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Colorectal Cancer Screening With Repeated Fecal Immunochemical Test Versus Sigmoidoscopy: Baseline Results From a Randomized Trial

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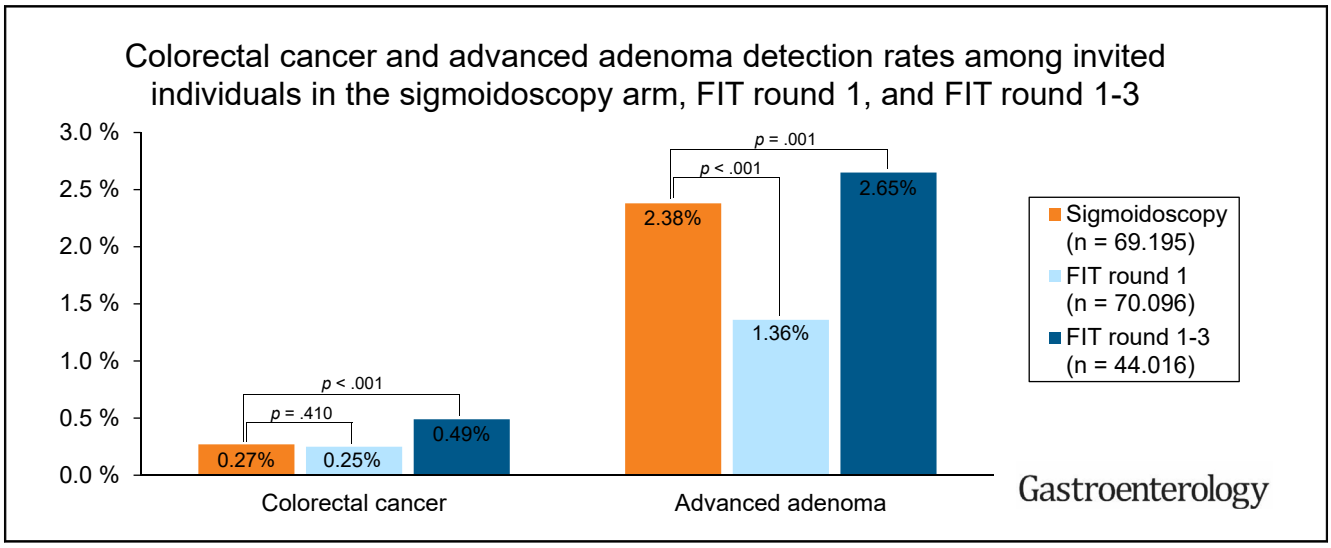

See editorial on page 1009.

BACKGROUND & 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 Southeast 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 of ≥10 mm, ≥3 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 2 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 (ORs) were calculated. **RESULTS:** We included 139,291 individuals: 69,195 randomized to sigmoidoscopy and 70,096 to FIT. The participation rate was 52% for sigmoidoscopy, 58% in the first FIT round, and 68% for 3 cumulative FIT rounds. Compared to sigmoidoscopy, the detection rate for CRC was similar in the

first FIT round (0.25% vs 0.27%; OR, 0.92; 95% confidence interval [CI], 0.75–1.13) but higher after 3 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 at 1.4% vs 2.4% (OR, 0.57; 95% CI, 0.53–0.62) but higher after 3 cumulative FIT rounds at 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 ($P = .13$). **CONCLUSIONS:** 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, Number: NCT01538550.

Keywords: Mass Screening; Screening Yield; Participation; Adverse Events.

CLINICAL AT

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 the detection and removal of premalignant precursor lesions (adenomas and serrated polyps). In 4 randomized trials with up to 17 years of 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 4 randomized trials with up to 30 years of follow-up. Meta-analyses have shown a 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 because of 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 FIT may also reduce CRC incidence.[8] However, to our knowledge, 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 recommendations with respect to the preferred screening method.[9] The International Agency for Research on Cancer 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 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 our knowledge, no randomized trials have compared the effectiveness of fecal occult blood testing with sigmoidoscopy screening on CRC mortality or incidence.

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.

In this article, 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 2 geographic areas in Southeast 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 FIT every second year for a maximum of 4 rounds. Randomization was performed by the Cancer Registry of Norway, using a computer-based algorithm and stratified by screening center, sex, 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 the first invitation were excluded from analyses. Enrollment in the FIT group (first round) ended in January 2017, when the predefined number of invited individuals was reached. Enrollment in the sigmoidoscopy group was completed in December 2018, and the last

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Abbreviations used in this paper: ADR, adenoma detection rate; BBPS, Boston bowel preparation scale; CI, confidence interval; CRC, colorectal cancer; FIT, fecal immunochemical test; gFOBT, guaiac-based fecal occult blood test; IQR, interquartile range; OR, odds ratio.

Most current article

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sigmoidoscopy was performed in May 2019. The data for the present study were obtained in April 2020. Accordingly, we included all screening data from the sigmoidoscopy group and the initial 3 FIT rounds, but because of ongoing screening, complete data from the third FIT round were available only 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 2 screening centers carried out the endoscopies. Most of the screening sigmoidoscopies and follow-up colonoscopies were performed by gastroenterology residents who were intensively trained (1-to-1 supervision by an experienced endoscopist) for 3 to 6 months before entering the trial. Quality assurance measures were closely monitored throughout the trial. Participants were invited by mail and reminded once if there was 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 result. Attenders in the sigmoidoscopy group provided written informed consent on attendance at the screening center, whereas 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 Southeast Norway (2011/1272) and is registered at clinicaltrials.gov (NCT01538550).

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) was available. At sigmoidoscopy, the endoscope was inserted as far as possible according to the allocated 20-minute time slot or until a lesion $\geq$10 mm was detected or limitations in bowel cleansing or patient discomfort did not permit further advancement. Repeated sigmoidoscopy was not offered in the case of an incomplete examination. Bowel cleansing was assessed by the endoscopist on a categorical 4-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 $\geq$10 mm, $\geq$3 adenomas, an adenoma with high-grade dysplasia or $\geq$25% villous architecture, or CRC. Polyps of $<$10 mm were usually removed during sigmoidoscopy.

Fecal Immunochemical Test

Each FIT screening consisted of a single fecal sample. A sampling kit and instructions were mailed together with the invitations. Participants were not asked to apply dietary restrictions or to discontinue anticoagulation or antiplatelet treatment ahead of sampling. Samples were mailed in a prepaid 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, participants were instructed to keep it in the refrigerator until the next day. All samples were analyzed with the OC-Sensor Diana (Eiken Chemical). 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 result and nonattenders were reinvited every second year, up to a maximum of 4 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. Before the colonoscopy, they were interviewed by a study nurse, either at the time of sigmoidoscopy or by phone for those with positive FIT results. 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: 1 sachet in the afternoon before the examination and the second dose 4 hours before 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 reinvited 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 histopathologic data from the sigmoidoscopies and colonoscopies were entered into a dedicated database. For all detected lesions, size, location, appearance (eg, pedunculated, sessile, or flat), and technique and completeness of removal were registered. CRC was defined as adenocarcinoma of the colon or rectum. An advanced adenoma was defined as an adenoma with either size $\geq$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 a size of $\geq$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' experiences, including satisfaction and abdominal pain during sigmoidoscopy and colonoscopy, was recorded using a questionnaire (data available only 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 prepaid envelope. Pain was categorized on a 4-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, radiologic intervention, or surgery. Perforation was defined as radiologic (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 10 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 this article, 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 10 years of mean follow-up. Type I error was set to .05.

Detection rates for neoplasia and serrated lesions were calculated both among invitees (intention-to-treat) and among attenders (those who attended the screening per protocol: attended sigmoidoscopy or returned at least 1 FIT sample). Because enrollment 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 (5-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 3 rounds of FIT (FIT_{1-3}), we included only individuals invited for the first time before January 1, 2015 (those who had been offered 3 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 (ORs) with 95% confidence intervals (CIs).

To illustrate participation rates by age, we used restricted cubic spline univariate logistic models,[20] with knots placed at the 4 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 κ was calculated to determine the agreement between the nonvalidated cleansing scale used in the trial and the Boston Bowel Preparation Scale (BBPS).[22] The Chi-squared test or Fisher exact test were used to compare proportions. All tests were 2 sided, and $P < .05$ was considered statistically significant. Statistical analyses were performed by using SAS software, version 9.4 (SAS Institute) and Stata statistical software, version 16.0 (StataCorp, College Station). 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 the first invitation, leaving 139,291 individuals for the intention-to-treat analyses (Figure 1); 69,195 were invited to sigmoidoscopy and 70,096 to FIT. The median age at first invitation was 63.3 years (interquartile range [IQR], 58.0–69.3) in the sigmoidoscopy group and 62.2 years (IQR, 56.6–68.1) in the FIT group (Table 1). A total of 44,016 (63%) individuals were included in the analyses of 3 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 3 cumulative FIT rounds (participation at least once) (Supplementary Table 1). Participation was higher in the FIT group compared to the sigmoidoscopy group for both men and women and for all age groups (Figure 2 and Supplementary Table 1). The participation rate was higher in women compared to men in the FIT arm, but no difference was seen for sigmoidoscopy screening (Supplementary Table 1).

Positivity Rates, Follow-Up Colonoscopies, and Surveillance

In the sigmoidoscopy group, 3378 (9.4%) attenders were referred for colonoscopy, of whom 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 13.0% and 16.2%, respectively (Figure 3). Colonoscopy compliance was approximately 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 5 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 vs 202 (0.27%) in the sigmoidoscopy group (OR, 0.92; 95% CI, 0.75–1.13). CRC detection rates were higher in FIT_{1-2} (0.37%; OR, 1.38; 95% CI, 1.15–1.66) and FIT_{1-3} (0.49%; OR, 1.87; 95% CI, 1.54–2.27) compared to sigmoidoscopy (Table 2 and 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, 0.59–0.65), whereas the advanced adenoma detection rate was higher in FIT_{1-3} (2.7%) compared to sigmoidoscopy (2.4%; OR, 1.14; 95% CI, 1.05–1.23) (Table 2 and Figure 3). Subgroup analyses by sex showed similar results (Supplementary Tables 2 and 3). For all CRC stages, the detection rate was higher after 3 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-}

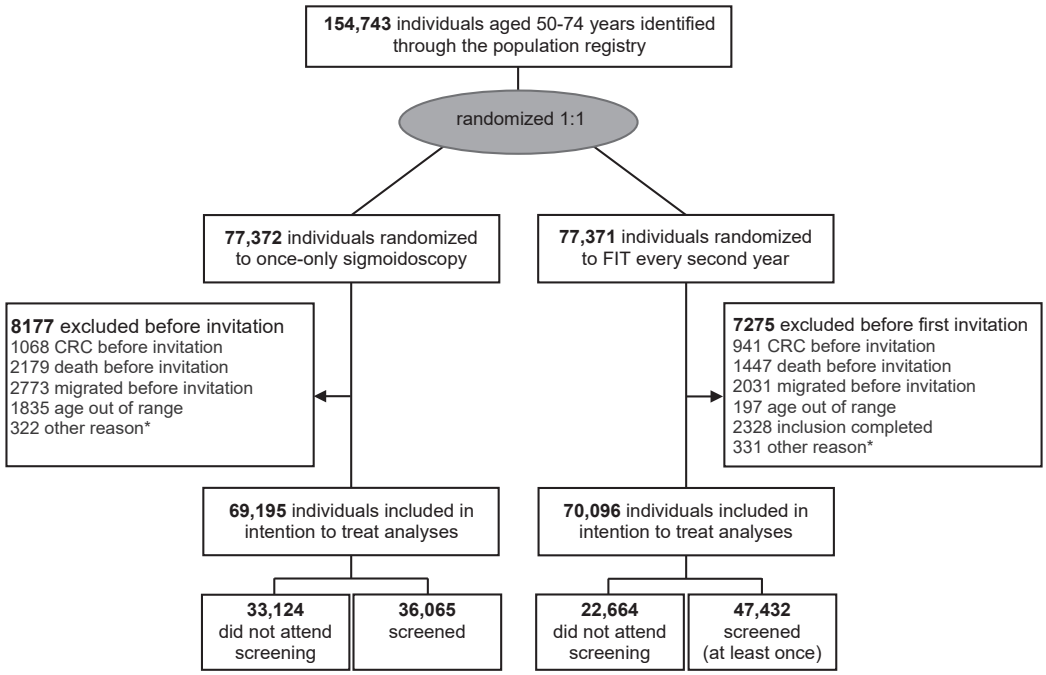

Figure 1. Flowchart. *Missing postal address (n = 581), postal address abroad (n = 60), withdrew consent (n = 3), randomization error (n = 2), invitation error (n = 7).

$_2$, 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, 1.16–1.72) and lower for adenomas (8.6% vs 17.6%; OR, 0.44; 95% CI, 0.42–0.46) and advanced adenomas (3.9% vs 4.6%; OR, 0.85; 95% CI, 0.79–0.92), respectively (Supplementary Table 4).

Table 1. Baseline Characteristics for Included Individuals

Characteristics	Sigmoidoscopy group	FIT group
Included individuals, n	69,195	70,096
Sex, n (%)		
Female	35,127 (50.8)	35,495 (50.6)
Male	34,068 (49.2)	34,601 (49.4)
Age at first invitation, y[a]		
Median (IQR)	63.3 (58.0–69.3)	62.2 (56.6–68.1)
50–59, n (%)	23,960 (34.6)	28,504 (40.7)
60–69, n (%)	30,081 (43.5)	29,223 (41.7)
≥70, n (%)	15,154 (21.9)	12,369 (17.6)
Screening center, n (%)		
Center 1	37,071 (53.6)	36,405 (51.9)
Center 2	32,124 (46.4)	33,691 (48.1)

[a]The median age at randomization for the initial 154,743 individuals was 60.0 years (IQR, 54.3–66.0) in both study groups.

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 those with positive results on FIT. The sigmoidoscopy feedback 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 result. 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 2 screening groups (Supplementary Table 5). The feedback questionnaire was completed by 7257 of 8940 individuals (81.2%). Of those, 1756 (24.2%) reported moderate or severe pain. A total of 9413 (91.9%) of the initial follow-up colonoscopies were performed by a screening-dedicated resident endoscopist, and the remaining were performed by gastroenterology consultants. The screening-dedicated endoscopists had higher ADRs at the initial colonoscopy subsequent to a positive FIT result (57.6% vs 49.6%, $P < .001$) and similar cecum intubation rates and patient-reported pain compared to gastroenterology consultants.

In a subsample of 1291 colonoscopies, bowel cleansing was characterized with both the 4-point scale and the BBPS;

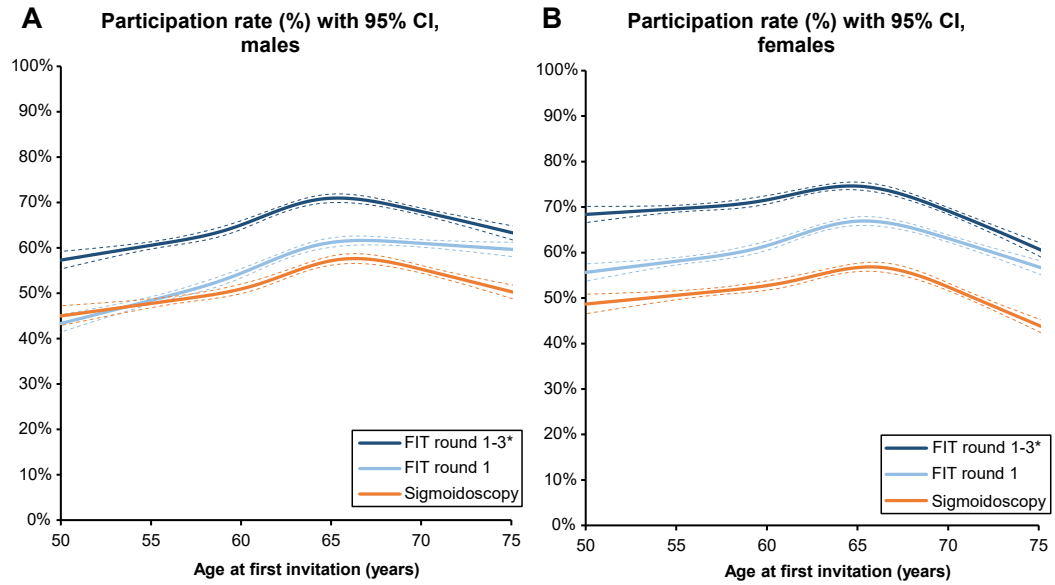

Figure 2. Participation rates by age in the sigmoidoscopy group, FIT round 1 and FIT rounds 1–3 for (*A*) men and (*B*) women, respectively. *Participation defined as at least once across FIT rounds.

1172 individuals (90.8%) had good or acceptable bowel cleansing on the 4-point scale, and 1146 (88.8%) had BBPS of $\geq$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 3 (0.01%) perforations (2 of these were most likely caused by the enema tip and 1 related to polypectomy, all conservatively treated) and 3 (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 1 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), and 6 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 older than 70 years, had a preexisting 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 already higher in the first round of FIT compared to sigmoidoscopy and increased in the second and third screening rounds. After 3 FIT screening rounds, more CRCs and advanced adenomas were detected than by sigmoidoscopy. Importantly, the adverse event rates did not differ between the 2 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, and no results for FIT have been 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 vs sigmoidoscopy screening included only 1 FIT round, were nonrandomized, had small sample sizes, or had poor participation rates in the sigmoidoscopy arm (28.1%–32.4%).[23–26] One of the trials, combining results from 3 Dutch screening cohorts, found higher detection rates for advanced neoplasia and CRC with 4 rounds of FIT compared to sigmoidoscopy.[24] However, the nonrandomized 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 1 round) compared to the published literature and the minimum target recommended by European Union 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 nonadvanced 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 nonadvanced adenomas over time. This may imply that once-only sigmoidoscopy detects most

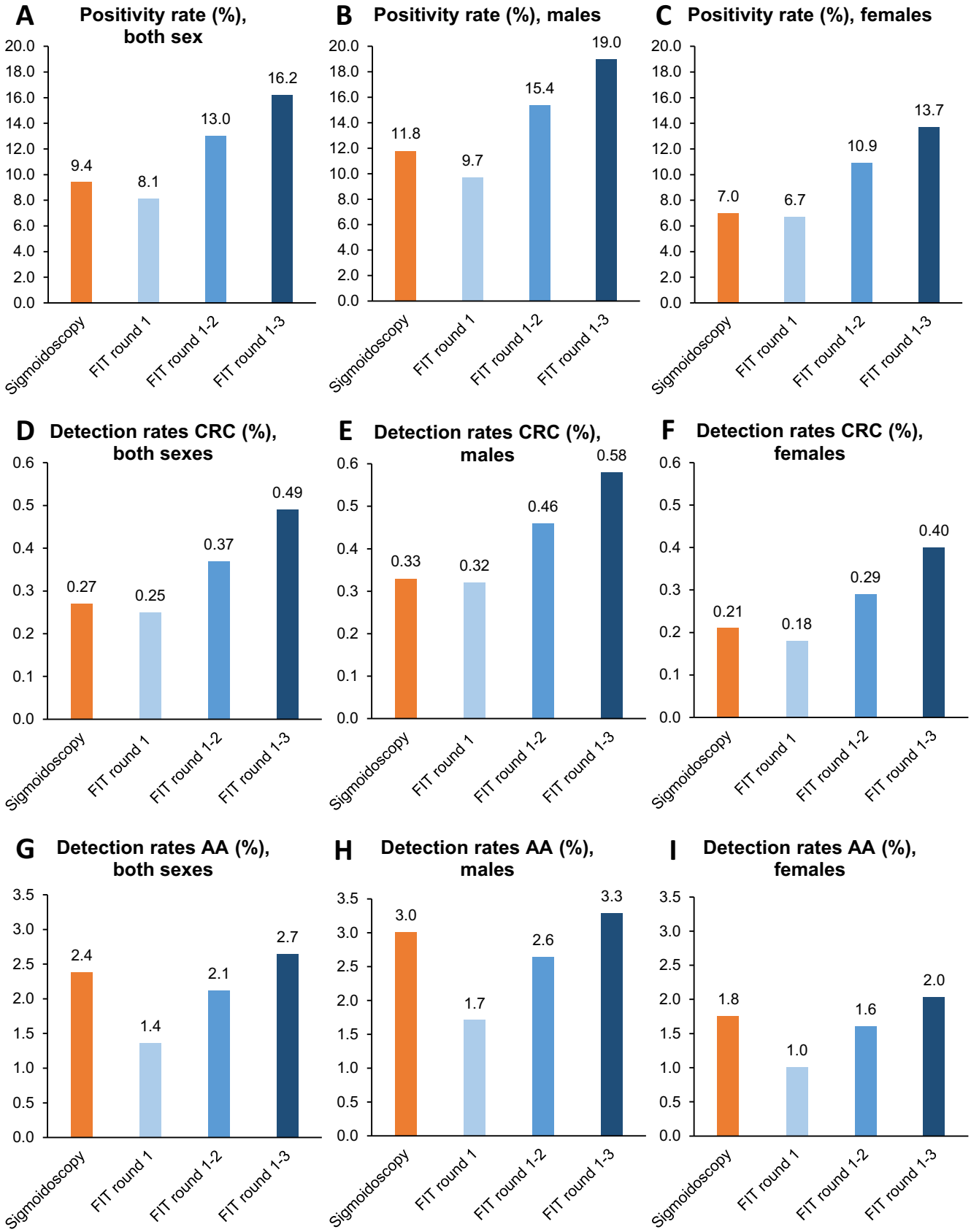

Figure 3. (*A–I*) Positivity rates and age-standardized detection rates CRC and advanced adenoma (AA) among invited individuals in the sigmoidoscopy group, FIT round 1 (FIT_1), FIT rounds 1–2 (FIT_{1-2}) and FIT round 1–3 (FIT_{1-3}) for both sexes, male and female.

Table 2. Findings Among Invited Individuals (Intention-to-Treat Analyses) in the Sigmoidoscopy Group, FIT Round 1, FIT Rounds 1–2, and FIT Rounds 1–3

	Sigmoidoscopy (n = 69,195)		FIT round 1 (n = 70,096)			FIT rounds 1–2 (n = 70,096)			FIT rounds 1–3 (n= 44,016)		
Finding	n	%[a]	n	%	OR (95% CI)[b]	n	%	OR (95% CI)[b]	n	%[a]	OR (95% CI)[b]
Colorectal cancer	202	0.27	173	0.25	0.92 (0.75–1.13)	260	0.37	1.38 (1.15–1.66)	210	0.49	1.87 (1.54–2.27)
Proximal[c]	21	0.03	41	0.06	2.08 (1.23–3.52)	77	0.11	3.92 (2.42–6.36)	63	0.15	5.47 (3.33–8.99)
Distal[c]	181	0.24	134	0.19	0.79 (0.64–0.99)	187	0.27	1.11 (0.90–1.36)	152	0.36	1.51 (1.21–1.87)
Stage I	130	0.17	87	0.12	0.72 (0.55–0.95)	133	0.19	1.10 (0.86–1.40)	101	0.24	1.40 (1.08–1.82)
Stage II	22	0.03	33	0.05	1.61 (0.94–2.77)	54	0.08	2.66 (1.62–4.37)	55	0.13	4.53 (2.76–7.46)
Stage III	40	0.06	40	0.06	1.06 (0.68–1.64)	56	0.08	1.47 (0.98–2.21)	45	0.11	1.96 (1.27–3.01)
Stage IV	10	0.01	13	0.02	1.37 (0.60–3.13)	17	0.02	1.82 (0.83–3.97)	9	0.02	1.67 (0.68–4.14)
Other cancer[d,e]	26	0.04	7	0.01	0.27 (0.12–0.61)	13	0.02	0.50 (0.25–0.97)	10	0.02	0.60 (0.29–1.26)
Adenoma[d]	6396	9.06	1793	2.56	0.27 (0.25–0.28)	3163	4.53	0.48 (0.46–0.50)	2485	5.79	0.62 (0.59–0.65)
Proximal[c]	1425	1.98	1040	1.49	0.76 (0.70–0.82)	1863	2.67	1.38 (1.28–1.48)	1474	3.45	1.81 (1.68–1.95)
Distal[c]	6126	8.68	1405	2.01	0.22 (0.20–0.23)	2447	3.50	0.38 (0.37–0.40)	1895	4.42	0.49 (0.46–0.51)
Advanced adenoma[d]	1699	2.38	950	1.36	0.57 (0.53–0.62)	1478	2.12	0.89 (0.83–0.96)	1132	2.65	1.14 (1.05–1.23)
Proximal[c]	271	0.37	275	0.39	1.08 (0.91–1.28)	428	0.61	1.68 (1.44–1.96)	331	0.77	2.19 (1.86–2.57)
Distal[c]	1577	2.21	787	1.13	0.51 (0.47–0.55)	1214	1.74	0.79 (0.73–0.85)	922	2.16	0.99 (0.91–1.07)
≥3 nonadvanced adenomas[d]	424	0.58	217	0.31	0.53 (0.45–0.63)	434	0.62	1.07 (0.94–1.23)	358	0.85	1.47 (1.27–1.69)
Advanced serrated lesions[d]	632	0.89	209	0.30	0.34 (0.29–0.39)	404	0.58	0.65 (0.58–0.74)	330	0.76	0.88 (0.77–1.00)
Proximal[c]	296	0.42	138	0.20	0.48 (0.39–0.59)	279	0.40	0.97 (0.82–1.14)	234	0.54	1.33 (1.12–1.59)
Distal[c]	409	0.58	83	0.12	0.21 (0.16–0.26)	146	0.21	0.36 (0.30–0.44)	109	0.25	0.44 (0.36–0.55)

[a]Age-standardized rates.
[b]Compared to sigmoidoscopy and adjusted by age.
[c]The sum may exceed the total number because of the possibility of findings in both the proximal and distal colon.
[d]Individuals with CRC detected at screening are excluded from analyses when calculating other cancers, adenomas, and serrated lesions.
[e]*Other cancer* includes screening-detected neuroendocrine tumors, squamous cell carcinomas, and lymphomas.

Table 3. Performance Measures and Severe Adverse Events at Sigmoidoscopy and Colonoscopy After a Positive Screening Test Result

Indicator	Sigmoidoscopy	Follow-up colonoscopy
Participating individuals, n	36,065	10,242
Intubation depth, *cm*, median (IQR)	50 (40–56)	N/A
Cecum intubated, n (%)	N/A	10,043 (98.1)
Withdrawal time ≥6 minutes, n (%)[a]	N/A	2015/2077 (97.0)
On-demand sedation or analgesia, n (%)	N/A	3206 (31.3)
Bowel cleansing quality, n (%)[b]		
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, n (%)[b]	24,800 (69.4)	9293 (92.1)
Adenoma detection rate, n (%)	5894 (16.3)	4073 (58.6)[c]
Major adverse events, n (%)		
Perforation	3 (0.01)	7 (0.07)
Significant bleeding[d]	3 (0.01)	67 (0.65)
Death	0 (0.00)	1 (0.01)
Patient-reported pain, n (%)[e]		
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, n (%)[e]		
Satisfied	22,949 (98.4)	6703 (97.9)
Not satisfied	374 (1.6)	141 (2.1)

N/A = not applicable.
[a]Proportion of complete diagnostic colonoscopies (no polypectomy or biopsy) with time from cecum to end of procedure of ≥6 minutes.
[b]Bowel cleansing quality missing for 355 sigmoidoscopy participants and 153 colonoscopy participants.
[c]In the FIT group (n = 6945).
[d]*Significant bleeding* was defined as requiring hospital admission, repeat endoscopy, blood transfusion, radiologic intervention, or surgery.
[e]Percentages among responding individuals (in years 2012–2018).

adenomas at a nonadvanced stage, whereas 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 because adenomas may transform to invasive lesions over time. These lesions might have been detected as noninvasive lesions if sigmoidoscopy screening was performed. Our trial aims at disentangling these most important features as it continues toward its primary endpoint of the comparison of CRC mortality and incidence after 10 years of follow-up. Presently, our data do not support any conclusion with respect to the superiority of any screening method. However, we believe that our results may be informative for researchers who work with screening modeling. The number of CRCs and advanced adenomas detected per screened individual in the present study is within the range reported from previous sigmoidoscopy[21,28–30] and FIT screening trials with comparable cutoffs (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 compared to sigmoidoscopy screening. This may be explained by FIT detecting bleeding in the entire colon, whereas sigmoidoscopy examines only the distal colon and rectum. We also show a difference in stage distribution between sigmoidoscopy and FIT in our trial, with a higher proportion of stage I CRC in the sigmoidoscopy group compared to 3 cumulative FIT rounds. However, the absolute number of stage I CRC detected was similar after 2 rounds of FIT and will be higher after 3 complete FIT rounds compared to sigmoidoscopy.

In our analyses of screened individuals (per-protocol analyses), CRC detection rates were higher after 3 rounds of FIT screening compared to sigmoidoscopy. The advanced adenoma detection rate increased with increasing FIT rounds but was still slightly lower after 3 FIT rounds compared to sigmoidoscopy. However, per-protocol analyses are difficult to interpret because of 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 a 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 after a positive FIT result (45% for men and 35% for women) 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 timeframe. However, this result requires sufficient resources (eg, experienced endoscopist trainers) available for teaching. The number of referrals for follow-up colonoscopy and for colonoscopy surveillance was higher after 3 rounds of FIT compared to sigmoidoscopy. Thus, the higher CRC and advanced adenoma detection is accompanied by 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, whereas FIT testing per se is not.[6,39]

Even with high-quality endoscopies, serious adverse events occur. The rates of significant bleedings (0.65%) and perforations (0.07%) among individuals having a colonoscopy in the present trial is in line with those 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 the number among 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. Second, 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 1 year at the time of first invitation between the 2 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%). Because the data set 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 nonstudy 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, approximately 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 2 arms at the time of randomization, but we cannot rule out that a previous colonoscopy history has had a different impact on screening uptake or findings at screening in the 2 arms. Also, our results may not be generalizable to populations with a different prevalence of colonoscopy history. In Norway, a national screening program will commence in 2021 with biennial FIT, starting at age 55 years. Although participants in the current trial will not be eligible for the national program, its introduction may influence the population's awareness of CRC and 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 2 trial arms differently. The final results will not be obtained until 10 years of follow-up. Even with this long timeframe, 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, because of increased awareness of serrated lesions over the last 2 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 that reported from both the UK flexible sigmoidoscopy trial (12.1% distal adenomas)[29] and the Italian randomized controlled trial of once-only sigmoidoscopy (SCORE-trial) trial (10.8% distal adenomas)[28] but in line with the Norwegian Colorectal Cancer Prevention (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 among the trials (any polyp sized $\geq$10 mm or biopsy-verified neoplasia in the NORCCAP trial, adenomas meeting high-risk criteria or any polyp $\geq$10 mm in the UK trial, and high-risk adenoma or any polyp $\geq$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 cutoff values. Finally, our results on participation and effects might not be generalizable to populations with other distributions of socioeconomic 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 3 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.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2020.11.037.

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Conflicts of interest
These authors disclose the following: Svein Oskar Frigstad reports personal fees from Tillotts Pharma, Janssen-Cilag, Pfizer, Takeda, Intercept Pharma, and AbbVie outside the submitted work. The remaining authors disclose no conflicts.

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Supplementary Table 1. Screening Participation, Positivity Rates, and Colonoscopy Attendance in the Sigmoidoscopy Group, FIT Round 1, FIT Rounds 1–2, and FIT Rounds 1–3 by Sex and by Age at First Invitation

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

[a]*Participation* is defined as at least once across FIT rounds.
[b]$P < .05$ compared to sigmoidoscopy, in favor of FIT.
[c]Percentages among individuals attending screening.
[d]$P < .05$ compared to sigmoidoscopy, in favor of sigmoidoscopy.
[e]Percentages among individuals with a positive screening test result.

Supplementary Table 2. Findings Among Invited Women in the Sigmoidoscopy Group, FIT Rounds 1, 1–2, and 1–3

	Sigmoidoscopy (n = 35,127)		FIT round 1 (n = 35,495)			FIT rounds 1–2 (n = 35,495)			FIT rounds 1–3 (n = 22,359)		
Finding	n	%[a]	n	%	OR (95% CI)[b]	n	%	OR (95% CI)[b]	n	%[a]	OR (95% CI)[b]
Colorectal cancer	79	0.21	64	0.18	0.86 (0.62–1.19)	102	0.29	1.36 (1.02–1.83)	89	0.40	1.96 (1.45–2.67)
Proximal[c]	12	0.03	23	0.06	2.03 (1.01–4.09)	41	0.12	3.64 (1.91–6.94)	37	0.17	5.59 (2.91–10.77)
Distal[c]	67	0.18	42	0.12	0.66 (0.45–0.98)	63	0.18	0.99 (0.70–1.40))	55	0.25	1.42 (0.99–2.03)
Stage I	49	0.13	33	0.09	0.71 (0.46–1.11)	48	0.14	1.03 (0.69–1.54)	37	0.17	1.31 (0.85–2.01)
Stage II	10	0.03	14	0.04	1.49 (0.66–3.36)	25	0.07	2.68 (1.29–5.59)	31	0.14	5.38 (2.63–11.02)
Stage III	14	0.04	11	0.03	0.82 (0.37–1.81)	22	0.06	1.63 (0.83–3.18)	17	0.08	2.08 (1.02 –4.25)
Stage IV	6	0.02	6	0.02	1.06 (0.34–3.30)	7	0.02	1.25 (0.42–3.73)	4	0.02	1.27 (0.36–4.55)
Other cancer[d,e]	9	0.03	4	0.01	0.45 (0.14–1.46)	8	0.02	0.90 (0.35–2.34)	5	0.02	0.85 (0.28–2.56)
Adenoma[d]	2545	7.15	695	1.96	0.26 (0.24–0.29)	1237	3.50	0.47 (0.44–0.51)	971	4.41	0.61 (0.56–0.65)
Proximal[c]	421	1.16	346	0.98	0.85 (0.74–0.99)	657	1.86	1.64 (1.45–1.86)	526	2.41	2.17 (1.90–2.47)
Distal[c]	2461	6.92	533	1.50	0.21 (0.19–0.23)	940	2.66	0.37 (0.34–0.40)	729	3.31	0.46 (0.43–0.51)
Advanced adenoma[d]	635	1.76	359	1.01	0.58 (0.51–0.66)	568	1.61	0.92 (0.82–1.03)	446	2.04	1.18 (1.05–1.34)
Proximal[c]	68	0.19	85	0.24	1.32 (0.96–1.81)	144	0.41	2.24 (1.67–2.99)	118	0.54	3.03 (2.24–4.10)
Distal[c]	607	1.68	299	0.84	0.50 (0.44–0.58)	471	1.33	0.79 (0.70–0.90)	367	1.68	1.01 (0.89–1.16)
≥3 nonadvanced adenomas[d]	113	0.31	63	0.18	0.58 (0.43–0.80)	138	0.39	1.28 (1.00–1.65)	111	0.51	1.68 (1.29–2.19)
Advanced serrated lesion[d]	302	0.84	103	0.29	0.35 (0.28–0.43)	202	0.57	0.68 (0.57–0.82)	166	0.75	0.91 (0.75–1.10)
Proximal[c]	152	0.42	69	0.19	0.46 (0.35–0.62)	147	0.42	0.99 (0.79–1.25)	131	0.59	1.44 (1.14–1.83)
Distal[c]	190	0.53	40	0.11	0.21 (0.15–0.30)	65	0.18	0.35 (0.26–0.46)	45	0.20	0.39 (0.28– 0.54)

[a]Age-standardized detection rates.
[b]Compared to sigmoidoscopy and adjusted by age.
[c]The sum may exceed the total number because of the possibility of findings in both the proximal and distal colon.
[d]Individuals with CRC detected at screening are excluded from analyses when calculating other cancers, adenomas, and serrated lesions.
[e]*Other cancer* includes screening detected neuroendocrine tumors, squamous cell carcinomas, and lymphomas.

Supplementary Table 3. Findings Among Invited Men in the Sigmoidoscopy Group, FIT Rounds 1, 1–2, and 1–3

	Sigmoidoscopy (n = 34,068)		FIT round 1 (n = 34,601)			FIT rounds 1–2 (n = 34,601)			FIT rounds 1–3 (n = 21,657)		
Finding	n	%[a]	n	%	OR (95% CI)[b]	n	%	OR (95% CI)[b]	n	%[a]	OR (95% CI)[b]
Colorectal cancer	123	0.33	109	0.32	0.96 (0.74–1.24)	158	0.46	1.39 (1.10–1.76)	121	0.58	1.81 (1.40–2.33)
Proximal[c]	9	0.02	18	0.05	2.14 (0.96–4.77)	36	0.10	4.29 (2.07–8.93)	26	0.12	5.30 (2.47–11.36)
Distal[c]	114	0.31	92	0.27	0.87 (0.66–1.15)	124	0.36	1.18 (0.91–1.52)	97	0.47	1.57 (1.19–2.06)
Stage I	81	0.21	54	0.16	0.73 (0.51–1.02)	85	0.25	1.14 (0.84–1.55)	64	0.31	1.46 (1.05–2.03)
Stage II	12	0.03	19	0.05	1.72 (0.83–3.54)	29	0.08	2.64 (1.34–5.17)	24	0.12	3.81 (1.90–7.66)
Stage III	26	0.07	29	0.08	1.19 (0.70–2.02)	34	0.10	1.38 (0.83–2.31)	28	0.14	1.89 (1.10–3.24)
Stage IV	4	0.01	7	0.02	1.83 (0.53–6.27)	10	0.03	2.66 (0.83–8.50)	5	0.02	2.26 (0.60–8.51)
Other cancer[d,e]	17	0.05	3	0.01	0.17 (0.05–0.59)	5	0.01	0.29 (0.11–0.78)	5	0.02	0.47 (0.17–1.28)
Adenoma[d]	3851	11.02	1098	3.18	0.27 (0.25–0.28)	1926	5.59	0.48 (0.45–0.51)	1514	7.23	0.63 (0.59–0.67)
Proximal[c]	1004	2.81	694	2.01	0.72 (0.65–0.79)	1206	3.50	1.27 (1.16–1.38)	948	4.53	1.67 (1.53–1.83)
Distal[c]	3665	10.48	872	2.53	0.22 (0.21–0.24)	1507	4.38	0.39 (0.37–0.42)	1166	5.58	0.50 (0.47–0.54)
Advanced adenoma[d]	1064	3.01	591	1.71	0.57 (0.51–0.63)	910	2.64	0.88 (0.81–0.96)	686	3.29	1.11 (1.01–1.23)
Proximal[c]	203	0.56	190	0.55	1.00 (0.82–1.22)	284	0.82	1.49 (1.25–1.79)	213	1.02	1.91 (1.57–2.32)
Distal[c]	970	2.75	488	1.41	0.51 (0.46–0.57)	743	2.16	0.78 (0.71–0.86)	555	2.66	0.97 (0.88–1.08)
≥3 nonadvanced adenomas[d]	311	0.86	154	0.45	0.51 (0.42–0.63)	296	0.86	0.99 (0.85–1.17)	247	1.20	1.40 (1.18–1.65)
Advanced serrated lesion[d]	330	0.93	106	0.31	0.33 (0.26–0.41)	202	0.59	0.63 (0.53–0.75)	164	0.78	0.84 (0.70–1.02)
Proximal[c]	144	0.41	69	0.20	0.49 (0.37–0.66)	132	0.38	0.94 (0.74–1.19)	103	0.49	1.22 (0.94–1.57)
Distal[c]	219	0.61	43	0.12	0.20 (0.14–0.28)	81	0.24	0.38 (0.29–0.49)	64	0.30	0.49 (0.37–0.65)

[a]Age-standardized detection rates.
[b]Compared to sigmoidoscopy and adjusted by age.
[c]The sum may exceed the total number because of the possibility of findings in both the proximal and distal colon.
[d]Individuals with CRC detected at screening are excluded from analyses when calculating other cancers, adenomas, and serrated lesions.
[e]*Other cancer* includes screening detected neuroendocrine tumors, squamous cell carcinomas, and lymphomas.

Supplementary Table 4. Findings Among Individuals Actually Screened (Per-Protocol Analyses) in the Sigmoidoscopy Group and FIT Rounds 1, 1–2, and 1–3

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

[a]Age-standardized detection rates.
[b]Compared to sigmoidoscopy and adjusted by age.
[c]The sum may exceed the total number because of the possibility of findings in both the proximal and distal colon.
[d]Individuals with CRC detected at screening are excluded from analyses when calculating other cancers, adenomas, and serrated lesions.
[e]*Other cancer* includes screening detected neuroendocrine tumors, squamous cell carcinomas, and lymphomas.

Supplementary Table 5. Performance Measures and Severe Adverse Events at Colonoscopy After a Positive Screening Test Result by Screening Method

Indicator	Follow-up colonoscopy after sigmoidoscopy	Follow-up colonoscopy after FIT	*P*
Individuals, n	3297	6945	
Cecum intubated, n (%)	3245 (98.4)	6798 (97.9)	.065
Withdrawal time ≥6 minutes, n (%)[a]	302/317 (95.3)	1713/1760 (97.3)	.047
On-demand sedation or analgesia, n (%)	944 (28.6)	2262 (32.6)	<.001
Bowel cleansing quality, n (%)[b]			
Good	2456 (75.3)	5020 (73.5)	.087
Acceptable	610 (18.7)	1368 (20.0)	
Partly poor	177 (5.4)	374 (5.5)	
Poor	19 (0.6)	65 (1,0)	
Adequate examination, n (%)[b]	3025 (92.7)	6268 (91.8)	.108
Adenoma detection rate, n (%)	N/A	4073 (58.6)	N/A
Major adverse events, n (%)			
Perforation	4 (0.12)	3 (0.04)	.222
Significant bleeding[c]	23 (0.70)	44 (0.63)	.707
Death	0 (0.00)	1 (0.01)	1.000
Patient reported pain, n (%)[d]			
None	823 (40.3)	1620 (38.7)	.001
Slight	762 (37.3)	1472 (35.2)	
Moderate	297 (14.5)	626 (15.0)	
Severe	160 (7.8)	466 (11.1)	
Patient satisfaction, n (%)[d]			
Satisfied	1988 (97.9)	4096 (97.8)	.886
Not satisfied	43 (2.1)	91 (2.2)	

N/A = Not applicable.

[a]The proportion of complete diagnostic colonoscopies (no polypectomy or biopsy) with a time from cecum to end of procedure of ≥6 minutes.

[b]Bowel cleansing quality was missing for 118 individuals at follow-up colonoscopy after FIT and 35 individuals after sigmoidoscopy.

[c]*Significant bleeding* is defined as requiring hospital admission, repeat endoscopy, blood transfusion, radiologic intervention, or surgery.

[d]Percentages among responding individuals (in years 2012 and 2014–2018).