Risk stratification for colorectal neoplasia detection in the Flemish colorectal cancer screening programme

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Abstract

Background: The quantitative faecal immunochemical test (FIT) detects pre-cancerous lesions and colorectal cancer (CRC). Current CRC screening programmes are based upon a binary FIT result. This study evaluates the possibility of personalised risk prediction, based on FIT, age and gender to gain more insight into improving discrimination between normal outcomes, pre-cancerous lesions, carcinoma in situ and CRC working towards a more tailored screening approach. Methods: In this retrospective study, from October 2013 until July 2016, data from 57,421 participants who underwent a colonoscopy after a positive FIT in the Flemish CRC screening programme were analysed using a multinomial multivariable logistic regression model. Results: A significant difference in risk of detecting neoplasia was found between the established risk profiles based on the combination of the quantitative FIT, age and gender. The odds for detecting CRC in men aged 74, with a FIT result of ≥1,000 ng/ml, was higher by a factor of 58.43 than that for women aged 56, with a FIT result of 75 ng/ml. Conclusion: A large difference in risk with regard to the detection of colorectal neoplasia was found, based on demographics of the population. For some participants, the chance of finding no anomalies was more than 60%. Including additional variables in a prediction model could further increase discrimination between outcomes and practicality.

Keywords	Early detection of cancer; Colorectal neoplasms; Occult blood; Risk factors; Decision making; Colonoscopy
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Highlights

- Based on a multinomial model large differences can be found in cancer detection based on simple population determinants.
- In Flanders, gender, age and the quantitative FIT result combined are strong predictors for pre-cancerous lesions, CIS and CRC detection where risk can be predicted for specific profiles.
- Differences in risk are of such magnitude that the GP and the participant should be informed of the increased risk, so that a more informed choice can be made about a follow-up colonoscopy.

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Risk stratification for colorectal neoplasia detection in the Flemish colorectal cancer screening programme.

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Abstract

Background: The quantitative faecal immunochemical test (FIT) detects pre-cancerous lesions and colorectal cancer (CRC). Current CRC screening programmes are based upon a binary FIT result. This study evaluates the possibility of personalised risk prediction, based on FIT, age and gender to gain more insight into improving discrimination between normal outcomes, pre-cancerous lesions, carcinoma in situ and CRC working towards a more tailored screening approach.

Methods: In this retrospective study, from October 2013 until July 2016, data from 57,421 participants who underwent a colonoscopy after a positive FIT in the Flemish CRC screening programme were analysed using a multinomial multivariable logistic regression model.

Results: A significant difference in risk of detecting neoplasia was found between the established risk profiles based on the combination of the quantitative FIT, age and gender. The odds for detecting CRC in men aged 74, with a FIT result of ≥1,000 ng/ml, was higher by a factor of 58.43 than that for women aged 56, with a FIT result of 75 ng/ml.

Conclusion: A large difference in risk with regard to the detection of colorectal neoplasia was found, based on demographics of the population. For some participants, the chance of finding no anomalies was more than 60%. Including additional variables in a prediction model could further increase discrimination between outcomes and practicality.

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1 Introduction

Colorectal cancer (CRC) is the third most common cancer in Europe.[1] With an increasing annual estimated incidence of 345,000 cases and a decreasing annual mortality of 152,000 cases, Europe accounts for 25% of the colorectal cancers worldwide.[2] In Flanders (a Belgian region) there is a CRC mortality level of 1800 people each year.[3] Most CRCs develop from polyps over the course of 10 to 15 years, since the growth of CRC is slow.[4] Regular screening aims to reduce CRC incidence and mortality through early detection and treatment of pre-cancerous lesions and CRC.[5]

Several countries with population-based CRC screening use a faecal immunochemical test (FIT) to detect (occult) blood in the stool, which is an indicator for the presence of (pre-)cancerous lesions and CRC.[6] In Flanders, a regional screening programme was implemented in October 2013[7], and has been evaluated to be a cost effective approach.[8] Current practice uses the FIT result in a binary way, which selects participants who require follow up by colonoscopy. In Flanders, a FIT cut-off discrimination of </≥75ng/ml is used.[9] Different countries use different cut-off values, for example, the Netherlands uses </≥275ng/ml.[10]

This current practice does not exploit the full potential of the FIT. There is room for improvement since in Flanders ~27% of the participants with a positive FIT (≥75 ng/ml) have a negative colonoscopy afterwards. In addition, 20% of the participants who have a positive FIT are not followed up by colonoscopy within 6 months.[9] Haemoglobin levels differ between colonoscopy findings and some determinants are independently associated with the occurrence of CRC, apart from the FIT result.[11, 12] Known predictors of CRC are older age[11, 12], male gender, obesity[13, 14], smoking[14], alcohol intake[15-18], inflammatory bowel disease[14], red and processed meat intake[14], prior screening results and family history of CRC or adenoma.[14, 19, 20] Considering that faecal haemoglobin level results are not easily transferable across countries and regions for CRC screening[21] and life style data are not always transferable between countries, Flanders cannot improve its screening programme accuracy based on foreign data. Therefore, to investigate the benefits of tailored screening approaches a study on Flemish regional data is necessary.

At this time, the number of predictors available in Flanders is limited. This study will explore the implications of an approach where quantitative FIT, combined with age and gender in screening follow-up, is associated with an increased discrimination between predicted probabilities of detecting pre-cancerous lesions, adenocarcinoma in situ (CIS) or CRC. This approach will be explored in participants who have been positively screened by the FIT within the Flemish CRC screening programme.

2 Methods

2.1 Study population of the Flemish CRC screening programme

In the Flemish region, CRC screening was initiated from October 2013 onwards and all eligible persons, aged 56 to 74 years were invited by letter to perform a FIT. Persons who were not eligible for screening were those

who had had a FIT in the past two years, had undergone a colonoscopy, had had a CRC diagnosis in the past ten years or persons who had had their colorectum fully removed. Data on exclusions were provided by the Belgian Cancer Registry (BCR). People who communicated that they did not want to participate were excluded by the Centre for Cancer Detection (CfCD).

2.2 Data sources

The data for this study was obtained from the BCR. The BCR is legally authorized to collect all data on new cancer diagnoses, resulting in a national population-based cancer registry. In addition, the laboratories for anatomical pathology are obliged to provide the BCR with all test results of colon specimens, regardless of the diagnosis. The BCR completes this Cyto-Histopathology register (CHP) with population-based reimbursement data from the Health Insurance Companies (HIC). The BCR couples these data with screening data available at the CfCD, in accordance with the latest data security guidelines and quality indicators.

2.3 Definitions

Colonoscopies were performed by gastroenterologists within routine practice and without specific guidelines or quality control. Individual colonoscopy findings were categorised as: normal or non-cancerous lesions (negative colonoscopy, inflammation, non-specific polyps, hyperplastic polyps etc.), pre-cancerous lesions (adenomas (sessile, serrated, tubular) with low-grade dysplasia and with/without a villous component), adenocarcinoma in situ (with high grade dysplasia) and (invasive) CRC. Detected CRCs were classified using the TNM classification system, where CIS is considered as TNM stage 0.[22] CIS is included to make a distinction between TNO 0 and ≥ 1 possible.

This categorisation was chosen over the classical non-advanced adenoma, advanced adenoma and CRC due to several reasons. Firstly, normal or non-cancerous lesions are used as a reference in the prediction model over the non-advanced adenoma, as we intend to also predict the detection of pre-cancerous lesions what would only be possible with this categorisation. Secondly, there is no colonoscopy register in Belgium, resulting in the lack of data on the size and number of lesions. It is therefore not possible to classify according to the classical approach.

Individuals with more than one lesion were classified according to the most advanced finding observed within 6 months after FIT. Four groups were established from the colonoscopy findings, as shown in Table 1. Risk factors considered were: age (56-74 years), gender and quantitative FIT results (75 ng/ml up to ≥1,000 ng/ml). FIT results of 1,000 ng/ml and more are considered as ≥1,000 because results above 1,000 ng/ml cannot be specifically quantified.

2.4 Faecal immunochemical test for haemoglobin

In Flanders, the FIT results are reported as nanograms of blood per millilitre of faeces (ng/ml). Internationally, the micrograms of haemoglobin per gram faeces (µg/gr) is oftentimes used. For generalisability regarding

the OC-sensor (FIT) results, a valid conversion is possible namely: (ng/ml result / 25)*5. The FIT uses antibodies specific for human haemoglobin and detects blood by immunoassay. FIT analysis measures the quantity of antibody bound to haemoglobin using a variety of methods. The analysis of the FIT is done by using the OC-Sensor Diana™ (Eiken Chemical, Tokyo, Japan). The range of the results extends from 50 ng/ml to ≥1,000 ng/ml. The haemoglobin value of 75 ng/ml was used as a positivity threshold. The quality control of both the FIT test and the rest of the screening programme is reported elsewhere.[9]

2.5 Statistical analyses

The FIT variable is non-normally distributed and is therefore approached as non-parametric for descriptive purposes, thus medians and interquartile ranges (IQR) are used. Differences in the median FIT result between colonoscopy findings was tested using the Kruskal-Wallis test, while pairwise differences were evaluated with a Pearson's chi-squared test. Multivariable multinomial logistic regression analysis was used to obtain insight into the association between the variables (age, gender, FIT) and the presence or absence of pre-cancerous lesions, CIS or CRC compared to the reference standard. The model's reference standard is the group of women (normal or non-cancerous lesions), age 56 with a FIT result of 75 ng/ml, since this group is most likely least at risk. Based on the reference standard, odds ratios (OR) and 95% confidence intervals (CI) are calculated. Predicted probabilities are calculated relative to the other outcomes based on the prediction model. ORs show the associations, while the predicted probabilities place the risk in the context of multiple outcomes and stay between 0 and 100%. For statistical significance and inclusion in the multivariable model a p-value of 0.05 and a CI coverage of 95% were used. The statistical analysis was performed using R: a language and environment for statistical computing.

2.6 Ethical consideration

Approval for the general Flemish CRC screening programme was given by the Commission for the Protection of Privacy with reference: SCSZG/13/194, number 13/091 on the date 17-09-2013. By participating in the screening programme all participants filled out an informed consent, explaining that personal information can be used for evaluation of the CRC screening programme and scientific research for improving the programme. This study used secondary data, collected and maintained at the BCR. Data was solely collected by conducting the CRC screening programme in Flanders and the identity of the participants was anonymised for the investigators by the BCR.

3 Results

After invitation by letter, 936,981 screening naïve individuals participated from October 2013 until July 2016 by returning their FIT. The population-based registries used in this study were considered complete for this time period. Subsequently, 72,055 participants were screened positive by FIT, as shown in Figure 1. Of these, 57,421 participants underwent a subsequent colonoscopy, which resulted in 38,913 participants with histopathology results and 18,359 participants where no sample was taken. This latter group was considered as having normal colonoscopy findings and was therefore included in the corresponding category.

["insert figure 1"]

Figure 1. Flowchart of the CRC screening programme participants from October 2013 to June 2016. * is included in normal and non-cancerous category.

An increase is observed between the determinants and the colonoscopy findings, as shown in Table 1. The FIT results are gradually increasing with the severity of the colonoscopy findings; from median 180 ng/ml (IQR 106-379) in normal and non-cancerous lesions, up to median 922 ng/ml (IQR 288-1,000) in CRC. The group who did not undergo a colonoscopy after a positive FIT result consisted of relatively more males compared to females (61% vs 39%). Also, the age distribution and median FIT results of 222 ng/ml (IQR 121-763) were comparable with the pre-cancerous lesions group.

["insert table 1"]

Median FIT results were significantly higher in the pre-cancerous lesions, CIS and CRC groups compared to the normal or non-cancerous lesions group, as shown in Figure 2 (P<.001). It should also be noted that 14,436 participants with a positive FIT result did not undergo a colonoscopy within 6 months.

["insert figure 2"]

Figure 2. Box and whisker plots of the difference between colonoscopy findings and FIT results. Significant pairwise differences (P<.001) and a difference of P<.001 between colonoscopy findings.

3.1 Risk stratification for pre-cancerous lesions, CIS and CRC

The multivariable model (Table 2) shows significant associations between the risk factors (gender, age and quantitative FIT result) and the detection of pre-cancerous lesions, CIS and CRC. Interaction terms in the model were not significant. Notable results are the stepwise increase of the association of pre-cancerous lesions, CIS and CRC detection with the increase of FIT results and older age.

["insert table 2"]

Informative results are the differences in predicted probabilities between colonoscopy findings, based upon the three risk factors calculated by the multinomial model. For example: the predicted probability difference of 15-20% between the detection of a normal outcome between males and females over the whole range of FIT and age, as derived from Figure 3. This means that detecting a normal finding after a positive FIT is much more likely in females compared to males, and especially younger females. To illustrate differences, some participant profiles are shown in Table 3. In addition, every participant profile (with categorised ages) and their predicted probability of detecting normal or non-cancerous lesions, pre-cancerous lesions, CIS and CRC can be derived from Figure 3.

Relative to the reference group, the group of men age 74 with a FIT result of ≥1,000 ng/ml had an increased odds of CRC detection by a factor of 58.43 (CI 52.89-64.55). Between these two groups, the probability of

finding a normal result for a 56-year-old woman with a FIT result of 75 ng/ml is 62%, while this is only 19% for a 74-year-old male with a FIT result of 1,000 ng/ml. The probability of finding CRC was 1% and 22%, respectively. Even if subgroups are created from these data, the findings are similar to the cases shown above due to the robustness of the model.

["insert table 3"]

["insert figure 3"]

Figure 3. Prediction of colonoscopy finding probabilities based upon the multivariable model including predictors for age, gender and quantitative FIT result.

4 Discussion

This study reported on a multinomial model that discriminated between normal outcomes and detecting (pre-)cancerous lesions after testing positive by FIT. This resulted in insightful results as a 56-year-old woman with a FIT result of 75 ng/ml had only a 1% chance of CRC detection by colonoscopy and 62% chance of detecting no anomalies. At the same time a 74-year-old male with a FIT result of 1,000 ng/ml had a 22% chance of CRC detection by colonoscopy and 19% chance of detecting no anomalies. We think that participants with a higher risk of cancer detection should be aware of this fact and informing all participants in the same way is less appropriate. This study could therefore really pave the way for informed decision making about CRC screening in Flanders (including pre-cancerous lesions).

This approach is in line with the recommendations of the Institute of Medicine[23] and the General Medical Council of the UK,[24] who promote informed decision making by informing prospective screening participants of their individual risk and allowing them to choose a screening test accordingly.[25] People should have the opportunity to be informed about their individual risk of pre-cancerous lesion and CRC detection. Several institutions advocate for clear communication and recommendation from the GPs to participants.[23, 24, 26, 27] Informed decision making is most likely associated with higher participation rates and compliance.[28] It should be clear that everyone with FIT ≥75ng/ml is advised to undergo a subsequent colonoscopy, while their individual risks differ considerably.

The probability of finding a pre-cancerous lesion in the reference group (56-year-old females with a FIT of 75 ng/ml) was still 35%. Creating a model where discrimination increases to the pragmatic extent, requires a more advanced discrimination between normal and neoplastic outcomes. Currently, however, participants are treated and informed in the same way within the CRC screening programme.

This study reported on the association between gender, age and quantitative FIT results and the detection of pre-cancerous lesions, CIS and CRC in non-symptomatic participants in the Flemish CRC screening programme which is consistent with other studies.[11, 29] However, the large sample size of 57,421 participants leads to a more precise risk stratification compared to other studies. This study views the question of possible quality improvement of the screening programme within the positively screened group where ~27% undergo a negative colonoscopy. The screening process needs to be improved to reduce the number of negative colonoscopies after a positive FIT. These are an unnecessary burden for the participants and are expensive in these large numbers (approximately €4.74 million per year for colonoscopies with no anomalies).[30]

Considering that negative colonoscopies occur over the whole range of FIT, adapting the FIT cut-off value per subgroup (e.g., increase cut-off in younger women or lower cut-off in older-men) would only shift the problem. Changing the FIT cut-off based on gender through multiple options could bring the differences between gender closer together in terms of accuracy or miss rates.[31] Increasing the FIT cut-off for women could lead to similar miss rates and positive predictive values between genders, but would decrease sensitivity and detection rates in females. Several of these considered options have their benefits and disadvantages. Nevertheless, the goal should be to reduce the negative colonoscopies and maintain the detection of pre-cancerous lesions and CRC.

A more promising approach could therefore be a personalized screening follow-up, based on a prediction model. Additional predictors, accompanied by the quantitative FIT, could make a more accurate prediction between participants with or without neoplasia. Natural considerations are gender and age but also other easily obtainable risk factors such as smoking, alcohol use, BMI, family history of CRC etc. In addition, we should also consider molecular and genetic markers, through molecular pathological epidemiology (MPE) for improving the early detection of CRC.[32] This brings the screening from a binary approach to an approach where probabilities are considered. It would be the most favourable approach for attaining fewer false positive colonoscopies and retaining the detection of pre-cancerous lesions, CIS and CRC.

Comparable results were found in a German study where the male gender and increasing FIT results were associated with an increased risk of detecting CRC (OR 1.9 and 2.4, respectively) while increasing age showed inconsistent results.[33] A Spanish study showed that increased risk of CRC was found based on the risk factors gender (male OR 2.07), age (60-69 OR 1.24) and FIT ng/ml (165-320, 325-885 and >885 OR 1.23, 2.00 and 3.80, respectively).[11] This latter study developed a risk matrix of 16 risk categories, where they found an (OR 11.46 fold) increase between risk categories.[11] Unfortunately, pre-cancerous lesions were not considered in these studies and this is an essential part of the screening programme. These European studies show less specific, but similar results compared to this study in terms of risk factors for CRC detection.

Limitations of this study were the absence of follow-up colonoscopy for negative FIT results (<75 ng/ml) which is related to the study design. As in Flanders (and many other European countries), a colonoscopy is not considered beneficial following a negative FIT as it induces extra risks and is therefore ethically not feasible. The screening programme used the age group 56-74, which does not conform to the European guidelines (50-74). However, multiple countries use this narrower target age for their screening

programmes.[6] Considering the recommendation of the EU to include the age range of 50-55, this would most likely increase the ratio between normal and pathological findings after a positive FIT with a subsequent colonoscopy. This means that the chance of performing an unnecessary colonoscopy after a positive FIT would be at least between 50-70% for women within the lower FIT and age range. This strongly suggests evaluating other or additional screening options.

Future research should therefore focus on gathering additional risk factors for inclusion in a prediction model by a prospective design. For example, by using a questionnaire with determinants indicated by prior studies such as alcohol intake and BMI.[34] Also of importance is the improvement of the comparability of the data collected from the various national CRC screening programmes. Multiple national CRC screening programmes use different tests, cut-off values, target ages, measurements and even terminology.[6] Belgium can improve this by implementing a colonoscopy registry and report according the international guidelines.

In conclusion: this study found an association between the risk factors of age, gender and quantitative FIT in detecting pre-cancerous lesions, CIS and CRC in Flanders. These results are similar to the risk factors reported internationally and could be of clinical relevance for both participants and GPs for informative purposes. More importantly, this approach proves the power of the multinomial model in discriminating between normal and (pre-)cancerous outcomes based on simple predictors. These results will be of importance in Flanders for further development of tailored screening and follow up in the near future, potentially improving both the accuracy and cost-effectiveness of the programme.

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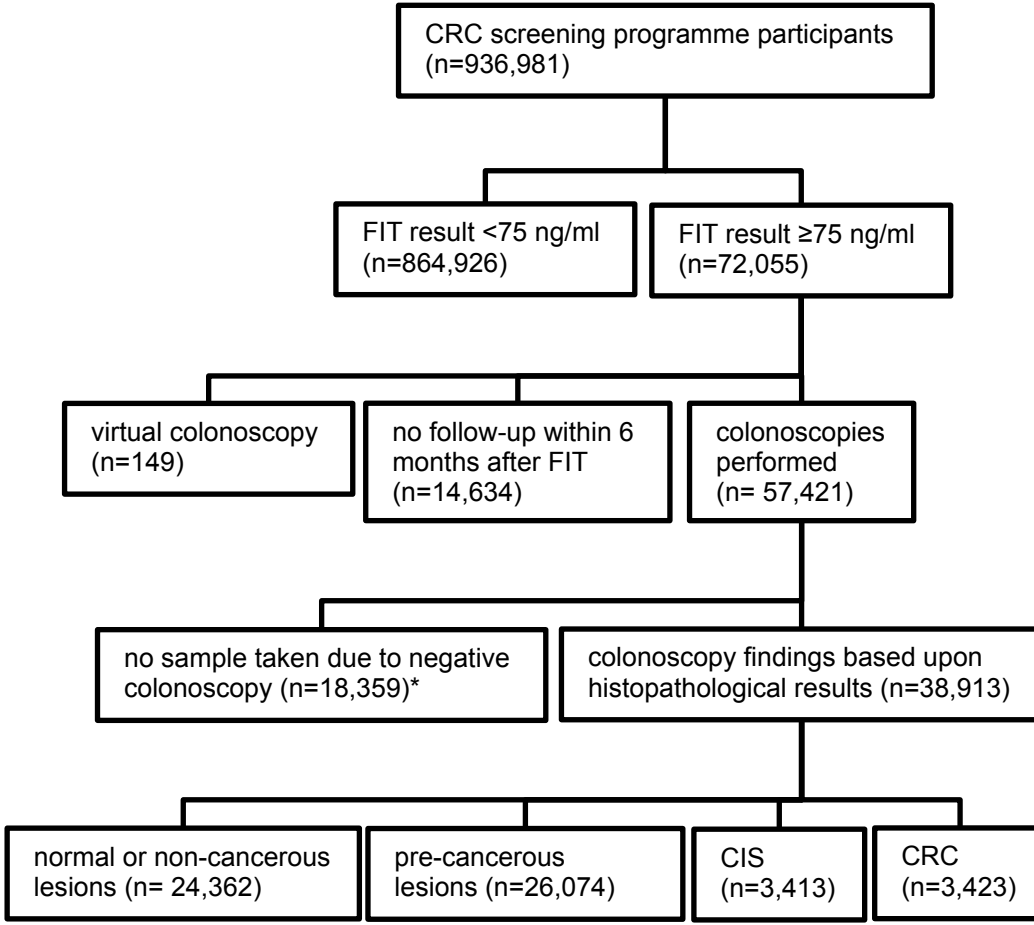
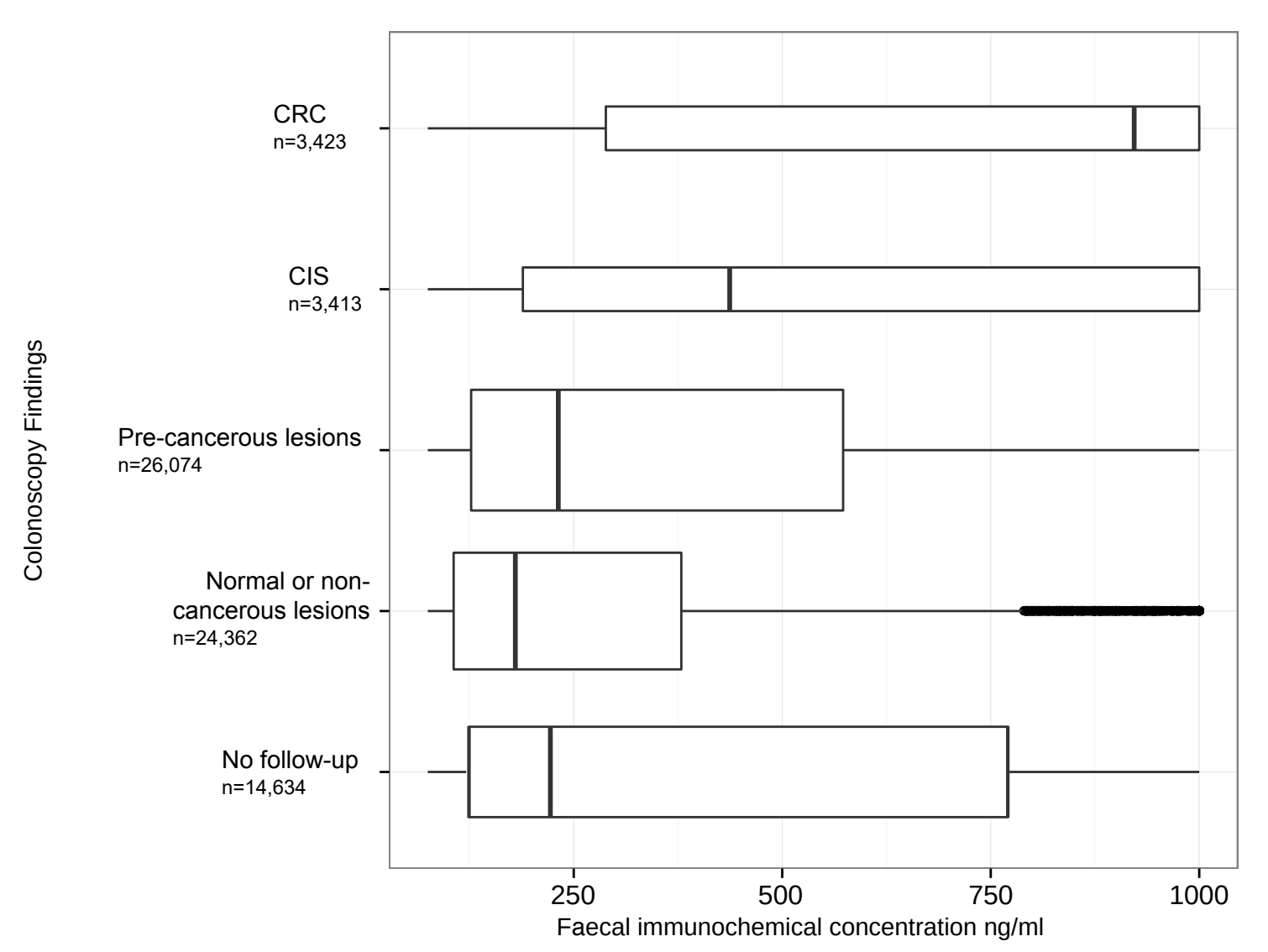

CRC screening programme participants (n=936,981)
FIT result <75 ng/ml (n=864,926)
FIT result ≥75 ng/ml (n=72,055)
virtual colonoscopy (n=149)
no follow-up within 6 months after FIT (n=14,634)
colonoscopies performed (n= 57,421)
no sample taken due to negative colonoscopy (n=18,359)*
colonoscopy findings based upon histopathological results (n=38,913)
normal or non-cancerous lesions (n= 24,362)
pre-cancerous lesions (n=26,074)
CIS (n=3,413)
CRC (n=3,423)


Colonoscopy Findings
CRC
n=3,423
CIS
n=3,413
Pre-cancerous lesions
n=26,074
Normal or non-cancerous lesions
n=24,362
No follow-up
n=14,634
250
500
750
1000
Faecal immunochemical concentration ng/ml

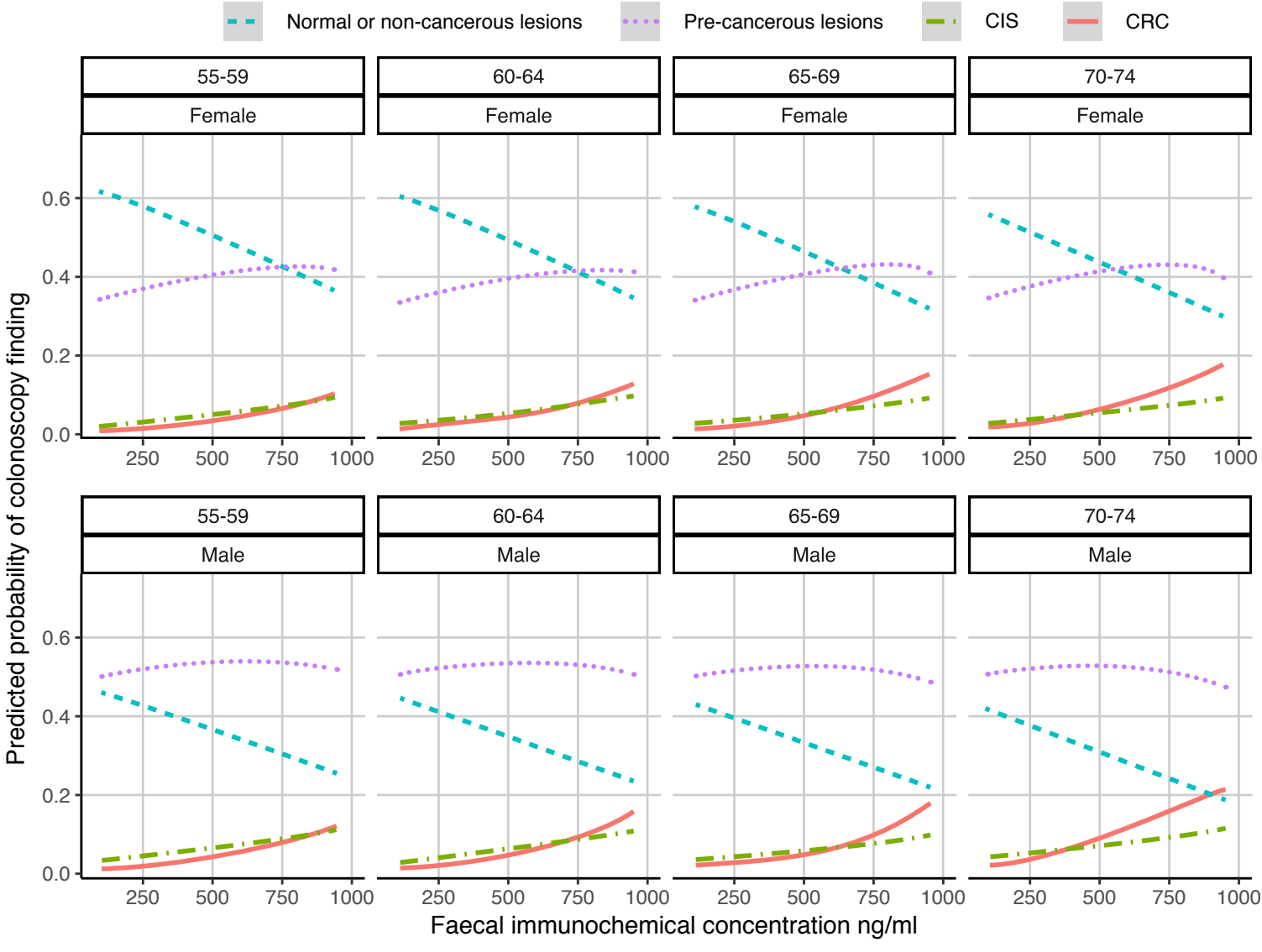

Normal or non-cancerous lesions
Pre-cancerous lesions
CIS
CRC
55-59
Female
60-64
Female
65-69
Female
70-74
Female
55-59
Male
60-64
Male
65-69
Male
70-74
Male
Predicted probability of colonoscopy finding
0.0
0.2
0.4
0.6
250
500
750
1000
Faecal immunochemical concentration ng/ml

Table 1. Study population demographics, FIT results and colonoscopy findings

Colonoscopy findings	N	Women	56-59y ♀&♂	60-64y ♀&♂	65-69y ♀&♂	70-74y ♀&♂	FIT results ng/ml Median (Interquartile range)
Normal or non-cancerous lesions	24,362	50.5%	18%	26%	27%	29%	180 (106-379)
Pre-cancerous lesions	26,074	34.5%	15%	28%	27%	30%	231.5 (127-573)
Carcinoma in situ	3,413	33.9%	14%	26%	30%	30%	437 (189-1000)
Colorectal Cancer	3,423	34.4%	11%	23%	29%	37%	922 (288-1000)
No colonoscopy follow-up	14,634	39%	15%	23%	29%	33%	222 (121-763)

Table 2. Multivariable model for the detection of pre-cancerous lesions, CIS and CRC according to gender, age and FIT results.

Pre-cancerous lesions	
Risk factors	
	OR (95% CI)*
Gender	
Female	1
Male	1.91 (1.84-1.98)
Age (years)	1.15 (1.09-1.21)
FIT (ng/ml)	1.98 (1.88-2.09)

CIS	
Risk factors	
	OR (95% CI)*
Gender	
Female	1
Male	1.90 (1.76-2.04)
Age (years)	1.24 (1.22-1.27)
FIT (ng/ml)	6.06 (5.52-6.64)

CRC	
Risk factors	
	OR (95% CI)*
Gender	
Female	1
Male	1.90 (1.84-2.14)
Age (years)	2.21 (2.16-2.27)
FIT (ng/ml)	14.56 (13.26-16.01)

1: reference group: female, 56 years of age, normal or non-cancerous lesions

FIT and Age are treated as quantitative variables in the multivariable model and reported as the OR for FIT ≥1,000 ng/ml and age 74 versus the reference group.

* All corresponding P-values <.001

Table 3. Participant profiles concerning the risk of detecting pre-cancerous lesions, CIS and CRC according to gender, age and FIT results.

Gender	Age	FIT (ng/ml)	Odds ratio (CI)	Normal Probability	Pre-cancerous Probability	CIS Probability	CRC Probability
Female	56	75	1	0.615	0.345	0.027	0.012
Female	74	1,000	32.22 (29.73-34.93)	0.307	0.393	0.103	0.197
Male	56	75	1.90 (1.84-2.14)	0.457	0.488	0.038	0.016
Male	74	1,000	58.43 (52.89-64.55)	0.191	0.465	0.121	0.222

1 Odds ratio of detecting invasive cancer relative to the reference standard (females, age 56 and FIT 75 ng/ml)

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Author statement:

W.v.d.V, G.V.H, M.P and S.H, conceived and planned the research. W.v.d.V, I.D.B and G.S carried out the analyses. All authors contributed to interpreting the results and provided critical feedback, helped shape the research, analysis and the manuscript. W.v.d.V wrote the manuscript and G.V.H, M.P and S.H supervised the project. All authors read the manuscript gave feedback and approved the final version for publication.