

## Randomized Clinical Trial

## Psychological effects of colorectal cancer screening: Participants vs individuals not invited

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### Abstract

#### AIM

To investigate the possible long-term psychological  
harm of participating in colorectal cancer (CRC)

screening in Norway.

### METHODS

In a prospective, randomized trial, 14294 participants (aged 50-74 years) were invited to either flexible sigmoidoscopy (FS) screening, or a faecal immunochemical test (FIT) (1:1). In total, 4422 screening participants (32%) completed the questionnaire, which consisted of the Hospital Anxiety and Depression Scale and the SF-12, a generic health-related quality of life (HRQOL) measurement, when invited to screening and one year after the invitation. A control group of 7650 individuals was invited to complete the questionnaire only, at baseline and one year after, and 1911 (25%) completed the questionnaires.

### RESULTS

Receiving a positive or negative screening result and participating in the two different screening modalities did not cause clinically relevant mean changes in anxiety, depression or HRQOL after one year. FS screening, but not FIT, was associated with an increased probability of being an anxiety case (score  $\geq 8$ ) at the one-year follow-up (5.6% of FS participants transitioned from being not anxious to anxious, while 3.0% experienced the reverse). This increase was moderately significantly different from the changes in the control group (in which the corresponding numbers were 4.8% and 4.5%, respectively),  $P = 0.06$ .

### CONCLUSION

Most individuals do not experience psychological effects of CRC screening participation after one year, while FS participation is associated with increased anxiety for a smaller group.

**Key words:** Colorectal cancer screening; Flexible sigmoidoscopy; Faecal immunochemical test; Anxiety; Health-related quality of life; Control group

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**Core tip:** Participation in cancer screening programmes might cause worries in the population outweighing the benefits of screening. However, the results from studies of psychological harm of colorectal cancer (CRC) screening remain inconsistent. This is the first randomized study to investigate long-term changes in anxiety from before CRC screening, and compare these changes to individuals not invited to screening. Based on sound methodology, our study show that most individuals have no psychological effect of receiving a positive screening result, or participating in CRC screening after one year. However, flexible sigmoidoscopy participation is associated with increased anxiety for a smaller, possibly anxious group.

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## INTRODUCTION

Colorectal cancer (CRC) is one of the most frequent causes of cancer-related deaths in both men and women in developed countries<sup>[1]</sup>. Randomized controlled trials have demonstrated that screening for CRC can reduce CRC incidence and mortality<sup>[2-4]</sup>. However, the total benefits and harm of national cancer screening programs are under debate. To save relatively few lives, a large number of people need to be screened<sup>[4]</sup>. The majority of participants will never develop cancer, but they may experience psychological stress from participation in the screening program.

Many studies report that receipt of a positive faecal occult blood test (FOBT) result is associated with anxiety in screening participants<sup>[5-9]</sup>. However, few studies have measured the long-term psychological consequences of CRC screening<sup>[6,8,10-12]</sup>, and the results of these studies are inconsistent. Only one study measured within-group changes<sup>[11]</sup>, and no studies have investigated the long-term changes in anxiety from before screening and compared these changes to those of individuals not invited to screening. Thus, knowledge of the long-term psychological effects of participating in CRC screening is limited.

The incidence of CRC in Norway, has increased rapidly since the 1950s<sup>[13]</sup>, and the lifetime risk of developing CRC for the average population is approximately 6%<sup>[14]</sup>. Accordingly, a randomized management trial, Bowel Cancer Screening in Norway (the BCSN pilot), was started in 2012 to compare the possible benefit of the two different screening modalities faecal immunochemical test (FIT) and flexible sigmoidoscopy (FS), on reductions in CRC incidence and mortality<sup>[15]</sup>. To evaluate the possible psychological harm of participation in the BCSN pilot, a sub-study was initiated. A random sample of the original cohort was invited to participate in the sub-study. The results of the short-term effects showed that receiving a positive CRC screening result or participating in CRC screening did not cause short-term anxiety, depression or decreased health-related quality of life (HRQOL) in participants<sup>[16]</sup>.

The primary aim of the current sub-study was to measure the long-term changes in anxiety, depression and HRQOL in participants receiving different primary screening results and in participants completing two different screening modalities during a one-year follow-up study. The secondary aim was to investigate whether the potential psychological changes observed were different or similar to changes in a control group.

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## MATERIALS AND METHODS

In the BCSN pilot, 140000 men and women aged 50-74 years in two defined geographical areas in South-East Norway are invited. From 2012-2018, they are randomized to receive an invitation to either a FS examination or screening with FIT (1:1). Individuals randomized to FIT receive a kit for taking a stool sample. Participants with a positive FS or FIT are invited to a work-up colonoscopy examination. In the present study, we invited a sub-sample of those invited to the main trial. A control group of sex- and age-matched individuals living in neighboring counties was randomly drawn from the Norwegian National Registry and invited to participate in the questionnaire study only.

Participants were invited to screening between September 2013 and July 2014 (FS group) and from October until December 2013 (FIT group). All participants received a questionnaire with the invitation together with a letter asking them to complete and return the questionnaire by a pre-paid return envelope or to complete the questionnaire online. One reminder was sent to participants who did not attend screening, but no reminders were sent to non-responders of the questionnaire. One year after the first invitation, participants who had completed the baseline questionnaire were invited to complete the questionnaire again.

### Questionnaire

The participant questionnaire consisted of two outcome measurements: the Hospital Anxiety and Depression scale (HADS) and the generic HRQOL questionnaire Short-Form Health Survey 12 (SF-12). Both measurements have been translated into Norwegian and validated in Norwegian background populations<sup>[17-19]</sup>.

The HADS consists of 14 questions, seven measuring anxiety and seven measuring depression<sup>[20]</sup>. Each question has four response options, ranging from 0-3, with a maximum total score of 21 for each scale. Higher scores indicate higher levels of anxiety or depression. For participants who lacked a response to one or two items on one subscale, missing values were substituted by the mean of the completed item scores. The subscale score of participants who lacked more than two items was set to missing.

The SF-12 consists of 12 questions; each question has response choices varying from two to six alternatives<sup>[21]</sup>. The 12 questions can be transformed into eight dimensional scores covering the physical and mental aspects of HRQOL. These dimensions are physical functioning (PF), role-physical (limitation associated with physical problems, RP), role-emotional (limitations associated with emotional problems, RE), mental health (MH), general health (GH), bodily pain (BP), vitality (energy and happiness, VT), and social functioning (SF). The dimension scores range

from 0-100, with higher scores indicating better HRQOL. Missing values were imputed following the recommendations of Ware and Kosinski<sup>[22]</sup>. If it was impossible to compute the value for one dimension, that dimensional score was deemed missing.

### Definitions

A positive FS is defined as the detection of advanced neoplasia (CRC, adenoma  $\geq 10$  mm, 3 or more adenomas, any polyp  $\geq 10$  mm, adenoma with high-grade dysplasia or villous components), and a positive FIT screening result is defined as the detection of human blood in the stool sample (cut-off  $> 75$   $\mu\text{g/L}$ ). Participants with a positive FS or FIT are referred for a colonoscopy. The main objective of this study was to investigate the potential anxiety caused by participation in a screening program among healthy participants who did not have screening-detected CRC. Thus, participants diagnosed with CRC from screening were excluded from the analyses.

For the HADS scale, cut-off levels are defined as a score of  $\geq 8$  for the possible presence of and  $\geq 11$  for the probable presence of "clinically meaningful degrees of mood disorder"<sup>[20]</sup>. In the current study, a score of  $\geq 8$  was defined as the cut-off for caseness for HADS-anxiety and HADS-depression, based on the results of a study of Norwegian patients visiting primary care physicians<sup>[23]</sup>.

Two-sided *P*-values  $< 0.05$  were considered statistically significant. The criterion for a clinically relevant mean change was defined as a change of  $\frac{1}{2}$  SD<sup>[24]</sup>, indicating the smallest change perceived by individuals as an actual change in condition. Cohen's *d* effect size above 0.5 as a medium effect size, or a clinically relevant change<sup>[25]</sup>. Therefore, our second criteria for a clinically relevant change was a value of Cohen's *d* above 0.5.

### Study outline

Participants first received the questionnaire with an invitation to CRC screening (baseline). They received the questionnaire for the second time with the results of their primary screening test (result), but before undergoing a potential colonoscopy. Six and 12 mo after receiving the invitation to screening, when participants had learned of their final screening results, participants who had completed the questionnaire at baseline received the questionnaire again. Control participants were invited to complete the questionnaire at baseline and at 6 and 12 mo following the first questionnaire.

The date of completion of the questionnaire was used to determine whether it had been completed before or after participation in screening. Consequently, questionnaires lacking a completion date were excluded. We were interested in the short-term reactions to the primary screening test results

in the second questionnaire. Therefore, result-questionnaires completed more than 60 d after the primary screening result or after work-up colonoscopy were excluded from the analyses of 4 time points. We accepted questionnaires that were completed within 5-8 mo following the invitation date as the 6-mo questionnaire, and questionnaires completed 11-15 mo after invitation were included as 1-year questionnaires.

Information regarding participants' nationality, marital status, education and occupation was obtained through the questionnaire. Education level was classified as low (primary school/high school) or high (minimum two years of college/university). Information regarding age and gender was obtained from the Norwegian National Registry.

### Participants

The number of individuals invited to participate in the psychological questionnaire study was 7270 for the FS group, 7024 for the FIT group, and 7650 for the control group. Participants who completed the questionnaire at baseline and after 1 year, as well as the screening examination for FS and FIT participants, were included in the main analyses. Additional analyses investigated changes over 4 time points, including all completed questionnaires.

Participants were ineligible for inclusion in the analyses if they had a previous CRC diagnosis or were deceased. Unattainable participants (invitation returned to sender) and participants who had moved out of the county were excluded. This study was approved by the Regional Ethics Committee of South-East Norway (REK approval no 2011/1272).

### Statistical analysis

To investigate the demographic differences between the three groups prior to screening,  $\chi^2$  tests were applied for categorical outcomes and ANOVA for continuous outcomes. Significant differences in the ANOVA analysis were further examined by contrast analysis to determine which groups differed from each other. The internal consistency of the two HADS subscales was tested by Cronbach's alpha.

To test for two- and three-way interaction effects between time (baseline and 1-year follow-up), primary screening results (positive and negative) and screening group (FIT and FS) on the outcome variables, ANOVAs analyses were applied. Next, we compared the mean change scores (from baseline to one-year follow-up) of the groups with positive and negative screening results, as well as of the two screening groups, with the change score in the control group. These analyses were completed with and without adjustment for participants' baseline values for the outcome. To investigate whether there were significant changes in outcome variables during the four time points, mixed models were applied, including all completed questionnaires at each time point. Two

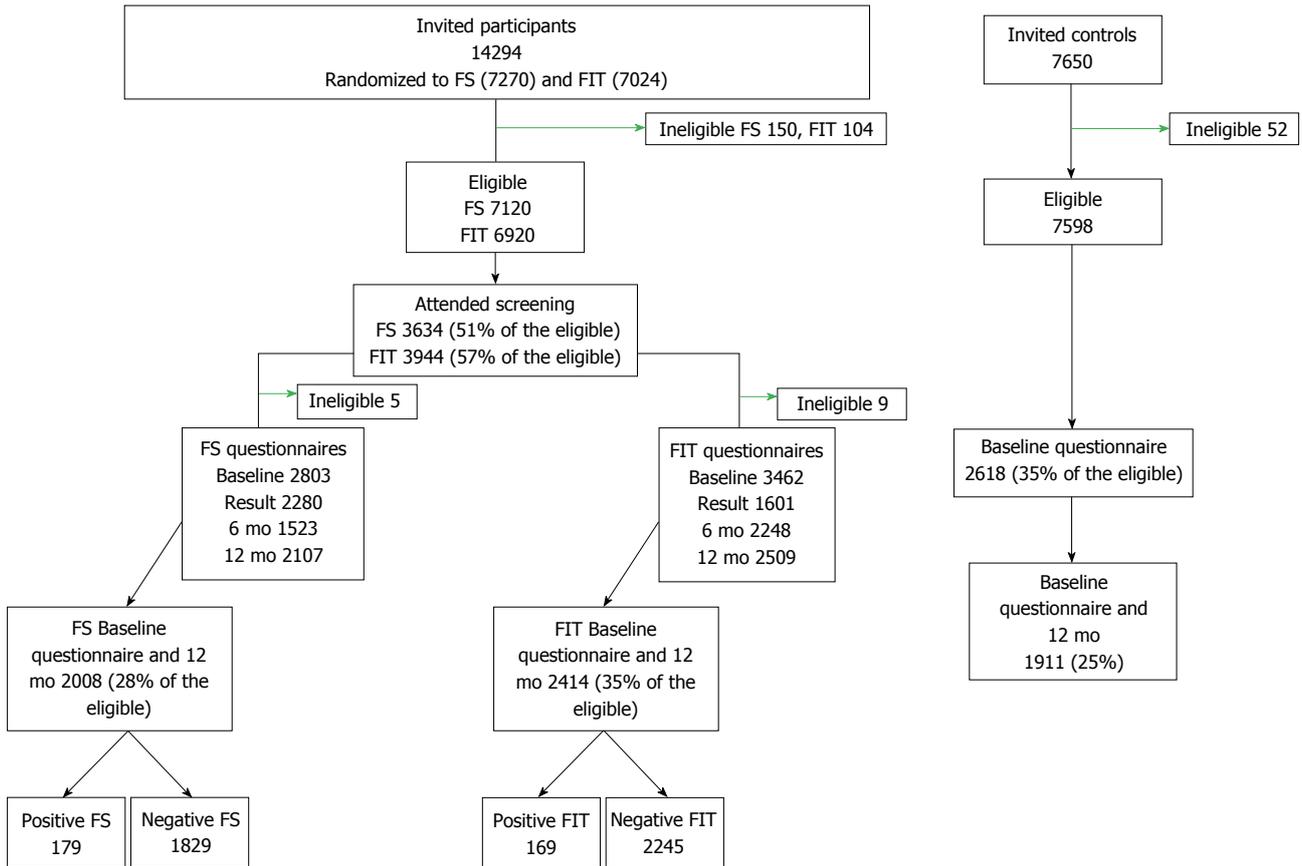
sensitivity analyses, using repeated measures ANOVA, were performed with the same aim for participants with complete data only (including only participants who had completed the questionnaire at all four time points) and for all participants who completed the baseline questionnaire, with participants' last completed questionnaire score carried forward when missing. Repeated measures analyses for binary outcomes were applied to test whether there were significant changes in the prevalence of participants with a score above the cut-off levels of anxiety and depression from baseline to one-year follow-up. Furthermore, we tested whether this change differed from the changes observed in the control group. These analyses were conducted with and without participants referred for surveillance colonoscopies. Age, sex, education, nationality, marital status and employment (and other HADS-score for HADS analyses) were included in all models to adjust for the effects of these variables. Statistical analyses were performed using SPSS v19 software. The statistical methods of this study were reviewed by statistician Edoardo Botteri from Cancer Registry of Norway.

## RESULTS

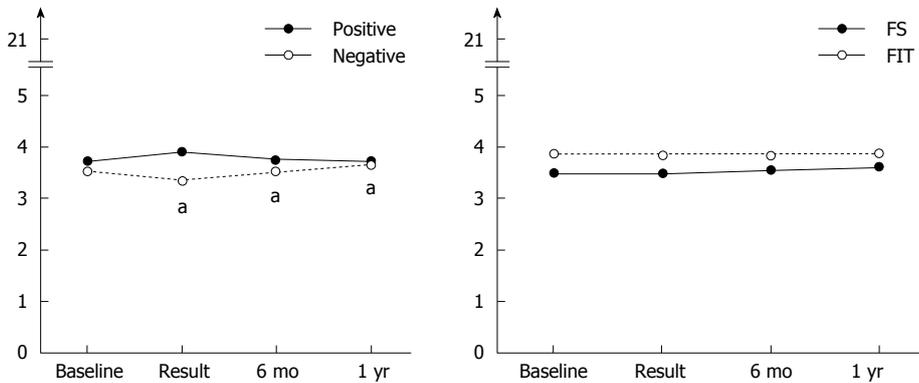
Of the 14294 individuals invited to screening, 7578 (53%) completed screening, of whom 4434 (32% of invited) completed the questionnaire both at invitation and at one-year follow-up: 2017 in the FS group and 2417 in the FIT group, respectively (Figure 1). Participants who received a CRC diagnosis during screening (13 in the FS and 12 in the FIT group) were excluded from all analyses. The 12-mo follow-up questionnaires were completed on an average of 340 d (range 88-426 FS) and 366 d (range 89-438 FIT) after screening participation, and 330 d (range 83-416) after colonoscopy for the screening positive. Among the individuals invited to the control group, 1911 (25%) completed the baseline and one-year follow-up questionnaires. Furthermore, 895 FS participants (13%) and 885 FIT participants (13%) completed the questionnaire at the four predefined time points.

The demographic data for each randomized group is shown in Table 1. The FS group displayed a higher mean age ( $M = 63.5$  years,  $SD = 7.0$ ) compared to the FIT group ( $M = 62.5$  years,  $SD = 6.6$ ),  $P < 0.01$ , as well as the control group ( $M = 62.7$  years,  $SD = 6.8$ ),  $P < 0.01$ . The HADS-anxiety and HADS-depression subscales had a Cronbach's alpha coefficients of 0.86 and 0.84, indicating good internal consistency.

Figure 2 shows participants' scores at baseline, after receiving screening results, after 6 mo and after 1 year, including all completed questionnaires (for n, see Figure 1). Participants' level of anxiety depended on both the screening results (positive versus negative) and time,  $P = 0.04$ . Anxiety increased immediately



**Figure 1** Flow-chart showing screening attendance and questionnaire response rate for the flexible sigmoidoscopy, faecal immunochemical test and control groups. Baseline questionnaires were completed prior to screening, and the result questionnaire after receiving the first screening result but before potential colonoscopy. FS: Flexible sigmoidoscopy; FIT: Faecal immunochemical test.



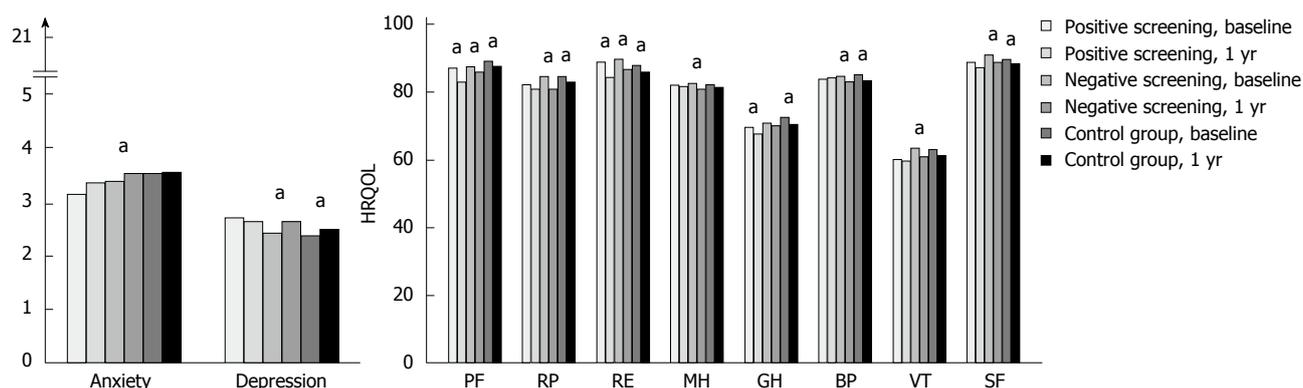
**Figure 2** Mean anxiety measured at four times in participants with positive and negative screening results and in the two screening groups. Baseline questionnaires were completed prior to screening, and the result questionnaire was completed after receiving the first screening result but before potential colonoscopy. Mixed models, <sup>a</sup>Contrast analyses. The mean score is statistically significantly different from the previous score. FS: Flexible sigmoidoscopy; FIT: Faecal immunochemical test.

after a positive result and decreased afterwards, while anxiety decreased after a negative result and increased afterwards. Participants with negative results reported statistically significantly less anxiety when receiving their results compared to baseline, which was also observed in the analyses of complete cases only and analyses with the last value carried forward (though the interaction effect was not significant). Some temporary improvements in HRQOL were observed

(Supplementary Tables 1 and 2).

**Participants with positive screening results**

Participants' scores for anxiety, depression and HRQOL at baseline and at 1 year follow up are shown in Figure 3. No statistically significant changes in anxiety were observed in participants with positive screening results from baseline to one-year follow-up. Table 2 shows the change in scores within each screening group



**Figure 3 Mean anxiety, depression and health-related quality of life scores at baseline and at 1-year follow-up for participants with positive and negative screening results and for the control group.** <sup>a</sup>The mean score at 1-year follow-up is statistically significantly different from the mean score at baseline. PF: Physical functioning; RP: Role-physical, limitation associated with physical problems; RE: Role-emotional, limitations associated with emotional problems; MH: Mental Health; GH: General health; BP: Bodily pain; VT: Vitality, energy and happiness; SF: Social Functioning.

**Table 1 Demographic characteristics of the three randomized groups measured at baseline**

	FS (Std residual)	FIT (Std residual)	Control (Std residual)	P comparing 3 groups
Norwegian nationality, %	95.9% (0.4)	94.6% (-0.2)	94.5% (-0.2)	0.08
Not married/cohabitant, %	18.0% (-2.0) <sup>1</sup>	20.0% (0.0)	22.0% (2.0) <sup>1</sup>	< 0.01
Higher education, %	45.3% (-0.8)	43.6% (-2.1) <sup>1</sup>	51.7% (3.2) <sup>1</sup>	< 0.01
Employed, %	48.9% (-0.9)	49.6% (-0.6)	52.9% (1.6) <sup>1</sup>	0.03
Women, %	50.1% (-1.0)	52.4% (0.6)	52.2% (0.4)	0.25
Mean age, yr	63.5	62.5	62.7	< 0.01 <sup>2</sup>

<sup>1</sup>Standardized residuals outside ± 1.96 are considered statistically significant; <sup>2</sup>ANOVA. FS: Flexible sigmoidoscopy; FIT: Faecal immunochemical test.

**Table 2 Mean anxiety, depression and health-related quality of life change scores from baseline to 1-year follow-up for participants with positive and negative screening results, the two screening groups and the control group**

	Control group	Positive (Cohen's d)	Negative (Cohen's d)	FS (Cohen's d)	FIT (Cohen's d)	Screening group (Cohen's d)
Anxiety	0.05	0.12 (-0.03)	0.13 (-0.04)	0.17 (-0.05)	0.09 (-0.02)	0.13 (-0.04)
Depression	0.15	-0.06 (0.10)	0.20 (-0.02)	0.20 (-0.02)	0.16 (-0.01)	0.19 (-0.02)
SF-12						
PF	-1.16	-3.83 <sup>1</sup> (0.14)	-1.50 (0.02)	-1.13 (-0.01)	-2.12 (0.05)	-1.71 (0.03)
RP	-1.86	-0.97 (-0.03)	-3.54 (0.05)	-4.05 <sup>1</sup> (0.06)	-2.77 (0.03)	-3.39 (0.04)
RE	-2.03	-3.37 (0.04)	-2.89 (0.03)	-2.04 (0.01)	-3.67 (0.05)	-2.99 (0.03)
MH	-0.41	-0.58 (0.01)	-1.28 (0.06)	-1.23 (0.05)	-1.20 (0.05)	-1.23 (0.05)
GH	-1.81	-2.09 (0.02)	-0.45 <sup>1</sup> (-0.09)	0.06 <sup>2</sup> (-0.12)	-1.08 (-0.05)	-0.57 <sup>1</sup> (-0.08)
BP	-1.57	0.57 (-0.11)	-1.11 (-0.02)	-0.73 (-0.04)	-1.18 (-0.02)	-1.01 (-0.03)
VT	-1.44	-0.19 (-0.06)	-1.93 (0.02)	-1.24 (-0.01)	-2.20 (0.04)	-1.8 (0.02)
SF	-1.10	-1.35 (0.01)	-1.47 (0.02)	-1.50 (-0.02)	-1.38 (0.02)	-1.46 (0.02)

ANOVA <sup>1</sup>The change from baseline to one year follow up is significantly different from the change observed in the control group. A Cohen's d effect size above 0.5 is defined as a clinically relevant change. HRQOL dimensions: PF: Physical functioning; RP: Role-physical, limitation associated with physical problems; RE: Role-emotional, limitations associated with emotional problems; MH: Mental Health; GH: General health; BP: Bodily pain; VT: Vitality, energy and happiness; SF: Social Functioning; FS: Flexible sigmoidoscopy; FIT: Faecal immunochemical test; HRQOL: Health-related quality of life.

**Table 3** Number of participants scoring above the cut-off for a case of anxiety ( $\geq 8$ ) at baseline and at 1-year follow-up in the different groups *n* (%)

Group			Anxiety at 1 yr follow up		<i>P</i> value <sup>1</sup>	<i>P</i> value <sup>2</sup>
			Non anxiety	Anxiety case		
Control group	Before screening	Non anxiety	1574 (82.5)	91 (4.8)	0.82	Ref.
		Anxiety case	87 (4.5)	57 (8.2)		
Screening	Before screening	Non anxiety	3660 (82.9)	250 (5.7)	< 0.01	0.11
		Anxiety case	164 (3.6)	343 (7.8)		
FS screening	Before screening	Non anxiety	1683 (84.0)	112 (5.6)	< 0.01	0.06
		Anxiety case	61 (3.0)	149 (7.4)		
FIT screening	Before screening	Non anxiety	1977 (82.0)	138 (5.7)	0.08	0.32
		Anxiety case	103 (4.3)	194 (8.0)		
Positive screening result	Before screening	Non anxiety	292 (84.0)	16 (4.6)	0.49	0.58
		Anxiety case	11 (3.2)	28 (8.2)		
Negative screening result	Before screening	Non anxiety	3368 (82.8)	234 (5.7)	< 0.01	0.11
		Anxiety case	153 (3.8)	315 (7.7)		

<sup>1</sup>The change observed within the group is statistically significant; <sup>2</sup>The change observed within the group is significantly different compared to the observed change within the control group. FS: Flexible sigmoidoscopy; FIT: Faecal immunochemical test.

compared to the changes in the control group. The only significant difference in change scores between participants with positive results and the control group was that participants with positive results had a greater worsening in the HRQOL dimension PF ( $M = -3.83$  vs  $M = -1.16$ ,  $P = 0.01$ , respectively).

#### **Participants with negative screening results**

At the 1-year follow-up, participants with negative results reported significantly more anxiety and a decreased HRQOL score compared to baseline (Figure 3). However, only the change in GH significantly differed from the control group, with the negative results group showing a smaller worsening in GH (Table 2).

#### **Effect of participation in screening**

The change scores observed in the FIT screening group were not statistically different from the changes in the control group (Table 2). FS participants showed a statistically significantly smaller worsening in GH and a greater worsening in RP compared to the changes in the control group.

Additionally, a significant increase in cases of anxiety (score  $\geq 8$ ) was observed among screening participants and FS participants from baseline to one year after screening (Table 3). However, the observed change in the screening group did not significantly differ from the change in the control group,  $P = 0.11$ . The increase in cases of anxiety within the FS group was marginally significantly different from the change observed in the control group,  $P = 0.06$ . The FS participants who changed from being non-cases to cases of anxiety had both a higher mean anxiety score ( $M = 5.2$ ,  $SD = 1.9$  vs  $M = 3.4$ ,  $SD = 3.3$ ) prior to screening and a higher mean change score ( $M = 4.4$ ,  $SD = 2.7$  vs  $M = 0.13$ ,  $SD = 2.3$ ) compared to the other screening participants. However, they did not differ from the other screening participants in terms of screening results or demographic variables.

None of the statistically significant mean changes observed fulfilled the criteria of a clinically relevant change (= change of  $\frac{1}{2}$  SD or Cohen's *d* of 0.5).

## **DISCUSSION**

This is the first randomized study to measure the long-term changes in anxiety from before CRC screening to one year after screening and to compare these changes with those of a control group. No clinically relevant change in anxiety, depression or HRQOL was documented in individuals receiving a positive CRC screening result one year after invitation to participate. Participants who received negative screening results reported decreased anxiety and improved HRQOL, but this effect was temporary and not clinically relevant. No clinically relevant psychological effects were observed in relation to FIT participation. In contrast, FS screening participants showed a marginally significant higher probability of being an anxiety case one year after screening compared to controls. The FS participants who progressed from not having anxiety to being considered an anxiety case showed a high anxiety level at baseline. Overall, for the vast majority, there were no clinically relevant psychological effects of participation in CRC screening, while for a small group of people, FS screening caused anxiety.

The results of the few previous studies on the psychological effects of CRC screening are inconsistent. Some studies find no effects of positive screening results on long-term general anxiety<sup>[6,10,12]</sup> or on HRQOL<sup>[11]</sup>, consistent with our results. Another study by Bobridge *et al*<sup>[8]</sup> documents higher anxiety in participants with positive compared to negative FIT results. However, due to comorbidities, these groups may differ prior to screening. For example, individuals experiencing gastrointestinal symptoms, such as anal fistula, are more likely both to have a false-positive FOBT and to be anxious<sup>[26,27]</sup>. Consequently,

the sample of participants receiving positive screening results is not necessarily comparable to those with a negative test, making within-participant measurements necessary. Furthermore, neither the effects documented in Bobridge's study<sup>[8]</sup>, or the mean changes observed in our study, fulfill the criteria for a clinically relevant change (of  $\frac{1}{2}$  SD<sup>[24]</sup>). Thus, there is little evidence for the concern that receiving a positive primary CRC screening result causes clinically relevant long-term anxiety.

In the present study, we observed a greater increase in the number of cases of anxiety in the FS screening group compared to the changes in the control group. Only one previous study has compared the psychosocial changes in CRC screening participants with a group not offered screening<sup>[12]</sup>. That study reported no increased anxiety in screening participants. The colonoscopy participants in that study were informed that their whole bowel had been visualized and that their risk of CRC was low, while our FS participants were informed that their whole bowel had not been visualized, which might have caused more insecurity. Importantly, the study mentioned above did not document within-group changes from before to after screening.

It would be interesting to compare psychological effects of colonoscopy screening with changes observed in the two screening modalities in the current study. However, because this is a pilot for a national CRC screening programme in Norway, it was decided to only include modalities with proven effect on CRC mortality in randomized controlled trials (RCT). Both FS and FIT meets this requirement<sup>[2]</sup>, while there are no results from RCT on colonoscopy screening available yet. As a consequence, no participants were invited to colonoscopy screening as a primary screening test in the BCSN pilot study.

In this study, FS screening was associated with an increase in cases of anxiety. One explanation of this finding could be that the participants who were referred to surveillance colonoscopies were the ones who become anxious, as they were awaiting further examinations. However, the results remained the same when we excluded these participants, and previous research shows no negative psychological effects of being offered surveillance colonoscopies<sup>[28,29]</sup>. While an increase in anxiety was observed among FS participants, there was no significant psychological effect of FIT screening. Invasive procedures are known to be associated with more anxiety<sup>[30]</sup>. Furthermore, FS differs from other screening procedures in that participants can follow the examination and observe any polyps. How participants interpret the presence of a polyp remains unclear, but this process can cause worries<sup>[28]</sup>. There are individual differences in how individuals process information about own health, and these differences influence the impact of the information received<sup>[31,32]</sup>. In our study, participants who progressed from being classified as

a non-anxiety case to a case of anxiety in the year following FS participation had a higher anxiety level prior to screening compared to the other screening participants. People with high self-rated anxiety can have cognitive biases, causing them to devote more attention to dangerous stimuli (such as cancers and an invitation to participate in a screening program due to being in a high-risk group) and to interpret mild threats as highly threatening<sup>[33]</sup>. This bias has been found to increase anxiety levels<sup>[34]</sup>. Further, anxious participants have a greater fear of cancer<sup>[35]</sup> and a higher perceived risk of developing CRC<sup>[36]</sup>, both of which are associated with higher anxiety in screening<sup>[37,38]</sup>. Future research should replicate our findings and investigate how anxious people might perceive screening as less distressing.

We observe no effect of FIT screening participation on anxiety, short- or long term. However, for FS screening we observe increased long-term anxiety in a sub-group, but there was no short-term effect<sup>[16]</sup>. One possible explanation is that the depth of peoples information processing depend on their emotional states<sup>[39]</sup>. Most people will have a negative screening result, and people experience positive emotions and relief after FS examination<sup>[12,31]</sup>. Positive emotion cause simple information processing, meaning that individuals think in terms of cancer or no cancer, and are relieved as they have not received a diagnosis of cancer. However, once the positive emotions disappear, individuals may process their screening experience deliberately. Individuals anxious about own health are especially likely to do so, because they are not reassured by CRC screening<sup>[31]</sup>. For example, they may process the presence and removal of polyps. Participants with negative screening results may focus on the fact that the whole bowel has not been visualized in the sigmoidoscopy examination, and consequently they did not receive the "all clear" result they may have expected. Some individuals who had all visible polyps removed during colonoscopy may be afraid that new polyps can develop. To individuals with high anxiety levels these health threats may be perceived as very threatening.

Previous research has reported decreased anxiety and improvements in HRQOL after receiving a negative CRC screening result<sup>[12,16,40-42]</sup>, in congruence with our results. The decreased anxiety might result from a decreased perceived risk of CRC, which could reduce motivation to maintain a healthy lifestyle. However, our results show that the decreased anxiety is temporary, disappearing within 1 year. This is reassuring, as short-term relief is less likely to create lasting health behavioral changes.

We used the HADS, a generic measure of anxiety, to identify psychiatric morbidity. However, a large meta-analysis of breast cancer screening showed that false-positive mammograms have negative effects on participants when measured by screening-specific measures, but not by generic measures<sup>[43]</sup>. In order to

investigate the potential harms of screening programs, it is important to document whether screening causes psychiatric morbidity, as well as screening-specific anxiety. Therefore, future research should replicate our study, using a cancer-specific anxiety measure, in order to get a complete understanding of the psychological effects of CRC screening.

### Limitations

Due to the prospective design of the current study, the number of participants who received a positive screening result was low, limiting our ability to detect statistically significant effects. The low response rate might limit the generalizability of our results. CRC screening attenders are more often married<sup>[44]</sup>, have a higher socioeconomic status<sup>[45]</sup> and better mental health<sup>[46]</sup> compared to non-attendees. Consequently, individuals who differ on these characteristics might respond differently towards screening attendance compared to our participants.

Participation in screening might be perceived as a benefit to the invited individuals. Selection bias in screening attendance might therefore differ from the determinants of compliance in the control group, which presented no immediate benefit to participants. However, the FS group and control group were similar in demographic variables, anxiety, depression and HRQOL prior to screening. Furthermore, the screening group and control group showed a similar change in depression and HRQOL over 1 year. We therefore believe that the greater increase in cases of anxiety in the FS compared to the control group was due to screening participation.

In conclusion, this study found no clinically relevant psychological harm of receiving a positive CRC screening result one year after invitation to undergo screening. FS screening participants, but not FIT participants, showed a marginally significant higher probability of having clinically meaningful anxiety one year after screening compared to controls. Thus, most participants who attend CRC screening do not experience clinically relevant long-term effects on anxiety, depression and HRQOL over one year. However, for a smaller, possibly anxious group, participation in FS screening may cause anxiety.

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## COMMENTS

### Background

Screening invites initially healthy people to be screened for cancer. The majority of participants will never develop cancer but might experience psychological stress from participation in the screening programme. It is important to determine the benefits and harms of screening.

### Research frontiers

The present study aimed to investigate possible long-term psychological harm of participation in colorectal cancer (CRC) screening in Norway. Participants are invited to flexible sigmoidoscopy (FS) screening or fecal immunochemical test (FIT).

### Innovations and breakthroughs

The results from previous research on psychological effects of CRC screening are inconsistent. While recommendations for psychosocial studies of screening recommend use of baseline and follow-up measures, and comparison to control groups, no study have investigated changes in anxiety from before CRC screening to after screening, and compared these changes to changes in a group not offered screening. This study is the first to do that, and the results show that participating in screening have no psychological effect on most participants, while FS screening cause increased anxiety in some participants. Participants with high levels of anxiety before screening might be vulnerable to get anxious from FS screening.

### Applications

It is important to understand benefit and harms of a screening programme, as more countries are considering implementation of CRC screening. Further research should focus on how to reduce anxiety in participants vulnerable to experience increased anxiety in FS screening.

### Peer-review

The paper is about the long-term psychological harm of participation in CRC screening in Norway. An interesting paper on the attitudes towards CRC screening that can help in designing future screening programs. Further research is still needed to find a definitive answer.

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