Systematic Review/Meta-analysis

Is water exchange superior to water immersion for colonoscopy? A systematic review and meta-analysis

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Abstract

Background/Aims: Recently, water exchange (WE) instead of water immersion (WI) for colonoscopy has been proposed to decrease pain and improve adenoma detection rate (ADR). This systematic review and meta-analysis is conducted to assess whether WE is superior to WI based on the published randomized controlled trials (RCTs).

Materials and Methods: We searched studies from PubMed, Cochrane Central Register of Controlled Trials, EMBASE, and MEDLINE. Only RCTs were eligible for our study. The pooled risk ratios (RRs), pooled mean difference (MD), and pooled 95% confidence intervals (CIs) were calculated by using the fixed-effects model or random-effects model based on heterogeneity.

Results: Five RCTs consisting of 2229 colonoscopies were included in this study. WE was associated with a significantly higher ADR than WI (RR = 1.18; CI = 1.05–1.32; $P = 0.004$), especially in right colon (RR = 1.31; CI = 1.07–1.61; $P = 0.01$). Compared with WI, WE was confirmed with lower pain score, higher Boston Bowel Preparation Scale score, but more infused water during insertion. There was no statistical difference between WE and WI in cecal intubation rate and the number of patients who had willingness to repeat the examination. Furthermore, both total procedure time and cecal intubation time in WE were significantly longer than that in WI (MD = 2.66; CI = 1.42–3.90; $P < 0.0001$; vs MD = 4.58; CI = 4.01–5.15; $P < 0.0001$).

Conclusions: This meta-analysis supports the hypothesis that WE is superior to WI in improving ADR, attenuating insertion pain and providing better bowel cleansing, but inferior in time and consumption of infused water consumption during insertion.

Keywords: Adenoma detection rate, cecal intubation time, pain score, water exchange, water immersion

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INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer globally and was the fourth leading cause of cancer death in 2012, accounting for 1.35 million newly diagnosed cases and 0.7 million deaths annually.[1,2]

Colonoscopy is important for diagnostic purposes and cancer surveillance and is almost irreplaceable for cancer screening in view of its potential to reduce the morbidity of CRC.[3-5] Besides, precursor lesions and early cancers can be detected early and removed by colonoscopy, which in turn could lead to the decline of mortality from colon cancer.[6]

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Traditionally, diagnostic colonoscopy began with air insufflation (AI) to inflate the colonic lumen to permit visualization and passage.[7] However, both the pain during insertion and the missed proximal lesions during withdrawal phase are two dominant challenges of unsedated gas insufflation screening colonoscopy, and the success rate of intubation is determined by the endoscopists' technical levels.[8,9] On the contrary, sedation might add to the burden of healthcare system by increased nursing, institutional and social costs, and space for recovery.[10,11]

Otherwise, water-aided colonoscopy, in which water is infused in lieu of gas insufflation to inflate the lumen during the insertion phase, has received renewed attention in the literature in recent years.[12] Several meta-analysis of randomized controlled trials (RCTs) comparing AI with water-aided colonoscopy suggested that the latter caused less pain during insertion than the former.[9,13] Water-aided colonoscopy can be categorized into two types, namely water immersion (WI) and water exchange (WE). WI is characterized by the infusion of water to facilitate cecal intubation and suction removal of residual water predominantly during withdrawal,[12,14,15] while WE is a recent modification of WI and is characterized by the clean water insertion to the cecum and removal of residual water predominantly during this phase.[7,12,14] In 2011, Leung *et al.*[8,16] first revealed that WE rather than WI was consistently associated with a greater attenuation of pain during insertion, which aroused global interest in the subject. Thereafter, a growing number of RCTs comparing WE and WI were performed to demonstrate that the former is superior to the latter one, both in lowering pain score and increasing adenoma detection rate (ADR). The aim of our systematic review and meta-analysis is to certify whether WE is a more effective diagnostic tool than WI, in terms of procedure-related and patient-related colonoscopic outcome.

MATERIALS AND METHODS

Search strategy

Recent randomized clinical trials relevant to the comparison of WE and WI to aid insertion of colonoscopy were identified by searching PubMed, Cochrane Central Register of Controlled Trials, EMBASE, and MEDLINE. The search period extended up to December 2017. The combinations of keywords used were ("water exchange" or "water immersion" or "water-assisted" or "water-aided" or "water related") and ("colonoscopy" or "colonoscopic"). References from all retrieved studies as well as review articles on this topic were scrutinized for more eligible trials. In addition, the ClinicalTrials.gov database was screened for information regarding unpublished trials and complementary information on published trials. Next, two reviewers independently assessed full papers of the selected references according to inclusion or exclusion criteria. Disagreements were resolved by discussion or by a third review author if needed.

Study selection criteria

Only RCTs comparing WE with WI during the insertion phase of colonoscopy were considered. Language and publication status of the trials included were not restricted. We included 18-to-85-year-old patients undergoing colonoscopy regardless of the procedural indications (screening, diagnostic, or treatment). Selected articles were required to have at least one of the following primary or secondary outcomes: (1) cecal intubation rate; (2) ADR; (3) right colon ADR; (4) total procedure time; (5) cecal intubation time; (6) withdrawal time; (7) pain score during insertion; (8) infused water during insertion; (9) willingness to repeat the examination; (10) Boston Bowel Preparation Scale (BBPS), an indicator to evaluate the quality of bowel preparation.

Exclusion criteria included: (1) 10 or fewer patients; (2) data of water-assisted colonoscopy could not be discriminated between WE and WI; (3) and animal studies. We also excluded six meeting abstracts since these were published online and the published papers were included in our systematic review and meta-analysis.

Data extraction and management

Two reviewers independently abstracted data from each included study using a standardized abstraction form. The data extraction was discussed, with decisions documented by a third reviewer if there was interobserver disagreement. The following data were extracted, verified, and recorded: characteristics of participants (number of patients enrolled ["total" and "per study arm" respectively], nationality, age, number and ratio of female and male, body mass index, history of previous abdominal surgery); characteristics of interventions (WE, WI, indications, sedation model, level of experience, and water temperature); and primary or secondary outcome measures (patient-related and procedure-related outcomes).

Assessment of risk of bias

Potential publication bias was investigated using a funnel plot.[17] The methodological quality of each included study was evaluated using the risk of bias as described in *Cochrane Handbook for Systematic Reviews of Interventions*.[18] The seven-item questionnaire was assessed on the following guidelines: (1) random sequence generation; (2) allocation

sequence concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessment; (5) incomplete outcome data; (6) selective reporting; (7) other bias. Each item has the response "high risk," "low risk," or "unclear risk." Assessment of studies was performed by two reviewers independently and consensus was reached after discussion if there existed disagreement.

Statistical analysis

The Review Manager (Cochrane Collaboration, Copenhagen, Denmark) and Stata version 14.0 (StataCorp, College Station, TX, USA) were used to analyze the data.

The pooled risk ratio (RR) and 95% confidence interval (95% CI) were calculated for dichotomous outcomes. For continuous outcomes, the pooled mean difference (MD) and 95% CI were calculated as appropriate.

Heterogeneity was assessed using the Chi-square test, and the data were considered heterogeneous if $P < 0.05$. The I^2 statistic was used to estimate the degree of heterogeneity. This measure describes the percentage of total variation across studies that results from heterogeneity rather than chance. A value of 25, 50, and 75% was considered to indicate low, moderate, and high heterogeneity, respectively. Data from individual trials were combined for meta-analysis if the interventions, patient groups, and outcomes (outcome reporting and scales of outcome measures) were sufficiently similar (to be determined by consensus). The fixed-effects model was used to pool data in the absence of heterogeneity. The random-effects model was used if significant heterogeneity was detected.

RESULTS

Search results

Overall, 106 potentially matched articles were identified through database search until December 2017. Four additional articles were found through the ClinicalTrials.gov. Figure 1 shows the process of paper selections. Five trials were finally included for meta-analysis. The characteristics of the studies are listed in Table 1. Quality of the included studies, as assessed using the risk of bias assessment tool described in the *Cochrane Handbook for Systematic Reviews of Interventions*, appears to be moderate because of potential detection bias in some articles [Figure S1].

Study characteristics

Participants

These five articles[19-23] were all RCTs, three conducted in Italy, two in Taiwan, Republic of China, including a total of 2229 participants. The number of male and female participants

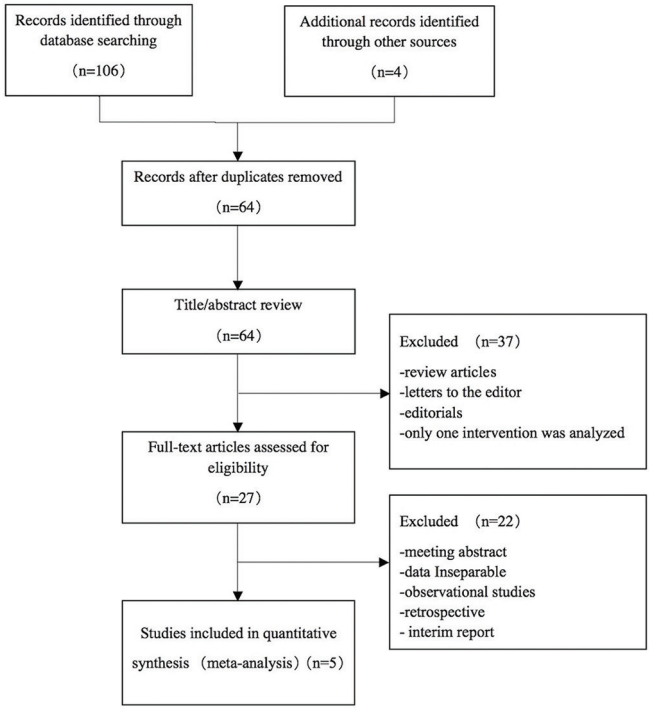

Figure 1: Selection of studies flowchart

was similar. The mean age of the study participants ranged from 53.0 to 61.4 years. Screening and diagnosis were the most frequent indications for colonoscopy.

Meta-analysis was conducted for 10 outcomes: (1) cecal intubation rate; (2) ADR; (3) right colon ADR; (4) total procedure time; (5) cecal intubation time; (6) withdrawal time; (7) pain score during insertion; (8) infused water during insertion; (9) willingness to repeat the examination; (10) BBPS [Table 2]

Primary outcomes

Cecal intubation rate

Five studies[19-23] with 2229 colonoscopies compared the cecal intubation rate between WE and WI. Irrespective of the colonoscopic method, mean cecal intubation rate ranged from 88.0 to 99.0%. In the final meta-analysis, cecal intubation rate was similar between WE and WI [RR = 1.01; CI = 1.00–1.03; $P = 0.14$; $I^2 = 15\%$] [Figure 2a].

Adenoma detection rate

ADR was assessed in three trials.[19,20,22] The meta-analysis involved a total of 1430 colonoscopies and the statistical results showed that WE had a significantly higher ADR than WI [RR = 1.18; CI = 1.05–1.32; $P = 0.004$; $I^2 = 0\%$] [Figure 2b].

Right colon ADR

Three trials[19,20,22] evaluated the right colon ADR using the proportion of patients with at least one adenoma.

Table 1: Baseline characteristics of studies included in the meta-analysis

References	Interventions	Publication	Methods	Country	Number	Male/Female	Age (years)	Body mass index
Hsieh *et al.* 2014	WE	Full text	RCT	Taiwan,	90	55 (61.1)/35 (38.9)	56.9 (10.3)	24.9 (2.9)
	WI			China	90	53 (58.9)/37 (41.1)	54.3 (11.4)	25.0 (3.3)
Cadoni *et al.* 2015-a	WE	Full text	RCT	Italy	186	110 (59.1)/76 (40.9)	59 (11.3)	26.5 (4.9)
	WI				197	116 (58.9)/81 (41.1)	60 (10.8)	25.9 (4.2)
Cadoni *et al.* 2015-b	WE	Full text	RCT	Italy	209	122 (58.4)/87 (41.6)	58 (14.4)	22.1 (4.7)
	WI				207	117 (56.5)/90 (43.5)	59 (12.5)	26.5 (5.1)
Cadoni *et al.* 2017	WE	Full text	RCT	Italy	408	224 (54.9)/184 (45.1)	61.4 (6.2)	26.4 (4.1)
	WI				408	223 (54.7)/185 (45.5)	61.0 (6.3)	26.4 (4.4)
Hsieh *et al.* 2017	WE	Full text	RCT	Taiwan,	217	121 (55.8)/96 (44.2)	55.7 (10.6)	24.1 (3.2)
	WI			China	217	110 (50.7)/107 (49.3)	55.9 (10.2)	24.3 (3.3)

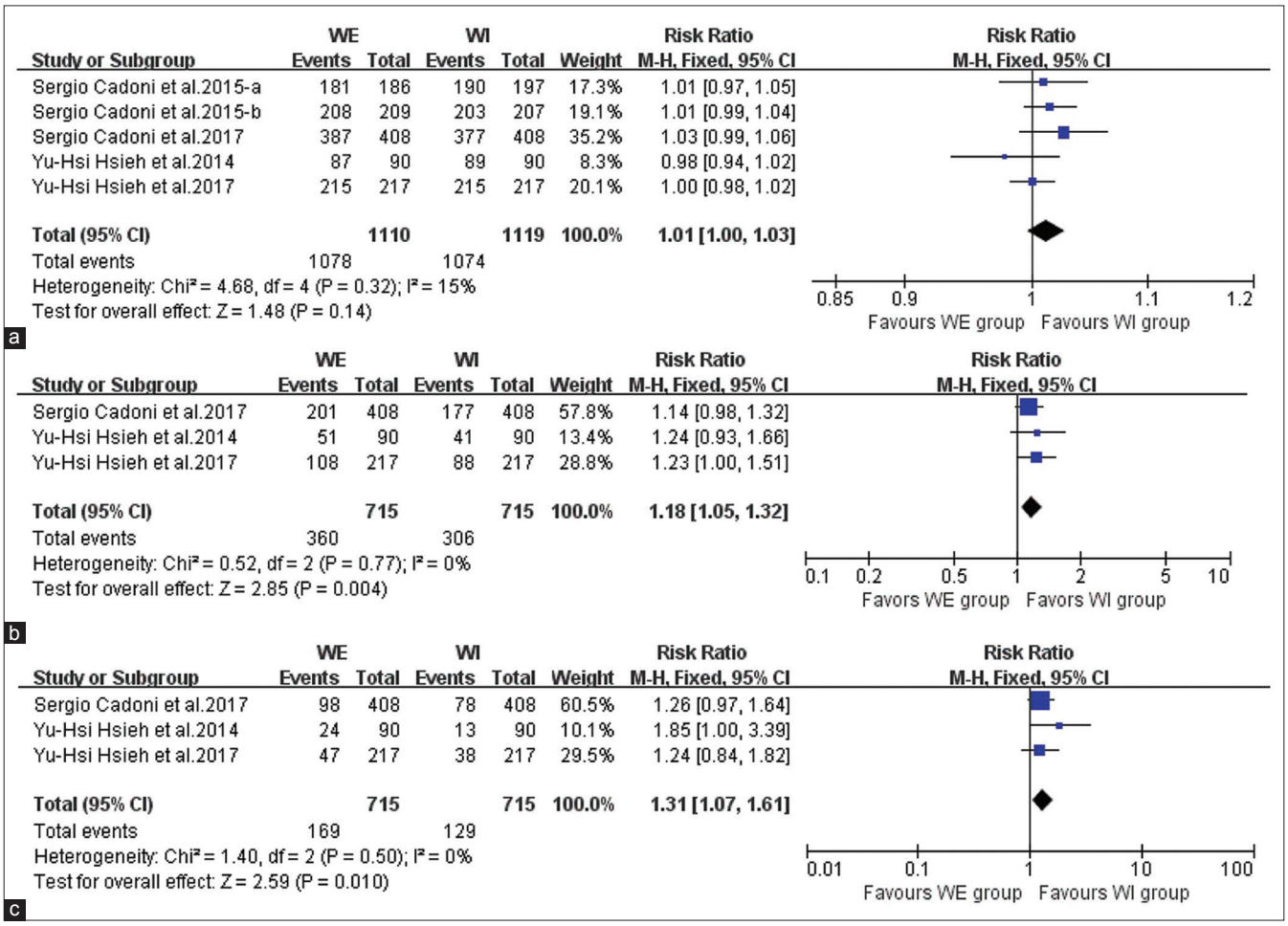

Figure 2: Forest plots of meta-analysis comparing the incidence of cecal intubation rate (a), adenoma detection rate (b), and right colon adenoma detection rate (c) between WE and WI. Studies are arranged by year, CI, confidence interval

The statistical results showed that WE had a higher right colon ADR [RR = 1.31; CI = 1.07–1.61; $P = 0.01$; $I^2 = 0\%$] [Figure 2c].

Secondary outcomes

Total procedure time

Total procedure time was reported in four included trials.[20-23] The article by Cadoni *et al.*[22] was excluded because it assessed data using median and interquartile range (IQR) instead of mean and SD. Statistical data revealed that total procedure time in WI was significantly longer than that in WE [MD = 2.66; CI = 1.42–3.90; $P < 0.0001$; $I^2 = 84\%$] [Figure 3a].

Cecal intubation time

Five studies[19-23] reported outcomes in terms of cecal intubation time. Only four trials[19-21,23] reported cecal intubation time as a mean average with standard deviation (SD). The large interstudy differences in the mean intubation time might contribute to the high heterogeneity in the pooled analysis of the mean difference ($I^2 = 98\%$). Meta-analysis of the data showed a reduction in cecal

Table 2: Distribution of factors among selected articles

References	Factors Cecal intubation rate	ADR	Right ADR	Pain score at insertion	Total procedure time	Cecal intubation time	Withdraw time
Cadoni *et al.* 2015-a	*				*	*	*
Cadoni *et al.* 2015-b	*			*	*	*	*
Cadoni *et al.* 2017	*	*	*				
Hsieh *et al.* 2014	*	*	*	*		*	*
Hsieh *et al.* 2017	*	*	*	*	*	*	*

*means that data of the analyzed factors are available in selected articles

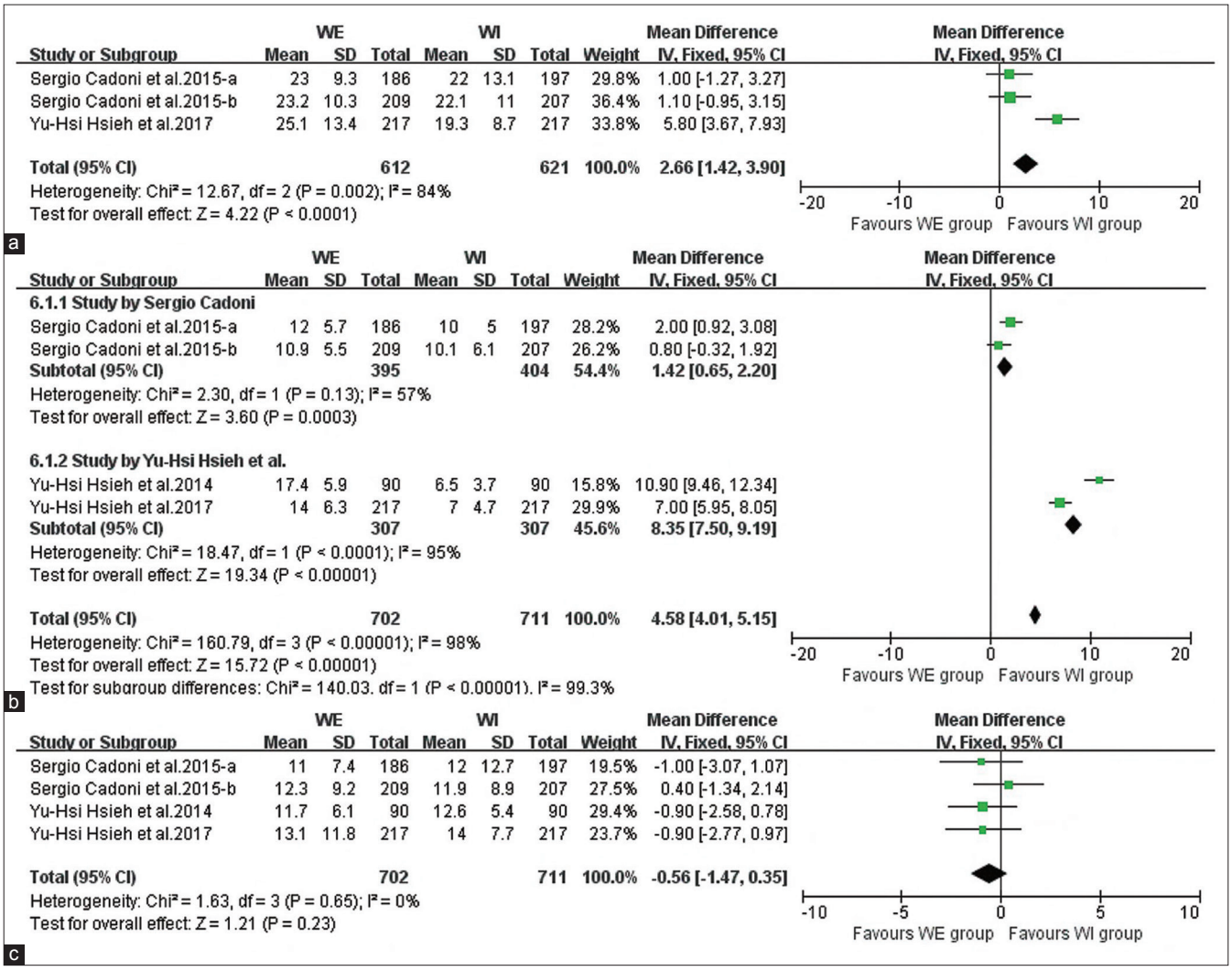

Figure 3: Forest plots of meta-analysis comparing the incidence of total procedure time (a), cecal intubation time (b), and withdraw time (c) between WE and WI. Studies arranged by year, CI, confidence interval

intubation time by 4.58 minutes in WI compared with WE [MD = 4.58; CI = 4.01–5.15; $P < 0.00001$; $I^2 = 98\%$] [Figure 3b]. Subgroup analysis also revealed a significant difference in cecal intubation time between two endoscopy centers (MD = 1.42; CI = 0.65–2.20; $P = 0.0003$; $I^2 = 57\%$ vs MD = 8.35; CI = 7.50–9.19; $P < 0.00001$; $I^2 = 95\%$).

Withdrawal time

All of these five studies[19-23] had evaluated the withdrawal time. The research by Cadoni *et al.*[22] was eliminated because it performed the results in median and IQR instead of mean and SD. Finally, with four studies included, there was no evidence of difference in the withdrawal time between WE and WI [MD = −0.56; CI = −1.47 to 0.35; $P = 0.23$; $I^2 = 0\%$] [Figure 3c].

Pain score during insertion

Four studies[19-21,23] investigated difference in pain score measured by 0 to 10 numeric rating scales (0 means no pain, 10 is the most severe or worst pain), while Cadoni *et al.*[21] was excluded without performing the results of SD. Pain score

was significantly lower in WE compared with WI [MD = −0.79; CI = −1.16 to − 0.42; $P < 0.0001$; $I^2 = 0\%$] [Figure 4a].

Infused water during insertion

Five trials[19-23] reported volume of infused water during insertion but only two of them[19,20] performed the results as a mean average in milliliter with SD. The volume of infused water during insertion in WI was smaller than that in WE [MD = 610.28; CI = 546.98–673.58; $P < 0.00001$; $I^2 = 47\%$] [Figure 4b].

Willingness to repeat the examination

To assess the satisfaction of the two examinations, four studies[19,21-23] evaluated the number of patients who had willingness to repeat the examination. This meta-analysis involved 893 and 902 patients who had experienced WE and WI, respectively. There was no difference between WE and WI [RR = 1.01; CI = 0.99–1.03; $P = 0.33$; $I^2 = 36\%$] [Figure 4c].

Boston Bowel Preparation Scale

Quality of bowel cleansing was assessed during withdrawal in four studies,[20-23] with Cadoni *et al.*[22] using median and IQR instead of mean and SD. Thus, only three RCTs were suitable to make an analysis. The score of each trial was presented in Figure 4d. Our meta-analysis showed that WE had significantly higher BBPS than WI [MD = 0.45; CI = 0.34–0.57; $P < 0.00001$; $I^2 = 0\%$] [Figure 4d].

Quality of the evidence

Quality of evidence of included RCTs appeared to be moderate or even low because of potential bias in some studies. However, we did not detect significant publication bias. Only five RCTs were included in our meta-analysis and the power of the tests was too weak to distinguish chance. Thus, we do not show these data [Figures S2-12 and Table S1].

DISCUSSION

Since Leung *et al.*[8] first came to the conclusion that WE was superior to WI for colonoscopy, a growing number of RCTs have attempted to make comparisons between WE and WI. In this systematic review and meta-analysis, we find that WE rather than WI during the insertion phase of colonoscopy is significantly associated with higher ADR (particularly in right colon), higher BBPS, and lower abdominal pain score. On the contrary, WE colonoscopy is characterized by a longer insertion phase and demanding more infused water.

Cecal intubation failures are always attributed to intolerable pain, diverticular substenosis, looping, acute angles, and obstructing cancer.[19,21,23] In our study, the analyzed results confirm cecal intubation rate is not significantly different between the two procedures. The reason may be that colonoscopists are all well-trained and the water could help them clean and expand bowel. Recent studies observed that WE was helpful in salvaging most of the failures and improved the success rate of cecal intubation in potentially difficult colonoscopies.[24-26] Nevertheless, Vemulapalli *et al.*[27] demonstrated that the use of WI offered the advantages of allowing cecal intubation in patients with known redundant colons by requiring an external stiffener less often. Therefore, colonoscopists are supposed to choose optimal colonoscopic methods depending on the difficulty and complexity of colonoscopies in clinical practice.

Secondly, the most important aspect to assess a colonoscopy is ADR, and data shows that 23–58% of interval CRCs are ascribed to missed lesions.[28] Our pooled data shows a superior ADR through WE rather than WI. The results show that WE had a higher ADR than WI in total and right colon ADR (cecum and ascending colon). Our results of BBPS show that WE performs better for colon cleanliness overall and may have contributed to the increase in ADR.[29] The underwater view might also be helpful to discover polyps hidden behind a fold or an angulation because suction-induced collapse of the colon by WE might change the contour of the colon and make a fold or an angulation less accentuated.[30] Researchers had reported a trend of more missed adenomas in the right side of the colon compared with the left[31] which might be of clinical significance. However, we find that the increase of ADR is likely due to longer examination time. Hsieh *et al.*[19] reported a 200% increase in cecal intubation time for the WE, when compared with WI. Rex *et al.*[32] pointed out that the increased ADR in the WE may be the result of more time spent on insertion rather than the method itself. Nonetheless, we believe that is insufficient data to make a statistical analysis of the association between ADR and cecal intubation time in our meta-analysis.

As far as time consumption is concerned, there is no difference in withdrawal time. However, WI demands less time for cecal intubation and the total procedure. It is mainly due to the time consumed in suctioning of the effluent.[33] WE, with split-dose bowl preparation, needs to clean residual gas and dispose off bubbles to avoid its interference with inspection.[24]

To assess the satisfaction of WE and WI, we compared the pain score, and the patients' willingness to repeat the

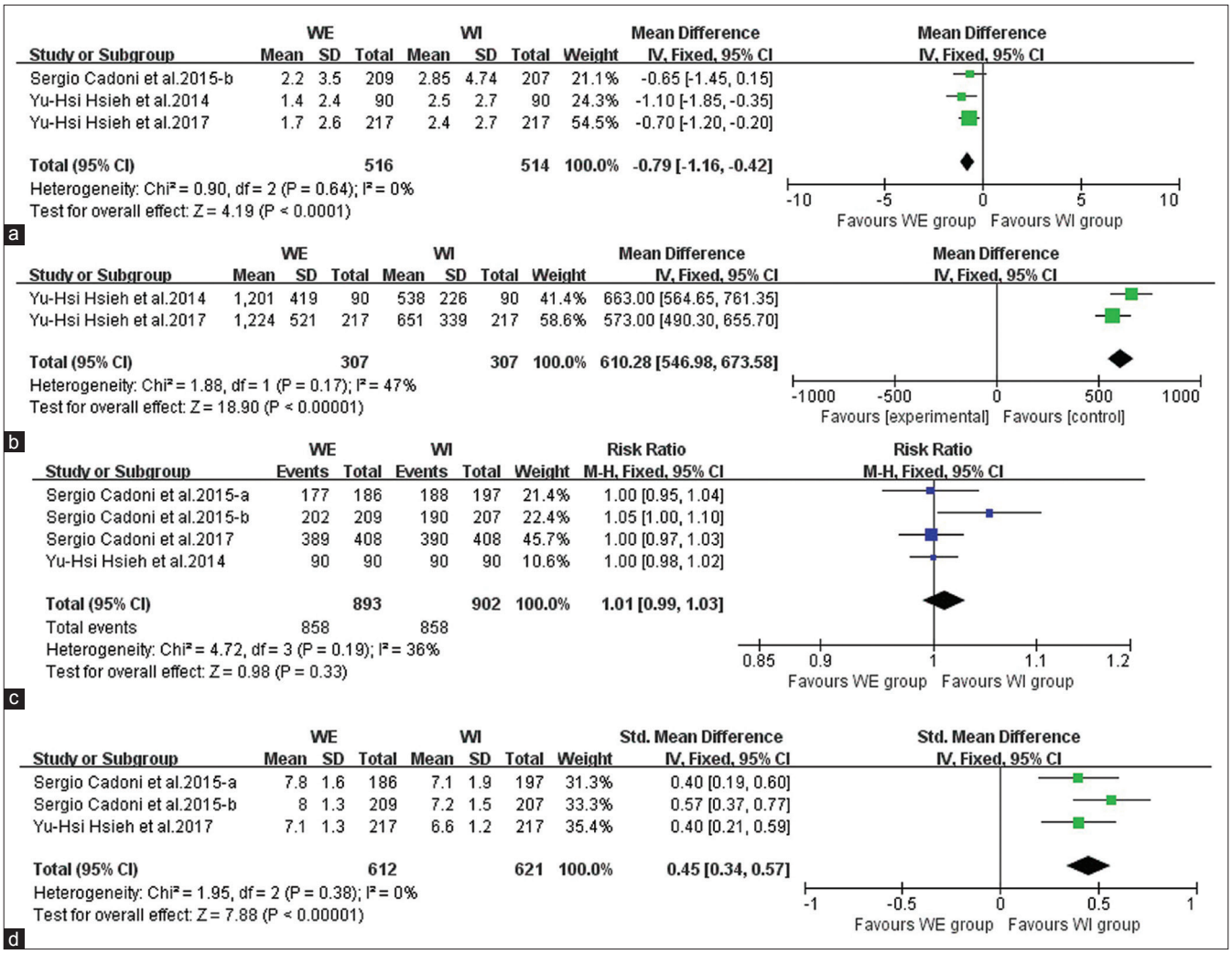

Figure 4: Forest plots of meta-analysis comparing the incidence of pain score during insertion (a), infused water during insertion (b), willingness to repeat the examination (c), and Boston Bowel Preparation Scale (d) between WE and WI. Studies arranged by year, CI, confidence interval

examination. The results show that WE could cause less pain but with no difference in the willingness of patients to repeat the examination. There are several plausible explanations for the pain produced during the examination. Loop formation at the sigmoid colon is associated with insertion pain.[34] Infusion of water could straighten the sigmoid and reduce loop formation at the rectosigmoid junction.[35] Besides, WE avoids lengthening of the colon and the aspiration of residual air pockets during WE further shortens the colon, which results in a shorter length of the instrument needed to achieve cecal intubation, and fewer attendant maneuvers, such as position change or abdominal pressure, to manage looping.[36] Thus, WE offers the best chance to complete more comfortable colonoscopies without the need of sedation.

Previous studies have demonstrated that the focused task of searching for lesions could potentially be distracted by withdrawal cleaning, leading to a lower yield of detected lesions.[8,29,37,38] The current data confirm that MD in water volume between WE and WI is even greater, by about 610.28 ml. More infused water is consumed to clear the view and minimize distension during this phase, which could avoid distraction of withdrawal cleaning which may affect WI and AI.[38] Thus, this could explain that WE does enhance the performance of investigators identifying lesions in the right colon at excellent segmental BBPS score.

The strength of the present systematic review and meta-analysis is that we included only RCTs and the methodological quality of most of them was high. However, the limitations of our study should not be ignored. The main weakness is that the eligible studies varied in several aspects, including difference in inclusion and exclusion criteria, characteristics of patient cohorts, sedation model, technical modality, colonoscopic skills level, and it is possible that methodological differences might have confounded the differences recorded across subgroups of

trials. A further limitation is that endoscopists, assistant nurses, and outcome assessors in some trials were not blinded, and as a consequence, the risk of bias is high and cannot be excluded. More importantly, all five clinical trials were designed and carried out by two investigative teams. Although it leads to low heterogeneity, yet the data may lack appeal and it may be difficult for other endoscopic centers to repeat the results. Besides, a sensitivity analysis could not be performed since only five studies met the inclusion criteria. Thus, we suggest that more multi-center, double-blinded RCTs should be carried out to confirm whether WE is superior to WI.

CONCLUSION

In conclusion, this is the first systematic review and meta-analysis to compare WE and WI colonoscopies. The attenuation of pain and higher detection of lesions suggest that WE is a superior insertion technique. Comparative data appeared to reveal that WE rather than WI was associated with longer cecal intubation time and larger infused water volume. Besides, WE is inferior to WI in bowel cleansing to help enhance the performance of investigators identifying lesions. Because of few RCTs from various endoscopic centers eligible in our study, the benefits of WE compared with WI should be further evaluated by additional multicenter and multinational RCTs for future meta-analysis.

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Conflicts of interest

There are no conflicts of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

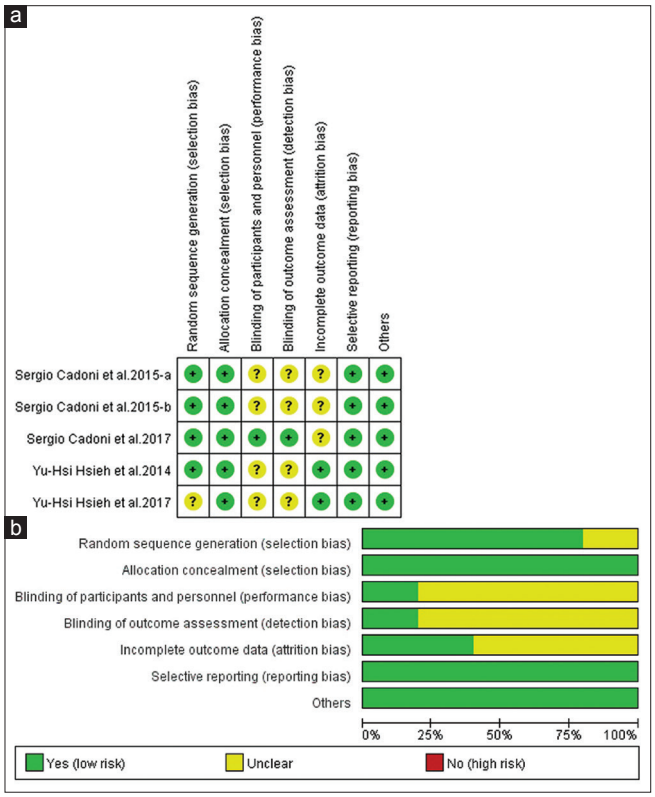

Figure S1: Risk of bias graph (a) and risk of bias summary (b)

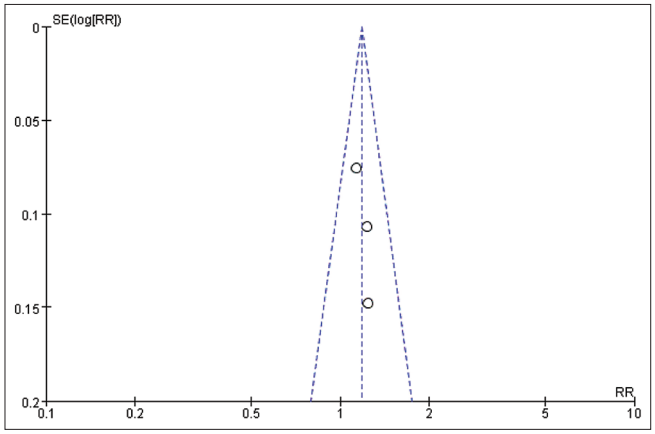

Figure S3: Funnel plot to explore the publication bias in the meta-analysis regarding adenoma detection rate

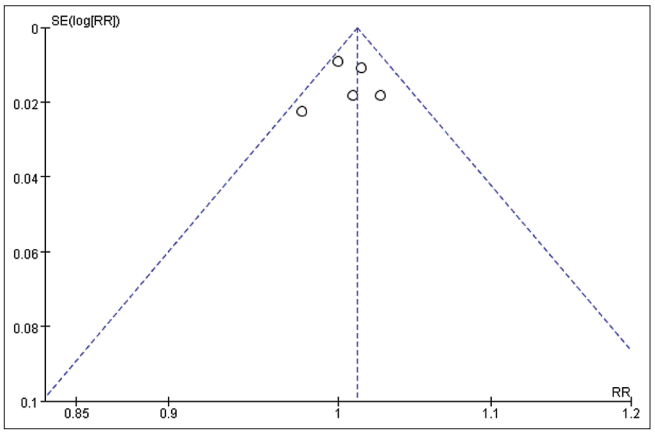

Figure S2: Funnel plot to explore the publication bias in the meta-analysis regarding cecal intubation rate

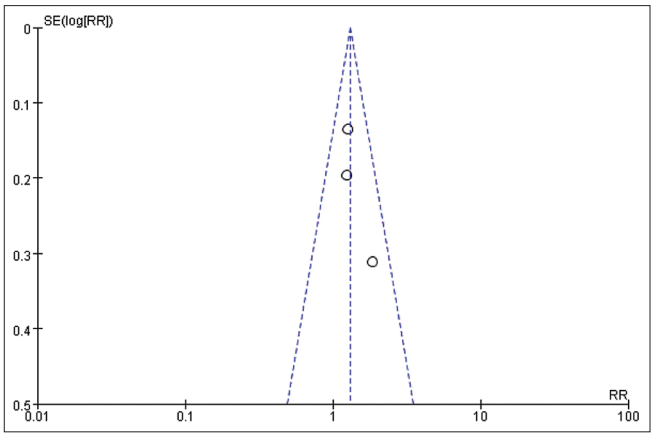

Figure S4: Funnel plot to explore the publication bias in the meta-analysis regarding right colon adenoma detection rate

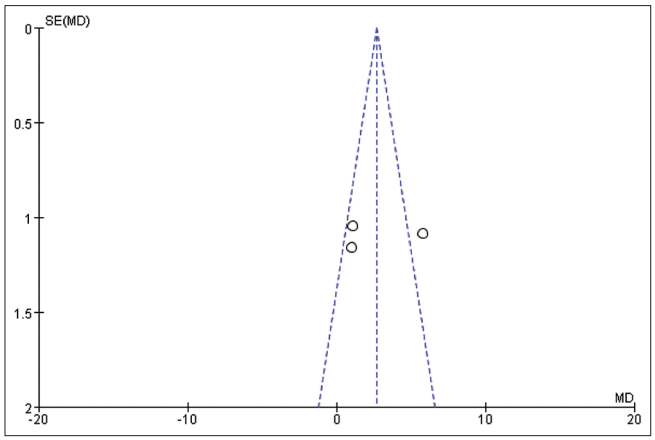

Figure S5: Funnel plot to explore the publication bias in the meta-analysis regarding total procedure time

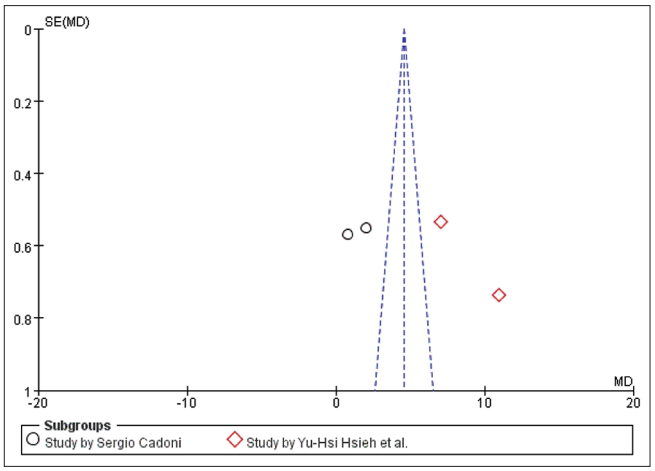

Figure S6: Funnel plot to explore the publication bias in the meta-analysis regarding cecal intubation time

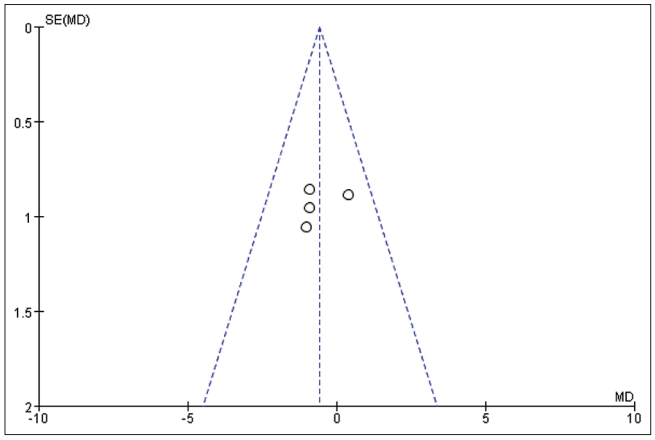

Figure S7: Funnel plot to explore the publication bias in the meta-analysis regarding withdraw time

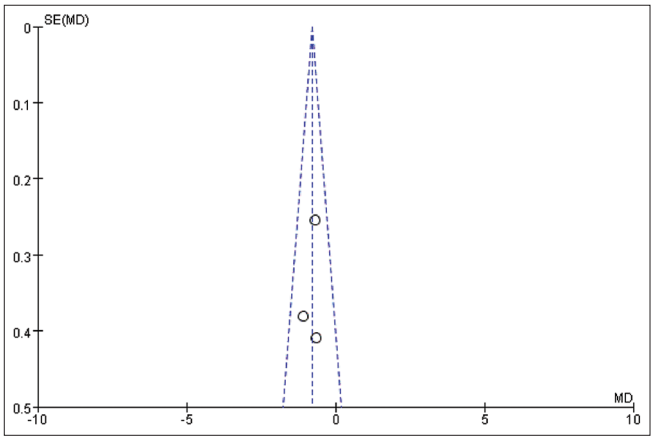

Figure S8: Funnel plot to explore the publication bias in the meta-analysis regarding pain score during insertion

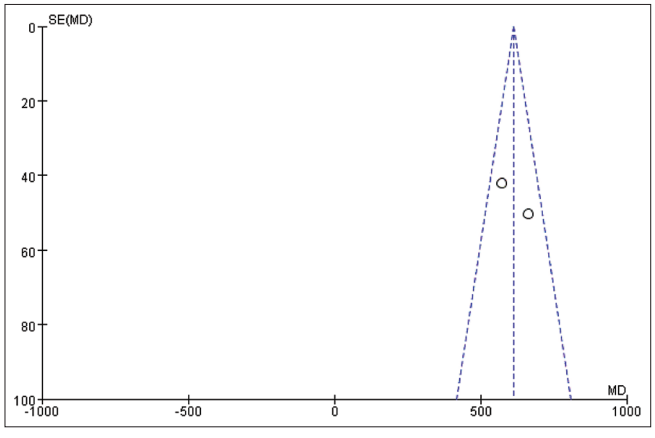

Figure S9: Funnel plot to explore the publication bias in the meta-analysis regarding infused water during insertion

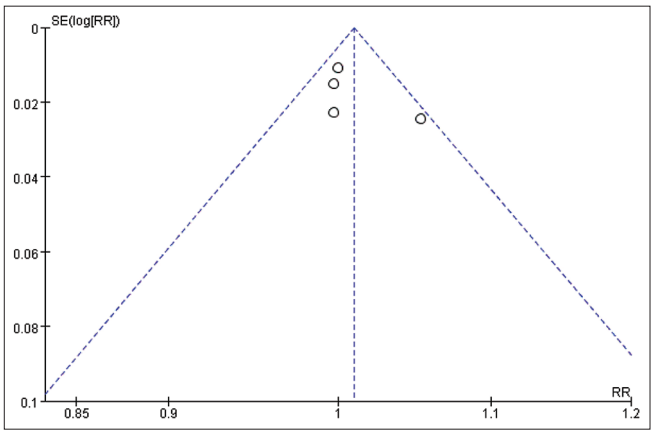

Figure S10: Funnel plot to explore the publication bias in the meta-analysis regarding willingness to repeat the examination

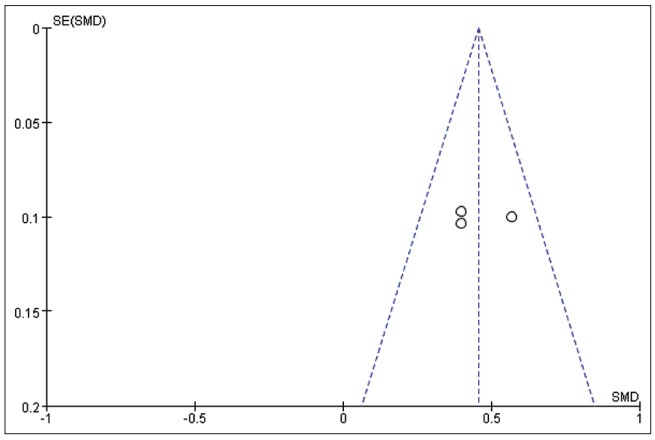

Figure S11: Funnel plot to explore the publication bias in the meta-analysis regarding Boston Bowel Preparation Scale

Summary of findings tables

1 Primary outcomes

Primary outcomes

Patient or population: patients with colonoscopy
Settings: Participants undergoing diagnostic, screening, or surveillance colonoscopy
Intervention: Water exchange colonoscopy
Comparision: Water immersion colonoscopy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Primary outcomes				
Cecal intubation rate	Study population		RR 1.01 (1 to 1.03)	2229 (5 studies)	⊕⊕⊖⊖ low[12]	
	960 per 1000	969 per 1000 (960 to 989)				
	Moderate					
	981 per 1000	991 per 1000 (981 to 1000)				
Right adenoma detection rate	Study population		RR 1.31 (1.07 to 1.61)	1430 (3 studies)	⊕⊕⊕⊖ moderate[1]	
	180 per 1000	236 per 1000 (193 to 290)				
	Moderate					
	175 per 1000	229 per 1000 (187 to 282)				
Adenoma detection rate	Study population		RR 1.18 (1.05 to 1.32)	1430 (3 studies)	⊕⊕⊕⊖ moderate[1]	
	428 per 1000	505 per 1000 (449 to 565)				
	Moderate					
	434 per 1000	512 per 1000 (456 to 573)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Footnotes

[1] Downgraded by 1 because a high risk of bias for 1 or more of the included studies was found for this outcome.

[2] Downgraded by 1 because heterogeneity existed between trials, which may be explained by different experience levels of endoscopists,
premedication, indications for colonoscopy, or age and sex of participants, although other explanations cannot be ruled out.

Figure S12: Summary of findings for the main comparison

Table S1: PRISMA Checklist

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	1-2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	none
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	2
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	2-3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	2
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	2-3
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	3
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	3
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	3
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	3-4
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	3

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	3
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	none
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	4
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	4
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	4-6
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	6
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	4
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	none
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	6-8
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	8
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	8
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	none

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.