Interventions to increase uptake of faecal tests for colorectal cancer screening: a systematic review.

Short title: Increasing uptake of tests for CRC screening

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ABSTRACT AND KEYWORDS

Introduction. International guidelines promote screening by faecal tests in asymptomatic people at average-risk of colorectal cancer (CRC) but uptake does not reach recommended levels in most countries.

Objective. The objective of the study was to synthetize evidence on 1) interventions aiming to increase uptake of faecal tests for CRC screening, in asymptomatic people at average risk of CRC, 2) interventions that targeted general practitioner (GP) involvement and 3) interventions that targeted non-responders or disadvantaged groups.

Methods. Systematic review of randomized controlled trials (RCT), searching Pubmed, Embase, and the Cochrane Library database, based on the Cochrane’s PRISMA-P 2015 guidelines. Risk of bias of included trials was assessed.

Results. From 24 included RCTs, the following interventions increase uptake of faecal tests: advance notification letter (OR 1.20 to 1.51), postal mailing (OR 1.30 to 2.89), written reminders (OR 1.31 to 7.70), telephone contacts with an advisor (OR 1.36 to 7.72). Three interventions demonstrated positive effects of GP involvement such as a GP signed invitation letter (OR 1.26), GP communication training (OR 1.22), or mailing reminders to GPs (OR 14.8). Inconclusive results were found for studies comparing different types of faecal tests, and those testing effectiveness of providing various type of written information.

Conclusion. Advance notification letters, postal mailing of the faecal tests, written reminders, and telephone contacts with an advisor increase patient uptake of faecal tests.
There was only limited evidence about the effect of GP involvement on screening test uptake, and a lack of studies focusing on non-responders or disadvantaged groups.

KEYWORDS

Colorectal cancer screening, FOBT, patient uptake, primary care, systematic review.
INTRODUCTION

In 2012, colorectal cancer (CRC) was the third most common cancer in men (746,000 cases) and the second most common in women (614,000 cases); annual mortality exceeds 500,000 (WHO, 2014). Screening programs conducted by government agencies slightly differ from one country to another (Benson et al., 2008; European Colorectal Cancer Screening Guidelines Working Group, 2013). However, in most countries, guidelines recommend 1) individualized assessment of risk for CRC in all adults, 2) starting screening at age 50 and in high-risk adults from 40 years, 3) using stool-based tests, flexible sigmoidoscopy, or colonoscopy, but always colonoscopy in high-risk people (European Colorectal Cancer Screening Guidelines Working Group, 2013; USPSTF, 2015). Screening can be stopped in adults over 75 years.

A minimum uptake is required to ensure screening efficiency, with suggested thresholds ranging from 65% to 75% (European Colorectal Cancer Screening Guidelines Working Group, 2013; Holme et al., 2013; NCI, 2005). Comparisons between a strategy based on colonoscopy and a strategy based on faecal test have shown that adherence was higher for screening by faecal test alone (Holme et al., 2013; Inadomi et al., 2012; Khalid-De Bakker et al., 2011), suggesting that screening should rely on faecal test completion. However participation rates in countries with organized screening programs based on faecal tests are low, ranging from 20% to 52%, and with disparities across socio-economic groups (Gellad et al., 2011).

In some countries, screening is organized independently of primary care and in others such as in France, policymakers decided that general practitioners (GPs) would be the only providers of FIT kits (French Ministry of Health, 2014). Factors associated with
lower participation rates include: female gender, younger participants, lower level of education, lower income, ethnic minorities and being unmarried (Wools et al., 2015). Identifying reproducible interventions that may be developed in a wider context is essential in order to maximize the efficacy of CRC screening programs. While French authorities have decided to organize FIT kit diffusion through GPs, we wondered whether there was evidence demonstrating the impact of GP involvement on patient uptake, and evidence of interventions that increased patient uptake among disadvantaged or hard-to-reach groups. *Another issue is the need to compile data regarding intervention's costs in order to analyse the cost-effectiveness of the corresponding interventions.*

The aim of the review was to investigate the following question: what randomized controlled trials (RCT) assessed interventions aiming at increasing uptake of faecal tests for CRC screening, in asymptomatic subjects at average risk of CRC?

**METHOD**

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2015) (Table 1).

**Inclusion and exclusion criteria**

The inclusion criteria for the studies included in this review were:

- design: RCT or cluster-RCT,
- setting: recruitment in a primary care or community setting, or at population level,
- population: asymptomatic adults at average risk of colorectal cancer.
Studies were excluded if: conducted in high-risk patients; targeted to specific patient groups (such as army veterans); no specification about participants; not reported in peer-reviewed publications; non-English or French language.

**Study identification and selection** (Moher et al., 2015)

We conducted a systematic search of PubMed, Embase, and the Cochrane Central Register of Controlled Trials, not limited by dates of publication, on September 1st 2015 (Text Box 1). We also hand searched reference lists of reviews and studies identified during the initial search. Abstracts and full texts were reviewed independently by two reviewers (CL and CR) for inclusion. Any disagreements about inclusion or exclusion were resolved by consensus and a third reviewer (AE) was consulted to resolve any remaining disagreements. When we identified multiple studies from the same authors investigating the same population or model, we reported them all as one study.

**Data extraction**

One reviewer (CL) extracted data on a form based on the Cochrane data extraction form (Cochrane Wounds Group, 2014). Studies were critically appraised by two reviewers (CL and CR) using the Cochrane Collaboration’s risk of bias tool (The Cochrane Collaboration, 2008), and discrepancies were resolved by consensus.

**Data synthesis and assessment of quality**

We performed narrative data synthesis, organizing the results by intervention in accordance with previous presentation from other authors (Senore et al., 2015), depending on whether the intervention focused on information to screening invitees,
physician practice, or test modalities. Quantitative synthesis was limited by the heterogeneity of the study designs and results presentation. In order to ensure consistency when reporting the impact of interventions, we re-calculated the number of patients, odds ratios, and/or p-values when these data were not provided explicitly in the manuscripts. The manuscript authors were contacted when the data provided did not allow recalculation of OR and/or p-values. For each study, we analyzed the following risks of bias: selection bias, performance bias and detection bias, attrition bias, reporting bias. These biases were classified in three categories (low, moderate, high), according to the PRISMA-P guidelines. We did not assess publication bias.

RESULTS

In total, 275 titles and abstracts were screened for eligibility utilizing the inclusion and exclusion criteria. Twenty-four studies were included in the review (Figure 1).

The main characteristics of studies are reported in Table 2. The trials varied in their design. Three studies targeted the clinician (GPs) for the interventions, and randomised by clinician (Aubin-Augé et al., 2014; Federici et al., 2006; Tinmouth et al., 2015). The other 21 studies targeted patients directly with the interventions, and randomised by patient (Baker et al., 2014; Birkenfeld et al., 2011; Cole et al., 2003, 2007; Federici et al., 2005; Gimeno-Garcia et al., 2009; Giorgi Rossi et al., 2011; Green et al., 2013; Hewitson et al., 2011; Hol et al., 2010; Hughes et al., 2005; Lee et al., 2009; Levi et al., 2011; MACS Group, 2006; Mant et al., 1992; Miller et al., 2005; Myers et al., 1991, 2014; Neter et al., 2014; Ore et al., 2001; Van Roon et al., 2011; Vinker et al., 2002).
The interventions reported in the included studies focused either on the test modalities (i.e. FIT vs gFOBT; 6 studies), on patient information (16 studies), or on physician practice (2 studies) (Table 3). Ten studies were based on complex interventions (Baker et al., 2014; Cole et al., 2007; Green et al., 2013; Hewitson et al., 2011; Hol et al., 2010; Mant et al., 1992; Miller et al., 2005; Myers et al., 1991; Neter et al., 2014; Vinker et al., 2002), which we report across different categories.

Screening uptakes varied markedly across studies, ranging from 1.2% to 82.2% (Table 3). In seven studies the uptake in the control group was less than 20%; in 12 studies it was from 20-40%; in seven studies it was from 40-60%; and in three it was over 60%. Screening uptake assessments were performed after various periods, ranging from 2 weeks to 24 months (Table 2). In nine studies, screening uptake was assessed before 6 months; in five studies it was performed between 6 months and one year; and in one it was performed at 12 and 24 months.

**Heterogeneous interventions**

**FIT vs gFOBT**

Six studies compared the use of FIT vs gFOBT kits (Birkenfeld et al., 2011; Cole et al., 2003; Federici et al., 2005; Hol et al., 2010; Hughes et al., 2005; Levi et al., 2011). Four concluded that using FIT rather than gFOBT significantly increased uptake of screening tests (OR from 1.29 to 2.14) (Cole et al., 2003; Federici et al., 2005; Hol et al., 2010; Hughes et al., 2005). In contrast, two studies based on large samples (16,132 and 12,537 people) found gFOBT was associated with higher uptake (OR= 0.86, OR = 0.92) (Birkenfeld et al., 2011; Levi et al., 2011).
Advanced notification letter

Two studies reported the positive impact of an advanced notification letter (Cole et al., 2007; Van Roon et al., 2011). They assessed the impact of mailing an information letter before the standard invitation, aiming to raise awareness of CRC screening among eligible people (OR ranging from 1.20 to 1.51). A third study also reported higher uptake after an advanced notification letter (31.7% vs 25.5%) but the difference was not statistically significant (p=0.051) (Mant et al., 1992).

Postal mailing of kits

Five studies reported that mailing kits to screening invitees increased uptake (OR ranging from 1.30 to 2.89) (Giorgi Rossi et al., 2011; Green et al., 2013; Mant et al., 1992; Ore et al., 2001; Tinmouth et al., 2015). Four of these studies compared a direct mailing of the kit vs a standard letter with invitation to collect a kit in a primary care clinic (Giorgi Rossi et al., 2011; Green et al., 2013; Mant et al., 1992; Ore et al., 2001). The fifth study focused on non-respondents to an initial mailed invitation (Tinmouth et al., 2015).

Frames of invitation messages

Five studies assessed the effect of different frames of invitation messages (varying presentation and content of the written information) (Cole et al., 2007; Hewitson et al., 2011; MACS Group, 2006; Myers et al., 1991; Neter et al., 2014). Three demonstrated increases in uptake, based on a leaflet containing information on FOBT (Hewitson et al., 2011), an “implementation intention” technique (Neter et al., 2014) or letting the participant choose between different screening tests (FOBT, colonoscopy, sigmoidoscopy, or CTC) (MACS Group, 2006. Two found no statistically significant
effect: one compared gain or loss framed messages in booklets sent with invitation letters (Myers *et al.*, 1991); the other evaluated an intervention to enhance awareness of risk of CRC based on advocacy messages (Cole *et al.*, 2007).

Reminders

Three studies demonstrated increased uptake ranging from 15.6% to 47.1% (OR ranging from 1.31 to 7.70), based on telephone and written reminders (Baker *et al.*, 2014; Green *et al.*, 2013; Myers *et al.*, 1991).

Tailored navigation

Four studies demonstrated increased uptake following a “navigation intervention” based on telephone calls by a counselor (OR from 1.36 to 7.72) (Green *et al.*, 2013; Myers *et al.*, 1991). In two or three arm RCTs, interventions included: an instruction call to patients within a week after kit mailing (telephone call about how to perform the test), a reminder phone call at 30 days if no tests were returned (Myers *et al.*, 1991); telephone assistance with a navigator after postal mailing of kits and mailed reminder letters (Baker *et al.*, 2014; Green *et al.*, 2013); personal navigator call to review mailed materials and explore preferences and barriers for screening (Myers *et al.*, 2014).

Video-based or computer-based interventions

Two studies assessed video-based or computer-based interventions. One reported a slight improvement of test uptake within 2 weeks after a video-based educational intervention (69.9% vs 54.4%, *p* = 0.044) (38). The second compared the effect of counseling provided by automatized informatics software to counseling by a nurse (Miller *et al.*, 2005), without showing any impact on uptake of screening tests (62% vs 63%).
Improving GP involvement

Finally, three studies reported interventions requiring GP involvement. Two showed increased uptake – from 12.2% to 15.3% (each statistically significant) (Aubin-Augé et al., 2014; Vinker et al., 2002) – while one was inconclusive (Hewitson et al., 2011). Aubin-Augé (2014) reported the impact of GP training focused on communication skills (increased screening uptake in the intervention arm (36.7% vs 24.5%; p = 0.03). Vinker (2002) demonstrated the impact of mailing reminders to GPs, rather than sending reminders to screening participants (OR = 14.8).

Focus on non-responders and disadvantaged groups

One study focused on non-responders (Tinmouth et al., 2015). Six authors reported that a higher socioeconomic status was associated with a higher uptake of screening test (Birkenfeld et al., 2011; Cole et al., 2003; Hol et al., 2010; Levi et al., 2011; Neter et al., 2014; Van Roon et al., 2011). However, none of them reported a specific impact of the experimented intervention on screening uptake inequalities in the corresponding populations. None of the studies assessed targeted interventions aiming to improve participation in disadvantaged groups.

Focus on intervention costs

Costs related to the intervention were reported in 4 studies, but there were wide variations in the data provided. Giorgi Rossi et al. (2011) assessed the cost of mailing FOBT (from 4.24 euros to 46.80, depending on whether the patient was a responder or not). The cost of performing a standard recall ranged from 3.29 to 18.30 (depending on whether the patient was a responder or not). Baker et al. (2014) evaluated the cost per completed test
at $43.13, based on a complex intervention with mailing, automated call, and text message. Green et al. (2013) reported costs ranging from $371 to $557 for interventions based on assisted care or navigated group.

DISCUSSION

Principal findings

From 24 randomized controlled studies, the following interventions increased uptake of faecal tests for CRC screening: advance notification letter (Cole et al., 2007; Van Roon et al., 2011), postal mailing (Giorgi Rossi et al., 2011; Green et al., 2013; Mant et al., 1992; Ore et al., 2001; Tinmouth et al., 2015), written reminders (MACS Group, 2006; Myers et al., 1991), telephone contacts with a navigator or a medical assistant (Baker et al., 2014; Green et al., 2013; Myers et al., 1991, 2014). Three interventions demonstrated positive effects of GP involvement (Aubin-Augier et al., 2014; Hewitson et al., 2011; Vinker et al., 2002) using a GP signed invitation letter, GP communication training or mailed reminders to GPs. Other studies assessed whether patient counseling could be provided by video or using automatized informatics software (Gimeno-Garcia et al., 2009; Miller et al., 2005). Inconclusive results were found for studies comparing FIT vs FOBT, and those testing effectiveness of different formats of written information. None of the interventions targeted participation in disadvantaged groups. Only one focused on non-responders (Tinmouth et al., 2015).

Strengths and weaknesses

Quality of the evidence
General evaluation showed risks of bias for most studies. None of the studies was blinded. Loss-to-follow-up and randomization were frequently unclear – reported in only eight studies (Aubin-Auger et al., 2014; Green et al., 2013; Lee et al., 2009; Levi et al., 2011; MACS Group, 2006; Miller et al., 2005; Ore et al., 2001; Van Roon et al., 2011). Only nine studies reported a power calculation (Aubin-Auger et al., 2014; Cole et al., 2003; Federici et al., 2006; Gimeno-Garcia et al., 2009; Hewitson et al., 2011; Hol et al., 2010; MACS Group, 2006; Miller et al., 2005; Van Roon et al., 2011). Selective reporting was estimated as moderate or high risk for 6 studies (Birkenfeld et al., 2011; Cole et al., 2007; Gimeno-Garcia et al., 2009; Mant et al., 1992; Ore et al., 2001; Vinker et al., 2002). Funding source was missing in 8 studies (Baker et al., 2014; Birkenfeld et al., 2011; Federici et al., 2005; Hewitson et al., 2011; Levi et al., 2011; Mant et al., 1992; Myers et al., 1991; Neter et al., 2014).

Most studies focused on an average-risk population aged from 50 to 74. Five studies included populations defined by other age thresholds (Cole et al., 2007; Hewitson et al., 2011; Lee et al., 2009; MACS Group, 2006; Mant et al., 1992) - such as 45-64 years (Mant et al., 1992) or 60-75 years (Lee et al., 2009) - but the related reasons were not provided.

Potential biases in the review process

Grey literature was not searched, potentially leading to publication bias. Interventions leading to null results are less likely to have been accepted for publication so the review may over-estimate apparent intervention effects.

Comparison with other studies

From observational studies, Vart et al. (2014) reported FIT characteristics that might improve CRC screening uptake: simplicity of tests, absence of dietary restrictions, less
stool manipulation and simplified procedures for analysis. Their meta-analysis also supported higher uptake rates in the FIT group. Both Vart’s and our review found greater uptake with FIT tests for studies in the earlier period (2003-2010). However these results were not confirmed by the two most recent studies performed with larger samples (Birkenfeld et al., 2011; Levi et al., 2011). The conflicting results may reflect that the first studies were performed in people who were asked to make dietary restrictions before the test, but dietary restrictions were not requested in the two later studies. Concerning stool DNA tests, previous authors reported that patients would prefer DNA test to colonoscopy (Cole et al., 2015; Abola et al., 2015) but we did not find studies comparing FIT and DNA tests and focusing on test uptake. A recent publication from Berger et al. (2016) reported an excellent participation rate with stool DNA tests (99%) but they did not discuss the selection bias.

This review provides evidence that various interventions increase test uptake and could be easily implemented: advance notification letter, postal mailing of screening tests, and written reminders. These results are consistent with the findings of previous reviews that included RCTs, but also observational, cross-sectional, experimental, and before and after studies (Camilloni et al., 2013; Sabatino et al., 2008; Senore et al., 2015). Camilloni et al. (2013) also concluded that postal and telephone reminders, mailed invitation letters signed by GPs, scheduled appointments and mailing kits to non-responders were effective interventions. Sabatino et al. (2008) reviewed 11 interventions to increase screening for cervical, breast and colon cancers. They reported that one-to-one education and reminders improve uptake rates for CRC screening tests.
Telephone contacts and involvement of navigators also led to higher uptake of screening tests, but these are more resource-intensive and may be difficult to implement in the usual screening setting. These results are consistent with the conclusions of Naylor et al. (2012) who focused on interventions that decrease racial and ethnic disparities toward CRC care and prevention. Naylor included 33 studies targeting African-American, Hispanic, and other minorities’ individuals. Navigation interventions – including specific elements such as language-adapted education materials in complex interventions – increased CRC screening uptake in these specific populations. However, all these interventions require recruiting navigators, training and making them available in the routine healthcare setting, and there is limited generalizable evidence for the whole population at average risk of colorectal cancer (Senore et al., 2015). Moreover, our focus on the costs associated with such interventions show that they would be associated with a multiplication of the costs (from 4€ to 500€ / completed test).

Further interventions could involve video or computer-based information. However, such information modalities might not be sufficient to convince people who are not concerned about colorectal cancer risk to consider screening. The positive effect observed for these interventions might also be due to a selection bias (see table 2).

There was limited evidence that training GPs is effective. Senore et al. (2015) suggested that giving feedback to providers about their screening rates may reinforce their commitment to promote screening. However, the original research leading to this statement was a “before vs after” study performed among resident physicians from 1993 to 1995 (Goebel et al., 1997), so that further research would be required in order to generalize these findings to private practice or other settings. Developing specific
communication skills may also be effective, but implementing changes in every day practice after formal continuing medical education is difficult. Concerning communication-based interventions direct to patients, they can be effective for chronic disease management, but there are difficulties in modifying preventive behaviors (Mehring et al., 2014; Hilberink et al., 2011; Butler et al., 2013). It may be hypothesized that general practitioners could enhance screening uptake, utilizing their long-term relationships with patients. However, there is a lack of well-designed trials involving GPs, while such studies could focus on barriers to test uptake.

The US guidelines promote letting patients choose between various screening strategies: faecal tests, colonoscopy, flexible sigmoidoscopy, or computed tomography colonography (USPSTF, 2016). However, various authors reported that screening uptake was lower with colonoscopy than with FIT (Segnan et al., 2007; Quintero et al., 2012; Inadomi et al., 2012). Recent publications suggested that patients might prefer computed tomography colonography (Gareen et al., 2015; Pooler et al., 2012). However, there is no evidence that one strategy would lead to better uptake (Ghanouni et al., 2014). Comparing test uptake is difficult because recommended intervals between tests are very different, depending on the test itself (Levin et al., 2008; Rex et al., 2009). Holme et al. (2013) aimed at providing data on flexible sigmoidoscopy attendance: on the population level, attendance rates were estimated at 38% and 10% in two studies (Atkin et al., 2010; Segnan et al., 2005), while it was only estimated between 0.3% and 3.4% in the third one (Simpson et al., 2000). In total, MACS et al. (2006,b) et Senore et al. (2015) concluded that offering people the option to choose between flexible sigmoidoscopy and FIT did not improve uptake.
Conclusion

Advance notification letters, postal mailing of the kits, written reminders, and telephone contacts with an advisor increase patient uptake of faecal tests. There is limited evidence about the effect of GP involvement on screening test uptake, and a lack of studies focusing on non-responders or disadvantaged groups.

REFERENCES


Table 1. PICO determinants of our review

<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Outcomes</th>
<th>Study design</th>
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</thead>
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<tr>
<td>Asymptomatic people at average risk of colorectal cancer</td>
<td>All interventions aiming to increase faecal test uptake</td>
<td>Intervention vs control group</td>
<td>Screening test uptake. Number of screened cancers</td>
<td>Randomized controlled trials</td>
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<tr>
<td>Author, year, setting</td>
<td>Sample</td>
<td>Design</td>
<td>Duration to assess uptake</td>
<td>Intervention</td>
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<tr>
<td>Aubin-Auger, 2015, France</td>
<td>45 GPs¹</td>
<td>Cluster RCT²</td>
<td>7 months</td>
<td>Implementation of a training course focused on communication skills among GPs</td>
</tr>
<tr>
<td>Baker, 2014, USA</td>
<td>450</td>
<td>RCT</td>
<td>6 months</td>
<td>1: Mailing an FIT³ kit. 2: Telephone and text reminders. 3: For non-respondents within 3 months, personal navigator contact</td>
</tr>
<tr>
<td>Myers, 2014, USA</td>
<td>764</td>
<td>RCT</td>
<td>6 months</td>
<td>Preference-based tailored navigation on CRC screening⁴</td>
</tr>
<tr>
<td>Neter, 2014, Israel</td>
<td>29 833</td>
<td>RCT</td>
<td>2 and 6 months</td>
<td>Use of the II (implementation intentions). 1: instruction leaflet sent to participants. 2: the leaflet contained suggestions for overcoming common problems that individuals face in attempting to perform FOBT, and an encouragement</td>
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<tr>
<td>Tinmouth, 2014, Canada</td>
<td>3 594</td>
<td>RCT</td>
<td>6 months</td>
<td>Addition of a gFOBT kit to a second mailed invitation</td>
</tr>
<tr>
<td>Green, 2013, USA</td>
<td>4 675</td>
<td>4 arms RCT</td>
<td>12 and 24 months</td>
<td>Use of a stepped-intensity intervention. 1: usual care: information letter and FOBT kit mailing. 2: automated care: in addition, a study database registry tracked when screening was due and</td>
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</tbody>
</table>

¹ GPs: General Practitioners  
² RCT: Randomized Controlled Trial  
³ FIT: Faecal Immunological Test  
⁴ CRC: Colorectal Cancer
automatically generated mailings. Non-respondents received a reminder letter.
3: assisted care: in addition, telephone assistance from a MA to complete screening.
4: navigated care: in addition, support from a nurse on questions or requests for an FOBT alternative. Medical assistants contacted navigated patients who did not request such alternative.

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Study Design</th>
<th>Intervention Details</th>
<th>Use of FIT</th>
<th>Risk</th>
<th>Advocacy</th>
<th>Advanced Notification</th>
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</thead>
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<tr>
<td>Birkenfeld, 2011, Israel</td>
<td>16 132</td>
<td>RCT</td>
<td>Use of FIT</td>
<td>Low</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
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<td>Hewitson, 2011, UK</td>
<td>1 288</td>
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<td>Use of educational letters. 1: GP’s endorsement letter, 2: enhanced procedural instruction leaflet, 3: GP’s letter plus leaflet, 4: control. An FOBT kit was sent a week after the first mailed letter.</td>
<td>Low</td>
<td>Moderate</td>
<td>Moderate</td>
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<td>Levi, 2011, Israel</td>
<td>12 537</td>
<td>RCT</td>
<td>Use of FIT</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Low</td>
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<td>Giorgi Rossi, 2011, Italy</td>
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<td>RCT</td>
<td>9 months</td>
<td>Direct kit-mailing</td>
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<td>Van Roon, 2011, Netherlands</td>
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<td>Use of a mailed advanced notification letter</td>
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<td>Gimeno-Garcia, 2009, Spain</td>
<td>158</td>
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<td>12 months</td>
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<td>Lee, 2009, USA</td>
<td>775</td>
<td>RCT</td>
<td>6 months</td>
<td>Use of a mailed educational reminder</td>
<td>Low</td>
<td>Low</td>
<td>Moderate</td>
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<td>RCT</td>
<td>12 months</td>
<td>Use of FIT, and patient mailed reminders</td>
<td>Low</td>
<td>Moderate</td>
<td>Low</td>
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<tr>
<td>Cole, 2007, Australia</td>
<td>2 400</td>
<td>4 arms RCT</td>
<td>2 weeks</td>
<td>Use of 3 different mailed information: risk, advocacy, advanced notification</td>
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<td>Moderate</td>
<td>High</td>
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<tr>
<td>MACS group, 2006, Australia</td>
<td>1 333</td>
<td>RCT</td>
<td>-</td>
<td>Use of choice between different screening tests (FIT, colonoscopy, Flexible sigmoidoscopy plus FIT)</td>
<td>Low</td>
<td>moderate</td>
<td>low</td>
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<tr>
<td>Cole, 2003, Australia</td>
<td>1 818</td>
<td>RCT</td>
<td>-</td>
<td>Use of FIT with spatula and FIT with brush (a more simple stool sample)</td>
<td>Low</td>
<td>moderate</td>
<td>Low</td>
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<tr>
<td>Study</td>
<td>Country</td>
<td>Sample Size</td>
<td>Design</td>
<td>Intervention</td>
<td>Duration</td>
<td>Outcome 1</td>
<td>Outcome 2</td>
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<td>Hughes, 2005, Australia</td>
<td>Australia</td>
<td>3358</td>
<td>RCT</td>
<td>Use of FIT</td>
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<td>moderate</td>
</tr>
<tr>
<td>Federici, 2005, Italy</td>
<td>Italy</td>
<td>7332</td>
<td>Cluster RCT</td>
<td>Use of FIT</td>
<td></td>
<td>moderate</td>
<td>moderate</td>
</tr>
<tr>
<td>Miller, 2005, USA</td>
<td>USA</td>
<td>204</td>
<td>RCT</td>
<td>Use of a computer-assisted intervention and a nurse counseling intervention</td>
<td>1 month</td>
<td>low</td>
<td>low</td>
</tr>
<tr>
<td>Vinker, 2002, Israel</td>
<td>Israel</td>
<td>2315</td>
<td>4 arms RCT</td>
<td>1: use of a reminder note to the physician. 2: patients received either a reminder letter or a phone call. One month later the non-responders received a follow-up reminder using the same method (the 4th arm if a control group)</td>
<td></td>
<td>moderate</td>
<td>moderate</td>
</tr>
<tr>
<td>Ore, 2001, Israel</td>
<td>Israel</td>
<td>2000</td>
<td>RCT</td>
<td>Direct kit-mailing</td>
<td>5 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mant, 1992, UK</td>
<td>UK</td>
<td>1588</td>
<td>4 arms RCT</td>
<td>1: mailed kit. 2: mailed kit with an invitation for a health check. 3: invitation for a health check, test offered at the health check. 4: just invited for the health check.</td>
<td></td>
<td>moderate</td>
<td>moderate</td>
</tr>
<tr>
<td>Myers, 1991</td>
<td></td>
<td>2201</td>
<td>RCT</td>
<td>Use of a booklet, telephone reminders and health education messages framed in &quot;loss&quot; terms as compared to those framed in &quot;gain&quot; terms.</td>
<td>3 months</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 3. Interventions and their related impact on patient uptake of screening tests

<table>
<thead>
<tr>
<th>Intervention and control</th>
<th>Uptake of test</th>
<th>OR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Use of FIT vs Gfobt</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Cole 2003</em></td>
<td>FIT with a spatula 39.6% vs 23.4%</td>
<td>2.14 [1.66-2.77]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>FIT with a brush 30.5% vs 23.4%</td>
<td>1.44 [1.10-1.87]</td>
<td>0.007</td>
</tr>
<tr>
<td><em>Hughes</em></td>
<td>FIT 38.7% vs 30.2%</td>
<td>1.93 [1.61-2.31]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><em>Federici</em></td>
<td>FIT 36.1% vs 30.4%</td>
<td>1.29 [1.17-1.43]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><em>Hol</em></td>
<td>Mailed FIT and reminders 61.5% vs 49.5%</td>
<td>1.63 [1.5-1.77]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><em>Birkenfeld</em></td>
<td>FIT vs FOBT 23.1% vs 24.6%</td>
<td>0.92 [0.85-0.99]</td>
<td>0.036</td>
</tr>
<tr>
<td><em>Levi</em></td>
<td>FIT vs FOBT 25.9% vs 28.8%</td>
<td>0.86 [0.80-0.94]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Advanced notification letter</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Van Roon</em></td>
<td>57.8% vs 51.5%</td>
<td>1.20 [1.07-1.34]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><em>Cole</em></td>
<td>25.2% vs 18.2%</td>
<td>1.51 [1.13-2.02]</td>
<td>0.004</td>
</tr>
<tr>
<td><em>Mant (1992)</em></td>
<td>31.7% vs 25.5%</td>
<td>1.35 [0.99-1.87]</td>
<td>0.051</td>
</tr>
<tr>
<td><strong>Postal mailing of FOBT kits</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Mant</em></td>
<td>25.5% vs 20.6%</td>
<td>1.31 [0.98-1.85]</td>
<td>0.112</td>
</tr>
<tr>
<td><em>Ore</em></td>
<td>19.9% vs 15.9%</td>
<td>1.31 [1.04-1.67]</td>
<td>0.021</td>
</tr>
<tr>
<td><em>Giorgi Rossi</em></td>
<td>14.6% vs 10.7%</td>
<td>1.42 [1.18-1.71]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><em>Giorgi Rossi</em></td>
<td>63.0% vs 56.8%</td>
<td>1.30 [1.12-1.5]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><em>Green</em></td>
<td>50.8% vs 26.3%</td>
<td>2.89 [2.42-3.45]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><em>Tinmouth</em></td>
<td>20.1% vs 9.6%</td>
<td>2.35 [1.93-2.90]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Presentation and content of written information</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Myers</em></td>
<td>Loss vs gain framed message 36% vs 40%</td>
<td>0.87 [0.73-1.03]</td>
<td>0.10</td>
</tr>
<tr>
<td><strong>MACS group</strong></td>
<td><strong>Shared decision making</strong></td>
<td>27.4% vs 18.6%</td>
<td>1.65 [1.04-2.64]</td>
</tr>
<tr>
<td>---------------</td>
<td>---------------------------</td>
<td>----------------</td>
<td>------------------</td>
</tr>
<tr>
<td><strong>Cole</strong></td>
<td>Advocacy messages, or messages focusing on risk</td>
<td>40.3% vs 36%</td>
<td>1.20 [0.95-1.53]</td>
</tr>
<tr>
<td><strong>Hewitson</strong></td>
<td>Enhanced procedural information leaflet</td>
<td>58.2% vs 52.2%</td>
<td>1.26 [1.01-1.58]</td>
</tr>
<tr>
<td><strong>Neter</strong></td>
<td>Implementation intention technique</td>
<td>71.4% vs 67.9%</td>
<td>1.18 [1.12-1.24]</td>
</tr>
</tbody>
</table>

**Written and telephone reminders**

| **Lee**       | Educational patient reminder by post | 64.6% vs 48.4% | 1.94 [1.45-2.60] | <0.001 |
| **Green**     | Mailed reminder letters | 57.5% vs 50.8% | 1.31 [1.11-1.55] | 0.001 |
| **Baker**     | Telephone and text message reminders | 73.8% vs 26.7% | 7.70 [4.98-12.03] | <0.001 |

**Telephone contacts with a navigator, medical assistant or nurse**

| **Myers**     | Instruction call | 48% vs 37% | 1.57 [1.27-1.92] | <0.001 |
| **Green**     | Telephone assistance | 64.7% vs 57.5% | 1.36 [1.14-1.61] | <0.001 |
| **Baker**     | Phone contact with a personal navigator for non-compliant patients | 82.2% vs 37.3% | 7.72 [4.91-12.3] | <0.001 |
| **Myers**     | Telephone contact with a navigator | 21.5% vs 15.3% | 1.51 [1.03-2.24] | 0.031 |

**Videos and computers**

| **Gimeno-Garcia** | Video-based educational intervention | 69.9% vs 54.4% | 1.91 [0.95-3.89] | 0.07 |
| **Miller**        | Counseling provided by automatized informatics software | 62% vs 63% | 0.96 [0.51-1.79] | 1 |

**Intervention requiring GP involvement**

| **Hewitson**     | GP-signed invitation letter | 58.1% vs 52.3% | 1.26 [1.01-1.58] | 0.044 |
| **Aubin-Auger**  | GP training focused on communication skills | 36.7% vs 24.5% | 1.22 [1.07-1.41] | 0.003 |
| **Vinker**       | Reminder sent to GPs | 16.5% vs 1.2% | 14.8 [8.1-29.6] | <0.001 |
FIGURE LEGENDS

Text Box 1. Search algorithms.

Figure 1. Flowchart of studies identification in this systematic review of RCT, assessing intervention to increase uptake to colorectal screening.
Text Box 1. Search algorithms.

**MEDLINE algorithm**
Filters: Clinical Trial; Randomized Controlled Trial; Review; English; French ; ((("Patient Compliance"[Mesh]) OR "Patient Participation"[Mesh])) AND ((("Mass Screening"[Mesh] OR "Early Detection of Cancer"[Mesh])) AND colorectal cancer) ; Filters: Clinical Trial; Randomized Controlled Trial; Review; English; French

**EMBASE algorithm**
'patient compliance'/exp OR 'patient participation'/exp AND ('mass screening'/exp OR 'early diagnosis'/exp) AND 'colorectal cancer'/exp AND ('review' OR 'clinical trial') AND ([english]/lim OR [french]/lim)

**COCHRANE LIBRARY**
systematic review of the CRC group publications
Figure 1. Flowchart of studies identification in this systematic review of RCT, assessing intervention to increase colorectal screening uptake.

Medline n=183  Embase n=92

Analysis based on title and abstracts n=275

Excluded n=220
- No data in the abstract (n=23)
- Non RCT (n=8)
- Protocol (n=10)
- No screening stage (n=28)
- No intervention (n=78)
- Colonoscopy program (n=48)
- No participation data (n=12)
- No average-risk population (n=13)

Full text analysis n=55

Excluded = 31
- No average-risk population (n=13)
- Colonoscopy (n=9)
- Review (n=1)
- Poor methodology (n=7)
- Non interventional study (n=1)

Included studies n=24