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Subsequent participation in organized FIT based screening following screen-derived colonoscopy – *A Danish nationwide cohort study*

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ABSTRACT

Introduction: In the Danish National Colorectal Cancer (CRC) screening program, participants with screen-detected low-risk adenomas are invited to a new faecal immunochemical test (FIT) screening after two years. However, participation rate in next FIT screening is unknown. We aimed to investigate this subsequent participation rate within the Danish CRC screening program.

Methods: This nationwide register-based study included participants aged 50–72 years registered with FIT screening in the Danish CRC screening program between January 1, 2016, and June 30, 2017. Participants were included if their index FIT was negative or if it was positive and the subsequent colonoscopy detected low-risk adenomas. Invitees were categorized as subsequent participants if they returned a FIT within 135 days following the invitation to screening. We estimated the relative risk for participation depending on screening outcome, age, and sex.

Result: 415,107 with a negative result and 5,550 with low-risk adenomas were included. 86.0% (85.9;86.1) of the invitees with a negative result participated in the subsequent screening, while 71.8% (70.6;73.0) of the invitees with low-risk adenomas participated subsequently. The risk of participation in the subsequent screening was significantly lower among all age groups of men and women with low-risk adenomas compared to similar groups with negative results.

Conclusion: Invitees with low-risk adenomas detected at their initial colonoscopy are less likely to participate in the subsequent screening than invitees with negative results. This association was found in all age groups and for both sexes. Further studies are necessary to assess whether non-attendance is more pronounced in specific subgroups.

1. Introduction

Colorectal cancer (CRC) is one of the most common cancer diagnoses worldwide (Ferlay et al., 2018). Overall CRC is ranked third in terms of incidence and second in terms of mortality. Worldwide, more than 1.9 million new cases are registered, and more than 900,000 people die from CRC (Bray et al., 2018; IARC, 2020) each year. Most organized CRC screening programs in Europe, use the guaiac fecal occult blood test (gFOBT) or the Fecal Immunochemical Test (FIT) (Ponti et al., 2017; Klabunde et al., 2015). Screening aims to detect CRCs at an earlier stage or already as precursors in order to reduce CRC morbidity and mortality (Fitzpatrick-Lewis et al., 2016; Karsa et al., 2012; Larsen et al., 2018; Stegeman et al., 2015; Hewitson et al., 2007). However, the magnitude and effect achieved by a CRC screening program depend on the participation rate (Karsa et al., 2012).

Currently, only 62.6 % of the invited citizens participate in the Danish national CRC screening program (Njor et al., 2018). Many factors have been shown to affect participation in the initial FIT test, follow-up colonoscopy, and continuous participation in organized CRC screening programs (Wools et al., 2016; Portillo et al., 2018; Unanue-Arza et al., 2021). Men and younger people have frequently been reported to have lower participation rates (Njor et al., 2018; Pallesen et al., 2021; Jäntti

Abbreviations: CI, Confidence Interval; CRC, Colorectal cancer; CRN, Civil register number; DCCG, The Danish Colorectal Cancer register; DCCSD, Database for Colorectal cancer screening; DCR, The Danish Cancer Registry; DNPR, The National Patient Register; FAP, Familial adenomatous polyposis; FIT, Fecal Immunochemical Test; IBD, Inflammatory bowel database; ICD, International Classification of Diseases; RR, Relative risk.

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et al., 2021; Solís-Ibinagagoitia et al., 2020; Artama et al., 2016; Blom et al., 2014; Gale et al., 2015; Navarro et al., 2017; Clarke et al., 2016), whereas older age is a barrier to follow-up colonoscopy (Thomsen et al., 2018; Deding et al., 2019; Hoeck et al., 2020). Comorbidity and low socio-economic status are also commonly described as barriers to participation in the CRC screening program (Pallesen et al., 2021; Thomsen et al., 2018; Deding et al., 2019; Deding et al., 2017; de Klerk et al., 2018; Kearns et al., 2018; Bhatia et al., 2021).

In Denmark, 90 % of the invited citizens with a positive FIT result adhere to a subsequent colonoscopy (Njor et al., 2018). Participants, who only get low-risk adenomas detected at their initial colonoscopy, are invited to a new FIT screening in the next screening round (The Danish Health Authority, 2012). In the general target population, previous participation in CRC screening is a strong predictor for future screening participation (Kirkøen et al., 2017; Saraste et al., 2018; Knudsen et al., 2017; Lo et al., 2015). Some participants with a screening-derived colonoscopy that is negative for CRC experience psychological dysfunction and cancer worry, but most participants express satisfaction with the screening and expect to participate again (Toft et al., 2019; Vermeer et al., 2020; Kirkegaard et al., 2019). However, to our knowledge, it is unknown how many of these future participants who actually participate in the screening program when invited again. Therefore, this study aims to investigate the subsequent screening participation rate for participants with low-risk adenomas at their initial colonoscopy in the Danish national CRC screening program.

2. Methods

2.1. Setting

The Danish national CRC screening program was initiated in 2014 with a four-year run-in period resulting in a screening interval between the first two screening rounds of two-four years. From the year 2018 and onwards the FIT test has been offered biennially to citizens aged 50–74 years (Njor et al., 2018; Danish Regions, 2017). Invitations are send by mail and include an invitation letter, information on CRC screening, guidelines on how to take the one sample FIT and the FIT kit, i.e. a sample bottle, faeces collection sheet, and the OC Sensor faecal immunochemical test [FIT]. The invitation specifies that citizens who are already participating in a surveillance program for CRC should not participate and those with Crohn's disease or ulcerative colitis should discuss with their physician whether the participation is relevant (Danish Regions, 2017; Danish Health Authority, 2016). In case of non-participation, the invitees receive a reminder letter within 45 days (The Danish Health Authority, 2012). Test-kit, return of test-kit as well as any subsequent follow-up colonoscopy and treatment are free of charge and part of the tax-funded health care system in Denmark (Mainz et al., 2015).

The returned FIT sample is analyzed and considered positive if the amount of blood exceeds the cut-off level of 100 ng/mL buffer (20 ug Hb/g Faces). By law participants with a positive test are invited to a subsequent colonoscopy within 14 days. The outcome from this colonoscopy is categorized as; clean colon, low-risk adenomas (1–2 adenomas $<$ 1 cm), medium-risk adenomas (3–4 adenomas $<$ 1 cm or adenomas ^{3}1–2 cm), high-risk adenomas (^{3}5 adenomas $<$ 1 cm or adenomas^{3} 2 cm) or detected CRC. The subsequent follow-up depends on

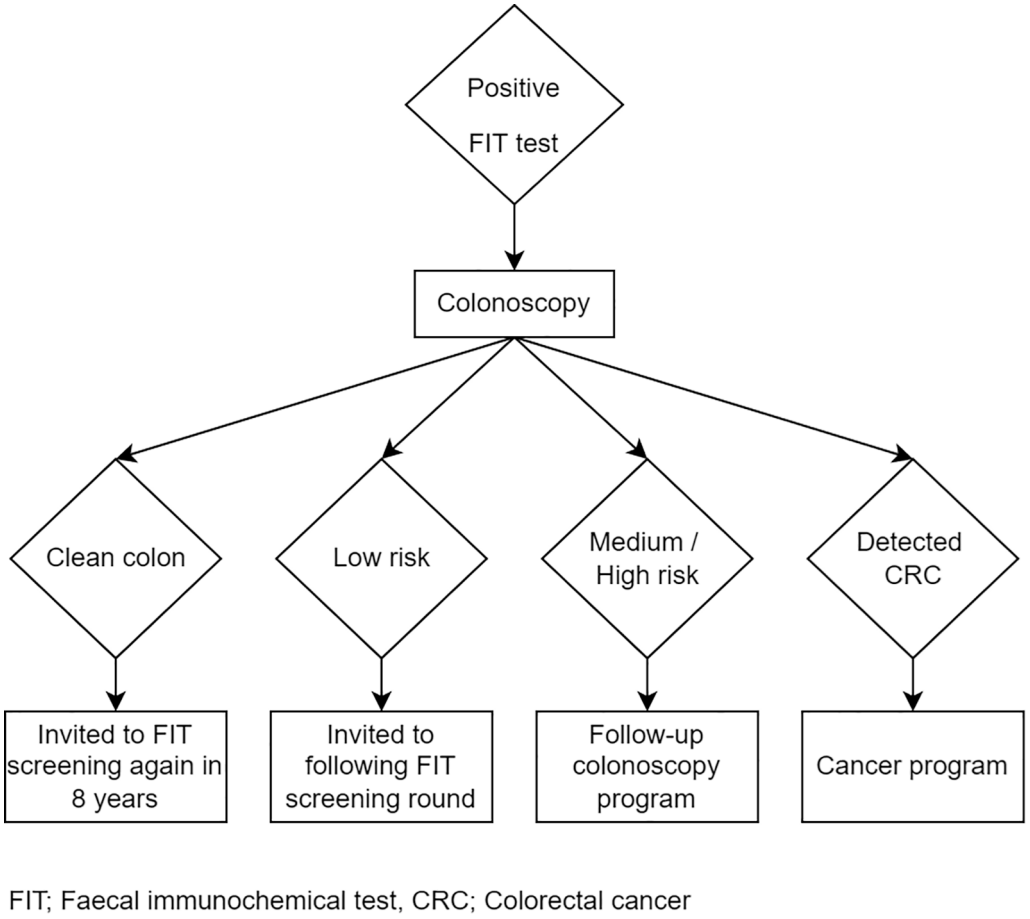

Fig. 1. Outcome and follow-up based on initial colonoscopy in the Danish national CRC screening program.

the outcome of the colonoscopy (Fig. 1). Participants with low-risk adenomas are invited to participate in the next FIT screening round (30).

2.2. Study population

This study is a nationwide register-based cohort study. The study population consists of participants aged 50–72 years registered with an index FIT between January 1, 2016, and June 30, 2017, in the Danish national CRC screening program. This population had an expected next invitation date in 2018–2020. Participants were included if their index FIT was negative or if their index FIT was positive and the initial colonoscopy(ies) performed in the next two months only detected low-risk adenomas. Participants with a previous CRC diagnosis, inflammatory bowel disease (IBD), and familial adenomatous polyposis (FAP) were

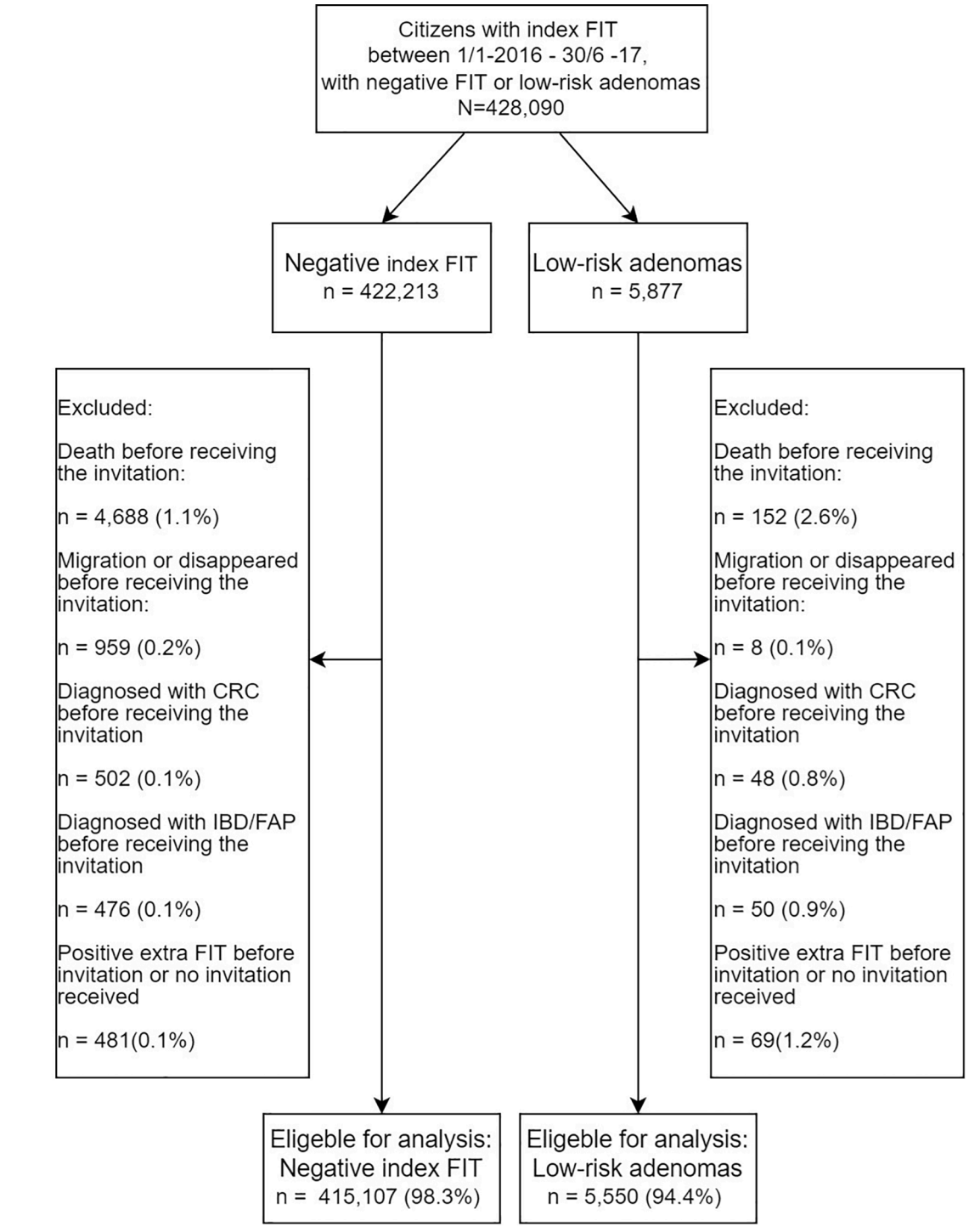

Fig. 2. Flowchart of in- and exclusion.

excluded from the study population.

Any diagnostic examination (colonoscopy, sigmoidoscopy, or CT-colonography) in the period between index FIT and the invitation to the second screening round was registered. Participants with low-risk adenomas who had a diagnostic examination within 14 days of their initial colonoscopy were not registered as having further diagnostic examinations, as we considered this an additional examination concerning the initial colonoscopy.

To evaluate the subsequent participation, we followed the participants until 135 days after they received the invitation to the second screening round. Participants were excluded from the analysis if they died, emigrated, or disappeared before the invitation was sent. We also excluded participants diagnosed with either CRC, IBD, or FAP during the follow-up period. Participants who had an additional FIT test, with a different result from the index FIT, between the date of index FIT and the date of receiving the invitation to the second screening round, were excluded, as a test before invitation would most likely be due to symptoms. For unknown reasons, some participants did not receive an invitation to the second screening round, and they were excluded from further analysis (Fig. 2). Participants were categorized as subsequent participants if they returned a stool sample within 135 days following the invitation to the second screening round.

2.3. Data sources

All residents in Denmark have a unique personal identifier, a civil register number (CRN) in the Danish civil registration system. The Danish civil registration system contains information on the date of birth, sex, emigration, and death (Pedersen, 2011).

Using the CRN, we linked the Danish quality database for Colorectal Cancer Screening (DCCSD) (RKKP, 2023), The National Patient Register (DNPR) (Lynge et al., 2011), the Danish Cancer Registry (DCR) (Gjerstorff, 2011), and the Danish Colorectal Cancer Register (DCCG) (Ingeholm et al., 2016).

Information on the dates of invitation, participation, and FIT results were obtained from DCCSD, which monitors the quality of the screening program. DCCSD gets information on invitations, participation, and FIT results from the administrative database IAM (RKKP, 2023).

Information on performed colonoscopies, sigmoidoscopies and CT colonographies based on procedure codes (KUJF32, KUJF35, KUJF42, KUJF45, UXCD80) as well as information on IBD and FAP were collected from DNPR. Information on IBD and FAP was based on the Danish version of the International Classification of Diseases (ICD), data on ulcerative colitis or Crohn's disease (ICD10 code DK51 and DK50) and FAP (ICD10 code DD126B or DD126F) were obtained from DNPR (Lynge et al., 2011; Schmidt et al., 2015). We classified participants as having low-risk adenomas if registered with a low-risk code (ZPY1E03) in DNPR (Lynge et al., 2011).

To exclude residents with CRC before the end of follow-up, we retrieved information on CRC diagnoses from DCCG, DCR, and DNPR (ICD 10 code: DC18, DC19, or DC20) (Lynge et al., 2011; Gjerstorff, 2011; Ingeholm et al., 2016).

2.4. Sensitivity analysis

We did a sensitivity analysis in which we excluded participants with a diagnostic examination (colonoscopy, sigmoidoscopy, or CT colonography) performed between their index FIT and the subsequent invitation to the second screening round. This analysis was made to ensure that subsequent participation was not affected by current surveillance not related to the CRC screening program.

2.5. Statistics

Age at index FIT was categorized into the following age groups: 50–54 years, 55–59 years, 60–64 years, 65–69 years, and 70–72 years.

We present the distribution of age and sex for participants with negative index FIT and participants with low-risk adenomas with number and percentage, respectively. We used a chi2 test to test whether these distributions were similar between the groups. Likewise, this was done among subsequent participants in the second screening round and is presented respectively for participants with negative index FIT and participants with low-risk adenomas. We also included the distribution of additional diagnostic examinations between index FIT or initial colonoscopy and the subsequent invitation.

We estimated the risk of subsequent participation in CRC screening for invitees with low-risk adenomas relative to invitees with negative index FIT. We included the explanatory variables sex (female or male) and the five year-age groups (50–54 years, 55–59 years, 60–64 years, 65–69 years, and 70–72 years).

Estimates are presented with 95 % confidence intervals (CI) and defined as statistically significant if the p-value < 0.05. All analyzes were performed using STATA statistical software version 17(Stata Corp, College Station, TX).

2.6. Ethics

According to EU's General Data Protection Regulation (article 30), the project was listed at the record of processing activities for research projects in Central Denmark Region (J. No.: 1–16-02–429-19). According to the Consolidation Act on Research Ethics Review of Health Research Projects, Consolidation Act number 1083 of 15 September 2017 section 14 (2) notification of medical database research projects to the research ethics committee system is only required if the project involves human biological material. Therefore, this study may be conducted without an approval from the committees.

3. Results

3.1. Study population

A total of 428,090 men and women were registered with an index FIT in the national Danish CRC screening program between January 1, 2016, and June 30, 2017, and included in this study. Of these 422,213 had a negative index FIT, while 5,877 had a positive index FIT and were categorized as only having low-risk adenomas at their screening-derived colonoscopies.

After exclusion 420,657 participants were eligible for further analysis. A total of 7,106 (1.7 %) participants were excluded from the negative group, while 327 (5.6 %) participants were excluded from the low-risk group. Participants were mainly excluded due to death before receiving the invitation to the second screening round (Fig. 2).

The age and sex composition were significantly different between participants with negative index FIT and participants with low-risk adenomas. Participants with low-risk adenomas at initial screening were in general older and more often males than participants with negative index FIT (Table 1).

Table 1
Characteristics of the study population for participants with negative index FIT and participants with low-risk adenomas. N = 420,657.

	Negative FIT		Low risk adenomas		p-value
	415,107	(98.7%)	5,550	(1.3%)	
Age n (%)					
50–54	88,360	(21.3)	737	(13.3)	
55–59	92,113	(22.2)	961	(17.3)	
60–64	89,621	(21.6)	1,271	(22.9)	
65–69	91,592	(22.1)	1,558	(28.1)	
70–72	53,401	(12.9)	1023	(18.4)	<0.001
Sex n (%)					
Female	226,589	(54.59)	2,317	(41.8)	
Male	188,518	(45.41)	3,233	(59.3)	<0.001

3.2. Subsequent participation

Overall 360,984 (85.8 %) of the invitees participated in the subsequent CRC screening round, by returning a FIT sample within 135 days. Among invitees with a negative index FIT 86.0 % (85.9;86.1) participated in the subsequent screening, while 71.8 % (70.6;73.0) of the invitees categorized with low-risk adenomas participated subsequently. The characteristics of the subsequent participants are presented in Table 2. In all age groups and for both sexes, the subsequent participation in the CRC screening program was lower for the group with low-risk adenomas.

3.3. Relative risk of subsequent participation

Having low-risk adenomas affected subsequent participation differently depending on age groups ($p < 0.001$) and the age groups affected subsequent participation differently for men and women($p < 0.001$). Therefore, we chose to present RR for the different age groups for men and women, respectively, instead of adjusting the estimates.

The risk of participating in the subsequent screening round in the CRC screening program was, for both men and women in all five age groups, significantly lower among invitees with previous low-risk adenomas than among invitees with a negative index FIT.

The relative risk of participating in the subsequent screening round was lowest for males at 50–59 years and lowest for females at age 55–59 years. At age 70–72 years the RR was 0.81 for both males (95 %CI: 0.77;0.85), and females (95 %CI:0.76;0.86). The estimated RRs are shown in Table 3.

3.4. Sensitivity analysis

Excluding invitees with a diagnostic examination before receiving the invitation to the second screening round, only affect the results slightly. When excluding these, 86.5% (86.4;86.6) of the invitees with negative index FIT participated subsequently, while 73.0% (71.8;74.2) invitees with low-risk adenomas participated in the subsequent CRC screening round.

Table 2
Characteristics of subsequent participants for the group with negative index FIT and the group with low-risk adenomas. N = 420,657.

	Negative index FIT n = 415,107 **Subsequent participants**		**p-value**	Low-risk adenomas n = 5,550 **Subsequent participants**		**p-value**
Total n (%)	356,998	(86.0)		3,986	(71.8)	
Female n(%)						
50–54 years	39,204	(81.0)		219	(68.9)	
55–59 years	43,742	(86.9)		291	(69.3)	
60–64 years	44,179	(89.8)		407	(78.0)	
65–69 years	45,107	(90.4)		461	(77.0)	
70–72 years	25,404	(88.4)	<0.001	327	(71.4)	0.002
Male n(%)						
50–54 years	30,226	(75.6)		247	(59.0)	
55–59 years	34,644	(82.9)		348	(64.3)	
60–64 years	35,184	(87.1)		528	(70.5)	
65–69 years	37,326	(89.5)		750	(78.2)	
70–72 years	21,982	(89.1)	<0.001	408	(72.2)	<0.001
Diagnostic examination n (%)						
Yes	16,478	(76.6)		228	(56.4)	
No	340,520	(86.5)	<0.001	758	(73.0)	<0.001

Table 3
Risk of subsequent participation for invitees with low-risk adenomas relative to invitees with negative index FIT. N = 419.575.

	50–54 years	55–59 years	60–64 years	65–69 years	70–72 years
	RR (CI 95%)	RR (CI 95%)	RR (CI 95%)	RR (CI 95%)	RR (CI 95%)
Male	0.78 (0.72;0.84)	0.78 (0.73;0.83)	0.81 (0.77;0.85)	0.87 (0.84;0.90)	0.81 (0.77;0.85)
Female	0.85 (0.79;0.92)	0.80 (0.75;0.85)	0.87 (0.83;0.91)	0.85 (0.81;0.89)	0.81 (0.76;0.86)

4. Discussion

4.1. Main findings

Participants only diagnosed with low-risk adenomas when participating in the National Danish CRC screening program are invited to the next FIT screening round. This study shows that only 72 % of these invitees chose to participate when invited to the next FIT screening round. Contrarily, 86 % of invitees with a negative index FIT choose to participate subsequently. The risk of participation in the subsequent screening round was lower among invitees with low-risk adenomas than among invitees with negative index FIT, in all age groups and for both males and females.

4.2. Strength and limitations

A major strength of this study is the use of high-quality Danish registers (Ingeholm et al., 2016; Schmidt et al., 2015; Thomsen et al., 2017; Erichsen et al., 2010). This reduces the risk of selection and information bias as the proportion of missing data is low, the validity of data is high, and the data is covering the entire population (Erichsen et al., 2010; Gjerstorff, 2011; Ingeholm et al., 2016; Lynge et al., 2011; Schmidt et al., 2015; Thomsen et al., 2017). Even though the databases have high completeness, registration errors may occur, but it is unlikely that this has systematically skewed the outcome of this study.

Compared to the negative group, a larger proportion of participants with low-risk adenomas were excluded due to not being invited again. It is unknown why these participants did not receive an invitation, some may have opted out of the CRC screening program, but there is also a risk that it is due to errors in the organization of the CRC screening program. Even if all 69 participants who did not receive an invitation would have been invited and participated in the subsequent screening FIT, the subsequent participation rate among participants with low-risk adenomas would only have increased slightly and would still be much lower than the subsequent participation rate for the participants with a negative index FIT.

We only included participants with low-risk adenomas, if the initial colonoscopy was performed within two months. This criterion was set following the Annual Report for Danish CRC screening (DCCSD, 2020). This exclusion criterion is only expected to have led to the exclusion of a very small proportion, as it is mandatory in Denmark that every-one with a positive FIT is offered a colonoscopy within 14 days (Danish Regions, 2017). The result is therefore not considered to be affected by this.

Invitees may have had adenomas detected outside the screening program between their index FIT and the second invitation. However, these adenomas would have been detected at a diagnostic examination, wherefore such invitees would have been excluded from our sensitivity analysis that only affected the results minorly.

Although the validity of the data in DNPR is high (Lynge et al., 2011), there is a risk that some may have been registered with a wrong risk code actually belonging to another risk group. When excluding all participants where there was any uncertainty regarding their risk code in

DNPR, this did not change the subsequent participation rate among participants with low-risk adenomas significantly. Excluding these participants resulted in an estimated subsequent participation rate of 2.1 % [70.8;73.4].

We did not have information about other relevant covariates, such as socio-economic status, comorbidity, alcohol intake, current smoking, obesity, and marital status which all may be associated with non-participation (Pallesen et al., 2021; Jäntti et al., 2021; Solís-Ibinagagoitia et al., 2020; Deding et al., 2017; Bhatia et al., 2021; Knudsen et al., 2017; Gram et al., 2021). This study uncovered the overall subsequent participation in the CRC screening program for invitees with low-risk adenomas at the initial colonoscopy, in the entire population. The participation rate can presumably be lower or higher in subgroups.

4.3. Discussion of the results and comparison with prior studies

To our knowledge, no prior studies have elucidated the subsequent participation rate among invitees with low-risk adenomas at their initial colonoscopy. However, the subsequent participation rate among all invitees (85.8 %) and our findings that participation is lowest among men and younger age groups, are consistent with the existing literature on participation in the second round of CRC screening (Blom et al., 2014; Clarke et al., 2016; Knudsen et al., 2017; Lo et al., 2015; van der Vlugt et al., 2017).

It has previously been shown that invitees who had a sigmoidoscopy screening are less likely to participate in subsequent screenings than invitees who had a FIT screening (Kirkøen et al., 2017).

The lower risk of participation among the oldest invitees may be due to the experience with the colonoscopy and the associated cleansing, which is more strenuous for the elderly (Day et al., 2011; Day and Velayos, 2015), although participants' experience with colonoscopy has generally been found positive (Ghanouni et al., 2016).

Based on previous studies about patients' experience with the initial colonoscopy, it is surprising that the subsequent participation rate was much lower for invitees with low-risk adenomas compared to invitees with a negative index FIT (Toft et al., 2019; Vermeer et al., 2020; Kirkegaard et al., 2019). A study that elucidated the experience four to six weeks after the examination found that the participants experienced the examination unpleasant, but all expected to get screened in the future (Kirkegaard et al., 2019). Another study found that after six months 5 % of the participants with no cancer detected at their initial colonoscopy regret their participation in the CRC screening program (Vermeer et al., 2020). So, it is conceivable that the proportion who regret their participation is not declining over time. The experiences with the initial colonoscopy were uncovered by interview studies or self-reported questionnaires (Toft et al., 2019; Vermeer et al., 2020; Kirkegaard et al., 2019), thus there is a risk of selection bias in the studies and the external validity is low. In the present study, the risk of selection bias is minimized and the study sheds light on the invitee's participation in the next screening round. Non-participation in the next screening round may be associated with regret of participation after a longer time than the mentioned studies have elucidated. These factors may explain why there is no agreement between the findings of this study and the existing literature.

It can be discussed whether the lower participation rate is due to the invitees regretting their participation or whether it may be due to insufficient communication and the organization of the CRC screening program. Invitees diagnosed with low-risk adenomas at the initial colonoscopy received the same information letter when invited to the second screening round. The information letter states that invitees should not participate if they are currently in a monitoring program for CRC (Danish Regions, 2017). There is a risk that some of the invitees are unsure whether they are in a monitoring program and therefore did not participate in FIT screening. In studies that have elucidated the non-participation among all invitees, some invitees explained that they did not participate in the CRC screening, because they assumed that screening was not necessary (Hall et al., 2015; Dressler et al., 2021). Some of the invitees with low-risk adenomas, may not find the subsequent screening necessary, because they received a colonoscopy and have been checked more closely, and therefore assume that they are not at risk of developing CRC (Llovet et al., 2018; Benito et al., 2018).

4.4. Implication for practice

The subsequent participation among invitees with previous low-risk adenomas should be studied further. It is relevant to study the association between previous low-risk adenomas and subsequent participation in CRC screening within different subgroups, with a focus on socio-economic status and comorbidity. Likewise, a qualitative study could be used to explore why many more of the invitees with low-risk adenomas did not participate in the subsequent FIT screening after their initial colonoscopy. A qualitative study might uncover whether it is the experience with the colonoscopy or the organization of the screening program or a third unknown factor that influences participation.

CRediT authorship contribution statement

Signe Bülow Therkildsen: Data curation, Formal analysis, Writing – original draft. **Pernille Thordal Larsen:** Conceptualization, Formal analysis, Data curation, Supervision, Writing – review & editing. **Sisse Njor:** Conceptualization, Formal analysis, Supervision, Writing – review & editing.

5. Conclusion

This register-based cohort study shows that invitees with low-risk adenomas detected at their initial colonoscopy are less likely to participate in the subsequent screening round compared to invitees with a negative index FIT. The result was found for all age groups and both sexes. Further studies are necessary to assess whether this non-participation is more pronounced in specific subgroups.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The authors do not have permission to share data.

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