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Original Research

Faecal haemoglobin concentration predicts all-cause mortality

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Abstract ***Background:*** Population-based screening for colorectal cancer by a faecal immunochemical test (FIT) is recommended by the European Union. Detectable faecal haemoglobin can indicate colorectal neoplasia as well as other conditions. A positive FIT predicts an increased risk of death from colorectal cancer but might also predict an increased risk of all-cause mortality.

Methods: A cohort of screening participants was followed using the Danish National Register of Causes of Death. Data were retrieved from the Danish Colorectal Cancer Screening Database supplemented with FIT concentrations. Colorectal cancer specific and all-cause mortality were compared between FIT concentration groups using multivariate cox proportional hazards regression models.

Findings: In 444,910 Danes invited for the screening program, 25,234 (5·7%) died during a mean follow-up of 56·5 months. Colorectal cancer caused 1120 deaths. The risk of colorectal cancer death increased with the increasing FIT concentration. The hazard ratios ranged from 2·6 to 25·9 compared to individuals with FIT concentrations <4 μg hb/g faeces. Causes other than colorectal cancer caused 24,114 deaths. The risk of all-cause death increased with the increasing FIT concentration, with the hazard ratios ranging from 1·6 to 5·3 compared to individuals with FIT concentrations <4 μg hb/g faeces.

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Interpretation: The risk of colorectal cancer mortality increased with the increasing FIT concentrations even for FIT concentrations considered negative in all European screening programs. The risk of all-cause mortality was also increased for individuals with detectable faecal blood. For colorectal cancer specific mortality and all-cause mortality, the risk was increased at the FIT concentrations as low as 4–9 μg hb/g faeces.

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1. Introduction

Systematic colorectal cancer (CRC) screening can reduce CRC mortality, and it has been introduced in 38 countries worldwide including more than 20 European countries [1,2]. A pan-national CRC screening programme is made freely available by the government in Denmark. All citizens aged 50–74 are invited to submit a faecal immunochemical test (FIT) sample followed by a colonoscopy if positive [3]. This approach follows the recommendations provided by the European Union [4].

The FIT quantifies the amount of haemoglobin in the stool, which correlates to the risk of neoplasia [5]. The choice of threshold concentrations, therefore, reflects not only clinical efficiency but also cost-efficiency and endoscopy capacity. It varies from 15 to 180 μg hb/g faeces between European countries [6], leading to variations in sensitivity. The statistically optimal threshold, where sensitivity and specificity are weighted equally, has been estimated to be 9 μg hb/g faeces [7], and the cost-efficiency may increase with the decreasing threshold concentrations, due to reduced cancer management costs [8]. We found that the risk of interval CRC (diagnosed outside a screening program between rounds) increased significantly at modest increases within the FIT result range considered negative [9] but the associated mortality is unknown. We have demonstrated an increase of 20% in all-cause mortality (excl. CRC deaths) in screening participants with a positive guaiac faecal blood test (gFOBT) [10]. However, the use of the gFOBT is a major limitation that leaves out a much desired nuance. Therefore, we aimed to investigate the all-cause and CRC specific mortality in screening participants in relation to their FIT concentration.

2. Methods

The study was conducted as a cohort study of CRC screening invitees, followed in the Danish National Register of Causes of Death. CRC screening using FIT was introduced in Denmark in 2014. During the first four years, all citizens aged 50–74 were invited to participate. A FIT concentration of 20 μg hb/g faeces (equivalent to a 100 ng/mL buffer) or higher is regarded as positive and elicited an invitation for a colonoscopy. Denmark is divided in five health care regions. We included all CRC screening invitees in the Region of Southern Denmark and included the FIT result up until 31st December 2017. A unique personal registration number (CPR) is assigned to all persons in Denmark [11], enabling us to merge information from the national registers.

2.1. National registers

The Danish CRC Screening Database (DCCSD) was created for monitoring and research purposes [12]. It holds a moderate to high validity, dependened on the variable category, but the validity for the provided exposures and covariates in the current study is high [13]. The National Register of Causes of Death [14] holds the main cause and any underlying causes of death for each individual in Denmark using the International Classification of Diseases 10th revision (ICD-10). The causes of death are registered when completing the death certificate as mandatory by law and adhering to the World Health Organisation rules [14].

2.2. Exposure

The exposure was the numerical FIT concentrations. They were obtained from the DCCSD, accompanied by the date of the test. FIT concentrations were provided from the database ranging from <7 to >199 μg hb/g faeces. As we were interested in comparing concentrations even lower than that, we obtained the specific uncensored FIT concentrations from 0 to 200 μg hb/g faeces for each individual from the Department of Biochemistry and Immunology (DBI), Lillebaelt Hospital, where all screening FIT samples are analysed. The details of the FIT procedures are provided by Plantener et al. [9] If the test date provided from DBI did not match the date from the DCCSD (plus/minus one day), the individual was excluded. The limit of quantification in this study was determined at 4 μg hb/g faeces (equivalent to 20 ng/mL buffer), based on an acceptance criterion of 20% (for details see Plantener et al. [9]). The reference group was therefore individuals with a FIT concentration <4 μg hb/g faeces, and the remaining individuals were divided into subgroups of 4–9, 10–19, 20–49, 50–99, 100–199 and > 199 μg hb/g faeces and non-participants.

2.3. Outcomes

The outcomes of interest were all-cause mortality and CRC specific mortality obtained from the National Register of Causes of Death [14]. All-cause mortality was defined as any death occurring later than the test date for participants and the invitation date for non-participants. CRC specific mortality was defined as death occurring later than the test/invitation date, with CRC registered as the main or the underlying cause of death (ICD-10 codes C18 and C20). All included individuals were followed from the time of test/invitation until their death, emigration or end of the follow-up 31st December 2020.

2.4. Covariates

Age, sex and results of any diagnostic follow-up after a positive FIT result were obtained from the DCCSD. Age was defined as age at the time of FIT and included as a categorical variable (49–59, 60–69 and 70 or older). Sex (female, male) was included as a categorical variable. Outcome from the diagnostic follow-up was included as a categorical variable grouped as no colonoscopy, negative colonoscopy, adenoma(s) or colorectal cancer.

2.5. Sample size

The age-standardised CRC mortality in Denmark is 23·6 per 100,000 individuals [15]. Assuming the increase in CRC mortality between the reference group and the highest FIT concentrations to be 12-fold [16], the sample should contain 4207 participants per group, with a power of 80% and a level of confidence at 95%. More than 100,000 individuals were invited for CRC screening per year in the Region. The participation rate was 67·8% during the first two years of screening [17], decreasing to 62–64%. The FIT positivity rate was 7% [3]. Therefore, including participants from the first four years, we expected a participating sample size of 260,000, of which 18,200 would be FIT positive. Missing data were expected to be rare. Assuming the FIT-positive individuals were distributed equally among the FIT concentration groups, each group would hold 4550 individuals. Of the remaining 241,800 individuals with a negative FIT result, 8% were expected in the 4–9 μg hb/g faeces group [9] and an assumption was made that the group with 10–19 μg hb/g faeces was comparable in size. Expected group sizes were, therefore, 200,000, 19,000, 19,000, 5,000, 5,000, 5,000 and 5000, respectively.

2.6. Statistical analysis

Descriptive statistical analyses were performed using the chi-squared test. Stratified cox proportional hazard regression models were conducted to estimate the hazard ratios (HR) for CRC specific mortality and all-cause mortality adjusted for age and sex. The baseline hazard function was stratified by diagnostic follow-up. In case of a competing event, the individual was censored. Censoring of individuals was caused by emigration. For the outcome of CRC mortality, individuals were also censored if dying from other causes. Schönfeld residuals were examined to verify the proportional hazard assumption. The significance level was set at 5% and 95% confidence intervals (CI) were calculated. As a sensitivity analysis, the cox proportional hazard regression model for non-CRC mortality was performed. The cumulative incidence function was used to create inverted cumulative incidence proportion curves using the Aalen-Johansen product-limit estimator to facilitate comparison with Kaplan–Meier survival curves showing the all-cause mortality. Excess mortality was calculated as the observed number of deaths minus the expected. Data management and statistical analyses were conducted using SAS software version 9.4 (SAS Institute Inc. SAS 9.4. Cary, North Carolina, USA) and RStudio statistical software package, Version 1.2.5019 [18]. Specific R packages used were Publish, Survival and Prodlim [19–21].

2.7. Ethics

All data in this study were stored on governmental secure logged servers and were pseudo-anonymised before the authors were granted access. Therefore, the computer code and raw data are not available. The study was approved by the Danish Data Protection Agency (journals 20/3609 and 18/39201) and by the Danish Patient Safety Authority (ref. 31-1521-150). As no intervention was performed, no ethical approval was needed.

2.8. Role of the funding source

The study was funded by the Odense University Hospital grants A3610 and A2359. The funding source had no involvement in the study and had no access to the data or manuscript. No author has received payment to contribute. All funding has been used for data and to secure storage. The funding source had no say in the decision to publish.

3. Results

A total of 447,356 individuals were invited for screening, and 290,587 individuals were registered with a FIT result in the Region of Southern Denmark from 1st March 2014 until 31st December 2017. In 0·5% of the subjects, the date from the DCCSD did not match those from the DBI and these were excluded. A further 0·02% were excluded because their diagnostic follow-up results or FIT concentrations were missing or their date of

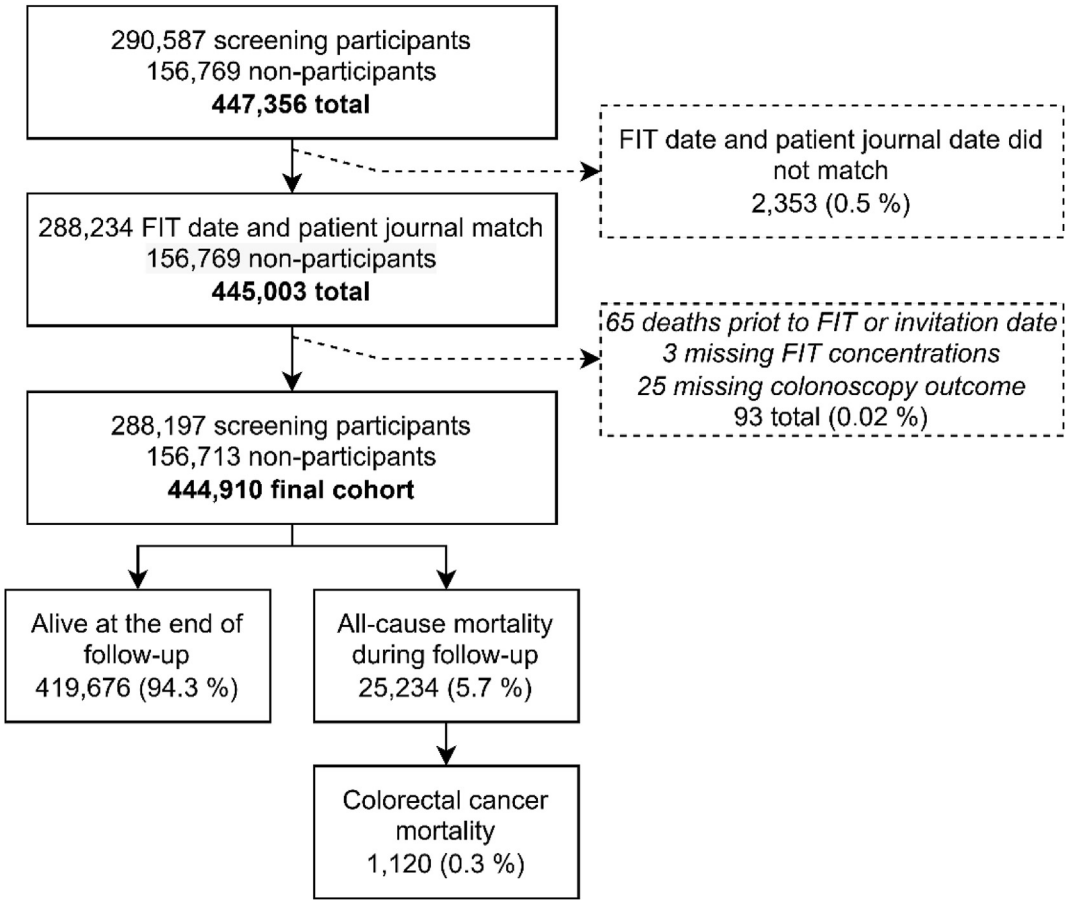

Fig. 1. flow of screening participants from inclusion until the end of follow-up.

death preceded their FIT date. It is possible to die after submitting the sample but prior to the test result. This left 444,910 individuals for analyses. Of these, 25,234 (5·7%) died during the follow-up. CRC was the main or underlying cause of death in 1120 cases (0·3% of the sample, 4·4% of deaths) (Fig. 1). In the same period, 24,114 (5·4% of the sample and 95·6% of deaths) individuals died of non-CRC related causes. The mean

Table 1
Frequencies of colorectal cancer and non-colorectal cancer related deaths in the cohort of 444,910 screening participants.

Variable	Subgroup	Survivors (%), n = 419,676	Non-colorectal cancer related deaths (%), n = 24,114	Colorectal cancer deaths (%), n = 1120	Total, n = 444,910	p-value
Faecal immunochemical test concentration, μg hb/g faeces	Non-participants	142,034 (90·6)	13,923 (8·9)	756 (0·5)	156,713	
	<4 μg	232,402 (97·0)	6999 (2·9)	156 (0·1)	239,557	
	4–9 μg	18,992 (94·6)	1037 (5·2)	38 (0·2)	20,067	
	10–19 μg	8068 (92·9)	582 (6·7)	36 (0·4)	8686	
	20–49 μg	8319 (92·5)	652 (7·3)	22 (0·2)	8993	
	50–99 μg	3738 (91·1)	349 (8·5)	14 (0·3)	4101	
	100–199 μg	2255 (90·6)	216 (8·7)	18 (0·7)	2489	
	>199 μg	3868 (89·9)	356 (8·3)	80 (1·9)	4304	<0·001
Sex	Female	212,661 (95·4)	9825 (4·4)	487 (0·2)	222,973	
	Male	207,015 (93·3)	14,289 (6·4)	633 (0·3)	221,937	<0·001
Age (years)	49–59	198,877 (97·7)	4507 (2·2)	179 (0·1)	203,563	
	60–69	142,215 (94·0)	8679 (5·7)	432 (0·3)	151,326	
	70 or older	78,584 (87·3)	10,928 (12·1)	509 (0·6)	90,021	<0·001
Diagnostic follow-up	No colonoscopy	403,676 (94·4)	22,947 (5·4)	1011 (0·2)	427,634	
	Clean colon	6313 (93·1)	453 (6·7)	14 (0·2)	6,78	
	Adenoma(s)	8728 (93·0)	639 (6·8)	16 (0·2)	9383	
	Colorectal cancer	959 (86·2)	75 (6·7)	79 (7·1)	1113	<0·001

follow-up was 56·5 months (1718 days, median = 1,736 and inter quartile range = 1371; 2096).

The proportion of individuals dying from CRC increased with the increasing FIT concentrations from 0·1% in the reference group to 1·9% in the group with 200 μg hb/g faeces or more. The same was seen for the citizens dying from non-CRC related causes, ranging from 2·9% in the reference group to 8·3% in the group with 200 μg hb/g faeces or more. More males than females died during the follow-up, but the proportions dying from CRC were similar at 0·2% for females and 0·3% for males. In individuals not undergoing a colonoscopy, in individuals with a negative colonoscopy and in those where adenomas were found, 0·2% died from CRC. If CRC was demonstrated at the colonoscopy, 7·1% died from CRC during the follow-up (Table 1). Results from the colonoscopies stratified by the FIT concentration subgroups are provided in Appendix A, Table A1. The excess mortality was 556 for non-CRC related deaths and 86 for CRC-related deaths in individuals with FIT concentrations of 4 μg hb/g faeces or more.

The cumulative incidence proportion of CRC deaths increased with the increasing FIT concentrations. Even though generally increasing, it dropped for those with concentrations from 20 to 50 μg hb/g faeces (the low range of positive tests) compared to the group below (the higher range of negative tests) and increased for the groups above. The group with FIT concentrations from 100 to 199 μg hb/g faeces exhibited a similar cumulative incidence proportion as the groups below until about 36 months of follow-up, where the incidence increased more rapidly. Non-participants were similar to those with FIT concentrations between 50 and 99 μg hb/g faeces (Fig. 2). The groups from 20 to 50 μg hb/g faeces and above are those who were offered diagnostic colonoscopy. All-cause mortality revealed a pattern of higher mortality with a higher FIT concentration, although it is worth noting that the mortality increase

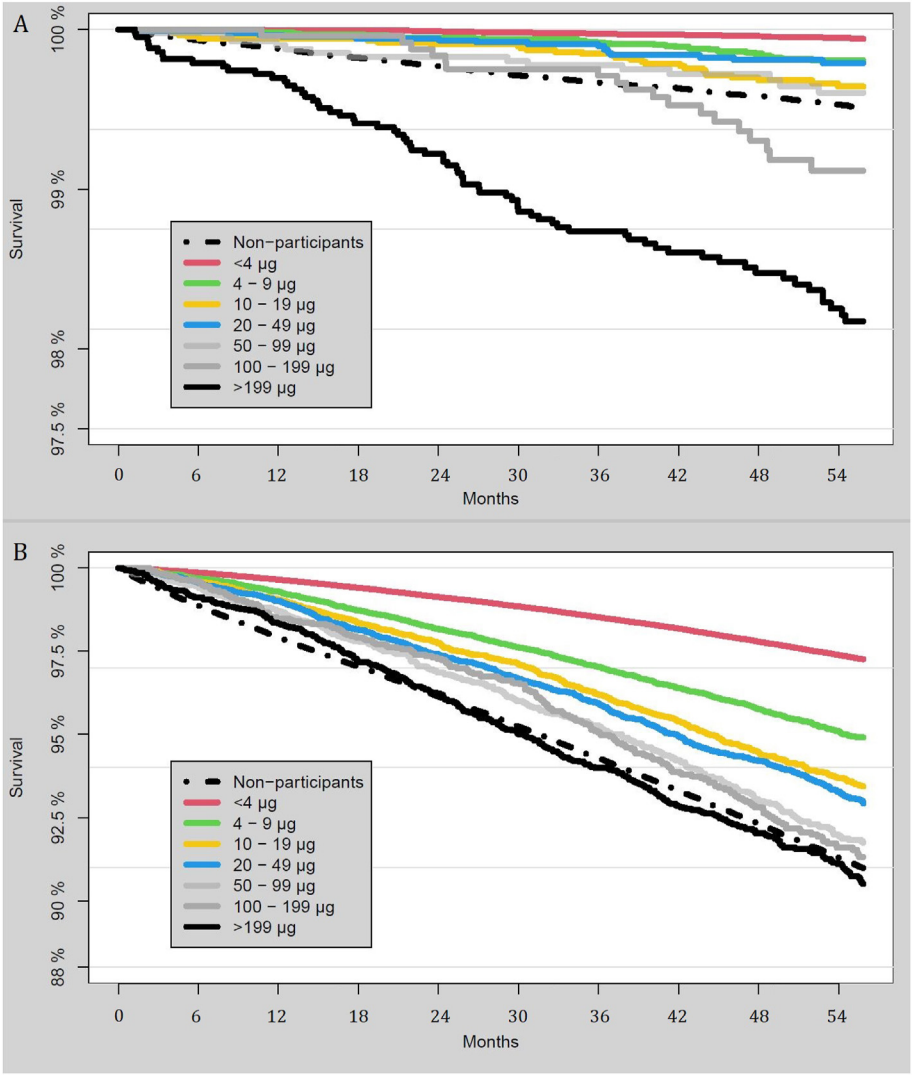

Fig. 2. inverted cumulative incidence proportion of colorectal cancer mortality (A), and the Kaplan−Meier curve for all-cause mortality (B) stratified by a faecal immunochemical test value.

between the groups was more pronounced for the lower concentration groups than the higher ones. Non-participants were similar to those with the highest FIT concentrations (Fig. 2).

The HR for CRC death ranged from 2·6 (CI 95% 1·8; 3·7) for FIT concentrations 4–9 μg hb/g faeces to 25·9 (CI 95% 16·0; 41·9) for FIT concentrations above 199, compared to reference. HR increased with the increasing FIT concentration, and all groups were at significantly higher risk of CRC death compared to reference. The HR for CRC death in non-participants was 8·4 (CI 95% 7·1; 10·0) compared to reference. Males were at an increased risk of CRC death, and the risk increased with increasing age (Fig. 3).

The HR for all-cause mortality ranged from 1·6 (CI 95% 1·5; 1·7) for FIT concentrations 4–9 μg hb/g faeces to 5·3 (CI 95% 4·6.; 6·0) for FIT concentrations above 199 compared to FIT concentrations below 4 μg hb/g faeces. HR increased with the increasing FIT concentration and all groups were at a significantly higher risk of death compared to reference. The HR for all-cause mortality in non-participants was 8·4 (CI 95% 7·1; 10·0) compared to reference. Males were at an increased risk compared to females, and the risk increased with increasing age (Fig. 4). Censoring CRC deaths only minimally affected the HR for all-cause mortality across FIT levels, although more so in the highest FIT concentration subgroups (Appendix A, Fig. A1).

The most common cause of death in the entire sample was malignant neoplasm of the bronchus and lung (ICD-10: C34), followed by other chronic obstructive pulmonary disease (ICD-10: J44), malignant neoplasms of the pancreas (ICD-10: C25), chronic ischaemic heart disease (ICD-10: I25) and malignant neoplasm of the colon (ICD-10: C18). Top five causes of death for each FIT concentration subgroup are detailed in appendix A, Table A2.

4. Discussion

The overall risk of death as well as CRC specific mortality increased significantly with the increasing FIT concentrations. Compared to reference, the increased FIT concentration was associated with a non-CRC excess mortality of 556 individuals and with a CRC excess mortality of 86 individuals in this cohort of 444,910 individuals. It is interesting that non-CRC mortality contributes with more than a 20-fold higher death number and is strongly associated with FIT concentration, but FIT-positive (20 μg hb/g faeces or higher) individuals without CRC are not subjected to any further investigations or interventions. The HR for CRC specific mortality was estimated to be 25·9 for the group with the highest FIT concentrations. For all-cause mortality, the HR was estimated to be 5·3 for individuals with the highest FIT concentrations. When comparing HR for CRC specific and all-cause mortality,

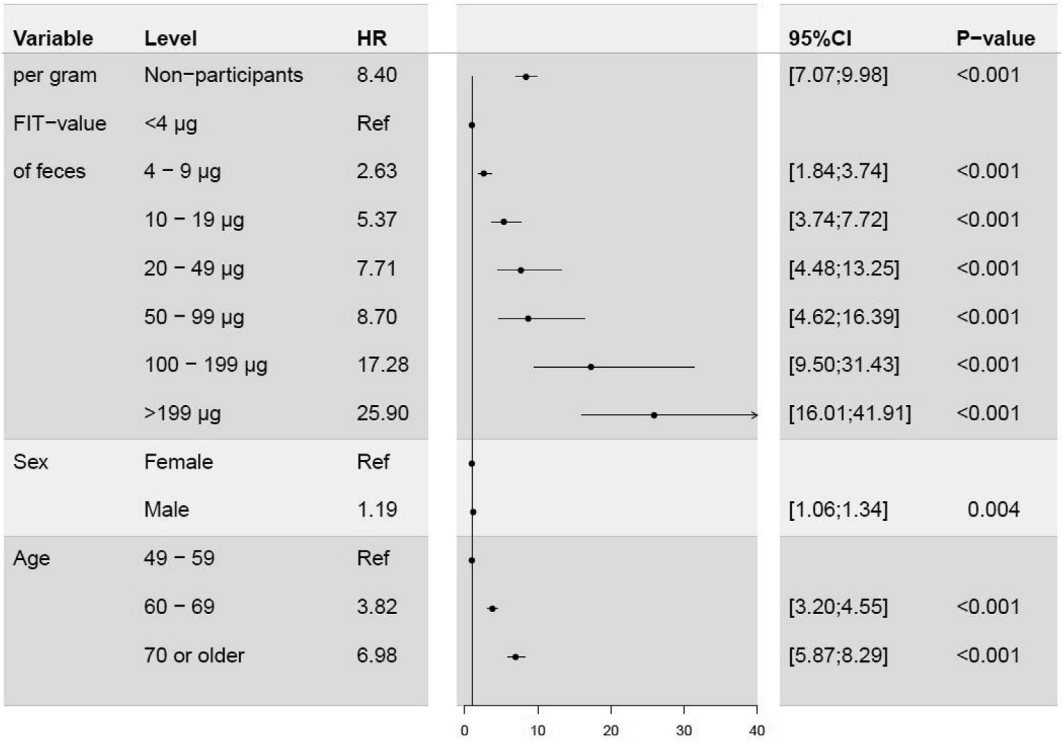

Fig. 3. Hazard ratios for colorectal cancer mortality from the multivariate cox proportional hazard regression model, with the baseline hazard function stratified by diagnostic follow-up, n = 444,910.

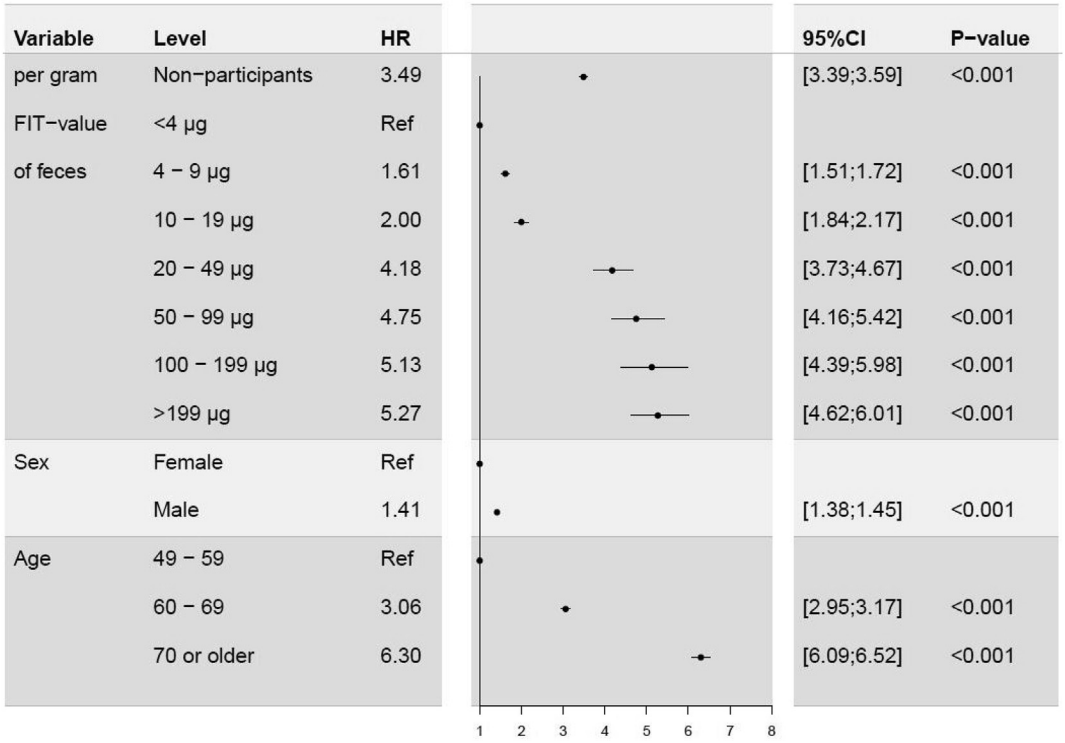

Fig. 4. Hazard ratios for all-cause mortality from the multivariate cox proportional hazard regression model with the baseline hazard function stratified by diagnostic follow-up, n = 444,910.

it should be kept in mind that participants in this population undergo both the treatment and secondary prevention, which reduce the HR significantly, while no intervention is directed against non-CRC mortality. These results are evident after a mean of 56·5 months of follow-up but the risks will likely further increase with a longer follow-up. Even modest increases in the FIT concentration predict an increased mortality risk. The groups with higher measurable yet negative FIT results were also at a significantly higher risk of both CRC specific and all-cause mortality. The FIT group with concentrations between 100 and 199 µg hb/g faeces revealed an interesting pattern of CRC specific mortality. The cancer incidence was comparable to that with lower concentrations for more than 3 years but then increased significantly. This could possibly be explained by adenomas or early cancers developing into invasive CRC over time. The cases with even higher FIT concentrations show increased mortality from day one, probably representing cases of advanced neoplasms at the time of testing.

In a recent study, we compared CRC screening individuals with a positive and negative stool sample, using the non-quantifiable gFOBT after 33 years of follow-up. The results showed that the risk of CRC mortality was four fold in gFOBT positives compared to negatives, while the all-cause mortality increased by 28 percent [10]. Similar findings were reported by others [16,22–24].

Only FIT-positive individuals were offered colonoscopy. This probably explains why the groups with FIT concentrations just below and just above the threshold concentration had a similar risk of CRC death. This is the positive effect of the screening program. It has repeatedly been shown that the FIT-based screening program does reduce the CRC specific death rate [1,25]. A significant impact on all-cause mortality, on the other hand, has been demonstrated in only one article including a very high number of participants [26].

The national registers used in this study have a high quality and validity [13,14]. We matched FIT concentrations from the DCCSD and the DBI to reduce misclassifications. The registers include individual covariate data with a low risk of information bias. The sample size was large, including all individuals submitting a sample. As all the individuals participating were identified and less than one percent were excluded, the risk of selection bias is limited. Use of anticoagulants can cause gastrointestinal bleeding, and there is a risk that all-cause mortality analyses may be affected by a positive FIT due to comorbidities treated with anticoagulants. But as the most common causes of death included chronic ischaemic heart disease for the entire sample, but not for the higher FIT concentration group, this potential bias is probably limited. The variability of FITs includes within-individual variability, between-individual variability and methodological variability. The biological variation for faecal haemoglobin is unknown. We

differentiated between concentrations down to 4 μg hb/g faeces as we accepted an analytical coefficient of variation of 20%, based on our prior research [9].

A recent register-based study revealed that the risk of CRC diagnosed by screening colonoscopy did not differ between individuals without adenomas and individuals with low risk adenomas [27]. It might therefore be worth considering if less resources should be used on low risk adenomas and if an intensified focus on individuals with high FIT concentrations and negative colonoscopies could add more benefit to the screening participants. It might also be worthwhile to consider the possible benefits of offering people with a high FIT concentration and negative colonoscopy, an active health surveillance to detect early signs of diseases other than CRC.

In conclusion, the risk of CRC-specific mortality increased with increasing FIT concentrations even for the subgroups with a FIT result below <20 μg hb/g faeces. The risk of all-cause (and non-CRC associated) mortality was also increased for individuals with detectable faecal blood. For both CRC-specific mortality and all-cause mortality, the risk was increased with increasing FIT concentrations from 4 μg hb/g faeces after a mean follow-up of 56·5 months.

Author contributions

UD conceived the idea for the study. UD, EP, JBM and LK sourced and curated the data. All authors contributed to the development of the methodology and data interpretation. The statistical analyses and figures were designed and performed by UD. LK has access to and verified the data. Funding was obtained by UD, LK, MKL and GB. Supervision was conducted by GB, RS, IAN, TBM, JSM and MKL. The original draft was done by UD and GB. All authors have reviewed and edited the manuscript prior to submission. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data sharing

The data from the current study will not be made available as this is not permitted by law. All data are stored at secured logged servers at Statistics Denmark.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2023.02.009.

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