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 recalculating 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-Auger *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 gFOFT; 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-Auger *et al.*, 2014; Vinker *et al.*, 2002) – while one was inconclusive (Hewitson *et al.*, 2011). Aubin-Auger (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-Auger *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

<u>Quality of the evidence</u>

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.

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Table 1. PICO determinants of our review

Population	Intervention	Comparison	Outcomes	Study design
Asymptomatic people at average risk of colorectal cancer	All interventions aiming to ncrease faecal test uptake	Intervention vs control group	Screening test uptake. Number of screened cancers	Randomized controlled trials

Table 2. Studies description

Author, year, setting	Sample	Design	Duration to assess uptake	Intervention	Risk of bias			
					Selection bias	Performance and detection bias	Attrition bias	Reporting bias
Aubin-Auger, 2015, France	45 GPs[1]	Cluster RCT[2]	7 months	Implementation of a training course focused on communication skills among GPs	low	low	low	low
Baker, 2014, USA	450	RCT	6 months	1: Mailing an FIT[3] kit. 2: Telephone and text reminders. 3: For non-respondents within 3 months, personal navigator contact	moderate	low	moderate	Low
Myers, 2014, USA	764	RCT	6 months	Preference-based tailored navigation on CRC screening[4]	low	moderate	low	low
Neter, 2014, Israel	29 833	RCT	2 and 6 months	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	moderate	high	moderate	Low
Tinmouth, 2014, Canada	3 594	RCT	6 months	Addition of a gFOBT kit to a second mailed invitation	moderate	moderate	low	low
Green, 2013, USA	4 675	4 arms RCT	12 and 24 months	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	Low	moderate	low	low

[1] GPs: General Practioners
[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 assitants contacted navigated patients who did not request such alternative.				
Birkenfled, 2011, Israel	16 132	RCT	-	Use of FIT	Low	Moderate	Moderate	Moderate
Hewitson, 2011, UK	1 288	4 arms RCT	20 weeks	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.	Low	Moderate	Moderate	Low
Levi, 2011, Israel	12 537	RCT	-	Use of FIT	Moderate	Moderate	Moderate	Low
Giorgi Rossi, 2011, Italy	4 219	RCT	9 months	Direct kit-mailing	Low	Moderate	Low	Low
Van Roon, 2011, Netherlands	5 000	RCT	8 months	Use of a mailed advanced notification letter	Low	Moderate	Low	Low
Gimeno-Garcia, 2009, Spain	158	RCT	12 months	Video-based educational intervention	moderate	Moderate	Moderate	High
Lee, 2009, USA	775	RCT	6 months	Use of a mailed educational reminder	Low	Low	Low	Low
Hol, 2009, Netherlands	15 011	RCT	12 months	Use of FIT, and patient mailed reminders	Low	Moderate	Low	Low
Cole, 2007, Australia	2 400	4 arms RCT	2 weeks	Use of 3 different mailed information: risk, advocacy, advanced notification	Moderate	Moderate	High	Moderate
MACS group, 2006, Australia	1 333	RCT	-	Use of choice between different screening tests (FIT, colonoscopy, Flexible sigmoidoscopy plus FIT)	low	moderate	low	Low
Cole, 2003, Australia	1 818	RCT	-	Use of FIT with spatula and FIT with brush (a more simple stool sample)	low	moderate	moderate	Low

Hughes, 2005, Australia	3 358	RCT	-	Use of FIT	moderate	moderate	moderate	Low
Federici, 2005, Italy	7 332	Cluster RCT	-	Use of FIT	moderate	moderate	moderate	Low
Miller, 2005, USA	204	RCT	1 month	Use of a computer-assisted intervention and a nurse counseling intervention	low	low	low	Low
Vinker, 2002, Israel	2 315	4 arms RCT	-	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)	moderate	moderate	high	High
Ore, 2001, Israel	2 000	RCT	5 months	Direct kit-mailing	moderate	moderate	low	High
Mant, 1992, UK	1 588	4 arms RCT	-	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.	moderate	moderate	high	High
Myers, 1991	2 201	RCT	3 months	Use of a booklet, telephone reminders and health education messages framed in "loss" terms as compared to those framed in "gain" terms.	moderate	moderate	high	Low

Table 3. Interventions and their related impact on patient uptake of screening tests

Intervention and control		Uptake of test	OR	p
Use of FIT vs Gfobt				
Cole 2003	FIT with a spatula	39.6% vs 23.4%	2.14 [1.66-2.77]	<0.001
	FIT with a brush	30.5% vs 23.4%	1.44 [1.10-1.87]	0.007
Hughes	FIT	38.7% vs 30.2%	1.93 [1.61-2.31]	<0.001
Federici	FIT	36.1% vs 30.4%	1.29 [1.17-1.43]	<0.001
Hol	Mailed FIT and reminders	61.5% vs 49.5%	1.63 [1.5-1.77]	<0.001
Birkenfeld	FIT vs FOBT	23.1% vs 24.6%	0.92 [0.85-0.99]	0.036
Levi	FIT vs FOBT	25.9% vs 28.8%	0.86 [0.80-0.94]	<0.001
Advanced notification letter				
Van Roon		57.8% vs 51.5%	1.20 [1.07-1.34]	<0.001
Cole		25.2% vs 18.2%	1.51 [1.13-2.02]	0.004
Mant (1992)		31.7% vs 25.5%	1.35 [0.99-1.87]	0.051
Postal mailing of FOBT kits				
Mant		25.5% vs 20.6%	1.31 [0.98-1.85]	0.112
Ore		19.9% vs 15.9%	1.31 [1.04-1.67]	0.021
Giorgi Rossi		14.6% vs 10.7%	1.42 [1.18-1.71]	<0.001
Giorgi Rossi		63.0% vs 56.8%	1.30 [1.12-1.5]	<0.001
Green		50.8% vs 26.3%	2.89 [2.42-3.45]	<0.001
Tinmouth		20.1% vs 9.6%	2.35 [1.93-2.90]	<0.001
Presentation and content of written information				
Myers	Loss vs gain framed message	36% vs 40%	0.87 [0.73-1.03]	0.10

MACS group	Shared decision making	27.4% vs 18.6%	1.65 [1.04-2.64]	0.027
Cole	Advocacy messages, or messages focusing on risk	40.3% vs 36%	1.20 [0.95-1.53]	0.14
Hewitson	Enhanced procedural information leaflet	58.2% vs 52.2%	1.26 [1.01-1.58]	0.044
Neter	Implementation intention technique	71.4% vs 67.9%	1.18 [1.12-1.24]	<0.001
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.