Colorectal cancer screening with faecal testing, sigmoidoscopy or colonoscopy: a systematic review and network meta-analysis

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ABSTRACT

Objective Evaluate effectiveness, harms and burdens of faecal blood testing, sigmoidoscopy and colonoscopy screening for colorectal cancer over 15 years.

Design We performed an update of a Cochrane systematic review, and performed network meta-analysis comparing randomised trials evaluating colorectal cancer screening with guaiac faecal occult blood test (gFOBT) (annual, biennial), faecal immunochemical test (FIT) (annual, biennial), sigmoidoscopy (once-only) or colonoscopy (once-only) in a healthy population, aged 50–79 years. We conducted subgroup analysis on sex. Follow-up >5 years was required for analysis of colorectal cancer incidence and mortality.

Results 12 randomised trials proved eligible. Compared with no-screening, we found high certainty evidence for sigmoidoscopy screening slightly reducing colorectal cancer incidence (relative risk (RR) 0.76; 95% confidence interval (CI) 0.61 to 0.75) (moderate certainty). No screening test reduced mortality nor incidence by more than six per 1000 screened over 15 years. Sigmoidoscopy had a greater effect in men, for both colorectal cancer incidence (women: RR 0.86; 95% CI 0.81 to 0.92, men: RR 0.75, 95% CI 0.71 to 0.79), and mortality (women: RR 0.85; 95% CI 0.71 to 0.96, men: RR 0.67; 95% CI 0.61 to 0.75) (moderate certainty).

Conclusions In a 15-year perspective, sigmoidoscopy reduces colorectal cancer incidence, while sigmoidoscopy, annual and biennial gFOBT all reduce colorectal cancer mortality. Sigmoidoscopy may reduce colorectal cancer incidence and mortality more in men than in women.

INTRODUCTION

Colorectal cancer is a major global health burden. It is the third most common cancer worldwide, and the second most cause of cancer-related deaths. Colorectal cancers may arise from precancerous lesions known as adenomas. Both adenomas and colorectal cancers can be visualised during sigmoidoscopy and colonoscopy. Even before symptoms occur, colorectal cancers might cause occult bleeding, which can be discovered by faecal blood tests known as guaiac faecal occult blood test (gFOBT) and the more recently developed faecal immunochemical test (FIT). gFOBT, FIT, sigmoidoscopy and colonoscopy are all used as screening methods for colorectal cancer.

Cancer screening are based on two different principles: early detection and prevention. Early detection of cancer enables treatment of cancer before it reaches an incurable state, and may thus reduce cancer mortality. Preventive cancer screening, on the other hand, is to detect and remove precursor lesions to cancers, such as colorectal adenomas. Thus, preventive screening may cause a reduction in both cancer incidence and subsequently mortality.

Prior systematic reviews and meta-analyses evaluating the effectiveness of colorectal cancer screening showed that sigmoidoscopy screening reduces colorectal cancer
Box 1  Linked articles in this BMJ Rapid Recommendation cluster

- Helsingen et al. Colorectal cancer screening with faecal immunochemical test, sigmoidoscopy or colonoscopy: a clinical practice guideline.16
  Summary of the results from the Rapid Recommendation process.
- Jodal et al. Colorectal cancer screening with faecal testing, sigmoidoscopy or colonoscopy: a systematic review and network meta-analysis.
  Systematic review and network meta-analysis of all available trials that assessed colorectal cancer screening.
- Buskermolen et al. Colorectal cancer screening with faecal immunochemical test, sigmoidoscopy or colonoscopy: a microsimulation modelling study.56
  Modelled estimates of benefits and harms of screening after 15 years for different levels of baseline risk of colorectal cancer.
- MAGICApp (http://magicproject.org/190220dist).
  Expanded version of results with multilayered recommendations, evidence summaries and decision aids for use on all devices.

We updated a previously published Cochrane systematic review search.4 The search previously ended in November 2012, while we updated the search until 17 December 2018. A trained medical librarian searched MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials for published randomised controlled trials, with no language restrictions (online supplementary appendix 1). We reviewed reference lists from eligible new trials and related reviews for additional citations.

Study selection
We imported all citations into Covidence (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia). Two reviewers (HCJ and LMH) independently screened titles, abstracts and full texts according to the eligibility criteria. Since this is an update of a previously published systematic review,4 we also screened the full texts of all the studies that were included and excluded at the full-text screening stage by the authors of the original review.

We considered all randomised controlled trials in any language comparing annual or biennial gFOBT or FIT, once-only sigmoidoscopy or once-only colonoscopy, compared with no-screening or to one another, in a healthy population aged 50–79 years, as requested by the panel.16 Outcomes of interest were colorectal cancer incidence and mortality, all-cause mortality, harms (bleeding, perforation, screening-related death and other major and minor complications as reported by trial authors) and burdens (need for further diagnostic workup including colonoscopy, procedure-related pain, psychological impact of a positive test and absence from work to prepare, perform and recover after the screening procedure).

Meta-analyses have shown that it takes at least 5 years from screening until an effect on colorectal cancer mortality or incidence can be observed.17 18 Thus, for analyses of colorectal cancer incidence and mortality, as well as all-cause mortality, we only included trials where follow-up was at least 5 years. Harms and burdens, on the
other hand, are experienced during or soon after the screening procedure, and thus no follow-up restrictions were applied to the analyses of these outcomes.

**Data extraction and rating of evidence**

Two reviewers (HCJ and JCA) independently extracted data using a standardised form. From each eligible trial we collected the following information: study characteristics (study design, description of intervention, study period), description of participants (number, screening adherence, age and sex distribution), length of follow-up and outcomes data (events and numbers of patients included for analyses in each group). Reviewers had a third party available to resolve disagreement, however it was not needed. The authors of studies that did not report all outcomes of interest (e.g., sex subgroups) were contacted.

Two reviewers (HCJ and LMH) independently assessed risk of bias using a modified version of the Cochrane tool, 

assessing the domains random sequence generation (selection bias), allocation concealment (selection bias), blinding (performance and detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other bias. For each domain, the risk of bias was judged as low or high. Reviewers had a third party available to resolve disagreement, however it was not needed. We followed the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach to rate the certainty of evidence of estimates derived from pairwise and network meta-analysis.

We rated direct, indirect and network meta-analysis (NMA) estimates separately. We used the lower certainty rating of the two pairwise estimates contributing as first-order loop for indirect comparisons. To rate the NMA estimates, we evaluated the ratings of the direct and indirect evidence and their coherence. Harms and burdens from screening will only occur in individuals attending screening, and is thus prognostic. Therefore, we evaluated the certainty of the evidence on harms and burdens using GRADE for assessment of evidence about prognosis.

**Data synthesis and analysis**

Intention-to-treat numbers were used for all analyses regarding incidence and mortality. In one of the trials, the ratio of screened to control participant differed in different age groups (1:3 vs 1:5:4), thus the average age in the screened and the control groups differed. Therefore, these two age groups are analysed as two separate trials in this NMA. We performed standard pairwise comparisons of each screening intervention versus no-screening, using a restricted maximum likelihood approach to estimate relative risks (RR) with 95% CIs. Between-study variances were made equal, and correlations were set to 0.5. We examined statistical heterogeneity among studies using the Cochran Q-test (significant if p<0.10) and the between-study variance tau. Furthermore, an NMA applying mixed-treatment models based on a random-effects model in a frequentist framework was performed to compare the different interventions, using the mvmeta program and network graphs package for Stata. We report RRs for direct, indirect and network estimates and associated 95% CIs. We used the node-splitting approach for the assessment of loop inconsistency. We used the mean risk of events in the comparison groups to calculate the absolute effects of treatment in a 15-year perspective. We performed a sensitivity analysis including the 30-year follow-up of one of the gFOBT trials, and another sensitivity analysis excluding the PLCO trial, as this trial included a second sigmoidoscopy screening episode 3 or 5 years after the initial screening. As the length of follow-up varies between the studies, we also performed sensitivity analyses using person-years as the denominator rather than number of participants, and we report HRs for network estimates.

Subgroup differences in incidence and mortality between women and men were analysed using a fixed-effect meta-analysis. To further explore the effect modification for sex, we used a one-stage multilevel meta-regression model including screening intervention, sex and interaction term between sex and intervention as fixed-effect covariates, and study as a random-effect covariate. Furthermore, we fit a meta-analysis using only within-study comparisons, that is, pooling the risk differences (the deft approach). We excluded studies that did not report outcomes separately for men and women.

Harms and burdens as selected by the guideline panel were analysed using meta-analyses for binomial data using the metaprop_one Stata package modelling random effects and exact CIs. Analysis of psychiatric harms was not possible due to differences in reporting, and is therefore only descriptive. All numbers on harms and burdens are presented as proportions of patients who underwent screening, that is, per-protocol numbers.

We used Stata V.15.1 for all data analyses (StataCorp, College Station, Texas, USA). We followed the reporting standards set by Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) and the PRISMA-NMA extension statement for all aspects of the review (online supplementary appendix 2).

**RESULTS**

**Description of included studies**

Our search yielded 8992 potentially relevant records. Combined with the result from the previously published review, a review of reference lists and updates of included trials published after our search was performed, a total of 12 different randomised trials described in 36 articles were included in this review (figure 1, table 1). Five trials included gFOBT screening, two included FIT screening, five included sigmoidoscopy screening and two included colonoscopy screening.

The included trials enrolled a total of 1325618 participants, from Denmark, Italy, the Netherlands, Norway,
All trials had at least one criterion at high risk of bias. For the outcomes of incidence and mortality, only one report was assigned high risk of bias for incomplete data, due to a high withdrawal of consent from the participants. None of the trials were assigned high risk of bias for selective reporting of the outcomes incidence and mortality, but several were so for harms and burdens (figure 2, online supplementary appendix 3).

Effects on incidence and mortality
Eight of the randomised trials had >5 years of follow-up, and were thus included in the analyses of incidence and mortality: four studies on gFOBT screening, and four on sigmoidoscopy screening (figure 3).

Sigmoidoscopy screening slightly reduced colorectal cancer incidence (RR 0.76; 95% CI 0.70 to 0.83) (figure 4) and colorectal cancer mortality (RR 0.74; 95% CI 0.69 to 0.80) (figure 5) compared with no-screening. In a 15-year perspective, this corresponds to a reduction of six (eight to four fewer) colorectal cancer cases per 1000 individuals screened, and a reduction of three (three to two fewer) colorectal cancer deaths per 1000 individuals screened. The certainty of evidence was high (table 2).

gFOBT screening made little or no difference on colorectal cancer incidence compared with no-screening, neither annually nor biennially (annual: RR 0.86; 95% CI 0.72 to 1.03, biennial: RR 0.95; 95% CI 0.87 to 1.04) (figure 4). Colorectal cancer mortality was slightly reduced for both annual and biennial gFOBT screening compared with no-screening (annual: RR 0.69; 95% CI 0.56 to 0.86, biennial: RR 0.88; 95% CI 0.82 to 0.93) (figure 5). In a 15-year perspective, this corresponds to a reduction of one (three fewer to one more) colorectal cancer case and one (two to one fewer) colorectal cancer death per 1000 screened individuals when screened biennially, and a reduction of four (seven fewer to one more) colorectal cancer cases and three (four to one fewer) colorectal cancer deaths per 1000 screened individuals when screened annually. The certainty of evidence for comparisons involving biennial gFOBT screening was high (table 2). The certainty of evidence was downgraded for all comparisons involving annual gFOBT screening due to serious imprecision, as this evidence is based on estimates from only one trial and the rate of events is low (table 2). Direct and indirect estimates are available in online supplementary table 1A.

Sigmoidoscopy screening slightly reduced colorectal cancer incidence (RR 0.80; 95% CI 0.71 to 0.91) (figure 4) and mortality (RR 0.85; 95% CI 0.77 to 0.93) (figure 5) compared with biennial gFOBT. In a 15-year perspective, this corresponds to an absolute reduction of six (eight fewer to three fewer) colorectal cancer cases and a reduction of two (three to one fewer) colorectal cancer deaths per 1000 individuals screened. The certainty of evidence was high (table 2).

Sigmoidoscopy compared with annual gFOBT screening probably had little or no difference on colorectal cancer incidence (RR 0.89; 95% CI 0.73 to 1.09) (figure 4) and mortality (RR 1.07; 95% CI 0.85 to 1.34) (figure 5),
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Design</th>
<th>Screening modality</th>
<th>Study period</th>
<th>Age</th>
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<th>Screening group (n)</th>
<th>Men/women (n)</th>
<th>Adherence (%)</th>
<th>Follow-up (years)</th>
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<td>Atkin</td>
<td>UK (UKFSST)</td>
<td>Volunteers</td>
<td>Sigmoidoscopy, once only</td>
<td>1994–1999</td>
<td>55–64</td>
<td>113178</td>
<td>57254</td>
<td>83 334 / 86 700</td>
<td>71</td>
<td>Median 17.1</td>
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<td>Schoen</td>
<td>US (PLCO)</td>
<td>Volunteers</td>
<td>Sigmoidoscopy, twice</td>
<td>1993–2001</td>
<td>55–74</td>
<td>77444</td>
<td>77443</td>
<td>76 678 / 78 209</td>
<td>83.5</td>
<td>Mortality median 16.8; Incidence median 15.8</td>
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<tr>
<td>Segnan</td>
<td>Italy (SCORE)</td>
<td>Volunteers</td>
<td>Sigmoidoscopy, once only</td>
<td>1995–1999</td>
<td>55–64</td>
<td>17144</td>
<td>17148</td>
<td>17 235 / 17 158</td>
<td>57.8</td>
<td>Mortality median 11.4; Incidence median 10.5</td>
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<td>Norway (NORCAP)</td>
<td>Population-based</td>
<td>Sigmoidoscopy, once only</td>
<td>1999–2001</td>
<td>50–64</td>
<td>79430</td>
<td>20780</td>
<td>49 191 / 49 601</td>
<td>65</td>
<td>Median 14.8</td>
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<td>Mandel</td>
<td>USA (Minnesota)</td>
<td>Volunteers</td>
<td>gFOBT, annually* and biennially†</td>
<td>1975–1992</td>
<td>50–80</td>
<td>15394</td>
<td>Annual: 15 570; Biennial: 15 587</td>
<td>Annual: 74 899 / 80 818; Biennial: 74 444 / 81 434</td>
<td>Annual: 90.2; Biennial: 89.9</td>
<td>Mortality: 30; Incidence: 18</td>
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<td>Denmark (Funen)</td>
<td>Population-based</td>
<td>gFOBT, biennially§</td>
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<td>45–75</td>
<td>30 966</td>
<td>30 967</td>
<td>29 714 / 32 219</td>
<td>66.7</td>
<td>Max 17</td>
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<td>Kewenter</td>
<td>Sweden (Gothenburg)</td>
<td>Population-based</td>
<td>gFOBT, biennially¶</td>
<td>1982–1995</td>
<td>60–64</td>
<td>34 164</td>
<td>34 144</td>
<td>NR</td>
<td>70</td>
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<td>gFOBT, biennially**</td>
<td>2004–2012</td>
<td>60–69</td>
<td>181 085</td>
<td>181 080</td>
<td>179 519 / 180 973</td>
<td>68.8</td>
<td>Median 4.5</td>
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<td>Quintero</td>
<td>Spain (COLONPREV)</td>
<td>Population-based</td>
<td>Colonoscopy, once only*/ FIT (15 µg/g), biennially**</td>
<td>2008–2011</td>
<td>50–69</td>
<td>NA</td>
<td>Colonoscopy: 28 708; FIT: 28 696</td>
<td>26 463 / 30 941</td>
<td>Colonoscopy: 24.6; FIT: 34.2</td>
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<td>Brethauer</td>
<td>Norway, Sweden, Poland, the Netherlands (NORDICC)</td>
<td>Population-based</td>
<td>Colonoscopy, once only</td>
<td>2009–2014</td>
<td>55–64</td>
<td>63 370</td>
<td>31 589</td>
<td>47 298 / 47 135</td>
<td>40.0</td>
<td>0</td>
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<td>Kirkøen</td>
<td>Norway (BCSN)</td>
<td>Population-based</td>
<td>Sigmoidoscopy, once only*/ FIT (15 µg/g), biennially**</td>
<td>2001–2008</td>
<td>50–74</td>
<td>76 50</td>
<td>Sigmoidoscopy: 7 270; FIT: 6 920</td>
<td>10 088 / 11 752</td>
<td>Sigmoidoscopy: 51; FIT: 57</td>
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Table 1 Continued

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<th>Study</th>
<th>Country</th>
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<th>Study period</th>
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<th>Men/women (n)</th>
<th>Adherence (%)</th>
<th>Follow-up (years)</th>
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</table>

*Eleven screening rounds over 15 years, with a 4-year hiatus.
††Six screening rounds over 15 years, with a 3-year hiatus.
‡Three to five screening rounds.
§Nine screening rounds.
¶Two to three screening rounds, interval between rounds maximum 10 years 2 months.

**Ongoing.

BCSN, Bowel Cancer Screening in Norway; COLONPREV, Colorectal Cancer Screening in Average-risk Population; FIT, faecal immunochemical test; gFOBT, guaiac faecal occult blood test; NORCCAP, Norwegian Colorectal Cancer Prevention trial; NORDICC, The Northern-European Initiative on Colorectal Cancer; PLCO, Prostate, Lung, Colorectal and Ovarian cancer screening trial; SCORE, Italian multicentre randomised controlled trial of once-only sigmoidoscopy; UKFSST, UK Flexible Sigmoidoscopy Screening Trial.
screening is based on estimates from only one trial and the rate of events is low (table 2).

Annual compared with biennial gFOBT screening probably has little or no difference on colorectal cancer incidence (RR 0.90; 95% CI 0.75 to 1.08) (figure 4), but probably reduced colorectal cancer mortality slightly (RR 0.79; 95% CI 0.64 to 0.98) (figure 5). In a 15-year perspective, this corresponds to an absolute reduction of three (seven fewer to two more) colorectal cancer cases, and three (four fewer to zero) colorectal cancer deaths per 1000 individuals screened. The certainty of evidence was downgraded due to serious imprecision, as the evidence of the effect of annual gFOBT screening is based on estimates from only one trial and the rate of events is low (table 2). Direct and indirect estimates are available in online supplementary table 1B.

All-cause mortality showed little or no difference among any of the screening interventions (online supplementary figure 1). For direct and indirect estimates, see online supplementary table 1A-B. The heterogeneity of the only loop in the network (annual gFOBT—biennial gFOBT—no-screening) could not be estimated due to insufficient observations, and reports of inconsistency are therefore abundant.

Sensitivity analyses including the 30-year follow-up of one of the gFOBT trials had no significant impact on the results. Sensitivity analysis excluding the PLCO trial on sigmoidoscopy screening (participants screened with sigmoidoscopy twice) had no significant impact of the results. A post hoc sensitivity analysis excluding the UKFSST trial on sigmoidoscopy was also performed, as this trial contributed to statistical heterogeneity in colorectal cancer incidence. This had no significant impact of the effect estimates, however moved the point estimates slightly towards the null. Therefore, this statistical heterogeneity was not considered a serious concern. Sensitivity analyses calculating hazard ratios (HR rather than RR, showed only minor differences, none of which affect the interpretation of the results (online supplementary figures 2-4).

Figure 4 Effect of different screening interventions on colorectal cancer incidence shown as relative risks (RR) with 95% CIs. gFOBT, guaiac faecal occult blood testing.

Sex differences
The subgroup analyses suggested a sex difference for sigmoidoscopy screening (table 3). Pairwise fixed-effect meta-analyses showed heterogeneity between the sexes for both colorectal cancer incidence (women: RR 0.89; 95% CI 0.81 to 0.92, men: RR 0.75; 95% CI 0.71 to 0.79, p=0.001) (figure 6) and mortality (women: RR 0.85; 95% CI 0.71 to 0.96, men: RR 0.67; 95% CI 0.61 to 0.75, p=0.006) (figure 7), but not for all-cause mortality (online supplementary figure 5). The one-stage multilevel model for sex and effect of sigmoidoscopy was statistically significant for interaction (incidence: p=0.001, mortality: p=0.015). Using the deft approach, we obtained similar results (colorectal cancer incidence risk difference 11% (95% CI 3% to 20%); colorectal cancer mortality risk difference 17% (95% CI 1% to 34%). We assessed the credibility of these observed subgroup differences to be moderate (online supplementary table 2), supporting a greater relative effect of sigmoidoscopy in men than in women, for reducing colorectal cancer incidence and mortality.

Harms and burdens
The gFOBT trials reported harms in different ways: three of the trials reported harms summarised after several screening rounds where only those who had attended the previous screening episode were re-invited, while the two other trials reported harms and total number of screening tests where all randomised participants were re-invited even though they chose not to attend the first or previous screening episodes. We therefore pooled the harms and burdens events from gFOBT screening trials data in two groups: 1) reported as a total from two to five screening rounds and 2) reported per performed screening test, assuming that harms and burdens were independent of the screening round. The sigmoidoscopy trials reported harms and burdens from the screening procedure including subsequent workup. Due to the differences in reporting, we were not able to pool estimates across screening interventions. All trials reported the total number of events. None of the trials, regardless of screening intervention, have reported harms and burdens following surveillance procedures.

Figure 5 Effect of different screening interventions on colorectal cancer mortality shown as relative risks (RR) with 95% CIs. FOBT, faecal occult blood testing.

Perforation and bleeding requiring hospitalisation
Eight out of the total of 11 trials reported on bleeding requiring hospitalisation and nine reported on perforations after screening, either from the screening procedure itself or subsequent workup. The risk of bleeding in the sigmoidoscopy trials was 3 (1–6) per 10000 (0.03%; 95% CI 0.01% to 0.06%) screening attenders, while for colonoscopy it was 17 (12–23) per 10000 (0.17%; 95% CI 0.12% to 0.23%) (figure 8). The risk of bleeding in the gFOBT trials were none (zero to one) per 10000 (0.00%; 95% CI 0.00% to
Table 2  Relative and absolute NMA effect estimates for incidence and mortality in a 15-year perspective comparing the different screening interventions and no-screening

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<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Difference (95% CI)</th>
<th>Certainty in effect estimates</th>
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<tr>
<td><strong>No-screening vs sigmoidoscopy screening</strong></td>
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<tr>
<td>Colorectal cancer incidence</td>
<td>RR 0.76 (95% CI 0.70 to 0.83) based on data from 614,397 patients in eight studies. Follow-up 10.5–19.5 years.</td>
<td>26 per 1000</td>
<td>20 per 1000</td>
<td>6 fewer per 1000 (8 fewer to 4 fewer)</td>
<td>High Sigmoidoscopy slightly reduces colorectal cancer incidence.</td>
</tr>
<tr>
<td>Colorectal cancer mortality</td>
<td>RR 0.74 (95% CI 0.69 to 0.80) based on data from 614,428 patients in eight studies. Follow-up 11.4–17.1 years.</td>
<td>10 per 1000</td>
<td>7 per 1000</td>
<td>3 fewer per 1000 (3 fewer to 2 fewer)</td>
<td>High Sigmoidoscopy slightly reduces colorectal cancer mortality.</td>
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<tr>
<td>All-cause mortality</td>
<td>RR 0.99 (95% CI 0.98 to 1.00) based on data from 614,431 patients in eight studies. Follow-up 11.4–19.5 years.</td>
<td>269 per 1000</td>
<td>266 per 1000</td>
<td>3 fewer per 1000 (5 fewer to 0)</td>
<td>High Sigmoidoscopy has little or no difference on all-cause mortality.</td>
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<tr>
<td><strong>No-screening vs biennial gFOBT screening</strong></td>
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<tr>
<td>Colorectal cancer incidence</td>
<td>RR 0.95 (95% CI 0.87 to 1.04) based on data from 598,865 patients in eight studies. Follow-up 10.5–19.5 years.</td>
<td>26 per 1000</td>
<td>25 per 1000</td>
<td>1 fewer per 1000 (3 fewer to 1 more)</td>
<td>High Biennial gFOBT screening has little or no difference on colorectal cancer incidence.</td>
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<td>Colorectal cancer mortality</td>
<td>RR 0.88 (95% CI 0.82 to 0.93) based on data from 598,933 patients in eight studies. Follow-up 11.4–19.5 years.</td>
<td>10 per 1000</td>
<td>9 per 1000</td>
<td>1 fewer per 1000 (2 fewer to 1 fewer)</td>
<td>High Biennial gFOBT screening slightly reduces colorectal cancer mortality.</td>
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<td>All-cause mortality</td>
<td>RR 1.00 (95% CI 0.99 to 1.01) based on data from 598,934 patients in eight studies. Follow-up 11.4–19.5 years.</td>
<td>269 per 1000</td>
<td>269 per 1000</td>
<td>0 fewer per 1000 (3 fewer to 3 more)</td>
<td>High Biennial gFOBT screening has little or no difference on all-cause mortality.</td>
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<td><strong>No-screening vs annual gFOBT screening</strong></td>
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<td>Colorectal cancer incidence</td>
<td>RR 0.86 (95% CI 0.72 to 1.03) based on data from 457,680 patients in eight studies. Follow-up 10.5–19.5 years.</td>
<td>26 per 1000</td>
<td>22 per 1000</td>
<td>4 fewer per 1000 (7 fewer to 1 more)</td>
<td>Moderate Annual gFOBT screening probably has little or no difference on colorectal cancer incidence.</td>
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<td>Colorectal cancer mortality</td>
<td>RR 0.69 (95% CI 0.56 to 0.86) based on data from 457,749 patients in eight studies. Follow-up 11.4–19.5 years.</td>
<td>10 per 1000</td>
<td>7 per 1000</td>
<td>3 fewer per 1000 (4 fewer to 1 fewer)</td>
<td>Moderate Annual gFOBT screening probably slightly reduces colorectal cancer mortality.</td>
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<td>Comparator</td>
<td>Intervention</td>
<td>Difference (95% CI)</td>
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<tr>
<td>All-cause mortality</td>
<td>RR 1.00 (95% CI 0.98 to 1.03) based on data from 457750 patients in eight studies. Follow-up 11.4–19.5 years.</td>
<td>269 per 1000</td>
<td>269 per 1000</td>
<td>0 fewer per 1000 (5 fewer to 8 more)</td>
</tr>
<tr>
<td>Biennial gFOBT vs sigmoidoscopy screening</td>
<td>Colorectal cancer incidence</td>
<td>RR 0.80 (95% CI 0.71 to 0.91) based on data from 328966 patients in eight studies. Follow-up 10.5–19.5 years.</td>
<td>28 per 1000</td>
<td>22 per 1000</td>
</tr>
<tr>
<td></td>
<td>Colorectal cancer mortality</td>
<td>RR 0.85 (95% CI 0.77 to 0.93) based on data from 329003 patients in eight studies. Follow-up 11.4–19.5 years.</td>
<td>12 per 1000</td>
<td>10 per 1000</td>
</tr>
<tr>
<td></td>
<td>All-cause mortality</td>
<td>RR 0.99 (95% CI 0.97 to 1.01) based on data from 329005 patients in eight studies. Follow-up 11.4–19.5 years.</td>
<td>438 per 1000</td>
<td>434 per 1000</td>
</tr>
<tr>
<td>Annual gFOBT vs sigmoidoscopy screening</td>
<td>Colorectal cancer incidence</td>
<td>RR 0.89 (95% CI 0.73 to 1.09) based on data from 187781 patients in five studies. Follow-up 10.5–18.0 years.</td>
<td>27 per 1000</td>
<td>24 per 1000</td>
</tr>
<tr>
<td></td>
<td>Colorectal cancer mortality</td>
<td>RR 1.07 (95% CI 0.85 to 1.34) based on data from 187819 patients in five studies. Follow-up 11.4–18.0 years.</td>
<td>8 per 1000</td>
<td>9 per 1000</td>
</tr>
<tr>
<td></td>
<td>All-cause mortality</td>
<td>RR 0.99 (95% CI 0.96 to 1.02) based on data from 187821 patients in five studies. Follow-up 11.4–18.0 years.</td>
<td>336 per 1000</td>
<td>333 per 1000</td>
</tr>
<tr>
<td>Biennial vs annual gFOBT screening</td>
<td>Colorectal cancer incidence</td>
<td>RR 0.90 (95% CI 0.75 to 1.08) based on data from 172249 patients in four studies. Follow-up 15.5–19.5 years.</td>
<td>28 per 1000</td>
<td>25 per 1000</td>
</tr>
</tbody>
</table>
0.01%) screening attenders in the trials reporting harms per two to five screening rounds, while it in the trial reporting harms per screening test was one (zero to one) per 10,000 screening tests (0.01%; 95% CI 0.00% to 0.01%) (figure 8). The risk of bleeding in the FIT trial was eight (3–14) per 10,000 (0.08%; 95% CI 0.03% to 0.14%) screening tests (figure 8). The risk of colorectal perforation in the sigmoidoscopy trials was three (one to four) per 10,000 (0.03%; 95% CI 0.01% to 0.04%) screening attenders, while for colonoscopy it was one (zero to three) per 10,000 (0.01%; 95% CI 0.00% to 0.03%) (figure 9). The risk of perforation in the gFOBT trials were one (one to two) per 10,000 (0.01%; 95% CI 0.01% to 0.02%) screening attenders in the trials reporting harms per two to five screening rounds, while it in the trial reporting harms per screening test was zero (zero to one) per 10,000 screening tests (0.00%; 95% CI 0.00% to 0.01%) (figure 9). The risk of perforation in the FIT trial was zero (zero to three) per 10,000 (0.00%; 95% CI 0.00% to 0.03%) screening tests (figure 9). The certainty of evidence for all screening interventions was downgraded to moderate due to risk of bias (online supplementary table 3A-B). The certainty of evidence for the gFOBT trials and FIT trial was downgraded further due to indirectness, with differences in the number of screening rounds (online supplementary table 3A and C).

Other physical harms and burdens
The mean risk of needing further workup due to findings at screening varied: 13% (95% CI 5% to 26%) in sigmoidoscopy trials, 7% (95% CI 7% to 8%) per screening test in the FIT trial, 5% (95% CI 5% to 5%) per screening test in gFOBT trials and 6% (95% CI 4% to 9%) per two to five gFOBT screening rounds (table 4 and supplementary table 3A-B). The confidence in the estimate of effect was downgraded to moderate certainty due to indirectness, resulting from differences in the number of screening rounds (gFOBT), and the differences in definitions of a positive screening test (online supplementary table 3A-B).

Surveillance of individuals with high-risk adenomas is recommended. The trials did not report the findings of high-risk adenomas consistently, however, we referred to reported adenoma characteristics and the European Society of Gastrointestinal Endoscopy guidelines to estimate surveillance need. We approximated those that will require surveillance as 1% (95% CI 1% to 2%) of screening attendees per two to five rounds with gFOBT screening, 2% (95% CI 2% to 3%) of screening attendees per FIT performed, 4% (95% CI 3% to 5%) of sigmoidoscopy screening attendees and 10% (95% CI 10% to 11%) of colonoscopy screening attendees (table 4 and supplementary table 3A-B). The certainty of evidence for all screening interventions was downgraded to moderate due to differences in the number of screening rounds. The certainty of evidence from the sigmoidoscopy trials were further downgraded to low, due to failure to report how information was obtained (online supplementary table 3A-B).

### Table 2

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Difference (95% CI)</th>
<th>Certainty in effect estimates</th>
<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal cancer mortality</td>
<td>RR 0.79 (95% CI 0.64 to 0.98) based on data from 172,324 patients in four studies. Follow-up 15.5–19.5 years.</td>
<td>Comparator Intervention</td>
<td>12 per 1000 9 per 1000</td>
<td>3 fewer per 1000 (4 fewer to 0)</td>
<td>Moderate (serious imprecision)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>RR 1.00 (95% CI 0.97 to 1.03) based on data from 172,324 patients in four studies. Follow-up 15.5–19.5 years.</td>
<td>438 per 1000 438 per 1000</td>
<td>0 fewer per 1000 (13 fewer to 13 more)</td>
<td>Moderate (serious imprecision)</td>
<td>Annual gFOBT screening probably has little or no difference on all-cause mortality compared with biennial gFOBT screening.</td>
</tr>
</tbody>
</table>

CI, confidence interval; gFOBT, guaiac faecal occult blood test; NMA, network meta-analysis; RR, relative risk.

### Other patient-important harms and burdens
All four sigmoidoscopy screening trials published reports on procedure-related pain, where 16% (95% CI 10% to 22%) reported moderate-to-severe pain during the procedure (online supplementary figure 6). Only one of the colonoscopy trials published a report on pain related to the procedure, where 21% (95% CI 19% to 22%) reported severe-to-moderate pain during the procedure, although no relation to sedation or air/CO2 insufflation was reported (online supplementary figure 6). The certainty of evidence of pain in sigmoidoscopy was downgraded to low certainty, due to probable selection bias in those who answered the questionnaires, as well as inconsistency between the trials (online supplementary table 3A). The certainty of evidence of pain in colonoscopy was high (online supplementary table 3B).
Table 3  Sex difference for sigmoidoscopy screening vs no-screening: relative and absolute NMA effect estimates for incidence and mortality in a 15-year perspective

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Difference in effect estimates</th>
<th>Certainty in effect estimates</th>
<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal cancer incidence, women</td>
<td>RR 0.86 (95% CI 0.79 to 0.93) based on data from 231,561 patients in four studies. Follow-up 10.5–17.1 years.</td>
<td>Comparator: 20 per 1000</td>
<td>Intervention: 17 per 1000</td>
<td>Difference (95% CI): 3 fewer per 1000 (4 fewer to 1 fewer)</td>
<td>High</td>
</tr>
<tr>
<td>Colorectal cancer incidence, men</td>
<td>RR 0.74 (95% CI 0.69 to 0.80) based on data from 226,424 patients in four studies. Follow-up 10.5–17.1 years.</td>
<td>Comparator: 29 per 1000</td>
<td>Intervention: 21 per 1000</td>
<td>Difference (95% CI): 8 fewer per 1000 (9 fewer to 6 fewer)</td>
<td>High</td>
</tr>
<tr>
<td>Colorectal cancer mortality, women</td>
<td>RR 0.86 (95% CI 0.73 to 1.01) based on data from 253,466 patients in four studies. Follow-up 14.8–19.5 years.</td>
<td>Comparator: 8 per 1000</td>
<td>Intervention: 7 per 1000</td>
<td>Difference (95% CI): 1 fewer per 1000 (2 fewer to 0)</td>
<td>High</td>
</tr>
<tr>
<td>Colorectal cancer mortality, men</td>
<td>RR 0.67 (95% CI 0.61 to 0.75) based on data from 245,245 patients in four studies. Follow-up 14.8–19.5 years.</td>
<td>Comparator: 12 per 1000</td>
<td>Intervention: 8 per 1000</td>
<td>Difference (95% CI): 4 fewer per 1000 (5 fewer to 3 fewer)</td>
<td>High</td>
</tr>
<tr>
<td>All-cause mortality, women</td>
<td>RR 0.99 (95% CI 0.95 to 1.03) based on data from 136,301 patients in two studies. Follow-up 14.8–17.1 years.</td>
<td>Comparator: 168 per 1000</td>
<td>Intervention: 166 per 1000</td>
<td>Difference (95% CI): 2 fewer per 1000 (8 fewer to 5 more)</td>
<td>High</td>
</tr>
<tr>
<td>All-cause mortality, men</td>
<td>RR 0.99 (95% CI 0.95 to 1.03) based on data from 132,525 patients in two studies. Follow-up 14.8–17.1 years.</td>
<td>Comparator: 250 per 1000</td>
<td>Intervention: 248 per 1000</td>
<td>Difference (95% CI): 2 fewer per 1000 (12 fewer to 8 more)</td>
<td>High</td>
</tr>
</tbody>
</table>

CI, confidence interval; NMA, network meta-analysis; RR, relative risk.

We identified four reports on the psychological impact of a positive screening test, two from sigmoidoscopy, and one from each gFOBT and FIT. One report on sigmoidoscopy screening used the short version of the Spielberger State-Trait Anxiety Inventory (STAI) to ask participants if they were worried about bowel cancer before and 3 months after sigmoidoscopy screening, and reported no significant psychological harms associated with positive screening results. One report on gFOBT screening measured anxiety using the original STAI, and reported that anxiety scores in a sample of 100 screening test false-positive patients were highest after the notification of a positive test, fell after a negative workup colonoscopy, and subsequently remained low. There were no data on the individuals who had a positive test, but did not attend the workup colonoscopy.

Another report on gFOBT screening measured worry at different time points during the screening process by using a questionnaire where the screening attenders reported their worry on a five-point scale ranging from ‘not at all’ to ‘extremely’. Sixty per cent reported to be extremely or very worried after receiving a positive gFOBT screening test result, an increase of 44 percentage points from when first receiving the invitation to screening. Concurrently, 15% reported negative effects on daily life ‘to a great deal’ when receiving the positive test result, compared with 5% when receiving the invitation to screening.

The most recent study, on sigmoidoscopy and FIT screening, reported no significant increase in anxiety and depression on the Hospital Anxiety and Depression Scale after a positive result in either sigmoidoscopy or FIT screening.
FIGURE 6  Sex differences on colorectal cancer incidence with sigmoidoscopy screening compared with no-screening. RR, relative risk.

FIGURE 7  Sex differences on colorectal cancer mortality with sigmoidoscopy screening compared with no-screening. RR, relative risk.

Discussion
Statement of principal findings
Screening with gFOBT or sigmoidoscopy slightly reduced colorectal cancer mortality in a 15-year perspective, based on high certainty evidence. Neither gFOBT nor sigmoidoscopy screening, however, had any effect on all-cause mortality. The absolute effects will depend on the baseline risk of the screening attenders, thus in the trials the absolute effect was one less colorectal cancer death per 1000 (0.1%) individuals screened with gFOBT biennially, and three fewer colorectal cancer deaths per 1000 (0.3%) individuals screened with gFOBT annually or once-only sigmoidoscopy.

Sigmoidoscopy screening also slightly reduced colorectal cancer incidence, based on high certainty evidence, where the absolute effect observed in the trials was six fewer colorectal cancer cases per 1000 (0.6%) individuals screened in a 15-year perspective. We found no significant difference between annual gFOBT and sigmoidoscopy screening on colorectal cancer incidence, but the certainty of evidence is moderate, as annual gFOBT has been evaluated in only one trial where rate of events is low. Biennial gFOBT had no effect on colorectal cancer incidence.

Compared with annual or biennial gFOBT, or no-screening, sigmoidoscopy is the most effective method for decreasing both colorectal cancer mortality and incidence in a 15-year perspective. However, sigmoidoscopy has a greater relative effect in men than in women: five fewer colorectal cancer cases and three fewer colorectal cancer deaths per 1000 (0.5% and 0.3%) screened individuals in men compared with in women. The reasons behind the greater relative effect in men than in

FIT, neither before or after the workup colonoscopy, regardless of colonoscopy result.

We also searched for data on absence for work to prepare for, attend and recover after the screening, as decided a priori by the guideline panel, but no data were identified in the included randomised trials.
Figure 8  Risk of bleeding requiring hospitalisation after screening and workup procedure shown as percentage of screening attenders with 95% CIs, unless otherwise mentioned. gFOBT, guaiac faecal occult blood test; FIT, faecal immunochemical test.

<table>
<thead>
<tr>
<th>Screening Procedure</th>
<th>Risk (95% CI)</th>
<th>Weight %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sigmoidoscopy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atkin</td>
<td>0.05 (0.03 to 0.06)</td>
<td>46.11</td>
</tr>
<tr>
<td>Segnan</td>
<td>0.01 (0.00 to 0.03)</td>
<td>24.90</td>
</tr>
<tr>
<td>Hoff</td>
<td>0.03 (0.01 to 0.08)</td>
<td>28.99</td>
</tr>
<tr>
<td>Subtotal</td>
<td>0.03 (0.01 to 0.06)</td>
<td>100.00</td>
</tr>
<tr>
<td>gFOBT per 2-5 screening rounds</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scholefield</td>
<td>0.00 (0.00 to 0.01)</td>
<td>65.19</td>
</tr>
<tr>
<td>Kewenter</td>
<td>0.00 (0.00 to 0.02)</td>
<td>34.81</td>
</tr>
<tr>
<td>Subtotal</td>
<td>0.00 (0.00 to 0.01)</td>
<td>100.00</td>
</tr>
<tr>
<td>gFOBT per screening test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mandel</td>
<td>0.01 (0.00 to 0.01)</td>
<td>100.00</td>
</tr>
<tr>
<td>FIT per screening test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quintero</td>
<td>0.08 (0.03 to 0.14)</td>
<td>100.00</td>
</tr>
<tr>
<td>Colonoscopy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quintero</td>
<td>0.24 (0.13 to 0.38)</td>
<td>28.69</td>
</tr>
<tr>
<td>Brethauer</td>
<td>0.14 (0.09 to 0.22)</td>
<td>71.31</td>
</tr>
<tr>
<td>Subtotal</td>
<td>0.17 (0.12 to 0.23)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Figure 9  Risk of colorectal perforation after screening and workup procedure shown as percentage of screening attenders with 95% CIs, unless otherwise mentioned. gFOBT, guaiac faecal occult blood test; FIT, faecal immunochemical test.
Table 4  Harms and burdens

<table>
<thead>
<tr>
<th>Screening method</th>
<th>Study</th>
<th>Met to screening</th>
<th>Workup procedure</th>
<th>Surveillance endoscopy*</th>
<th>Death &lt;30 days of procedure†</th>
<th>Death &lt;30 days of surgery</th>
<th>Major complications‡†</th>
<th>Miscellaneous§†</th>
<th>Pain¶</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sigmoidoscopy</td>
<td>Atkin41 46</td>
<td>40674</td>
<td>2131</td>
<td>1745</td>
<td>7</td>
<td>4</td>
<td>3</td>
<td>192</td>
<td>7947</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.02%</td>
<td>0.01%</td>
<td>0.01%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Schoen48 59</td>
<td>64658</td>
<td>15150</td>
<td>2153**</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>232</td>
</tr>
<tr>
<td></td>
<td>Segnan43</td>
<td>9911</td>
<td>832</td>
<td>395††</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>1833</td>
</tr>
<tr>
<td></td>
<td>Hof44 71</td>
<td>12960</td>
<td>2839</td>
<td>545**</td>
<td>NR</td>
<td>0</td>
<td>2</td>
<td>NR</td>
<td>283</td>
</tr>
<tr>
<td>Mean</td>
<td>(95% CI)</td>
<td></td>
<td></td>
<td></td>
<td>13%</td>
<td>4%</td>
<td>0.02%</td>
<td>0.01%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(5% to 26%)</td>
<td>(3% to 5%)</td>
<td>(0.01% to 0.04%)</td>
<td>(0.00% to 0.02%)</td>
<td></td>
</tr>
<tr>
<td>Mean (gFOBT per 2–5 screening rounds)</td>
<td>Scholefield 34 35</td>
<td>44838</td>
<td>2212</td>
<td>710</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>1 NA</td>
<td></td>
</tr>
<tr>
<td>Mean (gFOBT per screening test)</td>
<td>Mandel38</td>
<td>202116§§</td>
<td>17008</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NA</td>
</tr>
<tr>
<td>Mean (FIT per screening test)</td>
<td>Quintero39</td>
<td>10611</td>
<td>767</td>
<td>252**</td>
<td>NR</td>
<td>NR</td>
<td>2</td>
<td>NR</td>
<td>NA</td>
</tr>
</tbody>
</table>

Continued...
Screening method | Study | Met to screening | Workup procedure | Surveillance endoscopy* | Death <30 days of procedure† | Death <30 days of surgery | Major complications‡‡ | Miscellaneous§§ | Pain¶¶
---|---|---|---|---|---|---|---|---|---
Colonoscopy | Quintero72 | 5059 | NA | 493** | NR | NR | 11 | NR | NR
Brethauer70 | 12574 | NA | 1304†† | 0 | NR | 0 | 51 | 749
Mean (95% CI) | 10% | 0.00% | 0.02% | 0.41% | 21%

All numbers are number of screening participants, and percentages are calculated as percentage of participants met to screening, unless otherwise stated.

*According to ESGE guidelines, unless otherwise stated.
†Within 30 days of screening or diagnostic workup.
‡‡Bleeding, perforation and death excluded. Sigmoidoscopy: two myocardial infarctions, one pulmonary embolus, one burnt serosa syndrome and one fever of unknown cause. FIT: two individuals with hypotension or bradycardia. Colonoscopy: 10 individuals with hypotension or bradycardia, one desaturation.
§§Includes snare entrapment, vasovagal reactions, glutaraldehyde colitis and other events not requiring hospitalisation.
¶¶Per cent of those responded who reported moderate to severe pain during the procedure.
**Advanced adenoma.
††High-risk adenomas: advanced adenoma, or ≥3 adenomas.
***Adenomas >10 mm.
§§§Total number of screening tests performed (not number of individuals).
¶¶¶High-risk adenomas, 27 with low-risk distal adenomas with proximal polyps not sent to histology and 11 colorectal cancers endoscopically treated.
CI, confidence interval; ESGE, European Society of Gastrointestinal Endoscopy; FIT, faecal immunochemical test; gFOBT, guaiac faecal occult blood test; NA, not applicable; NR, not reported.
and do not report how data on harms and burdens were obtained, observational trials might provide further information on these outcomes. In addition, the absolute effects calculations are based on the mean risk of colorectal cancer incidence and mortality in the control groups of the different trials, which varies between the different trials. This might be due to the different calendar times at which the trials were performed, in addition to differences between the control groups of the different trials. All absolute risk reduction estimates assume that all individuals have mean risk. This is a strong assumption in the individual perspective, but represent the mean absolute effect in our target population of healthy individuals aged 50–79 years.

Findings in relation to other studies

Prior reviews show that sigmoidoscopy screening reduces colorectal cancer incidence, while both sigmoidoscopy and gFOBT reduce colorectal cancer mortality.4–7 This is the first review that includes follow-up from three of the major sigmoidoscopy trials exceeding 14.8 years,4–10 and we show that there is sustained effect of once-only sigmoidoscopy screening even 14.8 years after screening. This is also the first review that performs a network meta-analysis comparing the different screening test against one another with this long follow-up.

In addition, this is the first meta-analysis assessing the subgroup effect of sigmoidoscopy screening by sex with data from all four major sigmoidoscopy trials after 14.8 years of follow-up, demonstrating that there is a greater relative effect of reduction of both colorectal cancer incidence and mortality in men than in women.

Implications for clinicians and policy makers

Our review shows that sigmoidoscopy screening slightly reduces colorectal cancer incidence even 15 years after a once-only screening. Sigmoidoscopy, annual and biennial gFOBT all slightly reduce colorectal cancer mortality in the same time perspective. Sigmoidoscopy is likely to be more effective in men than in women both for colorectal cancer incidence and mortality. None of the screening interventions show effect on all-cause mortality. These results show that the relative effect of once-only sigmoidoscopy screening is maintained as long as 15 years after screening. Most guidelines today recommend rescreening 5–10 years after initial screening. This may now be safely extended to 15 years.

Harms and burdens were reported with large variation. The frequency of testing (annual or biennial for faecal blood tests) is important in the evaluation of possible harms and need of surveillance, as more frequent testing is likely to increase the rate of harms. The need for future surveillance reported in this study must be viewed critically for implications in contemporary practice, in particularly for gFOBT, where studies used sigmoidoscopy and barium contrast enemas, instead of colonoscopy, as the primary workup strategy after a positive screening test.

All trials on colorectal cancer screening mainly have participants of European origin, and there is paucity of data for other ethnicities.

Unfortunately, there are no reports on long-term effects on colorectal cancer incidence and mortality of FIT and colonoscopy. Colonoscopy and FIT both have higher sensitivity than gFOBT and colonoscopy, and are therefore likely to have a larger effect on incidence and mortality.55 However, these benefits must be weighed against increased harms and burdens such as more individuals in need of colonoscopy surveillance.

This review supported the development of an evidence-based clinical practice guideline, as reflected in the accompanying Rapid recommendations guideline.16

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Contributors HCJ drafted the protocol and the first draft of the review. HCJ, LMH and JCA performed data extraction. HCJ and LMH assessed risk of bias of included studies. HCJ and LE performed the statistical analyses. PV and LE supervised the study. HCJ, LMH, JCA, LL, PV and LE participated in writing the manuscript, interpretation of results and approval of the final version of the review. Corresponding author HCJ is the guarantor.

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Competing interests All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure and declare: no support from any organisation for the submitted work. POV is a member of the GRADE working group. JCA routinely see individuals eligible for colorectal cancer screening and is a co-writer on the American College of Gastroenterologists 2008 colorectal cancer screening guidelines. He is a member of the AGC, AGA, ASGE and the US Multi-Society Task Force for Colorectal Cancer Screening.

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Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No additional data available.

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