Participant-Related Risk Factors for False-Positive and False-Negative Fecal Immunochemical Tests in Colorectal Cancer Screening: Systematic Review and Meta-Analysis

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- OBJECTIVES:** Colorectal cancer (CRC) screening using fecal immunochemical tests (FIT) may reduce CRC-related mortality but its effectiveness is influenced by the limited accuracy of FIT. Identifying individuals at increased risk of a false FIT result could improve screening, but the available evidence is conflicting. We performed a systematic review and meta-analysis on risk factors for false-positive and false-negative FIT results in CRC screening.
- METHODS:** A systematic search in MEDLINE, EMBASE, and Cochrane Library identified publications (before 29 January 2017) on risk factors (known at time of FIT invitation) associated with false FIT results (presence/absence of advanced neoplasia) in a CRC screening setting. Risk of bias was assessed using QUIPS. In meta-analysis, summary relative risk ratios and corresponding 95% confidence intervals were calculated for each risk factor.
- RESULTS:** Of 518 records identified, 14 studies with 54,499 participants in total were included for analysis. In meta-analysis, male sex was associated with a significantly lower risk of false-positivity (RR 0.84, CI 0.74–0.94), whereas participants using non-steroidal anti-inflammatory drugs (NSAIDs) had a higher risk (RR 1.16, CI 1.06–1.27). The use of anticoagulants was most frequently studied, without a significant effect on FIT positivity. Males (RR 1.83, CI 1.53–2.19), participants with a family history for CRC (RR 1.61, CI 1.19–2.15), hyperglycemia (RR 1.29, CI 1.02–1.65), hypertension (RR 1.50, CI 1.14–1.98), obesity (RR 1.38, CI 1.11–1.71), and (former) smokers (RR 1.93, CI 1.52–2.45) were all at significantly higher risk for false-negative results. Age was not found to have a systematic effect on either FIT false-positivity or false-negativity in meta-analysis.
- CONCLUSIONS:** Multiple risk factors, known at time of FIT invitation, are associated with false FIT results in CRC screening. This information can be used to identify populations risking false reassurance after a negative result or unnecessary colonoscopy after a positive result, and to further optimize CRC screening effectiveness.

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INTRODUCTION

Population-based colorectal cancer (CRC) screening using fecal occult blood tests has shown to be effective in reducing the high burden of worldwide CRC-related mortality [1]. Fecal immunochemical tests (FIT) are replacing the former guaiac fecal occult blood (gFOBT) test as primary screening method because of their higher sensitivity, quantitative nature, and higher participation

rates [2, 3]. Compared to gFOBT, FIT is easier to use as it is a one-sample test and does not require dietary restrictions [3]. Yet, FIT is not a highly accurate test. Depending on the positivity cut-off used, no advanced neoplasia (AN) is detected at colonoscopy in 45–70% of FIT-positive participants [4–6]. Furthermore, up to 10% of participants with a negative FIT appear to have CRC or one of its precursor lesions [4, 7].

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False-negative FIT results can lead to false reassurance, which might delay CRC diagnosis if patients would develop symptoms. Negative FIT results could additionally decrease participation in successive rounds and may encourage participants to maintain an otherwise unhealthy lifestyle, due to the so-called ‘certificate of health effect’ [8, 9]. False-positive results can also be harmful because unnecessary colonoscopies are performed with a concomitant risk of complications, undeniable discomfort of the procedure, and healthcare costs. False-positive results further may cause psychological distress in participants, in between receiving the FIT result and the colonoscopy findings [10, 11].

Evidence-based knowledge on risk factors influencing FIT accuracy to detect AN may offer opportunities to increase the effectiveness of a CRC screening program. Multiple studies have shown that some participant-related factors, such as sex, age, smoking habits and the presence of hemorrhoids could influence FIT-positivity rates, lead to more false test results [12, 13]. The use of anticoagulants has been appointed as a potential source of false-positive results [14].

The available evidence is however conflicting and a review is missing, hampering strong conclusions and the development of recommendations to improve FIT accuracy. We performed a systematic review and meta-analysis of studies evaluating personal risk factors for either false-positive or false-negative FIT results, known at time of FIT invitation.

METHODS

The review is described in accordance with the PRISMA guidelines (Supplementary table 1) [15]. The protocol of this study was not included in an accessible registry. This review addressed the question: do participants in population-screening with a specific participant-related factor more often have a false-positive/false-negative FIT result compared to participants without that risk factor. We planned to select the risk factors as reported in the individual studies.

Search strategy and eligibility criteria

Databases Pubmed, Embase, and Cochrane were searched (29 January 2017) with the assistance of a specialized librarian, using MeSH terms and text words for colorectal cancer, screening, fecal immunochemical test, false-positivity, false-negativity, sensitivity, and specificity (Supplementary table 2).

Two reviewers (LV and CK) independently selected potentially eligible full-text articles from the search results by scanning title and abstract of all identified records. Reference lists of selected articles and reviews were scanned for other relevant publications. Any disagreement was solved through discussion. Potentially eligible articles were read in full-text to make final decisions about inclusion.

Eligible studies had assessed risk factors for false-positive/false-negative FIT results, defined as the presence or absence of AN (advanced adenoma and/or CRC) at colonoscopy; in a population-based screening program, a pilot program, or in a similar research setting. These inclusion criteria were chosen to minimize the chance of missing articles that reported false results as

secondary outcome. Excluded were studies only described in conference abstracts, letters to the editor, or in articles without quantitative results on the association of risk factors with false FIT results, which would preclude the calculation of relative risks. Also excluded were studies not available in full-text report after contacting the corresponding author.

Since we aimed at personal factors known at time of screening, we also excluded studies assessing the effect of changing positivity cutoffs only, the effect of number of FITs performed in one screening round, the effect of sample return period or season, and studies assessing risk factors found at colonoscopy.

Data extraction

Two authors (LV and CK) independently reviewed included articles and extracted relevant data using a standardized extraction form. Data were collected on publication year, study setting, data collection period, number of included patients, type of FIT used, FIT cutoff value for positivity, definition of a false FIT result (detection/no detection of AN), evaluated risk factors and total numbers of positive FIT results, total number of participants with and without risk factors and total of participants with and without AN at colonoscopy. Positivity cutoff values were reported in μg hemoglobin (Hb)/g feces and, where needed, converted from ng Hb/ml buffer [16].

Risk of bias assessment

The risk of bias of included studies was assessed using the QUIPS tool for prognostic reviews [17]. QUIPS includes the domains ‘prognostic factor measurement’ and ‘outcome measurement’, which were considered more appropriate to assess risk of bias of studies on risk factors than the comparable domains in QUADAS ‘index test’ and ‘reference test’ [18]. The other evaluated QUIPS domains were participation, study attrition, study confounding and statistical analysis and reporting. Risk of bias on each domain was graded as low, intermediate or high, following the recommendations of the Cochrane Prognosis Methods Group.

Data analysis and synthesis

To allow for meta-analysis, relative risks for reported risk factors were recalculated with the data in the study report. From 2×2 contingency tables, risk ratios for false-positive FIT results were calculated by dividing the proportion of false-positive results, relative to all FIT-positives, in the group with the risk factor by the proportion of false-positive results, relative to all FIT-positives, in the group without that risk factor. Similarly, false-negative relative risks were calculated using the false-negative proportions in each group.

For each risk factor, we calculated a summary estimate of the relative risk in meta-analysis, whenever this factor had been included in at least two study reports. We used Mantel-Haenszel’s random-effects method, and calculated 95% confidence intervals to assess statistically significance, relying on a predefined significance level of $p < 0.05$ [19]. Forest plots were composed for each meta-analysis. Heterogeneity was assessed with I^2 statistics [20]. An I^2 of $<25\%$ was considered low, 25–50% moderate, and $>50\%$ high heterogeneity. Funnel plots were screened to assess publication bias. We used Review Manager version 5.3.5 (The Nordic Cochrane

Centre, Copenhagen) for statistical (meta-)analyses. For reporting, risk factors are grouped into the broader categories demographic factors, medication use, medical history/comorbidities. A sensitivity analysis was performed with studies using the same positivity cutoff level of 20 µg Hb/g feces.

RESULTS

Study selection

The search strategy yielded 518 records (Fig. 1). We removed 109 duplicates, 354 records based on title and abstract, 13 conference abstracts, 1 letter, 3 abstracts without full text, 7 articles without relevant results [21–27], 10 articles only evaluating risk factors found at colonoscopy [4, 28–33] or organizational aspects [34–36], and 7 articles that reported insufficient data to calculate risk ratios [12, 13, 37–41]. This resulted in 14 articles included for review (Table 1) [14, 42–54].

Study characteristics

Included studies and their characteristics are summarized in Table 1. All data had been collected within an existing or pilot screening program with a cohort design, except for one study [14] that was part of a randomized controlled trial comparing FIT with colonoscopy screening. OC-Sensor was the most frequently used FIT brand. Positivity cutoffs varied between studies and between FIT brand (2 µg Hb/g feces to 50 µg Hb/g feces). The most fre-

quently used cutoff, in six studies, was 20 µg Hb/g feces. Diagnostic accuracy of FIT was calculated based on the detection of AN in all studies except two that additionally included intermediate-risk adenomas [43, 44].

Risk of bias across studies

Risk of bias evaluations for each study are shown in Supplementary figure 1. A high risk of bias for outcome measurement was assigned to five studies because of an undefined FIT brand or cutoff level for positivity, but overall risk of bias was considered limited. The risk of bias assessment did not lead to any exclusion of or correction in studies.

Risk factors for false-positive results

Risk factors and their association with false-positive FIT results in each study are described in Table 2a and summary results are presented in Table 3 (forest plots in Supplementary figures 2a–2I). The most frequently studied risk factors for false-positive results are the use of anticoagulants and antithrombotic drugs (10 results: [14, 44, 47, 51, 54]), sex (5 results: [44, 46, 49, 50, 53]), and age (5 results: [44–46, 53]).

The risk factor that was associated with a lower risk of false-positive results in meta-analysis was male sex (RR 0.84, CI 0.74–0.94, *P* 84%), and, in one study, elevated triglycerides (RR 0.85, CI 0.76–0.96) and age higher than 65 (RR 0.77, CI 0.65–0.92). In contrast, a higher risk of false-positive results was seen in participants using

Fig. 1 Study selection

Table 1 Study characteristics

Author, year	Setting	Number of participants	Study population (age and sex)	Type of FIT	FIT positivity cutoff	Outcome
Kim et al., 2017	Organized screening program Korea. 2013–2015.	3990	64.3 (mean) 54.1% male	OC-Sensor DIANA	20µg Hb/g feces	AN
Wieten et al., 2016	Pilot screening program The Netherlands. 2006–2008.	5986	61 (median) 48% male	OC-Sensor DIANA	10µg Hb/g feces	AN
Ibáñez-Sanz et al., 2016	Organized screening program Spain. 2013–2014.	472	Age total population missing 58.5% male	OC-Sensor DIANA	20µg Hb/g feces	Intermediate- or high-risk lesions ^a
Ibáñez-Sanz, et al., 2017	Organized screening program Spain. 2012–2014.	218	Age total population missing 39.4% male	OC-Sensor DIANA	20µg Hb/g feces	Intermediate- or high-risk lesions ^a
Wong et al., 2015	Opportunistic screening program Hong Kong. 2008–2012.	5339	57.7 (mean) 45% male	Hemosure	50µg Hb/g	AN
Symonds et al., 2015	Organized screening program Australia. 2008–2013.	2206	60.6 (median) 48.6% male	OC-Sensor DIANA	20µg Hb/g feces	AN
Kapidzic et al., 2015	Pilot screening program The Netherlands. 2006–2010.	11186	Age and sex total population missing	OC-Sensor Micro	10µg Hb/g feces	AN
Tsuji et al., 2015	Organized screening program Japan. 2011.	1016	67.9% male	Not reported, two sample	Not reported	AN
Bujanda et al., 2014	FIT arm of the COLONPREV trial, a RCT comparing one-time colonoscopy vs biennial FIT. 2008–2011.	6045	59.5 (mean) 64.4% male	OC-Sensor	15µg Hb/g feces	AN
Ng et al., 2013	Opportunistic screening program Hong Kong. 2008–2012.	4539	57.7 (mean) 45.3% male	Hemosure	50µg Hb/g feces	AN
Chang et al., 2014	Opportunistic screening program Taiwan. 2006–2009.	10884	54.1 (mean) 51.7% male	OC-Light	qualitative FIT method	AN
Cha et al., 2012	Organized screening program Korea. 2009–2010.	373	60.4 (mean) 72% male	OC-Sensor DIANA	20µg Hb/g feces	AN
Brenner et al., 2010	Opportunistic colonoscopy screening program Germany. 2005–2009.	1979	Age and sex total population missing	Ridascreen	2µg Hb/g feces	AN
Mandelli et al., 2011	Organized screening program Italy. 2007–2009.	266	Age and sex total population missing	Not reported	20µg Hb/g feces	AN

AN advanced neoplasia

AN (CRC or adenoma ≥ 10 mm, $\geq 25\%$ villous component or high grade dysplasia)

Cutoffs reported in µg Hb/g. Cutoffs in ng/ml converted: 20 µg Hb/g = 100 ng Hb/ml, 10 µg Hb/g = 50 ng Hb/ml

^aIntermediate- and high-risk lesions: 3–4 tubular adenomas < 10 mm with low-grade dysplasia or ≥ 1 adenoma 10–19 mm, ≥ 5 adenomas or ≥ 1 adenoma measuring ≥ 20 mm or CRC

non-steroidal anti-inflammatory drugs (NSAIDs) (RR 1.16, CI 1.06–1.27, P 0%) and, in individual studies, in participants with an anal fissure (RR 1.77, CI 1.38–2.25), a peptic ulcer (RR 1.25, CI 1.03–1.52) and those using proton pump inhibitors (RR 1.29, CI 1.09–1.52).

No significant associations were found for having hemorrhoids (RR 0.99, CI 0.93–1.97, P 93%), or the use of anticoagulants or antithrombotic drugs (RR 1.01, CI 0.96–1.06, P 0%). Only one study [47] reported a significantly lower risk of false-positivity when using low dose of aspirin (RR 0.46, CI 0.24–0.86), while in another study [46] the use of aspirin (or aspirin in combination with NSAIDs) was associated with a significantly higher risk of a false-positive result (RR 1.16, CI 1.05–1.28). Many other factors appeared to have no systematic effect on the proportion of

false-positive results: family history of CRC, socioeconomic status, obesity, diverticula, high blood pressure, hyperglycemia, low high-density lipoprotein (HDL), metabolic syndrome, menstruation or menopause, anemia, use of a selective serotonin reuptake inhibitor (SSRI) or use of (combined) medication, (a history of) smoking or drinking alcohol and participating in prior screening rounds.

Risk Factors for False-Negative Results

Risk factors for false-negative FIT results as evaluated in each study are summarized in Table 2b and summary results are presented in Table 3 (forest plots in Supplementary figures 2m–2r). Most frequently studied risk factors for false-negative FIT results were: sex (4 results: [33, 42, 43, 48]), family history of CRC (3 results: [46, 48, 52]) and obesity (3 results: [42, 46]).

Table 2a Individual risk ratios of risk factors for false-positive FIT results

Author, year	Significant association with false-positive FIT	Relative risk (95% CI)	No significant association with false-positive FIT	Relative risk (95% CI)
Kim, 2017	Hemorrhoids 82% vs not 72%	RR 1.14 (1.06–1.24)	Obesity 75% vs 75%	RR 1.00 (0.91–1.10)
	Elevated FBG 69% vs not 80%	RR 0.87 (0.79–0.96)	Metabolic syndrome 70% vs not 77%	RR 0.90 (0.81–1.00)
	Elevated TG (>150mg/dl) 66% vs not 78%	RR 0.85 (0.76–0.96)	Abdominal obesity (>80 women, >90 men) 75% vs not 75%	RR 1.00 (0.91–1.10)
			Elevated blood pressure > 130/85 mm Hg, or taking antihypertensive drugs 73% vs not 77%	RR 0.95 (0.87–1.04)
			Lower HDL (<40 mg/dl in men or <50 mg/dl in women) 70% vs not 76%	RR 0.91 (0.81–1.03)
			Diverticula 75% vs not 76%	RR 0.99 (0.87–1.11)
Wieten, 2016	Higher age >75, 53% vs <55, 74%	RR 0.71 (0.56–0.90)		
Ibáñez-Sanz, 2016	Hemorrhoids 66% vs not 44%	RR 1.63 (1.36–1.97)	Age 60–69 57% vs age 50–59 51%	RR 1.11 (0.94–1.32)
	Anal fissure 71% vs not 44%	RR 1.77 (1.38–2.25)	Low education 72% vs medium-high education 68%	RR 1.06 (0.92–1.21)
	Peptic ulcer 65% vs not 52%	RR 1.25 (1.03–1.52)	Anemia 50% vs not 49%	RR 1.02 (0.73–1.44)
	PPI use 65% vs not 50%	RR 1.29 (1.09–1.52)	Menstruation 81% vs menopause 81%	RR 1.01 (0.79–1.29)
	Male 45% vs female 66%	RR 0.69 (0.59–0.81)	NSAID use 63% vs not 53%	RR 1.18 (0.90–1.55)
	Initial screening 47% vs successive screening 58%	RR 0.82 (0.68–0.98)	Antiplatelet use 55% vs not 54%	RR 1.03 (0.80–1.31)
			Oral anticoagulants 50% vs not 54%	RR 0.93 (0.52–1.64)
			SSRI use 53% vs not 54%	RR 0.99 (0.74–1.31)
			Any medication (PPI and/or NSAIDs and/or antiplatelet agent and/or oral anticoagulants) 60% vs not 51%	RR 1.18 (1.00–1.40)
Wong, 2015	Use of NSAIDs or aspirin 93% vs not 80%	RR 1.16 (1.05–1.28)	BMI ≥ 25, 82% vs BMI < 25, 81%	RR 1.01 (0.92–1.11)
	Age >65, 64% vs age ≤65, 84%	RR 0.77 (0.64–0.92)	(ex) Smoker 84% vs non-smoker 81%	RR 1.05 (0.89–1.22)
	Age >60, 76% vs age ≤60, 84%	RR 0.90 (0.82–0.99)	(ex) Drinker alcohol 75% vs not 82%	RR 0.91 (0.78–1.06)
	Male 74% vs female 87%	RR 0.86 (0.79–0.94)	First-degree relatives with CRC 77% vs not 82%	RR 0.95 (0.82–1.09)
			Diabetes mellitus 84% vs not 81%	RR 1.04 (0.89–1.20)
			Hypertension 75% vs not 83%	RR 0.91 (0.82–1.01)
Symonds, 2015	Male 49% vs female 59%	RR 0.83 (0.75–0.92)	Age >70, 54% vs age <70, 53%	RR 1.01 (0.89–1.14)
	Age >60, 51% vs age <60, 59%	RR 0.86 (0.77–0.96)	Socioeconomic status low (quintile 1) 47% vs high (quintile 5) 52%	RR 0.90 (0.74–1.10)
			First round 52% vs previous FIT screening 55%	RR 0.96 (0.86–1.07)
Kapidzic, 2015	Male 50% vs female 63%	RR 0.81 (0.67–0.96)		
Tsuji, 2014			Antithrombotic drugs use 81% vs not 81%	RR 1.00 (0.91–1.09)
			Aspirin use 72% vs not 86%	RR 1.03 (0.93–1.14)
			Warfarin use 76% vs not 81%	RR 0.93 (0.78–1.12)
			Other antithrombotic drug use 82% vs not 81%	RR 1.02 (0.88–1.18)
Bujanda, 2014			Oral anticoagulant use 52% vs not 50%	RR 1.06 (0.69–1.61)
Ng, 2013			Family history of CRC 78% vs not 83%	RR 0.94 (0.81–1.08)
Mandelli, 2011			Use of anticoagulants 72% vs not 65%	RR 1.10 (0.88–1.37)
			Chronic low-dose aspirin use 71% vs not 69%	RR 1.03 (0.91–1.16)
Brenner, 2010	Use of low-dose aspirin 29% vs not 64%	RR 0.46 (0.24–0.86)		
Chang, 2014			Male 84% vs female 87%	RR 0.96 (0.91–1.01)

Table 2b Individual risk ratios of risk factors for false-negative FIT-results

Author, year	Significant association with false-negative FIT	Relative risk (95% CI)	No significant association with false-negative FIT	Relative risk (95% CI)
Kim, 2017	Male 10% vs female 4.8%	RR 2.09 (1.60–2.72)	Obesity (>25) 8.1% vs not 6.2%	RR 1.29 (0.97–1.72)
	Smoking 10.0% vs non-smoking 5.6%	RR 1.80 (1.39–2.31)	Elevated FBG 7.9% vs not 6.3%	RR 1.25 (0.94–1.67)
	Hemorrhoids 5.2% vs not 8.5%	RR 0.61 (0.45–0.83)	Metabolic syndrome 81% vs not 64%	RR 1.27 (0.94–1.71)
			Abdominal obesity 7.6% vs not 6.4%	RR 1.18 (0.89–1.57)
			Elevated blood pressure 7.7% vs not 5.9%	RR 1.30 (0.98–1.74)
			Elevated TG 7.2% vs not 6.8%	RR 1.06 (0.78–1.46)
			Lower HDL 6.7% vs not 6.9%	RR 0.97 (0.68–1.39)
			Diverticula 7.8% vs not 7.5%	RR 1.04 (0.69–1.56)
Ibáñez-Sanz, 2017			Male 18% vs female 14%	RR 1.30 (0.69–2.43)
Wong, 2015	Age > 65, 8.3% vs age ≤ 65, 4.6%	RR 1.79 (1.18–2.72)	Diabetes mellitus 6.7% vs not 4.7%	RR 1.41 (0.89–2.22)
	Age > 60, 7.1% vs age ≤ 60, 4.0%	RR 1.76 (1.33–2.33)	NSAIDs or aspirin use 6.0% vs not 4.8%	RR 1.26 (0.77–2.07)
	Male 6.3% vs female 3.7%	RR 1.71 (1.29–2.26)		
	BMI ≥ 25, 6.9% vs BMI < 25, 4.0%	RR 1.71 (1.29–2.26)		
	(ex)smoker 11% vs non-smoker 4.6%	RR 2.36 (1.51–3.69)		
	(ex) alcohol drinker 8.3% vs not 4.6%	RR 1.81 (1.23–2.66)		
	First degree relatives with crc 6.9% vs not 4.6%	RR 1.51 (1.05–2.15)		
	Hypertension 7.3% vs not 4.2%	RR 1.73 (1.29–2.31)		
Ng, 2013			Family history of CRC 4.7% vs not 3.1%	RR 1.50 (0.98–2.32)
Cha, 2012	First-degree relative CRC 13% vs not 3.8%	RR 3.52 (1.22–10.12)	Male 6% vs female 3.6%	RR 1.67 (0.66–4.24)
			No prior screening (barium or colonoscopy) 5.8% vs prior screening 3.5%	RR 1.67 (0.66–4.34)
			Prior diagnosis CRC 1.7% vs not 5.1%	RR 0.33 (0.05–2.46)

One study reported a significantly lower risk of false-negative results for participants with hemorrhoids (RR 0.61, CI 0.45–0.83). In meta-analysis, a higher risk of false-negative results was observed in males (RR 1.83, CI 1.53–2.19, I^2 0%), participants with a family history of CRC (RR 1.61, CI 1.19–2.15, I^2 14%), (former) smokers (RR 1.93, CI 1.52–2.45, I^2 9%), elevated fasting blood glucose (RR 1.29, CI 1.02–1.65, I^2 0%), obesity (RR 1.38, CI 1.11–1.71, I^2 43%), and hypertension (RR 1.50, CI 1.14–1.98, I^2 45%). Single studies have reported an effect of age > 60 (RR 1.76, CI 1.33–2.33) and > 65 (RR 1.79, CI 1.18–2.72) and (a history of) drinking alcohol (RR 1.81, CI 1.23–2.66).

No association with false-negative results was found for (known) diverticulosis, other elements of metabolic syndrome, NSAID or aspirin use, prior screening, or a previous CRC.

Sensitivity Analysis of Studies Using an Equal Positivity Cutoff

A sensitivity analysis of the six studies that used a positivity cutoff of 20 µg Hb/gr feces [42–44, 48, 51, 53], did not change the main conclusions. However, the analysis of NSAID use as risk factor was limited to one study, not showing a higher risk of a false-positive result (RR 1.18, CI 0.90–1.55). Similarly, hyperglycemia (RR 1.25, CI 0.94–1.67) and hypertension (RR 1.30, CI 0.98–1.74) did

not lead to a higher risk of a false-negative result. Some associations could not be evaluated because no studies with a 20 µg Hb/gr feces positivity cutoff included them: higher age and (a history of) drinking alcohol.

DISCUSSION

This systematic review shows that male sex is associated with a significantly lower risk of false-positive FIT results, while using NSAIDs is associated with a higher risk of a false-positive result. The use of anticoagulants has been studied frequently, but no systematic effect on FIT false-positivity was observed. Males, participants with a family history of CRC, with elements of the metabolic syndrome (obesity, hyperglycemia, hypertension), and (former) smokers were found to be at increased risk of false-negative results.

When interpreting this review several limitations should be acknowledged. First, data on FIT accuracy were compiled from different (pilot) screening programs, using different FIT brands and unequal cutoffs for positivity. Applying a higher cutoff level will lower sensitivity while increasing specificity, thus influencing the proportion of false-negative and false-positive screenees. However, since we compared the risks of any false result per study (proportion of participants with the risk factor vs. the proportion

Table 3 Meta-analysis of risk ratios for false-positive and false-negative FIT results

Risk factor category	Risk factor	False-positive risk studied (n)	Meta-analysis RR, 95% CI, I ²	False-negative risk studied (n)	Meta-analysis RR, 95% CI, I ²
Sex	Male sex	5	RR 0.84 (0.74–0.94) 84%	4	RR 1.83 (1.53–2.19) 0%
Age	Higher age > 60	3	RR 0.94 (0.82–1.06) 71%	1	RR 1.76 (1.33–2.33)
	>65	1	RR 0.77 (0.64–0.92)	1	RR 1.79 (1.18–2.72)
	>70	2	RR 0.86 (0.61–1.21) 85%		
Socioeconomic status	Low education Low SES	2	RR 0.99 (0.85–1.16) 43%		
Family history	First degree relative CRC/ Family history of CRC	2	RR 0.94 (0.85–1.04) 0%	3	RR 1.61 (1.19–2.15) 14%
Lifestyle	(Ex) smoker	1	RR 1.05 (0.89–1.22)	2	RR 1.93 (1.52–2.45) 9%
	(Ex) drinker (>2 units/wk)	1	RR 0.91 (0.78–1.06)	1	RR 1.81 (1.23–2.66)
Medication use: anti-coagulants	Antiplatelets Oral anticoagulants Antithrombotic drugs Aspirin Warfarin	10	1.01 (0.96–1.06) 0%		
Medication use: other	Proton pump inhibitor	1	RR 1.29 (1.09–1.52)		
	NSAID NSAID or aspirin	2	RR 1.16 (1.06–1.27) 0%	1	RR 1.26 (0.77–2.07)
	SSRI	1	RR 0.99 (0.74–1.31)		
	Any medication	1	RR 1.18 (1.00–1.40)		
Medical history/ comorbidities: Anorectal pathology	Hemorrhoids	2	RR 1.35 (0.93–1.97) 93%	1	RR 0.61 (0.45–0.83)
	Diverticula	1	RR 0.99 (0.87–1.11)	1	RR 1.04 (0.69–1.56)
	Anal fissure	1	RR 1.77 (1.38–2.25)		
Medical history/ comorbidities: Other	Peptic ulcer	1	RR 1.25 (1.03–1.52)		
	Menstruation	1	RR 1.01 (0.79–1.29)		
	Anemia	1	RR 1.02 (0.73–1.44)		
	Prior diagnosis CRC			1	RR 0.33 (0.05–2.46)
	First screening round	2	RR 0.90 (0.77–1.05) 57%	1	RR 1.67 (0.66–4.34)
Medical history/ comorbidities: Metabolic risk factors	Elevated FBG/ Diabetes mellitus	2	RR 0.94 (0.79–1.12) 75%	2	RR 1.29 (1.02–1.65) 0%
	Obesity/ BMI ≥ 25 High waist circumference	3	RR 1.00 (0.95–1.06) 0%	3	RR 1.38 (1.11–1.71) 43%
	Metabolic syndrome	1	RR 0.90 (0.81–1.00)	1	RR 1.27 (0.94–1.71)
	Elevated triglycerides	1	RR 0.85 (0.76–0.96)	1	RR 1.06 (0.78–1.46)
	Low HDL	1	RR 0.91 (0.81–1.03)	1	RR 0.97 (0.68–1.39)
	Elevated blood pressure	2	RR 0.93 (0.87–1.00) 0%	2	RR 1.50 (1.14–1.98) 45%

Italics: no meta-analysis

SES socio economic status, CRC colorectal cancer, NSAID non-steroidal anti-inflammatory drugs, SSRI serotonin reuptake inhibitor, FBG fasting blood glucose, BMI body mass index, HDL high-density lipoprotein

without that risk factor), differences in cutoff levels between studies should have little impact on the conclusions, as was shown in a sensitivity analysis of six studies using the same cutoff.

Seven studies that reported insufficient data (absolute numbers) to allow for relative risk calculation were excluded, limiting the precision of summary estimates. To allow for meta-analysis, individual risk factors were clustered in groups, leading to possible loss of detail in characterizing risk factors. For example, all types of anticoagulant and antithrombotic drugs had to be clustered. Lastly, reporting bias is possible with regard to the prevalence of hemorrhoids, since these lesions are frequently not included in systematic colonoscopy reporting systems.

Differences between subgroups in the risk of a false-negative FIT result and in the risk of a false-positive FIT result could be due to differences in prevalence, differences in accuracy, or a combination. A higher CRC prevalence in one subgroup will result in a higher risk of a false-negative result and a lower risk of a false-positive result, even in the absence of a difference in accuracy. A lower FIT sensitivity in a subgroup will generate more false-negatives, and a lower specificity will generate more false-positives (see supplementary material for a worked-out example). Due to the nature of the studies included in this review, we cannot distinguish between these causes as explanations for differences in the risk of false-negatives and false-positives.

Men are at lower risk of false-positive results and at higher risk of false-negative results. In single studies, similar conclusions have been drawn for participants at a higher age. This is likely related to the higher prevalence of CRC and AN in men and older individuals [55, 56], and raises the question whether the screening strategy should be optimized per subgroup. For men and older participants, the cutoff could be lowered to decrease the number of missed AN. Furthermore, the cutoff could be increased for women and younger participants to decrease the number of unnecessary colonoscopies in these populations. The most important question is the consequence of these modifications for the specificity of FIT in men and the sensitivity of FIT in women. Grobbee et al. assessed this balance and concluded that, for both sexes, a decrease in cutoff resulted in a relatively more rapid increase in sensitivity than the decline in specificity [57]. Alvarez et al. found similar results for men over 60 years old. In women younger than 60 years, a higher cutoff led to a significantly lower number of colonoscopies without modifying the detection rate of CRC [23]. Other than adjusting the cutoff for FIT-positivity, effectiveness by gender and age may be improved by adjusting the starting age of screening. Brenner et al. found that women reached equivalent levels of CRC risk as men when they are 4–8 years older, which might justify a postponed screening age for women [58]. Overall, this may support initiatives exploring the specific effect in specific screening populations of a lower cutoff for (older) men, a higher cutoff for (younger) women, or a postponed start of screening in women.

Currently, several research groups are investigating individual risk stratification for colonoscopy screening or colonoscopy referral after a positive FIT result. Among those are the Asia-Pacific Colorectal Screening (APCS) score and the Dutch risk stratification model of Stegeman et al. [59, 60]. Both models include age, family history for CRC and smoking for risk assessment, and APCS additionally includes sex. In our analysis, the same personal factors appeared to be prone for false-negative FIT results, which further supports the use of these factors in risk-based strategies. Possibly, hyperglycemia, obesity and hypertension could additionally be explored for inclusion in colonoscopy referral stratification models in FIT-based screening, since these factors are found to be related to more false-negative results, and are so far only partially explained by a concomitant higher incidence of AN [61, 62]. The influence of combinations of risk factors could be of interest when these are likely to interact, such as aspects of metabolic syndrome, lifestyle and the use of medication. Because of the way they were reported in the study reports, the effect of combined risk factors could not be assessed in this review, but future original studies provide this opportunity.

Although meta-analysis showed no significant increased risk of a false-positive FIT result for invitees with hemorrhoids, this risk is commonly believed by patients, and was demonstrated in individual studies [42, 44]. An assumed higher chance of false-positive results could restrain this group from participation in follow-up colonoscopy when receiving a positive FIT result. GPs could play a role in informing this specific group. Especially because, in contrast with risk factors such as male sex and higher age, the incidence of AN in this subgroup is similar to those without hemorrhoids.

In line with the European Screening recommendation that anti-coagulant drug restrictions in FIT screening are not indicated [3],

we showed that the use of aspirin or anticoagulant drugs does not increase FIT false-positivity in nine out of ten included studies. This may seem counter intuitive. One explanation could be that the absence of an effect is a consequence of both an increased and decreased risk of false-positive results. Anticoagulants could increase positivity and decrease false-positivity if AN is present but bleeds very little by itself. In contrast, anticoagulants could also increase false-positivity if other non-AN lesions are present and bleeding is provoked. Alternative explanations could point to molecular characteristics of AN and the exact mechanism of the anticoagulant used. For current practice, however, recent guidelines are adequate.

This study focused on personal risk factors and its influence on false FIT results. Other factors affecting FIT accuracy should also be acknowledged. Organizational aspects influencing FIT accuracy may for example include sample return times [34–36], season of return [34] or number of samples [33, 63]. Further, the colonic lesion itself may relate to the accuracy of FIT. For example, right-sided AN is associated with more false-negative FIT results than proximal lesions [33, 42, 64]. This is thought to be due to the degradation of hemoglobin during colon transit, the blood distribution through the stool [64], and a harder consistency of passing stool in the distal colon [65]. Similarly, the morphology of the lesion may relate to the (location specific) accuracy of FIT. FIT is less sensitive for the detection of sessile adenomas than for pedunculated adenomas [29, 32], and proximal adenomas are proportionately more often sessile than distal adenoma [66]. The relevance of studying other than personal factors should however be kept in mind, risks for a false FIT result evaluated during colonoscopy have limited value if risk-based stratification for colonoscopy is intended.

In theory, if advanced adenomas are missed with FIT in a first round but detected in a following round before their progression to CRC, the effectiveness of the screening program is not affected, in contrast to interval cancer. The limited evidence on personal risk factors for FIT interval is conflicting. Higher interval cancer rates were found for women in a gFOBT screening program [67–69], but no significant differences for sex or age were found in other studies [70–72].

Multiple personal risk factors, known at time of FIT invitation, could influence the proportion of false FIT results in CRC screening. Personalized screening strategies might increase the sensitivity of FIT and reduce the number of unnecessary colonoscopies.

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CONFLICTS OF INTEREST

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Colorectal cancer screening effectiveness is influenced by the suboptimal accuracy of FIT.
- ✓ Personal factors, such as sex, age, smoking habits, the presence of hemorrhoids, and the use of anti-coagulants have been associated with an increased risk of a false-positive or false-negative FIT result.

WHAT IS NEW HERE

- ✓ This is the first systematic review and meta-analysis summarizing the effect of personal factors on FIT accuracy.
- ✓ Male sex is associated with a lower risk of false-positive FIT results and using NSAIDs with a higher risk.
- ✓ No systematic effect of the use of anticoagulants on FIT false-positivity was found.
- ✓ Male sex, a family history of CRC, metabolic syndrome, and smoking are each associated with a higher risk of false-negative results.

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