOM |
| Buijs b | | | RCT | CCE2 | 48 | PEGAA | PEGAA + coffee | DOM |
| Buijs c | | | RCT | CCE2 | 60 | PEGAA | PEGAA | DOM |
| Kroijer [55] a | 2018 | Denmark | RCT | CCE2 | 60 | PEGAA | PEGAA | DOM |
| Kroijer b | | | RCT | CCE2 | 60 | PEGAA | Sulfate based solution | DOM |
| Kroijer c | | | RCT | CCE2 | 60 | PEGAA | PEGAA + GG | DOM |
| Ohmiya [56] a | 2018 | Japan | RCT | CCE2 | 152 | PEGAA | PEGAA + CO | MET or MgCit + MOS |
| Ohmiya b | | | RCT | CCE2 | 167 | PEGAA | PEGAA | MOS |

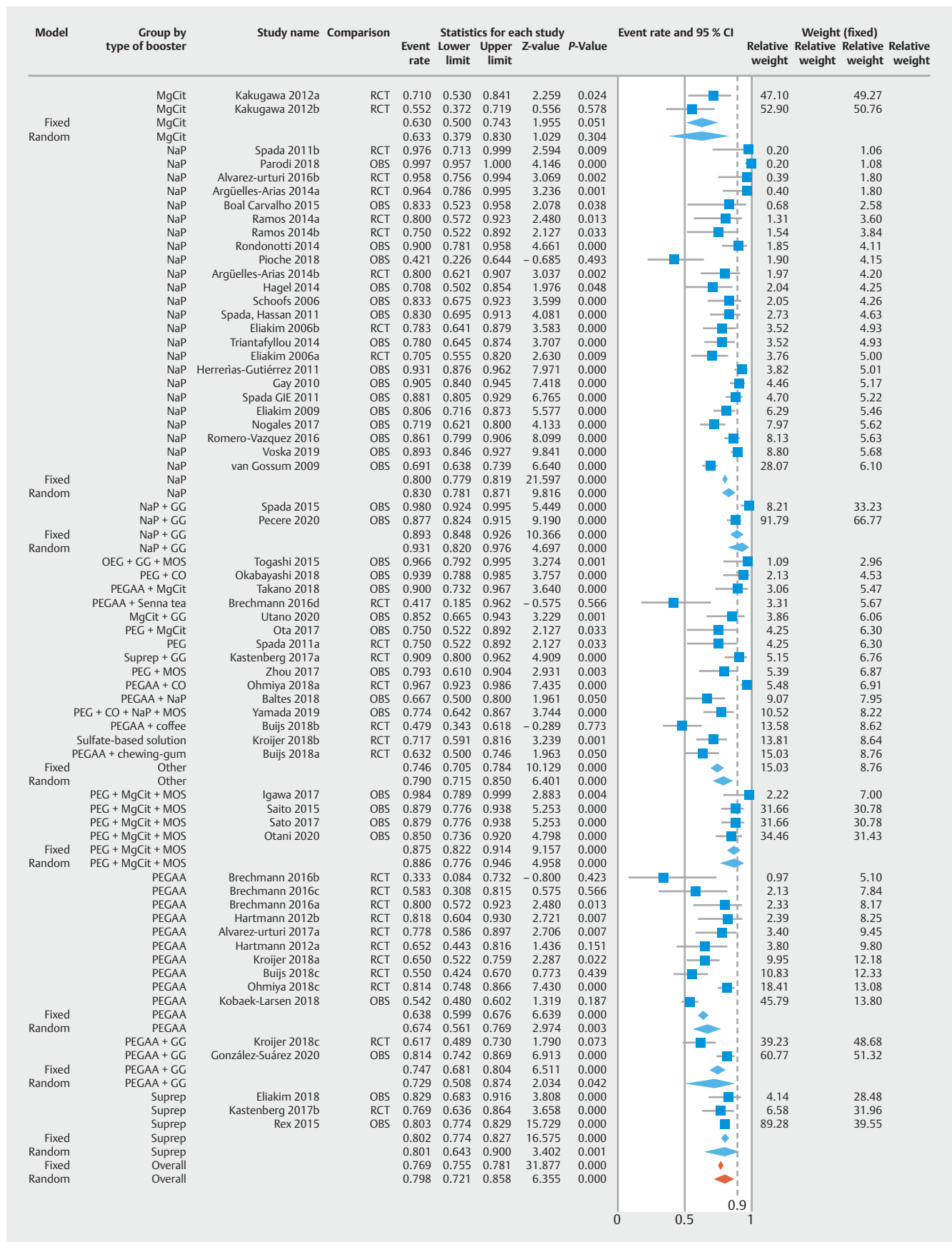
CCE, colon capsule endoscopy; CO, castor oil; DOM, domperidone; ERY, erythromycin; GG, Gastrografin; MET, metoclopramide; MgCit, magnesium citrate; MOS, mosapride; NA, not available; NaP, sodium phosphate; OBS, observational study; PEG, polyethylene glycol; PEGAA, polyethylene glycol and ascorbic acid; RCT, randomized controlled trial.

ed studies describes methods to address the risk of bias within their observations.

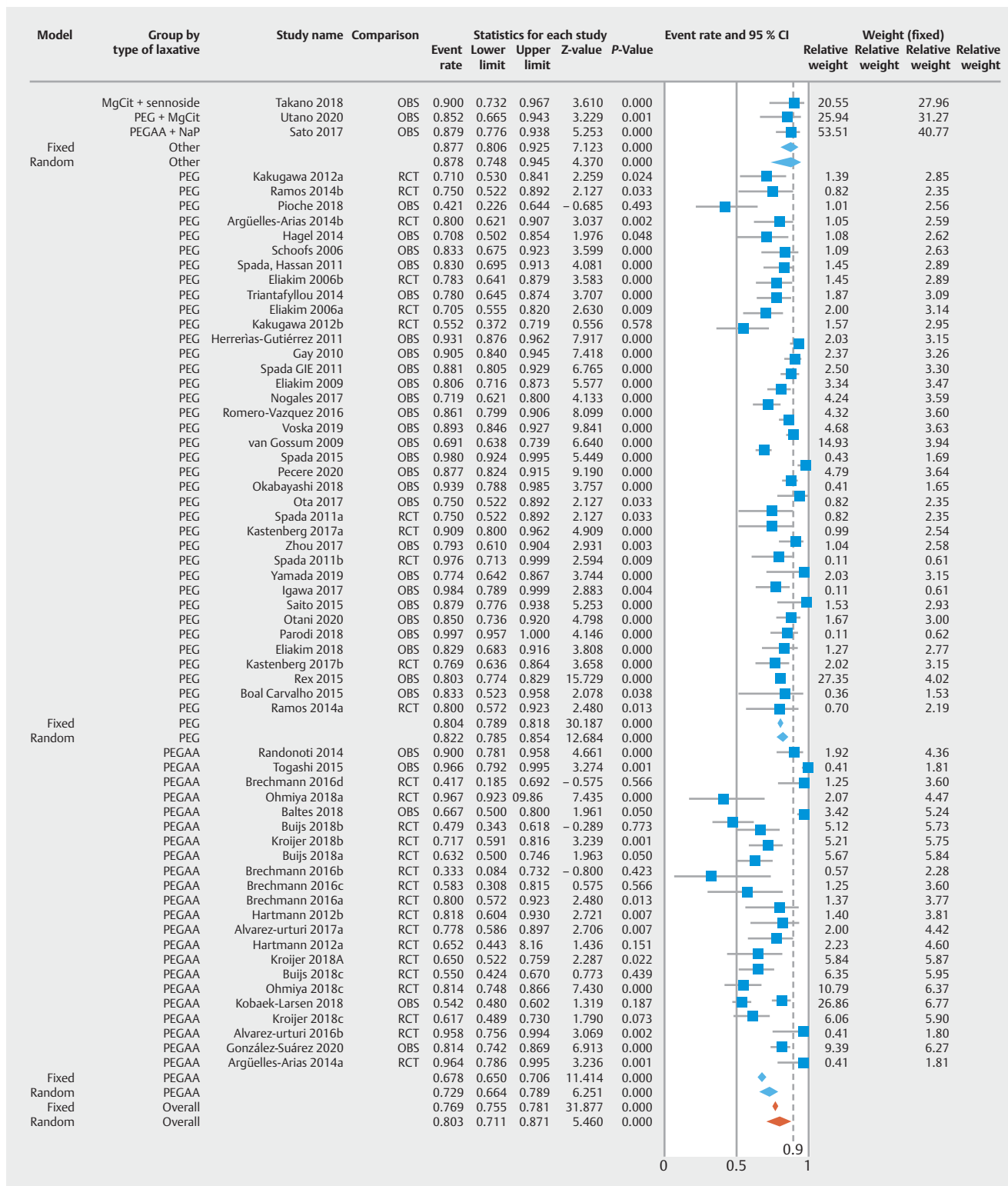
Regimen effects on CCE completion rate

Using a random-effects model, the overall pooled CCE CR was 0.798 (95% CI, 0.764–0.828). Between-study heterogeneity was present for CR by booster, laxative type, and prokinetic type ($I^2=96.25$, $P=0.000$). The most commonly used booster in the included studies was NaP ($n=24$); pooled CR of 0.830

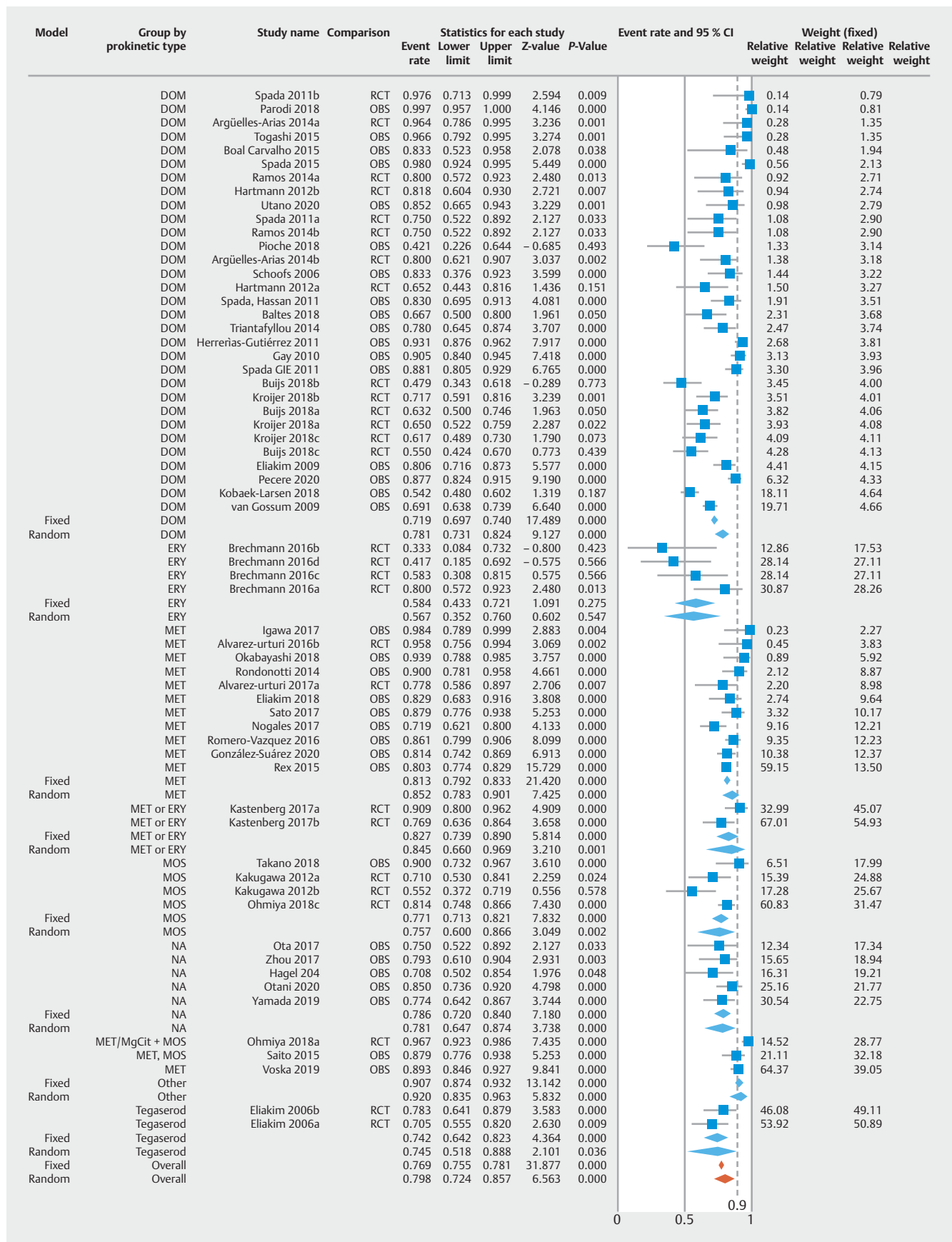
(95%CI, 0.781–0.871) (► **Fig. 2**). The highest completion rate was observed in studies ($n=2$) where NaP was used in combination with gastrografin (GG) (CR=0.931, 95% CI, 0.820–0.976). The CR for the most widely used laxative (PEG) was 0.822 (95% CI, 0.785–0.854) (► **Fig. 3**). The overall CR for studies using prokinetics was 0.798 (96% CI, 0.724–0.854) (► **Fig. 4**). A higher, but not statistically significant, CR was observed for studies in which prokinetic was administered (CR=0.801, 95% CI, 0.765–0.832) as compared to studies not using a prokinetic (CR=



► **Fig. 2** Forest plot of completeness by booster type. The dashed line represents 90 % CI, confidence interval; CO, castor oil; GG, Gastrografin; MgCit, magnesium citrate; MOS, mosapride; NaP, sodium phosphate; OBS, observational study; PEG, polyethylene glycol; PEGAA, polyethylene glycol and ascorbic acid; RCT, randomized controlled trial.



► **Fig. 3** Forest plot of completeness by laxative type. The dashed line represents 90 % CI, confidence interval; MgCit, magnesium citrate; NaP, sodium phosphate; OBS, observational study; PEG, polyethylene glycol; PEGAA, polyethylene glycol and ascorbic acid; RCT, randomized controlled trial.



► **Fig. 4** Forest plot by completeness by prokinetic type. The dashed line represents 90 %. CI, confidence interval; DOM, domperidone; ERY, erythromycin; MET, metoclopramide; MgCit, magnesium citrate; MOS, mosapride; NA, not available; OBS, observational study; RCT, randomized controlled trial

0.764, 95% CI, 0.612–0.869). Considerable heterogeneity was found between studies ($I^2 = 96.25$, $P = 0.000$).

The subgroup analyses revealed that CR differed regarding laxative type, type of laxative administration, booster type, prokinetics use, and prokinetics types with the highest observed CR for NaP+GG booster ($n = 2$, $ER = 0.931$, 95% CI: 0.820 to 0.976, $Z = 4.697$, $P = 0.000$), NaP-based booster ($n = 28$, $ER = 0.834$, 95% CI: 0.788 to 0.871, $Z = 10.640$, $P = 0.000$), split regimen of laxative ($n = 50$, $ER = 0.799$, 95% CI: 0.762 to 0.863) and type of prokinetics ($n = 3$, $ER = 0.920$, 95% CI: 0.835 to 0.888, $Z = 2.101$, $P = 0.000$). Except for split vs. non-split regimen of laxative administration and usage of prokinetics (Yes vs. No) there were significant heterogeneities between studies regarding all effect size moderators. The highest Q value was calculated for booster types ($Q = 19.581$, $df = 7$, $P = 0.007$) while the lowest for booster type grouped on NaP presence ($Q = 4.523$, $df = 1$, $P = 0.033$).

A meta-regression using a random-effects model revealed that the model utilizing different CR moderators (laxative total volume without booster, % of males, mean age, number of study participants, type of laxative with particular administration regimen (Split vs. non-split), type of booster, and usage and type of prokinetics), explained a total of 25% of variance within the event rates. A meta-regression using a random-effects model revealed that the model utilizing CCE device (CCE1 as reference group) had no impact on any of the studied outcomes (Cleanliness: $Q = 2.5$, $df = 3$, $P = 0.475$; Completeness: $Q = 1.98$, $df = 3$, $P = 0.5764$; Transit time: $Q = 1.26$, $df = 1$, $P = 0.2624$). Furthermore, the robustness of results we obtained were subjected to a sensitivity analysis (without subgroup analyses). The exclusion of one study at a time showed the results are not influenced by the effect size of only one study. The effect sizes ranged between 0.763 and 0.772 (random 0.768; lower limit: 0.734–0.741 and upper limit: 0.798–0.801; $P = 0.000$), 0.792 and 0.802 (random 0.798; lower limit: 0.758 – 0.802 and upper limit: 0.823–0.832; $P = 0.000$), 1.842 and 2.034 (random 1.972; standard error between 0.13–0.166, lower limit: 1.588–1.709 and upper limit: 2.097–2.36; $P = 0.000$) for cleanliness, completeness and transit time respectively.

Overall, an Egger's test suggested a publication bias regarding the event rate (Egger's test: $P = 0.0276$ (Supplementary Fig. 1). The Duval and Tweedie method adjusted values of 13 studies to left of mean; random model point estimate: 0.753; 95% CI: 0.712–0.789, Q value = 484.39.

Regimen effects on colon cleanliness

Using random-effects weights, the overall rate of ACR was 0.768 (95% CI, 0.735–0.797) (► Fig. 5). Between-study heterogeneity was present for ACR by booster, laxative, and prokinetic type ($I^2 = 96.25$, $P = 0.000$). Depending on the type of laxatives, ACR for PEG was 0.790 ($n = 37$, 95% CI, 0.750–0.826); for PEGAA 0.716 ($n = 22$, 95% CI, 0.663–0.7729). We did not find any effect of split-regimen compared to non-split regimen on ACR with rates with 0.766 (95% CI, 0.730–0.798) and 0.781 (95% CI, 0.690–0.850), respectively. Among boosters, PEG + MgCit ($n = 4$) had the highest rate of ACR = 0.953 (95% CI,

0.896–0.979) (► Fig. 6). The overall ACR for studies using prokinetics was 0.778 (95% CI, 0.697–0.843) (► Fig. 7) (Supplementary Fig. 2).

A meta-regression using a random-effects model revealed that the model utilizing the abovementioned moderators explained a total of 30% of variance within the event rates for cleanliness ($Q = 62.4$, $df = 23$, $P = 0.0000$). Overall, an Egger's test did not suggest a publication bias regarding the ACR (Egger's test: $P = 0.766$) (Supplementary Fig. 3).

Regimen effects on colonic transit time

Using random-effects weights, the overall mean CTT was 197.2 minutes (95% CI, 166.7–227.9). Between-study heterogeneity was present for CTT by booster and laxative type ($I^2 = 96.25$, $P = 0.000$). The subgroup analyses revealed that mean CTT differed regarding booster (► Fig. 8, Supplementary Fig. 2) and laxative types (► Fig. 9, Supplementary Fig. 2), with the lowest mean observed for PEG as laxative ($N = 10$, mean = 178.6, 95% CI, 191–291.7).

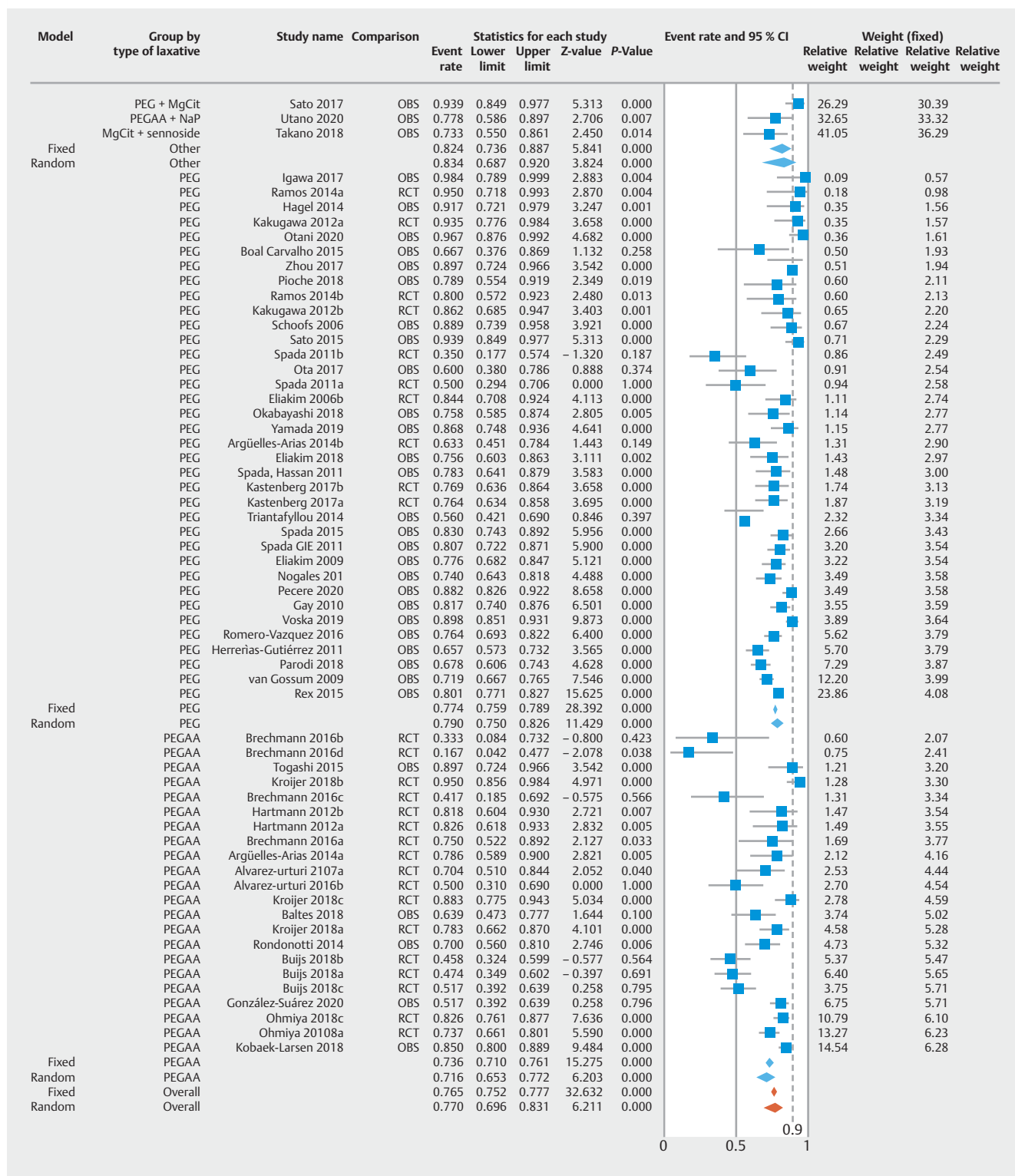
A meta-regression using a random-effects model with all study moderators was not possible due to problems with collinearity. Thus, all effect size moderators were separately analyzed. We were able to show that the variance in mean CTT was explained in 40% by booster type ($Q = 8.95$, $df = 2$, $P = 0.0114$), in 34% by laxative type ($Q = 4.38$, $df = 1$, $P = 0.0363$), in 44% by booster volume ($Q = 14.32$, $df = 1$, $P = 0.0002$), and in 43% with laxative volume with booster ($Q = 8.48$, $df = 1$, $P = 0.0036$).

Overall, an Egger's test suggested a publication bias regarding the CTT (Egger's test: $P = 0.00727$) (► Fig. 7–9). The Duval and Tweedie method adjusted values of 5 studies to left of mean; random model point estimate: 154.24; 95% CI: 118.81–189.66, Q value = 197.86.

Discussion

This is, to date, the most extensive systematic review and meta-analysis of studies that report colon cleanliness and completeness in CCE. Interestingly, by pooling all the included studies, both CCE CRs and colon cleansing are suboptimal. NaP was the most frequently used booster with a completion rate of 0.830 (95% CI, 0.781–0.871). We found that the highest rate of CCE completion was achieved in the two studies where NaP+GG booster was used with a CR of 0.931 (95% CI, 0.820 to 0.976). Regarding colon cleanliness, a single study reported adequate colonic cleanliness of 0.939 (95% CI, 0.849–0.977) using PEG + MgCit. PEG only was used in most studies with a reported pooled rate of adequate cleanliness of 0.790 (95% CI, 0.750–0.826). Boosters are, of course, required in CCE to increase the capsule completion rate and ensure complete visualization of the colonic and rectal mucosa.

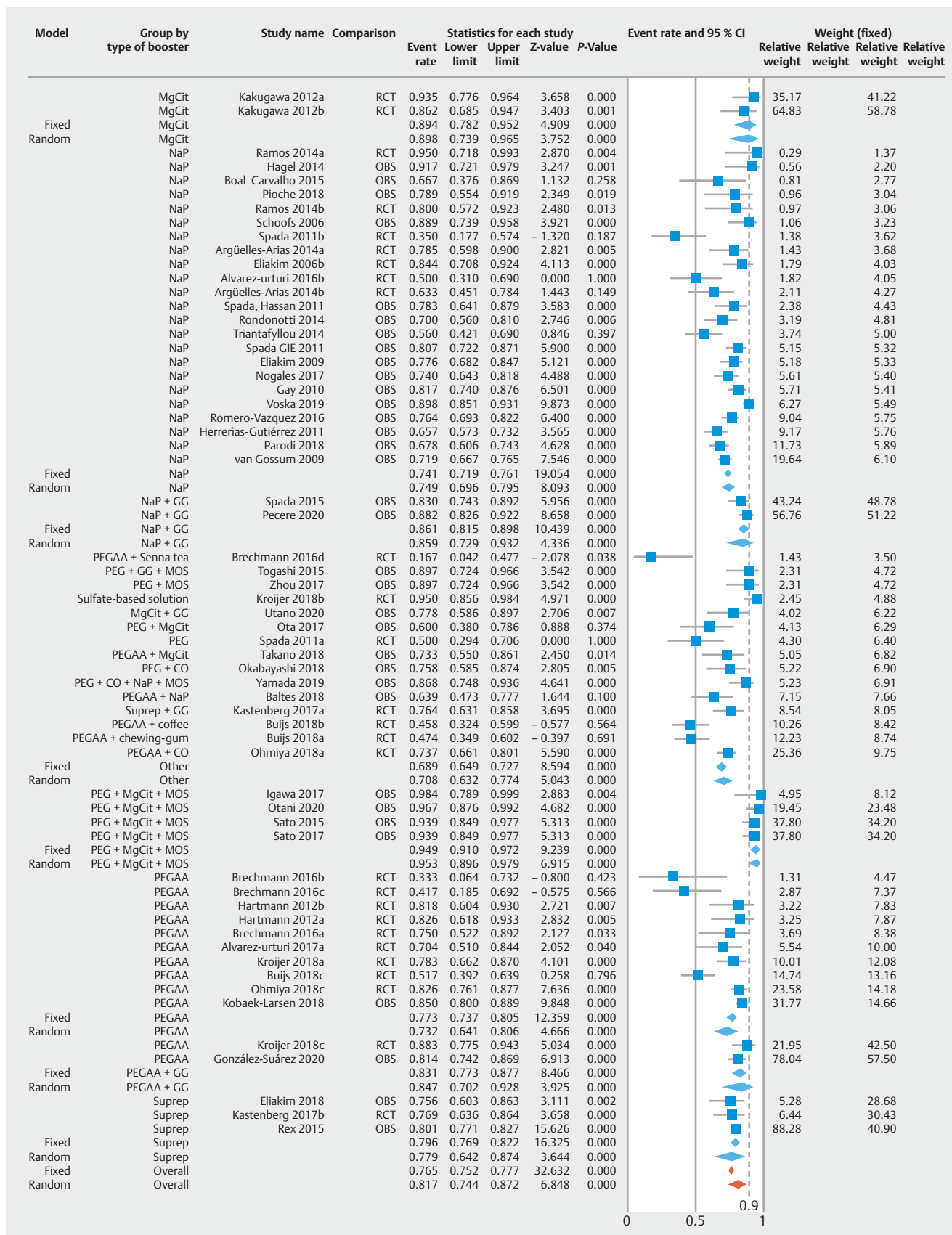
The European Society of Gastrointestinal Endoscopy (ESGE) recommends NaP-based boosters for CCE [57]. However, their usage is restricted by possible toxicity in patients with renal and cardiovascular disease, where serious electrolyte imbalance has been reported [58]. The recent ESGE-guidelines for flexible colonoscopy recommends against the routine use of



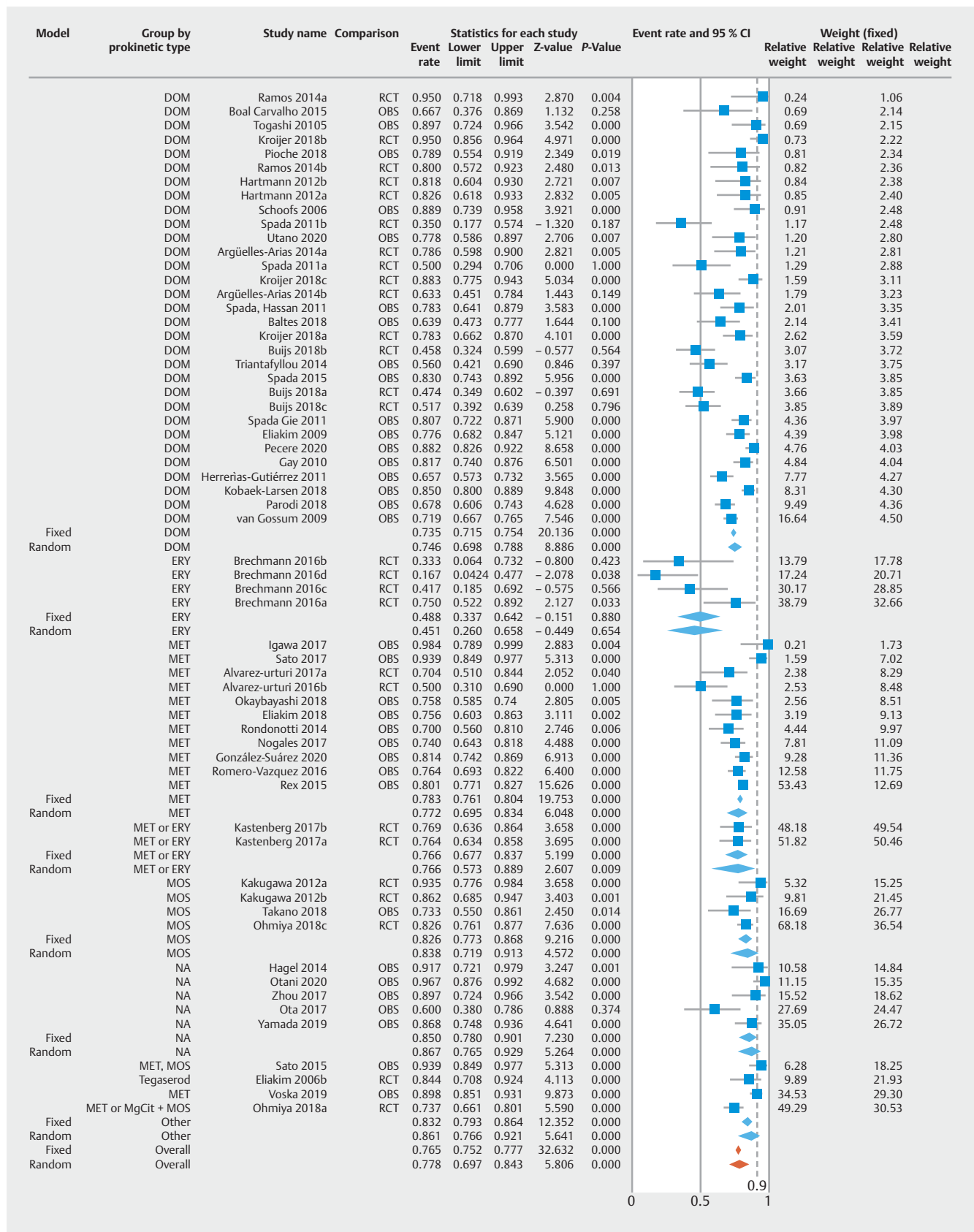
► **Fig. 5** Forest plot of cleanliness by laxative type. The dashed line represents 90 % CI, confidence interval; MgCit, magnesium citrate; NaP, sodium phosphate; OBS, observational study; PEG, polyethylene glycol; PEGAA, polyethylene glycol and ascorbic acid; RCT, randomized controlled trial.

oral NaP for bowel preparation [59]. Moreover, oral NaP solution has been withdrawn from the market in some countries [60]. The decreased use of NaP and attempt to replace it with

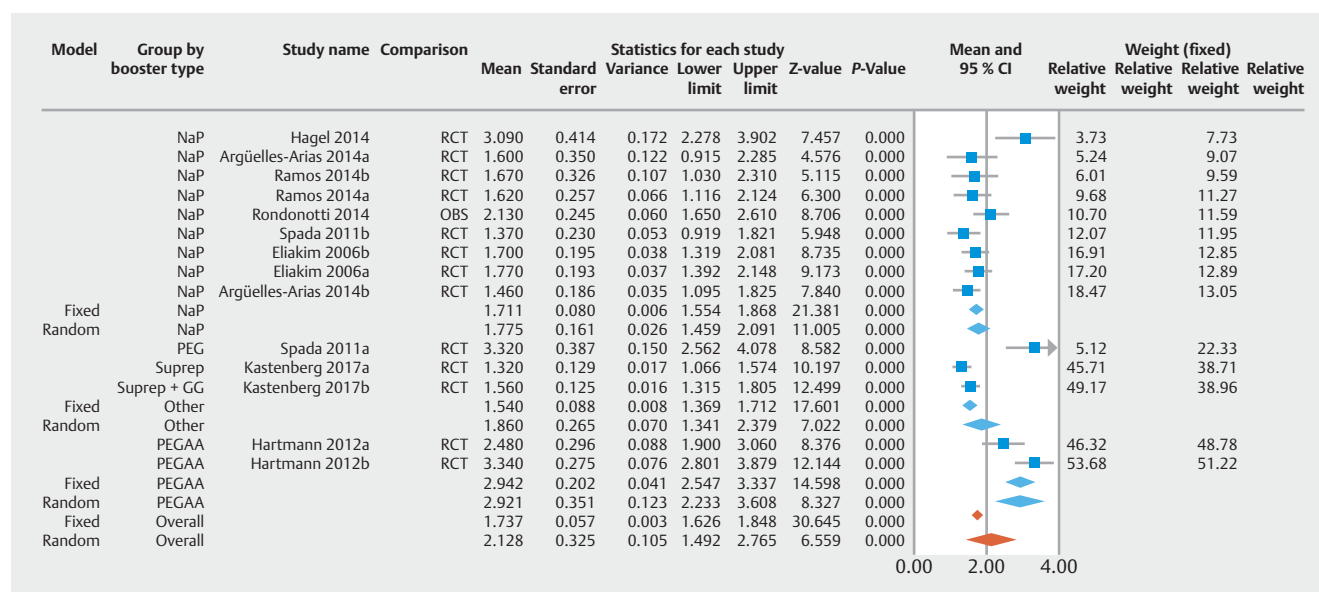
a new effective and safe booster is obvious in our review, showing that during the last 4 years, only seven of 29 (24 %) compar-



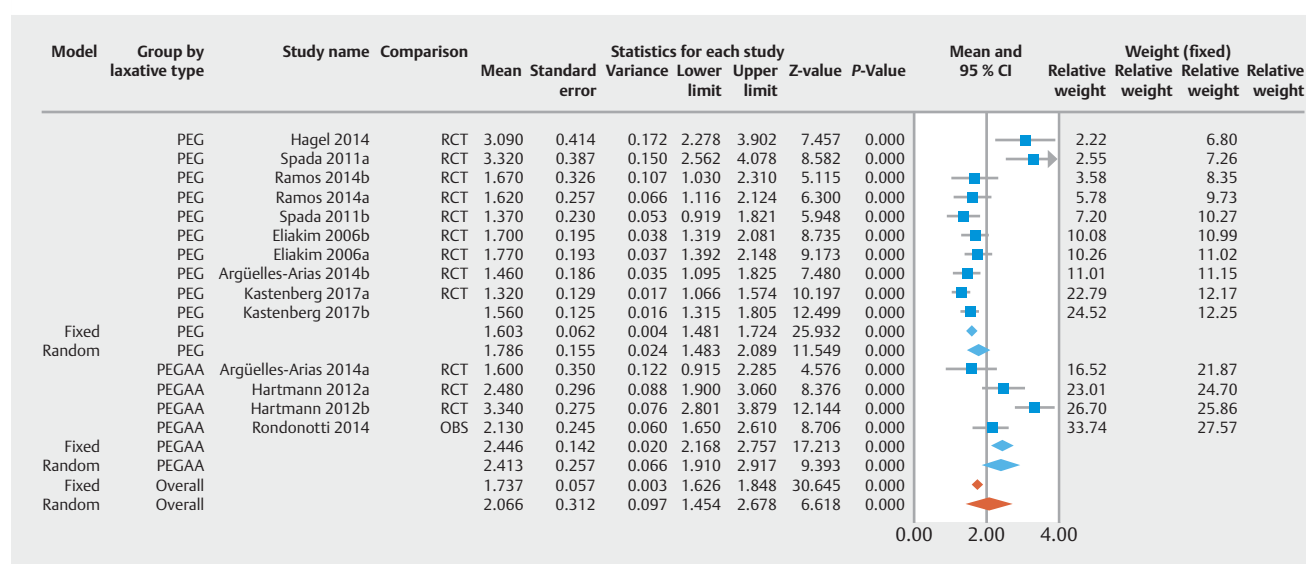
► **Fig. 6** Forest plot of cleanliness by booster type. The dashed line represents 90% CI, confidence interval; CO, castor oil; GG, Gastrografin; MgCit, magnesium citrate; MOS, mosapride; NaP, sodium phosphate; OBS, observational study; PEG, polyethylene glycol; PEGAA, polyethylene glycol and ascorbic acid; RCT, randomized controlled trial.



► **Fig. 7** Forest plot of cleanliness by prokinetic type. The dashed line represents 90%. CI, confidence interval; DOM, domperidone; ERY, erythromycin; MET, metoclopramide; MgCit, magnesium citrate; MOS, mosapride; NA, not available; OBS, observational study; RCT, randomized controlled trial.



► **Fig. 8** Forest plot of transit time by booster type. CI, confidence interval; GG, Gastrografin, NaP, sodium phosphate; OBS, observational study; PEGAA, polyethylene glycol and ascorbic acid; RCT, randomized controlled trial.



► **Fig. 9** Forest plot of transit time by laxative type. CI, confidence interval; OBS, observational study; PEG, polyethylene glycol; PEGAA, polyethylene glycol and ascorbic acid; RCT, randomized controlled trial.

ed to 21 of 35 (60%) in the previous years published studies included NaP booster in the CCE preparation regimen.

Recent research on CCE highlighted its diagnostic potential in different populations. Many countries have introduced a CRC screening program, which substantially increases the number of performed colonoscopies [61]. This high demand for colonoscopies raises concerns about the long-term sustainability of healthcare systems, especially in times of economic hardship or other occasions such as pandemics [62, 63]. A possible diagnostic alternative to relieve this burden is CCE. The technology of the CEE design is evolving and algorithms for polyp detection and quality of cleanliness is being developed [64]. Recent work

has shown promising results on a polyp matching algorithm with high accuracy compared to the reading of CCE by human readers [65]. Because CCE is only a diagnostic tool without the capabilities for biopsy or polyp removal, populations with a low prevalence of colorectal lesions, and therefore, low need for a subsequent colonoscopy are ideal for CCE. The introduction of CCE as a filter examination in screening programs comes with the caveat that a high completion rate and adequate bowel cleanliness are prerequisite [66, 67]. In a recent study by Cash et al. comparing the DY of CCE versus computed tomography colography (CTC) in a screening population, CCE was superior to CTC for detection of polyps ≥ 6 mm but inferior to colonosco-

py [68]. The CR and ACR of CCE should reach at least 90% according to quality parameters for flexible colonoscopy defined by international guidelines [69, 70].

The importance of adequate bowel cleanliness is emphasized because cancer and polyp miss rate are increased with inadequate visualization of the colonic mucosa [71]. A study of 253 participants from a screening population demonstrated high accuracy of CCE in detecting clinically significant polyps, but only 54% had adequate visualization of the colon [34]. Taking this into account, together with findings in this detailed review, completion and adequate colonic cleanliness rates need to be improved to meet the ESGE standards for colonoscopy and be a reliable alternative to CC. Currently, a large Danish RCT in a bowel cancer screening population is underway and the study is expected to be completed at the beginning of 2022 [72].

A previous systematic review from 2014, including 12 studies and 1,249 patients, found that PEG and NaP were the most used laxative and booster, respectively [73]. Our meta-analysis supports these findings; despite including 46 studies and a total of 5,003 patients, we were not able to show that PEG or NaP was superior to other used laxatives or boosters at a level of statistical significance. A major strength of our meta-analysis was a larger number of studies and > 5,000 patients who underwent CCE. Furthermore, most studies were of high quality with prospective designs. Certain limitations of this review should be addressed. Between-study heterogeneity was present for CR, ACR, and CTT indicated by high I^2 values, which need to be considered when interpreting the results. More well-designed protocolized studies would have enabled us to be more conclusive regarding the most optimal bowel preparation regimen. From a clinical standpoint, the quality of colon cleansing is dependent upon several factors, e.g., diet restriction, laxative type, laxative volume, laxative timing of administration, type of boosters, volume of boosters, number of boosters, timing of boosters etc, whereas, in our study we evaluate the impact of each major factor separately. Furthermore, we did not address the patient tolerability, which is a key factor to evaluate the applicability of a preparation regimen in clinical practice.

In terms of future research, we stress the need for large prospective studies on different bowel preparation regimens as much work remains to improve rates of completeness and adequate bowel cleanliness to qualify CCE as an equivalent to CC in certain settings. In parallel, patient tolerability of preparation regimens must be addressed in to avoid dropouts. In times of pandemics such as Covid-19, CCE might offer an important advantage compared to colonoscopy as it can be performed in out-patient clinics with minimal contact to health care personnel and patients [74].

Conclusions

In the largest systematic review and meta-analysis on CCE, we found that both CRs and ACRs are suboptimal. PEG laxative and NaP booster were the most commonly used. We were not able to show any superiority concerning completeness or cleanliness rate for any of the abundant laxatives or boosters at a level of

statistical significance. Well-designed studies focusing on the completeness or cleanliness of CCE should be performed to identify the optimal preparation regimen.

Competing interests

Dr. Koulaouzidis is consultant for Jinshan. He is director of iCERV Ltd and cofounder of AJM Medicaps Ltd. He has received a Given Imaging Ltd-ESGE grant, and material support for clinical research from SynMed/Intromedic. In the last 10 years, he has received honoraria and lecture fees from Jinshan, Dr Falk Pharma UK, and Ferring. He has also received educational travel support from Aquilant, Jinshan, Dr Falk Pharma, Almirall, Ferring, and has participated in advisory board meetings for Tillots, Ankon, and Dr Falk PharmaUK. Dr. Toth has received research grant from the Swedish Cancer Society and the Swedish ALF-agreement.

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