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Colorectal cancer screening with fecal immunochemical testing or primary colonoscopy: An analysis of health equity based on a randomised trial

U. Strömberg,[a]* C. Bonander,[a] M. Westerberg,[b] L.Å. Levin,[c] C. Metcalfe,[d] R. Steele,[e] L. Holmberg,[f,g] A. Forsberg,[h] and R. Hultcrantz[h]

[a]School of Public Health and Community Medicine, Institute of Medicine, Sahlgrenska Academy at University of Gothenburg, PO Box 463, Gothenburg SE-405 30, Sweden
[b]Department of Mathematics, Uppsala University, Box 480, Uppsala SE-751 06, Sweden
[c]Department of Health, Medicine and Caring Sciences, Linköping University, Linköping SE-581 83, Sweden
[d]Bristol Medical School: Population Health Sciences, University of Bristol, Canynge Hall, 39 Whatley Road, Bristol BS8 2PS, United Kingdom
[e]Department of Surgery, Population Health and Genomics, School of Medicine, University of Dundee, Ninewells Hospital, Dundee DD1 9SY, United Kingdom
[f]Translational Oncology and Urology Research (TOUR), School of Cancer and Pharmaceutical Sciences, King's College London, Guy's Hospital, St Thomas Street, London SE1 9RT, United Kingdom
[g]Department of Surgical Sciences, Uppsala University, Uppsala SE-751 85, Sweden
[h]Department of Medicine K2, Solna, Karolinska Institutet, Stockholm SE-171 76, Sweden

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Summary

Background We have addressed health equity attained by fecal immunochemical testing (FIT) and primary colonoscopy (PCOL), respectively, in the randomised controlled screening trial SCREESCO conducted in Sweden.

Methods We analysed data on the individuals recruited between March 2014, and March 2020, within the study registered with ClinicalTrials.gov, NCT02078804. Swedish population registry data on educational level, household income, country of birth, and marital status were linked to each 60-year-old man and woman who had been randomised to two rounds of FIT 2 years apart (n = 60,123) or once-only PCOL (n = 30,390). Furthermore, we geo-coded each study individual to his/her residential area and assessed neighbourhood-level data on deprivation, proportion of non-Western immigrants, population density, and average distance to healthcare center for colonoscopy. We estimated adjusted associations of each covariate with the *colonoscopy attendance* proportion *out of all invited* to respective arms; ie, the preferred outcome for addressing health equity. In the FIT arm, the test uptake and the colonoscopy uptake among the test positives were considered as the secondary outcomes.

Findings We found a marked socioeconomic gradient in the colonoscopy attendance proportion in the PCOL arm (adjusted odds ratio [95% credibility interval] between the groups categorised in the highest vs. lowest national quartile for household income: 2·20 [2·01–2·42]) in parallel with the gradient in the *test uptake* of the FIT × 2 screening (2·08 [1·96–2·20]). The corresponding gradient in the colonoscopy attendance proportion out of all invited to FIT was less pronounced (1·29 [1·16–1·42]), due to higher proportions of FIT positives in socioeconomically disadvantaged groups.

Interpretation The unintended risk of exacerbating inequalities in health by organised colorectal cancer screening may be higher with a PCOL strategy than a FIT strategy, despite parallel socioeconomic gradients in uptake.

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Keywords: Population; Cancer prevention; Screening uptake; Health equity; Socioeconomic status; Colorectal cancer

*Corresponding author.
E-mail address: ulf.stromberg@gu.se (U. Strömberg).

Research in context

Evidence before this study

This study addresses health equity in organised colorectal cancer (CRC) screening. We searched PubMed on November 10, 2021, using the following search terms: (uptake OR equity OR inequities OR inequalities) AND (socioeconomic) AND (cancer screening) AND (colorectal neoplasms OR colorectal cancer). Socioeconomic inequalities in the uptake of organised screening with fecal immunochemical testing (FIT) are well documented, whereas analogous reports for organised screening with primary colonoscopy (PCOL) are scarce.

Added value of this study

To our knowledge, this analysis is the first to address health equity based on two large intention-to-screen populations randomly invited to PCOL and FIT. Our analysis showed parallel, marked socioeconomic gradients in the (colonoscopy) uptake of a once-only PCOL strategy and the (test) uptake of a two rounds of FIT 2 years apart (FIT × 2) strategy. Yet, we found only small variations in the *colonoscopy attendance* proportion *at the intention-to-screen level* across various population groups in the FIT × 2 arm, due to higher proportions of FIT positives in socioeconomically disadvantaged groups.

Implications of all the available evidence

The unintended risk of exacerbating inequalities in health by an organised CRC screening program may be higher with a once-only PCOL strategy than a FIT × 2 strategy, despite parallel socioeconomic gradients in the uptake of each approach. Future cost-effectiveness evaluations should provide information about the health equity impacts of the alternative strategies and the trade-offs that may arise between equity and efficacy.

Introduction

Currently, the two most widely employed colorectal cancer (CRC) screening strategies are fecal immunochemical testing (FIT) and primary colonoscopy (PCOL). Socioeconomic inequalities in the uptake of organised screening with FIT are well documented.[1,2] However, it remains unclear whether such inequalities exacerbate health inequities. Work-up colonoscopy after a positive FIT detects existing invasive cancers, and colonoscopic removal of premalignant lesions is crucially important for preventing CRC.[3] To address health equity with regard to the potential health benefit of organised CRC screening from a population perspective, we analysed socioeconomic associations with the colonoscopy attendance proportion out of *all those invited* to FIT (ie, at the intention-to-screen level). This outcome depends on the test uptake, the proportion of test positives among the tested, and the work-up colonoscopy uptake among the test positives.

The health benefit of a PCOL strategy depends on the proportion of the invited who attend colonoscopy; ie, the PCOL uptake. Reports on socioeconomic inequalities in the uptake of organised screening with PCOL only are scarce.[2] Decreasing uptake with lower neighbourhood-level socioeconomic status has been reported in the PCOL arm of a randomised controlled trial (RCT) conducted in the regions of Amsterdam and Rotterdam (where colonography was tested as the alternative screening method).[4]

We aimed to evaluate the health equity attained by the FIT and PCOL screening strategies, respectively, in a nationwide RCT conducted in Sweden (SCREESCO [SCREEning of Swedish Colons]; ClinicalTrials.gov number NCT02078804).[5]

Methods

Study population

SCREESCO is a Swedish RCT with assignment of study subjects to one of three groups: once-only primary colonoscopy (PCOL arm), invitations to two rounds of high-sensitive FIT using a home test kit two years apart (FIT × 2 arm), or no intervention (control arm).[5]

Sweden is divided in 21 regions and each region is responsible for providing healthcare services. These regions are further organised into six collaborative health care regions. Two of the Swedish regions, which together form the health care region Stockholm-Gotland, started to implement CRC screening programmes in 2008/2009.[6] Eighteen of the other 19 regions, all naÿve to organised CRC screening, participated in the trial.

At the end of 2013, there were 437,000 registered inhabitants aged between 55 and 59 years (50.26% men) in the participating regions. SCREESCO started recruiting in March 2014, and finished the recruitment phase (including both invitations to FIT) in March 2020. The recruitment and screening procedures have been described in detail elsewhere.[5] In brief, the following approach was applied: Sixty-year-old men and women born in the period 1954–1958 were randomly selected and allocated to PCOL or FIT × 2. Randomised sampling of individuals from the population was performed within each combination of region and sex, and the number of individuals within each such stratum was defined following the population distribution. A randomised block method allocated individuals to the respective arms. In total, 31,440 individuals were randomised to the PCOL arm and 60,300 to the FIT × 2 arm. Ultimately, 30,400 (96.8%) and 60,137 (99.7%) were invited to each screening strategy. All invitees received a letter describing the study and a leaflet about CRC and screening (a reminder was sent after eight weeks). In

the PCOL arm, a second letter offered a scheduled time for a colonoscopy or to arrange a time by phone. In the FIT × 2 arm, the invitation letter included kits for stool samples and a positive FIT triggered an invitation to a colonoscopy identical to that offered to the colonoscopy group. Information on personal history of cancer was obtained from the Swedish Cancer Registry and 48 persons (21 in the PCOL arm, 27 in the FIT × 2 arm) with a previous CRC diagnosis did not attend colonoscopy.

The Ethics Committee at Karolinska Institutet approved the study, including the linkage to Swedish population registers for obtaining sociodemographic data (as described below).

Data

Individual data registered in the SCREESCO database up to February 2020 were sent to Statistics Sweden. Register holders in Sweden use the unique Swedish personal numbers for data linkage.[7] Statistics Sweden's population registry data on *educational level* (classified according to number of school years: >12 school years [corresponding to some education at university level] or ≤12 school years [no university education]), *household income* (disposable income per household per consumption unit [Statistics Sweden applies the following weights: 1·0 for single or living alone, 1·51 for cohabiting couple, 0·6 for each additional adult, 0·52 for first child 0–19 years, and 0·42 for each additional child 0–19 years] classified into national quartiles), *country of birth* (Western vs non-Western [Eastern Europe, Asia, Africa, and South America] countries), *marital status* (married, never married, or divorced/widowed/other), and *residential neighbourhood* (see below) were linked to each 60-year-old man/woman allocated to PCOL or FIT × 2. Time-varying data were assessed with regard to the year of invitation (first round in the FIT × 2 arm). Statistics Sweden delivered a pseudoanonymised data file for the present analysis.

Each study individual was geo-coded to residential neighbourhood at the time of (first) invitation, according to a small-area division of Sweden referred to as DeSO ("Demografiska StatistikOmråden" [in Swedish]). Statistics Sweden launched the DeSO division in 2018, to facilitate the monitoring of segregation and socioeconomic conditions in small geographic areas. In December 2018, the population sizes across the 5985 DeSO in Sweden varied between 653 and 4243. Strömberg and colleagues have demonstrated that these neighbourhoods can be used for monitoring influence of neighbourhood deprivation in public health.[8] They also suggested a DeSO-level deprivation index.[8] In the present analysis, we considered the following neighbourhood-level data: *deprivation* (neighbourhoods classified into national quintiles Q1 [least deprived] to Q5 [most deprived]), *proportion of non-Western immigrants* (proportion of inhabitants born in Eastern Europe, Asia, Africa, or South America in each neighbourhood assessed and, furthermore, classified into a national quintiles Q1-Q5), *population density* (total population size per km^2 in each neighbourhood assessed and, furthermore, classified into national quintiles Q1-Q5), and *distance to healthcare center* (straight line distance [km] from midpoint of neighbourhood to healthcare center for colonoscopy assessed and, furthermore, classified into quintiles Q1-Q5 based on all distances for the participating neighbourhoods). In the appendix, we provide maps visualizing the participating regions, neighbourhoods, healthcare centres for colonoscopy, and distances between neighbourhoods and healthcare centres (appendix Figure A1).

We defined the primary outcome of each study individual as *colonoscopy attendance or not* ie, a binary outcome taking the value 1 if the individual attended the healthcare center for colonoscopy after an invitation. For the individuals in the FIT × 2 arm, such an invitation was sent out provided a positive test in round 1 or 2 (410 individuals participated in a colonoscopy in both rounds[5]; their outcomes were set to 1). We also analysed *test attendance* (the test uptake) in the FIT × 2 arm, using binary outcomes equal to 1 for each individual who participated in the stool-based testing in round 1 or 2. In the FIT × 2 arm, we regarded the test uptake and the (work-up) colonoscopy uptake among the test positives as secondary outcomes in our evaluation of health equity.

Statistical methods

We modelled the colonoscopy attendance in the respective arms of the trial, and the test attendance in the FIT × 2 arm, using Bayesian logit models with individual-level and neighbourhood-level covariates. Missing data were classified in the dominant category of the covariate in question.

We obtained unadjusted odds ratios (ORs) with 95% credible interval (CI) from single-covariate models and adjusted ORs with 95% CI, together with predicted attendance proportions with 95% CI, from multivariable models with: (1) the individual-level covariates and (2) the neighbourhood-level covariates. The covariates *year of invitation* and *gender* were incorporated into both models. Neighbourhood-level random intercepts were modelled by including spatially unstructured, independent, and identically distributed Gaussian random effects in each model. In the modeling of neighbourhood-level associations (model 2), spatially structured random effects were enforced, using an intrinsic conditional autoregressive prior.[9,10] Thereby, in model 2, we allowed for attendance proportions to be more similar across adjacent neighbourhoods than those at distant locations. We specified a *minimally informative* prior on the hyper-parameters: logGamma(1, 0·0005).[10] The Appendix contains a detailed description of the statistical models.

The models were fitted by Integrated Nested Laplace Approximation (INLA) using the R-INLA software package.[10] All analyses were carried out in R version 4.0.0 (R Core Team, Vienna, Austria).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. US, CB, MW, LH, AF, and RH had access to the included study data. All authors agreed with the final decision to submit for publication.

Results

We excluded 24 individuals (10 in PCOL and 14 in FIT × 2) for whom we lacked register data necessary for the geocoding to residential neighbourhood. Two individuals had missing data on country of birth and 215 individuals had missing data on educational attainment; these data were classified into the categories "Western" and "no university education", respectively. Thus, the completed data sample for our analysis included 30,390 individuals invited to PCOL and 60,123 individuals invited to FIT × 2.

Table 1 shows that this large RCT yielded balanced covariate distributions between the two intention-to-screen populations (except for the covariate *year of invitation*[5]).

Individual-level associations with attendance among those invited to PCOL

In the PCOL arm, there was a pronounced variation in the attendance proportion around the overall proportion of 34·7% – between 20·3% and 40·7% (Table 1).

Women were less likely to attend colonoscopy than men (adjusted OR 0·87 [95% CI 0·83–0·91]; Table 2).

We found a marked socioeconomic gradient in the colonoscopy attendance proportion in the PCOL arm (adjusted OR 2·20 [95% CI 2·01–2·42] between the groups categorised in the highest vs. lowest national quartile for household income; Table 2). The colonoscopy attendance proportion was significantly lower among the people without university education compared to those with some university education (adjusted OR 0·75 [95% CI 0·71–0·79]), as well as among the non-Western immigrants compared to the people born in a Western country (adjusted OR 0·75 [95% CI 0·68 –0·84]) (Table 2). With regard to marital status, we found that the colonoscopy attendance proportion was higher among married persons (Table 2).

Individual-level associations with attendance among those invited to FIT × 2

In the FIT × 2 arm, the *colonoscopy* attendance proportion at the intention-to-screen level varied modestly around the overall proportion of 9·7% – between 7·7% and 10·4% across the population groups categorised by each covariate (Table 1). The *test* attendance proportion varied pronouncedly around the average of 55·3% – between 39·9% and 63·4% across the variously defined population groups (Table 1).

Women invited to the FIT × 2 arm were less likely to attend colonoscopy than men (adjusted OR women/men 0·90 [95% CI 0·86–0·95]), while the test attendance proportion was higher among women (adjusted OR women/men 1·35 [95% CI 1·31–1·40]) (Table 2). Men were more frequently tested positive than women (appendix Table A1).

The comparison between the groups categorised in the highest vs. lowest national quartile for household income showed a weaker association with the colonoscopy attendance at the intention-to-screen level (adjusted OR 1·29 [95% CI 1·16–1·42]) than with the test attendance (adjusted OR 2·08 [95% CI 1·96–2·20]) (Table 2). Furthermore, in comparison to the people with some university education, those without university education showed a similar colonoscopy attendance proportion at the intention-to-screen level (adjusted OR 0·99 [95% CI 0·94–1·06]), but a significantly lower test attendance proportion (adjusted OR 0·71 [0·69–0·74]) (Table 2). Hence, the socioeconomically related gradients in the colonoscopy attendance at the intention-to-screen level was notably less pronounced than the corresponding gradients in the test attendance (Table 2). These results can be explained by higher proportions of FIT positives and sufficiently high work-up colonoscopy uptakes in socioeconomically disadvantaged groups (appendix Table A1). For example, among the individuals in the lowest household income group who attended FIT, 20·7% (24·6% test positives among the tested × 78·4% work-up colonoscopy uptake) also attended colonoscopy, whereas the corresponding proportion among the individuals in the highest income group was 16·6% (17·7% × 93·8%) (appendix Table A1).

We obtained strikingly different associations of ethnic origin with the test and colonoscopy attendances at the intention-to-screen level in the FIT × 2 arm. The test attendance was higher among the non-Western immigrants (adjusted OR 1·14 [1·06–1·22]), whereas the colonoscopy attendance proportion out of those invited to the FIT × 2 arm was lower among the non-Western immigrants (adjusted OR 0·83 [0·74 –0·94]) (Table 2). The proportion of test positives out of all tested did not differ between the two groups reflecting ethnic origin, but the test-positive non-Western immigrants attended colonoscopy less frequently than the test positives from a Western country (appendix Table A1).

With regard to marital status, we found that the colonoscopy attendance proportion at the intention to screen level, as well as the test attendance proportion, was higher among married people (Table 2).

Covariate	Covariate distribution of the invited		Attendees out of the invited in each covariate category		
	PCOL,% (n)	FIT × 2,% (n)	PCOL Colonoscopy,% (n)	FIT × 2 Colonoscopy in round 1 or 2,% (n)	Test in round 1 or 2,% (n)
Year of invitation (first round in FIT × 2)					
2014	15·0% (4573)	14·5% (8726)	36·6% (1672)	11·7% (1024)	58·3% (5091)
2015	16·2% (4924)	36·6% (21,983)	34·9% (1717)	8·9% (1953)	55·9% (12,289)
2016	21·3% (6465)	42·6% (25,592)	34·5% (2228)	9·6% (2460)	53·9% (13,800)
2017 or later	47·5% (14,428)	6·4% (3822)	34·1% (4923)	10·1% (385)	54·3% (2076)
Gender					
Men	49·9% (15,159)	50·0% (30,034)	35·8% (5433)	10·1% (3038)	51·4% (15,451)
Women	50·1% (15,231)	50·0% (30,089)	33·5% (5107)	9·3% (2784)	59·2% (17,805)
Marital status					
Married	56·3% (17,123)	57·4% (34,540)	38·3% (6566)	10·2% (3506)	60·2% (20,778)
Never married	21·3% (6474)	20·0% (12,050)	28·7% (1861)	8·9% (1069)	46·1% (5559)
Divorced, widowed or other	22·4% (6793)	22·5% (13,533)	31·1% (2113)	9·2% (1247)	51·1% (6919)
Household disposable income per consumption unit					
National quartile 1	11·7% (3560)	12·0% (7209)	20·3% (722)	7·7% (555)	39·9% (2874)
National quartile 2	13·6% (4119)	13·6% (8200)	28·1% (1157)	9·5% (779)	48·5% (3975)
National quartile 3	26·7% (8108)	26·4% (15,869)	33·7% (2729)	9·5% (1513)	53·6% (8507)
National quartile 4	48·1% (14,603)	48·0% (28,845)	40·6% (5932)	10·3% (2975)	62·1% (17,900)
University education					
Yes	32·7% (9933)	32·1% (19,279)	40·7% (4045)	9·9% (1904)	63·4% (12,215)
No	67·3% (20,457)	67·9% (40,844)	31·7% (6495)	9·6% (3918)	51·5% (21,041)
Country of birth					
Western country	92·9% (28,229)	93·3% (56,071)	35·4% (9982)	9·8% (5498)	55·4% (31,067)
Non-Western country	7·1% (2161)	6·7% (4052)	25·8% (558)	8·0% (324)	54·0% (2189)
Neighbourhood deprivation (deprivation index divided into national quintiles Q1-Q5)					
Q1 (least deprived)	15·0% (4566)	15·1% (9108)	37·7% (1721)	10·3% (940)	60·6% (5518)
Q2	20·8% (6332)	20·6% (12,412)	37·4% (2366)	9·6% (1191)	57·2% (7107)
Q3	22·6% (6857)	22·8% (13,683)	36·4% (2498)	9·7% (1333)	56·4% (7722)
Q4	23·0% (6984)	22·8% (13,710)	33·5% (2337)	9·8% (1337)	54·1% (7414)
Q5 (most deprived)	18·6% (5651)	18·6% (11,210)	28·6% (1618)	9·1% (1021)	49·1% (5501)
Proportion of non-Western immigrants in neighbourhood (divided into national quintiles Q1-Q5)					
Q1 (≥ 0·000 to ≤ 0·014)	25·6% (7786)	26·1% (15,677)	38·9% (3027)	10·3% (1616)	57·9% (9071)
Q2 (> 0·014 to ≤ 0·023)	22·0% (6680)	21·8% (13,118)	36·0% (2404)	10·2% (1339)	57·0% (7481)
Q3 (> 0·023 to ≤ 0·036)	19·2% (5836)	19·6% (11,760)	34·4% (2008)	9·6% (1134)	55·5% (6521)
Q4 (> 0·036 to ≤ 0·060)	17·2% (5229)	16·8% (10,120)	33·7% (1761)	9·1% (916)	54·2% (5489)
Q5 (> 0·060 to ≤ 0·391)	16·0% (4859)	15·7% (9448)	27·6% (1340)	8·6% (817)	49·7% (4694)
Distance to healthcare center for colonoscopy (residential neighbourhood average distance [km] divided into quintiles Q1-Q5)					
Q1 (≥ 0·05 to ≤ 3·85)	19·9% (6036)	20·1% (12,075)	34·6% (2089)	9·2% (1107)	55·1% (6654)
Q2 (> 3·85 to ≤ 15·7)	20·3% (6163)	19·9% (11,936)	34·4% (2121)	9·9% (1184)	56·2% (6704)
Q3 (> 15·7 to ≤ 30·9)	20·1% (6095)	20·0% (12,008)	35·3% (2150)	9·7% (1166)	55·3% (6641)
Q4 (> 30·9 to ≤ 46·4)	19·8% (6005)	20·1% (12,096)	34·5% (2073)	9·3% (1128)	55·2% (6673)
Q5 (> 46·4 to ≤ 303)	20·0% (6091)	20·0% (12,008)	34·6% (2107)	10·3% (1237)	54·8% (6584)
Population density in neighbourhood (inhabitants per km^2 divided into national quintiles Q1-Q5)					
Q1 (≥ 0·0682 to ≤ 94·2)	26·7% (8115)	26·9% (16,180)	37·5% (3045)	10·4% (1680)	56·5% (9140)
Q2 (> 94·2 to ≤ 383)	22·3% (6762)	22·3% (13,435)	35·9% (2426)	10·0% (1340)	55·0% (7392)
Q3 (> 383 to ≤ 1470)	21·9% (6651)	21·4% (12,885)	34·1% (2265)	9·4% (1207)	56·3% (7253)
Q4 (> 1470 to ≤ 4850)	17·4% (5277)	17·3% (10,396)	33·3% (1757)	9·4% (978)	55·6% (5776)
Q5 (> 4850 to ≤ 57,500)	11·8% (3585)	12·0% (7227)	29·2% (1047)	8·5% (617)	51·1% (3695)

***Table 1*: Covariate distributions and attendance proportions observed among 30,390 60-year-old men and women in Sweden invited to once-only primary colonoscopy (PCOL) and 60,123 invited to biennial fecal immunochemical testing (FIT × 2).**

Covariate	PCOL			FIT × 2					
	Colonoscopy attendance (ie, uptake)			Colonoscopy attendance (out of all invited)			Test attendance (ie, test uptake)		
	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Predicted attendance proportion (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Predicted attendance proportion (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Predicted attendance proportion (95% CI)
Year of (first) invitation									
2014	1	1	0·41 (0·40–0·43)	1	1	0·13 (0·12–0·14)	1	1	0·63 (0·62–0·65)
2015	0·93 (0·85–1·01)	0·92 (0·84–1·00)	0·39 (0·38–0·41)	0·73 (0·68–0·79)	0·74 (0·68–0·80)	0·10 (0·09–0·10)	0·90 (0·86–0·95)	0·92 (0·87–0·97)	0·61 (0·60–0·62)
2016	0·91 (0·84–0·99)	0·90 (0·83–0·98)	0·39 (0·37–0·41)	0·80 (0·74–0·86)	0·80 (0·74–0·87)	0·10 (0·10–0·11)	0·83 (0·79–0·87)	0·84 (0·80–0·89)	0·59 (0·58–0·61)
2017 or later	0·90 (0·84–0·96)	0·89 (0·83–0·95)	0·39 (0·37–0·40)	0·84 (0·74–0·95)	0·85 (0·75–0·96)	0·11 (0·10–0·12)	0·85 (0·78–0·92)	0·85 (0·79–0·92)	0·59 (0·58–0·61)
Gender									
Men	1	1	0·41 (0·39–0·42)	1	1	0·11 (0·10–0·12)	1	1	0·56 (0·55–0·57)
Women	0·90 (0·86–0·95)	0·87 (0·83–0·91)	0·37 (0·36–0·39)	0·91 (0·86–0·96)	0·90 (0·85–0·95)	0·10 (0·09–0·11)	1·37 (1·33–1·42)	1·35 (1·31–1·40)	0·63 (0·62–0·64)
Marital status									
Married	1	1	0·39 (0·37–0·41)	1	1	0·10 (0·10–0·11)	1	1	0·41 (0·40–0·43)
Never married	0·65 (0·61–0·69)	0·75 (0·70–0·80)	0·32 (0·31–0·34)	0·86 (0·80–0·93)	0·89 (0·82–0·96)	0·09 (0·09–0·10)	0·57 (0·54–0·59)	0·70 (0·67–0·73)	0·49 (0·48–0·50)
Divorced, widowed or other	0·73 (0·68–0·77)	0·85 (0·80–0·91)	0·35 (0·33–0·37)	0·90 (0·84–0·96)	0·95 (0·88–1·01)	0·10 (0·09–0·11)	0·69 (0·67–0·72)	0·80 (0·76–0·83)	0·54 (0·53–0·55)
Household income									
Quartile 1	1	1	0·23 (0·21–0·24)	1	1	0·08 (0·08–0·09)	1	1	0·41 (0·40–0·43)
Quartile 2	1·54 (1·38–1·71)	1·47 (1·32–1·64)	0·30 (0·28–0·32)	1·26 (1·12–1·41)	1·23 (1·10–1·38)	0·10 (0·09–0·11)	1·42 (1·33–1·51)	1·36 (1·27–1·45)	0·49 (0·48–0·50)
Quartile 3	1·99 (1·82–2·19)	1·82 (1·65–2·00)	0·35 (0·33–0·36)	1·26 (1·14–1·40)	1·21 (1·10–1·35)	0·10 (0·09–0·11)	1·74 (1·65–1·84)	1·61 (1·52–1·71)	0·53 (0·52–0·54)
Quartile 4	2·69 (2·46–2·94)	2·20 (2·01–2·42)	0·39 (0·37–0·41)	1·38 (1·26–1·52)	1·29 (1·16–1·42)	0·10 (0·10–0·11)	2·47 (2·34–2·60)	2·08 (1·96–2·20)	0·59 (0·58–0·60)
University education									
Yes	1	1	0·46 (0·44–0·48)	1	1	0·11 (0·10–0·11)	1	1	0·67 (0·66–0·68)
No	0·68 (0·64–0·71)	0·75 (0·71–0·79)	0·39 (0·37–0·41)	0·97 (0·91–1·03)	0·99 (0·94–1·06)	0·10 (0·10–0·11)	0·61 (0·59–0·64)	0·71 (0·69–0·74)	0·59 (0·58–0·60)
Country of birth									
Western country	1	1	0·39 (0·37–0·41)	1	1	0·10 (0·10–0·11)	1	1	0·59 (0·58–0·60)
Non-Western	0·64 (0·58–0·70)	0·75 (0·68–0·84)	0·33 (0·30–0·35)	0·80 (0·71–0·90)	0·83 (0·74–0·94)	0·09 (0·08–0·10)	0·96 (0·90–1·03)	1·14 (1·06–1·22)	0·62 (0·61–0·64)

***Table 2*: Associations of sociodemographic and spatial covariates with colonoscopy attendance proportion among 30,390 60-year-old men and women in Sweden invited to primary colonoscopy (PCOL); and with test and colonoscopy attendance proportions among 60,123 invited to biennial fecal immunochemical testing (FIT × 2).**

Odds ratios (ORs) with 95% credible interval (CI) obtained from the corresponding Bayesian logistic regression model including a single covariate (unadjusted ORs) or all covariates (adjusted ORs). Predicted attendance proportions are also shown for each covariate. These predicted proportions were obtained by keeping each other covariate constant at their most common category (ie, [except for the varying covariate] Year of invitation = 2016, Marital status = married, Household income = quartile 4, University education = no, and Country of birth = Western), and taking the mean of the gender-specific predicted proportions.

The FIT uptake increased slightly between the first and second rounds (+0·9 percentage points). The change in FIT uptake over time differed somewhat between the population groups categorised in the highest vs. lowest national quartile for household income (+1·6 vs. −0·5 percentage points).

Neighbourhood-level associations

The socioeconomic gradients in the uptakes of PCOL and FIT × 2, respectively, were apparent also when categorizing population groups according to neighbourhood deprivation (appendix Table A2). By contrast, there was no such apparent gradient in the colonoscopy attendance proportion at the intention-screen-level of the FIT × 2 arm (appendix Table A2).

We found higher attendance proportions in the PCOL arm in neighbourhoods in close proximity to a screening center. The study persons living in the neighbourhoods classified in the distance quintiles Q2-Q4, ie, having a distance from the midpoint of their neighbourhood to the healthcare center for colonoscopy longer than 3·85 km (Table 1), showed lower adjusted ORs (varying between 0·86 [95% CI 0·77–0·96] and 0·88 [0·80–0·98]), as compared with those classified in Q1 (distance ≤3·85 km) (appendix Table A2).

Discussion

Based on the nationwide two-armed RCT SCREESCO conducted in Sweden, including 60,123 60-year-olds invited to CRC screening with a two rounds of FIT 2 years apart strategy and 30,390 invited to once-only primary colonoscopy, we found only small variations in the proportion who underwent colonoscopy out of *all invited* to FIT across variously defined population groups. In contrast, the colonoscopy attendance proportion in the PCOL arm was markedly lower in socioeconomically disadvantaged groups. The socioeconomic gradients in the uptake of the PCOL strategy were parallel with the corresponding gradients in the *test uptake* of the FIT × 2 strategy.

To our knowledge, this analysis is the first to compare colonoscopy attendance proportions between two large intention-to-screen populations randomly invited to FIT and PCOL, respectively, with consideration of several sociodemographic covariates. The large RCT design will have ensured comparable groups invited to the two screening approaches in terms of known and unknown confounders. Such comparability of the groups allocated to FIT × 2 and once-only PCOL strategies, may not be guaranteed in other RCTs that allow for a choice between FIT and PCOL within a screening arm. There are two other ongoing RCTs[11,12] which have been designed with separate FIT and PCOL arms, whereas another RCT[13] allowed for crossover between the PCOL and FIT arms and two other RCTs[14,15] have been designed to compare hybrid PCOL+FIT strategies against either PCOL or FIT as the control arm.

For each screening arm, FIT × 2 or PCOL, we considered *an invariable colonoscopy attendance proportion across variously defined population groups within the intention-to-screen population* as the primary criterion for attaining health equity, based on the rationale that an individual's potential health benefit related to CRC is conditional on colonoscopy. A limitation is that colonoscopy attendance in itself does not provide the full picture of the potential health benefit; the health outcome depends on the diagnostic yield, the effect of detecting a tumor earlier, and the long-term effect of polypectomy.

In screening with FIT, the predictive value of a positive test on the diagnostic yield may differ across various population groups; eg, if the risk of comorbidities that require anticoagulation therapy differs between population groups. On the other hand, the risk of CRC may also differ between population groups. Increased incidences of CRC, in particular stage II-IV tumours, with lower socioeconomic status have been observed among 55–74-year-old people in Sweden.[16] Most likely, in a FIT-followed-by-colonoscopy approach, the increasing likelihood of a positive FIT with deceasing socioeconomic status, as the present data from SCREESCO clearly indicate (appendix Table A1), helps to avoid exacerbation of health inequity. Steele and colleagues have reported increasing proportions of test positives with increasing neighbourhood deprivation in screening with biennial guaiac fecal occult blood test (gFOBT) in Scotland.[17] Furthermore, the present data from SCREESCO showed colonoscopy uptakes among the test positives in the FIT × 2 arm between 83·6% and 93·8% in all but two of the population groups that we considered (appendix Table A1). Lower uptakes were observed for the individuals born in a non-Western country (76·4%) and the individuals with a household income in the lowest national quartile (78·4%). Morris and colleagues have reported small socioeconomic variations in the colonoscopy uptake among the fecal occult blood test positives in the NHS Bowel Cancer Screening Programme in England (between 84·6% and 90·6%).[18]

The analysis of the PCOL arm revealed markedly lower colonoscopy attendance proportions in socioeconomically disadvantaged groups. However, we cannot infer exacerbated health inequities from these results with certainty. We have not addressed whether or not the diagnostic yield was higher among the attendees in socioeconomically disadvantaged groups. If so, the relation between the colonoscopy attendance proportion and the number of tumours detected earlier and potentially prevented may be inconsistent across different population groups. Analyses of sociodemographic variations in diagnostic yield among the attendees could generate further understanding about health inequities implied by the PCOL strategy.

A relatively small number of invitees were registered as participants in the SCREESCO database in the period March-December 2020 (delayed reporting occurred), ie, after the data for this analysis were prepared. Therefore, the total numbers of registered attendees in each arm were somewhat lower in the data set for the present analysis than reported in another report based on data registered until December 2020[5] (in the PCOL arm: 10,540 vs. 10,679 attendees; in the FIT × 2 arm: 33,256 vs 33,383 test attendees and 5822 vs 5876 colonoscopy attendees).

We had access to both individual-level and neighbourhood-level data. We used two types of models for estimation of 1) associations based on the individual-level data and 2) neighbourhood-level associations. Type 2 models may be applicable also in other countries where individual-level data are not available but neighbourhood-level data are commonly used. However, our analysis demonstrated that more distinct socioeconomic gradients can be obtained from individual-level data.

Several studies have analysed associations of ethnicity with the test uptake of organised FIT screening, using individual indicators of ethnicity and neighbourhood-based indicators of ethnic diversity.[1,2] Inferences from such studies should be made with caution due to possible residual confounding by socioeconomic factors. In our analysis of the test attendance proportion in the FIT × 2 arm, the unadjusted OR for non-Western immigrants versus people born in a Western country was estimated to be 0·96 (95% CI 0·90–1·03), whereas the multivariable adjustments changed the OR estimate to 1·14 (1·06–1·22). However, a comparable analysis, based on sociodemographic data linked to the organised FIT screening program in Denmark, has indicated lower test uptake among non-Western immigrants, even after adjustments for confounders.[19] Our analysis of the colonoscopy attendance proportion at the intention-to-screen level in the FIT × 2 arm showed a decreasing gradient across the two groups reflecting Western and non-Western origins. This results, in contrast to the increasing gradient in the test uptake, was understandable from the data showing that the test-positive non-Western immigrants attended colonoscopy less frequently than the test positives from a Western country (appendix Table A1).

Another noticeable result revealed that men attended more frequently in the PCOL screening than did women, while the test attendance proportion in the FIT × 2 arm was higher among women. Such gender differences have been reported previously.[2,20] Possible explanations may be that FIT participation is influenced by traditional gender roles in health, while women's embarrassment and worry for pain are more strongly linked to the invasive characteristics of colonoscopy.[2,21] Among the test attendees in the FIT × 2 arm, the proportion of test positives was higher among men than among women; this is probably related to biological factors rather than psychosocial/cultural factors.[5,20]

Future economic evaluations could provide information about the equity impacts of the alternative strategies and the trade-offs that may arise between equity in health and cost-effectiveness. A distributional cost-effectiveness analysis provides such information.[22,23] A comparative cost-effectiveness analyses of PCOL versus FIT based on early experiences of participation in the SCREESCO study have shown that screening with PCOL could be more cost-effective than FIT when lifelong effects and costs were considered.[24] Our finding indicates that PCOL screening might increase the inequalities in the population health distribution and, thereby, bringing to the fore the choice between efficacy and equal health distribution.

Previous research has emphasised efforts to reduce socioeconomic inequalities in the uptake of stool-based testing.[25] However, in the future efforts should be focused on reducing socioeconomic inequalities in the uptake of PCOL screening, and, in organised screening with FIT, increasing the colonoscopy uptake among the test positives, not least in groups of people from non-Western countries. We found that the distance to the endoscopy center could have an impact on the uptake of organised PCOL screening, rather than on the colonoscopy uptake of organised FIT screening with a home test kit (where the distance is of potential concern only for test positives invited to work-up colonoscopy). Whether the distance between home and endoscopy center affects the uptake of CRC screening has been addressed in a few studies, but with inconsistent results.[2] However, those results were obtained in settings with opportunistic rather than organised screening. Interestingly, for another type of organised screening, namely, atrial fibrillation screening aimed at men and women around 75 years of age, participation was improved greatly among socioeconomically disadvantaged people in Sweden by introducing a new screening center close to their neighbourhoods.[26]

In conclusion, the unintended risk of exacerbating inequalities in health by an organised CRC screening may be higher with a once-only PCOL strategy than a two rounds of FIT 2 years apart strategy, despite parallel socioeconomic gradients in the uptake of each approach. We recommend that future cost-effectiveness evaluations provide information about the health equity impacts of the alternative strategies and the trade-offs that may arise between equity and efficacy.

Contributors

US designed the study concept. AF, RH, MW, CB, and US obtained and managed data. US and CB designed the analytical approach. CB carried out the analysis. US designed presentation of results. US and LH wrote the first draft of the paper; all other authors contributed to

the revision and finalization of the paper. All authors helped with interpretation of results. The corresponding author was responsible for submitting the article for publication. RH, AF, LH, MW, CB, and US had full access to all data used in this study. CB, MW, and US checked and verified the data used in the analysis. Due to data permission restrictions, not all authors were able to access the individual-level data used in the study.

Declaration of interests

CB reports a grant from the Swedish Research Council for Health, Working life and Welfare under grant no. 2020–00962 to his institution. CM reports travel and subsistence expenses refunded from the study budget (no external funding of this). US reports grants from the Swedish Cancer Society under grant no. 20–0719 and the Swedish Research Council for Health, Working life and Welfare under grant no. 2020–00962 to his institution. All other authors have nothing to declare.

Data sharing statement

For data sharing questions, please contact study PI Rolf. Hultcrantz@ki.se. The study protocol and statistical analysis plan are available on request and are also filed with Lancet Gastroenterology and Hepatology. De-identified individual participant data that underlie the results reported in this article (text, tables, figures, and appendices), can be available to researchers after application to the SCREESCO Steering Committee. Researchers have to provide a methodologically sound proposal for a project that conforms with the Swedish Ethical Review Authority permit for the project. Researchers will have to sign a data access agreement. Data will be made available at a secure remote server to achieve the aims in the approved proposal. They will be available from 3 months after publication and ending three years after article publication. Proposals regarding the data underlying this article may be submitted up to two years after publication. The SCREESCO study will not carry the costs of external projects.

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Supplementary materials

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