BMJ Open Gastroenterology

Socioeconomic inequalities in interval colorectal cancer are explained by differences in faecal haemoglobin concentration and age: a register-based cohort study

Ulrik Deding ,[1,2] Morten Kobaek-Larsen,[1,2] Henrik Bøggild,[3] Lasse Kaalby ,[1,2] Marianne Kirstine Thygesen,[1,2] Gunnar Baatrup[1,2]

To cite: Deding U, Kobaek-Larsen M, Bøggild H, *et al*. Socioeconomic inequalities in interval colorectal cancer are explained by differences in faecal haemoglobin concentration and age: a register-based cohort study. *BMJ Open Gastro* 2023;**10**:e001113. doi:10.1136/bmjgast-2023-001113

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bmjgast-2023-001113).

Received 18 January 2023
Accepted 28 April 2023

[1]Department of Surgery, Odense University Hospital, Svendborg, Denmark
[2]Department of Clinical Research, University of Southern Denmark, Odense, Denmark
[3]Department of Health Science and Technology, Public Health and Epidemiology Group, Aalborg University, Aalborg, Denmark

Correspondence to
Ulrik Deding;
Ulrik.Deding@rsyd.dk

ABSTRACT

Objective To estimate the risk of interval colorectal cancer (CRC) in faecal immunochemical test (FIT) negative screening participants according to socioeconomic status.

Design In this register-based study, first round FIT negative (<20 µg hb/g faeces) screening participants (biennial FIT, citizens aged 50–74) were followed to estimate interval CRC risk. Multivariate Cox proportional hazard regression models estimated HRs based on socioeconomic status defined by educational level and income. Models were adjusted for age, sex and FIT concentration.

Results We identified 829 (0.7‰) interval CRC in 1 160 902 individuals. Interval CRC was more common in lower socioeconomic strata with 0.7‰ for medium-long higher education compared with 1.0‰ for elementary school and 0.4‰ in the highest income quartile compared with 1.2‰ in the lowest. These differences did not translate into significant differences in HR in the multivariate analysis, as they were explained by FIT concentration and age. HR for interval CRC was 7.09 (95% CI) for FIT concentrations 11.9–19.8 µg hb/g faeces, and 3.37 (95% CI) for FIT between 7.2 and 11.8 compared with those <7.2. The HR rose with increasing age ranging from 2.06 (95% CI 1.45 to 2.93) to 7.60 (95% CI 5.63 to 10.25) compared with those under 55 years.

Conclusion Interval CRC risk increased with decreasing income, heavily influenced by lower income individuals more often being older and having increased FIT concentrations. Individualising screening interval based on age and FIT result, may decrease interval CRC rates, reduce the social gradient and thereby increase the screening efficiency.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Population-based colorectal cancer screening has proven capable of decreasing cause-specific and all-cause mortality.
⇒ Guidelines recommend that screening programmes should aim to limit inequalities.
⇒ Social inequalities in colorectal cancer screening are evident in several stages of the process; faecal immunochemical test (FIT) participation, correct FIT sample collection, colonoscopy participation and risk of incomplete colonoscopy.

WHAT THIS STUDY ADDS

⇒ Social inequalities in interval colorectal cancer are evident in a National population-based screening programme using FIT, followed by optical colonoscopy in FIT positive individuals aged 50–74 years.
⇒ Individuals of lower income are at higher risk of interval colorectal cancer compared with their peers of higher-income groups.
⇒ Differences in risk between socioeconomic status subgroups are explained by differences in FIT concentration and age.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Population-based colorectal cancer screening programmes invite citizen based on their age and most use FIT to determine who is a candidate for optical colonoscopy.
⇒ Therefore, age and FIT results are easy available information in all FIT negative screening participants.
⇒ Screening programmes could increase efficiency, decrease the number of interval colorectal cancers and potentially limit the social gradient by differentiating the screening interval based on age and FIT result.

INTRODUCTION

Socioeconomic and demographic differences in colorectal cancer screening participation are evident worldwide.[1] Screening participation is associated with a reduction in both colorectal cancer mortality and all-cause mortality in long-term follow-up.[2] The higher mortality in non-participants may be due to higher stages of cancer at diagnosis, but advanced staged cancers detected in screening also holds better prognosis than cancers detected outside screening.[3] This

probably entails an increased mortality risk in lower socioeconomic subgroups due to their lower participation rates. European guidelines state that participation should not be limited by financial barriers and that one aim of screening is to reduce health inequalities.[4]

Nevertheless, social inequalities are evident in participation at both faecal immunochemical test (FIT) and colonoscopy.[5 6] The proportion of positive FIT samples and the risk of a following incomplete colonoscopy is higher in lower socioeconomic subgroups.[7 8] Why this is, has yet to be determined, but it has been established that lifestyle and health behaviour affects the risk of colorectal cancer.[9] In a North-American study, socioeconomic status has been identified as a predictor of the diversity in the colonic microbiota.[10] Lifestyle affects the risk of developing inflammatory bowel disease (IBD) and, in IBD patients, lifestyle affects the severity of disease,[11 12] while diet may also prevent the development of colorectal cancer.[13] Further, health behaviour such as smoking, alcohol and diet varies between socioeconomic subgroups[14 15] and may lead to increased risk of colorectal cancer. Whether this will be reflected in increased FIT concentrations is unknown. One possible explanation could be that lifestyle also affects the colonic microbiota and increases the risk of inflammation in the colon, entailing vasodilation and increased vascular permeability, swelling and redness,[16] which could then increase the risk of haemoglobin in the lumen when faeces come into contact with the mucosal lining. Further, the cell turnover increases when inflammation occurs, and the risk of cancers developing increases with cell proliferation.[17]

We know that the risk of interval cancer correlates to FIT value, sex and age in FIT negative individuals,[18–21] but whether a social gradient in the frequency of interval cancer exists is yet to be established. One study did not find statistically significant differences in interval colorectal cancer rates in FIT negative subjects by socioeconomic score, but was based on only 27 cases.[22]

We aimed to estimate the risk of interval colorectal cancer in FIT negative screening participant according to socioeconomic status.

METHODS

In this register-based study, individuals with a negative FIT (below 100 ng hb/mL buffer equivalent to 20 µg hb/g faeces) in the first round of the Danish Colorectal Cancer Screening Programme were identified. They were followed to estimate the risk of interval colorectal cancer defined as a colorectal cancer diagnosis before the next screening round. They were followed from the date of their negative FIT result until next screening invitation, death, emigration, lost to follow-up or end of follow-up 24 September 2018, whichever came first. The first round of screening in Denmark was rolled out over 4 years (2014–2017), after which citizens are repeatedly invited every 2 years. Follow-up in our study was therefore limited to 2 years in individuals who were not reinvited within 2 years. Individuals lost to follow-up or with missing data on exposure, outcomes or covariates were excluded from the analyses.

Registers

All data between registers were linked using the personal civil registration number assigned to all individuals in Denmark at birth or when immigrating.

The Danish Colorectal Cancer Screening Database (DCCSD) provided data on sex, age, date of screening participation, date of invitations and FIT results. The DCCSD is a clinical database with high validity for programme monitoring and research purposes.[23] It holds a high level of agreement (>90%) with hospital records, and receives data directly from the Invitation and Administration Module (IAM), which automatically plans and executes individuals' screening invitation trajectory. IAM uses the civil registration number, which includes the date of birth and sex of the citizen. Besides the IAM, the DCCSD also comprises data from the Danish National Patient Registry (DNPR) and the National Pathology registry.

The DNPR provided data on colorectal cancer diagnoses during follow-up. The DNPR was established in 1977 and holds information on all patient contacts with Danish hospitals, including diagnoses, procedures, treatments and dates. All diagnoses in the DNPR are registered using the International classification of Diseases (ICD) coding. The DNPR is the most comprehensive register and has since the year 2000 been the basis of all funding for public hospitals. Therefore, the registrations from public hospitals since then is assumed to be complete.[24] Colorectal cancer diagnoses were identified in the DNPR as ICD-10 codes 'C18' or 'C20', or ICD-8 codes '15300', '15301', '15302', '15309', '15319', '15329', '15339', '15380', '15389', '15399', '15409', '15410', '15411', '15419', or '15429'. ICD-8 codes were included in order to identify individuals with previous colorectal cancer as these were used up until the year 1993.

The Populations Education Registers (PER) provided data on the highest achieved level of education. The PER has a reported 0%–3% misclassifications and in 2008, 97% of the Danish population born between 1945 and 1990 have a registered level of education, but for immigrants this figure was lower (85%–90%).[25]

The Income Statistics Register (ISR) provided data on personal income. The ISR holds income information on anyone who has submitted a tax return form in Denmark and registers anyone economically active in Denmark. The ISR includes information on wages, entrepreneurial income, taxes, public transfer payments, public pensions, capital income, and private pension contributions and pay-outs. The ISR is complete and holds all registered income, however, any undeclared income cannot be covered by the register.[26]

Socioeconomic status

Socioeconomic status was assessed for each individual using educational level and income. These were treated as two separate exposures. Educational level was identified as highest level of completed education from the PER[25] at baseline and grouped as elementary school, high school or vocational education, short higher education, and medium-long higher education. We considered income as the annual individual income in the year previous to the FIT submission as registered in the ISR.[26] We then adjusted for inflation (year 2021) and categorised income by quartiles within the sample. The first income quartile was income below DKK208 897 (US$28 526), the second quartile was DKK208 897–DKK315 535 (US$28 526–US$43 088), the third quartile was DKK315 536–DKK447 865 (US$43 088–US$77 665), and the forth quartile was above DKK447 865 (US$77 665).

Covariates

Age was included in the models as a categorical variable grouped as <55, 55–59, 60–64, 65–69 and 70 years or above. Sex was included as a binary variable. FIT concentration was included as a categorical variable grouped as <7.2 µg hb/g faeces, 7.2–11.8 µg hb/g faeces and 11.9–19.8 µg hb/g faeces. Concentrations were reported as numerical values between below 35–99 ng hb/mL buffer in the DCCDS. This was translated into µg hb/g faeces resulting in a minimum value reported as below 7.2 and a maximum value of 19.8 µg hb/g faeces. FIT concentrations were measured in the screening programme using the OC-Sensor Diana instruments (Eiken Chemical Co, Japan).

Statistics

Baseline characteristics were compared using the χ^2 test. Multivariate Cox proportional hazards regression models were conducted, estimating the hazard rate ratio as a proxy for the risk of interval colorectal cancer based on socioeconomic status in a simple model including both income and educational level and in a full multivariate model additionally adjusting for age, sex and faecal haemoglobin concentration. The authors discussed whether faecal haemoglobin concentration was to be considered a confounder or if it mediated the effect of socioeconomic status on the risk of interval colorectal cancer. This discussion arose since, as suggested in the introduction, lifestyle and health behaviour are associated with the risk of colorectal cancer and are also associated with socioeconomic status. We also know that lifestyle mediates some, but not all, inequalities in health related to socioeconomic status.[27] FIT concentration may, therefore, simply be viewed as a marker of disease, but could also theoretically act as a proxy for lifestyle and behaviour in a mediation analysis. We, therefore, performed a series of regression models, as suggested by Baron and Kenny,[28] confirming that faecal haemoglobin concentration was not a mediator. Schönfeld residuals were evaluated to confirm the proportional hazards assumption, and interactions between each covariate and educational level and income, respectively, were explored by including interaction terms in the models. Cross-tables of age group and FIT concentrations stratified by socioeconomic status were provided. Finally, cumulative incidence proportions curves stratified by the strongest predictors of interval colorectal cancer were created. Level of statistical significance was set at 5% and 95% CIs were calculated. Data management and statistical analysis were performed using SAS software V.9.4 (SAS Institute) and R statistical software package V.4.1.3 (R Core Team, Vienna, Austria). Sensitivity analyses were performed conducting the multivariate regression model first including the interaction term of educational level and FIT concentration, then, stratified by FIT concentration, and last, while stratifying the baseline hazard function by FIT concentration. Further, we conducted marginal effects analysis exploring the pattern of this interaction. Marginal effects analysis was conducted in STATA V.17 (StataCorp. 2021. Stata Statistical Software: Release V.17, StataCorp).

RESULTS

In Denmark, 1 190 540 individuals submitted a FIT sample and had a negative test result in the first round of screening. Among these, we excluded 4718 (0.40%) individuals that were registered with previous colorectal cancer and 88 (0.07‰) individuals that were emigrated or dead prior to participation. A further 24 832 (2.1%) were excluded due to missing information on socioeconomic status. This left 1 160 902 (97.5%) individuals for final analyses, of whom 829 (0.7‰) were diagnosed with colorectal cancer before their next screening invitation (ie, within a maximum of 2 years) (figure 1).

Significant differences in the proportions of interval colorectal cancer among participants were observed between groups of educational level, income quartiles, FIT concentrations, sex and age group. Participants with elementary school as their highest completed educational level had a higher proportion of interval colorectal cancer than participants with higher educational levels. Also, the proportion of interval colorectal cancer decreased with increasing income. The highest proportions of interval colorectal cancer in the subgroups were seen in the eldest (1.6‰) and those with high negative faecal haemoglobin concentrations (2.1‰ and 4.6‰) (table 1).

Compared with those with elementary school as their highest level of education, only those with high school/vocational education had a significant lower risk of interval colorectal cancer from the simple model with an HR 0.83 (95% CI 0.71 to 0.98). The risks of interval colorectal cancer were significantly lower for those in the second (HR 0.60, 95% CI 0.51 to 0.71), third (HR 0.44, 95% CI 0.36 to 0.54) and fourth (HR 0.36, 95% CI 0.29 to 0.45) income quartiles compared with those with the lowest income in the simple model (figure 2).

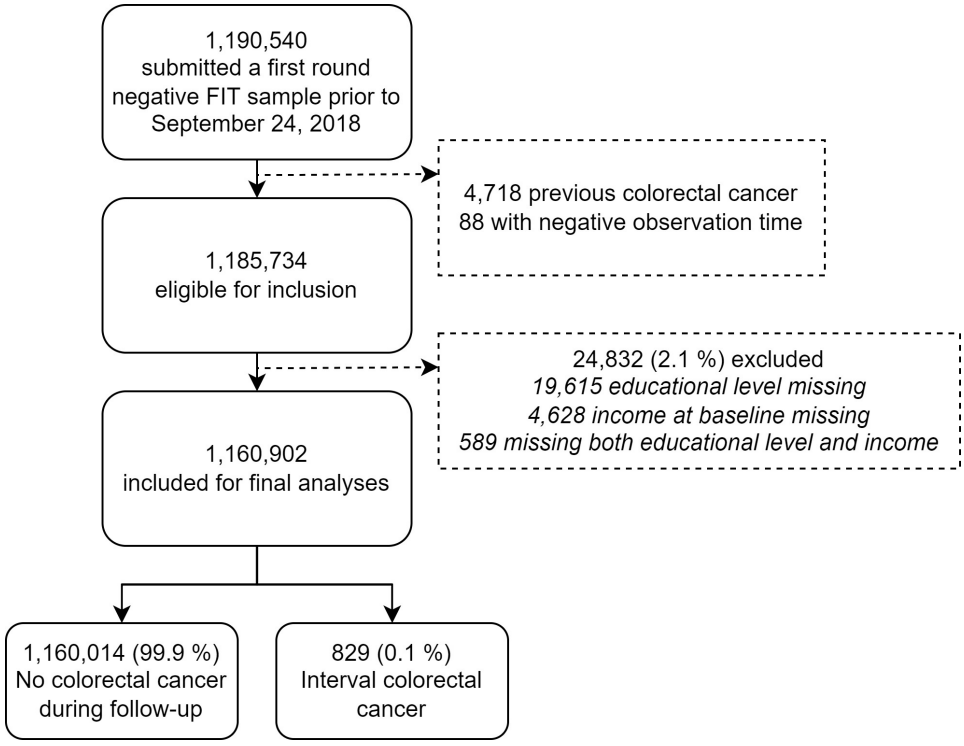


Figure 1 Flow of participants. FIT, faecal immunochemical test.

After adjusting for covariates, the only significant difference in risk for socioeconomic characteristics was a decreased risk for second income quartile (HR 0.76, 95% CI 0.64 to 0.91) compared with first quartile. The differences in risk were especially impacted by adjustments for FIT concentration and age. Sex also appeared to impact the results but to a lesser degree (figure 3). HR from the adjusted model were 3.37 (95% CI 2.81 to 4.04)

Table 1 Baseline characteristics stratified by interval colorectal cancer outcome

Variable	Subgroup	No interval CRC (%), n=1160073	Interval CRC (%), n=829	Total, n=1 160 902	P value
Educational	Elementary school	273585 (99.9)	262 (1.0)	273847	
level	High school/vocational	526835 (99.9)	357 (0.7)	527192	
	Short higher	272977 (99.9)	152 (0.6)	273129	
	Medium-long higher	86676 (99.9)	58 (0.7)	86734	<0.001
Income	1st quartile	286274 (99.9)	350 (1.2)	286624	
	2nd quartile	289176 (99.9)	207 (0.7)	289383	
	3rd quartile	291675 (99.9)	148 (0.5)	291823	
	4th quartile	292948 (100.0)	124 (0.4)	293072	<0.001
FIT	<7.2 µg hb/g faeces	1 061 440 (99.9)	551 (0.5)	1 061 991	
concentration	7.2–11.8 µg hb/g faeces	70227 (99.8)	148 (2.1)	70375	
	11.9–19.8 µg hb/g faeces	28406 (99.5)	130 (4.6)	28536	<0.001
Sex	Female	633880 (99.9)	413 (0.7)	634293	
	Male	526193 (99.9)	416 (0.8)	526609	0.006
Age	≤55 years	315678 (100.0)	55 (0.2)	315733	
	55–59 years	206014 (100.0)	71 (0.3)	206085	
	60–64 years	202699 (99.9)	115 (0.6)	202814	
	65–69 years	208501 (99.9)	226 (1.1)	208727	
	≥69 years	227181 (99.8)	362 (1.6)	227543	<0.001

CRC, colorectal cancer; FIT, faecal immunochemical test; hb, haemoglobin.

Variable	Subgroup	HR	95%CI	P−value
Educational level	Elementary school	Ref		
	High school/vocational	0.83	[0.71;0.98]	0.025
	Short higher	0.82	[0.67;1.01]	0.064
	Medium−long higher	1.17	[0.87;1.59]	0.303
Income quartiles	1st quartile	Ref		
	2nd quartile	0.60	[0.51;0.71]	<0.001
	3rd quartile	0.44	[0.36;0.54]	<0.001
	4th quartile	0.36	[0.29;0.45]	<0.001

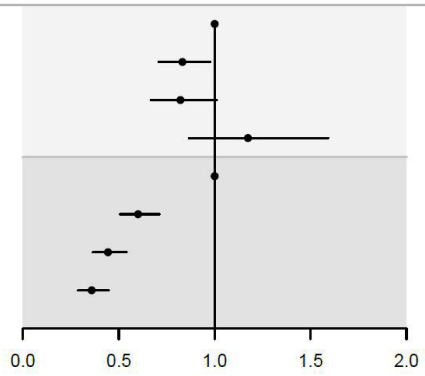


Figure 2 Risk of interval colorectal cancer based on socioeconomic characteristics from a simple cox proportional hazards regression model including educational level and income quartiles in the same model.

for FIT concentrations 7.2–11.8 µg hb/g faeces, and 7.09 (95% CI 5.85 to 8.59) for FIT concentrations 11.9–19.8 µg hb/g faeces compared with those with <7.2 µg hb/g faeces. Compared with those under 55 years, the age groups were all at significantly increased risk of interval colorectal cancer, with HR 2.06 (95% CI 1.45 to 2.93), 3.24 (95% CI 2.34 to 4.48), 5.70 (95% CI 4.20 to 7.75) and 7.60 (95% CI 5.63 to 10.25), respectively. Males were at increased risk compared with females (HR 1.16, 95% CI 1.01 to 1.33) in the adjusted model (figure 3). The only statistically significant interaction found was between educational level and FIT concentration, leading to a series of sensitivity analyses. Results from the sensitivity analysis with the inclusion of the interaction term of educational level and FIT concentration did not differ significantly from results presented in figure 3 (online supplemental appendix A, figure A1). The multivariate regression model stratified by FIT concentration did not reveal any significant differences in HRs for educational levels across the strata (online supplemental appendix A, figure A2) and the model stratifying the baseline hazard function by FIT concentration resulted in HRs equal to those of figure 3 (first decimal). The marginal effects analysis did not reveal a pattern of differing effects on the predicted HRs across educational levels from FIT concentrations (online supplemental appendix A, figure A3).

Larger proportions of individuals of lower socioeconomic status were seen in groups of increased FIT concentrations and higher age groups. For example, the proportions of individuals with FIT concentration 11.9–19.8 µg hb/g faeces were 1.8% for highest income quartile, increasing to 2.1%, 2.8% and 3.1% with decreasing income quartiles. Similar, proportions of individuals in the oldest group were 6.4% for the highest income quartile, increasing to 10.5%, 23.9% and 38.1% with decreasing income quartiles (table 2).

The cumulative incidence proportion curves illustrates how individuals aged 60 or older while also having an increased FIT concentration (7.2–19.8 µg hb/g faeces) were at significantly increased risk of interval colorectal cancer even before 100 days had passed since FIT result,

Variable	Subgroup	HR	95%CI	P−value
Educational level	Elementary school	Ref		
	High school/vocational	0.89	[0.76;1.05]	0.164
	Short higher	0.85	[0.69;1.05]	0.128
	Medium−long higher	1.10	[0.81;1.50]	0.528
Income quartiles	1st quartile	Ref		
	2nd quartile	0.76	[0.64;0.91]	0.003
	3rd quartile	0.87	[0.70;1.07]	0.187
	4th quartile	0.83	[0.65;1.06]	0.142
FIT concentration	<7.2 ug hb/g faeces	Ref		
	7.2−11.8 ug hb/g faeces	3.37	[2.81;4.04]	<0.001
	11.9−19.8 ug hb/g faeces	7.09	[5.85;8.59]	<0.001
Sex	Female	Ref		
	Male	1.16	[1.01;1.33]	0.042
Age (years)	Under 55	Ref		
	55−59	2.06	[1.45;2.93]	<0.001
	60−64	3.24	[2.34;4.48]	<0.001
	65−69	5.70	[4.20;7.75]	<0.001
	70 or older	7.60	[5.63;10.25]	<0.001

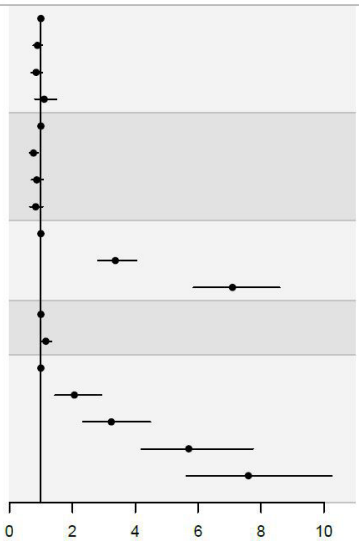


Figure 3 Risk of interval colorectal cancer based on socioeconomic characteristics and covariates from an adjusted cox proportional hazards regression model. FIT, faecal immunochemical test; hb, haemoglobin.

Table 2 Socioeconomic characteristics stratified by faecal haemoglobin concentration and age groups

	Faecal haemoglobin concentration					
Socioeconomic characteristic	**<7.2 µg hb/g faeces (%), n=1 061 991**		**7.2–11.8 µg hb/g faeces (%), n=70 375**		**11.9–19.8 µg hb/g faeces (%), n=28 536**	**Total, n=1 160 902**
Educational level						
Elementary school	246 654 (90.1)		19 143 (7.0)		8050 (2.9)	273 847
High school/vocational	481 334 (91.3)		32 504 (6.2)		13 354 (2.5)	527 192
Short higher	252 886 (92.6)		14 688 (5.4)		5555 (2.0)	273 129
Medium-long higher	81 117 (93.5)		4040 (4.7)		1577 (1.8)	86 734
Income						
1st quartile	257 958 (90.0)		19 897 (6.9)		8769 (3.1)	286 624
2nd quartile	262 082 (90.6)		19 082 (6.6)		8219 (2.8)	289 383
3rd quartile	269 084 (92.2)		16 607 (5.7)		6132 (2.1)	291 823
4th quartile	272 867 (93.1)		14 789 (5.0)		5416 (1.8)	293 072
Socioeconomic characteristic	**Age group**					
	Under 55 (%), n=315 733	**55–59 (%), n=206 085**	**60–64 (%), n=202 814**	**65–69 (%), n=208 727**	**≥70 (%), n=227 543**	**Total, n=1 160 902**
Educational level						
Elementary school	51 163 (18.7)	45 137 (16.5)	48 477 (17.7)	52 042 (19.0)	77 028 (28.1)	273 847
High school/vocational	154 673 (29.3)	92 217 (17.5)	88 013 (16.7)	96 142 (18.2)	96 147 (18.2)	527 192
Short higher	80 409 (29.4)	52 038 (19.1)	51 132 (18.7)	46 890 (17.2)	42 660 (15.6)	273 129
Medium-long higher	29 488 (34.0)	16 693 (19.2)	15 192 (17.5)	13 653 (15.7)	11 708 (13.5)	86 734
Income						
1st quartile	27 733 (9.7)	20 998 (7.3)	40 678 (14.2)	88 029 (30.7)	109 186 (38.1)	286 624
2nd quartile	52 885 (18.3)	40 721 (14.1)	64 041 (22.1)	62 625 (21.6)	69 111 (23.9)	289 383
3rd quartile	106 986 (36.7)	71 225 (24.4)	50 081 (17.2)	32 918 (11.3)	30 613 (10.5)	291 823
4th quartile	128 129 (43.7)	73 141 (25.0)	48 014 (16.4)	25 155 (8.6)	18 633 (6.4)	293 072

compared with individuals that are either below the age of 60 years or has an FIT concentration below 7.2, or both. After 2 years of follow-up, the cumulative incidence proportion was more than fivefold higher in the high risk group compared with low risk (figure 4). Cumulative incidence proportion curves illustrating the differences between age groups and FIT concentrations explicitly are included in online supplemental appendix A, figure A4,A5.

DISCUSSION

Social inequalities in interval colorectal cancer incidence were evident in the Danish Colorectal Cancer Screening programme, where interval cancers occurred more often in those with lower income. However, this association seems to be carried by an overrepresentation of older individuals and individuals with detectable faecal haemoglobin concentrations of 7.2 µg hb/g faeces or more in the lower income quartiles, as shown from the full multivariate regression analysis. No significant inequality was seen based on educational level from the adjusted regression model, whereas high school/vocational education held a significantly lower risk of interval cancer compared with elementary school in the simple model. In both models, a u-shaped pattern of the HRs was evident for educational level. Even though lifestyle and socioeconomic status in general holds a relationship of the higher the status the healthier the lifestyle, for some specific lifestyle choices, the pattern may be more u-shaped. As an example, alcohol intake is higher in the lowest and highest socioeconomic subgroups of the Danish population, while at the same time being a risk factor for colorectal cancer development.[29 30]

Interaction, mediation and marginal effects analyses did not indicate that the FIT concentration mediated the association between educational level and interval colorectal cancer. Even though it may seem plausible that income and age interacts, as individuals with increasing age have a higher likelihood of withdrawal from the work force, we did not find other significant interactions in the model. As FIT concentration and age is not used to determine screening interval, this means that individuals of lower income are by proxy at higher risk of interval colorectal cancer. We found that interval cancers were more common in men than women, contradicting previous finding from a Scottish sample,[31] although they

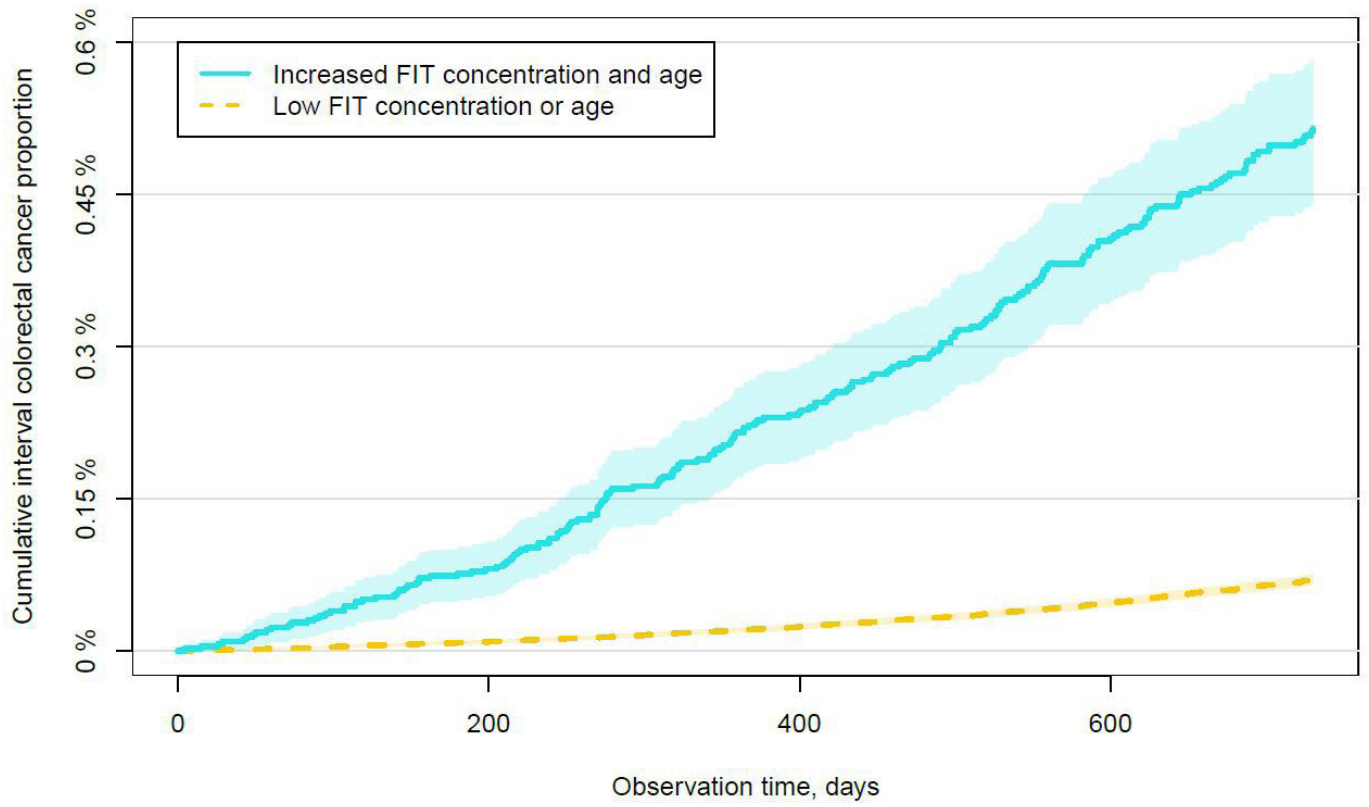


Figure 4 Cumulative incidence proportion curves of interval colorectal cancer stratified by risk predictors identified in multivariate cox proportional hazard regression model. Definitions: Increased FIT concentration, 7.2–19.8 µg hb/g faeces; increased age, 60 years or older. FIT, faecal immunochemical test; hb, haemoglobin.

used the guaiac-based faecal occult blood test (gFOBT) rather than the FIT as in the current study. This may affect the results if the FIT is more sensitive (compared with gFOBT) to left-sided cancers as opposed to right sided, as right-sided cancers were more common in women.[31] In the Dutch screening programme where the FIT is also employed, a higher incidence rate of interval cancers was seen in males compared with females[32] comparable to what we found. Regardless of which FIT positivity threshold is applied in screening, some cancers and precursor lesion will be missed. The threshold used in National screening programmes varies from 15 to 180 µg hb/g faeces (75–900 ng hb/mL buffer) between European countries with FIT-based screening.[33] A negative FIT result carries the risk of false reassurance[34] and neglect of symptoms. This could lead to a later stage cancer at time of diagnosis. It has been shown that interval cancers have a higher stage than screening detected cancers,[22] and stage at diagnosis is strongly associated with mortality.[35] To have the risk of false reassurance and risk of higher cancer stage at diagnosis differentiate between socioeconomic subgroups seems counterproductive in screening programmes that by European guidelines should aim to decrease inequalities in health.[4] Only one other study investigating the association between socioeconomic status and interval cancers was identified. The authors did not report any significant differences in interval cancer rate between socioeconomic subgroups in the FIT negative arm of their trial.[22] This may be either due to their low number of cases (n=27), due to their estimation of socioeconomic status relying on postal code means rather than individual assessments, or because no socioeconomic differences in interval colorectal cancer exists in the Netherlands. They did not adjust for age and FIT concentration, although with the power available it probably would not change the significance of their findings.

This register-based study enabled the inclusion of a large sample, needed for analyses of this rare outcome (0.71‰ in our sample with 2 years follow-up, and 1.72‰ in the Dutch sample with up to 2.3 years of follow-up).[22] The Danish National registers enable us to identify individual socioeconomic characteristics rather than relying on means of geographical area, which is often a limitation. The average age of retirement from the work force in Denmark is approximately 65 years old. As our measure of socioeconomic status relies on income the year before participation, there is a risk of pensioners with a low income but great wealth being categorised as lower socioeconomic status. As we included age groups in the full multivariate regression model, this possible bias will be limited to the results of the simple model. The results from the current study are limited to the first round of screening, and future research would need to confirm whether they can be generalised to consecutive rounds of colorectal cancer screening.

Most colorectal cancer screening programmes are targeting individuals based on their age, and usually within the range of 45–80 years. In programmes using the FIT as a first screening tool, a threshold must be determined. Therefore, all FIT-based screening programmes will have information on individual age and FIT concentration at participation. This information could possibly be used to individualise screening intervals according to risk of interval cancer. By decreasing the interval in high-risk individuals (eg, individuals above the age of 60 with an increased FIT concentration), we may be able to limit the number of interval cancers and decrease the social gradient. If at the same time the interval is increased in low-risk individuals, this can be done without adding additional FIT and colonoscopies to the screening programme, which would affect the cost of the programmes. The latter part would go against the guidelines, recommending that the interval should not exceed 2 years, but this is based on a low level of evidence,[4] which does not take individual risk assessment into account. Alternatively, the FIT concentration threshold for positivity could be differentiated by age. A recently published Dutch protocol describes how they aim to tailor personalised screening intervals based on prior faecal haemoglobin concentrations in the PERFECT-FIT trial.[36] The results from that trial will hopefully shed light on the effects of such a strategy, both in terms of clinical outcomes, social inequalities and cost-effectiveness. By employing a 'one screening interval fits all' strategy, we are leaving valuable and easy accessible information unused.

CONCLUSION

In a large sample of FIT negative screening participants, the proportion of interval colorectal cancer increased as income decreased. This was explained by the association of lower income individuals more often being of older age and having higher, yet negative, FIT concentrations than those with higher income. We propose individualising the screening interval in FIT negative participants, based on individual risk assessments from age and FIT concentration in order to decrease the total number of interval cancers while limiting the social gradient while likely increasing the overall efficiency of the programme.

Twitter Ulrik Deding @UlrikDeding

Contributors UD and MK-L conceived the idea for the study. UD and HB designed the statistical analysis plan. UD completed the data management and statistical analysis under the supervision of HB and GB. UD completed the first draft of the paper. UD, MK-L, HB, LK, MKT and GB revised and contributed to the manuscript. UD is the guarantor of the study.

Funding This work was supported by Odense University Hospital grant number A3610.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Data were stored on governmental secure logged servers and were pseudoanonymised before the authors were granted access. The study was approved by the Danish Data Protection Agency (journals 19/32137). No ethical approval or consent forms were needed according to Danish law, as a register-based approach was employed. This work was supported by Odense University Hospital grant number A3610.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available. Data were stored on governmental secure logged servers and were pseudoanonymised before the authors were granted access. These data can only be accessed after individual approval has been granted and the data contains personal individual information. the data can therefore not be shared.

ORCID iDs
Ulrik Deding http://orcid.org/0000-0002-8263-2989
Lasse Kaalby http://orcid.org/0000-0002-6721-3604

REFERENCES

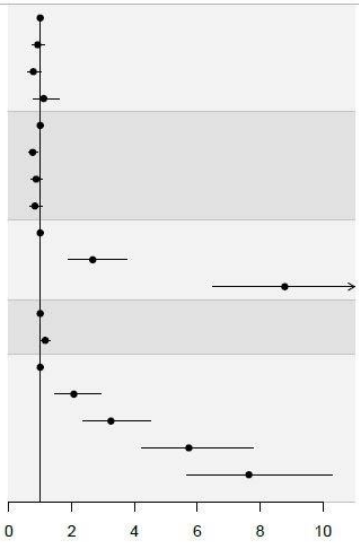
1 Mosquera I, Mendizabal N, Martín U, *et al*. Inequalities in participation in colorectal cancer screening programmes: a systematic review. *Eur J Public Health* 2020;30:416–25.
2 Shaukat A, Kaalby L, Baatrup G, *et al*. Effects of screening compliance on long-term reductions in all-cause and colorectal cancer mortality. *Clinical Gastroenterology and Hepatology* 2021;19:967–975.
3 Cardoso R, Guo F, Heisser T, *et al*. Overall and stage-specific survival of patients with screen-detected colorectal cancer in European countries: a population-based study in 9 countries. *Lancet Reg Health Eur* 2022;21:100458.
4 European Commission, Directorate-General for Health and Consumers, Executive Agency for Health and Consumers, World Health Organization. *European guidelines for quality assurance in colorectal cancer screening and diagnosis*. Publications Office, Available: https://data.europa.eu/doi/10.2772/1458
5 Deding U, Henig AS, Hindersson P, *et al*. Determinants of non-participation in colon examination following positive stool sample in colorectal cancer screening. *Eur J Public Health* 2019;29:1118–24.
6 Deding U, Henig AS, Salling A, *et al*. Sociodemographic predictors of participation in colorectal cancer screening. *Int J Colorectal Dis* 2017;32:1117–24.
7 Strömberg U, Bonander C, Westerberg M, *et al*. Colorectal cancer screening with fecal immunochemical testing or primary colonoscopy: an analysis of health equity based on a randomised trial. *EClinicalMedicine* 2022;47:101398.
8 Skau B, Deding U, Kaalby L, *et al*. Odds of incomplete colonoscopy in colorectal cancer screening based on socioeconomic status. *Diagnostics (Basel)* 2022;12:171.
9 Keum N, Giovannucci E. Global burden of colorectal cancer: emerging trends, risk factors and prevention strategies. *Nat Rev Gastroenterol Hepatol* 2019;16:713–32.
10 Miller GE, Engen PA, Gillevet PM, *et al*. Lower neighborhood socioeconomic status associated with reduced diversity of the colonic microbiota in healthy adults. *PLoS One* 2016;11:e0148952.
11 Rozich JJ, Holmer A, Singh S. Effect of lifestyle factors on outcomes in patients with inflammatory bowel diseases. *Am J Gastroenterol* 2020;115:832–40.
12 Khalili H, Ananthakrishnan AN, Konijeti GG, *et al*. Physical activity and risk of inflammatory bowel disease: prospective study from the nurses' health study cohorts. *BMJ* 2013;347:f6633.
13 Shivappa N, Godos J, Hébert JR, *et al*. Dietary inflammatory index and colorectal cancer risk-A meta-analysis. *Nutrients* 2017;9:1043.

14 Mackenbach JP, Stirbu I, Roskam A-JR, *et al*. Socioeconomic inequalities in health in 22 European countries. *N Engl J Med* 2008;358:2468–81.
15 Groth MV, Fagt S, Brøndsted L. Social determinants of dietary habits in Denmark. *Eur J Clin Nutr* 2001;55:959–66.
16 Janeway CJ, Travers P, Walport M, *et al*. Immunobiology: the immune system in health and disease. In: *Principles of innate and adaptive immunity*. 5th edn. New York: Garland Science, 2001.
17 Deschner EE. Cell turnover and colon tumor development. *Prev Med* 1987;16:580–5.
18 Bretagne J-F, Carlo A, Piette C, *et al*. Significant decrease in interval colorectal cancer incidence after implementing immunochemical testing in a multiple-round guaiac-based screening programme. *Br J Cancer* 2021;125:1494–502.
19 Zorzi M, Hassan C, Senore C, *et al*. Interval colorectal cancers after negative faecal immunochemical test in a 13-year screening programme. *J Med Screen* 2021;28:131–9.
20 Mancini S, Bucchi L, Giuliani O, *et al*. Proportional incidence of interval colorectal cancer in a large population-based faecal immunochemical test screening programme. *Digestive and Liver Disease* 2020;52:452–6.
21 Plantener E, Deding U, Madsen JB, *et al*. Using fecal immunochemical test values below conventional cut-off to individualize colorectal cancer screening. *Endosc Int Open* 2022;10:E413–9.
22 van der Vlugt M, Grobbee EJ, Bossuyt PMM, *et al*. Interval colorectal cancer incidence among subjects undergoing multiple rounds of fecal immunochemical testing. *Gastroenterology* 2017;153:439–47.
23 Thomsen MK, Njor SH, Rasmussen M, *et al*. Validity of data in the Danish colorectal cancer screening database. *Clin Epidemiol* 2017;9:105–11.
24 Lynge E, Sandegaard JL, Rebolj M. The Danish national patient register. *Scand J Public Health* 2011;39:30–3.
25 Jensen VM, Rasmussen AW. Danish education registers. *Scand J Public Health* 2011;39:91–4.
26 Baadsgaard M, Quitzau J. Danish registers on personal income and transfer payments. *Scand J Public Health* 2011;39:103–5.
27 Zhang Y-B, Chen C, Pan X-F, *et al*. Associations of healthy lifestyle and socioeconomic status with mortality and incident cardiovascular disease: two prospective cohort studies. *BMJ* 2021;373:n604.
28 Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J Pers Soc Psychol* 1986;51:1173–82.
29 Sundhedsstyrelsen [The Danish Health Authorities]. 2022. *Danskernes sundhed – Den Nationale Sundhedsprofil 2021 [Health of the Danes – The National Health Profile 2021]*. Copenhagen, 2022.
30 Mayén A-L, Viallon V, Botteri E, *et al*. A longitudinal evaluation of alcohol intake throughout adulthood and colorectal cancer risk. *Eur J Epidemiol* 2022;37:915–29.
31 Steele RJC, McClements P, Watling C, *et al*. Interval cancers in a FOBT-based colorectal cancer population screening programme: implications for stage, gender and tumour site. *Gut* 2012;61:576–81.
32 Breekveldt ECH, Toes-Zoutendijk E, van de Schootbrugge-Vandermeer HJ, *et al*. Factors associated with interval colorectal cancer after negative fit: results of two screening rounds in the Dutch FIT-based CRC screening program. *Int J Cancer* 2023;152:1536–46.
33 Senore C, Basu P, Anttila A, *et al*. Performance of colorectal cancer screening in the European Union member states: data from the second European screening report. *Gut* 2019;68:1232–44.
34 Barnett KN, Weller D, Smith S, *et al*. The contribution of a negative colorectal screening test result to symptom appraisal and help-seeking behaviour among patients subsequently diagnosed with an interval colorectal cancer. *Health Expect* 2018;21:764–73.
35 Joachim C, Macni J, Drame M, *et al*. Overall survival of colorectal cancer by stage at diagnosis: data from the Martinique cancer registry. *Medicine (Baltimore)* 2019;98:e16941.
36 Breekveldt ECH, Toes-Zoutendijk E, de Jonge L, *et al*. Personalized colorectal cancer screening: study protocol of a mixed-methods study on the effectiveness of tailored intervals based on prior f-hb concentration in a fit-based colorectal cancer screening program (perfect-fit). *BMC Gastroenterol* 2023;23:45.

Appendix A – Sensitivity analyses

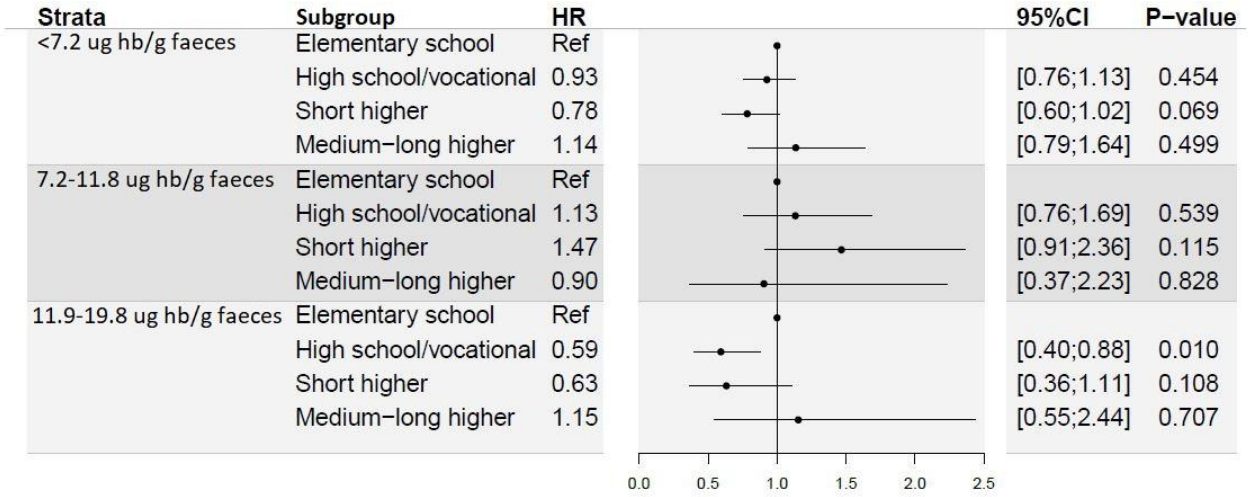
Fig. A1: Risk of interval colorectal cancer based on socioeconomic characteristics and covariates from adjusted cox proportional hazards regression model including interaction term for educational level and FIT concentration in the model

Variable	Subgroup	HR	95%CI	P−value
Educational level	Elementary school	Ref		
	High school/vocational	0.92	[0.76;1.13]	0.432
	Short higher	0.78	[0.60;1.01]	0.061
	Medium−long higher	1.11	[0.77;1.59]	0.574
Income quartiles	1st quartile	Ref		
	2nd quartile	0.76	[0.64;0.91]	0.002
	3rd quartile	0.87	[0.70;1.07]	0.178
	4th quartile	0.83	[0.65;1.06]	0.144
FIT concentration	<7.2 ug hb/g faeces	Ref		
	7.2-11.8 ug hb/g faeces	2.67	[1.90;3.77]	<0.001
	11.9-19.8 ug hb/g faeces	8.78	[6.47;11.92]	<0.001
Sex	Female	Ref		
	Male	1.16	[1.01;1.33]	0.040
Age (years)	Under 55	Ref		
	55−59	2.07	[1.46;2.95]	<0.001
	60−64	3.25	[2.35;4.51]	<0.001
	65−69	5.73	[4.22;7.79]	<0.001
	70 or older	7.64	[5.66;10.31]	<0.001



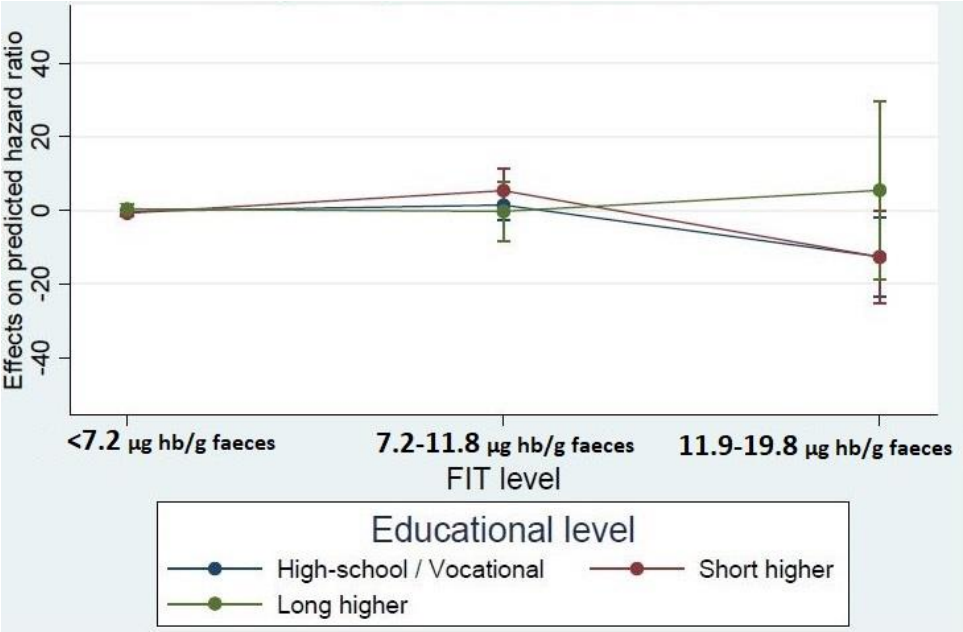
Abbreviations: FIT, Faecal immunochemical test; hb, haemoglobin

Fig. A2: Risk of interval colorectal cancer based on educational level from adjusted cox proportional hazards regression model stratified by FIT concentration



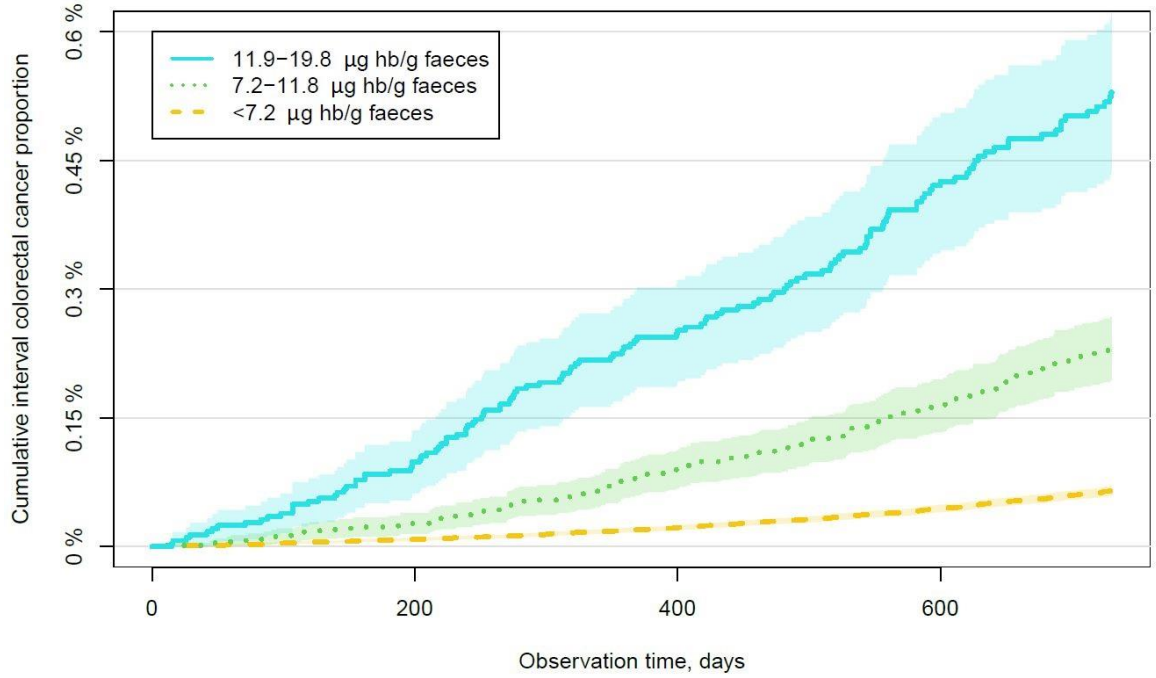
Abbreviations: FIT, Faecal immunochemical test; hb, haemoglobin

Fig. A3: Average marginal effects including 95% confidence intervals for the effect of educational levels on predicted hazard ratios for FIT concentrations with elementary school as reference



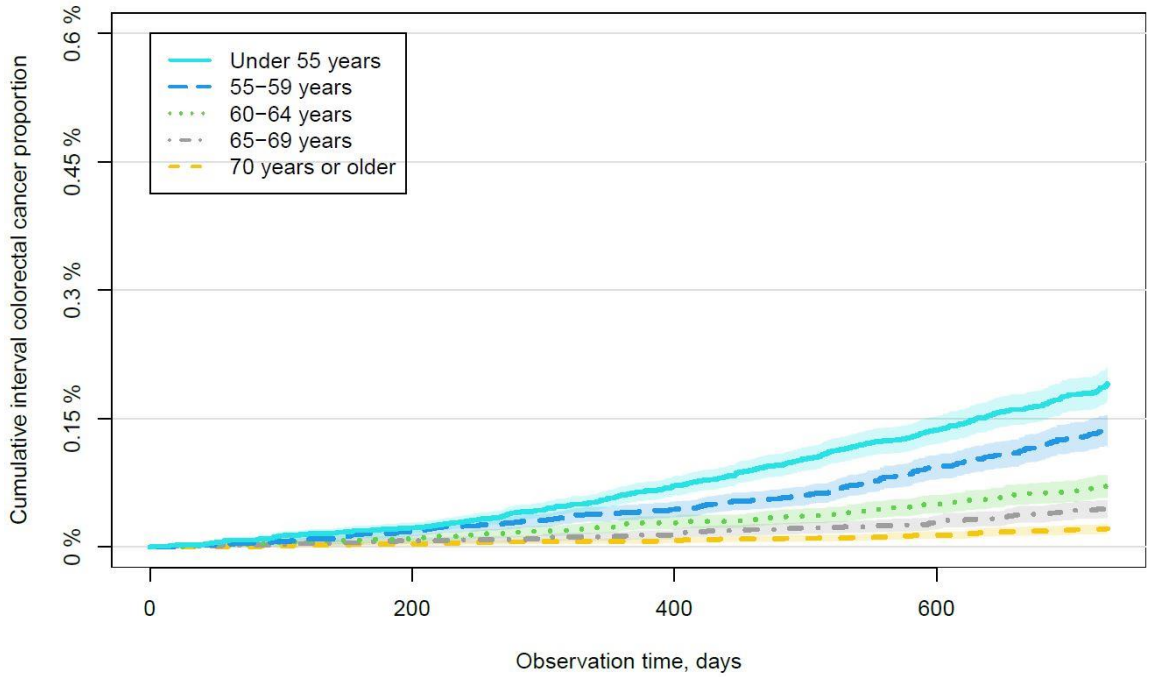
Abbreviations: FIT, Faecal immunochemical test; hb, haemoglobin

Fig. A4: Cumulative incidence proportion curves of interval colorectal cancer stratified by faecal haemoglobin concentration.



Abbreviations: FIT, Faecal immunochemical test.

Fig. A5: Cumulative incidence proportion curves of interval colorectal cancer stratified by age group.



Abbreviations: FIT, Faecal immunochemical test.