Impact of colorectal cancer screening on cancer-specific mortality in Europe: a systematic review

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ABSTRACT

Background: Populations differ with respect to their cancer risk and screening preferences, which may influence the performance of colorectal cancer (CRC) screening programs. This review aims to systematically compare the mortality effect of CRC screening across European regions.

Methods: Six databases including Embase, Medline, Web of Science, PubMed publisher, Google Scholar and Cochrane Library were searched for relevant studies published before March 2018. Bibliographic searches were conducted to select studies assessing the effect of various screening tests (guaiac fecal occult blood test [gFOBT]; flexible sigmoidoscopy [FS]; fecal immunochemical test [FIT]; and colonoscopy) on CRC mortality in Europe (PROSPERO Protocol: CRD42016042433). Abstract reviewing, data extraction and risk of bias assessment were conducted independently by two reviewers.

Results: A total of 18 studies were included; of which, 11 were related to gFOBT, 4 to FS, 2 to FIT, and 1 to colonoscopy; 8 were randomized clinical trials, and 10, observational studies, and an approximately equal number of studies represented Northern, Western, and Southern European regions. Among individuals invited to screening, CRC mortality reductions varied from 8% to 16% for gFOBT and from 21% to 30% for FS. When studies with a high risk of bias were considered, ranges were more extensive. The estimated effectiveness of gFOBT and FS screening appeared similar across different European regions.

Conclusions: CRC mortality impact of inviting individuals with similar adopted screening strategies (gFOBT or FS) may be consistent across several European settings.

INTRODUCTION

Colorectal cancer (CRC) is the second and the third leading cause of cancer death among men and women in Europe, with more than 242,000 deaths estimated in 2018.[2] The highest mortality rates were reported in Eastern Europe (Hungary and Slovakia), where CRC incidence rates have increased sharply in the last decades owing to changes in lifestyle factors.[2, 4] Screening has the potential to reduce the burden of CRC, with the scientific literature suggesting a reduction in CRC mortality ranging from 18% to 57% (depending on the screening test investigated).[73] In 2003, the European Council acknowledged the effectiveness of fecal occult blood testing (FOBT) screening and recommended the implementation of organised CRC screening for men and women aged 50-74 years in the European countries.[55]

However, CRC screening was not implemented homogenously across Europe. Existing organised programs differed in terms of target ages, screening interval and primary test.[57] In Finland, biennial guaiac FOBT (gFOBT) screening is offered to men and women aged 60-69 years, [62, 74] whereas in France and the United Kingdom (UK), biennial gFOBT is offered from the age of 50 to 74 years,[75, 76] and in the Netherlands, Spain, Slovenia, Ireland, Malta, and Hungary biennial fecal immunochemical test (FIT) screening is offered in various age ranges between 50 and 75 years.[57, 77-79] CRC screening also varies within the countries, for instance, in Italy. There, 112 regional CRC screening programs were gradually implemented during 2003-2012, some offering the FIT and some offering flexible sigmoidoscopy (FS).[63]

CRC screening implementation, performance and its geographical differences are currently monitored.[80] The first European Guidelines on quality assurance in CRC screening and diagnosis have been published, making standards and recommendations to improve CRC screening programmes (especially in quality assurance and the management of detected lesions).[81] The European Parliament has encouraged member states to invest more in reducing screening inequalities and stimulating early cancer diagnosis. To assist each country in reaching these goals, the European Commission funded the EU-TOPIA project (EU-Framework Programme, Horizon 2020 – 634753). EU-TOPIA will systematically evaluate the harms and benefits of existing screening programs for CRC in all European countries and identify ways to improve health outcomes and reduce screening inequalities of European Union (EU) citizens. As a first step, and to assess the appropriateness of various chosen screening policies, EU-TOPIA will review the evidence of the effectiveness of alternative screening strategies across European countries.

In this study, we systematically reviewed the literature on the effectiveness of screening in Europe, focussing on geographical disparities in the effectiveness of screening.

METHODS

We performed a systematic literature review following the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement.[82] This study was registered as part of a planned review, and its protocol was published on 6th July 2016 in PROSPERO (International prospective register of systematic reviews, CRD42016042433).[83]

Literature search

Systematic bibliographic searches were conducted on the databases Embase, Medline Ovid, Web of Science, PubMed publisher, Google Scholar and Cochrane Library to identify potentially relevant studies. All databases were searched from inception to 1st April 2016 (subsequently updated to 1st March 2018). The computer-assisted searches were designed and performed by a research librarian using controlled keywords to assess concepts related to screening, CRC and mortality among European countries (**Supplementary Table 2.1a-2.1b**). In addition, the search was augmented with a list of relevant, recently published, articles. All references were managed using Thomson Reuters Endnote X7.1, and duplicates were removed.

Study selection, data extraction, and quality assessment

Two investigators independently reviewed the titles and abstracts of all references identified by the literature search. A list of potential studies was retrieved considering the PICOS (population, intervention, control, outcome and study design) criteria defined in the study protocol (**Table 2.1**).[83] Inclusion criteria were defined to select relevant studies investigating the reduction in CRC mortality due to screening and focusing on populations invited to organised CRC screening programmes. To avoid exclusion of relevant references, studies that only reported CRC incidence reductions in the abstract were initially not excluded. Eligible articles were then reviewed in depth, and an additional selection was made applying the following eligibility criteria proposed by Elmunzer et al[73]: i) studies in which data or patients were duplicated in other manuscripts; ii) studies in which data were not reported for at least 5 years of follow-up; iii) studies in which the total number of events and participants were not reported for each study group or iv) studies that assessed only the effect on CRC incidence.

From each included article, the following data were extracted: first author; year of publication; country where the study was conducted; study design; screening modality; screening target population; follow-up information; sample size of the study and the reported estimates (with the corresponding 95% confidence intervals [95%CI]) of the CRC screening effect on cancer-specific mortality (as per the underlying cause of death from hospital or mortality registry, depending on the study). Information on adjustment for demographic differences between participants and non-participants in screening was also extracted.[84] For

Table 2.1. Inclusion and exclusion criteria

Category	Inclusion	Exclusion
Population	People invited to / participating in organised mass screening for colorectal cancer	
Interventions	organised screening for colorectal cancer (e.g. FS, gFOBT, FIT, colonoscopy)	
Controls	People not invited for/participating organised screening or people participating in opportunistic screening only	
Outcomes	Change in mortality due to colorectal cancer screening (colorectal cancer mortality reduction)	
Study design	Randomised controlled trials and observational studies, such as prospective and retrospective controlled cohort studies.	Study designs that do not directly assess the effect of screening. Systematic reviews, meta-analyses, modelling/ simulation studies, non-original research studies (e.g. editorials, letters) and abstracts only.
Language	English	

gFOBT: Guaiac fecal occult blood test; FIT: Fecal immunochemical test; and FS: Flexible sigmoidoscopy.

each included study, conflict of interest was reviewed and reported in **Supplementary Table 2.2**. Eligible articles were divided based on European areas (Northern, Western, Southern, and Eastern Europe) following the classification provided by EUROVOC Multilingual Thesaurus of the European Union.[85] To assess quality and bias, the studies were evaluated using validated evaluation tools. Randomized controlled trials (RCTs) were evaluated using the Cochrane Library criteria for systematic reviews of interventions and risk assessment. Observational studies were assessed using the criteria provided by the Newcastle-Ottawa Scale (NOS).[86, 87] In brief, risk of bias was categorized as follows: "high risk" was assigned to RCTs when at least one of the Cochrane Library criteria was assumed at high risk and to observational studies with an NOS score ≤ 4; "moderate risk" was assigned to RCTs when at least one of the Cochrane Library criteria was assumed at moderate risk and to observational studies where the NOS score ranged from 5 to 7 and "low risk" was assumed otherwise. Based on this categorisation, the results were interpreted by both excluding and including studies at high risk of bias to explore the impact of quality assessment on review conclusions. All studies were quality assessed independently by two reviewers. Disagreements between the two investigators were solved by consensus or consulting a third reviewer.

RESULTS

A total of 3,741 citations were retrieved through the initial searches (**Figure 2.1**). A subsequent updated bibliographic search provided 620 additional references. After removal of duplicates, 3,034 potentially relevant citations were identified, and 70 potential articles for detailed evaluation were selected based on the title and abstract review. Fifty-two of these articles were excluded due to the eligibility criteria (**Supplementary Table 2.3-2.4**), and thus, 18 were included in the final analysis.

The included articles varied based on region (7 from Northern Europe, 5 from Southern and 6 from Western), screening test assessed (11 for gFOBT, 3 for FS, 2 for FIT, 1 for FS in combination with FIT and 1 for colonoscopy), and study design (8 RCTs, 7 cohort studies and 3 case-control studies). No studies were retrieved from Eastern Europe.

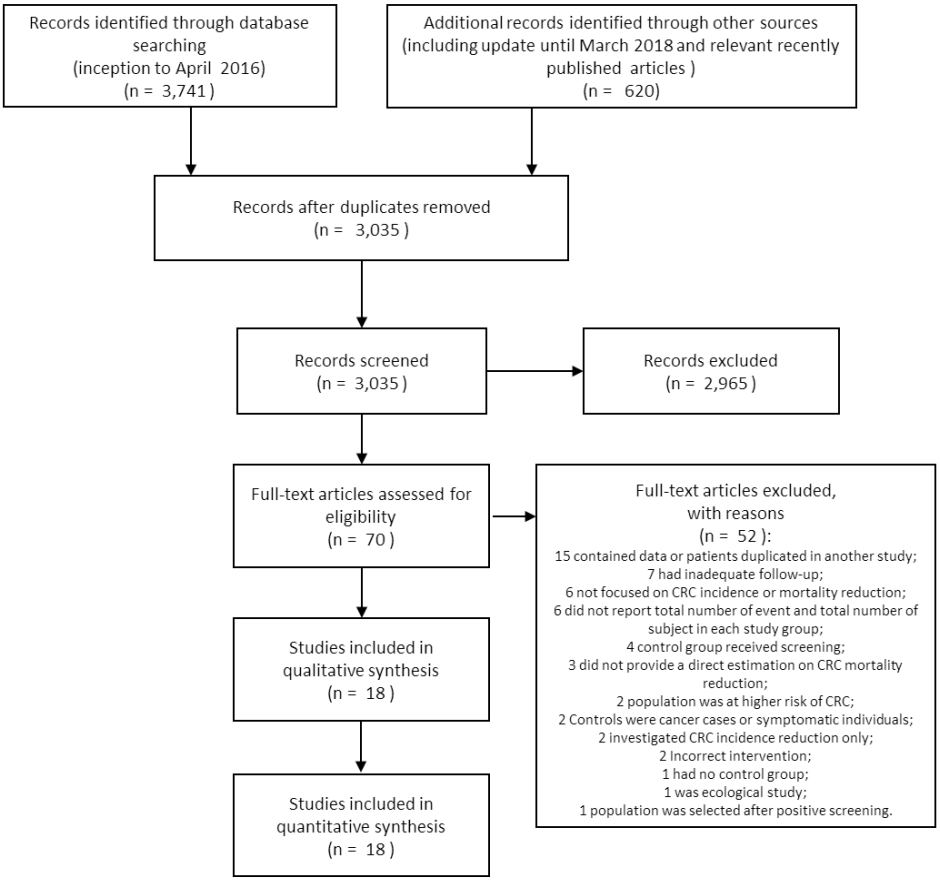

Figure 2.1. Flow chart for article search and selection process. CRC, colorectal cancer

Of the 8 RCTs, 4 assessed gFOBT (3 at low risk of bias and one moderate, **Supplementary Tables 2.5a-2.5b**); and 4 trials focused on FS (3 at low and one at high risk of bias caused by a possible bias in the random selection procedure, **Supplementary Tables 2.5c-2.5d**). Considering observational studies, risk of bias varied from 4 to 8 out of 9 on the NOS (**Supplementary Tables 2.6-2.7**): one study scored 4 (high risk of bias); 6 studies scored 5 or 6 and 3 studies scored 7 or 8 points.

What is the impact of gFOBT screening across Europe?

Effectiveness of gFOBT was investigated using various study designs and target ages: screening was offered to individuals between ages 45 and 74 or 75 years in two RCTs[32, 33] and a population-based cohort study;[88] between the ages 50 to 63-74 years in three cohort studies;[76, 89, 90] between the ages 60 and 64-69 years in two RCTs;[36, 62] and for anyone older than 40 years in two case-control studies.[91, 92] Despite these differences, the estimated impact of gFOBT screening did not vary substantially across studies. Among individuals invited to screening, gFOBT screening (participation rate ranging from 48 to 70%) decreased their CRC mortality by 8-16% compared with that of those not invited (**Table 2.2**, not including studies at high risk of bias).[32, 33, 36, 76, 88, 90] When studies at higher risk of bias were included, no effect on CRC mortality was documented in Finland (relative risk [RR] = 1.04, 95%CI: 0.84-1.3, study at moderate risk; and standardized mortality ratio [SMR] = 1.2, 95%CI: 0.75-1.7, at high risk of bias; **Figure 2.2**).[62, 89] For individuals participating in screening, the reduction in CRC mortality was up to 40%.[92] However, this effect was estimated only in observational studies (3 case-control and 3 cohort studies)[76, 88, 91-93] and may be confounded by demographic differences between participants and non-participants in screening. As shown by Libby et al, estimates for cancer-specific mortality reduction adjusted for confounding are significantly lower (RR = 0.83, 95%CI: 0.79-0.87) than unadjusted measures (RR = 0.73, 95%CI: 0.65-0.82).[76]

What is the impact of screening with the FIT in Europe?

Two observational studies assessed the effect of FIT screening on CRC mortality, both from Southern Europe (Italy; **Table 2.2**).[37, 94] Among individuals invited to FIT screening, incidence-based CRC mortality (i.e. CRC mortality in those with a confirmed CRC diagnosis in the local cancer registry) was 36% lower than that among those not invited (estimated with a maximum follow-up of 8 years).[37] The probability of dying from CRC was 41% lower in those who participated in FIT screening than in those who did not participate. However, this estimate was not adjusted for demographic differences between participants and non-participants.[94]

Table 2.2. Characteristics of the included studies investigating the effect of stool tests (gFOBT, or FIT).

Screening/ region/study	Country	Study type	Participants	Target age (years)	Screening interval (years)	Follow-up (years)	Participation rate (%)	Quality score[a]	Comparison provided	Correction for self-selection bias	RR (95%CI) for colorectal cancer mortality
gFOBT											
Northern Europe											
Lindholm et al	Sweden	RCT	34,144 invited 34,164 not invited[c]	60-64	N/A[e]	9	70	A	Invited vs not invited	-	0.84 (0.71-0.99)
Kronborg et al	Denmark	RCT	30,762 invited 30,966 not invited[c]	45-75	2	13.9	67	A	Invited vs not invited	-	0.84 (0.73-0.96)
Bjerrum et al	Denmark	Cohort	166,277 invited 1,240,348 not invited	50-74	Once	8.9	48	6/9	Invited vs not invited *Participants vs not invited*	- *No*	0.92 (0.86-0.99) *0.77 (0.67-0.90)*
Pitkaniemi et al	Finland	RCT	180,210 invited 180,282 not invited[c]	60-69	2	4.5	69	B[g]	Invited vs not invited	-	1.04 (0.84-1.28)
Malila et al	Finland	Cohort	1785 invited	50-63	N/A	9	69	4/9[h]	Invited vs control group[i]	-	1.17 (0.75-1.73)
Southern Europe											
Bertario et al	Italy	Case control	95 cases (16[b]) 475 controls[c] (109[b])	≥ 40	2	N/A	N/A	6/9	*Participants vs non-participants*	*No*	*0.64 (0.36-1.15)*
Zappa et al	Italy	Case control	206 cases (46[b]) 1,030 controls[c] (295[b])	≥ 41	2.5	N/A	N/A	5/9	*Participants vs non-participants*	*No*	*0.60 (0.40-0.90)*
Western Europe											
Scholefield et al	UK	RCT	76,056 invited 75,919 not invited[c]	45-74	2	19.5	57	A	Invited vs not invited	-	0.91 (0.84-0.99)
Libby et al	UK	Cohort	379,655 invited 379,655 not invited	50-69	2	8	61	7/9	Invited vs not invited *Participants vs not invited* *Participants vs not invited*	- *Yes* *No*	0.90 (0.83-0.99) *0.83 (0.79-0.87)* *0.73 (0.65-0.82)*

Table 2.2. Characteristics of the included studies investigating the effect of stool tests (gFOBT, or FIT). (*continued*)

Screening/ region/study	Country	Study type	Participants	Target age (years)	Screening interval (years)	Follow-up (years)	Participation rate (%)	Quality score[a]	Comparison provided	Correction for self-selection bias	RR (95%CI) for colorectal cancer mortality
Faivre et al	France	Case control	178 cases (92[b]) 712 controls (435[b])	45-80	2	N/A	N/A	7/9	Participants vs non-participants	No	0.67 (0.48-0.94)
Hamza et al	France	Quasi-experiment	45,642 invited 45,557 not invited	45-74	2	17.3	56	6/9	Invited vs not invited *Participants vs not invited*	- *No*	0.87 (0.80-0.94) *0.67 (0.59-0.76)*
FIT											
Southern Europe											
Ventura et al	Italy	Cohort	6,961 participants 26,285 non-participants[c]	50-70	2	10.7	N/A	8/9	*Participants vs non-participants*	*No*	*0.59 (0.37-0.93)*
Rossi et al	Italy	Cohort	171,785 invited	50-74	2	8 [d]	64	6/9	Invited vs not invited (incidence-based mortality)[d]	-	0.64 [d] (0.52-0.78)

N/A, not available; gFOBT, guaiac fecal occult blood test; FIT, fecal immunochemical test; RCT, randomised controlled trial; RR, relative risk; CI, confidence interval; CRC, colorectal cancer; UK, United Kingdom

Target age: ages targeted by the organised screening programme assessed in the study; follow-up: median follow-up time after initiation of the screening programme. RR: Standard mortality ratios, Hazard ratios, Odds ratio are presented as a RR. Screening effects estimated comparing participants and non-participants are shown in italics.

[a] Quality assessment made as per the Newcastle-Ottawa Scale and Cochrane Collaboration criteria for observational studies and RCTs, respectively; risk of bias for RCTs was categorised considering bias risk the final judgement of risk of bias as follow: A, low risk; B, moderate risk; and C, high risk.

[b] Exposed to screening;

[c] Controls were drawn from the same population as the intervention group;

[d] Maximum follow-up, this short follow-up might have an impact on the incidence-based mortality estimates (longer survival of individuals with screen-detected colorectal cancers);

[e] Study was designed with a not-regular screening interval;

[g] Limited follow-up time to assess CRC mortality reduction;

[h] Lack of information regarding representativeness of the exposed cohort, selection of the non-exposed, and ascertainment of the exposure;

[i] General Finnish population was set as thecontrol group.

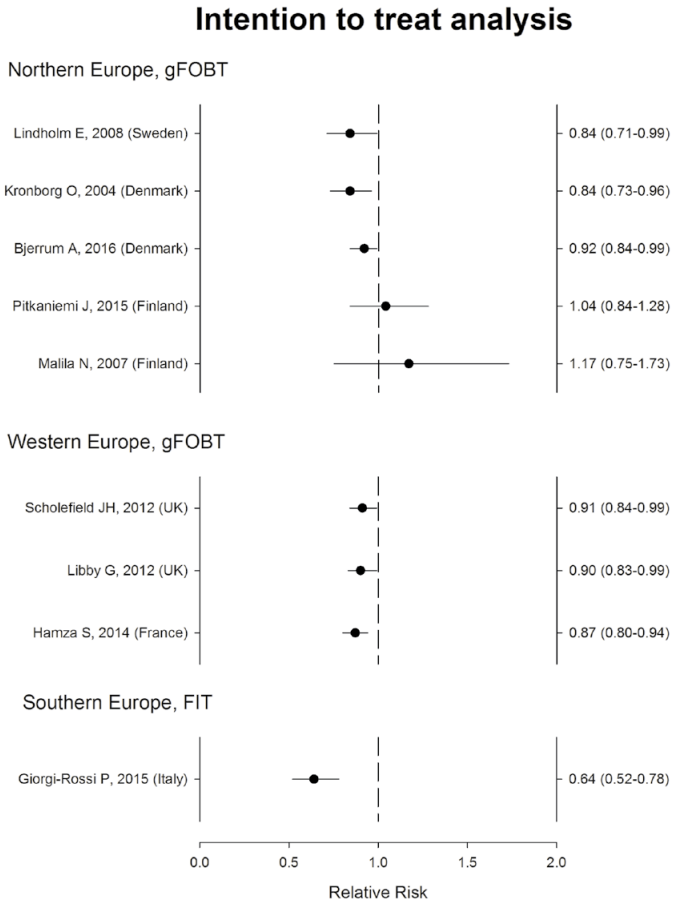

Figure 2.2. Impact of gFOBT and FIT screening per European region (intention-to-treat analysis). gFOBT, guaiac fecal occult blood test; FIT, fecal immunochemical test

What is the impact of once-in-a-lifetime FS screening across Europe?

The effect of offering FS screening was investigated by 4 RCTs (**Table 2.3**, and **Figure 2.3**).[28, 30, 34, 95] Studies differed based on screening participation (58-81%), sample size, age at screening (from 50-55 to 64 years), enrolment and risk of bias. The median follow-up varied from 10.9 to 21.0 years. Long-term outcomes (follow-up up to 21 years) and the effectiveness of FS in combination with FIT screening were investigated only in Northern Europe.[30, 95] CRC mortality reductions due to once-only FS screening ranged from 21% to 30% (point estimates; among those invited compared with among those not invited).[28, 30, 34] When FS was offered in combination with the FIT, probability of dying from CRC was 25% lower in the invited group than in the not-invited reference group (RR = 0.75, 95%CI: 0.57-0.99).[30]

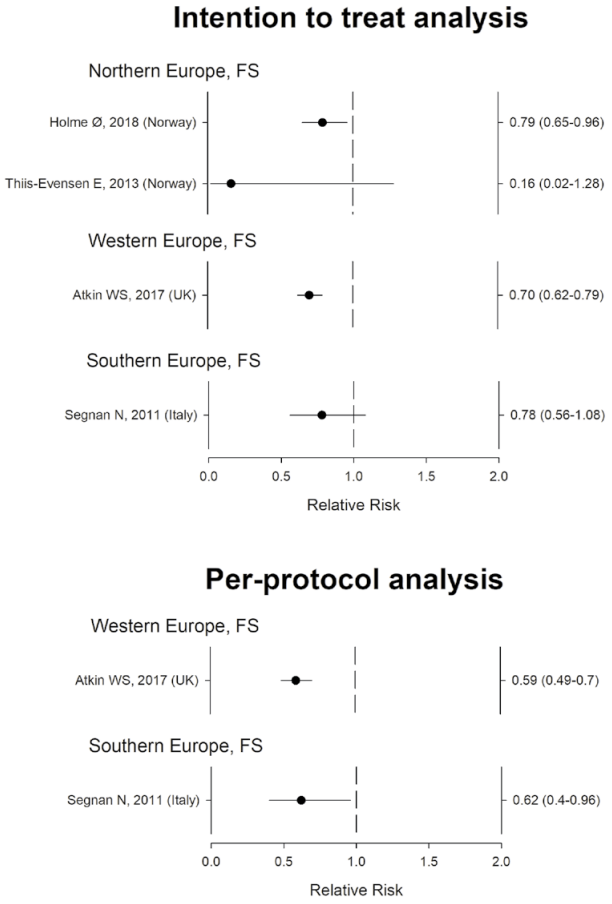

Figure 2.3. Impact of Flexible sigmoidoscopy screening per European region and THE type of assessment (intention-to-treat or per-protocol analysis). FS, flexible sigmoidoscopy.

Among participants in FS screening group, CRC mortality was 38-41% lower in the invited participants than in the not-invited control group (estimates adjusted for demographic differences in non-participants; **Figure 2.3**).[28, 34]

What is the impact of colonoscopy in Europe?

The effect of colonoscopy screening on CRC mortality was only evaluated in one Swiss study (**Table 2.3**).[96] In a closed prospective cohort study of 22,686 individuals, the reported risk reduction for CRC death was 88% (95%CI: 7%-99%) among those who participated in screening compared with among those who did not participate (not adjusted for demographic differences in non-participants).

Table 2.3. Characteristics of the included studies investigating the effect of endoscopy tests (FS, or colonoscopy).

Screening/Region Study	Country	Study type	Participants	Target age (years)	Screening interval (years)	Follow-up (years)	Participation rate (%)	Quality score[a]	Comparison provided	Correction for self-selection bias	RR (95%CI) for colorectal cancer mortality
FS											
Northern Europe											
Holme et al	Norway	RCT	10,283 invited to FS 10,289 invited to FS+FIT 78,220 not invited[d]	50-64	Once	15	61-65	A	Invited vs not invited Invited vs not invited	- -	0.79 (0.65-0.96) FS+FIT group: 0.75 (0.57-0.99)
Thiis-Evensen et al	Norway	RCT	400 invited 399 not invited[d]	50-59	Once (colonoscopy after 13 years[c])	21.7	81	C	Invited vs not invited	-	0.16 (0.02-1.28)
Southern Europe											
Segnan et al	Italy	RCT	17,136 invited 17,136 not invited[d]	55-64	Once	11.4	58	A	Invited vs not invited *Participants vs not invited (per-protocol analysis)*	- *Yes*	0.78 (0.56-1.08) *0.62 (0.40-0.96)*
Western Europe											
Atkin et al	UK	RCT	57,099 invited 112,939 not invited[d]	55-64	Once	17.1	71	A	Invited vs not invited *Participants vs not invited (per-protocol analysis)*	- *Yes*	0.70 (0.62-0.79) *0.59 (0.49-0.70)*

Table 2.3. Characteristics of the included studies investigating the effect of endoscopy tests (FS, or colonoscopy). (*continued*)

Screening/Region Study	Country	Study type	Participants	Target age (years)	Screening interval (years)	Follow-up (years)	Participation rate (%)	Quality score[a]	Comparison provided	Correction for self-selection bias	RR (95%CI) for colorectal cancer mortality
Colonoscopy											
Western Europe											
Manser et al	Switzerland	Cohort	1,912 participants 20,774 non-participants[d]	50-80	Once	6	N/A	6/9	*Participants vs non-participants*	*No*	*0.12 (0.01-0.93)*

N/A, not available; RR, relative risk; FIT, fecal immunochemical test; RCT, randomised controlled trial; RR, relative risk; CI, confidence interval; UK, United Kingdom; FS, flexible sigmoidoscopy.

Target age: ages targeted by the organised screening programme assessed in the study; follow-up: median follow-up time after initiation of the screening programme. RR = standard mortality ratios, hazard ratios, odds ratio are presented as a RR. Screening effects estimated comparing participants and non-participants are shown in italics.

[a] Quality assessment made as per the Newcastle-Ottawa Scale and Cochrane Collaboration criteria for observational studies and RCTs, respectively; risk of bias for RCTs was categorised considering bias risk the final judgement of risk of bias as follow: A, low risk; B, moderate risk; and C, high risk.

[c] Different screening period in the study design. (Both the control and intervention group were invited to participate in a colonoscopy investigation.)

[d] Controls were drawn from the same population as the intervention group.

How does the effect of CRC screening differ across Europe?

Effectiveness of FIT and colonoscopy screening was only investigated in a few countries, and therefore, a direct comparison across different European regions was not possible. For gFOBT, the effectiveness of screening in terms of CRC reduction mortality varied from 9 to 13% in Western Europe[33, 76, 88] to 16% in Northern Europe.[32, 36] For FS screening, effects on CRC mortality varied from a 21% to 30% reduction across European regions, when studies at high risk of bias were excluded.[28, 30, 34]

For individuals participating in screening (especially with gFOBT), demographic differences between participants and non-participants were not considered in the effect estimations, limiting the comparison between studies.

DISCUSSION

In this systematic review, we evaluated the variation in the effectiveness of different CRC screening strategies across European regions. To our knowledge, no previous studies have investigated the variation in screening effectiveness across countries, especially countries that share similar health goals such as EU member states. We found that citizens invited to CRC screening in some European countries were at lower risk of dying from CRC than those not invited: up to 30% for FS and to 16% for gFOBT (excluding studies with a high risk of bias). The effect of gFOBT and sigmoidoscopy screening varied only moderately between and within European regions, with variations ranging from 8% to 13% in Western to 16% in Northern Europe for the effect of gFOBT; and from 21% in Northern to 30% in Western Europe for the effect of FS. Moreover, evidence from RCTs showed consistent results across Europe, especially when the duration of follow-up was adequate (>10 years).

Screening with gFOBT was mainly conducted in Northern and Western Europe, varying in screening target ages and reporting different screening participation rates. Participation geographically varied across Europe, indicating a higher willingness to accept gFOBT screening among individuals included in studies conducted in Northern (67-70%) than in Western Europe (56-61%). Nevertheless, an 8-16% reduction in CRC mortality was found across Europe in those invited to gFOBT screening,[32, 33, 36, 76, 88, 90] and recent population-based cohort analyses, performed in Scotland and France, indicated a 10-13% lower risk of dying from CRC.[76, 88] Although two studies from Finland showed no impact on CRC mortality in that country, the small sample size (study at high risk, which was conducted by Malila et al.)[89] or limited follow-up (study at moderate risk of bias, which was conducted by Pitkaniemi et al.)[62] may explain those results. A recent modelling study (conducted by Chiu et al.)[97] supported the latter explanation, predicting a 9% CRC mortality reduction after 10 years of follow-up for the Finnish study of Pitkaniemi et al. For those persistently participating in gFOBT screening, effectiveness was higher (up to 40% lower CRC mortality), but this

effect was mainly observed in case-control studies that did not take into consideration the demographic differences between participants and non-participants.[88, 91-93] Therefore, these results may be biased and driven by other factors, such as different underlying CRC risks or the healthy screenee effect.

Offering FS once in a lifetime was associated with a reduction in CRC mortality ranging from 21% to 30% when studies at high risk of bias were excluded.[28, 30, 34] Variations in the screening participation rate and intervention group sample size may explain the slight difference in the effect range: compared with the UK RCT, the Italian and Norwegian trials had fewer individuals invited and participating in FS screening (sample size of the intervention group: 17,136-10,283 versus 57,099 individuals, respectively; participation rate: 58-65% versus 71%, respectively).[28, 30, 34]

It is important to note that evidence of the effectiveness of FS was reported only in RCTs based on predefined populations willing to accept this screening modality.[28, 34] At this time, few population-based organised screening programmes were implemented using this test (Italy [Piedmont], Norway, and England),[57, 98] and based on their monitoring data, FS screening uptake was found to be lower in the unselected population than that observed in the RCTs (i.e. ≥ 58%): response rates varied from 29% (Italy [Turin and Verona]) to 43% (England).[67] Nevertheless, FS has the possibility to better detect and remove adenomatous polyps (by participating in screening once in a life-time) and could be superior in reducing CRC mortality compared to at least gFOBT (if we restrict and compare only RCT results).

There was much less evidence for the effectiveness of FIT and colonoscopy screening. FIT was implemented mainly in Southern and Eastern Europe (Italy, Spain, Malta, Slovenia, and Hungary) and in a few countries in Western Europe (The Netherlands and Ireland).[57] However, almost all of these population-based screening programmes were implemented relatively recently, making it impossible at this point to observe a mortality effect. Until now, the impact of FIT in reducing CRC mortality was only reported in Italian studies.[37, 94] Opportunistic or pilot colonoscopy screening programmes have been implemented in more countries[57, 98] although evidence of their impact on CRC mortality is lacking, with only one European observational study providing information on the beneficial effect of participating in colonoscopy screening.[96] Three RCTs comparing FIT and colonoscopy screening are underway, but their results may not be available for another 10 years.[46, 47, 99]

Since 2003, the EU has recommended CRC screening for men and women, suggesting starting and ending gFOBT screening within the ages 50-74 years (the effectiveness of other CRC screening modalities was not yet assessed by RCTs at the time of the recommendation).[55] However, in 2012, new multidisciplinary, evidence-based European guidelines for quality assurance in CRC screening were proposed, reporting that the FIT, FS, and total colonoscopy might be commonly considered reasonable alternatives to gFOBT screening.[56] Our study suggests that the effect of FS and gFOBT on CRC mortality may be consistent across several European settings, indicating that FS screening is more effective than gFOBT.

Several studies have highlighted the impact of FS in reducing CRC incidence (another critical outcome of CRC screening),[28, 30, 34] whereas gFOBT seems not to have had a statistically significant effect on this outcome.[33] Although it may be reasonable to assume a higher efficacy from endoscopy screening than from gFOBT, the current recommended stool test across Europe is the FIT, which can achieve at least the same CRC mortality reduction as that observed with gFOBT (or potentially similar to that observed with FS),[37, 94] but with the additional effect on reducing CRC incidence.[37, 94] Thus, policymakers should consider test-specific effectiveness and population preferences (such as expected participation in screening) as the essential determinants in deciding which CRC screening program to implement. Results from a RCT in the Netherlands showed a far higher initial uptake with stool tests (FIT: 61.5% and gFOBT: 49.5%) than with endoscopy investigations (FS: 32.4%).[100] Similarly, annual screening participation rates were higher in Italian FIT screening programmes than in those adopting FS (compliance in 2011: FIT 47.1%; and FS 24.5%).[63] Nevertheless, FS is offered once in a lifetime, whereas screening with stool tests needs recurrent participation over several screening rounds to achieve their expected effects on CRC mortality. Considering initial uptake or annual participation rates instead of cumulative uptake over time may therefore not be appropriate, [67] especially in light of the recent data showing that there were significantly fewer regular participants than the participants in the first screening round.[101-103] In addition, potential constraints in endoscopy resources and harms of screening need to be considered by decision-makers. Depending on the type of screening, the demand for endoscopy may increase substantially. Shortage of colonoscopy capacity may reduce the potential benefit of the CRC screening (especially among those with lower social economic status). Increasing colonoscopy efficiency, training, and regulations may curb this demand, but at least 10-15 years are needed to completely overcome the shortage.[104] Furthermore, screening might lead to the overtreatment of some pre-cancerous lesions that would never develop into CRC, increasing risks of screening. In some rare cases, colonoscopy examinations could even cause severe complications or death (especially when polypectomy is performed).

Important limitations are evident and noteworthy. First, in assessing the effect of participating in screening, few studies corrected their estimates to take into account demographic differences among participants and non-participants, therefore affecting external comparability of their findings. Thus, any review of the effect of participating in screening between and within European regions may be affected by selection bias. Moreover, the evidence of effectiveness for various screening strategies was limited: evidence for FIT and colonoscopy screening was available only for a few countries, and it was impossible to compare their effectiveness across different European regions. The impact of these screening modalities was assessed mainly in observational studies distinguished by a selected group of individuals actively participating in screening (especially for colonoscopy). With such designs, the results are particularly prone to selection bias. In our review, we included some evidence

based on data collected in periods and populations with less favourable CRC survival (i.e. evidence for gFOBT screening in England and Denmark).[105] CRC survival has substantially increased in the last decades owing to improvements in surgical and medical oncology (especially in managing rectal carcinoma).[106, 107] Thus, the effect of gFOBT on CRC mortality may be overestimated in those studies. Finally, this study is limited by the absence of studies conducted in Eastern European countries. Considering the recent GLOBOCAN estimates, CRC mortality was higher in Central and Eastern Europe than in the European average in both men and women.[2] Hence, CRC screening could be more effective in that region.[108]

To conclude, this review highlights the beneficial effect of CRC screening across Europe. The impact on CRC mortality of inviting individuals with screening strategies adopting gFOBT or FS seem to be consistent across several European settings. As a consequence, to improve or implement CRC screening programmes, European policymakers should carefully consider national endoscopy resources and population preferences in conjunction with efficacy of screening modalities.

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Supplementary Table 2.1a. Computer-assisted search code according to reference databases.

Source	Selection code
Embase	(((‘large intestine cancer’/de OR ‘cecum cancer’/de OR ‘colon cancer’/exp OR colonoscopy/exp OR sigmoidoscopy/exp OR ‘occult blood’/de OR (((colon OR colorect* OR sigmoid* OR bowel OR ‘large intestine’ OR ‘large intestines’ OR cecum) NEAR/10 (cancer* OR neoplas* OR tumo* OR carcino* OR adenocarcin*)) OR colonoscop* OR sigmoidoscop*):ab,ti) AND (screening/exp OR ‘early diagnosis’/exp OR (screen* OR ((annual* OR periodic*) NEAR/3 examination*) OR (earl* NEAR/3 diagnos*)))) OR (‘occult blood test’/exp OR (((‘occult blood’ OR guaiac) NEAR/3 test*) OR ((fecal* OR faecal*) NEAR/3 immunochem*)):ab,ti)) AND (mortality/de OR ‘cancer mortality’/de OR (mortalit* OR (death NEXT/1 rate*)):ab,ti) NOT ([Conference Abstract]/lim OR [Letter]/lim OR [Note]/lim OR [Editorial]/lim) AND [english]/lim AND (europe/exp OR (europe* OR Andorra* OR Austria* OR Balkan* OR Belgi* OR Albania* OR Baltic-State* OR Bosnia* OR Herzegovina* OR Bulgaria* OR Croatia* OR Czech* OR Hungar* OR Kosovo* OR Macedonia* OR Moldova* OR Montenegr* OR Poland* OR polish* OR Belarus* OR Romania* OR Russia* OR Serbia* OR Slovakia* OR Slovenia* OR Ukraine* OR France* OR french OR German* OR Gibraltar* OR Great-Brit* OR uk OR united-kingdom* OR England* OR Scotland* OR Wales* OR welsh OR Greece* OR Ireland* OR Italy OR Italian OR Liechtenstein* OR Luxembourg* OR Monaco* OR Netherlands* OR dutch OR holland OR Portug* OR San-Marino* OR Scandinavia* OR Nordic* OR Denmark* OR danish OR Finland* OR finnish OR Iceland* OR Norwa* OR norwegian OR Sweden* OR swedish OR Spain* OR spanish OR Switzerland* OR swiss):ab,ti,ca,ta,cy,ad) AND (‘observational study’/exp OR ‘cohort analysis’/exp OR ‘longitudinal study’/exp OR ‘retrospective study’/exp OR ‘prospective study’/exp OR ‘health survey’/de OR ‘health care survey’/de OR ‘epidemiological data’/de OR ‘case control study’/de OR ‘cross-sectional study’/de OR ‘correlational study’/de OR ‘population research’/de OR ‘family study’/de OR ‘major clinical study’/de OR ‘multicenter study’/de OR ‘comparative study’/de OR ‘follow up’/de OR ‘clinical study’/de OR ‘clinical article’/de OR ‘clinical trial’/exp OR ‘randomization’/exp OR ‘intervention study’/de OR ‘open study’/de OR ‘community trial’/de OR ‘review’/exp OR ‘systematic review’/exp OR (((observation* OR epidemiolog* OR famil* OR comparativ* OR communit*) NEAR/6 (stud* OR data OR research)) OR cohort* OR longitudinal* OR retrospectiv* OR prospectiv* OR population* OR (national* NEAR/3 (stud* OR survey)) OR (health* NEAR/3 survey*) OR ((case OR cases OR match*) NEAR/3 control*) OR (cross NEXT/1 section*) OR correlation* OR multicenter* OR (multi* NEXT/1 center*) OR ‘follow up’ OR followup* OR clinical* OR trial OR random* OR review*):ab,ti)
Medline Ovid	(((exp “Colorectal Neoplasms”/ OR exp colonoscopy/ OR “Occult Blood”/ OR (((colon OR colorect* OR sigmoid* OR bowel OR “large intestine” OR “large intestines” OR cecum) ADJ10 (cancer* OR neoplas* OR tumo* OR carcino* OR adenocarcin*)) OR colonoscop* OR sigmoidoscop*).ab,ti.) AND (“Mass Screening”/ OR exp “Early Diagnosis”/ OR (screen* OR ((annual* OR periodic*) ADJ3 examination*)))) OR ((((“occult blood” OR guaiac) ADJ3 test*) OR ((fecal* OR faecal*) ADJ3 immunochem*)).ab,ti.)) AND (exp mortality/ OR (mortalit* OR (death ADJ rate*)).ab,ti.) NOT (letter OR news OR comment OR editorial OR congresses OR abstracts).pt. AND english.la. AND (exp europe/ OR (europe* OR Andorra* OR Austria* OR Balkan* OR Belgi* OR Albania* OR Baltic-State* OR Bosnia* OR Herzegovina* OR Bulgaria* OR Croatia* OR Czech* OR Hungar* OR Kosovo* OR Macedonia* OR Moldova* OR Montenegr* OR Poland* OR polish* OR Belarus* OR Romania* OR Russia* OR Serbia* OR Slovakia* OR Slovenia* OR Ukraine* OR France* OR french OR German* OR Gibraltar* OR Great-Brit* OR uk OR united-kingdom* OR England* OR Scotland* OR Wales* OR welsh OR Greece* OR Ireland* OR Italy OR Italian OR Liechtenstein* OR Luxembourg* OR Monaco* OR Netherlands* OR dutch OR holland OR Portug* OR San-Marino* OR Scandinavia* OR Nordic* OR Denmark* OR danish OR Finland* OR finnish OR Iceland* OR Norwa* OR norwegian OR Sweden* OR swedish OR Spain* OR spanish OR Switzerland* OR swiss).ab,ti,jn,cp,in.) AND (“observational study”/ OR exp “Cohort Studies”/ OR “Health Surveys”/ OR “Epidemiologic Studies”/ OR “Case-Control Studies”/ OR “Cross-Sectional Studies”/ OR “multicenter study”/ OR “comparative study”/ OR “clinical study”/ OR exp “clinical trials”/ OR “Random Allocation”/ OR “review”/ OR (((observation* OR epidemiolog*) ADJ6 (stud* OR data OR research)) OR cohort* OR longitudinal* OR retrospectiv* OR prospectiv* OR population* OR (national* ADJ3 (stud* OR survey)) OR (health* ADJ3 survey*) OR ((case OR cases OR match*) ADJ3 control*) OR (cross ADJ section*) OR correlation* OR multicenter* OR (multi* ADJ center*) OR “follow up” OR followup* OR clinical* OR trial OR random* OR review*).ab,ti.)

Supplementary Table 2.1a. Computer-assisted search code according to reference databases. (*continued*)

Source	Selection code
Cochrane	((((((colon OR colorect* OR sigmoid* OR bowel OR 'large intestine' OR 'large intestines' OR cecum) NEAR/10 (cancer* OR neoplas* OR tumo* OR carcino* OR adenocarcin*)) OR colonoscop* OR sigmoidoscop*):ab,ti) AND ((screen* OR ((annual* OR periodic*) NEAR/3 examination*) OR (earl* NEAR/3 diagnos*)))) OR ((((‘occult blood’ OR guaiac) NEAR/3 test*) OR ((fecal* OR faecal*) NEAR/3 immunochem*)):ab,ti)) AND ((mortalit* OR (death NEXT/1 rate*)):ab,ti) AND ((europe* OR Andorra* OR Austria* OR Balkan* OR Belgi* OR Albania* OR Baltic-State* OR Bosnia* OR Herzegovina* OR Bulgaria* OR Croatia* OR Czech* OR Hungar* OR Kosovo* OR Macedonia* OR Moldova* OR Montenegr* OR Poland* OR polish* OR Belarus* OR Romania* OR Russia* OR Serbia* OR Slovakia* OR Slovenia* OR Ukraine* OR France* OR french OR German* OR Gibraltar* OR Great-Brit* OR uk OR united-kingdom* OR England* OR Scotland* OR Wales* OR welsh OR Greece* OR Ireland* OR Italy OR Italian OR Liechtenstein* OR Luxembourg* OR Monaco* OR Netherlands* OR dutch OR holland OR Portug* OR San-Marino* OR Scandinavia* OR Nordic* OR Denmark* OR danish OR Finland* OR finnish OR Iceland* OR Norwa* OR norwegian OR Sweden* OR swedish OR Spain* OR spanish OR Switzerland* OR swiss))

Supplementary Table 2.1b. Computer-assisted search code according to reference databases.

Source	Selection code
Web-of-science	TS=(((((((colon OR colorect* OR sigmoid* OR bowel OR "large intestine" OR "large intestines" OR cecum) NEAR/10 (cancer* OR neoplas* OR tumo* OR carcino* OR adenocarcin*)) OR colonoscop* OR sigmoidoscop*)) AND ((screen* OR ((annual* OR periodic*) NEAR/2 examination*) OR (earl* NEAR/2 diagnos*)))) OR (((("occult blood" OR guaiac) NEAR/2 test*) OR ((fecal* OR faecal*) NEAR/2 immunochem*)))) AND ((mortalit* OR (death NEAR/1 rate*))) AND ((europe* OR Andorra* OR Austria* OR Balkan* OR Belgi* OR Albania* OR Baltic-State* OR Bosnia* OR Herzegovina* OR Bulgaria* OR Croatia* OR Czech* OR Hungar* OR Kosovo* OR Macedonia* OR Moldova* OR Montenegr* OR Poland* OR polish* OR Belarus* OR Romania* OR Russia* OR Serbia* OR Slovakia* OR Slovenia* OR Ukraine* OR France* OR french OR German* OR Gibraltar* OR Great-Brit* OR uk OR united-kingdom* OR England* OR Scotland* OR Wales* OR welsh OR Greece* OR Ireland* OR Italy OR Italian OR Liechtenstein* OR Luxembourg* OR Monaco* OR Netherlands* OR dutch OR holland OR Portug* OR San-Marino* OR Scandinavia* OR Nordic* OR Denmark* OR danish OR Finland* OR finnish OR Iceland* OR Norwa* OR norwegian OR Sweden* OR swedish OR Spain* OR spanish OR Switzerland* OR swiss)) AND (((observation* OR epidemiolog* OR famil* OR comparativ* OR communit*) NEAR/5 (stud* OR data OR research)) OR cohort* OR longitudinal* OR retrospectiv* OR prospectiv* OR population* OR (national* NEAR/2 (stud* OR survey)) OR (health* NEAR/2 survey*) OR ((case OR cases OR match*) NEAR/2 control*) OR (cross NEAR/1 section*) OR correlation* OR multicenter* OR (multi* NEAR/1 center*) OR"follow up" OR followup* OR clinical* OR trial OR random* OR review*)) AND DT=(article) AND la=(english)
Pubmed publisher	((("Colorectal Neoplasms"[mh] OR colonoscopy[mh] OR "Occult Blood"[mh] OR (((colon OR colorect*[tiab] OR sigmoid*[tiab] OR bowel OR "large intestine" OR "large intestines" OR cecum) AND0 (cancer*[tiab] OR neoplas*[tiab] OR tumor*[tiab] OR tumour*[tiab] OR carcino*[tiab] OR adenocarcin*[tiab])) OR colonoscop*[tiab] OR sigmoidoscop*[tiab])) AND ("Mass Screening"[mh] OR "Early Diagnosis"[mh] OR (screen*[tiab] OR ((annual*[tiab] OR periodic*[tiab]) AND examination*[tiab]))))) OR ((("occult blood test*[tiab] OR guaiac test*[tiab] OR ((fecal*[tiab] OR faecal*[tiab]) AND immunochem*[tiab])))) AND (mortality[mh] OR (mortalit*[tiab] OR (death rate*[tiab])))) NOT (letter[pt] OR news[pt] OR comment[pt] OR editorial[pt] OR congresses[pt] OR abstracts[pt]) AND english[la] AND english[la] AND (europe[mh] OR (europe* OR Andorra* OR Austria* OR Balkan* OR Belgi* OR Albania* OR Baltic-State* OR Bosnia* OR Herzegovina* OR Bulgaria* OR Croatia* OR Czech* OR Hungar* OR Kosovo* OR Macedonia* OR Moldova* OR Montenegr* OR Poland* OR polish* OR Belarus* OR Romania* OR Russia* OR Serbia* OR Slovakia* OR Slovenia* OR Ukraine* OR France* OR french OR German* OR Gibraltar* OR Great-Brit* OR uk OR united-kingdom* OR England* OR Scotland* OR Wales* OR welsh OR Greece* OR Ireland* OR Italy OR Italian OR Liechtenstein* OR Luxembourg* OR Monaco* OR Netherlands* OR dutch OR holland OR Portug* OR San-Marino* OR Scandinavia* OR Nordic* OR Denmark* OR danish OR Finland* OR finnish OR Iceland* OR Norwa* OR norwegian OR Sweden* OR swedish OR Spain* OR spanish OR Switzerland* OR swiss)) AND ("observational study"[pt] OR "Cohort Studies"[mh] OR "Health Surveys"[mh] OR "Epidemiologic Studies"[mh] OR "Case-Control Studies"[mh] OR "Cross-Sectional Studies"[mh] OR "multicenter study"[pt] OR "comparative study"[pt] OR "clinical study"[pt] OR "clinical trials"[pt] OR "Random Allocation"[mh] OR "review"[pt] OR (((observation*[tiab] OR epidemiolog*[tiab]) AND (stud*[tiab] OR data OR research)) OR cohort*[tiab] OR longitudinal*[tiab] OR retrospectiv*[tiab] OR prospectiv*[tiab] OR population*[tiab] OR (national*[tiab] AND (stud*[tiab] OR survey)) OR (health*[tiab] AND survey*[tiab]) OR ((case OR cases OR match*[tiab]) AND control*[tiab]) OR (cross section*[tiab]) OR correlation*[tiab] OR multicenter*[tiab] OR (multi center*[tiab]) OR "follow up" OR followup*[tiab] OR clinical*[tiab] OR trial OR random*[tiab] OR review*[tiab])) AND publisher[sb]
Google scholar	"colon|colorectal|colonic cancer|neoplasms|tumor|carcinoma"|colonoscopy|sigmoidoscopy screening|"annual|periodic examination "|"early diagnosis" mortality|"death rate" europe cohort|longitudinal|prospective|retrospective|trial|epidemiological|epidemiologic

Supplementary Table 2.2. Conflict of interest and/or statements of all included studies.

Study	Conflict of interest and/or funding statement
Pitkaniemi J, 2015	**Funding**: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors; **Competing interests**: None declared.
Malila N, 2007	No statement.
Lindholm E, 2008	**Funding**: The study was supported by the SwedishCancer Society, Assar Gabrielsson Foundation, Göteborgs Läkarsällskap, Inga-Britt and Arne Lundberg Research Foundation, Magnus Bergvall Foundation, Gunnar and Elisabeth Nilsson Foundation, Jubileumklinikens Foundation and Sahlgrenska University Hospital Foundation.
Kronborg O, 2004	No statement.
Bertario L, 1999	No statement.
Zappa M, 1997	No statement.
Hamza S, 2014	**Competing interests**: None.
Faivre J, 1999	**Funding**: This project was funded by the Europe Against Cancer Programme, INSERM, the Fonds National de Prévention, the Burgundy Regional Council and the French League Against Cancer.
Scholefield JH, 2012	**Funding**: This study was supported by the Medical Research Council with several project grants from 1987 to 2009 for data collection and trial administration; **Competing interests**: None.
Libby G, 2012	**Funding**: This work was supported by a grant from the Chief Scientist Office (Grant No CZH/6/4), Scottish Government Health Directorates to establish a bowel screening research unit.
Giorgi-Rossi P, 2015	**Funding**: None; **Competing interests**: None.
Ventura L, 2014	**Conflict of interest statement**: All authors declare to have not conflict of interest.
Thiis-Evensen E, 2013	**Funding**: This work was supported by the Norwegian Cancer Society (grant number E 96008/007). MK received research grants from the Norwegian Research Council (grant number 205243); **Competing interests**: Michael Bretthauer has received research support from Olympus, Fujinon, Ferring, CCS, and Falk Pharma. The other authors have nothing to report.

Supplementary Table 2.2. Conflict of interest and/or statements of all included studies. (*continued*)

Study	Conflict of interest and/or funding statement
Holme Ø, 2018	**Funding/Support**: The study was supported by research grants from the Norwegian government and the Norwegian Cancer Society. This work was funded by research grants from the Norwegian Cancer Society, the Research Council of Norway, the South-East Regional Health Authority of Norway, the Fulbright Foundation, Sørlandet Hospital Kristiansand, and the National Institutes of Health. **Conflict of Interest**: Dr. Holme reports personal fees from Norgine outside the submitted work. Dr. Herna´ n reports grants from the National Institutes of Health during the conduct of the study. Dr. Hoff reports personal fees from Amgen Norway during the conduct of the study. Authors not named here have disclosed no conflicts of interest. Disclosures can also be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M17-1441.
Segnan N, 2011	**Funding**: This work was supported by a grant from the Associazione Italiana per la Ricerca sul Cancro from 1995 to 1997 (1182/95 to Azienda Sanitaria Locale 1-Torino; N.S.) and a grant from the Italian National Research Council (CNR) (95.00539.PF39 and 96.00736.PF39 allocated to Azienda Sanitaria Locale 1-Torino; N.S.). The Istituto Oncologico Romagnolo (IOR), the Fondo "E Tempia," the University of Milano, and the Local Heath Unit Azienda Sanitaria Locale 1-Torino supported the implementation of the study in Rimini, Biella, Milano, and Torino, respectively, through own contribution within screening centers.
Atkin WS, 2017	**Funding**: National Institute for Health Research Efficacy and Mechanism Evaluation. **Conflicts of interest**: Authors declare that they have no conflicts of interest.
Manser CN, 2012	**Funding/Disclosure**: The initial screening study was supported by grants to Prof. Urs Marbet from the Swiss and Regional Cancer Leagues of Central Switzerland Glarus, the Gastroenterological Society GastroMed Swiss, and the Basel Foundation for Cancer Research. No other financial relationships relevant to this publication were disclosed.
Bjerrum A, 2016	**Funding/Support**: This research was supported by a grant of 25000 DKK from Copenhagen University Hospital, Herlev, to cover data retrieval from the Danish Health Registers. The research received no other funding from the public, commercial or not-for-profit sectors. **Competing interests**: None.

Supplementary Table 2.3. Characteristics of excluded studies.

Study	Reason for exclusion	Study	Reason for exclusion
Constantini AS, 2008	The study did not report the number of events and the total number of the participant in each study group.	Brenner H, 2001	Controls were cancer cases.
Senore C, 2015	Mortality data published in Segnan N, 2011. No update.	Goodyear SJ, 2008	Cohort selection not clear. No number of case per age.
Parente F, 2015	The study did not report the number of events and the total number of the participant in each study group.	Gill MD, 2012	Max follow-up less than 5 years.
Citarda F, 2001	Cases are selected after a positive colonoscopy examination.	Suttie SA, 2012	The study did not report the number of events and the total number of the participant in each study group.
Parente F, 2008	The study was focused on test performance characteristics. Moreover, follow-up less than 4 years.	Brenner H, 2016	The study did not report the number of events and the total number of the participant in each study group.
Bonelli L, 2006	Intervention was only previous negative screening.	Mansouri D, 2015	The study did not report the total number of the participant in each study group.
Zorzi M, 2015	No screening programs with at least of 5 years after the CRC screening introduction.	Rácz I, 2002	No control group.
Järvinen HJ, 2000	High risk population.	Jörgensen OD, 2002	Mortality data update in Kronborg O, 2004.
Wahrendorf J, 1993	No control group. All individual received FOBT.	Thiis-Evensen E, 1999	Mortality data update in Thiis-Evensen E, 2013.
Hardcastle JD, 1996	Mortality data update in Scholefield JH, 2012.	Kronborg O, 1997	Mortality data update in Kronborg O, 2004.
Mapp TJ, 1999	Mortality data update in Scholefield JH, 2012.	Kronborg O,1996	Mortality data update in Kronborg O, 2004.
Robinson MHE, 1999	Outcome was not CRC mortality or incidence reduction.	Lindholm E, 1995	Outcome was not CRC mortality or incidence reduction.
Robinson MH, 2000	Outcome was not CRC mortality or incidence reduction.	Kronborg O, 1992	Outcome was not CRC mortality or incidence reduction.
Lamah M, 2001	Moderate risk population.	Kronborg O, 1989	Max follow-up less than 5 years.
Scholefield JH, 2002	Mortality data update in Scholefield JH, 2012.	Hoff G, 2009	Mortality data update in Holme Ø, 2014.
Faivre J, 2004	Mortality data update in Hamza S, 2014.	Hoff G, 1996	Outcome was not CRC mortality or incidence reduction.

Supplementary Table 2.3. Characteristics of excluded studies. (*continued*)

Study	Reason for exclusion	Study	Reason for exclusion
Goodyear SJ, 2008	Study provided data on 30-days mortality after hospital admission.	Rasmussen M, 1999	Control group was not no screening or opportunistic screening.
Whynes DK, 2010	Outcome was not CRC mortality or incidence reduction.	Kewenter J, 1994a	Mortality data update in Lindholm E, 2008.
Courtney ED, 2013	No correct control group: symptomatic patients.	Kewenter J, 1994b	Mortality data update in Lindholm E, 2008.
Libby G, 2014	Study provided data on 30-days mortality after hospital admission.	Castells A, 2014	Control group was not no screening or opportunistic screening.
Saratzis A, 2015	Follow-up less than 2-3 years.	Quintero E, 2012	Control group was not no screening or opportunistic screening.
Hardcastle JD, 1989	Mortality data update in Scholefield JH, 2012.	Zorzi M, 2014	Ecologic study. Two screening areas.
Friedrich K, 2015	Study did not provide a direct estimation of CRC mortality reduction due to screening.	Mackay C, 2014	Study did not provide a direct estimation of CRC mortality reduction due to screening.
McClements PL, 2012	Study did not provide a direct estimation of CRC mortality reduction due to screening.	Brenner H, 2011	Intervention was only previous negative colonoscopy.
Brenner H, 2014	Outcome was CRC incidence reduction	Blom J, 2008	Outcome was CRC incidence reduction
Atkin WS, 2010	Mortality data update in Atkin WS, 2017.	Holme O, 2014	Mortality data update in Holme O, 2018.

Supplementary Table 2.5a. Risk of bias for randomized control trials.

Study	Entry[a]	Judgement	Support for judgement	Study	Entry[a]	Judgement	Support for judgement
Pitkaniemi J, 2015[62]	Random sequence generation (selection bias)	Lower risk	Quote: "The Finnish population-based screening program was individually randomized". Comment: Probably done. Randomization made a individuals level and was ordered through the Central Population Register. Information in previous publication (Manila N, 2005). Quote: "In January 2007, some controls (109 subjects) received a screening invitation due to problems in the software". Comment: Few individuals. It probably might not affect the estimated results.	Lindholm E, 2008[36]	Random sequence generation (selection bias)	Low risk	Quote: "Individuals were randomized into two groups of equal size". No indication about methods of randomization. Comment: Probably done.

Supplementary Table 2.5a. Risk of bias for randomized control trials. (*continued*)

Study	Entry[a]	Judgement	Support for judgement	Study	Entry[a]	Judgement	Support for judgement
	Blinding of outcome Assessment (detection bias)	Low risk	Incident CRC cases and CRC deaths were retrieved through record linkage with Finnish Cancer Registry and Statistics Finland.		Blinding of outcome Assessment (detection bias)	Low risk	Information on all CRC identified was obtained from the register at the Department of Pathology and the National cancer registry. A blinded independent reviewer evaluated all cases in which there was any uncertainty about cause of death.
	Incomplete outcome data Addressed (attrition bias)	Unclear risk	The study did not address this outcome.		Incomplete outcome data Addressed (attrition bias)	Unclear risk	The study did not address this outcome.
	Selective reporting (reporting bias)	Moderate risk	The study protocol is not available but it is clear that the published report include all expected outcomes. Comments: However, the study's follow-up was short and this might affect the results.		Selective reporting (reporting bias)	Low risk	The study protocol is not available but it is clear that the published reports include all expected outcomes.
	Final judgement	B	Moderate risk		Final judgement	A	Low risk

[a] Allocation concealment, Blinding of participant and personnel, Blinding of outcome assessment (patient-reported outcomes), and incomplete outcome data addressed (Short-term outcomes, 2-6 weeks) were not considered in the risk assessment of this analysis.

Supplementary Table 2.5b. Risk of bias for randomized control trials.

Study	Entry[a]	Judgement	Support for judgement	Study	Entry[a]	Judgement	Support for judgement
Kronborg O, 2004[32]	Random sequence generation (selection bias)	Low risk	Quote: "The design was described in detail in Kronborg O. et al (1987)". Kronborg O. (1987): "The two randomized groups were generated from two EDP files, The Central Person Register and the Patient File of the county".	Scholefield JH, 2012[33]	Random sequence generation (selection bias)	Low risk	Quote: "Randomization was by household" […] The methodology of the trial is described in more detail elsewhere (Hardcastle JD, 1996)". Comment: Probably done. Hardcastle JD, 1996. Central randomization of households identified from GP records (stratified by size, sex and average age of eligible members).
	Blinding of outcome Assessment (detection bias)	Low risk	Quote: "Death certificates are evaluated blindly. An impartial death review […] decides, whenever doubt exists, whether a person has died of colorectal cancer."		Blinding of outcome Assessment (detection bias)	Low risk	Clinical information and death certificates on CRC cases were reviewed. Verification was carried out blindly in the 95% of the cases.
	Incomplete outcome data Addressed (attrition bias)	Unclear risk	The study did not address this outcome.		Incomplete outcome data Addressed (attrition bias)	Low risk	Quote: "875 (0.6%) could not be traced by the Office for National Statistics or had emigrated and were therefore excluded from the analysis".

Supplementary Table 2.5b. Risk of bias for randomized control trials. (*continued*)

Study	Entry[a]	Judgement	Support for judgement	Study	Entry[a]	Judgement	Support for judgement
	Selective reporting (reporting bias)	Low risk	The study protocol is not available but it is clear that the published reports include all expected outcomes.		Selective reporting (reporting bias)	Low risk	The study protocol is not available but it is clear that the published reports include all expected outcomes.
	Final judgement	A	Low risk		Final judgement	A	Low risk

[a] Allocation concealment, Blinding of participant and personnel, Blinding of outcome assessment (patient-reported outcomes), and incomplete outcome data addressed (Short-term outcomes, 2-6 weeks) were not considered in the risk assessment of this analysis.

Supplementary Table 2.5c. Risk of bias for randomized control trials.

Study	Entry[a]	Judgement	Support for judgement	Study	Entry[a]	Judgement	Support for judgement
Thiis-Evensen E, 2013[95]	Random sequence generation (selection bias)	High risk	Quote: "Of these, 400 (born in the months of January, February, and March) were invited to FS screening examination (screening group), and 399 (no preference to month of birth) were allocated to control group (Hoff G et al. 1985)". In other reference (Thiis-Evensen E et al. 1999) the authors explained clearly the random allocation: screening group were selected only among born in January, February and March).	Segnan N, 2011[34]	Random sequence generation (selection bias)	Low risk	Randomization was performed in each center using a computer-generated random number sequence. Selection bias additional limited with the exclusion of 3880 eligible individuals from the random assignment in Genoa.
	Blinding of outcome Assessment (detection bias)	Low risk	CRC cases, CRC death and socioeconomic data were retrieved through record linkage from, respectively, Cancer Registry of Norway, Cause of Death Registry and Statistics Norway.		Blinding of outcome Assessment (detection bias)	Low risk	Information on outcomes were retrieved through record linkage from study databases and several sources: hospital discharge records, pathologic department files, regional mortality registries. In addition an independent panel of experts on cancer registries data assessed blindly clinical data of CRC cases and death certificates.

Supplementary Table 2.5c. Risk of bias for randomized control trials. (*continued*)

Study	Entry[a]	Judgement	Support for judgement	Study	Entry[a]	Judgement	Support for judgement
	Incomplete outcome data Addressed (attrition bias)	Unclear risk	The study did not address this outcome.		Incomplete outcome data Addressed (attrition bias)	Low risk	Intervention group: 1.6% (280) not traced. Control group: 1.9% (324) not traced.
	Selective reporting (reporting bias)	Unclear risk	The study protocol is not available.		Selective reporting (reporting bias)	Low risk	The study protocol is available and the published report include the primary outcomes. Trials: ISRCTN27814061
	Final judgement	C	High risk		Final judgement	A	Low risk

[a] Allocation concealment, Blinding of participant and personnel, Blinding of outcome assessment (patient-reported outcomes), and incomplete outcome data addressed (Short-term outcomes, 2-6 weeks) were not considered in the risk assessment of this analysis.

Supplementary Table 2.5d. Risk of bias for randomized control trials.

Study	Entry[a]	Judgement	Support for judgement	Study	Entry[a]	Judgement	Support for judgement
Holme Ø, 2018[30]	Random sequence generation (selection bias)	Low risk	Quote: "An independent body (IBM Norway) performed both randomization procedures using computerized algorithms".	Atkin WS, 2017[28]	Random sequence generation (selection bias)	Unclear risk	Randomization was stratified by trial centre, general practice within centre, and household type.
	Blinding of outcome Assessment (detection bias)	Low risk	CRC cases, CRC death and socioeconomic data were retrieved through record linkage from, respectively, Cancer Registry of Norway, Cause of Death Registry and Statistics Norway.		Blinding of outcome Assessment (detection bias)	Low risk	CRC cases and CRC death were retrieved through record linkage from National Health Service Central Register, Office for National Statistics, and Cancer Registries. Quote:"A second analysis was done after blinded verification of assignment of colorectal cancer as an underlying cause of death according to the rules described in the web appendix."

Supplementary Table 2.5d. Risk of bias for randomized control trials. (*continued*)

Study	Entry[a]	Judgement	Support for judgement	Study	Entry[a]	Judgement	Support for judgement
	Incomplete outcome data Addressed (attrition bias)	Low risk	Intervention group: 0.2%(34+19/20780) emigrated. Control group: 0.6%((478+3)/79430) emigrated or not traceable. (only 3 not traceable)		Incomplete outcome data Addressed (attrition bias)	Low risk	From Atkin 2010: Not traced 6 persons in intervention group and 6 in control group. 234 (<1%) individuals emigrated in intervention and 451 (<1%) in control group. From Atkin 2017: After the cohort was matched with the most recent data provided by national sources, 160 people were found to have died, 224 had colorectal cancer diagnosed and two had emigrated.
	Selective reporting (reporting bias)	Low risk	The study protocol is available and the published report include the primary outcomes. Trials: NCT0011912		Selective reporting (reporting bias)	Low risk	The study protocol is available and the published report include the primary outcomes.Trials: ISRCTN28352761
	Final judgement	A	Low risk		Final judgement	A	Low risk

[a] Allocation concealment, Blinding of participant and personnel, Blinding of outcome assessment (patient-reported outcomes), and incomplete outcome data addressed (Short-term outcomes, 2-6 weeks) were not considered in the risk assessment of this analysis.

Supplementary Table 2.6. Risk of bias in Case-Control studies according to Newcastle-Ottawa scale.

	Bertario L, 1999[91]	Zappa M, 1997[92]	Faivre J, 1999[93]
Selection			
Case definition¥	Definition adequate, with independent validation. "a colorectal cancer (CRC) death was defined as a case". Authors assessed cases using: death certificates and medical records. (*)	Record linkage. Cases were defined as individuals in according to: (i) living area covered by screening; (ii) diagnosis of primary cancer between 1984 and 1995, age 41–75; (iii) death for CRC before 30 June 1996. Those were collected by cancer and mortality registries.	Definition adequate, with independent validation. Cases were individuals enrolled in screening program and died for CRC. In the few instances in which the cause of death could not be easily determined, blinded expert – physician and pathologist – decided.(*)
Representativeness of the cases	Consecutive series of cases. CRC deaths among 21,879 individuals who agreed to participate to screening between 1978 and 1995. (*)	Consecutive series of cases. Well defined series of cases. (*)	Consecutive series of cases. Well defined series of cases. (*)
Control selection	Community controls. Controls were drawn from the same source. (*)	Community controls. Controls were drawn from the same source. (*)	Community controls. Controls were drawn from the same source. (*)
Control definition	No history of disease. "Controls were alive and free of CRC at the time of the index date of the corresponding case". (*)	No history of disease. "Controls were alive and free of CRC at the time of the index date of the corresponding case". (*)	No description of source. "A previous history of adenoma or non-fatal colorectal cancer first occurring after the diagnosis of the corr. Case was not grounds for exclusion".
Comparability			
Study controls for age	Cases and controls matched according to age quinquennium. (*)	Cases and controls matched according to age. (*)	Cases and controls matched according to year of birth. (*)
Any additional factors	Gender, area of birth, calendar year of admission into the screening programme. (*)	Gender, and place and length of residence. (*)	Gender, and place of residence. (*)

Supplementary Table 2.6. Risk of bias in Case-Control studies according to Newcastle-Ottawa scale. (*continued*)

	Bertario L, 1999[91]	Zappa M, 1997[92]	Faivre J, 1999[93]
Exposure			
Ascertainment	Medical record only.	Interview not blinded to case/control status. More information available for controls.	Secure record. Data from screening campaign's data files. (*)
Same method for case and control	No.	No. Direct interview for controls and more information available.	Yes. (*)
Non-Response rate	Quote: "Screening history for both cases and controls was determined". However, no information of completeness of this process.	No description of missing data on exposure..	Authors said available record. No description of missing data on exposure..
Final result	6/9	5/9	7/9

(*) The presence of this symbol means the study fitted the selected criteria; ¥ Since cancer registries in some countries have a very high percentage of histologically verified cases, which we qualified as independent validation, we did award a point on this question if the percentage of histologically verified colorectal cancer cases in the cancer registry used in the analysis was known to be above 95% according to the International Agency for Research on Cancer.

Supplementary Table 2.7a. Risk of bias in Cohort studies according to Newcastle-Ottawa scale.

	Selection			Comparability			Outcome			
Study	Representativeness of the exposed cohort	Selection of the non-exposed	Ascertainment of exposure	Absence of interest outcome at start of study	Study controls for age	Any additional factors	Assessment of outcome	Follow-up Length[a]	Adequacy of follow-up	Final result
Manila N, 2007[89]	No description of the derivation of the cohort of cases. Olny information on location (Järvenpää, Kerava, and Tampere).	Draw from a different source. External comparison with general finish population	No description. Authors did not report the source of screening information.	No.	Standardized incidence and mortality ratio for 5-years age-intervals. (*)	Gender, and five calendar periods. (*)	CRC incident cases and CRC deaths were retrieved through record linkage with Finish cancer registry and Statistics Finland. (*)	Yes. ~ 19.9 years. (*)	Not statement.	4/9
Giorgi-Rossi P, 2015[37]	Representative of the average population in the community. The study includes all the resident in Reggio-Emilia aged 50-69. (*)	Drawn from the same community. However, different period. (*)	Exposure not directly assessed at individual level. Intention-to-screen approach using 2 separate and defined cohorts.	No. No direct assessment of the outcomes at individual level.	Incidence rate ratio computed with Poisson regression adjusted for single year of age. (*)	Incidence rates further adjusted for gender. Mortality for calendar year. (*)	CRC cases and cancer deaths (only for CRC cases) were retrieved through record linkage with Reggio-Emilia Cancer Registry. (*)	Yes. Max 8 years for each cohort. (*) Note: Although in case of incidence-based mortality, 8 years might not be an adequate follow-up time.	No statement.	6/9

Supplementary Table 2.7a. Risk of bias in Cohort studies according to Newcastle-Ottawa scale. (*continued*)

	Selection			Comparability			Outcome			
Ventura L, 2014[94]	Representative of the average population in the community. The study includes all the resident aged 50-70 with first FIT during 1993-1999 due to screening in 24 Florentine municipalities. (*)	Drawn from the same community. No-exposed are no-participant to screening, excluded individuals with previous gFOBT. (*)	Secure record. Screening examination: attenders to FIT (screening program data). (*)	Yes. Quote: "We excluded all subjects […] for whom a CRC had been diagnosed before the enrolment period ".	Hazard ratio were adjusted for age. (*)	Hazard ratio for incidence were further adjusted for sex. No further adjustment for mortality.	CRC cases and CRC deaths were retrieved through record linkage with Tuscany cancer registry and Tuscany Death registry. (*)	Yes. ≥10.6 years. (*)	Ninety-seven (0.3%) emigrated and 323 subjects (0.97%) were lost to follow-up. No likely to introduce bias. (*)	8/9
Bjerrum A, 2016[90]	Representative of the average population in the community. The study includes all the resident in Vejle and half of Copenhagen. (*)	Draw from a different source. External comparison with rest of the country.	No description.	Yes. Several exclusions were made in the cohort definition. (*)	Hazard ratio were adjusted for age. (*)	Gender. (*)	Record linkage. Danish Cancer Registry, National Patient Registry, and Death Cause Register. (*)	Yes. 8.9. (*)	Not statement.	6/9

(*) The presence of this symbol means the study fitted the selected criteria and it was accounted in the final result; [a] Follow-up was assumed long enough to attribute a point if it was at least 8 years.

Supplementary Table 2.7b. Risk of bias in Cohort studies according to Newcastle-Ottawa scale.

	Selection				Comparability		Outcome			
Study	Representativeness of the exposed cohort	Selection of the non-exposed	Ascertainment of exposure	Absence of interest outcome at start of study	Study controls for age	Any additional factors	Assessment of outcome	Follow-up length[a]	Adequacy of follow-up	Final result
Libby G, 2012[76]	Representative of the average population in the community. Individuals selected from 3 three National Health Service Scottish boards to receive a FOBT. (*)	Draw from a different source. Controls selected from different boards.	Secure record. Data from the Information Services Division of NHS National Services Scotland. (*)	Yes. GPs excluded individuals before the screening. Furthermore, excluded individuals with CRC diagnosis or CRC hospital admission before screening. (*)	Controls were matched for age. (*)	In addition controls were matched for gender. (*)	CRC cases and CRC death were collected through record linkage with data from Scottish Cancer Registry, Scottish Morbidity records database and National Records of Scotland database. (*)	Yes. ~ 8 years. (*)	Not statement.	7/9
Manser CN, 2012[96]	Somewhat Representative of the average population in the community. All individuals aged 50 to 80 years in Uri and Glarus canton) were invited to screening. (*)	Drawn from the same community. No-exposed are no-participant to screening. (*)	Secure record. Surgeon databases in the region. Limited access to colonoscopy in the area, so completed awareness of people undergoing colonoscopy. (*)	Yes. Individuals with personal history of CRC or inflammatory bowel disease were excluded. (*)	Controls matched for age. (*)	In addition controls matched for gender. (*)	Self-report. CRC cases and information on CRC mortality were collected from databases of 3 hospital.	No. 6 years.	No statement.	6/9

Supplementary Table 2.7b. Risk of bias in Cohort studies according to Newcastle-Ottawa scale. (*continued*)

	Selection				Comparability		Outcome			
Hamza S, 2014[88]	Representative of the average population in the community. The study includes all the resident in 12 districts of Burgundy aged 45-74. (*)	Draw from a different source. All resident in other 17 districts.	Secure record. Data were collected from the screening monitoring institute. Test were performed from trained staff and results were interpreted and discussed by two technicians. (*)	No. The list of eligible individuals did not include subjects excluded by GPs because of life-threatening illnesses.	Standardized incidence and mortality ratios were computed adjusted for age. (*)	Additional for gender. (*)	CRC cases were collected through record linkage with Burgundy Cancer registry. Registry staff collected also information from pathology laboratories, hospitals, private surgeons, oncologist, gastroenterologist and GPs. (*)	Yes. ~ 17.3 years. (*)	Quote: "Among 16,238 individuals included in the study cohort who had died, the cause of death was missing for 6.9%".	6/9

(*) The presence of this symbol means the study fitted the selected criteria and it was accounted in the final result; [a] Follow-up was assumed long enough to attribute a point if it was at least 8 years.