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The national FIT-based colorectal cancer screening program in the Netherlands during the COVID-19 pandemic

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ABSTRACT

The COVID-19 pandemic has affected many healthcare services worldwide. Like many other nations, the Netherlands experienced large numbers of individuals affected by COVID-19 in 2020, leading to increased demands on hospitals and intensive care units. The Dutch Ministry of Health decided to suspend the Dutch biennial fecal immunochemical test (FIT) based colorectal cancer (CRC) screening program from March 16, 2020. FIT invitations were resumed on June 3. In this study, we describe the short-term effects of this suspension on a myriad of relevant screening outcomes. As a result of the suspension, a quarter of the individuals due for screening between March and November 2020 had not received their invitation for FIT screening by November 30, 2020. Furthermore, 57.8% of those who received a consecutive FIT between the restart and November 30, 2020, received it outside the upper limit of the standard screening interval (26 months). Median time between positive FIT and colonoscopy did not change as a result of the pandemic. Participation rates of FIT screening and follow-up colonoscopy in the months just before and during the suspension were significantly lower than expected, but returned to normal levels after the suspension. Based on the anticipated 2020 cohort size, we estimate that the number of individuals with advanced neoplasia currently detected up until November 2020 was 31.2% lower compared to what would have been expected without a pandemic. Future studies should monitor the impact on long-term screening outcomes as a result of the pandemic.

1. Introduction

The COVID-19 pandemic is having a profound impact worldwide. As of May 2021, over three million individuals have died from COVID-19 worldwide despite the implementation of rigorous regional and national measures to prevent infection (e.g. (partial) lockdowns, facial mask requirements, and contact tracing).(Dong et al., 2020; Hale et al., 2020) Many other patients with COVID-19 required hospitalization, including admission to intensive care units, which is challenging the provision of regular health care. To prevent overburdening of health systems and to ensure the safety of health care workers and patients, a lot of non-urgent health care worldwide was curtailed during the spring of 2020, including colonoscopies in colorectal cancer (CRC) screening programs.(Parasa et al., 2020) Likewise, the CRC screening program using a fecal immunochemical test (FIT) in the Netherlands was temporarily suspended for 11 weeks from March 16, 2020.

Suspending CRC screening may affect several screening outcomes. Individuals due for screening during the suspension did not receive their expected invitation until June 2020 or later. This may have led to increased intervals between two subsequent screening invitations or a delayed start of screening for those invited for the first time. Secondly, participation to FIT or follow-up colonoscopy may have decreased because of fear of infection with the coronavirus. Potentially, individuals whose screening was cancelled or delayed will present at a

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later moment with more advanced disease and worse outcomes.

In this study based on data from the Dutch CRC screening registry, we aimed to assess the short-term impact of the suspension of the Dutch CRC screening program due to the first wave of COVID-19 cases on various screening outcomes, including screening capacity, participation to FIT and follow-up colonoscopy, screening intervals, time between FIT and colonoscopy, and detection rates of CRC and advanced neoplasia (AN).

2. Methods

2.1. CRC screening in the Netherlands

The FIT-based screening program for CRC started in 2014 and was fully implemented in 2019. Individuals aged 55 to 75 years automatically receive an invitation and a FIT (FOB-Gold, Sentinel Diagnostics, Milan, Italy) every two years by mail, except those who explicitly indicate that they do not wish to participate in screening. A positive test result is defined as a FIT concentration of 47 microgram Hemoglobin per gram (μg Hb/g) feces or higher. All participants receive their result by mail. FIT-positive individuals automatically receive an appointment at a local accredited endoscopy clinic for an in-person intake, during which they receive information on the colonoscopy procedure and bowel preparation, and their ASA score is determined.(Bronzwaer et al., 2019) The screening organizations aim to plan the intake within 15 working days after a positive FIT result. Preferably within 15 days after intake, the FIT-positive individual undergoes a colonoscopy performed by an accredited endoscopist. All relevant screening data are captured in the national CRC screening database called ScreenIT. The Dutch CRC screening program is commissioned by the Dutch Ministry of Health and executed by the five regional screening organizations under supervision of the National Institute for Public Health and the Environment (RIVM).

2.2. Data collection

This study included aggregated data on the epidemiological situation of COVID-19 in the Netherlands, and aggregated data of the Dutch CRC screening program. Epidemiological data was extracted from publicly available databases of RIVM comprising of data of patients with PCR or CT (CO-RADS 4–5) proven COVID-19 from all hospitals and municipalities in the Netherlands.(COVID-19 dataset: National Institute for Health and the Environment (RIVM), n.d.) Data on the Dutch CRC screening program in 2018, 2019 and 2020 was extracted from ScreenIT. This dataset did not contain data on participation in colonoscopy intakes and pathology reports due to technical reasons. The screening data was recorded between January 1, 2018, and November 30, 2020, and extracted on December 15, 2020. Colonoscopy data was updated on March 26, 2021. Individuals participating in the screening program have the right to have their data excluded from analyses performed for scientific research. Consequently, data from approximately 700 individuals between 2014 and 2020 who objected to data exchange were excluded from the analysis. Ethical approval was not needed for this study.

2.3. Measures and definitions

The outcomes of interest were divided into five sections: screening capacity, screening interval, participation to FIT and colonoscopy, time to colonoscopy, and detection of CRC and AN. Outcomes of interest for screening capacity included the number of available and planned intake slots, and the number of FIT invitations sent. The number of FIT invitations sent is based directly on the number of intake slots that endoscopy clinics offer to the screening organizations seven weeks later. Prolonged screening interval was defined as an interval between two consecutive FIT invitations longer than 26 months, since the standard screening interval within the Dutch CRC screening program is 22–26 months. We measured the delay beyond 26 months in days. Individuals invited for their first screening round were not included in the analysis for this particular outcome.

For outcomes related to participation, we examined the participation rates with FIT and follow-up colonoscopy. The participation rate with FIT was defined as the percentage of individuals that had completed and returned the FIT out of all invitees. We included the participation rates up until September 2020, because the participation rates of October and November 2020 were largely incomplete at the time of data extraction. The participation rate to follow-up colonoscopy was the percentage of FIT-positive individuals attending the intake for whom a colonoscopy was planned. Time to colonoscopy was defined as the number of working days between a FIT-positive result and a colonoscopy.

Finally, we examined the reduction in detection of individuals with advanced neoplasia by comparing the observed detection with the expected number in a situation without COVID-19. The expected number of individuals with screen-detected AN was estimated using observed screening outcomes from 2020 (number of eligible individuals, FIT-positivity rate, and PPV of FIT), and expected participation to FIT and colonoscopy in 2020. Expected participation to FIT and colonoscopy 2020 was estimated using the mean participation rates of 2018 and 2019, because these years are the most comparable to 2020 with regard to age distribution of the screening population. To estimate the proportion of the effect attributable to the decline in participation, we performed the same calculation with the observed participation rates. Advanced neoplasia was defined as either CRC or an advanced adenoma, based on the judgement of the endoscopists. All endoscopists were trained with the NICE and JNET classifications.(Hewett et al., 2012; Sano et al., 2016)

2.4. Statistical analysis

We performed linear regression analyses to estimate the effects of COVID-19 on participation rates in FIT screening and follow-up colonoscopy. In the regression, we included participation to either FIT or follow-up colonoscopy as the dependent variables and dummy variables representing the suspension and recovery of the Dutch CRC screening program as independent variables. For the participation rates of follow-up colonoscopy, we assumed that the suspension occurred from March to May 2020. Recovery of the Dutch CRC screening program was assumed from June to November in 2020. Besides suspension and recovery, we also included variables for month and calendar year to correct for monthly and annual fluctuations in participation rate. For the participation rates to FIT, the same independent variables were used, but we left out the months April and May 2020, since there were no FIT invitations sent during this period. In addition, we performed a sensitivity analysis for FIT participation, in which we assumed that the effect of COVID-19 and the suspension already occurred in February.

Means, medians, and percentiles were calculated through standard data queries. *P*-values below 0.05 were considered to indicate statistically significant differences. Statistical analyses were performed with the R statistical package.(R Core Team, 2020)

3. Results

3.1. Suspension of CRC screening in the Netherlands

The Dutch Ministry of Health decided to temporarily suspend the Dutch CRC screening program on March 16, 2020 (Fig. 1). The screening organizations stopped sending FIT invitations and requested those who recently received a FIT invitation not to perform and return their FIT until further notice. Scheduled intakes and follow-up colonoscopies were allowed to go ahead. Based on an increase in available colonoscopy capacity and declining COVID-19 hospitalization rates, the decision was made on May 11 that there would be a phased restart of the screening program according to the first-in-first-out principle. From May 19,

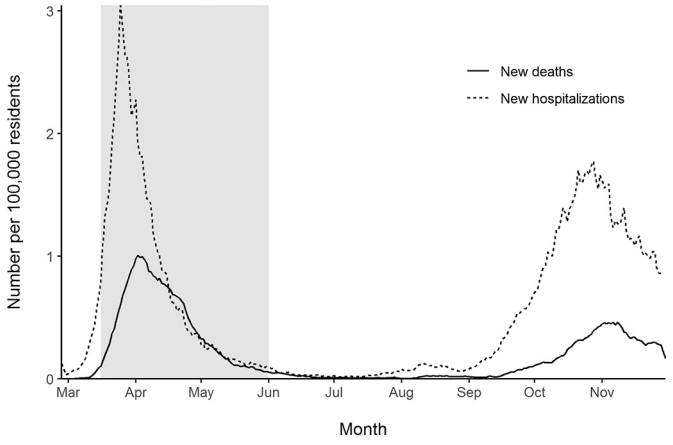

Fig. 1. 5-day rolling averages of daily new hospitalizations and deaths per 100,000 residents in de Netherlands due to COVID-19 in 2020. The grey area highlights the period in which the Dutch CRC screening program suspended the dispatch of FIT invitations.

individuals who were previously told to retain their FIT were invited to participate. Screening organizations dispatched new FIT invitations from June 3, according to the available capacity. Screening was resumed without alterations to standard screening processes.

3.2. Screening capacity

The number of available intake slots decreased drastically from April 2020, coinciding with a peak in the number of COVID-19 cases (Fig. 1, Fig. 2 and Table S1). The number of intake slots that were actually planned by the screening organizations decreased from March 2020, coinciding with the suspension of the screening program. The same was observed for the number of sent FIT invitations (Fig. 3). Following the restart of the program, the monthly volume of FIT invitations restored to pre-pandemic levels in July. Both the number of intake slots available and the proportion of planned slots were restored to pre-pandemic levels in September 2020.

There was a marked increase in FIT invitations sent in the second half of 2020: It increased by 25.7%, 39,9%, and 26.6% in September, October, and November 2020 respectively compared to the average number of invitations sent in these months in 2018 and 2019. Despite this catch-up, the total number of FIT invitations sent between March 1 and November 30, 2020 was 383,311 (23.5%) lower than in the same

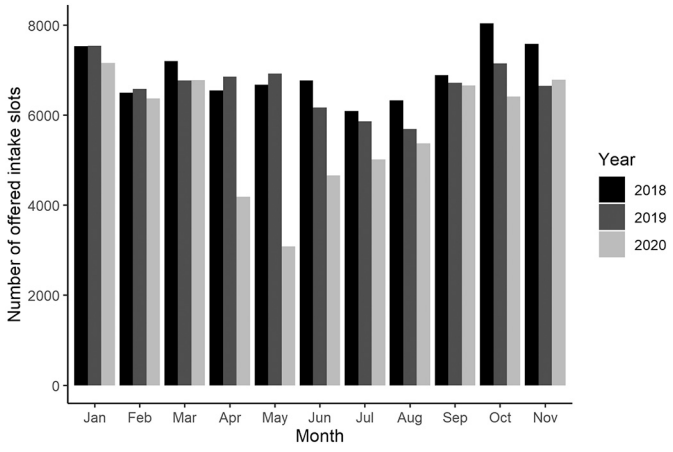

Fig. 2. Monthly number of intake slots for follow-up colonoscopy offered by the endoscopy centers in the Dutch CRC screening program in 2018, 2019 and 2020.

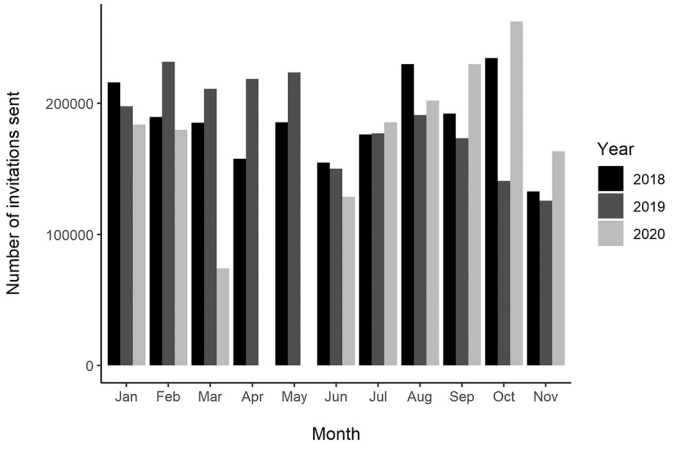

Fig. 3. Monthly number of invitations for FIT screening sent in the Dutch CRC screening program in 2018, 2019, and 2020.

period in 2018 and 2019.

3.3. Screening interval between two consecutive FIT invitations

Before the suspension, the percentage of individuals eligible for screening that received a consecutive FIT more than 26 months after their previous invitation was <1.0% (January 2018 – March 2020). In the months following the suspension, the percentage of individuals receiving their FIT after more than 26 months increased drastically: 85.5% of the individuals eligible for screening in June 2020 had a screening interval of more than 26 months (Table 1). This dropped to 39.2% in November 2020 as the rate of invitations increased late 2020. From the restart until November 30, 2020, 628.987 individuals (57.8%) had received the FIT invitation more than 26 months after their previous FIT invitation. The median delay for those who received a FIT after a 26-month interval was at most 45 days.

3.4. Participation to FIT screening and colonoscopy

FIT participation dropped to 66.7% and 64.7% in February and March 2020 respectively, compared to an average 71.7% and 71.5% in February and March 2018 and 2019. The drop corresponds directly to the time before and during the onset of strict lockdown measures and the suspension of the screening program in the Netherlands (Fig. 4A). Adjusted for monthly and annual fluctuations, and assuming the initiation of the pandemic in the Netherlands in March 2020, the drop in FIT participation in March 2020 was not statistically significant ($p = 0.09$) compared to all other months before and after the suspension. However, assuming the pandemic started in the Netherlands in February 2020, FIT participation significantly decreased by 4.0 percentage points in

Table 1
Absolute and relative number of invitations sent beyond the standard interval of 22–26 months in 2020. Median and interquartile range of days beyond the 26-month interval.

Month	Number of sent invitations	Number of sent invitations outside standard interval	%	Q25	Median	Q75
June	115,550	98,820	85.5%	17	23	32
July	177,047	124,709	70.4%	15	29	50
August	190,845	118,448	62.1%	21	43	58
September	216,419	117,209	54.2%	27	45	69
October	240,398	111,846	46.5%	23	32	62
November	147,703	57,955	39.2%	21	37	60

Abbreviations: Q25, 25-percentile quartile; Q75, 75-percentile quartile.

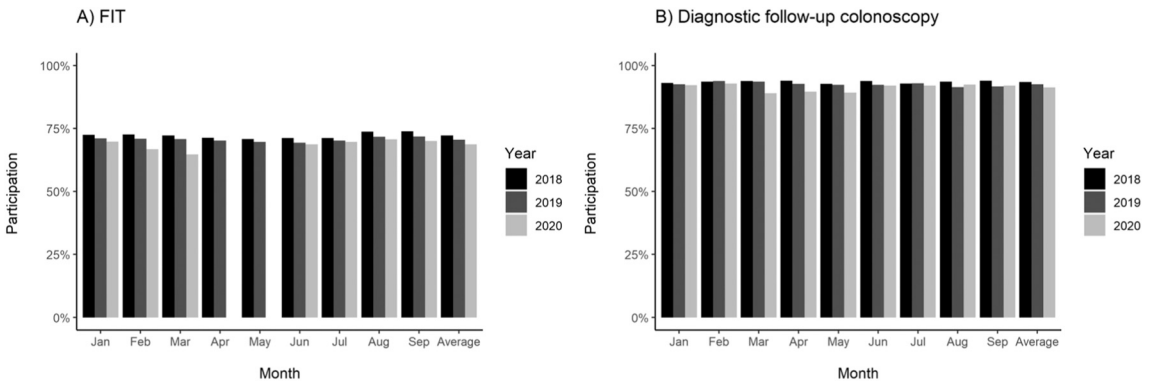

Fig. 4. Monthly participation to FIT (A) and diagnostic follow-up (B) screening in the Dutch CRC screening program in 2018, 2019 and 2020.

February and March 2020 compared to all other months ($p = 0.02$). After restart of the program (July – November 2020), FIT participation was not significantly different from previous years. Participation to follow-up colonoscopy was lower during the suspension and the coinciding first wave (Fig. 1, Fig. 4B). Linear regression analysis adjusting for monthly and annual fluctuations showed that the participation to follow-up colonoscopy was statistically significantly lower during the suspension of the screening program compared to all other months ($p < 0.0001$).

3.5. Time to follow-up colonoscopy after positive FIT

The median interval between a positive FIT and colonoscopy from January until November 2020 was similar to that in 2019 (both 20 working days). However, this interval increased to a median of 29 working days for participants who had received their result in March 2020 (Table 2). Participants who received their FIT result in and after April 2020 had a time to colonoscopy similar to pre-pandemic levels.

3.6. Effect of COVID-19 on detection of CRC and AN

Screening-related diagnoses of CRC and AN between January 1, 2020, and November 30, 2020, were markedly lower than during the same months in previous years (Table 3). Due to the effects of COVID-19 on participation rates and invitation volume, the number of individuals with screen-detected CRC or AN during this period was 31.2% lower than expected. In absolute terms, an estimated 5500 individuals with AN were estimated not to be detected due to the effects of COVID-19, of which around 800 would have been diagnosed with CRC. A substantial part of this difference, 21.4 percentage points, is estimated to be caused by the decrease in invitation volume.

Table 2
Monthly time to colonoscopy in 2020 based on date of positive FIT result. Appointments that were postponed at the request of the screenee are excluded. Time in working days.

Month	Individuals with a positive FIT and a colonoscopy	Q25	Median	Q75	% time to colonoscopy ≥30 working days
January	6024	14	18	25	14.6%
February	4639	16	22	40	30.8%
March	3606	19	29	54	47.7%
April	240	19	23	29	18.3%
May	308	12	16	21	10.4%
June	1512	10	13	18	8.8%
July	3343	12	16	22	12.2%
August	3815	12	16	21	10.2%
September	5026	14	18	23	12.1%
October	6307	17	21	27	17.5%
November	5320	19	25	34	32.4%

Abbreviations: FIT, fecal immunochemical test.

Table 3
Number of CRC, AA, and AN diagnoses and PPV (%) from January 1 to November 30 for 2018, 2019, and 2020.

	2018	2019	2020
CRC	3681 (6.4%)	3004 (5.7%)	1770 (5.0%)
AA	19,397 (33.8%)	16,004 (30.2%)	10,232 (28.7%)
AN	23,078 (40.3%)	19,008 (35.9%)	12,002 (33.7%)

Abbreviations: CRC, colorectal cancer; AA, advanced adenomas; AN, advanced neoplasia; PPV, positive predicted value.

4. Discussion

This study examined the short-term effects of the suspension of the Dutch FIT-based CRC screening program in response to the first wave of cases with COVID-19. We observed lower screening participation rates, more individuals with a prolonged screening interval, and fewer diagnoses of CRC and AN due to suspension. However, we also observed that the Dutch screening program was resilient as participation rates quickly bounced back following the suspension and the time to colonoscopy was hardly affected.

In line with previous studies, we observed a sharp decline in the number of CRC and AN diagnoses during the height of the first wave of COVID-19 cases.(Dinmohamed et al., 2020; de Pelsemaeker et al., 2021) We estimated that this number decreased by almost a third corrected for the decrease in invitation volume and participation rates. The majority of this decrease was driven by the drop in screening invitations during the suspension. One third of the effect can be attributed to a decrease in participation to FIT and colonoscopy, although this number may fall as individuals who declined screening with FIT and/or colonoscopy during COVID-19 may still reconsider their decision.

Our data indicates that only invitations sent in February and March were significantly less likely to be returned. This coincides with a period just before and during the suspension of the screening program and with a period with a high number of COVID-19 cases. The decrease could be explained by fear of infection, or because individuals, from an altruistic perspective, did not want to place further load on a strained healthcare system because of COVID-19. Another plausible explanation may be that individuals who were told not to return the FIT during the suspension, were less likely to return it when screening resumed. In contrast, FIT participation after the suspension was not significantly lower. Our findings differ from those of a Taiwanese study in a FIT-based screening program.(Cheng et al., 2020) This study showed that screening participation decreased by 3.5 percentage points in Q4 2019 and Q1 2020 compared to the same period in previous years, even though the number of COVID-19 cases was far lower in Taiwan compared to the Netherlands throughout the pandemic. One factor that may have contributed to

resilient participation rates in the Netherlands may have been media attention on the importance of screening in general and GP visits during COVID-19. There were no official public campaigns to boost CRC screening participation however.

Similar to FIT participation, we observed a decrease in participation to colonoscopy during COVID-19's first wave. Cheng et al. also noted a decrease in colonoscopy participation.(Cheng et al., 2020) For half of the individuals concerned in their study, fear of infection was the reason to cancel or reschedule the colonoscopy. We do not have data for the reasons behind the decrease in participation in our study. Since it occurred during a period with many cases of COVID-19, it may indicate a decrease in the willingness to undergo a colonoscopy due to fear of infection in the Netherlands as well.

Another cause of the drop in diagnoses was the effect of the suspension on the number of FIT invitations sent. This number decreased by almost a quarter between March and November 2020. Interestingly, the backlog was initially larger. From September 2020, we observed that screening organizations were catching up by increasing the invitation volume, supported by increased utilization of the available capacity (Table S1). If they manage to sustain this catch-up rate, the backlog may be cleared as soon as mid-2021, although future waves of COVID-19 cases may interfere. On top of this backlog, more than half of those who received a consecutive FIT during this period received it later than the standard screening interval of 26 months. The median interval of those with a prolonged interval was between 27 and 28 months. Finally, the average time from positive FIT to colonoscopy in 2020 did not change and stayed within the recommended 30 days.

It is feared that any significant delay in screening may lead to excess CRC-related mortality. Studies in FIT-positive individuals indicated that an increased time to colonoscopy of more than 6–12 months increased the risk of CRC-related mortality.(Corley et al., 2017; Forbes et al., 2020; Kaalby et al., 2019; Lee et al., 2019; Ricciardiello et al., 2020; Riley et al., 2020; Zorzi et al., 2020) Our data suggests that the suspension of the Dutch CRC screening program did not lead to such delays. Nevertheless, a comparative modelling study conducted on behalf of the COVID-19 and Cancer and Cancer Global Modelling Consortium (CCGMC) predicted that CRC-related deaths in the Netherlands could increase up to 0.3% between 2020 and 2050 in case of a 3 months disruption without catching up and with unaffected participation rates after restart.(de Jonge et al., 2021) This excess mortality could almost completely be mitigated in case of catching up missed individuals, which is already happening as can be observed in our study.

One of the strengths of this study is that we were able to analyze nationwide and up-to-date data on a myriad of relevant screening outcomes, including participation rates, screening intervals between two consecutive FITs, time to colonoscopy, and colonoscopy findings. This enables a broad view on the impact of COVID-19 on a biennial FIT-based program using mailed-out tests, a screening strategy some screening programs have considered to use during the pandemic as an alternative for primary colonoscopy or flexible sigmoidoscopy screening.(Gupta and Lieberman, 2020)

A limitation of this study is that we did not have individual data, which made certain analyses not possible. This includes corrections on our data for age and screening round, which may have accounted for some of the differences we have found between years, for example yield of FIT and participation rates. Furthermore, some data was not available in ScreenIT, for example data on the participation rates with intakes themselves and data on the reasons for colonoscopy non-attendance. Another limitation is that reported participation rates in 2020 may still rise, because individuals may return their FIT at a later moment. For this reason, we excluded the FIT invitations dispatched in October and November 2020 in the analysis of participation rates, since there was little time between these months and the date of data collection. Finally, data on CRC and AA detection was derived from colonoscopy reports rather than pathology reports. In the annual evaluation of CRC screening in the Netherlands, in which pathology reports are included, the number of individuals with AN was 24,538 and 21,140 in 2018 and 2019 respectively.(National Institute for Health and the Environment (RIVM), n.d.) In our study that is based on colonoscopy reports only, we found 23,078 and 19,008 individuals with AN in 2018 and 2019 respectively. This suggests that the actual and expected numbers of AN diagnoses in 2020 may be slightly higher than we reported.

5. Conclusion

Notwithstanding these limitations, this study clearly shows that the suspension of the CRC screening program in the Netherlands as a result of the emergence of COVID-19 has resulted in a large backlog of individuals who were due for screening and a 31.2% decline in the number of screen-detected individuals with AN. However, our data also suggests that once screening was resumed the participation to FIT remained high and that a part of the backlog could be cleared. In addition, the median delay between two consecutive FIT invitations due to the suspension was relatively short and the time to colonoscopy did not increase. Further studies are needed to assess the long-term impact of COVID-19 on CRC screening.

Declaration of Competing Interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ypmed.2021.106643.

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