Systematic review and meta-analysis : diagnostic accuracy of faecal immunochemical testing for haemoglobin (FIT) in detecting colorectal cancer for both symptomatic and screening population

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Abstract

Background : Colorectal cancer (CRC) is one of the most common cancers worldwide. A non-invasive test, with high sensitivity and specificity is essential for early detection, improved outcome and avoidance of unnecessary invasive tests. This study aims to evaluate the accuracy of the faecal immunochemical testing for haemoglobin (FIT) in the detection of CRC, both in symptomatic and screening population and to summarise the available evidence to date.

Methods : Search strategy was initially developed in MEDLINE and adapted for use in other databases. Studies were included if they had fulfilled the criteria. QUADAS-2 tool was used for quality assessment and data analysis performed using STATA 15 software.

Results : A total of 17 out of 92 articles were included in the final analysis. Within the symptomatic group (n= 6755), the overall pooled sensitivity and specificity of FIT to detect CRC was 0.90 (95% CI 0.87-0.92) and 0.87 (95% CI 0.83-0.90) respectively. In the screening population (n=24197), the pooled sensitivity and specificity of FIT to detect CRC was 0.69 (95% CI 0.54-0.81) and 0.94 (95% CI 0.94-0.95) respectively. Most analytics were comparable with cut off less than 20µg/g feces providing optimal sensitivity and specificity for symptomatic and screening populations respectively.

Conclusion : For the detection of CRC within the screening population, FIT has high specificity and sensitivity. In the symptomatic group, FIT's high sensitivity (90%) supports its role as a triage test to guide the selection of patients who require urgent lower gastrointestinal tract evaluation. (Acta gastroenterol. belg., **2019**, 82, **291-299**).

Key words : Faecal haemoglobin, colorectal cancer, screening

1. Introduction

Colorectal cancer is the fourth most common cancer in the UK. Early diagnosis is often difficult, owing to variable symptoms with poor specificity (1). Widlak et al (2) have shown that 40% of patients with alarm symptoms (rectal bleeding, weight loss or sudden change in bowel habits) who were referred by their primary care physicians, had completely normal investigations and only 6% had CRC. Unfortunately, many patients do not experience symptoms until the disease is very advanced. In these patients, an early triage test (e.g. faecal testing for haemoglobin (FIT) testing) may help to improve the outcome. A systematic review by Lee et al showed reasonably high specificity and sensitivity of FIT in asymptomatic population (3). Another systematic review by Westwood et al (4) of FIT was very limited, as it had only studied low risk symptomatic patients within the primary care setting.

FIT has gained credence in Europe as a screening test for CRC, as it is superior to faecal occult blood testing (guaiac based) ; the latter has poor sensitivity and specificity - 69% and 73% respectively (5,6). However, there is no consensus as of yet, on the optimal cut-off value to be applied, nor on the optimal analytical method to be used.

We sought to provide an updated, comprehensive review to investigate the diagnostic accuracy of FIT and cut off values for the detection of CRC in both symptomatic and screening populations.

2. Methods

A systematic review and meta-analysis was conducted to appraise the currently published data on the accuracy of FIT for the detection of CRC, in 1) symptomatic patients 2) screening patients, in comparison to colonoscopy. Studies published after 2007 were selected to reflect changes to FIT technology by manufacturers (improved detection and competitive pricing) as well as proof of concept work undertaken in Europe in this period. This review followed the guidance laid out in the Cochrane handbook for diagnostic accuracy reviews (7).

2.1 Data search strategy

Studies were identified by carrying out searches on the MEDLINE database, for keywords "faecal haemoglobin", "FIT" or "faecal immunochemical test" amongst the studies published up to and including the 25th of September 2018. Reference lists from accepted papers were also examined to identify additional studies.

2.2 Selection of studies

Inclusion criteria for the studies : (1) Assessment of accuracy of FIT to detect CRC, (2) Adults over the age of 16, (3) Colonoscopy as the gold standard test, (4)

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Reporting of true positive, false positive, true negative, false negative results or if they were able to be calculated from published data or provided by the authors upon contacting them, (5) studies published after 1st of January 2007. The exclusion criteria were as follows : (1) studies not published in English, (2) studies conducted in non-human subjects, (3) studies conducted on patients with established gastrointestinal diseases, (4) studies in which we were unable to locate, calculate or obtain from the author true positive, false positive, true negative, false negative results.

2.3 Quality assessment and data selection

The QUADAS-2 tool was used for this evaluation (8). If an agreement could not be made to include the paper in the study, an independent arbitrator (senior author) made the decision whether to include or exclude the paper. The following data was extracted from the papers : FIT results (true positive, false positive, true negative, false negative, sensitivity, specificity, PPV, NPV, positivity rate) ; total population undergoing FIT and colonoscopy ; cut off faecal haemoglobin concentration ; system used ; population characteristics ; outcome measures (CRC, adenomas). Papers which had discussed currently out-dated faecal occult blood or stool guaiac test, or which solely looked at faecal calprotectin, were excluded from the meta-analysis. For studies which did not contain all of the information needed to meet the inclusion criteria, the respective authors were contacted directly for the missing information.

2.4 Data analysis

A meta-analysis of the data was completed using the "Midas" command in the STATA 15 software to produce funnel plots for the sensitivity, specificity, PPV and NPV of FIT- in both the symptomatic and screening populations. Where available, different analytical methods for detecting FIT (e.g. OC-sensor, HM-JACKarc, Actim® faecal blood, OC Light, OC Fit-check, Enterix insure and RIDASCREEN systems) were evaluated. These are either quantitative or qualitative testing systems, which typically use various immunochemical methods to detect or measure the concentration of haemoglobin in faecal samples. As some studies had completed FIT testing using multiple cut-off values, these were included as separate data points in the forest plots. A receiver-operating characteristic curve of the data (using the "Midas" command in the STATA 15 software) was also created. The area under the curve was calculated, in order to assess the overall accuracy of FIT, for both the symptomatic and screening populations. As the majority of the included studies had used OC-sensor as their immunochemical testing system (either through OC-sensor Pedia or OC-sensor iO platform), additional subgroup analysis was carried out for the OC-sensor system.

3. Results

3.1 Literature searching and quality assessment

Overall, the search had identified 92 research articles. Of the 92 articles, 28 were excluded after an initial screening the title abstract. 64 full text articles were assessed for quality and data extraction. The results of this search are shown as a PRISMA diagram in Figure 1. In 10 studies, authors were contacted for clarification or for further data enquiries. Two of these (20%) replied with supporting information which were included in the final meta-analysis. Remaining studies were excluded as there was insufficient data to determine test accuracy of FIT to detect CRC.

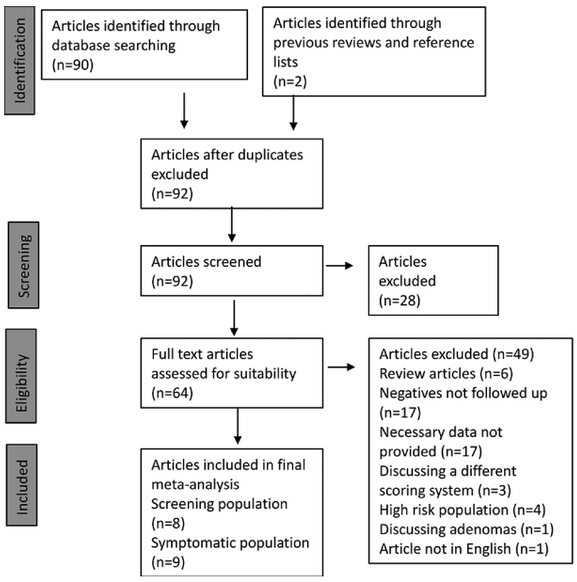

Figure 1. — PRISMA diagram detailing the selection process from literature searches through to final inclusion. The n= refers to the number of papers either included or excluded at that stage.

3.2 Analysis of the symptomatic population (N=6755)

Meta-analysis of the symptomatic population, sample size of 6755 (9 studies that fulfilled inclusion cirteria), was completed using data from three different FIT systems (OC-sensor, HM-JACKarc, Actim® faecal blood). Five studies used the OC-sensor, two used HM-JACKarc and one used the Actim® Faecal Blood system. Two studies used multiple cut-off values for faecal haemoglobin concentration (9,10). The rest of the studies used a single faecal haemoglobin concentration cut-off value. The cut-off values varied from 7µg/g feces to 50µg/g feces. However, 5 of the 9 studies in this review gave FIT performance outcome measures for the 10µg/g feces cut-off value (9,10,11,12,13). The prevalence of CRC in the study populations was 5.1%. All of the studies excluded patients without symptoms or history of established

gastrointestinal diseases. The age cut-off varied between the studies from >16 years to >40 years of age. The population, intervention, comparator and outcome for each of the studies, conducted in symptomatic patients, are summarised in Supplementary Table ST1 in the supplementary document.

3.2.1 Quality of included studies

Studies were quality assessed using the QUADAS-2 tool. The results of the performance of those studies are shown in Supplementary Table ST2. The QUADAS-2 score suggested that the greatest risk of bias was in the flow and timing section, where it was not clear how long had elapsed between FIT and endoscopy and whether the colonoscopist had been blinded to the FIT result.

3.2.2 Overall accuracy of FIT in symptomatic patients

The cumulative FIT performance data for CRC, including cut-off values and the systems used for each of the studies, is shown in Table 1. The overall pooled

Table 1. — **Summary of the diagnostic performance data of FIT for colorectal cancer in symptomatic patients**

Study	F-Hb cut-off (µgHb/g feces)	Machine	True Positive	False Positive	True Negative	False Negative	Total	Sensitivity	Specificity	PPV	NPV
Hogberg, 2017[14]	≥50	Actin Faecal Blood	7	119	246	1	373	87.5	67.4	5.60	99.6
Mowat, 2016[11]	≥10	OC Sensor	25	151	571	3	755	89.3	79.1	14.2	99.5
Steele, 2013[12]	≥10	OC Sensor	6	17	257	0	280	100	93.9	7.6	100
Widlak, 2017[2]	≥7	HM-JACKarc	21	28	377	4	430	84	93	44	99
Cubiella, 2014[21]	≥20	OC Sensor	85	156	534	12	787	87.6	77.4	35.3	97.8
Godber, 2016[13]	≥10	HM-JACKarc	11	116	380	0	507	100	76.6	8.7	100
Rodriguez-Alonso, 2015a[9]	≥10	OC Sensor	29	196	777	1	1003	96.7	79.9	12.9	99.9
Rodriguez-Alonso, 2015b[9]	≥15	OC Sensor	29	164	809	1	1003	96.7	83.1	15.0	99.9
Rodriguez-Alonso, 2015c[9]	≥20	OC Sensor	28	135	838	2	1003	93.3	86.1	17.2	99.8
Tehaar Sive Droste, 2011a[10]	≥10	OC Sensor	102	253	1693	10	2058	91.1	87	28.7	99.4
Tehaar Sive Droste, 2011a[10]	≥15	OC Sensor	102	219	1727	10	2058	91.1	88.7	31.8	99.4
Tehaar Sive Droste, 2011a[10]	≥20	OC Sensor	101	193	1753	11	2058	90.2	90.1	34.4	99.4
Tehaar Sive Droste, 2011a[10]	≥30	OC Sensor	95	158	1788	17	2058	84.8	91.9	37.5	99.1
Tehaar Sive Droste, 2011a[10]	≥40	OC Sensor	94	142	1804	18	2058	83.9	92.7	39.8	99
Widlak, 2018[24]	≥97	HM-JACKarc	28	37	490	7	562	80.0	93.0	44.0	99.0

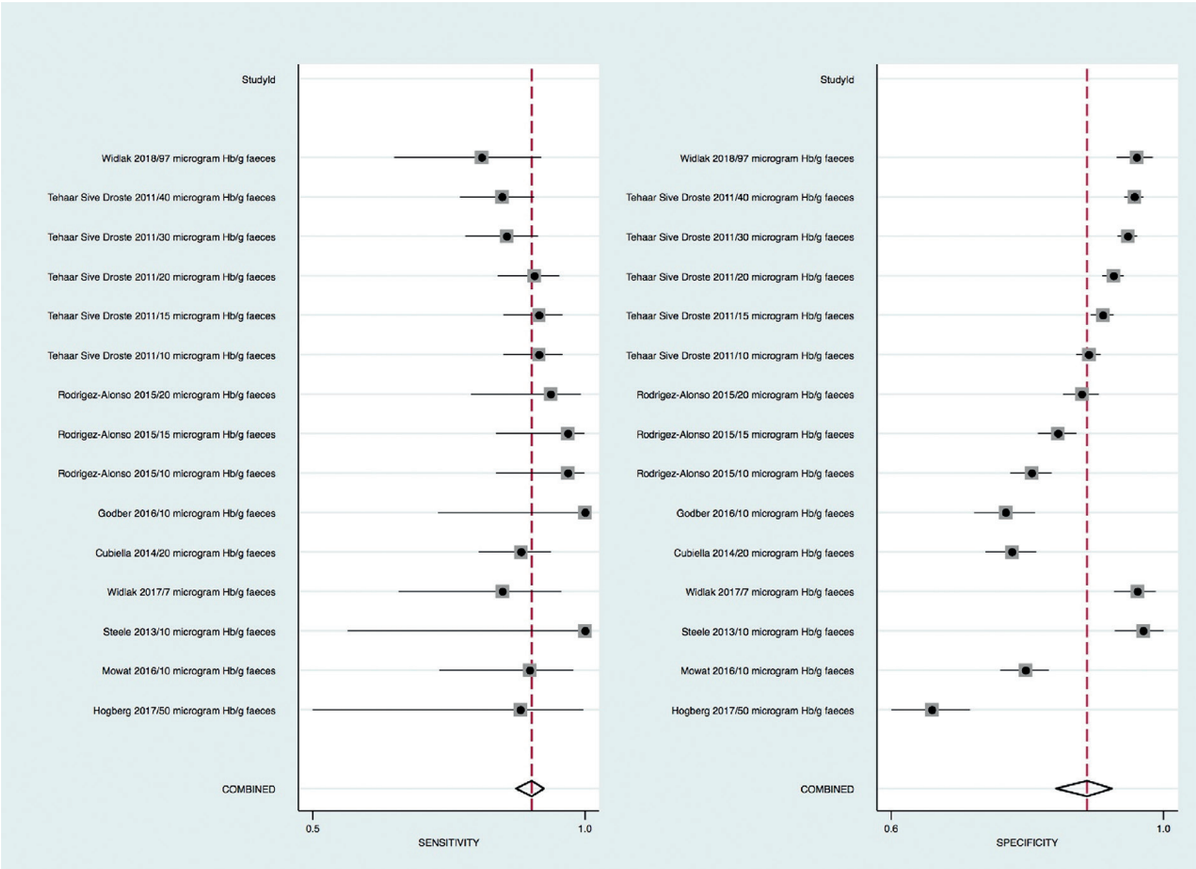

Figure 2. — Forest plot of sensitivity and specificity of FIT for detection of colorectal cancer in symptomatic patients. The pooled sensitivity was 0.90 and specificity 0.86 represented by the red dashed line.

sensitivity and specificity of FIT for CRC were 0.90 (95% CI 0.87-0.92) and 0.87 (95% CI 0.83-0.90) respectively. The positive likelihood ratio (ratio of the probability of a positive test in the disease positive population to the probability of a positive test among the disease negative population) was 6.8 (95% CI 5.3-8.7). The negative likelihood ratio (ratio of the probability of a negative test among the disease positive population to the probability of a negative test among the disease negative population) was 0.12 (95% CI 0.09-0.15) (Table 2). Forest plots summarising FIT test performance, in the symptomatic group, are shown in Figure 2.

A receiver operator characteristic curve (ROC), for all studies of FIT over multiple cut-off values for CRC (ranging from haemoglobin concentrations between 7-50µg/g feces) was produced and the area under the curve was calculated as 0.94 (0.92-0.96) (Figure 3). Using the average prevalence of CRC of 5.1%, pooled sensitivity of 0.90 and pooled specificity of 0.86, it can be calculated that 81.6% of colonoscopies could be avoided for exclusion of cancer but not for other enteric diseases ; (calculation 1 in supplementary document). It is important to understand, however, that these were only hypothetical maximum values and the true values were unlikely to be as high.

Table 2. — **Pooled sensitivity, specificity, positive likelihood ratio and negative likelihood ratio of FIT for colorectal cancer in symptomatic patients**

Parameter	Pooled value	95% CI lower value	95% CI Upper value
Sensitivity	0.90	0.87	0.92
Specificity	0.87	0.83	0.90
Positive Likelihood Ratio	6.8	5.3	8.7
Negative Likelihood Ratio	0.12	0.09	0.15
Diagnostic Odds Ratio	57	43	76

CI – Confidence Interval.

3.2.3 Subgroup analysis for OC-sensor analytical tool in symptomatic population

Five of the nine eligible studies used the OC-sensor system. For the OC-sensor system (using a cut-off value ranging from a Hb concentration of 10-40µg/g feces) the pooled sensitivity, specificity, positive likelihood ratio and negative likelihood ratio for CRC were 0.90 (95% CI 0.87-0.92), 0.88 (95% CI 0.84-0.91) 7.4 (95% CI 5.8-9.3) and 0.12 (95% CI 0.09-0.15) respectively (see Supplementary Table ST3 and Supplementary Figure SF1).

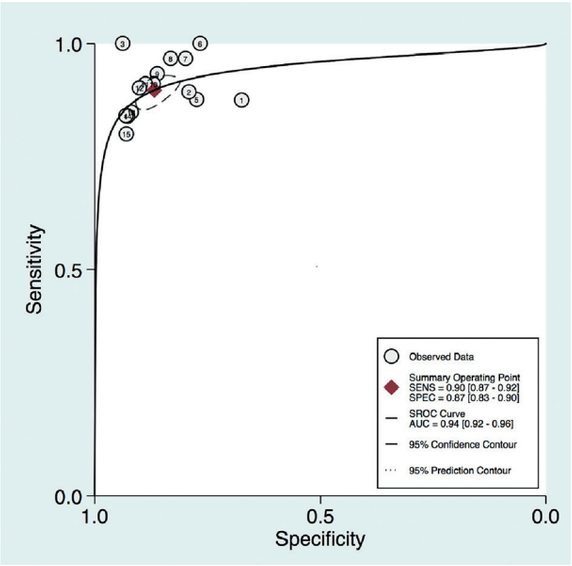

Figure 3. — Receiver operator characteristic curve of the sensitivity against specificity of FIT applying cut off values ranging from 7-50µg/g feces for detection of colorectal cancer.

For studies utilising the OC-sensor, multiple cut-off concentration values ranging from 10-40µg/g feces were applied. Analysis of the pooled sensitivity and specificity for a cut-off Hb concentration (range of 10-15µg/g feces) showed sensitivity of 0.93 (0.88-0.96) and specificity of 0.87 (0.82-0.90) (see Supplementary Table ST4 and supplementary Figure SF2 for a forest plot of this data). Applying a range between 20-40µg/g feces, resulted in an optimal pooled sensitivity and specificity of 0.87 (95% CI 0.84-0.90) and 0.89 (95% CI 0.84-0.92) respectively (see Supplementary Table ST5 and Supplementary Figure SF3 for a forest plot of this data).

A ROC was generated for the OC-sensor system, using the Hb concentration cut-off values (ranging from 10 - 40µg/g feces) quoted in the included studies for the FIT performance (Supplementary Figure SF4) (9,10,12,21). The area under the ROC curve was calculated as 0.95 (95% CI 0.93-0.97).

3.3 Analysis of the screening population (N=34,186)

Meta-analysis of the screening population included data from eight identified papers that fulfilled inclusion criteria. The number of participants in each study, ranged between 229 to 18296 (total sample size 34,186). All studies reported testing the participants of the screening population, who had not previously reported symptoms and who were a minimum of 50 years old. Three studies used the OC-sensor, one with OC-Light, one with OC-Fit-check, one with Enterix insure and one the RIDASCREEN system. Four of the studies used variable cut-off values, to measure the performance of the FIT system used. The population, intervention, comparator and outcome for each study, in the screening population, are shown in Supplementary Table ST6.

The quality of each of the articles was assessed using the QUADAS-2 tool ; the results of this assessment are shown in Supplementary Table ST7. The risk of bias was low in the studies included, as the screening population represented a random sample of the population. The degree of bias in the quantitative FIT tests and in the histological results, following colonoscopy, were minimal. The diagnostic accuracy data, including sensitivity, specificity, PPV and NPV for each of the studies included, are shown in Table 3. Results of the meta-analysis showed, a pooled sensitivity of 0.69 (95% CI 0.54-0.81) specificity of 0.94 (95% CI 0.94-0.95) respectively. The positive likelihood ratio was 12.2 (95% CI 10.1-14.7), the negative likelihood ratio was 0.33 (95% CI 0.21-0.51) and the diagnostic odds ratio was 37 (95% CI 20-70), see Figure 4 Forest plot. A ROC for all of the studies included, is shown in Figure 5. This includes all five analytical methods used in the eight studies and their cut-off concentrations ranging from 6-40µg Hb/g feces. The area under the curve was calculated as 0.95 (95% CI 0.93-0.96).

3.3.1 Subgroup analysis for OC-Sensor analytical tool in the screening population

Four of the eight studies used the OC-sensor machine.

As in the main meta-analysis, FIT cut-off concentration values ranged from 6-40µg Hb/g feces and the population sizes ranged from 779 to 2235. In this subgroup (total population 4126), the pooled sensitivity and specificity were 0.78 (95% CI 0.58-0.90) and 0.94 (95% CI 0.93-0.95) respectively and the Forest plot of this data is included in supplementary material – Supplementary Figure SF5.

In order to determine what effect different cut-off concentrations had on the sensitivity and specificity of the test in the detection of CRC, a meta-analysis was undertaken on the studies reporting different cut-off concentrations ; 6-15µgHb/g feces as well as 20-40µgHb/g feces. This showed, that applying a cut-off concentration in the range of 6-15µgHb/g feces, the pooled sensitivity and specificity were 0.75 (95% CI 0.46-0.91) and 0.94 (95% CI 0.92-0.95) respectively. Whilst applying a higher cut-off concentration range of 20-40µg Hb/g feces, the pooled sensitivity and specificity were 0.81 (95% CI 0.57-0.93) and 0.95 (95% CI 0.94-0.96) respectively. Supplementary Figure SF6 shows the ROC curve for all the studies using the OC-sensor system with FIT cut-off concentrations ranging from 6-40µgHb/g feces. The area under the curve was calculated as 0.95 (95% CI 0.93-0.97).

4. Discussion

4.1 Symptomatic population

Westwood et al (4) looked at the effectiveness of FIT as a triage tool in primary care setting within a low

Table 3. — **Summary of the diagnostic performance data of FIT for detection of colorectal cancer in the screening population**

Study	F-Hb cut-off (mg Hb/g feces)	Machine	True Positive	False Positive	True Negative	False Negative	Total	Sensitivity	Specificity	PPV	NPV
Brenner, 2013a[15]	³24.5	RIDASCREEN	9	102	2118	6	2235	60	95.4	8.1	99.7
Brenner, 2013b[15]	³7.95	RIDASCREEN	8	102	2118	7	2235	53.3	95.4	7.3	99.7
Brenner, 2013c[15]	³6.1	OC Sensor	11	99	2121	4	2235	73.3	95.5	10	99.8
Collins, 2012[23]	?	Enterix insure	9	19	181	20	229	31	90.5	32.1	90.1
Kallenberg, 2016a[16]	³10	OC Sensor	36	66	946	64	1112	36	93	35.3	93.7
Kallenberg, 2016b[16]	³15	OC Sensor	30	44	968	70	1112	30	96	40.5	93.3
Kallenberg, 2016c[16]	³20	OC Sensor	28	30	982	72	1112	28	97	48.3	93.2
Johnson, 2014[17]	³20	OC Fit-check	66	5	188	31	290	68	97.4	93	85.8
Hernandez, 2014a[18]	³10	OC Sensor	5	62	712	0	779	100	92	7.5	100
Hernandez, 2014b[18]	³15	OC Sensor	5	56	718	0	779	100	93	8.1	100
Hernandez, 2014c[18]	³20	OC Sensor	5	50	724	0	779	100	94	9.1	100
Hernandez, 2014d[18]	³23	OC Sensor	5	46	728	0	779	100	94	9.8	100
Hernandez, 2014e[18]	³30	OC Sensor	4	44	730	1	779	80	94	8.3	100
Hernandez, 2014f[18]	³40	OC Sensor	4	41	733	1	779	80	93	9.0	100
Chiu, 2013[19]	³10	OC Light	28	1302	18128	8	18296	78.6	92.8	1.65	99.9
de Wijkerslooth, 2012a[20]	³10	OC Sensor	7	114	1134	1	1256	88	91	6.0	100
de Wijkerslooth, 2012b[20]	³15	OC Sensor	6	82	1166	2	1256	75	93	7.0	100
de Wijkerslooth, 2012c[20]	³20	OC Sensor	6	65	1183	2	1256	75	95	8.4	100
Imperiale, 2014[25]	³20	OC Fit-check	48	472	9452	17	9989	73.8	94.9	9.2	99.8

risk symptomatic population. This limited review of 10 articles (up to 2015), showed FIT to be highly sensitive and specific and could be used as an effective tool in the selection of patients for colonoscopy. Since 2015, there have been several large published studies which have looked at the usefulness of FIT including cut off levels within a wider range of population groups.

This meta-analysis on symptomatic studies, comprising 6755 participants has identified a pooled sensitivity of 0.90 (95% CI 0.87-0.92) and specificity of 0.87 (95% CI 0.83-0.90) for FIT in the detection of CRC (accounting for low cancer prevalence). This would imply that around 1 in 10 cases of CRC could be missed. Clinicians would thus need to apply clinical judgement, in addition to the FIT result, to guide their decision on referral for investigations. It is not clear as to the outcome of those that test negative for FIT i.e. should this test be repeated or if another triage test should be used in adjunct. Widlak et al (2) report that just under 40% of those referred urgently for exclusion of CRC have normal colonoscopic findings.

Five of the nine included studies used the OC-sensor analytical method with little difference between the pooled sensitivity (difference of 0.00), specificity (difference of 0.02) and accuracy (difference of 0.01) when compared with other systems. This should however, be interpreted cautiously as there was little data on the other systems and were not used in direct comparison to the OC-sensor within the same cohort of patients.

It was also possible to explore the effects of different cut-off concentration values (of the OC-sensor system) with cut-off concentrations ranging between 10-15µg/g feces, showing the most optimal sensitivity of 0.93 (0.88-0.96) and specificity of 0.87 (0.82-0.90) respectively. Notwithstanding the overlapping confidence intervals, it was not possible to determine with statistical significance, which was the optimal FIT cut-off value.

4.2 Screening population

The meta-analysis of the screening studies had demonstrated variable performance of FIT for the detection of CRC, depending on the cut-off levels applied. As FIT was utilised in such a vast heterogenous population, it would be expected that the sensitivity would be lower. Some individuals may have had symptoms but not reported, whilst others may have had no indicators of colorectal disease at all. This wide variation in the presentation, may skew the ability of the test to be both sensitive and specific. However, for a screening test that

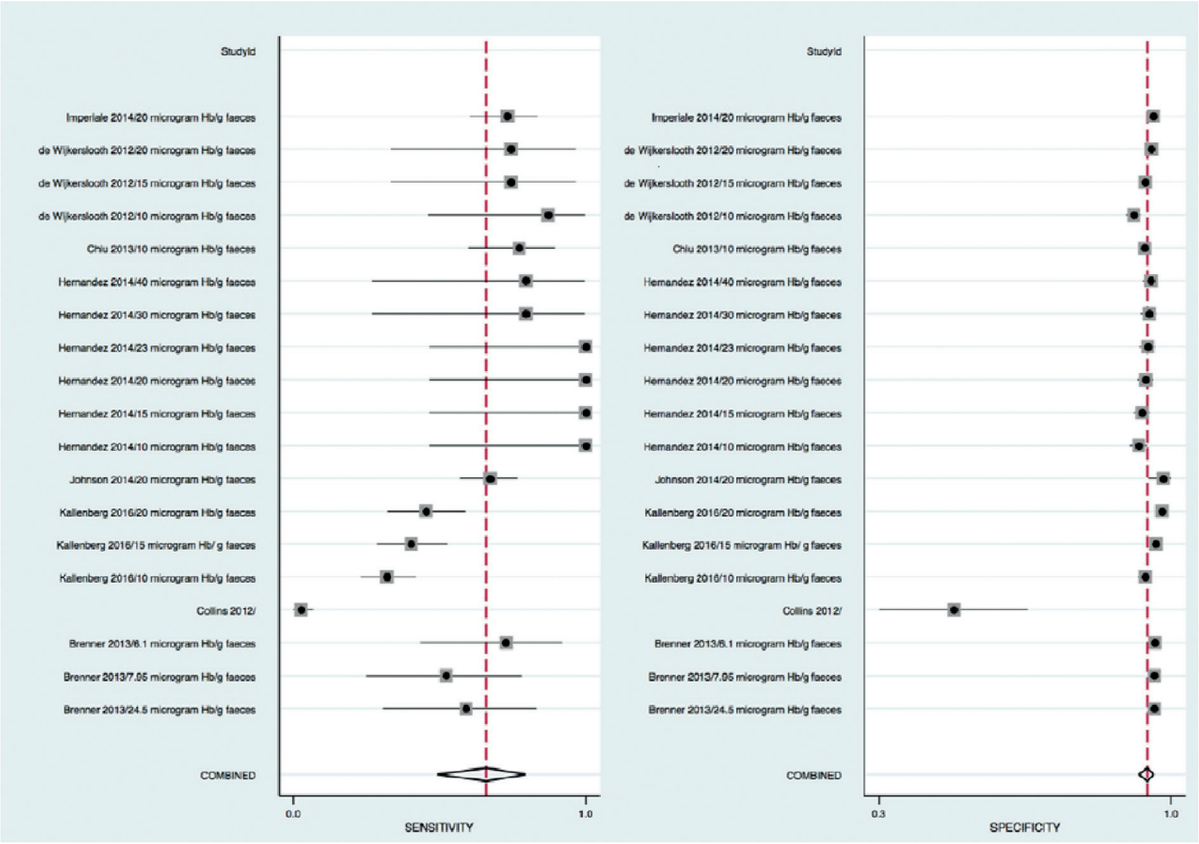

Figure 4. — A Forest plot showing the meta-analysis of the sensitivity and specificity data for FIT in screening population. The pooled sensitivity and specificity are 0.67 and 0.94 respectively and represented by the red dashed lines.

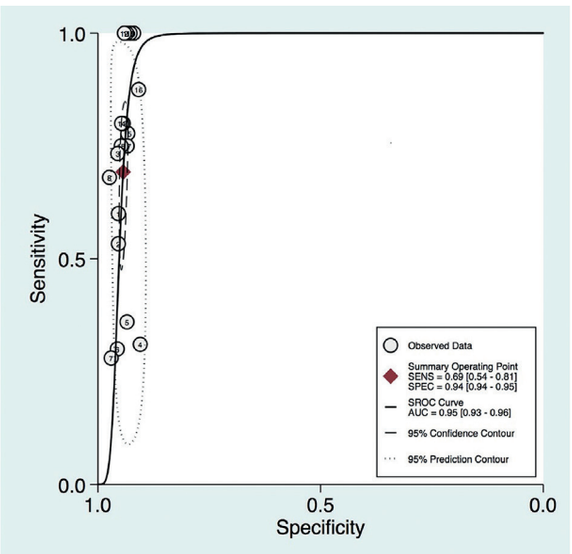

Figure 5. — A receiver-operator characteristic (ROC) curve using FIT in screening population applying cut off concentrations ranging between 6.1-40 µgHb/g feces.

aims to confirm the presence of a disease, a high specificity is ideal (22). It is likely that if low cut-off levels of FIT (e.g. <20µg Hb/g feces) were introduced for screening, very few CRC would be missed ; specificity of 94%. This would be a vast improvement on the specificity of 73% quoted for the currently used faecal occult blood test (5). The high area under the curve of 0.94 of the ROC curve, shown in Figure 3, further strengthens the evidence that FIT is an excellent screening test.

4.3 Limitations of this study

Several papers identified in the original searches had to be excluded, as the final outcome data was only available in those that tested positive for FIT and not for those that tested negative (26-38). Consequently, sensitivity and specificity could not be calculated. Other studies have suggested that the FIT result was dependent on sex and age of the patients, though it was not possible for this systematic review to take these factors into account (39,40). This study also did not compare the accuracy of FIT, in combination with other faecal biomarkers (such as faecal calprotectin, though emerging studies seem to report that it adds little to its diagnostic accuracy) (10-12,33).

5 Conclusion

FIT is a sufficiently accurate test that would significantly improve upon the current faecal occult

blood testing, with higher specificity whilst retaining a similar sensitivity in the screening population. Within the symptomatic group, there is good evidence to support the use of FIT as a triage tool to streamline current two-week services to determine those that require urgent investigations to exclude CRC.

Potential competing interests

None declared.

Specific author contributions

Author contributions: Stonestreet & Wooley: literature review, data collection, preparation of manuscript. Uthman: statistical analysis and manuscript preparation. Chandrapalan: critical revision and manuscript editing. Arasaradnam: design and concept, literature review, critical revision of the manuscript for important intellectual content. All authors have approved the final version of the manuscript.

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