Fecal immunochemical test based colorectal cancer screening
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Involvement of previous non-participants cannot fully compensate for lower participation in a second round of FIT-screening
ABSTRACT

Introduction: The effectiveness of colorectal cancer (CRC) screening programs depends on repeated participation. Little is known on later rounds in programs that use the fecal immunochemical test (FIT), in particular whether previous participants are likely to participate again, and if non-participants persist in declining. We compared overall participation in a second round to that in a first round, and evaluated differences in participation rates based on previous response.

Methods: Asymptomatic persons aged 50-74 years were invited to a second round of a FIT-based CRC screening pilot. We assessed the participation rate overall and within second round subgroups of previous participants, previous non-participants, and first time invitees. We also assessed whether participation rates were similar for males and females and for age groups.

Results: In the first screening round, 2,871 of 5,309 invitees returned the FIT (participation rate of 57%). This was higher than in the second in which 3,187 of 5,925 participated (54%; \(P=0.0008\)). Second round participation rate was 85% (2,034/2,385) among previous participants, 18% (325/1,826) among previous non-participants and 48% (828/1,714) among first time invitees (\(P<.0001\)). Overall, males and persons aged under 55 were less likely to participate.

Conclusions: Participation in a second round of FIT-screening was significantly lower than in the first round, largely due to a drop in participation in first round participants, and a relatively low response among first time invitees. This loss of uptake was partially compensated by a willingness to be screened in previous non-participants.
**INTRODUCTION**

Several clinical trials have shown that guaiac fecal occult blood test based (gFOBT) colorectal cancer (CRC) screening programs can reduce cancer related deaths\(^1\)\(^-\)\(^3\). Since test sensitivity of FOBTs is suboptimal in comparison to other screening tests\(^4\), screening programs using FOBTs rely on repeated participation to pursue a high program sensitivity. The effectiveness of a screening program is therefore affected by the level of participation in consecutive screening rounds.

Several screening programs using FOBT have shown a gradual decline in participation over consecutive screening rounds\(^5\)\(^-\)\(^8\). The gFOBT is increasingly being replaced by fecal immunochemical testing (FIT), which is known to have better patient acceptability, greater ease of use and higher participation rates\(^9\);\(^10\). It is unclear to what extent declining participation rates can also be expected in FIT-based population screening programs.

It is conceivable that participation in later screening rounds is affected by whether or not invitees responded positively to a previous invitation. Previous non-participants might be less willing to accept an invitation than persons who already participated in a previous round. Most previous studies about participation in consecutive screening rounds do not allow evaluation of uptake based on previous responses, since onetime non-participants were often not contacted in subsequent screening rounds\(^1\)\(^-\)\(^3\);\(^5\);\(^11\).

We evaluated participation in a second round of FIT-based population screening and compared it with participation in the first round. We analyzed differences in participation rate between previous participants, previous non-participants, and first time invitees to this second round.

**METHODS**

Data were collected in a second round of a FIT-based biennial CRC screening pilot in the Amsterdam region of the Netherlands. In the first round, reported in detail elsewhere\(^10\), eligible individuals had been randomly allocated to an invitation with a gFOBT or an invitation with a FIT. In the second round only FIT was used. In our analyses we focus only on invitees to FIT-based screening.

**Study population and setting**

The detailed study protocol for the second round is available elsewhere\(^12\). In summary, men and women at average risk for CRC, aged between 50 and 74 and living in the screening pilot catchment area, were eligible for inclusion. The catchment area was identical to that of the first round and consisted of three postal code areas within the surroundings of Amsterdam. Institutionalized individuals and persons that had tested positive and undergone colonoscopy in the first screening round were excluded. The latter group receives surveillance endoscopies based on their colonoscopy results, in line with the current Dutch guidelines on follow-up after polypectomy\(^13\). Persons who had been invited in the first round but no longer fulfilled eligibility criteria at the start of the second round were not reinvited; this included individuals who had recently turned 75 years and
those who had moved out of the catchment area between rounds. An invitation was sent to those who fulfilled the eligibility criteria at the start of the second round but had not been previously invited.

**Recruitment and Invitation**

A file containing all eligible individuals based on date of birth and postal code was extracted from the municipality’s population database. A centralized invitation procedure was used. All invitations and reminders were sent out by the regional Comprehensive Cancer Centre Amsterdam, an institution also responsible for the organization of the breast and cervical cancer screening programs in the region.

Eligible individuals received an invitation kit. These kits included a standard invitation letter, signed by the principal investigator, an information leaflet, a FIT (OC-Sensor by Eiken, Tokyo, Japan; single test at one occasion with cut-off level of 50ngHb/ml) with detailed instructions, and an informed consent form. The leaflet contained information on the background of screening and on the screening procedure itself. It emphasized that the effectiveness of screening relies on repeated participation. Invitees could perform the test at home and return the FIT with the signed informed consent form in a postage free envelope to the specialized laboratory of the Academic Medical Centre Amsterdam. A reminder was sent to non-participants after 2 weeks and again after 3 months.

All second round invitees were sent a questionnaire 2 weeks after the invitation. The questionnaire included questions about marital status, education level, employment status, ethnicity, and language spoken at home.

**Data-analysis**

Participation was defined as return of the FIT within three months. Invitees for the second round were classified into three subgroups: (1) previous participants; (2) previous non-participants and (3) first-time invitees. Previous participants are those that had been invited for the first round and had also participated in that round. Previous non-participants were invited for the first round but had not accepted that invitation. First-time invitees fulfilled eligibility criteria for the second round but not for the first round: these are those that had turned 50 years of age between rounds or had moved from elsewhere into the catchment area.

We calculated overall and subgroup participation rates. The participation rate was defined as the number of completed FITs returned relative to the number of tests sent out. We compared the overall participation rate in the second round to that in the first round of FIT-screening, including only invitees allocated to FIT in the first round in the analysis. In addition, participation rates within the second round were compared between previous participants, previous non-participants, and first-time invitees.

We evaluated whether differences in participation rate were similar for males and females and across age subgroups (50-54, 55-59, 60-64, 65-69, 70-75). In addition, we summarized demographic and socioeconomic characteristics of second round invitees and compared them between previous participants, previous non-participants and first-time invitees. All differences between groups were tested for significance using the Chi-square test statistic. All statistical analyses were done with the software package SPSS 16.0.
Ethics approval
Ethical approval was provided by the Dutch Health Council (2005/03WBO, The Hague, The Netherlands).

RESULTS
Invitees
Between June 2006 and February 2007 a total of 5,039 individuals had been invited to the first round of FIT-based screening in the Amsterdam region (Figure 1). Of these, 2,871 invitees (57%) had returned the test while 2,168 (43%) had not. Between August 2008 and October 2009, 5,925 persons were invited for the second screening round; this group included 2,385 first round participants, 1,826 first round non-participants, and 1,714 first-time invitees (newly eligible persons: recently turned 50 or moved into the area). A total of 486 first round participants and 522 first round non-participants were excluded from participation in the second round based on either non-eligibility (aged over 75 or moved out of the area) or because they had tested positive in the first round. Baseline characteristics of the invitees are summarized in Table 1.

Figure 1. Study flow.
Participation
Table 2 shows FIT participation rates in the second round and offers a comparison with FIT participation the first round. Overall 3,187 of 5,925 invitees participated in the second round (54%). The median time interval between invitation and test performance was 11 days (IQR: 5 to 24 days). The majority of persons responded after the initial invitation (1,847 (58%)), 42% responded after the reminders (1,340 persons) had been sent. Participation rate in the second round was significantly lower than in the first round: 3,187 of 5,925 second round invitees (54%) versus 2,871 of 5,039 first round invitees allocated to FIT (57%; p=0.0008).

Table 1. Baseline characteristics of invitees.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N</th>
<th>Mean age ± SD, years</th>
<th>Males, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First round (FIT group only)</td>
<td>5,039</td>
<td>60 ± 7</td>
<td>2,490 (49)</td>
</tr>
<tr>
<td>Second round</td>
<td>5,925</td>
<td>59 ± 7</td>
<td>2,937 (50)</td>
</tr>
<tr>
<td>Previous participants</td>
<td>2,385</td>
<td>61 ± 6</td>
<td>1,061 (45)</td>
</tr>
<tr>
<td>Previous non-participants</td>
<td>1,826</td>
<td>61 ± 6</td>
<td>1,000 (55)</td>
</tr>
<tr>
<td>First-time invitees</td>
<td>1,714</td>
<td>54 ± 6</td>
<td>876 (51)</td>
</tr>
</tbody>
</table>

Table 2. Participation rates of first and second round and within second round subgroups.

<table>
<thead>
<tr>
<th>Invitees, n</th>
<th>Participants, n (%)</th>
<th>RR for participation (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First round (FIT group only)</td>
<td>5,039</td>
<td>2,871 (57)</td>
</tr>
<tr>
<td>Second round</td>
<td>5,925</td>
<td>3,187 (54)</td>
</tr>
<tr>
<td>Previous participants</td>
<td>2,385</td>
<td>2,034 (85)</td>
</tr>
<tr>
<td>Previous non-participants</td>
<td>1,826</td>
<td>325 (18)</td>
</tr>
<tr>
<td>First-time invitees</td>
<td>1,714</td>
<td>828 (48)</td>
</tr>
</tbody>
</table>

* Compared to first round.
# Compared to previous participants.

Subgroups
Participation rates differed significantly between second round subgroups. Significantly more previous participants participated than previous non-participants: 85% versus 18% (P<.0002). These numbers also indicate that the 15% loss of uptake in previous participants - 351 of 2,385 previous participants did not take part in the second round - was compensated for by the 18% uptake in previous non-participants, where 325 of 1,826 invitees who were eligible but did not take part in the first round returned the FIT in the second round (P<0.0001).

Response to a first time invitation was lower in the second round, even when only persons aged 50-54 are compared. In the second round, response to a first time invitation
in this age subgroup was 50%, significantly lower than the 54% in same age group in the first round (P=0.026) (Table 3).

In both screening rounds, females were more likely to participate than males (Table 4). This difference was not observed within the subgroup of previous participants: there participation rates were similar for males and females. Table 3 shows participation rates stratified for age, with significant differences between age subgroups. In both rounds participation was lower in invitees under age 55. Previous participants had the shortest median time-interval between invitation and testing (10 days); previous non-participants the longest (20 days) (Table 5).

Furthermore, as can be appreciated from Table 5, response rates differed significantly between initial invitation and first reminder in previous participants and previous non-participants (p=0.006 and p=0.009) whereas there was no significant difference among first-time invitees (p=0.65).

### Table 3. Participation by age group.

<table>
<thead>
<tr>
<th>Age-group</th>
<th>50-54</th>
<th>55-59</th>
<th>60-64</th>
<th>65-69</th>
<th>70-75</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>First round (FIT group only)</td>
<td>794/1,466 (54)</td>
<td>760/1,267 (60)</td>
<td>561/935 (60)</td>
<td>424/709 (60)</td>
<td>312/590 (53)</td>
<td>0.001</td>
</tr>
<tr>
<td>Second round</td>
<td>1,004/1,995 (50)</td>
<td>774/1,388 (56)</td>
<td>616/1,095 (56)</td>
<td>439/776 (57)</td>
<td>331/596 (56)</td>
<td>0.002</td>
</tr>
<tr>
<td>Previous participants</td>
<td>366/436 (84)</td>
<td>590/690 (86)</td>
<td>478/556 (86)</td>
<td>336/396 (86)</td>
<td>250/295 (85)</td>
<td>0.89</td>
</tr>
<tr>
<td>Previous non-participants</td>
<td>68/376 (18)</td>
<td>92/506 (18)</td>
<td>76/412 (18)</td>
<td>50/275 (18)</td>
<td>33/216 (15)</td>
<td>0.89</td>
</tr>
<tr>
<td>First-time invitees</td>
<td>570/1,183 (48)</td>
<td>92/192 (48)</td>
<td>62/127 (49)</td>
<td>53/111 (48)</td>
<td>48/85 (57)</td>
<td>0.69</td>
</tr>
</tbody>
</table>

NOTE. All values are expressed as n (%).

### Table 4. Participation by gender.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Males</th>
<th>Females</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>First round</td>
<td>1299/2,490 (52)</td>
<td>1572/2,459 (62)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Second round</td>
<td>1,430/2,936 (49)</td>
<td>1,757/2,988 (59)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous participants</td>
<td>898/1,061 (85)</td>
<td>1,136/1,324 (86)</td>
<td>0.43</td>
</tr>
<tr>
<td>Previous non-participants</td>
<td>156/1,000 (16)</td>
<td>169/826 (21)</td>
<td>0.007</td>
</tr>
<tr>
<td>First-time invitees</td>
<td>376/876 (43)</td>
<td>452/838 (54)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

NOTE. All values are expressed as n (%).
**Table 5.** Timing of response.

<table>
<thead>
<tr>
<th></th>
<th>Previous participants</th>
<th>Previous non-participants</th>
<th>First time invitees</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n= 2,385</td>
<td>n= 1,826</td>
<td>n= 1,714</td>
<td></td>
</tr>
<tr>
<td>Median number of days between invitation and test performance (IQR)</td>
<td>10 (5-21)</td>
<td>20 (8.5-39)</td>
<td>13.5 (5-28)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Number responding, (%)</td>
<td>2,034 (85)#</td>
<td>325 (18)##</td>
<td>828 (48)###</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>After initial invitation</td>
<td>1,292 (54)</td>
<td>131 (7)</td>
<td>424 (25)</td>
<td></td>
</tr>
<tr>
<td>After first reminder (2 weeks)</td>
<td>699 (64)</td>
<td>168 (10)</td>
<td>351 (27)</td>
<td></td>
</tr>
<tr>
<td>After second reminder (3 months)</td>
<td>43 (11)</td>
<td>26 (2)</td>
<td>53 (6)</td>
<td></td>
</tr>
</tbody>
</table>

Significance of difference between initial response rate and response rate after first reminder
# p=0.006
## p=0.009
### p=0.65

A total of 2,313 second round invitees completed at least 1 item of the questionnaire: 1,501 of 2,385 previous participants (63%), 241 of 1,826 previous non-participants (13%) and 571 of 1,714 first time invitees (33%). Females and older persons more often returned the questionnaire (Table 6). As can be appreciated from Table 7, first round non-participants were more often single. First time invitees in the second round more often had a high educational level, they were more often employed, and included a larger proportion of persons of non-Dutch ethnicity. Previous participants more often spoke Dutch at home.

**Table 6.** Baseline characteristics of questionnaire participants and non-participants.

<table>
<thead>
<tr>
<th></th>
<th>Questionnaire participants (n=2,313)</th>
<th>Questionnaire non-participants (n=3,612)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males, n (%)</td>
<td>1,017 (44)</td>
<td>1,920 (53)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mean age ± SD, years</td>
<td>60 ±7</td>
<td>58 ±7</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

**DISCUSSION**

In the second round of a FIT-based CRC screening program pilot in the Netherlands, the proportion of FITs returned was smaller than in the first round, with strong differences in subgroups based on previous screening behavior. Previous participants were significantly more likely to return the test than previous non-participants. These differences were seen in both males and females and throughout all age groups.

Overall, females were more likely to participate, a gender effect that has been described before in a number of studies (1;14-16). Our observation that persons aged under 55 (and also those over 69 in the first round) were less likely to participate has also been described earlier(1;14). The effects of sex on participation were less strong in people who
Table 7. Socioeconomic characteristics of participants by second round subgroup.

<table>
<thead>
<tr>
<th>Marital status, n (%)</th>
<th>Previous Participants (n=1,501)</th>
<th>Previous non-participants (n=241)</th>
<th>First time Invites (n=571)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single</td>
<td>311 (20)</td>
<td>78 (33)</td>
<td>118 (20)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Married/unmarried partners</td>
<td>1,166 (78)</td>
<td>160 (66)</td>
<td>443 (78)</td>
<td></td>
</tr>
<tr>
<td>Widowed</td>
<td>24 (2)</td>
<td>3 (1)</td>
<td>10 (2)</td>
<td></td>
</tr>
<tr>
<td>Employment status, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employed</td>
<td>462 (37)</td>
<td>78 (35)</td>
<td>278 (60)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Retired</td>
<td>584 (46)</td>
<td>98 (46)</td>
<td>102 (22)</td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>216 (17)</td>
<td>39 (18)</td>
<td>84 (18)</td>
<td></td>
</tr>
<tr>
<td>Language at home, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>&lt;.002</td>
</tr>
<tr>
<td>Dutch</td>
<td>1,311 (88)</td>
<td>203 (85)</td>
<td>464 (83)</td>
<td></td>
</tr>
<tr>
<td>non-Dutch</td>
<td>173 (12)</td>
<td>37 (15)</td>
<td>97 (17)</td>
<td></td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Dutch</td>
<td>1,394 (95)</td>
<td>219 (92)</td>
<td>500 (90)</td>
<td></td>
</tr>
<tr>
<td>non-Dutch</td>
<td>81 (5)</td>
<td>18 (8)</td>
<td>57 (10)</td>
<td></td>
</tr>
<tr>
<td>Education level, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Low</td>
<td>364 (25)</td>
<td>56 (25)</td>
<td>105 (19)</td>
<td></td>
</tr>
<tr>
<td>Medium</td>
<td>671 (46)</td>
<td>99 (43)</td>
<td>233 (43)</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>412 (29)</td>
<td>73 (32)</td>
<td>206 (38)</td>
<td></td>
</tr>
</tbody>
</table>

NOTE. Numbers shown for survey responders only

had responded positively to the invitation in the first round: there participation rates were more comparable across age and sex subgroups.

To the best of our knowledge, data on participation in consecutive screening rounds in asymptomatic invitees have only been reported for gFOBT-based programs. A gradual decrease in participation rate was observed in most of these, similar to what we report here for FIT-based screening (5;6;8). Results from the first three rounds of the Scottish pilot, however, showed a recovery to 55% participation in the third round after an initial decrease from 55% to 53% in the second round (7). As one of few, this Scottish pilot has also looked at differences in participation rates between previous participants and previous non-participants and reported results similar to ours: 85% of first round participants completed testing in the second round compared to 14% of first round non-participants (7). Mandel and colleagues reported similar numbers for the first two rounds of the UK Bowel cancer screening pilot: uptake was high in those who had participated in the first round (81%), and low (13%) in those who did not respond in the first round. Compared to these previous studies, the slightly higher participation rate among previous non-participants in our study (21%) may be explained by the use of FIT rather than the gFOBT (9;10;17). While interpreting these comparisons, we should be aware that the Scottish and British populations may differ from the Dutch population in the current study.
We observed that the response to a first time invitation was 4 percentage points higher in the first round than in the second round within those aged 50-54 years: 54% versus 50%. In the Scottish pilot response to a first time invitation was 55% in the first round and 45% in the second round. In the British pilot these numbers were 52% and 45%.

It is interesting to note that in the groups of previous participants and previous non-participants a significant difference was observed between the response rate after the initial invitation and the response rate after the first reminder. This finding of the effectiveness of reminders on response rate could be of use in the implementation of future screening programs using FIT.

In this pilot, a larger proportion of previous participants had a low education level and a larger proportion of first time invitees had a high education level. In the literature, education level is most often positively associated with the chance of returning an FOBT (18-22). A study on participation in mammography screening in Denmark reported an inverse U-shaped association between education and participation: both persons that only completed primary school and academics were less willing to participate in screening than those with a medium education level (23). Several other studies have reported similar associations (24;25). The large proportion of persons with a high education level in first time invitees for the second round may at least partially explain the lower participation in that group.

First time invitees to the second round were significantly more often employed than previous participants, who were more often retired. Coughlin et al report a slightly higher uptake of FOBT-screening in retired persons compared to employed persons although this difference was not statistically significant (18). Analyses of our first screening round data have shown that time and priority setting were among the main reasons for not returning the FOBT (26). It is likely that employed persons have a busier schedule and assign a lower priority to performing the FOBT. Among previous participants, more persons of Dutch ethnicity were represented and a larger proportion of persons reported to speak Dutch at home. Several studies have shown disparities among different ethnic groups with ethnic minorities having an overall lower participation rate (27;28).

Whatever the underlying mechanisms, response to the first invitation seems to guide response to subsequent invitations. Around 15% of participants to the first round did not participate in the second round although the information leaflet explicitly emphasized that participation in subsequent rounds is as important as participation in the first round. Only half of the first time invitees in the second round participated. If this trend continues and 15% of these first time participants decline participation in a third round, overall participation will decrease further over consecutive screening rounds. A fraction of this loss of uptake may be compensated for by resumed participation of previous non-participants, of which apparently around one in five were willing to participate when invited to a second screening round although they had declined the invitation to the first round two years before. This underscores the need for extending the invitation to all persons eligible, including those who did not respond to invitations to previous screening rounds. Unfortunately, our study design did not allow us to collect more detailed information on the reasons underlying the decisions not to take part in the first round while returning the FIT in the second round.
Based on the significant differences in participation observed in this study, one could consider designing programs in which the information leaflet is conditional on previous responses, using other language and different approaches in previous non-participants and first time invitees. While this may complicate the development of screening programs, it could also lead to more balanced and better informed decision making. A better understanding of the reasons to take part in screening in previous non-participants may improve the architecture of screening programs. The ultimate goal is not to force people into screening, but to inform them properly about the benefits and harms of repeated FIT-screening and to reduce barriers to participation.
REFERENCE LIST


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