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SYSTEMATIC REVIEW

Adherence to colonoscopy in cascade screening of colorectal cancer: A systematic review and meta-analysis

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Key words
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Author contribution: W. W. designed the search strategy, performed the literature search, extracted and examined the data, analyzed and interpreted the data, and drafted the manuscript. J. H. devised the search strategy, performed the literature search, provided the statistical suggestions, and revised the manuscript. Y. Y. devised the search strategy, performed the literature search, and extracted and examined the data. S. T. performed the literature search and extracted the data. T. Y., J. F., D. M., and S. C. extracted the data. K. G., H. N. L., M. W., P. B., C. Y., Y. G., and M. C. S. W. interpreted the data and revised the manuscript. W. X. conceived and designed the study, revised the manuscript, and supervised the quality of the study throughout the conduct of the project. All authors have approved the final draft submitted.

Abstract

Background and Aim: This study aims to systematically evaluate adherence to colonoscopy and related factors in cascade screening of colorectal cancer (CRC) among average-risk populations, which is crucial to achieve the effectiveness of CRC screening.
Methods: We searched PubMed, Embase, Web of Science, and Cochrane Library for studies published in English up to October 16, 2020, and reporting the adherence to colonoscopy following positive results of initial screening tests. A random-effects meta-analysis was applied to estimate pooled adherence and 95% confidence intervals. Subgroup analysis and mixed-effects meta-regression analysis were performed to evaluate heterogeneous factors for adherence level.
Results: A total of 245 observational and 97 experimental studies were included and generated a pooled adherence to colonoscopy of 76.6% (95% confidence interval: 74.1–78.9) and 80.4% (95% confidence interval: 77.2–83.1), respectively. The adherence varied substantially by calendar year of screening, continents, CRC incidence, socioeconomic status, recruitment methods, and type of initial screening tests, with the initial tests as the most modifiable heterogeneous factor for adherence across both observational (Q = 162.6, $P < 0.001$) and experimental studies ($Q = 23.2$, $P < 0.001$). The adherence to colonoscopy was at the highest level when using flexible sigmoidoscopy as an initial test, followed by using guaiac fecal occult blood test, quantitative or qualitative fecal immunochemical test, and risk assessment. The pooled estimate of adherence was positively associated with specificity and positive predictive value of initial screening tests, but negatively with sensitivity and positivity rate.
Conclusions: Colonoscopy adherence is at a low level and differs by study-level characteristics of programs and populations. Initial screening tests with high specificity or positive predictive value may be followed by a high adherence to colonoscopy.

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Introduction

Colorectal cancer (CRC) ranks the third in cancer incidence and the second in cancer-related death worldwide.[1] Mass screening of CRC has been proven to reduce the incidence and mortality of the malignancy.[2,3] Cascade screening strategy, usually colonoscopy referral for individuals with abnormal initial screening results, has been recommended for average-risk populations, mainly for available resources and cost-effectiveness considerations.[4] In these guidelines, guaiac fecal occult blood test (gFOBT), fecal immunochemical test (FIT), flexible sigmoidoscopy (FS), computed tomography colonography, or questionnaire-based risk assessment (RA) were recommended to be used alone or combined as initial screening tests, followed by colonoscopy for those with abnormal results.[4–6] Despite the limited accuracy of the initial tests, the benefits of CRC screening can be maximized if all subjects with abnormal results would attend colonoscopy follow-up.[7]

In real-life screening practice, however, failure to attend colonoscopy is commonly observed worldwide, and this could greatly lower the efficiency of CRC screening programs.[8,9] In a systematic review investigating factors associated with incomplete diagnostic testing, mainly colonoscopy incompliance, the adherence to colonoscopy was found ranging from 35.3% to 99.2%.[10] A meta-analysis focusing on adherence to colonoscopy following a positive FOBT (gFOBT or FIT) in controlled studies reported a summary estimate of 72.5%.[11]

In this study, we conducted a systematic review to obtain a summary measure of colonoscopy adherence derived from broader scope of CRC screening programs in average-risk populations, and explored the determinants on the outcome. Addressing this knowledge gap will help clinicians and policy-makers to improve adherence to colonoscopy, which is an important performance indicator influencing the effectiveness of CRC screening.[12]

Methods

We conducted this systematic review according to a predefined protocol and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) statements.[13,14]

Search strategy and selection criteria. We systematically searched PubMed, Embase, Web of Science, and Cochrane Library from their inception through October 16, 2020, using a combination of Medical Subject Headings and free-text terms related to "colorectal", "cancer", "screening", "gFOBT", "FIT", "risk assessment", "sigmoidoscop*", and "colonoscopy", and limiting to studies published in English. We included experimental (randomized controlled trials and quasi-experimental studies) and observational studies based on general asymptomatic populations at an average risk for CRC.[8] The full search strategy is shown in Table S1. The electronic database search was supplemented with manual searches of the reference lists of related articles.

Search results were retrieved to an EndNote X9 (Clarivate Analytics, Boston, MA, USA) database, and duplicates were removed. After preliminary screening of titles or abstracts, three independent reviewer pairs (Y. Y. and S. C., S. T. and T. Y., and J. F. and D. M.) assessed the full text and reference lists of relevant publications according to the predefined eligibility criteria for final inclusion. Studies were considered eligible if the following inclusion criteria were met: (i) CRC screening was conducted in an average-risk population; (ii) cascade screening modalities were used, where gFOBT, FIT, RA, or FS alone or combined was adopted for initial screening followed by diagnostic colonoscopy if abnormal; and (iii) original data were available for computation of adherence to colonoscopy, the attendance rates of colonoscopy after positive screening, which were calculated as the number of positive subjects attending follow-up colonoscopy divided by the total number of subjects with positive screening results.

We excluded reviews, commentaries, letters, guidelines, and conference abstracts because these reports did not contain sufficient information for assessment. The limited number of studies using multi-target stool DNA test or other novel tests was excluded from this analysis. Pilot studies with results updated by formal studies were also excluded.

Data extraction. The three-pair reviewers independently extracted data from the included studies using a standardized data collection form, which included first author, year of publication, study period, country/area, study design, population characteristics, sample size, recruitment method, screening round, residence of subjects, initial screening tests used, positivity thresholds of FIT, sensitivity, specificity, positive predictive value (PPV), positivity rate (PR) of initial tests (or relevant data for calculation if available), and use of suboptimal diagnostic method (any alternative diagnostic method used when the colonoscopy could not be completed, e.g. FS, computed tomography colonography, and double-contrast barium enema). We also captured number of positive subjects and number of colonoscopies performed for computing adherence to colonoscopy. Of the 342 studies included, only 82 (24.0%) presented a specific timeframe to define adherence to colonoscopy, which varied from 7 to 730 days between positive screening and colonoscopy and had a median and interquartile range of 180 (60–365) days.

According to the positivity thresholds of FITs used in the included studies, we classified them into three groups: < 20, 20–40, and > 40 μg hemoglobin/g feces (μg/g). For studies using the unit of ng hemoglobin/mL buffer (ng/mL), we transformed it into μg/g to facilitate comparability of the findings.[15]

Incidence of CRC for the screened populations was available by screening year, country/area, and age range via the Global Burden of Disease results tool,[16] and additionally from the *Cancer Incidence in Five Continents* (CI5) (https://ci5.iarc.fr/CI5I-X/Pages/online.aspx, accessed November 10, 2020). Age-standardized incidence rate (ASRi) of CRC was further calculated based on the World Standard Population first presented by Segi[17] and modified by Doll *et al.*[18] Gross domestic product (GDP) per capita was obtained through the World Bank website[19] by screening year and country/area for a given screened population as a comprehensive proxy for insurance status of subjects, healthcare availability, and health service delivery, which were not available in most included studies.

Quality assessment. The paired reviewers assessed the quality of observational and experimental studies independently

using the Agency for Healthcare Research and Quality methodology checklist[20] and the tool recommended by the Cochrane Collaboration Handbook.[21] Each item was assigned an assessment index associated with the risk of bias classified as low, high, or unclear. An item was scored "0" if the answer was "high" or "unclear" and scored "1" if it was answered "low". The score ranged from 0 to 11 for observational studies with 0–3, 4–7, and 8–11 scores representing low, moderate, and high qualities, respectively, as previously described.[22] Similarly, the score ranged from 0 to 7 for experimental studies with 0–3, 4–5, and 6–7 scores representing low, moderate, and high qualities, respectively (Tables S2 and S3). The grading of recommendations assessment, development, and evaluation (GRADE) system was used to evaluate the strength of the overall weight of evidence.[23] All disagreements in the study selection, data extraction, and quality assessment were resolved by discussion with the third reviewer (J. H.) to achieve a consensus.

Statistical analysis. All data analyses were conducted using R (version 4.0.2). Meta-analysis was conducted separately for observational and experimental studies using the "meta" package. We combined a logit scale of adherence to colonoscopy, which was closest to normal distribution and based on the inverse variance method random-effects model. Pooled adherence along with 95% confidence intervals (CIs) was computed as the weighted average estimate of individual studies.

Subgroup analyses were performed to obtain pooled estimates by characteristics of screened populations and screening programs, including screening year, continent, age range of population, ASRi of CRC, GDP per capita, study design, study phase (pilot *vs* formal study), sample size, recruitment method, residence of subjects (urban, rural, or both), screening round, and initial tests adopted. Stratified analyses were also conducted by the sensitivity, specificity, PPV, and PR of the initial tests. Between-study heterogeneity was assessed using I^2 and Cochran's Q statistic.[24] Prediction intervals further provided a predicted range for the true estimate in an individual study.[25] Publication bias was assessed by visual inspection of asymmetry in funnel plots, followed by Egger's regression test and a weighted regression test recommended by Peters *et al*.[26–28]

Univariable and multivariable meta-regression analyses were further performed to explore the extent to which important study characteristics could explain anticipated heterogeneity, and thus identify moderators for adherence. Potential effect modification was also investigated by introducing interaction terms into the multivariable model, which was evaluated based on the likelihood ratio test, variance inflation factors, and Akaike information criterion. A permutation test was used to assess the robustness of the final model in resampled data.[29]

To assess the robustness of results and detect whether any study accounts for a large proportion of heterogeneity, several predefined sensitivity analyses were performed by: (i) removing observational studies with participants < 5000 or experimental studies with participants < 1000; (ii) removing studies using rare initial screening test (e.g. RA, fecal M2-pyruvate kinase, and fecal transferrin test); (iii) excluding studies with diagnosed CRC confirmed by suboptimal diagnostic method; (iv) removing studies with extreme value for adherence to colonoscopy ($< 50\%$ or $> 95\%$); (v) excluding low-quality studies with Agency for Healthcare Research and Quality or Cochrane score ≤ 3; and (vi) retaining studies using a timeframe within 180 days to define colonoscopy adherence.

All statistical tests were two sided with a P value of < 0.05 considered statistically significant.

Results

A total of 10 923 articles were identified through literature search. After removal of 3901 duplicates, we screened the titles and abstracts of 7022 articles and 55 relevant articles retrieved from the references cited by the included articles. After excluding 5956 articles according to the eligibility criteria, 1121 remained for full-text review and 224 articles were finally included, from which 245 observational and 97 experimental studies were extracted for meta-analyses (Fig. 1).

As shown in Table S4, the included articles were published from 1984 to 2020, which consist of screening programs performed between 1976 and 2019. Most articles were based on the studies conducted in Europe (n = 118), followed by Asia (n = 54), North America (n = 44), South America (n = 4), Oceania (n = 2), Africa (n = 1), and multiple continents (n = 1). Among 342 studies extracted on adherence to colonoscopy, 58 contained sensitivity and specificity of initial tests, 298 involved PPV, and 330 presented PR. The initial tests used in these populations included gFOBT (n = 95), FIT (n = 169), FS (n = 16), and RA (n = 8), as well as a combination of these tests, including parallel use of FOBTs (n = 10), parallel use of FOBT and RA (n = 11) or FS (n = 6), and serial use of tests (n = 5). Quality assessment for observational and experimental studies was shown in Tables S2 and S3, respectively. There were 132, 182, and 28 studies classified as having high, moderate, and low qualities, respectively.

The summarized adherence to colonoscopy from 245 observational studies was 76.6% (95% CI: 74.1–78.9) and was 80.4% (95% CI: 77.2–83.1) from 97 experimental studies. Significant heterogeneities in adherence were observed across observational studies (Q = 655 464.1, $P < 0.001$, I^2 = 100%) and experimental studies (Q = 7330.4, $P < 0.001$, I^2 = 98.7%) (Table 1). The between-study heterogeneity was also significant by screening year, continents, age range of populations, ASRi of CRC, and GDP per capita. The summarized adherence was significantly lower in studies conducted after 2009, in Asia or North America, or with lower ASRi. Low adherence was also observed in observational studies with the lowest level of GDP per capita, but in experimental studies with the highest level of GDP per capita.

Subgroup analyses by characteristics of screening programs showed significant subgroup differences in adherence to colonoscopy. Type of initial test was the most modifiable heterogeneous factor for adherence across both observational (Q = 162.6, $P < 0.001$) (Fig. 2a) and experimental (Q = 23.2, $P < 0.001$) studies (Fig. 2b). In observational studies, the adherence was 88.2% (95% CI: 84.2–91.2) when using parallel test of FOBTs and was 87.9% (95% CI: 78.0–93.7) when using FS alone, higher than 83.2% (95% CI: 80.0–86.0) when using gFOBT alone, and 76.0% (95% CI: 72.4–79.2) when using FIT alone. In experimental studies, the adherence was the highest in populations using parallel test of FOBT and FS (91.2%, 95% CI: 82.4–95.8) or using FS alone (90.2%, 95% CI: 82.4–94.8), followed by those using gFOBT alone (86.5%, 95% CI: 83.2–89.3) and using FIT alone (74.5%, 95% CI: 68.7–79.6). The overall estimate was also higher

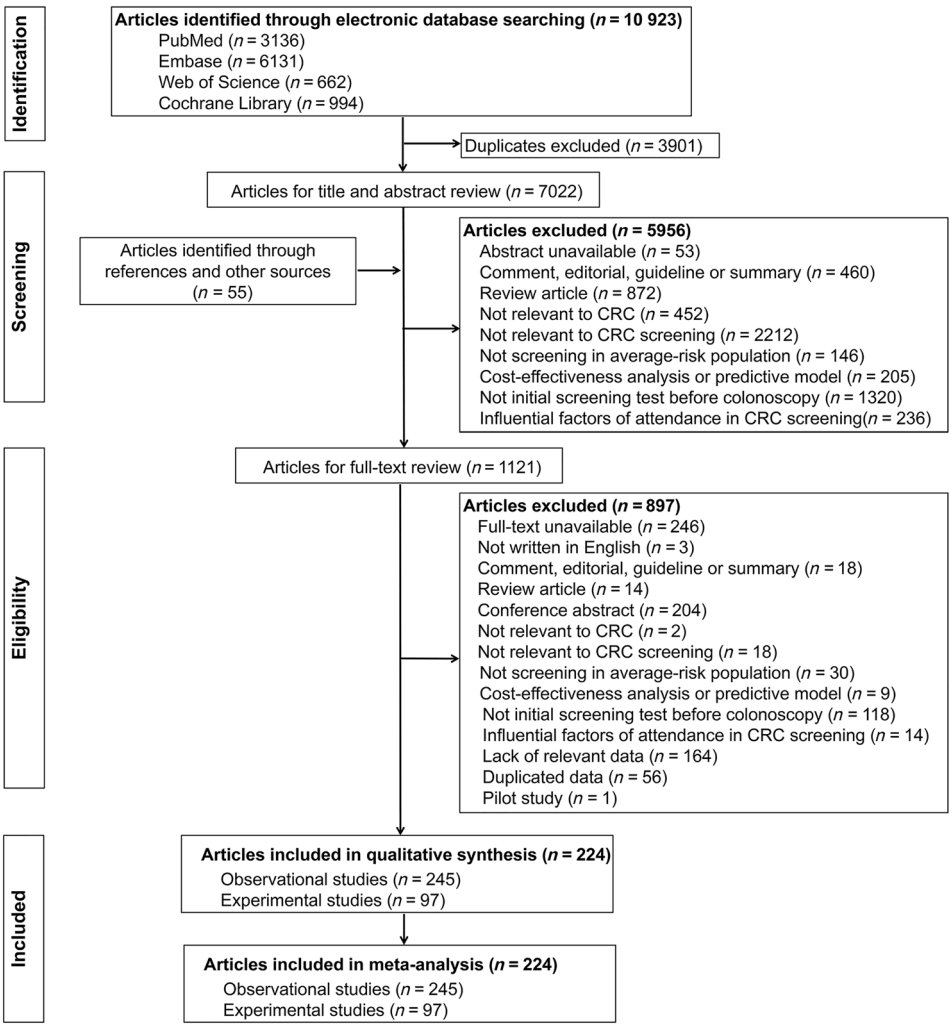

Figure 1 Study selection flow diagram.

when using quantitative FIT than using qualitative FIT in observational studies (79.7% *vs* 64.9%, $P < 0.001$), but was not in experimental studies ($P = 0.666$).

For other characteristics, a significant heterogeneity was observed for summarized adherence by recruitment method across observational studies (Fig. 2a). In experimental studies, a significantly lower pooled adherence was observed in organized screening settings, in populations living in urban areas, and in small-scale screening practice (Fig. 2b).

Considering the importance of initial screening tests on adherence to colonoscopy, we classified the sensitivity, specificity, PPV, and PR of the initial tests into quartile groups to evaluate heterogeneities of adherence by these indicators. As shown in Table 2, the summarized adherence differed by quartiles of sensitivity, PPV, and PR in observational studies, and by quartiles of sensitivity, specificity, and PR in experimental studies (P values < 0.001). We further summarized the adherence to colonoscopy regardless of observational or experimental studies, and found that adherence was significantly higher in studies using initial tests with higher levels of specificity and PPV, and lower levels of sensitivity and PR.

We then conducted a meta-regression analysis to investigate potential sources of heterogeneity on adherence to colonoscopy. As presented in Table 3, we found that the included observational studies were highly heterogeneous with respect to screening year, continent, ASRi of CRC, GDP per capita, recruitment method, and type of initial test used. The model with six predictors explained 63.11% of total between-study heterogeneity in adherence to colonoscopy ($P < 0.001$). Regarding the experimental studies, the continent, ASRi of CRC, residences of subjects, and type of initial test used were significant in the multivariable meta-regression model and accounted for only 25.16% of total between-study heterogeneity in adherence ($P < 0.001$) (Table 4). The permutation test provided consistent results to verify the robustness of the established models.

In sensitivity analyses of the study, the overall estimates of summarized adherence to colonoscopy were similar to those in the main analysis. However, in the analysis of 20 experimental studies

Table 1 Pooled adherence to colonoscopy in cascade screening of CRC by characteristics of screened populations

Characteristics	Observational studies					Experimental studies				
	No. of studies	Adherence (95% CI), %	Prediction interval, %	I^2 (%)	$Q^{\dagger}$	No. of studies	Adherence (95% CI), %	Prediction interval, %	I^2 (%)	$Q^{\dagger}$
Overall	245	76.6 (74.1–78.9)	29.5–96.2	100	655 464.1	97	80.4 (77.2–83.1)	41.1–96.0	98.7	7330.4
Calendar year of screening										
1976–1999	35	76.6 (70.7–81.6)	36.2–95.0	99.5	6710.6	33	88.2 (85.0–90.7)	61.7–97.2	98.7	2520.3
2000–2004	40	80.1 (75.0–84.5)	36.6–96.6	99.9	47 283.6	11	75.6 (65.0–83.8)	31.4–95.4	93.2	146.9
2005–2009	69	81.6 (76.9–85.5)	27.8–98.1	100	215 220.5	13	83.8 (77.6–88.5)	52.4–96.0	91.3	138.3
2010–2014	71	74.2 (69.3–78.6)	27.2–95.7	100	298 943.9	27	75.2 (67.6–81.5)	29.6–95.6	97.4	987.1
2015–2019	30	61.0 (48.1–72.5)	7.1–97.0	99.9	30 127.4	13	60.7 (46.6–73.2)	13.0–94.1	99.3	1835.8
Geographical continent[‡]										
Asia	65	59.7 (54.7–64.5)	22.7–88.2	100	216 951.7	15	73.0 (64.8–79.9)	35.0–93.1	98.7	1108.3
Europe	131	83.6 (81.7–85.4)	53.4–95.8	99.9	96 681.1	57	86.3 (83.7–88.5)	59.3–96.4	95.9	1382.7
North America	41	68.7 (65.0–72.1)	44.0–85.9	99.7	12 331.3	23	61.1 (50.9–70.4)	17.4–92.2	99.2	2736.0
South America	5	77.9 (75.0–80.6)	69.1–84.8	58.1	9.6	—	—	—	—	—
Age range of populations (years)										
$<$ 50 to all age above	43	70.1 (59.3–79.0)	9.3–98.2	99.9	52 510.9	25	82.1 (78.2–85.5)	56.5–94.2	94.7	452.3
50 to $\leq$ 75	140	79.4 (76.7–81.8)	38.0–96.0	99.9	256 104.8	49	76.4 (70.3–81.5)	28.0–96.4	98.5	3232.5
50 to $>$ 75	37	65.2 (59.8–70.2)	31.6–88.3	99.9	70 811.6	6	87.3 (79.0–92.6)	45.3–98.3	98.8	411.4
$>$ 50 to all age above	25	84.0 (81.8–86.0)	70.2–92.1	99.6	5363.2	17	84.5 (79.3–88.6)	53.7–96.2	98.3	915.2
ASRi of CRC (1/100 000) (by quartile)										
$\leq$ 89.56	64	67.5 (62.1–72.4)	25.4–92.7	99.9	64 077.4	22	77.8 (71.4–83.2)	39.1–95.1	98.6	1532.4
89.57–113.28	53	81.3 (77.3–84.8)	41.4–96.4	99.9	59 704.4	32	75.2 (66.6–82.1)	21.1–97.2	98.5	2122.9
113.29–135.95	62	77.6 (72.9–81.8)	30.6–96.5	100	273 414.4	23	80.4 (75.2–84.8)	49.1–94.6	94.1	371.6
$\geq$ 135.96	66	78.2 (74.8–81.2)	43.2–94.4	99.9	62 271.7	20	89.3 (85.0–92.5)	60.6–97.8	98.9	1751.1
GDP per capita ($US) (by quartile)										
$\leq$ 15 284	69	64.8 (59.6–69.6)	24.0–91.5	99.9	129 700.0	17	79.4 (72.3–85.1)	39.4–95.8	99.0	1683.8
15 285–29 568	60	76.0 (71.4–80.0)	33.5–95.2	100	149 684.4	26	86.5 (81.7–90.2)	51.0–97.5	98.2	1387.1
29 569–44 600	60	84.4 (82.6–86.1)	65.6–93.9	99.6	15 865.2	26	79.9 (70.6–86.8)	20.9–98.3	99.0	2446.4
$\geq$ 44 601	56	78.5 (75.1–81.5)	46.4–93.9	99.9	54 190.0	28	74.4 (65.7–81.5)	24.0–96.4	97.9	1311.3

[†]All P values less than 0.05 based on Cochran's Q statistic.

[‡]Insufficient evidence for assessment of studies from Oceania and Africa.

ASRi, age-standardized incidence rate; CI, confidence interval; CRC, colorectal cancer; GDP, gross domestic product.

using a timeframe $\leq$ 180 days to define adherence, the estimate was only 69.4%, lower than 80.4% in the main analysis including 97 trials (Fig. S1).

Funnel plots of logit-transformed adherence to colonoscopy suggested the presence of publication bias in observational studies but not in experimental studies (Fig. S2). Although the Egger regression asymmetry test was statistically significant for included observational studies ($P < 0.001$) and was marginally significant for experimental studies ($P = 0.052$), Peters test did not identify asymmetry in observational ($P = 0.299$) and experimental ($P = 0.637$) studies. Moreover, funnel plot of log-transformed adherence appeared symmetric in observational studies, and P values for Egger and Peters tests were more than 0.05. These results indicated that this meta-analysis was not affected by severe publication bias.

We further conducted subgroup analyses using log-transformed adherence to colonoscopy by characteristics of screening programs (Fig. S3) and sensitivity, specificity, PPV, and PR of initial screening tests (Table S5) in observational studies. The pooled adherences for each subgroup were not much different from those estimated using logit-scale transformation.

According to the GRADE working group methodology, the quality of evidence in the meta-analysis was summarized as low for observational studies and as high for experimental studies (Table S6).

Discussion

According to the guideline of European Union, an adherence to follow-up colonoscopy at above 90% in cascade screening of CRC is desirable to achieve screening benefits.[30] In this study, however, we observed suboptimal summarized adherence for observational (76.6%) or experimental (80.4%) studies, which varied between 8.9% and 100% across observational studies and from 7.2% to 100% across experimental studies in diverse screened populations and screening programs. Our findings indicate an urgent need to enhance colonoscopy attendance.

There could be a number of explanations for the large difference in adherence to colonoscopy across populations. Forbes *et al.*[31] indicated that factors at the levels of patient, physician, and system can influence colonoscopy adherence subsequent to a positive screening test. Most previous studies, however, have focused on

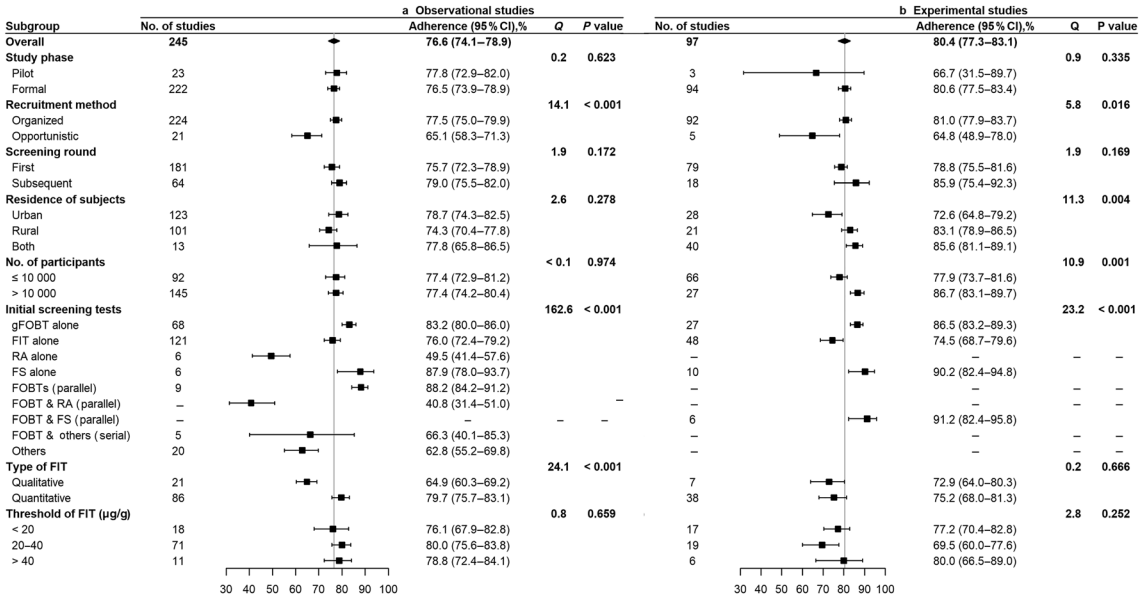

Figure 2 Summarized adherence to colonoscopy by characteristics of screening programs in (a) observational studies and (b) experimental studies. CI, confidence interval; FIT, fecal immunochemical test; FOBT, fecal occult blood test, including gFOBT and FIT; FS, flexible sigmoidoscopy; gFOBT, guaiac fecal occult blood test; RA, risk assessment.

Table 2 Pooled adherence to colonoscopy by sensitivity, specificity, positive predictive value, and positivity rate of initial screening tests for CRC

Characteristics	Overall					Observational studies					Experimental studies				
	No. of studies	Adherence (95% CI), %	I^2 (%)	*Q*	*P* value†	No. of studies	Adherence (95% CI), %	I^2 (%)	*Q*	*P* value	No. of studies	Adherence (95% CI), %	I^2 (%)	*Q*	*P* value
Sensitivity (%)				14.5	0.002				16.6	< 0.001				26.5	< 0.001
20.1–48.2	15	86.7 (75.7–93.1)	99.3			8	80.2 (59.5–91.8)	99.4			7	91.5 (85.8–95.1)	96.2		
48.3–66.2	14	89.2 (86.2–91.6)	96.5			9	90.2 (86.7–92.9)	97.6			5	87.6 (79.3–92.9)	90.7		
66.3–83.7	14	80.6 (76.8–83.8)	99.2			12	79.7 (75.7–83.3)	99.3			2	87.2 (81.3–91.4)	0		
83.8–100.0	15	86.1 (78.2–91.5)	100			14	86.9 (79.0–92.1)	100			1	70.6 (62.9–77.3)	-		
Specificity (%)				12.5	0.006				4.6	0.208				82.4	< 0.001
53.0–94.1	15	84.1 (75.7–90.0)	99.9			11	81.8 (70.9–89.3)	100			4	89.1 (76.8–95.2)	97.5		
94.2–96.2	14	85.6 (79.9–89.9)	99.7			13	84.2 (77.9–88.9)	99.7			1	96.2 (95.4–97.0)	-		
96.3–97.9	15	84.4 (82.3–86.3)	96.3			12	85.3 (83.1–87.2)	97			3	78.6 (70.4–85.0)	64.5		
98.0–99.3	14	89.1 (87.2–90.7)	89.1			7	88.2 (85.5–90.5)	94.4			7	90.0 (88.3–91.6)	0		
Positive predictive value (%)				25.4	< 0.001				32.2	< 0.001				2.7	0.436
0.0–3.4	78	71.5 (67.0–75.7)	100			50	67.1 (61.2–72.4)	100			28	79.3 (75.2–82.9)	97.6		
3.5–5.5	72	78.6 (75.6–81.3)	99.8			61	77.9 (74.6–80.9)	99.9			11	82.2 (75.6–87.3)	96.1		
5.6–7.9	75	84.0 (81.1–86.5)	99.8			67	84.2 (81.1–86.8)	99.8			8	83.3 (66.1–92.7)	98.8		
8.0–32.7	73	80.7 (77.1–83.8)	99.8			41	78.2 (72.9–82.7)	99.9			32	83.3 (80.2–86.0)	90.6		
Positivity rate (%)				43.4	< 0.001				44.9	< 0.001				16.6	< 0.001
0.2–3.2	83	85.3 (83.1–87.2)	99.7			61	84.8 (82.2–87.1)	99.8			22	86.6 (84.3–88.6)	66.4		
3.3–5.5	83	80.4 (77.8–82.7)	99.8			61	80.3 (77.3–82.9)	99.8			22	80.8 (75.0–85.5)	94.9		
5.6–9.0	81	74.3 (70.0–78.2)	100			59	72.8 (67.6–77.5)	100			22	77.9 (72.5–82.5)	96.3		
9.1–56.6	83	71.6 (66.6–76.1)	99.9			56	67.4 (61.4–72.9)	99.9			27	79.0 (72.8–84.1)	99.3		

†*P* values less than 0.05 considered statistically significant.
-, not applicable; CI, confidence interval; CRC, colorectal cancer.

the effect of age, sex, socioeconomic status, insurance type, screening history, and other factors at individual level.[32] In this study, we examined the influence of characteristics of the screened populations and screening programs on colonoscopy adherence at study level and found that in observational studies, the adherence varied greatly across populations by screening year, continent, ASRi of CRC, socioeconomic status, recruitment method, and type of initial test, which explained 63.11% of total heterogeneity

Table 3 Results of univariable and multivariable meta-regression analyses on adherence to colonoscopy in cascade screening for CRC from observational studies

Study-level variables	Univariable analyses					Multivariable analysis[†]		
	No. of studies	RR (95% CI)	*P* value by level	Heterogeneity explained (%)	Overall *P* value	No. of studies	Adjusted RR (95% CI)	*P* value by level
Calendar year of screening				< 0.01	< 0.001			
1976–2009	144	1.00 (ref)				132	1.00 (ref)	
2010–2019	101	0.59 (0.45–0.78)	< 0.001			90	0.70 (0.56–0.86)	0.001
Geographical continent				46.16	< 0.001			
Asia	65	1.00 (ref)				58	1.00 (ref)	
Europe	131	3.47 (2.74–4.40)	< 0.001			122	1.87 (1.36–2.57)	< 0.001
South America	5	2.80 (1.32–5.92)	0.007			5	2.58 (1.29–5.16)	0.007
North America	41	1.51 (1.11–2.07)	0.009			37	0.84 (0.58–1.21)	0.350
Age range of populations (years)				30.87	< 0.001			
< 50 to all age above	43	0.54 (0.40–0.74)	< 0.001			-	-	-
50 to ≤ 75	140	1.00 (ref)				-	-	-
50 to > 75	37	0.50 (0.36–0.69)	< 0.001			-	-	-
> 50	25	1.38 (0.95–2.01)	0.089			-	-	-
ASRi of CRC (1/100 000)	245	1.00 (1.00–1.01)	0.012	19.02	0.012	222	1.00 (0.99–1.00)	0.007
GDP per capita				42.85	< 0.001			
Low (< 29 569)	129	1.00 (ref)				115	1.00 (ref)	
High (≥ 29 569)	116	1.91 (1.56–2.34)	< 0.001			107	1.56 (1.24–1.96)	< 0.001
Study phase				4.01	0.807			
Formal	222	1.00 (ref)				-	-	-
Pilot	23	1.06 (0.67–1.66)	0.807			-	-	-
Sample size				0.04	0.968			
Small ($n \leq 10\,000$)	92	1.00 (ref)				-	-	-
Large ($n > 10\,000$)	145	1.01 (0.75–1.35)	0.968			-	-	-
Recruitment method				< 0.01	0.016			
Organized	224	1.00 (ref)				204	1.00 (ref)	
Opportunistic	21	0.56 (0.35–0.90)	0.016			18	0.66 (0.46–0.96)	0.027
Screening round				1.95	0.182			
First	181	1.00 (ref)				-	-	-
Subsequent	64	1.23 (0.91–1.65)	0.182			-	-	-
Residence of subjects				< 0.01	0.239			
Urban	123	1.00 (ref)				-	-	-
Rural	101	0.96 (0.50–1.84)	0.912			-	-	-
Both	13	0.79 (0.59–1.04)	0.094			-	-	-
Initial screening tests				26.72	< 0.001			
gFOBT alone	68	1.58 (1.18–2.13)	0.002			68	1.16 (0.92–1.46)	0.215
FIT alone	121	1.00 (ref)				120	1.00 (ref)	
RA alone	6	0.48 (0.21–1.09)	0.079			5	0.22 (0.11–0.42)	< 0.001
FS alone	6	2.30 (1.02–5.23)	0.046			5	3.20 (1.60–6.40)	0.001
FOBTs (parallel)	9	2.40 (1.24–4.65)	0.010			9	1.27 (0.77–2.08)	0.346

(Continues)

Table 3 (Continued)

Study-level variables	Univariable analyses					Multivariable analysis†		
	No. of studies	RR (95% CI)	*P* value by level	Heterogeneity explained (%)	Overall *P* value	No. of studies	Adjusted RR (95% CI)	*P* value by level
FOBT and RA (parallel)	10	0.22 (0.12–0.41)	< 0.001			10	0.30 (0.18–0.48)	< 0.001
FOBT and others (serial)	5	0.62 (0.26–1.49)	0.289			5	0.57 (0.30–1.10)	0.095
Use of suboptimal diagnostic method				< 0.01	0.187			
No	226	1.00 (ref)				-	-	-
Yes	19	1.41 (0.85–2.36)	0.187			-	-	-
Quality of studies				< 0.01	0.570			
High	95	1.00 (ref)				-	-	-
Moderate	134	1.05 (0.79–1.40)	0.711			-	-	-
Low	16	0.78 (0.44–1.38)	0.398			-	-	-

†VIFs less than 10 for all variables in the multivariable model, indicating no collinearity.

-, not applicable; ASRi, age-standardized incidence rate; CI, confidence interval; CRC, colorectal cancer; FIT, fecal immunochemical test; FOBT, fecal occult blood test, including gFOBT and FIT; FS, flexible sigmoidoscopy; GDP, gross domestic product; gFOBT, guaiac fecal occult blood test; RA, risk assessment; ref, reference; RR, risk ratio; VIFs, variance inflation factors.

in adherence; in experimental studies, the model including four significant predictors (continent, ASRi of CRC, residence of subjects, and type of initial test) accounted for only 25.16% of variation in adherence.

Generally, the characteristics of screened populations demonstrated unmodifiable (e.g. screening year or continent located) or relatively stable feature (e.g. age range, CRC incidence, or GDP per capita). Although these factors were not easily changed to improve adherence to colonoscopy, the differences in adherence by the factors may provide some clues for correlates of adherence. For instance, we found that the pooled adherence was lower in populations screened after 2009 than before. Given that populations in Asia or with low ASRi were more likely to be screened after 2009, one may speculate that these characteristics may be associated with a lower adherence to colonoscopy.

The characteristics of screening programs, on the other hand, can be modified to maximize the efficacy of CRC screening. In this study, the type of initial test was found to be the most heterogeneous factor for adherence to colonoscopy in both observational and experimental studies. Further analysis indicated that the heterogeneity by type of initial tests may be due to the varying specificities or PPVs of the initial tests used. Meta-regression analysis also demonstrated that type of initial test was the most important modifiable moderator for adherence. Although it is possible that unrecorded variables other than the test characteristics account for the observed differences, our results indicate that initial screening tests with high specificity or PPV may help to elevate adherence to colonoscopy, which has been observed in the comparison of three gFOBTs[33] and in a real-world setting.[34] The importance of test specificity for CRC screening programs was also specially addressed in other studies.[35,36] Our findings may have implications for the importance of choosing an initial test very carefully in a given jurisdiction or country to complete the full range of screening. Certainly, this analysis is an important step toward identifying determinants of colonoscopy adherence and bears implications for public health policy-making and practice.

It is of note that, of the 342 studies included in this analysis, only 82 presented a specific timeframe to define adherence to colonoscopy. The greatly varied timeframes (7–730 days) in these studies and in other programs[31,37] due to lack of a unified recommendation[38–40] may have contributed to the heterogeneities in adherence and biased our estimates of summarized adherence. In sensitivity analysis including studies using a timeframe within 180 days to define adherence, however, a comparable pooled adherence was obtained for observational studies, suggesting limited effect of the timeframe for colonoscopy in observational screening programs, in which most positive participants would attend colonoscopy follow-up as soon as possible for early diagnosis and treatment. Moreover, Liang and Dominitz[41] have proposed that, from the population-health perspective, the proportion of positive individuals attending subsequent colonoscopy is likely to be more important than the timely colonoscopy, particularly in screening programs with suboptimal follow-up. Therefore, our overall estimates of adherence to colonoscopy regardless of the varied timeframe provide a global overview on the key point in CRC screening.

Table 4 Results of univariable and multivariable meta-regression analyses on adherence to colonoscopy in cascade screening for CRC from experimental studies

Study-level variables	Univariable analyses					Multivariable analysis[†]		
	No. of studies	RR (95% CI)	*P* value by level	Heterogeneity explained (%)	Overall *P* value	No. of studies	Adjusted RR (95% CI)	*P* value by level
Calendar year of screening				13.30	< 0.001			
1976–2009	57	1.00 (ref)				-	-	-
2010–2019	40	0.42 (0.29–0.59)	< 0.001			-	-	-
Geographical continent				14.73	< 0.001			
Asia	15	1.00 (ref)				12	1.00 (ref)	
Europe	57	2.33 (1.44–3.79)	0.001			53	1.05 (0.53–2.07)	0.898
North America	23	0.58 (0.33–1.03)	0.061			18	0.35 (0.16–0.78)	0.010
Age range of populations (years)				7.59	0.053			
< 50 to all age above	25	1.45 (0.94–2.23)	0.089			-	-	-
50 to ≤ 75	49	1.00 (ref)				-	-	-
50 to > 75	6	2.11 (0.98–4.51)	0.055			-	-	-
> 50	17	1.71 (1.04–2.81)	0.034			-	-	-
ASRi of CRC (1/100 000)	97	1.01 (1.00–1.01)	0.011	< 0.01	0.011	83	1.01 (1.00–1.02)	0.027
GDP per capita				< 0.01	0.029			
Low (< 29 569)	43	1.00 (ref)				-	-	-
High (≥ 29 569)	54	0.66 (0.45–0.96)	0.029			-	-	-
Study phase				< 0.01	0.245			
Formal	94	1.00 (ref)				-	-	-
Pilot	3	0.50 (0.15–1.61)	0.245			-	-	-
Sample size				0.29	0.001			
Small ($n \leq 10\,000$)	66	1.00 (ref)				-	-	-
Large ($n > 10\,000$)	27	1.86 (1.29–2.68)	0.001			-	-	-
Recruitment method				0.39	0.068			
Organized	92	1.00 (ref)				-	-	-
Opportunistic	5	0.45 (0.19–1.06)	0.068			-	-	-
Screening round				< 0.01	0.050			
First	79	1.00 (ref)				-	-	-
Subsequent	18	1.62 (1.00–2.62)	0.050			-	-	-
Residence of subjects				< 0.01	0.005			
Urban	28	1.00 (ref)				27	1.00 (ref)	
Rural	21	1.88 (1.06–3.31)	0.030			17	1.50 (0.82–2.75)	0.186
Both	40	2.22 (1.37–3.61)	0.001			39	1.54 (0.96–2.47)	0.075
Initial screening tests				9.33	< 0.001			
gFOBT alone	27	2.22 (1.43–3.46)	< 0.001			26	1.90 (1.20–3.01)	0.006
FIT alone	48	1.00 (ref)				43	1.00 (ref)	
FS alone	10	3.08 (1.60–5.94)	0.001			10	2.79 (1.48–5.26)	0.002
FOBT and FS (parallel)	6	3.53 (1.60–7.78)	0.002			4	3.81 (1.54–9.43)	0.004
Use of suboptimal diagnostic method				< 0.01	0.140			
No	92	1.00 (ref)				-	-	-

(Continues)

Table 4 (Continued)

Study-level variables	Univariable analyses					Multivariable analysis[†]		
	No. of studies	RR (95% CI)	*P* value by level	Heterogeneity explained (%)	Overall *P* value	No. of studies	Adjusted RR (95% CI)	*P* value by level
Yes	5	1.89 (0.81–4.40)	0.140			-	-	-
Quality of studies				< 0.01	0.271			
High	37	1.00 (ref)				-	-	-
Moderate	48	0.97 (0.64–1.47)	0.887			-	-	-
Low	12	0.61 (0.32–1.14)	0.121			-	-	-

[†]VIFs less than 10 for all variables in the multivariable model, indicating no collinearity.

-, not applicable; ASRi, age-standardized incidence rate; CI, confidence interval; CRC, colorectal cancer; FIT, fecal immunochemical test; FOBT, fecal occult blood test, including gFOBT and FIT; FS, flexible sigmoidoscopy; GDP, gross domestic product; gFOBT, guaiac fecal occult blood test; ref, reference; RR, risk ratio; VIFs, variance inflation factors.

To our knowledge, this is the first systematic review that comprehensively estimates the pooled adherence to colonoscopy in cascade CRC screening using gFOBT, FIT, RA, or FS alone or combined for initial screening. Specifically, this review involved both experimental and observational studies and followed the recommendations of PRISMA and MOOSE, particularly on comprehensive retrieval of databases, robust data extraction, and quality assessment. Moreover, the large number of observational studies adequately powered our meta-analysis to provide the most comprehensive estimate of adherence to colonoscopy in average-risk populations on a global basis. Subgroup analyses according to a variety of characteristics of screened populations and screening programs provided clues for exploring heterogeneity. Meta-regression was further conducted to verify the main sources of heterogeneity and assess their influence on the outcome. In previous reviews on adherence to colonoscopy, however, they were merely focused on adherence to colonoscopy following a positive FOBT.[10,11]

This study is subject to several limitations. First, the screening programs included in this analysis were performed between 1976 and 2019, during which both FOBT and colonoscopy may have made a great progress in methodologies. The heterogeneities impose restrictions on drawing a clear conclusion. Second, we might have missed some articles due to language restriction and inclusion of studies that were published as full-text articles. We also recognized that most included studies were conducted in high-income settings. The situation in low-income and middle-income countries was not fully addressed because of unavailability of CRC screening in these countries.[5] Third, the publication bias may have imposed limitations on data interpretation for observational studies. Considering that publication bias was more likely to be detected in meta-analysis including a large number of studies and might be related with transformation method of the outcome variable,[42] we reconducted the meta-analyses using log-transformed adherence to colonoscopy. No publication bias was detected. Furthermore, the data on performance of initial tests were not available for some studies, which have limited our estimates on the relationship between accuracy of initial tests and adherence to colonoscopy. Moreover, possible unmeasured confounders like time from positive initial screening results to colonoscopy, insurance status, health service delivery, healthcare availability, and screening incentives may have influenced our results on moderators for adherence. Finally, heterogeneity was high with data derived from various settings and studies; this may have implications on the reliability of our findings. We therefore applied meta-regression to explore the sources of heterogeneity and verified the robustness of our results by multiple sensitivity analyses.

In conclusion, this systematic review presents the most up-to-date estimates on adherence to colonoscopy follow-up in cascade screening of CRC on a global scale. Our findings provide high-quality evidence demonstrating that the colonoscopy adherence is suboptimal overall and may be enhanced by selecting initial tests carefully. Further research is needed to elucidate the relationship between accuracy of initial tests and adherence to colonoscopy, identify sources of residual unexplained heterogeneity, and provide evidence for targeted interventions.

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