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Adherence to colorectal cancer screening: four rounds of faecal immunochemical test-based screening

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Background: The effectiveness of faecal immunochemical test (FIT)-based screening programs is highly dependent on consistent participation over multiple rounds. We evaluated adherence to FIT screening over four rounds and aimed to identify determinants of participation behaviour.

Methods: A total of 23 339 randomly selected asymptomatic persons aged 50–74 years were invited for biennial FIT-based colorectal cancer screening between 2006 and 2014. All were invited for every consecutive round, except for those who had moved out of the area, passed the upper age limit, or had tested positive in a previous screening round. A reminder letter was sent to non-responders. We calculated participation rates per round, response rates to a reminder letter, and differences in participation between subgroups defined by age, sex, and socioeconomic status (SES).

Results: Over the four rounds, participation rates increased significantly, from 60% (95% CI 60–61), 60% (95% CI 59–60), 62% (95% CI 61–63) to 63% (95% CI 62–64; *P* for trend < 0.001) with significantly higher participation rates in women in all rounds (*P* < 0.001). Of the 17 312 invitees eligible for at least two rounds of FIT screening, 12 455 (72%) participated at least once, whereas 4857 (28%) never participated; 8271 (48%) attended all rounds when eligible. Consistent participation was associated with older age, female sex, and higher SES. Offering a reminder letter after the initial invite in the first round increased uptake with 12%; in subsequent screening rounds this resulted in an additional uptake of up to 10%.

Conclusions: In four rounds of a pilot biennial FIT-screening program, we observed a consistently high and increasing participation rate, whereas sending reminders remain effective. The substantial proportion of inconsistent participants suggests the existence of incidental barriers to participation, which, if possible, should be identified and removed.

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Colorectal cancer (CRC) is a major cause of cancer-related death (Jemal *et al*, 2011) and its prognosis is largely dependent on stage at diagnosis. Population-based CRC screening aims to detect CRC in an early stage, and to detect and remove precursor lesions, thereby reducing CRC morbidity and mortality (Shaukat *et al*, 2013). Faecal occult blood test (FOBT)-based screening using guaiac FOBT (gFOBT) has been shown to result in a reduction in CRC-related mortality in a number of randomised controlled trials (Mandel *et al*, 1993; Hardcastle *et al*, 1996; Kronborg *et al*, 1996), with a 15% reduction in CRC-related mortality in a meta-analysis (Hewitson *et al*, 2008).

In the last decade, several studies have shown that the performance of the faecal immunochemical test (FIT) is superior to that of gFOBT (Allison *et al*, 2007; Hewitson *et al*, 2007; van Rossum *et al*, 2008). Although FIT-based randomised controlled trials with long-term follow-up are lacking, a recent observational study demonstrated a 22% reduction in CRC mortality in areas, where FIT-screening programs were implemented compared with areas without screening (Zorzi *et al*, 2015). However, FIT has a relatively low sensitivity for CRC and its precursors, and one round of FIT-screening results in a cancer miss rate of 12–25% depending on the cutoff used (de Wijkerslooth *et al*, 2012). Screening invitations are therefore usually repeated every 2 years, and the effectiveness of a FIT-screening program is highly dependent on participation in multiple rounds. Ideally, eligible invitees accept the invitation to be screened in every screening round (consistent participation; Gellad *et al*, 2011; Steele *et al*, 2013).

A high rate of consistent participation increases the program sensitivity of FIT screening (Winawer *et al*, 1993; Launoy *et al*, 1998; Zaubler *et al*, 2012; Nishihara *et al*, 2013). On the other hand, the success of a biennial FIT-based screening program might be overestimated if the willingness to participate in multiple rounds is low. Knowing possible determinants of inconsistent participation could help in targeting the information to specific groups. Previous studies showed, for example, that especially socioeconomically deprived persons are less likely to accept CRC-screening invitations (Wee *et al*, 2005; Pernet *et al*, 2010, 2014; Moss *et al*, 2012; Leuraud *et al*, 2013; Lo *et al*, 2015b).

Several studies on FOBT screening are available, usually reporting on participation rates in a single round. We aimed to examine patterns in participation in an invitational program of biennial FIT-based screening over four screening rounds and to identify possible predictors for consistent and inconsistent screening behaviour.

MATERIALS AND METHODS

Study population/study design. This study was performed in our ongoing pilot program of population-based CRC screening. Details about the design of our program have been described previously (van Rossum *et al*, 2008; Denters *et al*, 2013; Kapidiz *et al*, 2014; Stegeman *et al*, 2015). In short, demographic data of persons between 50 and 74 years living in the southwest and northwest of The Netherlands were obtained from municipal population registers. Selection of the regions in 2006 was based on a known average uptake of invitees for the national breast cancer screening program. For the southwest region, random samples were taken from the target population by a computer-generated algorithm (Tenalea, Amsterdam, The Netherlands). In the northwest region random samples of selected postal code areas were taken.

The study was conducted in a dynamic cohort. Persons in the target age range that had moved into the targeted postal code area at any time during the recruitment period were included, as well as those that reached the lower age limit of 50 years.

No national screening program had been implemented at the start of this pilot program, and thus the target population was screening naive when first contacted. In the Netherlands, a national FIT-based CRC screening program was gradually initiated from January 2014 onwards. Invitees for our cohort were not invited for the national program.

The selected persons were invited for each consecutive round, except for those who had moved out of the area, those that had passed the upper age limit, institutionalised people, invitees unable to give informed consent, and those who had tested positive in a previous screening round. In our information leaflet and in our informed consent form, persons with a history of inflammatory bowel disease, proctocolectomy, or CRC were advised not to participate CRC screening, but report this reason for non-participation back to our screening organisation via the informed consent form. Participants reporting a colonoscopy in the past 2 years during intake after a positive FIT result were excluded from further participation, as well as those with an estimated life expectancy of <5 years.

Recruitment took place between June 2006 and December 2014 (first round from June 2006 to February 2007; second round from August 2008 to June 2009; third round from February 2011 to February 2012; and fourth round from March 2014 to December 2014). During the first round, invitees from the northwest region were randomly allocated to receive either a gFOBT or a FIT as screening test. Invitees who received a gFOBT in this first round were excluded from our analyses.

Date of birth, sex, and postal codes of all invitees were collected using the municipal population register. Socioeconomic status (SES) was based on social status scores provided by the Netherlands Institute of Social Research (www.scp.nl). The social status score of a postal code area is based on the unemployment rate, education level, average income, and position on the labour market. Social status scores are available for almost all postal codes in the Netherlands. The average status score of 0 and the s.d. in the Netherlands in 2006 was used to divide persons into three categories into high (status scores >0.96), average (status scores between -0.96 and 0.96), and low SES (status scores <-0.96). The first available postal code of the invitee was used to categorise invitees.

FIT screening. Every 2 years, all invitees received a pre-announcement letter about the screening program by mail, followed 2 weeks later by an invitation kit containing an invitation letter, information leaflet, and a single FIT device with testing instructions. In the first, second, and third round, all invitees received an OC-Sensor (Eiken Chemical Co, Tokyo, Japan) as a FIT device. In the fourth round, invitees were randomised to receive either an OC-Sensor (Eiken Chemical Co, Tokyo, Japan) or a FOB Gold (Sentinel Diagnostics SpA, Milan, Italy). As no differences in participation behaviour were seen between the two tests, we included both arms in our analysis (Grobbee *et al*, 2016). The FIT devices were returned to one of our two selected specialised laboratories and dates of return were registered. A test positivity threshold of $\geq 10 \mu\text{g Hb g}^{-1}$ faeces was used. People with a positive FIT result were referred for colonoscopy.

All non-responders received a reminder letter by mail after 2–6 weeks. Date of dispatch was registered. A positive response after the reminder letter was defined as a FIT device arriving at the laboratory 3 or more days after sending out the reminder letter. This interval of 3 days was based on the mail system delivery times, which maximally take 3 days between sending and delivering. Date of dispatch of the reminder and date of return of the FIT device at the laboratories were recorded for calculating return time.

Statistical analysis. The participation rate was calculated as the number of participants relative to all eligible invitees. For each screening round, we calculated participation rates per sex. For our

analyses of adherence to FIT screening, we only included invitees who were eligible in at least two rounds to be able to observe the three different screening patterns (see below).

Differences in screening behaviour were used to assign participants to one of three groups: consistent participation (i.e., attending all rounds when eligible), inconsistent participation (i.e., attending at least once but less than the total times eligible), and non-participants (not participating in any round of FIT screening).

The percentage of consistent participants was defined as the number of invitees attending all rounds, for which they were eligible relative to the total number of invitees. The percentage of inconsistent participation was defined, as the number of invitees attending inconsistently relative to the total number of invitees. Similarly, the percentage of non-participants was defined as the number of invitees, who never responded to any of the screening invitations.

Differences in proportions between groups were evaluated for statistical significance using the χ^2 -test statistic. We evaluated participation over rounds with the χ^2 -test statistic for trend. Differences in medians between groups were tested using the Kruskal–Wallis test statistic. $P < 0.05$ were considered to correspond to statistically significant differences. Data analysis was performed using SPSS22 for Windows (SPSS Inc., Chicago, Ill, USA).

Ethics approval. The Dutch National Health Council approved the study. All included screenees gave written informed consent to participate in the study.

RESULTS

Population. Our dynamic cohort consisted of 23 339 invitees, of whom 323 had to be excluded because they did not meet the inclusion criteria; 49 invitees had moved out, 12 invitees had died, and 262 invitees met one or more of the exclusion criteria (see Materials and Methods section) leaving 23 016 eligible invitees.

Baseline characteristics of the eligible invitees are summarised in Table 1.

Participation. Over the four rounds, participation rates increased significantly, from 60% (95% CI 60–61), 60% (95% CI 59–60), 62% (95% CI 61–63) to 63% (95% CI 62–64), respectively (Figure 1; P for trend < 0.001). Differences between men and women over four rounds of FIT screening are shown in Figure 2, with significantly higher participation rates for women in all four rounds ($P < 0.001$).

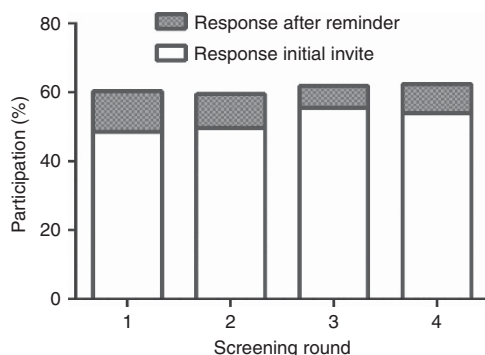


Figure 1. Overall participation per screening round with percentage distribution of type of response to participation (initial response vs response after reminder letter).

Adherence to screening and determinants of adherence. A total of 17 312 invitees were eligible for two or more rounds of FIT screening (Table 2). In this group, 8271 invitees (48%) were consistent participants and 4184 (24%) were inconsistent participants. Overall, 12 455 (72%) invitees participated at least once, whereas 4857 (28%) never participated in the FIT-screening program. Of the 8795 invitees that were eligible for all four rounds, 4345 (49%) participated in four rounds, 2370 (27%) in one or more rounds, and 2080 (24%) participated in none.

Table 3 lists the differences between consistent, inconsistent, and non-participants. Consistent participants were significantly older, more often female, and more likely to have a high SES.

Reminder letter. In the first screening round, 49% (95% CI 48–49) of the invitees responded within the first 2–6 weeks after receiving the initial invitation kit, and 12% (95% CI 11–12) participated after having been sent a reminder letter (Figure 1). The percentage of participants responding to the initial invitation increased after the first round, with participation rates of 50%, 56%, and 54% for the second, third, and fourth round, respectively. An additional uptake of up to 10% was observed after sending a reminder letter (Figure 1) within each round. On average, the FIT devices were returned within 15 days after sending a reminder letter (first round after 12 days (IQR 7–21); second round after 13 days (IQR 7–32); third round after 15 days (IQR 8–27); and fourth round after 14 days (IQR 7–28)).

DISCUSSION

In four rounds of a pilot biennial FIT-screening program, we observed consistently high and increasing participation rates of 60–63% in each round. Sending a reminder letter after an initial non-response resulted in an increased participation rate, adding 10–12% in each screening round. Almost half of the invitees that were eligible for two or more screening rounds were consistent participants, while almost a quarter never participated. Consistent participants were typically older, more often female, and more likely to have a high SES.

Strengths of our study include that our large cohort consists of an average risk population, comprising all the age ranges that are usually invited for CRC-screening programs worldwide. This population was screen naive when first approached, without the presence of any other CRC-screening initiatives in the population. Moreover, it covers four FIT-based screening rounds, although the majority of long-term studies so far were based on gFOBT-based

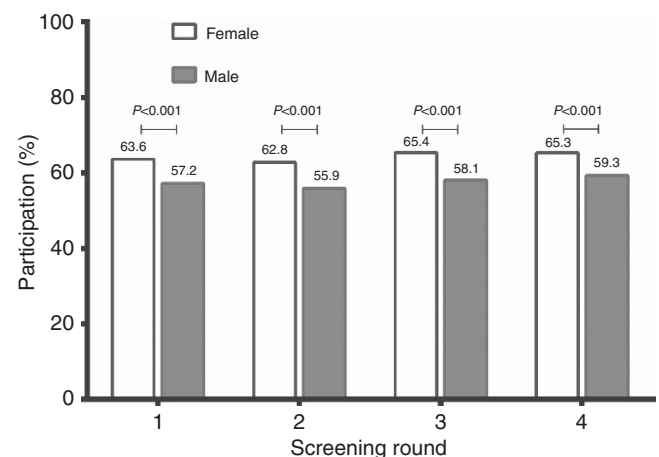


Figure 2. Participation rates per round of FIT-based screening subdivided by sex.

Table 1. Basic characteristics of eligible invitees of the dynamic FIT-based screening cohort

	Round 1	Round 2	Round 3	Round 4	P-value
Invitees ^a (n)	14.651	14.059	16.042	16.495	<0.001
Age (median; IQR)	59 (54–65)	60 (55–65)	59 (54–65)	61 (56–67)	<0.001
Sex (male; n (%))	7264 (50)	6880 (49)	7841 (49)	7955 (48)	0.127
SES (n (%))					<0.001
Low	1328 (9)	1412 (10)	1637 (10)	2281 (14)	
Average	10 602 (72)	10 004 (71)	11 296 (70)	11 117 (67)	
High	2721 (19)	2643 (19)	3094 (19)	3088 (19)	
Missing	0	0	15 (0.1)	9 (0.1)	

Abbreviations: FIT = faecal immunochemical test; IQR = interquartile range; SES = socioeconomic status.
^aEligible invitees.

Table 2. Adherence to FIT-based CRC screening over multiple rounds

Times eligible	Times participated (n, %)					Total
	0	1	2	3	4	
2	1766 (34%)	905 (17%)	2561 (49%)	—	—	5232
3	1011 (31%)	427 (13%)	482 (15%)	1365 (42%)	—	3285
4	2080 (24%)	656 (8%)	686 (8%)	1028 (12%)	4345 (49%)	8795
Total	4.857	1.988	3.729	2.393	4.345	17 312

Abbreviations: CRC = colorectal cancer; FIT = faecal immunochemical test. Analysis restricted to invitees who were eligible at least two screening rounds. Highlighted light purple blocks represent consistent participation.

Table 3. Determinants of FIT-screening participation behaviour

	Consistent (n = 8271, 48%)	Inconsistent (n = 4184, 24%)	Never (n = 4857, 28%)	P-value
Median age ^a (IQR)	57 (52–63)	55 (51–61)	55 (51–62)	<0.001
Males	45%	50%	54%	<0.001
SES ^a (%)				<0.001
Low	7%	11%	14%	
Average	71%	72%	70%	
High	22%	17%	16%	

Abbreviations: FIT = faecal immunochemical test; IQR = interquartile range; SES = socioeconomic status.
^aAge when first eligible.

screening. However, some study limitations have to be acknowledged. SES could only be assigned by postal code, as a proxy for individual-level SES. Regrettably, no data were available on the ethnicity of all invitees, nor their marital status, both factors that could also be associated with participation (El-Haddad *et al*, 2015). Our pilot program started in 2006, at a time when general awareness of CRC and CRC screening in The Netherlands was limited. That awareness has likely increased over time, especially after 2014, when a national Dutch CRC-screening program was launched. This might have positively affected participation rates in the third and fourth screening round in our pilot program. Moreover, in 2006, we selected our cohort based on uptake data from our national breast cancer screening program that has been implemented in 1990. We selected postal code areas within our regions with a known average uptake in breast cancer screening. This could have resulted in the relatively low proportion of low SES in our cohort.

Similar participation rates, ranging between 56 and 63%, have been reported for a pilot study over four rounds of biennial FIT screening in Italy (Crotta *et al*, 2012). Our percentage of consistent participants are in line with these data. Studies reporting on adherence to FIT screening over a longer time interval are scarce (Crotta *et al*, 2012; Kapidzic *et al*, 2014; Jensen *et al*, 2016). Most

reports are based on studies using gFOBT, reporting consistent adherence rates over multiple rounds, ranging from 39–44% (Steele *et al*, 2013; Pernet *et al*, 2014; Lo *et al*, 2015a).

As in several studies, women were more likely to participate in our FIT-screening program than men. A study from the United Kingdom also described sex differences in participation within a gFOBT-screening pilot consisting of three rounds (Moss *et al*, 2012). Denis *et al* (2015) reported an overall 6% higher participation rate for women in a first screening round within a gFOBT-screening program that consisted of four rounds, with a gradually decreasing difference over time. In contrast to these studies, the sex difference in our study remained comparable and significantly different, though this difference was small. A possible explanation could be that women are generally more familiar with the concept of screening. In The Netherlands, women are invited for cervical cancer screening every five years, since 1996 (invitations between the age of 30–60 years), and for breast cancer screening every 2 years, since 1990 (invitations between the age of 50–75 years). So far, no other national screening programs have targeted men. Yet the fact that the difference between participation in men and women did not decrease over four rounds, in contrast to what Denis *et al* reported, suggests that there may be other factors involved. Possibly, men are less likely to respond the mailed

invitations as compared to women and would, for instance, endorsement of the test by their general practitioner encourage them to participate.

A higher SES and older age were also significantly associated with consistent participation. These determinants for adherence to FIT screening are comparable with those in the previously reported one-time FOBT-screening studies and gFOBT-based CRC-screening studies (Wee *et al*, 2005; Pernet *et al*, 2010, 2014; Moss *et al*, 2012; Leuraud *et al*, 2013; Hurtado *et al*, 2015; Lo *et al*, 2015b). Pernet *et al* compared occasional participants with compliant participants in a gFOBT-screening program and also reported that occasional adherence was positively associated with living in socioeconomically deprived areas.

Response times for participation varied over screening rounds, with prompter participation in later screening rounds. A potential explanation could be that most invitees grew familiar with the program and the FIT as a screening test over successive rounds, thereby lowering the barrier to participate and to perform the test. An alternative, additional factor could be the increased awareness of CRC and CRC screening over time.

Response rates further increased after sending reminder letters to non-participants, and this effect was seen in each of the four rounds. Previous one-time screening studies with varying intervals for sending reminder letters also showed a positive effect on uptake from sending a reminder letter (Baron *et al*, 2008). Santare *et al* (2015) reported a very high proportion of 29% FIT devices returned (OC-Sensor) after sending a reminder letter after 21 days, but this was studied in Latvia, which has an opportunistic screening program with very low uptake (7.6%). Tinmouth *et al* (2015) reported a 9.7% increase in participation after sending a reminder letter in a gFOBT-based CRC screening after 6 months. Participation rates doubled after sending a new gFOBT kit. Our results indicate that sending a reminder letter to all non-responders after 6 weeks, in every screening round, consistently results in a positive contribution to overall participation and that reminders remain effective over multiple rounds.

About one in four invitees eligible for more than one round participated once or more often, but not in all screening rounds for which they had been invited. This indicates that the decision to participate in screening is not always the outcome of a one-time assessment. It is possible that eligible citizens change their behaviour in time, and one must acknowledge that also practical issues, such as work-related responsibilities, could prevent consistent participation.

Although screening uptake was high and increased over rounds, and about half of the FIT invitees were consistent participants, almost a quarter of the invitees never participated in any of the rounds of FIT screening. It would be relevant to investigate whether these invitees made an informed decision not to participate, or whether participation was hampered by barriers, such as limited health literacy, distrust of government initiated health initiatives, cost considerations, or other issues. Health literacy is an individual's capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions. Limited health literacy has been shown to be associated with a restricted use of preventive health services, such as cancer screening (Kobayashi *et al*, 2014). A questionnaire study performed in the second round of our pilot program of FIT screening showed that one of the more frequently reported reasons for non-participation in FOBT screening was lack of abdominal complaints, which suggests limitations in CRC knowledge in this group (Denters *et al*, 2015). Adequate CRC knowledge was found to be a strong predictor for participation in successive rounds (van Dam *et al*, 2013). It is conceivable that we need to diversify our invitation and information strategy, taking into account differences between groups, to achieve equity, enabling men and women, in all age groups, and socioeconomic

layers, in making well-informed decisions about participation in CRC screening.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

M van der Vlugt: study concept and design, acquisition of data; analysis and interpretation of data; drafting of the manuscript; and statistical analysis. EJ Grobbee: study concept and design; and analysis. Critical revision of the manuscript for important intellectual content. PMM Bossuyt: study concept and design; and statistical analysis. Critical revision of the manuscript for important intellectual content. E Bongers: made substantial contributions to the acquisition of data. Critical revision of the manuscript for important intellectual content. W Spijker: made substantial contributions to the acquisition of data. Critical revision of the manuscript for important intellectual content. EJ Kuipers: study concept and design. Critical revision of the manuscript for important intellectual content. I Lansdorp-Vogelaar: study concept and design. Critical revision of the manuscript for important intellectual content. M-L Essink-Bot: study concept and design. Critical revision of the manuscript for important intellectual content. MCW Spaander: study concept and design. Contributed to the acquisition of data. Critical revision of the manuscript for important intellectual content. E Dekker: study concept, and design and interpretation of data. Contributed to the acquisition of data. Critical revision of the manuscript for important intellectual content.

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