Novità dalla ricerca. Nuove valutazioni sull'efficacia della sigmoidoscopia:

analisi per età e sesso, effetto sulla mortalità generale

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Effectiveness of flexible sigmoidoscopy screening in men and women and different age groups: pooled analysis of randomised trials

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LETTERS

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OBSERVATION: BRIEF RESEARCH REPORT

Reanalysis of All-Cause Mortality in the U.S. Preventive Services Task Force 2016 Evidence Report on Colorectal Cancer Screening

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Effectiveness of flexible sigmoidoscopy screening in men and women and different age groups: pooled analysis of randomised trials

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In four large scale randomised trials,

flexible sigmoidoscopy screening has been shown to reduce both incidence and mortality from colorectal cancer, and one meta-analysis has shown consistent effects across the trials, with similar length of follow-up

The effect of flexible sigmoidoscopy screening in younger versus older individuals and in women versus men is currently unknown

To investigate the impact of sex and age on the effectiveness of flexible sigmoidoscopy screening, a collaboration between the investigators of three of the four large scale randomised trials was launched.

Methods

Examined data from three trials:

the US Prostate, Lung, Colorectal and Ovarian cancer screening trial (PLCO),

the Italian Screening for COlonREctum trial (SCORE),

and the NORwegian Colorectal CAncer Prevention trial (NORCCAP).

Invited the investigators of the UK Flexi Scope trial to participate, but declined.

Data from the Telemark Polyp Study, were not included owing to the trial's small size (799 enrolled individuals).

Methods

Accordingly, data from 60% of control participants and 67% of screening participants of all flexible sigmoidoscopy screening trials were available for analyses.

Table 1 | Characteristics of included studies investigating the effectiveness of flexible sigmoidoscopy to screen for colorectal cancer

Study	Population	Intervention	Period of inclusion	Age group (years)	No of screened participants/controls	No of men/ women	Follow-up (years, median)*
PLCO†	Volunteers at 10 screening centres in the USA	Flexible sigmoidoscopy at inclusion and after 3-5 years	1993-2001	55-74	77 431/77 433	76 670/78 194	11.9, 12.1
SCORE	Volunteers in six regions in Italy	Once only flexible sigmoidoscopy	1995-99	55-64	17 136/17 136	17 221/17 051	10.5, 11.4
NORCCAP	Identified through Population Registry in two regions in Norway	Once only flexible sigmoidoscopy. 50% also provided FIT	1999-2001	50-64	20 572/78 220	49 191/49 601	10.9

PLCO=Prostate, Lung, Colorectal and Ovarian cancer screening trial; SCORE=Screening Colon Rectum trial; NORCCAP=Norwegian Colorectal Cancer Prevention trial; FIT=faecal immunochemical test.
*Median follow-up on incidence and mortality, respectively, when separate.
†Numbers differ from original publication owing to withdrawal of consents and update of the study database.

Aggregated analyses

The investigators of the three trials provided aggregated data stratified by sex and age (in 5 year age groups), the number of individuals at risk, and the number of events (colorectal cancer cases and deaths) for each year of follow-up.

From the three groups, data on compliance with screening, follow-up colonoscopy, quality of bowel cleansing, and insertion depth during screening were collected

The distal colon was defined as the rectum and sigmoid, while the proximal colon was defined as the colon proximal to the sigmoid descending junction.

Results

Altogether, the three trials comprised 115 139 individuals randomised to screening and 172 789 individuals randomised to usual care; 144 846 (50.3%) were women and 143 082 (49.7%) were men.

Results

Incidence of colorectal cancer

A total of 1494 individuals in the screening group were diagnosed with colorectal cancer, compared with 2663 in the control group. This corresponds to a risk reduction of 21% (relative risk 0.79; 95% confidence interval 0.74 to 0.84), with no heterogeneity between the trials (I2=0%, P=0.67;

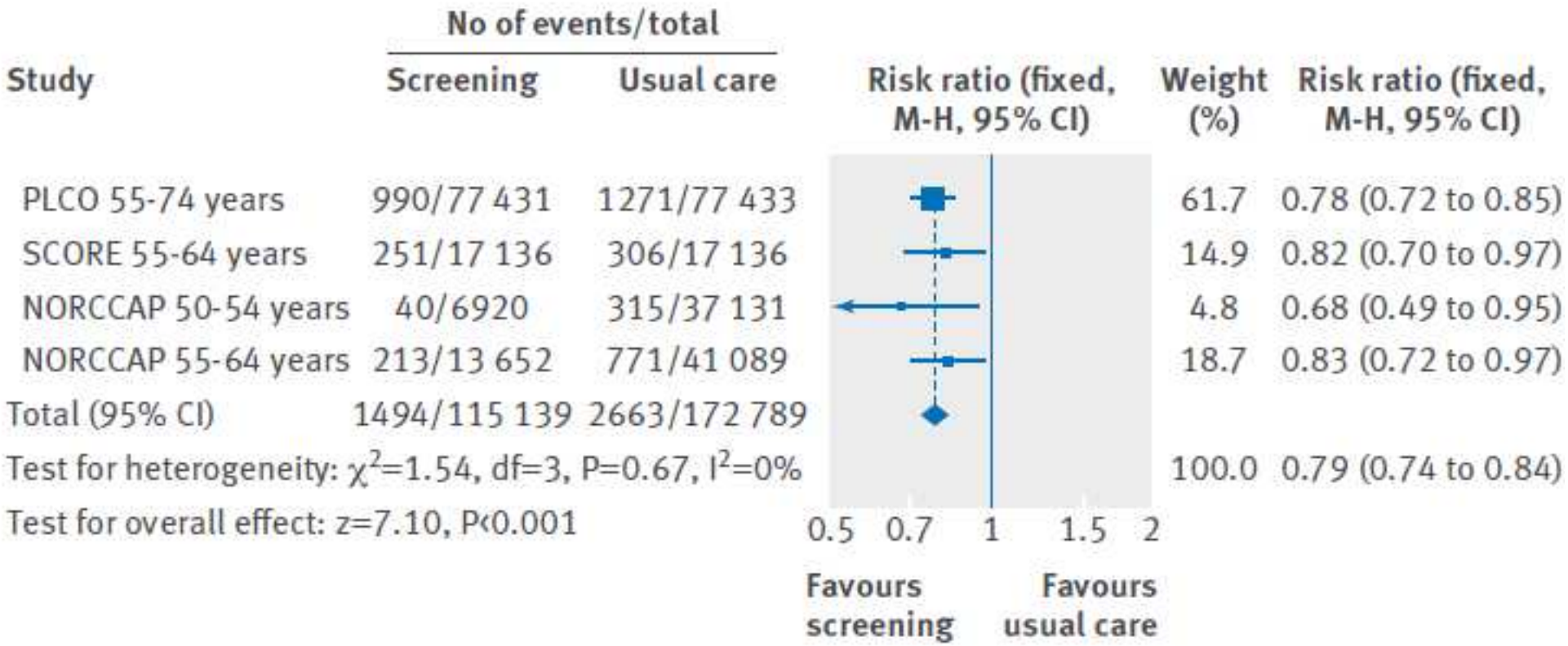

Fig 1 | Colorectal cancer incidence in the three trials comparing flexible sigmoidoscopy screening with usual care. Data from the NORCCAP trial are presented as two separate trials because the control: screening participants ratio was higher in the 50-54 year age group (5.4:1) than the 55-64 year age group (3:1). M-H=Mantel-Haenszel fixed effect model

Table 2 | Colorectal cancer incidence and mortality in pooled analysis. Results correspond to overall analysis (50-74 years), and age (≥60 years *v* <60 years) and sex stratified pairwise comparisons (screening group *v* control group) using Mantel-Haenszel fixed effect model. P values refer to the interaction terms between age and sex from a metaregression model including age, sex, interaction term, and indicator variables for each trial (see methods section)

	Screening group *v* control group			
	Colorectal cancer incidence (relative risk (95% CI))	P for interaction	Colorectal cancer mortality (relative risk (95% CI))	P for interaction
Colon and rectum				
Both sexes*	0.79 (0.74 to 0.84)		0.73 (0.64 to 0.83)	
Men†	0.76 (0.70 to 0.83)		0.67 (0.57 to 0.80)	
≥60 years‡	0.76 (0.68 to 0.84)		0.67 (0.55 to 0.82)	
<60 years§	0.76 (0.65 to 0.88)	0.12	0.67 (0.49 to 0.91)	0.55
Women¶	0.83 (0.75 to 0.92)		0.82 (0.67 to 1.00)	
≥60 years‡	0.90 (0.80 to 1.02)		0.88 (0.69 to 1.12)	
<60 years§	0.71 (0.59 to 0.84)		0.73 (0.53 to 1.02)	

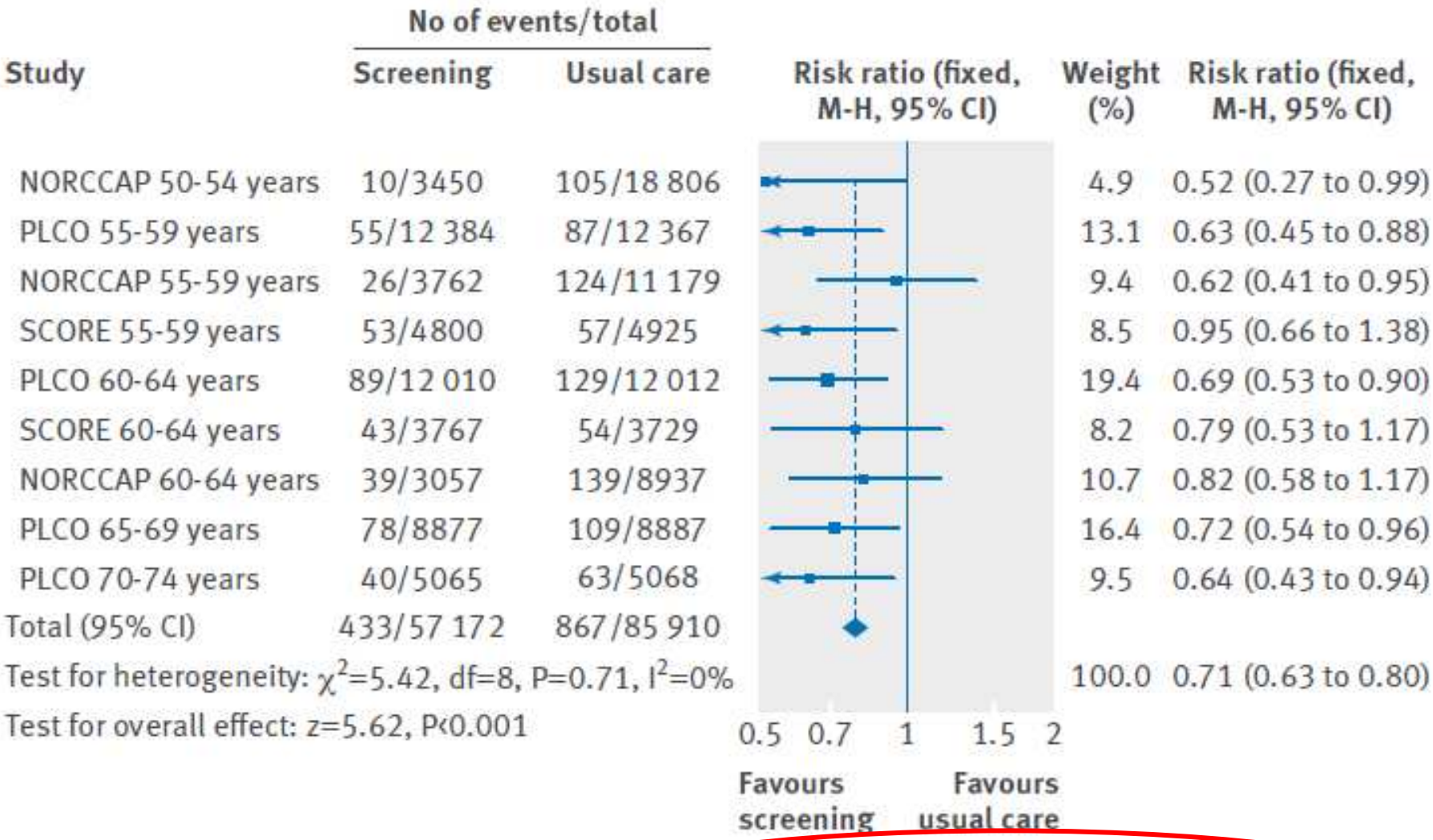

Fig 2 | Colorectal cancer incidence in the distal colon (rectum and sigmoid colon) in men, based on data from the three trials comparing flexible sigmoidoscopy screening with usual care. M-H=Mantel-Haenszel fixed effect model

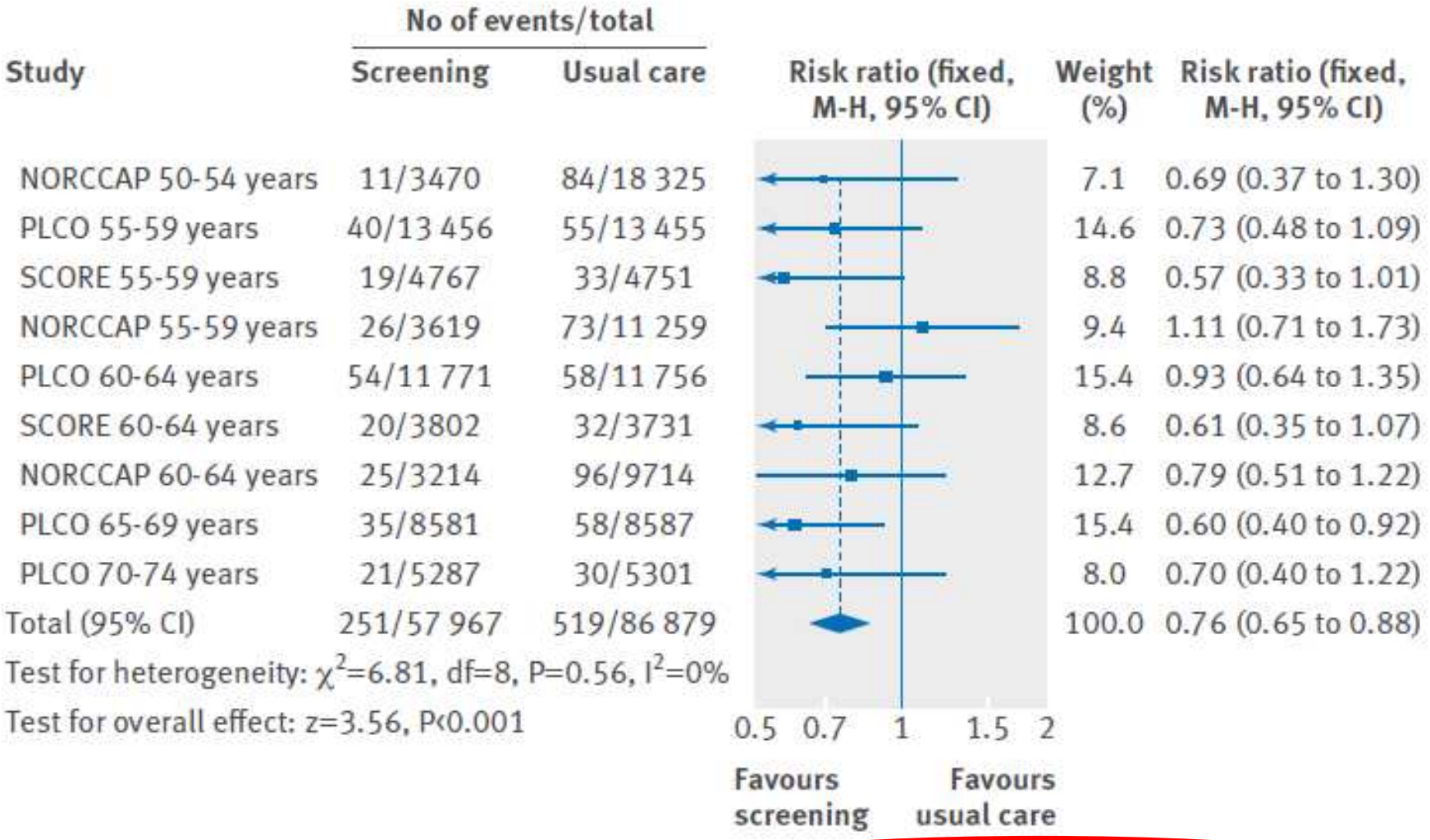

Fig 3 | Colorectal cancer incidence in the distal colon (rectum and sigmoid colon) in women, based on data from the three trials comparing flexible sigmoidoscopy screening with usual care. M-H=Mantel-Haenszel fixed effect model

	Screening group *v* control group			
	Colorectal cancer incidence (relative risk (95% CI))	P for interaction	Colorectal cancer mortality (relative risk (95% CI))	P for interaction
Distal colon				
Both sexes*	0.73 (0.66 to 0.80)		0.60 (0.49 to 0.72)	
Men†	0.71 (0.63 to 0.80)		0.51 (0.40 to 0.65)	
≥60 years‡	0.72 (0.62 to 0.84)		0.48 (0.35 to 0.64)	
<60 years§	0.69 (0.56 to 0.85)	0.66	0.58 (0.38 to 0.90)	0.39
Women¶	0.76 (0.65 to 0.88)		0.79 (0.58 to 1.09)	
≥60 years‡	0.74 (0.61 to 0.91)		0.85 (0.57 to 1.27)	
<60 years§	0.78 (0.61 to 0.99)		0.71 (0.42 to 1.18)	

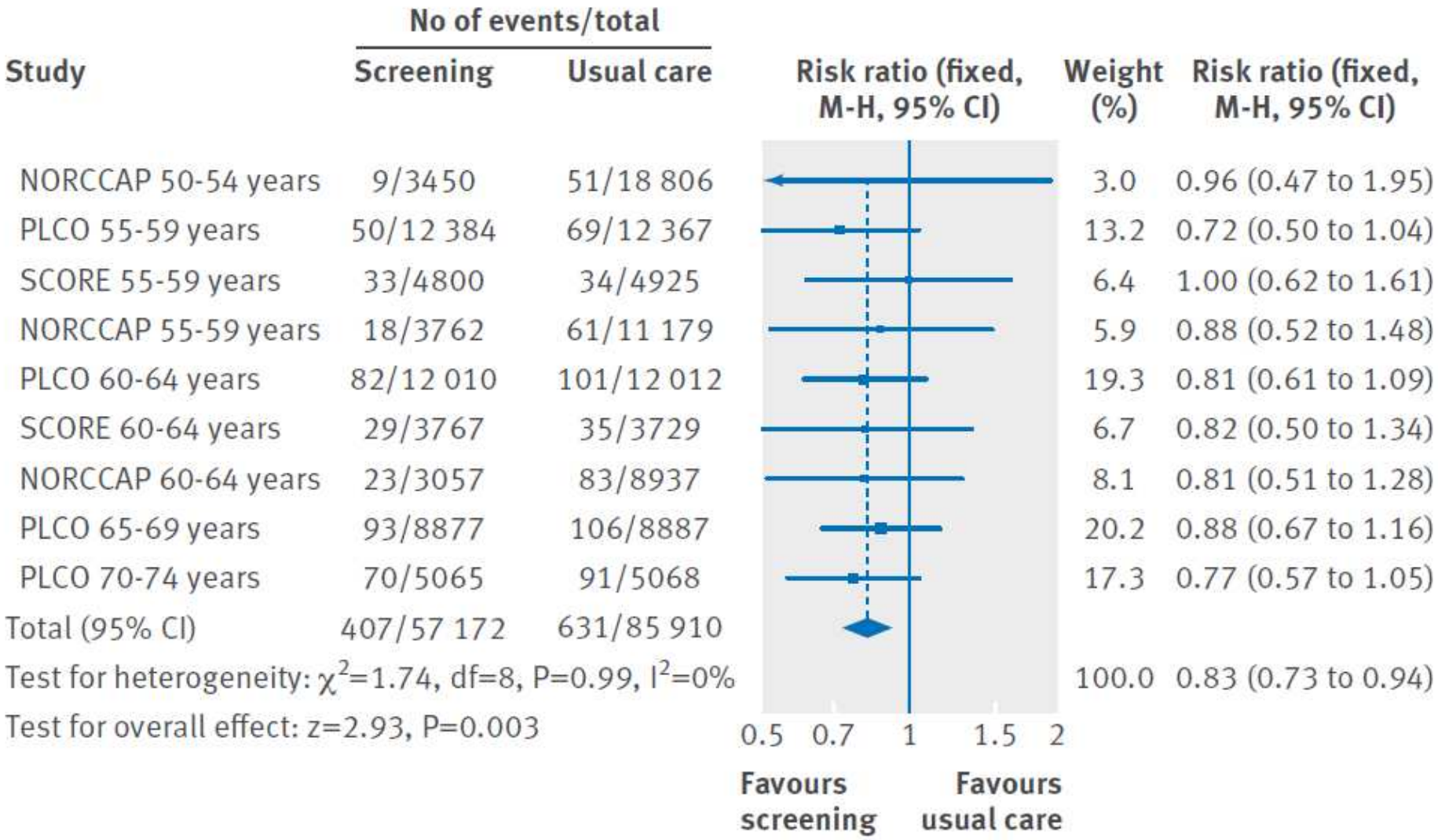

Fig 4 | Colorectal cancer incidence in the colon proximal to the sigmoid colon in men, based on data from the three trials comparing flexible sigmoidoscopy screening with usual care. M-H=Mantel-Haenszel fixed effect model

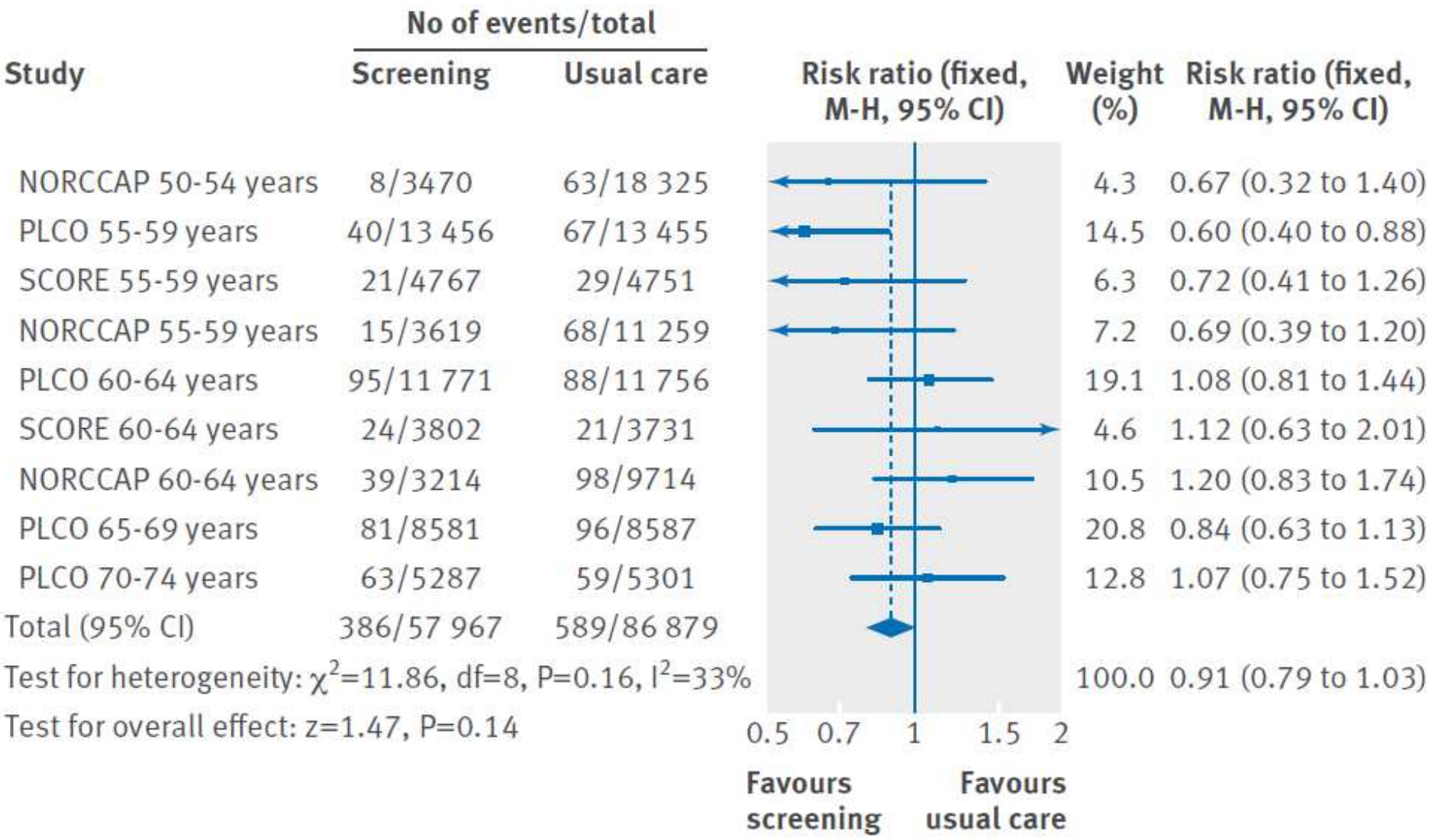

Fig 5 | Colorectal cancer incidence in the colon proximal to the sigmoid colon in women, based on data from the three trials comparing flexible sigmoidoscopy screening with usual care. M-H=Mantel-Haenszel fixed effect model

	Screening group *v* control group			
	Colorectal cancer incidence (relative risk (95% CI))	P for interaction	Colorectal cancer mortality (relative risk (95% CI))	P for interaction
Proximal colon				
Both sexes*	0.86 (0.79 to 0.93)		0.87 (0.73 to 1.04)	
Men†	0.83 (0.73 to 0.94)		0.89 (0.70 to 1.13)	
≥60 years‡	0.82 (0.71 to 0.95)		0.96 (0.73 to 1.28)	
<60 years§	0.84 (0.66 to 1.07)	0.04	0.71 (0.44 to 1.14)	0.61
Women¶	0.91 (0.79 to 1.03)		0.85 (0.66 to 1.10)	
≥60 years‡	1.03 (0.88 to 1.20)		0.89 (0.65 to 1.21)	
<60 years§	0.65 (0.50 to 0.84)		0.79 (0.51 to 1.23)	

Different results when restricting analysis to the 55-64 year age group

Several sensitivity analysis

- only individuals in the age group 55-64 years (the age range covered by all three trials included in the analysis):

  - flexible sigmoidoscopy screening reduces the incidence of colorectal cancer in the proximal colon in women younger than 60 too,

  - colorectal cancer mortality was statistically significantly reduced in men (0.70; 0.57 to 0.86) and in younger women (0.68; 0.47 to 0.98), but not in women aged 60 years and older (1.07; 0.77 to 1.48)

- the descending colon included in the definition of distal colon, and the results were comparable with those presented
- procedural characteristics (compliance with screening, colonoscopy referral rate, bowel cleansing, and insertion depth of the endoscope at the screening examination) included in univariate metaregression models: none of these procedural characteristics was statistically significant.
- the PLCO trial excluded because of its large size compared with SCORE and NORCCAP. The results were comparable with the main analysis

To explore whether the difference in effectiveness of screening could be attributable to the distribution of colorectal cancer in the distal and proximal colon among men and women in different age groups, the control group (no screening) was used to calculate the proportion of colorectal cancers in the distal (rectosigmoid) colon compared with the proximal colon

The proportion of distal versus proximal colorectal cancer was smaller for women than for men in all age groups. Proximal location of colorectal cancer occurs more frequently with increasing age. The distal/proximal ratio was about one in women aged 55-59, and less than one in those age 60 and over, while the same observation was made for men aged 70 and over.

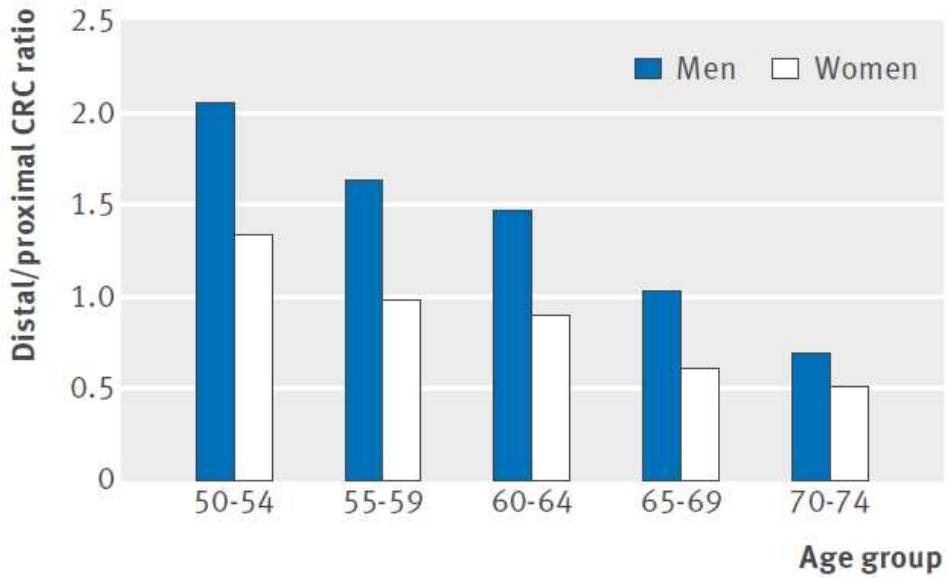

Fig 7 | Proportion of colorectal cancer (CRC) cases among men and women in the distal (rectosigmoid) and proximal colon (oral to the descending sigmoid junction) in the usual care groups in PLCO, SCORE, and NORCCAP trials. The age group indicates age at screening, and the distal/proximal ratio is calculated for the entire follow-up (median 10.5-11.9 years)

In recent years, it has become evident that colorectal cancer is a heterogeneous disease. Current screening strategies focus on the detection of adenomas, but adenomas— through the adenoma-carcinoma sequence —is only one of the precursors to colorectal cancer. About 16% of colorectal cancers develop through the serrated pathway, with the sessile serrated adenoma or polyp (SSA/P) as the precursor lesion.

These lesions are most often proximal, and in one study, 52% of individuals with advanced proximal serrated polyps (defined as SSA/P ≥10 mm with dysplastic features, or traditional serrated adenomas) did not have a distal lesion that could be detected at flexible sigmoidoscopy and which would trigger a full colonoscopy.

Thus, with increasing age, proximal SSA/P and proximal adenomas become more prevalent. A considerable proportion of these proximal polyps might not have a distal lesion that could trigger a full colonoscopy. The proportion without a distal adenoma might be more pronounced in women than men and could explain the difference that we observe in women in the present pooled analysis.

Conclusions

287 928 individuals were included in the pooled analysis; median follow-up was 10.5 to 12.1 years.

Screening reduced the incidence of colorectal cancer in men (relative risk 0.76; 95% confidence interval 0.70 to 0.83) and women (0.83; 0.75 to 0.92).

No difference in the effect of screening was seen between men younger than 60 and those older than 60.

Screening reduced the incidence of colorectal cancer in women younger than 60 (relative risk 0.71; 95% confidence interval 0.59 to 0.84), but not significantly in those aged 60 or older (0.90; 0.80 to 1.02).

Colorectal cancer mortality was significantly reduced in both younger and older men, and in women younger than 60.

Screening reduced colorectal cancer incidence to a similar extent in the distal colon in men and women, but there was no effect of screening in the proximal colon in older women with a significant interaction between sex and age group (P=0.04).

Whether other screening tools to more effectively detect proximal tumours—such as colonoscopy or the faecal occult blood test—offer a better alternative for older women is **currently unknown** and warrants further investigation

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OBSERVATION: BRIEF RESEARCH REPORT

Reanalysis of All-Cause Mortality in the U.S. Preventive Services Task Force 2016 Evidence Report on Colorectal Cancer Screening

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Background

The 2016 U.S. Preventive Services Task Force (USPSTF) evidence report on colorectal cancer screening concluded that no colorectal cancer screening methods reduce all-cause mortality. This conclusion was partially based on a meta-analysis of 4 randomized trials that compared flexible sigmoidoscopy screening with no screening. The meta-analysis aggregated results from the 2 age cohorts of 1 of the trials —the NORCCAP (Norwegian Colorectal Cancer Prevention) study— as if these cohorts were a single trial.

Aggregation of outcomes that have markedly different event rates, screening– control ratios, or both can create a Simpson paradox, a phenomenon where a finding exists in individual data groups that is absent or opposite when the groups are combined

The NORCCAP study involved 2 distinct trial cohorts because of a postscreening decision to expand the inclusion age to younger persons. The cohorts were randomly assigned separately. The additional age cohort (50 to 54 years) had a lower event rate and was randomly assigned with a screen– control ratio of 1:5.4 rather than the ratio of 1:3 used in the original older cohort (55 to 64 years)

Therefore, the metaanalysis in the USPSTF evidence report may be confounded because the aggregated NORCCAP results were used.

Objective:

To assess results of the NORCCAP study for a Simpson paradox and to repeat meta-analysis of all-cause mortality outcomes for screening flexible sigmoidoscopy using the 2 NORCCAP age cohorts as individual trials.

Methods:

Data for all-cause mortality were extracted from the 4 studies specified in the USPSTF evidence report. Only published data and intention-to-treat outcomes were used.

The 2 NORCCAP study age cohorts were included as individual trials using outcome data published in an author response to a comment

The fixed-effects model was chosen because of the lack of heterogeneity (I2 = 0%). Sensitivity analysis repeated the meta-analysis with multiple random-effects models (Sidik–Jonkman, maximum likelihood, restricted maximum likelihood, Hedges– Olkin, empirical Bayes, and DerSimonian–Laird).

Results

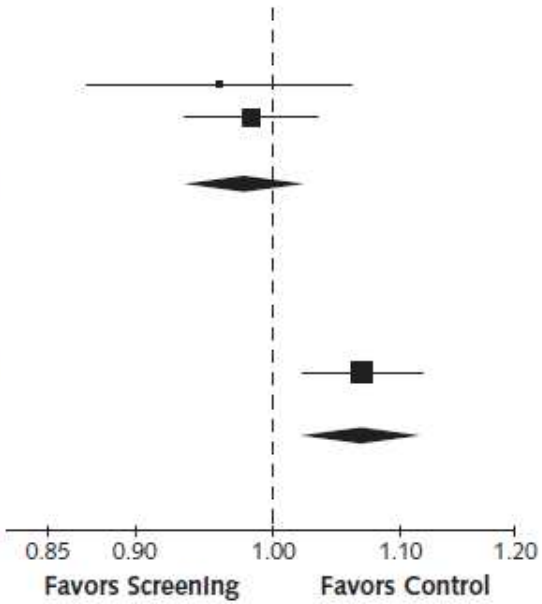
The relative risk (RR) for all-cause mortality favoring screening in the younger cohort of the NORCCAP study (ages 50 to 54 years) is 0.96 (95% CI, 0.87 to 1.06), whereas that for the older cohort (ages 55 to 64 years) is 0.98 (CI, 0.94 to 1.03).

The RR for the combined summary estimate of these 2 cohorts is 0.98 (CI, 0.94 to 1.02).

When the 2 cohorts are aggregated into a single group rather than combined meta-analytically as 2 separate groups, the RR for all-cause mortality is 1.07 (CI, 1.02 to 1.12), favoring no screening

Figure 1. RR for death in the NORCCAP individual cohorts versus the aggregate outcome.

Trial	Screening Deaths, *n*	Screening Persons, *n*	Screening Risk, %	Control Deaths, *n*	Control Persons, *n*	Control Risk, %	RR (95% CI)
Cohort outcomes							
NORCCAP							
Age 50–54 y	427	6920	6.17	2387	37 131	6.43	0.96 (0.87–1.06)
Age 55–64 y	1756	13 652	12.86	5375	41 089	13.08	0.98 (0.94–1.03)
Subtotal		20 572			78 220		0.98 (0.94–1.02)
Total events	2183			7762			
Heterogeneity: chi-square 0.18 ($P = 0.67$); $I^2 = 0\%$							
Test for overall effect: $Z = 0.95$ ($P = 0.34$)							
Aggregate outcomes*							
NORCCAP, all ages	2183	20 572	10.61	7762	78 220	9.92	1.07 (1.02–1.12)
Subtotal (95% CI)		20 572			78 220		1.07 (1.02–1.12)
Total events	2183			7762			
Heterogeneity: NA							
Test for overall effect: $Z = 2.93$ ($P = 0.003$)							



NA = not applicable; NORCCAP = Norwegian Colorectal Cancer Prevention; RR = relative risk.
* Showing Simpson paradox.

Results

Meta-analysis of all of the flexible sigmoidoscopy trials using the individual NORCCAP study cohorts shows that flexible sigmoidoscopy **reduces all-cause mortality (RR, 0.975 [CI, 0.959 to 0.992]; P = 0.004; I2 = 0%) at 11 to 12 years**

On the basis of the assumed risk for death in the U.S population of screening age (50 to 74 years), **the absolute risk reduction is 3.0 deaths per 1000 persons invited** to screening (CI, 1.0 to 4.9) after 11.5 years of follow-up.

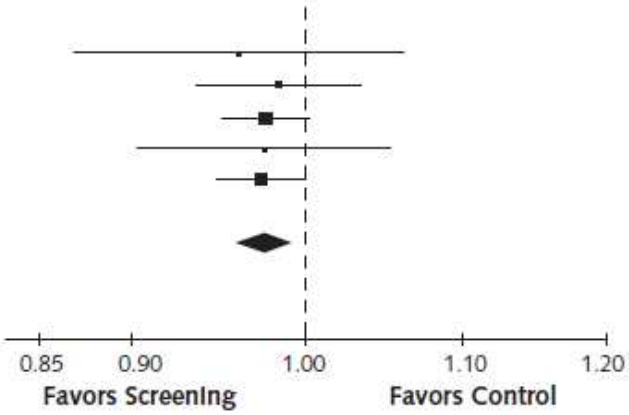
Sensitivity analysis showed no important change in outcome with use of different random-effects estimators or exclusion of any single trial.

Figure 2. RR for death with screening with flexible sigmoidoscopy in randomized controlled trials.

Trial	Screening			Control			RR (95% CI)
	Deaths, *n*	Persons, *n*	Risk, %	Deaths, *n*	Persons, *n*	Risk, %	
NORCCAP							
Age 50–54 y	427	6920	6.17	2387	37 131	6.43	0.96 (0.87–1.06)
Age 55–64 y	1756	13 652	12.86	5375	41 089	13.08	0.98 (0.94–1.03)
PLCO*	9390	77 445	12.12	9627	77 455	12.43	0.98 (0.95–1.002)
SCORE	1202	17 136	7.01	1233	17 136	7.20	0.97 (0.90–1.05)
UKFSST	6775	57 099	11.87	13 768	112 939	12.19	0.97 (0.95–1.0002)
Subtotal		172 252			285 750		0.975 (0.959–0.992)
Total events	19 550			32 390			

Heterogeneity: chi-square = 0.22 ($P = 0.99$); $I^2 = 0\%$

Test for overall effect: $Z = 2.90$ ($P = 0.004$)



NORCCAP = Norwegian Colorectal Cancer Prevention; PLCO = Prostate, Lung, Colorectal, and Ovarian; RR = relative risk; SCORE = Screening for Colon Rectum; UKFSST = U.K. Flexible Sigmoidoscopy Screening Trial.

* This trial reports a modified all-cause mortality that excludes deaths from prostate, lung, and ovarian cancer because the intervention group was also screened for those types of cancer.

Discussion

Aggregation of outcomes of the NORCCAP study in the USPSTF evidence report created a Simpson paradox that obscured the reduction in all-cause mortality by changing 2 statistically non significant reductions into a statistically significant increase.

This effect was large enough to nullify the reductions in all-cause mortality of the other trials in the meta-analysis.

A potential limitation of our meta-analysis of the trials is that the PLCO (Prostate, Lung, Colorectal, and Ovarian) cancer screening trial reports only modified all-cause mortality that excludes deaths from prostate, lung, and ovarian cancer because the intervention group was also screened for those types of cancer; however, exclusion of the PLCO trial does not change the result.

Another limitation is that we did not examine whether outcomes might vary by age and sex.

More than 50 years after the announcement of the first clinical trial of cancer screening,

a screening method has shown a reduction in the risk for death compared with no screening.

If the primary goal of screening is to reduce the risk for death,

then the evidence supporting flexible sigmoidoscopy is substantially stronger than that of other screening methods.

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Grazie per l’attenzione!