

Cap-assisted colonoscopy: a meta-analysis of high-quality randomized controlled trials



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Bibliography

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ABSTRACT

Background and study aims Standard colonoscopy (SC) is the preferred modality for screening for colon cancer; however, it carries a significant polyp/adenoma miss rate. Cap-assisted colonoscopy (CC) has been shown to improve

polyp/adenoma detection rate, decrease cecal intubation time and increase cecal intubation rate when compared to standard colonoscopy (SC). However, data on adenoma detection rate (ADR) are conflicting. The aim of this meta-analysis was to compare the performance of CC with SC for ADR among high-quality randomized controlled trials.

Patients and methods We performed an extensive literature search using MEDLINE, EMBASE, Scopus, Cochrane and Web of Science databases and abstracts published at national meetings. Only comparative studies between CC and SC were included if they reported ADR, adenoma per person (APP), cecal intubation rate, and cecal intubation time. The exclusion criterion for comparing ADR was studies with Jadad score ≤ 2 . The odds ratio (OR) was calculated using Mantel-Haenszel method. I^2 test was used to measure heterogeneity among studies.

Results Analysis of high-quality studies (Jadad score ≥ 3 , total of 7 studies) showed that use of cap improved the ADR with the results being statistically significant (OR 1.18, 95% CI 1.03–1.33) and detection of 0.16 (0.02–0.30) additional APP. The cecal intubation rate in the CC group was 96.3% compared to 94.5% with SC (total of 17 studies). Use of cap improved cecal intubation (OR 1.61, 95% CI 1.33–1.95) when compared to SC (P value < 0.001). Use of cap decreased cecal intubation time by an average of 0.88 minutes (95% CI 0.37–1.39) or 53 seconds.

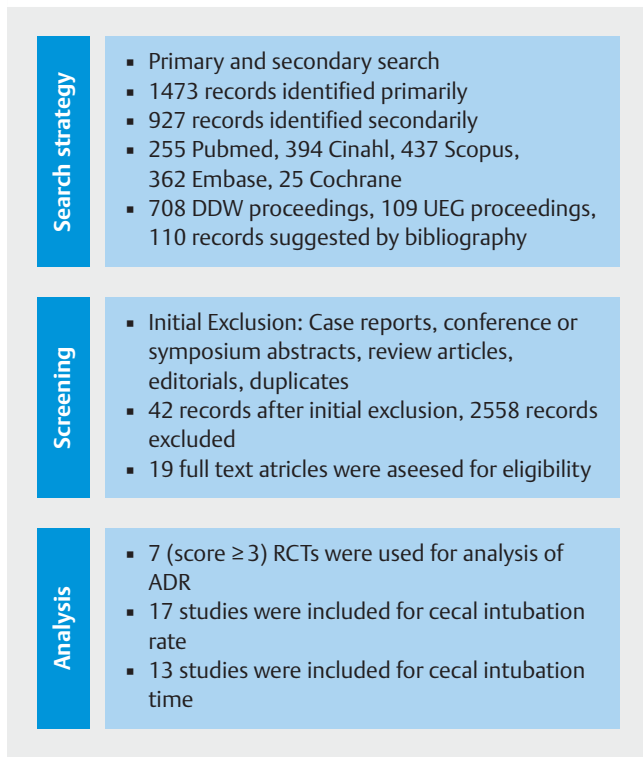
Conclusions Meta-analysis of high-quality studies showed that CC improved the ADR compared to SC.

Introduction

Population-based colorectal cancer (CRC) screening has been shown to reduce incidence of colon cancer and related mortality [1, 2]. Among patients at average risk, the most favored cancer prevention test is colonoscopy every 10 years, beginning at age 50 (45 for African-Americans) [3]. Screening per 1000 patients using colonoscopy, a gain of 270 life-years and a decrease in 24 deaths from CRC has been estimated [4].

However, despite being the reference standard, colonoscopy is far from a perfect test. Studies using compute tomography colonography have estimated the sensitivity of colonoscopy

for detecting advanced adenomas to be 88% [5]. Tandem colonoscopy studies have shown that up to one-quarter of polyps are missed during colonoscopy [6]. Adenoma detection rate (ADR) has been shown to be associated with interval colon cancer and related mortality [7, 8]. ADR $\geq 30\%$ for men and $\geq 20\%$ for women has been recommended as a quality indicator for colonoscopy [9]. Wide variations in ADRs for endoscopists have been reported [10, 11]. Therefore, various methods have been employed in attempts to improve ADR, including brief educational interventions [12], use of distal attachments such as caps [13], third-eye retroscopes, newer-generation wide-angle colonoscopes, cuffs and EndoRings.



► **Fig. 1** Study flow diagram depicting search strategy, screening and studies of cap-assisted colonoscopy identified for inclusion in the meta-analysis of adenoma detection rate.

Cap-assisted colonoscopy (CC) has been extensively studied as a modality to improve ADR. The cap is a straightforward attachment on the distal end of the endoscope that extends outward beyond the tip of the colonoscope to varying lengths. The cap helps in deflecting and flattening the mucosal folds, and by keeping the mucosa away from the lens prevents a red-out. These maneuvers expose the proximal aspects of colonic folds and thereby help in detecting polyps in these otherwise blind mucosal areas. Use of cap has been shown to decrease cecal intubation time, increase cecal intubation rate and improve polyp detection rate. However, data on ADR are rather conflicting. The aim of this meta-analysis was to compare the performance of CC with standard colonoscopy (SC) for ADR among high-quality randomized controlled trials (RCT).

Patients and methods

Search strategy

An electronic search was performed in MEDLINE, EMBASE, Google scholar, Cochrane database and Web of science. The search for studies of relevance was performed using the following key words and corresponding Medical Subject Heading/Entree terms when possible: “CAP assisted colonoscopy,” “colonoscopy with distal attachment,” “adenoma detection rate,” “adenoma per person,” “cecal intubation rate,” “cecal intubation time” with varying combinations with and/or. We retrieved 2558 abstracts (► **Fig. 1**). Abstracts published in major international conferences, including Digestive Disease Week, United Europe-

► **Table 1** Studies and their respective Jadad scores.

Study		Final score
Tada 1997	Paper	0
Matsushita 1998	Paper	1
Kondo 2007	Paper	3 (No ADR/APP reported)
Horiuchi 2008	Paper	3
Shida 2008	Paper	0
Takano 2008	Abstract	0
Lee 2009	Paper	1
Choi 2009	Paper	0
Harada 2009	Paper	1
Sato 2009	Prelim Report	3 (No ADR/APP reported)
Takeuchi 2010	Paper	3
Tee 2010	Paper	3 (No ADR/APP reported)
Dai 2010	Paper	0
Hewett 2010	Paper	3
Park 2012	Paper	3
Rastogi 2012	Paper	3
De Wijkerslooth 2012	Paper	4
Frieling 2013	Paper	3 (No ADR/APP reported)
Pohl 2015	Paper	3

an Gastroenterology Week and Asia Pacific Digestive Week over the past 10 years were manually searched. References from major trials and review articles were manually searched.

From the 2400 records, 2358 records were removed (1473 studies, 927 abstracts) because they were not relevant to the comparison between CC and SC. Of the remaining 42 records, 23 were excluded for the following reasons: duplicity, case report, review article, editorial, abstract only. Of the 19 full-text articles that were accepted, only 7 met the criteria of prospective RCTs, Jadad score ≥ 3 (see ► **Table 1**), reported ADR, and these studies were used for ADR and APP (adenomas detected per person) [14–20]. Of the 42 records, 17 studies were included that compared cecal intubation rate between CC and SC [14–30]. Thirteen studies were included that compared cecal intubation time between CC and SC [14–17, 19, 21–23, 25, 26, 30–32]. For analysis of cecal intubation and cecal intubation time, even studies with Jadad score < 3 were included. ADR alone was the primary aim of the study. We removed the constraints for cecal intubation time or rate as we wanted to be less stringent and more inclusive for these endpoints. While ADR is a cornerstone quality indicator for colonoscopy, the other two are not.

► **Table 2** Study characteristics.

Author	Country	Sample	CC	SC	Age	Male (%)
Tada et al. [32]	Japan	140	70	70	60	73
Matsushita et al. [26]	Japan	24	12	12	59	63
Kondo et al. [24]	Japan	456	221	235	61	60
Horiuchi et al. [16]	Japan	835	424	411	64	65
Shida et al. [28]	Japan	178	82	96	64	51
Takano et al. [29]	Japan	2502	1287	1215	NA	NA
Harada et al. [23]	Japan	592	289	303	63	66
Lee et al. [25]	Hong Kong	1000	499	501	53	46
Sato et al. [27]	Japan	221	110	111	NA	NA
Dai et al. [31]	China	250	121	129	51	54
Hewett et al. [15]	United States	100	52	48	62	57
Takeuchi et al. [20]	Japan	274	141	133	64	70
Tee et al. [30]	Australia	400	200	200	54	48
De Wijkerslooth et al. [14]	Netherlands	1339	656	683	60	51
Choi et al. [21]	Korea	228	114	114	NA	NA
Rastogi et al. [19]	United States	420	210	210	61	95
Park et al. [17]	Korea	600	300	300	62	52
Frieling et al. [22]	Germany	504	252	252	60 ± 15.5	182
Pohl et al. [18]	United States	1113	562	551	62	64

Data extraction

Two investigators (VN and MD) independently reviewed the studies and imported the data into a standardized form. In case of lack of consensus, the senior investigator (AR) reviewed the study independently and then made a final decision regarding the data point.

Data extracted were patient demographics, year of publication, study location, number of subjects, size of adenomas, number of adenomas detected, cecal intubation rate, cecal intubation time and study quality. Individual study and patient characteristics are shown in ► **Table 2**.

Statistical analysis

Meta-analyses were performed using Mantel-Haenszel method combining the results from different trials comparing CC and SC. Meta-Analysis was performed according to the PRISMA statement. A complete checklist is provided in ► **Table 3** [33]. A random effects model was used for statistical heterogeneity across trials and a fixed effect model was used if no significant heterogeneity was present. Relative risks (RR) with corresponding 95% CI were calculated. Heterogeneity was calculated using I^2 test. Publication bias was assessed using a funnel plot. Statistical analyses were performed using RevMan software (Review Manager version 5.3; The Nordic Cochrane Centre, Copenhagen, Denmark, The Cochrane Collaboration 2015).

Results

Adenoma detection rate

An initial pooled analysis of eight RCTs (5681 patients) was performed, which showed a numerically higher ADR in the CC group compared to the SC group, but results were not statistically significant (OR 1.08, 95% CI 0.97–1.21; I^2 56%) (► **Fig. 2a**). However, when only high-quality RCTs were included (Jadad score ≥ 3) as per the primary aim of this study, there were seven RCTs with a total of 4,681 patients (2,344 patients in the CC group, 2,337 patients in the SC group). We were unable to include some studies with a score of 3 or more, as they lacked information regarding ADR/APP [22, 24,30]. ADR was significantly higher in the CC group (OR 1.18, 95% CI 1.03–1.33) (► **Fig. 2b**). There was no significant heterogeneity in the ADR analysis ($I^2=0\%$). Publication bias for studies included for ADR was assessed using a funnel plot (► **Fig. 3**).

Analysis was also performed using a random effects model. Analysis of the seven high-quality RCTs using the random effects model showed significantly higher ADR in the CC group (OR 1.104, 95% CI 1.02–1.18) (► **Fig. 2c**).

Sensitivity analysis was not performed based on our stringent criteria to include only high-quality studies with Jadad score ≥ 3 which carry a very low risk for bias [34–36].

► **Table 3** PRISMA checklist.

TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Mentioned as meta-analysis
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:	A detailed abstract with the necessary information has been provided
INTRODUCTION			
Rationale/	3	Describe the rationale for the review in the context of what is already known.	Provided
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Provided
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.	Not applicable with Meta-analysis
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.	Provided
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.	Provided
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Provided
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).	Provided
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.	Provided
Data items	11	List and define all variables for which data were sought (e. g., PICOS, funding sources) and any assumptions and simplifications made.	Provided
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.	Provided
Summary measures	13	State the principal summary measures (e. g., risk ratio, difference in means).	Provided
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.	Provided
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).	Provided
Additional analyses	16	Describe methods of additional analyses (e. g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Provided
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.	Provided
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.	Provided
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).	Provided
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	Provided

Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Provided
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Provided
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Provided
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., health care providers, users, and policy makers).	Provided
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).	Provided
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Provided
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	Provided

Mean adenomas detected per person

Analysis for APP included six RCTs with 4,368 patients. There were 2184 patients in each group. Use of cap led to a mean difference of 0.16 (95% CI 0.02–0.30) additional APP (► Fig. 4). Significant heterogeneity was found in the studies reporting mean APP ($I^2=68\%$).

Large adenoma detection rate

Analysis for large adenomas (≥ 10 mm) included four RCTs with 2468 patients. There were 1247 patients in the CC group compared to 1221 patients in the SC group. Use of cap led to a statistically significantly higher rate of detection of large adenomas (OR 1.49, 95% CI 1.03–2.15, $P<0.005$) with heterogeneity of ($I^2=44\%$) (► Fig. 5).

Sessile serrated adenoma detection rate

Analysis for sessile serrated adenoma (SSA) included only three RCTs with 2872 patients. There were 1427 patients in the CC group compared to 1445 patients in the SC group. Use of cap did not lead to any significant difference in detection of SSA with (OR 1.12, 95% CI 0.66–1.88) and a significant heterogeneity of ($I^2=76\%$) (► Fig. 6).

Cecal intubation rate and time

Pooled analysis of 17 studies that included 5416 patients in the CC and 5401 patients in the SC groups were utilized to evaluate the cecal intubation rate (► Fig. 7a). The cecal intubation rate in the CC group was 96.3% compared to 94.5% with SC. Use of cap improved cecal intubation (OR 1.61, 95% CI 1.33–1.95) when compared to SC ($P<0.001$). Low heterogeneity was identified among studies ($I^2=2\%$).

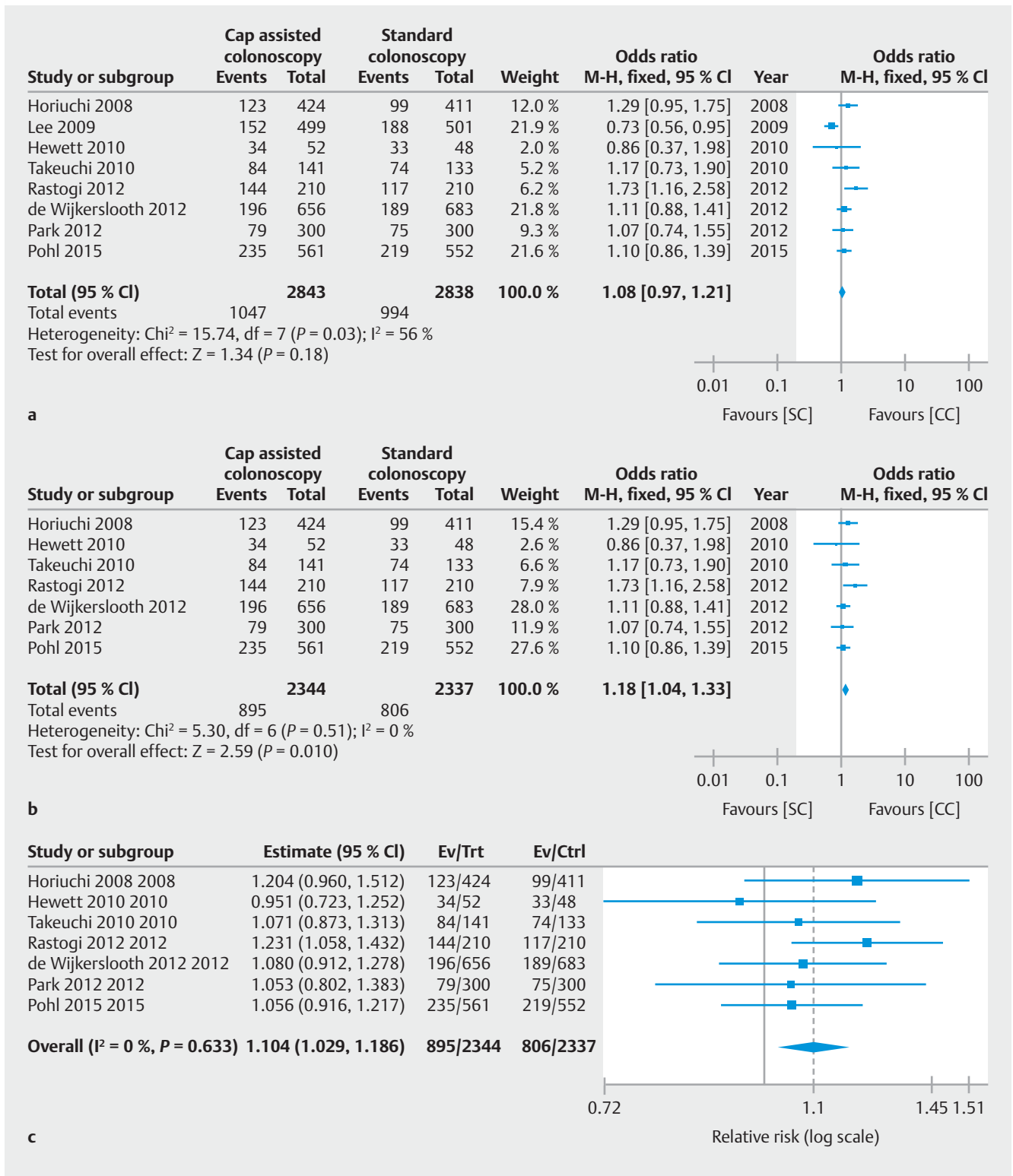
Thirteen studies were used to analyze the impact of cap on cecal intubation time (► Fig. 7b). The CC group included 3014 patients and the SC group included 3037 patients. Use of cap decreased the cecal intubation time by an average of 0.88 min-

utes (95% CI 0.37–1.39) or 53 seconds. However, significant heterogeneity was detected among these studies ($I^2=87\%$).

Discussion

Results of our meta-analysis indicate that use of cap improves detection of adenomas. An improvement in ADR, mean number of adenomas detected per patient and large adenomas was seen with CC. For ADR we included only trials with a Jadad score ≥ 3 to ensure only high-quality trials. The Jadad score is the most widely used scale to measure the quality of RCTs. Overall, we found seven RCTs with a Jadad score ≥ 3 . This study differs from a previous meta-analysis [13] in that we excluded the study by Lee [25] as it employed suboptimal techniques for randomization. Proper technique includes a statistician and computer-generated randomization, whereas in the study by Lee et al, only sealed envelopes were used without mention of statistician or a computer-generated sequence [25]. Furthermore, in that study, the quality of bowel preparation was significantly less satisfactory. They classified the quality of their bowel preparation into three categories: “excellent,” “fair,” and “poor.” In the results, they noted that a higher proportion of patients in the CC group had less satisfactory bowel preparation (excellent/fair/poor bowel preparation in CC group were 52.7:33.5:13.8% vs. SC group's 62.3:28.1:9.6%, respectively, $P=0.006$). They also reported an ADR that was lower with use of CAP. The inferior bowel preparation in the CC group could have negatively impacted the ADR. As a matter of fact, this is the only trial where use of CAP has been associated with lower ADR compared to standard colonoscopy. All other trials have shown either no difference or higher ADR with CAP.

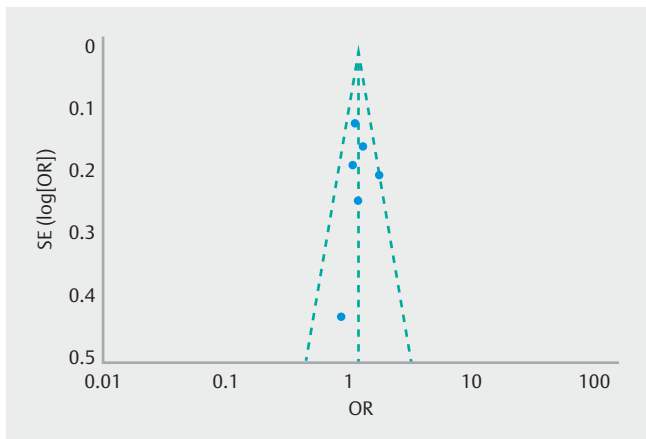
ADR is a quality indicator for colonoscopy and has been shown to be associated with improved outcomes related to interval cancer and colorectal cancer-related mortality. While this meta-analysis shows an overall improvement in ADR with CC, individual studies have shown variable results. The study



► **Fig. 2** Forest plot of pooled estimates of adenoma detection rate using cap-assisted colonoscopy compared to standard colonoscopy. **a** Results with all eligible studies. **b** Results with only high-quality studies (Jadad score ≥ 3). **c** Results with only high-quality studies using random effects.

by Pohl et al. [18] which was the largest study evaluating CC in the United States showed that the impact on the individual endoscopist ADR is variable. The range of impact was from

20% improvement to 15% decrease in the individual ADR with CC. They also showed that those who preferred

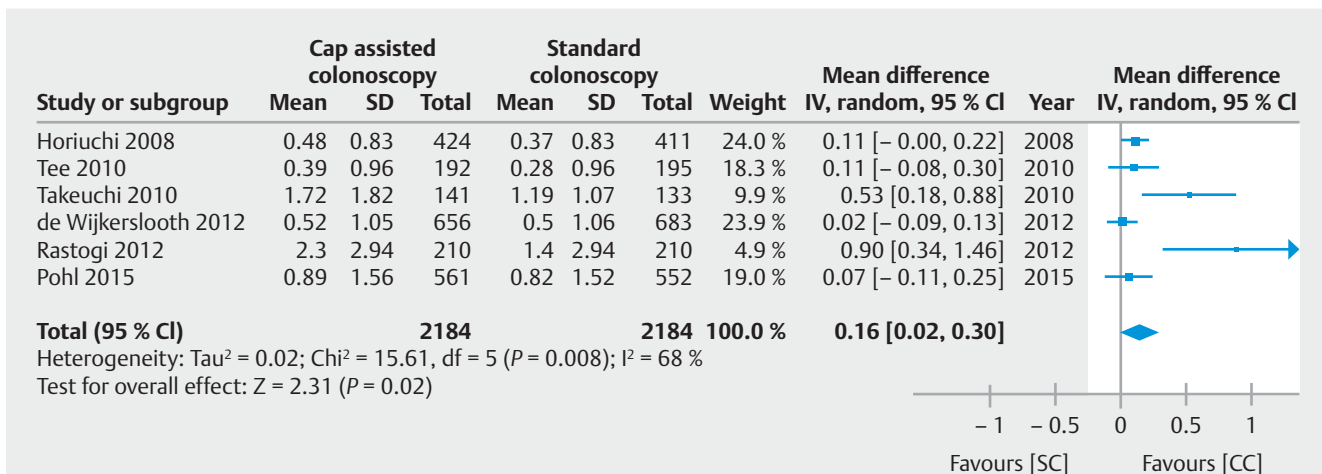


► Fig. 3 Funnel plot showing publication bias.

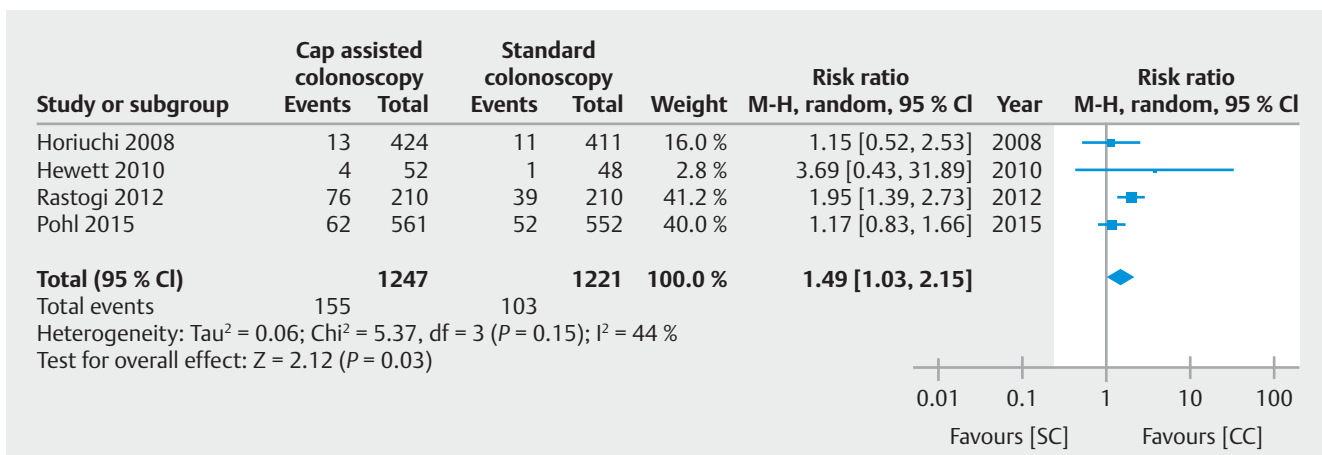
CAP showed an improvement in ADR. We have also shown an improvement in the average number of adenomas detected per patient.

CC also improved detection of large adenomas, however, a statistically significant improvement in mean number of diminutive adenomas was not found. We suspect this may be due, in part, to the differing sizes of small adenomas reported (5 mm vs. 6 mm). There was no significant improvement in detection of proximal adenomas or SSAs as the RCTs that were performed were not adequately powered to detect any difference in the above outcomes.

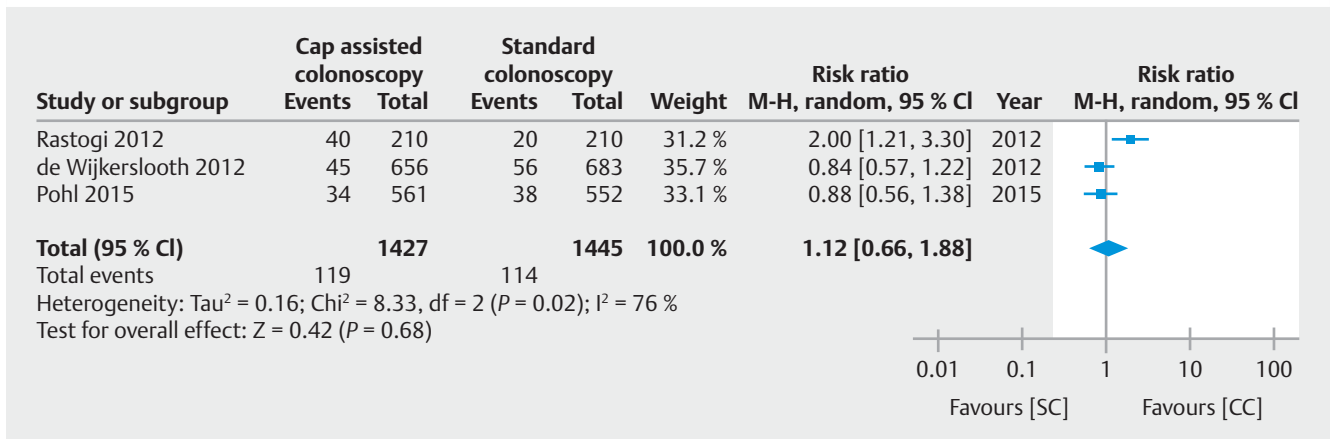
Our meta-analysis has some limitations. The study populations in the studies were very diverse with studies being performed in Asia, North America, and Europe. That, however, improves generalizability of the results. Given the obvious lack of blinding of the endoscopists and the nature of such studies evaluating devices to improve ADR, investigator bias is unavoidable. Endoscopist experience in the different studies also varies widely and could not be accounted for with respect to



► Fig. 4 Forest plot of pooled estimate of adenoma per person (APP) showing higher detection of average adenoma per person using cap compared to standard colonoscopy.



► Fig. 5 Figure plot of pooled estimate of adenomas > 10 mm, showing significant improved detection with CAP assisted colonoscopy compared to standard colonoscopy



► **Fig. 6** Figure plot of pooled estimate of sessile serrated adenoma (SSA) showing no significant improvement in the detection of proximal adenomas.

the impact of CC on ADR. Use of a cap with colonoscopy requires some training, adjustment, and experience. This factor was not adjusted for or studied in the trials, making it difficult to gauge the impact of that on the results.

A cap is a simple, inexpensive and easy-to-use tool to improve the quality of colonoscopy. The cost of the cap, albeit low, appears to be the only negative factor weighing against its use in daily clinical practice. To derive maximum benefit from cap, endoscopists need to gain experience with the device. As the cap projects outside the tip of the colonoscope, it may appear to limit the angle of view. This must be compensated for with adequate deflection of the tip and use of the edge of the cap to flatten the haustral folds to expose their proximal aspects and derive the maximum benefit. Furthermore, the benefit of CC has been shown to significantly extend visualization of the right colon in a colonoscopic training model [37]. Use of cap offers other secondary benefits such as improved cecal intubation rates and stabilization of the tip of the scope during polypectomy.

Conclusion

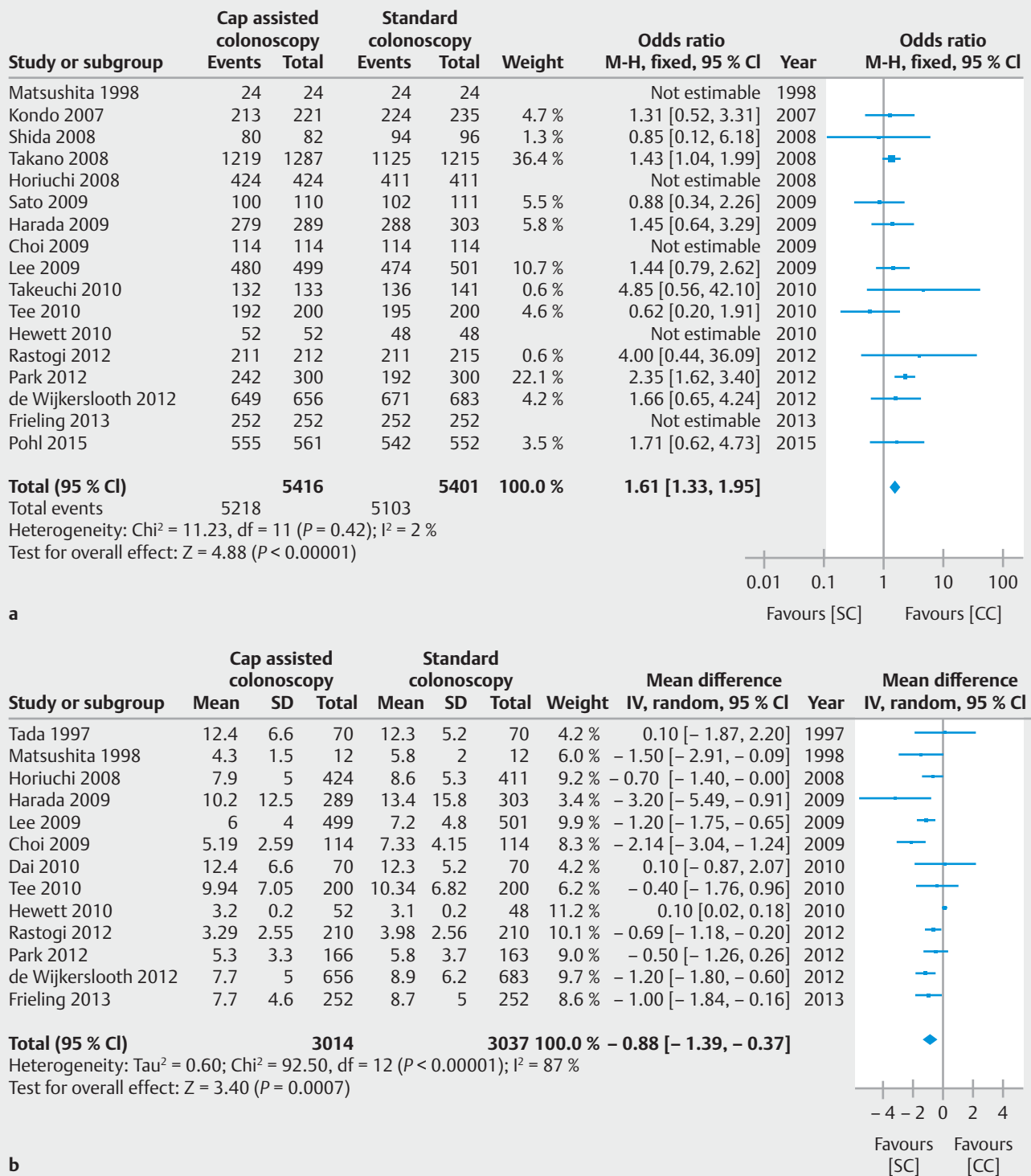
In conclusion, this meta-analysis showed that there is a marginal and statistically significant benefit to use of a cap during colonoscopy to improve ADR and cecal intubation rate and reduce cecal intubation time. Further research needs to be conducted to determine if there are specific patient subgroups that may benefit more from use of a cap, whether to train endoscopists in use of the device, and identify appropriate training methods.

Competing interest

None

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► **Fig. 7** Forest plot of pooled estimates of cecal intubation rate (a) and cecal intubation time (b) showing improved rates and lesser time with cap compared to standard colonoscopy

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