All-cause and non-colorectal cancer 1-year mortality among people having a faecal immunochemical test in primary care for investigation of symptoms of suspected colorectal cancer: an English cohort study

Francesca L Malcolm, Colin J Crooks, Joe West, David J Humes, Sinéad M Langan

Summary

Background High blood concentrations in stool, as determined by the faecal immunochemical test (FIT), in individuals screened for colorectal cancer are associated with increased mortality. To our knowledge, no studies to date have assessed whether this association is present in symptomatic individuals. Our objective was to estimate the risk of all-cause and non-colorectal cancer 1-year mortality in adults who have undergone a FIT after symptomatic presentation to primary care.

Methods In this regional retrospective cohort study, all adults (age ≥18 years) with symptoms of colorectal cancer who were tested with FIT in primary care in Nottingham, UK, between Nov 1, 2017, and Nov 30, 2022 were included. Patient data were retrieved from existing medical records. Associations between FIT and mortality were examined using Cox regression to produce adjusted hazard ratios (aHRs) comparing those with FIT results of 10 μg of haemoglobin per g or higher against those with results lower than 10 μg of haemoglobin per g. Standardised mortality ratios (SMRs) were derived using English data from the UK Office for National Statistics.

Findings 49 889 patients were included following their first FIT to investigate symptoms of colorectal cancer. The median age was 65 years (IQR 53–79); 27 912 (55·9%) patients were female and 21 977 (44·1%) were male. In the year following a symptomatic FIT, 1971 (4·0%) patients died, including 864 (8·3%) of 10 352 patients with a FIT result of 10 μg of haemoglobin per g or higher and 1107 (2·8%) of 39 537 with a FIT result lower than 10 μg of haemoglobin per g. After adjusting for age, sex, and year, there was evidence of increased all-cause mortality (aHR 1·96 [95% CI 1·79–2·14]) and non-colorectal cancer mortality (1·70 [1·55–1·88]) in those with a FIT result of 10 μg of haemoglobin per g or higher compared with those with a FIT result lower than 10 μg of haemoglobin per g. The overall cohort had higher mortality than the general English population (SMR 1·50 [95% CI 1·44–1·57]). The magnitude of the increase in mortality following a FIT result of 10 μg of haemoglobin per g or higher was greater in younger than in older patients and in female than in male patients compared with those with a FIT result lower than 10 μg of haemoglobin per g (HR for all-cause mortality was 3·83 [2·86–5·14] in female patients and 2·91 [2·21–3·85] in male patients at age 50 years *vs* 2·27 [1·98–2·60] in female patients and 1·73 [1·53–1·95] in male patients at age 80 years).

Interpretation Further understanding of the cause-specific mortality associations with symptomatic FIT has the potential to transform diagnostic pathways and subsequent treatment—particularly in younger and female patients, for whom the greatest excess all-cause mortality risks were observed at 1 year of follow-up.

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Colorectal Service, Nottingham University Hospitals NHS Trust, Nottingham, UK (F L Malcolm MSc); **School of Medicine, University of Nottingham, Nottingham, UK** (F L Malcolm, C J Crooks PhD, Prof J West PhD, D J Humes PhD); **Department of Non-Communicable Disease Epidemiology, Faculty of Epidemiology and Population Health, London School of Hygiene & Tropical Medicine, London, UK** (F L Malcolm, Prof S M Langan PhD); **National Institute for Health Research Nottingham Biomedical Research Centre, Nottingham University Hospitals NHS Trust and University of Nottingham, School of Medicine, Nottingham, UK** (F L Malcolm, C J Crooks, D J Humes); **Lifespan and Population Health, School of Medicine, University of Nottingham, Nottingham, UK** (J West); **Department of Clinical Medicine—Hepatology and Gastroenterology, Aarhus University, Aarhus, Denmark** (J West)

Correspondence to: Francesca L Malcolm, School of Medicine, University of Nottingham, Nottingham NG7 2UH, UK **francescaligori.malcolm@nottingham.ac.uk**

Introduction

Colorectal cancer is the third most common cancer and second highest cause of cancer death in the UK.[1] The faecal immunochemical test (FIT) is well established as an initial test for colorectal cancer because it enables detection of microscopic traces of blood in faeces, which could be caused by underlying colorectal cancer.[2] A large proportion of the population is now being tested each year with FIT because it is a non-invasive test that is used both in the bowel cancer screening programme and in patients with symptoms suggestive of colorectal cancer as a preliminary investigation in primary care.[3] The National Health Service (NHS) in England began to incentivise use of symptomatic FIT in 2023, in which year an estimated 2·1 million individuals underwent a symptomatic FIT.[4]

There is emerging evidence from population-based colorectal cancer screening that a raised FIT result (ie, high blood concentration in faeces) is associated with increased mortality that is unrelated to colorectal cancer.[5–8] A recent systematic review found that across seven screening cohorts, reporting 14 491 864 FIT results, the risk ratio of all-cause mortality with a raised FIT result was

Research in context

Evidence before this study

We searched Embase and MEDLINE on Feb 9, 2024, for observational or randomised studies published in English between Jan 1, 1980, and Feb 9, 2024, that incorporated the key search terms "colorectal cancer", "mortality", and "faecal immunochemical test". Seven cohort studies were identified that reported mortality following faecal immunochemical test (FIT) screening, all of which were deemed good quality on risk of bias assessment. Five studies identified from this search reported all-cause mortality excluding colorectal cancer; all showed that increased mortality associated with a raised screening FIT result was not fully attributable to deaths from colorectal cancer. This association has not been established in patients undergoing FIT to investigate symptoms suggestive of colorectal cancer, despite the rapid increase in the use of this test.

Added value of this study

To our knowledge, this is the first study to describe the association between raised symptomatic FIT and all-cause mortality and mortality from causes other than colorectal cancer. Our findings show an increase in mortality in participants with a symptomatic FIT result of 10 µg of haemoglobin per g or higher, which was not solely attributable to colorectal cancer deaths. The greatest excess mortality risks were seen in female patients and young patients, and this has not been described previously.

Implications of all the available evidence

The next steps are to examine causes of death following symptomatic FIT. Further understanding of the cause-specific mortality associations with symptomatic FIT has the potential to transform diagnostic pathways and subsequent treatment.

between 1·49 (95% CI 1·48–1·51) and 2·95 (2·85–3·05) compared with those with a normal result.[9] Estimates of hazard ratios (HRs) from Cox regression models were reported in six of the included papers, and all presented evidence of increased all-cause mortality after adjusting for confounders including age, sex, and comorbidities.[5–8,10] Moreover, the increase in all-cause mortality was not explained solely by colorectal cancer death, as mortality was shown to remain elevated when the outcome of mortality from any cause other than colorectal cancer was analysed.[9] For example, compared with individuals with a normal FIT result, increased mortality from non-colorectal cancer causes was observed in individuals with a raised screening FIT result in Taiwanese and Danish population cohorts.[5–8,10]

This recent systematic review[9] identified that the only papers reporting mortality following FIT were related to screening programmes and that no prior studies reported mortality following symptomatic FIT. Increasing numbers of individuals are undergoing FIT; UK national recommendations state that the association between raised symptomatic FIT and mortality needs to be further assessed.[11] Hypothetically, mortality is expected to be higher in symptomatic individuals with a raised FIT compared with screening patients with a raised FIT, because the presence of symptoms suggests a higher risk for underlying diseases, which subsequently contribute to mortality. Quantifying mortality outcomes in this group is essential to provide insight into the use of FIT beyond colorectal cancer diagnosis. The aim of this study was to analyse mortality following symptomatic FIT, compared with the general population, using the current standard thresholds for referral.

Methods

Study design and setting

In this retrospective, population-based cohort study, reported according to the Reporting of Studies Conducted using Observational Routinely Collected Health Data (known as RECORD) checklist,[12] we identified all adults who had undergone a symptomatic FIT processed within Nottingham University Hospitals (NUH) pathology services while registered with a general practice in the Nottingham City and South Nottingham Integrated Care Partnerships (Nottingham, UK), since Nov 1, 2017.

Patient-level data from the following sources are stored in the NUH Enterprise Data Warehouse, linked by a unique patient identification number:[13] the UK Office for National Statistics (ONS), which provides date of death;[14] the secondary care system Civica (known as Infoflex at the time of analysis),[15] where all cancer diagnoses are recorded; and the NHS Personal Demographics Service for demographic information including age, sex, and ethnicity.[16] Data were extracted from these sources on June 19, 2024. Before analysis, data were pseudo-anonymised and saved on a secure NUH research server that is accessible only by approved members of the research team (FLM and CJC). No patient identifiable data were accessible to the research team, and analyses were carried out within the NUH NHS Trust.

The cohort consisted of all adults (ie, aged ≥18 years) who underwent symptomatic FIT processed at NUH between Nov 1, 2017, and Nov 30, 2022. Date of entry into the cohort was defined as date of FIT and patients were followed up for 1 year. Censoring occurred at either date of death or 1 year after FIT. The final exit date was Nov 30, 2023. When an individual had completed more than one FIT within the study period, they were entered at the date of their first-ever FIT request until censoring and they could not re-enter the cohort after another FIT.

Ethical approval was obtained from the Health Research Authority and Health and Care Research Wales (Cardiff, UK; 312362, version 1.3). Ethics committee approval from the London School of Hygiene & Tropical Medicine (London, UK) was also granted (30026/RR/34169,

30026/RR/35470). No patient consent was required because routinely collected data were used and researchers did not have access to patient-level data. There was no direct patient involvement in this study design because it is a retrospective analysis of routinely collected data.

Data sources, covariates and exposures

The outcomes of interest were all-cause mortality and non-colorectal cancer mortality (ie, deaths from any cause other than colorectal cancer). Occurrence, date of death, and colorectal cancer deaths were derived from the ONS. Colorectal cancer diagnoses were derived from Civica. Previous work validating colorectal cancer outcomes using this cohort has shown that this approach is valid,[2] using International Classification of Disease 10th Revision codes C18–20. To define non-colorectal cancer deaths, an algorithm was developed that used the available data for colorectal cancer diagnosis (appendix p 2). Thus, to ascertain the number of non-colorectal cancer deaths, the total number of colorectal cancer deaths identified was subtracted from the total number of deaths from all causes.

As a comparator, English mortality data were used from open-source ONS mortality tables. The ONS reports yearly overall and disease-specific mortality rates by 5-year age band.[17] The English rates for all-cause mortality were used as a reference to estimate expected deaths from which to generate standardised mortality ratios (SMRs).[14]

Demographic factors were collected via electronic health records completed by general practitioners and included age (defined by year of birth), sex (categorised as male or female), and ethnicity (categorised as White, Black, Asian, other, mixed, or unknown). The calendar year in which FIT was performed was also collected. Missing data were examined in relation to FIT result.

FITs for investigation of patients with symptoms (ie, outside the national bowel cancer screening programme) are requested electronically by primary care clinicians. FIT kits are sent to the patient and returned via post. Completed tests are processed according to the manufacturer instructions using the UK National Institute for Health and Care Excellence endorsed OC-Sensor (Eiken Chemical, Tokyo, Japan) analyser within the Eastern Bowel Cancer Screening Programme laboratory (Nottingham, UK), and results are reported quantitively in μg of haemoglobin per g.[13] For this study, the exposure was defined by an individual's first recorded symptomatic FIT and categorised on the basis of the current national cutoff for symptomatic patients of 10 μg of haemoglobin per g.[11]

Statistical analysis

All analyses were conducted using R (version 4.2.4) within R Studio (2022.12.0+353). Descriptive statistics were used to examine the demographic characteristics comparing those with a FIT result lower than 10 μg of haemoglobin per g versus 10 μg of haemoglobin per g or higher. For continuous data, means (SD) were calculated for normally distributed data and medians (IQR) were used for non-normal data. Categorical variables were tested with the Pearson χ^2 test and continuous non-normal variables were tested with the Mann–Whitney *U* test.

A sample size was calculated based on the March, 2023, age-standardised English mortality rate (1008 per 100 000 person-years) and the adjusted HR (aHR) of 1·9 from the largest study examining mortality associated with raised screening FIT.[7,18] The total number of person-years of follow-up required for 90% power and α of 0·05 was 7350.

The crude rate per 1000 person years, rate differences, and crude rate ratios (RRs) of all-cause and non-colorectal cancer mortality with 95% CIs were calculated for the overall cohort and then by FIT result, age, and sex. SMRs were calculated by indirect standardisation.[17] Byar's approximation method was used to calculate SMR 95% CIs.[19]

Survival analysis methods were used to examine the cohort outcomes stratified by FIT result (<10 μg of haemoglobin per g *vs* ≥10 μg of haemoglobin per g). Kaplan–Meier curves were plotted and the log-rank test was used to assess whether the survival function differed between exposure groups.

See Online for appendix

Cox regression models were used to estimate crude HRs and aHRs comparing all-cause and non-colorectal cancer mortality between those with FIT results of 10 μg of haemoglobin per g and higher and those with results less than 10 μg of haemoglobin per g. Age, sex and year were considered to be a prior confounders and hence they were adjusted for in multivariable models. Ethnicity was not considered to be a confounder due to insufficient biological plausibility and hence was not included in modelling.[20] A test for linear trend was done to inform whether age should be fitted as a continuous or a categorical variable within adjusted models. To assess for evidence of effect modification, adjusted models with and without interaction terms were compared using likelihood ratio tests. Where there was evidence of interaction, stratum-specific HRs were derived. Subdistribution HRs for non-colorectal cancer mortality were estimated using a Fine–Gray model incorporating the colorectal cancer mortality as a competing risk.[21]

The proportional hazards assumption was checked graphically using log–log plots based on survival estimates. For the adjusted Cox models, this assumption was assessed using Schoenfeld residual plots and associated test statistics.[22] We found no suggestion that the proportional hazards assumption was violated (appendix pp 3–4).

Role of the funding source

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Results

A total of 56 989 symptomatic FIT results were available from the study period; 6236 results were excluded as these

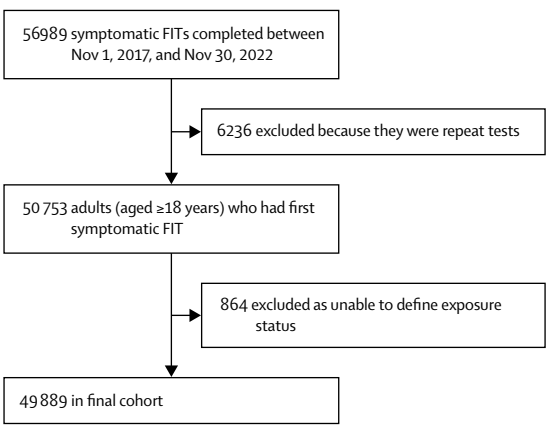

Figure: **Cohort creation flow diagram**
FIT=faecal immunochemical test.

	FIT <10 µg of haemoglobin per g (n=39 537)	FIT ≥10 of haemoglobin per g (n=10 352)	p value*
Sex			
Female	22 477 (56·9%)	5435 (52·5%)	..
Male	17 060 (43·1%)	4917 (47·5%)	<0·0001
Age at date of FIT, years	63 (52–75)	72 (59–81)	<0·0001
Year of FIT			
2017	282 (0·7%)	54 (0·5%)	..
2018	3866 (9·8%)	926 (8·9%)	..
2019	6568 (16·6%)	1664 (16·1%)	..
2020	7614 (19·3%)	2271 (21·9%)	..
2021	9161 (23·2%)	2484 (24·0%)	..
2022	12 046 (30·5%)	2953 (28·5%)	<0·0001
Ethnicity			
White	26 809 (67·8%)	7776 (75·1%)	..
Asian	1822 (4·6%)	289 (2·8%)	..
Black	957 (2·4%)	156 (1·5%)	..
Other	725 (1·8%)	151 (1·5%)	..
Mixed	323 (0·8%)	54 (0·5%)	..
Unknown or not defined†	8901 (22·5%)	1926 (18·6%)	<0·0001
Total person-time, person-years	38 963	9908	..
Follow-up time, days	365·25 (365·25–365·25)	365·25 (365·25–365·25)	<0·0001
Events			
Total deaths	1107 (2·8%)	864 (8·3%)	<0·0001
Non-colorectal cancer deaths	1080 (2·7%)	741 (7·2%)	<0·0001
Colorectal cancer deaths	27 (0·1%)	123 (1·2%)	<0·0001

Data are median (IQR) or n (%), unless otherwise stated. There were no missing data for age, sex, or year of FIT. FIT=faecal immunochemical test. *p values were calculated using the Pearson χ^2 test for categorical variables and Mann–Whitney *U* test for continuous variables. †Ethnicity was recorded as "declined after relevance of data collection given" in 3062 participants, "unknown" in 6233 participants, "not set" in eight participants, and "not stated" in 1524 participants.

Table 1: **Baseline characteristics and covariate data of the cohort, stratified by exposure group**

were repeat tests in individuals who had already completed a test. 864 were excluded because we could not define their exposure status due to their FIT result being recorded as lower than 20 µg of haemoglobin per g (figure). Hence, the cohort comprised 49 889 individuals who underwent a symptomatic FIT; 10 352 (20·8%) had a FIT result of 10 µg of haemoglobin per g or higher, and 39 537 (79·2%) had a FIT result lower than 10 µg of haemoglobin per g.

Baseline characteristics of the cohort by FIT category are shown in table 1. The overall median age was 65 years (IQR 53–79). Patients with a FIT result of 10 µg of haemoglobin per g or higher were older, with a median age of 72 years (IQR 59–81) compared with 63 years (52–75) in those with FIT results lower than 10 µg of haemoglobin per g (p<0·0001). Overall, there were more female than male patients in the cohort (27 912 [55·9%] of 49 889 *vs* 21 977 [44·1%], p<0·0001); however, male patients were more likely to have a FIT result of 10 µg of haemoglobin per g or higher than female patients (p<0·0001). The number of tests performed increased by calendar year, with the majority performed in 2022 (14 999 [30·1%]). A higher proportion of White patients had a FIT result of 10 µg of haemoglobin per g or higher than did patients of other ethnicities. Ethnicity was not recorded in 10 827 (21·7%) patients and those with missing data were categorised as unknown (table 1).

1971 deaths occurred within 1 year of follow-up. 864 (8·3%) of 10 352 patients with FIT results of 10 µg of haemoglobin per g or higher died versus 1107 (2·8%) of 39 537 with FIT results lower than 10 µg of haemoglobin per g. 150 (7·6%) deaths were due to colorectal cancer and 1821 (92·4%) were non-colorectal cancer deaths. The overall cohort survival probability at 1 year following FIT was 96·0% (95% CI 95·9–96·2). In those with FIT results lower than 10 µg of haemoglobin per g, survival probability was 97·2% (97·0–97·4) and for those with FIT results of 10 µg of haemoglobin per g or higher it was 91·7% (91·1–92·2; appendix pp 5–7).

The overall rate of all-cause mortality was 40·3 per 1000 person-years (95% CI 38·6–42·2) and the overall rate for non-colorectal cancer mortality was 37·3 per 1000 person-years (35·6–39·0). The rate of all-cause mortality was 87·21 per 1000 person-years (81·49–93·22) in patients with a FIT result of 10 µg of haemoglobin per g or higher compared with 28·41 per 1000 person-years (26·76–30·14) in those with a FIT result lower than 10 µg of haemoglobin per g (table 2). For non-colorectal cancer mortality, the rate was 74·79 per 1000 person-years (69·50–80·38) in patients with a FIT result of 10 µg of haemoglobin per g or higher versus 27·72 per 1000 person-years (26·09–29·42) in those with a FIT result lower than 10 µg of haemoglobin per g (table 3).

Results from crude and adjusted Cox regression models are shown in table 4., Initial unadjusted estimates for all-cause mortality gave a HR of 3·07 (95% CI 2·81–3·35) for patients with FIT results of 10 µg of haemoglobin per g or higher compared with those with FIT results lower than 10 µg of haemoglobin per g. Similarly, the unadjusted HR for non-colorectal cancer mortality in those with FIT results of 10 µg of haemoglobin per g or higher compared with those with FIT results lower than 10 µg of haemoglobin per g was 2·70 (2·47–2·96; table 4).

Multivariable models included age as a continuous variable because there was no evidence of departure from a

	Events*	Person-time, person-years*	Rate per 1000 person-years (95% CI)	Rate difference (95% CI)	Crude rate ratio (95% CI)
Overall cohort, <10 µg Hb/g	1110	38 960	28·41 (26·76–30·14)	..	1 (ref)
Overall cohort, ≥10 µg Hb/g	860	9910	87·21 (81·49–93·22)	58·80 (52·7–64·84)	3·07 (2·81–3·35)
Sex					
Female, <10 µg Hb/g	450	22 250	20·18 (18·36–22·14)	..	1 (ref)
Female, ≥10 µg Hb/g	400	5240	75·43 (68·18–83·25)	55·25 (47·58–62·92)	3·74 (3·27–4·28)
Male, <10 µg Hb/g	660	16 710	39·37 (36·42–42·49)	..	1 (ref)
Male, ≥10 µg Hb/g	470	4 670	100·40 (91·52–109·92)	61·04 (51·47–70·61)	2·55 (2·27–2·87)
Age					
<65 years,† <10 µg Hb/g	150	21 600	6·99 (5·92–8·20)	..	1 (ref)
<65 years,† ≥10 µg Hb/g	80	3660	20·51 (16·13–25·71)	13·52 (8·75–18·29)	2·93 (2·22–3·87)
≥65 years, <10 µg Hb/g	960	17 360	55·07 (51·63–58·67)	..	1 (ref)
≥65 years, ≥10 µg Hb/g	790	6250	126·22 (117·57–135·35)	71·16 (61·68–80·63)	2·29 (2·09–2·52)

*Rounded to nearest ten to prevent individual disclosure. †Cohort split at median age.

Table 2: **All-cause mortality rates, rate differences, and crude rate ratios stratified by faecal immunochemical test result, sex, and age**

	Events*	Person-time, person-years*	Rate per 1000 person-years (95% CI)	Rate difference (95% CI)	Crude rate ratio (95% CI)
Overall cohort, <10 µg Hb/g	1080	38 960	27·72 (26·09–29·42)	..	1 (ref)
Overall cohort, ≥10 µg Hb/g	740	9910	74·79 (69·50–80·38)	47·07 (41·44–52·71)	2·70 (2·46–2·96)
Sex					
Female, <10 µg Hb/g	440	22 250	19·73 (17·93–21·67)	..	1 (ref)
Female, ≥10 µg Hb/g	330	5240	63·40 (56·77–70·60)	43·67 (36·61–50·74)	3·21 (2·79–3·71)
Male, <10 µg Hb/g	640	16 710	38·35 (35·44–41·44)	..	1 (ref)
Male, ≥10 µg Hb/g	410	4670	87·56 (79·28–96·47)	49·21 (40·22–58·20)	2·28 (2·02–2·58)
Age					
<65 years,† <10 µg Hb/g	150	21 600	6·80 (5·75–8·00)	..	1 (ref)
<65 years,† ≥10 µg Hb/g	60	3660	15·59 (11·81–20·20)	8·78 (4·59–12·98)	2·29 (1·69–3·11)
≥65 years, <10 µg Hb/g	930	17 360	53·74 (50·35–57·30)	..	1 (ref)
≥65 years, ≥10 µg Hb/g	680	6250	109·42 (101·38–117·94)	55·68 (46·79–64·58)	2·04 (1·84–2·25)

*Rounded to nearest ten to prevent individual disclosure. †Cohort split at median age.

Table 3: **Non-colorectal cancer mortality rates, rate differences, and crude rate ratios stratified by faecal immunochemical test result, sex, and age**

linear trend (p>0·05). After adjusting for age, sex, and year in the multivariable Cox models, the aHR for all-cause mortality was 1·96 (95% CI 1·79–2·14) and for non-colorectal cancer mortality was 1·70 (1·55–1·88) in those with FIT results of 10 µg of haemoglobin per g or higher compared with lower than 10 µg of haemoglobin per g.

When examining for interaction, there was evidence that both age and sex modified the effect of FIT result on mortality. Cox models inclusive of interaction terms for these covariates provided a better fit than final adjusted models without interaction terms (likelihood ratio test, p<0·0001). To show these interactions, stratum-specific HRs were derived by age at 10-year intervals and sex (appendix p 8). Hazards of both all-cause and non-colorectal cancer mortality for people with FIT results of 10 µg of haemoglobin per g or higher compared with lower than 10 µg of haemoglobin per g was greater in younger patients and in female patients (appendix pp 9–10). For example, at age 50 years, the HR for all-cause mortality following a FIT result of 10 µg of haemoglobin per g or higher in female patients was 3·83 (95% CI 2·86–5·14) compared with 2·91 (2·21–3·85) in male patients. At age 80 years, the HR was 2·27 (1·98–2·60) in female patients and 1·73 (1·53–1·95) in male patients. The subdistribution HRs for non-colorectal cancer mortality (appendix p 11) were very similar to the Cox model estimates (table 4).

SMRs were calculated for all-cause and non-colorectal cancer mortality for the overall symptomatic FIT cohort and by exposure status (appendix p 11). Regardless of FIT result, the risk of mortality from all causes and causes other than colorectal cancer was observed to be increased in the symptomatic FIT cohort compared with the reference population. The SMR for all-cause mortality was 1·50 (95% CI 1·44–1·57) and for non-colorectal cancer mortality the SMR was 1·42 (1·36–1·49) compared with the expected rates based on the population within the year following symptomatic FIT. When examined by exposure status, mortality was further elevated in those with a FIT

	All-cause mortality			Non-colorectal cancer mortality		
	Hazard ratio (95% CI)	Wald test p value	Likelihood ratio test*	Hazard ratio (95% CI)	Wald test p value	Likelihood ratio test*
Model 1 (unadjusted model)	3·07 (2·81–3·35)	<0·0001	..	2·70 (2·47–2·96)	<0·0001	..
Model 2 (covariate: sex)	3·00 (2·75–3·29)	<0·0001	<0·0001	2·64 (2·40–2·90)	<0·0001	<0·0001
Model 3 (covariate: age)	1·98 (1·81–2·17)	<0·0001	<0·0001	1·72 (1·57–1·89)	<0·0001	<0·0001
Model 4 (covariate: year of FIT)	3·07 (2·81–3·35)	<0·0001	0·14	2·70 (2·46–2·96)	<0·0001	0·54
Model 5 (final model: adjusting for covariates sex, age, and year of FIT)	1·96 (1·79–2·14)	<0·0001	<0·0001	1·70 (1·55–1·88)	<0·0001	<0·0001

*Comparing unadjusted and adjusted models. FIT=faecal immunochemical test.

Table 4: **Cox model results for all-cause and non-colorectal cancer mortality, comparing patients with FIT results of 10 µg of haemoglobin per g or higher versus those with FIT results lower than 10 µg of haemoglobin per g**

result of 10 µg of haemoglobin per g or higher, with an SMR of 2·12 (1·98–2·26) for all-cause mortality and 1·86 (1·73–2·00) for non-colorectal cancer mortality compared with the reference. Although the magnitude of the mortality increase associated with FIT results lower than 10 µg of haemoglobin per g was smaller, the hazard was still higher than in the reference population.

Discussion

1-year all-cause and non-colorectal cancer mortality rates were almost doubled in people who had a symptomatic FIT result of 10 µg of haemoglobin per g or higher compared with those with a FIT result lower than 10 µg of haemoglobin per g. This excess mortality was not fully attributable to colorectal cancer deaths; after exclusion of deaths from colorectal cancer, mortality in patients with a FIT result of 10 µg of haemoglobin per g or higher the hazard ratio for non-colorectal cancer mortality was still 1·70 (95% CI 1·55–1·88).

We observed an even greater relative increase in the risk of mortality in female patients than in male patients, and in younger people than in older people, in those with a FIT result of 10 µg of haemoglobin per g or higher compared with those with a FIT result lower than 10 µg of haemoglobin per g. Thus, we highlight that younger patients and female patients undergoing symptomatic FIT are clinically significant groups in whom interventions to reduce mortality could have a particularly notable effect. The elevated risk in younger patients and female patients might indicate that FIT has potential as an additional diagnostic tool for these demographic groups. Alternatively, this finding might highlight diagnostic delay for these individuals due to incorrect clinical decisions made following a raised result.

A key strength of our study is that it uses population-level data, which include all adults who have undergone a symptomatic FIT within the region. The cohort was derived using one of the largest and longest established symptomatic FIT datasets to have been prospectively collated in real time.[13] Previous work has shown that this cohort provides validated, granular detail to sufficiently address a range of research questions related to colorectal cancer diagnosis.[13] We have used this rich data source to examine the outcomes of all-cause and non-colorectal cancer mortality with adjustment for a range of important covariates. Furthermore, comparison with the general population has provided additional valuable insight into how the outcomes can be viewed in a wider context. Follow-up to 1 year was selected to capture events occurring within the symptomatic period, which aligns with the methodology from our previous work examining colorectal cancer diagnosis.[13] Within screening, increased mortality following raised FIT has been reported up to 20 years following a test; hence, future studies of symptomatic cohorts with longer follow-up would be useful.[9]

Assessing the outcomes of both all-cause and non-colorectal cancer mortality allowed us to determine whether the increased risk of mortality observed in this cohort was purely due to colorectal cancer deaths. As FIT is primarily used to aid in the diagnosis of colorectal cancer, it would be reasonable to expect that any increase in all-cause mortality observed in individuals with FIT results of 10 µg of haemoglobin per g or higher would be attributable solely to excess deaths from colorectal cancer. Our results present evidence contrary to this hypothesis, because both the SMRs and Cox models provide strong evidence that non-colorectal cancer mortality was increased in those with FIT results of 10 µg of haemoglobin per g or higher.

Our study has several limitations. For instance, a recognised limitation of using data collected as part of routine clinical care for research is that they are not recorded purposely to address specific research questions.[12] Thus, the results presented are subject to potential biases due to misclassification and residual confounding from unmeasured factors. We can be confident that fact of death is fully ascertained due to the mandatory requirement for death registration in England, and hence expect misclassification for the outcome of all-cause mortality to be negligible. Because non-colorectal cancer death was defined as having no previous colorectal cancer diagnosis, a degree of misclassification might have occurred for this outcome, but we anticipate this to be negligible because within this population the number of deaths from non-registered cancers is expected to be minimal.

Although we expect our results to be representative of symptomatic individuals who completed FIT, the large

proportion of missing data for ethnicity might affect the generalisability of the results to the base population.[23] Additionally, we did not have the data available to examine outcomes of those who had a test requested but did not return it. A regional review of symptomatic FIT return, also in Nottingham, UK, found that 4·1% of requested tests were not completed.[23] FIT non-return has been found to be higher in male individuals, minority ethnic groups, and the least-deprived quintile.[23] As such, examination of mortality outcomes in individuals who did not return their FIT would be important given the increased mortality seen in those who completed a FIT compared with the general population. It is likely that risk of mortality would be higher still in non-returners due to sociodemographic factors and delayed diagnosis.

Another potential limitation is that we did not have information related to factors that might affect the association between FIT and death, including comorbidity, colonoscopy results, and use of antiplatelets or anticoagulants. Use of these medications decreases the sensitivity of FIT for colorectal cancer[24] and they are commonly prescribed in individuals with cardiovascular disease, a leading cause of death. However, we hypothesise that these factors might be on the causal pathway, in which case adjustment would not be appropriate. Even so, several previous population-based studies that adjusted for comorbidity, antiplatelet use, or both have shown strong evidence of the association of raised screening FIT and mortality.[5,7,10] Considering these and our own findings, we do not expect that residual confounding would fully explain the observed associations.

Our findings are consistent with estimates from population-based studies examining mortality following raised screening FIT, which show increased all-cause and non-colorectal cancer mortality versus those with a normal FIT;[9] however, our study is innovative because we investigated a symptomatic population. Previously reported crude estimates from screening studies observed risk of all-cause mortality to be between 1·5 and 2·9 times increased, and risk of non-colorectal cancer mortality to be between 1·37 and 2·8 times increased in comparison with those with normal FIT results.[7,8] The crude RRs derived from our cohort are akin to the highest previous estimate, which was reported in a Danish screening cohort study that used a FIT threshold of 20 μg of haemoglobin per g or higher and had a median follow-up of 3 years.[7] Our findings, in the context of previous publications, are likely to be attributable to the symptomatic population being at higher baseline risk than the presumably healthier asymptomatic screening population. Similarly, our aHRs were slightly higher than adjusted estimates reported in a South Korean screening cohort study of more than 6 million patients[8]—where all-cause mortality was 1·3 times increased and non-colorectal cancer mortality was 1·2 times increased following a so-called positive versus negative FIT. Likewise, a Danish cohort study, after accounting for demographics and comorbidity, reported HRs of 1·92 (95% CI 1·83–2·02) for all-cause mortality and 1·89 (1·79–1·98) for non-colorectal cancer mortality when comparing patients with a FIT result of 20–59 μg per g with those with a FIT result of 7·0 μg Hb per g of faeces or less.[7]

Another important consideration is the range of diseases associated with raised FIT, which might explain the increase in mortality. Upper gastrointestinal cancers might contribute to the mortality outcomes observed. Despite FIT being regarded as specific for colonic bleeding, the risk of gastrointestinal cancers proximal to the colon was increased in screening patients with raised FIT in Dutch and Korean populations.[25,26] In a small Spanish symptomatic cohort, a raised FIT was associated with gastrointestinal cancer mortality (HR 2·2 [95% CI 1·1–4·3]).[27]

Additionally, a narrative review summarising the evidence of associations between raised FIT and non-colorectal cancer disease postulated the mechanism that systemic inflammation caused by underlying chronic disease could lead to microscopic colonic inflammation and subsequent occult bleeding.[28] This review also highlighted that FIT might have use beyond colorectal cancer diagnosis and called for further examination of FIT as a potential biomarker for a range of chronic disease.[28] Several population-based cohort studies examining non-colorectal diseases associated with raised screening FIT have been conducted. These studies report increased risk of cardiovascular disease[5,10] and autoimmune diseases[29] in individuals with raised screening FIT compared with those with normal results. A study of 1 million screening individuals in South Korea found increased risk of rheumatoid and psoriatic arthritis with raised FIT, but highlighted that these outcomes could have been observed due to concurrent use of non-steroidal anti-inflammatory medications.[29] The presence of these associated diseases, along with the occurrence of cancers other than colorectal, perhaps explains the observed increased mortality with raised FIT; hence, further analysis of cause of death is warranted.

We found in our regional study in England that patients undergoing FIT for investigation of symptoms were at increased risk of mortality at 1 year following the test, and mortality was highest among those with FIT results of 10 μg of haemoglobin per g or higher. Both the risks of all-cause and non-colorectal cancer deaths were increased, and the relative risks were even greater among younger and female patients who were tested. Clinically, the findings are important as they highlight that individuals undergoing symptomatic FIT are an at-risk group at baseline. Considering these findings, the next steps are to examine causes of death, adjusting for competing risks following symptomatic FIT. Further understanding of the cause-specific mortality associations with symptomatic FIT has the potential to transform diagnostic pathways and subsequent treatment. Quantifying diseases with major contributions to mortality in this context could extend the use of symptomatic FIT beyond colorectal cancer diagnosis by indicating those requiring investigation other than or following

colonoscopy, with younger and female individuals—who have the highest relative increase in risk—being the groups with the most to gain.

Contributors

FLM performed the statistical analysis and drafted the manuscript. FLM, CJC, JW, and DJH conceptualised the study. CJC, JW, and DJH oversaw data acquisition. FLM and CJC accessed and verified the raw data. All authors contributed to the methodology, reviewed and edited the manuscript, had full access to all the data in the study, and had final responsibility for the decision to submit for publication.

Declaration of interests

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Data sharing

Data were collected by the UK National Health Service (NHS) as part of routine patient care. It is therefore not possible to share the original data outside the Nottingham University Hospitals NHS Trust as per the Data Protection Impact Assessment approval (IG0889).

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