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Colorectal cancer screening with repeated fecal immunochemical test versus sigmoidoscopy: baseline results from a randomized trial

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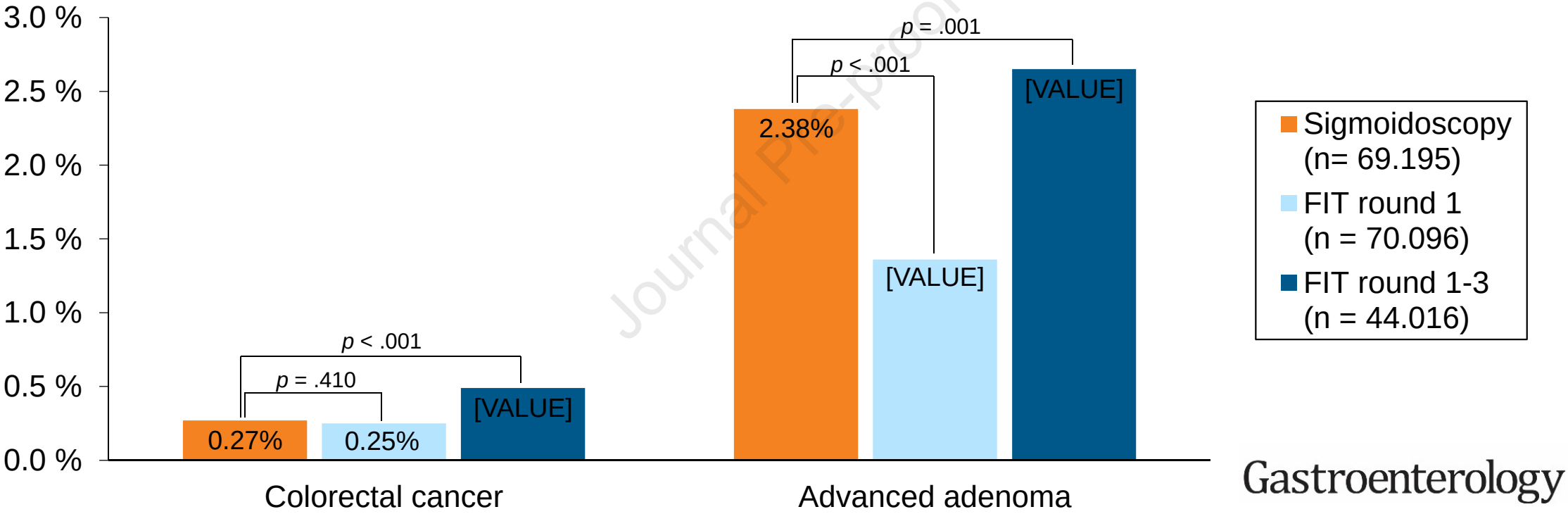
Colorectal cancer and advanced adenoma detection rates among invited individuals in the sigmoidoscopy arm, FIT round 1, and FIT round 1-3



Gastroenterology

Colorectal cancer screening with repeated fecal immunochemical test versus sigmoidoscopy: baseline results from a randomized trial

Short title: FIT versus sigmoidoscopy for CRC screening

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Abbreviations used in this paper

AA (advanced adenoma), ADR (adenoma detection rate), BBPS (Boston bowel preparation scale), CI (confidence interval), CRC (Colorectal cancer), gFOBT (Guaiac-based fecal occult blood test), FIT (fecal immunochemical test), K (Cohens Kappa), OR (odds ratio).

Author contributions:

Study concept and design: GH, GU, and MB

Acquisition, analysis, or interpretation of data: KRR, ALS, EB, GH, MB, GU, EN, PB, AJ, PKS, MEO, SOF, OD, ERN, NB, HK, AW, KAW, TdL, and ØH

Drafting of the manuscript: KRR, EB, and ØH.

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All authors approved the final report and are accountable for all aspects of this work. All authors had full access to all study data, take full responsibility for the accuracy of the data analysis, and have authority over submission preparation and decisions to submit for publication.

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Abstract

Background and aims: The comparative effectiveness of sigmoidoscopy and fecal immunochemical testing (FIT) for colorectal cancer (CRC) screening is unknown.

Methods: Individuals aged 50–74 years living in South-East Norway were randomly invited between 2012 and 2019 to either once-only flexible sigmoidoscopy or FIT screening every second year. Colonoscopy was recommended after sigmoidoscopy if any polyp ≥10 mm, ≥ three adenomas, any advanced adenomas, or CRC was found or subsequent to FIT > 15 µg hemoglobin/g feces. Data for this report were obtained after complete recruitment in both groups and included two full FIT rounds and part of the third round. Outcome measures were participation, neoplasia detection, and adverse events. Age-standardized detection rates and age-adjusted odds ratios (OR) were calculated.

Results: We included 139,291 individuals; 69,195 randomized to sigmoidoscopy and 70,096 to FIT. Participation rate was 52% for sigmoidoscopy, 58% in the first FIT round and 68% for three cumulative FIT rounds. Compared to sigmoidoscopy, detection rate for CRC was similar in the first FIT round (0.25% vs 0.27%, OR 0.92, 95% CI 0.75-1.13), but higher after three FIT rounds (0.49% vs 0.27%, OR 1.87, 95% CI 1.54-2.27). Advanced adenoma detection rate was lower in the first FIT round compared to sigmoidoscopy, 1.4% vs 2.4% (OR 0.57, 95% CI 0.53-0.62), but higher after three cumulative FIT rounds, 2.7% vs 2.4% (OR 1.14, 95% CI 1.05-1.23). There were 33 (0.05%) serious adverse events in the sigmoidoscopy group compared to 47 (0.07%) in the FIT group (p =.13).

Conclusion: Participation was higher and more CRC and advanced adenomas were detected with repeated FIT compared to sigmoidoscopy. The risk of perforation and bleeding was comparable. Clinicaltrials.gov (NCT 01538550).

Key words: mass screening; screening yield; participation; adverse events

Introduction

Colorectal cancer (CRC) is a major health burden with an estimated 1.8 million new cases worldwide in 2018.[1] Screening can reduce mortality by detection of asymptomatic early-stage cancer and prevent the disease by detection and removal of premalignant precursor lesions (adenomas and serrated polyps). In four randomized trials with up to 17 years follow-up, sigmoidoscopy screening (endoscopic examination of the rectum and sigmoid colon with subsequent colonoscopy if pathology is detected) has been shown to reduce CRC mortality by 22-31% and incidence by 18-26% compared to no screening.[2-5] Guaiac-based fecal occult blood testing (gFOBT) has been evaluated in four randomized trials with up to 30 years of follow-up. Meta-analyses have shown 14% reduction in CRC mortality, but no effect on CRC incidence.[6]

In recent years, fecal immunochemical testing (FIT) has replaced gFOBT as the preferred fecal screening test due to easier sampling, automatic test-reading and a quantitative measure of fecal hemoglobin concentration to allow adjustment of the threshold defining test positivity and thus, the sensitivity for adenomas and CRC.[7] At lower positivity thresholds, FIT has greater sensitivity for advanced adenomas and CRC compared with gFOBT used in the aforementioned randomized trials, and observational studies have suggested that iFOBT may also reduce CRC incidence.[8] However, no randomized trial evaluating the long term effectiveness of FIT on CRC mortality or incidence has been published.

Most international guidelines recommend CRC screening for average risk individuals between 50 and 75 years of age, although with differences in recommendation with respect to the preferred screening method.[9] The International Agency for Research on Cancer (IARC) recently concluded that there is insufficient evidence to rank screening tests in terms of effectiveness.[10] Evidence from randomized population-based clinical trials comparing different screening methods are required in order to provide clear recommendations. Several trials comparing the effect of FIT and colonoscopy screening on long-term CRC incidence and mortality are currently underway.[11] However, to date, no randomized trials have compared the effectiveness of fecal occult blood testing with sigmoidoscopy screening on CRC

mortality or incidence. In the present paper, we report the baseline findings from a large Norwegian randomized trial, including almost 140,000 individuals, comparing once-only sigmoidoscopy to FIT offered every second year.

Methods

Design and participants

In 2012, all individuals 50-74 years old (born between January 1, 1938 and December 31, 1962) living in two geographical areas in South-East Norway were identified through the population registry, and randomly assigned in a 1:1 ratio to be invited for either once-only flexible sigmoidoscopy, or to FIT every second year for a maximum of four rounds. Randomization was performed by the Cancer Registry of Norway, using a computer-based algorithm and stratified by screening center, gender and year of birth. No CRC screening program was available in Norway during the conduct of the trial. The first participants were invited in March 2012. Individuals who died, moved out of the area, reached the upper age limit, or received a CRC diagnosis before they were due for first invitation, were excluded from analyses. Enrolment in the FIT group (first round) ended in January 2017, when the predefined number of invited individuals was reached. Enrolment in the sigmoidoscopy group was completed in December 2018 and the last sigmoidoscopy was performed in May 2019. The data for the present study were obtained in April 2020. Accordingly, we include all screening data from the sigmoidoscopy group and the initial three FIT rounds, but due to ongoing screening, complete data from the third FIT round were only available for those invited for the first time before January 1, 2015 (63% of all individuals).

The trial is run by the Cancer Registry of Norway and two screening centers carried out the endoscopies. Most of the screening sigmoidoscopies and follow-up colonoscopies were performed by gastroenterology residents that were intensively trained (one- to-one supervision by an experienced endoscopist) for three to six months before entering the trial. Quality assurance measures were closely monitored throughout the trial. Participants were invited by mail and reminded once if no-response (no return of fecal sample or not attending sigmoidoscopy within 6 weeks). The mailed invitation included

detailed information about the randomized trial, the assigned screening method, risks and benefits of screening, and the follow up-colonoscopy in case of a positive test. Attenders in the sigmoidoscopy group provided written informed consent on attendance at the screening center, while return of the fecal sample was defined as consent in the FIT group. The trial was approved by the Regional Committee for Medical Research Ethics in South East Norway (2011/1272) and is registered at clinicaltrials.gov (NCT 01538550).

Flexible sigmoidoscopy

Bowel preparation for sigmoidoscopy was performed with a 240 mL sorbitol enema (Klyx®, Ferring Pharmaceuticals AS) administered on attendance. No sedation or analgesia was provided for sigmoidoscopy. The Olympus Exera II/III systems (Olympus H180DL/I, CF-HQ190L/I, PCF-PH190L/I, PCF-H190DL/I) were used for sigmoidoscopies and follow-up colonoscopies and CO_2 was the standard insufflation gas. During most of the examinations, a magnetic imaging system (ScopeGuide®, Olympus Europa, Hamburg, Germany) was available. At sigmoidoscopy, the endoscope was inserted as far as possible according to the allocated 20 minute time slot, or until a lesion ≥ 10 mm was detected, or limitations in bowel cleansing or patient discomfort did not permit further advancement. Repeated sigmoidoscopy was not offered in case of an incomplete examination. Bowel cleansing was assessed by the endoscopist on a categorical four-point rating scale as either poor, partially poor, acceptable, or good. A positive sigmoidoscopy (with subsequent referral to colonoscopy) was defined as: detection of any polyp ≥ 10 mm, ≥ three adenomas, an adenoma with high-grade dysplasia or ≥ 25% villous architecture, or CRC. Polyps < 10 mm were usually removed during sigmoidoscopy.

Fecal immunochemical test

Each FIT screening consisted of a single fecal sample. Sampling kit and instructions were mailed together with invitations. Participants were not asked to apply dietary restrictions or to discontinue anticoagulation or antiplatelet treatment ahead of sampling. Samples were mailed in a pre-paid envelope to the centralized laboratory at Oslo University Hospital. If the fecal sample could not be

mailed to the test laboratory on the day of collection, the participants were instructed to keep it in the refrigerator until the next day. All samples were analyzed using the OC-Sensor Diana (Eiken Chemical, Tokyo, Japan). The threshold defining a positive FIT was set to 15 µg hemoglobin/g feces (corresponding to 75 ng hemoglobin/ml buffer) and was decided after a literature search currently available at that time. At the laboratory, the fecal samples were analyzed on the day of arrival or stored at 4°C until analysis. In case of a non-analyzable FIT, a new test kit was sent to the participant. By design, attenders with a negative test and non-attenders were re-invited every second year, up to a maximum of four screening rounds, or until the upper age limit was reached.

Follow-up colonoscopies

Individuals with a positive screening result were scheduled for a follow-up colonoscopy. Prior to the colonoscopy, they were interviewed by a study nurse, either at time of sigmoidoscopy or by phone for FIT positives. Medical history data (including comorbidity, currently prescribed medication use, smoking, body mass index, cancer history, and gastrointestinal symptoms) were registered. Split dose bowel preparation (PicoPrep®, Ferring Pharmaceuticals) was recommended: one sachet in the afternoon prior to the examination and the second dose 4 hours prior to the colonoscopy. The same bowel cleansing rating scale was used as for sigmoidoscopy. Sedation or analgesia was mainly provided on demand. Individuals who had a colonoscopy were not re-invited to subsequent biennial rounds of FIT-testing. Attenders were referred for surveillance after colonoscopy in accordance with European guidelines.[12]

Data collection and outcome measures

Endoscopic and histopathological data from the sigmoidoscopies and colonoscopies were entered into a dedicated database. For all detected lesions: size, location, appearance (e.g. pedunculated, sessile or flat), and technique and completeness of removal was registered. CRC was defined as adenocarcinoma of the colon or rectum. An advanced adenoma was defined as an adenoma with either size ≥ 10 mm, villous components of at least 25%, or high-grade dysplasia. Advanced serrated lesions included any serrated lesions (hyperplastic polyp, sessile serrated lesion, or traditional serrated adenoma) with size

≥ 10 mm, or dysplasia.[13] We defined proximal lesions as lesions localized in colonic segments proximal to and including the splenic flexure and distal lesions as lesions localized in colonic segments distal to the splenic flexure.

An adequate colonoscopy was defined as intubation of the cecum with good or acceptable bowel cleansing. A sigmoidoscopy was considered adequate if the sigmoid-descending junction was reached, or the endoscope was inserted 35 cm without looping (verified by the external imager), and with good or acceptable bowel cleansing.

Information on patients' experience, including satisfaction and abdominal pain during sigmoidoscopy and colonoscopy, was recorded using a questionnaire (data only available for 2012-2018).[14] The participants received the questionnaire upon leaving the colonoscopy premises and were asked to complete the questionnaire the day after the procedure and to return it in a pre-paid envelope. Pain was categorized on a four-point rating scale as none, slight, moderate, or severe.

Adverse events occurring during or within 30 days after the procedure were assessed from the health trusts' electronic medical report system. We defined significant bleedings as bleedings that lead to hospitalization (≥ 1 day), blood transfusion, repeat endoscopy, radiological intervention, or surgery. Perforation was defined as radiological (computer tomography) findings consistent with intestinal perforation. Mortality within 30 days after endoscopy was obtained by linkage to the Norwegian population registry. For deaths occurring within 30 days, the patients' medical records were scrutinized by study medical personnel to assess whether the death was possibly related to the procedure.

CRC mortality after ten years is the primary endpoint of the main trial. Secondary endpoints include CRC incidence, overall mortality, cost-effectiveness, attendance rate, neoplasia detection rates, CRC stage at diagnosis, unwanted psychological[15, 16] and physical effects[17], and adverse events after endoscopy. In the current paper we present results for attendance rate, neoplasia detection, CRC stage at diagnosis and adverse events.

Statistical analysis

For sample size calculation in the main trial, we assumed a CRC mortality reduction of 30% in individuals invited to sigmoidoscopy[18] and 15% in individuals invited to FIT[19], compared to the general Norwegian population (no screening). Based on a mean annual CRC mortality rate of 76/100,000 for the first 10 years of follow-up (Norway 2010-2012), we calculated that 70,000 individuals per arm provided 80% power to detect a 50% difference in CRC mortality reduction between sigmoidoscopy and FIT, after ten years of mean follow-up. Type I error was set to 0.05.

Detection rates for neoplasia and serrated lesions were calculated both among invitees (intention-to-treat) and among attenders (those who attended screening per protocol; attended sigmoidoscopy or returned at least one FIT sample). Because enrolment by design was slower for sigmoidoscopy compared to FIT, individuals in the sigmoidoscopy group were older at invitation. Hence, we calculated age-standardized detection rates in the sigmoidoscopy group, using direct standardization with age at invitation in the first round of FIT (FIT_1) as the reference (five-year age groups). At the time of complete recruitment to the sigmoidoscopy group, 2 full FIT rounds had been completed, and the third round was ongoing. Accordingly, for the analysis of cumulative three rounds of FIT (FIT_{1-3}), we only included individuals invited for the first time before January 1, 2015 (those who had been offered three test-rounds). We fitted logistic regression models adjusted by age (as a continuous covariate) to compare the detection rates of neoplasia between the screening groups and report odds ratios (OR) with 95% confidence intervals (CI).

To illustrate participation rates by age, we used restricted cubic spline univariate logistic models,[20] with knots placed at the four percentiles of age. When calculating the adenoma detection rate (ADR) as a performance measure for sigmoidoscopy, we used a previously described algorithm, including both adenomas removed at sigmoidoscopy and adenomas detected at sigmoidoscopy but first removed at follow-up colonoscopy.[21] Cohen's κ was calculated to determine the agreement between the non-validated cleansing scale used in the trial and the Boston Bowel Preparation Scale (BBPS)[22]. All tests

were two-sided and $p < .05$ was considered statistically significant. Statistical analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC, USA) and Stata statistical software version 16.0 (StataCorp, College Station, TX, USA). All authors had access to the study data and reviewed and approved the final manuscript.

Results

Of 154,743 individuals randomized, 15,452 (10%) were excluded before first invitation, leaving 139,291 individuals for intention-to-treat analyses (Figure 1); 69,195 were invited to sigmoidoscopy and 70,096 to FIT. Median age at first invitation was 63.3 years (IQR 58.0 to 69.3) in the sigmoidoscopy group and 62.2 years (IQR 56.6 to 68.1) in the FIT group (Table 1). 44,016 (63%) individuals were included in the analyses of three cumulative FIT rounds. The participation rate for sigmoidoscopy screening was 52.1%, compared to 58.4% in the first FIT round and 68.4% after three cumulative FIT rounds (participation at least once, Supplementary Table A). Participation was higher in the FIT group compared to sigmoidoscopy for both men and women and for all age-groups (Figure 2, Supplementary Table A). The participation rate was higher in males compared to females in the FIT arm, but no difference were seen for sigmoidoscopy screening (Supplementary Table A).

Positivity rates, follow-up colonoscopies and surveillance

In the sigmoidoscopy group, 3378 (9.4%) attenders were referred for colonoscopy, of which 3297 (97.6%) underwent colonoscopy. Among attenders in FIT_1, 3317 (8.1%) had a positive test result. Cumulative positivity rates for FIT_{1-2} and FIT_{1-3} were 13.1% and 16.5%, respectively (Figure 3). Colonoscopy compliance was about 93% in both the first and subsequent FIT rounds among those testing FIT positive. Among the 6945 attenders who had a colonoscopy in the FIT group, 2749 (39.6%) were referred to polyp surveillance colonoscopy within five years, compared to 2158 (65.5%) of the 3297 individuals who had a colonoscopy in the sigmoidoscopy group.

Screen-detected lesions

In intention-to-treat analyses, 173 patients (0.25%) were diagnosed with CRC in FIT_1 versus 202 (0.27%) in the sigmoidoscopy group (OR 0.92, 95% CI 0.75 to 1.13). CRC detection rates were higher in FIT_{1-2} (0.37%, OR 1.38, 95% CI 1.15 to 1.66) and FIT_{1-3} (0.49% OR 1.87, 95% CI 1.54 to 2.27) compared to sigmoidoscopy (Table 2, Figure 3). The age-adjusted adenoma detection rate was lower in FIT_{1-3} (5.8%) compared to sigmoidoscopy (9.1%, OR 0.62, 95% CI 0.59 to 0.65), while the advanced adenoma detection rate was higher in FIT_{1-3} (2.7%) compared to sigmoidoscopy (2.4%, OR 1.14 95% CI 1.05 to 1.23; Table 2, Figure 3). Subgroup analyses by sex showed similar results (Supplementary Table B, Supplementary Table C). For all CRC stages, the detection rate was higher after three cumulative FIT rounds compared to sigmoidoscopy and the proportion of stage I-II vs stage III-IV CRC was similar in sigmoidoscopy, FIT_1, FIT_{1-2} and FIT_{1-3}. However the proportion of stage I CRC among individuals with cancer was lower in FIT_1, FIT_{1-2} and FIT_{1-3} compared to sigmoidoscopy (Table 2). The difference in detection rates of advanced adenomas and CRC between sigmoidoscopy and FIT_{1-3} was particularly pronounced for lesions located in the proximal colon (Table 2).

In per-protocol analyses, detection rates for CRC were higher in FIT_{1-3} compared to sigmoidoscopy (0.7% vs 0.5%, OR 1.42, 95% CI 1.16 to 1.72), and lower for adenomas (8.6% vs 17.6% OR 0.44, 95% CI 0.42 to 0.46) and advanced adenomas (3.9% vs 4.6%, OR 0.85, 95% CI 0.79 to 0.92), respectively (Supplementary Table D).

Endoscopy performance

Table 3 shows performance for sigmoidoscopy and follow-up colonoscopies. Adequate sigmoidoscopy screening was achieved for 24,800 (69.4%) attenders. The adenoma detection rate was 16.3% at sigmoidoscopy and 58.6% at follow-up colonoscopy in FIT positives. The sigmoidoscopy feed-back questionnaire was completed by 24,356 (69.8%) of 34,891 individuals. Moderate or severe abdominal pain was reported by 2412 (9.9 %) responders.

A total of 10,242 individuals had a colonoscopy after a positive screening test. The overall cecum intubation rate was 98.1% and the bowel cleansing was judged as good or acceptable in 93.7%. The

cecum intubation and bowel cleansing at colonoscopy did not differ between the two screening groups (Supplementary table E). The feed-back questionnaire was completed by 7257 of 8940 individuals (81.2%). Of those, 1756 (24.2%) reported moderate or severe pain. 9413 (91.9%) of the initial follow-up colonoscopies were performed by a screening-dedicated resident endoscopists, while the remaining were performed by gastroenterology consultants. The screening-dedicated endoscopists had higher ADR at the initial colonoscopy subsequent to a positive FIT (57.6% vs 49.6%, $p < .001$), and similar cecum intubation rate and patient reported pain compared to gastroenterology consultants.

In a subsample of 1291 colonoscopies, bowel cleansing was characterized with both the four-point scale and the Boston Bowel Preparation scale (BBPS); 1172 individuals (90.8%) had good or acceptable bowel cleansing on the four-point scale and 1146 (88.8%) had BBPS ≥ 2 in all segments (substantial agreement, $\kappa = 0.730$, 95% CI 0.676 - 0.785, $p < .001$).

Adverse events

Among 36,065 individuals attending sigmoidoscopy, there were three (0.01%) perforations (two of these were most likely caused by the enema tip and one related to polypectomy, all conservatively treated), and three (0.01%) significant bleedings. Two individuals died within 30 days of a diagnostic sigmoidoscopy. None of these deaths were considered related to the screening procedure.

Among the 10,242 participants who had at least one colonoscopy, 7 (0.07 %) perforations and 67 (0.65%) significant bleedings occurred, all related to polypectomy. One of the perforations was surgically treated (without stoma), while six were conservatively treated with antibiotics. Two individuals died within 30 days after colonoscopy. One of these deaths was probably related to the procedure. The person was above 70 years old, had a pre-existing coronary disease and died of an acute myocardial infarction within 24 hours after the colonoscopy.

In total, there were 33 (0.05%) significant bleedings or perforations (sigmoidoscopy and follow-up colonoscopy) among individuals invited in the sigmoidoscopy group compared to 47 (0.07%) significant bleedings or perforations among invitees in the FIT group (p = .13).

Discussion

In this large randomized trial, we show that both repeated FIT and once-only sigmoidoscopy are feasible screening methods. However, participation was higher already in the first round of FIT as compared to sigmoidoscopy and increased in the second and third screening round. After three FIT-screening rounds, more CRCs and advanced adenomas were detected than by sigmoidoscopy. Importantly, the adverse event rates did not differ between the two screening methods.

In contrast to screening sigmoidoscopy, biennial screening for fecal occult blood with gFOBT has not been shown to reduce CRC incidence in randomized trials, while no results for FIT are yet published. [6] No randomized trial comparing the effectiveness of repeated FIT with sigmoidoscopy screening on CRC mortality and incidence currently exists. Previous studies comparing detection rates of FIT versus sigmoidoscopy screening included only one FIT round, were non-randomized, had small sample sizes, or poor participation rates in the sigmoidoscopy arm (28.1- 32.4%).[23-26] One of the trials, combining results from three Dutch screening cohorts, found higher detection rates for advanced neoplasia and CRC with four rounds of FIT compared to sigmoidoscopy.[24] However, the non-randomized design and low participation at sigmoidoscopy makes interpretation difficult. Our participation rates were high both for sigmoidoscopy (52%) and for FIT (58% for the first round, 68% for at least one round) compared to the published literature and the minimum target recommended by EU guidelines (45%).[27]

The higher number of advanced adenomas among invited individuals in the FIT group compared to sigmoidoscopy in our trial, may indicate a potential effect not only on CRC mortality but also CRC incidence reduction. However, it needs to be considered that more non-advanced adenomas were

removed by sigmoidoscopy screening than in the FIT group. A higher detection rate of advanced adenomas with cumulative FIT rounds may be caused by transformation of non-advanced adenomas over time. This may imply that once-only sigmoidoscopy detect most adenomas at a non-advanced stage, while repeated FIT screening over time will detect more adenomas at an advanced stage. Thus, FIT screening may not be more effective than sigmoidoscopy screening to reduce CRC incidence. Also more CRCs might be detected in subsequent FIT rounds since adenomas may transform to invasive lesions over time. These lesions might have been detected as non-invasive lesions if sigmoidoscopy screening was performed. Our trial aims at disentangling these most important features as it will continue towards its primary endpoint of the comparison of CRC mortality and incidence after ten years follow-up. Presently, our data do not support any conclusion with respect to superiority of any screening method. But we believe that our results may be informative for researchers that work with screening modelling. The number of CRCs and advanced adenomas detected per screened in the present study is within the range reported from previous sigmoidoscopy[21, 28-30], and FIT screening trials with comparable cut-offs (10-20 µg hemoglobin/g feces).[23, 31-33]

Our result suggests that FIT screening might result in greater protection against proximal cancer development and death in the long-term, as compared to sigmoidoscopy screening. This may be explained by FIT detecting bleeding in the entire colon, while sigmoidoscopy is only examining the distal colon and rectum. We also show a difference in stage distribution between sigmoidoscopy and FIT in our trial with higher proportion of stage I CRC in the sigmoidoscopy group compared to three cumulative FIT rounds. However, the absolute number of stage I CRC detected was similar after two rounds of FIT and will be higher after three complete FIT rounds compared to sigmoidoscopy.

In our analyses of *screened* individuals (per protocol analyses), CRC detection rates were higher after three rounds of FIT screening compared to sigmoidoscopy. The advanced adenoma detection rate increased with increasing FIT rounds but was still slightly lower after three FIT rounds compared to sigmoidoscopy. However, per protocol analyses are difficult to interpret due to the inherent risk of selection bias.

The effect of a CRC screening program relies on high-quality colonoscopies with few adverse events. Most endoscopists in our trial had little endoscopy experience when they were recruited, but received intensive training and were closely monitored and given feedback on key quality indicators throughout the trial. The colonoscopy performance was excellent with cecum intubation rate of 98% and a bowel cleansing quality above the requirements for screening colonoscopies.[34] Also, the adenoma detection rate at follow-up colonoscopy in our trial (58.6%) is within the range of other FIT screening programs (37-65 %) [35-37] and higher than the benchmarks for colonoscopy following a positive FIT (45% for males and 35% for females) suggested by the US Multi-Society Task Force on Colorectal Cancer.[38]

Limited colonoscopy capacity is a bottleneck for endoscopic CRC screening. We show that recruitment and training of high-quality endoscopists is feasible within a rather short time frame. However, this result requires sufficient resources (e.g. experienced endoscopist trainers) available for teaching. The number of referrals for follow-up colonoscopy and for colonoscopy surveillance was higher after three rounds of FIT compared to sigmoidoscopy. Thus, the higher CRC and advanced adenoma detection is accompanied with an increased demand for colonoscopy. On the other hand, sigmoidoscopy is an invasive procedure associated with some discomfort, work-absenteeism, and risk of adverse events, while FIT testing per se is not.[6, 39]

Even with high-quality endoscopies, serious adverse events occur. The rate of significant bleedings (0.65%) and perforations (0.07%) among individuals having a colonoscopy in the present trial is in line with that reported from the English gFOBT screening program (0.65% bleeding and 0.06% perforation rate).[40] Importantly, we show that significant bleedings and perforations were equally frequent among those invited for sigmoidoscopy compared to those invited to FIT so far. However, with increasing rounds of FIT-screening, the number of adverse events in the FIT group may exceed those invited for sigmoidoscopy screening.

Almost one quarter of individuals undergoing colonoscopy reported moderate or severe pain. This is probably a consequence of providing sedation on-demand during colonoscopy and must be weighed against possible harms and disadvantages of more or deeper sedation. The reputation of the screening procedure should also be considered, as fear of pain has been shown to be a barrier to screening participation.[41] However, despite the relatively high rate of self-reported pain, the majority of screening attenders reported that they were satisfied with the examination.

The main strength of this study is the population design with no consent before inclusion - mimicking an organized screening program. Secondly, we included multiple FIT rounds in the analysis, which allows for a fair comparison on diagnostic yield compared to once-only sigmoidoscopy. Other strengths include the large sample-size; the relatively high participation rates at screening; and the availability of information on performance measures, adverse events, and patient experience in this trial.

The study also has limitations. First, the design of the study with all individuals being randomized at one point in time (in 2012) and a slower invitation rate for sigmoidoscopy led to a mean age difference of one year at the time of first invitation between the two study groups. To avoid a potential bias related to the increased prevalence of CRC and advanced adenomas by age,[42] we age-adjusted detection rates as described in the methods section. Another limitation is incomplete data from the third FIT round (63%). Since the dataset is large, however, we do not expect substantial changes in detection rates when the third round is complete. Third, we did not have any information of non-study colonoscopies performed before or during the course of the trial. Currently, there is no CRC screening program in Norway, and opportunistic screening is the indication for less than 5% of colonoscopies, according to the Norwegian colonoscopy quality registry (Gastronet).[43] According to a European survey from 2014, about 30% of the population aged 50-74 years in Norway have had a colonoscopy within the last 10 years.[44] Individuals with a previous colonoscopy were presumably equally distributed between the two arms at the time of randomization, but we cannot rule out that a previous colonoscopy history has had different impact on screening uptake or findings at screening in the two

arms. Also, our results may not be generalizable to populations with different prevalence of colonoscopy history. In Norway, a national screening program will commence in 2021 with biennial FIT, starting at age 55. Although participants in the current trial will not be eligible for the national program, its introduction may influence the population's awareness of CRC, as well as colonoscopy referral practice among physicians. It cannot be ruled out that implementation of a nationwide screening program may affect the long-term outcome in the two trial arms differently. The final results will not be obtained until 10 years of follow-up. Even with this long time-frame, results from large randomized trials like ours will offer important information for policy makers with regard to the upcoming screening program in Norway, and in other countries where screening programs are already in place or imminent.

Fourth, there is a risk that individuals in the same household were randomized to different arms of the trial. This might have influenced their behavior in ways relating to the exposure (screening method) or outcome (CRC). Fifth, due to increased awareness of serrated lesions over the last two decades, there is a possibility that serrated lesions may have been inconsistently classified during the trial. However, no significant increase in serrated lesion detection rates was seen over time (data not shown). Sixth, the high number of inadequate sigmoidoscopies may affect the detection rate in the sigmoidoscopy arm. However, adequate bowel preparation is not obtained as easily with enemas as with oral formulations used for full colonoscopy cleansing, and the adenoma detection at sigmoidoscopy in our trial was higher (16.3 %) than reported from both the UK flexible sigmoidoscopy trial (12.1% distal adenomas)[29] and the Italian SCORE trial (10.8% distal adenomas)[28], but in line with the NORCCAP trial (16.6 % any neoplasm)[45]. Of note, the age groups included were younger in NORCCAP (50-64 years) and the UK and Italian trials (55-64 years) compared to the present trial (50-74 years) and criteria for referral to colonoscopy differed between the trials (any polyp sized ≥10 mm or biopsy-verified neoplasia in the NORCCAP trial, adenomas meeting high risk criteria or any polyp ≥ 10 mm in the UK trial, and high risk adenoma or any polyp ≥ 5 mm in the Italian SCORE trial) making a direct comparison of ADR difficult.

It is worth mentioning that a threshold of 15 µg/g for FIT positivity in the current trial is relatively low, and our results may not be applicable to programs choosing other cut-off values. Finally, our results on participation and effects might not be generalizable to populations with other distributions of socio-economic background and education levels, but these data were not available in the current trial.

Conclusion

Baseline results from this randomized, comparative effectiveness trial showed higher detection rates for advanced adenomas and CRC with three cumulative FIT rounds compared to once-only sigmoidoscopy. Both methods are feasible in Norway with acceptable participation rates and comparable complication rates. Long-term follow-up data on CRC mortality and incidence are not expected until 10 years of follow-up.

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Author names in bold designate shared co-first authorship

Figure legends and footnotes

Figure 1. Flowchart

FIT = fecal immunochemical test. CRC = colorectal cancer.
* missing postal address (n=581), postal address abroad (n=60), withdrew consent (n=3), randomization error (n=2), invitation error (n=7)

Figure 2. Participation rates by age in the sigmoidoscopy group, FIT round 1 (FIT_1) and FIT round 1-3 (FIT_{1-3}) for males (A) and females (B), respectively

FIT = fecal immunochemical test. CI = confidence interval.
*Participation defined as at least once across FIT rounds.

Figure 3. Positivity rates and age-standardized detection rates for colorectal cancer and advanced adenoma among invited individuals in the sigmoidoscopy group, FIT round 1 (FIT_1), FIT round 1-2 (FIT_{1-2}) and FIT round 1-3 (FIT_{1-3}) for both sexes, males and females (A-I)

AA = advanced adenoma. FIT = fecal immunochemical test. CRC = colorectal cancer.

Table 1. Baseline characteristics for included individuals

Characteristic		**Sigmoidoscopy group**	**FIT group**
Included individuals		69,195 (100)	70,096 (100)
Sex	female	35,127 (50.8)	35,495 (50.6)
	male	34,068 (49.2)	34,601 (49.4)
Age at first invitation*	Median (IQR) years	63.3 (58.0 to 69.3)	62.2 (56.6 to 68.1)
	50-59 years	23,960 (34.6)	28,504 (40.7)
	60-69 years	30,081 (43.5)	29,223 (41.7)
	≥ 70 years	15,154 (21.9)	12,369 (17.6)
Screening Center	Center 1	37,071 (53.6)	36,405 (51.9)
	Center 2	32,124 (46.4)	33,691 (48.1)

Data are n (%) unless otherwise stated. FIT = fecal immunochemical test. IQR = interquartile range.
*median age at randomization for the initial 154,743 individuals was 60.0 years, IQR 54.3 to 66.0 in both study groups.

Table 2. Findings among invited individuals (intention to treat analyses) in the sigmoidoscopy group, FIT round 1 (FIT_1), FIT round 1-2 (FIT_{1-2}), and FIT round 1-3 (FIT_{1-3}).

	Sigmoidoscopy (n = 69,195)		**FIT round 1** (n = 70,096)			**FIT round 1-2** (n = 70,096)			**FIT round 1-3** (n= 44,016)		
	No	**%***	**No**	**%**	**OR (95% CI)†**	**No**	**%**	**OR (95% CI)†**	**No**	**%***	**OR (95% CI)†**
Colorectal cancer	202	0.27	173	0.25	0.92 (0.75 to 1.13)	260	0.37	1.38 (1.15 to 1.66)	210	0.49	1.87 (1.54 to 2.27)
Proximal‡	21	0.03	41	0.06	2.08 (1.23 to 3.52)	77	0.11	3.92 (2.42 to 6.36)	63	0.15	5.47 (3.33 to 8.99)
Distal‡	181	0.24	134	0.19	0.79 (0.64 to 0.99)	187	0.27	1.11 (0.90 to 1.36)	152	0.36	1.51 (1.21 to 1.87)
Stage I	130	0.17	87	0.12	0.72 (0.55 to 0.95)	133	0.19	1.10 (0.86 to 1.40)	101	0.24	1.40 (1.08 to 1.82)
Stage II	22	0.03	33	0.05	1.61 (0.94 to 2.77)	54	0.08	2.66 (1.62 to 4.37)	55	0.13	4.53 (2.76 to 7.46)
Stage III	40	0.06	40	0.06	1.06 (0.68 to 1.64)	56	0.08	1.47 (0.98 to 2.21)	45	0.11	1.96 (1.27 to 3.01)
Stage IV	10	0.01	13	0.02	1.37 (0.60 to 3.13)	17	0.02	1.82 (0.83 to 3.97)	9	0.02	1.67 (0.68 to 4.14)
Other cancer§¶	26	0.04	7	0.01	0.27 (0.12 to 0.61)	13	0.02	0.50 (0.25 to 0.97)	10	0.02	0.60 (0.29 to 1.26)
Adenoma§	6396	9.06	1793	2.56	0.27 (0.25 to 0.28)	3163	4.53	0.48 (0.46 to 0.50)	2485	5.79	0.62 (0.59 to 0.65)
Proximal‡	1425	1.98	1040	1.49	0.76 (0.70 to 0.82)	1863	2.67	1.38 (1.28 to 1.48)	1474	3.45	1.81 (1.68 to 1.95)
Distal‡	6126	8.68	1405	2.01	0.22 (0.20 to 0.23)	2447	3.50	0.38 (0.37 to 0.40)	1895	4.42	0.49 (0.46 to 0.51)
Advanced adenoma§	1699	2.38	950	1.36	0.57 (0.53 to 0.62)	1478	2.12	0.89 (0.83 to 0.96)	1132	2.65	1.14 (1.05 to 1.23)
Proximal‡	271	0.37	275	0.39	1.08 (0.91 to 1.28)	428	0.61	1.68 (1.44 to 1.96)	331	0.77	2.19 (1.86 to 2.57)
Distal‡	1577	2.21	787	1.13	0.51 (0.47 to 0.55)	1214	1.74	0.79 (0.73 to 0.85)	922	2.16	0.99 (0.91 to 1.07)
≥ 3 non-adv. adenoma§	424	0.58	217	0.31	0.53 (0.45 to 0.63)	434	0.62	1.07 (0.94 to 1.23)	358	0.85	1.47 (1.27 to 1.69)
Advanced serrated lesions§	632	0.89	209	0.30	0.34 (0.29 to 0.39)	404	0.58	0.65 (0.58 to 0.74)	330	0.76	0.88 (0.77 to 1.00)
Proximal‡	296	0.42	138	0.20	0.48 (0.39 to 0.59)	279	0.40	0.97 (0.82 to 1.14)	234	0.54	1.33 (1.12 to 1.59)
Distal‡	409	0.58	83	0.12	0.21 (0.16 to 0.26)	146	0.21	0.36 (0.30 to 0.44)	109	0.25	0.44 (0.36 to 0.55)

OR = Odds ratio. CI = Confidence interval.

* Age-standardized rates.

† Compared to sigmoidoscopy and adjusted by age.

‡ The sum may exceed the total number, due to the possibility of findings in both the proximal and distal colon.

§ Individuals with colorectal cancers detected at screening are excluded from analyses when calculating other cancers, adenomas, and serrated lesions.

¶ Other cancer includes screening detected neuroendocrine tumors, squamous cell carcinomas, and lymphomas.

Table 3. Performance measures and severe adverse events at sigmoidoscopy and colonoscopy following a positive screening test

	Sigmoidoscopy	Follow-up colonoscopy
Participating individuals	36,065	10,242
Intubation depth Median (IQR)	50 (40 - 56) cm	N/A
Cecum intubated	N/A	10,043 (98.1)
Withdrawal time ≥ 6 minutes[*]	N/A	2015/2077 (97.0)
On-demand sedation or analgesia	N/A	3206 (31.3)
Bowel cleansing quality[†]		
good	20,950 (58.7)	7476 (74.1)
acceptable	6580 (18.4)	1978 (19.6)
partly poor	7089 (19.9)	551 (5.5)
poor	1091 (3.1)	84 (0.8)
Adequate examination[†]	24,800 (69.4)	9293 (92.1)
Adenoma detection rate	5894 (16.3)	4073 (58.6)[‡]
Major adverse events		
Perforation	3 (0.01)	7 (0.07)
Significant bleeding[§]	3 (0.01)	67 (0.65)
Death	0 (0.00)	1 (0.01)
Patient reported pain[¶]		
none	14,975 (61.5)	2883 (39.7)
slight	6969 (28.6)	2618 (36.1)
moderate	1642 (6.7)	1047 (14.4)
severe	770 (3.2)	709 (9.8)
Patient satisfaction[¶]		
satisfied	22,949 (98.4)	6703 (97.9)
not satisfied	374 (1.6)	141 (2.1)

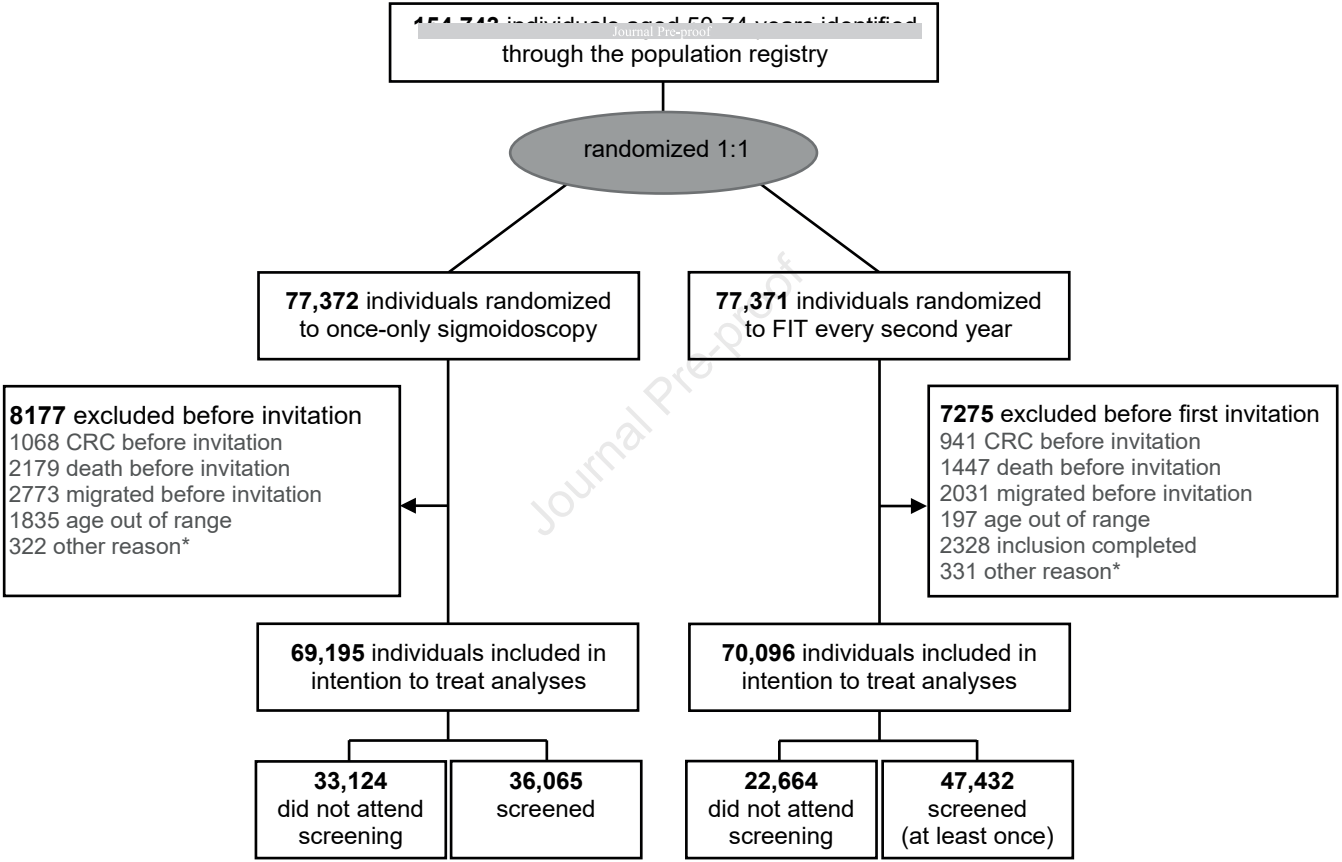
Data are n (%) if not otherwise stated. N/A = Not applicable. IQR = Interquartile range *Proportion of complete diagnostic colonoscopies (no polypectomy or biopsy) with time from cecum to end of procedure ≥ 6 minutes.

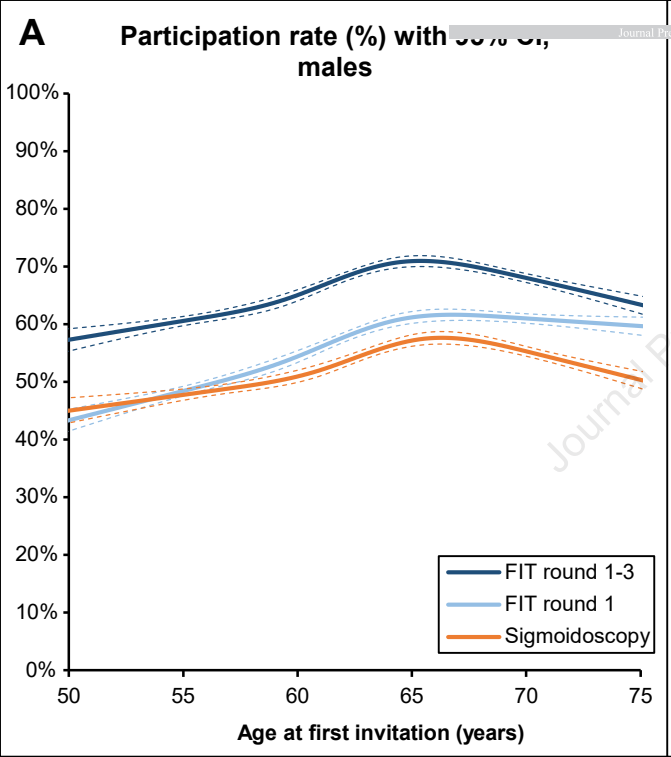
[†] Bowel cleansing quality missing for 355 sigmoidoscopy participants and 153 colonoscopy participants.

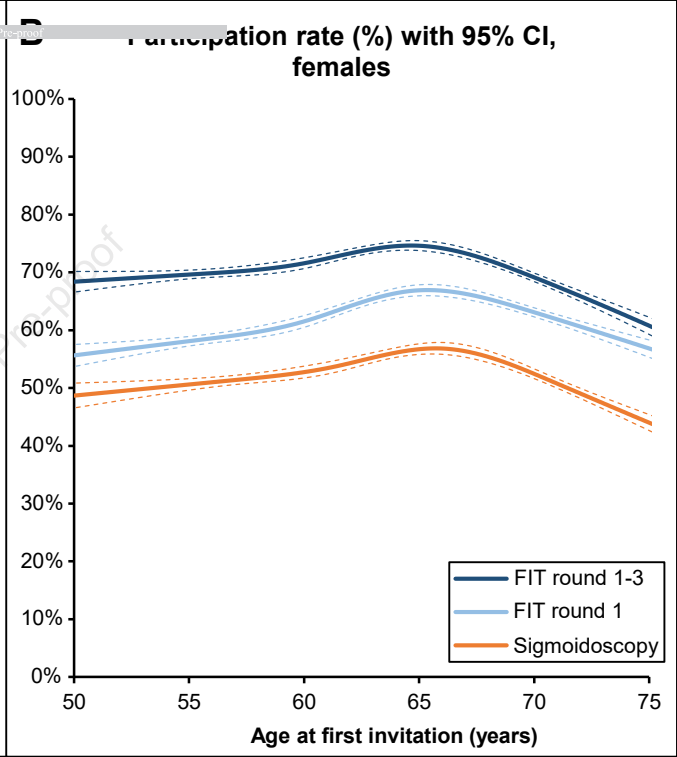
[‡] In the fecal immunochemical test (FIT) group (n = 6945)

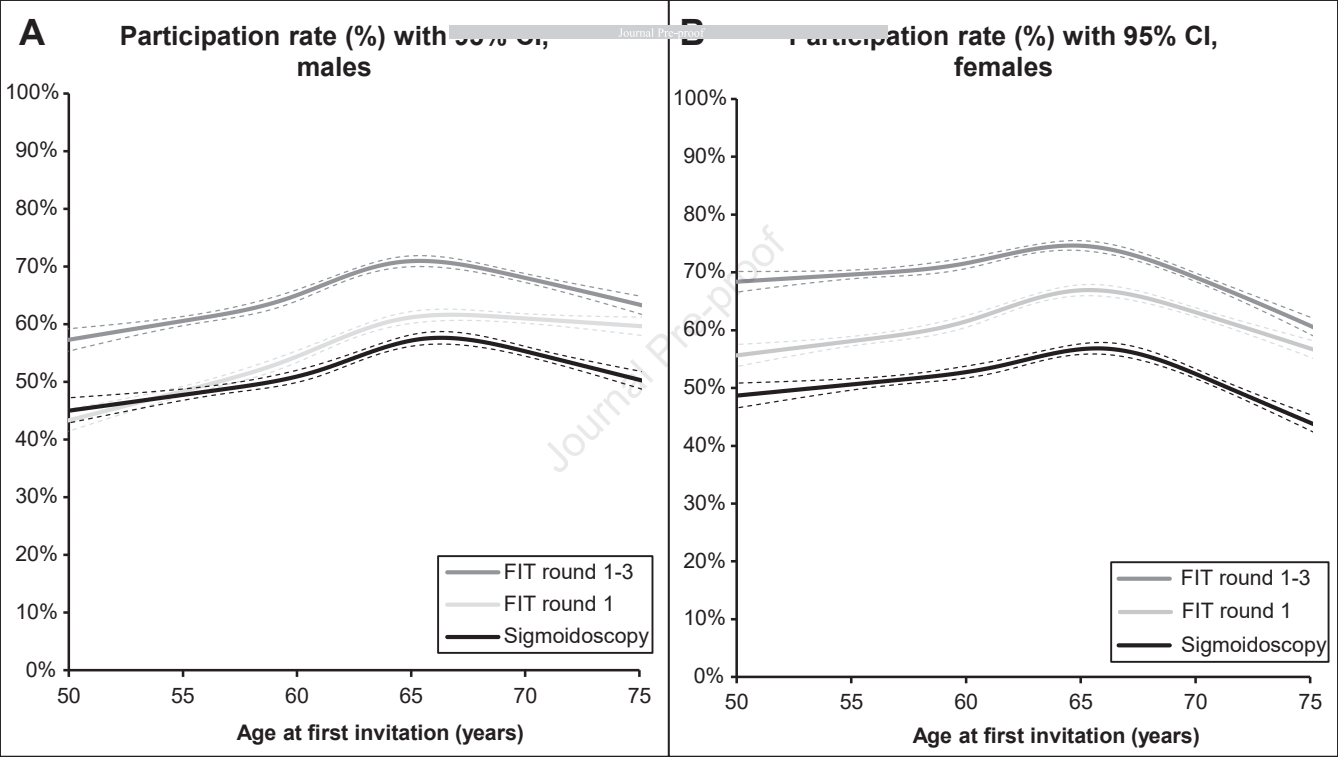
[§] Significant bleeding defined as requiring hospital admission, repeat endoscopy, blood transfusion, radiologic intervention, or surgery

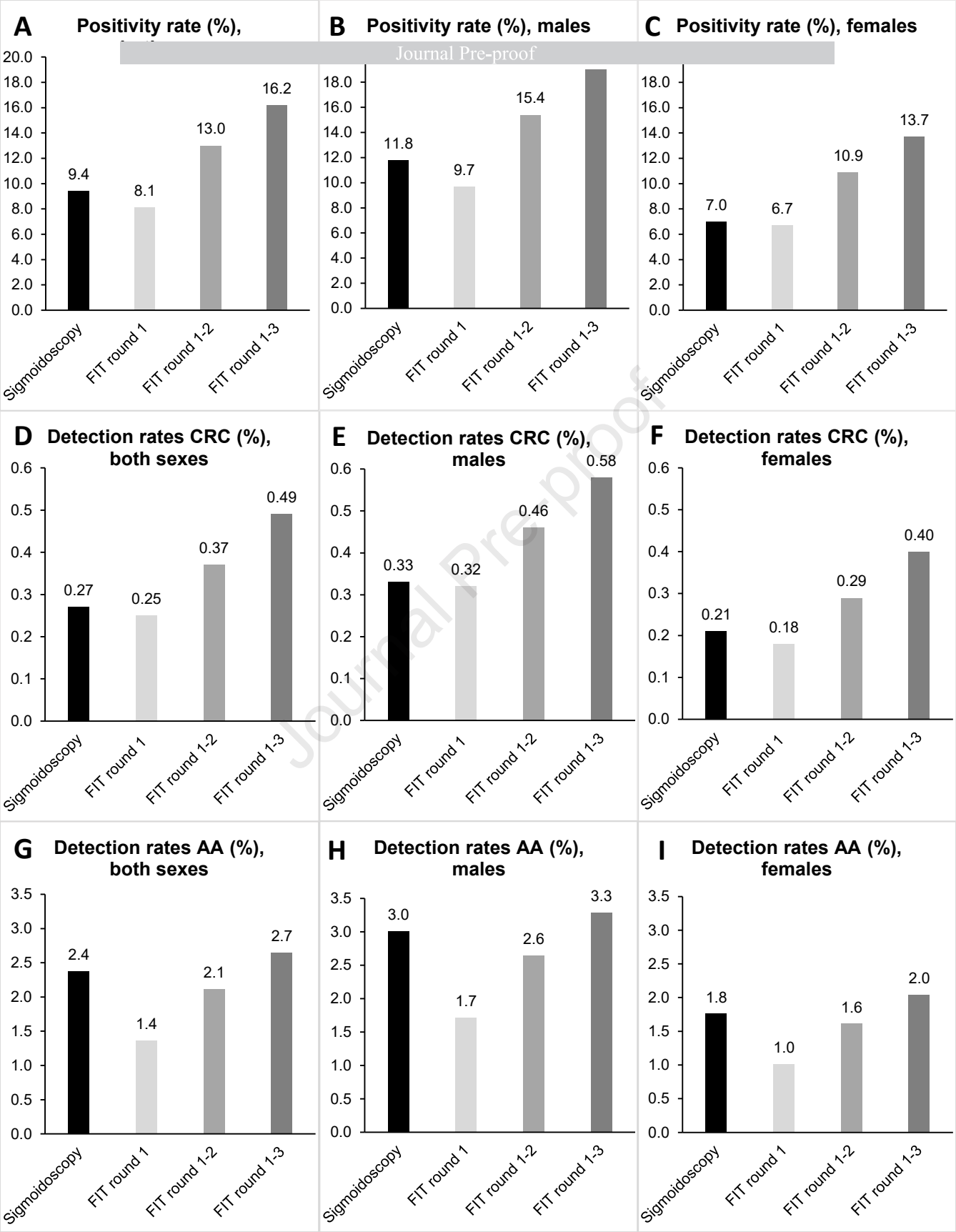
[¶] Percentages among responding individuals (in years 2012-2018)

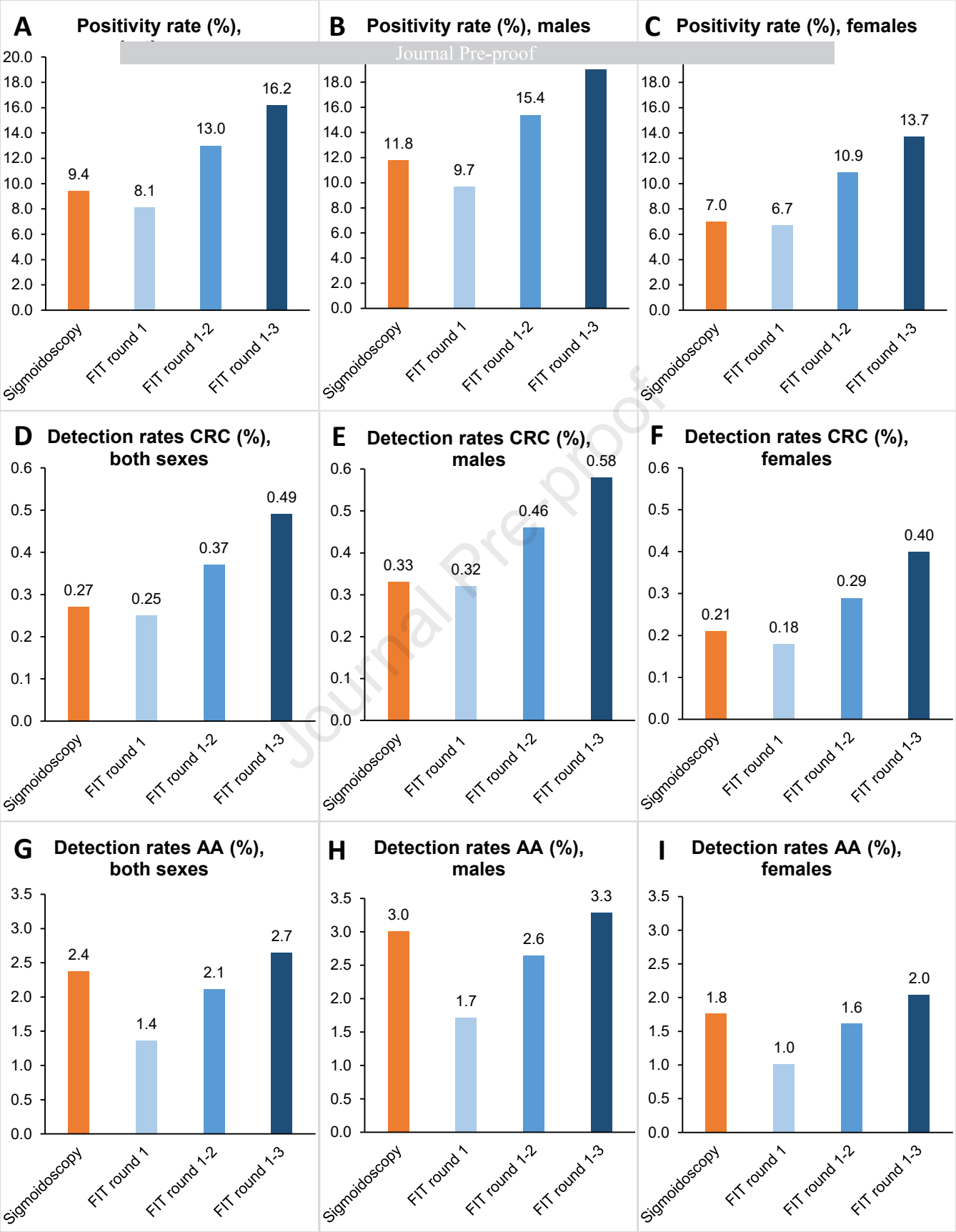












Supplementary Table A. Screening participation, positivity rates, and colonoscopy attendance in the sigmoidoscopy group, FIT round 1 (FIT_1), FIT round 1-2 (FIT_{1-2}) and FIT round 1-3 (FIT_{1-3}) by sex and by age at first invitation.

		Sigmoidoscopy (n = 69,195)	**FIT round 1** (n = 70,096)	**FIT round 1-2** (n = 70,096)	**FIT round 1-3** (n = 44,016)
Participating individuals*		**36,065 (52.1)**	**40,966 (58.4)**†	**45,687 (65.2)**†	**30,110 (68.4)**†
sex	females	18,246 (51.9)	21,791 (61.4)†	24,085 (67.9)†	15,854 (70.9)†
	males	17,8198 (52.3)	19,175 (55.4)†	21,602 (62.4)†	14,256 (65.8)†
age group	50-59 y	11,971 (50.0)	15,404 (54.0)†	17,696 (62.1)†	12,850 (66.1)†
	60-69 y	16,496 (54.8)	18,125 (62.0)†	20,000 (68.4)†	12,899 (71.6)†
	≥ 70 y	7598 (50.1)	7437 (60.1)†	7991 (64.6)†	4361 (66.4)†
Positive screening test‡		**3378 (9.4)**	**3317 (8.1)**§	**5958 (13.0)**†	**4883 (16.2)**†
sex	females	1275 (7.0)	1461 (6.7)	2627 (10.9)†	2173 (13.7)†
	males	2103 (11.8)	1856 (9.7)§	3331 (15.4)†	2710 (19.0)†
age group	50-59 y	812 (6.8)	947 (6.1)§	1832 (10.4)†	1724 (13.4)†
	60-69 y	1581 (9.6)	1517 (8.4)§	2787 (13.9)†	2326 (18.0)†
	≥ 70 y	985 (13.0)	853 (11.5)§	1339 (16.8)†	833 (19.1)†
Attended colonoscopy¶		**3297 (97.6)**	**3107 (93.7)**§	**5555 (93.2)**§	**4525 (92.7)**§
sex	females	1234 (96.8)	1361 (93.2)§	2441 (92.9)§	2010 (92.5)§
	males	2063 (98.1)	1746 (94.1)§	3114 (93.5)§	2515 (92.8)§
age group	50-59 y	794 (97.8)	901 (95.2)§	1728 (94.3)§	1610 (93.4)§
	60-69 y	1544 (97.7)	1423 (93.8)§	2604 (93.4)§	2154 (92.6)§
	≥ 70 y	959 (97.4)	783 (91.8)§	1223 (91.3)§	761 (91.4)§

Data are reported as n (%). FIT= fecal immunochemical test. y = age in years at time of first invitation.
* Participation defined as at least once across FIT rounds
† $p < .05$ compared to sigmoidoscopy, in favor of FIT.
‡ Percentages among individuals attending screening.
§ $p < .05$ compared to sigmoidoscopy, in favor of sigmoidoscopy.
¶ Percentages among individuals with a positive screening test.

Supplementary Table B. Findings among invited individuals in the sigmoidoscopy group, FIT round 1, 1-2, and 1-3, females.

	Sigmoidoscopy (n = 35,127)		FIT round 1 (n = 35,495)			FIT round 1-2 (n = 35,495)			FIT round 1-3[a] (n =22,359)		
	No	%*	No	%	OR (95% CI)[†]	No	%	OR (95% CI)[†]	No	%*	OR (95% CI)[†]
Colorectal cancer	79	0.21	64	0.18	0.86 (0.62 to 1.19)	102	0.29	1.36 (1.02 to 1.83)	89	0.40	1.96 (1.45 to 2.67)
Proximal[‡]	12	0.03	23	0.06	2.03 (1.01 to 4.09)	41	0.12	3.64 (1.91 to 6.94)	37	0.17	5.59 (2.91 to 10.77)
Distal[‡]	67	0.18	42	0.12	0.66 (0.45 to 0.98)	63	0.18	0.99 (0.70 to 1.40))	55	0.25	1.42 (0.99 to 2.03)
Stage I	49	0.13	33	0.09	0.71 (0.46 to 1.11)	48	0.14	1.03 (0.69 to 1.54)	37	0.17	1.31 (0.85 to 2.01)
Stage II	10	0.03	14	0.04	1.49 (0.66 to 3.36)	25	0.07	2.68 (1.29 to 5.59)	31	0.14	5.38 (2.63 to 11.02)
Stage III	14	0.04	11	0.03	0.82 (0.37 to 1.81)	22	0.06	1.63 (0.83 to 3.18)	17	0.08	2.08 (1.02 to 4.25)
Stage IV	6	0.02	6	0.02	1.06 (0.34 to 3.30)	7	0.02	1.25 (0.42 to 3.73)	4	0.02	1.27 (0.36 to 4.55)
Other cancer[§¶]	9	0.03	4	0.01	0.45 (0.14 to 1.46)	8	0.02	0.90 (0.35 to 2.34)	5	0.02	0.85 (0.28 to 2.56)
Adenoma[§]	2545	7.15	695	1.96	0.26 (0.24 to 0.29)	1237	3.50	0.47 (0.44 to 0.51)	971	4.41	0.61 (0.56 to 0.65)
Proximal[‡]	421	1.16	346	0.98	0.85 (0.74 to 0.99)	657	1.86	1.64 (1.45 to 1.86)	526	2.41	2.17 (1.90 to 2.47)
Distal[‡]	2461	6.92	533	1.50	0.21 (0.19 to 0.23)	940	2.66	0.37 (0.34 to 0.40)	729	3.31	0.46 (0.43 to 0.51)
Advanced adenoma[§]	635	1.76	359	1.01	0.58 (0.51 to 0.66)	568	1.61	0.92 (0.82 to 1.03)	446	2.04	1.18 (1.05 to 1.34)
Proximal[‡]	68	0.19	85	0.24	1.32 (0.96 to 1.81)	144	0.41	2.24 (1.67 to 2.99)	118	0.54	3.03 (2.24 to 4.10)
Distal[‡]	607	1.68	299	0.84	0.50 (0.44 to 0.58)	471	1.33	0.79 (0.70 to 0.90)	367	1.68	1.01 (0.89 to 1.16)
≥ 3 non-advanced adenoma[§]	113	0.31	63	0.18	0.58 (0.43 to 0.80)	138	0.39	1.28 (1.00 to 1.65)	111	0.51	1.68 (1.29 to 2.19)
Advanced serrated lesion[§]	302	0.84	103	0.29	0.35 (0.28 to 0.43)	202	0.57	0.68 (0.57 to 0.82)	166	0.75	0.91 (0.75 to 1.10)
Proximal[‡]	152	0.42	69	0.19	0.46 (0.35 to 0.62)	147	0.42	0.99 (0.79 to 1.25)	131	0.59	1.44 (1.14 to 1.83)
Distal[‡]	190	0.53	40	0.11	0.21 (0.15 to 0.30)	65	0.18	0.35 (0.26 to 0.46)	45	0.20	0.39 (0.28 to 0.54)

FIT = Fecal immunochemical test. OR = odds ratio. CI = confidence interval

* Age-standardized detection rates.

[†] Compared to sigmoidoscopy and adjusted by age

[‡] The sum may exceed the total number, due to the possibility of findings in both the proximal and distal colon

[§] Individuals with colorectal cancers detected at screening are excluded from analyses when calculating other cancers, adenomas, and serrated lesions.

[¶] Other cancer includes screening detected neuroendocrine tumors, squamous cell carcinomas, and lymphomas.

Supplementary Table C. Findings among invited individuals in the sigmoidoscopy group, FIT round 1, 1-2, and 1-3, males.

	Sigmoidoscopy (n = 34,068)		FIT round 1 (n = 34,601)			FIT round 1-2 (n = 34,601)			FIT round 1-3[a] (n = 21,657)		
	No	%*	No	%	OR (95% CI)[†]	No	%	OR (95% CI)[†]	No	%*	OR (95% CI)[†]
Colorectal cancer	123	0.33	109	0.32	0.96 (0.74 to 1.24)	158	0.46	1.39 (1.10 to 1.76)	121	0.58	1.81 (1.40 to 2.33)
Proximal[‡]	9	0.02	18	0.05	2.14 (0.96 to 4.77)	36	0.10	4.29 (2.07 to 8.93)	26	0.12	5.30 (2.47 to 11.36)
Distal[‡]	114	0.31	92	0.27	0.87 (0.66 to 1.15)	124	0.36	1.18 (0.91 to 1.52)	97	0.47	1.57 (1.19 to 2.06)
Stage I	81	0.21	54	0.16	0.73 (0.51 to 1.02)	85	0.25	1.14 (0.84 to 1.55)	64	0.31	1.46 (1.05 to 2.03)
Stage II	12	0.03	19	0.05	1.72 (0.83 to 3.54)	29	0.08	2.64 (1.34 to 5.17)	24	0.12	3.81 (1.90 to 7.66)
Stage III	26	0.07	29	0.08	1.19 (0.70 to 2.02)	34	0.10	1.38 (0.83 to 2.31)	28	0.14	1.89 (1.10 to 3.24)
Stage IV	4	0.01	7	0.02	1.83 (0.53 to 6.27)	10	0.03	2.66 (0.83 to 8.50)	5	0.02	2.26 (0.60 to 8.51)
Other cancer[§¶]	17	0.05	3	0.01	0.17 (0.05 to 0.59)	5	0.01	0.29 (0.11 to 0.78)	5	0.02	0.47 (0.17 to 1.28)
Adenoma[§]	3851	11.02	1098	3.18	0.27 (0.25 to 0.28)	1926	5.59	0.48 (0.45 to 0.51)	1514	7.23	0.63 (0.59 to 0.67)
Proximal[‡]	1004	2.81	694	2.01	0.72 (0.65 to 0.79)	1206	3.50	1.27 (1.16 to 1.38)	948	4.53	1.67 (1.53 to 1.83)
Distal[‡]	3665	10.48	872	2.53	0.22 (0.21 to 0.24)	1507	4.38	0.39 (0.37 to 0.42)	1166	5.58	0.50 (0.47 to 0.54)
Advanced adenoma[§]	1064	3.01	591	1.71	0.57 (0.51 to 0.63)	910	2.64	0.88 (0.81 to 0.96)	686	3.29	1.11 (1.01 to 1.23)
Proximal[‡]	203	0.56	190	0.55	1.00 (0.82 to 1.22)	284	0.82	1.49 (1.25 to 1.79)	213	1.02	1.91 (1.57 to 2.32)
Distal[‡]	970	2.75	488	1.41	0.51 (0.46 to 0.57)	743	2.16	0.78 (0.71 to 0.86)	555	2.66	0.97 (0.88 to 1.08)
≥ 3 non-advanced adenoma[§]	311	0.86	154	0.45	0.51 (0.42 to 0.63)	296	0.86	0.99 (0.85 to 1.17)	247	1.20	1.40 (1.18 to 1.65)
Advanced serrated lesion[§]	330	0.93	106	0.31	0.33 (0.26 to 0.41)	202	0.59	0.63 (0.53 to 0.75)	164	0.78	0.84 (0.70 to 1.02)
Proximal[‡]	144	0.41	69	0.20	0.49 (0.37 to 0.66)	132	0.38	0.94 (0.74 to 1.19)	103	0.49	1.22 (0.94 to 1.57)
Distal[‡]	219	0.61	43	0.12	0.20 (0.14 to 0.28)	81	0.24	0.38 (0.29 to 0.49)	64	0.30	0.49 (0.37 to 0.65)

FIT = Fecal immunochemical test. OR = odds ratio. CI = confidence interval

* Age-standardized detection rates.

[†] Compared to sigmoidoscopy and adjusted by age

[‡] The sum may exceed the total number, due to the possibility of findings in both the proximal and distal colon.

[§] Individuals with colorectal cancers detected at screening are excluded from analyses when calculating other cancers, adenomas, and serrated lesions.

[¶] Other cancer includes screening detected neuroendocrine tumors, squamous cell carcinomas, and lymphomas.

Supplementary Table D. Findings among individuals actually screened (per-protocol analyses) in the sigmoidoscopy group and FIT round 1, 1-2 and 1-3.

	Sigmoidoscopy (n = 36,065)	**FIT round 1** (n = 40,966)		**FIT round 1-2** (n = 45,687)		**FIT round 1-3** (n = 30,110)	
	Detection rate, %*	**Detection rate, %**	**OR (95% CI)†**	**Detection rate, %***	**OR (95% CI)†**	**Detection rate, %***	**OR (95% CI)†**
Colorectal cancer	0.53	0.42	0.80 (0.65 to 0.98)	0.58	1.10 (0.91 to 1.31)	0.73	1.42 (1.16 to 1.72)
Proximal‡	0.05	0.10	1.81 (1.07 to 3.06)	0.17	3.11 (1.92 to 5.03)	0.22	4.15 (2.52 to 6.81)
Distal‡	0.48	0.33	0.69 (0.55 to 0.86)	0.42	0.88 (0.71 to 1.08)	0.53	1.14 (0.92 to 1.42)
Stage I	0.34	0.21	0.62 (0.48 to 0.82)	0.30	0.87 (0.68 to 1.11)	0.35	1.06 (0.82 to 1.38)
Stage II	0.06	0.08	1.40 (0.82 to 2.40)	0.12	2.10 (1.28 to 3.45)	0.19	3.44 (2.09 to 5.65)
Stage III	0.11	0.10	0.92 (0.59 to 1.43)	0.12	1.17 (0.78 to 1.75)	0.16	1.48 (0.97 to 2.28)
Stage IV	0.03	0.03	1.19 (0.52 to 2.72)	0.04	1.44 (0.66 to 3.15)	0.03	1.27 (0.51 to 3.14)
Other cancer§¶	0.07	0.02	0.24 (0.10 to 0.54)	0.03	0.40 (0.20 to 0.77)	0.03	0.46 (0.22 to 0.96)
Adenoma§	17.58	4.40	0.22 (0.20 to 0.23)	7.01	0.35 (0.34 to 0.37)	8.57	0.44 (0.42 to 0.46)
Proximal‡	3.86	2.55	0.66 (0.61 to 0.71)	4.14	1.09 (1.01 to 1.16)	5.12	1.37 (1.27 to 1.48)
Distal‡	16.84	3.44	0.18 (0.17 to 0.19)	5.42	0.28 (0.27 to 0.30)	6.54	0.34 (0.33 to 0.36)
Advanced adenoma§	4.63	2.33	0.49 (0.46 to 0.54)	3.28	0.70 (0.65 to 0.75)	3.93	0.85 (0.79 to 0.92)
Proximal‡	0.73	0.67	0.94 (0.79 to 1.11)	0.95	1.33 (1.14 to 1.55)	1.16	1.66 (1.41 to 1.95)
Distal‡	4.30	1.93	0.44 (0.40 to 0.48)	2.69	0.62 (0.57 to 0.67)	3.20	0.74 (0.68 to 0.81)
≥ 3 non-advanced adenoma§	1.14	0.53	0.46 (0.39 to 0.55)	0.97	0.85 (0.74 to 0.97)	1.26	1.11 (0.96 to 1.28)
Advanced serrated lesion§	1.73	0.51	0.29 (0.25 to 0.34)	0.89	0.52 (0.46 to 0.59)	1.13	0.66 (0.58 to 0.76)
Proximal‡	0.81	0.34	0.42 (0.34 to 0.51)	0.62	0.77 (0.65 to 0.90)	0.80	1.01 (0.85 to 1.20)
Distal‡	1.12	0.20	0.18 (0.14 to 0.23)	0.32	0.29 (0.24 to 0.35)	0.37	0.34 (0.27 to 0.42)

FIT = Fecal immunochemical test. OR = odds ratio. CI = confidence interval

* Age-standardized detection rates.

† Compared to sigmoidoscopy and adjusted by age

‡ The sum may exceed the total number, due to the possibility of findings in both the proximal and distal colon.

§ Individuals with colorectal cancers detected at screening are excluded from analyses when calculating other cancers, adenomas, and serrated lesions.

¶ Other cancer includes screening detected neuroendocrine tumors, squamous cell carcinomas, and lymphomas.

Table E. Performance measures and severe adverse events at colonoscopy following a positive screening test by screening method.

	Follow-up colonoscopy after sigmoidoscopy	Follow-up colonoscopy after FIT	*p*
Individuals	3297	6945	
Cecum intubated	3245 (98.4)	6798 (97.9)	.065
Withdrawal time ≥ 6 minutes*	302/317 (95.3)	1713/1760 (97.3)	.047
On-demand sedation or analgesia	944 (28.6)	2262 (32.6)	<.001
Bowel cleansing quality†			
good	2456 (75.3)	5020 (73.5)	.087
acceptable	610 (18.7)	1,368 (20.0)	
partly poor	177 (5.4)	374 (5.5)	
poor	19 (0.6)	65 (1,0)	
Adequate examination†	3025 (92.7)	6268 (91.8)	.108
Adenoma detection rate	N/A	4073 (58.6)	N/A
Major adverse events			
Perforation	4 (0.12)	3 (0.04)	.158
Significant bleeding§	23 (0.70)	44 (0.63)	.707
Death	0 (0.00)	1 (0.01)	.491
Patient reported pain¶			
none	823 (40.3)	1,620 (38.7)	.001
slight	762 (37.3)	1,472 (35.2)	
moderate	297 (14.5)	626 (15.0)	
severe	160 (7.8)	466 (11.1)	
Patient satisfaction¶			
satisfied	1988 (97.9)	4096 (97.8)	0.886
not satisfied	43 (2.1)	91 (2.2)	

Data are n (%) if not otherwise stated. N/A = Not applicable. FIT = fecal immunochemical test.
*Proportion of complete diagnostic colonoscopies (no polypectomy or biopsy) with time from cecum to end of procedure ≥ 6 minutes.
† Bowel cleansing quality missing for 118 individuals at follow-up colonoscopy after FIT and 35 after sigmoidoscopy
§ Significant bleeding defined as requiring hospital admission, repeat endoscopy, blood transfusion, radiologic intervention, or surgery
¶ Percentages among responding individuals (in years 2012 and 2014-2018)

“Lay Summary”

In this randomized trial, the participation was higher and more colorectal cancers and advanced adenomas were detected after three rounds of fecal immunochemical testing, compared to sigmoidoscopy screening.

“What you need to know”

Background and Context: Screening with sigmoidoscopy or guaiac based fecal occult blood tests reduce colorectal cancer mortality in randomized controlled trials. The comparative effectiveness of sigmoidoscopy and immunochemical testing for fecal blood (FIT) is unknown.

New Findings: Baseline results from this randomized effectiveness trial show that more colorectal cancers and advanced adenomas were detected after three cumulative rounds of FIT compared to sigmoidoscopy screening. The risk of perforation and significant bleeding was comparable between the two screening modalities.

Limitations: Data not complete for third round FIT.

Impact: Experience gained so far provides valuable information for decision makers in implementing and improving organized CRC screening programs.