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Effect of chewing gum in bowel preparation for patients undergoing small bowel and colon capsule endoscopy: Systematic review with meta-analysis

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ABSTRACT

Background and study aims Quality of bowel preparation and successful transit are critical factors for complete small bowel capsule endoscopy (SBCE) and colon capsule endoscopy (CCE). The aim of this systematic review with meta-analysis was to assess the impact of chewing gum as part of the bowel preparation regimen on the completion rate in both SBCE and CCE.

Methods A systematic literature search was conducted in PubMed, Cochrane, Web of Science and Embase. Data were extracted upon quality assessment of included studies. Two reviewers conducted the screening process according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis. Eighty-four studies met the search criteria and four randomized controlled trials were included in the meta-analysis, these were assessed for bias using Minors. Pooled completion rate of SBCE studies was defined as the primary outcome.

Results Three randomized controlled trials were SBCE studies and one was a CCE study. The pooled completion rate (91%) was not significantly higher in SBCE patients who were given chewing gum after capsule ingestion compared to those who were not (85%). Variance information was not reported in all studies, and therefore, pooled transit time estimates could not be calculated.

Conclusions Chewing gum has a good safety profile but has only been used as a booster in one CCE study and a few SBCE studies. More prospective randomized controlled trials, therefore, are needed to investigate the efficacy of chewing gum for achieving complete capsule examination.

Introduction

Colon capsule endoscopy (CCE) was introduced in 2006 as a new modality for imaging the colonic mucosa [1]. It is sedation-free and may be able to reduce colonoscopy needs and minimize interaction with health care personnel [2]. For a long time, completion rates and the bowel preparation regimen for CCE have not been comparable to that for colonoscopy [3]. However, evidence is accumulating to suggest increased diagnostic accuracy and convenience for CCE as compared with optical colonoscopy [3,4]. This underscores the need for more

studies exploring how to improve completion rates for CCE to meet established standards for colonoscopy.

Small bowel capsule endoscopy (SBCE) was introduced 6 years earlier than CCE as a new imaging technique for observing the small bowel mucosa and today it is a well-established and accepted procedure in clinical practice [5, 6]. Prior studies have shown that accelerating SBCE transit time may increase the likelihood of a complete investigation [7]. However, the most optimal bowel preparation regimen for SBCE is yet to be determined [6].

The completion rate for capsule endoscopy is a limitation of both SBCE and CCE [3, 7]. Over the past decade, there has been significant improvement in bowel preparation regimens for both CCE and SBCE [5, 8]. As of now, the bowel preparation regimen for CCE is already more extensive than that for colonoscopy, and therefore, additional preparations should be introduced with caution. Some studies have investigated the ability to accelerate transit time by use of sham feeding to stimulate motor and sensory activity [9, 10]. Using chewing gum as a substitute for sham feeding has shown good results in accelerating motility throughout the gastrointestinal tract [9, 11, 12, 13].

This systematic review with meta-analysis aimed to assess the efficacy of chewing gum as a booster in bowel preparation regimens for patients undergoing either SBCE or CCE. The effectiveness was examined by comparing gastric transit time (GTT), small bowel transit time (SBTT), colon transit time (CTT), bowel cleanliness rate, and pooled estimates of complete investigations.

Methods

This systematic review was prepared according to PRISMA guidelines and registered in PROPSPERO (PROSPERO ID: CRD42022385214) without any further additions to the protocol after submission [14].

Literature search

A systematic literature search was performed in four electronic databases: PubMed, Embase, Cochrane, and Web of Science. The search string was initially developed for all four databases in three predefined search areas: investigation, comparator and outcome. The words for investigation were identifying studies on SBCE and/or CCE. Comparator words were used to identify but also limit the number of search hits in search of studies with a bowel preparation regimen involving chewing gum. Words for outcome were to further limit the number of search hits to studies with reported completion rates, effect on transit time and/or diagnostic yield. Both within and across the three search areas, search strings with relevant search terms were created and combined using Boolean expressions. The Boolean expression “OR” was used within search areas, and Boolean expression “AND” was used across search areas.

In addition, indexed search terms from the database thesauruses and free text search terms with truncation were included in the search strategy. The search strategy was then revised and edited by adding applicable MeSH terms, in collaboration with a research librarian from the University of Southern Denmark. This allowed the search strategy to be as comprehensive as possible to search multiple terms. The last search was performed on November 8, 2023. The search strategy is shown in Appendix A as **Table S1**, along with search strings in **Table S2**.

Reference screening

Endnote version X9 was used to process papers [15]. Two reviewers completed the entire screening process and data extraction to reduce risk of bias and validate eah other’s results (S.S.J. and U.D.) [16]. After excluding duplicates, titles and abstracts of all remaining citations were independently assessed for inclusion by the same two authors. If a discrepancy occurred and agreement could not be reached, the reference was evaluated by a third reviewer (T.B-M.). The third reviewer would decide whether the reference was eligible for inclusion. Following abstract and title screening, the same two authors independently assessed the relevant full-text manuscripts. No third opinions were necessary. Finally, one reviewer (S.S.J.) examined the references of each included study to identify any additional references of possible relevance that met the inclusion criteria. However, further studies were not retrieved.

Eligibility criteria

We included studies of patients who underwent SBCE or CCE for any indication. The bowel preparation regimen had to involve chewing gum and be compared with a standard bowel preparation regimen without chewing gum. Included studies had to be randomized controlled trials (RCTs), cross-sectional studies, or cohort studies. Studies not reporting the completion rate between groups were excluded. Eligible studies for inclusion had to be published in English, Danish, German, French, or Spanish; however, no non-English studies were retrieved. Case reports, conference abstracts, and reviews were excluded.

Data handling

Two authors (S.S.J and U.D.) performed data extraction from the included studies separately and discussed any discrepancies until a consensus was reached. ▶ **Table 1** shows an overview of the data extracted. Simultaneously, both authors assessed the quality of the included studies using the MINORS index [17].

Completion rate was defined as the proportion of investigations with complete transit. Complete transit was defined as visualization of the cecum for small bowel endoscopy and as visualization of the hemorrhoidal plexus or excretion within battery lifetime, along with acceptable bowel preparation for CCE. Completion rates were calculated as the number of complete examinations from the total number of procedures in the included studies. Additional descriptive data were retrieved; however, they were only used for descriptive reasons and not for subgroup analysis as initially intended due to the limited number of references.

▶ **Table 1** Data extracted for descriptive purposes and statistical analyses.

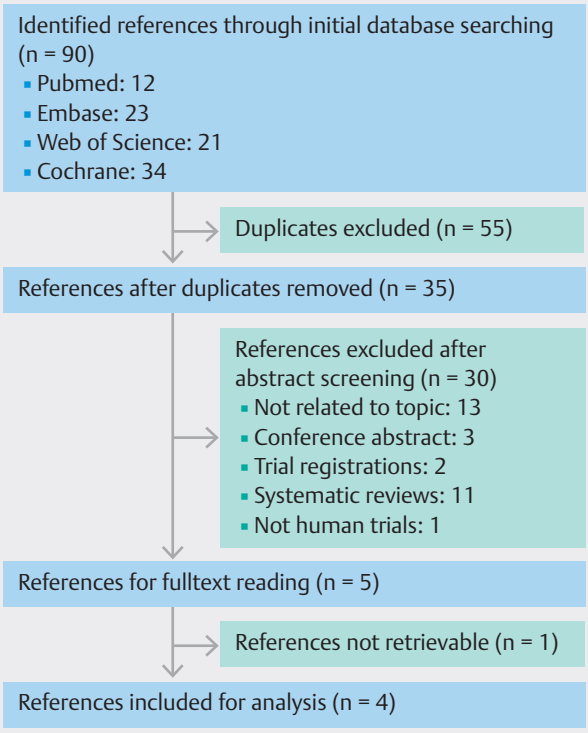
Number	Description
I	Number of individuals included in the study
II	Number of individuals with complete small bowel or colon capsule endoscopy
III	Descriptive data: first author, publication year, data origin (country), year of data collection, study type, single- or multicenter study, indications for either small bowel or colon capsule endoscopy, type of capsule, reported bowel/procedure preparation medicine (incl. boosters and contrast agents), type of bowel cleansing rate scale, transit time; total, gastric, small bowel and colon, participant characteristics, sex, and age distribution

Statistical analysis

All extracted data (▶ **Table 1**) were collected in Excel spreadsheets, whereafter they were imported to Stata 17 for further statistical analyses. The proportions of complete SBCE and CCE, including their 95% confidence intervals (CIs), were calculated for each study included in the analyses. These estimates were then pooled using Freeman-Tukey double arcsine transformation in random effects models using the Metaprop command [18]. Furthermore, as a sensitivity analysis, we repeated the calculation of these pooled estimates using fixed effects models. To evaluate the reliability of the results, the degree of heterogeneity was estimated by I^2 statistics for each pooled estimate. Furthermore, Egger's test was used to investigate potential small study effects and publication bias in each subgroup illustrated by funnel plots [19]. Stata 17 was used to conduct the analyses [18, 20].

Results

The final literature search resulted in 90 articles. Of those, 55 duplicates were removed and 30 articles were excluded after preliminary title and abstract screening. This left five articles for full-text screening. One of these references was not retrievable from any of the searched databases. Four studies were included after a full-text review, as shown in ▶ **Fig. 1** [21, 22, 23, 24]. No further articles were identified from the reference list screening of the included studies for full-text reading.



▶ **Fig. 1** Flow chart of literature search and study inclusion.

Characteristics of all four studies are presented in ▶ **Table 2**. Three studies investigated SBCE [21, 22, 23] and one evaluated CCE [24]. In the included studies, a total of 267 individuals received a bowel preparation regimen with chewing gum and 270 individuals received a bowel preparation regimen without chewing gum. The proportion of male individuals ranged from 44% to 66% and the median age ranged from 47 to 58 years be-

▶ **Table 2** Overview of study characteristics.

Publication, year	Country	Study type	Endoscopy type	Adverse events in chewing gum group	No. of cases/controls	MINORS score*
Apostolopoulos, 2008 [21]	Greece	Prospective, single-center	SBCE, PillCamSB1 (Given Imaging, Yoqneam, Israel)	0	47/46	22/24
Ou, 2014 [22]	Canada	Prospective, single-center	SBCE, PillCamSB2 (Given Imaging, Yoqneam, Israel)	0	60/62	24/24
Huang, 2021 [23]	China	Prospective, single-center	SBCE, PillCamSB2 (Medtronic, Minnesota, America)	Capsule retention (n = 3)	103/102	24/24
Buijs, 2018 [24]	Denmark	Prospective, single-center	CCE, PillCam2, (Given Imaging, Israel)	0	57/60	22/24

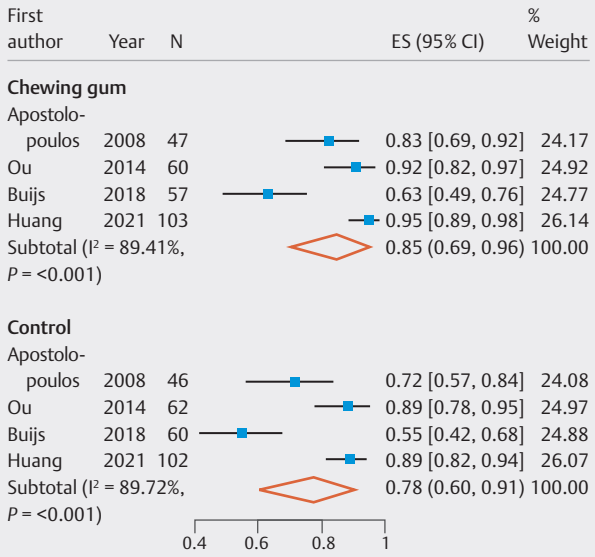
*Score from 0–24 for comparative studies.

▶ **Table 3** Bowel preparation regimens and administration of chewing gum in the included studies.

Publication	Bowel preparation regimen	Administration of chewing gum	Bowel preparation evaluation
Apostolopoulos, 2008 [21]	Day -5: Interrupt use of medication that could limit mucosal visualization Day -1: All day – clear liquids Evening – 45 mL of sodium phosphate (Fleet Phospho-Soda, Botania, Greece) with water Exam day: Fasting overnight, at least 8 hours prior to capsule endoscopy examination	1 piece of sugarless gum to be chewed for 30 minutes every 2 hours (maximum of four pieces total)	Bowel preparation evaluation scale proposed by the 2005 International Conference on Capsule Endoscopy
Ou, 2014 [22]	Day -5: Interrupt use of oral iron supplementation Day -1: Breakfast – soft diet Lunch -> rest of day – clear fluid diet 3.00 PM – 2 L polyethylene glycole electrolyte solution (PEG3350e) Exam day: Take nothing per mouth 2 hours before the scheduled appointment	1 piece of sugarless gum to be chewed for 20 minutes every 2 hours (maximum of four pieces total)	Not reported
Huang, 2021 [23]	Day -1: For dinner – clear liquids Exam day: Fasting overnight (at least 8 hours prior to undergoing SBCE) 4.00–5.00 – two sachets of polyethylene glycol electrolyte powder (59 g polyethylene glycol 4,000, 5.68 g sodium sulfate, 1.68 g sodium bicarbonate, 1.46 g sodium chloride, and 0.74 g potassium chloride per sachets) dissolved in 2 L of water (within 2 hours)	1 piece of sugarless gum to be chewed for 15 minutes every 30 minutes in the first hour (maximum of two pieces total)	Poor bowel preparation if < 75% of the mucosa was visualized
Buijs, 2018 [24]	Day -2: All day – 2 L water in addition to normal intake 2 times daily 1000 mg magnesium oxide (oral) Day -1: All day – clear liquids only Until 16.00 – white pasta with oil, only 17.00–19.00 – 1 L Moviprep followed by 1.5 L water Exam day: 6.00–7.30 – 1 L Moviprep followed by at least 1.5 L water 7.30–9.30 – No food/liquid ingestion ±10.00 – Ingestion of CCE with 20 mg domperidone (oral) After alarm – 0.75 L Moviprep followed by at least 0.6 L water + 3 hours – 0.25 L Moviprep followed by 0.2 L water + 2 hours – Bisacodyl enema	2 pieces of sugarless gum to be chewed for 30 minutes when capsule left stomach	Leighton-Rex scale

tween studies. All four studies were prospective, single-center RCTs conducted between 2008 and 2021 in Greece, Canada, China, and Denmark. In one study, SBCE was performed with the small bowel first-generation PillCam (Given Imaging Inc., USA) [21], in two studies, SBCE was performed with the small bowel second-generation PillCam (Given Imaging Inc., USA and Medtronic, USA) [22, 23], and in one study, CCE was performed with the second-generation colon PillCam2 (Given Imaging Inc., USA) [24]. In all studies, all individuals received dietary instructions before and during the capsule endoscopy procedure. Bowel preparation regimens are listed in ▶ **Table 3**. Only one study reported adverse events among the chewing gum group, with three cases of capsule retention in the chewing gum group and six capsule retentions in the control group [23].

Three studies used polyethylene glycol (PEG) solutions for bowel preparation [22, 23, 24] and one study used sodium phosphate [21]. The CCE study was the only study in which a



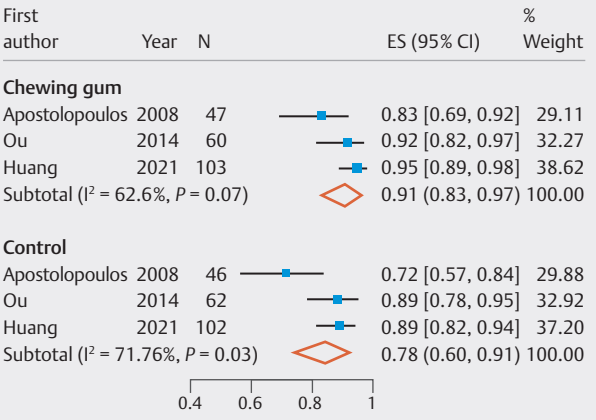
▶ **Fig. 2** Forest plot of estimated completion rates of capsule endoscopy with and without chewing gum in bowel preparation regimen. ES, estimated completion rate.

split-dose regimen was used and a booster solution was combined with prokinetics after capsule ingestion [24]. The booster was a PEG solution along with bisacodyl as the prokinetic agent. Among the studies, chewing gum dosage varied from two to a maximum of four pieces to be chewed after capsule ingestion at varying intervals. An overview of chewing gum administration is shown in ▶ **Table 3**.

Completion rate

The pooled estimated completion rate for capsule endoscopy with the chewing gum regimen was not significantly higher at 85% (95% CI 69%–96%) compared with 78% (95% CI 60%–91%) for the non-chewing gum regimen as shown in ▶ **Fig. 2**. Test of heterogeneity resulted in 89.41% (P <0.001) in the chewing gum groups and 89.72% (P <0.001) in the control groups. Sensitivity analyses using fixed effects models resulted in similar pooled estimates of 87% (95% CI 83%–91%) compared with 80% (95% CI 75%–85%) in the chewing gum and control groups, respectively.

Because of high heterogeneity, a sensitivity analysis excluding the CCE study was conducted to explore the potential impact on results. ▶ **Fig. 3** shows that heterogeneity was reduced in both the chewing gum group (62.60%, P = 0.07) and the control group (71.76%, P = 0.03). The pooled estimated completion rate for the chewing gum regimen (91%, 95% CI 83%–97%) was not significantly different from that for the standard regimen (85%, 95% CI 74%–93%) when limiting the analysis to SBCE studies. Sensitivity analyses using fixed effects models resulted in similar pooled estimates of 92% (95% CI 88%–95%) compared with 86% (95% CI 81%–90%) in the chewing gum group and control group respectively.



▶ **Fig. 3** Forest plot of estimated completion rates of small bowel capsule endoscopy with and without chewing gum in bowel preparation regimen. ES, estimated completion rate.

Bowel preparation

Only two studies reported an adequate bowel cleanliness rate; therefore, no pooled estimate was calculated [23,24]. One study reported an adequate bowel preparation rate of 100% in both the chewing gum and control groups; however, it was not stated how bowel cleanliness was evaluated [23]. Another study reported a 48% cleanliness rate in the chewing gum group and 52% in the control group based on the Leighton-Rex scale [24].

Transit time

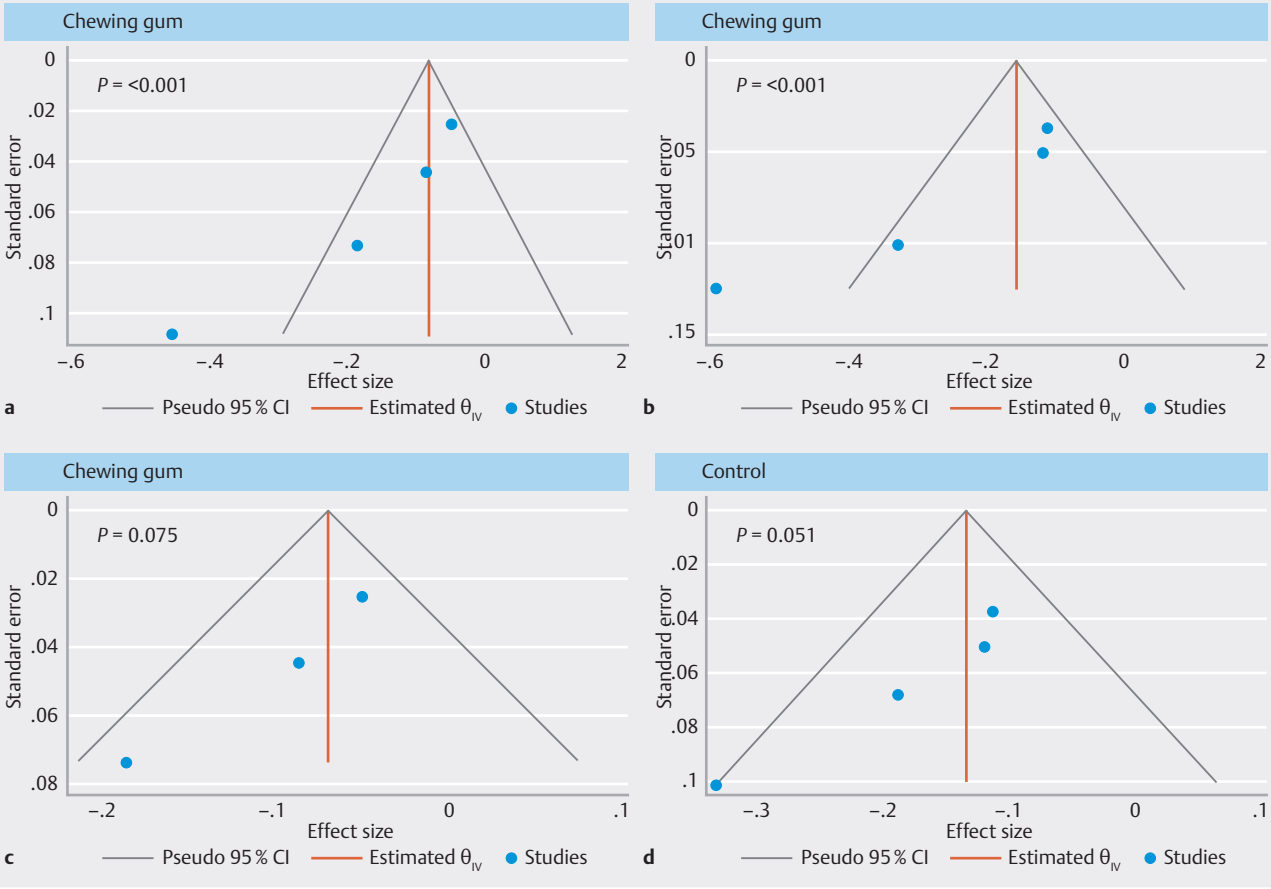
Pooled GTT, SBTT, and CTT estimates were not calculated because only one study reported variance information [21]. Median GTT ranged from 18.38 to 29.0 minutes and median SBTT ranged from 229.43 to 318.5 minutes in the chewing gum regimen groups. One study found a mean GTT of 40.81 SD ± 30.28 in the intervention group, and 56.41 SD ±42.77, as shown in ▶ **Table 4,** [21,22,23]. In the control groups, the median GTT ranged from 19.43 to 42.5 minutes, and the median SBTT ranged from 232.52 to 287.0 minutes with standard bowel preparation regimens. Lastly, a study found a mean SBTT of 229.05 SD ±75.99 in the intervention group and 266.69 SD ±69.88 in the control group, as shown in ▶ **Table 4** [21,22,23]. Only one study reported a significant impact for chewing gum in reducing both GTT and SBTT [21]. In addition, another study established a considerable GTT reduction but not for SBTT [23]. A third study found no significant influence on either GTT or SBTT [22]. The study on CCE did not find any difference between the intervention group and the control group regarding CTT and total transit time [24].

Publication bias and small study effects

Funnel plots are presented in ▶ **Fig. 4**. The Egger's tests were significant for both pooled estimates of completion rate in capsule endoscopy in the chewing gum group (P <0.001) and control group (P <0.001), (▶ **Fig. 4**, plots A and B). However, when the CCE study was removed and the analysis repeated, Egger's

▶ **Table 4** Overview of transit times in included small bowel capsule endoscopy studies.

Study	GTT		SBTT	
	Gum	Control	Gum	Control
Apostolopoulos, 2008 [21] mean ± SD	40.81±30.28	56.41±42.77	229.05±75.99	266.69±68.88
Ou, 2014 [22] median	18.38	19.43	229.43	232.52
Huang, 2021 [23] median	29.0	42.5	318.5	287



▶ **Fig. 4** Funnel plots visualizing the symmetry of the effect sizes for completion rate in small bowel and colon capsule endoscopy with and without chewing gum in the bowel preparation regimen. *P* values from Egger's tests provided for each plot. Plot A + B includes both small bowel capsule endoscopy and colon capsule endoscopy. Plot C + D includes only small bowel capsule endoscopy.

tests were no longer significant for either chewing gum groups ($P = 0.075$) or control groups ($P = 0.051$) (▶ **Fig. 4**, plots C and D).

Discussion

This review evaluated the effect of adding chewing gum to the bowel preparation regimen for capsule endoscopy. The primary finding was a non-significant improvement in the completion rate of 91% in SBCE patients who chewed gum during the procedure compared with a completion rate of 85% in control groups as shown in ▶ **Fig. 3**. When including the CCE study by Buijs et al. [24], the conclusion did not change. However, the completion rate for both intervention groups and control groups decreased. Including the CCE study by Buijs et al. [24] also introduced substantial heterogeneity, as shown in ▶ **Fig. 2**. The CCE study is the only study to date to explore the influence of chewing gum as a booster for CCE completion rate.

The included studies also evaluated transit times in capsule endoscopy within control and intervention groups. However, pooled analysis was not performed due to unavailable variance information. Even without the pooled analysis, we did see a tendency for chewing gum to positively affect transit times in the small bowel studies. GTT was significantly decreased by chewing gum, as shown in Apostolopoulos et al [21].

This is the only systematic review exploring chewing gum influence on completion rate and the only review in the current literature to compare transit times for both SBCE and CCE. Therefore, no other reviews were available for results comparison. However, a letter to the editor from 2013 describing 415 SBCE patients, of whom 207 had chewing gum administered as part of the bowel preparation regimen, described an equivalent pooled analysis of chewing gum impact on completion rate and transit time [25]. This meta-analysis comprised three studies, of which two are also included in this review [21,22]. The third study was non-retrievable for this review, as noted in ▶**Fig. 1** and the results paragraph. As our meta-analysis supports, those authors did not find an increased completion rate by adding chewing gum as a booster, but they did conclude an overall significant decrease in SBTT. However, the result was reported as non-applicable in clinical practice due to a lack of solid evidence. If the number of SBCE studies in this review had been larger and variance information had been provided for each study, transit times could have been pooled and compared to advance evidence. The three studies about SBCE all indicated that chewing gum had an accelerating effect on transit times. It is possible that in the future, chewing gum should be used for patients with low motility to speed up transit times. As previously mentioned, accelerating transit times in SBCE is associated with higher completion, underscoring the advantages of further exploration of the effect of chewing gum in that regard [7].

In the four studies included, administration of chewing gum varied. Apostolopoulos et al. and Ou et al. administered sugarless gum for as long as 8 hours, whereas Huang et al. and Buijs et al. administered sugarless chewing gum for as long as 4 hours [21,22,23,24]. The chewing gum administered for 8 hours could stimulate motor and sensory activity in both the stomach and small intestine; however, the chewing gum administered in Huang et al. and Buijs et al. stimulated only motor and sensory activity in the stomach. This might have influenced completion rates in the studies. However, the results do not indicate that administration of chewing gum for only 4 hours by Huang et al. produced a lower completion rate than was achieved in the two other SBCE studies [23].

With both SBCE and CCE, the bowel preparation regimen is essential to obtain a complete investigation. However, bowel preparation for CCE is more extensive than for colonoscopy because it is impossible to intervene in other ways than by administering boosters before or after capsule ingestion. This has resulted in numerous studies searching for the optimal composition of the bowel preparation regimen to increase acceptable bowel cleanliness and excretion rates [3]. In addition, add-on boosters such as castor oil, prucalopride, and a sulfate-based solution have influenced completion rates, suggesting that they have potential [26,27,28].

This review was strengthened by all included studies being prospective RCTs. Moreover, all included studies were quality assessed and scored high evaluations from the MINORS index. Limitations of this review include the low number of included studies (n = 4) and that all four studies were single-center reports. Therefore, the power of the analysis is limited, and the insignificant differences found between the pooled estimates may, in fact, be the result of type II errors. Furthermore, all studies were single-blinded and might have been candidates for hidden bias. This makes it challenging to support changes in clinical practice due to the need for external validity. However, because there might be a benefit from providing chewing gum during capsule transit, and the risks and costs associated are minuscule, it seems that it could be a reasonable add-on in patients with suspected decreased peristalsis. The data were too heterogeneous to include Buijs et al. in the pooled completion rate analysis because it was the only study to represent CCE [24]. This was also based on the fact that Egger's test demonstrated significant *P* values for all included studies when Buijs et al. was part of the test, but when excluded, *P* values were non-significant, as shown in ▶**Fig. 4**. This also suggests that this review was limited by small study effects and publication bias when Buijs et al. was part of the pooled completion rate estimates. Heterogeneity was still moderately high without Buijs et al., but this is to be expected from pooled analyses with few studies.

In terms of future research, more prospective and multicenter RCTs are warranted to disprove this review's findings. In addition, future issues that need addressing are the timing of booster administration and patient tolerability, regardless of which capsule endoscopy type or prokinetic agent is being evaluated. These might be critical factors in implementing changes in clinical practice, although evidence supporting this has yet to be established. Some of the studies included in this meta-analysis indicate that chewing gum might have a relevant advantage in accelerating transit times, which could be relevant to further investigation.

Conclusions

This meta-analysis did not find a significant difference in completion rate among patients receiving chewing gum as a booster in capsule endoscopy. With chewing gum's safety profile in consideration, more capsule endoscopy studies evaluating its efficacy can be performed with a low risk of causing complications. More CCE studies, in particular, are essential for proper evaluation of the actual impact of chewing gum as a booster in the bowel preparation regimen, and those data would enhance empirical evidence for analyses to be repeated. The findings about transit times are more optimistic, and it may be clinically relevant to consider use of chewing gum to decrease transit time, if further studies come to the same conclusion.

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Conflict of Interest

The authors declare that they have no conflict of interest.

Clinical trial

PROSPERO
CRD42022385214
prospective randomized controlled trial

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