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Acceptability of alternative technologies compared with faecal immunochemical test and/or colonoscopy in colorectal cancer screening: A systematic review

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Abstract

Objective: Colorectal cancer (CRC) is the third most common cancer and the second largest cause of cancer-related death worldwide. Current CRC screening in various countries involves stool-based faecal immunochemical testing (FIT) and/or colonoscopy, yet public uptake remains sub-optimal. This review assessed the literature regarding acceptability of alternative CRC screening modalities compared to standard care in average-risk adults.

Method: Systematic searches of MEDLINE, EMBASE, CINAHL, Cochrane and Web of Science were conducted up to February 3rd, 2022. The alternative interventions examined were computed tomography colonography, flexible sigmoidoscopy, colon capsule endoscopy and blood-based biomarkers. Outcomes for acceptability were uptake, discomfort associated with bowel preparation, discomfort associated with screening procedure, screening preferences and willingness to repeat screening method. A narrative data synthesis was conducted.

Results: Twenty-one studies met the inclusion criteria. Differences between intervention and comparison modalities in uptake did not reach statistical significance in most of the included studies. The findings do suggest FIT as being more acceptable as a screening modality than flexible sigmoidoscopy. There were no consistent significant differences in bowel preparation discomfort, screening procedure discomfort, screening preference and willingness to repeat screening between the standard care and alternative modalities.

Conclusion: Current evidence comparing standard colonoscopy and stool-based CRC screening with novel modalities does not demonstrate any clear difference in acceptability. Due to the small number of studies available and included in each screening comparison and lack of observed differences, further research is needed to explore factors influencing acceptability of alternative CRC modalities that might result in improvement in population uptake within different contexts.

Keywords

colorectal cancer screening, faecal occult blood test, faecal immunochemical test, flexible sigmoidoscopy, colon capsule endoscopy, computed tomography colonography, blood-based biomarker

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Introduction

Colorectal cancer (CRC) is the third most common cancer and the second largest cause of cancer-related death worldwide, with over 1.9 million new cases causing 935,000 deaths in 2020 globally.[1] Screening for CRC can be effective at reducing mortality, but uptake remains suboptimal.[2] Several tests can be used to screen for CRC, including stool-based tests and colonoscopy.

The faecal immunochemical test (FIT) is currently most commonly used to screen for CRC and uses antibodies to detect human blood in the stool. Colonoscopy is considered the gold standard of CRC screening due to its ability to

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examine the whole colon while simultaneously detecting and removing polyps.[2] Population-based colonoscopy screening has not been considered to be practicable in several countries due to the cost, capacity and expertise required[3] whilst it has been implemented in others with relatively limited coverage of the population at risk. For example, colonoscopy-based but opportunistic screening is used in the United States and Poland, rather than a population-based screening programme.[4] Stool-based screening may have significant false negatives depending on the threshold used for detection in a particular screening programme.[3] Hence, there is a need for an effective as well as patient-centred and less invasive screening test that is acceptable to participants.[5]

There are several alternative technologies that have been investigated for colorectal screening, including flexible sigmoidoscopy (FS), computed tomography (CT) colonography, colon capsule endoscopy and blood-based biomarkers,[5] which may have adequate sensitivity and specificity and fulfil criteria[6] to be used as a screening tool. Most of these are less invasive and/or often perceived as more patient-friendly than colonoscopy.[5] CRC screening uptake is consistently low among the underserved sections of the population.[7] Socioeconomic, ethnic and sociocultural factors also play a role in non-adherence with CRC screening. Individuals from areas with higher levels of social deprivation were less likely to participate in screening.[8] Zhu (2021)[9] reported that psychosocial barriers such as unpleasantness, embarrassment, pain and fear about a positive result were the most commonly reported barriers to colonoscopy screening among the Hispanic population.

Alternative technologies for CRC screening require systematic investigation of patient acceptability for their efficacy to be translated to effectiveness at a population level. Common parameters used in previous CRC screening studies to determine acceptability have included screening uptake, bowel preparation discomfort, screening procedure discomfort and screening preference.[10] There are limited studies assessing the acceptance of alternative technologies among average-risk populations.[11] Lin and colleagues[12] suggested that participants preferred CT colonography to colonoscopy in 16 of the 19 studies included in the review, but a pooled difference was not calculated. Khalid-de Bakker[13] reviewed comparative uptake of a range of CRC modalities in average-risk populations. Their study suggested higher uptake for stool-based modalities. Zhu et al.[14] conducted a meta-analysis comparing uptake between CT colonography and colonoscopy and found no significant difference. However, their review was limited by comparing one alternative modality to colonoscopy. The purpose of the current systematic review was to examine the acceptability of four alternative CRC screening methods currently available, with published data on their use, compared to standard care (colonoscopy and FIT).

Methods

The systematic review was registered on PROSPERO (reg. no. CRD42020203971) and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[15] Throughout all stages of the search, data extraction and quality appraisal, 15% of studies were double-checked for consistency by another member of the team (SG). All discrepancies were resolved through discussion. Data duplication was managed by removing duplications using a reference management software package (EndNote X9) and Rayyan,[16] followed by manual checking.

Search strategy

The literature from 1985 to February 3rd, 2022, was searched on electronic databases Medline, Embase, Cochrane, CINAHL and Web of Science using the terms listed in Table 1. A list of the search terms for the different databases are listed in Appendix 1 (see online Supplemental material). Studies published before 1985 were not included because the alternative interventions were not used in clinical practice prior to this date.

Eligibility criteria

Inclusion criteria were: (1) participants aged 45–86 years; (2) participants with average risk of CRC; (3) studies that compared colon capsule endoscopy, CT colonography, flexible sigmoidoscopy and/or blood biomarkers (e.g. Septin 9 or Epi proColon) with FOBT, FIT and/or colonoscopy. The exclusion criteria were: (1) studies that used a decision aid to increase CRC uptake; (2) participants who were previously non-adherent to screening and received a tailored intervention to encourage screening; (3) studies that did not report primary study data or used simulation models. This review was not limited to randomised controlled trials (RCTs); it also included studies that reported participants' perceptions and preferences to better understand acceptance of screening tests.

Selection process

Databases were searched with fixed search terms (Table 1) and all results were exported and saved onto EndNote. Articles were cross-referenced to look for relevant articles. Full texts of potentially eligible studies were reviewed. Discrepancies that arose were resolved by agreement between the two reviewers. If no agreement could be reached a third reviewer (SD) was consulted.

Data extraction and synthesis

A standardised form was used to extract the following study details: authors, year of publication, country, study design, screening intervention, screening comparator and study outcomes. Due to the heterogeneity of included studies, a narrative approach was used to synthesise key findings.[17] A p-value of <0.05 was used as a cut-off to determine significance of results reported.

Quality assessment

One author assessed the quality of all included studies using the Cochrane risk-of-bias (RoB 2) tool[18] to assess randomised studies and the ROBINS_I tool[19] for non-randomised studies.

Table 1. Population, intervention, comparator, outcomes (PICO) and search terms.

PICO	Description	Search terms
Population	Participants aged 45 to 86 years and who were at average risk of CRC	exp Colorectal Neoplasms/ or ((bowel or colorectral or colon) or adj3 (carcinoma* or neoplasm* or cancer)).mp or ("early detection of cancer" or early screening).mp or mass screening/ or (screen* or detection or test*)
Intervention	Colon capsule endoscopy, CT colonography, FS, blood biomarkers	(capsule endoscopy* or colon capsule or virtual camera or video endoscopy).mp or virtual endoscopy.mp or exp Colonography, Computed Tomographic/ or (virtual colonoscopy or CT colonoscopy).mp or Sigmoidoscopy/ or (flexible sigmoid* or flexible sigmoidoscopy).mp or blood testmp. or Hematologic tests/ or (epi procolon or septins or msept9).mp or septin9.mp or (blood bio* or blood-based or blood-based biomarker or liquid bio*).mp
Comparison	FOBT, FIT, colonoscopy	exp Colonoscopy/ or Occult Blood/ or fecal immunochemical testmp or faecal immunochemical testmp
Outcome	Acceptability - uptake, discomfort associated with bowel preparation, discomfort associated with screening procedure, screening preference, willingness to repeat screening modality	(acceptability* or acceptance).mp or (adherence* or attend* or attendance*) or (engage or engagement or interest or willing).mp or (uptake* or screening uptake).mp or (compliance* or complete*).mp or (intend or visit or choice or choose or chose).mp or patient preference/ or patient participation or participate*.mp or (knowledge or understanding or comprehension).mp or (decision making or decide or attitude or belief).mp or (perception or perceive or interest or value or decisional conflict).mp or (anxiety/ or discomfort).mp or (embarrassment or pain or experience).mp or satisfaction.mp or Personal Satisfaction/confidence* or fear or worry.mp

The Cochrane tool[18] assesses the likelihood of bias in studies across five domains: (1) randomisation bias, (2) intended intervention bias, (3) missing data bias, (4) outcome bias and (5) reporting bias. The risk of bias was judged as low, high or some concerns. Seven domains assessed using the ROBINS_I tool[19] were: (1) confounding bias, (2) participant selection bias, (3) intervention classification bias, (4) deviations from intended intervention bias, (5) missing data bias, (6) outcome bias and (7) reported bias. The risk of bias was judged as low, moderate or high. An RCT was graded higher than an observational study when evaluating the same outcome measure. Evidence from observational studies was used where no RCT data were available.

Results

Study selection

The initial search yielded 19,372 articles (Figure 1). After removing duplicates, 13,188 underwent title and abstract screening. Two-hundred and fifteen articles were assessed for full-text eligibility, of which 21 studies were included in the final analysis. Three of these used the same population cohort to assess uptake and measure acceptability,[31,34,36] but the findings were reported in separate studies.

Study characteristics

Key characteristics of the included studies are outlined in Table 2. Twelve studies were RCTs[20–31] and eight studies were observational.[32–40] To assess acceptability, studies compared participants who had completed a screening intervention or a comparator. Eight studies compared CT colonography and colonoscopy,[20–24,34–37,38] five studies compared FS and FIT,[25–28,39] four studies compared FS and colonoscopy,[21,26,36–37] four studies compared blood-based biomarker tests and FIT,[29–32] two studies compared colon capsule endoscopy and colonoscopy,[33,40] two studies compared CT colonography and FOBT[21,23] and one study compared CT colonography and FIT.[24]

Study quality

All of the randomised studies obtained a high risk of bias from the Cochrane RoB 2 tool,[18] as shown in Table 3, since participants were aware of their assigned intervention during the study. According to the ROBINS_I tool[19] shown in Table 4, two studies were assessed to be at high risk,[34–35] four studies moderate risk[32,37,39–40] and three studies low risk.[33,36,38] In two studies, participants were informed of their screening result prior to completing the questionnaire, which might have influenced the responses.[39–40]

Uptake

Five RCT studies compared uptake between CT colonography and colonoscopy[20–24] (Figure 2(a)). In two studies,[20–21]

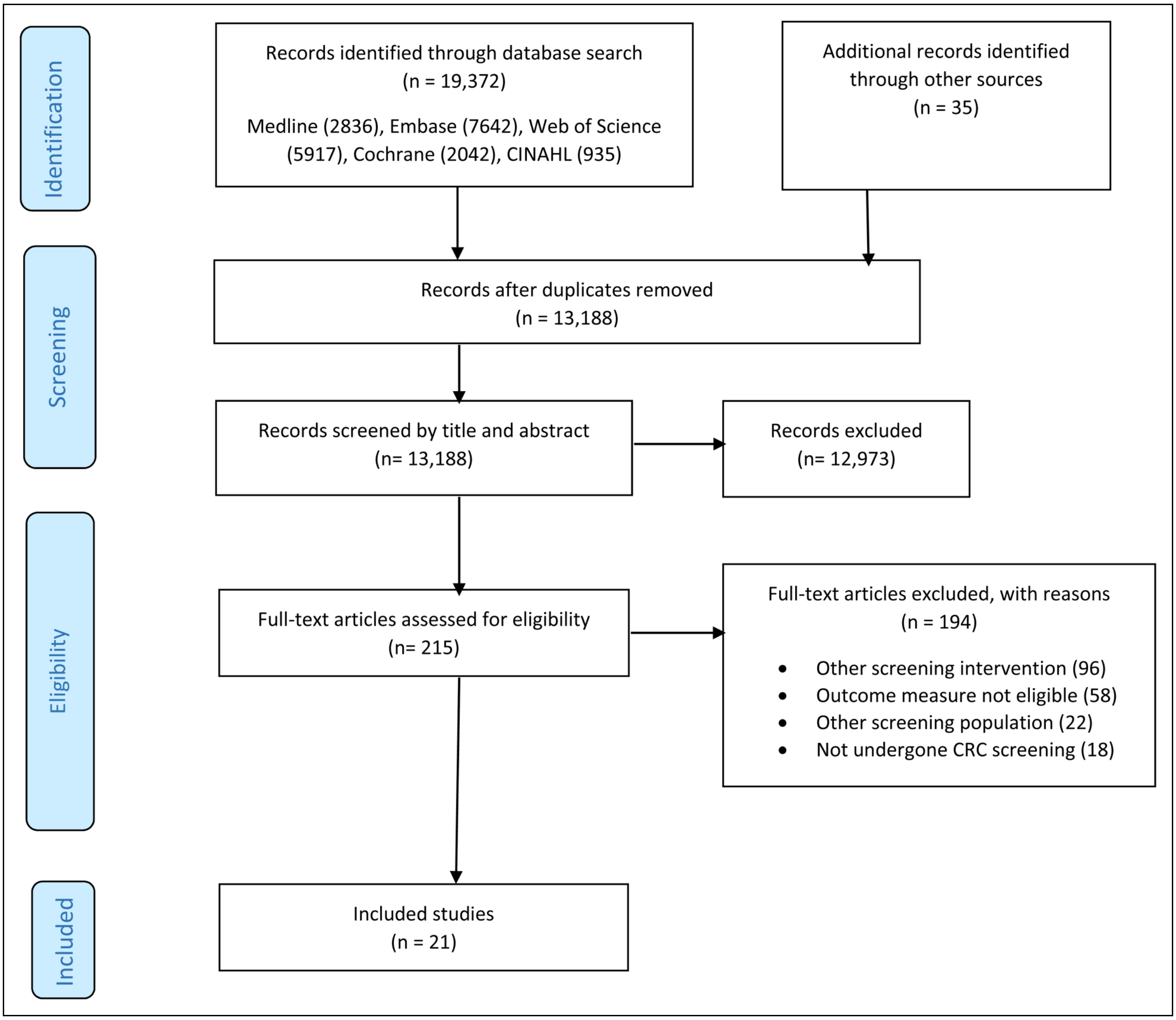

Figure 1. PRISMA flow diagram depicting study selection process.

differences in observed uptake were not statistically significant. In a third study by You,[23] the trial was stopped early; there was insufficient statistical power to detect relevant differences in uptake. In Stoop's study,[22] differences in observed uptake were statistically higher in CT colonography than colonoscopy (34% vs. 22%, $p < 0.001$). Similarly, differences in observed uptake in Sali's study[24] were significantly higher in both reduced (28.1%, $p < .001$) and full-preparation (25.2%, $p < .001$) CT colonography over colonoscopy (14.8%).

Four RCT studies compared uptake of FS and FIT[25–28] (Figure 2(b)). Uptake was higher with FIT compared to FS in two studies,[27–28] which totalled 150,000 participants. The other two studies[25–26] found no significant differences, but their combined sample size only accounted for a tenth of the total. In this review, Hol's study[27] was the only comparator of FS and FIT which included socio-economic status as a baseline characteristic. The results found participants from a higher socio-economic group were more likely to take part in both FS and FIT screening ($p < 0.05$). Three RCTs[29–31] and one observational[32] study compared uptake of blood-based test and FIT (Figure 2(c)). In two of these studies,[29–30] differences in observed uptake were not significant. In the third study, by Liles,[31] differences in observed uptake were higher in blood-based test than FIT (99.5% vs. 88.1%, $p < 0.001$). In the fourth study, by Ioannou,[32] there was no p-value stated to determine statistical difference.

Two RCTs compared uptake of CT colonography and FOBT.[21,23] Differences in observed uptake were not significant in Forbes[21] study and in You's study[23] the trial was stopped early. Segnan's RCT[26] was the only study that compared FS and colonoscopy uptake. After adjustment for demographic variables, the uptake was significantly higher in FS than colonoscopy (OR, 0.74; 95 percent CI: 0.68–0.80). Groth's observational study[33] was the only study that compared colon capsule endoscopy and colonoscopy uptake. The differences in observed uptake were not significant. Sali's RCT[24] was the only study that compared CT colonography and FIT. The differences in observed uptake were higher with FIT (50.4%, $p < 0.001$) than both reduced (28.1%) and full-preparation (25.2%) CT colonography.

Table 2. Key characteristics of included studies.

Study, (Country)	Study design	CRC screening intervention and comparator	Sample	Outcome measure	Summary of key findings	Quality appraisal
Scott et al. (2004) (Australia)[20]	RCT	CT colonography vs colonoscopy	Sample size invitees: CT colonography (n = 359), colonoscopy (n = 350). Age of participants: 50–55 years (53.0%), 65–69 years (47.0%). Gender: male (50.0%), female (50.0%).	Uptake	CT colonography (18.1% 65/359), colonoscopy (16.3%, 57/350), p = 0.82, no significant difference.	High risk
Forbes *et al* (2006) (Australia)[21]	RCT	CT colonography vs colonoscopy	Sample size invitees: CT colonography (n = 215), colonoscopy (n = 214). Age of participants: 50–54 years (49.5%), 65–69 years (50.5%). Gender: male (50.1%), female (40.9%).	Uptake	CT colonography (16.3%, 35/214), colonoscopy (17.8%, 38/214), no significant difference.	High risk
Stoop *et al* (2011) (Netherlands)[22]	RCT	CT colonography vs colonoscopy	Sample size invitees: CT colonography (n = 2920), colonoscopy (n = 5924). Age of participants: 50–59 years (45.9%), 60–75 years (54.2%). Gender: male (67.1%), female (32.9%).	Uptake	CT colonography (34%, 982/2920) had highest uptake compared to colonoscopy (22%, 1276/5924), (relative risk [RR] 1·56, 95% CI 1·46–1·68; p < 0·001).	High risk
You *et al* (2015) (Canada)[23]	RCT	CT colonography vs colonoscopy	Sample size invitees: CT colonography (n = 65), colonoscopy (n = 66). Age of participants: 50–70 years. Mean age: 58.7 years. Gender: male (52.5%), female (47.5%).	Uptake	CT colonography (76.9%), colonoscopy (80.3%), no p-value as trial was stopped early.	High risk
Sali *et al* (2016) (Italy)[24]	RCT	CT colonography vs colonoscopy	Sample size invitees: r-CT colonography (n = 2395), f-CT colonography (n = 2430), colonoscopy (n = 1036). Age of participants: 54–60 years (61.5%), 61–65 years (38.5%). Gender: male (46.4%), female (53.6%).	Uptake	r-CT colonography (28.1% 674/2395), f-CT colonography (25.2%, 612/2430), colonoscopy (14.8%, 153/1036). All differences between groups were statistically significant (P < .001).	High risk

(continued)

Table 2. (continued)

Study, (Country)	Study design	CRC screening intervention and comparator	Sample	Outcome measure	Summary of key findings	Quality appraisal
Kirkoen *et al* (2017) (Norway)[25]	RCT	FS vs FIT	Sample size invitees: FS (1700), FIT (1439). Age of participants: 50–74	Uptake	FS (52%), FIT (54%), no significant difference.	High risk
Segnan *et al* (2007) (Italy)[26]	RCT	FS vs FIT	Sample size invitees: FIT (6075), FS (6018). Age of participants: 55–59 years (59.5%), 60–64 years (40.5%). Gender: male (47.7%), female (52.3%)	Uptake	FS: 32.3% (1944/6018), FIT: 32.3% (1965/ 6075), no significant difference.	High risk
Hol *et al* (2009) (Netherlands)[27]	RCT	FS vs FIT	Sample size invitees: FS (5000), FIT (5007). Age of participants: 50–74	Uptake	61.5% (CI, 60.1 to 62.9%) for FIT and 32.4% (CI, 31.1 to 33.7%) for FS screening.	High risk
Randel *et al* (2021) (Norway)[28]	RCT	FS vs FIT	Sample size invitees: FS (69,165) FIT (70,096). Age of participants: 50–74 Gender: male (49.3%), female (50.7%).	Uptake	FIT 1st round had highest uptake (58.4%) compared to FS (52.1%), $p < 0.05$.	High risk
Symonds *et al* (2019) (Australia)[29]	RCT	Blood-based vs FIT	Sample size invitees: Blood-based (585), FIT (588). Gender: female (50.7%), male (49.3%). Age of participants: 50–74	Uptake	Blood-based test (5.3%, 31/585), FIT (3.6%, 21/ 588), $p > 0.05$.	High risk
Young *et al* (2021) (Australia)[30]	RCT	Blood-based vs FIT	Sample size invitees: blood test (293), FIT (292). Age of participants: 50–74. Gender: male (53.3%), female (47.7%)	Uptake	Blood-based test (13.3%, 39/293), FIT (12.0%, 35/292), 13.3%, $p = 0.88$.	High risk
Liles *et al* (2016) (USA)[31]	RCT	Blood-based vs FIT	Sample size invitees: Epi-proColon (203), FIT (210). Age of participants: 50–75. Gender: male (39.9%), female (60.1%) Ethnicity: Caucasian (85.7%), Others (14.3%).	Uptake	Blood-based test had highest uptake: (99.5%, 202/203), FIT (88.1%, 185.210), $p < 0.001$.	High risk
Ioannou *et al* (2021) (USA)[32]	Observational study	Blood-based vs FIT	Sample size invitees:	Uptake	Of 460 participants, none chose colonoscopy, 30 (6.5%) chose FIT and 430 (93.5%) chose blood-based test No p-value stated.	Moderate risk

(*continued*)

Table 2. (continued)

Study, (Country)	Study design	CRC screening intervention and comparator	Sample	Outcome measure	Summary of key findings	Quality appraisal
			460. Age of participants: >50 years. Gender: male (39%), female (61%)			
Forbes *et al* (2006) (Australia)[21]	RCT	CT colonography vs FOBT	Sample size invitees: CT colonography (215), FOBT (234).	Uptake	FOBT had highest uptake: (27.4%, 64/234), CT colonography (16.3%, 35/215), p = 0.005.	High risk
You *et al* (2015) (Canada)[23]	RCT	CT colonography vs FOBT	Sample size invitees: CT colonography (65), FOBT (67).	Uptake	CT colonography: (76.9%, 50/65), FOBT (64.2%, 43/67).	High risk
Segnan *et al* (2007) (Italy)[26]	RCT	FS vs colonoscopy	Sample size invitees: FIT (6075), FS (6018), colonoscopy (6021).	Uptake	FS: 32.3% (1944/6018), colonoscopy: 26.5% (1597/6021), (OR, 0.74; 95% CI: 0.68–0.80),	High risk
Groth *et al* (2012) (Germany)[33]	Observational study	Capsule endoscopy vs colonoscopy	Sample size invitees: 2150. Age of participants: >55 years. Gender: male, (49.3%), female (50.7%)	Uptake	Capsule endoscopy: (4.2%, 90/2150), colonoscopy: (1.6%, 34/2150).	Low risk
Sali *et al* (2016) (Italy)[24]	RCT	CT colonography vs FIT	Sample size invitees: r-CT colonography (2617), f-CT colonography (2625), FIT (9288). Age of participants: 54–65.	Uptake	FIT had highest uptake (50.4%), r-CT colonography: (28.1%), f-CT colonography: (25.2%). All differences between groups were statistically significant (P < .001).	High risk
Wijkerslooth *et al* (2011) (Netherlands)[34]	Observational study	CT colonography vs colonoscopy	Post-study questionnaire: CT colonography (n = 801/982), colonoscopy (n = 1009/1276). Age of participants: 50–74 years.	Bowel preparation discomfort	More burdensome in colonoscopy than CT colonography: (61% vs 16%, p < 0.001).	High risk
Gareen *et al* (2015) (USA)[35]	Observational study	CT colonography vs colonoscopy	Sample size invitees: 2310, participants. Age of participants: 55–86 years. Mean age: 58.4 years.	Bowel preparation discomfort	CT colonography participants reported more discomfort (81.3% vs 27.8%, p < 0.001) and more embarrassment (42.5% vs 26.0%, p < 0.001).	High risk
Nicholson and Korman (2005) (Australia)[36]	Observational study	FS vs colonoscopy	Sample size invitees: FS (191), colonoscopy (256). Gender: male (45%), female (55%).	Bowel preparation discomfort	BP ranked the worst part of procedure FS: 31%, colonoscopy 78% (p < 0.02).	Low risk
Senore *et al* (2011) (Italy)[37]	Observational study			Bowel		Moderate risk

(continued)

Table 2. (continued)

Study, (Country)	Study design	CRC screening intervention and comparator	Sample	Outcome measure	Summary of key findings	Quality appraisal
		FS vs colonoscopy	Sample size invitees: FS (1696), colonoscopy (1382).	preparation discomfort	BP symptom moderate/severe: FS (3.8%), colonoscopy (15.1%), not significant.	
Scott *et al* (2004) (Australia)[20]	RCT	CT colonography vs colonoscopy	Participants returned post-study questionnaire: CT colonography (n = 56), colonoscopy (n = 95).	Screening discomfort	Acceptability measured using median 100-point analogue scores (0 = most favourable, 100 = least favourable). Pain: CT computed tomography (23), colonoscopy (7.1). Satisfaction: CT computed tomography (6.5), colonoscopy (4.6). Embarrassment: CT computed tomography (10.2), colonoscopy (7.8).	High risk
Forbes *et al* (2006) (Australia)[21]	RCT	CT colonography vs colonoscopy	Post-study questionnaire: CT colonography (n = 37/38), colonoscopy (n = 62/63). Age of participants: 50–54 years and 65–69 years.	Screening discomfort	Acceptability measured using median 100-point analogue scores (0 = most favourable, 100 = least favourable). Pain score: CT colonography (20), colonoscopy (4.5). Satisfaction score: CT colonography (10), colonoscopy (4). Embarrassment score: CT colonography (6), colonoscopy (4).	High risk
Pickhardt *et al* (2003) (USA)[38]	Observational study	CT colonography vs colonoscopy	Sample size invitees: 1233 (81.5% returned post-study questionnaire). Age of participants: 50–79 years	Screening discomfort	CT colonography participants reported more discomfort (54.3% vs 38.1%, p < 0.001) and more acceptable in terms of convenience (68.3% vs 24.1%, p < 0.001).	Low risk
Wijkerslooth *et al* (2011) (Netherlands)[34]	Observational study	CT colonography vs colonoscopy	Participants returned post-study questionnaire: CT colonography (n = 801/982), colonoscopy (n = 1009/1276). Age of participants: 50–74 years.	Screening discomfort	CT colonography participants reported more pain (72% vs 47%, p < 0.001), more embarrassment (8% vs 5%, p < 0.001).	High risk
Forbes *et al* (2006) (Australia)[21]	RCT	FS vs colonoscopy	Sample size invitees: FS (39), colonoscopy (63).	Screening discomfort	Acceptability measured using median 100-point analogue scores (0 = most favourable, 100 = least	High risk

(continued)

Table 2. (continued)

Study, (Country)	Study design	CRC screening intervention and comparator	Sample	Outcome measure	Summary of key findings	Quality appraisal
					favourable). Pain: FS (18), colonoscopy (4.5). Satisfaction: FS (6), colonoscopy (4). Embarrassment: FS (10), colonoscopy (4).	
Nicholson and Korman (2005) (Australia)[36]	Observational study	FS vs colonoscopy	Sample size invitees: FS (191), colonoscopy (256). Gender: male (45%), female (55%).	Screening discomfort	Colonoscopy more comfortable (75% vs 18%; P < 0.001), embarrassment score not significantly different. No pain associated with colonoscopy and most individuals had a pain score of less than 3 (11-point scale) for FS.	Low risk
Senore *et al* (2011) (Italy)[37]	Observational study	FS vs colonoscopy	Sample size invitees: FS (1696), colonoscopy (1382).	Screening discomfort	No significant difference with pain and embarrassment levels.	Moderate risk
Hol *et al* (2010) (Netherlands)[39]	Observational study	FS vs FIT	Post-study questionnaire: FS (852/1124), FIT (530/659). Age of participants: 50–74	Screening discomfort	FS participants reported greater discomfort and embarrassment mean scores (p < 0.001).	Moderate risk
Scott *et al* (2004) (Australia)[20]	RCT	CT colonography vs colonoscopy	62 participants returned post-study questionnaire. Age of participants: 50–54 years and 65–69 years.	Screening preference	CT colonography (39%), colonoscopy (61%), p = 0.075, not significant.	High risk
Pickhardt *et al* (2003) (USA)[38]	Observational study	CT colonography vs colonoscopy	Sample size invitees: 1233 (81.5% returned post-study questionnaire).	Screening preference	CT colonography participants reported greater preference (49.8% vs 41.1%, p = 0.004).	Low risk
Gareen *et al* (2015) (USA)[35]	Observational study	CT colonography vs colonoscopy	Sample size invitees: 2310 participants.	Screening preference	CT colonography: 46.6%, (95% confidence interval [CI]: 44.5% –48.7%), colonoscopy: 25.0%, (95% CI: 23.3%–26.9%).	High risk
Groth *et al* (2012) (Germany)[33]	Observational study	Capsule endoscopy vs colonoscopy	Sample size invitees: 147	Screening preference	Capsule endoscopy (70.6%), colonoscopy (29.4%)	Low risk
Voska *et al* (2019) (Czech Republic)[40]	Observational study	Capsule endoscopy vs colonoscopy	Sample size invitees: 225	Screening preference	Capsule endoscopy (47.0%), colonoscopy (53.0%).	Moderate risk

(continued)

Table 2. (continued)

Study, (Country)	Study design	CRC screening intervention and comparator	Sample	Outcome measure	Summary of key findings	Quality appraisal
Scott *et al* (2004) (Australia)[20]	RCT	CT colonography vs colonoscopy	Post-study questionnaire: CT colonography (n = 56), colonoscopy (n = 95).	Willingness to repeat	Acceptability measured using median 100-point analogue scores (0 = most favourable, 100 = least favourable). Colonoscopy (4.5), CT colonography (11.0).	High risk
Forbes *et al* (2006) (Australia)[21]	RCT	CT colonography vs colonoscopy	Post-study questionnaire: CT colonography (n = 37/38), colonoscopy (n = 62/63).	Willingness to repeat	Acceptability measured using median 100-point analogue scores (0 = most favourable, 100 = least favourable). CT colonography (10), Colonoscopy (4).	High risk
Wijkerslooth *et al* (2011) (Netherlands)[34]	Observational study	CT colonography vs colonoscopy	Participants returned post-study questionnaire: CT colonography (n = 801/982), colonoscopy (n = 1009/1276).	Willingness to repeat	CT colonography (93%), colonoscopy (96%), p = 0.99, not significant.	High risk
Gareen *et al* (2015) (USA)[35]	Observational study	CT colonography vs colonoscopy	Sample size invitees: 2310 participants.	Willingness to repeat	Colonoscopy participants reported greater willingness to screen (96.6% vs 79% %, p < 0.001).	High risk
Kirkoen *et al* (2017) (Norway)[25]	RCT	FS vs FIT	Post-study questionnaire: FS (528), FIT (356) Age of participants: 50–74	Willingness to repeat	FS (90%), FIT (95%), not statistically significant.	High risk
Hol *et al* (2010) (Netherlands)[39]	Observational study	FS vs FIT	Post-study questionnaire: FS (852/1124), FIT (530/659). Age of participants: 50–74	Willingness to repeat	FIT (94.0%), FS (83.8%).	Moderate risk
Forbes *et al* (2006) (Australia)[21]	RCT	FS vs colonoscopy	Sample size invitees: FS (39), colonoscopy (63).	Willingness to repeat	Acceptability measured using median 100-point analogue scores (0 = most favourable, 100 = least favourable). FS (5), Colonoscopy (4).	High risk
Nicholson and Korman (2005) (Australia)[36]	Observational study	FS vs colonoscopy	Sample size invitees: FS (191), colonoscopy (256).	Willingness to repeat	FS (97.5%), colonoscopy (99.5%).	Low risk
Groth *et al* (2012) (Germany)[33]	Observational study	Capsule endoscopy vs colonoscopy	Sample size invitees: 147	Willingness to repeat	Capsule endoscopy (87%), colonoscopy (94%).	Low risk

CT: computed tomography, BP: bowel preparation, r-CT: reduced computed tomography, f-CT: full computed tomography, FS: flexible sigmoidoscopy, FIT: faecal immunochemical test.

Table 3. Risk of bias in randomised studies assessed by Cochrane Risk of bias 2.

	Randomisation bias	Intended intervention bias	Missing data bias	Outcome bias	Reporting bias	Overall bias
Scott 2004[20]	+	−	+	+	+	−
Forbes 2006[21]	+	−	+	+	+	−
Stoop 2011[22]	+	−	+	+	+	−
You 2015[23]	+	−	−	−	−	−
Sali 2016[24]	+	−	+	+	+	−
Kirkoen 2017[25]	+	−	+	+	+	−
Segnan 2007[26]	+	−	+	+	+	−
Hol 2009[27]	+	−	+	+	+	−
Randel 2021[28]	+	−	+	+	+	−
Symonds 2019[29]	+	−	+	+	+	−
Young 2021[30]	+	−	+	+	+	−
Liles 2016[31]	+	−	+	+	+	−

+ = Low risk, − = High risk.

Bowel preparation associated discomfort

Two observational studies[34–35] compared bowel preparation discomfort associated with CT colonography and colonoscopy. In Wijkerslooth's study,[34] bowel preparation being found burdensome was significantly higher for colonoscopy than CT colonography (73% vs. 32%, $p < 0.001$). They suggest this may be due to the increased fluid intake before colonoscopy, as opposed to the limited bowel preparation in CT colonography. In Gareen's study,[35] differences in bowel preparation discomfort were not statistically significant. Two observational studies[36–37] compared bowel preparation discomfort of FS and colonoscopy. In Nicholson's study,[36] bowel preparation discomfort was ranked the worst aspect in both colonoscopy (78%) and FS (31%) procedures ($p < 0.02$). In Senore's study,[37] differences in bowel preparation discomfort scores were not statistically significant.

Screening procedure associated discomfort

Four studies compared screening procedure discomfort between CT colonography and colonoscopy.[20–21,34,38] In two studies, discomfort was significantly higher for CT colonography than colonoscopy (p value<0.001).[34,38] In the other two studies, differences in median pain scores were not statistically significant.[20–21] Three studies compared screening procedure discomfort between FS and colonoscopy.[21,36–37] In two studies, differences in pain scores were not significant.[21,37] In Nicholson's study,[36] differences in discomfort were significantly higher for FS than colonoscopy ($p < 0.001$). Hol's study[39] was the only study that compared pain scores between FS and FIT. The mean pain score was unsurprisingly significantly higher with FS than FIT ($p < 0.001$).

Screening preference

Three studies compared screening preference between CT colonography and colonoscopy.[20,35,38] In two studies,[20,35] differences in screening preference were not significant. A questionnaire was used to capture participants' reasons for choosing a certain modality.[20,33] The reasons participants chose colonoscopy in Scott's study[20] included there was no obligation for a second procedure, they expected a more detailed examination and a preference for sedation. Conversely, the reasons participants chose CT colonography in Scott's study[20] included they expected it to take less time, be less painful, be less risky and not require sedation. In Pickhardt's study,[38] differences in screening preference were significantly higher for CT colonography than colonoscopy ($p = 0.004$).

Two studies compared screening preference between capsule endoscopy and colonoscopy.[33,40] In both studies, differences in screening preference were not statistically significant. In Groth's study,[33] the reasons participants preferred capsule colonoscopy were captured from questionnaires, and included that it sounded more pleasant, were afraid of colonoscopy pain, were afraid of sedation, and were afraid of colonoscopy problems. The reasons participants' favoured colonoscopy were because it allowed for biopsy and polypectomy in a single procedure and is the standard method.

Willingness to repeat screening modality at recommended screening interval

Four studies compared willingness to repeat screening between CT colonography and colonoscopy.[20–23,34–35] In three of the studies, there was no significant difference in willingness to repeat.[20–21,34] In Gareen's study,[35] the willingness to repeat colonoscopy was significantly higher than CT colonography (96.6% vs. 79%%, $p < 0.001$). Two studies compared willingness to repeat screening between FS and FIT[25,29] and neither study found a significant difference. Two studies compared willingness to repeat screening between FS and colonoscopy[21,36] and found no significant difference. The only study that evaluated willingness to repeat screening between colon capsule endoscopy and colonoscopy was Groth's[33] and showed no significant difference.

Discussion

This systematic review suggests that though there was no significant overall difference in acceptability between alternative

Table 4. Risk of bias in non-randomised studies assessed by ROBINS_I tool.

	Confounding bias	Participant selection bias	Intervention classification bias	Deviations from intervention bias	Missing data bias	Outcome bias	Reported bias	Overall bias
Ioannou[32] 2021	Low	Low	Low	Low	Low	Low	Moderate	Moderate
Groth[33] 2012	Low	Low	Low	Low	Low	Low	Low	Low
Wijkerslooth[34] 2011	Low	Low	Low	Low	Low	Low	High	High
Gareen[35] 2015	Low	Low	Low	Low	Low	Low	High	High
Nicholson[36] 2005	Low	Low	Low	Low	Low	Low	Low	Low
Senore[37] 2011	Low	Low	Low	Low	Low	Low	Moderate	Moderate
Pickhardt[38] 2003	Low	Low	Low	Low	Low	Low	Low	Low
Hol[39] 2010	Low	Low	Low	Low	Low	Low	Moderate	Moderate
Voska[40] 2019	High	Low	Low	Low	Low	Low	Moderate	Moderate

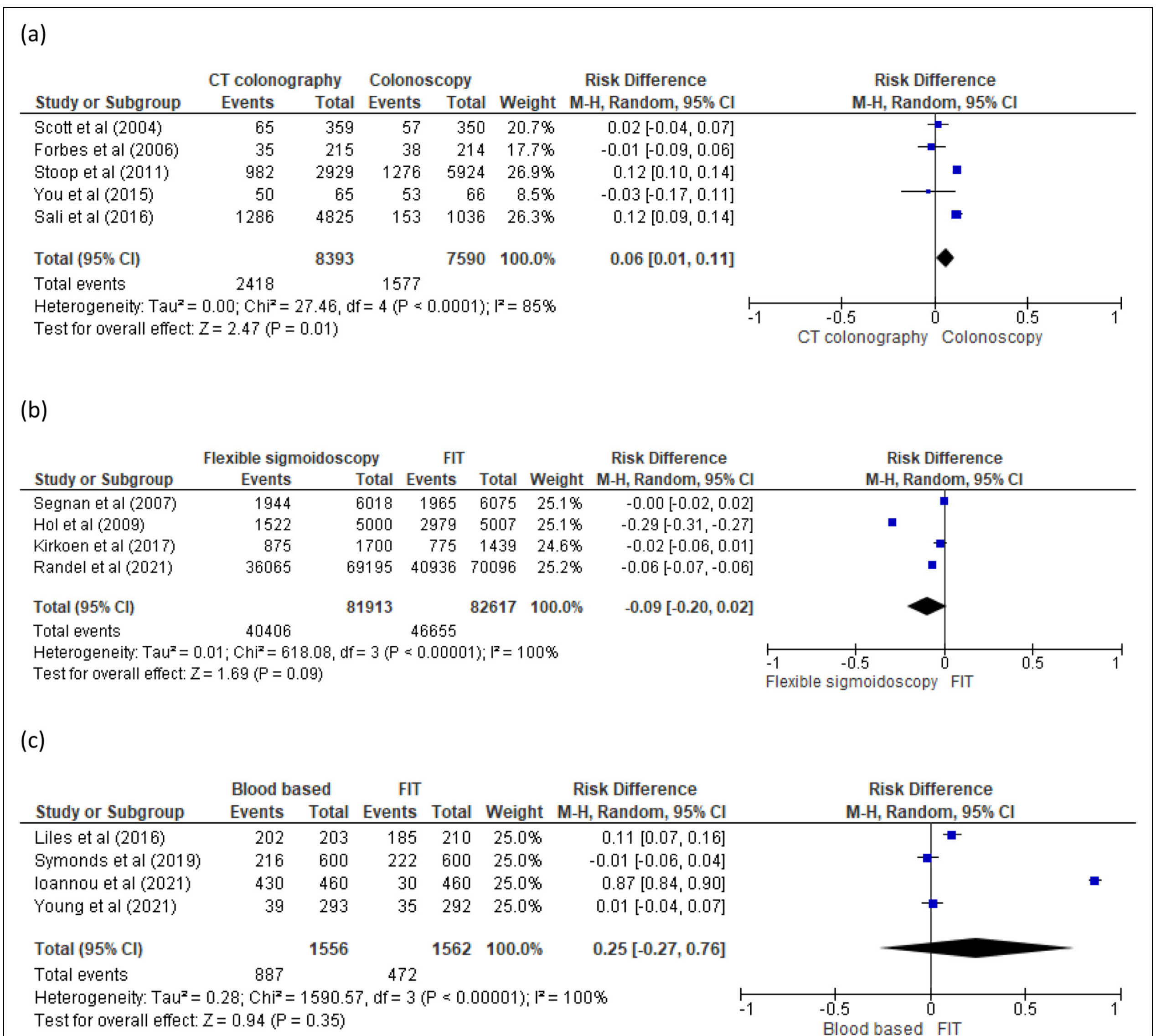

Figure 2. (a) Pooled results of uptake for computed tomography (CT) colonography and colonoscopy. (b) Pooled results of uptake for flexible sigmoidoscopy (FS) and FIT. (c) Pooled results of uptake for blood based and faecal immunochemical test (FIT).

modalities of screening, FIT seemed more acceptable than FS as evidenced by higher uptake and less discomfort experienced by participants. This review's findings are in agreement with Stracci,[41] who indicated FIT as being a more widely accepted screening test than FS.

The findings of Hol's study[27] are comparable to those of the English Bowel Screening Programme study,[42] which found those participants in the least deprived areas were more likely to participate (53.2%) in FS screening than those in the most deprived areas (32.7%). Previous synthesis of evidence has included these modalities in non-screening cohorts, e.g. for early detection of CRC in symptomatic patient groups where other and willingness to accept discomfort.[11–12,43] Mutneja's meta-analysis[44] did not include Kirkoen's study[25] and compared an additional two studies that were not eligible in this review. The bowel preparation requirement was found to be a common barrier to completing a colonoscopy. The percentage of participants in Wijkerslooth's study[34] who declined screening due to inconvenience of bowel preparation was significantly higher for colonoscopy than for CT colonography. This review's findings are similar to those of Cash's randomised trial,[45] which found no significant differences in screening preference between colonoscopy, colon capsule endoscopy and CT colonography.

This systematic review has a number of strengths. Firstly, a range of alternative screening modalities were compared to current standard of care screening by colonoscopy and FIT. Secondly, this review compared several parameters of acceptability measures, which included uptake, bowel preparation, screening discomfort, screening preference and willingness to repeat modality. Thirdly, this review focused on average-risk CRC individuals to understand their views of screening as opposed to those at high risk, who may be more motivated and consequently more likely to participate in screening anyway. Lastly, this review focused on studies of actual screening participants rather than studies of hypothetical screening scenarios or discrete choice experiments.

There are some limitations to this systematic review. There can be no definitive conclusion drawn on acceptability of alternative modality, because only a limited number of studies that fitted the inclusion criteria were possible to analyse. Secondly, the 21 studies included in the review were heterogeneous in study design, screening comparison and sample size, which were all limiting factors for why a meta-analysis was not conducted. Thirdly, studies differed as to where participants completed the post-screening questionnaire: at their homes or in hospital. Completing the questionnaire in a hospital setting may potentially influence a participant's response. Studies varied as to whether or not they informed participants of their screening result before completing the questionnaire, which could potentially influence participants' responses. Finally, there was no uniform reporting on the acceptability measures, which included use of a Likert scale, percentages and median 100-point analogue score. This made it difficult to interpret the significance of the results.

Due to the limited number of studies in each screening comparison, no definitive conclusion can be drawn on most acceptable alternative modality. The lack of significance in the study outcomes could be due to the specific nature of study population, small study sample sizes, mixture of study designs, different healthcare systems and limited context of demographic differences in the populations studied (different countries, ages, and socio-economic status). Other factors such as insurance status in some jurisdictions may also have an influence on screening modality preference.[46–47] However, this research adds to the limited evidence regarding bowel preparation acceptance, screening preference and willingness to repeat modality for non-invasive modalities. In the future, larger well-designed studies are needed comparing alternative CRC modalities with FIT and/or colonoscopy in order to facilitate meaningful comparison and complete a meta-analysis. Further qualitative studies are needed to explore compliance with bowel preparation, participants' screening preferences, and reasons for non-uptake in standard screening and alternative modality. In addition, future studies should include qualitative research analysing the acceptability of alternative screening modalities among individuals who are less likely to engage in routine CRC screening.

Several factors need to be considered before the consideration of colon capsule endoscopy and blood-based screening as population-based screening. These include a cost-effectiveness analysis, resource availability, views of healthcare organisations, practical implementation, need for subsequent second procedures and patient preferences. We believe this review is relevant to inform the context when there is increasing focus on blood-based cancer screening (including multiple cancer screening and early detection) tests as well as colon capsule endoscopy as potential screening modalities for CRC. It highlights the complex interplay between the effectiveness and acceptability of various tests and in different populations.

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Supplemental material

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