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Systematic review: Mortality associated with raised faecal immunochemical test and positive faecal occult blood results

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Summary

Background: Faecal haemoglobin (f-Hb) testing is used in colorectal cancer (CRC) screening and increasingly to guide the investigation in patients with symptoms suggestive of CRC. Studies have demonstrated increased mortality with raised f-Hb.

Aims: To assess the association of raised f-Hb with all-cause, non-CRC (any cause excluding CRC) and cause-specific mortality.

Methods: We searched Medline and Embase on 9 February 2024 to identify papers reporting mortality after faecal immunochemical (FIT) or guaiac faecal occult blood tests (gFOBT). The primary outcome was all-cause mortality following a positive compared to a negative test.

Results: The search identified 3155 papers. Ten met the inclusion criteria: three reported gFOBT and seven reported FIT results, as screening tests. These reported a total of 14,687,625 f-Hb results. Elevated f-Hb was associated with an increased risk of all-cause, non-CRC and cause-specific mortality including death from cardiovascular, digestive and respiratory diseases. Crude risk ratios for all-cause mortality with a positive versus negative test were derived from six papers (three reporting gFOBT, three FIT). An increased risk was demonstrated in five, with RRs ranging from 1.11 (95% CI: 1.06–1.16) to 2.95 (95% CI: 2.85–3.05). For non-CRC mortality risk, RRs ranged from 1.09 (95% CI: 1.04–1.15) to 2.79 (95% CI: 2.70–2.89). We did not perform meta-analysis due to a limited number of papers reporting suitable results for each type of f-Hb test.

Conclusions: All-cause, non-CRC and cause-specific mortality appear higher in those with raised f-Hb. Population-based studies are warranted to elicit whether this association occurs in symptomatic patients.

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1 | INTRODUCTION

Colorectal cancer (CRC) cases have almost doubled since 1990 with 2.1 million incident cases reported globally in 2019 with over a million deaths a year.[1] Screening programmes have utilised non-invasive stool tests such as guaiac faecal occult blood test (gFOBT) and faecal immunochemical test (FIT),[2,3] the latter of which is the cornerstone of CRC screening in the UK and various other countries due to its high sensitivity and specificity.[4,5] There has also been a rapid expansion of the use of FIT in patients with symptoms of CRC, FIT now acting as a gateway investigation in the UK for such patients.[6,7]

Faecal haemoglobin (f-Hb) is a biomarker in signalling the presence of colorectal neoplasms when using gFOBT/FIT.[5] Immunochemical tests also allow f-Hb concentrations to be quantified.[8,9] This has enabled studies to demonstrate increases in CRC mortality with incremental increases in f-Hb.[10] Currently, f-Hb testing is used in CRC screening to identify those who would benefit from further diagnostic tests such as colonoscopy[11,12] and in the UK in patients with symptoms suggestive of suspected CRC.

Raised f-Hb levels in the absence of CRC have led to studies examining other causes of faecal blood, for example, other digestive diseases[13,14] and the impact of medications that increase the risk of bleeding.[15–17] Recent work has also evaluated f-Hb as a possible marker that predicts the onset of inflammatory bowel disease[18] and its association with other chronic conditions, particularly cardiovascular diseases (CVDs).[19–22]

The association with elevated f-Hb and a range of diseases has led to studies investigating the relationship between elevated f-Hb with all-cause and cause-specific mortality.[23,24] It has also been suggested that elevated f-Hb levels may be a potential prognostic biomarker for chronic disease.[25] If patients are found to have a greater risk of mortality from specific chronic conditions, f-Hb results could also be utilised to identify patients who may benefit from further investigation for potential undiagnosed diseases when CRC has been excluded. This would be of particular importance in non-communicable, modifiable conditions such as CVD in which simple lifestyle interventions can be implemented with great benefit.[26,27] Whilst previously a systematic review has addressed mortality in patients screened with f-Hb compared to those who are unscreened, our focus is to assess differences between patients testing positive and negative.[28] Hence, the primary aim of this systematic review is to assess whether raised f-Hb is associated with all-cause mortality. Where reported, we will also analyse the secondary outcomes of the association of elevated f-Hb with non-CRC (any-cause excluding CRC) and cause-specific mortality.

2 | METHODS

2.1 | Search strategy

A systematic review was conducted according to the PRISMA statement.[29] Prospective registration was completed on PROSPERO. The search strategy was formulated to identify articles reporting the association of raised FIT or positive gFOBT and mortality (Appendix A). Three key concepts were explored: CRC, f-Hb measured as either FIT or gFOBT, and mortality. Medical subject headings, for Medline, and Embase subject headings terms were used to construct the search. The search was completed on 9 February 2024 and was limited to include articles published in English from 1980 to the search date.

2.2 | Inclusion and exclusion criteria

Full papers reporting an association between raised f-Hb (positive FIT/gFOBT) and all-cause, non-CRC (any cause other than CRC) or cause-specific mortality (in particular cardiovascular, respiratory and digestives disease) in adults (>18 years) versus adults with normal or negative f-Hb levels were included. All relevant randomised controlled trials, non-randomised trials and observational studies were considered for inclusion. Those reporting only CRC mortality, case series/ reports, letters, editorials, abstracts and systematic or narrative review articles were excluded.

2.3 | Study selection

Titles and abstracts were independently screened by three reviewers (A.Y., Z.W., and F.M.) using the Rayyan web application.[30] Two discrepancies were discussed and arbitrated by two senior authors (A.M. and D.H.). Similarly, full papers were independently evaluated by the same reviewers and further discrepancies were resolved by the senior authors for final inclusion.

2.4 | Data extraction

Independent data extraction was performed by two authors (A.Y. and F.M.) and recorded using Microsoft Excel.[31] This included title, year, authors, country, type of study, study period, primary aims; demographics of study participants, data and cause of death information sources, follow-up duration, type of stool test (FIT/gFOBT), stool analyser details, FIT positivity threshold, numbers of deaths reported (all-cause, non-CRC or cause-specific), adjusted (aHR) and unadjusted hazard ratios (HR), covariates used in model adjustment and mortality rates. Discrepancies were reviewed and resolved by the senior authors (AM/DH).

2.5 | Assessment of risk of bias

Bias assessment was undertaken using the Newcastle-Ottawa Scale (NOS) for non-randomised papers[32] and the revised Cochrane risk of bias tool (Version 2.0) for randomised controlled trials (RCT).[33]

2.6 | Data analysis

Papers were categorised according to the test used (FIT/gFOBT) and outcome reported (all-cause, non-CRC and cause-specific mortality). Primary outcome was the number of deaths due to all-cause in patients with positive f-Hb compared to those with negative results. Where quantitative FIT was reported, a 'positive' result was categorised according to the threshold described within the paper. Secondary outcomes were the number of non-CRC deaths and other specific causes of death (cancers other than colorectal, including cardiovascular, respiratory, digestive, neuropsychiatric, haematological and endocrine diseases).

It was deemed inappropriate to perform meta-analysis of reported HRs. Firstly, there were only two papers related to gFOBT that presented HRs. It was not possible to combine HRs for the FIT papers due to population overlap and reporting of multiple subgroups by FIT level as these did not align between papers. Hence to provide a comparable measure of effect between papers, we derived crude risk ratios (RR) and 95% confidence intervals (95% CI) from those reporting a raw number of deaths from all or non-CRC causes in patients with raised f-Hb compared to those testing negative. The Pearson's chi squared test of proportion was used to calculate *p*-values.

The RRs for all-cause mortality were calculated taking positive gFOBT/FIT as the exposure; the numerator was total deaths from all-causes in exposed divided by a total number of exposed patients and the denominator was total deaths from all-causes in unexposed divided by total unexposed patients. Similarly, for non-CRC mortality, the calculation used the risk of non-CRC death in the exposed as the numerator with the risk of non-CRC death in the unexposed as the denominator. In the case of a limited number of appropriate studies, only individual crude RRs were reported as in this setting pooled estimates would not provide a useful measure. Stata 18 was used to carry out statistical analysis.[34]

3 | RESULTS

3.1 | Search results

A total of 3155 individual search results were identified, of which 44 reports were assessed after abstract and title screening (Figure 1). Ten papers met the inclusion criteria: nine cohort studies and one RCT. These reported f-Hb results of 14,687,625 participants within CRC-screened programmes.

3.2 | General characteristics

Table 1 provides a summary of demographics, methodology, key outcomes of interest, characteristics and risk of bias assessment results of each included study. From this point, all papers will be referred to by their first author and year of publication. All papers were deemed 'good quality', scoring with a minimum NOS score of 7 out of 9 or 'low risk' on Cochrane risk of bias assessment.

Three papers reported gFOBT results, a total 195,761 patient's gFOBT results were reported and 3.4% were positive.[23,35,36] Seven papers reported FIT results of 14,491,864 participants: 6.1% were positive.[10,22,24,37–40] Due to reporting within overlapping time periods within the same population, there is potential for duplicate reporting of individuals (Table 1). Excluding the duplicate population results (Chien [2013], Moon [2021] and Deding [2023]), a total of

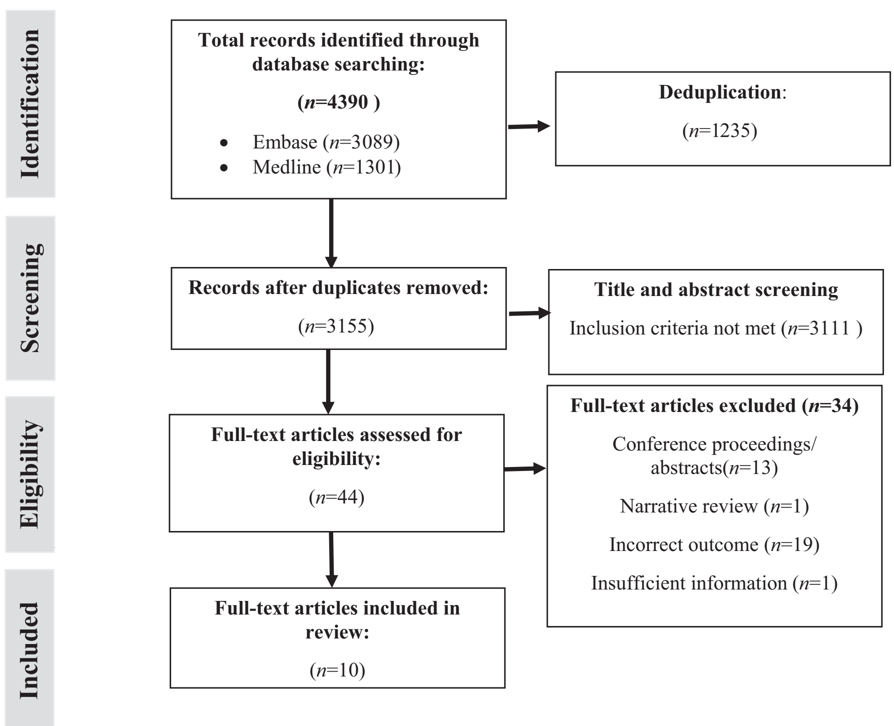

FIGURE 1 PRISMA flow diagram detailing the study selection and exclusion process.

TABLE 1 Summary of study demographics, methodology and risk of bias assessment results.

First author	Year	Country	Study type	Study period	Follow up time (years)	Age range	Test	Population
Whynes[35]	2010	England	RCT	1981–1991	11 (median)	45–74	gFOBT	English CRC screening trial
Libby[23]	2018	Scotland	Cohort	2000–2007	0–16 (range)	50–74	gFOBT	Scottish CRC screening patients
Kaalby[36]	2022	Denmark	Cohort	1985–1986	32–33 (range)	45–75	gFOBT	Hemoccult-II CRC screening trial
Chen[10]	2013	Taiwan	Cohort	1999–2008	3.5 (median)	40–79	FIT	KCIS & Tainan screening programmes
Chien[22]	2020	Taiwan	Cohort	1999–2004	8.43 (median)	≥40	FIT	KCIS[a] programme
Moon[37]	2021	South Korea	Cohort	2009–2012	6.79 (median)	≥50	FIT	South Korean National Health Insurance Service (NHIS) screening programme[b]
Jung[38]	2022	South Korea	Cohort	2009–2011	7–9 (range)	≥50	FIT	South Korean National Cancer Screening programme
Kaalby[24]	2023	Denmark	Cohort	2014–2017	2.7 (median)	50–75	FIT	DCCSP
Deding[39]	2023	Denmark	Cohort	2014–2018	4.7 (median)	50–74	FIT	DCCSP in Southern Denmark[c]
Wen[40]	2023	Taiwan	Cohort	1994–2017	20 (median)	≥20	FIT	MJ Health Management Institution Screening programme

Abbreviations: DCCSD, Danish Colorectal Cancer Screening Database; DRCD, Danish Registry of Cause of Death; KCIS, Keelung Community Integrated Screening; NHIS, National Health Insurance Service.

[a]Population overlap with Chen.

[b]Population overlap with Jung.

[c]Population overlap with Kaalby (2023).

[d]Revised Cochrane risk of bias assessment for randomised controlled trials.

[e]Newcastle-Ottawa Scale for non-randomised trials.

7,892,866 unique individual results (6.04% of which were raised) could be derived from the papers by Chen (2013), Jung (2022), Kaalby (2023) and Wen (2023).

The quantitative FIT threshold which determined 'positivity' was reported in six papers (Table 2). A threshold of ≥20 μgHb/g faeces or ≥100 ngHb/mL, the accepted equivalent based on alternative unit of measurement,[41] was used by Chen (2013), Chien (2013), Kaalby (2023) Deding (2023) and Wen (2023). The threshold reported by Moon (2021) varied according to brand and Jung (2022) reported qualitatively as either 'positive' or 'negative'. Table 2 presents further details of positivity thresholds, the total number of patients and total deaths by positive and negative f-Hb test results.

For the papers that reported a raw number of deaths, Table 3 summarises positive and negative patients by total number of deaths, non-CRC and CVD deaths, as this was the most commonly reported causes other than CRC. Across all papers, 6.0% of patients were positive, yet 9.1% of deaths were recorded in this group. This pattern was replicated in the percentage of deaths due to causes other than CRC and for deaths due to CVD. There was variation in the distribution of causes of death between papers; most notably in the two Danish FIT reports (Kaalby [2023], Deding [2023]), the percentage of deaths attributed to positive patients was approximately double what was reported in the other papers.

Table 4 compiles reported hazard and adjusted hazard ratios for the same three most frequent outcomes.

Meta-analysis was planned to incorporate papers reporting a number of deaths from all or non-CRC causes. However, due to the small number of papers reporting suitable results, three for gFOBT and three for FIT, we have not presented a pooled measure of effect in this context is not appropriate.

Mortality outcomes of interest reported	Data sources	Source of death data	Exclusion criteria	Risk of bias assessment results
All-cause, non-CRC mortality, other cancers, circulatory disease	Nottingham General Practise Database	Medical certificate of cause of death	Missing data	Low risk[d]
All-cause, non-CRC, other cancers, circulatory, respiratory, digestive diseases (excluding CRC)	Bowel Screening Scotland database	National Records of Scotland Database	Missing data	Good quality (8/9)[e]
All-cause, non-CRC, other cancers, CVD, respiratory, digestive diseases	Danish national registers on health & population, Danish national archives	DRCD & death certificates	Missing data	Good quality (9/9)[e]
All-cause	KCIS & Tainan screening programmes databases	National Cancer Registry	Not reported	Good quality (8/9)[e]
CVD	KCIS programme database	National death certificate data linkage	Pre-existing CVD	Good quality (8/9)[e]
All-cause, non-CRC	NHIS Database	NHIS Database	Pre-existing CVD, CRC	Good quality (8/9)[e]
All-cause, non-CRC, other cancers, circulatory, respiratory, digestive diseases (excluding CRC)	NHIS Database	Korea Statistical Office	Missing data, CRC, other cancers, IBD	Good quality (8/9)[e]
All-cause, non-CRC, other cancers, diabetes, CVD, respiratory diseases	DCCSD, Danish National Patient Register, the National Pathology Register	DRCD	Missing data	Good quality (8/9)[e]
All-cause	DCCSD	DRCD	Missing data	Good quality (9/9)[e]
All-cause, all-cancer, non-CRC, cardiovascular disease	MJ Health Management Screening database	National Death File linked to National Cancer Registry	Missing FIT data, previous cancer, history or medication for cerebrovascular disease or CVD (except isolated HTN)	Good quality (8/9)[e]

3.2.1 | All-cause mortality

Whynes (2010), Libby (2018) and Kaalby (2022) reported the association between a positive gFOBT and all-cause mortality. Libby (2018) and Kaalby (2022) reported higher all-cause mortality following positive tests demonstrated by the aHRs in Table 4. Libby (2018) reported a 1.76-fold risk of death from all-causes in the positive gFOBT group compared to negative patients (95% CI: 1.62–1.91, $p<0.001$). Likewise, Kaalby (2022) observed 1.28-fold higher all-cause mortality in gFOBT positive patients versus those testing negative (95%CI: 1.18–1.38, $p<0.001$). Conversely, Whynes (2010) found later age of death from all-causes in patients positive for gFOBT compared with those with negative results; the mean difference in age of death for negative women was −1.13 years (95% CI: −1.84 to −0.42) and −0.98 years (95% CI: −1.59 to −0.37) for men. This finding was attributed to the protective effect of a false positive result in terms of the increased likelihood that investigation for CRC would lead to diagnosis and treatment of other comorbidities.

All-cause mortality in relation to FIT was reported in six papers; these unanimously reported an association between increased all-cause mortality with raised FIT (Table 4). Both Chen (2013) and Wen (2023) utilised the trend test and demonstrated strong evidence of increasing all-cause mortality with incremental increases in FIT ($p<0.001$). Moon (2021) reported increased all-cause mortality patients with positive FIT with an aHR of 1.15 (95% CI: 1.07–1.23, $p=0.006$). Jung (2022) reported an increase in all-cause mortality of 29% in patients with positive FIT results (95% CI: 28–31%, $p<0.001$). Similarly, Kaalby (2023) demonstrated incremental increases in all-cause mortality with rising FIT; patients with FIT 20.0–59.90 μgHb/g

TABLE 2 Summary of total number of individuals f-Hb results reported, number positive versus negative tests and number of all cause deaths.

First author	Positivity threshold	Total number of patients	Positive patients	%	Negative patients	%	Total number of deaths	%	Total deaths in f-Hb positive patients	%	Total deaths in f-Hb negative patients	%
gFOBT												
Whynes	Positive/negative	41,146	2222	5.4	38,924	94.6	21,428	52.1	1162	5.4	20,266	94.6
Libby	Positive/negative	133,921	2714	2.0	131,207	98	13,226	9.9	594	4.5	12,632	95.5
Kaalby	Positive/negative	20,694	1766	8.5	18,928	91.5	10,068	48.7	946	9.4	9122	90.6
FIT												
Chen	≥100 ng Hb/mL	185,743	9315	5.0	176,428	95.0	–	–	–	–	–	–
Chien	≥100 ng Hb/ml	33,355	1590	4.8	31,765	95.2	–	–	–	–	–	–
Moon	Brand dependent[a]	6,277,446	370,140	5.9	5,907,306	94.1	11,253	0.2	920	8.2	10,333	91.8
Jung	Positive/negative	5,932,544	380,789	6.4	5,551,755	93.6	391,960	6.6	36,368	9.3	355,592	90.7
Kaalby	≥20.0 μgHb/g[b]	1,228,365	84,809	6.9	1,143,556	93.1	21,857	1.8	3921	17.9	17,936	82.1
Deding	≥20.0 μgHb/g[b]	288,197	19,887	6.9	268,310	93.1	10,555	3.7	1707	16.2	8848	83.8
Wen	≥20.0 μgHb/g[b]	546,214	13,636	2.5	532,578	97.5	54,296	9.9	2945	5.4	51,351	94.6
Total		14,687,625	886,868	6.0	13,800,757	94.0	534,641	3.7[§]	48,563	9.1	486,078	90.9

[a]SD Bioline FOB kits, Medex HM-JACK = 30 ng/mL, HemoTech NS-1000 = 40 ng/mL, OC-Hemocatch, FOB test, ASAN Easy Test FOB = 50 ng/mL, OC-sensor™ = 100 ng/mL.

[b]Equivalent to ≥100 ng Hb/ml

[§]Calculated with Chen and Chien total numbers excluded.

TABLE 3 Summary of number of overall, non-CRC and CVD deaths reported following positive and negative f-Hb tests.

First author	Deaths in positive patients	%	Deaths in negative patients	%	Non-CRC deaths	%	Non-CRC deaths in positive patients	%	Non-CRC deaths in negative patients	%	CVD deaths[a]	%	CVD deaths in positive patients	%	CVD deaths in negative patients	%
Whynes	1162	5.4	20,266	94.6	20,846	97.3	1050	5.0	19,796	95.0	–	–	–	–	–	–
Libby	594	4.5	12,632	95.5	12,709	96.1	510	4.0	12,199	96.0	3558	26.9	128	3.6	3430	96.4
Kaalby (2022)	946	9.4	9122	90.6	9693	96.3	882	9.1	8811	90.9	3668	36.4	340	9.3	3328	90.7
Moon	920	8.2	10,333	91.8	–	–	–		–		–			–	–	–
Jung	36,368	9.3	355,592	90.7	378,103	96.5	32,238	8.5	345,865	91.5	78,262	20.0	6530	8.3	71,732	91.7
Kaalby (2023)	3921	17.9	17,936	82.1	21,227	97.1	3634	17.1	17,593	82.9	5138	23.5	907	17.7	4231	82.3
Deding	1707	16.2	8848	83.8	10,191	96.5	1573	15.4	8618	84.6	–	–	–	–	–	–
Wen	2945	5.4	51,351	94.6	52,195	96.1	2546	4.9	49,649	95.1	11,436	21.1	549	4.8	10,887	95.2
Overall total	48,563	9.1	486,080	90.9	504,964	96.5	42,433	8.4	462,531	91.6	102,062	20.8	8454	8.3	93,608	91.7

[a]Classification of Circulatory and CVD deaths specified by ICD10 code I. Chen and Chien not featured in this table as raw number of deaths not reported.

TABLE 4 Summary of hazard ratios and adjusted hazard ratios for all-cause, non-CRC and CVD mortality following f-Hb test.

		All-cause mortality				All-cause mortality excluding CRC				CVD mortality			
Author	Comparator	HR	95% CI	aHR	95% CI	HR	95% CI	aHR	95% CI	HR	95% CI	aHR	95% CI
Libby	gFOBT positive versus negative	2.43	2.23–2.63**	1.76	1.62–1.91**	2.18	1.99–2.39**	1.58	1.45–1.73**	1.92	1.61–2.29**	1.28	1.07–1.53*
Kaalby (2022)	gFOBT positive versus negative	1.52	1.41–1.56**	1.28	1.18–1.38**	1.43	1.32–1.56**	1.20	1.10–1.30**	1.53	1.34–1.75**	1.22	1.07–1.39*
Chen	FIT 100–149 ng Hb/mL versus undetected	–	–	1.14	0.97–1.11	–	–	–	–	–	–	–	–
	FIT 150–249 ng Hb/mL versus undetected	–	–	1.35	1.14–1.61	–	–	–	–	–	–	–	–
	FIT 250–449 ng Hb/mL versus undetected	–	–	1.73	1.42–2.11	–	–	–	–	–	–	–	–
	FIT ≥450 ng Hb/mL versus undetected	–	–	1.78	1.54–2.07***	–	–	–	–	–	–	–	–
Chien	FIT ≥100 ng/mL versus undetected	–	–	–	–	–	–	–	–	–	–	1.73	1.13–2.66*
Moon	FIT positive versus negative	1.40	1.31–1.49†	1.15	1.07–1.23†	–	–	1.15	1.07–1.23*	–	–	–	–
Jung	FIT positive versus negative	1.53	1.51–1.55**	1.29	1.28–1.31**	1.39	1.38–1.41**	1.17	1.15–1.18**	1.36	1.32–1.37**	1.14	1.12–1.16**
Kaalby (2023)	FIT 20.0 to 59.9 versus ≤7.0 μg Hb/g	2.93	2.79–3.08**	1.92	1.83–2.02**	2.89	2.75–3.03**	1.89	1.79–1.98**	2.70	2.43–3.00*	1.64	1.48–1.83**
	FIT ≥60.0 versus ≤7.0 μg Hb/g	3.58	3.42–3.74**	2.20	2.10–2.30**	3.25	3.09–3.40**	1.98	1.89–2.08**	3.66	3.34–4.01**	2.09	1.90–2.29**
Deding	FIT 20 to 49 versus <4.0 μg Hb/g	–	–	4.18	3.73–4.67**	–	–	4.10	3.65–4.60**	–	–	–	–
	FIT 50 to 99 versus <4.0 μg Hb/g	–	–	4.75	4.16–5.42**	–	–	4.70	4.10–5.37**	–	–	–	–
	FIT 100 to 199 versus <4.0 μg Hb/g	–	–	5.13	4.39–5.98**	–	–	4.90	4.17–5.75**	–	–	–	–
	FIT >199 versus <4.0 μg Hb/g	–	–	5.27	4.62–6.01**	–	–	4.74	4.12–5.45**	–	–	–	–
Wen	FIT ≥20 versus <20 μg Hb/g	–	–	1.49	1.42–1.56	–	–	1.29	1.23–1.36	–	–	1.16	1.03–1.30
	FIT 20–59 versus <20 μg Hb/g	–	–	1.37	1.26–1.49	–	–	1.28	1.17–1.39	–	–	1.19	0.90–1.35
	FIT 60–119 versus <20 μg Hb/g	–	–	1.34	1.23–1.47	–	–	1.19	1.08–1.31	–	–	1.03	0.83–1.29
	FIT 120–199 versus <20 μg Hb/g	–	–	1.66	1.47–1.89	–	–	1.35	1.17–1.55	–	–	1.46	1.09–1.96
	FIT 200–299 versus <20 μg Hb/g	–	–	1.75	1.51–2.03	–	–	1.47	1.25–1.73	–	–	1.06	0.71–1.60
	FIT ≥300 versus <20 μg Hb/g	–	–	1.79	1.58–2.01***	–	–	1.41	1.23–1.62***	–	–	1.38	1.03–1.86††

Note: Covariants used in the calculation of adjusted hazard ratios: Libby: age, sex, deprivation and prescribed medicines that cause bleeding. Kaalby (2022): age, sex, income, education, bleeding at baseline and comorbidity. Chen: age and sex. Chien: age, sex, body mass index, smoking, alcohol drinking, regular exercise, systolic blood pressure, diastolic blood pressure, fasting glucose, total cholesterol, triglycerides, HDL cholesterol, white blood cell and drug usages for hypertension, diabetes, hyperlipidaemia. Moon: age, sex, smoking, alcohol consumption, regular exercise, diabetes mellitus, hypertension, dyslipidaemia, and body mass index. Jung: age, sex, smoking, alcohol consumption, BMI, Charlson Comorbidity Index, aspirin use. Kaalby (2023): age, sex, highest level of completed education, annual income, Charlson Comorbidity Index, diseases suspected of causing GI bleeding (e.g. inflammatory bowel disease, diverticular disease), prescription medication (e.g. aspirin). Deding: age and sex. Wen: age, sex, and non-steroidal anti-inflammatory agents.

*$p<0.05$. **$p<0.001$. ***$p<0.001$ on trend's test.

†p value not reported.

††$p=0.005$.

has an all-cause mortality aHR of 1.92 (95% CI: 1.83–2.02, $p<0.001$) which rose to 2.20 (95% CI: 2.10–2.30, $p<0.001$) for those with f-Hb≥60 µgHb/g when compared to patients with FIT<7.0 µgHb/g. Deding (2023) observed increased all-cause mortality with each incremental increase in FIT result with FIT<4 µgHb/g as the comparator; the highest aHR of 5.27 (95% CI: 4.62–6.01, $p<0.001$) was observed in patients with FIT ≥199 µgHb/g.

3.2.2 | Crude RRs for all-cause mortality

Crude RR calculation for all-cause mortality was possible for the six papers that reported a raw number of deaths; Whynes (2010), Libby (2018), and Kaalby (2022) reported gFOBT results and Jung (2022), Kaalby (2022) and Wen (2023) reported FIT results. The crude RRs and 95%CIs for all-cause mortality are summarised in Figure 2 and Table S1. It was not possible to derive RRs from Chen (2013) as a raw number of deaths were not published. The authors were contacted to request this information but there was no response. We have not presented crude RRs for Moon (2021) or Deding (2023) due to the overlap in populations with Jung (2022) and Kaalby (2023), respectively.

Evidence for increased risk of all-cause mortality in association with raised f-Hb was observed in five of the six papers from which crude RRs were derived. Libby (2018) and Kaalby (2022) demonstrated increased all-cause mortality associated with positive gFOBT, with RRs of 2.27 (95% CI: 2.11–2.45, $p<0.0001$) and 1.11 (95% CI: 1.06–1.16, $p<0.001$), respectively. Likewise for papers reporting FIT results the RRs demonstrated increased risk of all-cause mortality with raised FIT versus those testing negative. The estimated RRs were 1.49 (95% CI: 1.48–1.51, $p<0.0001$) from Jung (2022), 2.95 (95%CI: 2.85–3.05, $p<0.001$) from Kaalby (2023) and 2.24 (95% CI: 2.17–2.32, $p<0.0001$) from Wen (2023). Based on results reported by Whynes (2010), no difference in risk for all-cause mortality was observed with a RR of 1.00 (95% CI: 0.96–1.05, $p=0.8331$).

3.2.3 | Non-CRC mortality

Increased risk of non-CRC mortality was associated with positive gFOBT in Libby (2018) and Kaalby (2022). Compared to participants with a negative gFOBT, aHRs demonstrated those with a positive result had a 58% (95% CI: 45–70%, $p<0.0001$) and 20% (95% CI: 10–30%. $p<0.001$) higher risk of death from non-CRC causes, respectively. However, Whynes (2010) stated that when excluding CRC deaths, the 'composition of causes of death' was 'essentially similar' between the gFOBT positive and negative groups yet quantitative measurement was not presented.

An increased risk of non-CRC in those with a positive FIT was reported by Moon (2021), Jung (2022), Kaalby (2023), Deding (2023) and Wen (2023). Moon (2021) found a 15% increased risk of non-CRC death in positive patients in comparison to negative comparators (95% CI: 7%–23%, $p=0.006$). Jung (2022) reported a 17% greater risk of dying from all causes excluding CRC in the FIT-positive group (95% CI: 15%–18%, $p<0.001$). This association was further demonstrated by Kaalby (2023); aHR increased from 1.89 (95% CI: 1.79–1.98, $p<0.001$) for FIT 20–59.9 µgHb/g to 1.98 (95% CI: 1.89–2.08, $p<0.001$) in those with FIT≥60.0 µgHb/g. Furthermore, an estimated excess of 556 deaths from causes other than CRC was observed in those with raised FIT in the study by Deding (2023) with increasing aHRs for each incremental increase in FIT result (Table 4). Wen (2023) provided a summary measure of non-CRC mortality; aHR for non-CRC for FIT ≥20 versus <20 µg Hb/g was 1.29 (1.23 to 1.36). This paper also reported evidence of increasing non-CRC with incremental increases in FIT ≥20 µg Hb/g ($p<0.001$, trend test).

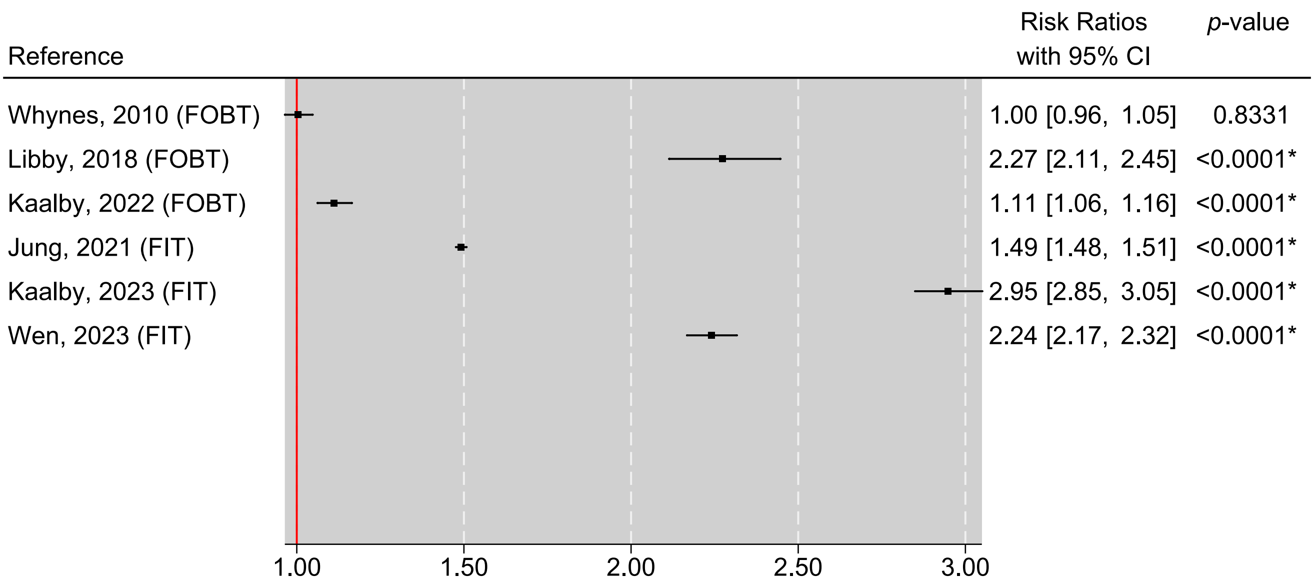

FIGURE 2 Forest plot summarising crude risk ratios for all-cause mortality with positive f-Hb compared to negative f-HB. *$p<0.05$.

3.2.4 | Crude RRs for non-CRC mortality

It was possible to derive crude RRs for non-CRC mortality from the results presented by Whynes (2010), Libby (2018) and Kaalby (2022) reporting gFOBT and Jung (2022), Kaalby (2022) and Wen (2023) reporting FIT. The risk of non-CRC mortality was increased with raised f-Hb in five of the six papers (Figure 3). A RR of 2.08 (95% CI: 1.92–2.25, $p<0.0001$) for non-CRC mortality with a positive gFOBT compared to a negative test was derived from Libby (2018) which reported the outcomes of the largest sample of gFOBT tests. Additionally, a modestly increased risk of non-CRC morality with positive gFOBT was derived from Kaalby (2022); RR 1.09 (95% CI: 1.04–1.15, $p=0.0004$). Crude RRs demonstrated an increased risk of non-CRC mortality associated with raised FIT. For Jung (2022), the RR of non-CRC mortality was 1.37 (95% CI: 1.36–1.39, <0.0001), for Kaalby (2023), the RR was 2.79 (95%CI: 2.70–2.89, $p<0.0001$), and from the results reported by Wen (2023), a RR of 2.06 (95%CI: 1.98–2.13, $p<0.0001$) was derived. No difference in non-CRC mortality was observed within the English participants in an early CRC screening trial published by Whynes (2010); the crude RR for non-CRC mortality was 0.97 (95% CI 0.93–1.01, $p=0.1245$).

Table S1 and Figures S1 and S2 present the aHRs and crude RRs for both all-cause and non-CRC mortality side by side to aid comparison. Overall, these uniformly convey increased mortality with positive f-Hb with no confidence interval crossing the null value.

3.3 | Cause-specific mortality

Whynes (2010) reported that 9.6% of deaths in positive patients were due to CRC compared to 2.3% of deaths in negative patients ($\chi^2=222.55, p<0.01$). However, no significant difference was observed in the percentage of deaths caused by other cancers, 23.1% in positive and 25.4% in negative patients ($\chi^2=2.86$, $p=0.09$). Comparable percentages of deaths due to CVD were also observed, 42.6% versus 42.0% in positive and negative patients, respectively ($\chi^2=0.16$, $p=0.69$). Cancers excluding CRC had a higher mortality in the positive groups as reported by Libby (2018) (aHR 1.40, 95% CI: 1.20–1.63, $p<0.0001$) and Kaalby (2022) (aHR 1.30, 95% CI: 1.12–1.51, $p<0.001$).

Libby (2018) reported raised mortality for circulatory (aHR 1.28, 95% CI: 1.07–1.53, $p=0.007$), respiratory (aHR 1.96, 95% CI: 1.53–2.51, $p<0.0001$), neuropsychological (aHR 1.66, 95% CI: 1.19–2.32, $p=0.003$) and haematological and endocrine (aHR 2.06, 95% CI: 1.26–3.36, $p=0.004$) diseases in positive patients. Comparatively, Kaalby (2022) found that participants with positive gFOBT had a greater risk of death from cardiovascular (aHR 1.22, 95% CI: 1.07–1.39, p=0.004), respiratory (aHR 1.19, 95% CI:1.01–1.40, $p=0.041$), and haematological and endocrine (aHR 1.58, 95% CI: 1.19–2.10, $p=0.001$) diseases when compared to their negative counterparts. Death caused by digestive disease, excluding CRC, increased in association with a positive gFOBT in both Libby (2018) (aHR 3.36, 95% CI: 2.50–4.51, $p<0.0001$) and Kaalby (2022) (aHR1.50, 95% CI: 1.07–2.10, $p=0.019$).

Four papers reported an association of raised FIT and increased risk of death from a range of specific causes (Chien [2020], Jung [2022], Kaalby [2023], Wen [2023]). Chien (2020) examined the relationship between raised FIT and risk of CVD death; at a FIT ≥100 ng/mL risk of cardiovascular death was 73% greater than in negative controls (95% CI: 13%–266%, $p=0.025$). Wen (2023) reported an increased risk of CVD mortality with FIT ≥20 µg with an overall aHR of 1.16 (95% CI: 1.03–1.30), and when examining CVD mortality and incremental increases in FIT ≥20 µg, there was evidence of dose-response relationship ($p=0.005$, trend test).

Jung (2022) and Kaalby (2023) found higher mortality from a range of diseases which was reported in association with FIT positivity. Excluding CRC death, Jung (2022) found other digestive diseases to be the most common cause of death for those with a positive FIT (aHR

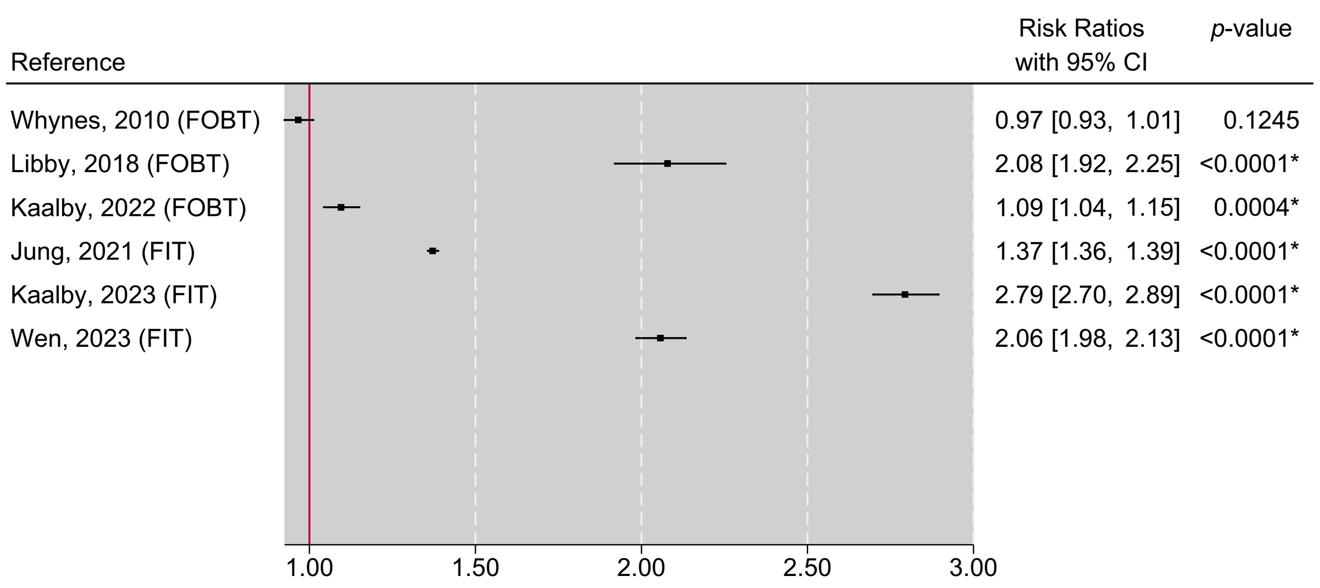

FIGURE 3 Forest plot summarising risk ratios for non-CRC mortality with positive f-Hb compared with negative f-HB. *$p<0.05$.

1.57, 95% CI: 1.48–1.66, $p<0.001$). Additionally, a 14% greater risk of death from cancers other than CRC (95% CI: 12%–16%, $p<0.0001$), CVD (95% CI: 11%–17%, $p<0.0001$) and respiratory disease (95% CI: 9%–19%, $p<0.0001$) was noted for those with a positive FIT. This group also had a greater mortality from haematological and endocrine disease (aHR 1.10, 95% CI: 1.04–1.17, $p=0.001$). Likewise, Kaalby (2023) reported increased risk of death with FIT 20.0–59.9μgHb/g from respiratory conditions (aHR 2.14, 95% CI: 1.95–2.35, <0.001), CVD (aHR 1.64, 95% CI: 1.48–1.83, $p<0.001$), other cancers (aHR 1.80, 95% CI: 1.67–1.91, <0.001) and diabetes (aHR 1.73, 95% CI: 1.27–2.35, $p=0.002$) compared to those with FIT<7.0μgHb/g. The same finding was upheld in those with FIT≥60μgHb/g with no overlap in confidence intervals and all $p<0.05$.

4 | DISCUSSION

4.1 | Summary—our findings

The objective of this systematic review was to investigate the association with elevated f-Hb, measured by either FIT or gFOBT and all-cause, non-CRC and cause-specific mortality. Ten articles from five countries investigated these various associations in patients undergoing CRC screening. The main finding was that the risk of mortality from all-causes was higher in those with positive gFOBT /FIT. Where FIT was reported quantitatively, this risk also increased with incremental increases in the f-Hb level. It would be reasonable to expect that the excess mortality exhibited in raised f-Hb would be purely attributed to a greater number of deaths from CRC, yet our findings indicate that increased mortality remained when CRC deaths were excluded. Elevated f-Hb was found to be associated with an increased risk of death from specific causes which included digestive diseases other than CRC, cardiovascular and respiratory disease.

4.2 | Strengths and Limitations

This is the first systematic review that has explored the association between raised f-Hb and all-cause and cause-specific mortality. We have summarised the available literature and highlighted the increased risk of mortality demonstrated. Overall, the papers comprised large population-based investigations which were rated highly when assessed with established risk of bias assessment tools. Particular strengths were the large sample sizes and length and completeness of follow-up.

The results are accrued largely from cohort studies using routinely collected data; such data sources were not created to answer study-specific research questions.[42] Therefore, it is crucial to acknowledge potential biases and recognise the impact of residual confounding either from incomplete or unmeasured risk factors.[43] An example of one such confounder is smoking which has been associated with raised f-Hb[44] and is a risk factor for all-cause and cause-specific mortality.[45] Hence, in papers that did not adjust for smoking, mortality associated with increased f-Hb may be overestimated.

Another factor to consider is non-compliance with colonoscopy following a positive screening test; this has been demonstrated to result in a twofold increased risk of CRC death at 10 years follow-up.[46] The elevated risk of CRC death in this group is expected due to delayed diagnosis and treatment, mortality from other causes is likely also increase as this group will include those in whom comorbidity and frailty contraindicate colonoscopy.[47] The impact of non-compliance with colonoscopy is not possible to determine from the included papers as none reported the outcomes within this specific subgroup. Nevertheless, non-CRC mortality was demonstrated to be consistently higher in positive patients in the four included papers which adjusted for comorbidity indicating that this association is unlikely to be fully explained by non-compliance.[24,36–38]

Qualities of ascertainment of cause of death and information bias, particularly misclassification, are other considerations. Whilst robust methods of ascertainment of cause of death included the use of data-linkage, independent validation of death certificates and the use of cancer and/or death registries these methods rely on the completeness of data,[48] the accuracy of the cause of death recorded,[43] correct coding and linkage.[49]

Misclassification of cause of death influences the magnitude of the associations, particularly in the context of cause-specific deaths.[50] The 'sticky-diagnosis' bias, which is well described within screening trials, would suggest that in relation to cause-specific mortality patients with raised f-Hb may be more likely to have death falsely attributed to CRC as CRC will be more commonly diagnosed within this group.[51] Thus, in papers that address causes-specific mortality, the presence of this bias could result in an overestimated CRC mortality and underestimated mortality from other causes within the raised f-Hb group. It is therefore probable that the true non-CRC mortality associated with raised f-Hb could be higher than observed within the reports in this review. The outcome measure of all-cause mortality should minimise the impact of misclassification, provided a minimal loss of follow-up, as it can be expected that death be accurately recorded.[50]

The main limitation of this review is the substantial heterogeneity between the included papers. This included inconsistency in the reported levels of f-Hb for the papers reporting FIT, the use of a variety of analysers to derive f-Hb results, varying exclusion criteria (supplementary information) and differential adjustments for confounders. Whilst there is consistency in the results between f-Hb test types, it is notable that all the papers reporting gFOBT were from Europe and whilst the majority of the FIT studies were undertaken in Asian. Geographic factors or dietary practices may influence the presence of faecal blood, potentially limiting the generalisability of the observed mortality outcomes across different populations.

Meta-analysis providing a pooled measure of effect has not been reported due to the small number of papers. This aligns with the methodology described by Borenstein et al. (2010) and is supported by the Cochrane Statistical Methods Group analysis recommendations for systematic review.[52,53]

Nevertheless, whilst there was variation between papers which could be attributed to differences in study settings, populations and follow-up times, the assimilated findings are congruent and indicate an increased risk of mortality associated with raised f-Hb.

4.3 | What is available in the literature

Whilst the association between elevated f-Hb and mortality has been described; the underlying mechanisms remain unclear and are likely multifactorial. Generalised inflammation is a proposed contributor which may lead to subclinical colonic inflammation and occult bleeding.[23] Inflammation is implicated in the development of cancers, and chronic disease such as CVD and type 2 diabetes,[54–56] with the severity linked to mortality risk.[57–59] Studies have also demonstrated an association between raised f-Hb and diseases with inflammatory components such as metabolic syndrome and diabetes as well as immune-mediated conditions including rheumatoid arthritis and systemic lupus erythematosus.[21,60,61]

Another hypothesis is the impact of chronic blood loss in faeces and the resultant decrease in blood haemoglobin levels. Anaemia is known to impact all-cause mortality[10,62] and is associated with an increased risk of cardiovascular and cancer mortality.[63,64] With regard to CVD death, it has been theorised that patients with CVD are more likely to be prescribed medications that can cause gastrointestinal bleeding (e.g. anti-platelets, anti-coagulants).[25] Counter to this, a recent meta-analysis found that the accuracy of f-Hb testing was not affected by concurrent antiplatelet or anticoagulant use.[65] Interestingly, one of the large population-based cohort studies included in our review which excluded patients with pre-existing CVD and adjusted for smoking, obesity, dyslipidaemia and hypertension found a statistically significant increased risk development of CVD, and cardiovascular death was demonstrated in those with raised f-Hb.[22]

The potential mechanisms related to inflammation and chronic blood loss suggest that factors resulting in raised f-Hb and associated increased mortality are likely multifactorial. Regardless, we can deduce that elevated f-Hb is a marker of poor health.

Over the past 10 years, symptomatic FIT has expanded from use in pilot pathways at a handful of pioneering centres to endorsement in national guidelines.[66] Joint recommendations from the Association of Coloproctology of Great Britain and Ireland and the British Society of Gastroenterology published in 2022 and guidance by NICE in 2023 advocate the use of FIT, with a positivity threshold of ≥10 μgHb, to determine urgent onward referral in patients presenting to primary care with signs and symptoms of suspected CRC.[6,7] The need for further studies is of particular importance with the rapid growth in the use of FIT to triage symptomatic patients and with the planned lowering in the UK screening programme of the FIT threshold and age for participation.[67]

5 | CONCLUSION AND CLINICAL SIGNIFICANCE

The evidence we have presented adds impetus for further focused efforts to improve understanding of the causes and significance of raised f-Hb and associated increased mortality outside the context of CRC diagnosis. These findings suggest the potential utility of f-Hb as a marker of undiagnosed inflammatory disease states or as a marker of chronic disease.

Chronic non-communicable diseases comprise the majority of the global disease burden and are the most common causes of preventable mortality worldwide.[68] In patients with raised f-Hb, there may be an opportunity to undertake further investigation to identify and guide intervention to optimise other underlying chronic conditions. With the overarching aim of screening being to 'prevent earlier deaths' and to 'improve quality of life by detecting a condition at a stage where treatment can be more effective', the future of using f-Hb within this context may be wider reaching than purely to diagnose CRC.[69] The concept of 'false-positive FIT' will perhaps be reframed as evidence emerges; targeted investigation for other diseases when CRC has been excluded may need to be considered in patients with raised f-Hb. We therefore highlight the importance of further examination of the predictive role of f-Hb in relation to mortality and disease outcomes in those with raised f-Hb who do not have CRC or other colonic pathology at colonoscopy.

Further research is required particularly with the increasing use of FIT not only within screening programmes but as a tool to investigate patients with bowel symptoms.[6,7,67] A study of the relationship between f-Hb and mortality within symptomatic cohorts should be undertaken to determine whether they would have comparable findings to screening populations, as in patients without CRC their symptoms could be a manifestation of other diseases.

AUTHOR CONTRIBUTIONS

Francesca Ligori Malcolm: Conceptualization; methodology; investigation; formal analysis; project administration; writing – original draft; writing – review and editing. **Anjali K. D. S. Yapa:** Investigation; conceptualization; methodology; writing – original draft; writing – review and editing; formal analysis. **Zhen Yu Wong:** Investigation; writing – review and editing. **Alastair James Morton:** Writing – review and editing; conceptualization; investigation; methodology; formal analysis. **Colin Crooks:** Conceptualization; methodology; writing – review and editing; supervision. **Joe West:** Writing – review and editing; supervision; conceptualization; methodology. **Ayan Banerjea:** Writing – review and editing; conceptualization; methodology; supervision. **David Humes:** Conceptualization; methodology; supervision; visualization; writing – review and editing.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

STUDY REGISTRATION

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AUTHORSHIP

Guarantor of the article: Francesca Ligori Malcolm acts as guarantor for the article. All authors have approved the final version of the manuscript.

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SUPPORTING INFORMATION

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

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APPENDIX A

SEARCH STRATEGY

Embase: 3089.

1	Exp colorectal cancer/ or colorectal carcinoma/	409,698
2	colon cancer/ or colon tumour/ or rectum carcinoma/ or colon carcinoma/ or rectum cancer/ or rectum tumour/	200,446
3	large intestine cancer/ or large intestine carcinoma/	732
4	intestine cancer/	5970
5	exp colon/	116,756
6	("colorectal cancer" or "colorectal tumo?r" or "colorectal malig*" or "colorectal carcinoma" or "colorectal adenocarcinoma"). mp.	312,305
7	("rect* cancer" or "rect* tumo?r" or "rect* malig*" or "rect* carcinoma" or "rect* adenocarcinoma").mp.	89,088
8	("large intestin* cancer" or "large intestin* tumo?r" or "large intestin* malig*" or "large intestin* carcinoma" or "large intestin* adenocarcinoma").mp.	1173
9	((colon* adj3 cancer) or (cancer adj3 bowel) or (cancer adj3 colorect*) or (malig* adj3 bowel) or (malig* adj3 colorect*) or (tumo?r* adj3 bowel) or (tumo?r* adj3 colorect*)).mp.	403,710
10	occult blood/ or occult blood test/ or occult blood test kit/	18,768
11	colorectal cancer detection kit/	179
12	((FIT adj2 cancer) or "f?ecal immuno?chem*" or "f?ecal h?emoglobin" or "f-Hb" or f?ecal h?emorrhage or "f?ecal bl??d").mp.	5060
13	("gFOBT" or "FOB test" or "guaiac" or "occult bl?d" or occult h?emorrhage).mp.	2125
14	((f?ec* adj2 h?emoglobin) or (f?ec* adj2 immuno?chem*) or (stool adj2 bl?d) or (f?ec* adj2 occult) or (stool adj2 test)).mp.	13,466
15	cancer mortality/ or all cause mortality/ or mortality rate/ or mortality/	1,278,723
16	death/ or "cause of death"/	479,722
17	fatality/	106,319
18	(fatal* or mortality or death* or died or surviv* or lethal or dead* or decease*).mp.	5,859,529
19	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	619,568
20	10 or 11 or 12 or 13 or 14	25,151
21	19 and 20	14,135
22	15 or 16 or 17 or 18	5,859,529
23	21 and 22	4606
24	case study/	110,792
25	case report/	3,113,143
26	letter.pt.	1,326,568
27	editorial.pt.	810,224
28	note.pt.	989,946
29	review.pt.	3,286,427
30	24 or 25 or 26 or 27 or 28 or 29	9,197,290
31	23 not 30	3225
32	limit 31 to em = 198,001–202,406	3086

Ovid MEDLINE(R): 1301.

1	Exp colorectal neoplasms/	246,865
2	Colonic Neoplasms/	80,196
3	intestine, large/ or colon/	74,718
4	("colorectal cancer" or "colorectal tumo?r" or "colorectal malignanc*" or "colorectal adenocarcinoma" or "colorectal carcinoma").mp.	155,480
5	("rect* cancer" or "rect*malignanc*" or "rect* tumo?r*" or "rect* adenocarcinoma" or "rec* carcinoma").mp.	38,399
6	("large intestin* cancer" or "large intestin*malignanc*" or "large intestin* tumo?r*" or "large intestin* adenocarcinoma" or "large intestin* carcinoma").mp.	219
7	(bowel or colorect* or large intestin*).mp.	415,756
8	((colon* adj3 cancer) or (cancer adj3 bowel) or (cancer adj3 colorect*) or (malig* adj3 bowel) or (malig* adj3 colorect*) or (tumo?r* adj3 bowel) or (tumo?r* adj3 colorect*)).mp.	206,727
9	Occult Blood/	6496
10	((FIT adj2 cancer) or f?ecal immuno?chemi* or "f?ecal h?emoglobin" or "f?ecal h?emorrhage" or f?ecal immuno* or "f-Hb"). mp	2652
11	("gFOBT" or "guaiac f?ecal occult blood test" or "guaiac" or "FOB test" or "occult blood" or "occult haemorrhage" or "stool test" or "stool occult blood").mp.	10,091
12	((f?ec* adj2 h?emoglobin) or (f?ec* adj2 immuno?chemi*) or (stool adj2 bl?d) or (f?ec* adj2 occult) or (stool adj2 test)).mp.	7906
13	mortality/ or "cause of death"/ or fatal outcome/ or survival rate/	347,943
14	Death/ or "Cause of Death"/	74,783
15	((mortality adj2 all? cause) or (death adj2 all? cause) or (fatal* adj2 all? cause) or fatal* or mortality or death).mp.	2,388,434
16	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	581,613
17	9 or 10 or 11 or 12	12,229
18	16 and 17	8233
19	13 or 14 or 15	2,435,081
20	18 and 19	1879
21	Case Reports/	2,411,891
22	letter.pt.	1,258,670
23	editorial.pt.	695,049
24	review.pt.	3,338,721
25	21 or 22 or 23 or 24	7,304,435
26	20 not 25	1338
27	limit 26 to dt="19,800,101–20,240,209"	1301