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Sex- and Age-Stratified Outcomes of Colonoscopy Versus Faecal Immunochemical Testing: Post-Analysis of the COLONPREV Study

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ABSTRACT

Background: Colorectal cancer (CRC) screening is effective and cost-effective in average-risk individuals. The COLONPREV study recently showed that individuals invited to a faecal immunochemical test (FIT) were more likely to participate in screening than those invited to colonoscopy, and that FIT-based screening was non-inferior to colonoscopy with respect to CRC-related mortality and CRC incidence.

Objective: To assess whether the outcomes of colonoscopy- and FIT-based screening differ according to sex and age in the invited population.

Methods: Presumptively healthy men and women aged 50–69 years were randomised to either a one-time screening colonoscopy or biennial FIT. In this analysis, we report participation and crossover rates, CRC-related mortality, CRC incidence, all-cause mortality, and diagnostic yield for both screening strategies, stratified by sex and by age group (50–59 and 60–69 years).

Results: The eligible population consisted of 26,332 individuals assigned to colonoscopy and 26,719 assigned to FIT. As expected, participation and crossover rates were higher in women than in men and in older individuals compared with younger individuals. Participation was also consistently higher in those invited to FIT screening than in those assigned to colonoscopy across both sexes and age groups. The observed reductions in CRC-related mortality and CRC incidence, which were consistent across both screening strategies, were independent of sex or age. However, CRC-related mortality, all-cause mortality, and CRC incidence remained higher in men and older participants than in women and younger participants. Colonoscopy screening showed a higher diagnostic yield of premalignant precursor lesions across all demographic subgroups.

Antoni Castells and Enrique Quintero Both authors contributed equally to this work.

Conclusion: Participation and reductions in CRC-related mortality and incidence were consistent across sex and age groups for both FIT- and colonoscopy-based screening strategies. The higher baseline risk observed in men could not be fully mitigated by screening.
Trial Registration: ClinicalTrials.gov: NCT00906997

1 | Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide and the second leading cause of cancer-related death [1, 2]. Evidence from several studies have shown that CRC screening is effective and cost-effective in average-risk individuals [3–6]. Recommended CRC screening strategies fall into two broad categories: stool tests (looking for occult blood or exfoliated DNA) and structural exams (flexible sigmoidoscopy, colonoscopy, CT colonography, and endoscopic capsule) [7]. Of them, occult blood detection using a faecal immunochemical test (FIT) and colonoscopy are the most widely employed approaches [8–10], with the former predominantly implemented in Europe and Australia and the latter in the US [11].

We have recently published long-term results of the COLONPREV study [12, 13], the first randomised controlled trial comparing colonoscopy and FIT head-to-head, demonstrating that individuals invited to FIT were more likely to participate in screening than those invited to colonoscopy. More importantly, the FIT-based screening programme appeared not to be inferior to one based on primary colonoscopy in terms of CRC-related mortality and CRC incidence. In addition, whereas there were no differences in the number of subjects in whom CRC was detected, colonoscopy was demonstrated to be superior to FIT in detecting colorectal polyposis, and advanced and non-advanced colorectal lesions [12, 13].

Sex, gender and age are important determinants of health that influence environmental and occupational exposures, risk-taking behaviours, access to health care, patterns of health-seeking behaviour, use of health services, and perceptions of health care, which in turn relate to disease prevalence and treatment outcomes [14, 15]. More specifically, sex and gender have also been shown to influence the development and progression of CRC [16]. Therefore, it is essential to consider their potential impact when interpreting the results of any preventive, diagnostic, or therapeutic strategy, mainly those informing public health policies [17, 18]. This fact is especially relevant in CRC screening, since it has been suggested that women are disadvantaged compared to men, particularly in programmes that use FIT [19]. Indeed, FIT positivity is lower in women and, therefore, a smaller proportion of them are invited for further investigation [20]. Moreover, although participation and adherence to FIT screening are consistently higher than those in men, the yield of neoplastic lesions is lower in women [21]. Finally, FIT-based screening programmes seem associated with a lower CRC incidence and mortality reduction in women than in men [22].

In this post hoc analysis, we report participation and crossover rates, CRC-related mortality, CRC incidence and all-cause mortality, and diagnostic yield of premalignant precursor lesions in both screening strategies stratified by sex and age, a critical information to establish whether colonoscopy and FIT performance may vary based on such outcomes.

2 | Material and Methods

The COLONPREV study is a pragmatic, non-inferiority, randomised controlled trial carried out in 8 Spanish regions with the participation of 15 tertiary hospitals, which was designed to assess the effectiveness of one-time colonoscopy and biennial FIT for reducing CRC-related mortality at 10 years [12, 13].

The study protocol was approved by the ethical committee of the Hospital Clínic of Barcelona (approval number 2006/3379), and all participants provided written informed consent.

2.1 | Study Population

Presumptively healthy men and women 50–69 years of age were eligible for enrolment in this study. Exclusion criteria were ascertained after randomisation by means of a questionnaire at the local screening office, and included personal history of CRC, adenoma or inflammatory bowel disease, family history of hereditary or familial CRC (i.e., 2 or more first-degree relatives with CRC or one diagnosed before the age of 60) [23, 24], severe comorbidity, and previous colectomy. Patients were also temporarily excluded if they had already received faecal occult blood testing in the past 2 years, or sigmoidoscopy or colonoscopy within the past 5 years, or if they had symptoms requiring additional work-up; these patients were eligible for the trial once previous screening tests had expired or if the results of clinical work-up were negative.

2.2 | Randomisation

Participants were randomly allocated to one-time colonoscopy or biennial FIT in a ratio of 1:1 prior to invitation. Individuals were sent a pre-invitation presentation letter containing information on CRC screening and the rationale for this study. Two weeks later, an invitation letter was sent indicating the specific group in which the subject was assigned. Two additional reminder letters were mailed three and 6 months after invitation to non-responders. Subjects agreeing to participate in the study received an appointment to the local screening office where they completed the questionnaire. The study design allowed for crossover between both screening strategies.

Eligible individuals who did not participate in the baseline screening round were able to participate in the study at any time if they fulfiled the above-mentioned inclusion/exclusion

Key Summary

- Summary of the established knowledge on this subject:
  - Several studies have shown that colorectal cancer (CRC) screening is effective and cost-effective in average-risk individuals (i.e., men and women aged 50 or older without personal or family history of CRC).
  - The COLONPREV study, the first randomised controlled trial comparing colonoscopy and FIT head-to-head, has demonstrated that individuals invited to FIT were more likely to participate in screening than those invited to colonoscopy, being FIT-based screening programme not inferior to one based on primary colonoscopy in terms of CRC-related mortality and CRC incidence.
  - It is unknown, however, whether these results depend on the sex and age of the invited population. This fact is especially relevant in CRC screening, since it has been suggested that women are disadvantaged compared to men, particularly in programmes that use FIT.
- What are the significant and/or new findings of this study?
  - The results of this post hoc analysis indicated that both screening strategies exhibited comparable effectiveness (i.e., participation rate, CRC-related mortality, CRC incidence, and precursor lesion diagnostic yield) across different sex and age categories.
  - Analysis of primary and secondary endpoints confirmed that the COLONPREV study results are applicable to the entire target population, without requiring adjustment for these demographics in personalised screening approaches.

criteria; they continued being allocated to the initial randomization group, except those who required to crossover to the alternative one. Finally, individuals not participating in the COLONPREV study could have been invited to participate in institutional FIT-based screening programs as each Spanish region gradually introduced them.

2.3 | Study Interventions

In individuals undergoing colonoscopy, bowel cleansing and sedation were performed as previously described [25]. All colonoscopies were performed by experienced endoscopists (> 200 colonoscopies per year) [26].

FIT strategy consisted of one single sample using the automated semiquantitative OC-sensor (Eiken Chemical, Tokyo, Japan), without specific diet or medication restrictions. Samples were processed at each regional reference hospital. Cut-off level for indicating the work-up colonoscopy was established at 15 μg (first round) or 20 μg (subsequent screening rounds) of haemoglobin per gram of faeces [20].

Further details on study population, randomisation, study interventions, quality assurance programme, and sample size calculation have been reported previously [12, 13].

2.4 | Outcomes

Influence of age and sex on the study outcomes was assessed according to the intention-to-screen contrast. Secondary analyses also evaluated their influence according to the as-screened and per-protocol contrasts [13]. Individuals were excluded from these analyses if they attended the screening office and met one or more exclusion criteria. Of note, subjects who did not attend the screening office and consequently did not provide information about exclusion criteria were classified as eligible and included in the analyses.

Among participants in the study, any colorectal examination for screening, surveillance, and diagnostic purposes was registered in an online electronic case-report form and stored in a central database. This information was confirmed by consultation of both regional screening programs and hospital databases. Among non-participants, information was limited to survival data, development of CRC, and participation in institutional screening programs.

The primary endpoint of COLONPREV was death from CRC at 10 years (CRC-related mortality). Secondary endpoints were participation, risk of CRC (incidence), diagnostic yield of screen-detected premalignant precursor lesions, and risk of death from any cause (all-cause mortality; post hoc outcome) at 10 years. Definitions of CRC-related death and criteria for the diagnosis of CRC and premalignant lesions have also been reported previously [12, 13].

Follow-up time was calculated from the date of randomisation to the date when any permanent exclusion criterion, absent at the baseline evaluation, was identified, diagnosis of CRC (for analyses of CRC incidence), death from CRC (for analyses of CRC-related mortality), death from causes other than CRC, or to the end of follow-up (i.e., December 31st, 2021), whichever came first. In CRC-related mortality analyses, non-CRC-related deaths were treated as censoring events.

Screening participation was defined as the number of subjects undergoing screening divided by the number of eligible subjects in each arm. With respect to individuals undergoing FIT, they were considered participants if they completed at least one FIT and the work-up colonoscopy if a positive test occurred.

Diagnostic yield of screen-detected premalignant precursor lesions (i.e., polyposis, advanced lesions, and non-advanced lesions) was the number of subjects with true positive results divided by the number of eligible subjects in the intention-to-screen analysis [13].

Detection rate of screen-detected premalignant precursor lesions was calculated as the number of subjects with true positive results divided by the number of subjects who actually underwent testing in the as-screened analysis [13].

2.5 | Statistical Analysis

Outcomes were stratified by sex and age at randomisation. Sex was categorised as female or male according to the information

of the Community Health Registry of each autonomous region, which constituted the primary source for identifying the study population. With respect to age, individuals were classified into two age groups: 50 to 59 and 60–69 years old.

The cumulative 10-year risks of CRC-related mortality, CRC incidence, and all-cause mortality were calculated using the Kaplan-Meier estimator. Risks were compared using ratios (RR) and differences, with 95% confidence intervals (95% CI), computed via the Delta approximation.

For participation and crossover rates, diagnostic yield and detection rate, differences between groups were also expressed as RR, with 95% CI.

There was no prespecified plan to adjust for multiple testing. The widths of the 95% CI were not adjusted for multiple testing and cannot be used in place of hypothesis tests. Nevertheless, multivariate analyses were performed to confirm whether sex and age influenced the main screening outcomes. For this purpose, both logistic regression (participation and crossover rates) and Cox regression (CRC-related mortality, CRC incidence and all-cause mortality) analyses were used.

3 | Results

The eligible population included 26,332 individuals assigned to the colonoscopy arm and 26,719 to the FIT arm. Female participants represented 52.8% of each group, with 13,916 in the colonoscopy arm and 14,102 in the FIT arm. The mean age at randomisation was 58.8 ± 5.7 years in both study groups (Supporting Information S1: Table S1 and Figures S1 and S2).

As expected, participation and crossover rates were higher in women and older individuals than in men and younger individuals, whereas CRC-related and all-cause mortality and CRC incidence were higher in men and older individuals than in women and younger individuals (Supporting Information S1: Table S2).

Interestingly, when screening participation was determined by calendar year (Supporting Information S1: Table S3), the data indicate a trend ($p < 0.03$) of a higher proportion of men among early adopters compared to those who participated in subsequent years. Moreover, among individuals who underwent FIT screening, men and older adults were significantly more likely ($p < 0.001$) to adhere to FIT testing than women and younger individuals (Supporting Information S1: Table S4).

3.1 | Participation and Crossover Rates

Among subjects eligible to undergo colonoscopy, 5293 subjects accepted the proposed strategy, whereas 3074 were screened by FIT, thus resulting in a participation rate of 31.8%. Among subjects eligible to undergo FIT, 10,525 subjects accepted the proposed strategy, whereas 126 were screened by colonoscopy, thus resulting in a participation rate of 39.9%. This difference in participation between study arms was maintained in both women (RR, 0.79; 95% CI, 0.76–0.81) and men (RR, 0.81; 95% CI, 0.78–0.84) and across the two age groups (50–59 years old: RR, 0.79; 95% CI, 0.76–0.82; 60–69 years old: RR, 0.80; 95% CI, 0.78–0.83) (Table 1).

The crossover rate was consistently higher among individuals in the colonoscopy arm who opted for FIT screening compared with those in the FIT arm who chose colonoscopy. This pattern was more pronounced in women (RR, 27.28; 95% CI, 21.32–34.91) than in men (RR, 22.06; 95% CI, 17.08–28.48), and the difference increased with age (50–59 years old: RR, 19.19; 95% CI, 15.20–24.21; 60–69 years old: RR, 32.58; 95% CI, 24.75–42.88) (Table 1).

3.2 | Colorectal Cancer-Related Mortality

At 10 years, the risk of death from CRC was comparable between individuals in the colonoscopy arm and those in the FIT arm, across all sex (women: RR, 0.78; 95% CI, 0.43–1.39; men: RR, 1.02; 95% CI, 0.64–1.64) and age categories (50–59 years old:

TABLE 1 | Participation and crossover rates stratified by sex and age.

Endpoint/Stratum	Colonoscopy arm	FIT arm	Risk ratio (95% CI)
Participation rate			
Women (n = 28,018)	4478 (32.2%)	5773 (40.9%)	0.79 (0.76–0.81)
Men (n = 25,033)	3889 (31.3%)	4878 (38.7%)	0.81 (0.78–0.84)
50–59 years old (n = 29,159)	4124 (28.6%)	5350 (36.3%)	0.79 (0.76–0.82)
60–69 years old (n = 23,892)	4243 (35.6%)	5301 (44.3%)	0.80 (0.78–0.83)
Crossover rate			
Women (n = 28,018)	1750 (12.6%)	65 (0.5%)	27.28 (21.32–34.91)
Men (n = 25,033)	1324 (10.7%)	61 (0.5%)	22.06 (17.08–28.48)
50–59 years old (n = 29,159)	1388 (9.6%)	74 (0.5%)	19.19 (15.20–24.21)
60–69 years old (n = 23,892)	1686 (14.1%)	52 (0.4%)	32.58 (24.75–42.88)

Abbreviations: FIT, faecal immunochemical test; 95% CI, 95% confidence interval (risk ratio computed with the Delta approximation).

RR, 1.02; 95% CI, 0.56–1.86; 60–69 years old: RR, 0.86; 95% CI, 0.54–1.35) (Table 2 and Figure 1).

3.3 | Colorectal Cancer Incidence

The risk of CRC at 10 years was similar in both study groups, regardless of sex (women: RR, 0.86; 95% CI, 0.67–1.12; men: RR, 0.96; 95% CI, 0.79–1.18) and age (50–59 years old: RR, 0.97; 95% CI, 0.75–1.25; 60–69 years old: RR, 0.89; 95% CI, 0.73–1.09) (Table 2 and Figure 2).

3.4 | All-Cause Mortality

After 10 years of follow-up, the risk of death from any cause was also similar between the colonoscopy and FIT arms. This consistency was observed regardless of sex (women: RR, 0.97; 95% CI, 0.87–1.07; men: RR, 1.01; 95% CI, 0.94–1.09) and age (50–59 years old: RR, 1.00; 95% CI, 0.90–1.10; 60–69 years old: RR, 0.99; 95% CI, 0.92–1.06) (Table 2 and Supporting Information S1: Figure S3).

3.5 | Diagnostic Yield and Detection Rate of Premalignant Precursor Lesions

Colorectal polyposis was diagnosed more frequently in participants assigned to the colonoscopy arm compared with those in the FIT arm across all sex and age categories (Table 3). The diagnostic yield of advanced lesions was also greater among individuals in the colonoscopy group than in those in the FIT group, without differences by sex or age. In addition, non-advanced lesions were identified more often in the colonoscopy arm than in the FIT arm, regardless of demographic factors (Table 3). Similar results were observed with respect to the detection rate (Supporting Information S1: Table S5), when analyses were referred to individuals who had actually undergone testing (as-screened contrast).

3.6 | As-Screened and Per-Protocol Analyses

In the Supplementary material, we have provided additional sex and age-stratified data based on the as-screened (Supporting Information S1: Figures S4–S5) and per-protocol (Supporting

TABLE 2 | Colorectal cancer-related mortality, colorectal cancer incidence and all-cause mortality stratified by sex and age.

	Colonoscopy arm		FIT arm		Colonoscopy versus FIT	
Endpoint/ stratum	**Individuals**	**10-Yr risk % (95% CI)**	**Individuals**	**10-Yr risk % (95% CI)**	**Risk difference (95% CI)**	**Risk ratio % (95% CI)**
Colorectal cancer-related mortality						
Women	20	0.15 (0.08–0.21)	26	0.19 (0.12–0.26)	−0.04 (−0.14–0.06)	0.78 (0.43–1.39)
Men	35	0.30 (0.20–0.40)	34	0.29 (0.19–0.39)	0.01 (−0.13–0.15)	1.02 (0.64–1.64)
50–59 years old	21	0.15 (0.09–0.21)	21	0.15 (0.08–0.21)	0.00 (−0.09–0.09)	1.02 (0.56–1.86)
60–69 years old	34	0.30 (0.20–0.40)	39	0.35 (0.24–0.47)	−0.05 (−0.20–0.10)	0.86 (0.54–1.35)
Colorectal cancer incidence						
Women	106	0.78 (0.64–0.93)	125	0.91 (0.75–1.07)	−0.12 (−0.34–0.09)	0.86 (0.67–1.12)
Men	180	1.53 (1.30–1.75)	189	1.58 (1.36–1.81)	−0.06 (−0.37–0.26)	0.96 (0.79–1.18)
50–59 years old	115	0.82 (0.67–0.97)	122	0.85 (0.70–1.00)	−0.03 (−0.24–0.18)	0.97 (0.75–1.25)
60–69 years old	171	1.52 (1.29–1.74)	192	1.70 (1.46–1.94)	−0.18 (−0.51–0.14)	0.89 (0.73–1.09)
All-cause mortality						
Women	685	4.97 (4.61–5.34)	719	5.14 (4.77–5.51)	−0.17 (−0.68–0.35)	0.97 (0.87–1.07)
Men	1304	10.65 (10.10–11.19)	1315	10.54 (10.00–11.07)	0.11 (−0.66–0.88)	1.01 (0.94–1.09)
50–59 years old	720	5.03 (4.67–5.38)	738	5.03 (4.68–5.39)	−0.01 (−0.51–0.50)	1.00 (0.90–1.10)
60–69 years old	1269	10.85 (10.28–11.41)	1296	10.98 (10.42–11.55)	−0.14 (−0.94–0.66)	0.99 (0.92–1.06)

Abbreviations: FIT, faecal immunochemical test; 95% CI, 95% confidence interval (risk difference and ratio computed via the Delta approximation).

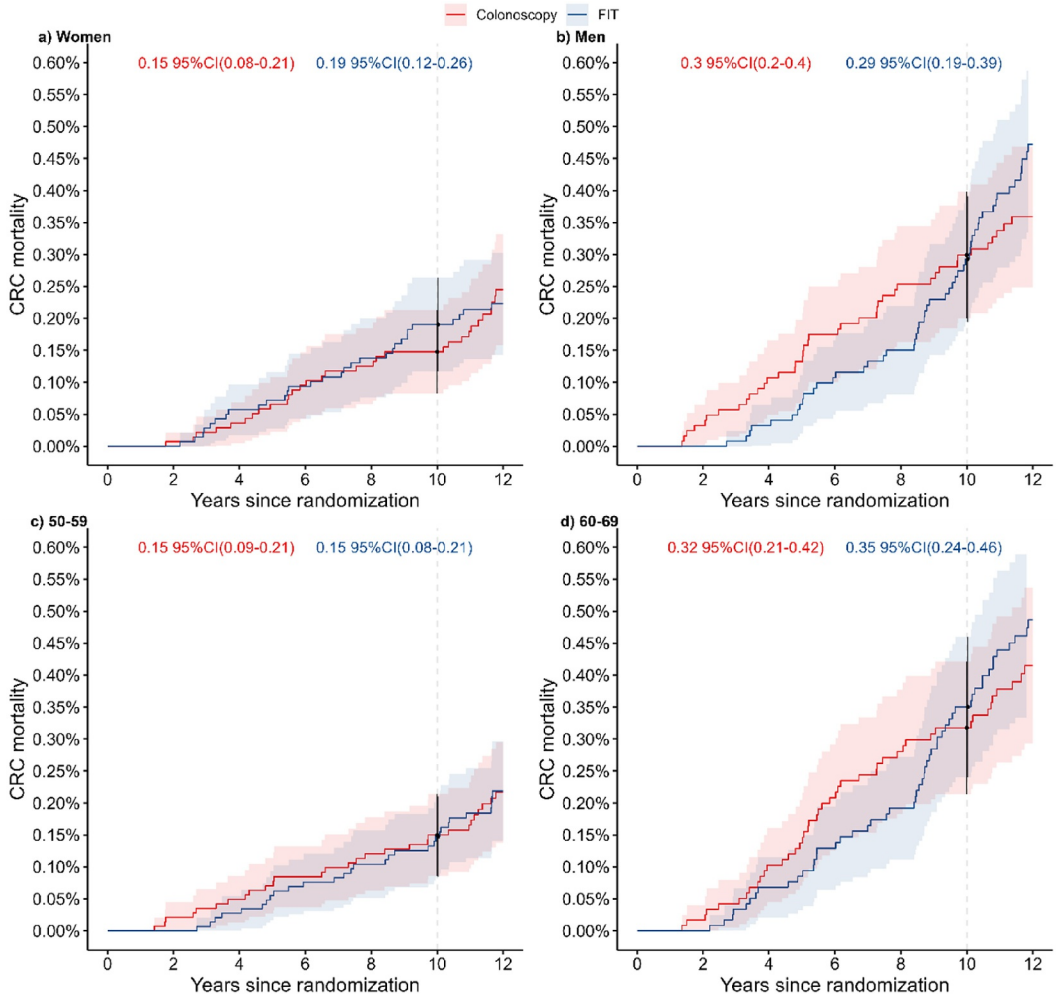

FIGURE 1 | Cumulative risk of death from CRC at 10 years stratified by sex and age. Panels a and b display findings for women and men, respectively, while panels c and d present results for individuals aged 50–59 and 60–69 years, respectively. FIT, faecal immunochemical test; 95% CI, 95% confidence interval.

Information S1: Figures S6–S7) analyses. These results confirmed that reductions in CRC-related mortality and CRC incidence for both FIT and colonoscopy screening strategies were consistent across all sex and age groups.

4 | Discussion

The results of this post hoc analysis indicated that both screening strategies exhibited comparable effectiveness across different sex and age categories. Participation rates were greater among individuals invited to FIT screening compared with those allocated to colonoscopy, with this pattern observed consistently for both men and women, as well as across the two age groups. Furthermore, the FIT-based programme proved to be noninferior to the colonoscopy-based approach in reducing both CRC-related mortality and CRC incidence irrespective of sex and age. Finally, colonoscopy screening showed a higher diagnostic yield for premalignant precursor lesions in all demographic subgroups.

The COLONPREV study was the first randomised controlled trial comparing head-to-head colonoscopy and FIT-based screening in terms of CRC-related mortality and CRC incidence [12, 13]. The findings indicated that both screening strategies yielded equivalent long-term outcomes, a result largely attributed to the higher acceptance of FIT compared with primary colonoscopy. Given the influence of these results on public health policy, it was crucial to determine whether the observed equivalence remained consistent across all sex and age groups. Analysis of both primary and secondary endpoints confirmed that these conclusions are applicable to the entire target population, thus suggesting that there is no need to adjust for sex or age in personalised screening approaches [27]. Indeed, CRC-related mortality and CRC incidence were higher in men and older individuals than in women and younger individuals, thus probably reflecting differences in their intrinsic CRC risk [28] rather than a differential response to a particular screening strategy [29].

As mentioned above, the findings from this analysis also underscore the significant role of demographic factors in CRC incidence, CRC-related mortality, and participation rates. Notably, women tend to have higher rates of screening participation and a lower likelihood of developing CRC or dying from this disease, whereas older adults are more likely to participate

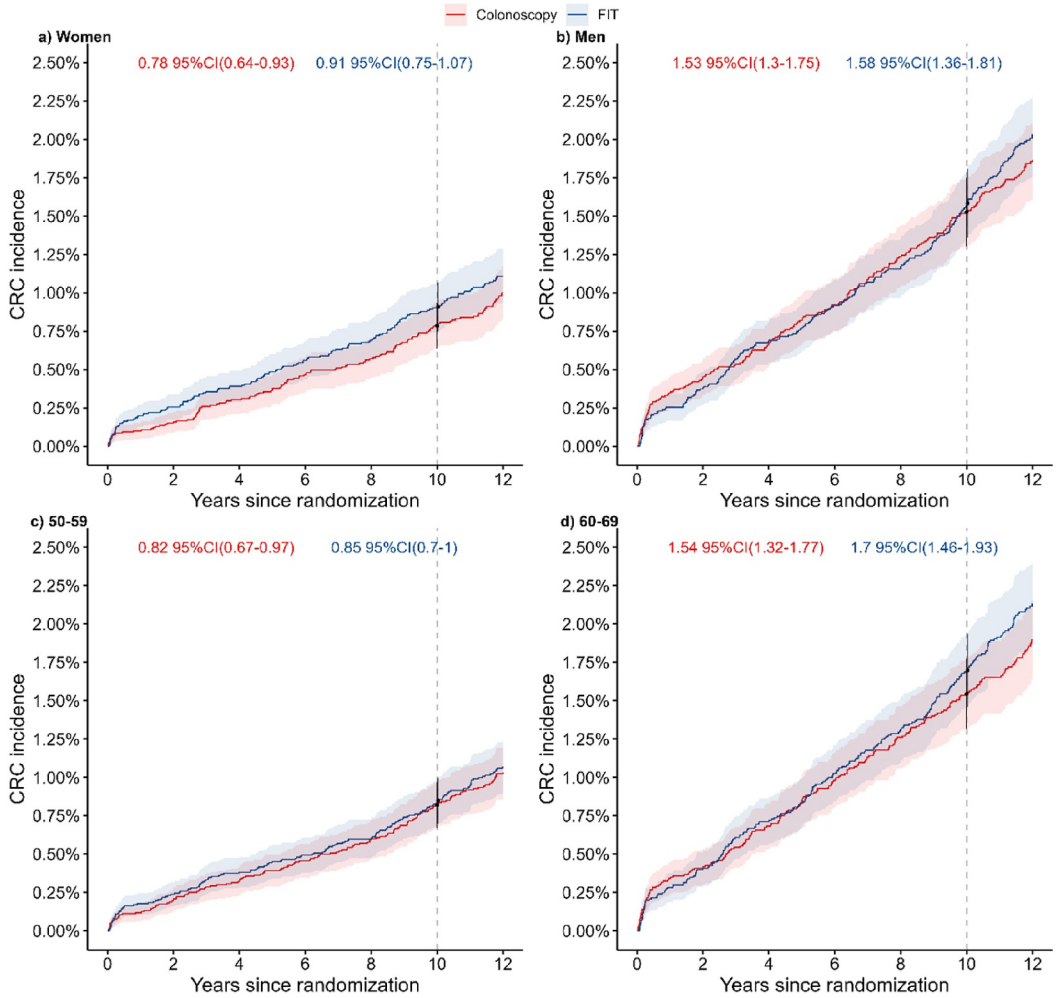

FIGURE 2 | Cumulative risk of CRC at 10 years stratified by sex and age. Panels a and b display findings for women and men, respectively, while panels c and d present results for individuals aged 50–59 and 60–69 years, respectively. FIT, faecal immunochemical test; 95% CI, 95% confidence interval.

in screening but face greater risks of CRC incidence and mortality than their younger counterparts. Collectively, these patterns imply that underlying CRC risk may blunt the net benefit of current screening strategies. Therefore, enhancing both the effectiveness and acceptance of existing screening methods remains crucial. Increasing the sensitivity of screening tools could lead to better detection of advanced premalignant lesions and, over time, a reduction in CRC incidence. Similarly, the adoption of non-invasive, accessible, and affordable screening approaches would likely boost participation and adherence among the target population. Strategies aimed at optimising both diagnostic yield and participant engagement should be prioritised as the main goals of research in CRC screening.

Our study has several strengths. It is derived from the first randomised controlled trial comparing colonoscopy to FIT for programmatic CRC screening at the population level and following a pragmatic approach. The closed cohort was randomised prior to invitation, and crossover between screening groups was permitted, allowing for a genuine evaluation of acceptance and participation for each strategy. The large sample size and extended follow-up were sufficient to assess key screening outcomes, namely CRC-related mortality and CRC incidence. Additionally, the use of intention-to-screen analysis minimised bias and ensured reliable results with respect to sex and age differences. Finally, the participation pattern, where women are more likely to participate in screening than men, mirrors trends seen in most countries, including CRC screening programmes in Spain [21, 30, 31].

We are also aware of some limitations. First, gender was not specifically recorded in the COLONPREV trial. As a result, we were unable to evaluate differences arising from socially constructed roles, behaviours, and identities, which may also influence study outcomes [14, 15]. Second, although adequately powered to assess the primary endpoint of the study (i.e., CRC-related mortality), the number of events observed within certain subgroups was low. This resulted in wide confidence intervals for these categories, which restricted the precision and interpretability of these specific findings. Third, data regarding sociodemographic, lifestyle, and dietary factors were not accessible in this study. As these variables may affect the outcomes, it is important to acknowledge the limitation of not being able to adjust for their potential influence when interpreting the findings of this analysis. Finally, the relatively low participation observed in the COLONPREV study is a limitation for the

TABLE 3 | Diagnostic yield of screen-detected premalignant precursor lesions[a] stratified by sex and age.

Stratum	Lesion	Colonoscopy arm	FIT arm	Risk ratio (95% CI)
Female (n = 28,018)	Colorectal polyposis	11 (0.1%)	3 (0.0%)	3.72 (1.04–13.32)
	Advanced colorectal lesion[b]	293 (2.1%)	219 (2.1%)	1.36 (1.14–1.61)
	Non-advanced colorectal lesion[c]	520 (3.7%)	152 (1.1%)	3.47 (2.90–4.15)
Male (n = 25,033)	Colorectal polyposis	35 (0.3%)	16 (0.1%)	2.22 (1.23–4.01)
	Advanced colorectal lesion[b]	560 (4.5%)	411 (3.3%)	1.38 (1.22–1.57)
	Non-advanced colorectal lesion[c]	656 (5.3%)	239 (1.9%)	2.79 (2.41–3.23)
50–59 years old (n = 29,159)	Colorectal polyposis	29 (0.2%)	11 (0.1%)	2.70 (1.35–5.40)
	Advanced colorectal lesion[b]	377 (2.6%)	298 (2.0%)	1.29 (1.11–1.50)
	Non-advanced colorectal lesion[c]	578 (4.0%)	206 (1.4%)	2.87 (2.45–3.36)
60–99 years old (n = 23,892)	Colorectal polyposis	17 (0.1%)	8 (0.1%)	2.13 (0.92–4.95)
	Advanced colorectal lesion[b]	476 (4.0%)	332 (2.8%)	1.44 (1.26–1.65)
	Non-advanced colorectal lesion[c]	598 (5.0%)	185 (1.5%)	3.25 (2.76–3.82)

Abbreviations: FIT, faecal immunochemical test; 95% CI, 95% confidence interval (risk ratio computed via the Delta approximation).
[a]The diagnostic yield was calculated as the number of subjects with true positive results divided by the number of subjects who were eligible to undergo testing (intention-to-screen analysis) and limited to screen-detected lesions.
[b]Advanced lesion was defined as an adenoma measuring 10 mm or more in diameter, with villous architecture (> 25%), high-grade dysplasia or intramucosal carcinoma, or a serrated lesion measuring 10 mm or more in diameter or with dysplasia.
[c]Non-advanced lesion was defined as a tubular adenoma measuring less than 10 mm in diameter with low-grade dysplasia or a serrated lesion measuring less than 10 mm in diameter without dysplasia.

current analysis as well as for the previous published main results [12, 13]. Indeed, since participation is a major determinant of programmatic screening success, higher adherence rates achieved through different invitation and/or organisational approaches could significantly affect screening outcomes (i.e., CRC-related mortality) not only within each group but also in terms of the differences between the colonoscopy and FIT arms.

In summary, the results of the COLONPREV study were consistent across age and sex groups, supporting the robustness of its conclusions. Indeed, analysis of primary and secondary endpoints confirmed that its results are applicable to the entire target population, without requiring adjustment for these demographics in personalised screening approaches. Nevertheless, the independent association of sex and age with study outcomes highlights the importance of improving both the effectiveness and acceptance of current screening methods. Finally, the comprehensive data on the performance of colonoscopy and FIT presented in this article may offer valuable insight for upcoming meta-analyses and clinical guidelines, enhancing the global understanding and application of CRC screening strategies.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Supporting Information S1: ueg270169-sup-0001-suppl-data.docx.