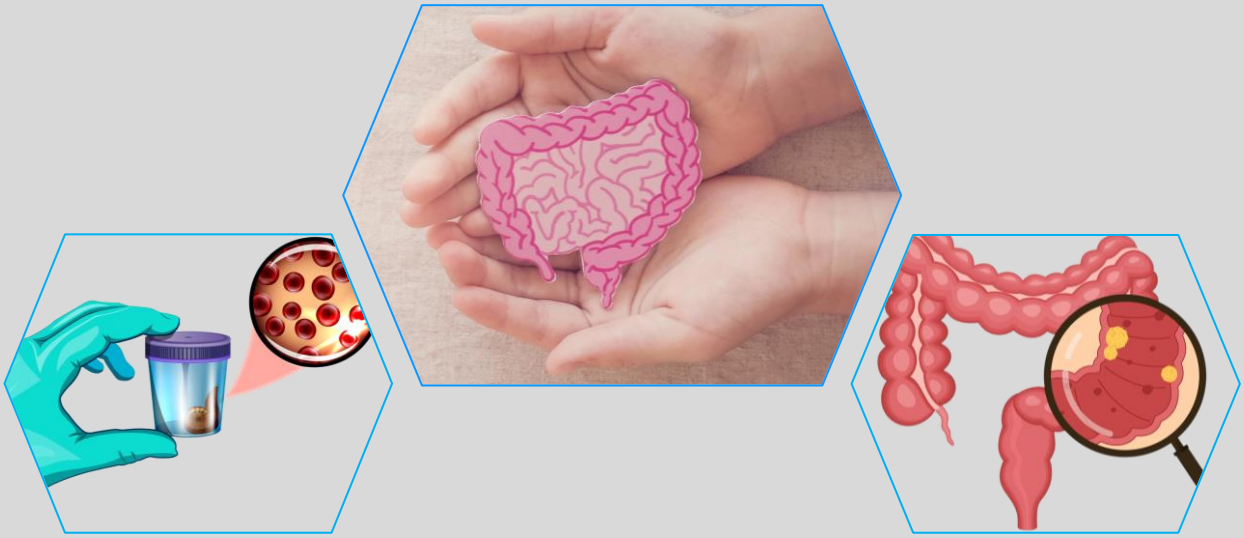
Colorectal Cancer Screening in Flanders:
Impact, Challenges, and Recommendations

PhD thesis submitted for the degree of Doctor of Medical Sciences
at the University of Antwerp to be defended by:

Thuy Ngan TRAN



Promotors: Prof. dr. Guido Van Hal
Prof. dr. Marc Peeters
Dr. Sarah Hoeck

University of Antwerp
Faculty of Medicine and Health Sciences
Antwerp, 2023

Colorectal Cancer Screening in Flanders: Impact, Challenges, and Recommendations

Thuy Ngan Tran

Colorectal Cancer Screening in Flanders: Impact, Challenges, and Recommendations
PhD thesis, University of Antwerp, Belgium

Cover design and layout: Thuy Ngan Tran & Tien Dat Bui

Cover images: Shutterstock (https://www.shutterstock.com)

Printing: Universitas

University of Antwerp
Faculty of Medicine and Health Sciences

Colorectal Cancer Screening in Flanders: Impact, Challenges, and Recommendations

Dikkedarmkankerscreening in Vlaanderen: Impact, Uitdagingen en Aanbevelingen

PhD thesis submitted for the degree of Doctor of Medical Sciences
at the University of Antwerp to be defended by

THUY NGAN TRAN

Antwerp, 2023

MEMBERS OF THE JURY

Internal Jury Members:

Prof. dr. Sven Francque, University of Antwerp, Antwerp, Belgium

Prof. dr. Peter Van Bogaert, University of Antwerp, Antwerp, Belgium

External Jury Members:

Prof. dr. Danny De Looze, Ghent University, Ghent, Belgium

Prof. dr. Iris Lansdorp-Vogelaar, Erasmus University Medical Center, Rotterdam, The Netherlands

Promotors:

Prof. dr. Guido Van Hal, University of Antwerp, Antwerp, Belgium

Prof. dr. Marc Peeters, University of Antwerp, Antwerp, Belgium

Dr. Sarah Hoeck, University of Antwerp, Antwerp, Belgium

Table of contents

List of abbreviations

aOR	adjusted Odds Ratio	iFOBT	Immunochemical Faecal Occult Blood Test
APC	Annual Percentage Change	IK	Intervalkanker
BCR	Belgian Cancer Registry	IMA-AIM	Het InterMutualistisch Agentschap
BI	Betrouwbaarheidsinterval	IQR	Interquartile Range
CBSS	Crossroads Bank for Social Security	KRAS	Kirsten Rat Sarcoma
CCD	Centre for Cancer Detection	MLH1	MutL Homolog 1
CCR	Centre Communautaire de Référence	MSI	Microsatellite Instability
CI	Confidence Interval	OR	Odds Ratio
CIMP	CpG Island Methylator Phenotype	PEG	Polyethylene Glycol
CIN	Chromosomal Instability	PEG-ELS	Polyethylene Glycol-Electrolyte Solutions
CRC	Colorectal Cancer	PPV	Positive Predictive Value
CTC	Computed Tomography Colonography	PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
DAG	Directed Acyclic Graph	QALY	Quality-Adjusted Life-Year
DC	Diagnostic Colonoscopy	QR	Quick Response
DDK	Dikkedarmkanker	SEPT9	Septin 9
DNA	Deoxyribonucleic Acid	SES	Socioeconomic Status
EU	European Union	SMS	Short Message Service
EUR	Euro	STROBE	STrengthening the Reporting of OBservational studies in Epidemiology
FCD	Fecal Collection Devices	TNM	Tumor-Nodes-Metastasis
FIT	Faecal Immunochemical Test	TV	Television
FOBT	Faecal Occult Blood Test	UK	United Kingdom
GEE	Generalized Estimating Equations	US	United States
gFOBT	Guaiac Faecal Occult Blood Test	USA	United States of America
GP	General Practitioner	WHO	World Health Organization
IC	Interval Cancer	WSR	age-Standardised Rate using the Word global standard population
ICER	Incremental Cost-Effectiveness Ratio		

Chapter 1

General introduction

1.1. The burden of colorectal cancer

Colorectal cancer (CRC) poses a significant health challenge due to its high incidence and mortality. It ranks as the third most prevalent cancer worldwide, accounting for 10% of all cancer cases and the second leading cause of cancer-related deaths, contributing to 9.4% of total cancer-related deaths.[1] Recent estimates indicate that in 2020 alone, there were approximately 1.9 million new CRC cases and 935,000 CRC-related deaths, highlighting its substantial impact on the global burden of cancer.[1]

The global incidence of CRC is on the rise due to population aging, dietary changes and the increasing prevalence of risk factors such as obesity, smoking and sedentary lifestyles.[2,3] While CRC incidence is increasing in non-Western countries, developed countries continue to bear the greatest burden of CRC. Among regions worldwide, Europe records the highest rates of CRC.[1] Recent 2020 statistics show that in Europe, CRC ranks second in terms of both cancer diagnosis (520,000 new cancer cases, 12.9% of total cancer cases) and cancer-related mortality (250,000 deaths, 6.8% of cancer-related deaths).[4]

In Belgium, based on 2021 statistics, CRC is the third most common cancer in both males (4387 new cases, 10.8% of all cancer cases) and females (3494 new cases, 10.2%) (**Figure 1**).[5] In terms of mortality, CRC is the second leading cause of cancer-related deaths in 2020 when considering both sexes combined (2484 deaths, 8.3% of cancer-related deaths).[6]

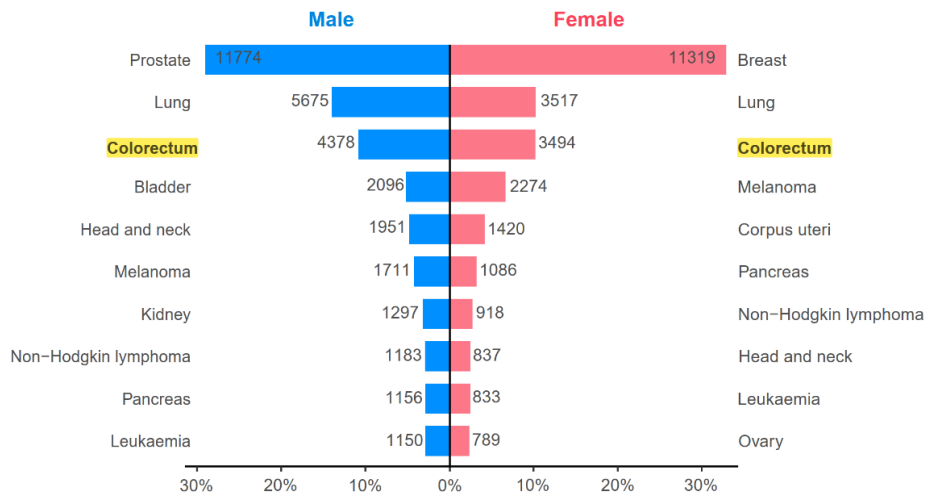


Figure 1. The absolute numbers and percentages of the ten most common cancers by sex in Belgium 2021 (Source of data: Belgian Cancer Registry[5])

Prior to the implementation of population-based CRC screening (October 2013), in 2012, Flanders documented 2948 new CRC cases in males (WSR – age-standardised rate using the Word global standard population: 46.0 new cases/100,000 person-years (py)) and 2312 CRC cases in females (WSR 30.2/100,000 py), along with 785 CRC-related deaths in males (WSR 10.3 CRC-related deaths/100,000 py) and 677 CRC-related deaths in females (WSR 6.6/100,000 py).[5,7,8]

1.2. CRC is an ideal candidate for population-based screening

The high incidence and mortality rates of CRC, coupled with its slow development and progression, lack of symptoms in the early stages, detectable precancerous lesions and evidence of reduced mortality and cost-effectiveness of screening, make it an ideal candidate for population-based screening.

1.2.1. CRC has slow development and progression

CRC commonly originates from benign, precancerous polyps, undergoing a slow progression over a period of 10 to 20 years. This slow progression presents an opportunity for early detection and intervention through screening.[9-11] Polyps are abnormal tissue growths on the inner lining of the colon or rectum and have the potential to become cancerous.[12] Among polyp

types, adenomatous polyps or adenomas carry a higher risk of developing into cancer, although the actual progression to cancer only occurs in fewer than 10% of cases. Adenomas are common in the population, with an estimated prevalence of approximately 20% by age 55, which further rises to 36% by age 75. Among individuals aged 75 and above, the prevalence of adenomas exceeds 40%.[13] The classical adenoma-carcinoma sequence by Fearon and Vogelstein,[14] describing the progression from normal colonic mucosa to small tubular adenomas, larger adenomas with advanced histologic features (villous features, high-grade dysplasia), and eventually to cancer, forms a fundamental framework for understanding and managing colonic adenomas. In this framework, adenomatous polyps (adenomas) are identified as the principal precursors of CRC, driven by the progressive accumulation of critical mutations, mainly chromosomal instability (CIN) and KRAS mutations,[14,15] accounting for the majority (70-80%) of CRC cases.[16]

Beyond the classical adenoma-carcinoma sequence, an increasingly recognised alternative is the 'serrated pathway', estimated to account for approximately 15-30% of CRC cases.[16] This pathway is characterised by serrated precursor lesions, forming a diverse group that includes hyperplastic polyps, sessile serrated lesions, traditional serrated adenomas, and mixed polyps.[17] While hyperplastic polyps were previously considered benign, specific subtypes are now recognised as precursors to non-adenomatous cancers within the serrated pathway.[17] Within this framework, certain hyperplastic polyps have the potential to progress to other serrated polyps, including sessile serrated adenomas, traditional serrated adenomas or mixed polyps, eventually evolving to CRC.[18]

Notably, CRCs arising from the serrated pathway are disproportionately represented in CRC interval cancers.[17,19] Among the subtypes of serrated lesions, sessile serrated lesions, predominantly located in the proximal colon, are of particular interest. These lesions are often overlooked by endoscopists due to their proximal location and subtle endoscopic features.[20] Sessile serrated lesions exhibit sessile or flat morphology, with proximal lesions more likely to be flat than distal ones.[17] They may resemble folds in the lining of the colon, displaying pale colour, indistinct borders, and are often covered with mucus.[17,20] Even when detected, they are more prone to incomplete resection.[20] Sessile serrated lesions are also missed more by screening with faecal occult blood test (FOBT) due to their flat nature, resulting in smaller areas in contact with faeces, the presence of mucus covering, and a lower likelihood of bleeding than

conventional adenomas.[17,20,21] A study by Heigh et al. (2014) demonstrated the limited ability of faecal immunochemical test (FIT) at both 10 and 20 µg/g (50 and 100 ng/ml) thresholds in detecting sessile serrated lesions.[22] Specifically, at the specificity cut-off of 95%, FIT at 20 µg/g failed to detect any sessile serrated polyps, while at specificity cut-off of 91%, FIT at 10 µg/g detected only 10% of sessile serrated polyps.

Additionally, it is plausible that a proportion of interval cancers may arise from tumours with more aggressive characteristics after a true negative colonoscopy or FIT. Serrated lesions progress through a sequential molecular process, with early events involving the activation of BRAF or, less commonly, KRAS mutations in hyperplastic polyps.[17] A significant molecular feature marking the transformation of sessile serrated lesions to more advanced stages (sessile serrated lesions with dysplasia or carcinomas) is CpG island methylator phenotype positivity (CIMP+), either with or without MLH1 methylation.[20] The MLH1 gene, a DNA mismatch repair gen, is frequently methylated under CIMP+ conditions. MLH1 silencing leads to high microsatellite instability (MSI-high). When a sessile serrated lesion becomes MSI-high due to MLH1 silencing, it is highly likely to advance into a sessile serrated lesion with dysplasia and transform rapidly into a carcinoma.[20] This rapid progression may contribute to both FIT interval cancers and post colonoscopy CRCs, particular in the proximal colon.

TNM staging

As cancer cells proliferate, they form a tumour within the colon or rectum. Initially, the tumour grows slowly and remains localized within the inner layers of the intestinal wall (known as local invasion), without spreading beyond the intestinal wall.[23] However, if left undetected and untreated, CRC can advance to more aggressive stages, wherein it invades deeper layers of the colon or rectum wall and may penetrate blood vessels or lymphatic vessels. Typically, cancer cells spread first to lymph nodes near the tumour, and then they can also travel through the bloodstream to distant organs like the liver or lungs, or within the abdominal cavity affecting areas like the ovary. The process of cancer cell dissemination through blood or lymphatic vessels is referred to as metastasis.[11]

The staging of CRC reflects the extent of its spread and plays a crucial role in treatment decisions and prognosis assessment. The TNM staging system, widely used in clinical settings, includes the following stages[24]:

- Stage 0: Carcinoma in situ, confined to the mucosa without invading beyond the inner lining

of the colon or rectum.

- Stage I: Invasion into the submucosa (T1) or muscularis propria (T2) of the colon or rectum, without lymph node involvement (N0) or distant metastasis (M0).
- Stage II: Penetration into the subserosa (T3) or through the layers of the muscle to the lining of the abdomen, called the visceral peritoneum (T4a), without lymph node involvement (N0) or distant metastasis (M0).
- Stage III: Invasion of nearby structures (T4b) or presence of regional lymph node involvement (N1/N1c or N2) at any T stage, without distant metastasis (M0).
- Stage IV: Presence of distant metastasis (M1), regardless of the T and N status.

1.2.2. CRC is typically asymptomatic in early stages

In the early stages, CRC often remains asymptomatic. This silent progression means that the cancer develops and grows without noticeable signs or symptoms in the body. As the disease advances, symptoms may appear, but they are often nonspecific and can be mistaken for benign conditions. These symptoms include abdominal pain or discomfort, changes in bowel habits, a feeling of incomplete bowel emptying, intermittent diarrhoea or constipation, blood in the stool, unintentional weight loss and fatigue.[25-28] While evidence from systematic reviews and meta-analyses has consistently demonstrated an association between rectal bleeding and CRC,[26,27,29] the diagnostic value of the other symptoms such as changes in bowel habits, abdominal pain and bloating remains uncertain.[28,30] By the time CRC symptoms become apparent, the disease has often reached an advanced stage, resulting in poor survival rates and requiring extensive and costly treatment.

The asymptomatic nature of CRC in the early stages highlights the significance of regular screening. By detecting CRC at an early stage or precancerous lesions, screening can facilitate timely interventions prior to the onset of symptoms.

1.2.3. Colorectal precancerous lesions are detectable and screening tools are available

CRC screening enables the detection of not only CRC but also precancerous lesions, particularly adenomatous polyps. Currently the two most common CRC screening methods are colonoscopy and faecal occult blood tests (FOBT). Colonoscopy, considered the gold standard,

provides direct visualization of the colon, allowing for the identification and removal of abnormal lesions during the procedure. FOBT, a less invasive alternative, detects occult blood in the stool, which indicates the presence of early-stage cancer or precancerous lesions. Individuals with a positive FOBT result are often referred to undergo a follow-up colonoscopy for the removal of abnormal lesions. Timely detection and removal of these lesions contribute to a reduced risk of invasive cancer and improved prognosis.[25,31]

1.2.4. CRC screening improves survival and reduces mortality

The early detection of localized CRC through screening enhances treatment effectiveness and increases chances of favourable outcomes. Additionally, screening aims to identify and remove precancerous lesions before they progress into invasive cancer, leading to improved overall survival rates and reduced mortality and incidence rates of CRC over time at the population level.[32,33]

CRC screening serves as an effective preventive intervention and plays a crucial role in improving CRC survival rates, as evidenced by the substantial difference in 5-year survival rate between stage I (96%) and stage IV CRC (19%) (statistics in Flanders) (**Figure 2**).[34] The implementation of population-based screening has demonstrated a notable reduction in CRC-related mortality.[35-40] The guaiac FOBT (gFOBT) has shown a mortality reduction of 14-16%.[35-38,41,42] More recently, the faecal immunochemical test (FIT) has been introduced as a superior screening method, offering enhanced sensitivity, a user-friendly sampling design and quantitative test results.[43,44] Observational studies have shown that FIT can reduce CRC mortality by 8.8%-52% over a period of 7-16 years.[39,40]

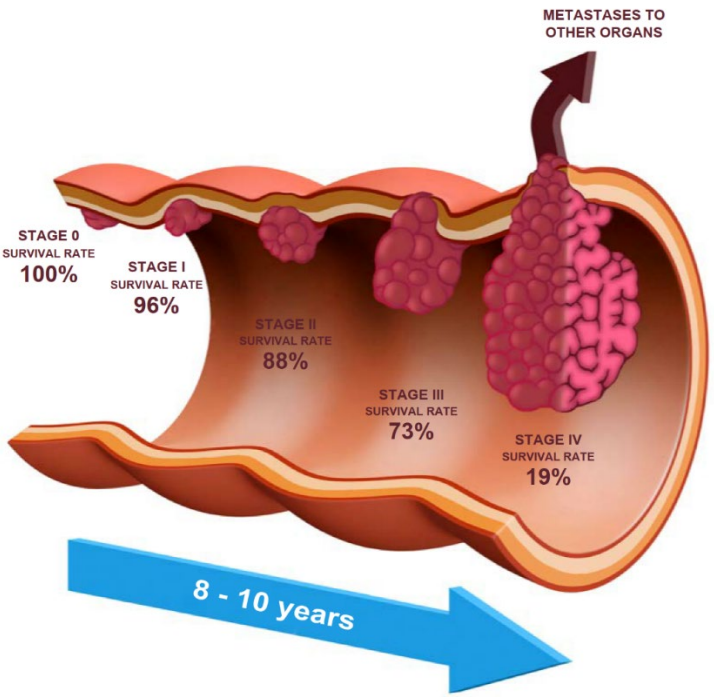


Figure 2. The 5-year relative survival of colorectal cancer by stage in Flanders. (Source of image: Centre for Cancer Detection[34])

1.2.5. CRC screening is cost-effective

Cost-effectiveness analyses have consistently supported the benefits of early detection, prevention of advanced CRC, and improved treatment outcomes, demonstrating that the benefits outweigh the costs of CRC screening. Detecting and managing CRC at an early stage is generally more cost-effective than treating advanced-stage cancer.[45-47] By implementing efficient screening strategies, healthcare systems can optimize resource allocation and maximize the impact on population health while minimizing financial burdens.

According to the principles for population screening outlined by the World Health Organization (WHO), the implementation of screening programmes should be based on a favourable cost-benefit balance.[48] In most developed countries, an acceptable threshold is set at an incremental cost of $50,000 or less per an additional year of life gained.[49] For CRC screening, all the established screening strategies have consistently demonstrated cost-effectiveness ratios below $50,000 per life-year gained when compared to no screening. For example, a systematic review focussing on CRC screening in the US reported cost-effectiveness estimates ranging from

$5,691 to $17,805 per life-year gained for gFOBT, $12,477 to $39,359 for sigmoidoscopy, $13,792 to $22,518 for the combination of gFOBT and sigmoidoscopy, and $9,038 to $22,012 for colonoscopy screening.[46] In Europe, the cost-effectiveness of CRC screening using stool-based test (gFOBT and FIT) has demonstrated even more favourable results, with cost-effectiveness ratios mostly below $10,000 per life-year gained.[50-54]

1.3. Progress and adoption of population-based CRC screening in Europe

In the light of increasing evidence of the benefits and cost-effectiveness of CRC screening,[35,36,38,46,54-56] the Council of the European Union (EU) has urged the member states since 2003 to establish population-based CRC screening programmes, accompanied by quality assurance measures.[57] While several effective screening options exist and have demonstrated cost-effectiveness compared to no screening, their specific cost-effectiveness varies depending on factors such as background risk, screening protocol, targeted age range, programme organisation and acceptability of the methods.[45,58] These factors have contributed to variations in screening policies across programmes. The first report on CRC screening in the EU (2008) revealed that as of 2008, population-based CRC screening programmes had been introduced in only 12 member states, with most programmes still in early rollout or pilot phases.[59]

In 2010, the European Commission released comprehensive guidelines on quality assurance in CRC screening and diagnosis.[58] These guidelines, along with a written declaration on the fight against CRC issued in November 2010,[58,60] recommended the establishment of population-based screening programmes for CRC by EU member states. Experts widely supported the use of FOBT as the first-line screening test in the CRC screening programmes.

Following the publication of the EU guidelines for quality assurance in CRC screening and diagnosis published in 2010,[58] the European Commission funded a second report on cancer screening programmes in the member states.[61] Published in 2017, this report provided updated information on the status and organisation of population-based cancer screening, while gathering quantitative data for comparative evaluation of programme performance across countries and regions, using the quality indicators outlined in the guidelines. By 2017, a total of 23 countries/regions had implemented a population-based CRC screening programme, mostly using stool-based tests (gFOBT or FIT) as the primary screening method and total colonoscopy as the follow-up method after a positive gFOBT/FIT result.[61,62]

1.4. Implementation of population-based CRC screening in Flanders

1.4.1. The call for implementing a population-based CRC screening programme in Flanders

In February 2007, the Flemish Government called for a pilot CRC screening programme to assess the feasibility and potential benefits of implementing CRC screening among individuals aged 50-74 years in Flanders.[63] Prior to this, Flanders had established a breast cancer screening programme since 2001, but its participation rate was relatively low at around 48% compared to neighbouring countries.[64,65] The effectiveness of any screening programme relies greatly on the participation rate.[66] Given the suboptimal participation rate in the existing breast cancer screening programme, there were uncertainties about the response of the target population to the invitation to participate in the pilot CRC screening programme. Additionally, Flanders had limited experience with men and women collecting their own stool samples for CRC screening, as previous experiences primarily focused on women and breast cancer screening. The sensitive nature of stool sample collection raised concerns about the acceptability and feasibility of this procedure among the target population.

Therefore, a pilot CRC screening programme was necessary in Flanders to gain insights into the potential participation rate in general, and when utilizing specific invitation strategies such as sending the test kit to individuals' home via mail or through their GP. Additionally, it was crucial to investigate individuals' attitudes towards the process of self-administered stool sampling, examining whether it would be viewed as a challenging and inconvenient or as straightforward and user-friendly task. The perception of stool sample collection as a taboo could significantly impact the participation rate.[64]

1.4.2. Test selection for population-based CRC screening in Flanders

While colonoscopy is the predominant method for CRC screening in the United States (US),[67] it is not recommended for population-based CRC screening in European countries for various reasons, including limited endoscopic capacity,[68,69] insufficient evidence from randomized trials,[57] and the population's preference for non-invasive screening alternatives.[70,71] Additionally, the decision-making process for developing screening guidelines and policies differs between the US and Europe. In the US, guidelines have been issued by professional

societies and organisations, which prioritize effectiveness, without taking into account financial constraints or resources availability.[72,73] In contrast, many European countries rely on national bodies to make and implement decisions, obliging them to consider a broader set of factors including capacity, costs, available resources and the effectiveness of alternative screening options.[45]

To date, the EU guidelines have recommended only FOBT for CRC screening.[58] In the planning phase of the pilot CRC screening programme in Flanders around 2008, randomised controlled trials (RCTs) had provided substantial evidence of the effectiveness of gFOBT in reducing CRC-related mortality by 14-16%.[35-38,41,42] However, evidence regarding the impact of FIT on CRC-related mortality was limited to observational studies.[74-76] Nevertheless, population-based screening studies consistently demonstrated that FIT exhibited significantly higher sensitivity for advanced adenomas and CRC compared to gFOBT.[77-83] FIT also offers other advantages over gFOBT, including better specificity for human haemoglobin, no dietary or medication restrictions, the requirement of only one sample, and the ability to adjust positivity rates based on quantitative results.[70,80-82,84,85] In contrast, gFOBT requires the collection of three consecutive samples, involves a cumbersome stool sampling process, and imposes dietary restrictions. As a result, FIT was reported to yield significant higher participation rates compared to gFOBT in RCTs.[70,83-85]

Following a thorough evaluation,[86] the Belgian Superior Health Council recommended the adoption of FIT over gFOBT for population-based CRC screening in Flanders. This preference for FIT was based on its superior attributes, including a more user-friendly sampling process, higher participation rates, increased sensitivity for advanced adenomas and CRC, and improved cost-effectiveness. Among the available immunochemical tests for CRC screening programmes in Europe at the time, OC Sensor was chosen over FOB Gold due to its extensive testing, widespread usage, significantly higher sensitivity, and better test stability. To achieve an optimal balance between test performance and colonoscopy capacity, and taking costs into account, a one-sample FIT (OC Sensor; Eiken, Japan) with a cut-off value of approximately 20 µg Hb/g (15-25 µg Hb/g) was recommended to attain a positive test rate of 3-5%.[86]

1.4.3. Comparison of invitation strategies: sending the test kit via mail or GPs

The pilot study to assess the feasibility of implementing population-based CRC screening in

Flanders was conducted in 2009.[63] Two invitation strategies were compared: direct mail invitations with a FIT kit (mail-group) and invitations without a FIT kit, followed by kit provision at the GP's office (GP group). The FIT kit was provided free of charge, while the cost of GP consultation was charged to the participant (with a personal contribution ranging from 4 to 6 EUR after health insurance). The participation rate was significantly higher in the mail-group (52.3%) than in the GP-group (27.7%). Barriers to participation in the GP-group might include the need to schedule an appointment with GP, travel distance, consultation cost, waiting time, and lack of a regular GP. However, obtaining the FIT kit at GP's office after receiving the invitation letter allowed for additional screening information from the GP such as medical exclusion criteria, test explanation, the screening process, possible test results and follow-up procedures.[63]

When the two invitation strategies were combined, the pilot CRC screening programme achieved a response rate of 42%, slightly below the minimum acceptable rate of 45% recommended by the EU guidelines, which was considered promising.[58] Given the significantly higher response rate in the group that received the FIT kit directly included in the mailed invitation, compared to the group that received the FIT kit at the GP's office, the Flemish CRC screening programme decided to adopt this strategy for sending screening invitations in the official programme.

1.4.4. Public perception of stool testing for CRC screening in the Flemish population

In addition to assessing participation rates based on different invitation strategies (FIT kit sent via mail or at GP's office), the Flemish pilot CRC screening programme aimed to investigate the perception of the Flemish population towards self-administered stool sampling for CRC screening.[64] If stool sampling was perceived as a sensitive or taboo subject, it could have a negative impact on participation rates. However, the results indicated that the process of obtaining a stool sample using FIT was well-accepted among the Flemish population, as 90% of respondents found it easy to perform.

Regarding the need for professional guidance, while the mail group relied primarily on an information leaflet and written test instructions for practical guidance on using the test, 94% of this group found the screening materials clear and convincing, and were motivated to participate. Additionally, 65% expressed satisfaction with receiving the FIT kit by mail. Only a

small percentage (8%) desired additional guidance from their GP on obtaining the stool sample.[64]

Non-participants cited various reasons for their decision not to participate, including feeling healthy without complaints (25%), absence of cancer cases in their neighbourhood (9%), or a preference for private examinations with a physician (8%). Only 5% found obtaining a stool sample to be bothersome, 1% considered it impractical, and 3% expressed fear of test results.[64]

These findings suggest that the FIT was perceived as a user-friendly stool sampling device, and stigma related to stool sampling was not apparent in the Flemish population.[64]

1.4.5. Gradual expansion of target screening ages in the Flemish CRC screening programme

Flanders adheres to the EU guidelines by implementing CRC screening for individuals aged 50-74 years.[58] However, due to the large size of the target population, the screening programme was introduced gradually. The target screening age range was expanded over time as follows: 2013: 66–74 years (even ages only); 2014: 56–74 years (even ages only); 2015–2016: 56–74 years; 2017: 55–74 years; 2018: 53–74 years; 2019: 51–74 years; 2020: 50–74 years. This phased approach has also been adopted by other CRC screening programmes, such as those in the Netherlands[87] and Finland.[88]

Unlike in certain countries where phased rollouts were driven by the need to increase colonoscopy capacity gradually,[89,90] Flanders did not encounter colonoscopy capacity challenges. A simulation evaluation was conducted to assess the adequacy of the available capacity in Flanders for performing colonoscopies after a positive FIT result from the CRC screening programme.[91] The simulation employed parameters based on findings from the prior pilot study,[91] including a participation rate of 40%, a test positive rate of 5.3%, and a follow-up colonoscopy rate of 85.5%, along with the size of the Flemish target population of 1.9 million, number of 320 gastroenterologists at the time of assessment. The findings indicated that approximately 1.2 extra colonoscopies per gastroenterologist per week would be required, and all the gastroenterologists involved in this evaluation confirmed that this capacity requirement was highly achievable in Flanders.[91] The decision to adopt a phased rollout in Flanders resulted from two main reasons: 1) The extensive administrative process delayed the launch of the official programme until October 2013, allowing for only a three-month implementation period

for the first year (2013), thereby limiting the initial inclusion to a small population; 2) A phased approach enabled better financial and practical preparations.

1.4.6. Implementation of the screening programme in October 2013

The Flemish population-based CRC screening programme was officially implemented in October 2013 by the Centre for Cancer Detection (CCD) after completing all the necessary preparations. The programme provides a free FIT kit (mailed) every two years to eligible individuals aged 50-74 years, with a phased implementation based on age (see **Section 1.4.5**). Exclusions from screening invitations include individuals with a validated CRC diagnosis (based on both hospital and laboratory data) in the past 10 years, a CRC diagnosis based only on laboratory results in the past 3 years, a stool test in the past 2 years, a virtual colonoscopy in the past 4 years, a complete colonoscopy in the past 10 years, or a total colectomy (excluded permanently).[92]

The invitation package includes an invitation letter, an information leaflet providing general details about the CRC screening programme, a participation form, a FIT kit containing collection paper and user instructions, product information in three official national languages (Dutch, French, and German), a bag, and a prepaid return envelope with a pre-printed laboratory address (**Figure 3**). Upon participation, individuals submit a stool sample for analysis to measure human haemoglobin levels. Both the FIT kit and laboratory analyses are provided free of charge. Ten weeks after the initial invitation, non-participants receive a reminder letter (without a FIT kit) either by email if the person has a valid email address in the programme's database or by post otherwise.[92]

Figure 3. The invitation package of the Flemish population-based CRC screening programme. (Source of image: Centre for Cancer Detection[93])

The positivity cut-off of FIT for the previous OC Sensor test was set at 15 µg Hb/g, while the current FOB Gold test (starting from February 2021) has a cut-off of 8.5 µg Hb/g. After sample analysis, participants and their GPs receive screening results within 10 calendar days. While the EU guidelines recommend a maximum time of 15 calendar days between the test and result receipt,[58] the CCD has applied a stricter norm of maximum 10 days to ensure faster delivery of results to participants, particularly in cases of a positive result, enabling timely follow-up if necessary. In 2021, nearly all participants (99.6%) in Flanders receive their results within 10 calendar days after screening participation.[94] Individuals with a positive FIT result are advised to undergo a colonoscopy. They have the option to be referred by their GP or directly schedule an appointment with a preferred gastroenterologist. The Belgian health insurance provides partial reimbursement for the cost of a diagnostic colonoscopy, with individuals covering the

remaining expenses (mean average of 85 EUR, accounting for about 13% of the total amount).[95] During the colonoscopy, any detected polyps and adenomas are removed if feasible and biopsied if needed. Participants who have a negative colonoscopy after a positive FIT result are exempt from FIT screening for the next 10 years. Histological findings from biopsies or removed lesions during the colonoscopy procedure are recorded by the Belgian Cancer Registry (BCR).[92]

1.4.7. Health economic analysis to evaluate the cost-effectiveness of the Flemish CRC screening programme

The first cost-effectiveness evaluation for the Flemish CRC screening programme was conducted in 2015.[96] This evaluation employed a two-part health economic model: a screening model including the various steps of CRC screening and a Markov model projecting the natural progression of CRC in individuals aged 50+ over a 20-year period. A comparison was made between scenarios with and without population-based CRC screening. The effectiveness of screening was measured using quality-adjusted life-years (QALYs). The primary outcome of the analysis was the Incremental Cost-Effectiveness Ratio (ICER), calculated by the difference in costs between the screening and no screening scenarios over 20 years, divided by the difference in QALYs. Additionally, the relative reduction in CRC-related mortality resulting from the implementation of population-based screening over the same 20-year period was estimated.

According to the simulation model, the Flemish CRC screening programme would save 0.012 QALYs per man aged 50+ and 0.005 QALYs per woman aged 50+, with incremental costs of €23 and €20, respectively. Thus, the cost-effectiveness ratio for the programme, compared to no screening, would be €1,912/QALY for men and €3,851/QALY for women over 20 years. Furthermore, the programme was expected to lead to a 23% reduction in CRC-related mortality for men and a 19% reduction for women over the same 20-year timeframe. The implementation of population-based screening would result in a shift in the distribution of detected CRCs, with a higher proportion of CRCs detected at stage I and a lower proportion at stage II, III, and IV. Initially, the programme would detect more cancers, but after approximately 8 years, the number of detected tumours would decrease to a lower level compared to no screening. The impact of the programme was anticipated to be more pronounced in men due to their higher CRC prevalence and incidence compared to women.[96]

The findings suggest that the Flemish CRC screening programme is highly cost-effective and would bring about a significant decrease in CRC-related mortality. It was anticipated that the actual outcomes would even exceed the estimates provided by the simulation model. This is because the model slightly underestimated the number of detected cancers, as it only considered the prevalence of polyps identified within the screening programme and did not account for those identified outside the programme. As a result, there might be an underestimation of the true number of polyps.

1.4.8. Results from the first round of the Flemish population-based CRC screening programme

The results of the first round of population-based CRC screening in Flanders during the 2013 start-up period, including participation rate, FIT positivity rate, colonoscopy compliance following a positive FIT, and follow-up outcomes, were published in 2016.[92] In this first round, individuals aged 66, 68, 70, 72 and 74 years were invited for screening. The participation rate was 48.4%, exceeding the minimum acceptable rate of 45% recommended by the EU guidelines.[58]

The positive predictive value (PPV) for invasive CRCs was 8.2%, falling within the expected range for population-based CRC screening programme.[58] However, the overall FIT positivity rate was 10.1%, with a detection rate of 6.6‰ for invasive CRCs. The PPV for advanced adenomas was 16.9% and for non-advanced adenomas was 36.5%. The detection rates for advanced and non-advanced adenomas were 13.6‰ and 29.8‰, respectively. These values are higher compared to the results from other population-based programmes.[58] It is important to consider that these indicators tend to be higher in the first screening round and among first-time participants due to a greater number of prevalent cases.[97] Additionally, the first round of the Flemish CRC screening programme targeted only older individuals (66-68-70-72-74 years), whose positivity rates are higher than the younger populations.[92,98] Moreover, it should be noted that the reported PPV and detection rates for 'adenomas' in CRC screening programmes may not always specify whether they include only advanced adenomas or both advanced and non-advanced adenomas together. The follow-up colonoscopy rate for individuals with a positive FIT result in the first round was 78.1%, below the acceptable threshold of 90% recommended by EU guidelines.[58,92]

1.5. Research gaps

1.5.1. The need for a comprehensive scientific evaluation of the impact of the Flemish CRC screening programme, particularly on mortality

While the 2015 simulation study suggested that the Flemish population-based CRC screening programme is highly cost-effective and could significantly reduce CRC-related mortality,[96] it is important to acknowledge that the study relied on several assumptions and data outside of Flanders. To accurately assess the programme's outcomes, actual data is needed to determine if the observed outcomes align with the initial estimations and expectations. This simulation study estimated a 23% reduction in CRC-related mortality for men and 19% reduction for women over a 20-year period following the implementation of population screening. The CRC incidence was projected to decrease below the level observed without screening after 8 years. Moreover, it was anticipated that the actual outcomes would surpass the model's estimations, as the model only considered polyps identified within the screening programme and not those outside, potentially leading to an underestimation of the true number of polyps.[96]

In addition, since 2019, the Belgian Cancer Registry, in collaboration with the Centre for Cancer Detection, has conducted an annual descriptive analysis to examine the evolution of CRC incidence in Flanders following the implementation of organised screening. The findings from the descriptive analysis already indicated positive trends, with an initial surge followed by a significant decline in CRC incidence and a shift towards earlier stages, affirming the effectiveness of CRC screening in detecting a greater number of CRC cases at an earlier stage.[99] However, a more comprehensive scientific evaluation of the programme's impact on CRC incidence, mortality and survival was planned, awaiting a longer follow-up period. It has been suggested that a comprehensive evaluation of the effectiveness of a population-based CRC screening programme should cover a minimum period of 4-10 years.[100] In Flanders, as of 2021, CRC incidence data was available until 2019, and mortality data until 2018, allowing for a thorough analysis of the impact of the CRC screening programme over a 5-6-year period after its initiation (see **Chapter 2**).

The impact of population-based CRC screening programmes can vary across countries and regions due to differences in screening uptake, background rate, follow-up duration, and FIT cut-off values. For instance, Spain reported a 9% reduction in CRC mortality after 7 years of

biennial FIT screening (cut-off 20 µg Hb/g),[39] Northern California achieved a 52% reduction after 16 years of annual FIT screening (cut-off 20 µg Hb/g),[40] while the Netherlands did not observe a significant reduction after 6 years of biennial FIT screening (cut-off 47 µg Hb/g).[101] Several countries and regions without CRC screening programmes are planning their implementation in the near future.[102,103] Thus, investigating the impact of the Flemish CRC screening programme, with its specific characteristics, would provide valuable evidence for enhancing existing screening strategies and guiding the initiation of new programmes.

1.5.2. Maximizing response rate in organised CRC screening in Flanders: exploring outside FOBT screening, inconsistent participation, and population preferences

The effectiveness of population-based CRC screening relies not only on the use of proper screening tests but also on achieving high participation rates among the target population. The Flemish CRC screening programme, like others, has made continuous efforts to enhance screening uptake to ensure more people can benefit from timely CRC detection, improved treatment, and better prognosis, which can ultimately lead to a reduction in CRC-related morbidity and mortality at the population level.

Since the implementation of the Flemish CRC screening programme, the response rate has consistently remained around 50%, except for a higher rate of 54.6% in 2016 for unknown reasons and a lower rate of 48.7% in 2020 due to the COVID-19 pandemic (**Figure 4**).[94,104-110] Breaking the stagnation of these figures and expanding the reach of the population CRC screening present significant challenges. Prior to this PhD, a quantitative study investigated the demographic and socioeconomic characteristics of screening non-participants, complemented by a qualitative focus group study exploring the barriers and facilitators to CRC screening.[111,112] Based on the findings of these studies, several measures were implemented, such as simplifying the participation form to reduce participant burden, utilizing infographics to present screening information, and emphasizing the importance of screening even in the absence of symptoms. However, the impact of these measures on screening uptake has been limited thus far.

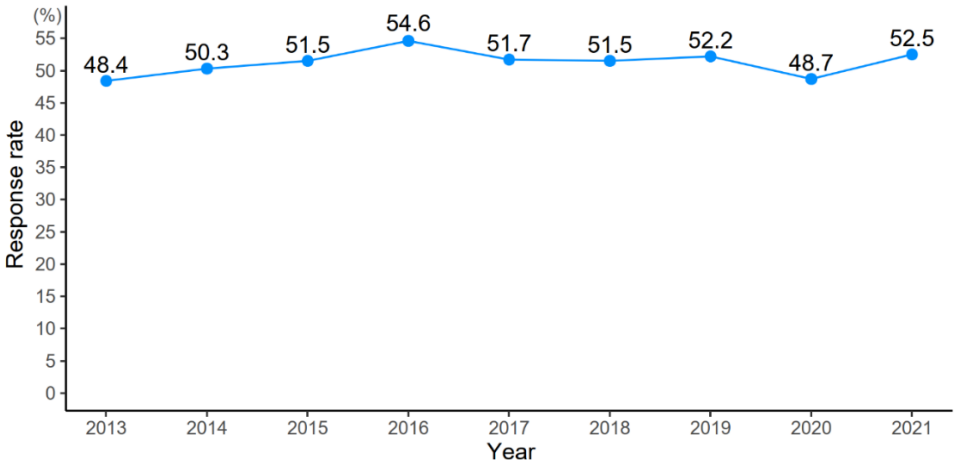


Figure 4. Response rates of population-based colorectal cancer screening in Flanders during 2013-2021 (Source of data: Centre for Cancer Detection[94,104-110])

Considering the importance of improving response rate in Flanders, this PhD research further investigates the topic by enhancing study methodologies and exploring screening non-participation from alternative perspectives.

Regarding research methodology improvement, the previous quantitative study that investigated the demographic and socioeconomic characteristics of non-participants was unable to consider several important factors such as education level and health-related determinants due to data unavailability. However, we have recently discovered a valuable source, the 'Provincie In Cijfers' databank, which provides readily available area-level data on various demographic, socioeconomic and health-related factors. Many of these factors are provided at the statistical sector level, closely approximating the individual level.[113] Notably, this databank contains data on education level and health-related factors such as GP visits, disabilities, and chronic diseases, which have been shown in the literature to be associated with cancer screening participation.[111,114-118] Building upon this discovery, we proposed linking the data on demographic, socioeconomic, and health-related factors from the 'Provincie In Cijfers' databank with screening data from the CCD to provide a better understanding of the relationships between demographic, socioeconomic and health-related characteristics and patterns of CRC screening (see **Chapter 3**).[113,119]

To gain insights into the response rate of the Flemish CRC screening programme from alternative perspectives, this PhD research investigated three specific areas. Firstly, an analysis

was conducted to examine CRC screening using FOBTs outside the organised screening programme (see **Chapter 3**). This was done because screening outside the programme could potentially have a negative impact on participation rates within the programme. Additionally, it also raised concerns about cost, lack of systematic result registration, follow-up information, and quality assurance. Flanders possesses a unique advantage of having data on GP-prescribed FOBTs outside the screening programme, which is registered through nomenclature codes used in health insurance claims. The objective of our analysis was to identify factors associated with the use of FOBTs outside the screening programme and explore their interrelationships with screening participation within the programme.

Secondly, previous research focused primarily on non-participation in general, with comparatively less attention given to the phenomenon of inconsistent participation within individuals. Exploring the motives behind individuals' decisions to opt-in or opt-out of screening, particularly their transition from non-participation in the previous round to participation in the current round, or vice versa, presented an intriguing area of investigation. Prior research conducted outside Flanders has identified procrastination, fear of cancer, and a lack of awareness regarding the importance of repeat screening as key factors influencing CRC screening adherence.[120-122] It is important to recognise that the reasons for inconsistent participation in CRC screening are influenced by local context and culture. Therefore, conducting a study among inconsistent participants in Flanders would provide valuable knowledge about this phenomenon within the specific regional context (see **Chapter 4**).

Thirdly, while most decisions regarding the organisation of CRC screening in Flanders, such as the selection of primary screening test, follow-up method, screening interval, and dissemination of screening information, have mainly been based on expert opinions and scientific evidence, limited consideration has been given to the preference of the general population regarding CRC screening tests and the delivery of screening information. To address this gap, the first step would involve conducting a comprehensive review of recent evidence on the general population's acceptance and perceptions of both conventional and emerging CRC screening tests (see **Chapter 5**). The findings from this review would provide valuable insights for improving the participation rate of the Flemish CRC screening programme. Previous research has shown that individual preferences for a specific test significantly influence their decision to participate.[123,124] Several factors play a role in this decision-making process,

including perceived test accuracy, invasiveness, discomfort, preparation requirements, pain, risk reduction, procedural complexity, costs, screening interval, embarrassment, and faecal aversion.[125,126] Notably, some individuals may choose to decline screening if their preferred test option is not available.[127,128] However, most population-based CRC screening programmes currently employ one single first-line test for the entire screening population.[43]

1.5.3. The potential of optimizing FIT cut-off and screening interval to address FIT interval cancers in the Flemish CRC screening programme

In the pursuit of improving screening uptake, the Flemish CRC screening programme has also recognised associated challenges, including an increase in the number of FIT interval cancers (FIT-IC). FIT-IC refers to CRC detected during the interval period between scheduled screenings when participants are expected to be protected by the screening programme. The occurrence of FIT-ICs is a significant quality indicator for FIT-based CRC screening programmes.[58]

FIT-IC is considered undesirable in the context of CRC screening. Previous studies have reported proportions of FIT-ICs ranging from 7% to 51% using FIT cut-offs between 10 and 80 µg Hb/g faeces in two-year interval programmes.[129-133] The presence of FIT-ICs indicates potential missed or undetected cancers during the screening process with FIT, which can result in delayed diagnosis and consequential impacts on patient outcomes, including advanced stages, increased disease burden, more invasive treatments, and reduced survival rates.[129,132,134]

Therefore, CRC screening programmes have made great efforts to understand the characteristics of FIT-ICs and reduce their occurrence. Previous research has identified specific subgroups, such as women[130,133,135,136] and older people,[135,137] who are at a higher risk of experiencing FIT-ICs. The use of a single FIT cut-off and screening interval for the entire screening population may lead to inequities among these subgroups. Consequently, studies have advocated for personalized approaches that individualize FIT cut-off and screening interval, aiming to promote equity and improve the effectiveness of FIT-based CRC screening programmes.[133,138-140]

The Flemish CRC screening programme, like other programmes, has strived to understand FIT-ICs and minimize their occurrence to enhance programme efficacy. While a prior study examined the characteristics of screen-detected and interval cancers within the programme, it was limited by data availability from October 2013 to July 2017, resulting in only univariable

analyses being performed without adjusting for potential confounders due to a small sample size.[135] To overcome this limitation, we aimed to utilize data covering a broader timeframe from October 2013 to December 2018 to investigate the factors associated with FIT-IC occurrence compared to screen-detected CRCs using multivariable logistic regression analyses where potential confounders could be adjusted, to validate the previous findings. More importantly, we sought to explore the impact of lowering the FIT cut-off or shortening the screening interval on reducing the occurrence of FIT-ICs within the Flemish CRC screening programme (see **Chapter 6**).

1.6. Objectives

This PhD research aims to achieve the following objectives:

- To evaluate the impact of the Flemish population-based CRC screening programme on CRC incidence, mortality and survival
- To investigate the suboptimal response rate of the Flemish population-based CRC screening programme by examining three key aspects: screening with outside FOBTs, reasons for inconsistent participation, and population's preferences for CRC screening
- To identify the characteristics of FIT interval cancers and explore potential strategies to optimize FIT cut-off and screening interval to reduce the occurrence of FIT interval cancers within the Flemish CRC screening programme

1.7. Thesis outline

The thesis is structured into seven chapters, each serving a specific purpose:

Chapter 1: Introduction

This chapter provides a comprehensive overview of CRC, CRC screening, and the implementation of population-based CRC screening in Europe, with a particular focus on the process of implementing the CRC screening programme in Flanders, Belgium. It also presents the research gaps that this PhD research aims to address and outlines the main objectives of the thesis.

Chapters 2 to 6: Individual research studies

These chapters consist of five individual studies grouped into three parts:

Part 1: Assessing the impact of the Flemish CRC screening programme (Chapter 2)

This quantitative study evaluates the impact of the Flemish population-based CRC screening programme on CRC incidence, mortality, and survival after six years of implementation.

Part 2: Investigating the suboptimal response rate of the programme (Chapters 3-5)

This part includes three studies that examine different aspects of the programme's suboptimal response rate:

- **Chapter 3**: A quantitative study investigating screening with outside FOBT, relative to screening with inside FIT.
- **Chapter 4**: A survey-based study exploring the motivations behind inconsistent screening participation.
- **Chapter 5**: A review of population's preferences for CRC screening

Part 3: Optimizing FIT interval cancers within the programme (Chapter 6)

This quantitative study identifies the characteristics of FIT interval cancers within the Flemish CRC screening programme and explores strategies to optimize FIT cut-off and screening interval to reduce the occurrence of FIT interval cancers within the programme.

Chapter 7: Discussion and conclusion

The final chapter, **Chapter 7**, presents a comprehensive discussion of the most important findings, their implications, and the considerations and limitations of the methodologies employed in the individual studies. It also includes thoughts on future perspectives for the Flemish CRC screening programme. This chapter concludes with key conclusions and recommendations based on the findings of this PhD research.

*It should be noted that the conceptualization, data collection and preliminary data analyses of the study presented in **Chapter 4** were conducted prior to this PhD research. However, during the course of this PhD, refinements were made to the methods of data analysis, result preparation, and result presentation to ensure suitability for the publication of the study's findings.*

1.8. Terminology clarification

To ensure accurate comparisons of response rate (also referred to as participation rate or screening uptake) and screening coverage among countries, establishing clear definitions and

calculation methods is crucial. In the Flemish CRC screening programme, the following definitions and calculation methods are used:

Response rate (participation rate, screening uptake) within 12 months after invitation for year 20XX:

- *Definition:* Response rate within 12 months after invitation for year 20XX is defined as the percentage of individuals invited for CRC screening in that year who participated within 12 months after the invitation date, out of the total number of individuals invited.
- *Method of calculation*:
    - ✓ Numerator: All invited individuals for CRC screening who participated within 12 months after the invitation date.
    - ✓ Denominator: All invited individuals for CRC screening.
    - ✓ Calculation: Response rate = (Numerator/Denominator) * 100

Coverage for year 20XX (within the screening programme):

- *Definition:* Coverage for year 20XX is defined as the percentage of individuals in the total target population (individuals aged 50-74 years in Flanders) who are covered by CRC screening through one of the following options:
    - ✓ Participating in the screening programme in 20XX or 20XX-1
    - ✓ Being excluded from screening invitation due to a validated CRC diagnosis based on both hospital and laboratory data (past 10 years), a CRC diagnosis based only on laboratory results (past 3 years), total colectomy, a complete (past 10 years) or virtual colonoscopy (past 4 years) after a positive FIT result within the screening programme.
    - ✓ Having had a validated CRC diagnosis based on both hospital and laboratory data (past 10 years), a CRC diagnosis based only on laboratory results (past 3 years), total colectomy, a complete (past 10 years) or virtual colonoscopy (past 4 years) that is not related to a prior positive FIT result within the screening programme.
- *Method of calculation*:
    - ✓ Numerator: all individuals in Flanders aged 50-74 years who are covered by CRC screening through one of the specific options listed above.
    - ✓ Denominator: all individuals in Flanders aged 50-74 years

- ✓ Calculation: Coverage = (Numerator/Denominator) * 100

The Centre for Cancer Detection issues an annual monitoring report of the Flemish CRC screening programme, presenting the main indicators, interpretations, and recommendations for programme improvement.[94] Detailed calculation methods for these indicators are also made publicly available.[141]

References

1. Sung, H., Ferlay, J., Siegel, R.L., Laversanne, M., Soerjomataram, I., Jemal, A. et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71:209-249.
2. Ferlay, J., Shin, H.R., Bray, F., Forman, D., Mathers, C. & Parkin, D.M. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer. 2010;127:2893-2917.
3. Pilleron, S., Sarfati, D., Janssen-Heijnen, M., Vignat, J., Ferlay, J., Bray, F. et al. Global cancer incidence in older adults, 2012 and 2035: A population-based study. Int J Cancer. 2019;144:49-58.
4. Dyba, T., Randi, G., Bray, F., Martos, C., Giusti, F., Nicholson, N. et al. The European cancer burden in 2020: Incidence and mortality estimates for 40 countries and 25 major cancers. Eur J Cancer. 2021;157:308-347.
5. Belgian Cancer Registry (2023). *Annual tables*, https://kankerregister.org/default.aspx?PageId=643 Accessed 30 June 2023.
6. International Agency for Research on Cancer (IARC). Belgium fact sheets. (2021).
7. Belgian Cancer Registry. Cancer Burden in Belgium. (Brussels, 2016).
8. Belgian Cancer Registry. Cancer fact sheet Colorectal cancer Belgium, Incidence year 2020. (Brussels, 2022).
9. Kelloff, G.J., Schilsky, R.L., Alberts, D.S., Day, R.W., Guyton, K.Z., Pearce, H.L. et al. Colorectal adenomas: a prototype for the use of surrogate end points in the development of cancer prevention drugs. Clin Cancer Res. 2004;10:3908-3918.
10. Rawla, P., Sunkara, T. & Barsouk, A. Epidemiology of colorectal cancer: incidence, mortality, survival, and risk factors. Prz Gastroenterol. 2019;14:89-103.
11. American Cancer Society. Colorectal Cancer Facts & Figures 2011-2013. (Atlanta: American Cancer Society, 2011).
12. Simon, K. Colorectal cancer development and advances in screening. Clin Interv Aging. 2016;11:967-976.
13. Williams, A.R., Balasooriya, B.A. & Day, D.W. Polyps and cancer of the large bowel: a necropsy study in Liverpool. Gut. 1982;23:835-842.
14. Fearon, E.R. & Vogelstein, B. A genetic model for colorectal tumorigenesis. Cell. 1990;61:759-767.
15. Pino, M.S. & Chung, D.C. The chromosomal instability pathway in colon cancer. Gastroenterology. 2010;138:2059-2072.
16. Satorres, C., Garcia-Campos, M. & Bustamante-Balen, M. Molecular Features of the Serrated Pathway to Colorectal Cancer: Current Knowledge and Future Directions. Gut Liver. 2021;15:31-43.
17. East, J.E., Atkin, W.S., Bateman, A.C., Clark, S.K., Dolwani, S., Ket, S.N. et al. British Society of Gastroenterology position statement on serrated polyps in the colon and rectum. Gut. 2017;66:1181-1196.
18. Yamane, L., Scapulatempo-Neto, C., Reis, R.M. & Guimaraes, D.P. Serrated pathway in colorectal carcinogenesis. World J Gastroenterol. 2014;20:2634-2640.
19. JE, I.J., Vermeulen, L., Meijer, G.A. & Dekker, E. Serrated neoplasia-role in colorectal carcinogenesis and clinical implications. Nat Rev Gastroenterol Hepatol. 2015;12:401-409.
20. Macken E. *Questions and answers about quality of colonoscopy in Belgium* Doctor of Medical Sciences thesis, University of Antwerp, (2022).
21. Waldock, A., Ellis, I.O., Armitage, N.C., Turner, D.R. & Hardcastle, J.D. Histopathological assessment of bleeding from polyps of the colon and rectum. J Clin Pathol. 1989;42:378-382.

22. Heigh, R.I., Yab, T.C., Taylor, W.R., Hussain, F.T., Smyrk, T.C., Mahoney, D.W. et al. Detection of colorectal serrated polyps by stool DNA testing: comparison with fecal immunochemical testing for occult blood (FIT). PLoS One. 2014;9:e85659.

23. Liu, H.T., Chen, S.Y., Peng, L.L., Zhong, L., Zhou, L., Liao, S.Q. et al. Spatially resolved transcriptomics revealed local invasion-related genes in colorectal cancer. Front Oncol. 2023;13:1089090.

24. Brierley, J.D., Gospodarowicz, M.K. & Wittekind, C. (eds). *TNM Classification of Malignant Tumours*. 8th edn, (John Wiley & Sons, Inc.: Oxford, UK ; Hoboken, NJ, 2017).

25. Kuipers, E.J., Grady, W.M., Lieberman, D., Seufferlein, T., Sung, J.J., Boelens, P.G. et al. Colorectal cancer. Nat Rev Dis Primers. 2015;1:15065.

26. Astin, M., Griffin, T., Neal, R.D., Rose, P. & Hamilton, W. The diagnostic value of symptoms for colorectal cancer in primary care: a systematic review. Br J Gen Pract. 2011;61:e231-243.

27. Ford, A.C., Veldhuyzen van Zanten, S.J., Rodgers, C.C., Talley, N.J., Vakil, N.B. & Moayyedi, P. Diagnostic utility of alarm features for colorectal cancer: systematic review and meta-analysis. Gut. 2008;57:1545-1553.

28. Jellema, P., van der Windt, D.A., Bruinvels, D.J., Mallen, C.D., van Weyenberg, S.J., Mulder, C.J. et al. Value of symptoms and additional diagnostic tests for colorectal cancer in primary care: systematic review and meta-analysis. BMJ. 2010;340:c1269.

29. Adelstein, B.A., Macaskill, P., Chan, S.F., Katelaris, P.H. & Irwig, L. Most bowel cancer symptoms do not indicate colorectal cancer and polyps: a systematic review. BMC Gastroenterol. 2011;11:65.

30. Olde Bekkink, M., McCowan, C., Falk, G.A., Teljeur, C., Van de Laar, F.A. & Fahey, T. Diagnostic accuracy systematic review of rectal bleeding in combination with other symptoms, signs and tests in relation to colorectal cancer. Br J Cancer. 2010;102:48-58.

31. Stracci, F., Zorzi, M. & Grazzini, G. Colorectal cancer screening: tests, strategies, and perspectives. Front Public Health. 2014;2:210.

32. Lee, Y.C., Hsu, C.Y., Chen, S.L., Yen, A.M., Chiu, S.Y., Fann, J.C. et al. Effects of screening and universal healthcare on long-term colorectal cancer mortality. Int J Epidemiol. 2019;48:538-548.

33. Zorzi, M., Fedeli, U., Schievano, E., Bovo, E., Guzzinati, S., Baracco, S. et al. Impact on colorectal cancer mortality of screening programmes based on the faecal immunochemical test. Gut. 2015;64:784-790.

34. Centre for Cancer Detection (Population-based colorectal cancer screening) *Advantages [Voordelen]*, https://dikkedarmkanker.bevolkingsonderzoek.be/nl/ddk/voordelen Accessed 7 July.

35. Mandel, J.S., Bond, J.H., Church, T.R., Snover, D.C., Bradley, G.M., Schuman, L.M. et al. Reducing mortality from colorectal cancer by screening for fecal occult blood. Minnesota Colon Cancer Control Study. N Engl J Med. 1993;328:1365-1371.

36. Hardcastle, J.D., Chamberlain, J.O., Robinson, M.H.E., Moss, S.M., Amar, S.S., Balfour, T.W. et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. The Lancet. 1996;348:1472-1477.

37. Hewitson, P., Glasziou, P., Irwig, L., Towler, B. & Watson, E. Screening for colorectal cancer using the faecal occult blood test, Hemoccult. Cochrane Database Syst Rev. 2007;2007:CD001216.

38. Kronborg, O., Fenger, C., Olsen, J., Jørgensen, O.D. & Søndergaard, O. Randomised study of screening for colorectal cancer with faecal-occult-blood test. The Lancet. 1996;348:1467-1471.

39. Keys, M.T., Serra-Burriel, M., Martinez-Lizaga, N., Pellise, M., Balaguer, F., Sanchez, A. et al. Population-based organized screening by faecal immunochemical testing and colorectal cancer mortality: a natural experiment. Int J Epidemiol. 2021;50:143-155.

40. Levin, T.R., Corley, D.A., Jensen, C.D., Schottinger, J.E., Quinn, V.P., Zauber, A.G. et al. Effects of Organized Colorectal Cancer Screening on Cancer Incidence and Mortality in a Large Community-Based Population. Gastroenterology. 2018;155:1383-1391 e1385.

41. Heresbach, D., Manfredi, S., D'Halluin P, N., Bretagne, J.F. & Branger, B. Review in depth and meta-analysis of controlled trials on colorectal cancer screening by faecal occult blood test. Eur J Gastroenterol Hepatol. 2006;18:427-433.

42. Kerr, J., Day, P., Broadstock, M., Weir, R. & Bidwell, S. Systematic review of the effectiveness of population screening for colorectal cancer. N Z Med J. 2007;120:U2629.

43. Schreuders, E.H., Ruco, A., Rabeneck, L., Schoen, R.E., Sung, J.J., Young, G.P. et al. Colorectal cancer screening: a global overview of existing programmes. Gut. 2015;64:1637-1649.

44. Tinmouth, J., Lansdorp-Vogelaar, I. & Allison, J.E. Faecal immunochemical tests versus guaiac faecal occult blood tests: what clinicians and colorectal cancer screening programme organisers need to know. Gut. 2015;64:1327-1337.

45. Lansdorp-Vogelaar, I., Knudsen, A.B. & Brenner, H. Cost-effectiveness of colorectal cancer screening - an overview. Best Pract Res Clin Gastroenterol. 2010;24:439-449.

46. Pignone, M., Saha, S., Hoerger, T. & Mandelblatt, J. Cost-effectiveness analyses of colorectal cancer screening: a systematic review for the U.S. Preventive Services Task Force. Ann Intern Med. 2002;137:96-104.

47. Lin, J.S., Perdue, L.A., Henrikson, N.B., Bean, S.I. & Blasi, P.R. Screening for Colorectal Cancer: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA. 2021;325:1978-1998.

48. Wilson, J.M. & Jungner, Y.G. [Principles and practice of mass screening for disease]. Bol Oficina Sanit Panam. 1968;65:281-393.

49. Weinstein, M.C. How much are Americans willing to pay for a quality-adjusted life year? Med Care. 2008;46:343-345.

50. Berchi, C., Bouvier, V., Reaud, J.M. & Launoy, G. Cost-effectiveness analysis of two strategies for mass screening for colorectal cancer in France. Health Econ. 2004;13:227-238.

51. Lejeune, C., Arveux, P., Dancourt, V., Bejean, S., Bonithon-Kopp, C. & Faivre, J. Cost-effectiveness analysis of fecal occult blood screening for colorectal cancer. Int J Technol Assess Health Care. 2004;20:434-439.

52. Macafee, D.A., Waller, M., Whynes, D.K., Moss, S. & Scholefield, J.H. Population screening for colorectal cancer: the implications of an ageing population. Br J Cancer. 2008;99:1991-2000.

53. Whynes, D.K. & Nottingham, F.O.B.S.T. Cost-effectiveness of screening for colorectal cancer: evidence from the Nottingham faecal occult blood trial. J Med Screen. 2004;11:11-15.

54. Hristova, L. & Hakama, M. Effect of screening for cancer in the Nordic countries on deaths, cost and quality of life up to the year 2017. Acta Oncol. 1997;36 Suppl 9:1-60.

55. Gyrd-Hansen, D. The relative economics of screening for colorectal cancer, breast cancer and cervical cancer. Crit Rev Oncol Hematol. 1999;32:133-144.

56. Norum, J. Prevention of colorectal cancer: a cost-effectiveness approach to a screening model employing sigmoidoscopy. Ann Oncol. 1998;9:613-618.

57. The Council of the European Union (2003). *Council recommendation of 2 December 2003 on cancer Screening (2003/878/ec)*, https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2003:327:0034:0038:EN:PDF Accessed 30 June 2003.

58. Segnan, N., Patnick, J. & von Karsa, L. (eds). *European guidelines for quality assurance in colorectal cancer screening and diagnosis*. 1st edn, (Publications Office of the European Union: Luxembourg, 2010).

59. Cancer Screening in the European Union Report on the implementation of the Council Recommendation on cancer screening first report. (Brussel: European Communities, 2008).

60. Union, E. (2010). *Written declaration on the fight against bowel cancer in the European Union Declaration of the European Parliament of 25 November 2010 on fighting colorectal cancer in the European Union*, https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52010XP0451 2010.

61. Cancer Screening in the European Union (2017), Report on the implementation of the Council Recommendation on cancer screening. (Brussels: European Commission, 2017).

62. Senore, C., Basu, P., Anttila, A., Ponti, A., Tomatis, M., Vale, D.B. et al. Performance of colorectal cancer screening in the European Union Member States: data from the second European screening report. Gut. 2019;68:1232-1244.

63. Van Roosbroeck, S., Hoeck, S. & Van Hal, G. Population-based screening for colorectal cancer using an immunochemical faecal occult blood test: a comparison of two invitation strategies. Cancer Epidemiol. 2012;36:e317-324.

64. Van Hal, G., Hoeck, S. & Van Roosbroeck, S. Screening for colorectal cancer: sense and sensibilities. Eur J Cancer. 2011;47 Suppl 3:S156-163.

65. Otto, S.J., Fracheboud, J., Looman, C.W., Broeders, M.J., Boer, R., Hendriks, J.H. et al. Initiation of population-based mammography screening in Dutch municipalities and effect on breast-cancer mortality: a systematic review. Lancet. 2003;361:1411-1417.

66. Boyle, P., Autier, P., Bartelink, H., Baselga, J., Boffetta, P., Burn, J. et al. European Code Against Cancer and scientific justification: third version (2003). Ann Oncol. 2003;14:973-1005.

67. National Cancer Institute (NIH) (2017). *Low-Tech Outreach Methods Improve Colorectal Cancer Screening*, https://www.cancer.gov/news-events/cancer-currents-blog/2017/colorectal-cancer-screening-outreach Accessed 03 July 2017.

68. Macfarlane, B., Leicester, R., Romaya, C. & Epstein, O. Colonoscopy services in the United Kingdom. Endoscopy. 1999;31:409-411.

69. van Putten, P.G., van Leerdam, M.E. & Kuipers, E.J. The views of gastroenterologists about the role of nurse endoscopists, especially in colorectal cancer screening. Aliment Pharmacol Ther. 2009;29:892-897.

70. Hol, L., van Leerdam, M.E., van Ballegooijen, M., van Vuuren, A.J., van Dekken, H., Reijerink, J.C. et al. Screening for colorectal cancer: randomised trial comparing guaiac-based and immunochemical faecal occult blood testing and flexible sigmoidoscopy. Gut. 2010;59:62-68.

71. Segnan, N., Senore, C., Andreoni, B., Arrigoni, A., Bisanti, L., Cardelli, A. et al. Randomized trial of different screening strategies for colorectal cancer: patient response and detection rates. J Natl Cancer Inst. 2005;97:347-357.

72. Force, U.S.P.S.T., Davidson, K.W., Barry, M.J., Mangione, C.M., Cabana, M., Caughey, A.B. et al. Screening for Colorectal Cancer: US Preventive Services Task Force Recommendation Statement. JAMA. 2021;325:1965-1977.

73. Wolf, A.M.D., Fontham, E.T.H., Church, T.R., Flowers, C.R., Guerra, C.E., LaMonte, S.J. et al. Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society. CA Cancer J Clin. 2018;68:250-281.

74. Saito, H., Soma, Y., Koeda, J., Wada, T., Kawaguchi, H., Sobue, T. et al. Reduction in risk of mortality from colorectal cancer by fecal occult blood screening with immunochemical hemagglutination test. A case-control study. Int J Cancer. 1995;61:465-469.

75. Saito, H., Soma, Y., Nakajima, M., Koeda, J., Kawaguchi, H., Kakizaki, R. et al. A case-control study evaluating occult blood screening for colorectal cancer with hemoccult test and an immunochemical hemagglutination test. Oncol Rep. 2000;7:815-819.

76. Nakajima, M., Saito, H., Soma, Y., Sobue, T., Tanaka, M. & Munakata, A. Prevention of advanced colorectal cancer by screening using the immunochemical faecal occult blood test: a case-control study. Br J Cancer. 2003;89:23-28.

77. Rozen, P., Knaani, J. & Samuel, Z. Comparative screening with a sensitive guaiac and specific immunochemical occult blood test in an endoscopic study. Cancer. 2000;89:46-52.

78. Ko, C.W., Dominitz, J.A. & Nguyen, T.D. Fecal occult blood testing in a general medical clinic: comparison between guaiac-based and immunochemical-based tests. Am J Med. 2003;115:111-114.

79. Smith, A., Young, G.P., Cole, S.R. & Bampton, P. Comparison of a brush-sampling fecal immunochemical test for hemoglobin with a sensitive guaiac-based fecal occult blood test in detection of colorectal neoplasia. Cancer. 2006;107:2152-2159.

80. Allison, J.E., Sakoda, L.C., Levin, T.R., Tucker, J.P., Tekawa, I.S., Cuff, T. et al. Screening for colorectal neoplasms with new fecal occult blood tests: update on performance characteristics. J Natl Cancer Inst. 2007;99:1462-1470.

81. Guittet, L., Bouvier, V., Mariotte, N., Vallee, J.P., Arsene, D., Boutreux, S. et al. Comparison of a guaiac based and an immunochemical faecal occult blood test in screening for colorectal cancer in a general average risk population. Gut. 2007;56:210-214.

82. Dancourt, V., Lejeune, C., Lepage, C., Gailliard, M.C., Meny, B. & Faivre, J. Immunochemical faecal occult blood tests are superior to guaiac-based tests for the detection of colorectal neoplasms. Eur J Cancer. 2008;44:2254-2258.

83. van Rossum, L.G., van Rijn, A.F., Laheij, R.J., van Oijen, M.G., Fockens, P., van Krieken, H.H. et al. Random comparison of guaiac and immunochemical fecal occult blood tests for colorectal cancer in a screening population. Gastroenterology. 2008;135:82-90.

84. Hoffman, R.M., Steel, S., Yee, E.F., Massie, L., Schrader, R.M. & Murata, G.H. Colorectal cancer screening adherence is higher with fecal immunochemical tests than guaiac-based fecal occult blood tests: a randomized, controlled trial. Prev Med. 2010;50:297-299.

85. Rabeneck, L., Rumble, R.B., Thompson, F., Mills, M., Oleschuk, C., Whibley, A. et al. Fecal immunochemical tests compared with guaiac fecal occult blood tests for population-based colorectal cancer screening. Can J Gastroenterol. 2012;26:131-147.

86. Superior Health Council (2013). *Immunochemical Faecal Occult Blood Tests for Colorectal Cancer Screening*, https://www.health.belgium.be/sites/default/files/uploads/fields/fpshealth_theme_file/hgr_8901_advies_colorectaal.pdf Accessed 19 July 2013.

87. The National Institute for Public Health and the Environment (RIVM). Framework for the execution of the Dutch colorectal cancer screening programme. (BA Bilthoven, The Netherlands, 2021).

88. Finnish Cancer Registry (2022). *Colorectal cancer screening*, https://cancerregistry.fi/screening/colorectal-cancer-screening/#:~:text=The%20Government%20amended%20the%20Government,women%20aged%2060%E2%80%9368%20years. Accessed 04 July 2022.

89. National Institute for Public Health and the Environment. Lessons learned from the introduction of the colorectal cancer screening programme. (2020).

90. Malila, N., Anttila, A. & Hakama, M. Colorectal cancer screening in Finland: details of the national screening programme implemented in Autumn 2004. J Med Screen. 2005;12:28-32.

91. Hoeck, S., Van Roosbroeck, S. & Van Hal, G. Pilot project for population-based colorectal cancer screening [Pilootproject bevolkingsonderzoek naar dikkedarmkanker]. (2011).

92. Hoeck, S., Pringels, S., Kellen, E., Van Herck, K., Martens, P., Van Limbergen, E. et al. First results of the Flemish colorectal cancer screening program : start-up- period late 2013. Acta Gastroenterol Belg. 2016;79:421-428.

93. Centre for Cancer Detection (Population-based colorectal cancer screening) *How is colorectal cancer detected [Hoe wordt dikkedarmkanker opgespoord?]*, https://dikkedarmkanker.bevolkingsonderzoek.be/nl/ddk/hoe-wordt-dikkedarmkanker-opgespoord Accessed 07 July.

94. Centre for Cancer Detection (2022). *Monitoring report of the Flemish Colorectal Cancer Screening Programme 2022*, https://dikkedarmkanker.bevolkingsonderzoek.be/sites/default/files/2022-12/Jaarrapport%202022_0.pdf Accessed 9 July 2022.

95. Meeus, A. & Demyttenaere, B. Study colonoscopy [Studie colonoscopie]. (Nationaal Verbond van Socialistische Mutualiteiten: Sint-Jansstraat 32-38, 1000 Brussel 2020).

96. Fobelets, M. & Pil, L. The cost-effectiveness of population-based colorectal cancer screening in Flanders: a health economic evaluation [De kosteneffectiviteit van het bevolkingsonderzoek naar dikkedarmkanker in Vlaanderen: gezondheidseconomische evaluatie]. (2015).

97. Kapidzic, A., Grobbee, E.J., Hol, L., van Roon, A.H., van Vuuren, A.J., Spijker, W. et al. Attendance and yield over three rounds of population-based fecal immunochemical test screening. Am J Gastroenterol. 2014;109:1257-1264.

98. Rabeneck, L., Tinmouth, J.M., Paszat, L.F., Baxter, N.N., Marrett, L.D., Ruco, A. et al. Ontario's ColonCancerCheck: results from canada's first province-wide colorectal cancer screening program. Cancer Epidemiol Biomarkers Prev. 2014;23:508-515.

99. Belgian Cancer Registry. Addendum annual report Flemish population screenings 2019: Evolution of colorectal cancer incidence in Flanders 2004-2017 [Addendum Jaarfiche Vlaamse bevolkingsonderzoeken 2019: Evolutie incidentie van dikkedarmkanker Vlaanderen 2004-2017]. (Brussels, 2019).

100. Lee, S.J., Boscardin, W.J., Stijacic-Cenzer, I., Conell-Price, J., O'Brien, S. & Walter, L.C. Time lag to benefit after screening for breast and colorectal cancer: meta-analysis of survival data from the United States, Sweden, United Kingdom, and Denmark. BMJ. 2013;346:e8441.

101. Breekveldt, E.C.H., Lansdorp-Vogelaar, I., Toes-Zoutendijk, E., Spaander, M.C.W., van Vuuren, A.J., van Kemenade, F.J. et al. Colorectal cancer incidence, mortality, tumour characteristics, and treatment before and after introduction of the faecal immunochemical testing-based screening programme in the Netherlands: a population-based study. The Lancet Gastroenterology & Hepatology. 2021; 10.1016/s2468-1253(21)00368-x

102. Gini, A., Jansen, E.E.L., Zielonke, N., Meester, R.G.S., Senore, C., Anttila, A. et al. Impact of colorectal cancer screening on cancer-specific mortality in Europe: A systematic review. Eur J Cancer. 2020;127:224-235.

103. Cardoso, R., Guo, F., Heisser, T., Hackl, M., Ihle, P., De Schutter, H. et al. Colorectal cancer incidence, mortality, and stage distribution in European countries in the colorectal cancer screening era: an international population-based study. The Lancet Oncology. 2021;22:1002-1013.

104. Centre for Cancer Detection (2015). *Monitoring report of the Flemish Colorectal Cancer Screening Programme 2015*, https://dikkedarmkanker.bevolkingsonderzoek.be/sites/default/files/2022-03/Jaarrapport%202015.pdf Accessed 9 July 2015.

105. Centre for Cancer Detection (2016). *Monitoring report of the Flemish Colorectal Cancer Screening Programme 2016*, https://dikkedarmkanker.bevolkingsonderzoek.be/sites/default/files/2022-03/Jaarrapport2016.pdf Accessed 9 July 2016.

106. Centre for Cancer Detection (2017). *Monitoring report of the Flemish Colorectal Cancer Screening Programme 2017*, https://dikkedarmkanker.bevolkingsonderzoek.be/sites/default/files/2022-03/Jaarrapport2017.pdf Accessed 9 July 2017.

107. Centre for Cancer Detection (2018). *Monitoring report of the Flemish Colorectal Cancer Screening Programme 2018*, https://dikkedarmkanker.bevolkingsonderzoek.be/sites/default/files/2022-03/Jaarrapport%202018.pdf Accessed 9 July 2018.

108. Centre for Cancer Detection (2019). *Monitoring report of the Flemish Colorectal Cancer Screening Programme 2019*, https://dikkedarmkanker.bevolkingsonderzoek.be/sites/default/files/2022-03/Jaarrapport2019.pdf Accessed 9 July 2019.

109. Centre for Cancer Detection (2020). *Monitoring report of the Flemish Colorectal Cancer Screening Programme 2020*, https://dikkedarmkanker.bevolkingsonderzoek.be/sites/default/files/2022-03/Jaarrapport%202020_0.pdf Accessed 9 July 2020.

110. Centre for Cancer Detection (2021). *Monitoring report of the Flemish Colorectal Cancer Screening Programme 2021*, https://dikkedarmkanker.bevolkingsonderzoek.be/sites/default/files/2022-03/Jaarrapport%202021%20BVO%20naar%20kanker_0.pdf Accessed 9 July 2021.

111. Hoeck, S., Van Roy, K. & Willems, S. Barriers and facilitators to participate in the colorectal cancer screening programme in Flanders (Belgium): a focus group study. Acta Clin Belg. 2022;77:37-44.

112. Hoeck, S., van de Veerdonk, W., De Brabander, I. & Kellen, E. Does the Flemish colorectal cancer screening programme reach equity in FIT uptake? Eur J Public Health. 2019;29:1108-1114.

113. Data & Analysis of five Flemish provinces *Provinces in numbers [Provincies In Cijfers]*, https://provincies.incijfers.be/databank Accessed 07 July.

114. Kellen, E., Nuyens, C., Molleman, C. & Hoeck, S. Uptake of cancer screening among adults with disabilities in Flanders (Belgium). J Med Screen. 2020;27:48-51.

115. Shin, D.W., Chang, D., Jung, J.H., Han, K., Kim, S.Y., Choi, K.S. et al. Disparities in the Participation Rate of Colorectal Cancer Screening by Fecal Occult Blood Test among People with Disabilities: A National Database Study in South Korea. Cancer Res Treat. 2020;52:60-73.

116. Frederiksen, B.L., Jorgensen, T., Brasso, K., Holten, I. & Osler, M. Socioeconomic position and participation in colorectal cancer screening. Br J Cancer. 2010;103:1496-1501.

117. Wools, A., Dapper, E.A. & de Leeuw, J.R. Colorectal cancer screening participation: a systematic review. Eur J Public Health. 2016;26:158-168.

118. Fon Sing, M., Leuraud, K. & Duport, N. Characteristics of French people using organised colorectal cancer screening. Analysis of the 2010 French Health, Healthcare and Insurance Survey. Prev Med. 2013;57:65-68.

119. Centre for Cancer Detection (2023). *Population screening statistics [Bevolkingsonderzoek InCijfers]*, https://bevolkingsonderzoek.incijfers.be//jive?cat_open_code=ddk_extern Accessed 22 June 2023.

120. Green, B.B., BlueSpruce, J., Tuzzio, L., Vernon, S.W., Aubree Shay, L. & Catz, S.L. Reasons for never and intermittent completion of colorectal cancer screening after receiving multiple rounds of mailed fecal tests. BMC Public Health. 2017;17:531.

121. Christy, S.M., Schmidt, A., Wang, H.L., Sutton, S.K., Davis, S.N., Chavarria, E. et al. Understanding Cancer Worry Among Patients in a Community Clinic-Based Colorectal Cancer Screening Intervention Study. Nurs Res. 2018;67:275-285.

122. Duncan, A., Turnbull, D., Gregory, T., Cole, S.R., Young, G.P., Flight, I. et al. Using the Transtheoretical Model of Behaviour Change to describe readiness to rescreen for colorectal cancer with faecal occult blood testing. Health Promot J Austr. 2012;23:122-128.

123. Benning, T.M., Dellaert, B.G., Dirksen, C.D. & Severens, J.L. Preferences for potential innovations in non-invasive colorectal cancer screening: A labeled discrete choice experiment for a Dutch screening campaign. Acta Oncol. 2014;53:898-908.

124. Wong, M.C., Ching, J.Y., Chan, V.C., Lam, T.Y., Luk, A.K., Ng, S.C. et al. Informed choice vs. no choice in colorectal cancer screening tests: a prospective cohort study in real-life screening practice. Am J Gastroenterol. 2014;109:1072-1079.

125. Mansfield, C., Tangka, F.K., Ekwueme, D.U., Smith, J.L., Guy, G.P., Jr., Li, C. et al. Stated Preference for Cancer Screening: A Systematic Review of the Literature, 1990-2013. Preventing Chronic Disease. 2016;13:E27.

126. Cole, S.R., Zajac, I., Gregory, T., Mehaffey, S., Roosa, N., Turnbull, D. et al. Psychosocial variables associated with colorectal cancer screening in South Australia. Int J Behav Med. 2011;18:302-309.

127. Wolf, R.L., Basch, C.E., Zybert, P., Basch, C.H., Ullman, R., Shmukler, C. et al. Patient Test Preference for Colorectal Cancer Screening and Screening Uptake in an Insured Urban Minority Population. Journal of Community Health. 2016;41:502-508.

128. Chatrath, H. & Rex, D.K. Potential screening benefit of a colorectal imaging capsule that does not require bowel preparation. Journal of Clinical Gastroenterology. 2014;48:52-54.

129. Portillo, I., Arana-Arri, E., Idigoras, I., Bilbao, I., Martínez-Indart, L., Bujanda, L. et al. Colorectal and interval cancers of the Colorectal Cancer Screening Program in the Basque Country (Spain). World J Gastroenterol. 2017;23:2731-2742.

130. Zorzi, M., Fedato, C., Grazzini, G., Stocco, F.C., Banovich, F., Bortoli, A. et al. High sensitivity of five colorectal screening programmes with faecal immunochemical test in the Veneto Region, Italy. Gut. 2011;60:944-949.

131. Mlakar, D.N., Bric, T.K., Škrjanec, A.L. & Krajc, M. Interval cancers after negative immunochemical test compared to screen and non-responders' detected cancers in Slovenian colorectal cancer screening programme. Radiol Oncol. 2018;52:413-421.

132. van der Vlugt, M., Grobbee, E.J., Bossuyt, P.M.M., Bos, A., Bongers, E., Spijker, W. et al. Interval Colorectal Cancer Incidence Among Subjects Undergoing Multiple Rounds of Fecal Immunochemical Testing. Gastroenterology. 2017;153:439-447 e432.

133. Digby, J., Fraser, C.G., Carey, F.A., Lang, J., Stanners, G. & Steele, R.J. Interval cancers using a quantitative faecal immunochemical test (FIT) for haemoglobin when colonoscopy capacity is limited. J Med Screen. 2016;23:130-134.

134. Steel, M.J., Bukhari, H., Gentile, L., Telford, J. & Schaeffer, D.F. Colorectal adenocarcinomas diagnosed following a negative faecal immunochemical test show high-risk pathological features in a colon screening programme. Histopathology. 2021;78:710-716.

135. van de Veerdonk, W., Hoeck, S., Peeters, M., Van Hal, G., Francart, J. & De Brabander, I. Occurrence and characteristics of faecal immunochemical screen-detected cancers vs non-screen-detected cancers: Results from a Flemish colorectal cancer screening programme. United European Gastroenterol J. 2020;8:185-194.

136. Giorgi Rossi, P., Carretta, E., Mangone, L., Baracco, S., Serraino, D. & Zorzi, M. Incidence of interval cancers in faecal immunochemical test colorectal screening programmes in Italy. Journal of Medical Screening. 2017;25:32-39.

137. Selby, K., Jensen, C.D., Lee, J.K., Doubeni, C.A., Schottinger, J.E., Zhao, W.K. et al. Influence of Varying Quantitative Fecal Immunochemical Test Positivity Thresholds on Colorectal Cancer Detection: A Community-Based Cohort Study. Ann Intern Med. 2018;169:439-447.

138. Chiu, H.M., Lee, Y.C., Tu, C.H., Chen, C.C., Tseng, P.H., Liang, J.T. et al. Association between early stage colon neoplasms and false-negative results from the fecal immunochemical test. Clin Gastroenterol Hepatol. 2013;11:832-838 e831-832.

139. Steele, R.J., Stanners, G., Lang, J., Brewster, D.H., Carey, F.A. & Fraser, C.G. Interval cancers in a national colorectal cancer screening programme. United European Gastroenterol J. 2016;4:587-594.

140. Selby, K., Levine, E.H., Doan, C., Gies, A., Brenner, H., Quesenberry, C. et al. Effect of Sex, Age, and Positivity Threshold on Fecal Immunochemical Test Accuracy: A Systematic Review and Meta-analysis. Gastroenterology. 2019;157:1494-1505.

141. Centre for Cancer Detection. Definitions and calculation methods for the monitoring report 2022 of the Flemish CRC screening programme (2022).

PART I

EVALUATING THE IMPACT OF FIT-BASED COLORECTAL CANCER SCREENING IN FLANDERS

Chapter 2

The impact of a six-year existing screening programme using the faecal immunochemical test in Flanders (Belgium) on colorectal cancer incidence, mortality and survival: a population-based study

Thuy Ngan Tran[1,2], Sarah Hoeck[1,2] , Harlinde De Schutter[3], Sharon Janssens[3], Marc Peeters[4,5] and Guido Van Hal[1,2]

1. Centre for Cancer Detection, 8000 Bruges, Belgium

2. Family Medicine and Population Health (FAMPOP), Faculty of Medicine and Health Sciences, University of Antwerp, 2610 Antwerp, Belgium

3. Research Department, Belgian Cancer Registry, 1210 Brussels, Belgium

4. Department of Oncology, Antwerp University Hospital, 2650 Edegem, Belgium

5. Integrated Personalized & Precision Oncology Network (IPPON), University of Antwerp, 2610 Antwerp, Belgium

(Published in *Int J Environ Res Public Health. 2023;20(2):1654*)

2.1. Abstract

Background: The faecal immunochemical test (FIT) has been increasingly used for organised colorectal cancer (CRC) screening. We assessed the impact of a six-year existing FIT screening programme in Flanders (Belgium) on CRC incidence, mortality and survival.

Methods: The Flemish CRC screening programme started in 2013, targeting individuals aged 50–74 years. Joinpoint regression was used to investigate trends of age-standardised CRC incidence and mortality among individuals aged 50–79 years (2004–2019). Their 5-year relative survival was calculated using the Ederer II method.

Results: We found that FIT screening significantly reduced CRC incidence, especially that of advanced-stage CRCs (69.8/100,000 in 2012 vs. 51.1/100,000 in 2019), with a greater impact in men. Mortality started to decline in men two years after organised screening implementation (annual reduction of 9.3% after 2015 vs. 2.2% before 2015). The 5-year relative survival was significantly higher in screen-detected (93.8%) and lower in FIT non-participant CRCs (61.9%) vs. FIT interval cancers and CRCs in never- invited cases (67.6% and 66.7%, respectively).

Conclusions: Organised FIT screening in Flanders clearly reduced CRC incidence (especially advanced-stage) and mortality (in men, but not yet in women). Survival is significantly better in screen-detected cases vs. CRCs in unscreened people. Our findings support the implementation of FIT organised screening and the continued effort to increase uptake.

2.2. Introduction

Worldwide, colorectal cancer (CRC) represents a considerable portion of the overall cancer burden, accounting for one in every ten cancer cases and deaths [1]. In Flanders, among the most common types of cancer, CRC ranks second in women after breast cancer and third in men after prostate and lung cancer. Concerning CRC alone, the CRC incidence is higher in men than in women, with age-standardised (world standard population) CRC incidence rates of 31.9/100,000 and 22.8/100,000 person-years, respectively, for men and women in 2020 [2].

Most CRCs develop from benign polyps over a long natural history of at least 10 years [3], and screening techniques are available for detecting and treating the disease at early premalignant stages, making CRC one of the most preventable cancers [4,5]. The European Guidelines

recommend faecal occult blood test (FOBT) as the primary CRC screening tool [6]. The guaiac FOBT was reported to reduce CRC-related mortality by 15.0–33.0% [7,8]. More recently, the faecal immunochemical test (FIT) has been shown to be superior to the guaiac FOBT in terms of sensitivity, user-friendly sampling design and quantitative result [9].

Although several studies have demonstrated the effect of FIT screening on reducing CRC incidence and mortality, few of them used standardised parameter estimates [10,11], which restricts the comparison with other studies. Additionally, the magnitude of screening impact varies due to differences in screening uptake, background rate, length of follow-up and FIT cut-off. CRC mortality declined by 8.8% after 7 years of implementing biennial FIT screening (cut-off 20 µg Hb/g) in Spain [10] and a reduction of 52% was observed after 16 years of annual FIT screening (cut-off 20 µg Hb/g) in northern California (US) [12], while no significant reduction was observed after 6 years of biennial FIT screening (cut-off 47 µg Hb/g) in the Netherlands [11].

FIT screening programmes worldwide (in pilot phase or started recently) are currently using different screening strategies, with FIT cut-offs ranging from 15 to 80 µg Hb/g and screening intervals of one or two years, depending on their desired diagnostic value and colonoscopy capacity [13]. A number of countries and regions where no CRC screening programmes are in place yet are planning to implement one in the near future [14,15].

High-quality and generalisable data on the effectiveness of specific strategies for CRC screening are crucial to improve the existing screening programmes or to provide evidence for the initiation of a new one. Such information also enables the target population to make an informed decision about their screening participation. In this study, we investigated the impact of a six-year existing FIT organised screening programme in Flanders on age- standardised CRC incidence, mortality and relative survival.

2.3. Methods

2.3.1. The Flemish organised CRC screening programme

The Flemish CRC screening programme, offering a free FIT (by mail) every two years, started in October 2013 with a stepwise implementation by age, resulting in all target ages of 50–74 years included in 2020 (2013: 66–74 years, only even ages; 2014: 56–74 years, only even ages; 2015–

2016: 56–74 years; 2017: 55–74 years; 2018: 53–74 years; 2019: 51–74 years; 2020: 50–74 years). Exclusion criteria include a CRC diagnosis in the past 10 years, performance of a stool test in the past 2 years, a virtual colonoscopy in the past 4 years, a complete colonoscopy in the past 10 years or a total colectomy. An FIT positivity cut-off of 15 µg Hb/g was used. Individuals with a FIT+ result are recommended to undergo a follow-up colonoscopy. In 2019, the response rate of the programme was 51.5%; the FIT sensitivity, positive predictive value and detection rate for invasive CRCs were 72.4%, 3.3% and 0.16%, respectively [16].

2.3.2. Study design, outcomes and study population

Our study is a retrospective, observational, population-based study.

Firstly, we investigated trends of CRC incidence during 2004–2019 and mortality during 2004–2018 in the population aged 50–79 years. In addition to ages of 50–74 years (target screening ages), we also included ages of 75–79 years to capture the long-term effect of screening after people reach the upper age limit for screening.

Secondly, we assessed 5-year relative survival among individuals diagnosed with CRC at ages of 50–74 years during 2004–2019. Study subjects were censored at the date of death, end of the study period (15 July 2021) or date of the last follow-up when they were known to be alive. Five screening status subgroups were defined, including screen-detected CRC, FIT-interval cancer, post-colonoscopy CRC after a FIT+, CRC in FIT non-participants and never-invited (definitions in **Table 1**).

Table 1. Definitions of screening status subgroups.

Subgroup	Definition
Screen-detected CRC	CRC diagnosed after a FIT+ result, within six months after the first follow-up colonoscopy and before the next recommended FIT invitation (24 months).
FIT-interval cancer	CRC diagnosed after a negative FIT result and before the next recommended FIT invitation (24 months).
Post-colonoscopy CRC after a FIT+	CRC diagnosed after a FIT+ result but later than six months after the first follow-up colonoscopy and before the next recommended colonoscopy examination (10 years, 4 years and 2 years for a complete, virtual and incomplete colonoscopy, respectively).
CRC in FIT non-participant	CRC diagnosed but no FIT participation recorded after screening invitation.
CRC in never-invited*	CRC occurred before the start of the screening programme. CRC occurred after the start of the screening programme but in individuals whose ages were not yet included in the target screening ages at the time (e.g., age 50 during 2013–2019).

CRC, colorectal cancer; FIT, faecal immunochemical test. *CRC cases that were diagnosed during an individual's period of exclusion from CRC screening (a CRC diagnosis ≤ 10 years, an opportunistic FOBT ≤ 2 years, a full colonoscopy ≤ 10 years or a virtual colonoscopy ≤ 4 years) were excluded from our analysis of relative survival.

Our goal was to assess the impact of screening on the relative survival of individuals that adhered to the programme's recommendations. Thus, we left out cases that were excluded from CRC screening invitation and those that had a deviated follow-up after a FIT+ result taken inside the organised screening programme, including another follow-up rather than a colonoscopy, a combination of different follow-up techniques or no follow-up at all. Since survival by stage was investigated in this study, cases that were suspected of having undergone pre-operative treatment (neo-adjuvant treatment)—presenting with a higher clinical vs. pathological stage—were also excluded.

2.3.3. Data sources

Data on CRC incidence and tumour and patient characteristics were retrieved from the Belgian Cancer Registry (BCR) [17]. Tumour stage was determined using the applicable TNM edition at the time of diagnosis and was classified as early-stage (stages I and II) or advanced-stage (stages III and IV) [18–20]. Pathological staging was prioritised over clinical staging, except in the presence of clinical distant metastases, which were always considered stage IV. In the case of multiple lesions, the first primary invasive tumour was retained [12]. Demographic population data including life tables were retrieved from Statistics Belgium—Statbel (publicly available data) [21].

The following data were linked and transferred to the BCR for research purposes following authorisation (reference number 13/091) from the Committee for the Protection of Privacy, which is now the Information Security Committee [22,23]: data on individuals' vital status were obtained from the data linkage between the BCR and the Belgian Crossroads Bank for Social Security (CBSS) based on social security number [24]. Cause of death was derived from the death certificates, collected by the regional authority ('Agentschap Zorg en Gezondheid' for Flanders). Data on FIT screening history (screening invitation, screening participation and FIT result) were extracted from the database of the Flemish Centre for Cancer Detection (CCD). Information on follow-up colonoscopy was based on reimbursement data from the Intermutualistic Agency (IMA-AIM) that are collected from seven health insurance companies in Belgium. These data are complete for 99% of cases due to the compulsory health insurance in Belgium.

2.3.4. Statistical analysis

2.3.4.1. Sample size

In total, 55,688 invasive CRCs during 2004–2019 and 14,146 CRC-related deaths during 2004–2018 in people aged 50–79 years were included in the analysis of CRC incidence and mortality, and 35,796 CRCs in people aged 50–74 years during 2004–2019 were included in the analysis of relative survival.

2.3.4.2. Missing data

Throughout 2004–2019, the staging information of about 6.6% of CRCs was registered with an unspecified code or left blank by data providers. These CRCs were included in the "unknown" stage category in our analyses.

2.3.4.3. Main analysis

Age-specific and truncated age-standardised (world standard population) CRC incidence and mortality rates were calculated as the number of new CRC cases and CRC-related deaths, respectively, per 100,000 person-years (py) for each year during the study period.

Trends of CRC incidence and mortality were investigated using Joinpoint regression analyses. Changes in the evolution of the rates, indicated by joinpoints (where the slope of the regression function changes), were identified and annual percentage change (APC) was calculated.

Relative survival was calculated as the ratio of the observed and expected survival for a comparable group of the general population matched by age, sex and calendar year. The expected survival was calculated using the Ederer II method and the Flemish life tables [25,26]. The log-rank test was performed to compare survival rates among the screening status subgroups.

We used the Joinpoint regression Software (version 4.9.0.0; US National Cancer Insti- tute) and RStudio Software (version 1.3.1056; RStudio, PBC, Boston, MA, USA) for data analyses. A p-value of < 0.05 (two-sided) was considered statistically significant.

2.3.5. Privacy and ethics

The secondary use and linkage of the databases involved was approved on 17 September 2013 (updated on 20 March 2018), with reference number 13/091, by the Committee for the Protection of Privacy, which is now the Information Security Committee [22,23]. Approval from an ethical committee was not necessary given the fact that this retrospective study does not fall under the Belgian legislation for ethical committee approval (Law of 7 May 2004 regarding experiments on human persons (art. 3, Section 2)). Participants in the Flemish CRC screening programme fill in a written informed consent agreeing that personal information can be used for scientific research and for the evaluation of the programme. Our reporting adheres to the STROBE guidelines for observational studies (**Table S1**) [27].

2.4. Results

In total, 55,688 CRC cases during 2004–2019 and 14,146 CRC-related deaths during 2004–2018 in people aged 50–79 years were included in the analyses of CRC incidence and mortality trends. A subgroup of 35,796 CRCs in people aged 50–74 years during 2004–2019 was included in the analysis of 5-year relative survival (**Figure 1**).

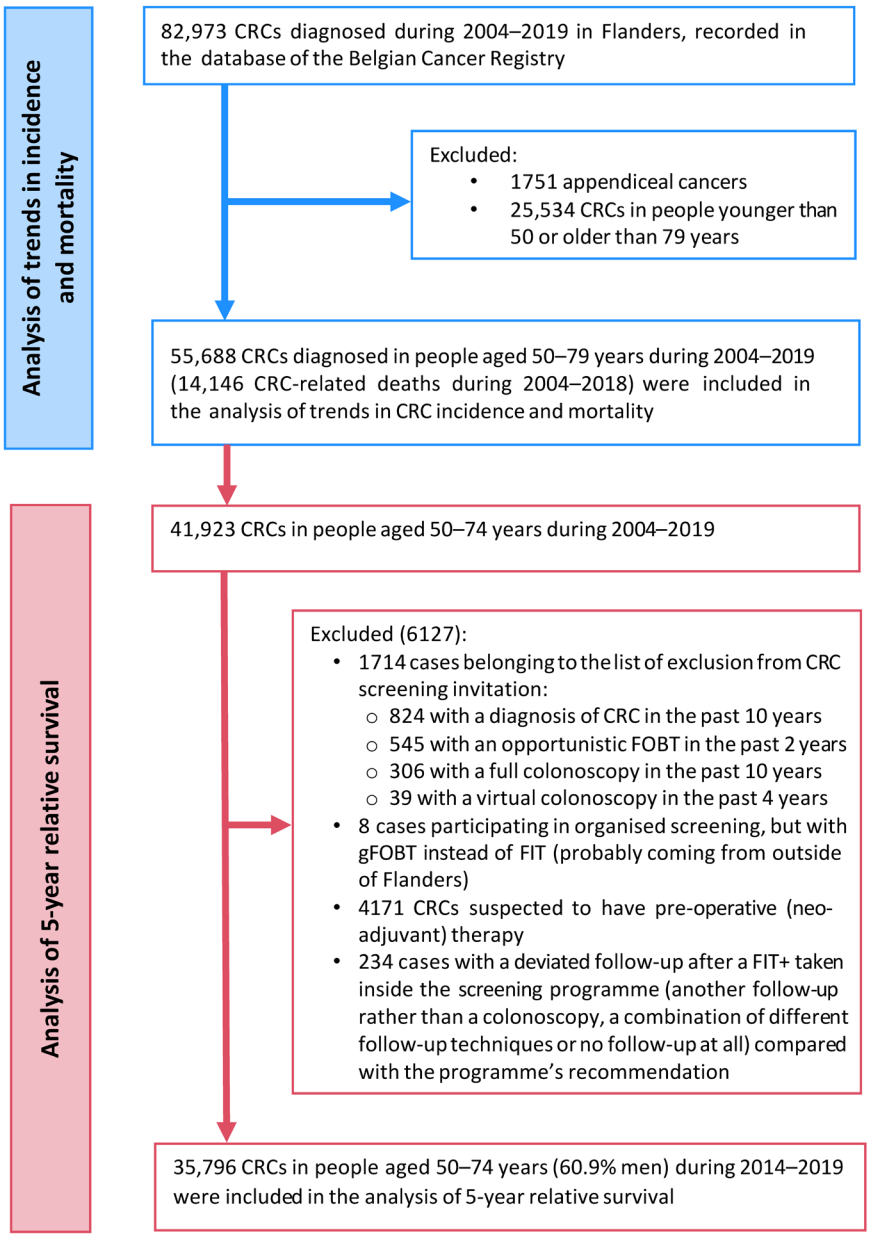


Figure 1. Flowchart of inclusion of study subjects in the study.

2.4.1. Trends of CRC incidence and mortality by gender

After the screening programme started in 2013, age-standardised CRC incidence initially increased and reached a peak in 2014 and then decreased drastically to a lower rate compared to before organised screening (134.5/100,000 py in 2019 vs. 191.9/100,000 py in 2012 for men;

96.9/100,000 py in 2019 vs. 116.9/100,000 py in 2012 for women). The impact was greater in men than in women. The annual percentage change (APC [95%CI]) for the periods before and after the peak in 2014 was 1.4% [0.6 to 2.3] and −9.4% [−11.4 to −7.3] for men and 0.9% [−0.2 to 2.0] and −6.1% [−9.1 to −3.1] for women, respectively (**Figure 2a**).

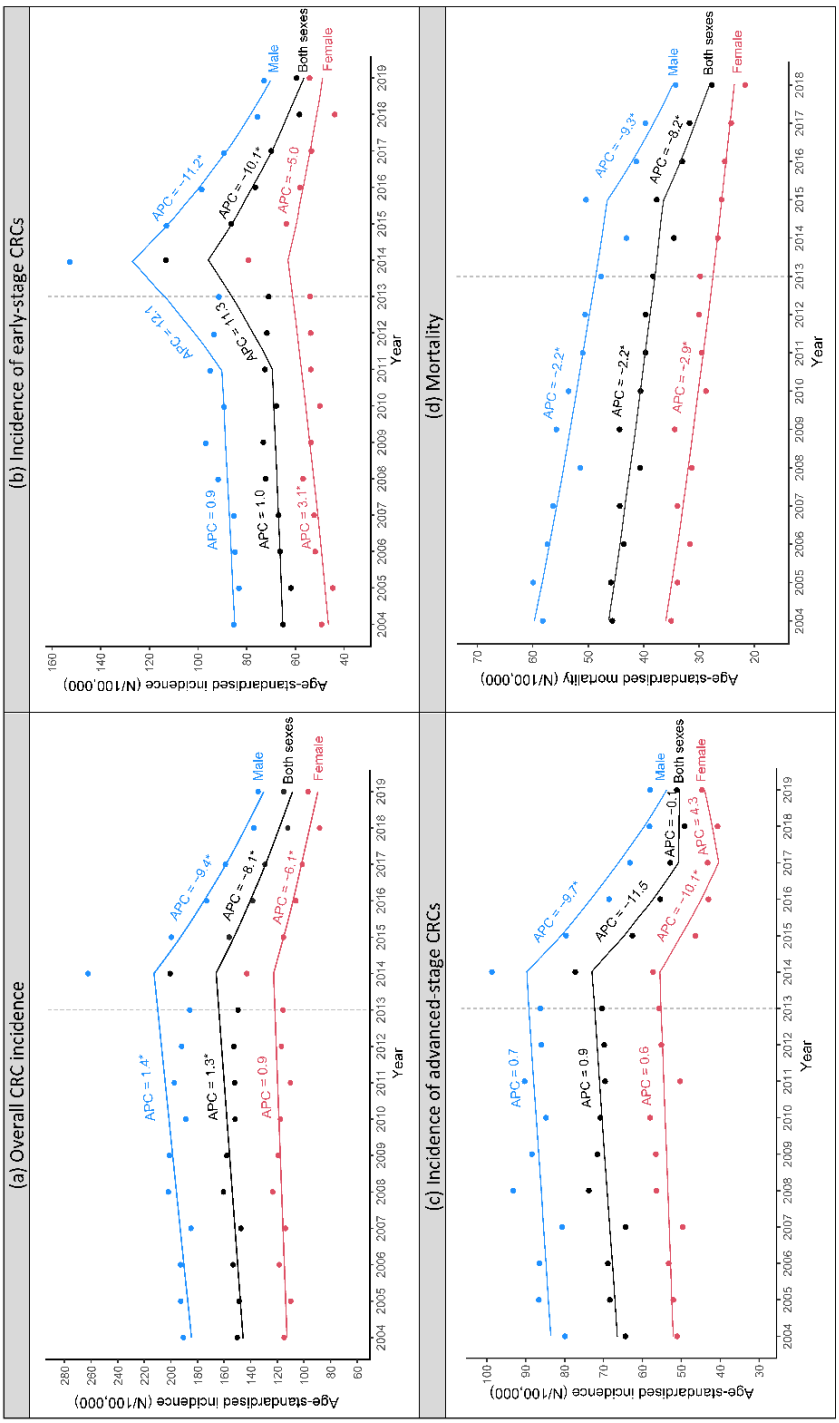


Figure 2. Trends of age-standardised CRC incidence and mortality, stratified by gender, in people aged 50–79 years in Flanders, Belgium, during 2004–2019 (incidence) and 2004–2018 (mortality). (a) Overall CRC incidence. (b) Incidence of early-stage CRCs. (c) Incidence of advanced-stage CRCs. (d) Mortality. The transparent dashed line presents the year when the organised colorectal cancer screening programme was initiated in Flanders. CRC, colorectal cancer; APC, annual percentage change; * statistically significant

The increase in incidence after screening implementation was more pronounced for early-stage CRCs than advanced-stage CRCs. The early-stage CRC incidence rose sharply between 2013 and 2014 and then decreased steadily between 2014 and 2019 to a similar (for women) or slightly lower rate (for men). In contrast, the incidence of advanced-stage CRCs only increased slightly during 2013–2014 and then decreased drastically to a significantly lower rate compared to before the start of organised screening (58.0/100,000 py in 2019 vs. 85.9/100,000 py in 2012 for men; 44.7/100,000 py in 2019 vs. 55.1/100,000 py in 2012 for women). There was a slight increase in advanced-stage CRC incidence in women during 2017–2019 (APC 4.3%, not statistically significant) (**Figure 2b,c**).

Age-standardised CRC-related mortality was already decreasing gradually in both men and women before the implementation of organised screening. However, a sharper decline was observed in men starting from two years after the implementation of the screening programme (APC −9.3% [−15.2 to −3.0] after 2015 vs. −2.2% [−3.1 to −1.4] before 2015). No change in mortality trend during the study period was found in women (**Figure 2d**).

2.4.2. Trends of CRC incidence and mortality by age group

Figure 3a presents the trends of age-specific CRC incidence, which were completely in line with the stepwise introduction by age cohorts of the screening programme. Being included right from the start in 2013, the incidence in age groups of 65–69 and 70–74 years reached a peak in 2014. A similar peak was observed in 2015 for 55–59 and 60–64 years since these ages were only included since 2014. As the youngest group, 50–54 years, was only included since 2018, an increase in its incidence was observed during 2018–2019.

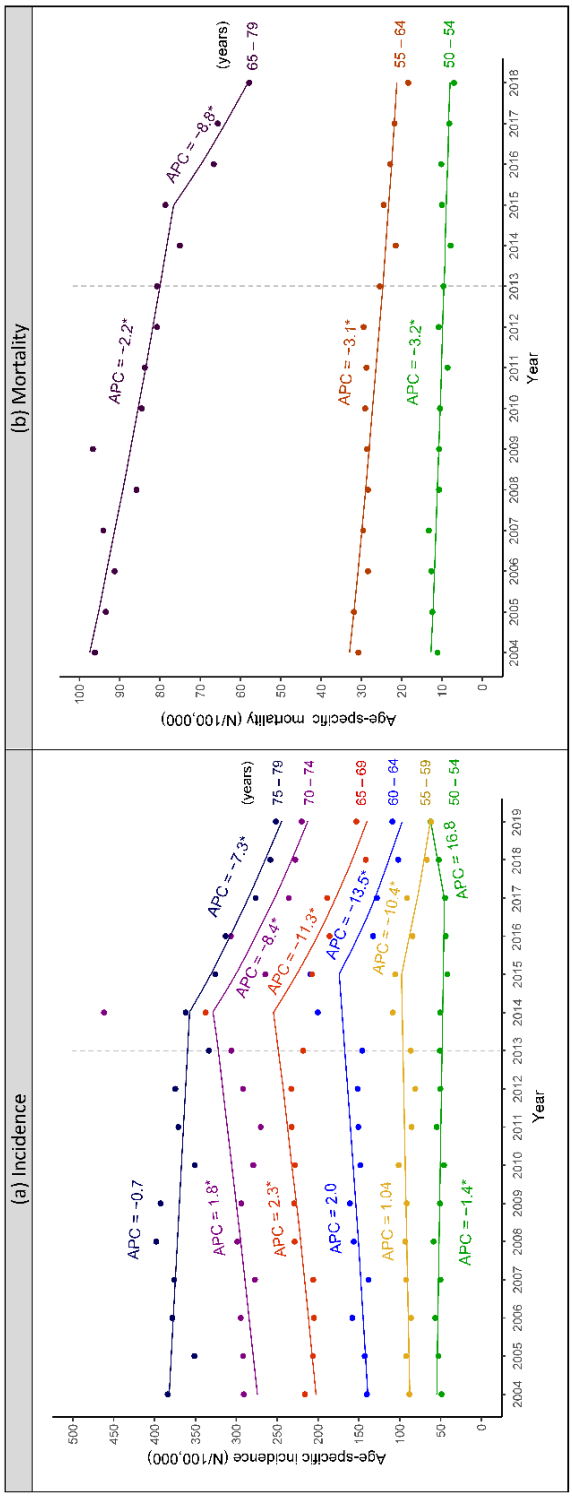


Figure 3. Trends of age-specific CRC incidence and mortality in people aged 50–79 years in Flanders, Belgium, during 2004–2019 (incidence) and 2004–2018 (mortality). (**a**) Incidence. (**b**) Mortality. The transparent dashed line presents the year when the organised colorectal cancer screening programme was initiated in Flanders. CRC, colorectal cancer; APC, annual percentage change; * statistically significant

The impact of organised screening continued after screened individuals reached the upper age limit for screening. CRC incidence in the group of 75–79 years decreased substantially (APC −7.3% [−10.4 to −4.1]) during 2014–2019 to a significantly lower rate compared to before the start of the screening programme (251.6/100,000 py in 2019 vs. 374.6/100,000 py in 2012).

Although CRC-related mortality decreased gradually during the study period, no change in trend of mortality was identified when each 5-year age group was assessed separately (**Figure S1**). When the groups with a similar incidence trend (a peak reached in 2014 or 2015 or no peak observed yet) were combined, a change in the trend of mortality was captured for the group above 65 years, with a sharper decline from 2015 onwards (APC −8.8% [−14.7 to −2.5] after 2015 vs. −2.2% [−3.0 to −1.3] before 2015) (**Figure 3b**).

2.4.3. Relative survival by screening status

In total, 4959 screen-detected CRCs, 905 FIT-interval cancers, 4555 CRCs in FIT non-participants and 25,353 CRCs in never-invited cases were included in the relative survival analyses. The results for the post-colonoscopy CRC subgroup are shown in our Supplementary Materials due to its small sample size (24 cases) **(Table S2**, **Figures S2** and **S3** and **supplementary text**).

Table 2 presents the study subjects' characteristics. The majority in all subgroups were men (60.3–63.7%), except for the FIT-interval cancer group (sexes almost equally distributed). There was no major difference in the mean age among the subgroups (64.4–66.5 years). The mean time between FIT participation and CRC diagnosis was significantly longer among FIT-interval cancers vs. screen-detected CRCs (425.0 vs. 77.9 days).

Table 2. Characteristics of study subjects included in the analysis of 5-year relative survival: people aged 50–74 years at time of CRC diagnosis during 2004–2019 in Flanders, Belgium (grouped by CRC screening status).

	Screen-Detected CRC (N = 4959)	**FIT-Interval Cancer (N = 905)**	**CRC in Never-Invited (N = 25,353)**	**FIT Non-Participant CRC (N = 4555)**
Men	3157 (63.7%)	468 (51.7%)	15,298 (60.3%)	2854 (62.7%)
Mean age (years) ± SD	65.7 ± 5.8	66.5 ± 5.4	64.4 ± 6.9	66.2 ± 5.6
Stage				
I	2532 (51.0%)	234 (25.9%)	4352 (17.2%)	845 (18.6%)
II	799 (16.1%)	151 (16.7%)	5880 (23.2%)	980 (21.5%)
III	1185 (23.9%)	249 (27.5%)	7325 (28.9%)	1257 (27.6%)
IV	325 (6.6%)	241 (26.6%)	5723 (22.6%)	1321 (29.0%)
Unknown	118 (2.4%)	30 (3.3%)	2073 (8.2%)	152 (3.3%)
Mean time between FIT and diagnosis (days)	77.9	425.0	-	-

CRC, colorectal cancer; FIT, faecal immunochemical test.

The 5-year relative survival decreased with increasing stage: 95.5% for stage I, 87.6% for stage II, 75.7% for stage III and only 20.3% for stage IV CRCs. The 5-year relative survival of unknown-stage CRCs was also low (56.1%) (**Figure 4a**). The proportion of early-stage CRCs (I or II) among the screen-detected CRCs was significantly higher than the other subgroups (67.1% vs. 40.1–42.6%) (**Figure 4b** and **Table 2**). As a result, the 5-year relative survival of screen-detected CRCs was significantly higher than the survival of the other subgroups (93.8% vs. 61.9–67.6%, *p*-values < 0.01) (**Figure 5**). Among CRCs in FIT non-participants, never-invited cases and FIT-interval cancers, CRCs in FIT non-participants had a significantly lower 5-year relative survival than the other two subgroups (61.9% vs. 66.7–67.6%, *p*-values < 0.01) (**Figure 5**) due to a higher proportion of advanced-stage CRCs (especially stage IV) compared to CRCs in never-invited cases and a lower proportion of early-stage CRCs (especially stage I) compared to FIT-interval cancers (**Figure 4b** and **Table 2**).

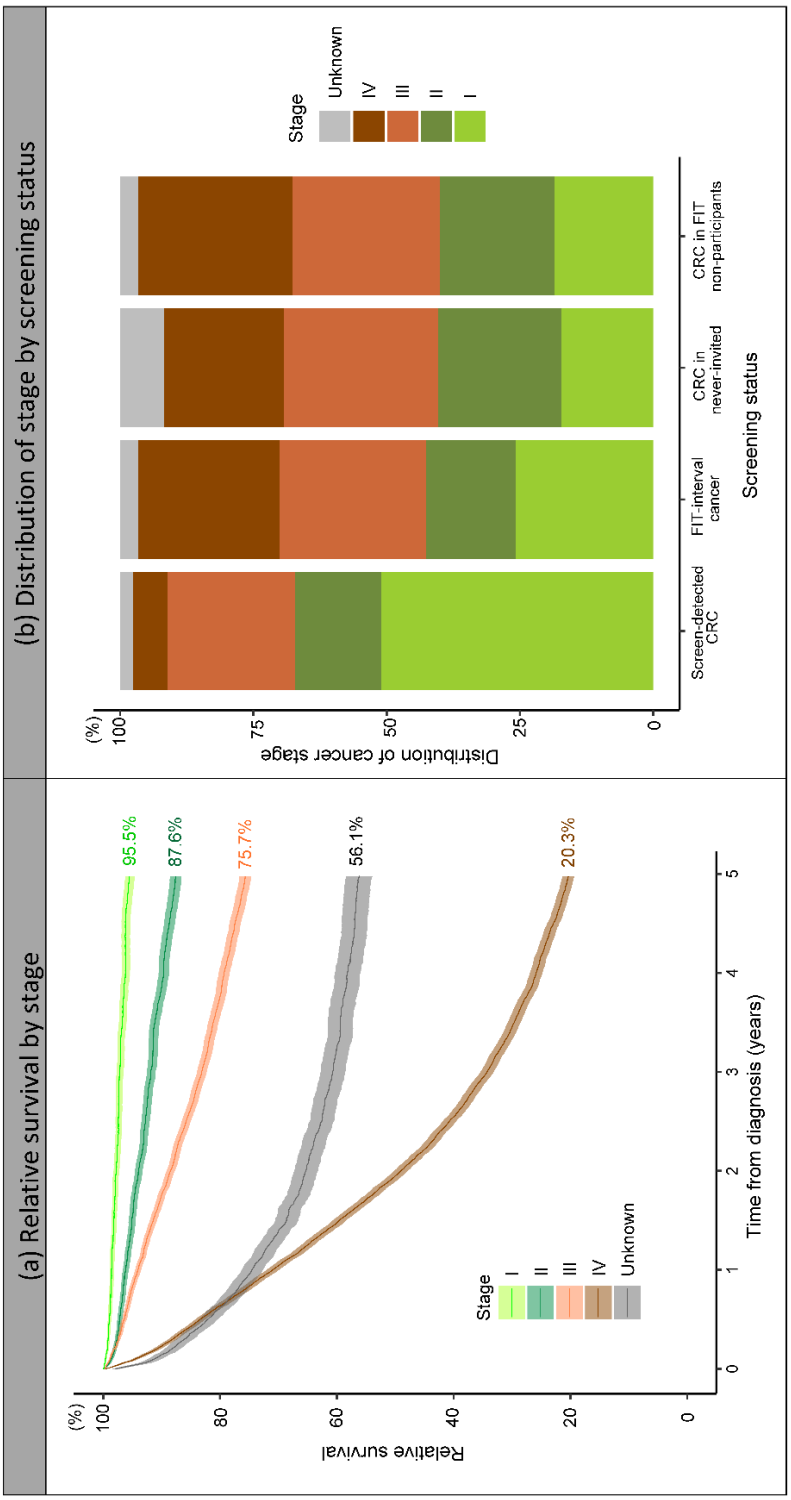


Figure 4. The 5-year relative survival by tumour stage and the distribution of tumour stage by screening status. (**a**) Relative survival by stage. (**b**) Distribution of stage by screening status. CRC, colorectal cancer; FIT, faecal immunochemical test

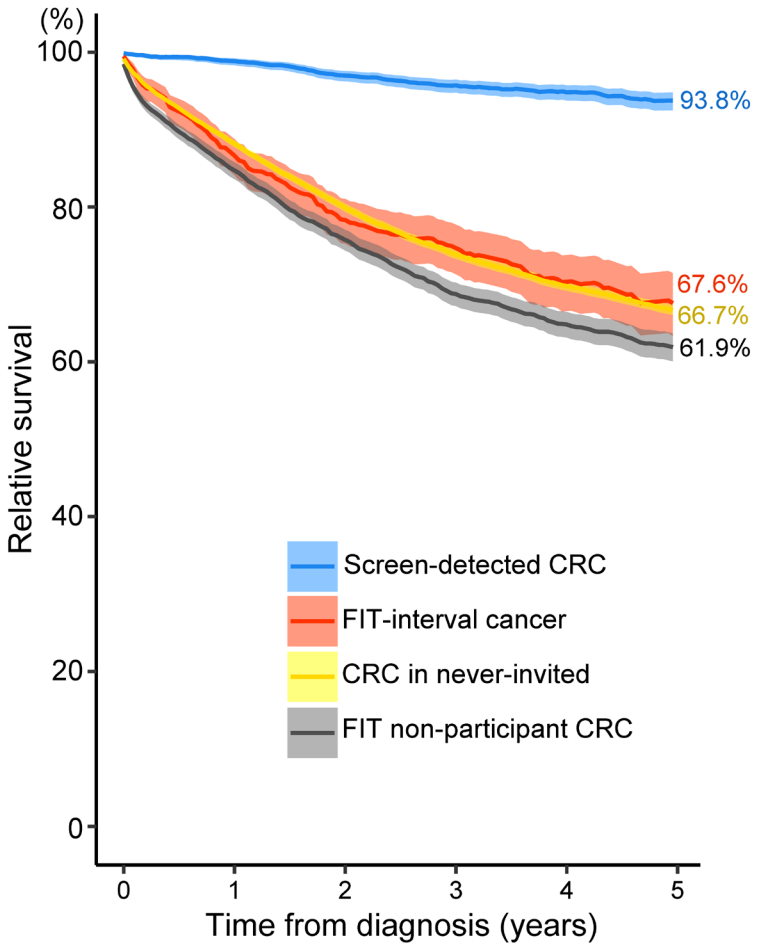


Figure 5. Five-year relative survival by screening status. CRC, colorectal cancer; FIT, faecal immunochemical test.

2.5. Discussion

We investigated the impact of a six-year existing FIT screening programme in Flanders on CRC incidence, mortality and relative survival. The implementation of organised screening induced a sharp rise in early-stage CRC incidence, followed by a gradual decrease to a similar (women) or slightly lower rate (men). Conversely, advanced-stage CRC incidence only increased slightly

but then decreased drastically to a significantly lower rate compared to before the implementation of organised screening. The impact of screening was more pronounced in men than in women and continued after individuals reached the upper age for screening. The effect of screening on mortality has already been observed in men and the group older than 65 years, but not yet in women and the younger groups. The 5-year relative survival was significantly higher in screen-detected CRCs and significantly lower in FIT non-participant CRCs compared to FIT-interval cancers and CRCs in never-invited cases, who shared a similar survival rate.

The observed trend of CRC incidence after the implementation of organised FIT screening in Flanders is similar to other countries where a high screening uptake (>50%) was rapidly achieved, such as the Netherlands, Slovenia and Denmark. A sharp increase in incidence (mostly early-stage CRCs) in the first 1–2 years after the initiation of the screening programme was noted in these countries, followed by a progressive decrease (both early- and advanced-stage CRCs) [11,15]. Organised screening thus resulted in an immediate increase in prevalent asymptomatic cases. These mainly comprised early-stage CRCs that, without organised screening, would take years to become symptomatic and be detected. In alignment with these observations, we observed a sharp peak in incidence right after the start of organised screening for early-stage CRCs but only a slight one for advanced-stage CRCs.

After the peak, however, advanced-stage CRC incidence decreased drastically to a significantly lower level than before the screening programme started. This decrease in advanced-stage CRC incidence resulted from a massive detection of early asymptomatic cases before they progressed into advanced stages. At the same time, screening enables the detection and removal of precursors, leading to a reduction in CRC incidence in the long term [15,28]. In Flanders, the overall CRC incidence decreased steadily from the peak in 2014 (200.6/100,000 py)—one year after the start of the programme—to a significantly lower level (115.2/100,000 py in 2019 vs. 152.7/100,000 py in 2012). A similar reduction in CRC incidence has been observed in Italy, Basque Country (Spain), northern California (US) and Taiwan [12,28–30].

The down-staging effect of CRC screening, i.e., shifting towards an earlier stage at diagnosis, has been well reported in the literature. In line with results from Slovenia, northern Italy and Basque Country (Spain) [31–33], almost 70% of CRCs detected within the Flemish screening programme, compared to only around 40% of CRCs in FIT-non-participants and never-invited cases, were in stages I and II. The Australian National Bowel Cancer Screening Program also

reported 171% higher odds of being diagnosed at an earlier stage among screen-detected vs. screening non-participant CRCs [34].

The ultimate goal of CRC screening is to reduce CRC-related mortality through the down-staging effect (resulting in better treatment options and prognosis), together with a reduction in incidence in the long term [35,36]. Compared with CRC incidence, which is immediately influenced after screening implementation, the impact on CRC-related mortality is delayed and less pronounced [11]. In Flanders, CRC-related mortality was already decreasing steadily before the start of organised screening, probably due to improvements in treatment and patient care [37]. A steeper decline in mortality (indicating an additional impact of screening) was captured starting from two years after screening implementation, mainly in men (annual reduction of 9.3% after 2015 vs. 2.2% before 2015). Other FIT programmes have also reported various impacts of FIT screening on mortality according to levels of screening implementation, progress in incidence reduction, baseline mortality and length of follow-up [15]. Based on data from Italy, Spain, the US and Taiwan, FIT organised screening reduced CRC-related mortality by 9–52% after a follow-up duration of 6–16 years [10,12,28,29,36,38,39].

In line with previous studies [11,31,40], we observed a more pronounced impact of organised FIT screening on both CRC incidence and mortality in men than in women. There are two possible reasons: (1) CRC incidence and mortality are generally higher in men [13], and the effect is therefore expected to be greater in men; (2) the FIT is more sensitive in men [36,41]. A clear illustration shown in this study is the difference in the trend of advanced-stage CRC incidence during 2017–2019 between men and women (**Figure 2c**): the advanced-stage CRC incidence continued to decrease in men while it increased slightly in women. Such a slight increase in advanced-stage CRC incidence in women was observed because the decreasing pattern due to the detection (and treatment) of asymptomatic CRCs and precancerous lesions through active screening was cancelled out by the increasing pattern due to the entry of two new age cohorts each year in 2018 and 2019 in Flanders (leading to the detection of a large number of prevalent CRCs). In contrast, the decreasing pattern was still more predominant than the increasing pattern in men during this period. Likewise, a change in mortality trend (sharper decline) was already observed starting from two years after the start of the screening programme in men, but not yet in women.

Previous studies have suggested lowering the FIT cut-off or shortening the screening interval in

women to narrow the gap in the test's diagnostic performance between men and women [40,42–45]. However, our prior research has shown that in the context of the Flemish screening programme, where a low FIT cut-off of 15 µg Hb/g was already used for both sexes, lowering the FIT cut-off from 15 to 10 µg Hb/g or shortening the screening interval from two years to one year would only have a minimal impact on reducing FIT-interval cancers [41]. To address the reduced FIT sensitivity in women, new screening techniques may be required to replace or supplement the FIT for CRC screening in women [42,46,47].

Our findings aligned completely with the stepwise extension by age of the Flemish screening programme. The age cohorts included earlier experienced the effect of screening sooner. Specifically, those above 65 years old who entered the target population from the start in 2013 had a peak in incidence in 2014, while the 50–54 years group, included since 2017, had an increase in incidence during 2018–2019. The impact on mortality was already observed in those aged above 65 years but not yet in the younger population, for the following possible reasons: (1) CRC mortality is higher in the older population, and the impact is therefore more visible; (2) since ages above 65 years were included right from the start, these people could benefit from screening earlier with more screening rounds [29]; (3) since CRC takes years to develop and people with even advanced CRC still have a certain survival, time is required to observe an impact of screening on mortality. Therefore, the effect of screening on mortality is more apparent in older people who participated in screening in their earlier age. Notably, our results demonstrated that the screening effect continues after people reach the upper age limit for screening (i.e., 74 years). After six years of screening implementation, we have already observed a significant reduction in CRC incidence in the group aged 75–79 years.

In addition to incidence and mortality, we also investigated the impact of FIT screening on relative survival by screening status. In line with previous findings [30–33,48–51], we found that the 5-year relative survival was significantly higher among screen-detected CRCs (93.8%) and significantly lower among non-participant CRCs (61.9%) compared to FIT-interval cancers and CRCs in never-invited cases (67.6% and 66.7%, respectively). This finding strongly confirms the benefit of FIT screening on CRC-related survival and the importance of optimizing screening uptake in the target screening population. Note that, although considered undesirable events, the 5-year relative survival of FIT-interval cancers did not differ significantly from that of CRCs in never-invited cases (CRCs diagnosed when organised screening was not yet available).

The combined approach of evaluating the impact of FIT screening on both survival and mortality is an important strength of the current study. This combined approach minimised the influence of lead time bias on our interpretations of screening effects [52]. Specifically, if the increased survival in screen-detected CRCs was merely due to lead time bias (screening only brought forward time of diagnosis without affecting the disease course), CRC-related mortality would not have decreased after the implementation of organised FIT screening. We found the opposite in this study.

Our findings also did not support the theory of length bias. According to this theory, screening would detect more slowly progressing cancers, leading to an overestimation of survival time in screen-detected CRCs. If this occurred, one would normally expect FIT-interval cancers—those escaping FIT screening—to have worse survival than non-screening CRCs. However, our findings and those from previous studies have shown a similar or even better survival in FIT-interval cancers than in CRCs diagnosed without screening [33,34,53]. Note that this result might also be affected by the healthy user bias, i.e., that subjects who participated in screening are likely to be healthier than those who did not [54]. Future research taking into account subjects' lifestyles and health-seeking behaviours as well as length bias is needed to validate the findings from ours and previous studies which showed that survival in FIT interval cancers is better than or similar to that of CRCs diagnosed without screening [33,34,53,54].

Another strength of this study is the use of register-based data, which eliminated information and selection biases. Moreover, we used the relative survival parameter in which survival of the CRC population is compared with the matched (age, sex and calendar year) general population. Thus, age, sex and improvement of general treatment and care over time (proxied by calendar year) were sufficiently controlled for in our analysis. Improvement in CRC-specific treatment was, however, only partially adjusted for with the use of relative survival since the CRC population benefits from CRC-specific treatment advances to a greater extent compared with the general population. Other potential biases due to opportunistic screening, pre-operative treatment and specific reasons leading to exclusion from CRC screening were also considered in our methodologies.

We could not account for changes in lifestyle factors over time in our trend analyses. Nevertheless, we expected the magnitude of such an influence on our results to be small due to two reasons: (1) there is no evidence of a substantial change in the adoption of low-CRC-risk

behaviours in Flanders during the study period [15]; (2) a general change in lifestyle would induce similar trends in early- and advanced-stage CRC incidence. However, we observed totally different patterns in incidence for early- and advanced-stage CRCs after the implementation of the screening programme, for which screening is apparently a more plausible explanation.

2.6. Conclusions

Our data showed a clear impact of FIT organised screening on improving CRC survival and reducing incidence and mortality, with a more pronounced effect in men than in women. The impact of screening continued after people reached the upper target age for screening (i.e., older than 74 years). Our findings support the timely implementation of organised FIT screening programmes where they are not yet in place and the improvement of the existing ones. To maximise the impact of screening, increasing screening uptake is crucial.

Supplementary materials

Table S1 – The STROBE research checklist for observational studies in epidemiology applied in the current study.

	Item No	Recommendation	Page No.
Title and abstract	1	Title	1
		Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	1-2
Objectives	3	State specific objectives, including any prespecified hypotheses	2
Methods			
Study design	4	Present key elements of study design early in the paper	2
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	2-4
Participants	6	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	2-3 Figure 1
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers.	2-4
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	2-4
Bias	9	Describe any efforts to address potential sources of bias	3-4 (combined with 14&15 - Discussion)
Study size	10	Explain how the study size was arrived at	4-5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses.	10 (Table 2) Figure 3 shows how age was categorised

Statistical methods	12	Describe all statistical methods, including those used to control for confounding	4
		Describe any methods used to examine subgroups and interactions	4
		Explain how missing data were addressed	4
		If applicable, explain how loss to follow-up was addressed	2
		Describe any sensitivity analyses	Not applicable
Results			
Participants	13	Report numbers of individuals at each stage of study	4-5
		Give reasons for non-participation at each stage	Not applicable
		Consider use of a flow diagram	Figure 1
Descriptive data	14	Characteristics of study participants	10
		Number of participants with missing data	4
		Follow-up time	4 (combined with 2 – Methods)
Outcome data	15	Report numbers of outcome events or summary measures over time	4
Main results	16	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	5-12
		Report category boundaries when continuous variables were categorized	Not applicable
		If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-12
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14-15

Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	14-15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

Table S2. Characteristics of the study subjects in subgroups by screening status, with the post-colonoscopy CRC subgroup included (the last column).

	Screen-detected CRC (N=4,959)	**FIT-interval cancer (N=905)**	**CRC in never-invited (N=25,353)**	**FIT non-participant CRC (N=4,555)**	**Post-colonoscopy CRC (N=24)**
Men	3,157 (63.7%)	468 (51.7%)	15,298 (60.3%)	2,854 (62.7%)	14 (58.3%)
Mean age (years) ± SD	65.7 ± 5.8	66.5 ± 5.4	64.4 ± 6.9	66.2 ± 5.6	68.5 ± 4.9
Mean time between FIT and diagnosis (days)	77.9	425.0	-	-	993.8
Stage					
I	2,532 (51.0%)	234 (25.9%)	4,352 (17.2%)	845 (18.6%)	3 (12.5%)
II	799 (16.1%)	151 (16.7%)	5,880 (23.2%)	980 (21.5%)	0 (0%)
III	1185 (23.9%)	249 (27.5%)	7,325 (28.9%)	1257 (27.6%)	12 (50%)
IV	325 (6.6%)	241 (26.6%)	5,723 (22.6%)	1321 (29.0%)	8 (33.3%)
Unknown	118 (2.4%)	30 (3.3%)	2,073 (8.2%)	152 (3.3%)	1 (4.2%)

CRC: Colorectal cancer; FIT, Faecal immunochemical test

Supplementary text: Relative survival of the post-colonoscopy colorectal cancer subgroup

As introduced in the main manuscript, we present our results on individual relative survival of the "post-colonoscopy colorectal cancer (CRC) after an organised FIT+" subgroup in this Supplementary Materials due to the small sample of the subgroup (24 cases during 2013-2019). Similar to the screen-detected CRC, FIT non-participant and never-invited subgroups, the majority of the post-colonoscopy CRC subgroup were men (58.3%) and its mean age at diagnosis was slightly higher than the other subgroups (68.5 vs. 64.4-66.5 years, respectively). The mean time between FIT participation and CRC diagnosis among post-colonoscopy CRCs were 12.8 times and 2.3 times longer than screen-detected CRCs and FIT-interval cancers (Table S2). With regards to tumour stage distribution, 83.3% of CRCs in this subgroup were at an advanced stage III or IV while this proportion among screen-detected CRCs was only 30.5% and among FIT-interval cancers, CRCs in FIT non-participants and never-invited was 51.5-56.6% (Table S2 and Figure S2).

Among the subgroups by screening status investigated in this study, post-colonoscopy CRCs had the lowest 5-year relative survival of 50.9% (screen-detected CRCs: 93.8%, FIT-interval cancers: 67.6%, CRC in never-invited: 66.7%, CRCs in FIT non-participant CRCs: 61.9%) (Figure S3). When comparing with the 5-year relative survival between post-colonoscopy CRCs vs. the other subgroups, significance level was only reached in the comparison between post-colonoscopy CRCs and screen-detected CRCs (due to a large difference of >40%) but not in the comparisons with the other subgroups (due to the limited number of post-colonoscopy CRCs: 24 cases). To sufficiently study the survival of post-colonoscopy CRCs after FIT+, a longer study period (to provide an adequate sample size) or a different study methodology is required.

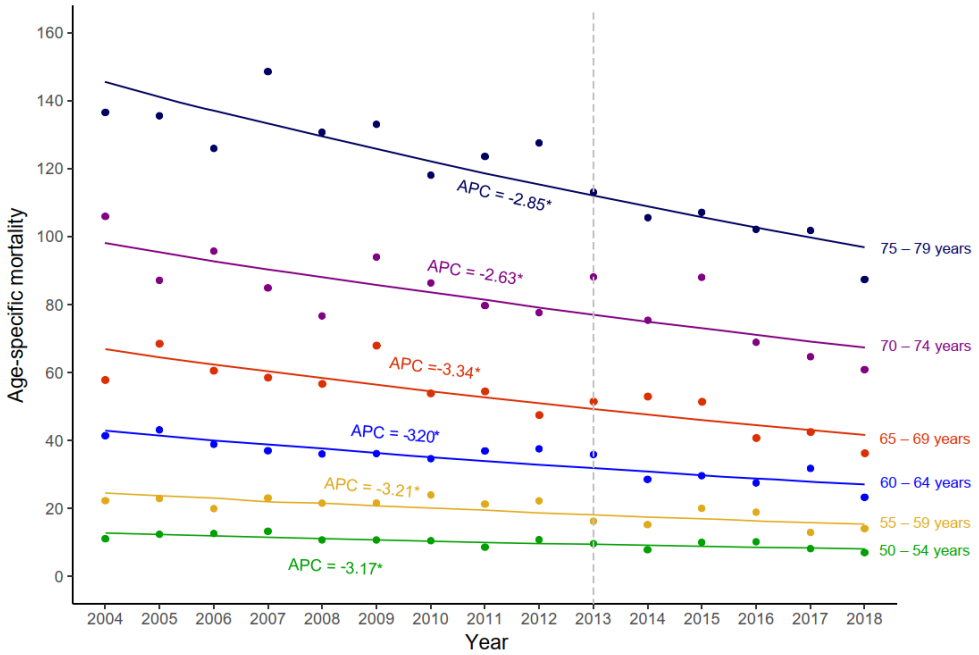


Figure S1. Trends of age-specific CRC mortality in people aged 50-79 years in Flanders, Belgium during 2004-2018 (by individual 5-year age group). The transparent dashed line presents the year when the organised colorectal cancer screening programme was initiated in Flanders. CRC, colorectal cancer; APC, annual percentage change; *statistically significant

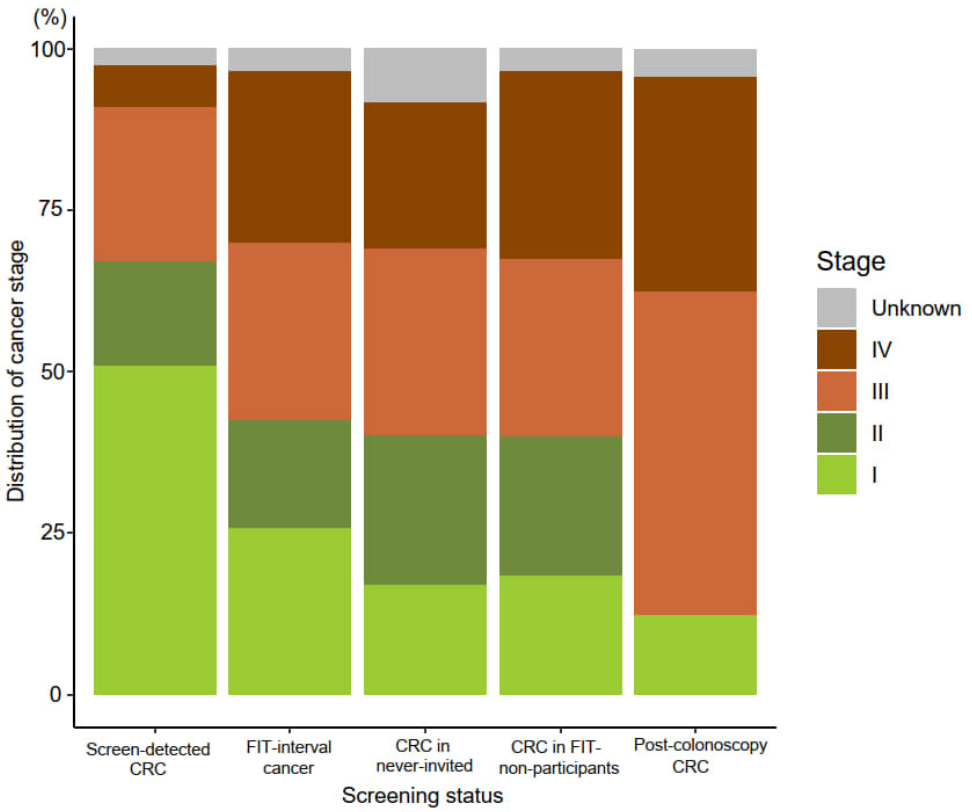


Figure S2. Distribution of CRC stage by screening status, with the post-colonoscopy CRC subgroup included. CRC, colorectal cancer, FIT, faecal immunochemical test

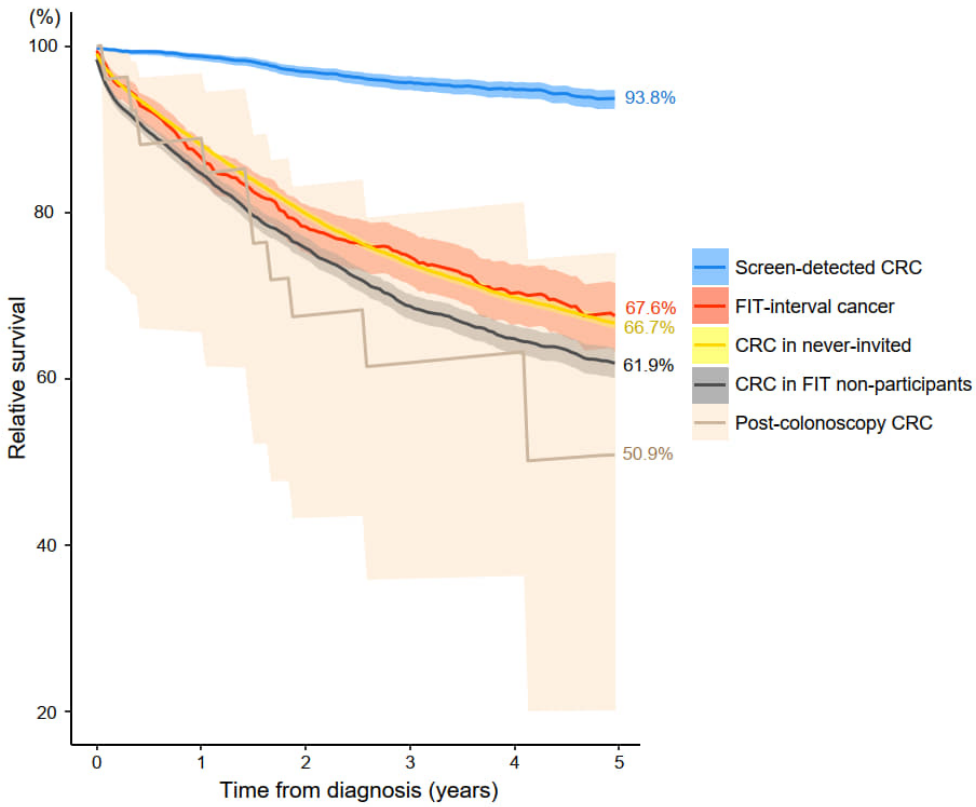


Figure S3. Five-year relative survival by screening status, with the post-colonoscopy CRC subgroup included. CRC, colorectal cancer, FIT, faecal immunochemical test.

References

1. Bray, F.; Ferlay, J.; Soerjomataram, I.; Siegel, R.L.; Torre, L.A.; Jemal, A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J. Clin. 2018, 68, 394–424. https://doi.org/10.3322/caac.21492.
2. Belgian Cancer Registry. Cancer Fact Sheet Colorectal Cancer: Belgium 2020. Availabe online: https://kankerregister.org/media/docs/CancerFactSheets/2020/Cancer_Fact_Sheet_ColorectalCancer_2020.pdf (accessed on 6 January 2023).
3. Morson, B.C. The evolution of colorectal carcinoma. Clin. Radiol. 1984, 35, 425–431. https://doi.org/10.1016/s0009-9260(84)80033-1.
4. Larsen, M.B.; Njor, S.; Ingeholm, P.; Andersen, B. Effectiveness of Colorectal Cancer Screening in Detecting Earlier-Stage Disease-A Nationwide Cohort Study in Denmark. Gastroenterology 2018, 155, 99–106. https://doi.org/10.1053/j.gastro.2018.03.062.
5. Helsingen, L.M.; Kalager, M. Colorectal Cancer Screening—Approach, Evidence, and Future Directions. NEJM Evid. 2022, 1. https://doi.org/10.1056/EVIDra2100035.
6. Ponti, A.; Anttila, A.; Ronco, G.; Senore, C.; Basu, P.; Segnan, N.; Tomatis, M.; Žakelj, M.P.; Dillner, J.; Fernan, M.; et al. Cancer Screening in the European Union. Report on the implementation of Council Recommendation on Cancer Screening; European Commission: Brussels, Belgium, 2017.
7. Mandel, J.S.; Bond, J.H.; Church, T.R.; Snover, D.C.; Bradley, G.M.; Schuman, L.M.; Ederer, F. Reducing mortality from colorectal cancer by screening for fecal occult blood. Minnesota Colon Cancer Control Study. N. Engl. J. Med. 1993, 328, 1365–1371. https://doi.org/10.1056/NEJM199305133281901.
8. Hardcastle, J.D.; Chamberlain, J.O.; Robinson, M.H.E.; Moss, S.M.; Amar, S.S.; Balfour, T.W.; James, P.D.; Mangham, C.M. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. Lancet 1996, 348, 1472–1477. https://doi.org/10.1016/s0140-6736(96)03386-7.
9. Tinmouth, J.; Lansdorp-Vogelaar, I.; Allison, J.E. Faecal immunochemical tests versus guaiac faecal occult blood tests: What clinicians and colorectal cancer screening programme organisers need to know. Gut 2015, 64, 1327–1337. https://doi.org/10.1136/gutjnl-2014-308074.
10. Keys, M.T.; Serra-Burriel, M.; Martinez-Lizaga, N.; Pellise, M.; Balaguer, F.; Sanchez, A.; Bernal-Delgado, E.; Castells, A. Population-based organized screening by faecal immunochemical testing and colorectal cancer mortality: A natural experiment. Int. J. Epidemiol. 2021, 50, 143–155. https://doi.org/10.1093/ije/dyaa166.
11. Breekveldt, E.C.H.; Lansdorp-Vogelaar, I.; Toes-Zoutendijk, E.; Spaander, M.C.W.; van Vuuren, A.J.; van Kemenade, F.J.; Ramakers, C.R.B.; Dekker, E.; Nagtegaal, I.D.; Krul, M.F.; et al. Colorectal cancer incidence, mortality, tumour characteristics, and treatment before and after introduction of the faecal immunochemical testing-based screening programme in the Netherlands: A population-based study. Lancet Gastroenterol. Hepatol. 2021, 7, 60–68. https://doi.org/10.1016/s2468-1253(21)00368-x.
12. Levin, T.R.; Corley, D.A.; Jensen, C.D.; Schottinger, J.E.; Quinn, V.P.; Zauber, A.G.; Lee, J.K.; Zhao, W.K.; Udaltsova, N.; Ghai, N.R.; et al. Effects of Organized Colorectal Cancer Screening on Cancer Incidence and Mortality in a Large Community-Based Population. Gastroenterology 2018, 155, 1383–1391.e5. https://doi.org/10.1053/j.gastro.2018.07.017.
13. Schreuders, E.H.; Ruco, A.; Rabeneck, L.; Schoen, R.E.; Sung, J.J.; Young, G.P.; Kuipers, E.J. Colorectal cancer screening: A global overview of existing programmes. Gut 2015, 64, 1637–1649. https://doi.org/10.1136/gutjnl-2014-309086.
14. Gini, A.; Jansen, E.E.L.; Zielonke, N.; Meester, R.G.S.; Senore, C.; Anttila, A.; Segnan, N.; Mlakar,

D.N.; de Koning, H.J.; Lansdorp-Vogelaar, I.; et al. Impact of colorectal cancer screening on cancer-specific mortality in Europe: A systematic review. Eur. J. Cancer 2020, 127, 224–235. https://doi.org/10.1016/j.ejca.2019.12.014.

15. Cardoso, R.; Guo, F.; Heisser, T.; Hackl, M.; Ihle, P.; De Schutter, H.; Van Damme, N.; Valerianova, Z.; Atanasov, T.; Májek, O.; et al. Colorectal cancer incidence, mortality, and stage distribution in European countries in the colorectal cancer screening era: An international population-based study. Lancet Oncol. 2021, 22, 1002–1013. https://doi.org/10.1016/s1470-2045(21)00199-6.

16. Centre for Cancer Detection. Monitoring Report 2021 of the Flemish Colorectal Cancer Screening Programme. Availabe online: https://dikkedarmkanker.bevolkingsonderzoek.be/nl (accessed on 5 May 2022).

17. Van Eycken, L.; Haustermans, K. Current role and future perspectives of the Belgian Cancer Registry in quality of cancer projects. Belg. J. Med. Oncol. 2010, 4, 216–222.

18. International Union Against Cancer (UICC). TNM Classification of Malignant Tumours, 6th ed.; Sobin, L.H., Wittekind, C., Eds.; Wiley: New York, NY, USA, 2002.

19. International Union Against Cancer (UICC). TNM Classification of Malignant Tumours, 7th ed.; Sobin, L.H., Gospodarowicz, M.K., Wittekind, C., Eds.; Wiley-Blackwell: Chichester, UK, 2009.

20. International Union Against Cancer (UICC). TNM Classification of Malignant Tumours, 8th ed.; Brierley, J.D., Gospodarowicz, M.K., Wittekind, C., Eds.; John Wiley & Sons: Oxford, UK; Hoboken, NJ, USA, 2017.

21. Statbel (Belgium in figures). Life Expectancy and Life Tables [Sterftetafels en Levensverwachting]. Availabe online: https://statbel.fgov.be/en/themes/population/mortality-life-expectancy-and-causes-death/life-expectancy-and-life-tables#figures (accessed on 10 March 2022).

22. Committee for the Protection of Privacy (Commissie voor de Bescherming van de Persoonlijke Levenssfeer). SCSZG/18/064. Availabe online: https://www.ehealth.fgov.be/ehealthplatform/file/view/AWJNUKfuJW4b-4n3_A_Z?filename=13-091-n064-bevolkingsonderzoek%20dikkedarmkanker-gewijzigd%20op%2020%20maart%2020....pdf (accessed on 2 September 2022).

23. eHealth. Informatieveiligheidscomité (Information Security Committee). Availabe online: https://www.ehealth.fgov.be/ehealthplatform/nl/informatieveiligheidscomite (accessed on 9 November 2022).

24. Crossroads Bank for Social Security (CBSS). Documentation. Availabe online: https://www.ksz-bcss.fgov.be/nl/documents-list (accessed on 15 May 2022).

25. Belgian Cancer Registry. Cancer Survival in Belgium. Availabe online: https://kankerregister.org/media/docs/publications/CancerSurvivalinBelgium.PDF (accessed on 15 May 2022).

26. Ederer, F.; Axtell, L.M.; Cutler, S.J. The relative survival rate: A statistical methodology. Natl. Cancer Inst. Monogr. 1961, 6, 101–121.

27. von Elm, E.; Altman, D.G.; Egger, M.; Pocock, S.J.; Gotzsche, P.C.; Vandenbroucke, J.P.; Initiative, S. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: Guidelines for reporting observational studies. BMJ 2007, 335, 806–808. https://doi.org/10.1136/bmj.39335.541782.AD.

28. Chiu, H.M.; Jen, G.H.; Wang, Y.W.; Fann, J.C.; Hsu, C.Y.; Jeng, Y.C.; Yen, A.M.; Chiu, S.Y.; Chen, S.L.; Hsu, W.F.; et al. Long-term effectiveness of faecal immunochemical test screening for proximal and distal colorectal cancers. Gut 2021, 70, 2321–2329. https://doi.org/10.1136/gutjnl-2020-322545.

29. Giorgi Rossi, P.; Vicentini, M.; Sacchettini, C.; Di Felice, E.; Caroli, S.; Ferrari, F.; Mangone, L.; Pezzarossi, A.; Roncaglia, F.; Campari, C.; et al. Impact of Screening Program on Incidence of Colorectal Cancer: A Cohort Study in Italy. Am. J. Gastroenterol. 2015, 110, 1359–1366. https://doi.org/10.1038/ajg.2015.240.

30. Mar, J.; Arrospide, A.; Larranaga, I.; Iruretagoiena, M.L.; Imaz, L.; Gorostiza, A.; Ibarrondo, O. Impact of an organised population screening programme for colorectal cancer: Measurement after first and second rounds. J. Med. Screen 2021, 28, 122–130. https://doi.org/10.1177/0969141320921893.

31. Tepes, B.; Mlakar, D.N.; Stefanovic, M.; Stabuc, B.; Grazio, S.F.; Zakotnik, J.M. The impact of 6 years of the National Colorectal Cancer Screening Program on colorectal cancer incidence and 5-year survival. Eur. J. Cancer Prev. 2021, 30, 304–310. https://doi.org/10.1097/CEJ.0000000000000628.

32. Parente, F.; Vailati, C.; Boemo, C.; Bonoldi, E.; Ardizzoia, A.; Ilardo, A.; Tortorella, F.; Cereda, D.; Cremaschini, M.; Moretti, R. Improved 5-year survival of patients with immunochemical faecal blood test-screen-detected colorectal cancer versus non-screening cancers in northern Italy. Dig. Liver Dis. 2015, 47, 68–72. https://doi.org/10.1016/j.dld.2014.09.015.

33. Idigoras Rubio, I.; Arana-Arri, E.; Portillo Villares, I.; Bilbao Iturribarria, I.; Martinez-Indart, L.; Imaz-Ayo, N.; de la Cruz, M.; de Castro, V.; Lopez de Munain, A.; Torrejon Perez, I.; et al. Participation in a population-based screening for colorectal cancer using the faecal immunochemical test decreases mortality in 5 years. Eur. J. Gastroenterol. Hepatol. 2019, 31, 197–204. https://doi.org/10.1097/MEG.0000000000001338.

34. Australian Institute of Health and Welfare. Analysis of Bowel Cancer Outcomes for the National Bowel Cancer Screening Program. Availabe online: https://www.aihw.gov.au/reports/cancer-screening/analysis-of-bowel-cancer-outcomes-nbcsp-2018/summary (accessed on 11 April 2022).

35. Lee, Y.C.; Hsu, C.Y.; Chen, S.L.; Yen, A.M.; Chiu, S.Y.; Fann, J.C.; Chuang, S.L.; Hsu, W.F.; Chiang, T.H.; Chiu, H.M.; et al. Effects of screening and universal healthcare on long-term colorectal cancer mortality. Int. J. Epidemiol. 2019, 48, 538–548. https://doi.org/10.1093/ije/dyy182.

36. Zorzi, M.; Fedeli, U.; Schievano, E.; Bovo, E.; Guzzinati, S.; Baracco, S.; Fedato, C.; Saugo, M.; Dei Tos, A.P. Impact on colorectal cancer mortality of screening programmes based on the faecal immunochemical test. Gut 2015, 64, 784–790. https://doi.org/10.1136/gutjnl-2014-307508.

37. Welch, H.G.; Robertson, D.J. Colorectal Cancer on the Decline--Why Screening Can't Explain It All. N. Engl. J. Med. 2016, 374, 1605–1607. https://doi.org/10.1056/NEJMp1600448.

38. Ventura, L.; Mantellini, P.; Grazzini, G.; Castiglione, G.; Buzzoni, C.; Rubeca, T.; Sacchettini, C.; Paci, E.; Zappa, M. The impact of immunochemical faecal occult blood testing on colorectal cancer incidence. Dig. Liver Dis. 2014, 46, 82–86. https://doi.org/10.1016/j.dld.2013.07.017.

39. Chiu, H.M.; Chen, S.L.; Yen, A.M.; Chiu, S.Y.; Fann, J.C.; Lee, Y.C.; Pan, S.L.; Wu, M.S.; Liao, C.S.; Chen, H.H.; et al. Effectiveness of fecal immunochemical testing in reducing colorectal cancer mortality from the One Million Taiwanese Screening Program. Cancer 2015, 121, 3221–3229. https://doi.org/10.1002/cncr.29462.

40. White, A.; Ironmonger, L.; Steele, R.J.C.; Ormiston-Smith, N.; Crawford, C.; Seims, A. A review of sex-related differences in colorectal cancer incidence, screening uptake, routes to diagnosis, cancer stage and survival in the UK. BMC Cancer 2018, 18, 906. https://doi.org/10.1186/s12885-018-4786-7.

41. Tran, T.N.; Peeters, M.; Hoeck, S.; Van Hal, G.; Janssens, S.; De Schutter, H. Optimizing the colorectal cancer screening programme using faecal immunochemical test (FIT) in Flanders, Belgium from the "interval cancer" perspective. Br. J. Cancer 2022, 126, 1091–1099. https://doi.org/10.1038/s41416-021-01694-2.

42. Chiu, H.M.; Lee, Y.C.; Tu, C.H.; Chen, C.C.; Tseng, P.H.; Liang, J.T.; Shun, C.T.; Lin, J.T.; Wu, M.S. Association between early stage colon neoplasms and false-negative results from the fecal immunochemical test. Clin. Gastroenterol. Hepatol. 2013, 11, 832–838.e2. https://doi.org/10.1016/j.cgh.2013.01.013.

43. Digby, J.; Fraser, C.G.; Carey, F.A.; Lang, J.; Stanners, G.; Steele, R.J. Interval cancers using a quantitative faecal immunochemical test (FIT) for haemoglobin when colonoscopy capacity is limited. J. Med. Screen 2016, 23, 130–134. https://doi.org/10.1177/0969141315609634.

44. Steele, R.J.; Stanners, G.; Lang, J.; Brewster, D.H.; Carey, F.A.; Fraser, C.G. Interval cancers in a national colorectal cancer screening programme. United Eur. Gastroenterol. J. 2016, 4, 587–594. https://doi.org/10.1177/2050640615624294.

45. Selby, K.; Levine, E.H.; Doan, C.; Gies, A.; Brenner, H.; Quesenberry, C.; Lee, J.K.; Corley, D.A. Effect of Sex, Age, and Positivity Threshold on Fecal Immunochemical Test Accuracy: A Systematic Review and Meta-analysis. Gastroenterology 2019, 157, 1494–1505. https://doi.org/10.1053/j.gastro.2019.08.023.

46. Imperiale, T.F.; Ransohoff, D.F.; Itzkowitz, S.H.; Levin, T.R.; Lavin, P.; Lidgard, G.P.; Ahlquist, D.A.; Berger, B.M. Multitarget stool DNA testing for colorectal-cancer screening. N. Engl. J. Med. 2014, 370, 1287–1297. https://doi.org/10.1056/NEJMoa1311194.

47. Ferrari, A.; Neefs, I.; Hoeck, S.; Peeters, M.; Van Hal, G. Towards Novel Non-Invasive Colorectal Cancer Screening Methods: A Comprehensive Review. Cancers 2021, 13, 1820. https://doi.org/10.3390/cancers13081820.

48. Ibanez-Sanz, G.; Mila, N.; Vidal, C.; Rocamora, J.; Moreno, V.; Sanz-Pamplona, R.; Garcia, M. Positive impact of a faecal-based screening programme on colorectal cancer mortality risk. PLoS ONE 2021, 16, e0253369. https://doi.org/10.1371/journal.pone.0253369.

49. Gutierrez-Stampa, M.A.; Aguilar, V.; Sarasqueta, C.; Cubiella, J.; Portillo, I.; Bujanda, L. Colorectal Cancer Survival in 50- to 69-Year-Olds after Introducing the Faecal Immunochemical Test. Cancers 2020, 12, 2412. https://doi.org/10.3390/cancers12092412.

50. Li, X.; Zhou, Y.; Luo, Z.; Gu, Y.; Chen, Y.; Yang, C.; Wang, J.; Xiao, S.; Sun, Q.; Qian, M.; et al. The impact of screening on the survival of colorectal cancer in Shanghai, China: A population based study. BMC Public Health 2019, 19, 1016. https://doi.org/10.1186/s12889-019-7318-8.

51. Mengual-Ballester, M.; Pellicer-Franco, E.; Valero-Navarro, G.; Soria-Aledo, V.; Garcia-Marin, J.A.; Aguayo-Albasini, J.L. Increased survival and decreased recurrence in colorectal cancer patients diagnosed in a screening programme. Cancer Epidemiol. 2016, 43, 70–75. https://doi.org/10.1016/j.canep.2016.06.003.

52. McClements, P.L.; Madurasinghe, V.; Thomson, C.S.; Fraser, C.G.; Carey, F.A.; Steele, R.J.; Lawrence, G.; Brewster, D.H. Impact of the UK colorectal cancer screening pilot studies on incidence, stage distribution and mortality trends. Cancer Epidemiol. 2012, 36, e232–e242. https://doi.org/10.1016/j.canep.2012.02.006.

53. Vicentini, M.; Zorzi, M.; Bovo, E.; Mancuso, P.; Zappa, M.; Manneschi, G.; Mangone, L.; Giorgi Rossi, P.; Colorectal Cancer Screening, I.s.w.g. Impact of screening programme using the faecal immunochemical test on stage of colorectal cancer: Results from the IMPATTO study. Int. J. Cancer 2019, 145, 110–121. https://doi.org/10.1002/ijc.32089.

54. Shrank, W.H.; Patrick, A.R.; Brookhart, M.A. Healthy user and related biases in observational studies of preventive interventions: A primer for physicians. J. Gen. Intern. Med. 2011, 26, 546–550. https://doi.org/10.1007/s11606-010-1609-1.

PART II

EXPLORING POTENTIAL AREAS FOR IMPROVING COLORECTAL CANCER SCREENING UPTAKE IN FLANDERS

Chapter 3

Population-based data reveal factors associated with organised and non-organised colorectal cancer screening: an important step towards improving coverage

Thuy Ngan Tran[1], Guido Van Hal[1,2], Marc Peeters[3,4], Svetlana Jidkova[2,5], Harlinde De Schutter[6] and Sarah Hoeck[1,2]

1. Family Medicine and Population Health (FAMPOP), Faculty of Medicine and Health Sciences, University of Antwerp, 2610 Antwerp, Belgium

2. Centre for Cancer Detection, 8000 Bruges, Belgium

3. Department of Oncology, Antwerp University Hospital, 2650 Antwerp, Belgium

4. Integrated Personalized & Precision Oncology Network (IPPON), University of Antwerp, 2610 Antwerp, Belgium

5. Department of Public Health and Primary Care, Ghent University, 9000 Ghent, Belgium

6. Research Department, Belgian Cancer Registry, 1210 Brussels, Belgium

(Published in *Int J Environ Res Public Health. 2021;18(16):8373*)

3.1. Abstract

Aims: We investigated factors associated with organised and non-organised colorectal cancer screening using faecal occult blood tests, based on data from 308 municipalities in Flanders (6.6 million residents, 57% of Belgium) during 2015–2017.

Methods: Logistic regression with generalized estimating equations was used to assess the associations between municipal characteristics and organised and non-organised screening coverages.

Results: Factors associated ***negatively with both organised and non-organised screening***: percentage of people aged 70–74 in the target population [OR (odds ratios) = 0.98, 95%CI (confidence interval): 0.97–0.99 and OR = 0.98, 95%CI: 0.96–0.999, respectively]; ***negatively with organised screening***: average income [OR = 0.97, 95%CI: 0.96–0.98], percentage of people with a non-Belgian/Dutch nationality [OR = 0.962, 95%CI: 0.957–0.967]; ***positively with organised screening***: percentages of men in the target population [OR = 1.13, 95%CI: 1.11–1.14], jobseekers [OR = 1.12, 95%CI: 1.09–1.15] and people with at least one general practitioner (GP) visit in the last year [OR = 1.04, 95%CI: 1.03–1.05]; ***positively with non-organised screening***: number of patients per GP [OR = 1.021, 95%CI: 1.016–1.026], percentage of people with a global medical dossier handled by a preferred GP [OR = 1.025, 95%CI: 1.018–1.031].

Conclusions: This study helps to identify the hard-to-reach subpopulations in CRC screening, and highlights the important role of GPs in the process of promoting screening among non-participants and encouraging non-organised participants to switch to organised screening.

3.2. Introduction

Worldwide, colorectal cancer (CRC) ranks third in terms of cancer incidence and second in terms of mortality [1]. In Flanders, colorectal cancer was the second most common cancer in females and third in males in 2018, with low incidences before the age of 50 (<22.4/100,000 person-years (py) for ages 45–49) but gradually increasing rates for older age groups. Incidence rates ranged, for males and females respectively, from 59.9/100,000 py and 48.0/100,000 py for ages 50–54 up till 280.5/100,000 py and 184.8/100,000 py for ages 70–74 [2].

Flanders, the most populated region of Belgium (57% of the country's population) [3], had 4,954 new CRC cases and 1,617 CRC deaths in 2017 [2]. Regular screening is an excellent preventive intervention for CRC: the 5-year relative survival rate for stage I CRC is 94.7% while for stage IV CRC it is only 16.2% (Flanders, 2000–2018) [2]. Organised screening is the only screening strategy for CRC recommended by the European Council since it ensures equity of access and quality control [4,5]. In Flanders, the organised CRC screening programme has been in place since 2013, offering a free biennial faecal occult blood test (FOBT, immunochemical type) to all eligible individuals aged 50–74.

Despite the recognised benefits of organised CRC screening, only just over half of the target population in Flanders participate in the organised screening programme [6]. Some of them, instead, undergo a non-organised FOBT. The main issues with non-organised FOBTs are that they are not free-of-charge; results and follow-up in-formation are not systematically registered, and quality is not systematically controlled by the organised CRC screening programme, the cancer registry or any other authorities. Therefore, it is crucial to identify factors associated with organised and non-organised FOBT screening. Unfortunately, comprehensive data on non-organised FOBTs are currently lacking [7].

A unique strength of the CRC screening programme in Flanders is the ability to obtain data on non-organised FOBTs (prescribed by GPs and specialists). In this study, we investigated factors associated with organised and non-organised FOBT screening coverages at a municipality level. Our findings will help to guide targeted interventions to increase CRC screening among non-participatory individuals or encourage non-organised participants to switch to organised screening.

3.3. Methods

3.3.1. Flanders and its organised CRC screening programme

Flanders is the most populated region of Belgium (6.6 million, 57% of Belgian population) [3]. It comprises 308 municipalities with populations varying from ~90 to 520,900, of which 19–40% were at eligible ages for CRC screening (2015–2017). The organised CRC screening programme in Flanders has been in place since 2013 and is coordinated by the Centre for Cancer Detection. The programme offers a free FOBT (immunochemical type) every two years to all citizens aged

50–74 using a centralized invitation procedure (target ages were extended gradually from 56–74 in 2013 to 50–74 in 2020). During the study period, the target screening ages were 56–74 in 2015–2016 and 55–74 in 2017. People were excluded from the screening invitation list if they had had a stool test in the past two years, a virtual colonoscopy in the past four years or a complete colonoscopy in the past ten years, were diagnosed with CRC in the past ten years or had undergone a total colectomy (excluded permanently).

3.3.2. Study population and data sources

We included data from all 308 municipalities in Flanders in 2015–2017. Data on organised FOBT screening coverage, gender and age-specific proportions of the screening population were obtained from the Centre for Cancer Detection.

Data on non-organised FOBTs, identified by nomenclature codes used in health insurance claims, are available at the Belgian Cancer Registry which receives these data from the health insurance companies. In Flanders, individuals who have had an FOBT in the past two years, regardless of whether it was an organised or non-organised test, are excluded from screening invitations. Four times per year, the Centre for Cancer Detection receives data on non-organised FOBTs from the Belgian Cancer Registry in order to prepare the screening invitation list. These data were used in the current study as a source of information regarding non-organised FOBTs.

Data on other demographic, socioeconomic and health-related municipal characteristics were retrieved from the publicly accessible database of the Flemish provincial authorities (https://provincies.incijfers.be/databank (accessed on 17 August 2020)) and were linked to the data on screening coverage.

3.3.3. Main outcomes

The main outcomes are the annual organised CRC screening coverage and the annual non-organised CRC screening coverage from 2015 to 2017.

3.3.4. Determinants considered

Figure 1 presents twenty demographic, socioeconomic and health-related municipal characteristics included as potential factors associated with organised and non-organised FOBT

screening coverages.

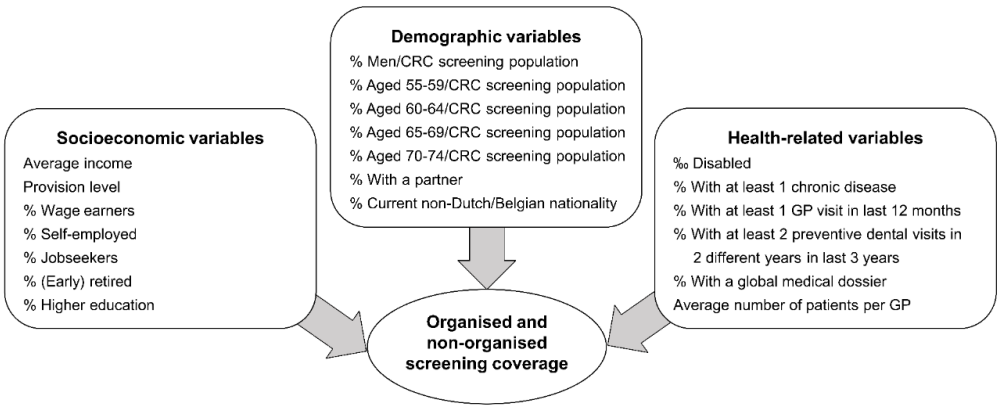


Figure 1. Potential municipal characteristics associated with organised and non-organised colorectal cancer screening using faecal occult blood test.

Variable explanation

Proportions of genders and age groups were measured for the target CRC screening population in each municipality. Other variables were measured for the total population of a municipality and were used as a proxy for the characteristics of the target CRC screening population. Current nationality combines Belgian and Dutch because language and cultural barriers seem irrelevant for Dutch people (Dutch is the official language in Flanders) [8]. Municipal average income is calculated by the total net taxable income divided by the number of inhabitants. Municipal provision is measured by the available supply as regards education, care, public and commercial services, personal services, hotels-restaurants-cafes, retail trade, culture/recreation and sport; and is classified into seven levels [9]. Distribution of positions in the labour market was characterized by the percentage of the four main positions (wage-earners, self-employed, jobseekers and (early) retired). The percentage of residents aged 18–24 studying at a college/university (higher education) was used as a proxy for education level. Disabled people are registered by the Directorate General for Disabled Persons as losing at least one third of the average earning capacity or being unable to perform daily activities. GP visits and preventive dental visits were defined as the percentage of people who had had at least one GP visit in the last 12 months and at least three preventive dental visits in two different years in the last three years, respectively. The global medical dossier formally indicates the patient's

preferred GP, who handles the dossier and follows the patient's medical history. Other variables are self-explanatory (details on https://provincies.incijfers.be/databank (accessed on 17 August 2020)).

3.3.5. Covariates

We used the causal directed acyclic graph (DAG) approach to identify covariates for adjustment when assessing the associations between municipal characteristics and the organised/non-organised screening coverages. We constructed causal diagrams of the study variables and selected covariates, taking into account the between-variable relationships. The final list of covariates for adjustment is presented in **Table 1**. The detailed DAGs showing the pathways among the variables before and after adjusting for covariates are included in **Supplementary Figure S1**. The relationships among the included variables were defined based on our prior knowledge about the Flemish context and the organised programme, independently of the study data. The use of the DAG approach helps to avoid bias due to over-adjusting for variables that may behave statistically like confounders (collider bias) [10].

Table 1. List of covariates for adjustment in multivariable analyses to estimate the association between each municipal characteristic (listed under 'main determinant of assessment') and organised/non-organised FOBT screening coverages.

Main determinant of assessment	Covariates for adjustment in multivariable analyses
Men/CRC screening population	Year
Age groups/CRC screening population	Provision level, year
With a partner	Age groups/CRC screening population, year
Current non-Belgian/Dutch nationality	Provision level, year
Average income	With a partner, age groups/CRC screening population, current non-Belgian/Dutch nationality, chronic disease, disability, education level, provision level, men/CRC screening population, position in labour market, year
Provision level	Year
Position in labour market	Age groups/CRC screening population, current non-Belgian/Dutch nationality, disability, education level, provision level, men/CRC screening population, year
Education level [§]	GP visit, with a partner, age groups/CRC screening population, average income, current non-Belgian/Dutch nationality, chronic disease, disability, provision level, men/CRC screening population, global medical dossier, position in labour market, preventive dental visit, year
Disability	Provision level, year
Chronic disease	Age groups/CRC screening population, current non-Belgian/Dutch nationality, disability, education level, provision level, men/CRC screening population, year
GP visit	Age groups/CRC screening population, average income, chronic disease, disability, education level, men/CRC screening population, preventive dental visit, year
Preventive dental visit	With a partner, age groups/CRC screening population, current non-Belgian/Dutch nationality, chronic disease, education level, men/CRC screening population, global medical dossier, position in labour market, year
Global medical dossier	With a partner, age groups/CRC screening population, current non-Belgian/Dutch nationality, chronic disease, education level, men/CRC screening population, position in labour market, preventive dental visit, year
Average number of patients per GP	Provision level, year

[§] For education level, covariates for adjustment could only be identified for estimating the direct effect (not mediated via other variables) of this factor on the study outcomes.

3.3.6. Statistical analysis

3.3.6.1. Missing data

For privacy reasons, figures were not displayed for cells with < 5 events. As missing data was minimal (1.5%) and solely due to privacy concerns, complete case analysis was applied.

3.3.6.2. Sample size

For logistic regression, at least 10 outcome events per determinant are required [11]. We included 20 determinants while having 308 municipalities that carried data on organised and non-organised screening coverages (study outcomes). Therefore, our sample size could provide sufficient statistical power.

3.3.6.3. Main analysis

Continuous variables were described with medians (interquartile range) and categorical variables were described with numbers (proportions). Each person was assigned a screening status for organised screening (covered versus not covered by an organised FOBT) and for non-organised screening (covered versus not covered by a non-organised FOBT), so the study outcomes are grouped binomial. To evaluate the associations between the determinants and the annual screening coverage of the two screening strategies, we used logistic regression with generalized estimating equations (GEE) to account for the correlation of repeated measurements of municipalities' characteristics and screening coverage each year during the study period. Crude and adjusted odds ratios (ORs) were reported with 95% confidence intervals (95% CIs). Multicollinearity in multivariate models was checked using variance inflation factors (VIFs). p-values less than 0.05 (two-sided) were considered statistically significant. All analyses were performed with R (version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria)).

3.3.7. Ethics

For secondary aggregated data, ethical approval was not required. Our reporting adheres to the STROBE guidelines for observational studies [12].

3.4. Results

3.4.1. Municipal characteristics

The demographic, socioeconomic and health-related characteristics of the 308 study municipalities in 2015–2017 are summarised in **Table 2**. Their organised and non-organised FOBT screening coverages are presented in **Figure 2**. The median organised screening coverage increased from 36.4% in 2015 to 38.0% in 2016 and 40.1% in 2017, whereas the median non-

organised screening coverage decreased from 4.8% in 2015 to 3.9% in 2016 and 3.3% in 2017. A wide variation in organised and non-organised screening coverages existed among municipalities. There were municipalities with extremely low organised screening coverage and municipalities with extremely high non-organised screening coverage (presented with outlier points in **Figure 2**).

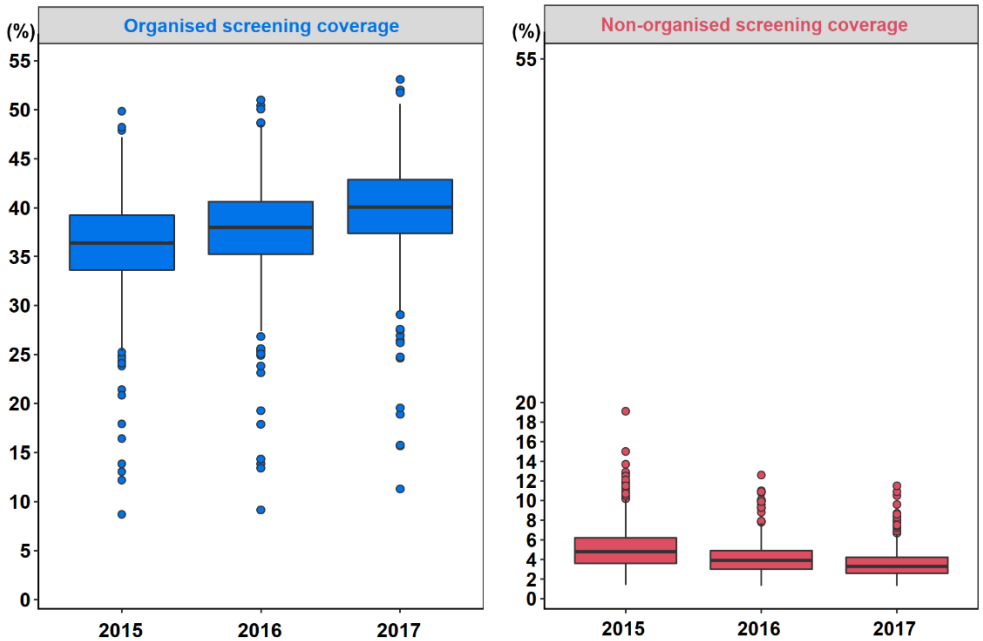


Figure 2. Organised and non-organised faecal occult blood test screening coverage of 308 municipalities in Flanders, 2015–2017. The outlier points show that there are a number of municipalities with extremely low organised screening coverage (below 1.5 times the interquartile range) and municipalities with extremely high non-organised screening coverage (above 1.5 times the interquartile range).

Table 2. Demographic, socioeconomic and health-related characteristics of all 308 municipalities in Flanders, 2015–2017.

	Median (IQR), unless stated otherwise		
	2015 (*n* = 303) †	**2016 (*n* = 303) †**	**2017 (*n* = 304) †**
Demographic characteristics			
% Men/CRC screening population	50.1 (49.2–50.8)	50.0 (49.2–50.8)	50.0 (49.3–50.8)
Age groups			
% 55–59/CRC screening population	25.9 (24.9–26.9)	25.6 (24.8–26.5)	30.0 (29.2–31.3)
% 60–64/CRC screening population	28.5 (27.8–29.5)	28.5 (27.8–29.2)	26.6 (25.9–29.2)
% 65–69/CRC screening population	25.8 (24.9–26.6)	25.1 (24.3–25.9)	25.1 (24.3–25.9)
% 70–74/CRC screening population	19.7 (18.8–20.6)	20.6 (19.7–21.8)	19.9 (19.0–21.0)
% With a partner	52.7 (51.1–53.9)	52.6 (51.1–53.8)	52.6 (50.9–53.7)
% Current non-Belgian/Dutch nationality	2.6 (1.90–4.20)	3.0 (2.1–4.6)	3.3 (2.3–4.8)
Socioeconomic characteristics			
Average income (per 1000 EUR) ‡	19.2 (18.1–20.6)	19.3 (18.1–20.9)	19.9 (18.7–21.4)
Provision level (Number, percentage)			
Level 1 (lowest)	59 (19.5%)	59 (19.5%)	60 (19.7%)
Level 2	65 (21.5%)	65 (21.5%)	65 (21.4%)
Level 3	81 (26.7%)	81 (26.7%)	81 (26.6%)
Level 4	53 (17.5%)	53 (17.5%)	53 (17.4%)
Level 5	18 (5.9%)	18 (5.9%)	18 (5.9%)
Level 6	14 (4.6%)	14 (4.6%)	14 (4.6%)
Level 7 (highest)	13 (4.3%)	13 (4.3%)	13 (4.3%)
Position in labour market			
% Wage earners	36.6 (34.8–37.9)	36.6 (34.5–37.9)	36.8 (34.8–38.1)
% Self-employed	7.9 (6.9–9.2)	8.0 (7.0–9.3)	8.1 (7.1–9.5)
% Jobseekers	1.8 (1.5–2.2)	1.8 (1.7–2.1)	1.6 (1.3–1.9)
% (Early)retired	19.7 (18.5–20.9)	19.9 (18.8–21.1)	20.1 (19.0–21.2)
% Higher education	44.4 (39.1–49.2)	44.8 (39.8–49.7)	45.5 (40.8–51.1)
Health-related characteristics			
‰ Disabled	6.4 (5.0–7.9)	6.5 (5.1–7.9)	6.4 (5.0–7.8)
% With at least 1 chronic disease	9.7 (8.8–10.6)	10.4 (9.6–10.5)	11.0 (10.1–12.1)
% With at least 1 GP visit in last 12 months	84.2 (82.1–86.0)	84.9 (82.7–86.6)	84.4 (82.3–86.4)
% With at least 2 preventive dental visits in 2 different years in last 3 years	34.7 (31.0–37.6)	37.4 (33.5–40.6)	40.1 (36.1–43.4)
% With a global medical dossier	74.8 (69.0–80.6)	78.4 (73.5–82.7)	82.0 (77.0–85.3)
Average number of patients per GP (per 100 patients) ‡	14.1 (12.1–16.2)	14.5 (12.6–16.8)	14.7 (12.5–17.4)

The percentages of men and age groups were captured for the colorectal cancer screening population in each municipality. Other characteristics were captured for the whole population in each municipality and were used as proxies for the colorectal cancer screening population. † Number of municipalities included in the analysis, for which data for all the study variables were available (cell ≥ 5 events). ‡ For statistical purposes, average income was divided by 1000 and average number of patients per GP was divided by 100 before inclusion into analyses. IQR, interquartile range; CRC, colorectal cancer.

3.4.2. Factors associated with organised and non-organised screening coverage

Multicollinearity in multivariate models was low (VIFs: 1.0–5.2). Associations between municipal characteristics and organised and non-organised FOBT screening coverages are graphically presented in **Figure 3** and detailed in **Tables 3 and 4**.

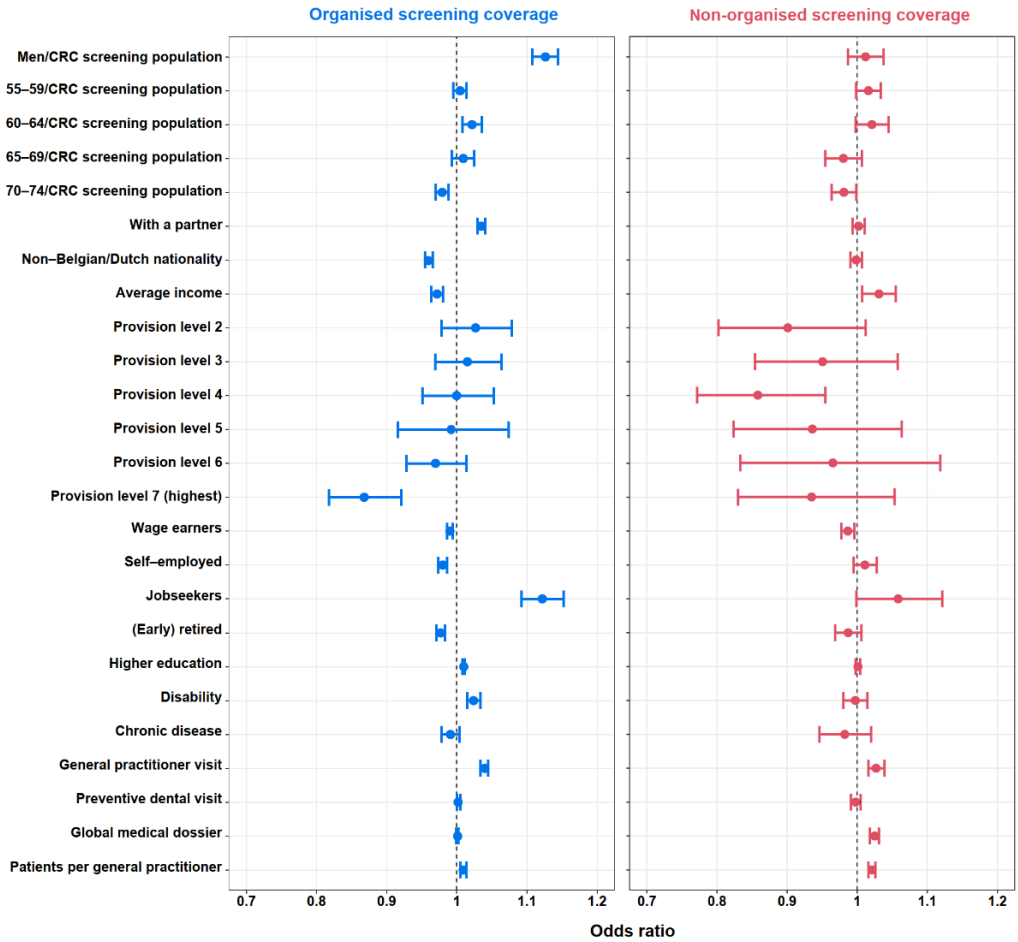


Figure 3. Associations between municipal characteristics with organised and non-organised screening coverages, presented with adjusted odds ratios and 95% confidence intervals.

Table 3. Univariable and multivariable associations between municipal characteristics and organised FOBT screening coverage.

	Univariable analyses			Multivariable analyses		
	OR	**95% CI**	***p* Value**	**OR**	**95% CI**	***p* Value**
Demographic characteristics						
Men/CRC screening population (%)	1.13	1.11–1.15	<0.001 *	1.13	1.11–1.14	<0.001 *
Age categories						
55–59/CRC screening population (%)	1.02	1.01–1.03	<0.001 *	1.005	0.995–1.014	0.37
60–64/CRC screening population (%)	0.986	0.973–0.9996	0.044 *	1.02	1.01–1.04	0.002 *
65–69/CRC screening population (%)	0.983	0.971–0.995	0.005 *	1.01	0.99–1.03	0.27
70–74/CRC screening population (%)	0.98	0.97–0.99	<0.001 *	0.98	0.97–0.99	<0.001 *
With a partner (%)	1.035	1.029–1.041	<0.001 *	1.035	1.029–1.040	<0.001 *
Current non-Belgian/Dutch nationality (%)	0.969	0.964–0.975	<0.001 *	0.962	0.957–0.967	<0.001 *
Socioeconomic characteristics						
Average income (per 1000 EUR) ‡	1.003	0.988–1.018	0.71	0.97	0.96–0.98	<0.001 *
Provision level						
Level 1 (lowest)	(ref)			(ref)		
Level 2	1.03	0.98–1.08	0.31	1.03	0.98–1.08	0.29
Level 3	1.02	0.97–1.07	0.54	1.02	0.97–1.06	0.52
Level 4	1.000	0.948–1.054	0.99	1.000	0.951–1.053	0.99
Level 5	0.99	0.91–1.08	0.83	0.99	0.92–1.07	0.83
Level 6	0.97	0.92–1.02	0.21	0.97	0.93–1.01	0.17
Level 7 (highest)	0.87	0.81–0.93	<0.001 *	0.87	0.82–0.92	<0.001 *
Position in labour market						
Wage earners (%)	1.02	1.01–1.03	<0.001 *	0.990	0.986–0.994	<0.001 *
Self-employed (%)	1.003	0.990–1.016	0.67	0.98	0.97–0.99	<0.001 *
Jobseekers (%)	0.92	0.90–0.95	<0.001 *	1.12	1.09–1.15	<0.001 *
(Early)retired (%)	1.004	0.994–1.014	0.42	0.977	0.971–0.983	<0.001 *
Higher education (%)	1.007	1.003–1.010	<0.001 *	1.010	1.008–1.011	<0.001 *
Health-related characteristics						
Disability (‰)	1.02	1.01–1.03	<0.001 *	1.024	1.015–1.034	<0.001 *
Chronic disease (%)	1.04	1.02–1.06	<0.001 *	0.991	0.978–1.004	0.18
GP visit (%)	1.043	1.040–1.047	<0.001 *	1.04	1.03–1.05	<0.001 *
Preventive dental visit (%)	1.017	1.014–1.021	<0.001 *	1.002	1.000–1.005	0.051
Global medical dossier (%)	1.019	1.017–1.021	<0.001 *	1.001	0.999–1.002	0.37
Patients per GP (per 100 patients) ‡	1.010	1.005–1.015	<0.001 *	1.009	1.005–1.014	<0.001 *

‡ For statistical purposes, average income was divided by 1000 and average number of patients per GP was divided by 100 before inclusion into analyses. * Statistically significant. FOBT, faecal occult blood test.

Table 4. Univariable and multivariable associations between municipal characteristics non-organised FOBT screening coverage.

	Univariable analyses			Multivariable analyses		
	OR	**95% CI**	***p* Value**	**OR**	**95% CI**	***p* Value**
Demographic characteristics						
Men/CRC screening population (%)	1.01	0.98–1.04	0.61	1.01	0.99–1.04	0.36
Age categories						
55–59/CRC screening population (%)	0.97	0.96–0.99	<0.001 *	1.016	0.999–1.034	0.07
60–64/CRC screening population (%)	1.07	1.05–1.10	<0.001 *	1.021	0.998–1.045	0.08
65–69/CRC screening population (%)	1.05	1.03–1.07	<0.001 *	0.98	0.95–1.01	0.14
70–74/CRC screening population (%)	0.97	0.96–0.99	0.002 *	0.981	0.964–0.999	0.037 *
With a partner (%)	1.002	0.992–1.012	0.68	1.002	0.994–1.011	0.64
Current non-Belgian/Dutch nationality (%)	0.997	0.989–1.005	0.51	0.998	0.990–1.007	0.71
Socioeconomic characteristics						
Average income (per 1000 EUR) ‡	1.001	0.985–1.016	0.95	1.03	1.01–1.06	0.010 *
Provision level						
Level 1 (lowest)	(ref)			(ref)		
Level 2	0.90	0.80–1.02	0.09	0.90	0.80–1.01	0.08
Level 3	0.95	0.85–1.06	0.38	0.95	0.85–1.06	0.35
Level 4	0.86	0.77–0.96	0.008 *	0.86	0.77–0.95	0.005 *
Level 5	0.94	0.82–1.07	0.35	0.94	0.82–1.06	0.31
Level 6	0.97	0.83–1.13	0.66	0.97	0.83–1.12	0.63
Level 7 (highest)	0.94	0.82–1.07	0.32	0.94	0.83–1.05	0.27
Position in labour market						
Wage earners (%)	1.002	0.993–1.010	0.74	0.987	0.977–0.996	0.005 *
Self-employed (%)	1.01	0.99–1.02	0.53	1.011	0.995–1.028	0.17
Jobseekers (%)	1.03	0.99–1.08	0.16	1.058	0.999–1.122	0.054
(Early)retired (%)	0.987	0.976–0.997	0.012 *	0.99	0.97–1.01	0.18
Higher education (%)	1.005	1.003–1.008	<0.001 *	1.001	0.998–1.004	0.53
Health-related characteristics						
Disability (‰)	0.9996	0.9821–1.0174	0.96	0.997	0.980–1.015	0.76
Chronic disease (%)	0.96	0.94–0.98	<0.001 *	0.98	0.95–1.02	0.35
GP visit (%)	1.011	1.001–1.021	0.038 *	1.03	1.02–1.04	<0.001 *
Preventive dental visit (%)	0.997	0.992–1.003	0.32	0.998	0.991–1.005	0.55
Global medical dossier (%)	1.004	1.000–1.008	0.033 *	1.025	1.018–1.031	<0.001 *
Patients per GP (per 100 patients) ‡	1.018	1.013–1.024	<0.001 *	1.021	1.016–1.026	<0.001 *

‡ For statistical purposes, average income was divided by 1000 and average number of patients per GP was divided by 100 before inclusion into analyses. * Statistically significant FOBT, faecal occult blood test.

3.4.2.1. Factors associated with both organised and non-organised screening coverages:

A higher average income was associated with a lower organised screening coverage (OR = 0.97, 95%CI: 0.96–0.98) but a higher non-organised screening coverage (OR = 1.03, 95%CI: 1.01–1.06). A higher percentage of people aged 70–74 in the target screening population was associated with lower screening coverages by both screening strategies (organised screening: OR = 0.98, 95%CI: 0.97–0.99; non-organised screening: OR = 0.98, 95%CI: 0.96–0.999).

A higher percentage of people with at least one GP visit in the last year was associated with higher screening coverages by both screening strategies (organised screening: OR = 1.04, 95%CI: 1.03–1.05; non-organised screening: OR = 1.03, 95%CI: 1.02–1.04). Compared to organised screening coverage, the association between non-organised screening coverage with average number of patients per GP (OR = 1.021, 95%CI: 1.016–1.026) was more pronounced.

3.4.2.2. Factors associated with only organised screening coverage:

The highest provision level (OR = 0.87, 95%CI: 0.82–0.92) and a higher percentage of people with non-Belgian/Dutch nationality (OR = 0.962, 95%CI: 0.957–0.967) were associated with a lower organised screening coverage.

Regarding the distribution of labour positions, a higher percentage of jobseekers was associated with a higher organised screening coverage (OR = 1.12, 95%CI: 1.09–1.15). Organised screening coverage was also positively associated with education level (OR = 1.010, 95%CI: 1.008–1.011), the percentage of people with a partner (OR = 1.035, 95%CI: 1.029–1.040), disability (OR = 1.024, 95%CI: 1.015–1.034) and more men in the target CRC screening population (OR = 1.13, 95%CI: 1.11–1.14).

3.4.2.3. Factors associated with only non-organised screening coverage:

A higher percentage of people with a global medical dossier handled by a preferred GP was associated with a higher non-organised screening coverage (OR = 1.025, 95%CI: 1.018–1.031).

3.5. Discussion

Our findings suggest several hard-to-reach subpopulations in CRC screening. Higher average income, lower average education level and a higher percentage of people with non-Belgian/Dutch nationality were associated with a lower organised screening coverage. More

older people (70–74) in the target population were associated with lower coverages for both organised and non-organised screening. GPs were shown to have an important role in improving CRC screening coverage: a higher percentage of people with a GP visit in the last year was associated with higher coverage for both screening strategies, whereas a higher average number of patients per GP and a high percentage of people with a global medical dossier handled by a preferred GP were associated with a higher non-organised screening coverage.

In this study, we could not compare the organised and non-organised FOBT screening coverages in Flanders with other regions/countries because they do not have data on non-organised FOBTs and have therefore not reported these indicators. However, in terms of screening uptake, the FOBT screening uptake in Flanders was 51.5–54.6% (2015–2018) [6], within the range of screening uptake reported in other European countries 15.3–71.3% [5].

A lower FOBT screening coverage (both organised and non-organised) was observed in municipalities with more people in the oldest target age group (70–74). The negative association between older age and participation in FOBT screening has also been reported in other European countries [5]. Older people often suffer multiple health issues and have a lower perceived life expectancy, which is linked to poorer CRC screening [13]. Other health priorities might also limit their screening participation. However, it should be noted that the benefits of CRC screening for this group still outweigh its risks. At age 75, a Flemish man and woman still have an average life expectancy of 9.9 and 12.5 years, respectively [14]. The higher CRC incidence in the group aged 70–74 could also contribute to the lower organised screening coverage in municipalities with more people aged 70–74 in the target screening population, since those diagnosed with CRC were excluded from the invitation list of the screening programme and could no longer participate and be counted in the category “coverage by organised screening”.

The success of organised CRC screening programmes in removing financial barriers to screening with the provision of free FOBTs has been proven in previous studies in which no association between organised FOBT uptake and income was found [7,15]. Our study (Flanders, Belgium), in agreement with two other studies (Korea and Manitoba, Canada) [7,16], even found that income was associated negatively with organised but positively with non-organised screening. The increase in non-organised screening coverage with income is to be expected, since non-organised FOBTs are not free-of-charge. However, the fact that this is observed alongside a

decrease in organised screening coverage is worrisome. As organised FOBTs are population-based and free-of-charge, some people might perceive these organised FOBTs to be of lesser quality and opt for non-organised tests [17]. Further research is needed to test this hypothesis and if it is proven, it is crucial for the Flemish screening programme to reassure the target population that the quality of the organised tests is systematically reviewed by the screening programme, and highlight the additional advantages of having their screening history, results and follow-up information systematically monitored.

Our study found a lower organised FOBT screening coverage in municipalities with a higher percentage of people with non-Belgian/Dutch nationality. The negative association between non-Belgian/Dutch nationality and organised CRC screening has also been shown in a previous Flemish study at the individual level [8]. Two main reasons for FOBT non-participation reported by migrants in Flanders are language issues and embarrassment when talking about CRC screening and stool samples [18]. As screening invitations are written in Dutch, many non-Dutch speaking people expressed a lack of screening information. Some even mistook the invitations for advertisements and discarded them. Older migrants admitted that they depended on their children to translate screening materials but found it uncomfortable talking about CRC screening and stool collection [18]. Language issues also limit migrants' communication with GPs and prevent them from obtaining screening information.

A lower organised screening coverage in migrants may also explain the lower organised screening coverage in municipalities with the highest provision level. These municipalities, with better job opportunities and access to services, have a higher percentage of residents with nationalities other than Belgian/Dutch (9.2%) compared to municipalities with a lower provision level (2.9–4.8%) [19]. It is also possible that with more accessible and concentrated healthcare services, more people underwent 'preventive' colonoscopies and were excluded from organised screening.

In agreement with previous studies at the individual level [20,21], we found a positive association between education level and FOBT screening coverage. This suggests that the gap in FOBT screening between people with high and low education levels still exists and needs to be addressed. In general, it is easier for highly educated people to obtain and comprehend screening information. They also understand the importance of screening better.

Along with the well-reported association between FOBT screening (both organised and non-

organised) and GP visits [15,18], we found pronounced associations between non-organised screening coverage with the average number of patients per GP and the percentage of people who had a global medical dossier handled by a preferred GP. On the one hand, GPs showed a positive impact on promoting CRC screening in the target population. On the other hand, it appeared that despite the availability of the organised programme, some GPs still prescribed a non-organised FOBT to patients instead of referring them to the organised programme. These likely include older GPs who have a large number of patients but are less familiar with screening practices. A previous evaluation also revealed that in Flanders, some GPs were unaware of specific elements of the screening programme. While the recommended follow-up after a positive organised FOBT is a colonoscopy, some GPs prescribed a non-organised FOBT, hoping for a second positive result in order to convince patients to undergo a colonoscopy. Others did not know that in the case of a lost/expired test, GPs or patients can contact the organised programme for another free test [14]. Our findings highlight the importance of providing GPs with sufficient and accurate information about the organised screening programme so that they can effectively assist patients in making informed decisions about screening.

Regarding labour position distribution, municipalities with a higher percentage of jobseekers had a higher organised FOBT screening coverage, while municipalities with a higher percentage of wage earners and the self-employed had a lower organised FOBT screening coverage. One possible reason is that jobseekers have more time to complete a stool test at home. Less time for sample collection at home has been reported as a reason for individuals not choosing FOBT as their preferred CRC screening method compared to (hypothetical) blood and saliva sampling [22]. A previous Flemish study at the individual level also found negative associations between organised FOBT screening with wage earners and being self-employed [8]. It was not possible to compare our findings regarding the association between employment and FOBT screening with other countries due to different systems of employment classification [15,16,20].

The positive association between having a partner and organised FOBT screening has been well-reported in previous studies [20,23]. In this study, we also found a higher organised FOBT screening coverage in municipalities with a higher percentage of people with a partner. Those who have a partner have a higher sense of responsibility towards themselves and their partner and are more likely to engage in healthy lifestyles [24]. Communication between a couple can also promote each other's awareness and involvement in screening [24]. Co-invitation (inviting

partners together) has been suggested as a potential measure to increase CRC screening uptake [25].

Prior literature has reported inconsistent results regarding the association between having a disability and FOBT screening due to different ways of classifying disabilities (type and severity) [26–28]. Although we could not classify disabilities further due to data unavailability, we found a general positive association between the percentage of people with a disability and organised screening coverage. People with disabilities normally value health more highly and are more conscious about preventive care. They contact GPs/specialists more frequently and are more likely to receive screening recommendations [21]. Moreover, disabled people may have financial problems and appreciate the free organised FOBT. This test is also convenient for them since it is mailed to their home and no transportation is needed.

An interesting result that we found with the use of data at the municipality level is that more men in the screening population were associated with a higher organised screening coverage. This finding seemed counter-intuitive at first sight, since previous studies have shown that women are more likely to participate in CRC screening than men [8,20,23,29–31]. However, a closer data inspection revealed that in Flanders, within a municipality, the screening coverage in women was higher compared to men, but among municipalities, more men in the screening population were associated with a higher screening coverage in both men and women, leading to a higher overall screening coverage. A higher rate of positive screening results and adenoma/CRC detection has been consistently reported in men compared to women [5,6,32]. One possible explanation for our finding is that in municipalities with more men in the screening population, resulting in a higher rate of positive results and adenoma/CRC detection in men, people are more exposed to CRC-related information and experiences, and are therefore made more aware and more likely to participate in screening.

A key strength of this study is the ability to obtain data on non-organised FOBT screening, which is currently lacking in other regions/countries. Moreover, the use of administrative data eliminated selection and recall bias associated with self-reported data. Since the amount of missing data was small (1.5%), selection bias due to missing data was unlikely. Collider bias was avoided with the use of DAG to identify covariates for adjustment (details in Methods).

Several limitations need to be acknowledged. Firstly, our results at the municipality level may be subject to ecological fallacy, meaning some associations may not hold true at the individual

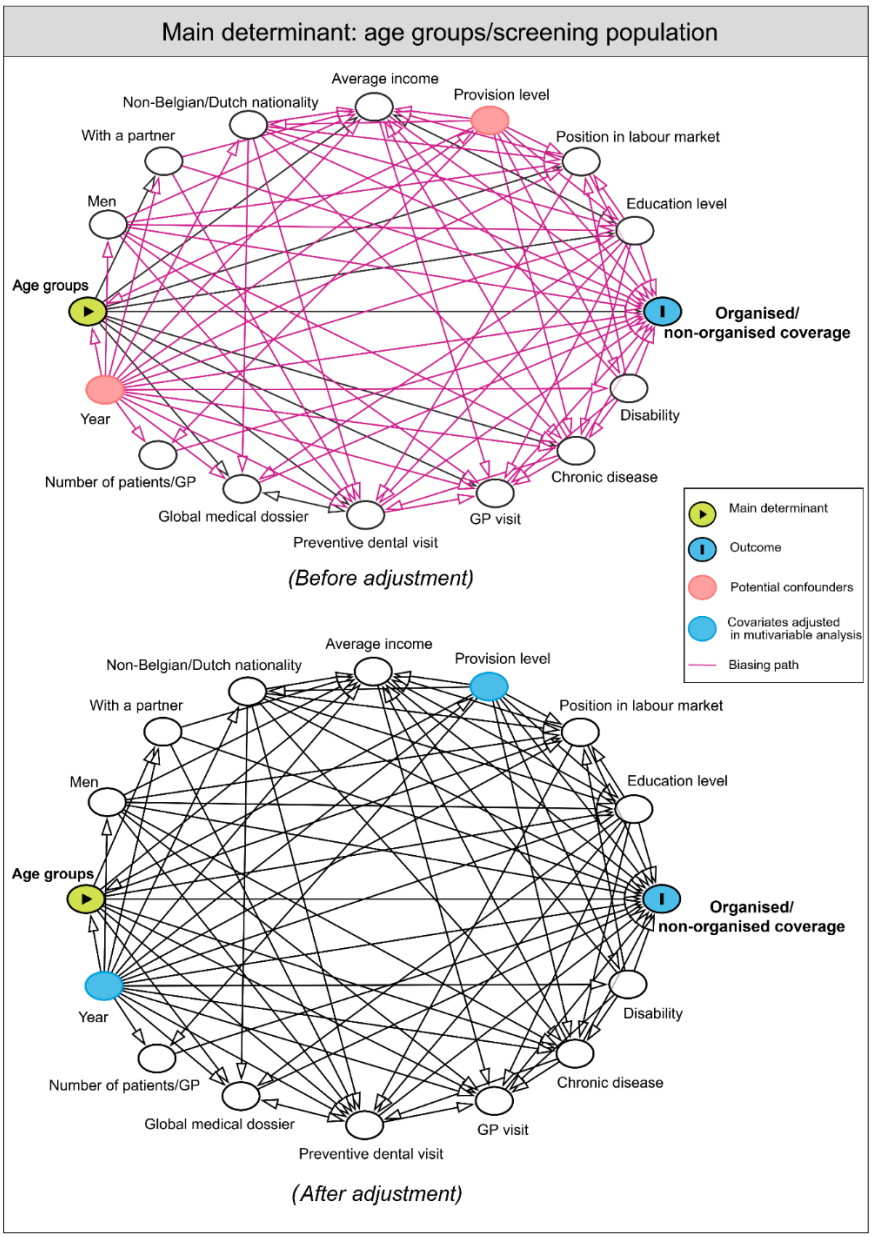
level. Secondly, most of the independent variables were measured for the complete municipality population and used as proxies for the screening population. Nevertheless, the surrounding environment has proven to influence individuals' health behaviours and decisions significantly [33], and our results substantiate previous findings at individual level. Thirdly, we could not include non-organised FOBTs ordered from pharmacies/online because data were unavailable. Non-organised screening coverage might be underestimated. Fourthly, data on reasons for the prescription of non-organised FOBTs was unavailable, so we could not judge whether a non-organised FOBT was taken for a screening or diagnostic/therapeutic reason. Some of the non-organised FOBTs might be appropriately prescribed for a specific indication which fell outside the remit of the organised screening programme. Finally, although it has been well reported that the younger group (50–59) participate less in FOBT screening [5,8,15,29,30], we could not fully assess the association between this age group and FOBT screening coverage since ages 50–54 were not yet included in the target age range in the study period.

3.6. Conclusions

Our findings showed that higher average income, lower education level and non-Belgian/Dutch nationality were related to a lower organised FOBT screening coverage while older age (70–74) was related to lower screening coverages for both organised and non-organised screening. GP visits were positively associated with screening coverages for both screening strategies, highlighting the important role of GPs in promoting CRC screening among the target population. The associations between the average number of patients per GP and having a global medical dossier handled by a preferred GP with non-organised screening coverage were more pronounced compared to organised screening coverage. Efforts are needed to provide GPs with sufficient and accurate information about organised and non-organised CRC screening so that they can effectively assist patients in making informed decisions about screening. It is also crucial to identify and address barriers to CRC screening, especially organised CRC screening, in the subpopulations with lower screening coverage. The aim is to first and foremost promote screening among non-participants so that they are covered by screening (regardless of the screening strategy). Additionally, from both economic and organisational points of view, those who have undertaken non-organised FOBTs for CRC screening should be encouraged to switch to organised screening. Future research at a lower geographical or individual level and

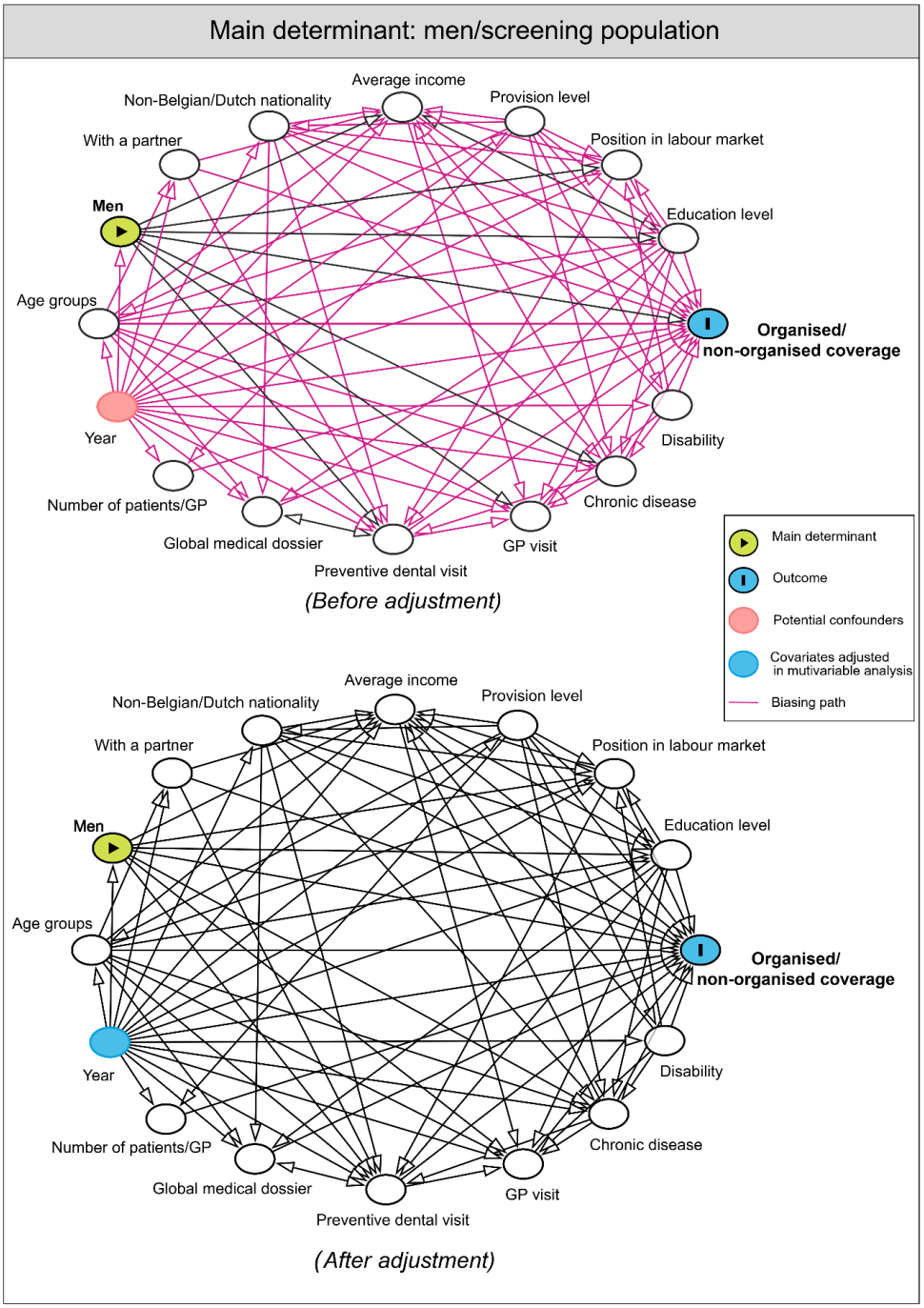
more in-depth investigation into the barriers to FOBT screening in specific subpopulations are needed to verify our findings.

Supplementary materials

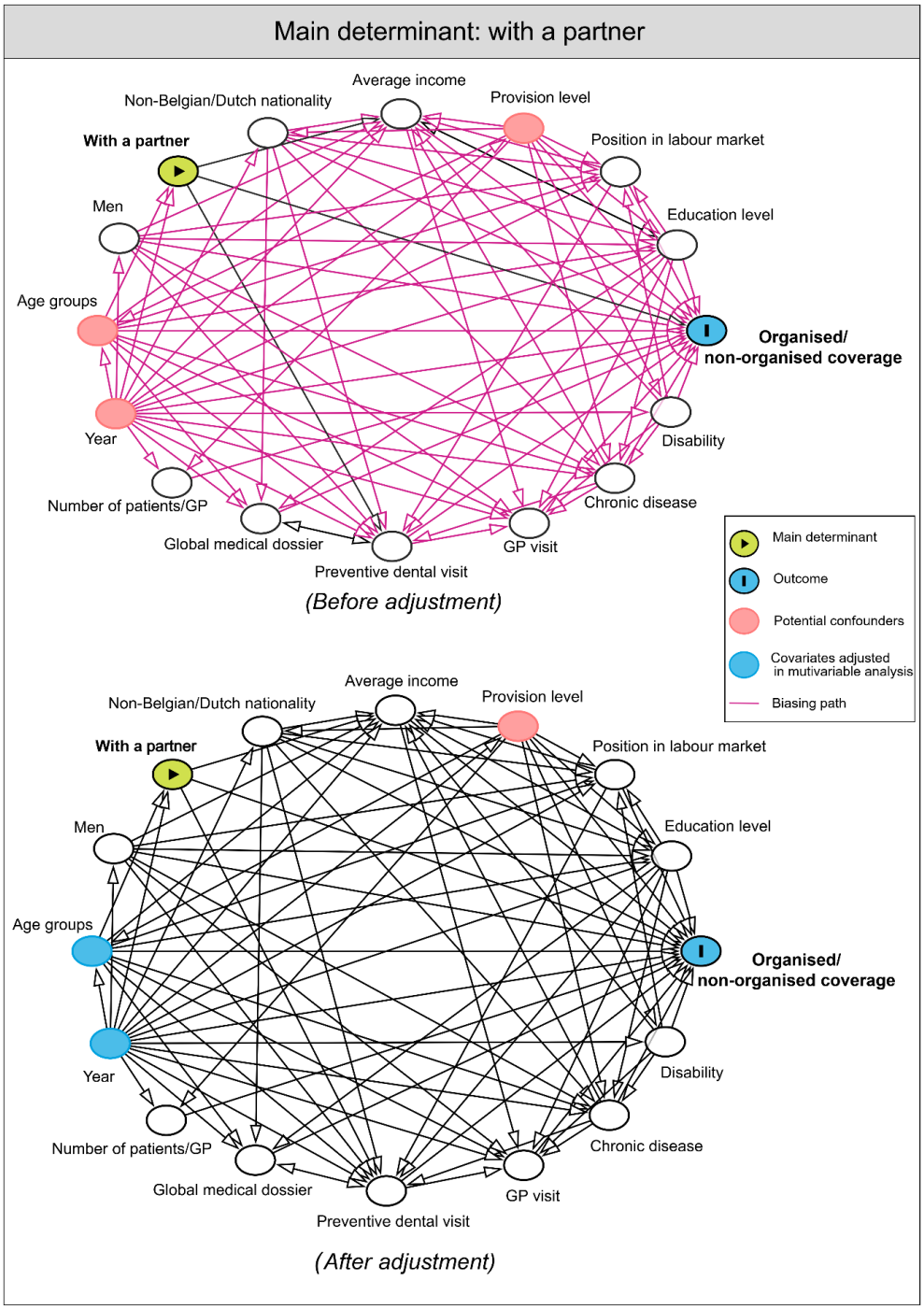


Supplementary Figure S1 Causal directed acyclic graphs (DAGs) constructed to identify covariates for adjustment in multivariable analyses. After covariate adjustment, no causal paths (indicated by purple lines) are present.

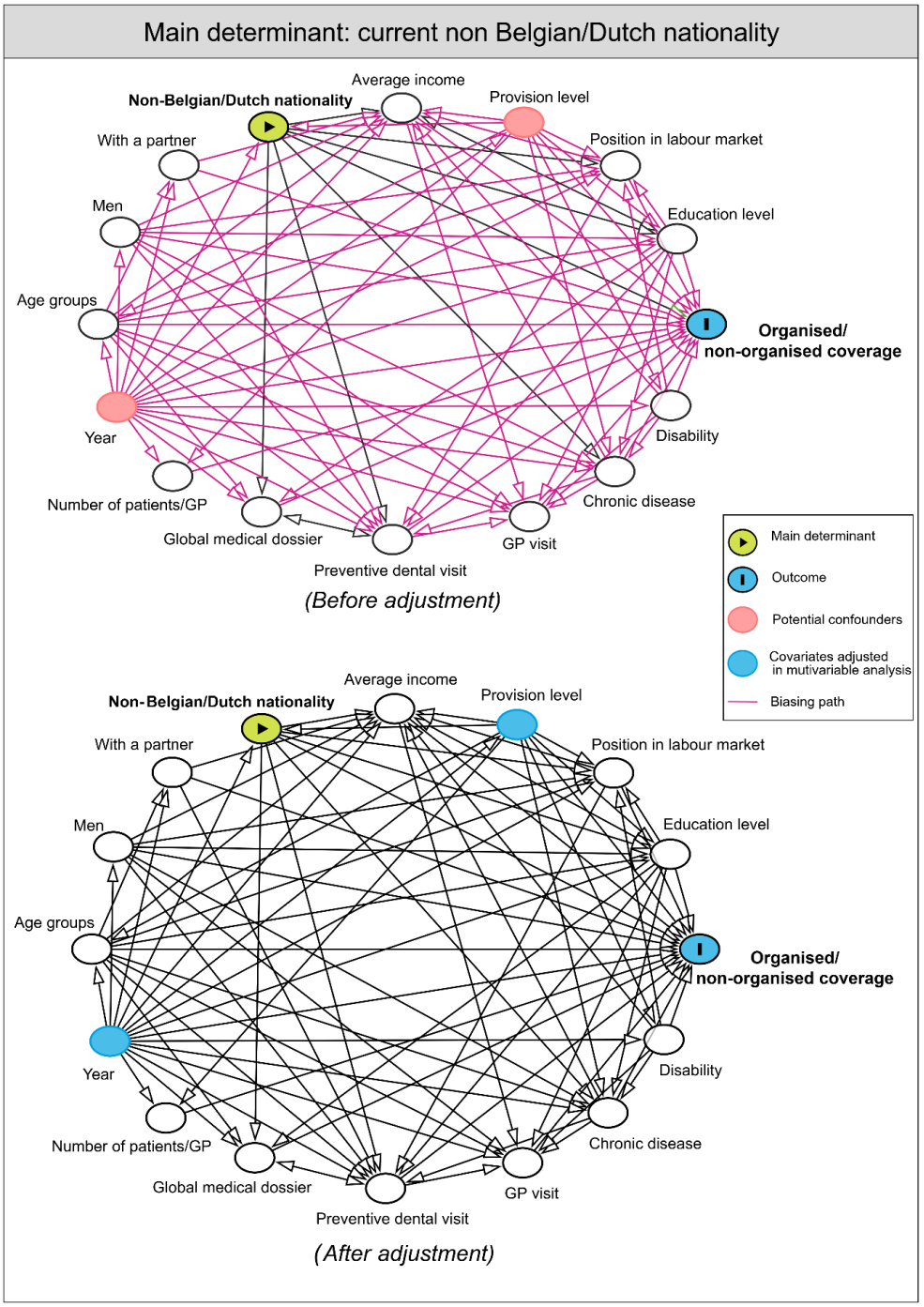
Supplementary Figure S1 Continued.



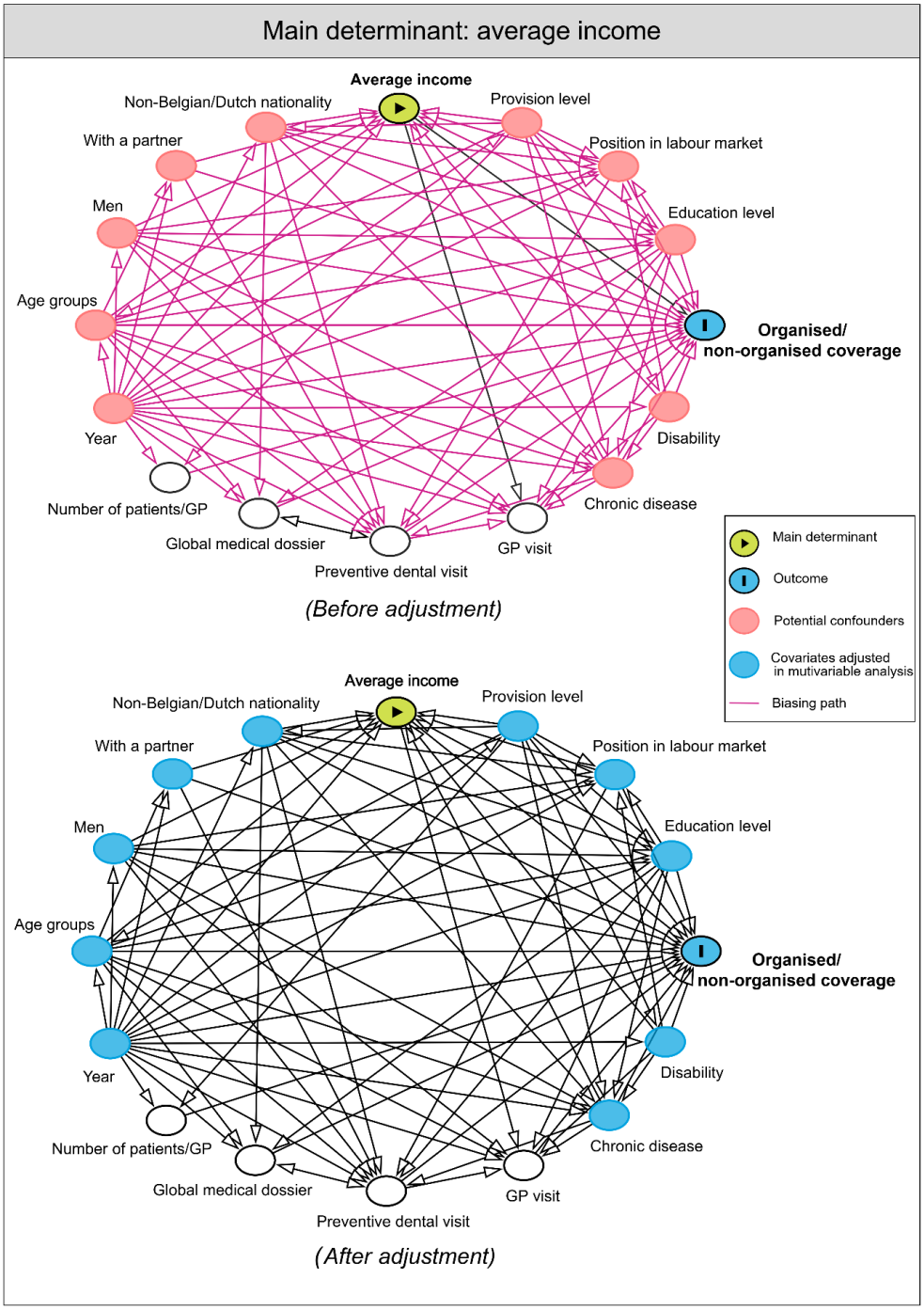
Supplementary Figure S1 Continued.



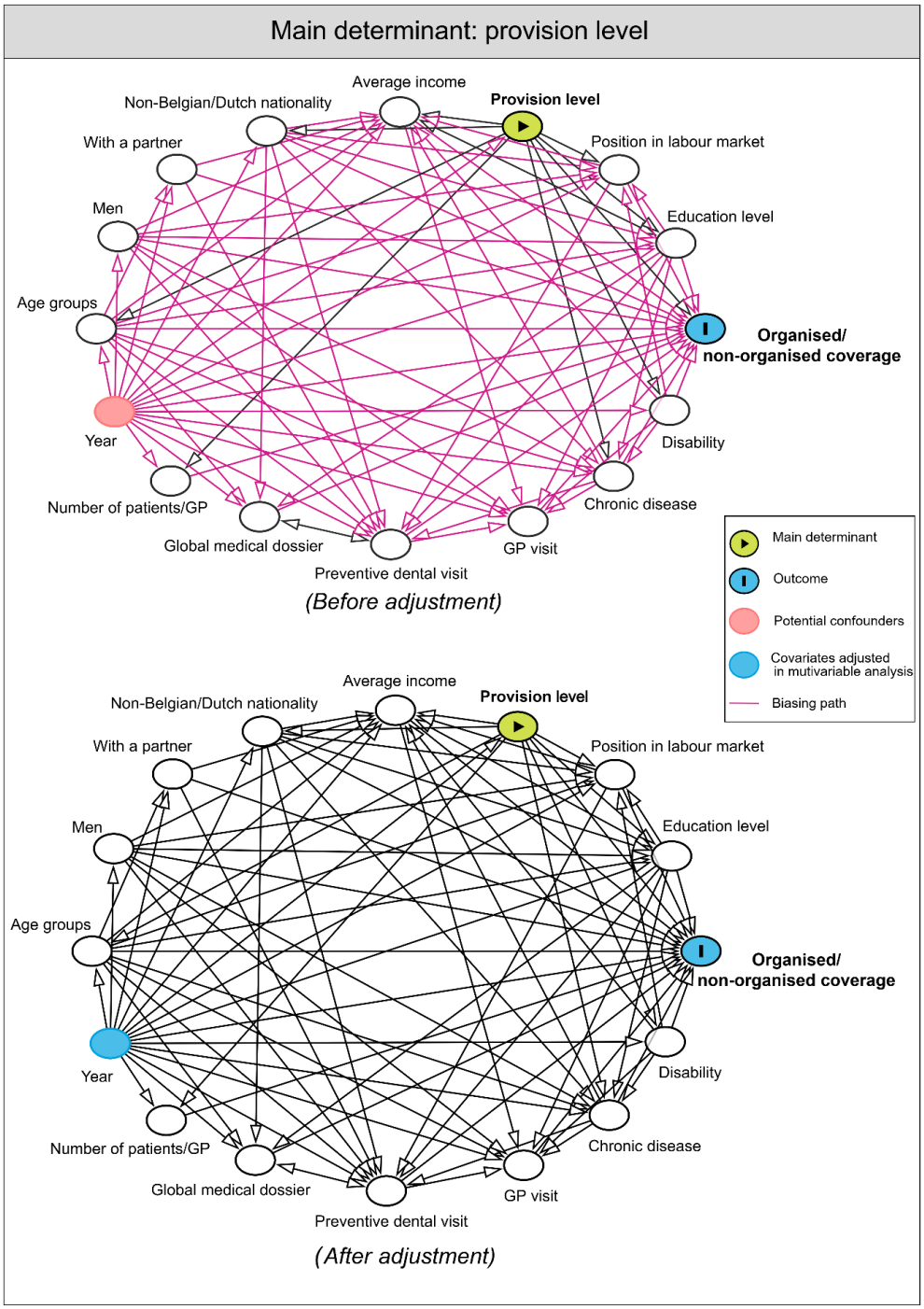
Supplementary Figure S1 Continued.



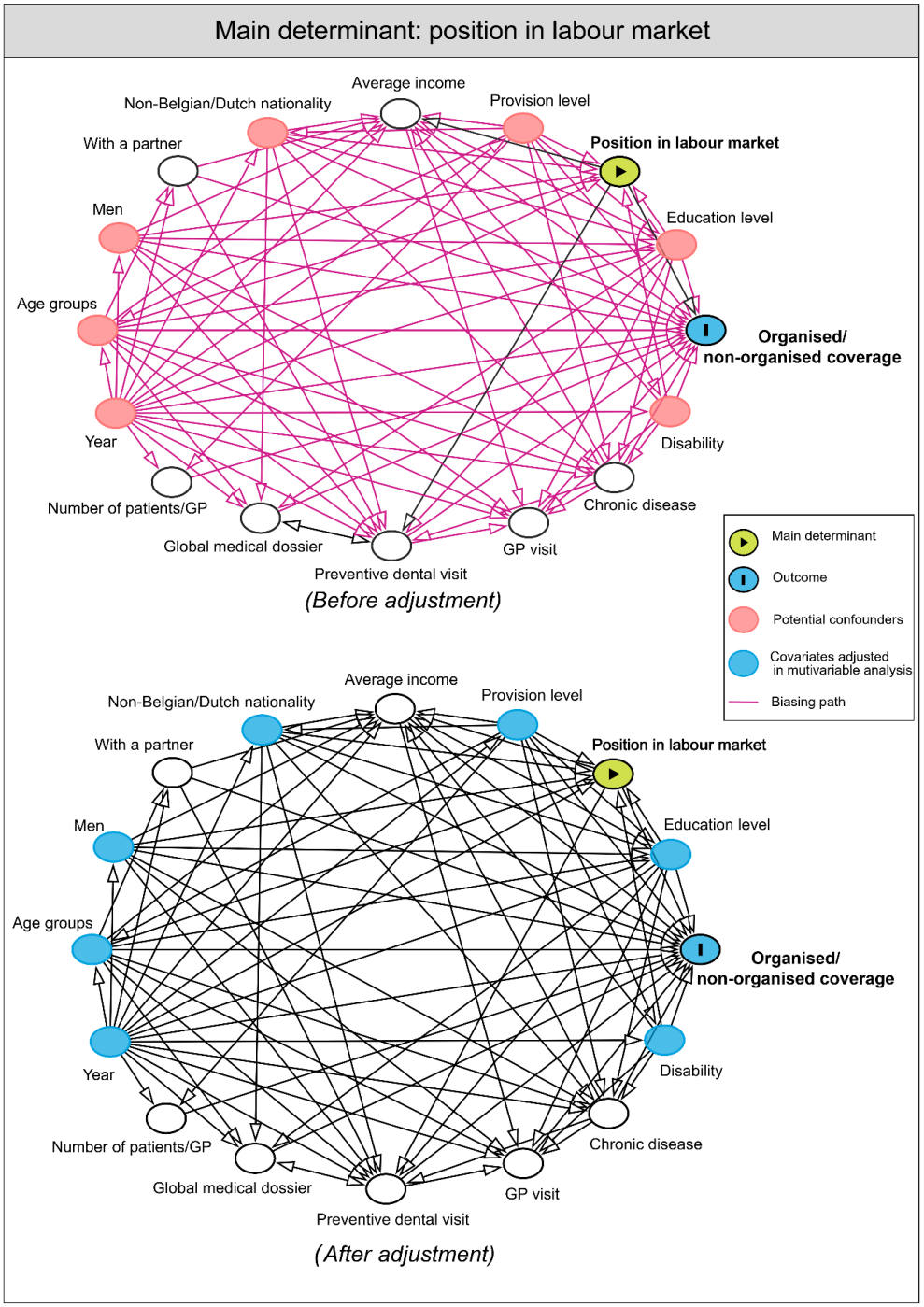
Supplementary Figure S1 Continued.



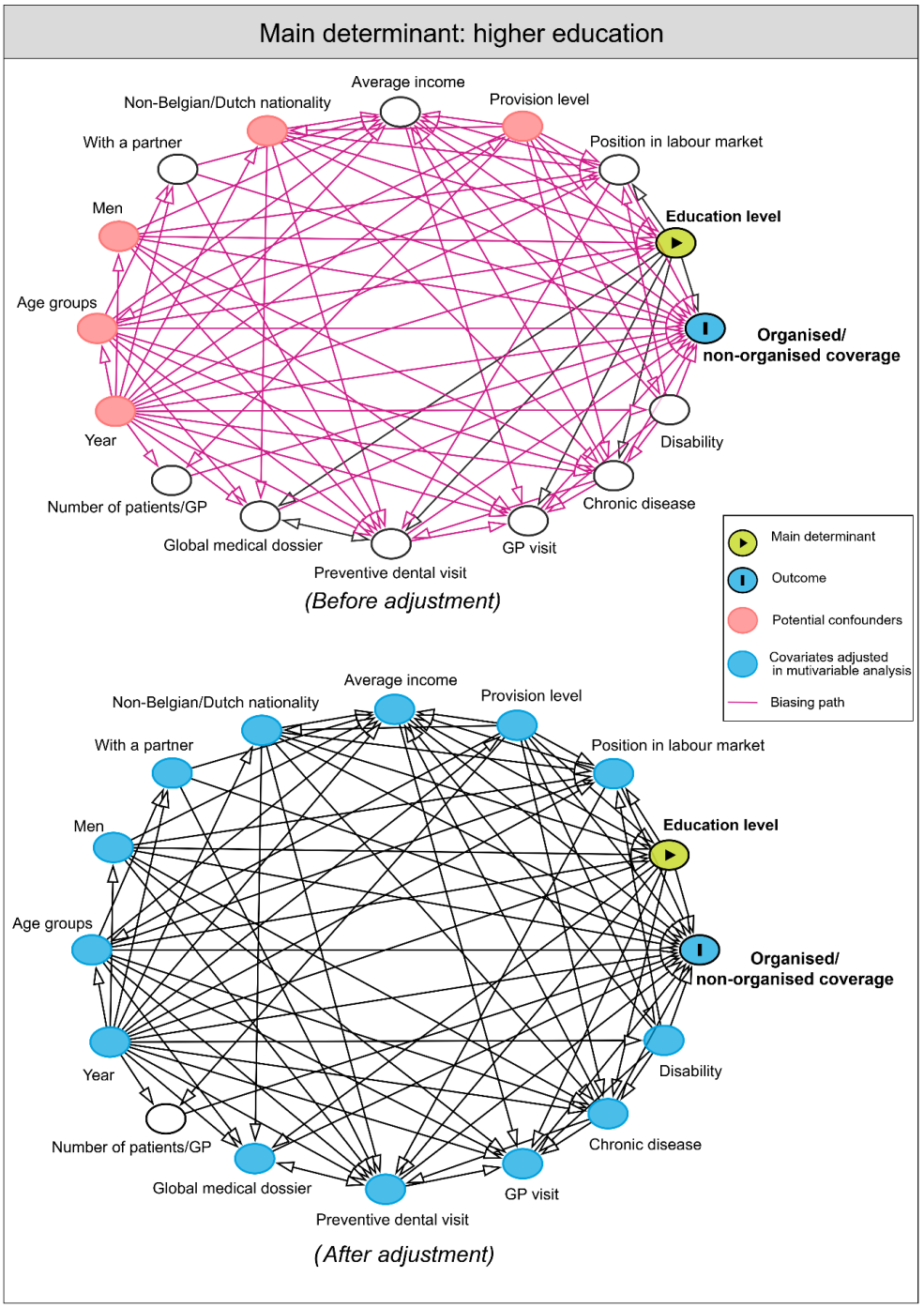
Supplementary Figure S1 Continued.



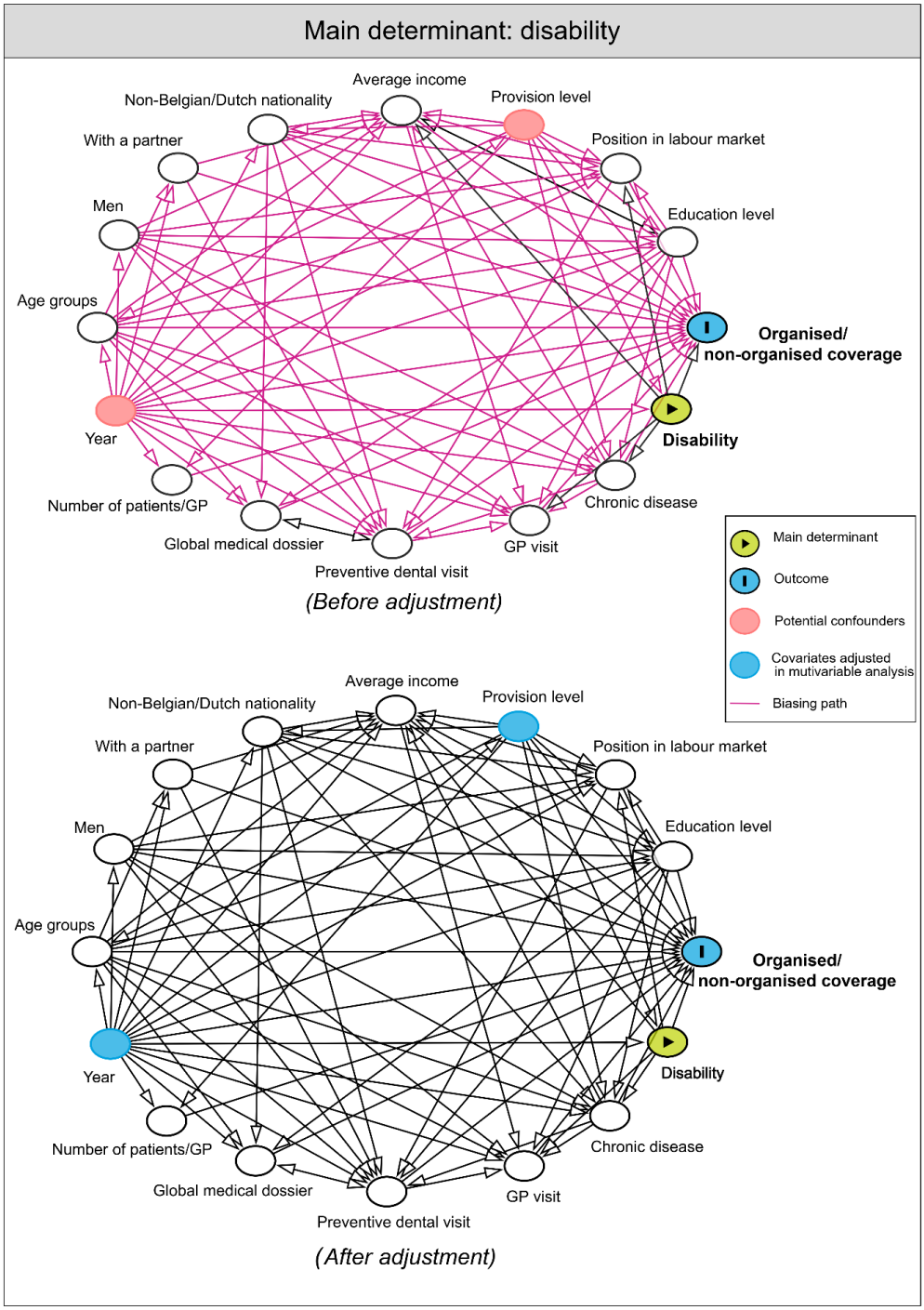
Supplementary Figure S1 Continued.



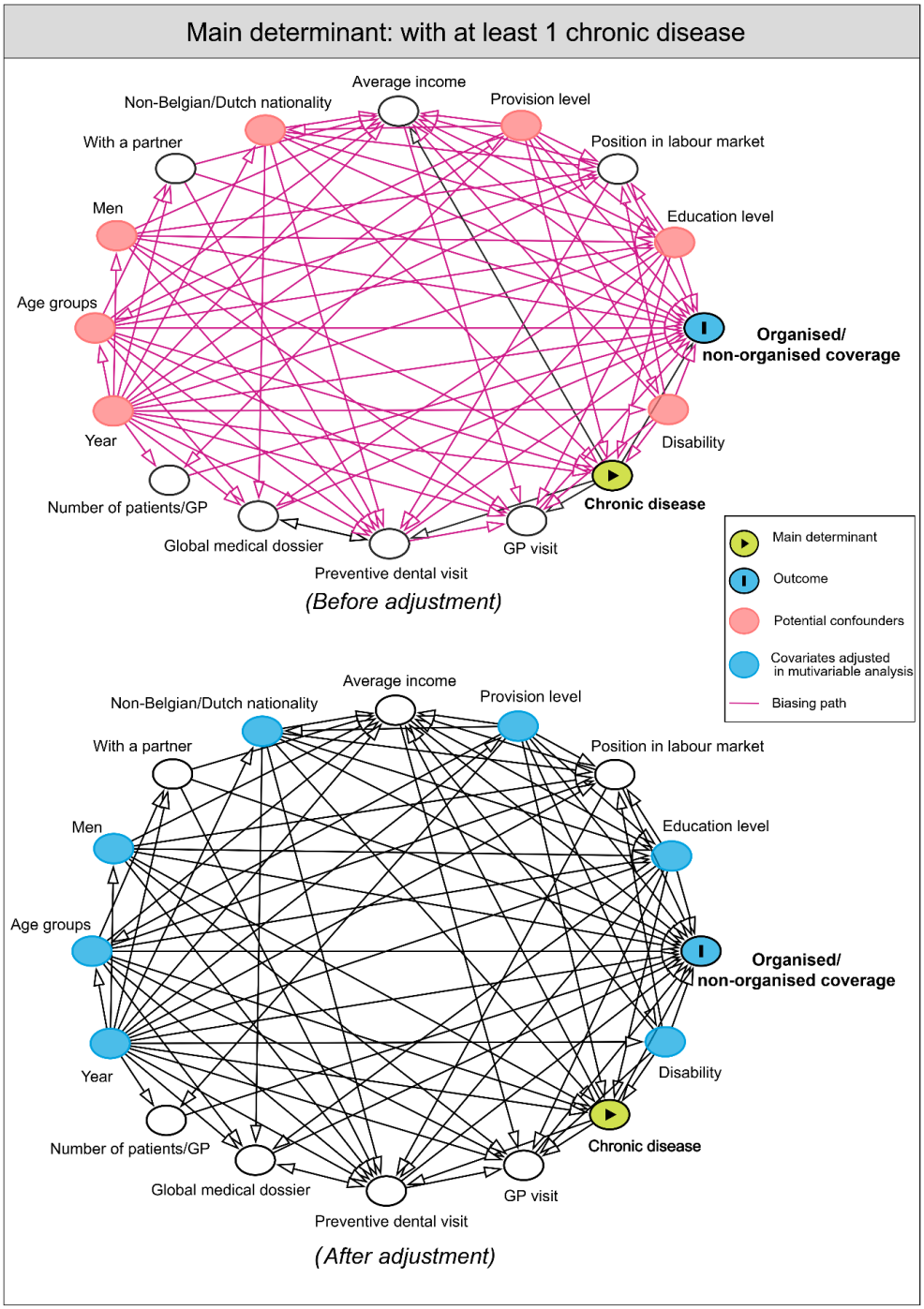
Supplementary Figure S1 Continued.



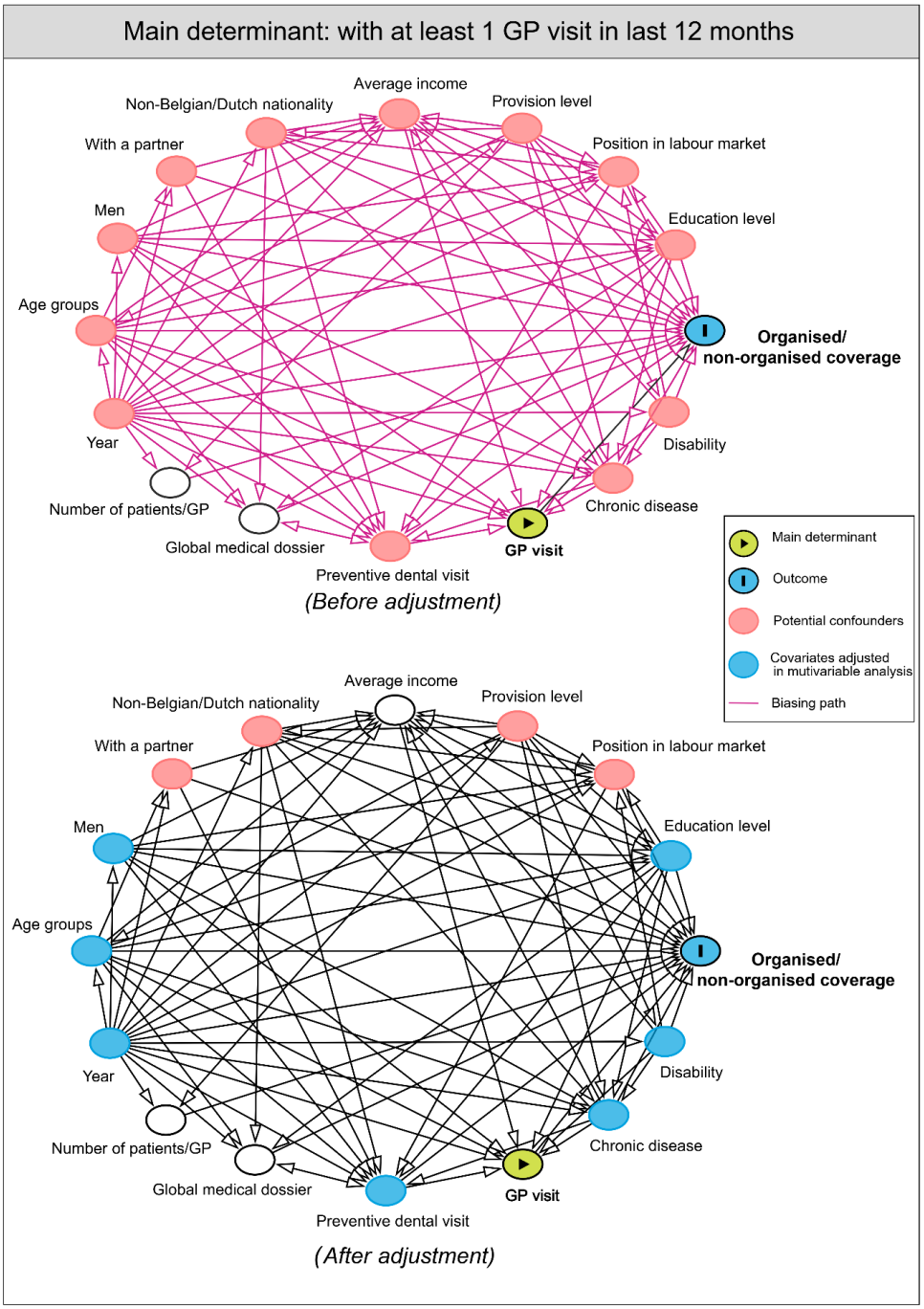
Supplementary Figure S1 Continued.



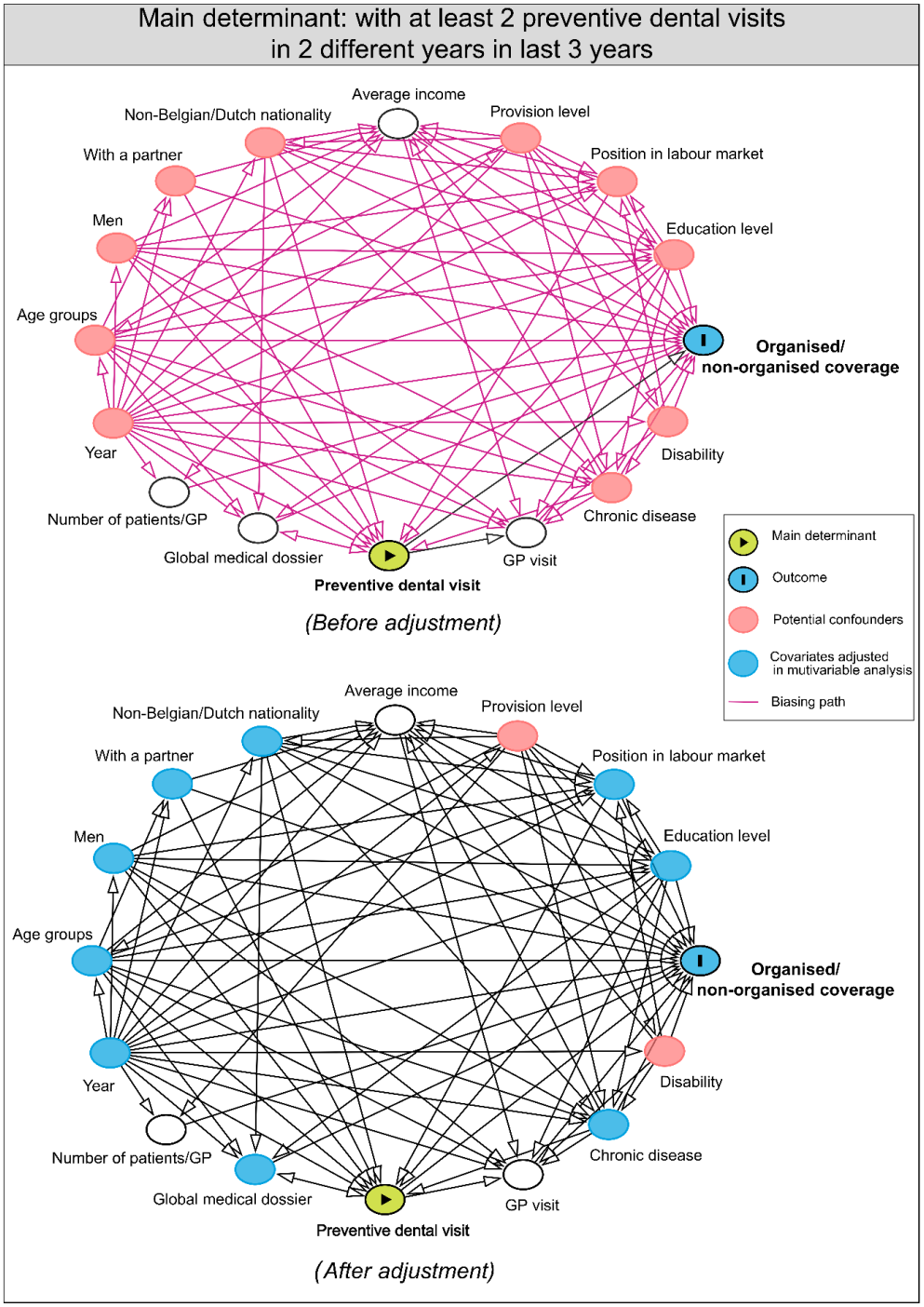
Supplementary Figure S1 Continued.



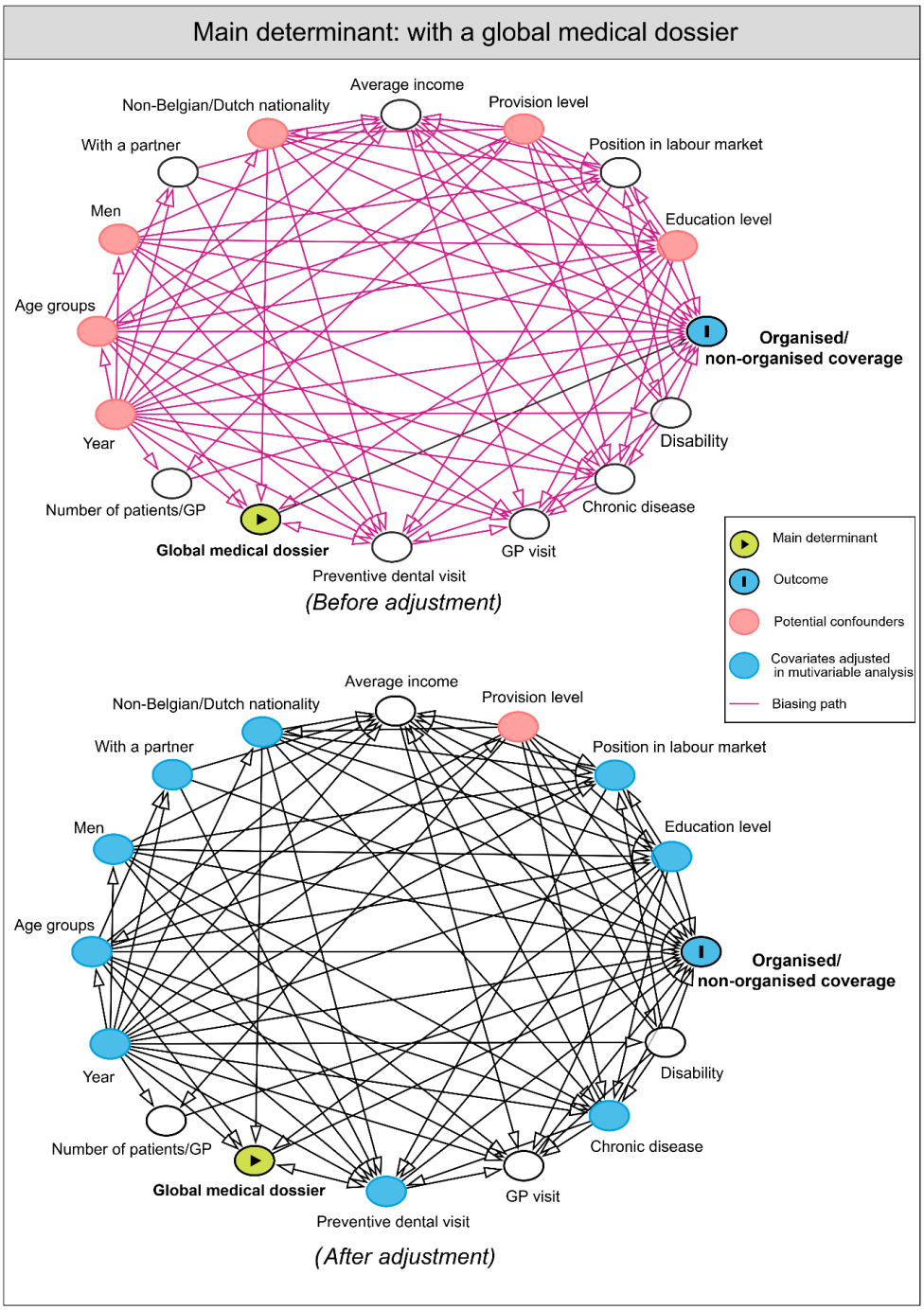
Supplementary Figure S1 Continued.



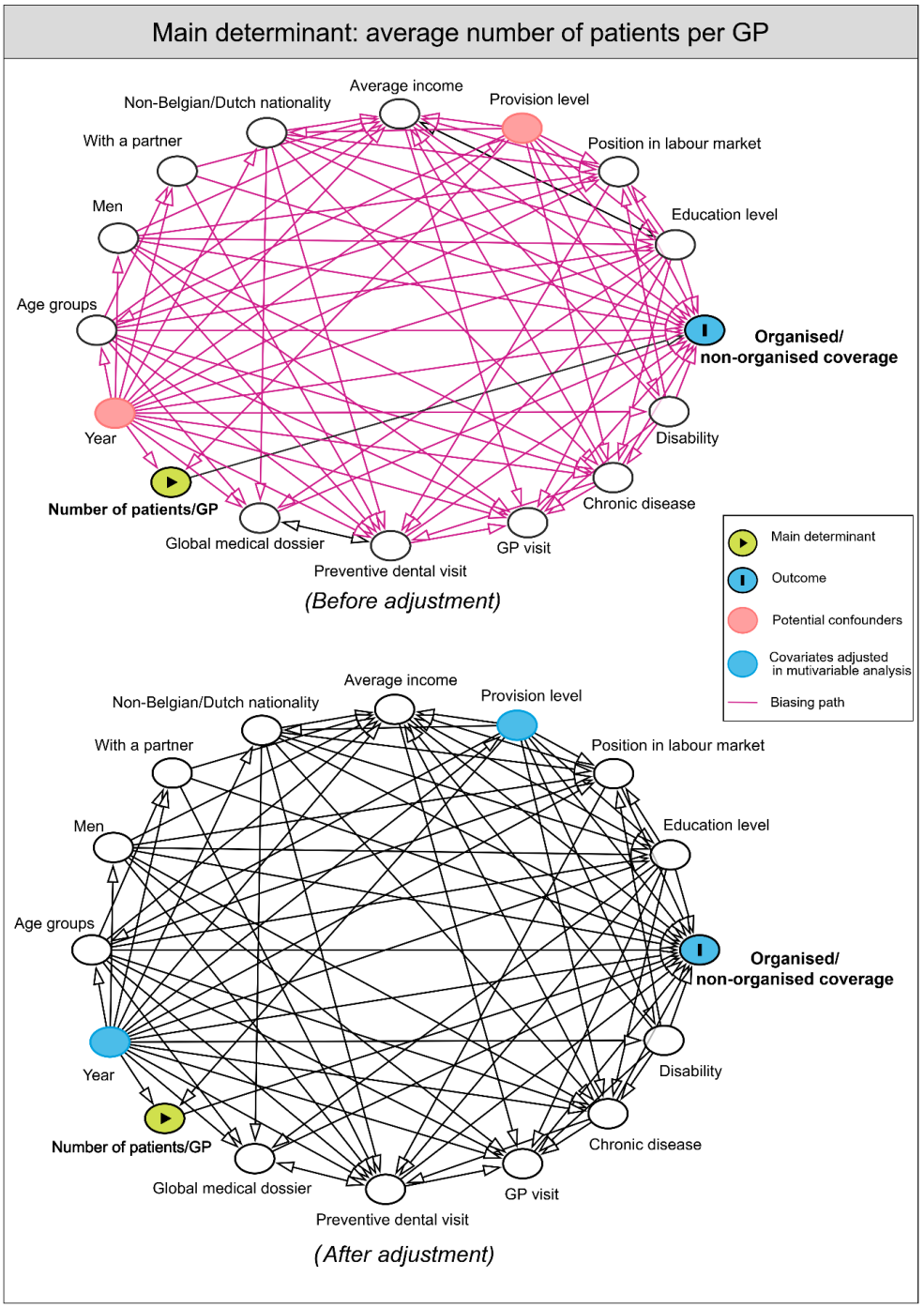
Supplementary Figure S1 Continued.



Supplementary Figure S1 Continued.



Supplementary Figure S1 Continued.



References

1. Bray, F.; Ferlay, J.; Soerjomataram, I.; Siegel, R.L.; Torre, L.A.; Jemal, A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J. Clin. 2018, 68, 394–424.
2. Belgian Cancer Registry. Requesting Specific Data 2020. Available online: https://kankerregister.org/Requesting%20specific%20data (accessed on 30 October 2020)
3. STATBEL. Structure of the Population 2020. Available online: https://statbel.fgov.be/en/themes/population/structure-population (accessed on 16 February 2021)
4. Publications Office of the European Union. European Guidelines for Quality Assurance in Colorectal Cancer Screening and Diagnosis, 1st ed.; Segnan, N., Patnick, J., von Karsa, L., Eds.; Publications Office of the European Union: Luxembourg, Luxembourg, 2010.
5. Ponti, A., Anttila, A., Ronco, G., Senore, C., Basu, P., Segnan, N., Tomatis, M., Žakelj, M.P., Dillner, J., Fernan, M.; et al. Cancer Screening in the European Union. Report on the implementation of Council Recommendation on Cancer Screening. Brussels: European Commission 2017. Available online: https://ec.europa.eu/health/sites/health/files/major_chronic_diseases/docs/2017_cancerscreening_2ndreportimplementation_en.pdf (accessed on 16 February 2021)
6. Center for Cancer Detection. Monitoring Report of the Flemish Colorectal Cancer Screening Programme 2020. Available online: https://www.bevolkingsonderzoek.be/sites/default/files/atoms/files/Jaarrapport%202020.pdf (accessed on 1 December 2020)
7. Decker, K.M.; Demers, A.A.; Nugent, Z.; Biswanger, N.; Singh, H. Reducing income-related inequities in colorectal cancer screening: Lessons learned from a retrospective analysis of organised programme and non-programme screening delivery in Winnipeg, Manitoba. BMJ Open 2016, 6, e009470.
8. Hoeck, S.; van de Veerdonk, W.; De Brabander, I.; Kellen, E. Does the Flemish colorectal cancer screening programme reach equity in FIT uptake? Eur. J. Public Health 2019, 29, 1108–1114.
9. De Maesschalck, F.; Van Hecke, E. Equipment Level of the Flemish Municipalities 2018. Available online: https://www.west-vlaanderen.be/sites/default/files/2018-12/Uitrustingsgraad-van-de-vlaamse-gemeenten-typologie-.pdf (accessed on 17 August 2020)
10. Sauer, B.; Brookhart, M.; Roy, J.; VanderWeele, T.J. Covariate Selection. In Developing a Protocol for Observational Comparative Effectiveness Research: A User's Guide. Velentgas, P., Dreyer, N., Nourjah, P., et al., Eds.; Agency for Healthcare Research and Quality: Rockville, MD, USA, 2013; pp. 93–108.
11. Peduzzi, P.; Concato, J.; Kemper, E.; Holford, T.R.; Feinstein, A.R. A simulation study of the number of events per variable in logistic regression analysis. J. Clin. Epidemiol. 1996, 49, 1373–1379.
12. von Elm, E.; Altman, D.G.; Egger, M.; Pocock, S.J.; Gøtzsche, P.C.; Vandenbroucke, J.P. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: Guidelines for reporting observational studies. BMJ 2007, 335, 806–808.
13. Kobayashi, L.C.; von Wagner, C.; Wardle, J. Perceived Life Expectancy Is Associated with Colorectal Cancer Screening in England. Ann. Behav. Med. 2017, 51, 327–336.
14. Hoeck, S.; Hoste, J.; Vandeputte, L.; Dekker, N. Colorectal Cancer Screening 2017. Available online: https://www.domusmedica.be/sites/default/files/Richtlijn%20Dikkedarmkankerscreening.pdf (accessed on 6 November 2020)
15. Fon Sing, M.; Leuraud, K.; Duport, N. Characteristics of French people using organised colorectal cancer screening. Analysis of the 2010 French Health, Healthcare and Insurance Survey. Prev. Med. 2013,

57, 65–8.

16. Suh, M.; Choi, K.S.; Lee, H.Y.; Hahm, M.I.; Lee, Y.Y.; Jun, J.K.; Park, E.C. Socioeconomic Disparities in Colorectal Cancer Screening in Korea: A Nationwide Cross-Sectional Study. Medicine (Baltim.) 2015, 94, e1368.

17. Turnbull, E.; Priaulx, J.; de Kok, I.; Lansdorp-Vogelaar, I.; Anttila, A.; Sarkeala, T.; Senore, C.; Segnan, N.; Csanádi, M.; Pitter, J.; et al. Results of a health systems approach to identify barriers to population-based cervical and colorectal cancer screening programmes in six European countries. Health Policy 2018, 122, 1206–1211.

18. Hoeck, S.; Van Roy, K.; Willems, S. Barriers and facilitators to participate in the colorectal cancer screening programme in Flanders (Belgium): A focus group study. Acta Clin. Belg. 2020, 1–8. doi: 10.1080/17843286.2020.1783906

19. Statistics Flanders. Population by Nationality 2019. Available online: https://www.statistiekvlaanderen.be/en/population-by-nationality-0 (accessed on 18 August 2020)

20. Frederiksen, B.L.; Jorgensen, T.; Brasso, K.; Holten, I.; Osler, M. Socioeconomic position and participation in colorectal cancer screening. Br. J. Cancer 2010, 103, 1496–501.

21. Wools, A.; Dapper, E.A.; de Leeuw, J.R. Colorectal cancer screening participation: A systematic review. Eur. J. Public Health 2016, 26, 158–68.

22. Osborne, J.M.; Flight, I.; Wilson, C.J.; Chen, G.; Ratcliffe, J.; Young, G.P. The impact of sample type and procedural attributes on relative acceptability of different colorectal cancer screening regimens. Patient Prefer. Adherence 2018, 12, 1825–1836.

23. Artama, M.; Heinävaara, S.; Sarkeala, T.; Prättälä; R; Pukkala, E.; Malila, N. Determinants of non-participation in a mass screening program for colorectal cancer in Finland. Acta Oncol. 2016, 55, 870–874.

24. Lewis, M.A.; Rook, K.S. Social control in personal relationships: Impact on health behaviors and psychological distress. Health Psychol. 1999, 18, 63–71.

25. van Jaarsveld, C.H.; Miles, A.; Edwards, R.; Wardle, J. Marriage and cancer prevention: Does marital status and inviting both spouses together influence colorectal cancer screening participation? J. Med. Screen 2006, 13, 172–6.

26. Kellen, E.; Nuyens, C.; Molleman, C.; Hoeck, S. Uptake of cancer screening among adults with disabilities in Flanders (Belgium). J. Med. Screen 2020, 27, 48–51.

27. Shin, D.W.; Chang, D.; Jung, J.H.; Han, K.; Kim, S.Y.; Choi, K.S.; Lee, W.C.; Park, J.H.; Park, J.H. Disparities in the Participation Rate of Colorectal Cancer Screening by Fecal Occult Blood Test among People with Disabilities: A National Database Study in South Korea. Cancer Res. Treat 2020, 52, 60–73.

28. Iezzoni, L.I.; Kurtz, S.G.; Rao, S.R. Trends in colorectal cancer screening over time for persons with and without chronic disability. Disabil. Health J. 2016, 9, 498–509.

29. Portillo, I.; Arana-Arri, E.; Gutiérrez-Ibarluzea, I.; Bilbao, I.; Luis Hurtado, J.; Sarasqueta, C.; Idigoras, I.; Bujanda, L. Factors related to the participation and detection of lesions in colorectal cancer screening programme-based faecal immunochemical test. Eur. J. Public Health 2018, 28, 1143–1148.

30. Pornet, C.; Dejardin, O.; Morlais, F.; Bouvier, V.; Launoy G. Socioeconomic determinants for compliance to colorectal cancer screening. A multilevel analysis. J. Epidemiol. Community Health 2010, 64, 318–324.

31. Sun, J.; March, S.; Ireland, M.J.; Crawford-Williams, F.; Goodwin, B.; Hyde, M.K.; Chambers, S.K.; Aitken, J.F.; Dunn, J. Socio-demographic factors drive regional differences in participation in the National Bowel Cancer Screening Program—An ecological analysis. Aust. N. Z. J. Public Health 2018, 42, 92–97.

32. van de Veerdonk, W.; Hoeck, S.; Peeters, M.; van Hal, G.; Francart, J.; de Brabander, I.

Occurrence and characteristics of faecal immunochemical screen-detected cancers vs non-screen-detected cancers: Results from a Flemish colorectal cancer screening programme. United Eur. Gastroenterol J. 2020, 8, 185–194.

33. McAlister, A.L.; Perry, C.L.; Parcel, G.S. How individuals, environments, and health behaviors interact: Social cognitive theory. In Health Behavior and Health Education: Theory, Research and Practice, 4th ed; Glanz, K., Rimer, B.K., Viswanath, K., Eds.; Jossey-Bass: San Francisco, CA, USA, 2008.

Chapter 4

Self-reported reasons for inconsistent participation in colorectal cancer screening using FIT in Flanders, Belgium

Sarah Hoeck[1,2] and Thuy Ngan Tran[1,2]

1. Centre for Cancer Detection, 8000 Bruges, Belgium

2. Social Epidemiology and Health Policy, University of Antwerp, 2610 Antwerpen, Belgium

(Published in *Gastrointest. Disord. 2023; 5(1):1-14*)

4.1. Abstract

Background: In Flanders, the uptake in the population-based colorectal cancer (CRC) screening program (using fecal immunochemical test, FIT) is suboptimal (~50%). This study explored the reasons for inconsistent participation in FIT screening among irregular participants in Flanders.

Methods: An online survey with both open questions and fixed statements was sent to irregular participants (2016–2018) in the Flemish CRC screening program. A reminder email followed eight weeks after the first email. Data analysis used both qualitative and quantitative approaches. Post-stratification weights based on gender, age group, and the first two digits of the postcode were employed to reduce non-response bias.

Results: In total, 5328 out of 19,592 irregular participants responded to the survey. While the main reasons not to participate were related to 'postponing participation' and 'having other priorities', the main reasons to participate were related to the importance of (preventive) health checks. The role of general practitioners (GPs) in promoting CRC screening also emerged as an important theme among the respondents' answers (based on fixed statements).

Conclusions: The study reported the main reasons for inconsistent participation in FIT screening for CRC in Flanders. The findings are helpful in guiding tailored interventions to increase FIT screening uptake in the region.

4.2. Introduction

The Flemish colorectal cancer (CRC) screening program uses a centralized invitation procedure: invitations (with leaflet and fecal immunochemical test, FIT) are sent by the Centre for Cancer Detection (CCD) by post. Participation is free of charge. The target population (50–74 years old) receives a new invitation 24 months after their last screening (or after their last invitation for non-participants) [1]. The cost of diagnostic colonoscopy (DC) following a positive fecal immunochemical test (FIT) screening is reimbursed by the Belgian healthcare system with a certain percentage out-of-pocket expense.

The screening uptake has varied from 48.4% to 52.5% since the start of the program in 2013 and is suboptimal [2,3]. During 2017–2021, among individuals with at least two invitation rounds, 45% were adherent to all the invitations, 14% were irregular participants, and 40%

were non-responsive to all invitations [internal data CCD]. In Flanders, the five-year relative survival rate for CRC (2014–2018) is 74.9% [4], and it is even 97.6% for Stage I compared with only 18.7% for Stage IV [5]. These results highlight the clinical importance of participation in CRC screening and screening adherence.

Reasons not to participate in CRC screening have been widely documented, and comprise a 'lack of symptoms', 'feeling healthy', 'no family CRC history', 'general lack of knowledge', 'being unaware of the usefulness of CRC screening', 'fear of cancer', 'fear of a positive result', 'fear of a follow-up colonoscopy', and 'lack of a provider recommendation' [6–17]. In Flanders, 'fear of cancer', 'shame', and 'feeling healthy' have emerged as key barriers to screening [18]. Prior research conducted among irregular participants in Catalonia, Spain, and Florida, US, indicated that 'procrastination' [19], 'cancer fear' and 'being unaware of the need to repeat screening' play a role in CRC screening (non)adherence [20–22].

It is known that the reasons for inconsistent participation in CRC screening are dependent on the local context and culture. Since this topic has not been researched in Belgium, we conducted the current study to investigate the reasons behind people's decision to (re)start or skip participation in CRC screening in Flanders (57% of the Belgian population). Our results help to understand the potential triggers to CRC screening by FIT that can be encouraged as well as barriers to screening that can be addressed by, for example, adapting communication materials or strategies in informing the target population in order to eventually increase re(start) FIT screening.

4.3. Results

4.3.1. Sociodemographic characteristics of the survey respondents

In total, 5328 of the 19,592 invitees (27.6%) responded to the survey, of whom 640 (12.0%) responded after the reminder email. The sociodemographic characteristics of the survey respondents are presented in **Table 1**. More men (55.0%) vs. women and more younger people aged 59–64 years (57.9%) vs. 65–75 years responded to the survey. The majority of respondents had a Belgian nationality (92.4%), spoke Dutch (the local language in Flanders) at home (97.4%), and were married or cohabiting without children living at home (59.9%). Three quarters of them had higher than a secondary education, 87.3% were full-time/part-time

employees or retired. Almost 87% of the respondents were in a fair or good financial situation (neutral/easy/very easy) and 89% did not have to suspend a medical appointment or medical procedure due to financial problems.

Table 1. Sociodemographic characteristics of the survey respondents (absolute numbers and unweighted percentages).

Variable	Category	N (%)
Sex	Male	2932 (55.0)
	Female	2396 (45.0)
Age	59–64	3085 (57.9)
	65–69	1479 (27.8)
	70–75	764 (14.3)
Nationality at birth	Belgian	4922 (92.4)
	Dutch	107 (5.6)
	other	51 (2.6)
Spoken language at home	Dutch	1871 (97.4)
	French	30 (1.6)
	Other	19 (1.0)
Highest educational level	No degree or primary	134 (7.0)
	Lower secondary	344 (17.9)
	Higher secondary	699 (36.4)
	Higher education	741 (38.6)
	Other	2 (0.1)
Economic status	(Early)retirement	1036 (54.0)
	Employee (full-time or part-time)	639 (33.3)
	Jobseeker	48 (2.5)
	Minimum wage/social allowance	5 (0.3)
	Full-time housewife/houseman and others	63 (3.3) + 6 (0.3)
	Allowance for long-term illness/allowance for disabled	123 (6.4)
Living situation	Cohabitant or married without children living at home	1150 (59.9)
	Cohabitant or married with children living at home	264 (13.8)
	Single with children living at home (with or without partner that lives elsewhere)	67 (3.5)
	Single (including widow)	439 (22.9)
Financial situation	Very difficult	59 (3.1)
	Difficult	192 (10.0)
	Neutral	950 (49.5)
	Easy	530 (27.6)
	Very easy	82 (9.5)
	Missing	7 (0.4)
Ever suspended a medical appointment/procedure due to financial problems?	Yes	207 (10.8)
	No	1709 (89.0)
	Missing	4 (0.2)
Total		5328 (100)

4.3.2. Results of survey questions

4.3.2.1. Reasons not to participate

Figures 1 and **2** present reasons not to participate in FIT screening answered by the respondents in open questions and fixed statements (applicable or not), grouped into subthemes. Categories with <20 answers were left out. Only 297 respondents (5.6%) did not fill in the open question or filled in 'I don't know'. **Figure 1** summarizes reasons not to participate that were reported in both the open answers as fixed statements; **Figure 2** summarizes reasons not to participate that were reported only in one source but not the other.

The most reported reasons not to participate in screening in both the open question (~50% of reasons) and fixed statements were related to postponing FIT participation and having other priorities ('put the FIT aside and forgot it', 'delay participation', 'not interested', 'laziness', or 'have another cancer/other health problems'). It appeared that non-participation due to 'fear', 'personal feelings and perceptions' were selected more when given as fixed statements compared with when given as a free-text answer to the open question. For instance, 'I feel good' and 'I had no complaints or symptoms' were selected by 49.4% and 46.0% of respondents in fixed statements but were only given in the answers to the open question by 2.8% of respondents. 'Unpleasant sampling procedure' and 'fear of a false positive FIT' were also selected more as a reason not to participate when given as fixed statements, compared with open answers. Other reasons not to participate, given both in open answers and fixed statements, include FIT/sampling problems ('FIT and invitation lost'; 'sampling procedure failed') and lack of understanding ('insufficiency of Dutch language'; 'unclear instruction leaflet').

At the same time, there are reasons not included in the literature (and not given as fixed statements) but mentioned by respondents in Flanders: no FIT available (e.g., 'no invitation received, possibly due to moving house or staying abroad', 9.7%) and 'FIT by GP or specialist was negative' (3.4%). These reasons seem to be typical of the Flemish context. Several reasons (**Figure 2**) were selected when given in fixed statements but did not appear in the open answers, e.g., 'My GP (general practitioner) did not talk with me about it (FIT screening)' (applicable for 11.2%), or 'I don't want to know if I have cancer' (6.9%).

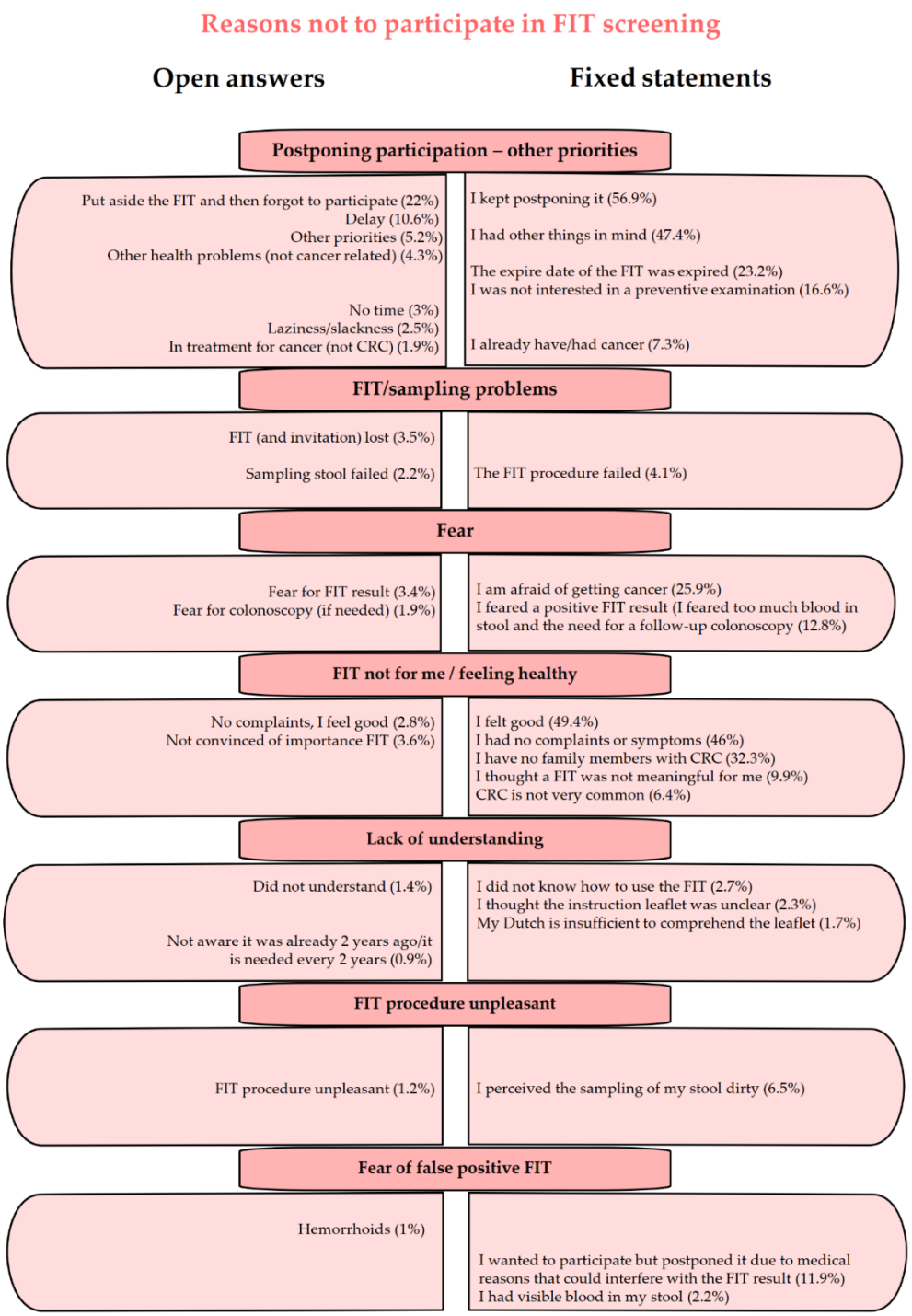


Figure 1. Reasons not to participate in FIT screening among irregular participants in Flanders which are common between individuals' self-reported open answers and given fixed statements (Q1 and S1).

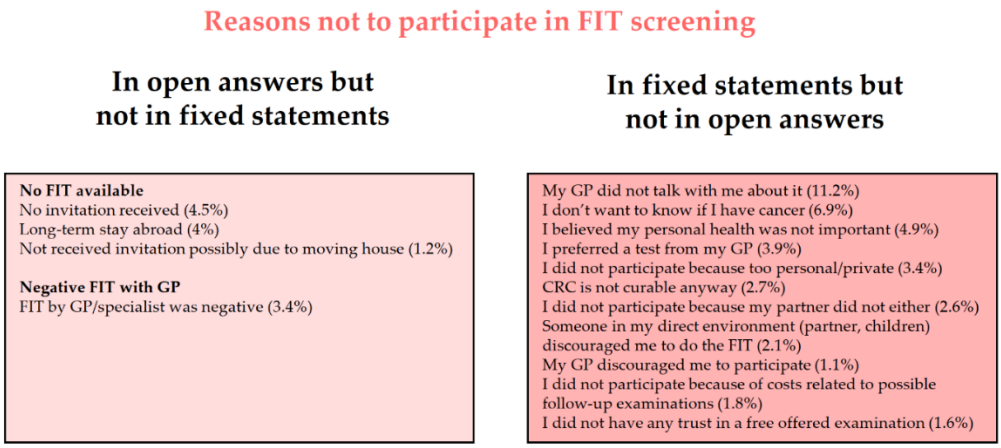


Figure 2. Reasons not to participate in FIT screening among irregular participants in Flanders which are based on either the individuals' self-reported open answers or given fixed statements (Q1 and S1) but not the other. GP: general practitioner.

4.3.2.2. Reasons to Participate

Figures 3 and **4** present reasons for FIT screening participation, grouped into subthemes, by respondents in both the open question and fixed statements (**Figure 3**) or only in the open question but not in fixed statements (**Figure 4**). Categories with <20 answers were left out. Only 79 respondents (2.3%) did not fill in the open question or filled in 'I don't know'.

The most reported reasons to participate in screening in both the open question (40% of reasons in open answers) and fixed statements were related to the importance of (preventive) health checks: e.g., 'better to prevent than to cure' and 'importance of my health'. Some other reported reasons to participate can be grouped into 'advised by others to participate' (~13% of reasons given in the open question) and 'confronted with CRC and fear'. Although only 23 respondents (0.7%) indicated 'fear of cancer' as a reason to participate in the open answers, more than 40% indicated it in the fixed statement as being a reason to participate. In the subtheme 'awareness of the (increased) risk of CRC', 'CRC as a common cancer' was selected by the respondents among the fixed statements to be a reason to participate, while this was not filled in as an open answer. Other subthemes captured in both open answers and fixed statements were 'easy screening offer' (e.g., 'test is free') and 'information and media' (e.g.,

'information event about CRC screening', while media comprises information about the ongoing Flemish CRC screening program in newspapers, social media, and TV and radio campaigns).

The reasons to participate that were not given as fixed statements, but were mentioned by the respondents, mainly referred to a previous non-participation, e.g., 'regretted previous non-participation' and 'no other priorities this time'.

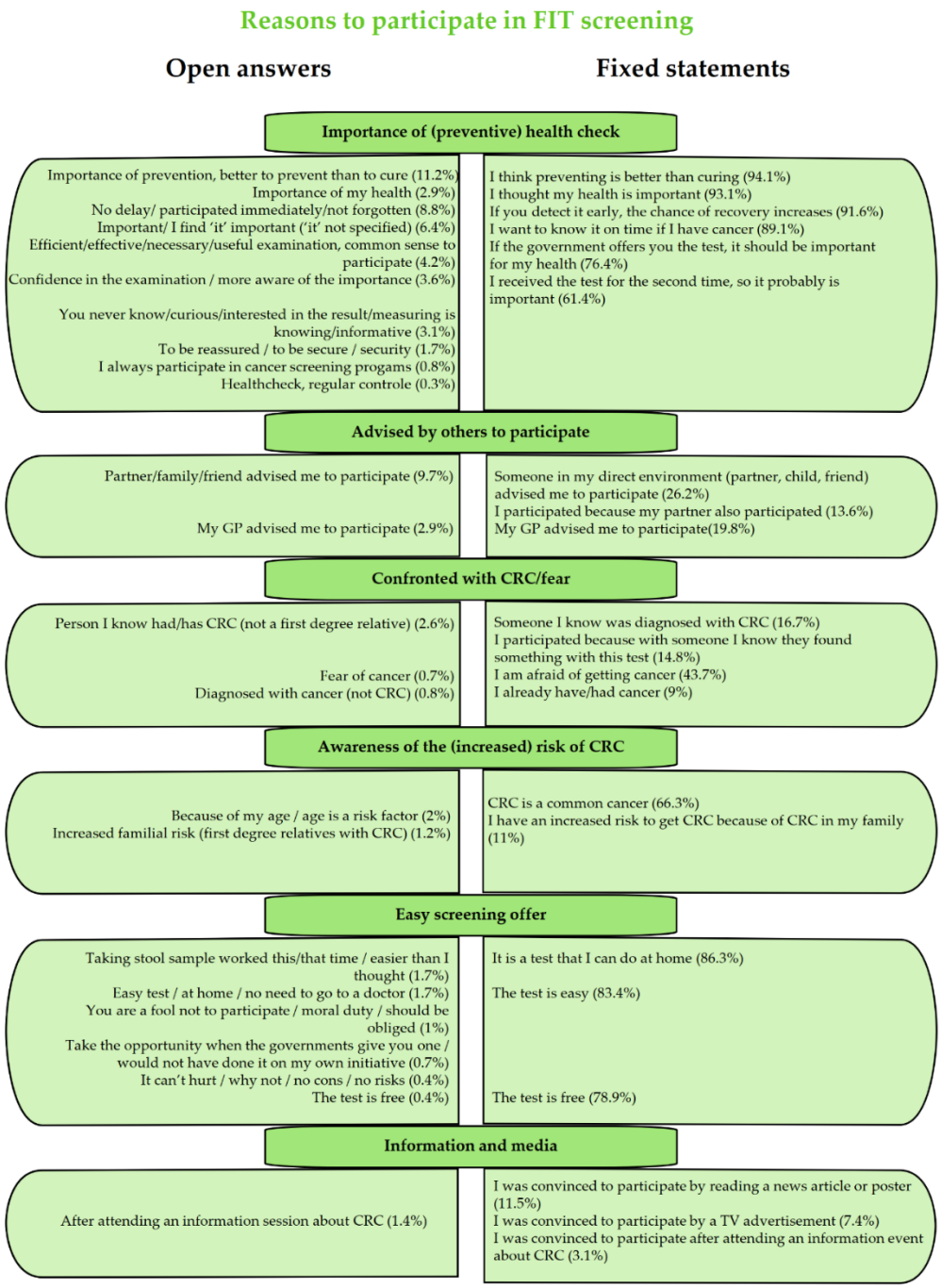


Figure 3. Reasons to participate in FIT screening among irregular participants in Flanders which are common between individuals' self-reported open answers and given fixed statements (only delayed entries N = 3401) (Q2 and S2). GP: general practitioner.

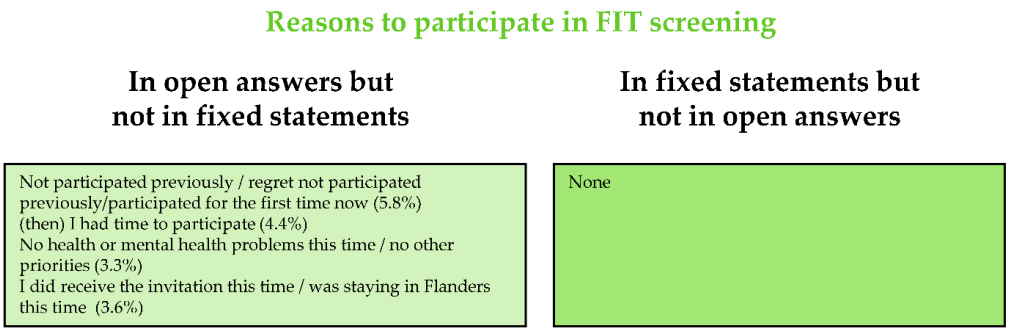


Figure 4. Reasons to participate in FIT screening among irregular participants in Flanders which are based on either the individuals' self-reported open answers or given fixed statements (Q2 and S2) but not the other (only delayed entries N = 3401).

4.3.2.3. Role of GPs, leaflets and media

Table 2 below summarizes given statements about the need for more information and the possible role of GPs in FIT participation. The majority rather or completely agreed that 'the invitation and leaflet contained enough information to make a decision to participate or not' (83.4%), that 'the leaflet provided sufficient information about the importance of repeating the test every two years' (81.9%), and that 'the sampling instructions were clear enough' (89%). Fewer than half of the respondents (42.4%) were aware that a new test could be requested for free. More than 65% of the respondents agreed with the statement that 'their GP should mention the FIT invitation' and more than 40% agreed with the statement that 'they would have participated earlier if their GP had recommended FIT for CRC screening'.

Table 2. Results of survey statements about 'the need for more information after the FIT invitation and the role of the GPs (S3)' in absolute numbers and weighted percentages.

Statements	Weighted absolute number of respondents agreed with the statement *
The invitation and leaflet contain enough information to make myself decide whether or not to participate.	4442 (83.4%)
After receiving the FIT invitation, I needed more information from my GP/doctor.	510 (9.6%)
After reading the FIT invitation and leaflet, I still had some questions.	390 (7.3%)
Leaflet provides sufficient explanation about the importance of repeating the test every two years.	4365 (81.9%)
Leaflet provides enough information about disadvantages of the test.	2607 (48.9%)
Leaflet provides enough information about advantages of the test.	4222 (79.3%)
Instructions are clear enough to take a stool sample.	4742 (89.0%)
I am aware that I can request a new test for free.	2260 (42.4%)
My GP should mention the FIT invitation spontaneously with his/her patients.	3468 (65.1%)
If my GP would have advised the FIT, I would have participated earlier.	2212 (41.5%)
CRC screening program should be more publicized through media.	3419 (64.2%)

* Indicated in table if respondents rather agreed or completely agreed with the statement.

4.3.2.4. Intention for future participation

Among the survey respondents, more than 95% (weighted N = 5058) answered they would participate in the future in the CRC screening program (Q3), 2.5% did not know, and 2.5% (weighted N = 135) responded 'not willing to participate in the future'. 'Under specialist follow-up due to a positive FIT result' and 'no longer in the target population (>74 years)' are the most reported reasons of not wanting to participate in the future. The second most reported reasons are linked with different disadvantages of CRC screening. Other reasons are listed in **Table 3** below.

Table 3. Reasons for no future FIT participation (Q3).

Reason	Total (Weighted) (N = 135)
Under specialist follow-up due to a positive FIT or no longer in the target population (>74 years)	68 (50.4%)
Disadvantages of screening, distrust in FIT result (false positive and false negative), fear of positive FIT result and fear of colonoscopy, fear of cancer	24 (17.8%)
Other mental and/or physical complaints	19 (14.1%)
Feeling healthy, cancer does not happen to me, no complaints	5 (3.7%)
Not specified and others	19 (14.1%)

4.4. Discussion and conclusion

This study explored the barriers and triggers to (re)participate in or skip FIT screening among irregular participants in Flanders. To make use of the evidence reported in the literature as well as to capture the context-specific information in Flanders that has not been documented, we used both open questions and fixed statements. We found that some themes emerged in both approaches while other themes only emerged in one approach but not in the other. The two approaches complement each other: while fixed statements remind respondents of the main reasons for inconsistent participation that they could not recall in a short time, open questions help to identify the reasons that are specific for Flanders (not documented in the literature).

We found '**procrastination**, postponing, and having other priorities' to be the main reasons for not being adherent to FIT screening (based on both open questions and fixed statements). The literature has already indicated delay, other priorities [6,17,19,23], and forgetfulness [24] as common reasons not to participate. '**Fear**' (of a positive FIT result, of having cancer, and/or of a colonoscopy) also emerged in both the open question and fixed statements, as a reason for being nonadherent to screening. Fear as a reason for CRC screening nonadherence is given elsewhere [17]. Interestingly, fear (being afraid of getting cancer) also came up as a motivation to participate in the program. Benito et al. (2018) [20] already indicated that fear works in two ways: it can both facilitate CRC screening adherence and prevent further screening. Similarly, religion acts as both a facilitator and a barrier to CRC screening [25–27]. In our study, only 19/3401 (0.6%) delayed entries and 8/1927 (0.4%) dropouts indicated religion as their reason not to participate in FIT screening (fixed statement). At the same time, 44/3401 (1.3%) delayed entries filled in religion as their reason to participate in FIT screening (open answer). The low percentages of respondents selecting 'religion' show that religion is only a minor factor to

facilitate or prevent FIT screening in Flanders. As a result, it was not included in our main results.

In the current study, reasons linked to '**fear**', '**FIT is not for me**', and '**feeling healthy**' were given more often in fixed statements compared with open answers. These reasons seem to be very common among respondents; however, they are not ranked very highly in terms of importance since the respondents did not mention these when they needed to give only one main reason. Both the lack of knowledge or perceived need of CRC screening and not feeling that participation is personally necessary have been well documented [6,19,28,29]. We found that '**no FIT available**' (e.g., no invitation received or long-term stay abroad) as a reason for non-participation only emerged in open questions but not in fixed statements, suggesting that this is a context-specific issue of Flanders.

The most important reason for participating in FIT screening—recorded in both open answers and fixed statements—was the '**importance of (preventive) health checks**'. This is an important reason stated in the literature as well [19,30]. '**Advised by others to participate**' (by partner, children, and GP) was indicated as an important reason to participate, especially in the fixed statements. The importance of social influences for people to participate has also be reported by others [19,22,30,31].

Although only a minority (9.6%) agreed with the statement that they needed more information from a GP after reading the invitation, 65% indicated that a GP should mention the FIT invitation spontaneously and more than 40% would have participated earlier if their GP had advised it. The **role of the GP** also occurred differently depending on the approach: in fixed statements, 'My GP did not talk with me about FIT screening' emerged as a reason not to participate, while in open answers, 'a negative FIT result by the GP' (after a previous positive one in the screening program) was mentioned as a reason not to participate. A GP recommendation has been well reported as an important trigger to participate in CRC screening [17,19,20,28,29,32].

According to the results from fixed statements about the **information in the leaflet and instructions** on how to use the FIT, the majority of respondents thought that the information was clear enough to decide whether to participate. The **FIT invitation by mail** was perceived as an easy offer that triggered participation. Green et al. [19] also indicated that the convenience of mailing and doing the test at home is a screening facilitator. Berg-Beckhoff (2022) indicated that 'when given the FIT offer' was an important reason to participate [33]. Only in open answers, '**regret of not having participated previously**' was indicated as a trigger to participate

in the current screening round. Although 'feeling good' and 'no CRC in the family' were not given in open answers as a reason for being nonadherent to FIT screening, many respondents found those reasons applicable when given as fixed statements.

Based on the survey results, in particular the 'postponing participation' and 'having other priorities', some adjustments have been made to the invitation, leaflet, and the national campaign in Flanders: in the leaflet, the sentence 'put the kit near the toilet' was added. In the campaign, 'no excuse' was launched as a central theme. These reasons could also result from socially desirable responding.

Recent systematic reviews clearly indicate that outreach interventions based on (a combination of) phone calls, pre- and post-FIT text messaging, mail reminders, and provider alerts improve FIT uptake. Tailored patient messages and financial initiatives do not seem to increase CRC screening [34–36]. Huf et al. [37] indicated that serial motivational text messaging with an opt-out design can substantially improve FIT uptake. In an opt-out design, FIT is mailed unless the person opted out of screening while in an opt-in design, FIT is mailed only if the person actively opted in to participate. Somsouk et al. [38] also found that a mailed informational postcard (usual care) combined with up to two phone calls, followed by a mailed FIT and up to two reminder phone calls (if FIT was not returned within two weeks), improved FIT uptake.

In 2022, the Flemish CRC screening program started a pilot project in which a second reminder (by email only) is sent after the first standard reminder (10 weeks after the invitation) in order to increase screening uptake. In a second step, the screening program is investigating if sending an SMS reminder (after the second reminder by email) can increase adherence as well. Apparently, telephone numbers (as well as the email addresses) are predominantly available in ever-participants or individuals that also participated in the other screening programs organised by the CCD. Their contact information is available in the system if they agreed with the use of their contact details for the CRC screening program. Text messaging and telephone-based interventions appear very promising to increase FIT uptake in Flanders, but the impact relies heavily on the availability of accurate phone numbers in the system. A telephone intervention pilot among non-participants has recently been set up in Flanders and preliminary results show that telephone numbers were only available and correct for a minority (<15%) of non-participants.

'Feeling good', 'not having symptoms', and 'no CRC in the family' have also been addressed in

the leaflet and information materials of the Flemish program in terms of the aim of screening. These materials highlight that the aim of the test is 'screening', meaning that the target individuals need to participate when they do not yet have any symptoms. Fewer than half of the respondents were aware that a free FIT could be requested if needed (e.g., a lost or expired test), so this information has been added in the leaflet and to the website of the screening program. A significant proportion of irregular participants stated that their previous non-participation was only temporarily due to a specific reason (e.g., I participated because 'I had time this year', 'I received the invitation this year', or 'I was in Belgium'). It appears that they would normally participate when the temporary situation was over.

Our study highlights the need to strengthen the role of GPs in promoting CRC screening and screening adherence among their patients. Survey respondents would have participated (earlier) if their GP had advised them to do so. This indicates 'GP not talking about CRC screening' as a reason for their patients' non-participation. GPs might need to do this proactively (not related to an immediate invitation) since some patients do not even know what information about CRC screening they can expect from their GPs. They agreed with the fixed statements about the role of GPs in informing and promoting CRC screening to them, but they did not mention this theme themselves in the open answers. The CCD is planning a pilot to test if a one-minute motivational talk can increase CRC adherence among non-participants.

An important limitation of this study is that the online survey was only sent to ever-participants who provided the CCD with a valid email address. These included more men, at younger ages (e.g., 59–64 years old), with a higher socio-economic status, higher educational level, and speaking the local language. Therefore, our results might not be representative for the entire eligible population. However, the focus of the study is to increase adherence to CRC screening among inconsistent participants; tackling never-participants will be our next step. Furthermore, with a large sample size, our study could still capture the responses of 764 people in the oldest age category (70–75 years, 14.3% of the study population), 250 people with a (very) difficult financial situation (13%) of which approximately 200 (11%) ever suspended a medical procedure because of financial reasons, 134 persons with the lowest educational level—no degree or only primary degree (7%)—and 49 people speaking a language other than Dutch (2.6%).

In conclusion, this study investigated the reasons for (re)starting or skipping FIT screening

among irregular participants in the Flemish CRC screening program by exploring their responses to both fixed statements and open questions via an online survey. The most reported reasons not to participate in FIT screening were related to 'postponing participation' and 'having other priorities', whereas the most reported reasons to participate were related to the importance of (preventive) health checks. A large proportion of respondents agreed with statements about the influence of GPs on their decision to participate in CRC screening.

Based on the survey results, adjustments have been made to the screening materials (invitation, leaflets) and campaigns of the Flemish CRC screening program. The CCD is also developing several other interventions to increase FIT uptake in Flanders, including sending a second reminder email after the first reminder letter, contacting non-participants by telephone, and launching community projects that involve community healthcare workers in having face-to-face conversations with non-participants in order to sensibilize them on the importance of FIT screening.

4.5. Materials and methods

4.5.1. Study design – online survey

The current study is a cross-sectional study in which we combined qualitative (categorized open questions) and quantitative approaches (fixed statements and closed questions). An online email survey (in Dutch) was sent in October 2019 to the irregular participants of the 2016–2018 survey seasons, including (1) delayed entries: those who did not participate after their previous FIT invitation in 2016, but participated after the most recent one in 2018; and (2) dropouts: those who participated after their previous FIT invitation in 2016 but did not participate after the most recent one in 2018 in the Flemish CRC screening program. A reminder email was sent to the entire study population (due to the anonymous approach) eight weeks after the first email (December 2019). The survey was based on the literature [6,8,19,20,22,30] and the results of 26 telephone interviews among irregular participants in the Flemish CRC screening program, and was piloted on an external panel before being performed in the eligible population. Only participants who had once provided a valid email address in their participation form (sent together with their stool sample) received a link to the online survey.

4.5.2. Overview of the survey questions

The survey questions concerning reasons for inconsistent participation—(re)starting or skipping a screening round—during 2016–2018 in the Flemish CRC screening program are given below. We used a combined approach in which we provided both fixed statements (**Table 4** and **Supplementary Tables S1–S3**) based on a search of the literature [6,8,19,20,22,30] and previous research in Flanders [18], and open questions to answer with free text (**Table 4**). Note that only one main answer per respondent to each open question was included, while with fixed statements, people were allowed to select all statements that were applicable to them. The two methods of obtaining information complemented each other: the fixed statements helped to remind respondents of the most reported reasons in a similar setting in other countries and regions, while with open questions, we could capture reasons that are specific to the Flemish context or that have not been recorded in the literature. All the questions and statements were asked to both delayed entries and dropouts, except for the questions and statements on reasons to participate, which were only asked of the delayed entries since we were specifically interested in understanding the motivations that drove people to (re)start FIT screening in the current round. Based on this knowledge, we could develop and provide tailored interventions to increase FIT screening in Flanders.

Table 4. Summary of the open survey questions and fixed statements.

Theme	Content of open questions (Q) or statements (S)
Reasons not to participate	Q1: Why did you not participate in 2016 (delayed entries)/2018 (dropouts)? (open question) S1: What has influenced the decision not to participate? (31 statements)
Reasons not to participate	Q2: Why did you participate in 2018? (open question, delayed entries only) S2: What has influenced the decision to participate? (22 statements, delayed entries only)
Role of GPs/ leaflets/media	S3: Opinions about the role of the general practitioner (GP)/information in invitation and leaflet. (11 statements)
Intention for future participation	Q3: Would you participate in the future? *If not:* Why not? (open question)

4.5.3. Statistical analysis

4.5.3.1. Post-stratification weights

Non-response bias is common in survey studies. This bias occurs when individuals with certain characteristics over- or under-respond to a survey. Our preliminary findings showed significant

differences between respondents and non-respondents in terms of gender (male/female), age group (59–64/65–69/70–74 years), and the first two digits of their postcode (15–39/80–99) (all *p*-values < 0.001). More specifically, males responded more to our survey compared with females (55% of respondents vs. 51% of non-respondents were males). More people aged 59–64 years, but fewer people aged 70–75 years responded to our survey (ages 59–64 years: 58% among respondents vs. 51% among non-respondents; ages 70–75 years: 14% among respondents vs. 21% among non-respondents). While some areas—presented by the first two postcode digits—had a larger proportion of respondents vs. non-respondents (e.g., 29: 5.5% among respondents vs. 4.9% among non-respondents, 90: 5.1% among respondents vs. 4.1% among non-respondents), other areas had a lower proportion of respondents vs. non-respondents (e.g., 18: 1.8% among respondents vs. 2.4% among non-respondents, 99: 1.9% among respondents vs. 2.3% among non-respondents) (**Supplementary Tables S4–S6**).

To reduce non-response bias, we constructed post-stratification weights based on gender, age group, and the first two digits of the postcode [39]. Each respondent was assigned with a weight—corresponding to the person's profile which is a combination of gender, age group, and the first two digits of the respondent's postcode—so that when we adjusted for the post-stratification weights in our analyses, the distribution of the respondent population (5328 subjects) would replicate the distribution of the total study population (19,468 subjects) to whom we sent the survey in terms of gender, age group, and the first two digits of the postcode [40]. For ease of presentation, each weighted number of the respondents presented in our results (after applying post-stratification weights) was rounded to the nearest integer.

4.5.3.2. Main data analysis

We used the SPSS (version 25) to collect and openly code information from respondents' answers to the open questions (qualitative data) and analyze the data thematically. The absolute numbers and the corresponding percentages of respondents who had certain answers or selected certain statements were presented. All quantitative analyses were performed using RStudio software (version 1.3.1056; RStudio, PBC, Boston, MA, USA).

4.5.4. Privacy and ethics

Response to the online survey served as informed consent. No ethical approval was needed. Respondents' anonymity was ensured throughout the study. No incentive was given.

Supplementary materials

Supplementary Table 1. Statements 1 - What has influenced the decision not to participate (31 statements)

I did not participate because… [applicable yes or no]
I kept postponing it
I had other things in mind
The expire date of the FIT was expired
I was not interested in a preventive examination
I already have/had cancer
The FIT procedure failed
I am afraid of getting cancer
I feared a positive FIT result (I feared to much blood in stool and the need for a follow-up colonoscopy
I felt good
I had no complaints or symptoms
I have no family members with CRC
I thought a FIT was not meaningful for me
CRC is not very common
I did not know how to use the FIT
I thought the instruction leaflet was unclear
My Dutch is insufficient to comprehend the leaflet
I perceived the sampling of my stool dirty
I wanted to participate but postponed it due to medical reasons that could interfere with the FIT result
I had visible blood in my stool
My GP did not talk with me about it
I don’t want to know if I have cancer
I believed my personal health was not important
I preferred a test from my GP
I did not participate because too personal/private
CRC is not curable anyway
I did not participate because my partner did not either
Someone in my direct environment (partner, children) discouraged me to do the FIT
My GP discouraged me to participate
I did not participate because of costs related to possible follow-up examinations
I did not have any trust in a free offered examination
I did not participate because of my religion

Supplementary Table 2. Statements 2 – What has influenced the decision to participate? (22 statements, delayed entrees only)

I participated because… [applicable yes or no]
I think preventing is better than curing
I thought my health is important
If you detect it early, the chance of recovery increases
I want to know it on time if I have cancer
If the government offers you the test, it should be important for my health
I received the test for the second time, so it probably is important
Someone in my direct environment (partner, child, friend) advised me to participate
I participated because my partner also participated
My GP advised me to participate
Someone I know was diagnosed with CRC
I participated because with someone I know they found something with this test
I am afraid of getting cancer
I already have/had cancer
CRC is a common cancer
I have an increased risk to get CRC because of CRC in my family
It is a test that I can do at home
The test is easy
The test is free
I was convinced to participate by reading a news article or poster
I was convinced to participate by a TV advertisement
I was convinced to participate after attending an information event about CRC
I participated because of my religion

Supplementary Table 3. Statements 3: Opinions about the GP role, information in the invitation and leaflet (11 statements)

Opinions about the GP role, information in invitation and leaflet **Answering categories: disagree strongly disagree OR neutral/no opinion OR agree/strongly agree**
The invitation and leaflet contain enough information to make myself decide whether or not to participate
After receiving the FIT invitation, I needed more information from my GP/doctor
After reading the FIT invitation and leaflet I still had some questions
Leaflet provides sufficient explanation about the importance of repeating the test every two years
Leaflet provides enough information about disadvantages of the test
Leaflet provides enough information about advantages of the test
Instructions are clear enough to take a stool sample
I am aware that I can request a new test for free
My GP should mention the FIT invitation spontaneously with his/her patients
If my GP would advise the FIT, I would have participated earlier
CRC screening program should be more publicized through media

Supplementary Table 4. Gender difference between the response and non-response groups to the survey

	Response	Non-response	P-value (Fisher exact)
Male	2932 (55.0%)	7256 (51.0%)	<0.001
Female	2396 (45.0%)	6959 (49.0%)	

Supplementary Table 5. Age difference between the response and non-response groups to the survey

	Response	Non-response	P-value (Fisher exact)
59-64	3085 (57.9%)	7203 (50.7%)	
65-69	1479 (27.8%)	3974 (28.0%)	< 0.001
70-75	764 (14.3%)	3038 (21.3%)	

Supplementary Table 6. Postcode difference (first 2 digits) between the response and non-response groups to the survey

Postcode first 2 digits	Response	%	Non-response	%	P-value (Fisher exact)
29	291	5.46	702	4.94	< 0.001
90	273	5.12	577	4.06	
28	213	4.00	469	3.30	
30	208	3.90	512	3.60	
35	203	3.81	598	4.21	
91	188	3.53	518	3.64	
21	187	3.51	463	3.26	
36	174	3.27	465	3.27	
26	173	3.25	499	3.51	
25	169	3.17	433	3.05	
92	165	3.10	410	2.88	
20	164	3.08	392	2.76	
22	162	3.04	394	2.77	
84	161	3.02	468	3.29	
39	159	2.98	401	2.82	
17	147	2.76	403	2.84	
23	145	2.72	392	2.76	
85	143	2.68	388	2.73	
24	135	2.53	305	2.15	
98	135	2.53	333	2.34	
83	113	2.12	373	2.62	
88	106	1.99	347	2.44	
31	103	1.93	201	1.41	
99	99	1.86	327	2.30	
18	98	1.84	341	2.40	
87	93	1.75	352	2.48	
32	91	1.71	236	1.66	
37	90	1.69	216	1.52	
33	89	1.67	215	1.51	
86	89	1.67	294	2.07	
80	84	1.58	152	1.07	
19	83	1.56	216	1.52	
93	82	1.54	218	1.53	
89	73	1.37	266	1.87	
94	68	1.28	211	1.48	
38	60	1.13	181	1.27	

16	53	0.99	208	1.46
82	50	0.94	124	0.87
15	48	0.90	125	0.88
34	48	0.90	86	0.61
96	46	0.86	177	1.25
97	35	0.66	97	0.68
95	32	0.60	130	0.91

References

1. Hoeck, S.; van de Veerdonk, W.; De Brabander, I. Do socioeconomic factors play a role in nonadherence to follow-up colon-oscopy after a positive faecal immunochemical test in the Flemish colorectal cancer screening programme? Eur. J. Cancer Prev. 2020, 29, 119–126.
2. Centre for Cancer Detection & Belgian Cancer Registry. 2021. Monitoring Report of the Flemish Colorectal Cancer Screening Programme. 2021. Available online: https://dikkedarmkanker.bevolkingsonderzoek.be/sites/default/files/2022-03/Jaarrapport%202021%20BVO%20naar%20kanker_0.pdf (accessed on 26 April 2022).
3. Website Bevolkingsonderzoek In Cijfers. Available online: https://bevolkingsonderzoek.incijfers.be//jive?cat_open_code=ddk_extern (accessed on 16 December, 2022).
4. Belgian Cancer Register (BCR). Cancer Fact Sheet, Colorectal Cancer, ICD10: C18-20. BCR: Brussels, Belgium, 2018. Available online: https://kankerregister.org/media/docs/CancerFactSheets/2018/Cancer_ Fact_Sheet_ColorectalCancer_2018.pdf (ac-cessed 16 December, 2022).
5. Hoeck, S.; De Schutter, H.; Van Hal, G. Why do participants in the Flemish colorectal cancer screening program not undergo a diagnostic colonoscopy after a positive fecal immunochemical test?. Acta Clin. Belg. 2022, 77, 760–766. https://doi.org/10.1080/17843286.2021.1980675.
6. Hall, N.J.; Rubin, G.P.; Dobson, C.; Weller, D.; Wardle, J.; Ritchie, M.; Rees, C.J. Attitudes and beliefs of non-participants in a population-based screening programme for colorectal cancer. Health Expect. 2015, 18, 1645–1657. https://doi.org/10.1111/hex.12157.
7. van Dam, L.; Korfage, I.J.; Kuipers, E.J.; Hol, L.; van Roon, A.H.; Reijerink, J.C.; van Ballegooijen, M.; van Leerdam, M.E. What influences the decision to participate in colorectal cancer screening with faecal occult blood testing and sigmoidoscopy? Eur. J. Cancer 2013, 49, 2321–2330.
8. Bradley, D.T.; Treanor, C.; McMullan, C.; Owen, T.; Graham, A.; Anderson, D. Reasons for non-participation in the Northern Ireland Bowel Cancer Screening Programme: A qualitative study. BMJ Open 2015, 5, e008266. https://doi.org/10.1136/bmjopen-2015-008266.
9. Palmer, C.K.; Thomas, M.C.; Von Wagner, C.; Raine, R. Reasons for non-uptake and subsequent participation in the NHS Bowel Cancer Screening Programme: A qualitative study. Br. J. Cancer 2014, 110, 1705–1711. https://doi.org/10.1038/bjc.2014.125.
10. Woudstra, A.J.; Dekker, E.; Essink-Bot, M.L.; Suurmond, J. Knowledge, attitudes and beliefs regarding colorectal cancer screening among ethnic minority groups in the Netherlands—A qualitative study. Health Expect. 2015, 19, 1312–1323.
11. Dawson, G.; Crane, M.; Lyons, C.; Burnham, A.; Bowman, T.; Travaglia, J. A qualitative investigation of factors influencing participation in the bowel screening in New South Wales. Health Promot. J. Aust. 2016, 27, 48–53. https://doi.org/10.1071/he15026.
12. Chapple, A.; Ziebland, S.; Hewitson, P.; McPherson, A. What affects the uptake of screening for bowel cancer using a faecal occult blood test (FOBt): A qualitative study. Soc. Sci. Med. 2008, 66, 2425–2435. https://doi.org/10.1016/j.socscimed.2008.02.009.
13. Honein-AbouHaidar, G.N.; Kastner, M.; Vuong, V.; Perrier, L.; Daly, C.; Rabeneck, L.; Straus, S.; Baxter, N.N. Systematic Review and Meta-study Synthesis of Qualitative Studies Evaluating Facilitators and Barriers to Participation in Colorectal Cancer Screening. Cancer Epidemiol. Biomark. Prev. 2016, 25, 907–917. https://doi.org/10.1158/1055-9965.epi-15-0990.

14. Keighley, M.R.B.; O'Morain, C.; Giacosa, A.; Ashorn, M.; Burroughs, A.; Crespi, M.; Delvaux, M.; Faivre, J.; Hagenmuller, F.; Lamy, V.; et al. Public awareness of risk factors and screening for colorectal cancer in Europe. Eur. J. Cancer Prev. 2004, 13, 257–262. https://doi.org/10.1097/01.cej.0000136575.01493.9b.

15. Wee, C.C.; McCarthy, E.P.; Phillips, R.S. Factors associated with colon cancer screening: The role of patient factors and phy-sician counseling. Prev. Med. 2005, 41, 23–29. https://doi.org/10.1016/j.ypmed.2004.11.004.

16. Berkowitz, Z.; Hawkins, N.A.; Peipins, L.A.; White, M.C.; Nadel, M.R. Beliefs, Risk Perceptions, and Gaps in Knowledge as Barriers to Colorectal Cancer Screening in Older Adults. J. Am. Geriatr. Soc. 2008, 56, 307–314. https://doi.org/10.1111/j.1532-5415.2007.01547.x.

17. Kroupa, R.; Ondrackova, M.; Kovalcikova, P.; Dastych, M.; Pavlik, T.; Kunovsky, L.; Dolina, J. Viewpoints of the target pop-ulation regarding barriers and facilitators of colorectal cancer screening in the Czech Republic.. World J. Gastroenterol. 2019, 25, 1132–1141. https://doi.org/10.3748/wjg.v25.i9.1132.

18. Hoeck, S.; Van Roy, K.; Willems, S. Barriers and facilitators to participate in the colorectal cancer screening programme in Flanders (Belgium): A focus group study. Acta Clin. Belg. 2022, 77, 37–44. https://doi.org/10.1080/17843286.2020.1783906.

19. Green, B.B.; BlueSpruce, J.; Tuzzio, L.; Vernon, S.W.; Shay, L.A.; Catz, S.L. Reasons for never and intermittent completion of colorectal cancer screening after receiving multiple rounds of mailed fecal tests. BMC Public Health 2017, 17, 531. https://doi.org/10.1186/s12889-017-4458-6.

20. Benito, L.; Farre, A.; Binefa, G.; Vidal, C.; Cardona, A.; Pla, M.; García, M. Factors related to longitudinal adherence in colorectal cancer screening: Qualitative research findings. Cancer Causes Control 2018, 29, 103–114. https://doi.org/10.1007/s10552-017-0982-z.

21. Christy, S.M.; Schmidt, A.; Wang, H.-L.; Sutton, S.K.; Davis, S.N.; Chavarria, E.; Abdulla, R.; Quinn, G.; Vadaparampil, S.T.; Schultz, I.; et al. Understanding Cancer Worry among Patients in a Community Clinic-Based Colorectal Cancer Screening Intervention Study. Nurs. Res. 2018, 67, 275–285. https://doi.org/10.1097/nnr.0000000000000275.

22. Duncan, A.; Turnbull, D.; Gregory, T.; Cole, S.R.; Young, G.P.; Flight, I.; Wilson, C. Using the Transtheoretical Model of Be-haviour Change to describe readiness to rescreen for colorectal cancer with faecal occult blood testing. Health Promot. J. Aust. 2012, 23, 122–128. https://doi.org/10.1071/he12122.

23. Dominitz, J.A. Barriers and Facilitators to Colorectal Cancer Screening. Gastroenterol. Hepatol. 2021, 17, 550–552.

24. Ylitalo, K.R.; Camp, B.G.; Meyer, M.R.U.; Barron, L.A.; Benavidez, G.; Hess, B.; Laschober, R.; Griggs, J.O. Barriers and Facil-itators of Colorectal Cancer Screening in a Federally Qualified Health Center (FQHC). J. Am. Board Fam. Med. 2019, 32, 180–190. https://doi.org/10.3122/jabfm.2019.02.180205

25. Dressler, J.; Johnsen, A.; Madsen, L.; Rasmussen, M.; Jorgensen, L. Factors affecting patient adherence to publicly funded colorectal cancer screening programmes: A systematic review. Public Health 2021, 190, 67–74. https://doi.org/10.1016/j.puhe.2020.10.025.

26. Kretzler, B.; König, H.-H.; Hajek, A. Religious Attendance and Cancer Screening Behavior. Front. Oncol. 2020, 10, 583925. https://doi.org/10.3389/fonc.2020.583925.

27. Dharni, N.; Armstrong, D.; Chung-Faye, G.; Wright, A.J. Factors influencing participation in colorectal cancer screening-a qualitative study in an ethnic and socio-economically diverse inner city population. Health Expect. 2017, 20, 608–617. https://doi.org/10.1111/hex.12489.

28. Wang, H.; Roy, S.; Kim, J.; Farazi, P.A.; Siahpush, M.; Su, D. Barriers of colorectal cancer screening

in rural USA: A systematic review. Rural Remote Health 2019, 19, 5181. https://doi.org/10.22605/RRH5181.

29. Cooper, C.P.; Gelb, C.A. Opportunities to Expand Colorectal Cancer Screening Participation. J. Women's Heal. 2016, 25, 990–995. https://doi.org/10.1089/jwh.2016.6049.

30. Gordon, N.P.; Green, B.B. Factors associated with use and non-use of the Fecal Immunochemical Test (FIT) kit for Colorectal Cancer Screening in Response to a 2012 outreach screening program: A survey study. BMC Public Health 2015, 15, 546. https://doi.org/10.1186/s12889-015-1908-x.

31. Clarke, N.; Kearney, P.M.; Gallagher, P.; McNamara, D.; O'Morain, C.A.; Sharp, L. Negative emotions and cancer fatalism are independently associated with uptake of Faecal Immunochemical Test-based colorectal cancer screening: Results from a pop-ulation-based study. Prev. Med. 2021, 145, 106430.

32. Goodwin, B.C.; Crawford-Williams, F.; Ireland, M.J.; March, S. General practitioner endorsement of mail-out colorectal cancer screening: The perspective of nonparticipants. Transl. Behav. Med. 2020, 10, 366–374. https://doi.org/10.1093/tbm/ibz011.

33. Berg-Beckhoff, G.; Leppin, A.; Nielsen, J.B. Reasons for participation and non-participation in colorectal cancer screening. Public Health 2022, 205, 83–89. https://doi.org/10.1016/j.puhe.2022.01.010.

34. Facciorusso, A.; Demb, J.; Mohan, B.P.; Gupta, S.; Singh, S. Addition of Financial Incentives to Mailed Outreach for Promoting Colorectal Cancer Screening: A Systematic Review and Meta-analysis. JAMA Netw. Open 2021, 4, e2122581.

35. Issaka, R.B.; Avila, P.; Whitaker, E.; Bent, S.; Somsouk, M. Population health interventions to improve colorectal cancer screening by fecal immunochemical tests: A systematic review. Prev. Med. 2019, 118, 113–121. https://doi.org/10.1016/j.ypmed.2018.10.021.

36. Roy, S.; Dickey, S.; Wang, H.-L.; Washington, A.; Polo, R.; Gwede, C.K.; Luque, J.S. Systematic Review of Interventions to Increase Stool Blood Colorectal Cancer Screening in African Americans. J. Community Health 2021, 46, 232–244. https://doi.org/10.1007/s10900-020-00867-z.

37. Huf, S.W.; Asch, D.A.; Volpp, K.G.; Reitz, C.; Mehta, S.J. Text Messaging and Opt-out Mailed Outreach in Colorectal Cancer Screening: A Randomized Clinical Trial. J. Gen. Intern. Med. 2021, 36, 1958–1964. https://doi.org/10.1007/s11606-020-06415-8.

38. Somsouk, M.; Rachocki, C.; Mannalithara, A.; Garcia, D.; Laleau, V.; Grimes, B.; Issaka, R.B.; Chen, E.; Vittinghoff, E.; Shapiro, J.A.; et al. Effectiveness and Cost of Organized Outreach for Colorectal Cancer Screening: A Randomized, Controlled Trial. J. Natl. Cancer Inst. 2020, 112, 305–313. https://doi.org/10.1093/jnci/djz110.

39. Royal, K.D. Survey research methods: A guide for creating post-stratification weights to correct for sample bias. Educ. Health Prof. 2019, 2, 48. https://doi.org/10.4103/ehp.ehp_8_19.

40. European Social Survey. Documentation of ESS Post-Stratification Weights. Available online: https://www.europeansocialsurvey.org/docs/methodology/ESS_post_stratification_weights_documentation.pdf (accessed on 27 October 2022).

Chapter 5

Colorectal cancer screening: Have we addressed concerns and needs of the target population?

Thuy Ngan Tran[1], Allegra Ferrari[1], Sarah Hoeck[1,2], Marc Peeters[3,4] and Guido Van Hal[1,2]

1. Family Medicine and Population Health (FAMPOP), Faculty of Medicine and Health Sciences, University of Antwerp, 2610 Antwerp, Belgium

2. Colorectal Cancer Screening Program, Centre for Cancer Detection, 8000 Bruges, Belgium

3. Department of Oncology, Antwerp University Hospital, 2650 Antwerp, Belgium

4. Department of Oncology, Faculty of Medicine and Health Sciences, University of Antwerp, 2610 Antwerp, Belgium

(Published in *Gastrointest. Disord. 2021; 3(4):173-203*)

5.1. Abstract

Background: Despite the recognized benefits of colorectal cancer (CRC) screening, uptake is still suboptimal in many countries. In addressing this issue, one important element that has not received sufficient attention is population preference. Our review provides a comprehensive summary of the up-to-date evidence relative to this topic.

Methods: Four OVID databases were searched: Ovid MEDLINE® ALL, Biological Abstracts, CAB Abstracts, and Global Health. Among the 742 articles generated, 154 full texts were selected for a more thorough evaluation based on predefined inclusion criteria. Finally, 83 studies were included in our review.

Results: The general population preferred either colonoscopy as the most accurate test, or fecal occult blood test (FOBT) as the least invasive for CRC screening. The emerging blood test (*SEPT9*) and capsule colonoscopy (nanopill), with the potential to overcome the pitfalls of the available techniques, were also favored. Gender, age, race, screening experience, education and beliefs, the perceived risk of CRC, insurance, and health status influence one's test preference.

Conclusions: To improve uptake, CRC screening programs should consider offering test alternatives and tailoring the content and delivery of screening information to the public's preferences. Other logistical measures in terms of the types of bowel preparation, gender of endoscopist, stool collection device, and reward for participants can also be useful.

5.2. Introduction

Worldwide, colorectal cancer (CRC) is the third most commonly diagnosed and the second most deadly cancer, with an estimation of 1.93 million new CRC cases and 0.94 million CRC-related deaths in 2020 [1]. Screening is an excellent preventive intervention to detect pre-cancerous polyps and tumors at an early stage and reduce the mortality and morbidity of CRC [2-4]. Current international guidelines recommend two main screening methods for CRC: colonoscopy as the gold standard test and fecal occult blood tests (guaiac fecal occult blood test – gFOBT or fecal immunochemical test – iFOBT/FIT) as the standard first-line test for population-based CRC screening [5-8]. Other less common screening modalities include stool DNA test (sDNA), sigmoidoscopy, computed tomography colonography (CTC), barium enema

and capsule colonoscopy [6, 9, 10].

Despite the recognized benefits that screening offers, CRC screening uptake around the world is still suboptimal, with the rates below 50% in many countries and regions [11-14]. Considerable efforts have been made to increase CRC screening uptake. However, most of the measures taken have only considered the perspectives of scientific literature and experts [15, 16]. One important element that has not received adequate attention is the preference of the general population for CRC screening tests.

Previous studies have shown that individual preference for a specific test can influence a person's decision to participate in screening [17-19]. As a result, providing the screening population with their test of choice can increase screening uptake [17-19]. One's acceptance and utilization of a screening test depends highly on the person's attitude and barriers such as perceived test accuracy, the extent of invasiveness, discomfort, pain and risk reduction, the complexity of the screening procedure, the length of screening interval, preparation requirements, embarrassment, and stool aversion (stool-based tests) [20-25]. Notably, it has been observed that a segment of the population would rather forgo screening if their test of choice is not available [26-29]. Yet, most of the population-based CRC screening programs up to present only use one default first-line test for the entire screening population [30].

In addition, prior evidence shows that the preferences of the target population for CRC screening tests have not been well understood and, in many cases, there is a great discrepancy between physicians' perception of their patients' preferences and their actual preferences [31]. In a study by Redwood et al. [31], patients reported travel and bowel preparation as the main barriers to colonoscopy, while physicians thought that fear of pain and test invasiveness were the main barriers for their patients. The difference between patients and physicians in the ranking for other colonoscopy attributes were also noted, including concerns about anesthesia (29% vs. 72%), the need for dependent care (22% vs. 66%), embarrassment (18% vs. 57%) or whether the procedure is time-consuming (16% vs. 48%). Similarly, in a study by Ling et al. [32], while the patients' hierarchy of test preferences was FOBT (43%), followed by colonoscopy (40%), FOBT plus sigmoidoscopy (12%), barium enema (3%), and sigmoidoscopy alone (2%), physicians recommended FOBT plus sigmoidoscopy most often (54%), followed by FOBT (23%), sigmoidoscopy (15%), and colonoscopy (3%) (none recommended barium enema). Disagreement in test preference between patients and physicians can have a negative impact

on patients' willingness to adhere to screening and the outcome of their screening experiences [33,34]. Unfortunately, previous findings suggest that physicians are often unwilling to comply with patient preference when it differs from their own [33,35].

A number of reviews have synthesized the available information on the advantages and disadvantages of the available CRC screening tests from the perspectives of experts [36–39]. In the past fifteen years, many single studies have also attempted to investigate the preference of the general population for both the conventional and emerging CRC screening techniques; however, an up-to-date review on this topic is currently lacking [40]. In this review, we aim to systematically summarize the existing findings and evidence on (1) Population preferences for CRC screening tests and the main reasons for their choices; (2) Individuals' characteristics that influence test preference; (3) The actual participation in screening in relation to the stated preferences; (4) The perceived barriers to a specific test and potential measures to address the barriers; and (5) Population's willingness to pay for CRC screening. Knowledge stemming from this comprehensive review can be helpful to guide policies and interventions to increase CRC screening uptake.

5.3. Results

5.3.1. Population preference for CRC screening tests

There are two prominent trends in population preference for CRC screening tests reported in previous studies: people preferred either the most accurate test (visual or structural test: colonoscopy) [29,31,41–51] or the least invasive one (stool-based test: fecal occult blood test (FOBT) or stool DNA (sDNA) test) [26,28,52–58]. While both tests are highly recommended by international guidelines [5–8], with colonoscopy recommended as the gold standard test and stool-based test (iFOBT or gFOBT) as the standard first-line test for population-based CRC screening, population preference for colonoscopy and stool-based tests, as well as the other available screening techniques, has not been systematically reviewed.

The following paragraphs, which are graphically summarized below, attempt to present population preference for CRC screening tests reported in literature (**Table 1**) and the reasons for their choices (**Figure 1**).

Figure 1. Word clouds (in which the size of each word indicates its frequency or importance) of the most cited barriers and facilitators to colorectal cancer screening—Created with https://worditout.com/ (accessed on 20 August 2021). Definitions: Barriers = factors that could limit or restrict participation in colorectal cancer screening; Facilitators = factors that could either promote or be perceived as the most important attributes that facilitate decision making towards participation in colorectal cancer screening.

Table 1. Studies that reported colonoscopy or stool-based test as population's most preferred test and the corresponding percentages of respondents that selected the tests.

Author, Year	Setting	Methods	Sample size	Most preferred test	% Respondents choosing the preferred test	Tests compared
Moreno et al., 2019 [41]	USA; 2016	Survey	215	colonoscopy	80.6%	Colonoscopy vs. stool-based tests vs. CTC
Cho et al., 2017 [42]	South Korea, 2016	Questionnaire	396	colonoscopy	68.7%	Colonoscopy vs. FIT
Jung et al., 2009 [43]	South Korea; 2006	Questionnaire (followed by telephone questionnaire)	51	colonoscopy	64.7%	Colonoscopy vs. CTC
Imaeda et al., 2010 [44]	USA	Survey	92	colonoscopy	62%	Colonoscopy vs. FOBT vs. sigmoidoscopy vs. colon capsule vs. CTC
Omran et al., 2015 [45]	Jordan; 2014	Survey	713	colonoscopy	60.4%	Colonoscopy vs. sigmoidoscopy vs. FOBT
Calderwood et al., 2011 [46]	USA; 2008–2010	Survey	100	colonoscopy	59%	Colonoscopy vs. FOBT vs. sDNA vs. CTC
Redwood et al., 2019 [31]	USA; 2017	Survey	1616	colonoscopy	58%	Colonoscopy vs. sDNA
Palmer et al., 2010 [47]	USA; 2007	In-depth personal interview	60	colonoscopy	57%	Colonoscopy vs. FOBT vs. barium enema vs. sigmoidoscopy
Chatrath and Rex, 2014 [29]	USA	Survey	502	colonoscopy	57%	Colonoscopy vs. FOBT vs. colon capsule
Sandoval et al., 2021 [48]	Switzerland; 2016	Survey	1260	colonoscopy	54.9%	Colonoscopy vs. FOBT
Schroy et al., 2007 [49]	USA; 2002–2003	Survey	263	colonoscopy	51.6%	Colonoscopy vs. FOBT vs. sigmoidoscopy vs. sigmoidoscopy plus FOBT vs. barium enema vs. sDNA
Ruffin et al., 2009 [50]	USA	Focus group interview and survey	93	colonoscopy	49%	Colonoscopy vs. FOBT vs. sigmoidoscopy vs. barium enema

Hawley et al., 2012 [51]	USA; 2004–2006	Telephone survey	1224	colonoscopy	41.1%	Colonoscopy vs. FOBT vs sigmoidoscopys barium enema
Lachter et al., 2008 [52]	Israel	Questionnaire and follow-up telephone call	100	FOBT	84%	Colonoscopy vs. FOBT vs. sigmoidoscopy vs. barium enema
Qumseya et al., 2014 [53]	Palestine	Self-administered questionnaire	1352	FOBT	79%	Colonoscopy vs. FOBT
Zhu et al., 2021 [54]	USA; 2019	Pannel survey	1595	sDNA	>65%	Colonoscopy vs. sDNA vs. FOBT
Bonello et al., 2016 [55]	UK	Questionnaire	491	FOBT	60.8%	Colonoscopy vs. FIT
Brenner et al., 2014 [56]	USA and Australia; 2011	Online survey	920	FOBT	55.9%	Colonoscopy vs. FOBT vs. sigmoidoscopy ys radiological test
Wolf et al., 2016 [26]	USA; 2011–2013	Questionnaire	528	stool-based	54.5%	Colonoscopy vs. stool-based test
DeBourcy et al., 2008 [28]	USA; 2007	Survey	323	FOBT	53%	Colonoscopy vs. FOBT
Schroy et al., 2005 [57]	USA; 2001–2003	Survey	4042	sDNA	45%	Colonosocpy vs. FOBT vs. sDNA test
Phisalprapa et al., 2021 [58]	Thailand; 2017–2018	Discrete choice experiment questionnaire	400	FOBT	38.2%	Colonoscopy vs. FIT vs. barium enema vs. CTC vs. sigmoidoscopy

5.3.1.1. Preference for colonoscopy

Colonoscopy was reported as the most preferred test in almost half of the studies regarding this topic that had been selected (13 studies, 4 countries: USA, South Korea, Jordan and Switzerland) [29,31,41–51]. In these studies, colonoscopy was offered together with either only one other test (FOBT [42,48], CTC [43], or multi-target stool DNA test [31]), or a group of the available tests including stool-based tests [41] (FOBT [29,44–47,49–51] or sDNA [46,49]), sigmoidoscopy [44,45,47,49–51], CTC [41,44,46], colon capsule [29,44], barium enema [47,49–51] and FOBT plus barium enema [49]. The percentages of individuals selecting colonoscopy as their first-choice test ranged from 41.1% to 80.6% [29,31,41–51].

Accuracy was the most commonly reported reason for favoring colonoscopy [28,43,46,49,50,59]. Colonoscopy was seen as a thorough and revealing test [47], with high sensitivity [44,60,61] and could help to avoid false-positives [60]. Other valued attributes of colonoscopy included long screening intervals (normally 10 years) [46,49,59], capacity to remove polyps [43,60], no need for a follow-up test [44,50], thoroughness of information provided [50], and absence of pain thanks to anesthesia [50].

Previous studies have also reported that individuals were more willing to undergo a colonoscopy if recommended by their physician [45,51]. At the same time, these studies indicate a strong tendency among physicians to practice and recommend colonoscopy over other tests. In a study by Wolf et al. (2016) [26], 34% of the physicians responded that they did not have stool-based tests available, or they did have stool-based tests available but never recommended them to their patients. They were concerned that their patients would not complete the kits properly (e.g., not returning kits, improper sample storage) and the test accuracy was not sufficient, with a high rate of false positives and a certain rate of false negatives. A few answered that they could make no money when offering an FOBT or were not aware that FOBT was also recommended in the current guidelines [26].

Notably, even in populations where the majority favored colonoscopy, there was always a subgroup that were strongly averse to colonoscopy and would not undergo CRC screening unless an alternative option was available [26–29]. The most common reasons for their aversion to colonoscopy were bowel preparation [42], examination procedure [42], invasiveness and pain/discomfort [50,62], fear of the procedure [62], need for anesthesia [50], cost and time consuming [28] (See also Section 5.3.4.1).

5.3.1.2. Preference for stool-based tests (FOBT and sDNA)

Stool-based tests were the second most commonly stated as population's preferred tests for CRC screening, with FOBT more commonly reported (six studies, six countries (Isarael, Palestine, UK, USA, Australia, and Thailand)) [28,52,53,55,56,58] than sDNA (two studies, only in USA [54,57]). In these studies, FOBT was offered either with only colonoscopy [28,53,55,59] or with a group of the available tests including colonoscopy [52,56,58], sigmoidoscopy [52,56,58], and radiological tests [56] (barium enema [52,58] and/or CTC [58]). sDNA testing was compared with colonoscopy [54,57,61], FOBT [54,57,61], sigmoidoscopy [61], virtual colonoscopy [61] and barium enema [61]. The percentages of individuals choosing stool-based test as their most favored screening test ranged from 38.2% to 84% [26,28,52–58].

Test ease and convenience (simple sample collection and no need for preparation) was the most common reason stated among the respondents who selected stool-based test as their preferred test [28,47,50,55,59,61–64]. An equally valued attribute of stool-based test was its non-invasiveness (less likely to cause harm/complication, less pain and discomfort) [46,47,49,55,59,61,62].

The next commonly mentioned advantage of stool-based test is short interval (every one or two years) [49,50,55]. Frequent testing was perceived to provide screening participants with reassurance of a good health [49,65,66]. Many respondents also considered the non-invasive stool-test to be a preliminary test before other more invasive tests would be required [50].

Another recognized benefit of stool-based tests is that they can usually be performed at home and distributed by mail, which enhances individuals' privacy [47,50,62,67]. Van Dam et al. found that FOBT acceptance rate declined when individuals were required to take the test at hospital. The authors suggested two possible reasons including the lack of access to the testing centers and the absence of comfort compared to home sample collection [67].

In some countries where FOBT was used in the population-based screening programs, the higher preference for FOBT could also be due to the population's high familiarity with this test [56]. Interestingly, people who selected a stool-based test as their first-choice test tended to choose the alternative stool-based test, if offered, as their second-choice test over the other non-stool-based tests such as colonoscopy [26,46,63] and CTC [46,63]. These individuals were often afraid of colonoscopy because of the use of laxatives for bowel preparation, sedation, or

complications. They preferred a convenient and non-invasive test for routine screening even though the test is less accurate compared to colonoscopy [26].

From the user's perspective, sDNA and FOBT share many similarities since both are non-invasive stool-based tests which can be conveniently performed at home. However, Schroy et al. (2005) found that sDNA testing was rated as having simpler sample collection process compared to FOBT, which resulted in a higher level of comfort for participants in their study. The authors suggested that this might be due to the difference in the sample containers used between the two types. The sample container for sDNA could be directly mounted onto the toilet seat, so no direct manipulation of stool was required as it is, instead, for FOBT. People also perceived sDNA as more accurate than FOBT due to its more sophisticated and advanced technology [57]. Research has shown superior sensitivity of multitarget stool DNA testing (mt-sDNA) for detecting CRC and advanced precancerous lesions compared to FIT (47-50% vs 25-31%). However, mt-sDNA demonstrates lower specificity compared to FIT (87-93% vs 95-97%) [68-70]. In 2014, the United States Food and Drug Administration approved mt-sDNA testing for CRC screening in the average-risk population [69]. While FOBT (FIT in specific) is now the most commonly used test in population-based CRC screening [30], sDNA remains relatively uncommon in many countries and regions.

The most commonly reported reasons for not favoring stool-based tests are unpleasant sample collection [42, 62], sample storage and transportation [42] (See also Section 5.3.4.2).

5.3.1.3. Preference for computed tomography colonography (CTC)

CTC was reported to be preferred by the population over colonoscopy in 3 studies (conducted in the USA and UK) in which only the two tests were compared with each other [27, 60, 71]. In these studies, respondents selected CTC over colonoscopy due to convenience [27], less invasiveness [20, 60], lower level of discomfort [71], unpleasant experience with the previous colonoscopy [27], embarrassment with colonoscopy [71], primary care provider recommendation [27], and safety concerns related to the individual's health status [27].

Participants found CTC more convenient than colonoscopy because CTC can be performed in a shorter examination time (a few minutes) [27, 32, 43] and does not require sedation [27]; therefore, daily life activities are less interrupted, e.g., the person can drive to and from the procedure. In contrast, patients under sedation used in colonoscopy are advised against

operating machinery for at least 24 h after the procedure [72, 73]. Lack of transportation has been reported as an important practical barrier to CRC screening with colonoscopy [74-76].

CTC has been reported to be a safer procedure compared to colonoscopy in terms of perforation rate. Unlike colonoscopy which requires the insertion and maneuvering of a flexible tube to the proximal end of the colon, participants with CTC undergo gas insufflation using a small rectal catheter. Although extremely uncommon, perforation due to CTC can occur during the process of gas insufflation or the insertion of the rectal catheter through the rectal wall [77]. The rate of CTC-related perforation in literature ranged from 0.009% to 0.059% [78-80]. In many cases [80], CTC was performed for a diagnostic indication rather than screening. Thus, the rate of perforation related to screening CTC is expected to be even lower than the reported figures [80]. In comparison, the rate of colonoscopy-related perforation was about 0.1% [81-83]. The risk is even higher when polypectomy is performed during colonoscopy [84, 85].

In contrast, Jung et al. (2009) [43] recorded a higher degree of abdominal pain, abdominal discomfort, and loss of dignity for CTC compared to colonoscopy. These findings defer from those of the previous studies in which the respondents preferred CTC over colonoscopy [27, 60, 71]. According to Jung et al., this difference might be due to the quality of sedation. In their study, all participants were satisfied with sedation during colonoscopy, which might attribute to a higher level of contentment with colonoscopy and their preference for colonoscopy over CTC.

Another reason for the population's preference for CTC over colonoscopy reported by Moawad et al. (2010) was the physician's recommendation [27]. However, the authors explained that physicians at the study institution were more likely to recommend CTC to their patients because at the time, CTC was shown in two large studies to be as sensitive as colonoscopy in detecting polyps of ≥10 mm [86, 87], and had been endorsed as an acceptable option for CRC screening by the American Cancer Society, American College of Radiology, and US Multi-Society Task Force on Colorectal Cancer [10]. Physicians' willingness to recommend CTC over the other screening tests might also be due to the typical ease of referral, expedited follow-up for significant colonic (any polyp ≥6 mm) and extra-colonic findings, and the unique no-fee provision of care at the study institution as a military treatment facility [27].

Two of the three studies that found the population's preference for CTC over colonoscopy expressed concerns about potential selection bias that could have impacted their results. In

Gareen et al.'s study (2015) [71], the study subjects comprised those who chose to participate in the National CTC Trial, suggesting their willingness to undergo CTC. Similarly, in the study by Moawad et al. (2010), the study participants had already chosen to undergo CTC for screening when queried about their test preference [27].

Reasons for people's aversion to CTC include gas insufflation [60], claustrophobic feeling [60], the need to return for a colonoscopy for polyp removal when polyps are detected [71, 88], abdominal pain, abdominal discomfort, and a loss of dignity [43]. While in colonoscopy, a patient is sedated and the procedure is typically performed in an isolated space, CTC is often performed (with colon inflation) on a fully conscious patient in a relatively open space, which may increase the patient's anxiety, discomfort and loss of dignity [43]. In a study by Akerkar et al. [89], participants who experienced a higher level of pain, discomfort and loss of dignity in the CTC group would be willing to wait for almost five weeks longer to have a colonoscopy instead of a CTC (See also Section 5.3.4.1).

5.3.1.4. Preference for blood test (SEPT9) and capsule colonoscopy (nanopill)

SEPT9 and capsule colonoscopy have shown the potential to address the pitfalls of the current available tests with test convenience and a low level of harm. Vuik et al's systematic review (2021) highlighted a high accuracy of capsule colonoscopy in detecting CRC and polyps, which is comparable to that of colonoscopy, despite a moderate completion rate ranging from 57% to 92% [90]. However, given the novelty of SEPT9 and capsule colonoscopy, their application in population-based CRC screening requires consideration of various factors, including guideline development, health economic considerations, and costs to participants.

In general, Australians expressed a preference for blood sampling over stool sampling because of sampling convenience [64, 91, 92]. In the two studies conducted in Germany [93] and the USA [94], the SEPT9 blood test was the most preferred test by the study population when offered with the other available screening tests including FOBT, colonoscopy and sigmoidoscopy. In the study by Adler et al. (2014), people favored SEPT9 since it could, at the same time, avoid fear, discomfort and concern about bowel preparation and the colonoscopy procedure itself, and remove the aversion to the handling of stool samples [93]. The majority of the population has previously taken a blood test and has high trust of the test [93]. Almost no negative aspects of SEPT9, including fear of needles, were mentioned by the study participants. In the study by Taber et al. (2014) where focus groups were informed of SEPT9's

high sensitivity in detecting CRC - up to 90 of 100 cancers (compared to colonoscopy detecting 95 of 100 cancers or advanced lesions, sigmoidoscopy detecting 70-80 of 100 cancers or advanced lesions, and gFOBT detecting 24-50 of 100 cancers or advanced lesions), many survey participants expressed a preference for SEPT9 due to its high accuracy [94].

Recent meta-analysis by Song et al. (2017) [95] and a review by Wang et al. (2018) [96] showed that SEPT9 was superior to FIT in detecting CRC in a symptomatic population, with higher sensitivity (75.6% for SEPT9 vs. 67.1% for FIT) and relatively comparable specificity (90.4% for SEPT9 and 92.0% for FIT). However, in an asymptomatic population, the performance of SEPT9 appeared to be lower than FIT and FIT-DNA tests, with lower sensitivity (68.0% for SEPT9 vs. 79.0% for FIT and 92.3% for FIT-DNA) and lower specificity (80.0% for SEPT9 vs. 94.0% for FIT and 86.6% for FIT-DNA) [95]. Despite its diagnostic value for advanced-stage CRCs (stages III-IV), the SEPT9 gene methylation assay demonstrated a limited ability to detect early-stage cancers and CRC precursors. Its sensitivity in detecting stage I CRC, advanced adenomas, and polyps (>1 cm) was shown to be approximately 35%, 11.2%, and, and 22%, respectively [96-98]. Additionally, the study by Zajac et al. (2016) showed that although respondents to their survey stated a preference for blood screening over FIT, the likelihood of engaging in blood screening was significantly lower compared to home-based FIT [92]. This underlines the fact that the population's decision making for CRC screening is driven by multiple factors, and test preference is only one of them.

Groothuis-Oudshoorn et al. (2014) [99] demonstrated the potential of capsule colonoscopy when used for CRC screening to reduce the percentage of people preferring no screening from 19.2% (when FIT was used) to 16.7%. The main reasons for which individuals preferred capsule colonoscopy were screening technique, sensitivity and preparation (less intensive preparation required). Capsule colonoscopy outperforms other tests due to its state-of-the-art technological basis and test convenience, however, at the expense of cost [99].

5.3.2. Individuals' characteristics influencing test preference

5.3.2.1. Gender

Women tended to prefer non-invasive test (FOBT) over the other more invasive tests (especially colonoscopy) [55, 59, 100]. This aligns with the observations that men had a more positive attitude towards colonoscopy than women [101] and women had lower rates of screening with

colonoscopy than men [102, 103]. Compared to men, women were more concerned about pain, discomfort, embarrassment, and complications related to colonoscopy and the possibility of cancer detection [103, 104]. After experiencing colonoscopy, women also reported a higher level of pain [105] and discomfort [106], and lower willingness to undergo a future colonoscopy, compared to men [107].

At the same time, more women than men expressed a preference for blood sampling [64]; and more women considered barium enema as their least-preferred test [50].

5.3.2.2. Age

Previous studies have consistently shown a decrease in willingness to undergo colonoscopy with age [29, 41, 44, 71], probably because of increasing concerns about sedation and complications [44]. Cho et al. (2017) [42] also reported a significantly higher preference for FIT among elderly participants.

Compared to older people, younger people were more concerned about colon preparation and missing work due to colonoscopy [44]. In the study by Redwood et al. (2019), people aged <60 years had a higher preference for sDNA than their older counterparts [31].

5.3.2.3. Screening experience

People with prior experience with colonoscopy were more willing to undergo a future colonoscopy [29], and were less likely to prefer stool-based test over colonoscopy [54]. Fear and concerns about colonoscopy seem to decrease once the test has been experienced. The same trend is observed for stool-based tests. Previously screened subjects with stool-based tests were more likely to favor FOBT/sDNA compared to unscreened subjects [31, 54, 64, 92]. This implies that when one selects a test for CRC screening, the person's familiarity with the test can overcome the perceived barriers [64].

5.3.2.4. Ethnicity

All the included studies that explored the association between ethnicity and preferences for CRC screening tests were conducted in the US. Caucasian Americans were more likely to prefer stool-based tests and SEPT9 [26, 49, 94] while African Americans were more likely to prefer colonoscopy/sigmoidoscopy [49, 50]. When combining self-reported race and prior experience (with any CRC screening technique), Taber et al. (2014) [94] found that unscreened African Americans tended to prefer colonoscopy, followed by screened Caucasian Americans and unscreened Hispanic Americans. In the same study, 43% of unscreened Caucasian Americans did not select colonoscopy as either their first- or second-choice test, suggesting a particular aversion to colonoscopy in this group.

5.3.2.5. Education level and belief

Two studies conducted in USA and Australia found that people with higher education preferred stool-based test more than those with lower education [49, 64]. However, a Palestinian study found a lower acceptability of colonoscopy, but not FOBT, in those with education below secondary school level compared to those with higher education. Religious objection to screening and fatalistic beliefs were also linked with a lower acceptability of colonoscopy in this study [53]. The authors suggested that these results might be typical of Palestine since fatalism is a central belief in Islam. Fatalism has been shown to influence individuals' attitudes towards cancer screening [108-110]. Palestinians also seem to have a strong religious objection to colonoscopy compared to FOBT because colonoscopy is more invasive, intimidating and may contradict some of their religious values [53].

In a Jordan study, preference for colonoscopy was also reported to be associated with a belief that CRC screening is costly [45]. People might assume that tests with higher costs have a higher accuracy and quality [111].

5.3.2.6. Perceived risk of CRC

Higher perceived risk of CRC or presence of symptoms were related to a greater willingness to undergo colonoscopy compared to less invasive tests (stool-based tests and CTC) [60, 112, 113]. In contrast, average-risk individuals (with no symptoms; or a genetic test indicating an average risk) tended to choose FOBT as their most preferred test [112].

5.3.2.7. Insurance status

Uninsured people were more likely to prefer stool-based tests over colonoscopy compared to insured people [54]. This suggests cost-related barriers to CRC screening.

5.3.2.8. Health status

People with fair or poor health status seemed to be less concerned about sensitivity than people with good to excellent health status and were less likely to select colonoscopy as their test of choice [44]. Although known as the most accurate test available, colonoscopy is also related to a higher risk of complications and therefore is not suitable for people with ill health.

5.3.3. Intention to participate and actual participation in relation to the stated preference

Previous studies have presented a consistent observation that participants who preferred colonoscopy were more likely to complete a colonoscopy compared to those preferring another test [26, 51, 71]. Even when people stated that they preferred another test rather than colonoscopy, in their actual screening participation, many of them underwent colonoscopy. In fact, colonoscopy was the most commonly chosen test when people did not receive their preferred test [26, 51, 52]. For example, in an English study (Wolf 2016), 78% of those who stated a preference for stool-based test remained unscreened. In the same study, regardless of the test chosen based on one's preference, up to 80% of those screened were screened with colonoscopy. The two studies by Palmer et al. (2010) [47] and Sandoval et al. (2021) [48] also showed that individuals who were adherent to CRC screening were more likely to choose colonoscopy as their preferred test while those who were non-adherent to CRC screening were more likely to choose stool-based tests. Participants with up-to-date screening were more concerned about test accuracy, unlike participants without up-to-date screening who were more concerned about the risks of colonoscopy and its costs [48].

Other observations on individuals' intention to participate or their actual participation came from single studies. In the study conducted by Zajac et al. (2016) [92], a dichotomous choice between blood and FIT screening initially revealed a higher preference among participants for blood testing. However, the dynamics shifted when participants encountered four scenarios, separately for blood and stool testing, involving varying levels of external contact—ranging from home tests with no contact to three points of contact (two GP appointments and one visit to a collection centre). In this assessment, the likelihood ratings for home-based FIT were

significantly higher, with a score of 4.15 on a 5-point Likert Scale (ranging from not at all likely to definitely likely), compared to all blood-related scenarios: home blood (4.01), blood with one visit (3.75), blood with two visits (3.17), and blood with three visits (2.79). The findings suggest that, despite the initial preference for blood testing, the convenience of home-based FIT significantly surpassed that of blood sample collection [92]. The majority (91%) of those who underwent sDNA testing were willing to use the test again [63]. Annual capsule colonoscopy showed the potential to bring about a higher screening uptake compared to biennial FIT, but the difference was modest (from 75.8% to 78.8%) [99].

5.3.4. Barriers to participation in CRC screening and potential addressing measures

5.3.4.1. Visual (or structural) tests: colonoscopy, sigmoidoscopy and capsule colonoscopy

While the American Cancer Society guidelines recommend visual technologies, including colonoscopy and CT colonography, for screening the average-risk population [6], the European Guidelines for Quality Assurance in Colorectal Cancer Screening and Diagnosis recommend FOBT as the primary test in population-based CRC screening programmes, where colonoscopy play a crucial role as the gold standard for evaluating the status of individuals with a positive FOBT result [5]. Colonoscopy is not recommended as the primary test for screening the average-risk population according to the EU guidelines due to cost, invasiveness, limited endoscopic capacity, and insufficient evidence from randomized trials. Instead, colonoscopy surveillance is only recommended for individuals at increased risk (e.g., those with a positive FOBT result) [5].

Despite the well-known advantages of these visual techniques, colonoscopy in particular, are well known (e.g., high accuracy, the ability to screen and treat at the same time, longer screening intervals), they still present certain downsides (e.g., invasiveness, discomfort and the need for bowel preparation) that negatively affect screening compliance [36].

For this reason, the following paragraphs attempt to collect and describe the main barriers and facilitators to screening with visual tests perceived by the public that were listed in literature.

Barriers to screening with visual tests

Aside from logistical barriers to participate in screening, such as "lack of time" [44, 52, 114], the literature clearly shows that important psychological barriers also exist. In fact, respondents of different ages, from different countries and healthcare systems, often express the same difficulties in participating in colonoscopy-based screening programs due to their perceived invasiveness [20, 29, 41, 52, 61, 67, 99, 114-117], which causes fear and anxiety [52, 115] related to the procedure and preparation.

Embarrassment [115, 116, 118-120] surrounding the procedure and the interaction with the healthcare professionals involved – especially in those cases in which the individual preference for the sex or, in some cases, ethnicity [118] of the examiner is not met – are yet other main reported obstacles to participation.

The perceived invasiveness of colonoscopy is often expressed by participants as fear of pain [20, 52, 61, 67, 115, 121] and discomfort [117, 122], anxiety regarding sedation [41, 44, 71, 115, 123] and preparation, fear of "insertion of tubes" [41] and needles [115], and concerns for privacy.

Feeling of "disgust" is also commonly reported [52, 115]. Bowel preparation in particular, described as "horrible" from subjects interviewed by Dyer et al. [115], represents a significant barrier to screening [20, 41, 58, 60, 61, 67, 114, 115, 124]. Standard colonoscopy preparations are made of nonabsorbable solutions such as Polyethylene glycol (PEG)-electrolyte solutions (PEG-ELS) [125] that, because of the laxative action [20, 60, 67] and the large volume [126] – around 4 L– that must be ingested, can prevent the participants from completing the preparation [127].

Radiological tests, alternative to colonoscopy, such as CTC and barium enema, present downsides as well. In fact, even if nowadays barium enema procedures are not often carried out, when requested as alternative to colonoscopy, they similarly require a laxative preparation and the procedure involves a tube that delivers the barium solution and air (double-contrast) into the colon [128], which may cause the person to feel bloating and discomfort [20, 67]. On the other hand, CTC also requires a laxative preparation and, in order to correctly visualize the colon, the distention of the colon by inserting air with an insufflator [129]. In this regard, Gareen et al. [71], who investigated population's preference for CTC and colonoscopy, found that

participant-reported discomfort was more commonly worse than expected for CTC (32.9%) than for colonoscopy (5.0%) ($p<0.001$). Moreover, women - more likely, in general, to express a preference for the sex of the examiner - were more likely to express a preference in this regard when having the CTC examination (44.5%) than when undergoing colonoscopy (24.3%).

Preference for provider's gender

Because endoscopic procedures are often perceived as invasive and uncomfortable, it is understandable that the endoscopist's gender can influence a person's attitude towards screening. Among the studies included in this review, seven evaluated gender preferences among CRC screening participants [52, 71, 118-120, 130, 131].

Females in particular appear to be more likely to express a preference for the sex of the examiner, as reported by Chong et al. [130] - who found that 70% of the female subjects (vs. 62.8% of males) who participated in their study expressed a gender preference -, Zapatier et al. [118] - who found that 30.8% of the female subjects (vs. 20.4% of males) expressed a gender preference ($P= 0.02$) – and Lachter et al. [52] - who found that 46% of the female subjects (vs. 22% of males) expressed a preference for a same-gender endoscopist ($P = 0.086$).

The most commonly cited reasons behind same gender preference are "feeling more comfortable" [52], "less embarrassed" [119] and the feeling, as reported by Menees et al. [120], that "the same gender was more empathetic", "a better listener" and also "technically better". In fact, sometimes the same gender preference would even influence people's willingness to pay (or pay more) and to wait in order to have their preference met [120, 131].

In summary, evidence shows that participant's "same gender" preference for the provider represents an important barrier that should be considered when organizing a screening program. However, not all individuals tend to express a gender preference, and some prefer an opposite gender endoscopist. The reason behind this, as reported by Khara et al. [131], may lie in health practices and habits: the majority of them, predominantly females, have male primary care providers and male gynecologists.

Potential addressing measures for increasing participation with visual tests

Test attributes considered to be the most important and the hierarchy of information participants desire to receive represent a good exemplification of facilitators to CRC screening adherence. In this regard, respondents from the included studies give great importance to test

accuracy [123], high sensitivity for detecting polyps [117, 124] and the opportunity to detect and treat them in the same procedure [117, 123]. People want to be informed of the risks of the procedure, as well as practical aspects [132] (with some asking for detailed, step by step explanations of what is going to happen and what to expect from the test [115]), and its benefits (e.g., how many cases of CRC or CRC-related deaths could be prevented by screening [132]). In general, the degree of satisfaction with information provided correlates with the degree of comfort during colonoscopy [133].

In addition, addressing existing barriers such as the discomfort produced by bowel preparation could itself facilitate individuals' participation: studies show that CRC screening participants have a preference for non-laxative [60] and low-volume [126] preparations. In fact, some of the included studies have investigated alternatives to the commonly used standard preparation PEG-ELS 4L, such as Sodium Phosphate (NaP) tablets [134], Mannitol solutions [135] and low-volume preparations such as Moviprep® AscPEG- 2L (PEG combined with ascorbic acid) and CitraFleet® PiMg (sodium picosulfate combined with magnesium citrate) [126].

NaP tablets, for example, were preferred over the PEG solution by 66% of the 53 participants interviewed by Gurudu et al. [134]. In the study performed by Piñerúa-Gonsálvez et al. [135], the PEG solution was also less chosen to be used again in future colonoscopies compared to the mannitol solution (71.4% of the individuals in the PEG group vs. 82.9% of the individuals in the mannitol group). Finally, Rodríguez de Miguel et al. [126] who, studied PEG-ELS 4L-related adverse effects compared to the low volume preparations on a cohort of 292 individuals, found that participants using PEG-ELS 4L required antiemetics more often compared to the AscPEG-2L and PiMg groups (22.4% vs 2.1% and 8.2%, respectively; $p < 0.0001$). The AscPEG-2L and PiMg groups also presented with less nausea, thirst and headache than those treated with PEG-ELS 4L (12.5% vs 23.5%, $p = 0.047$; 7.3% vs 23.5%, $p = 0.002$ and 6.2% vs 18.4%, $p = 0.010$, respectively). The evidence underlines how low-volume preparations, in general, appear to be better tolerated than the standard solution PEG-ELS 4L.

Moreover, having a choice among a range of colon-cleansing preparations for their next colonoscopy, as well as suggestions to alleviate the process, were consistently cited as facilitators [115, 134].

Another major issue that prevents screening participation is concern for privacy. This, however, could be addressed by ensuring a protected environment and usage of adequate tools. For

example, Aamar et al. [136], investigated whether the use of a novel disposable patient garment (Privacy Pants®; Dignity Garment, Madison, MS, USA), which increases coverage, could reduce embarrassment and increase colonoscopy acceptance. Their results were noteworthy, with increased privacy - compared to the traditional gown - reported by 76% of the participants. This tool was associated with high rates of respect and satisfaction and decreased embarrassment during the procedure. The utilization this new disposable garment is shown in **Figure 2**.

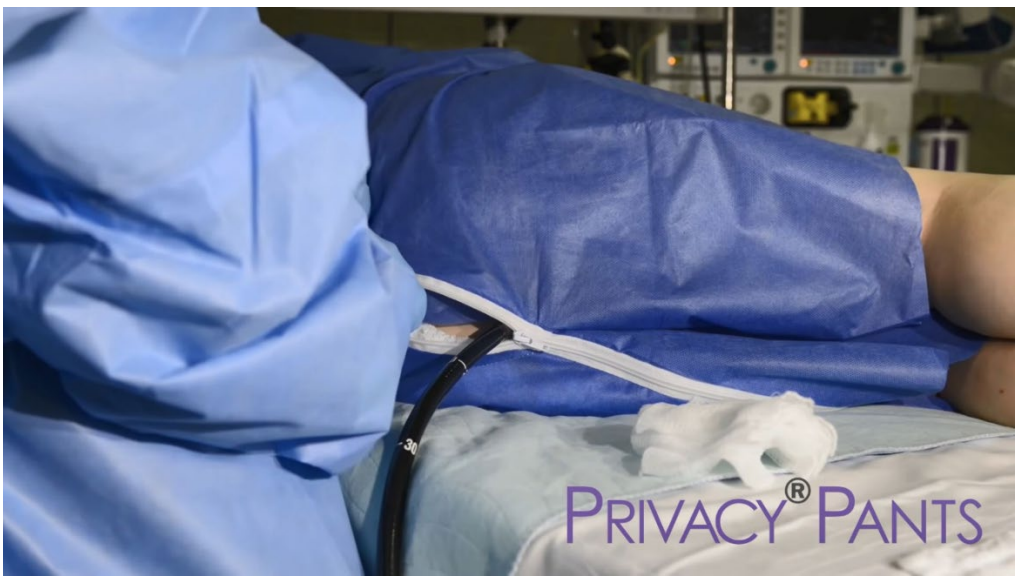


Figure 2. Illustrative image showing the utilization of the Privacy Pants® during colonoscopy—Retrieved from Dignity Garments (https://www.youtube.com/watch?v=tK8QplfW-ME (accessed on 1 September 2021)) [129].

It should be noted that among the most appreciated attributes of visual tests, there is a set of features common to one particular technique: capsule endoscopy. This test does not require sedation and it is minimally invasive, therefore does not cause major embarrassment and discomfort that are frequently reported with the other structural techniques. Moreover, being available also during weekends, it appears more attractive to people with busy schedules [118]. In a study by Rex and Liberman [123] (2012) involving 308 individuals, capsule colonoscopy (Check-Cap®) was chosen by 43% of individuals with a prior colonoscopy and by 69% of individuals who declined colonoscopy before ($p<0.0001$). Furthermore, Chatrath and Rex [29] who, in 2014, performed a similar investigation by proposing colonoscopy, FOBT, and Check-Cap as screening alternatives, found that Check-Cap was preferred to FOBT as an

alternative to colonoscopy, most likely because of its higher sensitivity (80% for CRC and 50% for large polyps vs. 70% for CRC and 35% for large polyps) and ease of administration.

5.3.4.2. Stool-based tests: FIT/gFOBT and sDNA test

Stool-based tests (FIT/gFOBT) and, with regards to the guidelines presently in place in the US, sDNA testing are currently recommended by international guidelines as the standard first-line tests for CRC screening in the average-risk population [6-8]. However, similarly to their above-mentioned structural counterparts, these tests present certain disadvantages and barriers to participation. For example, feelings of embarrassment and discomfort and lower accuracy, which leads to higher false-positive rates compared to structural tests, are not always considered acceptable by participants [138] and can negatively affect compliance [36].

Barriers to screening with stool-based tests

The main barriers reported by individuals undergoing stool-based screenings are caused by "interaction with feces" [139] that, generally, brings along feelings of "disgust" [122, 140], "shame"[140], "discomfort" and "embarrassment" [122].

Stool collection in particular, with troubles in "using paper to catch the sample", "getting the stool sample into the tube" and "labelling the test", seems to represent the biggest obstacle to screening participation with stool-based tests [122, 141, 142].

In order to address the practical difficulties experienced by participants, some authors explored possible tools that could simplify participation. Among these are the so-called fecal collection devices (FCDs) - employing external collecting containers such as single-use flushable paper-based products and reusable plastic designs.

These, however, as reported by Morling et al. [141], who investigated the preferences of 679 individuals, are less preferred than the standard container methods (44.6% found the sample collection with the FCD more difficult vs. only 38.4% found it easier). In contrast, in the study by Shin et al. [143], the sampling bottle - consisting of "a small tube comprising a thin and long sampling probe with a grooved, spiraling tip and a twistable structure to open the cap" (typically employed in OC-Sensor quantitative FIT) was preferred over the conventional FOBT container (79.9% being satisfied with the sampling bottle vs. 73% with the conventional container). The intention to undergo future screening was also higher in the group preferring the sampling bottle compared to the conventional container (aOR 1.78 [1.28-2.48]). Although

with rather contrasting opinions, small tube openings were generally disliked [122, 144] and the use of such devices would decrease people's willingness to participate.

Potential addressing measures for increasing participation with stool-based tests

In line with what has been said, ease of use [122, 140-144] was consistently cited as one of the main factors that could facilitate stool-based screening uptake, with participants requesting "clarity of instructions" [141], "simpler instructions" [122] and "simple and large font instructions" [142].

The objective difficulties experienced by individuals in understanding and following kits' instructions are witnessed by the need, expressed by many, of having a healthcare professional that could help them [115, 139], for example, by performing the test in a mobile screening van or in hospital setting [139]. In general, "having an appointment with a healthcare professional" [139] was perceived as a facilitator to taking the test, not only with the instructions and help provided, but also with the follow-up support [142].

On the other hand, some authors have underlined how interaction with healthcare workers could cause embarrassment for some: Ellis et al. [145] and Ramezani Doroh et al. [67] reported that interviewed participants most often preferred their home as the sampling location. Similarly, Stoltzfus et al. [146] reported how self-sampling, by overcoming healthcare access barriers, tends to help the people feel "in charge of their own care" resulting in a greater sense of independence and convenience.

On the same page, people's preferences for returning samples were mixed. For example, 51% and 46.7% of the 820 participants interviewed by Ellis et al. [145] preferred returning the stool sample by post and taking the sample to the general practitioner, respectively. In a study by Worthley et al. [147], 5/44 responses regarding methods to encourage screening participation expressed a need for an "alternative to mail" to return stool samples.

In general, "limiting the need for interaction with feces" [139, 142] is an important aspect of stool-based screening that could be addressed by "using tests that require only one sample" [139, 142], "including disposable gloves" [122], "including an antibacterial wipe and extra sheets of paper" [122] and, in general, by providing "better equipment" for stool sample collection [114].

A summary of the main perceived barriers and facilitators to both structural and stool-based

tests is shown is included in **Figure 3**.

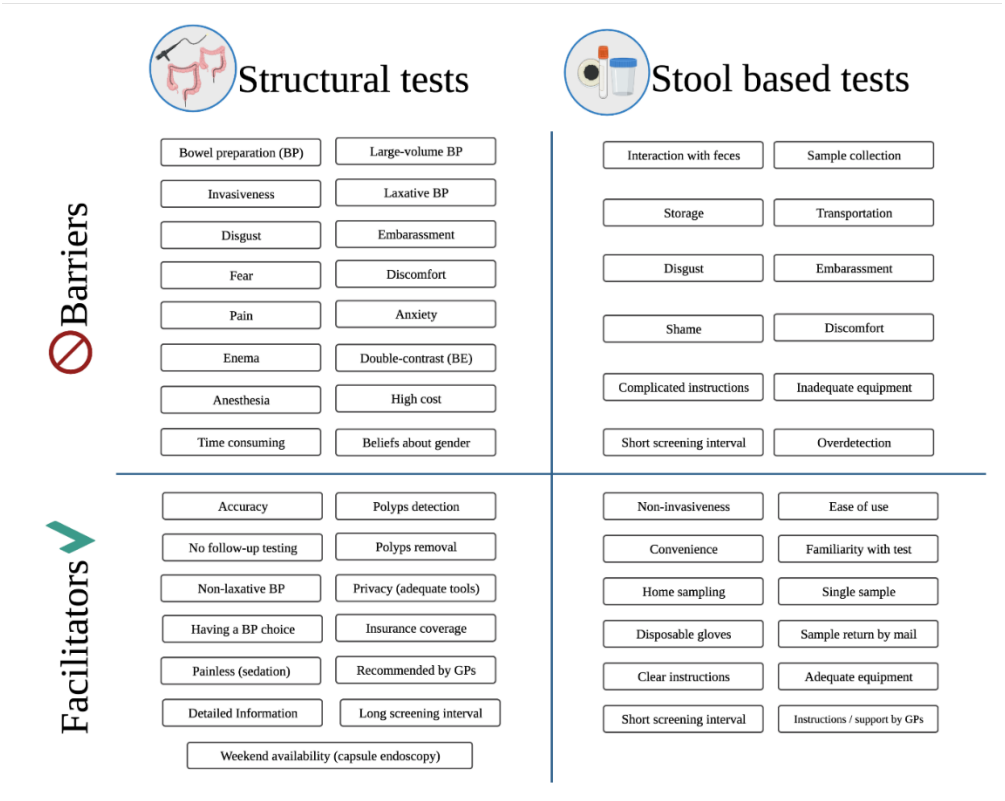


Figure 3. Main perceived barriers and facilitators to structural and stool-based tests—Created with https://biorender.com/ (accessed on 8 September 2021). Abbreviations: BP = bowel preparation; BE = barium enema; GP = general practitioners.

5.3.4.3. General preferences

Other barriers to CRC screening in general

Regardless the type of test, the included articles show a specific trend in terms of perceived barriers to screening. In particular, feelings of embarrassment [99, 114-116, 122, 123], discomfort [117, 122, 135], disgust [52, 115, 122, 140] and fear of pain [20, 44, 52, 67, 114, 115, 121, 146] were common across various study populations undergoing different procedures.

Studies have found that these generalized feelings of anxiety and fear often translate into an attempt to avoid bad news. For example, a study conducted in Czech Republic by Kroupa et al. [114] involving 498 individuals showed that 30.1% did not want to undergo screening tests for

fear of a positive test result. Similarly, subjects interviewed by Gwede et al. [62] preferred a "lighter tone" when receiving information regarding CRC disease and screening. In general, providing too many details, for example, regarding stool sampling methods [145] or invasive follow-up tests [148] was perceived as a barrier that could decrease screening participation.

Lack of interest [114] and lack of time [44, 52, 114], with the latter expressed, for example, as concern for "missing work" [44] were also commonly cited as an obstacle to participation.

Other potential addressing measures for increasing participation in CRC screening

Conveniently, some of the above-mentioned participant-reported barriers to screening can be addressed by an equal number of participant-reported facilitators and suggestions. For example, one of the strategies that could be implemented to address people's lack of interest for screening is, first of all, adequate information campaign. People's suggestions in this regard include providing "major information before the offering of a test" [147], more reminders [147], billboards, commercials, newspaper articles [62], personalized print materials such as books, magazines and other publications [149], celebrity endorsement [139] and "better publicity with a focus on sedation and reduction of inconvenience" [114].

While people seem to dislike automated phone calls [150], video decision aids (DAs) were appreciated by participants interviewed by Brackett et al. [151], Coughlin et al. [149], and Gwede et al. [62], with the latter suggesting that a physician should serve as the narrator. In this regard, many studies reported that suggestions by a physician, particularly if this was the patient's general practitioner, could positively influence screening participation [46, 50, 52, 53, 62, 114-116, 122, 141, 145, 147, 152]. For example, participants interviewed by Gordon and Green [122] reported that they would undergo screening "if the doctor told them why it is important for them to get screened". Similarly, patients interviewed by Worthley et al. [147] said that it was important for them to "understand their physician's rationale for recommending a test over another".

With regards to decision making, of the 2,119 participants interviewed by Messina et al. [153], 50% preferred to share decision making with their physician, 25% preferred to make decisions after considering their physician's opinions, 16% preferred their physician to make all screening decisions and 5% preferred to make decisions alone. Similarly, of the 100 subjects interviewed by Calderwood et al. [46] 53% said the physician and patient should equally share decision

making, 20% preferred to make decisions alone, 13% said that the physician should make screening decisions, 7% said that decisions should be made mostly by the patient and another 7% preferred decisions to be made mostly by the physician. In contrast, most individuals interviewed by Ruffin et al. [50] reported that the test choice should be up to the physician "because of their training, knowledge, and inclination to be directive". In general, patients expressed a desire to be able to discuss with their provider about different screening options [146, 154, 155].

On the subject of information campaign, a campaign launched in Lebanon in the international CRC month of March 2017 included a series of outreach events which employed a "giant inflatable colon model" as an interactive educational tool. Baassiri et al. [156], by analyzing the data of 782 participants, found that touring the inflatable colon model significantly improved participants' awareness and knowledge about CRC (81.2% after visiting the inflatable colon - vs. 19.2% before - knew the recommended age range for CRC screening), increased their willingness to participate in screening (78.6% vs. 70%) and their comfort discussing CRC screening (86.6% vs. 76.6%), ($p< 0,001$). **Figure 4** displays an example of inflatable colon model in use in awareness campaigns.

Figure 4. Giant inflatable colon on display at the Henry Ford Hospital as a part of Colorectal Cancer Awareness Month.- A Healthier Michigan (9 April 2021), Inflatable colon [Photograph]. Retrieved from https://www.flickr.com/photos/healthiermi/13266807653 (accessed on 1 September 2021) [157].

On the one hand, these results open a way to the new, interactive and informative tools to enhance people's awareness of CRC screening and therefore, increase their screening uptake. However, lack of time remains an important issue preventing many individuals from participating in screening programs as well as attending these outreach events. In fact, different studies have underlined that "shorter travel time" to the hospitals or health clinics definitely facilitates participation in screening programs [154, 155, 158].

Another important issue that should be addressed in order to enhance screening participation lies in healthcare accessibility [146, 154, 159], particularly for women [159]. In this regard, participants suggested "improving existing relationships with providers", "being given a referral for screening or specialist" and "ease/speed of scheduling follow-up appointments".

Finally, with regards to the test attributes considered as the most important to participants, the available literature indicates that, in general, the "ideal" test would be a low-cost, non-invasive test that does not require sedation, does not require preparation, does not involve radiation, has a low probability of pain and complications, is characterized by a high accuracy and significant mortality reduction and is offered with less frequency [20, 41, 58-61, 67, 91, 115, 117, 123, 132, 160]. Although creating a test that could meet these expectations is certainly challenging, it appears clear that, in order to maximize uptake in CRC screening programs, efforts of the scientific community should point in this direction.

5.3.5. Willingness to pay, costs and rewards in CRC screening

Healthcare access does not always come free of charge; for this reason, researchers have explored how costs of screening and health insurance coverage influence individual's screening uptake [50, 53, 62, 146, 154, 155]. For example, participants interviewed by both Ruffin et al. [50] and Stoltzfus et al. [146] reported that test cost and insurance coverage "would likely influence their motivation to use one screening modality over another". Pignone et al. [155] have pointed out that many would feel "discouraged from participating in a program where they had to bear large costs". In this regard, in a study performed by Qumseya et al. [53] in Palestine, out of 1,352 respondents, 10% and 15% said they could not afford at all to pay for FOBT and colonoscopy, respectively.

In general, percentages of participants willing to pay out of pocket expenses for CRC screening

vary across different settings. In a US study by Calderwood et al. [46] involving 100 persons, when the participants were asked if they would still pick their first-choice test if it was not covered by healthcare insurance, 24% said "yes" regardless of the cost, 25% said "maybe" depending on the cost, 29% said "no", and 22% were uncertain. Similarly, 83% of the 68 American participants interviewed by Ho et al. [161] stated that they would not be willing to pay out-of-pocket the fees if insurance did not cover the test. In contrast, 91.7% of the 1,240 participants interviewed by Zhou et al. [121] in China, said that they were willing to pay for screening.

With regards to the amount that people would be willing to pay for CRC testing, studies included in this review reveal fluctuating trends [45, 58, 61, 91, 112, 117, 121, 161, 162], with the mean values ranging around $100-200 for both structural (e.g., colonoscopy and CTC) and stool-based testing (e.g., FOBT and sDNA).

These analyses also underline that the differences in people's willingness to pay depend not only on the type of test, but also on its attributes. For example, some individuals would be willing to pay more for a test that "removed polyps", that can "avoid discomfort" by, for example, employing sedatives [117] or that requires "longer intervals", "no bowel preparation", and causes "less complications" [58]. Participants would also pay more for a test with a 90% cancer detection rate, compared to 80% [91] or, more in general, a test that found "most cancer", compared to "some cancer" [117]. The specifications of these studies are provided in **Table 2**.

Table 2. Population's willingness to pay for specific colorectal cancer screening tests and/or features.

Author/Year	Setting	Sample size	"Payable" amount (mean values)	Test type and/or features
Ho et al., 2010 [161]	USA	68	**$244**	CTC
Hollinghurst et al., 2016 [162]	UK; 2011–2012		35% = between **£1 and £100** 21% = between **£101 and £300** 10% = between **£301 and £700** 16% = **over £700** 17% = would not pay	Colonoscopy
Mansfield et al., 2018 [117]	USA; 2014–2015	2067	64% = would choose it if it was free 17% = would pay the cost of **$200**	Colonoscopy (over FIT)
			Up to **$1416**	A test that found "most cancer" (compared to "some cancer")
			Up to **$989**	A test that removed polyps
			Up to **$690**	Avoiding discomfort (eg. using a sedative)
Marshall et al., 2009 [20]	Canada and USA; 2005	501	**$232**	CTC
			$222	sDNA
Omran et al., 2015 [45]	Jordan; 2014	713	65.5% = up to **$706** 25.5% = would wait up to 6 months to get free service 9% = would refuse colonoscopy	Prompt colonoscopy if recommended by physician
Osborne et al., 2018 [91]	Australia	1282	**$13, $8, $21** respectively.	Blood, saliva and stool based-test, respectively
			$87 and **$1**, respectively.	90% and 80% cancer detection rate, respectively
Phisalprapa et al., 2021 [58]	Thailand; 2017–2018	400	**$189, $142, $183, $154**, and **$251**	Colonoscopy, flexible sigmoidoscopy, double-contrast barium enema, CTC and FIT, respectively.
			$3	For every 1% increase in mortaliy risk reduction
			$46	5-year interval
			$45	Less complications
			$38	No bowel preparation
Van Bebber et al., 2007 [112]	USA; 2005	1087	**$150** (mean), in particular: 37% = **$150** 23% = **$20** 17% = would not pay	Genetic tests
Zhou et al., 2018 [121]	China	1240	29.2% = less than **¥100** 20.7% = **¥100–¥199** 14.8% = **¥200–¥299** 13.0% = **¥300–¥399** 22.4% = **more than ¥400**	CRC screening

*****1 US Dollar ($) ≈ 6.5 Chinese Yuan (¥).

In general, those with a higher income, higher education level or a previous diagnosis of cancer were willing to pay more for screening [112, 121, 162]. The participants' gender – surprisingly, male in particular - was also significantly associated with willingness to pay for CRC screening [45, 112, 121].

Since testing costs can pose a significant barrier to CRC screening participation, some programs have tried to promote community participation by financially "rewarding" screening participants. Authors have, in fact, described that individuals would be more likely to be screened if given a small ($10) [154] or large (around $100) [91, 155] reward. It appears that even small rewards (e.g., in the form of coupons) that could serve to repay gas expenses (for travelling to the hospital) or a day off work, especially in low-income communities, could serve as an important facilitator to screening participation.

5.4. Discussion and conclusions

Despite it being of fundamental importance for the success of any CRC screening program, the general population's preference in this context has not gained sufficient attention. Our study provides a comprehensive summary of the up-to-date knowledge on this topic. In this review, the PRISMA guidelines for reporting systematic reviews and meta-analyses were adopted where applicable (e.g., search strategy, selection of studies and data extraction) [163]. However, it was not possible to assess the quality of the studies because of the diversity of study designs and populations.

It should be noted that a large amount of information provided in this review regards colonoscopy, the most commonly reported "preferred" test by the general population. The preponderance of this topic may be due to the large number of studies conducted in USA (42/83 of the studies included) where opportunistic colonoscopy screening is more common than in other countries (e.g., EU countries where many population-based CRC screening programs use FOBT) [164]. For this reason, in order to obtain a more complete understanding of population preferences concerning CRC screening tests, more studies should be conducted in a wider variety of settings.

Overall, the present study points out the main issues that need to be considered in the organization of a CRC screening program: information for participants on one hand and logistical/organizational measures in place on the other.

With regards to information for participants, there are two main aspects that should be considered: individual previous knowledge/experience and the information that is provided to them. As for the latter, our review points out that the general population prefer receiving CRC screening information in more tailored and interactive ways which also use a "lighter tone" in contrast to fear appeals. This requires a more welcoming and open environment for the target population to express their needs and concerns about CRC screening. Multicultural and multilingual outreach programs and campaigns which enable individuals to feel respected and in charge of their own health are also strongly desired. In this regard, suggestions and information directly provided by physicians, particularly if they are the patients' general practitioners, appear to positively influence participation by providing a trustworthy/authoritative voice that can support decision making.

Moreover, providers who wish to advocate for one screening test option over another should be trained on how to properly educate people about its advantages, focusing, in particular, on features of the tests that people consider more important. These are either the test accuracy, the therapeutic effect and the low frequency required in the case of visual or structural tests [28, 49, 50, 55] or, even if it comes with the price of a lower test accuracy, the convenience/ease of use and reduced invasiveness in the case of stool-based tests [49, 65, 66]. Interestingly, both long screening intervals (ten-year), like those in colonoscopy based programs [46, 49, 59], and short screening intervals (one- or two-year), like those in stool-based programs [49, 50, 55], could be perceived as advantages by the general population and could ultimately aid in increasing compliance. By providing more accurate results, colonoscopy-based programs require less frequent testing while more frequent testing employed in programs using stool-based tests can give participants more reassurance of well-being since they are screened every one or two years.

With regards to perceived invasiveness, it should be noted that a number of newer and promising screening technologies that employ biomarkers such as panels of methylated genes (e.g., SEPT9), microRNAs (miRNA) and protein panels, which can be performed on both blood, stool and, in some cases, urine samples, may become available on the market in the near future [36, 165, 166]. However, there is currently not yet a clear recommendation about the clinical use of these tests. It may be possible, as we previously hypothesized [36], that thanks to the features of ease-of-collection and non-invasiveness, these novel screening techniques, by

meeting patient preferences, will improve screening uptake [165, 166]. Since none of the retrieved studies (up to July 2021) have investigated population preferences for biomarker-based screening tests, further research is needed to validate this hypothesis.

Additionally, people perceive different test characteristics as being advantageous depending on their perceived risk of CRC [60, 112]. Specific backgrounds, such as family history or prior detection of polyps, place a person at a higher risk for CRC. Those who know someone with CRC may also perceive their own risk of CRC to be higher than average [113]. Prior qualitative research has shown that people with a higher-than-average perceived risk tend to choose a more invasive screening test (colonoscopy) while people with an average perceived risk prefer a less invasive one (FOBT) [112, 113]. These observations seem to reinforce the use of stool-based tests in average risk population-based CRC screening programs. However, in order to validate this hypothesis, further quantitative research conducted in screening settings is needed.

At the same time, due to the above-mentioned perceived barriers to CRC screening (Section 5.3.4), there is a relevant portion of individuals strongly reluctant towards colonoscopy or stool-based tests regardless of their previous or potential knowledge on the matter. Although both knowledge and beliefs have been shown to be associated with preference, beliefs tend to be more predictive of screening uptake, especially when they are supported by previous negative experiences [26]. As a consequence, the adaption of CRC screening programs to participants' preferences by offering alternative CRC screening tests possesses a great potential to increase screening uptake.

In fact, when it comes to logistical/organizational measures in place, it seems that one of the most central issues to consider is the possibility to offer a range of options in terms of the screening tests (e.g., FOBT vs. colonoscopy vs. others) as well as the features of a specific test (e.g., high vs. low-volume or laxative vs. non-laxative bowel preparations for colonoscopy; or conventional kits vs. newer sample collection devices for stool-based tests).

Many studies corroborate this hypothesis, for example, Chatrath and Rex [29] have reported that, among their study population, 76% of the subjects who declined colonoscopy were willing to undergo alternate forms of screening. Similarly, 97% of the participants in the study by Adler et al. [93] who refused a colonoscopy were willing to accept a non-invasive test. Indeed, one third of people interviewed by Moawad et al. [27] would not have undergone CRC screening if

CTC had not been available as alternative to colonoscopy.

This data also underlines the fact that a preference for a specific test is limited to the options which are known to the people, e.g., if a person only knows about colonoscopy, it cannot be expected that the person prefers CTC or FIT instead. Clearly, providing complete, simple and clear information to the participant is of no less importance than providing screening alternatives.

In resource-limited settings where it is impractical to offer a range of options, other potential methods of boosting CRC screening uptake also exist. For example, if one test is offered as the default test but a portion of people persistently decline it, an alternative test can then be proposed to this specific subgroup. In these regards, the newer convenient screening technologies such as blood tests or capsule endoscopy that can be provided in the physician's office could be useful to enhance screening participation.

In addition to providing alternatives, facilitating logistical aspects of a screening test can also improve participants' feelings and attitudes towards it. Among these are initiatives that may help reduce healthcare access disparities and barriers, especially in lower socioeconomic status neighborhoods. For example, meeting participants' preferences regarding the gender of endoscopist or systems of incentives and rewards that could encourage individuals in financial difficulties to prioritize their health.

Although most current guidelines recommend 50 years as the starting age for average risk CRC screening [5, 167, 168], recent studies have showed an increase in CRC incidence among younger individuals [169-172]. In the US, both the guidelines of the American Cancer Society and US Preventive Services Task Force have, in 2018 and 2021, respectively, lowered the age for initiation of screening from 50 to 45 years [6, 173]. Recent data (2021) from three European tertiary centers also suggests that the incidence of rectal cancers in adults aged ≤39 is increasing, with the disease likely to be more advanced at presentation compared to the older population (≥50 years). According to the authors, the lack of screening programs directed towards this age group may lead to late diagnosis and underestimation of symptoms [174].

Since age has been shown to be associated with individual preference for screening test [29, 31, 41, 42, 44, 71], the findings of our review need to be interpreted with caution in settings where younger adults (≤50 years) are also included in the CRC screening target group. In fact,

further research is needed to investigate CRC screening preference in the younger population and identify the best approach that can optimize screening modalities across age groups [175]. For example, according to Mehta et al. (2021) [175], the lowering of the starting age for screening in the US creates an opportunity to promote stool-based testing, particularly in individuals aged ≤50 years, who have a lower risk of CRC compared to the older counterparts.

Finally, prior evidence has shown that physicians may as well have a strong preference towards one CRC screening test over another, with a general tendency to recommend colonoscopy to their patients [44]. The findings of our review, however, demonstrate that, in order to boost screening participation, patients' preferences and concerns need to be taken into account. We believe that, to guide their patients' informed choice, physicians need to be, first and foremost, provided with up-to-date information about the available screening options, their attributes, and their perceived advantages and disadvantages. Therefore, changes in international guidelines and protocols that support and guide clinicians on these themes are needed to strengthen physicians' role in facilitating patients' decision-making process and increasing levels of CRC screening uptake.

To conclude, we trust the present collection of information and evidence can serve as a helpful updated guide of CRC screening population's preferences, concerns and needs, meant for healthcare providers engaged in the organization of CRC screening programs.

5.5. Methods

On 25/07/2021 a comprehensive search was carried out in OVID and the following databases were used:

- Ovid MEDLINE® ALL;
- Biological Abstracts;
- CAB Abstracts;
- Global Health

The bibliographic search was conducted using the following string (**Table 3**).

Table 3. Bibliographic search strategy.

	Search History	Results (n)
1	exp Colorectal Neoplasms/	236,253
2	exp Early Detection of Cancer/	29,324
3	exp Patient Preference/	9598
4	exp "patient acceptance of health care"/or patient compliance/or patient participation/	169,803
5	3 or 4	177,822
6	1 and 2 and 5	829
7	exp "surveys and questionnaires"/or health care surveys/or health surveys/or patient health questionnaire/or self-report/	1,108,317
8	6 and 7	427
9	screening.ab,kf,ti.	970,991
10	(Colorectal Cancer or Bowel Cancer or Colon Cancer).ab,kf,ti.	225,573
11	("prefer*" or willingness*" or "accept*").ab,kf,ti.	1,641,532
12	("questionnaire*" or "survey*").ab,kf,ti.	2,133,496
13	9 and 10 and 11 and 12	692
14	13 or 8	1070
15	limit 14 to english language	1027
16	limit 15 to yr = "2005-Current"	943
17	remove duplicates from 16	742

The automatic search identified 1070 articles. Of these, 201 were excluded through automatic duplicates removal. Once the duplicates had been removed, titles and abstracts obtained from the bibliographic search were screened in accordance with the PICo framework [176]:

- Population: General population or population at average risk for colorectal cancer (e.g., studies on subjects with genetic/familial risk or cancer patients only were excluded).
- Phenomena of interest: Preference, acceptability, compliance or willingness to undergo one or more screening tests, measured by survey, questionnaire or interview. Only direct measurement of participants' preferences was taken into consideration (e.g., studies employing methodologies investigating factors associated with uptake as an indirect measurement of participants' preferences were not included).
- Context: Colorectal cancer screening (i.e., studies on other types of gastrointestinal cancers were excluded).
- Other considerations: We restricted our search to only original articles (reviews, systematic reviews, meta-analyses and other types of secondary research were excluded), written in English and published between January 2005 and July 2021.

Of 742 titles/abstracts evaluated, 588 records—either secondary studies or those considered irrelevant—were removed. Subsequently, full texts of potentially eligible studies were assessed by applying the set of inclusion and exclusion criteria described above. Of 154 reports assessed for eligibility, 83 papers were finally included in this review. The whole selection and screening process is shown in **Figure 5**.

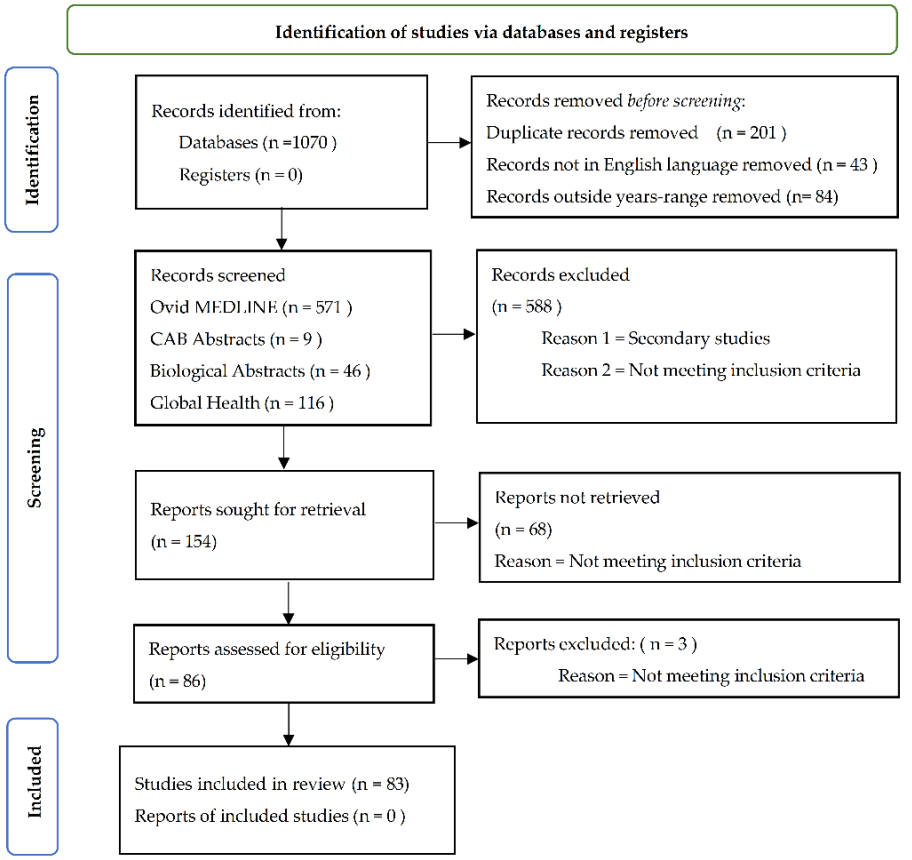


Figure 5. Selection and Screening Process. Adapted from the PRISMA guidelines by Page et al (2020) [163]. For more information, visit: http://www.prisma-statement.or (accessed on 1 August 2021).

Data from the selected studies were extracted and entered into an Excel sheet. The following information was collected (if relevant): Authors and year of publication; Study setting; Study design; Study population and/or Inclusion/Exclusion criteria; Sample size; Any statistical measure related to relevant outcomes; Main results and other potentially relevant information.

References

1. Xi, Y.; Xu, P., Global colorectal cancer burden in 2020 and projections to 2040. *Transl Oncol* **2021,** 14, (10), 101174.
2. Brenner, H.; Stock, C.; Hoffmeister, M., Effect of screening sigmoidoscopy and screening colonoscopy on colorectal cancer incidence and mortality: systematic review and meta-analysis of randomised controlled trials and observational studies. *BMJ* **2014,** 348, g2467.
3. Hewitson, P.; Glasziou, P.; Watson, E.; Towler, B.; Irwig, L., Cochrane systematic review of colorectal cancer screening using the fecal occult blood test (hemoccult): an update. *Am J Gastroenterol* **2008,** 103, (6), 1541-9.
4. Giorgi Rossi, P.; Vicentini, M.; Sacchettini, C.; Di Felice, E.; Caroli, S.; Ferrari, F., et al., Impact of Screening Program on Incidence of Colorectal Cancer: A Cohort Study in Italy. *Am J Gastroenterol* **2015,** 110, (9), 1359-66.
5. von Karsa, L.; Patnick, J.; Segnan, N.; Atkin, W.; Halloran, S.; Lansdorp-Vogelaar, I., et al., European guidelines for quality assurance in colorectal cancer screening and diagnosis: Overview and introduction to the full Supplement publication. *Endoscopy* **2013,** 45, (1), 51-59.
6. Wolf, A. M. D.; Fontham, E. T. H.; Church, T. R.; Flowers, C. R.; Guerra, C. E.; LaMonte, S. J., et al., Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society. *CA Cancer J Clin* **2018,** 68, (4), 250-281.
7. Segnan, N.; Patnick, J.; von Karsa, L.; eds., *European guidelines for quality assurance in colorectal cancer screening and diagnosis*. 1st ed.; Publications Office of the European Union: Luxembourg, 2010.
8. Ponti, A.; Anttila, A.; Ronco, G.; Senore, C.; Basu, P.; Segnan, N., et al. *Cancer Screening in the European Union. Report on the implementation of Council Recommendation on Cancer Screening*; Brussels: European Commission, 2017.
9. Geiger, T. M.; Ricciardi, R., Screening options and recommendations for colorectal cancer. *Clin Colon Rectal Surg* **2009,** 22, (4), 209-17.
10. Levin, B.; Lieberman, D. A.; McFarland, B.; Smith, R. A.; Brooks, D.; Andrews, K. S., et al., Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. *CA Cancer J Clin* **2008,** 58, (3), 130-60.
11. Worthington, J.; Lew, J. B.; Feletto, E.; Holden, C. A.; Worthley, D. L.; Miller, C., et al., Improving Australian National Bowel Cancer Screening Program outcomes through increased participation and cost-effective investment. *PLoS One* **2020,** 15, (2), e0227899.
12. Moutel, G.; Duchange, N.; Lievre, A.; Orgerie, M. B.; Jullian, O.; Sancho-Garnier, H., et al., Low participation in organized colorectal cancer screening in France: underlying ethical issues. *Eur J Cancer Prev* **2019,** 28, (1), 27-32.
13. Ni, K.; O'Connell, K.; Anand, S.; Yakoubovitch, S. C.; Kwon, S. C.; de Latour, R. A., et al., Low Colorectal Cancer Screening Uptake and Persistent Disparities in an Underserved Urban Population. *Cancer Prev Res (Phila)* **2020,** 13, (4), 395-402.
14. Palmer, C. K.; Thomas, M. C.; McGregor, L. M.; von Wagner, C.; Raine, R., Understanding low colorectal cancer screening uptake in South Asian faith communities in England--a qualitative study. *BMC Public Health* **2015,** 15, 998.
15. Alberti, L. R.; Garcia, D. P.; Coelho, D. L.; De Lima, D. C.; Petroianu, A., How to improve colon cancer screening rates. *World J Gastrointest Oncol* **2015,** 7, (12), 484-91.
16. Dougherty, M. K.; Brenner, A. T.; Crockett, S. D.; Gupta, S.; Wheeler, S. B.; Coker-Schwimmer, M., et al., Evaluation of Interventions Intended to Increase Colorectal Cancer Screening Rates in the United States: A Systematic Review and Meta-analysis. *JAMA Intern Med* **2018,** 178, (12), 1645-1658.

17. Inadomi, J. M.; Vijan, S.; Janz, N. K.; Fagerlin, A.; Thomas, J. P.; Lin, Y. V., et al., Adherence to colorectal cancer screening: a randomized clinical trial of competing strategies. *Archives of Internal Medicine* **2012,** 172, (7), 575-82.

18. Benning, T. M.; Dellaert, B. G.; Dirksen, C. D.; Severens, J. L., Preferences for potential innovations in non-invasive colorectal cancer screening: A labeled discrete choice experiment for a Dutch screening campaign. *Acta Oncol* **2014,** 53, (7), 898-908.

19. Wong, M. C.; Ching, J. Y.; Chan, V. C.; Lam, T. Y.; Luk, A. K.; Ng, S. C., et al., Informed choice vs. no choice in colorectal cancer screening tests: a prospective cohort study in real-life screening practice. *Am J Gastroenterol* **2014,** 109, (7), 1072-9.

20. Marshall, D. A.; Johnson, F. R.; Phillips, K. A.; Marshall, J. K.; Thabane, L.; Kulin, N. A., Measuring patient preferences for colorectal cancer screening using a choice-format survey. *Value in Health* **2007,** 10, (5), 415-30.

21. Mansfield, C.; Tangka, F. K.; Ekwueme, D. U.; Smith, J. L.; Guy, G. P., Jr.; Li, C., et al., Stated Preference for Cancer Screening: A Systematic Review of the Literature, 1990-2013. *Preventing Chronic Disease* **2016,** 13, E27.

22. van Dam, L.; Hol, L.; de Bekker-Grob, E. W.; Steyerberg, E. W.; Kuipers, E. J.; Habbema, J. D., et al., What determines individuals' preferences for colorectal cancer screening programmes? A discrete choice experiment. *Eur J Cancer* **2010,** 46, (1), 150-9.

23. Hol, L.; de Jonge, V.; van Leerdam, M. E.; van Ballegooijen, M.; Looman, C. W. N.; van Vuuren, A. J., et al., Screening for colorectal cancer: Comparison of perceived test burden of guaiac-based faecal occult blood test, faecal immunochemical test and flexible sigmoidoscopy. *European Journal of Cancer* **2010,** 46, (11), 2059-2066.

24. Cole, S. R.; Zajac, I.; Gregory, T.; Mehaffey, S.; Roosa, N.; Turnbull, D., et al., Psychosocial variables associated with colorectal cancer screening in South Australia. *Int J Behav Med* **2011,** 18, (4), 302-9.

25. Chapple, A.; Ziebland, S.; Hewitson, P.; McPherson, A., What affects the uptake of screening for bowel cancer using a faecal occult blood test (FOBt): a qualitative study. *Soc Sci Med* **2008,** 66, (12), 2425-35.

26. Wolf, R. L.; Basch, C. E.; Zybert, P.; Basch, C. H.; Ullman, R.; Shmukler, C., et al., Patient Test Preference for Colorectal Cancer Screening and Screening Uptake in an Insured Urban Minority Population. *Journal of Community Health* **2016,** 41, (3), 502-8.

27. Moawad, F. J.; Maydonovitch, C. L.; Cullen, P. A.; Barlow, D. S.; Jenson, D. W.; Cash, B. D., CT colonography may improve colorectal cancer screening compliance. *American Journal of Roentgenology* **2010,** 195, (5), 1118-1123.

28. DeBourcy, A. C.; Lichtenberger, S.; Felton, S.; Butterfield, K. T.; Ahnen, D. J.; Denberg, T. D., Community-based preferences for stool cards versus colonoscopy in colorectal cancer screening. *Journal of General Internal Medicine* **2008,** 23, (2), 169-174.

29. Chatrath, H.; Rex, D. K., Potential screening benefit of a colorectal imaging capsule that does not require bowel preparation. *Journal of Clinical Gastroenterology* **2014,** 48, (1), 52-4.

30. Schreuders, E. H.; Ruco, A.; Rabeneck, L.; Schoen, R. E.; Sung, J. J.; Young, G. P., et al., Colorectal cancer screening: a global overview of existing programmes. *Gut* **2015,** 64, (10), 1637-49.

31. Redwood, D. G.; Blake, I. D.; Provost, E. M.; Kisiel, J. B.; Sacco, F. D.; Ahlquist, D. A., Alaska native patient and provider perspectives on the multitarget stool DNA test compared with colonoscopy for colorectal cancer screening. *Journal of Primary Care & Community Health* **2019,** 10, (54).

32. Ling, B. S.; Moskowitz, M. A.; Wachs, D.; Pearson, B.; Schroy, P. C., Attitudes Toward Colorectal Cancer Screening Tests. *J Gen Intern Med* **2001,** 16, (12), 822-30.

33. Schroy, P. C., 3rd; Duhovic, E.; Chen, C. A.; Heeren, T. C.; Lopez, W.; Apodaca, D. L., et al., Risk Stratification and Shared Decision Making for Colorectal Cancer Screening: A Randomized Controlled Trial. *Med Decis Making* **2016,** 36, (4), 526-35.

34. McQueen, A.; Bartholomew, L. K.; Greisinger, A. J.; Medina, G. G.; Hawley, S. T.; Haidet, P., et al., Behind closed doors: physician-patient discussions about colorectal cancer screening. *J Gen Intern Med* **2009,** 24, (11), 1228-35.

35. Rimer, B. K.; Briss, P. A.; Zeller, P. K.; Chan, E. C.; Woolf, S. H., Informed decision making: what is its role in cancer screening? *Cancer* **2004,** 101, (5 Suppl), 1214-28.

36. Ferrari, A.; Neefs, I.; Hoeck, S.; Peeters, M.; Van Hal, G., Towards Novel Non-Invasive Colorectal Cancer Screening Methods: A Comprehensive Review. *Cancers (Basel)* **2021,** 13, (8).

37. Issa, I. A.; Noureddine, M., Colorectal cancer screening: An updated review of the available options. *World J Gastroenterol* **2017,** 23, (28), 5086-5096.

38. Bailey, J. R.; Aggarwal, A.; Imperiale, T. F., Colorectal Cancer Screening: Stool DNA and Other Noninvasive Modalities. *Gut and Liver* **2016,** 10, (2).

39. Kuipers, E. J.; Rosch, T.; Bretthauer, M., Colorectal cancer screening--optimizing current strategies and new directions. *Nat Rev Clin Oncol* **2013,** 10, (3), 130-42.

40. Ghanouni, A.; Smith, S. G.; Halligan, S.; Plumb, A.; Boone, D.; Yao, G. L., et al., Public preferences for colorectal cancer screening tests: a review of conjoint analysis studies. *Expert Rev Med Devices* **2013,** 10, (4), 489-99.

41. Moreno, C. C.; Jarrett, T.; Vey, B. L.; Mittal, P. K.; Krupinski, E. A.; Roberts, D. L., Patient Knowledge Regarding Colorectal Cancer Risk, Opinion of Screening, and Preferences for a Screening Test. *Current Problems in Diagnostic Radiology* **2019,** 48, (1), 50-52.

42. Cho, Y. H.; Kim, D. H.; Cha, J. M.; Jeen, Y. T.; Moon, J. S.; Kim, J. O., et al., Patients' Preferences for Primary Colorectal Cancer Screening: A Survey of the National Colorectal Cancer Screening Program in Korea. *Gut & Liver* **2017,** 11, (6), 821-827.

43. Jung, H. S.; Park, D. K.; Kim, M. J.; Yu, S. K.; Kwon, K. A.; Ku, Y. S., et al., A Comparison of Patient Acceptance and Preferences Between CT Colonography and Conventional Colonoscopy in Colorectal Cancer Screening. *Korean Journal of Internal Medicine* **2009,** 24, (1), 43-47.

44. Imaeda, A.; Bender, D.; Fraenkel, L., What Is Most Important to Patients when Deciding about Colorectal Screening? *Journal of General Internal Medicine* **2010,** 25, (7), 688-693.

45. Omran, S.; Barakat, H.; Muliira, J. K.; Bashaireh, I.; Batiha, A. M., Assessment of Jordanian Patient's Colorectal Cancer Awareness and Preferences towards CRC Screening: Are Jordanians Ready to Embrace CRC Screening? *Asian Pacific Journal of Cancer Prevention: Apjcp* **2015,** 16, (10), 4229-35.

46. Calderwood, A. H.; Wasan, S. K.; Heeren, T. C.; Schroy, P. C., 3rd, Patient and Provider Preferences for Colorectal Cancer Screening: How Does CT Colonography Compare to Other Modalities? *International Journal of Cancer Prevention* **2011,** 4, (4), 307-338.

47. Palmer, R. C.; Midgette, L. A.; Mullan, I. D., Colorectal cancer screening preferences among African Americans: which screening test is preferred? *Journal of Cancer Education* **2010,** 25, (4), 577-81.

48. Sandoval, J. L.; Relecom, A.; Ducros, C.; Bulliard, J. L.; Arzel, B.; Guessous, I., Screening Status as a Determinant of Choice of Colorectal Cancer Screening Method: A Population-Based Informed Survey. *Gastrointestinal Tumors* **2021,** 8, (2), 63-70.

49. Schroy, P. C., 3rd; Lal, S.; Glick, J. T.; Robinson, P. A.; Zamor, P.; Heeren, T. C., Patient preferences for colorectal cancer screening: how does stool DNA testing fare? *American Journal of Managed Care* **2007,** 13, (7), 393-400.

50. Ruffin, M. T. I.; Creswell, J. W.; Jimbo, M.; Fetters, M. D., Factors influencing choices for colorectal cancer screening among previously unscreened African and Caucasian Americans: findings from a triangulation mixed methods investigation. *Journal of Community Health* **2009,** 34, (2), 79-89.

51. Hawley, S. T.; McQueen, A.; Bartholomew, L. K.; Greisinger, A. J.; Coan, S. P.; Myers, R., et al., Preferences for colorectal cancer screening tests and screening test use in a large multispecialty primary care practice. *Cancer* **2012,** 118, (10), 2726-2734.

52. Lachter, J.; Leska-Aharoni, T.; Warum, D.; Eliakim, R., Overcoming barriers to colorectal cancer screening tests. *Israel Medical Association Journal: Imaj* **2008,** 10, (8-9), 621-6.

53. Qumseya, B. J.; Tayem, Y. I.; Dasa, O. Y.; Nahhal, K. W.; Abu-Limon, I. M.; Hmidat, A. M., et al., Barriers to colorectal cancer screening in Palestine: a national study in a medically underserved population. *Clinical Gastroenterology & Hepatology* **2014,** 12, (3), 463-9.

54. Zhu, X.; Parks, P. D.; Weiser, E.; Fischer, K.; Griffin, J. M.; Limburg, P. J., et al., National survey of patient factors associated with colorectal cancer screening preferences. *Cancer Prevention Research* **2021,** 14, (5), 603-614.

55. Bonello, B.; Ghanouni, A.; Bowyer, H. L.; MacRae, E.; Atkin, W.; Halloran, S. P., et al., Using a hypothetical scenario to assess public preferences for colorectal surveillance following screening-detected, intermediate-risk adenomas: annual home-based stool test vs. triennial colonoscopy. *BMC Gastroenterology* **2016,** 16, 113.

56. Brenner, A.; Howard, K.; Lewis, C.; Sheridan, S.; Crutchfield, T.; Hawley, S., et al., Comparing 3 values clarification methods for colorectal cancer screening decision-making: a randomized trial in the US and Australia. *Journal of General Internal Medicine* **2014,** 29, (3), 507-513.

57. Schroy, P. C., 3rd; Heeren, T. C., Patient perceptions of stool-based DNA testing for colorectal cancer screening. *American Journal of Preventive Medicine* **2005,** 28, (2), 208-14.

58. Phisalprapa, P.; Ngorsuraches, S.; Wanishayakorn, T.; Kositamongkol, C.; Supakankunti, S.; Chaiyakunapruk, N., Estimating the preferences and willingness-to-pay for colorectal cancer screening: an opportunity to incorporate the perspective of population at risk into policy development in Thailand. *Journal of Medical Economics* **2021,** 24, (1), 226-233.

59. Xu, Y.; Levy, B. T.; Daly, J. M.; Bergus, G. R.; Dunkelberg, J. C., Comparison of patient preferences for fecal immunochemical test or colonoscopy using the analytic hierarchy process. *BMC Health Services Research* **2015,** 15, 175.

60. Ghanouni, A.; Smith, S. G.; Halligan, S.; Plumb, A.; Boone, D.; Magee, M. S., et al., Public perceptions and preferences for CT colonography or colonoscopy in colorectal cancer screening. *Patient Education & Counseling* **2012,** 89, (1), 116-21.

61. Marshall, D. A.; Johnson, F. R.; Kulin, N. A.; Ozdemir, S.; Walsh, J. M.; Marshall, J. K., et al., How do physician assessments of patient preferences for colorectal cancer screening tests differ from actual preferences? A comparison in Canada and the United States using a stated-choice survey. *Health Economics* **2009,** 18, (12), 1420-39.

62. Gwede, C. K.; Koskan, A. M.; Quinn, G. P.; Davis, S. N.; Ealey, J.; Abdulla, R., et al., Patients' perceptions of colorectal cancer screening tests and preparatory education in federally qualified health centers. *Journal of Cancer Education* **2015,** 30, (2), 294-300.

63. Berger, B. M.; Schroy, P. C., 3rd; Rosenberg, J. L.; Lai-Goldman, M.; Eisenberg, M.; Brown, T., et al., Colorectal cancer screening using stool DNA analysis in clinical practice: early clinical experience with respect to patient acceptance and colonoscopic follow-up of abnormal tests. *Clinical Colorectal Cancer* **2006,** 5, (5), 338-43.

64. Osborne, J. M.; Wilson, C.; Moore, V.; Gregory, T.; Flight, I.; Young, G. P., Sample preference for colorectal cancer screening tests: blood or stool? *Open Journal of Preventive Medicine* **2012,** 2, (3), 326-331.

65. de Bekker-Grob, E. W.; Hol, L.; Donkers, B.; van Dam, L.; Habbema, J. D.; van Leerdam, M. E., et al., Labeled versus unlabeled discrete choice experiments in health economics: an application to colorectal cancer screening. *Value in Health* **2010,** 13, (2), 315-23.

66. Cantor, S. B.; Volk, R. J.; Cass, A. R.; Gilani, J.; Spann, S. J., Psychological benefits of prostate cancer screening: the role of reassurance. *Health Expect* **2002,** 5, (2), 104-13.

67. Ramezani Doroh, V.; Delavari, A.; Yaseri, M.; Emamgholipour Sefiddashti, S.; Akbarisari, A., Preferences of Iranian average risk population for colorectal cancer screening tests. *International Journal of Health Care Quality Assurance* **2019,** 32, (4), 677-687.

68. Imperiale, T. F.; Ransohoff, D. F.; Itzkowitz, S. H.; Levin, T. R.; Lavin, P.; Lidgard, G. P., et al., Multitarget stool DNA testing for colorectal-cancer screening. *N Engl J Med* **2014,** 370, (14), 1287-97.

69. Berger, B. M.; Levin, B.; Hilsden, R. J., Multitarget stool DNA for colorectal cancer screening: A review and commentary on the United States Preventive Services Draft Guidelines. *World J Gastrointest Oncol* **2016,** 8, (5), 450-8.

70. Redwood, D. G.; Asay, E. D.; Blake, I. D.; Sacco, P. E.; Christensen, C. M.; Sacco, F. D., et al., Stool DNA Testing for Screening Detection of Colorectal Neoplasia in Alaska Native People. *Mayo Clin Proc* **2016,** 91, (1), 61-70.

71. Gareen, I. F.; Siewert, B.; Vanness, D. J.; Herman, B.; Johnson, C. D.; Gatsonis, C., Patient willingness for repeat screening and preference for CT colonography and optical colonoscopy in ACRIN 6664: the National CT Colonography trial. *Patient preference & adherence* **2015,** 9, 1043-51.

72. Vargo, J. J., Doc, can I drive home? *Am J Gastroenterol* **2009,** 104, (7), 1656-7.

73. Riphaus, A.; Gstettenbauer, T.; Frenz, M. B.; Wehrmann, T., Quality of psychomotor recovery after propofol sedation for routine endoscopy: a randomized and controlled study. *Endoscopy* **2006,** 38, (7), 677-83.

74. Green, A. R.; Peters-Lewis, A.; Percac-Lima, S.; Betancourt, J. R.; Richter, J. M.; Janairo, M. P., et al., Barriers to screening colonoscopy for low-income Latino and white patients in an urban community health center. *J Gen Intern Med* **2008,** 23, (6), 834-40.

75. McLachlan, S. A.; Clements, A.; Austoker, J., Patients' experiences and reported barriers to colonoscopy in the screening context--a systematic review of the literature. *Patient Educ Couns* **2012,** 86, (2), 137-46.

76. Iannaccone, R.; Catalano, C.; Mangiapane, F.; Murakami, T.; Lamazza, A.; Fiori, E., et al., Colorectal polyps: detection with low-dose multi-detector row helical CT colonography versus two sequential colonoscopies. *Radiology* **2005,** 237, (3), 927-37.

77. Kato, T.; Muroya, T.; Goda, T.; Takabayashi, K.; Sasaki, K.; Takahashi, T., et al., Iatrogenic Colonic Perforation due to Computed Tomographic Colonography. *Case Rep Gastroenterol* **2015,** 9, (2), 171-8.

78. Sosna, J.; Blachar, A.; Amitai, M.; Barmeir, E.; Peled, N.; Goldberg, S. N., et al., Colonic perforation at CT colonography: assessment of risk in a multicenter large cohort. *Radiology* **2006,** 239, (2), 457-63.

79. Burling, D.; Halligan, S.; Slater, A.; Noakes, M. J.; Taylor, S. A., Potentially serious adverse events at CT colonography in symptomatic patients: national survey of the United Kingdom. *Radiology* **2006,** 239, (2), 464-71.

80. Pickhardt, P. J., Incidence of colonic perforation at CT colonography: review of existing data and implications for screening of asymptomatic adults. *Radiology* **2006,** 239, (2), 313-6.

81. Levin, T. R.; Zhao, W.; Conell, C.; Seeff, L. C.; Manninen, D. L.; Shapiro, J. A., et al., Complications of colonoscopy in an integrated health care delivery system. *Ann Intern Med* **2006,** 145, (12), 880-6.

82. Zubarik, R.; Fleischer, D. E.; Mastropietro, C.; Lopez, J.; Carroll, J.; Benjamin, S., et al., Prospective analysis of complications 30 days after outpatient colonoscopy. *Gastrointest Endosc* **1999,** 50, (3), 322-8.

83. Anderson, M. L.; Pasha, T. M.; Leighton, J. A., Endoscopic perforation of the colon: lessons from a 10-year study. *Am J Gastroenterol* **2000,** 95, (12), 3418-22.

84. Laanani, M.; Coste, J.; Blotiere, P. O.; Carbonnel, F.; Weill, A., Patient, Procedure, and Endoscopist Risk Factors for Perforation, Bleeding, and Splenic Injury After Colonoscopies. *Clin Gastroenterol Hepatol* **2019,** 17, (4), 719-727 e13.

85. Benazzato, L.; Zorzi, M.; Antonelli, G.; Guzzinati, S.; Hassan, C.; Fantin, A., et al., Colonoscopy-related adverse events and mortality in an Italian organized colorectal cancer screening program. *Endoscopy* **2021,** 53, (5), 501-508.

86. Pickhardt, P. J.; Choi, J. R.; Hwang, I.; Butler, J. A.; Puckett, M. L.; Hildebrandt, H. A., et al., Computed tomographic virtual colonoscopy to screen for colorectal neoplasia in asymptomatic adults. *N Engl J Med* **2003,** 349, (23), 2191-200.

87. Johnson, C. D.; Chen, M. H.; Toledano, A. Y.; Heiken, J. P.; Dachman, A.; Kuo, M. D., et al., Accuracy of CT colonography for detection of large adenomas and cancers. *N Engl J Med* **2008,** 359, (12), 1207-17.

88. van Gelder, R. E.; Birnie, E.; Florie, J.; Schutter, M. P.; Bartelsman, J. F.; Snel, P., et al., CT colonography and colonoscopy: assessment of patient preference in a 5-week follow-up study. *Radiology* **2004,** 233, (2), 328-37.

89. Akerkar, G. A.; Yee, J.; Hung, R.; McQuaid, K., Patient experience and preferences toward colon cancer screening: a comparison of virtual colonoscopy and conventional colonoscopy. *Gastrointest Endosc* **2001,** 54, (3), 310-5.

90. Vuik, F. E. R.; Nieuwenburg, S. A. V.; Moen, S.; Spada, C.; Senore, C.; Hassan, C., et al., Colon capsule endoscopy in colorectal cancer screening: a systematic review. *Endoscopy* **2021,** 53, (8), 815-824.

91. Osborne, J. M.; Flight, I.; Wilson, C. J.; Chen, G.; Ratcliffe, J.; Young, G. P., The impact of sample type and procedural attributes on relative acceptability of different colorectal cancer screening regimens. *Patient preference & adherence* **2018,** 12, 1825-1836.

92. Zajac, I. T.; Duncan, A.; Turnbull, D.; Wilson, C.; Flight, I., Blood-based screening for bowel cancer may not resolve suboptimal screening participation in Australia. *Aust N Z J Public Health* **2016,** 40, (4), 337-41.

93. Adler, A.; Geiger, S.; Keil, A.; Bias, H.; Schatz, P.; deVos, T., et al., Improving compliance to colorectal cancer screening using blood and stool based tests in patients refusing screening colonoscopy in Germany. *BMC Gastroenterology* **2014,** 14, 183.

94. Taber, J. M.; Aspinwall, L. G.; Heichman, K. A.; Kinney, A. Y., Preferences for blood-based colon cancer screening differ by race/ethnicity. *American Journal of Health Behavior* **2014,** 38, (3), 351-361.

95. Song, L.; Jia, J.; Peng, X.; Xiao, W.; Li, Y., The performance of the SEPT9 gene methylation assay and a comparison with other CRC screening tests: A meta-analysis. *Sci Rep* **2017,** 7, (1), 3032.

96. Wang, Y.; Chen, P. M.; Liu, R. B., Advance in plasma SEPT9 gene methylation assay for colorectal cancer early detection. *World J Gastrointest Oncol* **2018,** 10, (1), 15-22.

97. Church, T. R.; Wandell, M.; Lofton-Day, C.; Mongin, S. J.; Burger, M.; Payne, S. R., et al., Prospective evaluation of methylated SEPT9 in plasma for detection of asymptomatic colorectal cancer. *Gut* **2014,** 63, (2), 317-25.

98. Grutzmann, R.; Molnar, B.; Pilarsky, C.; Habermann, J. K.; Schlag, P. M.; Saeger, H. D., et al., Sensitive detection of colorectal cancer in peripheral blood by septin 9 DNA methylation assay. *PLoS One* **2008,** 3, (11), e3759.

99. Groothuis-Oudshoorn, C. G.; Fermont, J. M.; van Til, J. A.; Ijzerman, M. J., Public stated preferences and predicted uptake for genome-based colorectal cancer screening. *BMC Medical Informatics & Decision Making* **2014,** 14, 18.

100. Clarke, N.; Sharp, L.; Osborne, A.; Kearney, P. M., Comparison of uptake of colorectal cancer screening based on fecal immunochemical testing (FIT) in males and females: a systematic review and meta-analysis. *Cancer Epidemiol Biomarkers Prev* **2015,** 24, (1), 39-47.

101. Hol, L.; de Bekker-Grob, E. W.; van Dam, L.; Donkers, B.; Kuipers, E. J.; Habbema, J. D. F., et al., Preferences for colorectal cancer screening strategies: a discrete choice experiment. *British Journal of Cancer* **2010,** 102, (6), 972-980.

102. Segnan, N.; Senore, C.; Andreoni, B.; Azzoni, A.; Bisanti, L.; Cardelli, A., et al., Comparing attendance and detection rate of colonoscopy with sigmoidoscopy and FIT for colorectal cancer screening. *Gastroenterology* **2007,** 132, (7), 2304-12.

103. Denberg, T. D.; Melhado, T. V.; Coombes, J. M.; Beaty, B. L.; Berman, K.; Byers, T. E., et al., Predictors of nonadherence to screening colonoscopy. *J Gen Intern Med* **2005,** 20, (11), 989-95.

104. Wong, R. K.; Wong, M. L.; Chan, Y. H.; Feng, Z.; Wai, C. T.; Yeoh, K. G., Gender differences in predictors of colorectal cancer screening uptake: a national cross sectional study based on the health belief model. *BMC Public Health* **2013,** 13, 677.

105. Shah, S. G.; Brooker, J. C.; Thapar, C.; Williams, C. B.; Saunders, B. P., Patient pain during colonoscopy: an analysis using real-time magnetic endoscope imaging. *Endoscopy* **2002,** 34, (6), 435-40.

106. Park, D. I.; Kim, H. J.; Park, J. H.; Cho, Y. K.; Sohn, C. I.; Jeon, W. K., et al., Factors affecting abdominal pain during colonoscopy. *Eur J Gastroenterol Hepatol* **2007,** 19, (8), 695-9.

107. Ussui, V. M.; Silva, A. L.; Borges, L. V.; Silva, J. G.; Zeitune, J. M.; Hashimoto, C. L., What are the most important factors regarding acceptance to the colonoscopy?: study of related tolerance parameters. *Arq Gastroenterol* **2013,** 50, (1), 23-30.

108. Azaiza, F.; Cohen, M.; Awad, M.; Daoud, F., Factors associated with low screening for breast cancer in the Palestinian Authority: relations of availability, environmental barriers, and cancer-related fatalism. *Cancer* **2010,** 116, (19), 4646-55.

109. Jun, J.; Oh, K. M., Asian and Hispanic Americans' cancer fatalism and colon cancer screening. *Am J Health Behav* **2013,** 37, (2), 145-54.

110. Powe, B. D., Fatalism among elderly African Americans. Effects on colorectal cancer screening. *Cancer Nurs* **1995,** 18, (5), 385-92.

111. Ryan, M.; Watson, V.; Entwistle, V., Rationalising the 'irrational': a think aloud study of discrete choice experiment responses. *Health Econ* **2009,** 18, (3), 321-36.

112. Van Bebber, S. L.; Liang, S. Y.; Phillips, K. A.; Marshall, D.; Walsh, J.; Kulin, N., Valuing personalized medicine: willingness to pay for genetic testing for colorectal cancer risk. *Personalized Medicine* **2007,** 4, (3), 341-350.

113. Howard, K.; Salkeld, G.; Pignone, M.; Hewett, P.; Cheung, P.; Olsen, J., et al., Preferences for CT colonography and colonoscopy as diagnostic tests for colorectal cancer: a discrete choice experiment. *Value Health* **2011,** 14, (8), 1146-52.

114. Kroupa, R.; Ondrackova, M.; Kovalcikova, P.; Dastych, M.; Pavlik, T.; Kunovsky, L., et al., Viewpoints of the target population regarding barriers and facilitators of colorectal cancer screening in the Czech Republic. *World Journal of Gastroenterology* **2019,** 25, (9), 1132-1141.

115. Dyer, K. E.; Shires, D. A.; Flocke, S. A.; Hawley, S. T.; Jones, R. M.; Resnicow, K., et al., Patient-Reported Needs Following a Referral for Colorectal Cancer Screening. *American Journal of Preventive Medicine* **2019,** 56, (2), 271-280.

116. Yusoff, H. M.; Daud, N.; Noor, N. M.; Rahim, A. A., Participation and barriers to colorectal cancer screening in Malaysia. *Asian Pacific Journal of Cancer Prevention: Apjcp* **2012,** 13, (8), 3983-7.

117. Mansfield, C.; Ekwueme, D. U.; Tangka, F. K. L.; Brown, D. S.; Smith, J. L.; Guy, G. P., Jr., et al., Colorectal Cancer Screening: Preferences, Past Behavior, and Future Intentions. *The Patient: Patient-Centered Outcomes Research* **2018,** 11, (6), 599-611.

118. Zapatier, J. A.; Kumar, A. R.; Perez, A.; Guevara, R.; Schneider, A., Preferences for ethnicity and sex of endoscopists in a Hispanic population in the United States. *Gastrointestinal Endoscopy* **2011,** 73, (1), 89-97, 97.e1-4.

119. Nicholson, F. B.; Korman, M. G., Acceptance of flexible sigmoidoscopy and colonoscopy for screening and surveillance in colorectal cancer prevention. *Journal of Medical Screening* **2005,** 12, (2), 89-95.

120. Menees, S. B.; Inadomi, J. M.; Korsnes, S.; Elta, G. H., Women patients' preference for women physicians is a barrier to colon cancer screening. *Gastrointestinal Endoscopy* **2005,** 62, (2), 219-23.

121. Zhou, Q.; Li, Y.; Liu, H.; Liang, Y.; Lin, G., Willingness to pay for colorectal cancer screening in Guangzhou. *World Journal of Gastroenterology* **2018,** 24, (41), 4708-4715.

122. Gordon, N. P.; Green, B. B., Factors associated with use and non-use of the Fecal Immunochemical Test (FIT) kit for Colorectal Cancer Screening in Response to a 2012 outreach screening program: a survey study. *BMC Public Health* **2015,** 15, 546.

123. Rex, D. K.; Lieberman, D. A., A survey of potential adherence to capsule colonoscopy in patients who have accepted or declined conventional colonoscopy. *Journal of Clinical Gastroenterology* **2012,** 46, (8), 691-695.

124. Ghanouni, A.; Halligan, S.; Taylor, S. A.; Boone, D.; Plumb, A.; Stoffel, S., et al., Quantifying public preferences for different bowel preparation options prior to screening CT colonography: a discrete choice experiment. *BMJ Open* **2014,** 4, (4), e004327.

125. Hassan, C.; East, J.; Radaelli, F.; Spada, C.; Benamouzig, R.; Bisschops, R., et al., Bowel preparation for colonoscopy: European Society of Gastrointestinal Endoscopy (ESGE) Guideline - Update 2019. *Endoscopy* **2019,** 51, (8), 775-794.

126. Rodriguez de Miguel, C.; Serradesanferm, A.; Lopez-Ceron, M.; Carballal, S.; Pozo, A.; Balaguer, F., et al., Ascorbic acid PEG-2L is superior for early morning colonoscopies in colorectal cancer screening programs: a prospective non-randomized controlled trial. *Gastroenterologia y Hepatologia* **2015,** 38, (2), 62-70.

127. ASGE Standards of Practice Committee, Bowel preparation before colonoscopy. *Gastrointest Endosc* **2015,** 81, (4), 781-94.

128. Mayo Clinic Barium enema. https://www.mayoclinic.org/tests-procedures/barium-enema/about/pac-20393008 (23 August 2021).

129. UCSF Department of Radiology & Biomedical Imaging Prepare for a Virtual CT Colonoscopy scan. https://radiology.ucsf.edu/patient-care/prepare/virutal-ct-colonoscopy (23 August 2021).

130. Chong, V. H., Gender preference and implications for screening colonoscopy: impact of endoscopy nurses. *World Journal of Gastroenterology* **2012,** 18, (27), 3590-3594.

131. Khara, H. S.; Suthar, D.; Bergenstock, M.; Berger, A.; McKee, J. L.; Stewart, D., et al., Identifying Gender Barriers for Colorectal Cancer Screening and Assessing the Need for a Multigender Endoscopy Team: A Prospective Multicenter Study. *American Journal of Gastroenterology* **2021,** 22, 22.

132. Dreier, M.; Krueger, K.; Walter, U., Patient-rated importance of key information on screening colonoscopy in Germany: a survey of statutory health insurance members. *BMJ Open* **2018,** 8, (7), e019127.

133. Voiosu, A.; Tantau, A.; Garbulet, C.; Tantau, M.; Mateescu, B.; Baicus, C., et al., Factors affecting colonoscopy comfort and compliance: a questionnaire based multicenter study. *Romanian Journal of Internal Medicine* **2014,** 52, (3), 151-7.

134. Gurudu, S. R.; Li, F.; Fleischer, D. E.; Sharma, V. K.; Heigh, R. I.; Crowell, M. D., et al., Patient Preference and Acceptance with Sodium Phosphate Tablet Preparation for Colonoscopy. *Digestive Diseases & Sciences* **2009,** 54, (7), 1555-1559.

135. Pin Erua-Gonsa Lvez, J. F.; Zambrano-Infantino, R. D. C.; Baptista, A.; Sulbaran, M.; Camaray, N., Assessment of tolerance and acceptability between mannitol solution and polyethylene glycol as bowel preparation for colonoscopy: a three-center study. *Revista de Gastroenterologia del Peru* **2020,** 40, (1), 7-12.

136. Aamar, A.; Butt, Z.; Madhani, K.; Hussain, I.; Garsten, J.; Aslanian, H., Effect of a Novel Patient Garment on Perceived Privacy during Colonoscopy: A Simple Approach to Minimize Embarrassment. *Gastroenterology research & practice* **2019,** 2019, 2467101.

137. Dignity Garments. (2016). *How to use Privacy Pants* [YouTube video]. https://www.youtube.com/watch?v=tK8QplfW-ME (assessed on 1 September 2021).

138. Van den Bruel, A.; Jones, C.; Yang, Y.; Oke, J.; Hewitson, P., People's willingness to accept overdetection in cancer screening: population survey. *Bmj* **2015,** 350, (4).

139. Bradley, D. T.; Treanor, C.; McMullan, C.; Owen, T.; Graham, A.; Anderson, D., Reasons for non-participation in the Northern Ireland Bowel Cancer Screening Programme: a qualitative study. *BMJ Open* **2015,** 5, (9), e008266.

140. Deutekom, M.; Rossum, L. G. M. v.; Rijn, A. F. v.; Laheij, R. J. F.; Fockens, P.; Bossuyt, P. M. M., et al., Comparison of guaiac and immunological fecal occult blood tests in colorectal cancer screening: the patient perspective. *Scandinavian Journal of Gastroenterology* **2010,** 45, (11), 1345-1349.

141. Morling, J. R.; Barke, A. N.; Chapman, C. J.; Logan, R. F., Could stool collection devices help increase uptake in bowel cancer screening programmes? *Journal of Medical Screening* **2018,** 25, (4), 174-177.

142. Pham, R.; Cross, S.; Fernandez, B.; Corson, K.; Dillon, K.; Yackley, C., et al., "Finding the Right FIT": Rural Patient Preferences for Fecal Immunochemical Test (FIT) Characteristics. *Journal of the American Board of Family Medicine: JABFM* **2017,** 30, (5), 632-644.

143. Shin, H.; Suh, M.; Choi, K.; Hwang, S.; Jun, J.; Han, D., et al., Higher satisfaction with an alternative collection device for stool sampling in colorectal cancer screening with fecal immunochemical test: a cross-sectional study. *BMC Cancer* **2018,** 18, (365).

144. de Klerk, C. M.; Wieten, E.; van der Steen, A.; Ramakers, C. R.; Kuipers, E. J.; Hansen, B. E., et al., Participation and Ease of Use in Colorectal Cancer Screening: A Comparison of 2 Fecal Immunochemical Tests. *American Journal of Gastroenterology* **2019,** 114, (3), 511-518.

145. Ellis, R. J. B.; Wilson, S.; Holder, R. L.; McManus, R. J., Different faecal sampling methods alter the acceptability of faecal occult blood testing: a cross sectional community survey. *European Journal of Cancer* **2007,** 43, (9), 1437-1444.

146. Stoltzfus, K. C.; Popalis, M. L.; Reiter, P. L.; Moss, J. L., Perspectives on self-sampling for cancer screening among rural and urban women: Multilevel factors related to acceptability. *Journal of Rural Health* **2021,** 18, 18.

147. Worthley, D. L.; Cole, S. R.; Esterman, A.; Mehaffey, S.; Roosa, N. M.; Smith, A., et al., Screening for colorectal cancer by faecal occult blood test: why people choose to refuse. *Internal Medicine Journal* **2006,** 36, (9), 607-610.

148. Benning, T. M.; Dellaert, B. G.; Severens, J. L.; Dirksen, C. D., The effect of presenting information about invasive follow-up testing on individuals' noninvasive colorectal cancer screening participation decision: results from a discrete choice experiment. *Value in Health* **2014,** 17, (5), 578-87.

149. Coughlin, S. S.; Berkowitz, Z.; Hawkins, N. A.; Tangka, F., Breast and colorectal cancer screening and sources of cancer information among older women in the United States: results from the 2003 Health Information National Trends Survey. *Preventing Chronic Disease* **2007,** 4, (3).

150. Albright, K.; Richardson, T.; Kempe, K. L.; Wallace, K., Toward a trustworthy voice: increasing the effectiveness of automated outreach calls to promote colorectal cancer screening among African Americans. *Permanente Journal* **2014,** 18, (2), 33-7.

151. Brackett, C.; Kearing, S.; Cochran, N.; Tosteson, A. N.; Blair Brooks, W., Strategies for distributing cancer screening decision aids in primary care. *Patient Education & Counseling* **2010,** 78, (2), 166-8.

152. Benito, L.; Farre, A.; Binefa, G.; Vidal, C.; Cardona, A.; Pla, M., et al., Factors related to longitudinal adherence in colorectal cancer screening: qualitative research findings. *Cancer Causes & Control* **2018,** 29, (1), 103-114.

153. Messina, C.; Lane, D.; Grimson, R., Colorectal Cancer Screening Attitudes and PracticesPreferences for Decision Making. *American Journal of Preventive Medicine* **2005,** 28, (5), 439-446.

154. Martens, C. E.; Crutchfield, T. M.; Laping, J. L.; Perreras, L.; Reuland, D. S.; Cubillos, L., et al., Why Wait Until Our Community Gets Cancer?: Exploring CRC Screening Barriers and Facilitators in the Spanish-Speaking Community in North Carolina. *Journal of Cancer Education* **2016,** 31, (4), 652-659.

155. Pignone, M. P.; Crutchfield, T. M.; Brown, P. M.; Hawley, S. T.; Laping, J. L.; Lewis, C. L., et al., Using a discrete choice experiment to inform the design of programs to promote colon cancer screening for vulnerable populations in North Carolina. *BMC Health Services Research* **2014,** 14, 611.

156. Baassiri, A.; El-Harakeh, M.; Itani, A.; Nassar, F. J.; Safi, R.; Dassouki, Z., et al., Giant Inflatable Colon Model Enhances Lebanese Community Knowledge and Intention for Colorectal Cancer Screening. *JCO Global Oncology* **2020,** 6, 167-173.

157. A Healthier Michigan. (2021). *Inflatable colon* [Photograph]. https://www.flickr.com/photos/healthiermi/13266807653 (assessed on 1 September 2021).

158. Banks, J.; Hollinghurst, S.; Bigwood, L.; Peters, T. J.; Walter, F. M.; Hamilton, W., Preferences for cancer investigation: a vignette-based study of primary-care attendees. *Lancet Oncology* **2014,** 15, (2), 232-40.

159. Brewer, K. C.; Peacock, N. R.; Ferrans, C. E.; Campbell, R. T.; Polite, B.; Carnahan, L., et al., Gender- and Race-Based Differences in Barriers and Facilitators to Early Detection of Colon Cancer. *Journal of Women's Health* **2020,** 29, (9), 1192-1202.

160. Nayaradou, M.; Berchi, C.; Dejardin, O.; Launoy, G., Eliciting population preferences for mass colorectal cancer screening organization. *Medical Decision Making* **2010,** 30, (2), 224-233.

161. Ho, W.; Broughton, D. E.; Donelan, K.; Gazelle, G. S.; Hur, C., Analysis of barriers to and patients' preferences for CT colonography for colorectal cancer screening in a nonadherent urban population. *American Journal of Roentgenology* **2010,** 195, (2), 393-397.

162. Hollinghurst, S.; Banks, J.; Bigwood, L.; Walter, F. M.; Hamilton, W.; Peters, T. J., Using willingness-to-pay to establish patient preferences for cancer testing in primary care. *BMC Medical Informatics & Decision Making* **2016,** 16, 105.

163. Page, M. J.; McKenzie, J. E.; Bossuyt, P. M.; Boutron, I.; Hoffmann, T. C.; Mulrow, C. D., et al., The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* **2021,** 372, n71.

164. Hultcrantz, R., Aspects of colorectal cancer screening, methods, age and gender. *J Intern Med* **2021,** 289, (4), 493-507.

165. Sammarco, G.; Gallo, G.; Vescio, G.; Picciariello, A.; De Paola, G.; Trompetto, M., et al., Mast Cells, microRNAs and Others: The Role of Translational Research on Colorectal Cancer in the Forthcoming Era of Precision Medicine. *J Clin Med* **2020,** 9, (9).

166. Moazzendizaji, S.; Sevbitov, A.; Ezzatifar, F.; Jalili, H. R.; Aalii, M.; Hemmatzadeh, M., et al., microRNAs: small molecules with a large impact on colorectal cancer. *Biotechnol Appl Biochem* **2021**.

167. Canadian Task Force on Preventive Health, C., Recommendations on screening for colorectal cancer in primary care. *CMAJ* **2016,** 188, (5), 340-348.

168. Wilkins, T.; McMechan, D.; Talukder, A., Colorectal Cancer Screening and Prevention. *Am Fam Physician* **2018,** 97, (10), 658-665.

169. Peterse, E. F. P.; Meester, R. G. S.; Siegel, R. L.; Chen, J. C.; Dwyer, A.; Ahnen, D. J., et al., The impact of the rising colorectal cancer incidence in young adults on the optimal age to start screening: Microsimulation analysis I to inform the American Cancer Society colorectal cancer screening guideline. *Cancer* **2018,** 124, (14), 2964-2973.

170. Meester, R. G. S.; Peterse, E. F. P.; Knudsen, A. B.; de Weerdt, A. C.; Chen, J. C.; Lietz, A. P., et al., Optimizing colorectal cancer screening by race and sex: Microsimulation analysis II to inform the American Cancer Society colorectal cancer screening guideline. *Cancer* **2018,** 124, (14), 2974-2985.

171. Montminy, E. M.; Zhou, M.; Maniscalco, L.; Abualkhair, W.; Kim, M. K.; Siegel, R. L., et al., Contributions of Adenocarcinoma and Carcinoid Tumors to Early-Onset Colorectal Cancer Incidence Rates in the United States. *Ann Intern Med* **2021,** 174, (2), 157-166.

172. Vuik, F. E.; Nieuwenburg, S. A.; Bardou, M.; Lansdorp-Vogelaar, I.; Dinis-Ribeiro, M.; Bento, M. J., et al., Increasing incidence of colorectal cancer in young adults in Europe over the last 25 years. *Gut* **2019,** 68, (10), 1820-1826.

173. U. S. Preventive Services Task Force, Screening for Colorectal Cancer: US Preventive Services Task Force Recommendation Statement. *JAMA* **2021,** 325, (19), 1965-1977.

174. Foppa, C.; Francesca Bertuzzi, A.; Cianchi, F.; Carvello, M.; Maroli, A.; Wolthuis, A. M., et al., Rectal Cancer in Adolescent and Young Adult Patients: Pattern of Clinical Presentation and Case-Matched Comparison of Outcomes. *Dis Colon Rectum* **2021,** 64, (9), 1064-1073.

175. Mehta, S. J.; Morris, A. M.; Kupfer, S. S., Colorectal Cancer Screening Starting at Age 45 Years-Ensuring Benefits Are Realized by All. *JAMA Netw Open* **2021,** 4, (5), e2112593.

176. Joanna Briggs Institute *Joanna Briggs Institute Reviewers' Manual: 2014 Edition*; South Australia: University of Adelaide, 2014.

PART III

OPTIMIZING

FIT CUT-OFF AND SCREENING INTERVAL

TO ADDRESS FIT INTERVAL CANCERS IN FLANDERS

Chapter 6

Optimizing the colorectal cancer screening programme using faecal immunochemical test (FIT) in Flanders, Belgium from the "interval cancer" perspective

Thuy Ngan Tran[1], Marc Peeters[2,3], Sarah Hoeck[1,4], Guido Van Hal[1,4], Sharon Janssens[5], and Harlinde De Schutter[5]

1. Family Medicine and Population Health (FAMPOP), Faculty of Medicine and Health Sciences, University of Antwerp, Antwerp, Belgium

2. Department of Oncology, Antwerp University Hospital, Antwerp, Belgium

3. Integrated Personalized & Precision Oncology Network (IPPON), University of Antwerp, Belgium

4. Centre for Cancer Detection, Bruges, Belgium

5. Research Department, Belgian Cancer Registry, Brussels, Belgium

(Published in *Br J Cancer. 2022;126(7):1091-1099*)

6.1. Abstract

Background: Interval cancer (IC) is a critical issue in colorectal cancer (CRC) screening. We identified factors associated with ICs after faecal immunochemical test (FIT) screening and explored the impact of lowering FIT cut-off or shortening screening interval on FIT-ICs in Flanders.

Methods: FIT participants diagnosed with a CRC during 2013-2018 were included. Factors associated with FIT-ICs were identified using logistic regression. Distributions of FIT results among FIT-ICs were examined.

Results: In total, 10,122 screen-detected CRCs and 1,534 FIT-ICs were included (FIT-IC proportion of 13%). FIT-ICs occurred more frequently in women (OR 1.58 [95% CI 1.41–1.76]) and ages 70–74 (OR 1.35 [1.14–1.59]). FIT-ICs were more often right sided (OR 3.53 [2.98–4.20]), advanced stage (stage IV: OR 7.15 [5.76–8.88]), and high grade (poorly/undifferentiated: OR 2.57 [2.08–3.18]). The majority (83–92%) of FIT ICs would still be missed if FIT cut-off was lowered from 15 to 10 µg Hb/g or screening interval was shortened from two to one year.

Conclusions: FIT-ICs were more common in women, older age, right sided location, advanced stage and high grade. In Flanders, lowering FIT cut off (to 10 µg Hb/g) or shortening screening interval (to one year) would have a minimal impact on FIT-ICs.

6.2. Introduction

Worldwide, colorectal cancer (CRC) accounts for one in every ten cancer cases and deaths. Between 2012 and 2018, the number of patients diagnosed with CRC in Europe increased from 447,000 to 500,000 while the number of those who died from this disease increased from 215,000 to 242,000.[1] In Flanders (57% of the Belgian population), CRC is the second most common cancer in women and third in men. In 2018, the age-standardized (world standard population) CRC incidence rates for men and women were 33.8/100,000 and 24.1/100,000 person-years, respectively.[2]

CRC screening helps to detect precancerous lesions and tumours at an early stage and can therefore reduce CRC-related mortality. Faecal occult blood test is recommended for organised CRC screening by the European guidelines.[3] Guaiac faecal occult blood test (gFOBT) has been

shown to reduce CRC-related mortality by 15.0–33.0%.[4-6] In recent years, faecal immunochemical test (FIT) is a more preferred screening test by many CRC screening programmes since it offers a higher sensitivity compared to gFOBT.[7] Among the organised screening programmes that use FIT, each programme implements a different screening strategy: a different FIT cut-off (15–80 µg Hb/g) or screening interval (one-year or two-year), depending on its desired diagnostic values and capacity of follow-up colonoscopy after a positive FIT.[7] Research is still ongoing to identify the optimal screening strategy for each programme.

The optimization of a screening programme needs to be approached from different angles. The occurrence of FIT interval cancers (FIT-ICs) is an important quality indicator of any screening programme using FIT. FIT-IC is defined as CRC diagnosed after a negative FIT and before the next recommended examination.[3] The proportion of FIT-ICs ranged from 7% to 51% in previous studies with a FIT cut-off between 10 and 80 µg Hb/g (two-year screening interval).[8-13] In addition, FIT-ICs have been shown to be associated with more advanced stage, higher grade and more aggressive histotype, resulting in reduced survival compared to screen-detected CRCs.[8,12,14,15] The European guidelines recommend monitoring interval cancers as a parameter of programme effectiveness.[3]

Prior research has pointed out several subgroups who are at a higher risk of having FIT-IC such as women[9,13,16-19] and older age.[16,20] These individuals may be disadvantaged when only a single FIT cut-off is used for the whole screening population. Therefore, many studies have advocated individualizing FIT usage in CRC screening to increase equity across subgroups and improve the performance of the screening programmes.[13,21-23] Gender-specific FIT cut-offs have been introduced in several screening programmes to narrow the gap between men and women in the test's diagnostic performance, especially sensitivity, such as 80 µg Hb/g for men and 40 µg Hb/g for women in Sweden,[24,25] or 70 µg Hb/g for men and 25 µg Hb/g for women in Finland[26]. Shortening screening interval has also been suggested as a possible measure for subgroups with a lower FIT sensitivity.[21]

In Flanders, the organised CRC screening programme has been in place since 2013, which offers a free biennial FIT to all individuals in the target population using a centralized invitation procedure. During the study period (2013–2018), the programme used a uniform FIT cut-off of 75 ng Hb/ml (15 µg Hb/g) and a uniform screening interval (two-year) for all screening

individuals aged 53-74 years. However, like other CRC screening programmes, the Flemish programme is attempting to determine the optimal screening strategy to optimize its efficacy. The objectives of the current study were to identify factors associated with the risk of having a FIT-IC versus a screen-detected CRC and explore the impact of lowering FIT cut-off or shortening screening interval on reducing FIT-ICs in the context of the Flemish CRC screening programme. These findings can provide valuable information on the directions of personalizing CRC screening using FIT for the Flemish screening programme as well as for other countries and regions.

6.3. Methods

6.3.1. Flanders and its CRC screening programme

Flanders is the most populated region of Belgium (6.6 million inhabitants, 57% of Belgian population).[27] The CRC screening programme in Flanders has been in place since October 2013 and offers a free biennial quantitative FIT (OC-sensor, Eiken Chemical Co, Tokyo, Japan) to all citizens eligible for CRC screening. During the study period, the target screening ages were extended gradually from 56–74 in 2013 to 53–74 in 2018 (up to 50–74 in 2020). People were excluded from the screening invitation list if they had had a stool test in the past two years, a virtual colonoscopy in the past four years or a complete colonoscopy in the past ten years, had been diagnosed with CRC in the past ten years or had had a total colectomy (excluded permanently). The positivity cut-off of FIT was ≥15 µg Hb/g [or 75 ng Hb/ml, conversion formula: µg Hb/g faeces = (ng Hb/ml buffer) × 2 mL buffer / 10 mg faeces collected]. In 2018, the response rate of the Flemish CRC screening programme was 51.5% (~670,000 invitations sent out). The FIT sensitivity values were 72.4% and 86.3%, positive predictive values were 3.7% and 4.1%, and detection rates were 0.17% and 0.19%, respectively, for invasive and in situ cancers.[28]

After a positive FIT, patients are advised to undergo a colonoscopy ordered either through their GP or by consulting a gastroenterologist. During the study period, follow-up colonoscopy was not included as part of the population-based CRC screening programme in Flanders and there was also no centralised colonoscopy quality register in Belgium. Data on the performance of a follow-up colonoscopy after a positive FIT, based on the reimbursement data from health insurance companies, was available at the Belgian Cancer Registry and used to create an

exclusion list (as detailed above) for the CRC screening programme for the next invitation round.[16]

6.3.2. Study population and data sources

The study population included all eligible individuals for CRC screening (53–74 years) who participated in the Flemish CRC screening programme between October 2013 (start of the programme) and December 2018 (the latest year for which all required data were complete) and were subsequently diagnosed with either a screen-detected CRC or FIT-IC in the same period. A screen-detected CRC and FIT-IC were defined by the screening programme as follows:

- Screen-detected CRC was defined as a CRC diagnosed after a positive FIT, within six months after the first follow-up colonoscopy and before the next recommended FIT invitation (24 months).
- FIT-IC was defined as a CRC diagnosed after a negative FIT and before the next recommended FIT invitation (24 months).

Data on individuals' screening history (FIT result and follow-up colonoscopy) were retrieved from the database of the Flemish Centre for Cancer Detection and were linked with data on tumour characteristics (location, stage and differentiation grade) from the population-based Belgian Cancer Registry. The Belgian Cancer Registry collects information regarding new CRC diagnoses based on obligatory notifications provided by the oncological care programmes and the laboratories for pathological anatomy. Validated data are currently available for Flanders from 2001–2018 with an estimated >98% completeness. In the case of multiple lesions, only the most advanced finding was retained (e.g., prioritizing invasive lesions over in situ lesions). The applicable TNM edition at the time of diagnosis was used (TNM 7th edition for incidence years 2013–2016 and TNM 8th edition for incidence years 2017–2018).[29,30] A combined TNM stage was determined by prioritizing pathological staging over clinical staging, except in the presence of clinical distant metastases which were always considered stage IV. Tumour location was classified as right side (from the cecum to the transverse colon), left side (from the splenic flexure to the sigmoid colon) or rectum.[8,9,18] Differentiation grade was classified as well-differentiated (grade 1), moderately-differentiated (grade 2) and poorly/undifferentiated (grade 3–4).[8,14,31,32]

6.3.3. Statistical analysis

6.3.3.1. Sample size

All 11,656 FIT participants between October 2013 and December 2018 who were subsequently diagnosed with either a screen-detected CRC (N=10,122) or FIT-IC (N=1,534) in the same period were included for all the analyses; except in the analyses regarding tumour location where we only included 10,111 screen-detected CRCs and 1,528 FIT-ICs because two CRCs with an overlapping location and 15 CRCs in the right side of the colon but detected with an incomplete colonoscopy were removed.

6.3.3.2. Missing data

Data on gender, age at FIT screening and cancer diagnosis were known for all study subjects. About 14% of the tumours had an unknown stage, 38% had an unknown location and 47% had an unknown differentiation grade. In such cases, the data providers (oncological care programmes and/or laboratories for pathological anatomy) filled in the variables with an unspecified code or left them blank (although the fields were mandatory in the registration form). In our data analyses, these observations were included under the "unknown" category.

6.3.3.3. Main analysis

Continuous variables were described with medians (interquartile ranges) and categorical variables were described with numbers (percentages). Logistic regression was used to assess the associations between individuals' and tumours' characteristics and the risk of having a FIT-IC versus a screen-detected CRC. Crude and adjusted odds ratios (for age and gender) with 95% confidence intervals were reported. In this study, stage I was used as the reference to enable the comparison with other studies where only stages I–IV were included.[8,10-12,31] FIT-IC proportions for different profiles combining individuals' and tumours' characteristics were presented. FIT-IC proportion was calculated as the number of FIT-ICs divided by the total number of FIT-ICs and screen-detected CRCs and presented as percentage to enhance comprehension.[11,12,16] We also examined the distributions of FIT results among FIT-ICs in the first/second year of the screening interval and by patients' and tumours' characteristics to explore the impact of shortening FIT screening interval or lowering FIT cut-off on reducing FIT-ICs. There is discrepancy among guidelines regarding whether to include in situ cancers in the definition of colorectal carcinoma (TNM and Japanese classification systems) or not (European

and US classification systems).[3,30,33] To facilitate the comparison of our findings with those of other studies, we present, where it is possible, the results for in situ cancers as a separate group from invasive cancers.

P-values less than 0.05 (two-sided) were considered statistically significant. All analyses were performed with RStudio (version 1.3.1056; RStudio, PBC, Boston, MA).

6.3.4. Privacy and ethics

When participating in the Flemish CRC screening programme, each person fills out a written informed consent stating that personal information can be used for evaluating and improving the screening programme and for scientific research. Data used in the current study relied on recurrent data exchanges between the Flemish Centre for Cancer Detection and Belgian Cancer Registry, for which approval was given by the Belgian Privacy Commission on 17 September 2013 and amended on 2 July 2019, with reference IVC/KSZG/19/236, number 13/091.[34] Only pseudonymized data were used for this study, and results are reported in an aggregated way. The study protocol conforms to the principles of the Declaration of Helsinki. Our reporting adheres to the STROBE guidelines for observational studies (**Supplementary Table 1**).[35]

6.4. Results

6.4.1. Characteristics of the study population

In total, 11,656 CRCs diagnosed after FIT screening were included, with a FIT-IC proportion of 13%. The number of CRCs decreased gradually each year from 3,174 in 2014 to 1,524 in 2018. Most of the study subjects were male (64.5%). The median age at FIT screening was 66 years. A large proportion of the tumours were classified as “unknown” for location (38.3%), stage (14.0%) or differentiation grade (46.7%). Among the tumours with known categories, the majority presented in the left side of the colon or rectum (5,680/7,188; 79.0%), at stage I or in situ (7,184/10,019; 72.0%) and were moderately differentiated (3,577/6,209; 57.0%) (**Table 1**).

Table 1. Characteristics of individuals who participated in the Flemish colorectal cancer screening programme during 2013–2018 and were subsequently diagnosed with either a screen-detected or interval colorectal cancer.

Characteristics	Number (%) N=11,656
Screen-detected CRCs + FIT-ICs per incidence year	
2013	143 (1.2%)
2014	3,174 (27.2%)
2015	2,687 (23.1%)
2016	2,192 (18.8%)
2017	1,936 (16.6%)
2018	1,524 (13.1%)
Gender	
Male	7,516 (64.5%)
Age at FIT screening	
Median (IQR)	66 (61–70)
53–59	2,035 (17.5%)
60–69	6,290 (54.0%)
70–74	3,331 (28.6%)
Tumour location	
Right side	1,506 (12.9%)
Left side	2,761 (23.7%)
Rectum	2,919 (25.0%)
Unknown	4,468 (38.3%)
Overlap	2 (~0%)
Tumour stage	
In situ	4,470 (38.3%)
I	2,714 (23.3%)
II	1,060 (9.1%)
III	1,269 (10.9%)
IV	506 (4.3%)
Unknown	1,637 (14.0%)
Differentiation grade	
Well differentiated	1,752 (15.0%)
Moderately differentiated	3,577 (30.7%)
Poorly and undifferentiated	880 (7.5%)
Unknown	5,447 (46.7%)
Outcome	
FIT-ICs	1,534 (13.2%)

CRC: Colorectal cancer; FIT, Faecal immunochemical test; IC, Interval cancer; IQR, Interquartile range

6.4.2. Factors associated with the risk of having a FIT-IC versus a screen-detected CRC

The risk of having a FIT-IC versus a screen-detected CRC was 1.6 times higher in women vs. men (OR = 1.58 [1.41–1.76]) and 1.4 times higher in people aged 70–74 compared to ages 53-59 (OR = 1.35 [1.14–1.59]). Regarding tumours' characteristics, the risk of having FIT-IC was 3.5 times

higher for tumours in the right side of the colon (OR = 3.53 [2.98–4.20]) and twice higher for those in the rectum (OR = 2.01 [1.72–2.37]) compared to those in the left side; 7.2 times higher for stage IV compared to stage I (OR = 7.15 [5.76–8.88]); and 2.6 times higher for poorly/undifferentiated lesions compared to well-differentiated lesions (OR = 2.57 [2.08–3.18]) (**Table 2**).

Table 2. Univariable and multivariable associations between individuals' and tumours' characteristics and risk of having an interval cancer versus a screen-detected cancer after screening with a faecal immunochemical test.

Characteristics	Category	Screen-detected CRC (%) N=10,122§	Interval CRCs (%) N=1,534§	Crude OR	p-value	aOR (95% CI)	p-value
Gender†	Male	6,670 (66%)	846 (55%)	Ref		Ref	
	Female	3,452 (34%)	688 (45%)	1.57 (1.41–1.75)	*<0.001**	1.58 (1.41–1.76)	*<0.001**
Age at FIT screening†	53–59	1,800 (18%)	235 (15%)	Ref		Ref	
	60–69	5,483 (54%)	807 (53%)	1.13 (0.97–1.32)	*0.129*	1.16 (0.99–1.35)	*0.067*
	70–74	2,839 (28%)	492 (32%)	1.33 (1.13–1.57)	*<0.001**	1.35 (1.14–1.59)	*<0.001**
Location‡	Left	2,503 (25%)	258 (17%)	Ref		Ref	
	Right	1,077 (11%)	414 (27%)	3.73 (3.15–4.43)	*<0.001**	3.53 (2.98–4.20)	*<0.001**
	Rectum	2,431 (24%)	488 (32%)	1.95 (1.66–2.29)	*<0.001**	2.01 (1.72–2.37)	*<0.001**
	Unknown	4,100 (41%)	368 (24%)	0.87 (0.74–1.03)	*0.104*	0.89 (0.75–1.05)	*0.171*
Stage‡				Ref			
	I	2,438 (24%)	276 (18%)			Ref	
	II	881 (9%)	179 (12%)	1.80 (1.46–2.20)	*<0.001**	1.75 (1.42–2.14)	*<0.001**
	III	1,031 (10%)	238 (16%)	2.04 (1.69–2.46)	*<0.001**	2.04 (1.69–2.47)	*<0.001**
	IV	278 (3%)	228 (15%)	7.25 (5.85–8.99)	*<0.001**	7.15 (5.76–8.88)	*<0.001**
	Unknown	1,434 (14%)	203 (13%)	1.25 (1.03–1.52)	*0.023**	1.28 (1.06–1.55)	*0.012**
	In situ	4,060 (40%)	410 (27%)	0.89 (0.76–1.05)	*0.163*	0.91 (0.78–1.08)	*0.296*
Differentiation grade‡	Well differentiated	1,551 (15%)	201 (13%)	Ref		Ref	
	Moderately differentiated	3,078 (30%)	499 (33%)	1.25 (1.05–1.49)	*0.012**	1.23 (1.03–1.46)	*0.023**
	Poorly/undifferentiated	657 (6%)	223 (15%)	2.62 (2.12–3.24)	*<0.001**	2.57 (2.08–3.18)	*<0.001**
	Unknown	4,836 (48%)	611 (40%)	0.98 (0.83–1.16)	*0.769*	0.99 (0.83–1.17)	*0.874*

FIT, Faecal immunochemical test; CRC, Colorectal cancer; OR, Odds ratio; aOR, Adjusted odds ratio.

†For the variables "gender" and "age at FIT screening" that were assessed at the time of FIT screening, "age at FIT screening" and "gender" were adjusted for in the multivariable analyses, respectively.

‡For the variables "location", "stage" and "differentiation grade" that were assessed at the time of cancer diagnosis, age at cancer diagnosis and gender were adjusted for in the multivariable analyses.

§In the analysis of tumour location, only 10,111 screen-detected CRCs and 1,528 FIT-ICs were included. Two CRCs with overlapping location and 15 CRCs in the right side of the colon but detected with an incomplete colonoscopy were excluded from the analysis.

*Statistically significant (p-value < 0.05)

Figure 1 illustrates the increase in FIT-IC proportion when tumour stage (the strongest factor associated with an increased risk of having a FIT-IC) was combined with the other factors. FIT-IC proportion was 45% when considering stage IV alone but increased to 49% when stage IV was combined with age 70–74; 55–56% when stage IV was combined with female gender or poorly/undifferentiated grade and to 63% when stage IV was combined with right side location.

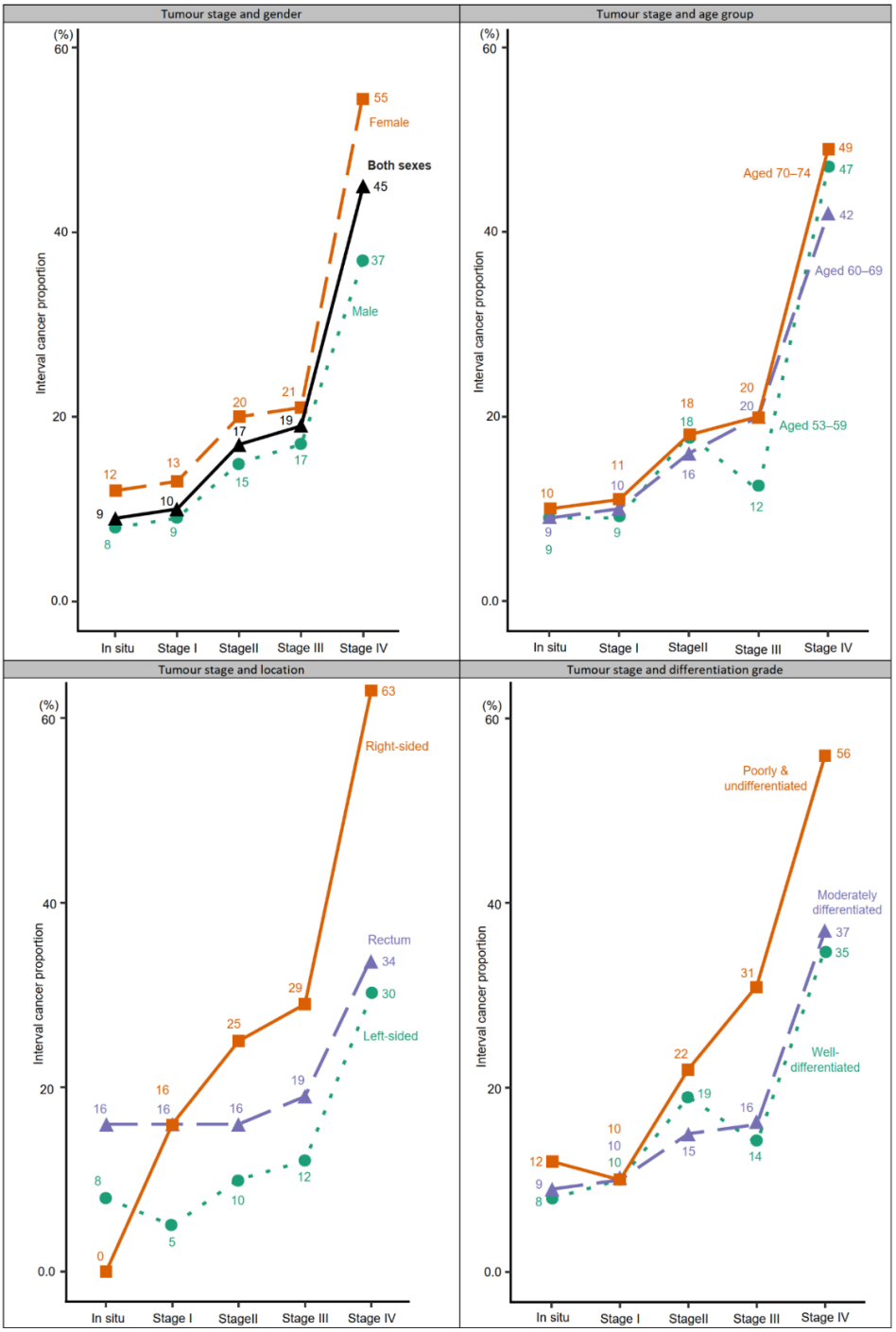


Figure. 1. Proportions of interval cancer after a faecal immunochemical test, by tumour stage alone and when tumour stage is combined with other risk factors including gender, age group, tumour location and differentiation grade.

6.4.3. Distribution of FIT results among FIT-ICs in the first/second year of screening interval and by patients' and tumours' characteristics

The number of FIT-ICs increased during the two-year screening interval (**Figure 2**). More than sixty percent (922/1,534) of FIT-ICs were detected in the second year. According to the distributions of FIT results (**Figure 3** and **Supplementary Table 1**), 83-92% FIT-ICs in both sexes, all age groups, tumour locations and stages had a low quantitative FIT result of ≤ 10 µg Hb/g. This majority of FIT ICs would not be picked up if the FIT cut-off was lowered from 15 to 10 µg Hb/g. Similarly, 89% of the FIT-ICs detected in the second year of the two-year screening interval also had a low FIT result of ≤ 10 µg Hb/g, suggesting that most FIT-ICs would still be missed even if the screening interval was shortened from two to one year, given the current FIT cut-off of 15 µg Hb/g.

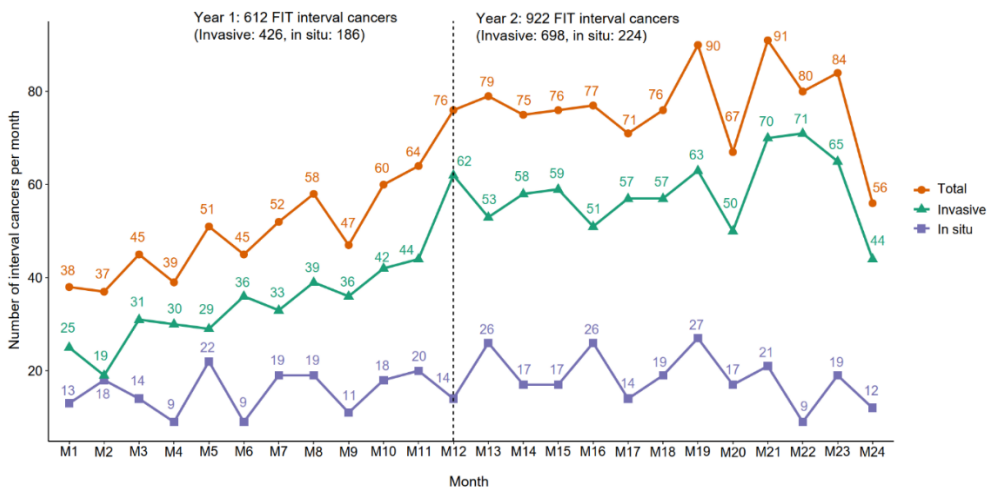


Figure. 2. The numbers of interval cancers (invasive, in situ and total) after a faecal immunochemical test in the first and the second year of the two-year screening interval (M1–M24: month 1 to month 24 after FIT screening).

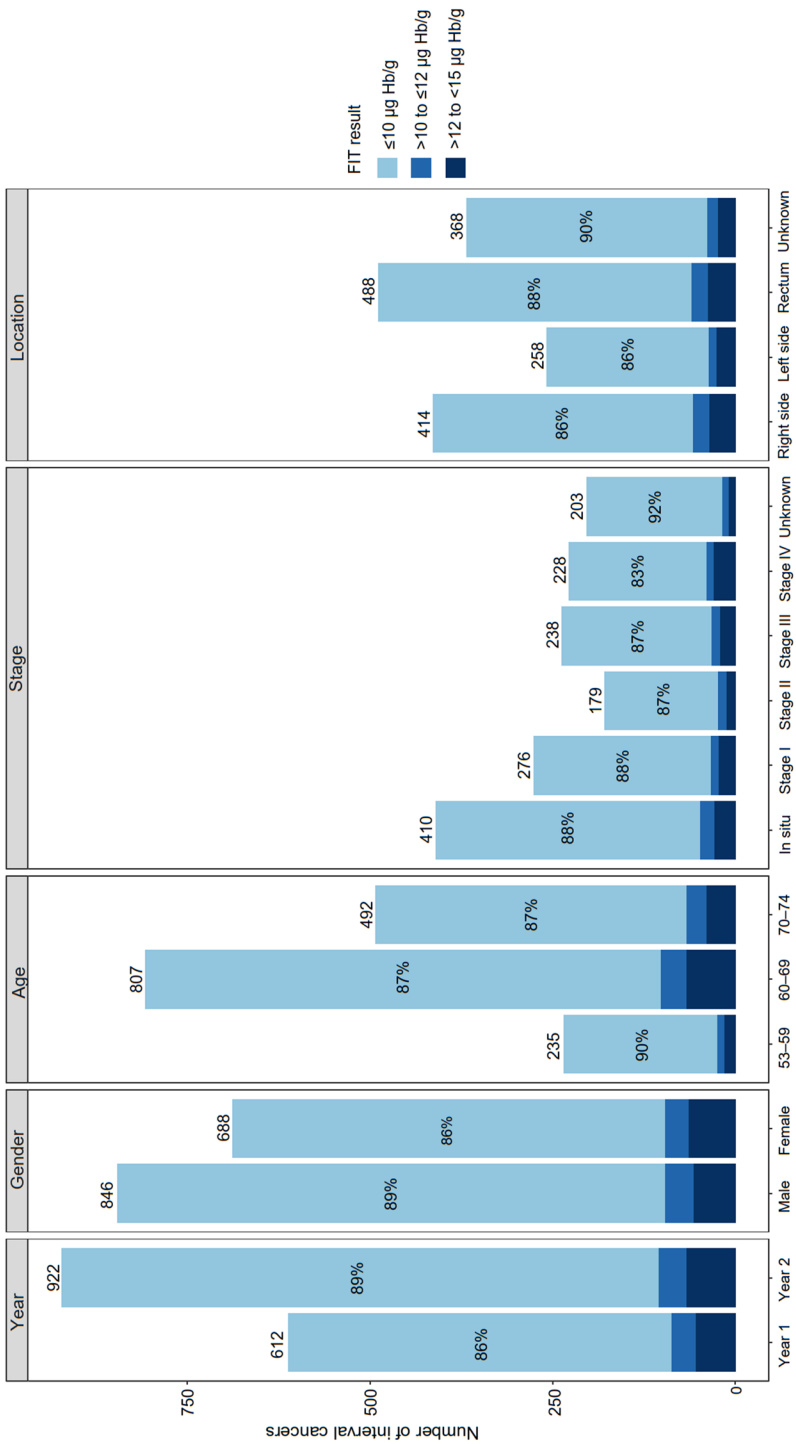


Figure. 3. Distributions of quantitative results of faecal immunochemical test (FIT) among FIT-interval cancers, stratified by the first/second year of the screening interval, genders, age groups, tumour stages and tumour locations.

6.5. Discussion

Using data of all screen-detected CRCs and FIT-ICs diagnosed in FIT participants for CRC screening in Flanders during 2013–2018, we identified several factors associated with a higher risk of having a FIT-IC versus a screen-detected CRC. These include female gender, older age, right side and rectum locations, advanced stage and high grade. The majority (83–92%) of FIT-ICs in both the first and second year of the two-year screening interval and all subgroups had a low FIT result of ≤ 10 µg Hb/g, indicating a minimal impact of shortening the screening interval from two years to one year or lowering the FIT cut-off from 15 µg Hb/g (the current cut-off) to 10 µg Hb/g on reducing FIT-ICs.

The FIT-IC proportion in Flanders during 2013–2018 was 13%, which lies within the range of FIT-IC proportion of 7–23% in other screening programmes using a FIT cut-off between 10 and 20 µg Hb/g.[8-12] Our study also supports previous findings that ICs after a negative faecal occult blood test are more common in women,[9,13,16-19] older people,[16,20,36] in the right side of the colon[8,9,11,16-19,22] or in the rectum,[10,17,37] at a more advanced stage[8-14,16,22,31,37] and with a higher grade,[14,31] compared to screen-detected CRCs. Prior literature has proposed several explanations for these associations but definitive conclusions have not been reached.

The fact that women have a higher risk of having FIT-IC than men might be due to lower blood haemoglobin concentrations,[17,20,38] a longer colonic transit time leading to a greater degree of haemoglobin degradation,[39] or a higher proportion of harder-to-detect, right-sided cancers.[17,20,22,40] The last proposed reason might contribute modestly to the explanation since after adjusting for tumour location, we found almost the same association between gender and the risk of having a FIT-IC versus a screen-detected CRC (OR 1.53 [1.36–1.71]), showing 1.53 times higher risk of having a FIT-IC in women, independently of location.

Although a number of studies have shown a lower FIT sensitivity in older people,[16,20,36] no possible explanations for this association have been given. Fraser et al (2014) reported increasing faecal haemoglobin concentrations with age (50–69 years) for both men and women in the screening populations for CRC.[39] With a higher faecal haemoglobin concentration and a higher CRC incidence rate, we would normally expect a higher FIT sensitivity in the older age group; it is interesting that studies have found the inverse. We also tested the possibility that CRCs diagnosed in older people presented at a more advanced stage and therefore were missed

more by FIT. However, this hypothesis was not supported by our data since the association between the oldest age group (70–74) and the risk of having a FIT-IC versus a screen-detected CRC remained (OR 1.31 [1.11–1.56]) after we adjusted for tumour stage in addition to gender. It is a question of future research to investigate the possible reasons for the lower sensitivity of FIT in the older age group.

Prior research has reported a higher proportion of nonpolypoid (flat) tumours in the right side compared to the left side of the colon.[21,41] These tumours tend to have a higher risk of malignant transformation and invasiveness at a relatively smaller size.[41,42] Due to the smaller areas in contact with faeces and sparser vasculature in the mucosa, they bleed less and are less sensitive to FIT.[21,43] A longer transit time from the right side may also lead to a greater degree of haemoglobin degradation, and therefore more false-negative results occur with right-sided tumours.[17,19,21,44] Selby et al (2018) reported a significantly lower faecal haemoglobin level of the right-sided cancers among FIT screenees compared to that of the left-sided cancers (12.4 versus 60.0 µg Hb/g; $p < 0.001$).[20]

Regarding a higher risk of being a FIT-IC for tumours in the rectum compared to the left side location, erythrocytes in blood released from rectum lesions may not have been sufficiently haemolysed during a short passage through the rectum, and therefore do not yield a positive result to a FIT.[13,37] In the same study by Selby et al, the faecal haemoglobin level of the rectal cancers was also significantly lower than that of the left-sided cancers (24.4 versus 60.0 µg Hb/g, $p < 0.001$).[20] Another possible explanation is that rectal bleeding more often presents with bright red blood in faeces, which is easier to notice. Screening participants generally have a heightened awareness of signs of blood in their faeces. Once they notice bright red blood in faeces, they tend to consult with primary care promptly.[22] It cannot be ruled out that low FIT effectiveness for tumours in the right colon or rectum may also stem from lesions that grow more rapidly.[41,42,45]

Compared to screen-detected CRCs, FIT-ICs exhibited a higher grade and aggressive histotype (signet ring cell and mucinous carcinomas).[14] However, it is still unclear to what degree FIT-ICs are due to FIT false-negative tests or a faster growth pathway of high-grade and aggressive histotype tumours. A recent study by Steel et al reported a mean time of 10.9 ± 2.9 months from FIT screening to diagnoses of all ICs and 11.6 ± 7.2 months from FIT screening to diagnoses of high-grade and aggressive histotype ICs.[14] The more advanced stage of FIT-ICs compared to

screen-detected CRCs might be because FIT is known to be less sensitive for flat, right-sided and poorly or undifferentiated lesions,[14,46-48] tumours with these characteristics may be missed more often by FIT. Once these tumours are detected later on when symptoms appear, they are already at an advanced stage. A proportion of these ICs may also originate from tumours with more aggressive characteristics and worse behaviour, which actually arose after a true negative FIT.[14,15] Our findings reinforce the current advice to screening participants not to regard a negative FIT result as a "certificate of health". Instead, they need to be vigilant and seek primary care promptly when any signs or symptoms appear.[22,49,50]

To reduce FIT-ICs, previous studies have also suggested personalizing FIT cut-offs, for example, using a lower cut-off in the subgroups with a lower FIT sensitivity such as women and older people.[13,21-23] However, our data showed that in Flanders, lowering FIT cut-off from 15 to 10 µg Hb/g would only have a limited impact on reducing FIT-ICs since more than 83% of FIT-ICs had a low FIT result of ≤ 10 µg Hb/g across genders, age groups, tumour locations and stages. Although the FIT test used in the Flemish screening programme could theoretically detect up to 3 µg Hb/g faeces, the quantitative results between 3–10 µg Hb/g were considered (quantitatively) unreliable due to large deviations. Therefore, lowering FIT cut-off to below 10 µg Hb/g would not be a suitable option for the test used. Prior research has reported around 75% of FIT-ICs with a low level of haemoglobin (< 10 µg Hb/g) and 19.4–44% with an undetectable level (0 µg Hb/g).[11-13] This implies that the majority of FIT-ICs would still be missed even with a drastic reduction in the FIT cut-off.

Gender-specific cut-offs have also been introduced/piloted in several screening programmes, for example, 40 µg Hb/g for women and 80 µg Hb/g for men in Sweden;[24,25] or 25 µg Hb/g for women and 70 µg Hb/g for men in Finland.[26] In Flanders, a much lower FIT cut-off of 15 µg Hb/g has already been applied for all screening individuals. Our results suggest that 15 µg Hb/g should be the lowest FIT cut-off that a CRC screening programme should aim for, regardless of the patient's gender and age. This recommendation is supported by a recent study by Vanaclocha-Espi et al (2021) which found the optimal FIT cut-off of around 15 µg Hb/g for the subgroup of women aged 60–69, which had the lowest FIT sensitivity among the subgroups evaluated (women and men, aged 50–59 and 60–69).[51]

Many studies have also highlighted a substantial increase in colonoscopy demand for only a marginal gain in sensitivity by lowering FIT cut-off.[13,20,52] For example, the Scottish Bowel

Screening Programme reported that halving the FIT cut-off in their programme from 80 µg Hb/g to 40 µg Hb/g faeces would reduce the FIT-IC proportion from 50.8% to 45.9%, but would increase the number of colonoscopies required by 58.6%.[13] An American screening programme predicted that lowering the FIT cut-off in their programme from 20 µg Hb/g to 10 µg Hb/g would increase the programme's sensitivity by only 3% (from 76.3% to 79.3%) while increasing the number of positive results per one cancer case detected from 52 to 85.[20]

In agreement with Giorgi Rossi et al,[18] we also observed more FIT-ICs in the second year than the first year of the two-year screening interval (60% of all ICs). The difference in the number of FIT-ICs between the second and the first year was 310 cases. It seems, at first glance, that shortening the FIT screening interval from two to one year during the study period might have helped to reduce this number of FIT-ICs.[21] However, 89% of FIT-ICs in the second year were found to have a low FIT result at screening of ≤ 10 µg Hb/g, suggesting that the majority of ICs would still be missed even when the screening interval was shortened to one year. One might also argue that the FIT results were obtained at the time of screening and as tumours progressed between the first and second year, FIT results might get higher and reach the positive cut-off. The proportion of such tumours seemed to be modest since our data showed that 83–92% of FIT-ICs across all tumour stages had a low FIT result of ≤ 10 µg Hb/g. Thus, in the programmes where a low FIT cut-off of 15 µg Hb/g is implemented, shortening screening interval from two to one year seems to produce only a marginal impact on reducing FIT-ICs.

Meanwhile, a CRC screening programme should also consider the impact of screening interval on screen-detected CRCs and the related costs. Specifically, when the screening interval of a two-year programme was shortened to one year, the number of prevalent cases detected among individuals entering the screening programme for the first time would be almost similar (same population and same target screening ages). The main difference is that after the first screening round, the population would repeat screening right the next year in the one-year programme, instead of waiting for two years in the two-year programme. A proportion of the screen-detected incident CRCs in the two-year programme would be diagnosed one year earlier in the one-year programme. This, however, comes at the cost of having the whole screening population undergo FIT every year instead of every two years (Flanders: ~850,000 individuals in 2020),[28] meaning doubling the entire process of screening invitation, FIT provision, result analyses and follow-up with colonoscopy after a positive FIT.

With data from a population-based screening programme of the largest region in Belgium, which used a FIT cut-off within the common range of 10–20 µg Hb/g, our results can be widely generalized to other CRC screening programmes. The large sample size allowed us to stratify our results by multiple participants' and tumours' characteristics.

Several limitations need to be acknowledged. Firstly, since data on both FIT participation and cancers were retrieved between October 2013 and December 2018, data on screen-detected CRCs and FIT-ICs following FITs taken in the latest years (2017–2018) might be incomplete, resulting in an underestimation of both screen-detected CRC and FIT-ICs, with an expected larger extent for FIT-ICs. As a result, FIT-IC proportion might be underestimated, especially for the latest screening years. Secondly, the administrative data used in this study contained sizable proportions of tumours with unknown location, stage, or differentiation grade. Future research can benefit from using pathology reports to supplement missing or non-specific information. Lastly, data on molecular characteristics of tumours are lacking in the current study. We plan to analyse pathology reports to study the difference in molecular characteristics between screen-detected CRCs and FIT-ICs, especially those at an advanced stage, in the next step.

6.6. Conclusions

We identified several factors associated with a higher risk of having a FIT-IC versus a screen-detected CRC, including female gender, older age, right side and rectum locations, advanced stage, and high grade. Our findings suggest that 15 µg Hb/g should be the lowest FIT cut-off (OC-sensor) that one CRC screening programme should go for, regardless of individuals' characteristics. In the Flemish CRC screening programme where a low FIT cut-off (15 µg Hb/g) is implemented, shortening the screening interval from two years to one year is likely to have only a marginal impact on reducing FIT ICs. With the current screening strategy, cancers may still appear after a negative FIT, often at a more advanced stage and with a higher grade compared to screen-detected CRCs. It is important to empower and inform the target population that despite a negative FIT result, they should carefully monitor the symptoms of CRC and visit their GPs when symptoms appear.

Supplementary materials

Supplementary Table 1 The STROBE research checklist for observational studies in epidemiology applied in this study.

	Item No	Recommendation
Title and abstract	1	Title *Optimizing the colorectal cancer screening programme using faecal immunochemical test (FIT) in Flanders, Belgium from the "interval cancer" perspective*
		Provide in the abstract an informative and balanced summary of what was done and what was found ***Background*** *Interval cancer (IC) is a critical issue in colorectal cancer (CRC) screening. We identified factors associated with ICs after faecal immunochemical test (FIT) screening and explored the impact of lowering FIT cut-off or shortening screening interval on FIT-ICs in Flanders.* ***Methods*** *FIT participants diagnosed with a CRC during 2013 2018 were included. Factors associated with FIT ICs were identified using logistic regression. Distributions of FIT results among FIT-ICs were examined.* ***Results*** *In total, 10,122 screen-detected CRCs and 1,534 FIT-ICs were included (FIT-IC proportion of 13%). FIT-ICs occurred more frequently in women (OR 1.58 [95% CI 1.41–1.76]) and ages 70–74 (OR 1.35 [1.14–1.59]). FIT-ICs were more often right sided (OR 3.53 [2.98–4.20]), advanced stage (stage IV: OR 7.15 [5.76–8.88]), and high grade (poorly/undifferentiated: OR 2.57 [2.08–3.18]). The majority (83–92%) of FIT ICs would still be missed if FIT cut-off was lowered from 15 to 10 µg Hb/g or screening interval was shortened from two to one year.* ***Conclusions*** *FIT-ICs were more common in women, older age, right sided location, advanced stage and high grade. In Flanders, lowering FIT cut off (to 10 µg Hb/g) or shortening screening interval (to one year) would have a minimal impact on FIT-ICs.*
Introduction		
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported *Worldwide, colorectal cancer (CRC) accounts for one in every ten cancer cases and deaths. Between 2012 and 2018, the number of patients diagnosed with CRC in Europe increased from 447,000 to 500,000 while the number of those who died from this disease increased from 215,000 to 242,000.[1] In Flanders (57% of the Belgian population), CRC is the second most common cancer in women and third in men. In 2018, the age-standardized (world standard population) CRC incidence rates for men and women were 33.8/100,000 person-years and 24.1/100,000 person-years, respectively.[2]* *CRC screening helps to detect precancerous lesions and tumours at an early stage and can therefore reduce CRC-related mortality. Faecal occult blood test is recommended for organised CRC screening by the European guidelines.[3] Guaiac faecal occult blood test (gFOBT) has been shown to reduce CRC-related mortality by 15.0–33.0%.[4-6] In recent years, faecal immunochemical test (FIT) is a more preferred screening test by many CRC screening programmes since it offers a higher sensitivity compared to gFOBT.[7] Among the organised screening programmes that use FIT, each programme implements a different screening strategy: a different FIT cut-off (15–80 µg Hb/g) or screening interval (one-year or two-year), depending on its desired diagnostic values and capacity of follow-up colonoscopy after a positive FIT.[7] Research is still ongoing to identify the optimal screening strategy for each programme.* *The optimization of a screening programme needs to be approached from different angles. The occurrence of FIT interval cancers (FIT-ICs) is an important quality indicator of any screening programme using FIT. FIT-IC is defined as CRC diagnosed after a negative FIT and before the next recommended examination.[3] The proportion of FIT-ICs ranged from 7% to 51% in previous studies with a FIT cut-off between 10 and 80 µg Hb/g (two-year screening interval).[8-13] In addition, FIT-ICs have been shown to be associated with more advanced stage, higher grade and more aggressive histotype, resulting in reduced survival compared to screen-detected CRCs.[8,12,14,15] The European guidelines recommend monitoring interval cancers as a parameter of programme effectiveness.[3]* *Prior research has pointed out several subgroups who are at a higher risk of having FIT-IC such as women[9,13,16-19] and older age.[16,20] These individuals may be disadvantaged when only a single FIT cut-off is used for the whole screening population. Therefore, many studies have advocated individualizing FIT usage in CRC screening to increase equity across subgroups and improve the performance of the screening programmes.[13,21-23] Gender-specific FIT cut-offs have been introduced in several screening programmes to narrow the gap between men and women in the test's diagnostic performance, especially sensitivity, such as 80 µg Hb/g for men and 40 µg Hb/g for women in Sweden,[24,25] or 70 µg Hb/g for men and 25 µg Hb/g for women in Finland[26]. Shortening screening interval has also been suggested as a possible measure for subgroups with a lower FIT*

		sensitivity.[21] *In Flanders, the organised CRC screening programme has been in place since 2013, which offers a free biennial FIT to all individuals in the target population using a centralized invitation procedure. During the study period (2013–2018), the programme used a uniform FIT cut-off of 75 ng Hb/ml (15 µg Hb/g) and a uniform screening interval (two-year) for all screening individuals aged 53-74 years. However, like other CRC screening programmes, the Flemish programme is attempting to determine the optimal screening strategy to optimize its efficacy.*
Objectives	3	State specific objectives, including any prespecified hypotheses *The objectives of the current study were to identify factors associated with the risk of having a FIT-IC versus a screen-detected CRC and explore the impact of lowering FIT cut-off or shortening screening interval on reducing FIT-ICs in the context of the Flemish CRC screening programme.*
Methods		
Study design	4	Present key elements of study design early in the paper *An observational study using data on screen-detected CRCs and FIT-ICs between October 2013 (start of the programme) and December 2018 (the latest year for which all required data were complete).*
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection ***Flanders and its CRC screening programme*** *Flanders is the most populated region of Belgium (6.6 million inhabitants, 57% of Belgian population).*[27] *The CRC screening programme in Flanders has been in place since October 2013 and offers a free biennial quantitative FIT (OC-sensor, Eiken Chemical Co, Tokyo, Japan) to all citizens eligible for CRC screening. During the study period, the target screening ages were extended gradually from 56–74 in 2013 to 53–74 in 2018 (up to 50–74 in 2020). People were excluded from the screening invitation list if they had had a stool test in the past two years, a virtual colonoscopy in the past four years or a complete colonoscopy in the past ten years, had been diagnosed with CRC in the past ten years or had had a colectomy (excluded permanently). The positivity cut-off of FIT was ≥15 µg Hb/g [or 75 ng Hb/ml, conversion formula: µg Hb/g faeces = (ng Hb/ml buffer) × 2 mL buffer / 10 mg faeces collected]. In 2018, the response rate of the Flemish CRC screening programme was 51.5% (~670,000 invitations sent out). The FIT sensitivity values were 72.4% and 86.3%, positive predictive values were 3.7% and 4.1%, and detection rates were 0.17% and 0.19%, respectively, for invasive and in situ cancers.*[28] *After a positive FIT, patients are advised to undergo a colonoscopy ordered either through their GP or by consulting a gastroenterologist. During the study period, follow-up colonoscopy was not included as part of the population-based CRC screening programme in Flanders and there was also no centralised colonoscopy quality register in Belgium. Data on the performance of a follow-up colonoscopy after a positive FIT, based on the reimbursement data from health insurance companies, was available at the Belgian Cancer Registry and used to create an exclusion list (as detailed above) for the CRC screening programme for the next invitation round.*[16] ***Study population and data sources*** *The study population included all eligible individuals for CRC screening (53–74 years) who participated in the Flemish CRC screening programme between October 2013 (start of the programme) and December 2018 (the latest year for which all required data were complete) and were subsequently diagnosed with either a screen-detected CRC or FIT-IC in the same period.*
Participants	6	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *A screen-detected CRC and FIT-IC were defined by the screening programme as follows:* *- Screen-detected CRC was defined as a CRC diagnosed after a positive FIT, within six months after the first follow-up colonoscopy and before the next recommended FIT invitation (24 months).* *- FIT-IC was defined as a CRC diagnosed after a negative FIT and before the next recommended FIT invitation (24 months).* *Data on individuals' screening history (FIT result and follow-up colonoscopy) were retrieved from the database of the Flemish Centre for Cancer Detection and were linked with data on tumour characteristics (location, stage and differentiation grade) from the population-based Belgian Cancer Registry. The Belgian Cancer Registry collects information regarding new CRC diagnoses based on obligatory notifications provided by the oncological care programmes and the laboratories for pathological anatomy. Validated data are currently available for Flanders from 2001–2018 with an estimated >98% completeness. In the case of multiple lesions, only the most advanced finding was retained (e.g., prioritizing invasive lesions over in situ lesions). The applicable TNM edition at the time of diagnosis was used (TNM 7th edition for incidence years 2013–2016 and TNM 8th edition for incidence years 2017–2018).*[29,30] *A combined TNM stage was determined by prioritizing pathological staging over clinical staging, except in the presence of clinical distant metastases which were always considered stage IV. Tumour location was classified as right side (from the cecum to the transverse colon), left side (from the splenic flexure to the sigmoid colon) or rectum.*[8,9,18] *Differentiation grade was classified as well-differentiated (grade 1), moderately-differentiated (grade 2) and poorly/undifferentiated (grade 3–4).*[8,14,31,32]

		(*b*) For matched studies, give matching criteria and number of exposed and unexposed: *Not applicable*
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. *Exposures:* *Individuals' characteristics* *Gender* *Age at FIT screening* *Tumours' characteristics* *Location* *Stage* *Differentiation grade* *Outcomes: The risk of having a FIT-IC versus a screen-detected CRC* *Covariates* *For the variables "gender" and "age at FIT screening" that were assessed at the time of FIT screening, "age at FIT screening" and "gender" were adjusted for in the multivariable analyses, respectively.* *For the variables "location", "stage" and "differentiation grade" that were assessed at the time of cancer diagnosis, age at cancer diagnosis and gender were adjusted for in the multivariable analyses.*
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group ***Sources of data*** *Data on individuals' screening history (FIT result and follow-up colonoscopy) were retrieved from the database of the Flemish Centre for Cancer Detection and were linked with data on tumour characteristics (location, stage and differentiation grade) from the population-based Belgian Cancer Registry. The Belgian Cancer Registry collects information regarding new CRC diagnoses based on obligatory notifications provided by the oncological care programmes and the laboratories for pathological anatomy. Validated data are currently available for Flanders from 2001–2018 with an estimated >98% completeness. In the case of multiple lesions, only the most advanced finding was retained (e.g., prioritizing invasive lesions over in situ lesions).* ***Exposures*** *The applicable TNM edition at the time of diagnosis was used (TNM 7th edition for incidence years 2013–2016 and TNM 8th edition for incidence years 2017–2018).[29,30] A combined TNM stage was determined by prioritizing pathological staging over clinical staging, except in the presence of clinical distant metastases which were always considered stage IV. Tumour location was classified as right side (from the cecum to the transverse colon), left side (from the splenic flexure to the sigmoid colon) or rectum.[8,9,18] Differentiation grade was classified as well-differentiated (grade 1), moderately-differentiated (grade 2) and poorly/undifferentiated (grade 3–4).[8,14,31,32]* ***Outcomes*** *A screen-detected CRC and FIT-IC were defined by the screening programme as follows:* *- Screen-detected CRC was defined as a CRC diagnosed after a positive FIT, within six months after the first follow-up colonoscopy and before the next recommended FIT invitation (24 months).* *- FIT-IC was defined as a CRC diagnosed after a negative FIT and before the next recommended FIT invitation (24 months).*
Bias	9	Describe any efforts to address potential sources of bias *Administrative data were used for all the study variables, thus eliminating the common selection and recall bias associated with self-reported data.*
Study size	10	Explain how the study size was arrived at *All 11,656 FIT participants between October 2013 and December 2018 who were subsequently diagnosed with either a screen-detected CRC (N=10,122) or FIT-IC (N=1,534) in the same period were included for all the analyses; except in the analyses regarding tumour location where we only included 10,111 screen-detected CRCs and 1,528 FIT-ICs because two CRCs with an overlapping location and 15 CRCs in the right side of the colon but detected with an incomplete colonoscopy were removed.*
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. *Age at FIT screening was categorized into three groups: 53-59, 60-69 and 70-74. Other variables were originally categorical.*
Statistical methods	12	Describe all statistical methods, including those used to control for confounding *Continuous variables were described with medians (interquartile ranges) and categorical variables were described with numbers (percentages). Logistic regression was used to assess the associations between individuals' and tumours' characteristics and the risk of having a FIT-IC versus a screen-detected CRC. Crude and adjusted odds ratios (for age and gender) with 95% confidence intervals were reported. In this study, stage I was used as the reference to enable the comparison with other studies where only stages I–IV were included.[8,10-12,31] FIT-IC proportions for different profiles combining individuals' and tumours' characteristics were presented. FIT-IC proportion was calculated as the number of FIT-ICs divided by the total number of FIT-ICs and screen-detected CRCs and presented as percentage to enhance comprehension.[11,12,16] We also examined the distributions of FIT results among FIT-ICs in the first/second year of the screening interval and by patients'*

		and tumours' characteristics to explore the impact of shortening FIT screening interval or lowering FIT cut-off on reducing FIT-ICs. There is discrepancy among guidelines regarding whether to include in situ cancers in the definition of colorectal carcinoma (TNM and Japanese classification systems) or not (European and US classification systems).[3,30,33] To facilitate the comparison of our findings with those of other studies, we present, where it is possible, the results for in situ cancers as a separate group from invasive cancers. *P-values less than 0.05 (two-sided) were considered statistically significant. All analyses were performed with RStudio (version 1.3.1056; RStudio, PBC, Boston, MA).*
		Describe any methods used to examine subgroups and interactions: *Not applicable.*
		Explain how missing data were addressed: *Data on gender, age at FIT screening and cancer diagnosis were known for all study subjects. About 14% of the tumours had an unknown stage, 38% had an unknown location and 47% had an unknown differentiation grade. In such cases, the data providers (oncological care programmes and/or laboratories for pathological anatomy) filled in the variables with an unspecified code or left them blank (although the fields were mandatory in the registration form). In our data analyses, these observations were included under the "unknown" category.*
		If applicable, explain how loss to follow-up was addressed: *Not applicable.*
		Describe any sensitivity analyses: *Not applicable.*
Results		
Participants	13*	Report numbers of individuals at each stage of study: *In total, 11,656 CRCs diagnosed after FIT screening were included, with a FIT-IC proportion of 13%. The number of CRCs decreased gradually each year from 3,174 in 2014 to 1,524 in 2018.*
		Give reasons for non-participation at each stage: *Not applicable.*
		Consider use of a flow diagram: *Not applicable.*
Descriptive data	14*	Characteristics of study participants: *Most of the study subjects were male (64.5%). The median age at FIT screening was 66 years. A large proportion of the tumours were classified as "unknown" for location (38.3%), stage (14.0%) or differentiation grade (46.7%). Among the tumours with known categories, the majority presented in the left side of the colon or rectum (5,680/7,188; 79.0%), at stage I or in situ (7,184/10,019; 72.0%) and were moderately differentiated (3,577/6,209; 57.0%) (**Table 1**).*
		Number of participants with missing data: *Data on gender, age at FIT screening and cancer diagnosis were known for all study subjects. About 14% of the tumours had an unknown stage, 38% had an unknown location and 47% had an unknown differentiation grade. In such cases, the data providers (oncological care programmes and/or laboratories for pathological anatomy) filled in the variables with an unspecified code or left them blank (although the fields were mandatory in the registration form). In our data analyses, these observations were included under the "unknown" category.*
		Follow-up time: *between October 2013 and December 2018*
Outcome data	15*	Report numbers of outcome events or summary measures over time: *In total, 11,656 CRCs diagnosed after FIT screening were included, with a FIT-IC proportion of 13% (Table 1).*
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). ***Factors associated with the risk of having a FIT-IC versus a screen-detected CRC*** *The risk of having a FIT-IC versus a screen-detected CRC was 1.6 times higher in women vs. men (OR = 1.58 [1.41–1.76]) and 1.4 times higher in people aged 70–74 compared to ages 53-59 (OR = 1.35 [1.14–1.59]). Regarding tumours' characteristics, the risk of having FIT-IC was 3.5 times higher for tumours in the right side of the colon (OR = 3.53 [2.98–4.20]) and twice higher for those in the rectum (OR = 2.01 [1.72–2.37]) compared to those in the left side; 7.2 times higher for stage IV compared to stage I (OR = 7.15 [5.76–8.88]); and 2.6 times higher for poorly/undifferentiated lesions compared to well-differentiated lesions (OR = 2.57 [2.08–3.18]) (**Table 2**).* ***Figure 1** illustrates the increase in FIT-IC proportion when tumour stage (the strongest factor associated with an increased risk of having a FIT-IC) was combined with other factors. FIT-IC proportion was 45% when considering stage IV alone but increased to 49% when stage IV was combined with age 70–74; 55–56% when stage IV was combined with female gender or poorly/undifferentiated grade and to 63% when stage IV was combined with right side location.* ***Distribution of FIT results among FIT-ICs in the first/second year of screening interval and by patients' and tumours' characteristics*** *The number of FIT-ICs increased during the two-year screening interval (**Figure 2**). More than sixty percent (922/1,534) of FIT-ICs were detected in the second year. According to the distributions of FIT results (**Figure 3** and **Supplementary Table 1**), 83-92% FIT-ICs in both sexes, all age groups, tumour locations and stages had a low quantitative FIT result of ≤ 10 μg Hb/g. This majority of FIT-ICs would not be picked up if the FIT cut-off was lowered from 15 to 10 μg Hb/g. Similarly, 89% of the FIT-ICs detected in the second year of the two-year screening interval also had a low FIT result of ≤ 10 μg Hb/g, suggesting that most FIT-ICs would still be missed even if the screening interval was shortened from two to one year, given the current FIT cut-off of 15 μg Hb/g.* Make clear which confounders were adjusted for and why they were included

		For the variables "gender" and "age at FIT screening" that were assessed at the time of FIT screening, "age at FIT screening" and "gender" were adjusted for in the multivariable analyses, respectively. *For the variables "location", "stage" and "differentiation grade" that were assessed at the time of cancer diagnosis, age at cancer diagnosis and gender were adjusted for in the multivariable analyses.*
		Report category boundaries when continuous variables were categorized: *Not applicable.*
		If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period: *Not applicable.*
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses: *Not applicable.*
Discussion		
Key results	18	Summarise key results with reference to study objectives *Using data of all screen-detected CRCs and FIT-ICs diagnosed in FIT participants for CRC screening in Flanders during 2013–2018, we identified several factors associated with a higher risk of having a FIT-IC versus a screen-detected CRC. These include female gender, older age, right side and rectum locations, advanced stage and high grade. The majority (83–92%) of FIT-ICs in both the first and second year of the two-year screening interval and all subgroups had a low FIT result of ≤ 10 µg Hb/g, indicating a minimal impact of shortening the screening interval from two years to one year or lowering the FIT cut-off from 15 µg Hb/g (the current cut-off) to 10 µg Hb/g on reducing FIT-ICs.*
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias *Several limitations need to be acknowledged. Firstly, since data on both FIT participation and cancers were retrieved between October 2013 and December 2018, data on screen-detected CRCs and FIT-ICs following FITs taken in the latest years (2017–2018) might be incomplete, resulting in an underestimation of both screen-detected CRC and FIT-ICs, with an expected larger extent for FIT-ICs. As a result, FIT-IC proportion might be underestimated, especially for the latest screening years. Secondly, the administrative data used in this study contained sizable proportions of tumours with unknown location, stage or differentiation grade. Future research can benefit from using pathology reports to supplement missing or non-specific information. Lastly, data on molecular characteristics of tumours are lacking in the current study. We plan to analyse pathology reports to study the difference in molecular characteristics between screen-detected CRCs and FIT-ICs, especially those at an advanced stage, in the next step.*
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence: *The FIT-IC proportion in Flanders during 2013–2018 was 13%, which lies within the range of FIT-IC proportion of 7–23% in other screening programmes using a FIT cut-off between 10 and 20 µg Hb/g.[8-12] Our study also supports previous findings that ICs after a negative faecal occult blood test are more common in women, [9,13,16-19] older people,[16,20,36] in the right side of the colon[8,9,11,16-19,22] or in the rectum,[10,17,37] at a more advanced stage[8-14,16,22,31,37] and with a higher grade,[14,31] compared to screen-detected CRCs. Prior literature has proposed several explanations for these associations but definitive conclusions have not been reached.* *The fact that women have a higher risk of having FIT-IC than men might be due to lower blood haemoglobin concentrations,[17,20,38] a longer colonic transit time leading to a greater degree of haemoglobin degradation,[39] or a higher proportion of harder-to-detect, right-sided cancers.[17,20,22,40] The last proposed reason might contribute modestly to the explanation since after adjusting for tumour location, we found almost the same association between gender and the risk of having a FIT-IC versus a screen-detected CRC (OR 1.53 [1.36–1.71]), showing 1.53 times higher risk of having a FIT-IC in women, independently of location.* *Although a number of studies have shown a lower FIT sensitivity in older people,[16,20,36] no possible explanations for this association have been given. Fraser et al (2014) reported increasing faecal haemoglobin concentrations with age (50–69 years) for both men and women in the screening populations for CRC.[39] With a higher faecal haemoglobin concentration and a higher CRC incidence rate, we would normally expect a higher FIT sensitivity in the older age group; it is interesting that studies have found the inverse. We also tested the possibility that CRCs diagnosed in older people presented at a more advanced stage and therefore were missed more by FIT. However, this hypothesis was not supported by our data since the association between the oldest age group (70–74) and the risk of having a FIT-IC versus a screen-detected CRC remained (OR 1.31 [1.11–1.56]) after we adjusted for tumour stage in addition to gender. It is a question of future research to investigate the possible reasons for the lower sensitivity of FIT in the older age group.* *Prior research has reported a higher proportion of nonpolypoid (flat) tumours in the right side compared to the left side of the colon.[21,41] These tumours tend to have a higher risk of malignant transformation and invasiveness at a relatively smaller size.[41,42] Due to the smaller areas in contact with faeces and sparser vasculature in the mucosa, they bleed*

less and are less sensitive to FIT.[21,43] A longer transit time from the right side may also lead to a greater degree of haemoglobin degradation, and therefore more false-negative results occur with right-sided tumours.[17,19,21,44] Selby et al (2018) reported a significantly lower faecal haemoglobin level of the right-sided cancers among FIT screenees compared to that of the left-sided cancers (12.4 versus 60.0 µg Hb/g; p < 0.001).[20]

Regarding a higher risk of being a FIT-IC for tumours in the rectum compared to the left side location, erythrocytes in blood released from rectum lesions may not have been sufficiently haemolysed during a short passage through the rectum, and therefore do not yield a positive result to a FIT.[13,37] In the same study by Selby et al, the faecal haemoglobin level of the rectal cancers was also significantly lower than that of the left-sided cancers (24.4 versus 60.0 µg Hb/g, p < 0.001).[20] Another possible explanation is that rectal bleeding more often presents with bright red blood in faeces, which is easier to notice. Screening participants generally have a heightened awareness of signs of blood in their faeces. Once they notice bright red blood in faeces, they tend to consult with primary care promptly.[22] It cannot be ruled out that low FIT effectiveness for tumours in the right colon or rectum may also stem from lesions that grow more rapidly.[41,42,45]

Compared to screen-detected CRCs, FIT-ICs exhibited a higher grade and aggressive histotype (signet ring cell and mucinous carcinomas).[14] However, it is still unclear to what degree FIT-ICs are due to FIT false-negative tests or a faster growth pathway of high-grade and aggressive histotype tumours. A recent study by Steel et al reported a mean time of 10.9 ± 2.9 months from FIT screening to diagnoses of all ICs and 11.6 ± 7.2 months from FIT screening to diagnoses of high-grade and aggressive histotype ICs.[14] The more advanced stage of FIT-ICs compared to screen-detected CRCs might be because FIT is known to be less sensitive for flat, right-sided and poorly or undifferentiated lesions,[14,46-48] tumours with these characteristics may be missed more often by FIT. Once these tumours are detected later on when symptoms appear, they are already at an advanced stage. A proportion of these ICs may also originate from tumours with more aggressive characteristics and worse behaviour, which actually arose after a true negative FIT.[14,15] Our findings reinforce the current advice to the screening participants not to regard a negative FIT result as a "certificate of health". Instead, they need to be vigilant and seek primary care promptly when any signs or symptoms appear.[22,49,50]

To reduce FIT-ICs, previous studies have also suggested personalizing FIT cut-offs, for example, using a lower cut-off in the subgroups with a lower FIT sensitivity such as women and older people.[13,21-23] However, our data showed that in Flanders, lowering FIT cut-off from 15 to 10 µg Hb/g would only have a limited impact on reducing FIT-ICs since more than 83% of FIT-ICs had a low FIT result of ≤ 10 µg Hb/g across genders, age groups, tumour locations and stages. Although the FIT test used in the Flemish screening programme could theoretically detect up to 3 µg Hb/g faeces, the quantitative results between 3–10 µg Hb/g were considered (quantitatively) unreliable due to large deviations. Therefore, lowering FIT cut-off to below 10 µg Hb/g would not be a suitable option for the test used. Prior research has reported around 75% of FIT-ICs with a low level of haemoglobin (< 10 µg Hb/g) and 19.4–44% with an undetectable level (0 µg Hb/g).[11-13] This implies that the majority of FIT-ICs would still be missed even with a drastic reduction in the FIT cut-off.

Gender-specific cut-offs have also been introduced/piloted in several screening programmes, for example, 40 µg Hb/g for women and 80 µg Hb/g for men in Sweden;[24,25] or 25 µg Hg/g for women and 70 µg Hg/g for men in Finland.[26] In Flanders, a much lower FIT cut-off of 15 µg Hg/g has already been applied for all screening individuals. Our results suggest that 15 µg Hg/g should be the lowest FIT cut-off that a CRC screening programme should aim for, regardless of the patient's gender and age. This recommendation is supported by a recent study by Vanaclocha-Espi et al (2021) which found the optimal FIT cut-off of around 15 µg Hg/g for the subgroup of women aged 60–69, which had the lowest FIT sensitivity among the subgroups evaluated (women and men, aged 50–59 and 60–69).[51]

Many studies have also highlighted a substantial increase in colonoscopy demand for only a marginal gain in sensitivity by lowering FIT cut-off.[13,20,52] For example, the Scottish Bowel Screening Programme reported that halving the FIT cut-off in their programme from 80 µg Hb/g to 40 µg Hb/g faeces would reduce the FIT-IC proportion from 50.8% to 45.9%, but would increase the number of colonoscopies required by 58.6%.[13] An American screening programme predicted that lowering the FIT cut-off in their programme from 20 µg/g to 10 µg/g would increase the programme's sensitivity by only 3% (from 76.3% to 79.3%) while increasing the number of positive results per one cancer case detected from 52 to 85.[20]

In agreement with Giorgi Rossi et al,[18] we also observed more FIT-ICs in the second year than the first year of the two-year screening interval (60% of all ICs). The difference in the number of FIT-ICs between the second and the first year was 310 cases. It seems, at first glance, that shortening the FIT screening interval from two to one year during the study period might have helped to reduce this number of FIT-ICs.[21] However, 89% of FIT-ICs in the second year were found to have a low FIT result at screening of ≤ 10 µg Hb/g,

		suggesting that the majority of ICs would still be missed even when the screening interval was shortened to one year. One might also argue that the FIT results were obtained at the time of screening and as tumours progressed between the first and second year, FIT results might get higher and reach the positive cut-off. The proportion of such tumours seemed to be modest since our data showed that 83–92% of FIT-ICs across all tumour stages had a low FIT result of ≤ 10 µg Hb/g. Thus, in the programmes where a low FIT cut-off of 15 µg Hb/g is implemented, shortening screening interval from two to one year seems to produce only a marginal impact on reducing FIT-ICs. *Meanwhile, a CRC screening programme should also consider the impact of screening interval on screen-detected CRCs and the related costs. Specifically, when the screening interval of a two-year programme was shortened to one year, the number of prevalent cases detected among individuals entering the screening programme for the first time would be almost similar (same population and same target screening ages). The main difference is that after the first screening round, the population would repeat screening right the next year in the one-year programme, instead of waiting for two years in the two-year programme. A proportion of the screen-detected incident CRCs in the two-year programme would be diagnosed one year earlier in the one-year programme. This, however, comes at the cost of having the whole screening population undergo FIT every year instead of every two years (Flanders: ~850,000 individuals in 2020),[28] meaning doubling the entire process of screening invitation, FIT provision, result analyses and follow-up with colonoscopy after a positive FIT.* *With data from a population-based screening programme of the largest region in Belgium, which used a FIT cut-off within the common range of 10–20 µg Hb/g, our results can be widely generalized to other CRC screening programmes. The large sample size allowed us to stratify our results by multiple participants' and tumours' characteristics.*
Generalisability	21	Discuss the generalisability (external validity) of the study results *With data from a population-based screening programme of the largest region in Belgium, which used a FIT cut-off within the common range of 10–20 µg Hb/g, our results can be widely generalized to other CRC screening programmes.*
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based *The authors received no specific funding for this work.*

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

Supplementary Table 2 Distributions of quantitative results of faecal immunochemical test (FIT) among FIT-interval cancers, stratified by the first/second year of the screening interval, genders, age groups, tumour stages and tumour locations.

	FIT-ICs (µg Hb/g)				Screen-detected cancers
	≤10	>10 to ≤12	> 12 to <15	<15 (negative)	≥15 (positive)
Year					
Year 1	525 (85.8%)	33 (5.4%)	54 (8.8%)	612 (100%)	9925
Year 2	817 (88.6%)	39 (4.2%)	66 (7.2%)	922 (100%)	197
Gender					
Male	750 (88.7%)	39 (4.6%)	57 (6.7%)	846 (100%)	6670
Female	592 (86%)	33 (4.8%)	63 (9.2%)	688 (100%)	3452
Age at FIT screening					
53–59	211 (89.8%)	9 (3.8%)	15 (6.4%)	235 (100%)	1800
60–69	705 (86.6%)	36 (5.5%)	66 (7.9%)	807 (100%)	5483
70–74	426 (87.6%)	27 (4.2%)	39 (8.2%)	492 (100%)	2839
Tumour stage					
In situ	362 (88.3%)	20 (4.9%)	28 (6.8%)	410 (100%)	4060
Stage I	243 (88.0%)	11 (4.0%)	22 (8.0%)	276 (100%)	2438
Stage II	156 (87.2%)	11 (6.1%)	12 (6.7%)	179 (100%)	881
Stage III	206 (86.6%)	12 (5.0%)	20 (8.4%)	238 (100%)	1031
Stage IV	189 (82.9%)	10 (4.4%)	29 (12.7%)	228 (100%)	278
Unknown stage	186 (91.6%)	8 (3.9%)	9 (4.4%)	203 (100%)	1434

FIT, Faecal immunochemical test; IC, Interval cancer

References

1 Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R.L., Torre, L.A. & Jemal, A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394-424.

2 Belgian Cancer Registry (2020). *Cancer Fact Sheet Colorectal Cancer: Belgium 2018*, https://kankerregister.org/media/docs/CancerFactSheets/2018/Cancer_Fact_Sheet_ColorectalCancer_2018.pdf Accessed 30 August 2020.

3 Segnan, N., Patnick, J. & von Karsa, L. (eds). *European guidelines for quality assurance in colorectal cancer screening and diagnosis*. 1st edn, (Publications Office of the European Union: Luxembourg, 2010).

4 Mandel, J.S., Bond, J.H., Church, T.R., Snover, D.C., Bradley, G.M., Schuman, L.M. et al. Reducing mortality from colorectal cancer by screening for fecal occult blood. Minnesota Colon Cancer Control Study. N Engl J Med. 1993;328:1365-1371.

5 Kronborg, O., Fenger, C., Olsen, J., Jørgensen, O.D. & Søndergaard, O. Randomised study of screening for colorectal cancer with faecal-occult-blood test. The Lancet. 1996;348:1467-1471.

6 Hardcastle, J.D., Chamberlain, J.O., Robinson, M.H.E., Moss, S.M., Amar, S.S., Balfour, T.W. et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. The Lancet. 1996;348:1472-1477.

7 Schreuders, E.H., Ruco, A., Rabeneck, L., Schoen, R.E., Sung, J.J., Young, G.P. et al. Colorectal cancer screening: a global overview of existing programmes. Gut. 2015;64:1637-1649.

8 Portillo, I., Arana-Arri, E., Idigoras, I., Bilbao, I., Martínez-Indart, L., Bujanda, L. et al. Colorectal and interval cancers of the Colorectal Cancer Screening Program in the Basque Country (Spain). World J Gastroenterol. 2017;23:2731-2742.

9 Zorzi, M., Fedato, C., Grazzini, G., Stocco, F.C., Banovich, F., Bortoli, A. et al. High sensitivity of five colorectal screening programmes with faecal immunochemical test in the Veneto Region, Italy. Gut. 2011;60:944-949.

10 Garcia, M., Domenech, X., Vidal, C., Torne, E., Mila, N., Binefa, G. et al. Interval cancers in a population-based screening program for colorectal cancer in catalonia, Spain. Gastroenterol Res Pract. 2015;2015:672410.

11 Mlakar, D.N., Bric, T.K., Škrjanec, A.L. & Krajc, M. Interval cancers after negative immunochemical test compared to screen and non-responders' detected cancers in Slovenian colorectal cancer screening programme. Radiol Oncol. 2018;52:413-421.

12 van der Vlugt, M., Grobbee, E.J., Bossuyt, P.M.M., Bos, A., Bongers, E., Spijker, W. et al. Interval Colorectal Cancer Incidence Among Subjects Undergoing Multiple Rounds of Fecal Immunochemical Testing. Gastroenterology. 2017;153:439-447 e432.

13 Digby, J., Fraser, C.G., Carey, F.A., Lang, J., Stanners, G. & Steele, R.J. Interval cancers using a quantitative faecal immunochemical test (FIT) for haemoglobin when colonoscopy capacity is limited. J Med Screen. 2016;23:130-134.

14 Steel, M.J., Bukhari, H., Gentile, L., Telford, J. & Schaeffer, D.F. Colorectal adenocarcinomas diagnosed following a negative faecal immunochemical test show high-risk pathological features in a colon screening programme. Histopathology. 2021;78:710-716.

15 Richter, J.M., Pino, M.S., Austin, T.R., Campbell, E., Szymonifka, J., Russo, A.L. et al. Genetic mechanisms in interval colon cancers. Dig Dis Sci. 2014;59:2255-2263.

16 van de Veerdonk, W., Hoeck, S., Peeters, M., Van Hal, G., Francart, J. & De Brabander, I. Occurrence and characteristics of faecal immunochemical screen-detected cancers vs non-screen-detected cancers: Results from a Flemish colorectal cancer screening programme. United European Gastroenterol J. 2020;8:185-194.

17 Steele, R.J., McClements, P., Watling, C., Libby, G., Weller, D., Brewster, D.H. et al. Interval cancers in a FOBT-based colorectal cancer population screening programme: implications for stage, gender and tumour site. Gut. 2012;61:576-581.

18 Giorgi Rossi, P., Carretta, E., Mangone, L., Baracco, S., Serraino, D. & Zorzi, M. Incidence of interval cancers in faecal immunochemical test colorectal screening programmes in Italy. Journal of Medical Screening. 2017;25:32-39.

19 Morris, E.J., Whitehouse, L.E., Farrell, T., Nickerson, C., Thomas, J.D., Quirke, P. et al. A retrospective observational study examining the characteristics and outcomes of tumours diagnosed within and without of the English NHS Bowel Cancer Screening Programme. Br J Cancer. 2012;107:757-764.

20 Selby, K., Jensen, C.D., Lee, J.K., Doubeni, C.A., Schottinger, J.E., Zhao, W.K. et al. Influence of Varying Quantitative Fecal Immunochemical Test Positivity Thresholds on Colorectal Cancer Detection: A Community-Based Cohort Study. Ann Intern Med. 2018;169:439-447.

21 Chiu, H.M., Lee, Y.C., Tu, C.H., Chen, C.C., Tseng, P.H., Liang, J.T. et al. Association between early stage colon neoplasms and false-negative results from the fecal immunochemical test. Clin Gastroenterol Hepatol. 2013;11:832-838 e831-832.

22 Steele, R.J., Stanners, G., Lang, J., Brewster, D.H., Carey, F.A. & Fraser, C.G. Interval cancers in a national colorectal cancer screening programme. United European Gastroenterol J. 2016;4:587-594.

23 Selby, K., Levine, E.H., Doan, C., Gies, A., Brenner, H., Quesenberry, C. et al. Effect of Sex, Age, and Positivity Threshold on Fecal Immunochemical Test Accuracy: A Systematic Review and Meta-analysis. Gastroenterology. 2019;157:1494-1505.

24 Ribbing Wilen, H., Saraste, D. & Blom, J. Gender-specific cut-off levels in colorectal cancer screening with fecal immunochemical test: A population-based study of colonoscopy findings and costs. J Med Screen. 2021;28:439-447.

25 Blom, J., Lowbeer, C., Elfstrom, K.M., Sventelius, M., Ohman, D., Saraste, D. et al. Gender-specific cut-offs in colorectal cancer screening with FIT: Increased compliance and equal positivity rate. J Med Screen. 2019;26:92-97.

26 Sarkeala, T., Farkkila, M., Anttila, A., Hyoty, M., Kairaluoma, M., Rautio, T. et al. Piloting gender-oriented colorectal cancer screening with a faecal immunochemical test: population-based registry study from Finland. BMJ Open. 2021;11:e046667.

27 STATBEL (2020). *Structure of the population*, https://statbel.fgov.be/en/themes/population/structure-population Accessed 16 Feb 2020.

28 Centre for Cancer Detection (2021). *Monitoring Report of the Flemish Colorectal Cancer Screening Programme*, https://www.bevolkingsonderzoek.be/sites/default/files/atoms/files/Jaarrapport%202021%20BVO%20naar%20kanker.pdf Accessed 3 December 2021.

29 Sobin, L.H., Gospodarowicz, M.K. & Wittekind, C. (eds). *TNM Classification of Malignant Tumours*. 7th edn, (Wiley-Blackwell: Chichester, West Sussex, UK, 2009).

30 Brierley, J.D., Gospodarowicz, M.K. & Wittekind, C. (eds). *TNM Classification of Malignant Tumours*. 8th edn, (John Wiley & Sons, Inc.: Oxford, UK ; Hoboken, NJ, 2017).

31 Asteria, C.R., Lucchini, G., Guarda, L., Ricci, P., Pagani, M. & Boccia, L. The detection of interval colorectal cancers following screening by fecal immunochemical test may predict worse outcomes and prompt ethical concerns: a 6-year population-based cohort study in a full district. Eur J Cancer Prev. 2019;28:17-26.

32 Vicentini, M., Zorzi, M., Bovo, E., Mancuso, P., Zappa, M., Manneschi, G. et al. Impact of screening programme using the faecal immunochemical test on stage of colorectal cancer: Results from the IMPATTO study. Int J Cancer. 2019;145:110-121.

33 Yao, T. & Shiono, S. Differences in the pathological diagnosis of colorectal neoplasia between the East and the West: Present status and future perspectives from Japan. Dig Endosc. 2016;28:306-311.

34 Belgian Privacy Commission (2019). *IVC/KSZG/19/236*, https://www.ehealth.fgov.be/ehealthplatform/file/view/AWvhE2PqnF_Mkwg-mMCV?filename=13-091-n236-bevolkingsonderzoek%20dikkedarmkanker-gewijzigd%20op%202%20juli%202019.pdf Accessed 3 December 2019.

35 von Elm, E., Altman, D.G., Egger, M., Pocock, S.J., Gotzsche, P.C., Vandenbroucke, J.P. et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. BMJ. 2007;335:806-808.

36 Shin, A., Choi, K.S., Jun, J.K., Noh, D.K., Suh, M., Jung, K.W. et al. Validity of fecal occult blood test in the national cancer screening program, Korea. PLoS One. 2013;8:e79292.

37 Tazi, M.A., Faivre, J., Lejeune, C., Bolard, P., Phelip, J.M. & Benhamiche, A.M. Interval cancers in a community-based programme of colorectal cancer screening with faecal occult blood test. Eur J Cancer Prev. 1999;8:131-135.

38 McDonald, P.J., Strachan, J.A., Digby, J., Steele, R.J. & Fraser, C.G. Faecal haemoglobin concentrations by gender and age: implications for population-based screening for colorectal cancer. Clin Chem Lab Med. 2011;50:935-940.

39 Fraser, C.G., Rubeca, T., Rapi, S., Chen, L.S. & Chen, H.H. Faecal haemoglobin concentrations vary with sex and age, but data are not transferable across geography for colorectal cancer screening. Clin Chem Lab Med. 2014;52:1211-1216.

40 Kim, S.E., Paik, H.Y., Yoon, H., Lee, J.E., Kim, N. & Sung, M.K. Sex- and gender-specific disparities in colorectal cancer risk. World J Gastroenterol. 2015;21:5167-5175.

41 Chiu, H.M., Lin, J.T., Chen, C.C., Lee, Y.C., Liao, W.C., Liang, J.T. et al. Prevalence and characteristics of nonpolypoid colorectal neoplasm in an asymptomatic and average-risk Chinese population. Clin Gastroenterol Hepatol. 2009;7:463-470.

42 Soetikno, R.M., Kaltenbach, T., Rouse, R.V., Park, W., Maheshwari, A., Sato, T. et al. Prevalence of nonpolypoid (flat and depressed) colorectal neoplasms in asymptomatic and symptomatic adults. JAMA. 2008;299:1027-1035.

43 Doubeni, C.A., Corley, D.A., Quinn, V.P., Jensen, C.D., Zauber, A.G., Goodman, M. et al. Effectiveness of screening colonoscopy in reducing the risk of death from right and left colon cancer: a large community-based study. Gut. 2018;67:291-298.

44 Doubeni, C.A. & Levin, T.R. In Screening for Colorectal Cancer, Is the FIT Right for the Right Side of the Colon? Ann Intern Med. 2018;169:650-651.

45 Launoy, G., Smith, T.C., Duffy, S.W. & Bouvier, V. Colorectal cancer mass-screening: Estimation of faecal occult blood test sensitivity, taking into account cancer mean sojourn time. Int J Cancer. 1997;73:220-224.

46 Ciatto, S., Martinelli, F., Castiglione, G., Mantellini, P., Rubeca, T., Grazzini, G. et al. Association of FOBT-assessed faecal Hb content with colonic lesions detected in the Florence screening programme. Br J Cancer. 2007;96:218-221.

47 Cross, A.J., Wooldrage, K., Robbins, E.C., Kralj-Hans, I., MacRae, E., Piggott, C. et al. Faecal immunochemical tests (FIT) versus colonoscopy for surveillance after screening and polypectomy: a diagnostic accuracy and cost-effectiveness study. Gut. 2019;68:1642-1652.

48 Imperiale, T.F., Ransohoff, D.F., Itzkowitz, S.H., Levin, T.R., Lavin, P., Lidgard, G.P. et al. Multitarget stool DNA testing for colorectal-cancer screening. N Engl J Med. 2014;370:1287-1297.

49 Barnett, K.N., Weller, D., Smith, S., Steele, R.J., Vedsted, P., Orbell, S. et al. The contribution of a negative colorectal screening test result to symptom appraisal and help-seeking behaviour among patients subsequently diagnosed with an interval colorectal cancer. Health Expect. 2018;21:764-773.

50 Hallifax, R., Lacey, M., Bevis, P., Borley, N.R., Brooklyn, T. & Wheeler, J.M.D. Slipping through the bowel cancer screening programme. Colorectal Dis. 2012;14:844-847.

51 Vanaclocha-Espi, M., Ibanez, J., Molina-Barcelo, A., Valverde-Roig, M.J., Nolasco, A., Perez-Riquelme, F. et al. Optimal cut-off value for detecting colorectal cancer with fecal immunochemical tests according to age and sex. PLoS One. 2021;16:e0254021.

52 Berry, E., Miller, S., Koch, M., Balasubramanian, B., Argenbright, K. & Gupta, S. Lower Abnormal Fecal Immunochemical Test Cut-Off Values Improve Detection of Colorectal Cancer in System-Level Screens. Clin Gastroenterol Hepatol. 2020;18:647-653.

Chapter 7

General discussion

7.1. Main findings and implications

This chapter presents a comprehensive discussion of the key findings from this PhD research and their implications for the Flemish population-based CRC screening programme, as well as future perspectives. Methodological considerations and limitations of the individual studies are also discussed.

Please note that this discussion focuses solely on the novel findings that are directly applicable to the current context of the Flemish CRC screening programme. For example, the results from **Chapter 5** regarding colonoscopy as the primary test for CRC screening (based on the predominance of US-based studies in our review), are not covered in this section, as they are more relevant to the context of opportunistic colonoscopy screening in the US. Similarly, findings that merely confirmed previous research, such as the characteristics of FIT interval cancers in **Chapter 6**, are also not extensively discussed. Further details regarding these specific findings can be found in the respective individual studies.

Furthermore, it is important to acknowledge that the conceptualisation, data collection, and preliminary data analysis of the study presented in **Chapter 4** were conducted prior to this PhD research. The measures implemented in the screening programme based on these findings were developed independently of this PhD. However, during the course of this PhD, refinements were made to the methods of data analysis, result preparation, and result presentation to ensure suitability for the publication of the study's findings.

7.1.1. The FIT-based CRC screening programme in Flanders has proven to be effective

The primary objectives of any CRC screening programme are to detect CRCs early, improve prognosis and reduce CRC-related mortality and incidence in the long term.[1,2] Therefore, close monitoring of the programmes' performance and its alignment with expectations is important. Since 2019, the Belgian Cancer Registry in collaboration with the Centre for Cancer Detection (CCD), has conducted an annual descriptive analysis of the impact of the Flemish CRC screening programme on CRC incidence and stage distribution.[3] The findings have shown a positive trend, with a notable initial increase in CRC incidence followed by a significant decrease and a shift towards earlier stages, thus affirming the effectiveness of FIT screening in Flanders in detecting a higher number of CRC cases at an earlier stage.

In 2021, after six years of implementation, the follow-up period for the Flemish CRC screening programme was considered sufficient for a comprehensive scientific evaluation of its impact on CRC incidence (early and advanced stage), mortality and survival in Flanders. The results of this assessment are presented in **Chapter 2**. Despite the relatively short follow-up period, the programme has demonstrated initial successes in detecting CRCs at earlier stages, improving survival and reducing CRC-related mortality.[4]

Following its introduction in 2013, the programme initially led to a sharp increase in incidence of early-stage CRC within a year, which was followed by a steady decrease until 2019, reaching a slightly lower rate than before the programme's initiation. In contrast, the incidence of advanced-stage CRC only increased slightly during 2013-2014 and then decreased drastically to a significantly lower rate than the pre-programme rate. FIT screening has proven to be effective in detecting asymptomatic CRC cases at an early stage, preventing their progression to advanced stages with symptoms, and thereby resulting in a significant reduction in the incidence of advanced-stage CRC. Furthermore, by identifying and removing precursors, screening can help reduce the overall incidence of CRC over time. In Flanders, there is already evidence of a reduction in incidence, with the overall CRC incidence steadily decreasing from its peak in 2014 (200.6/100,000 py) to a significantly lower rate in 2019 compared to the pre-programme rate in 2012 (115.2/100,000 py vs. 152.7/100,000 py).[4]

Consistent with results reported from other regions and countries,[5-7] Flanders demonstrated a remarkable down-staging effect of CRC screening, with 70% of screen-detected CRCs being at an early stage (I or II) compared to only around 40% for CRCs in non-participants or those not yet invited to participate in the screening programme (CRCs that occurred before the initiation of the screening programme or after its initiation but in individuals whose ages were not yet included in the target screening ages). The 5-year relative survival for screen-detected CRCs was very high at 94% whereas it was only 62% and 67% for CRCs in FIT non-participants and never-invited individuals, respectively.[4]

In addition to improving survival, FIT screening in Flanders has also contributed to a decrease in CRC-related mortality, although the impact was only evident in men in our evaluation conducted in 2021 (an annual percentage decrease of 8.2% in CRC-related mortality starting two years after FIT screening implementation vs. 2.2% before the programme's initiation). The greater impact of FIT screening in men can be attributed to their higher CRC incidence and

mortality, as well as the higher sensitivity of FIT in detecting CRC in men compared to women. It is anticipated that the effect of screening on mortality in women will become apparent as the follow-up period extends.[4]

Our findings affirm the effectiveness of the CRC screening programme in reducing the burden of CRC in Flanders. These results have been made publicly accessible on the programme's website and effectively communicated to GPs and pharmacists through an informative yearly infosheet distributed during CRC awareness month (March) since 2021.[8] The aim is to encourage their active involvement in promoting CRC screening among their patients. The CCD also intends to create a simplified version of the infosheet, utilising lay language and incorporating more infographics, specifically tailored for the target screening population. Ultimately, showcasing the positive impact of the screening programme itself would serve as the most compelling 'advertisement' to motivate individuals to participate in screening and experience its benefits.[9]

Furthermore, beyond the context of Flanders, our findings support the timely implementation of organised FIT screening programmes in areas where they are not yet established, as well as the improvement of existing programmes. The reported impact of FIT screening on mortality worldwide has varied (ranging from 9% to 52% reduction after 6-16 years) due to differences in screening implementation levels, baseline CRC incidence and mortality, screening target age range, FIT cut-off, screening interval and length of follow-up period.[2,10-15] Our findings show that in settings similar to Flanders, a noticeable reduction in CRC-related mortality can be achieved within a relatively short period (less than 10 years) after the implementation of population FIT screening.

Lastly, continuous monitoring and evaluation are vital for the ongoing improvement of any cancer screening programme. The Flemish CRC screening programme plans to assess its impact regularly (every 2-3 years) to monitor the evolution of results and take timely actions as necessary.

7.1.2. Enhancing screening participation is essential for maximizing the programme's effectiveness

Despite initial achievements, the Flemish CRC screening programme has not yet reached its full potential in terms of screening participation. The current annual participation rate in CRC screening in Flanders slightly exceeds 50%,[9] meeting the minimum acceptable rate of at least 45% recommended by EU guidelines but still falling below the desirable rate of at least 65%.[16] Strikingly, about a quarter of the target population has never participated in any CRC screening rounds.[9] To address this challenge, the CCD has dedicated significant efforts to understand the characteristics of this lesser-reached population in order to inform the development of tailored interventions that can enhance their participation in CRC screening. This PhD research has identified and further examined several crucial determinants of CRC screening participation in the Flemish population, including taking FOBTs outside the screening programme, language barriers, delayed participation, misconceptions about the necessity of screening, and role of GPs.[17-19]

7.1.2.1. FOBT use outside the screening programme and its impact on participation rate within the programme

Thanks to the registration of FOBTs prescribed by GPs using nomenclature codes in health insurance claims, we were able to explore factors associated with screening coverage through an FOBT outside the screening programme in Flanders, as detailed in **Chapter 3**.[17] The study revealed that GP contact is the primary determinant linked to higher screening coverage with FOBTs outside the programme. Surprisingly, some GPs continued to prescribe outside FOBTs to their patients despite the availability of the organised CRC screening programme. An evaluation in 2017 discovered that certain GPs prescribed an additional outside FOBT after a positive FIT result within the screening programme, aiming to confirm the first positive result and persuade patients to undergo a colonoscopy.[20] Another common reason for GPs to prescribe an outside FOBT is when a patient has lost the FIT provided by the screening programme or when the first test has expired. In our study conducted in 2019 among irregular participants,[19] 42% of more than 5300 survey respondents stated that they were unaware that they could request a new free test from the screening programme if needed.[19]

To address this issue, since 2020, the Flemish CRC screening programme has emphasized in the

information leaflet and on its website that GPs or patients can contact the programme for another free test in the case of a lost or expired test.[21,22] At the same time, the annual report provided to GPs regarding follow-up after a positive FIT result also underscores that a second FOBT outside the screening programme after an inside positive FIT is not a correct follow-up; instead, individuals with a positive FIT result are recommended to undergo a colonoscopy. An example of the list of patients with an incorrect follow-up after a positive FIT result given in this report is presented in **Figure 1** below:

Patiënten met geen of incorrecte follow-up na FIT+ uit het BVO DDK

Nr.	RR	Naam	Voornaam	Datum laboresultaat FIT	Type van (incorrecte) follow-up	Datum follow-up *
1	[redacted]			13-02-2018	stoelgangtest	20-06-2018
2				06-03-2018	geen follow-up	nvt
3				30-03-2018	geen follow-up	nvt
4				27-04-2018	geen follow-up	nvt
5				03-05-2018	geen follow-up	nvt
6				14-05-2018	geen follow-up	nvt
7				01-06-2018	geen follow-up	nvt
8				31-07-2018	geen follow-up	nvt
9				13-08-2018	geen follow-up	nvt
10				07-09-2018	geen follow-up	nvt
11				12-09-2018	geen follow-up	nvt
12				12-10-2018	geen follow-up	nvt
13				06-11-2018	geen follow-up	nvt
14				04-12-2018	geen follow-up	nvt
15				11-12-2018	volledige colonoscopie	15-07-2021

Figure 1. An example of a list of patients with an incorrect follow-up after a positive FIT result within the Flemish colorectal cancer screening programme. This list is included in the programme's annual report provided to GPs regarding follow-up after a positive FIT result.

Theoretically, screening with a FOBT outside the screening programme can negatively affect the participation rate within the programme because individuals opt for an outside test instead of an inside one for screening purposes.[9] However, the effect of this practice seems to be limited, indicated by the generally low and continuously declining coverage associated with FOBT use outside the screening programme in Flanders. During the study period from 2015 to 2017,[17] the coverage with outside FOBTs decreased from 5.4% to 3.7% and further declined to 2.5% in 2021.[23] It should be noted that these figures include outside FOBTs used for both screening and diagnostic purposes, as the available data did not allow us to distinguish between the two (See also **Section 7.2.5**). Thus, the proportion of outside FOBTs used solely for screening purposes is even smaller than the reported figures.

Moreover, it is worth recognising that even with an outside FOBT, an individual is still covered by screening, which is more favourable than no screening at all. Nonetheless, an outside FOBT is associated with various issues, including being non-free of charge, lacking systematic

registration of screening results and follow-up information, and lacking adequate quality control by the screening programme, the cancer registry, or any other authorities. From both economic and organisational perspectives, individuals who have opted for non-organised FOBTs for CRC screening should be encouraged to shift to organised screening. However, one remaining challenge in using a test within the screening programme, after a GP has convinced a patient to undergo CRC screening, is the time required for the programme to complete administrative processes. These processes include identifying the person, checking the person's eligibility for screening, preparing the invitation package (including the test kit), and mailing it, which may take up to three weeks. This could be a reason why some GPs are tempted to provide their patients with an outside FOBT, which is already readily available at their clinics. The CCD is aware of this issue and is actively working to accelerate the provision of the test kits to individuals who have requested the kits from the screening programme, either directly or through their GPs.

7.1.2.2. Language barriers to CRC screening

In line with previous findings in Flanders,[24,25] our study in **Chapter 4**[17] revealed a lower coverage rate by the organised CRC screening programme among individuals with a migrant background (non-Belgian/Dutch nationality). Language barriers and discomfort discussing CRC screening and stool samples were identified as the primary concerns among non-participants with a migrant background.[17,24]

Previous interviews with Turkish migrants in Flanders highlighted their limited knowledge about CRC screening, with many expressing their need for more information.[24] Difficulties in understanding written information in Dutch made it challenging for them to make informed decisions about screening participation. Some even mistook the screening invitation for an advertisement and discarded it. Older migrants (first generation) relied heavily on their children to understand the information in the invitation letter and leaflet but at the same time, felt uncomfortable discussing CRC screening and stool samples with them. Language barriers among migrants persist in their communication with their GPs, limiting their access to screening information from their GPs.[17,24]

To address the issue of people misperceiving the invitation letter as an advertisement, modifications have been made to the invitation envelop since 2019. The text "Free test for CRC screening" has now been included and the specific logo of the CRC screening programme has

replaced the uniform Population Screening logo.[26] However, due to strict language regulations in Belgium that require the use of Dutch in all administrative communications in Flanders, including the materials of a population screening programme, the text "Free test for CRC screening" could only be added in Dutch. This constraint limits the effectiveness of the measure in addressing the initial problem, as it primarily affects individuals with inadequate Dutch language proficiency who are prone to perceiving the invitation letter as an advertisement.

In the same interviews with Turkish migrants,[24] the provision of translated information (even if only partial) was cited as a facilitator for CRC screening. The website of the Flemish CRC screening programme offers screening materials, including the invitation letter, participation form, user instructions, leaflet and reminder letter, in 10 languages apart from Dutch (German, Italian, Spanish, Russian, Romanian, Arabic, English, French, Polish and Turkish).[27] However, the challenge lies in effectively informing people who need these translations and ensuring their accessibility to the materials. Currently, the invitation letter, leaflet and user instructions (in the invitation package) all include a QR code that provides easy access to the programme website where the translations are available. However, as these documents in the invitation package are in Dutch, individuals with limited Dutch language proficiency may be less likely to scan the QR code and learn about the availability of the translated screening materials on the programme website. GPs can also play a role in informing people about the translations. However, limited Dutch language ability remains a significant challenge for a considerable proportion of people with a migrant background, both through the invitation package or GP channels. This situation creates a paradox where people who need translation support are required to possess a certain level of Dutch proficiency to become aware of the translations provided on the programme website, which are designed to assist those with limited Dutch language skills. It should be noted the CCD is aware of this situation, but the issue persists due to the strict language legislation imposed by the Belgian government, which is beyond the control of the Flemish CRC screening programme.

In early 2023, almost 715,000 individuals with a foreign nationality lived in Flanders, comprising approximately 11% of the total population.[28] Among them, about 21% come from the Netherlands and face no difficulty understanding the screening materials in Dutch.[28] Additionally, some people with a non-Belgian/Dutch nationality have acquired a certain level of Dutch language proficiency, enabling them to comprehend the screening materials.

However, it is likely that a significant proportion of this group still encounter language barriers when dealing with the CRC screening process. According to Google Analytics data, the website of the Flemish CRC screening programme was accessed by 185,820 visitors in 2022, with 86.7% assessing the website in Dutch and 13.3% using a non-Dutch language.[29] Considering that roughly 840,000 individuals are invited for CRC screening each year in Flanders,[99] it is estimated that about one fifth of the target population visited the programme's website in 2022, although this calculation might be slightly overestimated due to potential visitors outside the target population.

Interpreting these figures presents a significant challenge as data on the languages spoken by people is not available. Among the majority (4/5) of the target population who did not visit the programme website, the reasons for not doing so could differ between Dutch and non-Dutch speaking individuals. Dutch-speaking people likely received sufficient information from the screening materials provided in the invitation package by the CCD, while many non-Dutch speaking people may have struggled to understand the provided screening materials and remained unaware of the programme's website with translated materials. Furthermore, it is worth noting that among the one fifth of the target population who accessed the programme's website, only 13.3% used it in a non-Dutch language,[29] indicating an under-utilization of the available translations on the website.

Another option to address language barriers is the presence of an interpreter. However, many healthcare workers view the use of interpreters as time-consuming.[30-32] This can be addressed by offering multiple consultations, longer appointments, and increased funding for such consultations. Previous research suggests improving incentives for GPs to engage in longer consultations in challenging and complex cases.[33,34] However, the use of interpreters may not always be effective, as some may give unclear information due to limited cultural understanding.[35] Patients have also raised concerns about confidentiality with the use of external interpreters.[35,36] Another alternative is to involve a younger relative as a translator, although some patients find this uncomfortable when sharing sensitive information.[37] In addressing this issue, multiple digital language translation apps have been developed and tested but have demonstrated inconsistent translation accuracy due to complex factors such as variations in dialects and vocal tones in speech-to-speech translation.[38]

7.1.2.3. 'Postponing participation', 'no time' and 'having other priorities' as main reasons for screening non-participation

In the CCD survey conducted among individuals with irregular screening participation, detailed in **Chapter 4**[19], 'postponing participation', 'no time' and 'having other priorities' were identified as the primary reasons for non-participation in CRC screening in Flanders. Based on these findings, adjustments have been made to the information leaflet, user instructions and CRC screening campaign.[9,21,39] Specifically, the instruction 'put the kit near the toilet' has been added to the screening materials.[21,39] In the 'BLABLABLA campaign' launched during the CRC awareness month in March 2021, 'no excuses' was featured as the main theme.[9] The campaign utilized various media channels such as posters on buses, newspapers, TV, radio, Facebook and YouTube. However, despite all these efforts from the CCD, the annual participation rate has not changed much over the years, implying a limited impact of these interventions. It is possible that the reasons for non-participation in CRC screening given by survey respondents were influenced by socially desirable responding.[19,40]

To address the challenges of 'postponing screening', time constraints, and competing priorities leading to non-participation, measures regarding reminders have also been implemented by the screening programme. In 2022, the programme piloted sending a second reminder letter via email (as a cost-saving measure) 10 weeks after the first reminder letter. This digital reminder letter was sent to individuals with a valid email address in the programme's system, including those who have previously participated in at least one of the three cancer screening programmes (colorectal, breast and cervical cancer) and have consented the use of their email addresses for programme evaluation and research purposes. If the email was not opened, the reminder letter was then sent to the person by post. Findings from this pilot study (not yet published) showed a significant 11.3% increase in response rate for the group receiving the second reminder letter compared to the group not receiving it (32.2% vs. 20.9%). Currently, the impact of sending a third reminder letter via email to those who did not participate after the second reminder is being assessed in 2023. To optimize cost efficiency, no subsequent reminder letter by post will be sent if this reminder email is not opened. Furthermore, the programme is also planning to explore the effects of sending a text message reminder on screening participation.[19]

7.1.2.4. Misperceptions regarding the necessity of screening in asymptomatic individuals

In the same survey study (**Chapter 4**),[19] 'feeling good', 'not having symptoms' and 'no CRC in the family' also emerged as another prominent set of reasons for non-participation in CRC screening in Flanders. The perception of being in a good health seems to be associated with a decreased sense of screening's relevance,[41-44] originating from a lack of knowledge and the misconception that CRC screening is only necessary when symptoms are present.[45-47]

Feeling healthy and absence of symptoms as significant barriers to CRC screening participation have been consistently reported in previous studies, including the pilot study preceding the implementation of the Flemish CRC screening programme.[24] Right from its start, the screening materials have always emphasized that the intrinsic objective of screening is to target individuals without complaints, highlighting the importance of recognising that most cases of CRC do not exhibit noticeable symptoms at early stages.[19] Despite the programme's extensive efforts to raise awareness and underscore the significance of cancer screening in detecting cancer at an early stage before symptoms manifest, the perception of feeling healthy persists as a barrier to CRC screening.

Addressing these misconceptions is crucial, and healthcare providers, especially GPs, play a significant role in clarifying these misconceptions among their patients.[48] Public education programmes that incorporate peer testimonials are also instrumental in raising awareness, correcting misperceptions regarding the relevance of screening in asymptomatic individuals and fostering open discussions on CRC.[18,46,49] In this regard, the CCD has issued a short article containing peer testimonials and additional explanations to address the most common misconceptions about CRC screening.[50] For example, it clarifies the need to participate in screening even when experiencing no symptoms, or the necessity of undertaking the test every two years despite a previous negative test result. This article is made accessible on the website of the Flemish CRC screening programme,[50] and disseminated to different organisations, such as the loco-regional health consultation and organisation Logo's (Locoregionaal gezondheidsoverleg en -organisatie), local authorities, and health insurance organisations, for distribution through various channels. Furthermore, the notification letter sent to individuals who did not participate in the last three screening rounds also highlights the fact that CRC is typically asymptomatic in early stages and underscores the importance of screening.

7.1.2.5. The facilitating role of GPs in enhancing patient participation and adherence to CRC screening

Our investigation into factors influencing CRC screening coverage, both within and outside the screening programme in Flanders (**Chapter 3**), identified the crucial role of GPs in promoting CRC screening: higher rates of GP visits in the previous year were associated with increased coverage for both screening approaches; a higher number of patients per GP and a higher proportion of people with a global medical dossier managed by a preferred GP were linked to higher non-organised screening coverage.[17] As mentioned in **Subsection 7.1.2.1**, despite the availability of the screening programme, some GPs still prescribed outside FOBTs to their patients, potentially to confirm the initial positive FIT result within the programme and persuade them to undergo a colonoscopy. Additionally, in cases of expired or lost tests, some GPs prescribed an outside FOBT instead of referring patients to the screening programme. In the CCD 2019 survey targeting irregular participants,[19] some respondents cited a negative FIT result by their GP as a reason for not participating in the screening programme. At the same time, a large proportion of the survey respondents acknowledged the significant influence of GPs on their decision to participate in CRC screening: 65% indicated that GPs should spontaneously mention the FIT screening invitation, and over 40% would have participated earlier in the current or previous screening round(s) if advised by their GP. Existing literature consistently emphasizes the role of GP recommendation as a facilitator for CRC screening participation.[47,51-57]

Our review on population's preference regarding CRC screening (**Chapter 5**) further highlights the vital role played by GPs in promoting screening participation and ensuring adherence among their patients.[18] The general population demonstrates a preference for receiving tailored and interactive CRC screening information in a supportive and open setting that allows them to express their needs and concerns. GPs are widely recognised as reliable and trustworthy sources of information and guidance, assisting individuals in making informed decisions about CRC screening.[18]

Therefore, it is essential to strengthen the involvement of GPs in promoting participation and ensuring adherence to CRC screening. GPs may need to adopt a proactive approach by integrating discussions on CRC screening into consultations that may have a different primary focus, considering that some patients are even unaware of the information they can receive

from their GPs regarding CRC screening. While a large proportion of respondents in the CCD survey study (**Chapter 4**)[19] agreed with the provided statements concerning the role of GPs in informing and promoting CRC screening, they did not spontaneously mention this aspect in their open-ended responses. The misconception that the absence of symptoms justifies non-participation could also be effectively addressed by GPs, as discussed in **Subsection 7.1.2.4**.

The CCD highly acknowledges the significant role of GPs in addressing the barriers to screening among non-participants who have not been successfully reached by the screening programme despite extensive efforts. Starting from 2023, the CCD plans to provide GPs with an annual list of non-participants among their patients who have not responded to the last two invitations. This enables GPs to proactively engage with these patients, offering CRC screening information, addressing potential barriers, and encouraging participation.[9] Additionally, the CCD is launching a pilot project to evaluate the impact of a one-minute motivational talk delivered by GPs on screening uptake among non-participants in their patients.[19] Since 2022, GPs have also been receiving an annual report from the CCD, containing data on rates of appropriate follow-ups after a positive FIT result (**Figure 2**). This report provides details about each GP's performance in the most recent 3 years for which the data is available, compared to that of all GPs in the same primary care zone (eerstelijnszone), in the same province, and in the entire Flemish region. The report also includes information on patients with inappropriate follow-ups, allowing GPs to improve their performance and enhance their patients' adherence to screening (see **Figure 1**, **Subsection 7.1.2.1**). It further emphasizes that using an outside FOBT is not an appropriate follow-up after a positive FIT result; instead, patients with a positive FIT result should be referred for a colonoscopy.

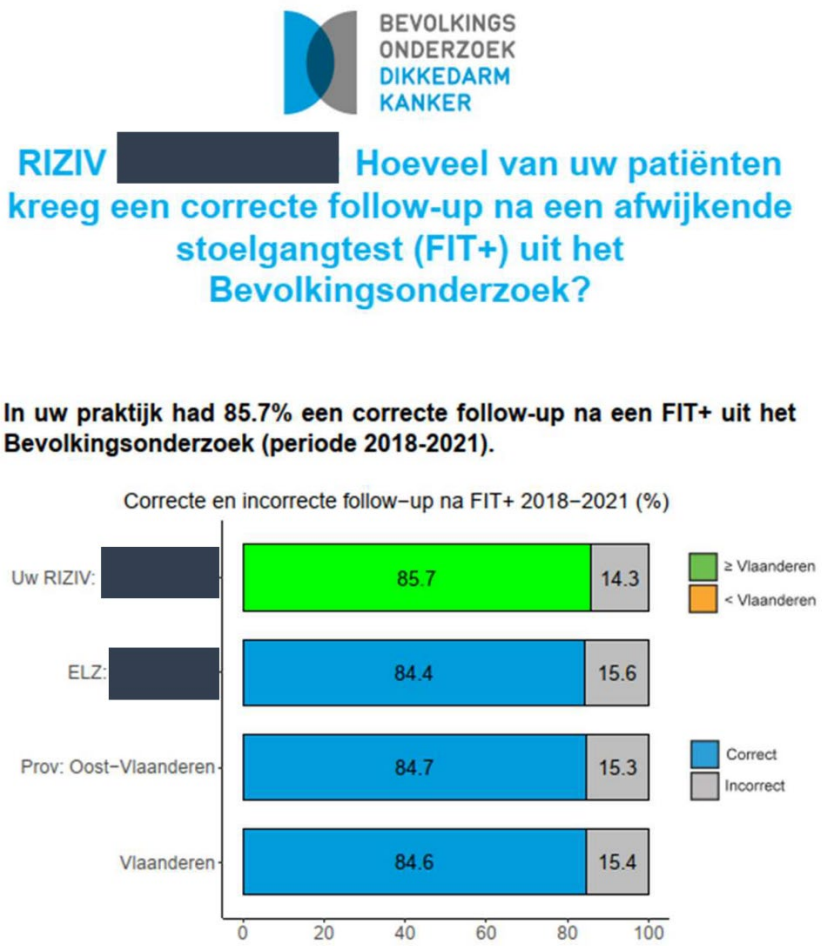


Figure 2. A screenshot of the first page of the Centre for Cancer Detection's annual report to GPs about rates of appropriate follow-ups after a positive FIT result.

However, language barriers between patients with limited Dutch proficiency and their GP pose a persistent challenge, as discussed in **Subsection 7.1.2.2**. Individuals with migrant background often hesitate to contact GPs unless they have urgent or chronic medical needs.[24,46]

At the same time, the limited awareness among certain GPs regarding the option to request another free test from the screening programme in cases of lost or expired tests, as well as the prescription of outside FOBTs to patients with a positive FIT result within the screening programme, highlights the need for improved knowledge among GPs regarding specific elements of the screening programme. It is thus crucial to consistently furnish GPs with up-to-date and accurate information about the screening programme, enabling them to effectively

guide their patients in making well-informed decisions about CRC screening.[17,18,18]

7.1.3. Optimizing FIT cut-off and screening interval to enhance CRC screening effectiveness in Flanders

Interval cancer is a crucial indicator in monitoring and evaluating cancer screening programmes. In the previous **Section 7.1.2** and its subsections, we emphasized the significance of increasing screening uptake to maximize the cost-effectiveness of the screening programme. However, it is important to recognise that as screening participation increases, the occurrence of FIT-IC also increases. While lowering FIT cut-off or shortening screening interval can reduce the occurrence of FIT-IC to some extent, it also results in increased false positive rates and substantial cost escalation. Therefore, the screening programmes need to carefully assess the benefits and drawbacks of implementing such measures.

7.1.3.1. The selection of the FIT cut-off and screening interval in Flanders is considered optimal in terms of FIT interval cancer

In our study outlined in **Chapter 6**,[58] we evaluated the optimization of the FIT cut-off and screening interval selection in Flanders with regard to FIT interval cancer (FIT-IC). Our findings indicate that lowering the FIT cut-off from 15 to 10 µg Hb/g would only have a minimal impact on reducing FIT-ICs because over 83% of FIT-ICs exhibited a low FIT result of ≤ 10 µg Hb/g in both the first and second year of the two-year screening interval, across genders, age groups, tumour locations, and stages.[58] These results align with previous studies reporting approximately 75% of FIT-ICs with low haemoglobin levels (<10 µg Hb/g) and 19–44% with undetectable levels (0 µg Hb/g),[59-61] suggesting that the majority of FIT-ICs would still be missed despite a drastic reduction in the FIT cut-off. Although the FIT used in the Flemish CRC screening programme detects up to 3 µg Hb/g faeces theoretically, the quantitative results between 3–10 µg Hb/g were deemed (quantitatively) unreliable due to significant deviations. Consequently, lowering the FIT cut-off to below 10 µg Hb/g would not be a practically suitable option given the limitations of the test.

Based on our results, we recommend that 15 µg Hb/g should be the minimum FIT cut-off (OC Sensor) that a CRC screening programme should aim for, regardless of the patient's gender and age. This recommendation is supported by a recent study by Vanaclocha-Espi *et al* (2021) which identified an optimal FIT cut-off of approximately 15 µg Hb/g for women aged 60–69, who

exhibited the lowest FIT sensitivity among the evaluated groups (women and men, aged 50–59 and 60–69).[62] Since FIT is more sensitive in men,[2,58] a minimum FIT cut-off of 15 µg Hb/g is also applicable for men. Furthermore, our findings support a screening interval of 2 years as the optimal interval for CRC screening in Flanders when using a FIT cut-off of 15 µg Hb/g.

While reducing the FIT cut-off and shortening screening interval only have a minimal impact on reducing FIT-ICs, implementing such measures can have significant consequences, including increased colonoscopy demands, colonoscopy-related complications and associated costs. Several studies have highlighted a substantial increase in colonoscopy demand relative to a marginal sensitivity gain when the FIT cut-off is lowered.[61,63,64] The higher number of colonoscopies performed (due to the increased referral rates resulting from the lower FIT cut-off) would detect more advanced adenomas and CRCs but also lead to a significant rise in false positive results. The increase in false positives is expected to be much greater than the increase in true positives, which would lead to a significant decline in the positive predictive value of the test. Additionally, the rise in the number of colonoscopies performed would also be associated with an increased incidence of colonoscopy-related complications.

Shortening the screening interval would accelerate the detection of incident CRCs but would also result in significant additional costs. When the screening interval is reduced from two to one year, the number of prevalent cases detected among individuals entering the screening programme for the first time remains relatively the same (due to the same population and target screening ages). The main difference is that in the one-year programme, the screening population undergoes repeated screening the following year, whereas in the two-year programme, they wait for two years between screenings. As a result, a portion of incident CRCs detected in the second year of the two-year programme would be diagnosed one year earlier in the one-year programme. However, this advantage comes at the expense of requiring the entire screening population to undergo FIT screening annually rather than biennially (Flanders: ~870,000 individuals in 2020),[9] doubling the entire process of screening invitation, FIT provision, result analysis and subsequent follow-up with colonoscopy after a positive FIT.

Although FIT-IC is considered an ‘adverse event’ in FIT-based CRC screening, its impact on individual prognosis appears to be limited. A false negative FIT result may result in false reassurance and discourage individuals with CRC-related symptoms from seeking medical assistance, potentially leading to cancer detection at a later stage compared to no screening.

However, previous research has shown a similar stage distribution (40% early stages I & II) between CRCs detected by symptoms and interval cancers following negative FIT results.[65,66] Similarly, our study on the impact of FIT screening found no significant differences in stage distribution and 5-year relative survival between FIT-ICs and CRCs diagnosed without screening.[4] While this is reassuring, individuals with symptoms after a negative FIT result are strongly advised to promptly seek medical help.

7.1.3.2. Continuous monitoring and regular evaluations of FIT performance are important

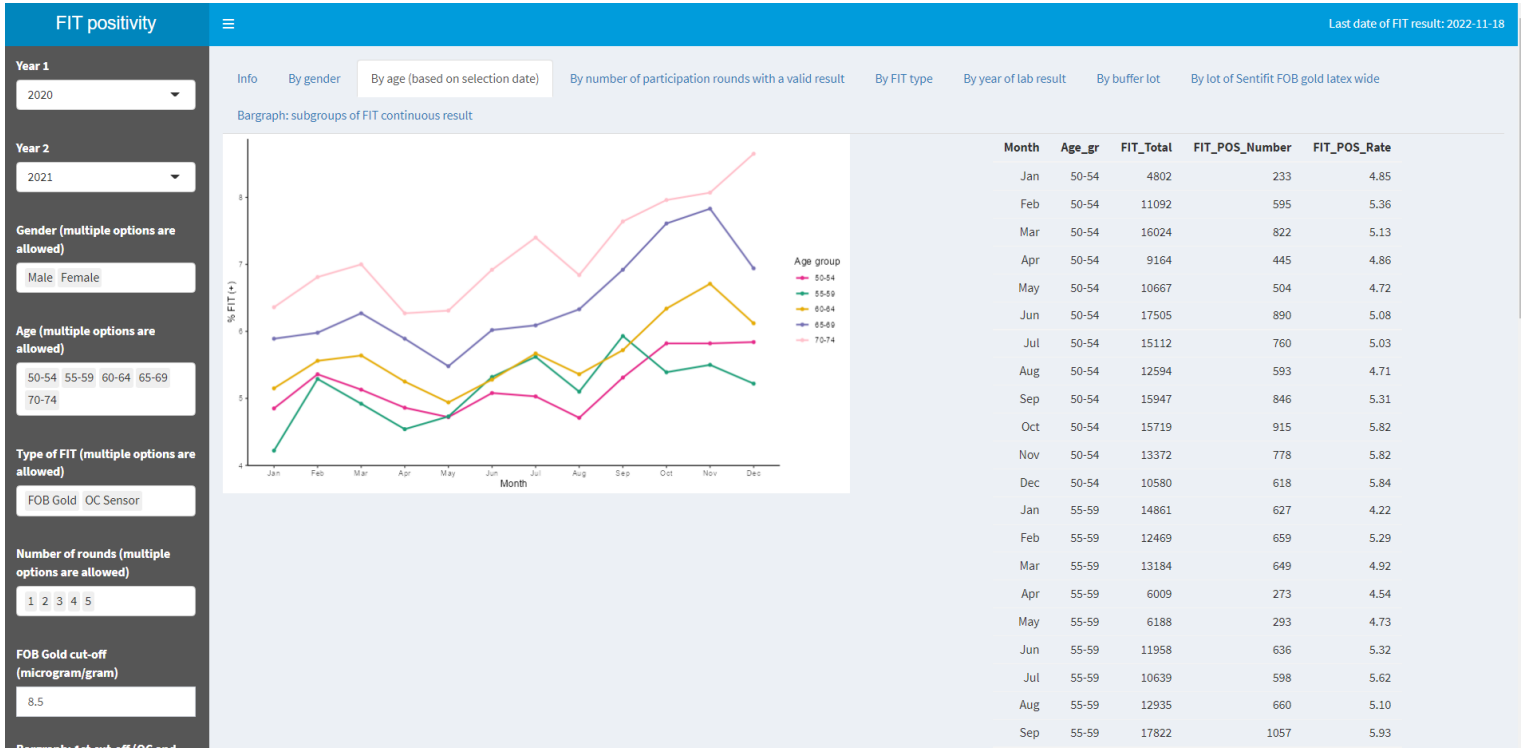
Based on the arguments presented in the previous **Subsection 7.1.3.1**, the Flemish CRC screening programme has decided to maintain the screening interval and the cut-off of the FIT used at the time of our study. Simultaneously, the programme has diligently monitored the FIT positivity rates, especially since the introduction of the new FIT test FOB Gold (Sentinel, Italy) in February 2021, replacing the previous OC Sensor (Eiken, Japan). Although the cut-off of the new FOB Gold test (8.5 µg Hb/g) was selected to yield a similar positivity rate (around 5.9%[9]) as that of the previous OC Sensor, differences in performance and subsequent impact between the two tests may exist. Hence, continuous monitoring and regular evaluations of FIT performance are essential.

The Flemish CRC screening programme has closely monitored the performance of FOB Gold in comparison to OC Sensor, reporting all key test indicators (adenoma and cancer detection rate, interval cancer, positive predictive value, sensitivity, specificity, and lab error rates) in the programmes' annual monitoring report. In recent years, monitoring and evaluations of FIT performance have been conducted on a more frequent basis (monthly) within smaller groups to promptly identify and address any atypical patterns. To facilitate effective monitoring, a user-friendly interactive dashboard was developed in 2022,[67] enabling users to track monthly FIT positivity rates over the years and make comparisons based on the following variables and their combinations:

- Year
- Gender
- 5-year age group
- Type of FIT (OC Sensor vs FOB Gold)
- Number of screening rounds
- FIT quantitative cut-off

- Buffer lot
- Reagent lot

This interactive dashboard also enables users to adjust the FIT cut-off and observe corresponding changes in FIT positivity rates. **Figure 3** below provides a screenshot of the FIT positivity dashboard, displaying the monthly FIT positivity rates by age group among the target CRC screening population in Flanders during the period of 2020-2021.



Month	Age_gr	FIT_Total	FIT_POS_Number	FIT_POS_Rate
Jan	50-54	4802	233	4.85
Feb	50-54	11092	595	5.36
Mar	50-54	16024	822	5.13
Apr	50-54	9164	445	4.86
May	50-54	10667	504	4.72
Jun	50-54	17505	890	5.08
Jul	50-54	15112	760	5.03
Aug	50-54	12594	593	4.71
Sep	50-54	15947	846	5.31
Oct	50-54	15719	915	5.82
Nov	50-54	13372	778	5.82
Dec	50-54	10580	618	5.84
Jan	55-59	14861	627	4.22
Feb	55-59	12469	659	5.29
Mar	55-59	13184	649	4.92
Apr	55-59	6009	273	4.54
May	55-59	6188	293	4.73
Jun	55-59	11958	636	5.32
Jul	55-59	10639	598	5.62
Aug	55-59	12935	660	5.10
Sep	55-59	17822	1057	5.93

Figure 3. A screenshot of the FIT positivity dashboard used in the Flemish CRC screening programme to monitor monthly FIT positivity rate.

7.2. Methodological considerations and limitations

This section will cover the discussions on the key methodological considerations and limitations encountered in the included studies.

7.2.1. Assessing the impact of FIT screening on both CRC survival and mortality: a combined approach

In our study assessing the impact of FIT screening (**Chapter 2**),[4] we adopted a combined approach to evaluate the impact of screening on both CRC-related relative survival and mortality. This comprehensive approach was designed to mitigate the influence of lead time bias, a well-known bias in previous cancer screening studies, on our interpretations of screening effects.[68] Lead time bias occurs when screening detects a disease at an earlier time point than it would have been diagnosed based on symptoms, resulting in prolonged survival time from diagnosis without affecting mortality.[69] Therefore, relying solely on survival analysis is insufficient to draw conclusions about the impact of cancer screening on patient prognosis. Our findings demonstrated improved survival in screen-detected CRC cases compared to unscreened individuals, along with a decline in CRC-related mortality in men, starting two years after the initiation of the screening programme.

Another common bias encountered in survival-based studies investigating the impact of cancer screening is length bias. This bias arises when screening detects predominantly slow-progressing cancers, leading to an overestimation of survival time for screen-detected CRCs.[69] However, our findings did not support this theory which suggests that as FIT interval cancers escape FIT screening, they would exhibit worse survival than CRCs in unscreened individuals. Instead, our study, along with previous research, showed comparable or even superior survival for FIT-ICs compared to CRCs diagnosed without screening.[70-72] However, it is important to acknowledge the potential influence of healthy user bias, wherein screening participants tend to be healthier than non-participants.[73] Unfortunately, we were unable to account for this bias in our study. Future investigations should consider incorporating subjects' lifestyles and health-seeking behaviours to validate our findings and those of previous studies which suggest comparable or better survival for FIT-ICs compared to CRCs diagnosed without screening.[70-73] Length bias can also be addressed in randomized controlled trials which ensure comparability between the groups being compared concerning the rates of slow- and fast-progressing

tumours.

7.2.2. Tackling non-response bias in survey research using post-stratification weights

Non-response bias is a common issue in survey research, where individuals with specific characteristics exhibit over- or under-response tendencies. In our survey study focusing on irregular participants (**Chapter 4**),[19] we addressed this bias by employing post-stratification weights in all analyses.[74] These weights were constructed based on gender, age group, and the first two digits of the postcode, as these variables exhibited significant disparities between survey respondents and non-respondents. By incorporating these weights, we aimed to attain a respondent sample that closely resembled the total survey population in terms of gender, age group and postcode, thereby enhancing the representativeness of our results for the survey population.[75]

However, our study was susceptible to sampling bias as the online survey was restricted to individuals with a valid email address registered in the CCD's system. These individuals were ever-participants in one of the three cancer screening programmes (colorectal, breast and cervical cancer) in Flanders who had given consent for their email addresses to be used for evaluation and research purposes. Previous explorations conducted by the Flemish CRC screening programme revealed that individuals with an email address in the programme's system are more likely to be male, younger, possess higher socioeconomic status and educational level, and speak the local language.[19] As a result, our findings may not be fully representative of the entire eligible population.

Nonetheless, our study primarily focused on improving adherence to CRC screening among inconsistent participants who had already engaged in screening at least once, with the majority of them having registered their email addresses in the CCD's system. Furthermore, despite the sampling bias, our study with a large sample size could capture responses from 764 individuals in the oldest age category (70-75 years), 250 individuals facing significant financial challenges, 134 individuals with the lowest educational level (no degree or primary degree only), and 49 individuals speaking languages other than Dutch.[19] To mitigate the impact of sampling bias, future research could consider alternative channels (e.g., social media, community gatherings) to engage individuals who have not participated in any of the three cancer screening programmes and thus lack an email address in the CCD's system.

7.2.3. Ecological fallacy: limitation of area-level analysis

In our study investigating factors associated with FOBT screening coverage inside and outside the screening programme (**Chapter 3**),[17] we relied on municipality-level data, which introduced the potential issue of ecological fallacy, whereby associations observed at the area level may not necessarily hold true at the individual level.[76] However, the significant influence of the surrounding environment on individuals' health behaviours and decisions has been established.[77] Moreover, most of the associations identified in our study align with prior individual-level research conducted in Flanders.[25]

In this study, to explore the relationships between specific characteristics and CRC screening behaviours, we linked screening data from the Flemish CRC screening programme with data from a publicly available resource 'Provincies In Cijfers' at the municipality level.[78] Acquiring individual-level data is often time-consuming and resource-intensive, while readily available area-level data in the 'Provincies In Cijfers' databank offer valuable insights into demographic, socioeconomic, and health-related factors, many at statistical sector level, which closely approximates individual-level data. Our study represents the first investigation in Flanders examining the associations between health-related variables (such as GP visits, number of patients per GP, proportion of patients with a global medical dossier managed by a preferred GP) and FOBT screening coverage inside and outside the CRC screening programme. Our findings provide a basis for future research conducted at the individual level to validate and further investigate the observed associations. For instance, our results suggest that despite the availability of the organised screening programme, some GPs still prescribe FOBTs outside the programme, possibly due to reasons such as lost/expired tests or the need for an additional stool test to confirm the initial positive FIT result within the programme. Future studies can delve into the reasons behind the use of outside FOBTs, and examine specific hypotheses, including whether individuals with higher income prefer more expensive outside tests over the free mass screening test for perceived higher test quality.[79]

7.2.4. The use of register-based data offered high quality information at a large scale while effectively minimizing selection and recall bias

In this PhD research, aside from the review and survey studies (**Chapters 4 & 5**),[18,19] the remaining three studies (**Chapters 2, 3 & 6**) utilized administrative data, which involved linking

CRC screening data from the CCD with various datasets, including demographic, socioeconomic and health-related data from the 'Provincies In Cijfers' databank,[17] cancer diagnosis and tumour characteristics from the Belgian Cancer Registry, reimbursement data related to cancer screening from the Intermutualistic Agency (IMA-AIM),[58] vital status data from the Belgian Cross-roads Bank for Social Security (CBSS) and cause of death data from death certificates collected by the regional authority ('Agentschap Zorg en Gezondheid' for Flanders).[4] By employing administrative data, selection and recall bias inherent in self-reported data was avoided. Additionally, the use of registered-based data covering the entire CRC screening population in Flanders facilitated high-quality data at a large scale, ensuring sufficient sample size for our studies.

7.2.5. The issue of incomplete data in the studies concerning FIT interval cancers and coverage by FOBT outside the screening programme

In our study regarding FIT-ICs (**Chapter 6**),[58] data on FIT participation and cancer diagnoses were collected for the same timeframe. However, due to the requirement of a two-year follow-up period to capture all screen-detected and FIT-ICs diagnosed during the two-year screening interval, the data on screen-detected cancers and FIT-ICs following FIT participation in the last two years were incomplete. This could result in an underestimation of both screen-detected CRCs and FIT-ICs, with a potentially larger impact on FIT-ICs. Additionally, our study could only include screening and cancer data until 2018, limiting the dataset to a maximum of three screening rounds per person. Despite the incompleteness of cancer data for the last two years, we anticipated that it would have a limited impact on our main findings regarding factors associated with FIT-IC occurrence compared to screen-detected cancer, as well as the distribution of FIT quantitative results across diagnosis year (first or second year of the two-year interval), gender, age, tumour stage and location. To address this issue of incomplete data, future research with a longer follow-up should be conducted, including complete data on cancer cases up to the most recent year available and incorporating FIT screening data from two years prior to the year of cancer diagnosis to ensure a complete two-year follow-up period.

In our study investigating factors related to coverage by FOBT taken outside the screening programme (**Chapter 3**),[17] the availability of data on GP-prescribed FOBTs outside the screening programme in Flanders was a notable strength. However, this data did not capture all outside FOBTs, as a portion of them could be obtained from pharmacies, online sources, or ordered by

companies for their employees, for which data was unavailable due to possible lack of registration with nomenclature codes. Furthermore, the recorded information for GP-prescribed FOBTs only indicated test registration without specifying whether the test was used for screening or diagnostic purposes following a positive test within the screening programme. It is possible that some outside FOBTs were appropriately prescribed for specific indications beyond the scope of the organised screening programme. In cases where outside tests were taken as diagnostic tests after an initial FIT within the screening programme, they did not impact coverage by organised screening since individuals had already participated in the programme prior to the outside test.

7.3. Future perspectives

7.3.1. Insufficient evidence for expanding the Flemish CRC screening programme at present

While the European guidelines have maintained the recommended starting age of 50 years for CRC screening for over a decade,[16] the American Cancer Society recently revised their recommendations and lowered the starting age to 45 years.[80] In April 2023, the Austrian National Committee for Cancer Screening issued a recommendation to implement a nationwide organised CRC screening programme in Austria, targeting all adults aged 45-75 years.[81] The rationale behind lowering the starting age for CRC screening is based on the observed increase in CRC incidence among individuals under 50 years old.[82-84] However, the current evidence in Flanders does not support expanding the CRC screening programme by reducing the starting screening age, lowering the FIT cut-off, or shortening the screening interval. Over a 19-year period (2001-2019), CRC incidence in Flanders did not show a clear increase among the 45-49 age group, and the incidence in this age group was significantly lower than the incidence in the age groups that belong to the target group of the Flemish population-based CRC screening programme.[85,8682] Therefore, reducing the target age for CRC screening in Flanders does not appear justifiable.[85]

Additionally, our study in **Chapter 6** demonstrated that the selection of FIT cut-off and screening interval in Flanders is considered optimal for detecting FIT interval cancers so far. In fact, while reducing the FIT cut-off and shortening the screening interval may have a minimal

impact on reducing FIT-ICs, implementing such measures can result in significant implications, including increased demand for colonoscopies, associated complications and additional costs. Hence, no adjustments to the FIT cut-off or screening interval are currently deemed necessary in Flanders.

The focus of the Flemish CRC screening programme at present should be on optimizing its existing strategy rather than expanding the programme. Potential areas for improvement include the introduction of pre-invitations and additional reminders, increased involvement of GPs and other stakeholders, incorporation of risk stratification, and adoption of alternative screening tools.

7.3.2. Improving screening response rate with additional reminders and pre-invitations

In the CCD survey study (**Chapter 4**),[19] 'postponing participation', 'no time' and 'having other priorities' were identified as primary reasons for non-participation in specific screening rounds among irregular participants. To address this issue, the Flemish CRC screening programme has implemented various measures. For example, the information leaflet now includes an instruction 'put the kit near the toilet', and since 2021, the programme's campaigns during CRC Awareness Month (March) have centred around the theme of 'no excuse'. However, these initiatives have shown limited impact on improving screening uptake. Consequently, the programme is now adopting more proactive approaches, such as implementing additional reminder letters and and potentially introducing a pre-invitation.

In 2022, the programme initiated a pilot project to assess the effect of a second reminder letter, sent via email 10 weeks after the first standard reminder letter, on response rate. This digital reminder targeted individuals with a valid email address in the CCD's system, including previous participants in the Flemish colorectal, breast or cervical cancer screening programme who had given consent for their email addresses to be used for evaluation and research purposes. If the email remained unopened, the reminder letter was subsequently sent by post. Preliminary unpublished results from this pilot study demonstrated an 11.3% increase in the response rate among recipients of the second reminder letter compared to those who received the standard reminder letter only. Based on the findings, the programme plans to expand the implementation of the second reminder letter. Additionally, given the cost-effectiveness of this

measure, another pilot study is scheduled for 2023 to evaluate the impact of a third reminder letter, also sent via email, to non-participants after the second reminder letter. The programme also intends to explore the impact of sending text message reminders on participation rate.[19]

The use of a pre-invitation, which is an advance notification letter providing information on CRC and the benefits of screening, and informing about the upcoming invitation, has proven effective in increasing participation rates (3-4%).[87] This approach generates early awareness, which is reinforced by subsequent screening materials, and is particularly valuable in populations with low awareness of CRC and screening benefits. Furthermore, this measure enhances cost efficiency by allowing individuals who do not intend to participate in a specific round to opt out in advance, thereby saving resources by preventing the unnecessary mailing of invitation materials.[87] These cases are then excluded from the total number of invitations sent (denominator in response rate calculation), leading to an overall increase in response rate.

The option to opt out of a specific screening round or permanently has been available in the Flemish CRC screening programme since its establishment, as communicated through the screening invitation, leaflet and the programme website. However, these materials are typically more familiar to individuals who have previously participated rather than first-time invitees. Currently, Flanders has not implemented a pre-invitation system yet, resulting in individuals being able to opt out only after receiving the invitation package, leading to unnecessary invitations being sent in these cases. Additionally, the existing opt-out system in Flanders has shown limited effectiveness so far, with few non-participants contacting the CCD to inform of their intent not to participate. Therefore, the CCD does not expect the pre-invitation to drastically alter the situation, but it remains an option worthy of consideration.

The CCD is currently assessing the cost implications of introducing the pre-invitation. One potential cost-saving measure is to send the pre-invitation electronically via email, thereby reducing printing and mailing costs. However, the recurring challenge is that the programme's database only contains email addresses of individuals who have ever participated in the Flemish colorectal, breast or cervical cancer screening programme. Given that breast and cervical cancer screening are only limited to women and breast cancer screening shares the same starting age as colorectal cancer screening, a considerable number of first-time invitees to CRC screening will not yet have an email address registered in the programme's system. Nonetheless, the programme considers the approach of sending an electronic pre-invitation as

an extra low-cost measure to improve participation rates and thus does not aim to cover the entire target population, but rather targets the first-time invitees and irregular participants that already have a valid email address available in the CCD's system.

7.3.3. Enhancing engagement of GPs, local authorities and health insurance organisations to reach underserved populations

A crucial aspect of population screening is respecting the autonomy of individuals to decide whether or not to participate in screening. However, the decision-making process is heavily influenced by the available information about the screening programme, with various stakeholders playing a role in disseminating this information. While it is acceptable for individuals to make an informed choice not to participate, it is unfortunate when decisions are based on insufficient or deficient information. Therefore, it is important to ensure that the key information about screening reaches the entire population.

As discussed in **Subsection 7.1.2.5**, GPs are widely recognised as trustworthy sources of information for their patients. In recent years, the CCD has actively engaged GPs in promoting CRC screening. Starting in 2023, the programme will provide GPs with an annual list of non-participants among their patients who have not responded to the last two invitations. This enables GPs to proactively engage with these patients, providing CRC screening information, addressing barriers, and encouraging participation.[9] Additionally, the CCD is initiating a pilot project to assess the impact on screening uptake of a one-minute motivational talk delivered by GPs to non-participants among their patients.[19] Since 2022, GPs have also received an annual report from the programme containing data on the rates of appropriate follow-ups after a positive FIT result. This report includes details of patients who did not have an appropriate follow-up, allowing GPs to improve their performance and enhance adherence to screening in their patients (see **Figure 1**, **Subsection 7.1.2.1** & **Figure 2**, **Subsection 7.1.2.5**).

CRC screening uptake remains consistently low among individuals with low socioeconomic status (SES), including those with a low education level or a migrant background.[24,25,88,89] In Flanders, the loco-regional health consultation and organisation Logo's (Locoregionaal gezondheidsoverleg en -organisatie) and Health insurance organisations have implemented targeted community projects to improve CRC participation in communities with low participation rates, often characterised by a substantial proportion of individuals with low SES.

When a community project is planned in a municipality, screening invitations in that community are strategically postponed and rescheduled to align with the project's timeline. The first pilot of such community project was launched in the Tienen municipality in 2022 where community health workers engaged with individuals at the local market, providing information about population-based CRC screening in Flanders and distributing toilet rolls wrapped with the CRC screening information leaflet. The project's activities were also made public though local newspapers. Preliminary unpublished results indicate positive effects of these community projects on increasing CRC screening uptake among non-participants. The CCD will publish detailed results, along with recommendations for necessary adjustments to enhance the effectiveness of these community projects once the evaluation is completed.

Health insurance companies are also regarded as reliable sources of information in Belgium. With an extensive coverage of the Belgian compulsory health insurance (over 99% of the country's inhabitants),[90] health insurance organisations present a promising channel for reaching the lesser-reached groups that the programme has not been able to engage. Currently, the CCD is investigating the potential effect on screening participation rates of health insurance organisations informing individuals about CRC screening just prior to sending out invitations.

7.3.4. Integration of risk stratification in population-based CRC screening

The incorporation of risk stratification in CRC screening has been extensively discussed as a means to optimize the effectiveness of screening. Risk stratification methods consider patient characteristics such as age, gender, lifestyle and genetic variants, as well as screening history, including previous FIT results. By tailoring screening invitations based on individual risk levels, population-based screening can allocate its advantages and disadvantages more equitably. This approach allows a greater focus on individuals at higher risk for CRC and minimise the burden on those at lower risk. For instance, individuals at high risk for CRC can benefit from shorter screening intervals, while those at low risk can benefit from extended screening intervals.

Recent research has highlighted the potential of CRC risk stratification based on previous FIT results. Individuals with Hb concentrations below but near the established cut-off value have shown an increased risk of detecting advanced adenomas and CRC in the subsequent round compared to those with very low baseline concentrations.[91-101] For instance, an investigation of

the Scottish bowel screening programme (using a FIT cut-off of 80 µg Hb/g faeces) found that compared to Hb concentrations of 0.0-19.9 µg Hb/g faeces, the odds of detecting advanced adenomas or CRCs in the subsequent round were 14.3 times higher for individuals with initial Hb concentrations of 20.0-39.9 µg Hb/g faeces, and 38 times higher for those with concentrations of 60.0-79.9 µg Hb/g faeces.[100] Similarly, in a study conducted in the Netherlands (using a FIT cut-off of 47 µg Hb/g faeces), individuals with Hb concentrations of 15-47 µg Hb/g faeces in the previous round exhibited up to 23 times higher odds of detecting advanced neoplasms in the subsequent round compared to individuals with no detectable Hb concentrations in the previous round.[101]

The biological explanation for these findings is the gradual bleeding of adenomas during their progression to carcinoma, suggesting that even low Hb levels can be indicative of adenoma presence.[95] Hence, individuals with Hb concentrations slightly below the established cut-off in the previous screening round may benefit from more rigorous screening, such as shorter screening intervals. In contrast, individuals with very low Hb concentrations in the previous screening round may require less frequent screening intervals.

Personalised screening using previous FIT results offers notable advantages over factors such as diet, lifestyle or family history. The association between previous FIT results and screening outcomes in the subsequent round demonstrates superior capability in distinguishing individuals at high and low risks for CRC compared to lifestyle or family history.[94,102,103] Another advantage of using previous FIT results lies in the availability of data. While FIT results from the previous rounds are readily available in the screening programme systems, obtaining information on diet, lifestyle, or family history often requires the use of questionnaires or other methods, which could potentially compromise screening participation.

The potential of using previous FIT results for risk stratification is promising. However, in the specific context of Flanders, careful consideration is necessary. The Flemish CRC screening programme has already employed a notably low FIT cut-off of 15 µg Hb/g faeces with the previous FIT OC Sensor and 8.5 µg Hb/g faeces with the current FIT FOB Gold (the switch was made in February 2021). The determination of thresholds for shorter, unchanged or longer screening intervals based on previous FIT results requires thorough investigations and discussions, taking into account the potential increase in CRC and advanced adenoma detection, along with the associated costs. Another important aspect to consider is the

response of the target population to this change in the screening strategy. Over nearly 10 years of implementation, all eligible individuals have undergone screening every two years. Introducing shorter screening intervals for individuals with previous FIT results near the established cut-off may be perceived as advantageous for them. However, those with very low previous FIT results would receive less frequent screenings than what they are used to, which could potentially lead to a reduced sense of protection through population screening.

Several lifestyle factors, including smoking, consumption of processed and red meat, alcohol intake, and obesity, have been linked to an increased risk of CRC.[104-106] Conversely, physical activity, calcium supplements, and consumption of dairy products have shown protective effects against CRC.[105,107,108] However, none of these factors individually exhibits a sufficiently strong association with CRC risk to be used in risk stratification. Even when combined, the risk prediction models based on multiple lifestyle factors still demonstrate limited ability to identify individuals at risk of developing CRC.[102] Additionally, polygenic factors have been recognised as significant contributors to CRC risk. The use of a polygenic test, which calculates a risk score based on specific alleles, allows for the identification of individuals with a higher risk of CRC compared to the average population.[109] Nevertheless, the integration of this approach into population-based CRC screening remains uncommon at present.

The Flemish CRC screening programme currently maintains a cautious stance, awaiting further evidence before implementing risk stratification. More reliable risk prediction models and refined algorithms to determine optimal screening strategies are needed. At the same time, risk stratification may pose new logistical and ethical challenges. For example, as mentioned above, individuals with a low estimated CRC risk based on previous FIT results may exhibit reluctance towards extended screening intervals. Moreover, the impact of personalised strategies on screening adherence is uncertain and can manifest in different ways. Individuals who are aware of their high risk for CRC may feel more inclined to participate, while those with a low estimated risk may choose to opt out due to their perceived low risk and the belief that participation is unnecessary. Thus, more research is needed to evaluate the advantages, disadvantages, feasibility and cost-effectiveness of risk stratification.

7.3.5. New approaches for CRC screening beyond the FIT

The cost-effectiveness of the current FIT poses a challenge for alternative screening tests to

surpass it.[110] When evaluating a new screening test, affordability is a crucial factor for its sustainability in population-level implementation. Additionally, the new test should demonstrate comparable or superior sensitivity and specificity to the FIT.

Offering alternative screening tests is a potential strategy for the Flemish CRC screening programme to improve screening participation among individuals who decline the FIT due to specific reasons, such as cultural taboos associated with stool tests. In Flanders, around 25% of the target population has never responded to any CRC screening invitations. Alternative screening options can be made available to those who decline the FIT. Another application of alternative tests (which are typically more specific but also more costly than the FIT) is for triaging individuals after a positive FIT result in order to reduce unnecessary colonoscopies, minimize associated adverse events, and enhance the positive predictive value of screening. Such intermediate tests may be particularly suitable for participants with relatively low risks of CRC based on their screening history and other relevant risk factors.

Among the emerging test modalities for CRC screening, other stool-based tests such as multitarget FIT, stool DNA test or multi-target stool DNA test, and video endoscopy show promise. However, their cost-effectiveness is still questionable given their high costs and logistical complexities associated with sample handling, which may not outweigh the marginal additional benefits.[110]

A multi-target stool DNA test, incorporating quantitative molecular assays for aberrantly methylated *BMP3* and *NDRG4* promoter regions, mutant *KRAS*, and *β*-actin (a reference gene for human DNA quantity), along with an immunochemical assay for human haemoglobin, has been shown to exhibit higher sensitivity in detecting CRCs and advanced precancerous lesions compared to FIT, with an absolute difference of nearly 20 percentage points. However, this test shows lower specificity for both CRC and advanced precancerous lesions, with absolute difference ranging from 6.6 to 8.3 percentage points.[111] Additionally, the multi-target stool DNA requires more complex sample logistics and is considered less cost-effective compared to FIT.[112]

Another stool-based test, known as the 'multi-target FIT', developed in the Netherlands, shows more promising outcomes. This test combines multiple proteins and exhibits a superior sensitivity for advanced neoplasia compared to the FIT, while maintaining a similar specificity. For example, the combination of haemoglobin, calprotectin, and serpin family F member 2 [serpinF2] yields a cross-validated sensitivity of 43% for advanced neoplasia, surpassing the

FIT's sensitivity of 37.3%. Notably, the cross-validated sensitivity for advanced adenomas increases from 28% to 38% for the multi-target FIT compared to the FIT. Preliminary assessments indicate that the multi-target FIT could be a cost-effective alternative to the FIT and a potential option for population-based CRC screening.[113,114]

The video capsule, a swallowable pill equipped with one or two cameras, provides a non-invasive means of capturing images of the entire intestine. Compared with one camera, two cameras provide a broader field of view and enables images to be captured from different angles.[115] The video capsule can be used both as a primary screening test and a follow-up tool after a positive stool test. One notable advantage of this technique is that it allows for convenient at-home bowel examination. However, considering its cost, it is currently more suitable as a follow-up examination option. By serving as an intermediate test between FIT and colonoscopy, the video capsule can effectively reduce the number of unnecessary colonoscopies and associated complications. It is considered a safe and effective method for detecting CRC and advanced precancerous lesions, with a sensitivity comparable to that of colonoscopy. Nevertheless, one remaining limitation of video capsule is its moderate completion rate, ranging from 57% to 92%, indicating that it fails to capture images of the entire intestine in 8% to 43% of the cases.[116] Furthermore, individuals in whom polyps are found still need to undergo a colonoscopy for polyp removal.

7.4. Main conclusions and recommendations

7.4.1. Main conclusions

- In Flanders, FIT-based CRC screening has significantly reduced CRC incidence, particularly advanced-stage cases, with a greater impact on men. Screen-detected cases exhibit improved survival compared to unscreened individuals. While CRC-related mortality has decreased in men, the effect in women is expected to become evident with longer follow-up.
- The use of FOBT outside the screening programme appears to have limited impact on screening participation within the programme due to low and declining coverage associated with outside FOBTs (below 2.5% in 2021). However, screening with outside FOBTs poses challenges such as cost, lack of systematic result registration and follow-up information, and

inadequate quality control. Encouraging a shift to organised screening is important.

- Language barriers remain a significant challenge for individuals with a migrant background in Flanders, as screening materials are only available in Dutch. Although the Flemish programme is aware of this situation, the issue persists due to strict language legislation imposed by the Belgian government.
- The most common reasons for non-participation in a specific round among irregular participants are 'postponing participation', 'no time' and 'having other priorities'. Another prominent set of reasons for non-participation includes 'feeling good', 'lack of symptoms', and 'no family history of CRC', indicating a lack of knowledge and the misconception that CRC screening is only necessary when symptoms are present.
- GPs play a crucial role in providing information, promoting CRC screening, and ensuring screening adherence, and addressing potential barriers and misconceptions in their patients.
- The selection of FIT cut-off and screening interval in Flanders is considered optimal in terms of FIT interval cancers. Lowering FIT cut-off or shortening screening interval would have minimal impact on the occurrence of FIT interval cancers. Continuous monitoring and evaluation of FIT performance are essential for maintaining effectiveness.

7.4.2. Recommendations

- Our findings support the implementation of FIT organised screening in countries and regions without existing programmes. Maintaining a high response rate is important to ensure programme effectiveness.
- In Flanders, the current evidence does not support expanding the CRC screening programme by reducing the starting age, lowering FIT cut-off, or shortening screening interval. Instead, optimization of the existing strategy should be the focus, with regular monitoring and evaluation for continuous improvement.
- Introducing pre-invitations and additional reminders can be effective in addressing the issue of procrastination in CRC screening participation in Flanders.
- The involvement of GPs, local authorities, and health insurance organisations should be strengthened to reach the underserved populations. It is crucial to provide these stakeholders with sufficient, accurate and up-to-date information about the screening

programme.

- Considerations can be given to incorporating risk stratification in the screening programme, particularly based on previous FIT results, to customise screening invitations. This approach prioritizes individuals at higher risk for CRC while minimizing burden for those at lower risk.
- The Flemish programme can explore the use of promising emerging tests to improve its efficacy. For example, the stool-based 'multi-target FIT', which combines multiple proteins, offers superior sensitivity for advanced neoplasia while maintaining a similar specificity compared to the FIT, and is considered a cost-effective alternative for FIT in population-based CRC screening. The video capsule, with a comparable sensitivity to colonoscopy, can be valuable for triaging individuals after a positive FIT result, reducing unnecessary colonoscopies and associated adverse events.

References

1. Lee, Y.C., Hsu, C.Y., Chen, S.L., Yen, A.M., Chiu, S.Y., Fann, J.C. et al. Effects of screening and universal healthcare on long-term colorectal cancer mortality. Int J Epidemiol. 2019;48:538-548.
2. Zorzi, M., Fedeli, U., Schievano, E., Bovo, E., Guzzinati, S., Baracco, S. et al. Impact on colorectal cancer mortality of screening programmes based on the faecal immunochemical test. Gut. 2015;64:784-790.
3. Belgian Cancer Registry. Addendum annual report Flemish population screenings 2019: Evolution of colorectal cancer incidence in Flanders 2004-2017 [Addendum Jaarfiche Vlaamse bevolkingsonderzoeken 2019: Evolutie incidentie van dikkedarmkanker Vlaanderen 2004-2017]. (Brussels, 2019).
4. Tran, T.N., Hoeck, S., De Schutter, H., Janssens, S., Peeters, M. & Van Hal, G. The Impact of a Six-Year Existing Screening Programme Using the Faecal Immunochemical Test in Flanders (Belgium) on Colorectal Cancer Incidence, Mortality and Survival: A Population-Based Study. Int J Environ Res Public Health. 2023;20:
5. Tepes, B., Mlakar, D.N., Stefanovic, M., Stabuc, B., Grazio, S.F. & Zakotnik, J.M. The impact of 6 years of the National Colorectal Cancer Screening Program on colorectal cancer incidence and 5-year survival. Eur J Cancer Prev. 2021;30:304-310.
6. Parente, F., Vailati, C., Boemo, C., Bonoldi, E., Ardizzoia, A., Ilardo, A. et al. Improved 5-year survival of patients with immunochemical faecal blood test-screen-detected colorectal cancer versus non-screening cancers in northern Italy. Dig Liver Dis. 2015;47:68-72.
7. Idigoras Rubio, I., Arana-Arri, E., Portillo Villares, I., Bilbao Iturribarrria, I., Martínez-Indart, L., Imaz-Ayo, N. et al. Participation in a population-based screening for colorectal cancer using the faecal immunochemical test decreases mortality in 5 years. Eur J Gastroenterol Hepatol. 2019;31:197-204.
8. Centre for Cancer Detection (2022). *Infosheet for GPs (Infosheet voor de huisartsen)*, https://dikkedarmkanker.bevolkingsonderzoek.be/sites/default/files/2023-03/Infosheet%20huisartsen_2023.pdf Accessed 22 June 2022.
9. Centre for Cancer Detection (2022). *Monitoring report of the Flemish Colorectal Cancer Screening Programme 2022*, https://dikkedarmkanker.bevolkingsonderzoek.be/sites/default/files/2022-12/Jaarrapport%202022_0.pdf Accessed 9 July 2022.
10. Giorgi Rossi, P., Vicentini, M., Sacchettini, C., Di Felice, E., Caroli, S., Ferrari, F. et al. Impact of Screening Program on Incidence of Colorectal Cancer: A Cohort Study in Italy. Am J Gastroenterol. 2015;110:1359-1366.
11. Ventura, L., Mantellini, P., Grazzini, G., Castiglione, G., Buzzoni, C., Rubeca, T. et al. The impact of immunochemical faecal occult blood testing on colorectal cancer incidence. Dig Liver Dis. 2014;46:82-86.
12. Keys, M.T., Serra-Burriel, M., Martinez-Lizaga, N., Pellise, M., Balaguer, F., Sanchez, A. et al. Population-based organized screening by faecal immunochemical testing and colorectal cancer mortality: a natural experiment. Int J Epidemiol. 2021;50:143-155.
13. Levin, T.R., Corley, D.A., Jensen, C.D., Schottinger, J.E., Quinn, V.P., Zauber, A.G. et al. Effects of Organized Colorectal Cancer Screening on Cancer Incidence and Mortality in a Large Community-Based Population. Gastroenterology. 2018;155:1383-1391 e1385.
14. Chiu, H.M., Jen, G.H., Wang, Y.W., Fann, J.C., Hsu, C.Y., Jeng, Y.C. et al. Long-term effectiveness of faecal immunochemical test screening for proximal and distal colorectal cancers. Gut. 2021;70:2321-2329.
15. Chiu, H.M., Chen, S.L., Yen, A.M., Chiu, S.Y., Fann, J.C., Lee, Y.C. et al. Effectiveness of fecal immunochemical testing in reducing colorectal cancer mortality from the One Million Taiwanese Screening Program. Cancer. 2015;121:3221-3229.

16. Segnan, N., Patnick, J. & von Karsa, L. (eds). *European guidelines for quality assurance in colorectal cancer screening and diagnosis*. 1st edn, (Publications Office of the European Union: Luxembourg, 2010).

17. Tran, T.N., Van Hal, G., Peeters, M., Jidkova, S., De Schutter, H. & Hoeck, S. Population-Based Data Reveal Factors Associated with Organised and Non-Organised Colorectal Cancer Screening: An Important Step towards Improving Coverage. Int J Environ Res Public Health. 2021;18:

18. Tran, T.N., Ferrari, A., Hoeck, S., Peeters, M. & Van Hal, G. Colorectal Cancer Screening: Have We Addressed Concerns and Needs of the Target Population? Gastrointestinal Disorders. 2021;3:173-203.

19. Hoeck, S. & Tran, T.N. Self-Reported Reasons for Inconsistent Participation in Colorectal Cancer Screening Using FIT in Flanders, Belgium. Gastrointestinal Disorders. 2022;5:1-14.

20. Hoeck, S., Hoste, J., Vandeputte, L. & Dekker, N. Colorectal cancer screening [Dikkedarmkankerscreening]. (2017).

21. Centre for Cancer Detection (2022). *Leaflet colorectal cancer screening*, https://dikkedarmkanker.bevolkingsonderzoek.be/sites/default/files/2022-03/DDK-FO-ALG-50-2020.pdf Accessed 26 June 2022.

22. Centre for Cancer Detection (2023). *Questions about the screening invitation: I lost my inviation package. What now? [Ik ben mijn uitnodigingspakket kwijt. Wat nu?]*, https://dikkedarmkanker.bevolkingsonderzoek.be/nl/ddk/ik-ben-mijn-uitnodigingspakket-kwijt-wat-nu Accessed 22 June 2023.

23. Centre for Cancer Detection (2023). *Population screening statistics [Bevolkingsonderzoek InCijfers]*, https://bevolkingsonderzoek.incijfers.be//jive?cat_open_code=ddk_extern Accessed 22 June 2023.

24. Hoeck, S., Van Roy, K. & Willems, S. Barriers and facilitators to participate in the colorectal cancer screening programme in Flanders (Belgium): a focus group study. Acta Clin Belg. 2022;77:37-44.

25. Hoeck, S., van de Veerdonk, W., De Brabander, I. & Kellen, E. Does the Flemish colorectal cancer screening programme reach equity in FIT uptake? Eur J Public Health. 2019;29:1108-1114.

26. Centre for Cancer Detection (Population-based colorectal cancer screening) *How is colorectal cancer detected [Hoe wordt dikkedarmkanker opgespoord?]*, https://dikkedarmkanker.bevolkingsonderzoek.be/nl/ddk/hoe-wordt-dikkedarmkanker-opgespoord Accessed 07 July.

27. Centre for Cancer Detection (2023). *Population screening: Colorectal cancer*, https://dikkedarmkanker.bevolkingsonderzoek.be/nl Accessed 24 June 2023.

28. Statistics Flanders (Statistiek Vlaanderen) (2023). *Population by nationality [Bevolking naar nationaliteit]*, Accessed 20 July 2023.

29. Google Analytics (2022). *Usage statistics for dikkedarmkanker.bevolkingsonderzoek.be*, https://analytics.google.com/analytics/web/#/report-home/a89745403w133161560p137180668 Accessed 20 July 2022.

30. Chandrakumar, A., Hoon, E., Benson, J. & Stocks, N. Barriers and facilitators to cervical cancer screening for women from culturally and linguistically diverse backgrounds; a qualitative study of GPs. BMJ Open. 2022;12:e062823.

31. Dumky, H., Fridell, K., Leifland, K. & Metsala, E. Breast cancer screening and immigrant women-A scoping review of attendance, knowledge, barriers and facilitators. Nurs Open. 2023; 10.1002/nop2.1865

32. Wang, A.M.Q., Yung, E.M., Nitti, N., Shakya, Y., Alamgir, A.K.M. & Lofters, A.K. Breast and Colorectal Cancer Screening Barriers Among Immigrants and Refugees: A Mixed-Methods Study at Three Community Health Centres in Toronto, Canada. J Immigr Minor Health. 2019;21:473-482.

33. Moen, K.A., Terragni, L., Kumar, B. & Diaz, E. Cervical cancer screening among immigrant women in Norway- The healthcare providers' perspectives. Scand J Prim Health Care. 2018;36:415-422.

34. Haycock, J., Grivell, N., Redman, A., Saini, B., Vakulin, A., Lack, L. et al. Primary care management of chronic insomnia: a qualitative analysis of the attitudes and experiences of Australian general practitioners. BMC Fam Pract. 2021;22:158.

35. Suwankhong, D. & Liamputtong, P. Early Detection of Breast Cancer and Barrier to Screening Programmes amongst Thai Migrant Women in Australia: A Qualitative Study. Asian Pac J Cancer Prev. 2018;19:1089-1097.

36. March, S., Villalonga, B., Sanchez-Contador, C., Vidal, C., Mascaro, A., Bennasar, M.L. et al. Barriers to and discourses about breast cancer prevention among immigrant women in Spain: a qualitative study. BMJ Open. 2018;8:e021425.

37. Parajuli. Access to breast cancer screening - perception, and perceived barriers among older Bhutanese refugee women resettled in Australia: A qualitative study.

38. Dew, K.N., Turner, A.M., Choi, Y.K., Bosold, A. & Kirchhoff, K. Development of machine translation technology for assisting health communication: A systematic review. J Biomed Inform. 2018;85:56-67.

39. Centre for Cancer Detection (2023). *How do I take the stool test? [Hoe doe ik de stoelgangtest?]*, https://dikkedarmkanker.bevolkingsonderzoek.be/sites/default/files/2022-03/stoelgangtest.pdf Accessed 24 June 2023.

40. Paulhus, D.L. Socially Desirable Responding on Self-Reports. In: *Encyclopedia of Personality and Individual Differences* 10.1007/978-3-319-28099-8_1349-1 Ch. Chapter 1349-1, 1-5 (2017).

41. Dawson, G., Crane, M., Lyons, C., Burnham, A., Bowman, T. & Travaglia, J. A qualitative investigation of factors influencing participation in bowel screening in New South Wales. Health Promot J Austr. 2016;27:48-53.

42. Christy, S.M., Schmidt, A., Wang, H.L., Sutton, S.K., Davis, S.N., Chavarria, E. et al. Understanding Cancer Worry Among Patients in a Community Clinic-Based Colorectal Cancer Screening Intervention Study. Nurs Res. 2018;67:275-285.

43. Duncan, A., Turnbull, D., Gregory, T., Cole, S.R., Young, G.P., Flight, I. et al. Using the Transtheoretical Model of Behaviour Change to describe readiness to rescreen for colorectal cancer with faecal occult blood testing. Health Promot J Austr. 2012;23:122-128.

44. Dominitz, J. Barriers and Facilitators to Colorectal Cancer Screening. Gastroenterol Hepatol (N Y). 2021;17:550-552.

45. Palmer, C.K., Thomas, M.C., von Wagner, C. & Raine, R. Reasons for non-uptake and subsequent participation in the NHS Bowel Cancer Screening Programme: a qualitative study. Br J Cancer. 2014;110:1705-1711.

46. Honein-AbouHaidar, G.N., Kastner, M., Vuong, V., Perrier, L., Daly, C., Rabeneck, L. et al. Systematic Review and Meta-study Synthesis of Qualitative Studies Evaluating Facilitators and Barriers to Participation in Colorectal Cancer Screening. Cancer Epidemiol Biomarkers Prev. 2016;25:907-917.

47. Kroupa, R., Ondrackova, M., Kovalcikova, P., Dastych, M., Pavlik, T., Kunovsky, L. et al. Viewpoints of the target population regarding barriers and facilitators of colorectal cancer screening in the Czech Republic. World J Gastroenterol. 2019;25:1132-1141.

48. Van Hal, G., Hoeck, S. & Van Roosbroeck, S. Screening for colorectal cancer: sense and sensibilities. Eur J Cancer. 2011;47 Suppl 3:S156-163.

49. Crookes, D.M., Njoku, O., Rodriguez, M.C., Mendez, E.I. & Jandorf, L. Promoting colorectal cancer screening through group education in community-based settings. J Cancer Educ. 2014;29:296-303.

50. Centre for Cancer Detection (2023). *Promotional article: Population-based colorectal cancer screening [Publireportage Bevolkingsonderzoek Dikkedarmkanker]*, https://dikkedarmkanker.bevolkingsonderzoek.be/sites/default/files/2023-01/Publireportage%20Bevolkingsonderzoek%20Dikkedarmkanker.pdf Accessed 20 July 2023.

51. Green, B.B., BlueSpruce, J., Tuzzio, L., Vernon, S.W., Aubree Shay, L. & Catz, S.L. Reasons for never and intermittent completion of colorectal cancer screening after receiving multiple rounds of mailed fecal tests. BMC Public Health. 2017;17:531.

52. Benito, L., Farre, A., Binefa, G., Vidal, C., Cardona, A., Pla, M. et al. Factors related to longitudinal adherence in colorectal cancer screening: qualitative research findings. Cancer causes & control: CCC. 2018;29:103-114.

53. Wang, H., Roy, S., Kim, J., Farazi, P.A., Siahpush, M. & Su, D. Barriers of colorectal cancer screening in rural USA: a systematic review. Rural Remote Health. 2019;19:5181.

54. Cooper, C.P. & Gelb, C.A. Opportunities to Expand Colorectal Cancer Screening Participation. J Womens Health (Larchmt). 2016;25:990-995.

55. Goodwin, B.C., Crawford-Williams, F., Ireland, M.J. & March, S. General practitioner endorsement of mail-out colorectal cancer screening: The perspective of nonparticipants. Transl Behav Med. 2020;10:366-374.

56. Hall, N.J., Rubin, G.P., Dobson, C., Weller, D., Wardle, J., Ritchie, M. et al. Attitudes and beliefs of non-participants in a population-based screening programme for colorectal cancer. Health Expect. 2015;18:1645-1657.

57. Hewitson, P., Ward, A.M., Heneghan, C., Halloran, S.P. & Mant, D. Primary care endorsement letter and a patient leaflet to improve participation in colorectal cancer screening: results of a factorial randomised trial. Br J Cancer. 2011;105:475-480.

58. Tran, T.N., Peeters, M., Hoeck, S., Van Hal, G., Janssens, S. & De Schutter, H. Optimizing the colorectal cancer screening programme using faecal immunochemical test (FIT) in Flanders, Belgium from the "interval cancer" perspective. Br J Cancer. 2022;126:1091-1099.

59. Mlakar, D.N., Bric, T.K., Škrjanec, A.L. & Krajc, M. Interval cancers after negative immunochemical test compared to screen and non-responders' detected cancers in Slovenian colorectal cancer screening programme. Radiol Oncol. 2018;52:413-421.

60. van der Vlugt, M., Grobbee, E.J., Bossuyt, P.M.M., Bos, A., Bongers, E., Spijker, W. et al. Interval Colorectal Cancer Incidence Among Subjects Undergoing Multiple Rounds of Fecal Immunochemical Testing. Gastroenterology. 2017;153:439-447 e432.

61. Digby, J., Fraser, C.G., Carey, F.A., Lang, J., Stanners, G. & Steele, R.J. Interval cancers using a quantitative faecal immunochemical test (FIT) for haemoglobin when colonoscopy capacity is limited. J Med Screen. 2016;23:130-134.

62. Vanaclocha-Espi, M., Ibanez, J., Molina-Barcelo, A., Valverde-Roig, M.J., Nolasco, A., Perez-Riquelme, F. et al. Optimal cut-off value for detecting colorectal cancer with fecal immunochemical tests according to age and sex. PLoS One. 2021;16:e0254021.

63. Berry, E., Miller, S., Koch, M., Balasubramanian, B., Argenbright, K. & Gupta, S. Lower Abnormal Fecal Immunochemical Test Cut-Off Values Improve Detection of Colorectal Cancer in System-Level Screens. Clin Gastroenterol Hepatol. 2020;18:647-653.

64. Selby, K., Jensen, C.D., Lee, J.K., Doubeni, C.A., Schottinger, J.E., Zhao, W.K. et al. Influence of Varying Quantitative Fecal Immunochemical Test Positivity Thresholds on Colorectal Cancer Detection: A Community-Based Cohort Study. Ann Intern Med. 2018;169:439-447.

65. Toes-Zoutendijk, E., Kooyker, A.I., Elferink, M.A., Spaander, M.C.W., Dekker, E., Koning, H.J. et al. Stage distribution of screen-detected colorectal cancers in the Netherlands. Gut. 2018;67:1745-1746.

66. Toes-Zoutendijk, E., Kooyker, A.I., Dekker, E., Spaander, M.C.W., Opstal-van Winden, A.W.J., Ramakers, C. et al. Incidence of Interval Colorectal Cancer After Negative Results From First-Round Fecal Immunochemical Screening Tests, by Cutoff Value and Participant Sex and Age. Clin Gastroenterol Hepatol. 2020;18:1493-1500.

67. Centre for Cancer Detection (2022). *FIT positivity dashboard*, https://cvko.shinyapps.io/FIT_positivity/ Accessed 9 July 2022.

68. McClements, P.L., Madurasinghe, V., Thomson, C.S., Fraser, C.G., Carey, F.A., Steele, R.J. et al. Impact of the UK colorectal cancer screening pilot studies on incidence, stage distribution and mortality trends. Cancer Epidemiol. 2012;36:e232-242.

69. Gates, T. Screening for cancer: concepts and controversies. Am Fam Physician. 2014;90:625-631.

70. Idigoras Rubio, I., Arana-Arri, E., Portillo Villares, I., Bilbao Iturribarria, I., Martinez-Indart, L., Imaz-Ayo, N. et al. Participation in a population-based screening for colorectal cancer using the faecal immunochemical test decreases mortality in 5 years. Eur J Gastroenterol Hepatol. 2019;31:197-204.

71. Australian Institute of Health and Welfare (2018). *Analysis of bowel cancer outcomes for the National Bowel Cancer Screening Program*, https://www.aihw.gov.au/reports/cancer-screening/analysis-of-bowel-cancer-outcomes-nbcsp-2018/summary Accessed 11 April 2018.

72. Vicentini, M., Zorzi, M., Bovo, E., Mancuso, P., Zappa, M., Manneschi, G. et al. Impact of screening programme using the faecal immunochemical test on stage of colorectal cancer: Results from the IMPATTO study. Int J Cancer. 2019;145:110-121.

73. Shrank, W.H., Patrick, A.R. & Brookhart, M.A. Healthy user and related biases in observational studies of preventive interventions: a primer for physicians. J Gen Intern Med. 2011;26:546-550.

74. Royal, K. Survey research methods: A guide for creating post-stratification weights to correct for sample bias. Education in the Health Professions. 2019;2:

75. European Social Survey (2014). *Documentation of ESS post-stratification weights*, https://www.europeansocialsurvey.org/docs/methodology/ESS_post_stratification_weights_documentation.pdf Accessed 9 July 2014.

76. Piantadosi, S., Byar, D.P. & Green, S.B. The ecological fallacy. Am J Epidemiol. 1988;127:893-904.

77. Glanz, K., Rimer, B.K., Viswanath, K. & eds. *Health Behavior and Health Education: Theory, Research, and Practice*. 4th edn, (Jossey-Bass: San Francisco, CA, 2008).

78. Data & Analysis of five Flemish provinces *Provinces in numbers [Provincies In Cijfers]*, https://provincies.incijfers.be/databank Accessed 07 July.

79. Turnbull, E., Priaulx, J., de Kok, I., Lansdorp-Vogelaar, I., Anttila, A., Sarkeala, T. et al. Results of a health systems approach to identify barriers to population-based cervical and colorectal cancer screening programmes in six European countries. Health Policy. 2018;122:1206-1211.

80. Wolf, A.M.D., Fontham, E.T.H., Church, T.R., Flowers, C.R., Guerra, C.E., LaMonte, S.J. et al. Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society. CA Cancer J Clin. 2018;68:250-281.

81. Gartlehner, G., Schernhammer, E., Lax, S.F., Preusser, M., Bachler, H., Tietzer, H. et al. Screening for colorectal cancer : A recommendation statement of the Austrian National Committee for Cancer Screening. Wien Klin Wochenschr. 2023; 10.1007/s00508-023-02209-0

82. Siegel, R.L., Fedewa, S.A., Anderson, W.F., Miller, K.D., Ma, J., Rosenberg, P.S. et al. Colorectal Cancer Incidence Patterns in the United States, 1974-2013. J Natl Cancer Inst. 2017;109:

83. Ansa, B.E., Coughlin, S.S., Alema-Mensah, E. & Smith, S.A. Evaluation of Colorectal Cancer Incidence Trends in the United States (2000-2014). J Clin Med. 2018;7:

84. Vuik, F.E., Nieuwenburg, S.A., Bardou, M., Lansdorp-Vogelaar, I., Dinis-Ribeiro, M., Bento, M.J. et al. Increasing incidence of colorectal cancer in young adults in Europe over the last 25 years. Gut. 2019;68:1820-1826.

85. van de Veerdonk, W., Van Hal, G., Peeters, M. & Hoeck, S. Should Flanders consider lowering its target age for colorectal cancer screening to 45-49? Cancer Epidemiol. 2019;61:172-175.

86. Belgian Cancer Registry. The incidence of colorectal cancer among 45- to 49-year-olds in Flanders, 2001-2019 [De incidentie van dikkedarmkanker bij 45- tot 49-jarigen in Vlaanderen, 2001-2019]. (Brussels, 2022).

87. van Roon, A.H., Hol, L., Wilschut, J.A., Reijerink, J.C., van Vuuren, A.J., van Ballegooijen, M. et al. Advance notification letters increase adherence in colorectal cancer screening: a population-based randomized trial. Prev Med. 2011;52:448-451.

88. Frederiksen, B.L., Jorgensen, T., Brasso, K., Holten, I. & Osler, M. Socioeconomic position and participation in colorectal cancer screening. Br J Cancer. 2010;103:1496-1501.

89. Wools, A., Dapper, E.A. & de Leeuw, J.R. Colorectal cancer screening participation: a systematic review. Eur J Public Health. 2016;26:158-168.

90. Berete, F., Demarest, S., Charafeddine, R., Bruyere, O. & Van der Heyden, J. Comparing health insurance data and health interview survey data for ascertaining chronic disease prevalence in Belgium. Arch Public Health. 2020;78:120.

91. Ciatto, S., Martinelli, F., Castiglione, G., Mantellini, P., Rubeca, T., Grazzini, G. et al. Association of FOBT-assessed faecal Hb content with colonic lesions detected in the Florence screening programme. Br J Cancer. 2007;96:218-221.

92. Digby, J., Fraser, C.G., Carey, F.A., McDonald, P.J., Strachan, J.A., Diament, R.H. et al. Faecal haemoglobin concentration is related to severity of colorectal neoplasia. J Clin Pathol. 2013;66:415-419.

93. Fraser, C.G., Mathew, C.M., McKay, K., Carey, F.A. & Steele, R.J. Automated immunochemical quantitation of haemoglobin in faeces collected on cards for screening for colorectal cancer. Gut. 2008;57:1256-1260.

94. Grobbee, E.J., Schreuders, E.H., Hansen, B.E., Bruno, M.J., Lansdorp-Vogelaar, I., Spaander, M.C.W. et al. Association Between Concentrations of Hemoglobin Determined by Fecal Immunochemical Tests and Long-term Development of Advanced Colorectal Neoplasia. Gastroenterology. 2017;153:1251-1259 e1252.

95. Auge, J.M., Pellise, M., Escudero, J.M., Hernandez, C., Andreu, M., Grau, J. et al. Risk stratification for advanced colorectal neoplasia according to fecal hemoglobin concentration in a colorectal cancer screening program. Gastroenterology. 2014;147:628-636 e621.

96. Chen, L.S., Yen, A.M., Chiu, S.Y., Liao, C.S. & Chen, H.H. Baseline faecal occult blood concentration as a predictor of incident colorectal neoplasia: longitudinal follow-up of a Taiwanese population-based colorectal cancer screening cohort. Lancet Oncol. 2011;12:551-558.

97. Senore, C., Zappa, M., Campari, C., Crotta, S., Armaroli, P., Arrigoni, A. et al. Faecal haemoglobin concentration among subjects with negative FIT results is associated with the detection rate of neoplasia at subsequent rounds: a prospective study in the context of population based screening programmes in Italy. Gut. 2020;69:523-530.

98. Buron, A., Roman, M., Auge, J.M., Macia, F., Grau, J., Sala, M. et al. Changes in FIT values below the threshold of positivity and short-term risk of advanced colorectal neoplasia: Results from a population-based cancer screening program. Eur J Cancer. 2019;107:53-59.

99. van de Veerdonk, W., Van Hal, G., Peeters, M., De Brabander, I., Silversmit, G. & Hoeck, S. Risk stratification for colorectal neoplasia detection in the Flemish colorectal cancer screening programme. Cancer Epidemiol. 2018;56:90-96.

100. Digby, J., Fraser, C.G., Carey, F.A., Diament, R.H., Balsitis, M. & Steele, R.J. Faecal haemoglobin concentration is related to detection of advanced colorectal neoplasia in the next screening round. J Med Screen. 2017;24:62-68.

101. Kooyker, A.I., Toes-Zoutendijk, E., Opstal-van Winden, A.W.J., Spaander, M.C.W., Buskermolen, M., van Vuuren, H.J. et al. The second round of the Dutch colorectal cancer screening program: Impact of an increased fecal immunochemical test cut-off level on yield of screening. Int J Cancer. 2020;147:1098-1106.

102. Jeon, J., Du, M., Schoen, R.E., Hoffmeister, M., Newcomb, P.A., Berndt, S.I. et al. Determining Risk of Colorectal Cancer and Starting Age of Screening Based on Lifestyle, Environmental, and Genetic Factors. Gastroenterology. 2018;154:2152-2164 e2119.

103. Slattery, M.L., Levin, T.R., Ma, K., Goldgar, D., Holubkov, R. & Edwards, S. Family history and colorectal cancer: predictors of risk. Cancer Causes Control. 2003;14:879-887.

104. Huxley, R.R., Ansary-Moghaddam, A., Clifton, P., Czernichow, S., Parr, C.L. & Woodward, M. The impact of dietary and lifestyle risk factors on risk of colorectal cancer: A quantitative overview of the epidemiological evidence. International Journal of Cancer. 2009;125:171-180.

105. American Cancer Society. Colorectal Cancer Facts & Figures 2011-2013. (Atlanta: American Cancer Society, 2011).

106. Ferrari, P., Jenab, M., Norat, T., Moskal, A., Slimani, N., Olsen, A. et al. Lifetime and baseline alcohol intake and risk of colon and rectal cancers in the European prospective investigation into cancer and nutrition (EPIC). Int J Cancer. 2007;121:2065-2072.

107. Samad, A.K., Taylor, R.S., Marshall, T. & Chapman, M.A. A meta-analysis of the association of physical activity with reduced risk of colorectal cancer. Colorectal Dis. 2005;7:204-213.

108. Cho, E., Smith-Warner, S.A., Spiegelman, D., Beeson, W.L., van den Brandt, P.A., Colditz, G.A. et al. Dairy foods, calcium, and colorectal cancer: a pooled analysis of 10 cohort studies. J Natl Cancer Inst. 2004;96:1015-1022.

109. Saunders, C.L., Kilian, B., Thompson, D.J., McGeoch, L.J., Griffin, S.J., Antoniou, A.C. et al. External Validation of Risk Prediction Models Incorporating Common Genetic Variants for Incident Colorectal Cancer Using UK Biobank. Cancer Prev Res (Phila). 2020;13:509-520.

110. Lansdorp-Vogelaar, I., Knudsen, A.B. & Brenner, H. Cost-effectiveness of colorectal cancer screening - an overview. Best Pract Res Clin Gastroenterol. 2010;24:439-449.

111. Imperiale, T.F., Ransohoff, D.F., Itzkowitz, S.H., Levin, T.R., Lavin, P., Lidgard, G.P. et al. Multitarget stool DNA testing for colorectal-cancer screening. N Engl J Med. 2014;370:1287-1297.

112. Lansdorp-Vogelaar, I., Goede, S.L., Bosch, L.J.W., Melotte, V., Carvalho, B., van Engeland, M. et al. Cost-effectiveness of High-performance Biomarker Tests vs Fecal Immunochemical Test for Noninvasive Colorectal Cancer Screening. Clin Gastroenterol Hepatol. 2018;16:504-512 e511.

113. de Klaver, W., Wisse, P.H.A., van Wifferen, F., Bosch, L.J.W., Jimenez, C.R., van der Hulst, R.W.M. et al. Clinical Validation of a Multitarget Fecal Immunochemical Test for Colorectal Cancer Screening : A Diagnostic Test Accuracy Study. Ann Intern Med. 2021;174:1224-1231.

114. Bosch, L.J.W., de Wit, M., Pham, T.V., Coupe, V.M.H., Hiemstra, A.C., Piersma, S.R. et al. Novel Stool-Based Protein Biomarkers for Improved Colorectal Cancer Screening: A Case-Control Study. Ann Intern Med. 2017;167:855-866.

115. Triantafyllou, K., Papanikolaou, I.S., Papaxoinis, K. & Ladas, S.D. Two cameras detect more lesions in the small-bowel than one. World J Gastroenterol. 2011;17:1462-1467.

116. Vuik, F.E.R., Nieuwenburg, S.A.V., Moen, S., Spada, C., Senore, C., Hassan, C. et al. Colon capsule endoscopy in colorectal cancer screening: a systematic review. Endoscopy. 2021;53:815-824.

Appendices

Summary

Colorectal cancer (CRC) is a significant global challenge, ranking as the third most prevalent cancer and the second leading cause of cancer-related deaths. In Belgium, based on 2021 statistics, CRC is the third most common cancer in both males (4387 new cases, 10.8% of all cancer cases) and females (3494 new cases, 10.2%). In terms of mortality, CRC is the second leading cause of cancer-related deaths in 2020 when considering both sexes combined (2484 deaths, 8.3% of cancer-related deaths).

The high incidence and mortality rates, coupled with detectable precancerous lesions, slow development, lack of early-stage symptoms, and evidence of reduced mortality and cost-effectiveness, make CRC an ideal candidate for population-based screening. Since 2003, the Council of the European Union has urged member states to establish population-based CRC screening programmes. By 2017, 23 countries/regions had implemented such programmes, primarily using stool-based test (gFOBT or FIT) as the primary screening method.

In Flanders, a pilot CRC screening programme was initiated in 2009 to assess its feasibility and potential benefits. In October 2013, the Flemish population-based CRC screening programme was officially implemented. The programme provides eligible individuals aged 50-74 years with a free FIT kit every two years, with phased implementation based on age. A simulation study conducted in 2015 demonstrated that the programme is highly cost-effective and has the potential to significantly reduce CRC-related mortality.

However, the simulation study relied on several assumptions and data from outside Flanders. Actual data is needed to accurately assess the programme's outcomes and determine whether the observed outcomes align with initial estimations and expectations. Descriptive analysis has shown the effectiveness of screening in detecting a greater number of cases at an earlier stage. However, a more comprehensive scientific evaluation of the program's impact on CRC incidence, mortality, and survival has been planned, pending a longer follow-up period.

In Flanders, as of 2021, CRC incidence data was available until 2019, and mortality data until 2018, allowing for a thorough analysis of the impact of the CRC screening programme on CRC incidence, mortality and survival after six years of implementation (results presented in **Chapter 2**). The analyses included a total of 55,688 invasive CRC cases during 2004–2019, 14,146 CRC-related deaths during 2004–2018 in individuals aged 50–79 years for the analysis

of CRC incidence and mortality, and 35,796 CRC cases in individuals aged 50–74 years during 2004–2019 for the analysis of relative survival. Joinpoint regression was used to investigate trends of age-standardized CRC incidence and mortality. Five-year relative survival was calculated using the Ederer II method. FIT screening in Flanders significantly reduced CRC incidence, especially that of advanced-stage CRCs (69.8/100,000 in 2012 vs. 51.1/100,000 in 2019), with a greater impact observed in men. Mortality started declining in men two years after the implementation of organised screening, with an annual reduction of 9.3% after 2015 compared to 2.2% before 2015. The 5-year relative survival was significantly higher in screen-detected (93.8%) and lower in FIT non-participant CRCs (61.9%) vs. FIT interval cancers and CRCs in never-invited cases (67.6% and 66.7%, respectively). The effect of screening on reducing mortality in women is expected to become evident with longer follow-up.

Despite the benefits offered by screening, the response rate has consistently remained around 50%. In this PhD research, the suboptimal response rate within the programme was investigated through an examination of screening with FOBTs outside the programme, reasons for inconsistent participation, and population's preferences for CRC screening. The quantitative study in **Chapter 3** investigated factors associated with screening coverage with outside FOBT, relative to coverage with FIT inside the programme. Data from the CCD on CRC screening coverage, both inside and outside the screening program, for 308 municipalities in Flanders during 2015–2017 were linked with data on demographic, socioeconomic, and health-related municipal characteristics from the 'Provincies In Cijfers' databank for the same period. Logistic regression with generalized estimating equations was employed to assess the associations between municipal characteristics and organised and non-organised screening coverages. The findings highlighted the crucial role of GPs in promoting CRC screening, as a higher percentage of people who had visited a GP in the last year were associated with higher screening coverages for both screening strategies (organised screening: OR = 1.04, 95% CI: 1.03–1.05; non-organised screening: OR = 1.03, 95% CI: 1.02–1.04). Furthermore, a higher average number of patients per GP and a higher percentage of people with a global medical dossier managed by a preferred GP were associated with higher non-organised screening coverage (OR = 1.021, 95% CI: 1.016–1.026 and OR = 1.025, 95% CI: 1.018–1.031, respectively). The study also identified significantly lower screening coverage within the programme among individuals with a migrant background (non-Belgian/Dutch nationality) (OR = 0.962, 95%CI: 0.957–0.967). Language barriers remain a significant challenge for individuals with a migrant background in Flanders, as screening

materials are only available in Dutch.

Screening with outside FOBTs appears to have limited impact on the response rate within the programme due to low and decreasing coverage. During our study period from 2015 to 2017, the screening coverage with outside FOBTs decreased from 5.4% to 3.7% and further dropped to 2.5% in 2021. However, outside FOBTs pose challenges, including cost, lack of systematic result registration and follow-up information, and inadequate quality control. Hence, promoting a shift towards organised screening is crucial.

Previous research has predominantly focused on non-participation in general, with limited attention given to the phenomenon of inconsistent participation within individuals. To explore this area further, the CCD conducted a survey-based study (**Chapter 4**) among inconsistent participants in the Flemish CRC screening programme. An online survey was distributed to irregular participants 2016-2018. Data analysis employed both qualitative and quantitative approaches. Post-stratification weights were applied to address non-response bias. Out of 19,592 irregular participants, 5,328 responded to the survey. Among these respondents, the most common reasons (~50% of respondents) for non-participation in a specific round were 'postponing participation', 'insufficient time', and 'prioritizing other commitments'. Another notable set of reasons for non-participation included 'feeling healthy' and 'lack of symptoms', with over 46% of respondents agreeing with these statements, indicating a lack of knowledge and the misconception that CRC screening is necessary only when symptoms are present. The influence of GPs emerged as an important facilitator to screening, as more than 65% expressed the desire for their GP to mention the FIT invitation spontaneously, and over 40% stated they would have participated earlier if advised by their GP.

Decisions regarding CRC screening in Flanders have primarily relied on expert opinions and scientific evidence, with limited consideration given to population's preferences concerning screening test and information delivery. In **Chapter 5**, we conducted a comprehensive review in this topic, searching in four OVID databases: Ovid MEDLINE® ALL, Biological Abstracts, CAB Abstracts, and Global Health. Among the initially identified 742 articles, 154 full texts were evaluated based on predefined criteria, resulting in the inclusion of 83 studies in the review. The general population expressed a preference for colonoscopy as the most accurate test, or FOBT as the least invasive option for CRC screening. The review also emphasized the vital role of GPs in promoting CRC screening and ensuring adherence. The general population expressed

a desire for tailored and interactive CRC screening information provided in a supportive and open setting that accommodates individual needs and concerns. GPs were recognised as reliable and trustworthy sources of information, assisting individuals in making informed decision about CRC screening.

In its efforts to enhance screening uptake, the Flemish CRC screening programme has also taken measures to address associated challenges, including an increase in the number of FIT interval cancers (FIT-IC). The occurrence of FIT-ICs is a significant quality indicator for FIT-based CRC screening programmes. Our study in **Chapter 6** aimed to investigate the characteristics of FIT-IC within the Flemish programme and assess the impact of lowering FIT cut-off or shortening screening interval on reducing FIT-IC occurrence. The analyses included 11,656 FIT participants diagnosed with screen-detected CRC (N=10,122) or FIT-IC (N=1,534) between October 2013 and December 2018. Results from multivariable logistic regression showed that FIT-ICs were more common in women (OR 1.58 [95% CI 1.41–1.76]), older age 70–74 years (OR 1.35 [1.14–1.59]), right sided location (OR 3.53 [2.98–4.20]), and advanced stage (stage IV: OR 7.15 [5.76–8.88]). Lowering FIT cut-off 15 to 10 µg Hb/g or shortening screening interval from two to one year would have minimal impact on the occurrence of FIT interval cancers, as the majority (83–92%) of FIT ICs would still be missed even with a lower FIT cut-off of 10 µg Hb/g or a shortened screening interval of one year. Continuous monitoring and evaluation of FIT performance are essential for maintaining the programme effectiveness.

In conclusion, the population-based CRC screening programme in Flanders has proven effective in significantly reducing CRC incidence, mortality and improving survival. Our findings support the implementation of FIT organised screening in countries and regions without existing programmes. Although screening with FOBTs outside the screening programme has limited impact on the response rate within the programme, it poses challenges related to cost, inadequate result registration and follow-up, and insufficient quality control. Encouraging a shift to organised screening is important. Persistent challenges include language barriers for individuals with a migrant background, the issue of postponed screening due to time constraints and competing priorities, and the misconception that CRC screening is only necessary when symptoms are present. GPs play a vital role as trusted sources of information, promoting CRC screening, and addressing barriers and misconceptions among their patients. The chosen FIT cut-off and screening interval in Flanders are considered optimal with regards

to FIT-IC, as lowering FIT cut-off or shortening screening interval would have minimal impact on the occurrence of FIT interval cancers.

The current evidence does not support expanding the CRC screening programme by reducing the starting age for screening, lowering the FIT cut-off, or shortening the screening interval. Instead, the focus should be on optimizing the existing screening strategy, along with regular monitoring and evaluation for continuous improvement. Introducing pre-invitations and additional reminders can be effective in addressing procrastination in CRC screening participation. Strengthening the involvement of GPs, local authorities, and health insurance organisations seems beneficial in reaching underserved populations. To enhance screening effectiveness, the programme may consider incorporating risk stratification based on previous FIT results to tailor screening invitations. Emerging tests can be explored to be used as an alternative for FIT as the primary screening test (e.g., multi-target FIT) or triaging individuals after a positive FIT to reduce unnecessary colonoscopies and associated adverse events (e.g., video capsule).

Samenvatting

Dikkedarmkanker (DDK) is een belangrijke wereldwijde uitdaging, het is de op twee na meest voorkomende kanker en de op een na belangrijkste oorzaak van kankergerelateerde sterfgevallen. In België, op basis van statistieken uit 2021, is DDK de op twee na meest voorkomende kanker bij zowel mannen (4387 nieuwe gevallen, 10,8% van alle kankergevallen) als vrouwen (3494 nieuwe gevallen, 10,2%). Wat betreft mortaliteit is DDK in 2020 de op een na belangrijkste oorzaak van kankergerelateerde sterfgevallen, bij zowel mannen als vrouwen samen (2484 sterfgevallen, 8,3% van alle kankergerelateerde sterfgevallen).

De hoge incidentie- en sterftecijfers, samen met detecteerbare voorstadia, trage ontwikkeling, gebrek aan symptomen in een vroeg stadium en bewijs van verminderde oorzaakspecifieke sterfte en kosteneffectiviteit, maken DDK tot een ideale kandidaat voor screening op grote schaal. Sinds 2003 heeft de Raad van de Europese Unie lidstaten aangespoord om DDK-screeningsprogramma's op te zetten. Tegen 2017 hadden 23 landen/regio's dergelijke programma's geïmplementeerd, voornamelijk gebruikmakend van de stoelgangtest (gFOBT of FIT) als primaire screeningsmethode.

In Vlaanderen werd in 2009 een piloot-DDK-screeningsprogramma gestart om de haalbaarheid en potentiële voordelen ervan te beoordelen. In oktober 2013 werd het DDK-screeningsprogramma officieel geïmplementeerd in gans Vlaanderen. Het programma voorziet in gratis FIT-kits om de twee jaar voor in aanmerking komende personen in de leeftijd van 50-74 jaar, met een gefaseerde implementatie op basis van leeftijd. Een simulatiestudie uitgevoerd in 2015 toonde aan dat het programma zeer kosteneffectief is en het potentieel heeft om de DDK-gerelateerde sterfte aanzienlijk te verminderen.

De simulatiestudie was echter gebaseerd op verschillende aannames en gegevens buiten Vlaanderen. Werkelijke gegevens zijn nodig om de resultaten van het programma nauwkeurig te beoordelen en te bepalen of de waargenomen resultaten overeenkomen met de oorspronkelijke schattingen en verwachtingen. Descriptieve analyse heeft de effectiviteit van screening aangetoond bij het detecteren van een groter aantal gevallen in een vroeger stadium. Een meer uitgebreide wetenschappelijke evaluatie van het effect van het programma op de incidentie, mortaliteit en overleving van DDK is echter gepland, in afwachting van een langere follow-upperiode.

In 2021 waren gegevens beschikbaar over DDK incidentie tot 2019, en mortaliteitsgegevens tot 2018, waardoor een grondige analyse mogelijk was van de impact van het DDK-screeningsprogramma op de incidentie, mortaliteit en overleving van DDK na zes jaar implementatie, in Vlaanderen (resultaten gepresenteerd in **Hoofdstuk 2**). De studie omvatte in totaal 55.688 invasieve DDK-gevallen tijdens 2004-2019 en 14.146 DDK-gerelateerde sterfgevallen tijdens 2004-2018 bij personen in de leeftijd van 50-79 jaar. Voor de analyse van relatieve overleving werden 35.796 DDK-gevallen bij personen in de leeftijd van 50-74 jaar tijdens 2004-2019 opgenomen. Joinpoint-regressie werd gebruikt om trends in leeftijdsgestandaardiseerde DDK-incidentie en mortaliteit te onderzoeken. De vijfjaarsrelatieve overleving werd berekend met behulp van de Ederer II-methode. FIT-screening in Vlaanderen heeft de DDK-incidentie significant verminderd, vooral die van gevorderd stadium DDK (69,8/100.000 in 2012 vs. 51,1/100.000 in 2019), met een groter effect bij mannen. De sterfte begon bij mannen te dalen twee jaar na de invoering van georganiseerde screening, met een jaarlijkse daling van 9,3% na 2015 in vergelijking met 2,2% vóór 2015. De vijfjaarsrelatieve overleving was significant hoger bij screening-gedetecteerde DDKs (93,8%) en lager bij DDKs van niet-deelnemers aan FIT (61,9%) in vergelijking met FIT-interval kankers en DDKs bij nooit-uitgenodigden (67,6% en 66,7%, respectievelijk). Het effect van screening op het verminderen van de sterfte bij vrouwen zal naar verwachting zichtbaar worden bij een langere follow-up.

Ondanks de voordelen van screening blijft de responsgraad stabiel rond 50%. In dit PhD onderzoek werd de suboptimale responsgraad binnen het programma onderzocht door te kijken naar screening met FOBT's buiten het programma, redenen voor inconsistente deelname en de voorkeuren van de bevolking voor DDK-screening. De kwantitatieve studie in **Hoofdstuk 3** onderzocht factoren die verband houden met de dekkingsgraad met FOBT buiten het programma, in vergelijking met dekking met FIT binnen het programma. Gegevens van Het Centrum voor Kankeropsporing (CvKO) over de dekkingsgraad, zowel binnen als buiten het screeningprogramma, voor 308 gemeenten in Vlaanderen tijdens 2015-2017 werden gekoppeld aan gegevens over demografische, sociaaleconomische en gezondheidsgerelateerde gemeentelijke kenmerken uit de databank 'Provincies In Cijfers' voor dezelfde periode. Logistische regressie met ‘generalised estimating equations’ werd gebruikt om de verbanden tussen gemeentelijke kenmerken en georganiseerde en niet-georganiseerde dekkingsgraad te beoordelen. De bevindingen benadrukten de cruciale rol van huisartsen bij het bevorderen van DDK-screening, aangezien een hoger percentage mensen dat het afgelopen

jaar een huisarts had bezocht, werd geassocieerd met een hogere dekkingsgraad voor beide screeningstrategieën (georganiseerde screening: OR = 1,04, 95% BI: 1,03-1,05; niet-georganiseerde screening: OR = 1,03, 95% BI: 1,02-1,04). Bovendien werden een hoger gemiddeld aantal patiënten per huisarts en een hoger percentage mensen met een globaal medisch dossier geassocieerd met een hogere niet-georganiseerde dekkingsgraad (OR = 1,021, 95% BI: 1,016-1,026 en OR = 1,025, 95% BI: 1,018-1,031, respectievelijk). De studie identificeerde ook een significant lagere dekkingsgraad binnen het programma bij mensen met een migratieachtergrond (niet-Belgische/Nederlandse nationaliteit) (OR = 0,962, 95% BI: 0,957-0,967). Taalbarrières blijven een belangrijke uitdaging voor mensen met een migratieachtergrond in Vlaanderen, aangezien de uitnodiging met bijhorende folder en gebruiksaanwijzing alleen beschikbaar is in het Nederlands.

Screening met FOBT's buiten het programma lijkt een beperkte impact te hebben op de responsgraad binnen het programma vanwege beperkte en dalende aantallen. Tijdens onze onderzoeksperiode van 2015 tot 2017 daalde de dekking met FOBT's buiten het programma van 5,4% tot 3,7% en daalde dit verder tot 2,5% in 2021. Er zijn echter uitdagingen verbonden aan FOBT's buiten het programma, waaronder kosten, het ontbreken van systematische registratie van resultaten en follow-upinformatie, en ontoereikende kwaliteitscontrole. Het bevorderen van een verschuiving naar georganiseerde screening is daarom cruciaal.

Eerdere onderzoeken hebben zich voornamelijk gericht op non-participatie in het algemeen, met beperkte aandacht voor inconsistente deelname. Om dit verder te verkennen, voerde het CvKO een op enquêtes gebaseerde studie uit (**Hoofdstuk 4**) onder inconsistente deelnemers aan het Vlaamse DDK-screeningsprogramma. Een online enquête werd tussen 2016 en 2018 verspreid onder onregelmatige deelnemers. De data-analyse gebeurde zowel via kwalitatieve als kwantitatieve benaderingen. Post-stratificatiegewichten werden toegepast om non-responsbias aan te pakken. Van de 19.592 onregelmatige deelnemers reageerden 5.328 op de enquête. Onder deze respondenten waren de meest voorkomende redenen (~50% van de respondenten) voor niet-deelname in een specifieke screeningsronde 'uitstelgedrag ', 'geen tijd' en 'prioriteit geven aan andere medische en niet medische verplichtingen'. Andere opvallende redenen voor niet-deelname waren 'zich gezond voelen' en 'gebrek aan symptomen', wat door meer dan 46% van de respondenten werd aangegeven, wat wijst op een gebrek aan kennis en de misvatting dat DDK-screening alleen nodig is wanneer symptomen

aanwezig zijn. De invloed van huisartsen bleek een belangrijke facilitator van screening, aangezien meer dan 65% de wens uitsprak dat hun huisarts de FIT-uitnodiging spontaan zou vermelden, en meer dan 40% verklaarde eerder te hebben deelgenomen als ze door hun huisarts waren geadviseerd.

Beslissingen met betrekking tot DDK-screening in Vlaanderen zijn voornamelijk gebaseerd op expertmeningen en wetenschappelijk bewijs, met beperkte aandacht voor de voorkeuren van de bevolking met betrekking tot de screeningstest en informatievoorziening. In **Hoofdstuk 5** voerden we een uitgebreide review uit over dit onderwerp, waarbij we zochten in vier OVID-databases: Ovid MEDLINE® ALL, Biological Abstracts, CAB Abstracts en Global Health. Van de 742 oorspronkelijk geïdentificeerde artikelen werden 154 volledige teksten beoordeeld op basis van vooraf bepaalde criteria, resulterend in de inclusie van 83 studies in de review. De algemene bevolking gaf de voorkeur aan colonoscopie als de meest nauwkeurige test, of FOBT als de minst invasieve optie voor DDK-screening. De review benadrukte ook de cruciale rol van huisartsen bij het bevorderen van DDK-screening en het waarborgen van participatietrouw. De algemene bevolking gaf de wens aan voor op maat gemaakte en interactieve informatie over DDK-screening, verstrekt in een ondersteunende en open setting die tegemoetkomt aan individuele behoeften en zorgen. Huisartsen werden erkend als vertrouwenspersonen, die mensen helpen bij het nemen van geïnformeerde beslissingen over DDK-screening.

In haar inspanningen om de responsgraad te verhogen, heeft het Vlaamse DDK-screeningsprogramma ook maatregelen genomen knelpunten, waaronder een toename van FIT-interval kankers (FIT-IK), aan te pakken. Het optreden van FIT-IK's is een belangrijke kwaliteitsindicator voor FIT-gebaseerde DDK-screeningsprogramma's. Ons onderzoek in **Hoofdstuk 6** had tot doel de kenmerken van FIT-IK binnen het Vlaamse programma te onderzoeken en de impact van verlaging van de FIT-drempelwaarde of inkorten van het screeninginterval te beoordelen om het optreden van FIT-IK te verminderen. De analyses omvatten 11.656 FIT-deelnemers bij wie DDK werd vastgesteld na screening (N=10.122) of FIT-IK (N=1.534) tussen oktober 2013 en december 2018. Resultaten van multivariate logistische regressie toonden aan dat FIT-IK's vaker voorkwamen bij vrouwen (OR 1,58 [95% BI 1,41-1,76]), in de oudere leeftijdsgroep 70-74 jaar (OR 1,35 [1,14-1,59]), in de rechterzijde gelokaliseerd zijn (OR 3,53 [2,98-4,20]) en in een gevorderd stadium (stadium IV: OR 7,15 [5,76-8,88]). Het verlagen van de FIT-drempelwaarde van 15 naar 10 µg Hb/g of het inkorten van het

screeninginterval van twee naar één jaar zou een minimale impact hebben op het optreden van FIT-IK, aangezien de meerderheid (83-92%) van de FIT-IK's nog steeds zou worden gemist, zelfs bij een lagere FIT-drempelwaarde van 10 µg Hb/g of een verkort screeninginterval van één jaar. Voortdurende monitoring en evaluatie van de FIT-prestaties zijn essentieel voor het behoud van de effectiviteit van het programma.

Concluderend blijkt het DDK-screeningsprogramma in Vlaanderen effectief in het verminderen van de incidentie, mortaliteit en verbetering van de overleving van DDK. Onze bevindingen ondersteunen de implementatie van georganiseerde FIT-screening in landen en regio's zonder bestaande programma's. Hoewel screening met FOBT's buiten het programma beperkte impact heeft op de responsgraad binnen het programma, brengt het uitdagingen met zich mee op het gebied van kosten, ontoereikende registratie van resultaten en follow-upinformatie en onvoldoende kwaliteitscontrole. Het bevorderen van een verschuiving naar georganiseerde screening is daarom belangrijk. Aanhoudende uitdagingen zijn taalbarrières voor mensen met een migratieachtergrond, het probleem van niet-deelname vanwege uitstelgedrag en concurrerende prioriteiten, en de misvatting dat DDK-screening alleen nodig is bij aanwezigheid van symptomen. Huisartsen spelen een cruciale rol als vertrouwenspersoon, bij het bevorderen van DDK-screening en het aanpakken van barrières en misvattingen bij hun patiënten. De gekozen FIT-drempelwaarde en screeninginterval in Vlaanderen worden als optimaal beschouwd met betrekking tot FIT-IK, omdat het verlagen van de FIT-drempelwaarde of het verkorten van het screeninginterval een minimale impact zouden hebben op het optreden van FIT-IK.

Het huidige bewijsmateriaal ondersteunt geen uitbreiding van het DDK-screeningsprogramma door de startleeftijd voor screening te verlagen, de FIT-drempelwaarde te verlagen of het screeninginterval te verkorten. In plaats daarvan moet de focus liggen op het optimaliseren van de bestaande screeningsstrategie, samen met regelmatige monitoring en evaluatie voor voortdurende verbetering. Het introduceren van voor-aankondigingen en extra herinneringen kan effectief zijn bij het aanpakken van uitstelgedrag bij DDK-screening. Het versterken van de betrokkenheid van huisartsen, lokale autoriteiten en ziektekostenverzekeraars lijkt gunstig om ondergescreende populaties te bereiken. Om de effectiviteit van screening te verbeteren, kan overwogen worden om risicoclassificatie op basis van eerdere FIT-resultaten op te nemen om screeningsuitnodigingen op maat te maken. Opkomende tests kunnen worden verkend als

alternatief voor FIT als primaire screeningsmethode (bijvoorbeeld multi-target FIT) of voor het triëren van individuen na een positieve FIT om onnodige colonoscopieën en gerelateerde nadelige gebeurtenissen te verminderen (bijvoorbeeld video-capsule).

Supplement 1. Overview of colorectal cancer screening programmes in the three regions of Belgium - Flanders, Brussels, and Wallonia

While this PhD thesis primarily focuses on the colorectal cancer (CRC) screening programme in Flanders, it is acknowledged that some readers may also be interested in a brief introduction of the CRC screening programmes in the other two regions of Belgium, namely Wallonia and Brussels. This supplement provides an overview of the CRC screening programmes in all three regions of Belgium. It also offers a description of the evolution of CRC incidence before and after the implementation of organised CRC screening in each region. To our knowledge, there has been no published similar data regarding CRC stage distribution and mortality for Wallonia and Brussels.

It should be noted that drawing direct and accurate comparisons among the three screening programmes across these regions is challenging due to the distinct characteristics of these programmes and their separate organisational structures. Such comparisons are not the primary objective of this PhD research, and reliable assessments would require extensive and comprehensive research beyond the scope of this PhD research. For a short summary of the main features of the CRC screening programmes in Flanders, Wallonia and Brussels, please refer to **Table 1**.

Since the initiation of population-based CRC screening, participation rate in Flanders has consistently remained at around 50% of the individuals invited for screening.[1] In Brussels, the participation rate was 35.8% (2022), while in Wallonia, it was around 25% (2019) [unpublished data].

Table 1. Overview of the colorectal cancer screening programmes in three regions of Belgium - Flanders, Brussels and Wallonia[2]

Region	Flanders (since 2013)[3]	Brussels (since 2018)[4] (2009-2018 invited by CCR)	Wallonia (since 2009)[5]
Organisation coordinating CRC screening	Centrum voor Kankeropsporing (CvKO) https://dikkedarmkanker.bevolkingsonderzoek.be/	BruPrev https://www.bruprev.be/fr/colotest	Le Centre Communautaire de Référence (CCR) https://www.ccref.org/
Pilot/Start	Pilot 2008-2010 Official start: October 2013	Pilot from 11/2018 till present	No pilot Official start: March 2009
Screening test	Faecal immunochemical test (FIT)	2009-2018: same as Wallonia Since 09/2018: FIT	2009-2015: gFOBT 2016 onwards: FIT
Screening interval	Biannually	Biannually	Biannually
Cost for participant	FIT participation within the screening programme: free of charge Follow-up colonoscopy and visiting GP: not free of charge, partly reimbursed by health insurance	FIT participation within the screening programme: free of charge Follow-up colonoscopy and visiting GP: not free of charge, partly reimbursed by health insurance	FIT participation within the screening programme: free of charge Follow-up colonoscopy and visiting GP: not free of charge, partly reimbursed by health insurance
Target population	Asymptomatic persons at average risk within an age range 2013: 66-74, only even ages 2014: 56-74, only even ages 2015-2016: 56-74 2017: 55-74 2018: 53-74 2019: 51-74 2020: 50-74	Asymptomatic persons at average risk within an age range 2018-present: 50-74	Asymptomatic persons at average risk within an age range 2009-present: 50-74
Invitation strategy	FIT sent by mail	2009-2018: same as Wallonia From 2018: FIT collected at the pharmacy. Two years after the first participation, FIT sent by mail to home address.	2009-2015: gFOBT sent by mail. From March 2015: FIT collected at GPs or ordered online via CCR website. Two years after the first participation, FIT sent by mail to home address.
Reminder letter	After 10 weeks, no FIT included	No reminder letter	After 4 months, no FIT included
Result letter	To participant: FIT- result via email (or post in case no email address), FIT+ result via both email and post To GP: all results via eHeath	To participant To GP: all results via eHealth Box, and also via post in FIT+ cases	To participant: FIT+ result, or no registered GP To GP: all results via eHealth Box and also via

	Box		post in FIT+ cases
Exclusion criteria	• FIT within or outside the organised programme in the last 2 years • Colonoscopy in the last 10 years or virtual colonoscopy in the last 4 years • Colectomy (permanent) or CRC diagnosis in the last 10 years • Request for exclusion	• FIT within the organised programme in the last 2 years • Colonoscopy in the last 5 years or virtual colonoscopy in the last 4 years • Colectomy (permanent) or CRC diagnosis in the last 10 years • Request for exclusion	• FIT within the organised programme in the last 2 years • Colonoscopy in the last 5 years or virtual colonoscopy in the last 4 years • Colectomy (permanent) or CRC diagnosis in the last 10 years • Request for exclusion
FIT positive threshold	OC Sensor: 75 ng/ml (15 µg/g) Fob Gold: 50 ng/ml (8.5 µg/g) (the switch was made in February 2021)	FIT (OC Sensor): 75 ng/ml (15 µg/g)	FIT (OC Sensor): 75 ng/ml (15 µg/g)
Failsafe when no follow-up colonoscopy is performed after a positive FIT	Since 2019 24 months after a positive FIT without a follow-up colonoscopy, a letter is sent to the participant and GP with advice to still undergo a colonoscopy	6 months after a positive FIT without a follow-up colonoscopy, a reminder is sent to participant.	No

Figure 1 illustrates the evolution in CRC incidence prior to and following the implementation of organised CRC screening in the three regions during 2004-2017.[6] Specific incidence data focussing solely on the target screening ages and above are not available; the published data cover all age groups.

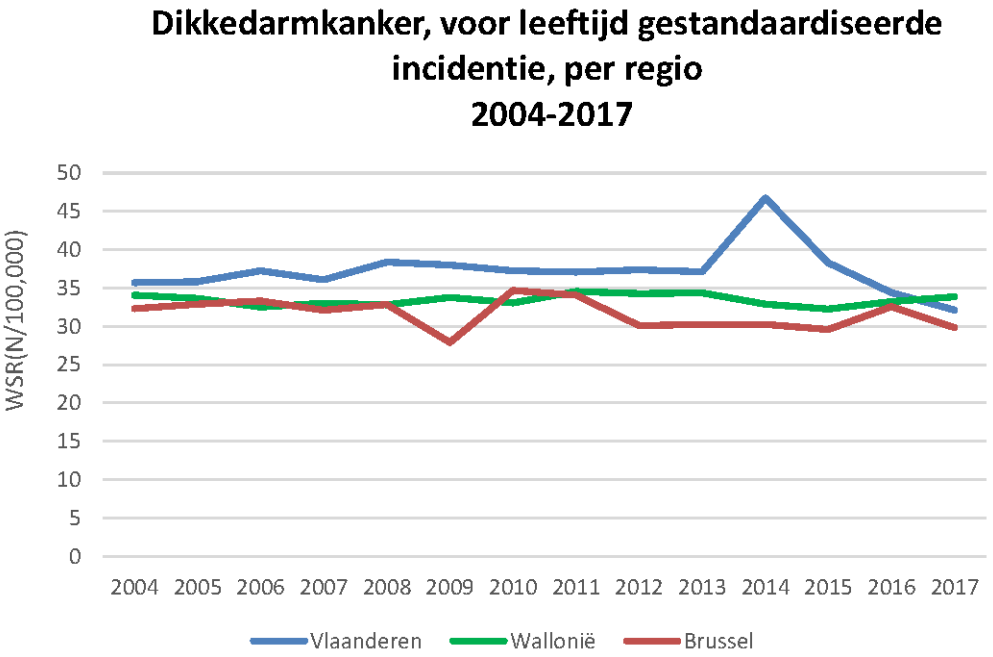


Figure 1. Evolution of age-standardized incidence (WSR - age-standardised rate using the Word global standard population, per 100.000) in Flanders, Wallonia and Brussels during 2004-2017, all ages included. (Source of figure: Belgian Cancer Registry[6])

In Flanders, the impact of organised CRC screening (starting in October 2013) on CRC incidence is evident. Age-standardised CRC incidence sharply rose from 37.3/100,000 person-years (py) before 2013 to 46.8/100,000 py in 2014, subsequently decreasing substantially to 32.2 /100,000 py in 2017, significantly lower than the pre-programme level.

Compared to Flanders, the impact of organised screening on CRC incidence is less apparent in Brussels. In 2009, when organised CRC screening was initiated in March (with invitations jointly sent with Wallonia by CCR - Le Centre Communautaire de Référence), CRC incidence notably decreased to 28.0/100,000 py, compared to the preceding years where it ranged around 32.0-33.0/100,000 py. Subsequently, the incidence increased to approximately 34.0/100,000 py during 2010-2011, then reduced to 30.0//100,000 py in 2012 and maintained a stable rate

between 2012 and 2015. A slight increase to 32.7/100,000 py was noted in 2016, probably attributed to the switch from gFOBT to FIT, as FIT is known to yield higher participation rate and higher sensitivity.[7] The incidence then decreased to 29.8/100,000 py in 2017, slightly lower than the pre-screening level.

In Wallonia, CRC incidence has remained quite stable, ranging between 32.3/100,000 py and 34.7/100,000 py from 2004 to 2017. This suggests that the organised CRC screening using gFOBT, as well as of the subsequent transition to FIT in 2016, has not yielded a noticeable impact.

References

1 Centre for Cancer Detection (2022). *Monitoring report of the Flemish Colorectal Cancer Screening Programme 2022*, https://dikkedarmkanker.bevolkingsonderzoek.be/sites/default/files/2022-12/Jaarrapport%202022_0.pdf Accessed 9 July 2022.

2 van de Veerdonk, W. *Colorectal cancer screening in Flanders: towards an optimal performance* PhD thesis, University of Antwerp.

3 Centre for Cancer Detection *Population-based colorectal cancer screening (Flanders)*, https://dikkedarmkanker.bevolkingsonderzoek.be/nl Accessed 22 August.

4 BruPrev *Colorectal cancer screening (Brussels)*, https://www.bruprev.be/fr/colotest Accessed 22 August.

5 Le Centre Communautaire de Référence (CCR) *Colorectal cancer screening programme (Wallonia)*, https://www.ccref.org/ Accessed 22 August.

6 Belgian Cancer Registry. Addendum annual report Flemish population screenings 2019: Evolution of colorectal cancer incidence in Flanders 2004-2017 [Addendum Jaarfiche Vlaamse bevolkingsonderzoeken 2019: Evolutie incidentie van dikkedarmkanker Vlaanderen 2004-2017]. (Brussels, 2019).

7 Guo, F., De Brabander, I., Francart, J., Candeur, M., Polus, M., Van Eycken, L. et al. Benefits of switching from guaiac-based faecal occult blood to faecal immunochemical testing: experience from the Wallonia-Brussels colorectal cancer screening programme. Br J Cancer. 2020;122:1109-1117.

List of publications

Publications in this thesis

1. **Tran, T. N.**, Hoeck, S., De Schutter, H., Janssens, S., Peeters, M., & Van Hal, G. (2023). The Impact of a Six-Year Existing Screening Programme Using the Faecal Immunochemical Test in Flanders (Belgium) on Colorectal Cancer Incidence, Mortality and Survival: A Population-Based Study. International journal of environmental research and public health, 20(2), 1654. https://doi.org/10.3390/ijerph20021654
2. Hoeck, S.; **Tran, T.N**. (2023). Self-Reported Reasons for Inconsistent Participation in Colorectal Cancer Screening Using FIT in Flanders, Belgium. Gastrointestinal Disorders, 5(1), 1–14. https://doi.org/10.3390/gidisord5010001
3. **Tran, T. N.**, Peeters, M., Hoeck, S., Van Hal, G., Janssens, S., & De Schutter, H. (2022). Optimizing the colorectal cancer screening programme using faecal immunochemical test (FIT) in Flanders, Belgium from the "interval cancer" perspective. British journal of cancer, 126(7), 1091–1099. https://doi.org/10.1038/s41416-021-01694-2
4. **Tran, T.N.**; Ferrari, A.; Hoeck, S.; Peeters, M.; Van Hal, G. (2021). Colorectal Cancer Screening: Have We Addressed Concerns and Needs of the Target Population? Gastrointestinal Disorders, 3(4), 173–203. https://doi.org/10.3390/gidisord3040018
5. **Tran, T. N.**, Van Hal, G., Peeters, M., Jidkova, S., De Schutter, H., & Hoeck, S. (2021). Population-Based Data Reveal Factors Associated with Organised and Non-Organised Colorectal Cancer Screening: An Important Step towards Improving Coverage. International journal of environmental research and public health, 18(16), 8373. https://doi.org/10.3390/ijerph18168373

Other publications

1. Ferrari, A., **Tran, T. N.**, Hoeck, S., Peeters, M., Goossens, M., Van Hal, G. (2023). Relationship between health-related determinants and adherence to breast and colorectal cancer screening: a population-based study in Flanders, Belgium. European Journal of Public Health, ckad206. https://doi.org/10.1093/eurpub/ckad206
2. Chan, J. T. N., Nguyen, V., **Tran, T. N.**, Nguyen, N. V., Do, N. T. T., van Doorn, H. R., & Lewycka, S. (2023). Point-of-care testing in private pharmacy and drug retail settings: a narrative review. BMC infectious diseases, 23(1), 551. https://doi.org/10.1186/s12879-023-08480-w
3. **Tran, T.N.**; Hoeck, S.; Janssens, S., Peeters, M.; Van Hal, G. (2023). De impact van FIT-screening op de incidentie, mortaliteit en overleving van darmkanker in Vlaanderen.

OncoHemato, 17(3), 3.

4. **Tran, T.N.**; Hoeck, S.; Peeters, M.; Van Hal, G. (2022). Teleurstellende deelname aan het Bevolkingsonderzoek Dikkedarmkanker in de faciliteitengemeenten: is de taalbarrière het enige probleem? Medi-Sfeer, 708, 41–44.
5. Ferrari, A.; **Tran, T.N.**; Hoeck, S.; Peeters, M.; Goossens, M.; Van Hal, G. (2022). Differences and Similarities in Breast and Colorectal Cancer Screening Uptake among Municipalities in Flanders, Belgium. Gastrointestinal Disorders, 4(2), 84–96. https://doi.org/10.3390/gidisord4020010
6. **Tran, T. N.**, Vu, D. H., Nguyen, H. A., Abrams, S., Bruyndonckx, R., Nguyen, T. T., Tran, N. M., Trinh, T. A., Do, T. H. G., Pham, H. N., Nguyen, G. B., & Coenen, S. (2022). Predicting mortality in intensive care unit patients infected with Klebsiella pneumoniae: A retrospective cohort study. Journal of infection and chemotherapy: official journal of the Japan Society of Chemotherapy, 28(1), 10–18. https://doi.org/10.1016/j.jiac.2021.09.001
7. **Tran, T.N.**, Van Hal, G., Peeters, M., Jidkova, S., Hoeck, S. (2021). Provinciale responsverschillen in het Vlaamse Bevolkingsonderzoek Dikkedarmkanker : inzichten uit gemeentelijke socio-demografische en gezondheidsgerelateerde kenmerken. Tijdschrift voor geneeskunde, 77(9), 724–738. https://doi.org/10.47671/TVG.77.21.144
8. Kebede, W., Abebe, G., Gudina, E. K., Kedir, E., **Tran, T. N.**, & Van Rie, A. (2021). The role of chest radiography in the diagnosis of bacteriologically confirmed pulmonary tuberculosis in hospitalised Xpert MTB/RIF-negative patients. ERJ open research, 7(1), 00708–2020. https://doi.org/10.1183/23120541.00708-2020
9. Nguyen, K. D., **Tran, T. N.**, Nguyen, M. T., Nguyen, H. A., Nguyen, H. A., Jr, Vu, D. H., Nguyen, V. D., & Bagheri, H. (2019). Drug-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in vietnamese spontaneous adverse drug reaction database: A subgroup approach to disproportionality analysis. Journal of clinical pharmacy and therapeutics, 44(1), 69–77. https://doi.org/10.1111/jcpt.12754
10. Nguyen, T. M., Tran, T. H., **Tran, T. N.**, Nguyen, M. H., Can, T. N., Phan, T. P., Nguyen, H. A., Ngo, Q. C. (2019). Analysis of the actual use of antibiotics for acute exacerbation of chronic obstructive pulmonary disease in the Respiratory Centre of Bach Mai Hospital, Vietnam. Pharmaceutical journal, 10:3-8. (http://canhgiacduoc.org.vn/SiteData/3/UserFiles/DH%202019%20so%2010%20tr3-8-%20final.pdf)

PhD portfolio

PhD candidate: Thuy Ngan Tran

PhD period: December 2019 – December 2023

Department: Family Medicine and Population Health (FAMPOP)

Promotors: Prof. dr. Guido Van Hal

Prof. dr. Marc Peeters

Dr. Sarah Hoeck

Competence category	Type of activity	Name of activity	Year	Points
Research skills and techniques	Courses	E-sources Biomedical Sciences	2019-2020	0.2
		Excel: intermediate tips and tricks	2020-2021	0.7
		Creative Problem Solving	2020-2021	0.6
		Cochrane Systematic Review Course for Doctoral Schools	2020-2021	2.1
		Essential tools for R	2020-2021	2.4
		Multilevel analysis	2020-2021	1.5
		Generalized linear models	2020-2021	1.3
		Survival analysis	2020-2021	1.5
		Time series analysis	2020-2021	2.0
		Building Dashboards with shinydashboard	2021-2022	0.4
		Building Web Applications with Shiny in R	2021-2022	0.4
		Case Studies Building Web Applications with Shiny in R	2021-2022	0.4
		Intermediate DAta visualization with ggplot2	2021-2022	0.4
		Introduction to Data Visualization with ggplot2	2021-2022	0.4
		Reporting with R Markdown	2021-2022	0.4
		Systematic review	2021-2022	2.1
		Joining Data into SQL	2022-2023	0.4

		Intermediate SQL	2022-2023	0.4
		Introduction to SQL	2022-2023	0.2
		Data Manipulation in SQL	2022-2023	0.4
		Joining data with data.table in R	2022-2023	0.4
		Data manipulation with data.table in R	2022-2023	0.4
	Reviewing manuscript	Factors related to tuberculosis and survival of its patients in Kermanshah province during 2009-2019 (Journal of Preventive Medicine and Hygiene)	2021-2022	0.1
		Intensive care unit-acquired pneumonia caused by Klebsiella pneumoniae in China: risk factors and prediction model of mortality (Annals of Palliative Medicine)	2021-2022	0.1
		COVID-19 related decline in cancer screenings most pronounced for elderly patients and women in Germany – A claims data analysis (Journal of Cancer Research and Clinical Oncology)	2022-2023	0.1
		The accuracy of the FIT in detecting advanced neoplasm is higher in young people aged 40 to 49 years: An analysis based on sex and age (Journal of Cancer)	2022-2023	0.1
	Co-reader for master thesis	Co-reader for two master theses (Biomedical Sciences) Welke factoren bepalen de participatiegraad aan borstkankerscreening onder vrouwen van de Marokkaanse gemeenschap? (Abou Allal Sanae) Barrières en factoren voor deelname aan het Bevolkingsonderzoek Dikkedarmkanker in Vlaanderen: Een onderzoek onder inwoners van Marokkaanse afkomst (El Fikri Ahlam)	2022-2023	0.2
	Lecture/workshop	Eighth ASCID evening symposium on Current Viral Epidemics	2020-2021	0.3
		Attending the 14th European Public Health Conference 2021	2021-2022	1.5
		Attending Kankercongres 2021	2021-2022	0.4
		Attending the 2nd DiCE Colorectal Cancer Screening Summit	2021-2022	0.3
	Attending Antwerp Doctoral Day	How to create impact from your PhD	2021-2022	0.1
		Managing your career as a PhD	2021-2022	0.1
		More insight into your competence profile: to create a personal development plan	2021-2022	0.1
	Attend research day	Cancer Research Day - UAntwerp	2022-2023	0.6
Research environment	Peer review committee	Peer review commission doctoral study programme	2021-2022	0.8
	Courses	Mind the GAP	2022-2023	1.0
Research management	Courses	Project management	2019-2020	2.1
		Word: Long Documents	2020-2021	0.7
Personal effectiveness	Courses	Achieving your goals and performing more successfully in your PhD	2019-2020	2.4
		Personal Effectiveness	2020-2021	2.1
	International publication (co-	The role of chest X-ray in the diagnosis of bacteriologically confirmed pulmonary tuberculosis in hospitalised Xpert MTB/RIF-negative patients (ERJ Open Research)	2020-2021	1.5

	author)	Differences and Similarities in Breast and Colorectal Cancer Screening Uptake among Municipalities in Flanders, Belgium (Gastrointestinal Disorders)	2022-2023	1.5
	International publication (first author)	Population-Based Data Reveal Factors Associated with Organised and Non-Organised Colorectal Cancer Screening: An Important Step towards Improving Coverage (International Journal of Environmental Research and Public Health)	2021-2022	3.0
		Colorectal Cancer Screening: Have We Addressed Concerns and Needs of the Target Population? (Gastrointestinal Disorders)	2021-2022	3.0
		Optimizing the colorectal cancer screening programme using faecal immunochemical test (FIT) in Flanders, Belgium from the "interval cancer" perspective (British Journal of Cancer)	2021-2022	3.0
		Predicting mortality in intensive care unit patients infected with Klebsiella pneumoniae: A retrospective cohort study (Journal of Infection and Chemotherapy)	2021-2022	3.0
		The Impact of a Six-Year Existing Screening Program Using the Faecal Immunochemical Test in Flanders (Belgium) on Colorectal Cancer Incidence, Mortality and Survival: A Population-Based Study (International Journal of Environmental Research and Public Health)	2022-2023	3.0
	National publication (first author)	Provinciale responsverschillen in het Vlaamse Bevolkingsonderzoek Dikkedarmkanker: inzichten uit gemeentelijke socio-demografische en gezondheidsgerelateerde kenmerken (Tijdschrift voor Geneeskunde)	2021-2022	2.0
	National publication (co-author)	Analysis of the actual use of antibiotics for acute exacerbation of chronic obstructive pulmonary disease in the Respiratory Centre of Bach Mai Hospital, Vietnam (Pharmaceutical journal)	2021-2022	1.0
	National publication without peer review (first author)	Teleurstellende deelname aan het Bevolkingsonderzoek Dikkedarmkanker in de faciliteitengemeenten: is de taalbarrière het enige probleem? (Medi-Sfeer)	2022-2023	1.0
	International publication (last author)	Self-Reported Reasons for Inconsistent Participation in Colorectal Cancer Screening Using FIT in Flanders, Belgium (Gastrointestinal Disorders)	2022-2023	3.0
Communication skills	Courses	Giving presentations in English	2019-2020	1.5
		Writing academic papers	2019-2020	1.2
		Communicating effectively	2019-2020	1.2
		PowerPoint	2019-2020	0.7
		Creating a scientific poster	2020-2021	0.6
		Analytic Storytelling	2021-2022	1.4
	Teaching in higher education	Teaching 2 practical sessions in the course "Clinical Epidemiology" of the Master of Epidemiology	2020-2021	0.6
		Teaching 2 practical sessions in the course "Clinical Epidemiology" of the Master of Epidemiology	2021-2022	0.8
		Teaching practical session '14-day mortality assignment' in the course 'Clinical Epidemiology'	2022-2023	0.2
		Teaching practical session 'Data management' in the course 'Data management and Statistical	2022-2023	0.6

		Softwares		
		Teaching practical session 'Reports and dashboards' in the course 'Data management and Statistical Softwares'	2022-2023	0.6
		Teaching practical session 'Pneumonia assignment' in the course Clinical Epidemiology	2022-2023	0.4
	Giving a presentation at an international conference	Factors associated with organised and non-organised colorectal cancer screening (14th European Public Health Conference 2021)	2021-2022	3.0
	Mid-term presentation of PhD research in DEC	Impact of the colorectal cancer screening programme in Flanders and rooms for improvement	2022-2023	3.0
	Poster presentation	Poster presentation: FIT screening in Flanders has effectively decreased colorectal cancer incidence and mortality and increased survival of the target population (UA Cancer Research Day)	2022-2023	0.5
		Poster presentation: Understanding the molecular and histopathological differences between FIT screen-detected and interval colorectal cancers using data from pathology reports: a study protocol (UA Cancer Research Day)	2022-2023	0.5
Networking and teamwork	Courses	Leadership and teamwork	2019-2020	3.5
		Cross-cultural intelligence	2019-2020	1.0
		Optimizing cooperation in international research groups	2019-2020	1.0
Career management	Courses	Grow your future career	2019-2020	2.1
		What does it mean to be a researcher in 21st century academia?	2021-2022	1.2
		Total		**82.7**

Acknowledgements

The journey of the past four years has been a profound period of growth for me, not only in my knowledge and research skills but also in life. I started my PhD in December 2019, right before the onset of the COVID-19 pandemic, presenting unforeseen challenges. Yet, these difficulties became invaluable lessons that shaped not only my academic pursuits but also my understanding of myself, my aspirations, and my career paths.

I would like to take this opportunity to express my gratitude to all those who have directly or indirectly contributed to my experiences during these significant four years.

First and foremost, my heartfelt thanks to my esteemed supervisors, Guido, Sarah, and Marc. I could not have asked for a better research group to be a part of. The guidance and support you have offered me throughout this journey have been truly invaluable.

Guido, thank you for your trust in me! It was a pleasant surprise to receive your email offering this PhD on Monday, July 29, 2019. The surprise came from the fact that, although you were my PPP professor during the Master of Epidemiology, we did not have the opportunity to work together then. I understand that selecting a PhD student to work with for a typical duration of four years is not always an easy task, which involves more than just assessing grades and skills; it's also about the person themselves, ensuring a good team dynamic. Therefore, I really appreciate the 'risk' you took in offering the position to me even before our first talk. During the PhD, whenever I felt overwhelmed and lacked confidence in myself, I often revisited that very first email for encouragement.

You have always been a kind, gentle, and supportive supervisor. Even on your busiest days filled with meetings, you always made time for me when I had questions. You are incredibly patient, and I never felt pressure from you. You just have your unique ways of reminding your students to complete their tasks. You create a very pleasant and supportive working environment for those around you. I don't know how you manage it in your busy schedule, but throughout my PhD, whenever I needed your feedback for my work, your responses were always very thorough, thoughtful and helpful, and returned promptly. Thanks for being such a wonderful supervisor!

Sarah, my dear 'rough and tough' supervisor, thank you for always being there for me during the past four years! This PhD has benefited a lot from many of your great ideas as the manager of the Flemish CRC screening programme. Even before I joined CvKO, you had already given me insights into how the programme works, its advantages, and the difficulties it faced. You shared stories about the programme's organisational aspects, going beyond what I could obtain from just reading literature and reports. While some of the stories were not directly related to a specific research question in my PhD, in the end, all the pieces came together, providing me with a better understanding of the screening programme. This understanding was instrumental in deriving 'meaning' from data and figures. Also, thanks a lot for introducing me to CvKO; and now, I am proud to be a part of it.

With 'rough and tough', of course, it is not about being 'rough and tough' to me or other colleagues but about your attitude when facing challenges, a quality I have learned from you and am still learning. You never mind confronting uncomfortable situations to protect your students and colleagues when necessary, and always in a polite, professional, and respectful way. As your student, I always felt 100% trusted, supported, and protected. That is the kind of supervisor any PhD student would dream of. Personally, you have always been very sweet, warm, and caring. You are there for me not just when I need help and support for my PhD research but also when I need help in life. You have been a constant source of advice and support, and I am truly grateful for that!

Marc (Peeters), without you, there would not have been this PhD in the first place, for which I am deeply thankful. Unlike with Guido and Sarah, whom I talk to very often, I only met you during the meetings where we discussed the results of my PhD. You did not know it, but I was always really excited about those meetings because I knew you would always bring some other interesting ways of looking into the analyses, ideas about extra explorations, and how to dig deeper into the data. While Guido, Sarah, and I focused more on epidemiology, you brought perspectives from the clinical side, which always made a great combination.

Besides my supervisors, I am also deeply grateful for the guidance and support I received from my advisors and colleagues from the collaborating organisations, including the

Belgian Cancer Registry (BCR), the Insurance Intermutualistic Agency (IMA-AIM) and the Federal Public Service (FPS) Health, Food Chain Safety and Environment.

Thank you, Harlinde, for all your thoughtful and constructive feedback and suggestions for my work. You are an excellent advisor, and I truly admire your knowledge and research skills. I learned a lot from the way you analysed things, approaching them from different perspectives, providing various hypotheses, and suggesting ways for me to explore those hypotheses. Your feedback was always very detailed, with clear instructions and the reasons why you suggested each point. I thoroughly enjoyed the time working with you and am very grateful to have had you as an advisor for my PhD.

Thank you, Sharon and Joanna, for your invaluable help and input during my PhD. I appreciate your efforts in making all the necessary arrangements for obtaining the data from the BCR, as well as IMA, FOD VVVL in a timely manner for my PhD research. Your encouragement at each critical point of my PhD meant a lot to me!

Thank you, Roselien for providing advice on the ethical aspects of the included studies. Thank you, Inge, for your help and willingness to answer all my questions at the beginning of my PhD.

Thank you, Koen (Van Herck), for taking on the task of guiding and supporting me in the last part of my PhD after Harlinde. Although it has not been long since I had the chance to work with you, I am already very impressed by your expertise and research skills. When you review a work, you really make time for it and give all very thorough and constructive feedback, along with thoughtful suggestions. I hope I will have the opportunity to work with you and learn more from you in the coming projects.

I would also like to thank Xavier from IMA and colleagues from FOD VVVL for assisting in preparing the data for our study on colonoscopy complications. Although it was initially intended for this PhD, it was excluded in the end due to not aligning with the central theme throughout the PhD. Nevertheless, we are confident that it will soon result in a valuable publication.

I would like to extend my gratitude to the internal jury members, Prof. Sven Francque and Prof. Peter Van Bogaert, for dedicating their time to reviewing my work and providing

constructive and helpful feedback throughout the trajectory of my PhD. Additionally, I want to express my thanks to the external jury members, Prof. Danny De Looze and Prof. Iris Lansdorp-Vogelaar, for their critical evaluation, and valuable constructive feedback on the PhD thesis, which I truly appreciate.

I also wish to express my gratitude to my colleagues at the Centre for Cancer Detection (CvKO). Special thanks to Dr. Patrick Martens and the research board for approving the included studies in this PhD. I am so thankful that, after 2.5 years as a PhD student working on CvKO data, CvKO warmly welcomed me as an employee last year. The past year has provided me with a deeper and more thorough understanding of the colorectal cancer screening programme, as well as the breast and cervical cancer screening programmes. This enhanced understanding has been instrumental in enabling me to discuss the results of my PhD in a more comprehensive manner.

I would like to thank Ms. Svetlana Jidkova, for her assistance in explaining CvKO data to me when I first started working with it. Thank you, Svetlana, for preparing the data and for providing your input for the first study in my PhD.

I would like to thank my dear colleagues in the data team at CvKO. I want to acknowledge Marc (Van Cauwenberghe) for his support in offering me flexibility over the past few months. This allowed me to complete my tasks at CvKO optimally while simultaneously finalising my PhD. A special thank you to Patrick (Beyltjens) and Marieke for your continuous encouragement. The understanding and support of you all have been invaluable to me.

I would like to thank Sofie for being a very warm and kind colleague who has done a great job fostering a strong bond among members in the team wherever she is. Thank you, Sofie, for teaching me to approach data from a different perspective. You reminded me for example, while achieving a 95% rate of people receiving their screening results on time is already an accomplishment to be proud of, the remaining 5% also holds significance. Every individual matters, they could be our family members, friends, and relatives. Thank you for being so warm-hearted and for all the enjoyable conversations we've had.

Thank you, Ina, Sandra, Marjoke, Charlotte, and the other colleagues at CvKO whom I

have not had a chance to get to know more personally, for a warm welcome to CvKO. I've promised myself to learn Dutch diligently after finishing this PhD, so that I can get to know you better.

I would like to thank my colleagues and fellow PhD students in the Social Epidemiology & Health Policy group for adding vibrant colours to my PhD journey. Hanna, you're not just a colleague but also a dear friend. We have connected so well, sharing the highs and lows of our PhD experiences as well as life, creating beautiful moments that I truly treasure. Thank you, Deborah, for bringing your lovely and positive vibes to the office, even when it's only 'twice per month'. I admire your hard work and appreciate how effortlessly you maintain a 'chill' manner each time we meet. To Allegra, thank you for the fantastic experiences we've had working together. Your dedication, hard work, and ability to enjoy life to the fullest are truly admirable. Looking forward to more fruitful collaborations in the future. Charlotte and Febe, thank you for the interesting conversations during lunch. Thank you all for creating such a positive and supportive group!

Thank you, Wessel, for sharing your experiences and offering advice at the beginning of my PhD journey. I appreciate the opportunity to contribute to the preparation of the Orient application, which was a valuable experience for me. Your successful completion of your PhD has always been a source of inspiration for me throughout my PhD.

Thank you, Koen (De Schrijver), for always bringing interesting discussions to our office, from research, to sport, to culture, and more. And it was not just talks; you sometimes also brought us delicious cookies and chocolates.

I would like to thank Ms. Kristin Deby for her assistance in organising all the administrative steps in between. Thank you, Kristin, for all the instructions and help you have provided me along the way, especially during the stages of preparing for the PhD thesis and defence. Without you, things would not have gone so smoothly.

I would like to express my gratitude to all my professors from the Master of Epidemiology, University of Antwerp. They provided me with a very solid foundation for further development. After the completion of the master's programme, I have always had

confidence in my research skills, methodological knowledge, and data analysis abilities. While I may not know everything, I am assured that I possess the fundamental knowledge and skills to continually advance and grow.

Last but not least, I want to express my deepest gratitude to my family for their unconditional love and support.

Thank you, Dat, my loving husband, for always being there for me, and for putting up with me during times when I was at my lowest. Your patience in listening to all my irrational stories, from days of highs to lows, is truly appreciated. I'm confident that you've witnessed significant growth in me throughout this PhD journey. We often joke about how I initially approached my PhD, recognising that I might not have taken the smart and efficient route. However, we both agree that we learn from these less-than-smart approaches to become smarter, and there are no shortcuts. Thanks for lifting my spirits, teaching me not to take things too seriously, and encouraging me to pursue what I love for my own fulfilment, not to prove anything to others. Thank you for showing me how to gain genuine confidence - something that doesn't require achieving something grand or chasing external validation, but rather finding contentment within myself and taking pride in what I do.

I'm also grateful for the sound suggestions you provided for my research, even though you work in a completely different field as an engineer. Your fresh perspective has been a valuable advantage, offering great ideas whenever I found myself stuck.

Thank you, Minh, my beloved son, for being my greatest source of energy. Whenever I feel tired, just talking to you, watching you play and laugh, and hugging you in my arms energize me, making me feel so much better. This PhD journey has not only been a learning experience for me but for you as well. You've learned R, HTML, Python, Google Docs, and Google Forms by yourself, becoming mommy's helpful assistant. You have been a constant reminder for me to find happiness in what I have. One evening, after a long day of data analysis when my eyes were tired, you came to me and said, 'Mommy, I envy you. I was allowed to have only two hours programming today, but you had the whole day working with codes.' That’s very true, my dear; I should appreciate it. You're an understanding, sweet, and gentle boy who's always ready to protect your mom. When

you see me with a busy schedule, you always make an effort to arrange something nice for us to watch or enjoy together at the end of the day. You generously share the nicest bites and the best things you have with mommy.

I hope this PhD has been an opportunity for both your dad and me to show you that things don't come easy without time and effort. However, when we pursue things that we love and are passionate about, we willingly face challenges because we know they add colours to our journey and contribute to our growth.

To my parents, my parents-in-law, my brother, my sister-in-law, I'm deeply grateful for your unconditional love and support. I look forward to expressing my thanks to you in person when we visit you during the Christmas holiday.

Among those who have provided me with help and support throughout the years, I may have forgotten to mention a few, but please rest assured that I am grateful for each and every one of you!

About the author

Thuy Ngan Tran was born in 1989 in Hanoi, Vietnam. She pursued her study in Pharmacy at the Hanoi University of Pharmacy, Vietnam, from 2007 to 2012, earning a bachelor's degree in Pharmacy. Following her undergraduate study, she dedicated five years to working as a drug information specialist and researcher at the Vietnam National Centre for Drug Information and Adverse Drug Reactions Monitoring. Her research during this time mainly focussed on adverse drug reactions reporting and monitoring, as well as antimicrobial resistance. From September 2017 to July 2019, she undertook the Master in Epidemiology programme at the University of Antwerp, Belgium, supported by a fully funded scholarship from the Flemish Interuniversity Council for University Development Cooperation (VLIR-UOS). In December 2019, she began her PhD journey, focussing on 'Colorectal cancer screening in Flanders' at the Department of Family Medicine and Population Health (FAMPOP), University of Antwerp, under the supervision of Prof. dr. Guido Van Hal, Prof. dr. Marc Peeters, and Dr. Sarah Hoeck. In August 2022, she started working as a data analyst at the Centre for Cancer Detection (CvKO), Belgium. She completed her PhD in December 2023, and the findings of her research are presented in this thesis.