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Association between use of low-dose aspirin and detection of colorectal polyps and cancer in a screening setting

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ABSTRACT

Background: The possible protective effect of aspirin on risk of colorectal cancer (CRC) is still highly debated.
Methods: We used data from Bowel Cancer Screening in Norway, a trial randomizing individuals from general population, aged 50-74 years, to flexible sigmoidoscopy or faecal immunochemical test (FIT), to study the association between aspirin use and detection of CRC and two CRC precursors: adenomas and advanced serrated lesions (ASL). Prescriptions of low-dose aspirin were obtained from Norwegian prescription database. Logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs).
Results: Among 64,889 screening participants (24,159 sigmoidoscopy, 40,730 FIT), 314 (0.5%) had CRC, 6,208 (9.6%) adenoma and 659 (1.0%) ASL. Overall and short-term use (<3 years) of low-dose aspirin, versus no use, were not associated with any colorectal lesion. Long-term use (≥3 years) was associated with lower detection of CRC (overall OR 0.66, 95%CI 0.46-0.93; sigmoidoscopy: 0.56, 0.33-0.97; FIT: 0.72, 0.45-1.15), adenomas in sigmoidoscopy arm (overall OR 0.95, 95%CI 0.87-1.03; sigmoidoscopy: 0.89, 0.80-0.99; FIT: 1.03, 0.89-1.18), but not ASLs. We did not observe significant differences in the effect of aspirin according to the location of colorectal lesions.
Conclusion: Our results suggest that long-term use of aspirin might have a protective effect against adenomas and colorectal cancer, but not ASLs.

1. Introduction

Worldwide, colorectal cancer (CRC) has the third-highest incidence of all cancers, with more than 1.9 million new cases in 2020 [1]. Over the last three decades, there have been decreasing trends in incidence [1–3], mainly due to improved lifestyle behaviours and the implementation of screening programs [4,5].

Chemoprevention is an additional strategy that has been long studied to lower the incidence of CRC, with aspirin being the most studied agent for chemoprevention of CRC and its precursor lesions [6,7]. In the last three decades, several observational studies have shown promising results on the association between aspirin use and primary prevention of colorectal adenomas [8,9] and cancer [8,10–13]. Yet, some other studies, including randomized controlled trials (RCTs), have not confirmed those results, neither for adenomas [14] nor for CRC [14–16], especially in individuals older than 70 years [17,18], and for limited duration of aspirin use [19,20]. A possible explanation for these conflicting findings might be the large variations in the administration plans of aspirin in the different studies, including dosage and duration of use [8,21,22]. Notably, while in 2016 the U.S. Preventive Services Task Force recommended the initiation of low-dose aspirin for CRC prevention in

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average-risk adults aged 50-59 years [23], after the recent contradictory findings, the same task force removed that recommendation in 2022 [24].

Only a few studies investigated aspirin use as primary prevention for CRC and colorectal polyps taking into account the histopathological and molecular features of these lesions. There is promising evidence of a protective effect of aspirin on adenomas [8,9], but the effect of aspirin on serrated lesions is largely unknown. Though one study found a protective effect of aspirin against large serrated polyps [25], two other studies found no association between use of aspirin and cancers believed to originate from serrated lesions [26,27].

The possible protective effect of aspirin against colorectal neoplasia, optimal administration plan and mechanism of action remain highly debated. Moreover, the evidence of aspirin's effects according to the molecular and histopathological features, stage, and anatomical site of lesions is still unclear. In a large Norwegian CRC screening trial, we investigated the association between the use of aspirin and detection of CRC and colorectal polyps according to the lesions' stage, site, and histopathological characteristics.

2. Methods

2.1. Design and population

This cross-sectional study uses data from the randomized pilot trial of Bowel Cancer Screening in Norway (BCSN) [28]. In this trial, 140,000 individuals were invited to either sigmoidoscopy or faecal immunochemical test (FIT) in a 1:1 randomized fashion [28]. For the present study, we extracted data in 2017, before the enrolment in the sigmoidoscopy arm was completed, and included 24,159 participants who attended sigmoidoscopy and 40,930 who attended the first round of FIT between 2012 and 2017. Participants with a positive FIT (> 15 microgram haemoglobin per gram faeces) or positive sigmoidoscopy (any polyp ≥ 10 mm, ≥3 adenomas, any advanced adenomas, or CRC) were invited to attend a follow-up colonoscopy [28]. Two hundred FIT-positive attendees did not undergo a colonoscopy and were excluded from this study.

Sociodemographic data were retrieved from Statistics Norway (SSB) and included marital status (recategorized as married or having a cohabitant/not married or not having a cohabitant), immigration status (Norwegian/immigrant), education (primary school/secondary (high school)/≤4 years university/>4 years university), employment status (employed/unemployed/ outside of workforce or retired), and household income (recategorized in quartiles). Only individuals born outside of Norway to non-Norwegian parents were defined as immigrants. Age, sex, and screening centre were retrieved from the BCSN trial database. Data on medication prescriptions covering four years before screening invitation were obtained from the Norwegian Prescription Database (NorPD), which does not include over-the-counter use of medications. To be used as a proxy for co-morbidities, we included drugs used in diabetes (anatomical therapeutic chemical (ATC) code A10), antithrombotic agents (group B01, drugs other than aspirin), cardiac therapy (C01), diuretics (C03), antihypertensives including beta-blockers (C07), calcium channel blockers (C08), agents acting on the renin-angiotensin system (C09), psycholeptics (N05), antidepressants (N06A), drugs for obstructive airway diseases (R03). Where prescriptions included a combination of different drug/drug classes, it was included in both agents' categories. The data from the two registries, SSB and NorPD were linked to the screening data using 11-digit unique Norwegian personal identification numbers.

2.2. Main exposure

Data on exposure to aspirin (ATC codes B01AC06, B01AC56) were available only for the four years before invitation. All the retrieved aspirin prescriptions had low-dose formulations (<325 mg). We divided the exposure period into four distinct years. If an individual received two prescriptions in one of the four years, then he/she was considered a user in that specific year. If an individual was a user for three or four years, then he/she was considered a long-term user (≥3 years). If an individual was a user for one or two years, then he/she was considered a short-term user (<3 years). All other individuals were considered non-users. In some analyses, we combined short and long-term users in the broader category of users.

2.3. Outcome

Using the most advanced lesion for each participant, findings were categorized as: no lesions, non-advanced adenomas (any adenoma measuring <1 cm, without high-grade dysplasia, and less than 25% villous features), advanced adenomas (any adenoma with size ≥1 cm, with at least 25% villous features, or high-grade dysplasia), non-advanced serrated polyps (hyperplastic polyps <1 cm in diameter and sessile serrated polyps/adenomas <1 cm in diameter and without dysplasia), advanced serrated lesions (ASL; traditional serrated adenomas or any serrated polyp with diameter size ≥1 cm, or with dysplasia) [28], and CRC.

2.4. Statistical analysis

In participants with multiple lesions, the most severe one was chosen as the outcome of interest. However, in some cases, the choice of the most severe lesion was arbitrary (e.g., in the presence of both advanced adenoma and advanced serrated polyp). Therefore, we ran different multinomial logistic regression models according to the lesion of interest. For CRC and adenoma, we used a multinomial model with the following outcome categories, ordered by severity: CRC, adenoma, any serrated polyps, and no lesion. For serrated polyps, we used a multinomial model with the following outcome categories, ordered by severity: CRC, any serrated polyps, adenoma, and no lesion. For non-advanced and advanced adenomas, we used a multinomial model with the following outcomes, ordered by severity: CRC, advanced adenoma, non-advanced adenoma, any serrated polyps, and no lesion. For non-advanced and advanced serrated polyps, we used a multinomial model with the following outcomes, ordered by severity: CRC, advanced serrated polyps, non-advanced serrated polyps, adenomas, and no lesion. We estimated the association between aspirin use (or long-term aspirin use) and the detection of colorectal lesions, with no-use as the reference exposure category and no lesion as the reference outcome category, reporting odds ratios (OR) with 95% confidence intervals (CI). In the model for CRC and adenoma, we further separated CRCs into distal and proximal CRCs, and into stage 1 and stage ≥ 2 CRCs. We studied the association between use of aspirin and characteristics of adenomas in participants who were not diagnosed with CRC, including proximal location (from caecum to and including splenic flexure), distal location (distal to splenic flexure including rectum) [28], size ≥1 cm, presence of ≥25% villous features, and high-grade dysplasia in five distinctive multinomial models. In each model, we considered adenomas with that feature, adenomas without that feature, any serrated polyps, and no lesion as the outcome categories.

All estimates for aspirin use were adjusted for continuous age in years (integer), sex, screening centre, marital status, immigration status, education, employment status, household income, and current use (≥2 prescriptions in the 12 months before the screening

invitation) of certain medications (ATC codes A10, B01, C01, C03, C07, C08, C09, N05, N06A, R03) as proxy for the presence of comorbidities at the time of invitation. We had missing values only for education and income, and we used a separate category for them in the multivariable models.

We investigated the heterogeneity of the estimates between screening arms and sex strata using the Cochran's Q test, and between CRC and adenomas' sites, and CRC stages using the Wald test. All tests were 2-sided, and p-values <0.05 were considered statistically significant. Statistical analyses were performed with R software, version 3.6.1 and the VGAM package was used for multinomial regression.

2.5. Ethical statement

The randomized trial was approved by the Regional Committee for Medical Research Ethics in South East Norway (2011/1272). The CRC screening participants provided written informed consent on attendance at the screening centre (the sigmoidoscopy arm) or by return of the faecal sample (FIT arm). The Regional Committee for Medical Research Ethics in South East Norway approved use of registry-based data on everyone who were invited, regardless of consent. Trial registration number and date of registration are NCT 01538550 (clinicaltrials.gov), February 24, 2012.

3. Results

Of the 64,889 attenders in the screening, 24,159 were in the sigmoidoscopy arm, and 40,730 were in the FIT arm. Among sigmoidoscopy attenders, 2,372 (9.8%) had a positive sigmoidoscopy. Among FIT attenders, 3,100 (7.6%) had a positive FIT. Of all attenders, 11,608 (17.9%) individuals were aspirin users (Table 1). All users were prescribed low-dose aspirin, with 117,254 (85.1%) of prescriptions being 75 mg aspirin and 20,553 (14.9%) 160 mg aspirin. In both arms, use of aspirin was more common in males, individuals who were older, retired, and had lower education and income. In total, 314 (0.5%) participants had CRCs, 3,800 (5.9%) adenomas, 4,170 (6.4%) serrated lesions, and 2,408 (3.7%) both adenomas and serrated lesions.

Compared to no use, use of aspirin (OR 0.82; 95%CI 0.61-1.11) or short-term use of aspirin (<3 years) (OR 1.39; 95%CI 0.90-2.14) were not associated with the detection of CRC (Fig. 1). However,

Table 1
Attenders' characteristics and detected lesions by use of aspirin overall and by arm.

	Sigmoidoscopy and FIT		Sigmoidoscopy		FIT	
	All attenders n (col %)	Aspirin users n (row %)	All attenders n (col %)	Aspirin users n (row %)	All attenders n (col %)	Aspirin users n (row %)
All	64889 (100.0)	11608 (17.9)	24159 (100.0)	4282 (17.7)	40730 (100.0)	7326 (18.0)
Sex						
Females	33927 (52.3)	4530 (13.4)	12250 (50.7)	1603 (13.1)	21677 (53.2)	2927 (13.5)
Males	30962 (47.7)	7078 (22.9)	11909 (49.3)	2679 (22.5)	19053 (46.8)	4399 (23.1)
Age (years)						
50-55	11164 (17.2)	685 (6.1)	4033 (16.7)	258 (6.4)	7131 (17.5)	427 (6.0)
56-60	14606 (22.5)	1558 (10.7)	5474 (22.7)	571 (10.4)	9132 (22.4)	987 (10.8)
61-65	14115 (21.8)	2380 (16.9)	5291 (21.9)	871 (16.5)	8824 (21.7)	1509 (17.1)
66-70	14471 (22.3)	3568 (24.7)	5298 (21.9)	1269 (24.0)	9173 (22.5)	2299 (25.1)
>70	10533 (16.2)	3417 (32.4)	4063 (16.8)	1313 (32.3)	6470 (15.9)	2104 (32.5)
Education						
Primary school	10677 (16.5)	2331 (21.8)	3681 (15.2)	787 (21.4)	6996 (17.2)	1544 (22.1)
Secondary (high school)	30376 (46.8)	5775 (19.0)	11324 (46.9)	2152 (19.0)	19052 (46.8)	3623 (19.0)
≤4 years university	16802 (25.9)	2464 (14.7)	6459 (26.7)	934 (14.5)	10343 (25.4)	1530 (14.8)
>4 years university	6704 (10.3)	967 (14.4)	2590 (10.7)	390 (15.1)	4114 (10.1)	577 (14.0)
Missing	330	71 (21.5)	105	19 (18.1)	225	52 (23.1)
Employment status						
Employed	41560 (64.0)	5562 (13.4)	15867 (65.7)	2145 (13.5)	25693 (63.1)	3417 (13.3)
Unemployed	297 (0.5)	55 (18.5)	104 (0.4)	18 (17.3)	193 (0.5)	37 (19.2)
Outside of workforce/retired	23032 (35.5)	5991 (26.0)	8188 (33.9)	2119 (25.9)	14844 (36.4)	3872 (26.1)
Household income (Norwegian Krone)						
Q1[a] (<559098)	16221 (25.0)	3687 (22.7)	5659 (23.4)	1264 (22.3)	10562 (25.9)	2423 (22.9)
Q2 (559098-833440)	16221 (25.0)	3349 (20.6)	6078 (25.2)	1268 (20.9)	10143 (24.9)	2081 (20.5)
Q3 (833441-1210060)	16219 (25.0)	2571 (15.9)	6145 (25.4)	960 (15.6)	10074 (24.7)	1611 (16.0)
Q4 (>1210060)	16221 (25.0)	2001 (12.3)	6274 (26.0)	790 (12.6)	9947 (24.4)	1211 (12.2)
Missing	7	0 (0.0)	3	0 (0.0)	4	0 (0.0)
Marital status						
Married/Having a cohabitant	51913 (80.0)	9280 (17.9)	19438 (80.5)	3441 (17.7)	32475 (79.7)	5839 (18.0)
Not married/Not having a cohabitant	12976 (20.0)	2328 (17.9)	4721 (19.5)	841 (17.8)	8255 (20.3)	1487 (18.0)
Immigration status						
Norwegian	60751 (93.6)	10968 (18.1)	22810 (94.4)	4078 (17.9)	37941 (93.2)	6890 (18.2)
Immigrant	4138 (6.4)	640 (15.5)	1349 (5.6)	204 (15.1)	2789 (6.8)	436 (15.6)
Most severe finding at the screening						
No lesion	54197 (83.5)	9562 (17.6)	15674 (64.9)	2758 (17.6)	38523 (94.6)	6804 (17.7)
Serrated polyps	4170 (6.4)	666 (16.0)	3924 (16.2)	619 (15.8)	246 (0.6)	47 (19.1)
Adenomas	3800 (5.9)	812 (21.4)	2674 (11.1)	539 (20.2)	1126 (2.8)	273 (24.2)
Adenomas and serrated polyps	2408 (3.7)	497 (20.6)	1745 (7.2)	334 (19.1)	663 (1.6)	163 (24.6)
CRC	314 (0.5)	71 (22.6)	142 (0.6)	32 (22.5)	172 (0.4)	39 (22.7)

CRC: colorectal cancer; FIT: faecal immunochemical test.
[a] Q1 – Q4: Quartiles for household income

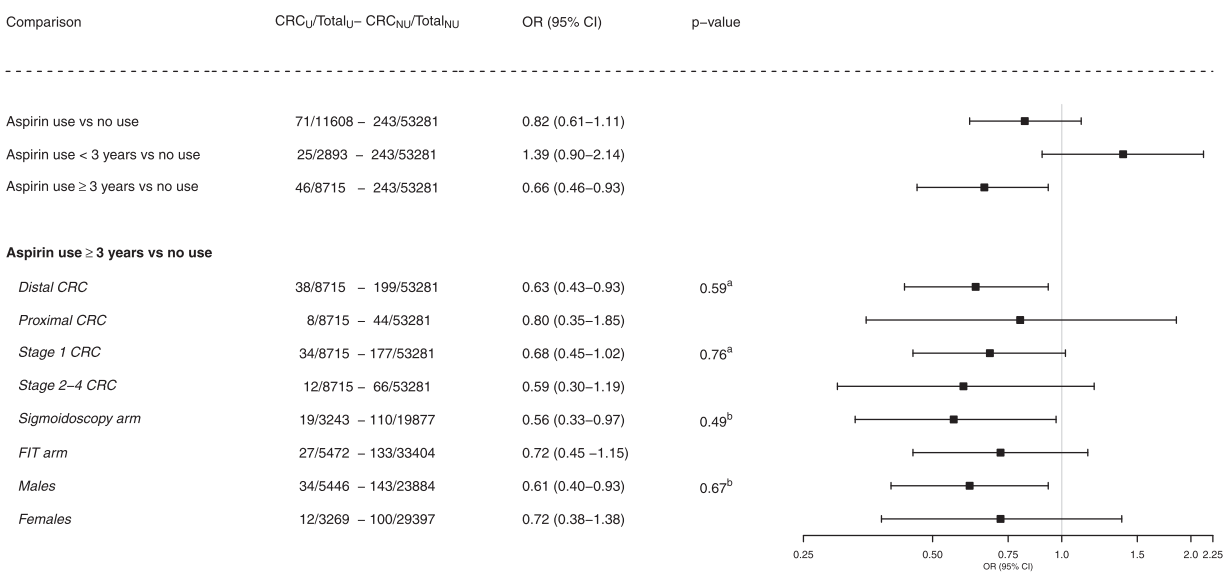

Fig. 1. Association between aspirin and detection of colorectal cancer. CRC: colorectal cancer; FIT: faecal immunochemical test; U: user; NU: non-user. Odds ratios (OR) and 95% confidence interval (CI) were adjusted for age, sex, screening centre, marital status, immigration status, education, employment status, household income, and use of antidiabetics, psycholeptics, antidepressants, cardiac therapy, antithrombotic agents, drugs for obstructive airway diseases, beta-blockers, agents acting on the renin-angiotensin system, calcium channel blockers, and diuretics. Reference for each estimate is no use of aspirin.
[a] *P*-value from Wald test comparing ORs between outcome strata; [b] *P*-value from Cochran's Q test comparing ORs between subgroups of the population.

long-term use of aspirin (≥3 years) was associated with a lower detection of CRC (OR 0.66; 95%CI 0.46-0.93) compared to no use. When comparing long-term use to no use, no significant differences were observed between CRC location ($P_{heterogeneity}$ = 0.59), CRC stage (P = 0.76), screening arm (P = 0.49) and sex (P = 0.67).

In the overall cohort, long-term use of aspirin, compared to no use, was not associated with a lower detection of adenomas (OR 0.95; 95%CI 0.87-1.03) (Table 2), but it was associated with a lower detection of serrated polyps (OR 0.86; 95%CI 0.79-0.93). No significant differences were observed between locations of adenomas (OR 0.94; 95%CI 0.86-1.02 for distal adenoma, OR 0.98; 95%CI 0.86-1.12 for proximal adenoma, $P_{heterogeneity}$= 0.60).

In the sigmoidoscopy arm, long-term aspirin use, compared to no use, was associated with lower detection of any adenoma (OR 0.89; 95%CI 0.80-0.99; non-advanced adenomas 0.89; 95%CI 0.79-1.01, advanced adenomas 0.88; 95%CI 0.74-1.06; Table 3), serrated polyps (OR 0.80; 95%CI 0.72-0.89), non-advanced serrated polyps (OR 0.79; 95%CI 0.71-0.88), but not ASLs (OR 0.97; 95%CI 0.72-

Table 2
Association between long-term use of aspirin (≥3 years) and detection of colorectal lesions in screening attenders, overall and according to gender.

	All	Females	Males	p-value[a]
CRC				
OR (95% CI)	0.66 (0.46-0.93)	0.72 (0.38-1.38)	0.61 (0.40-0.93)	0.67
Cases$_U$/Total$_U$-Cases$_{NU}$/Total$_{NU}$	46/8715-243/53281	12/3269-100/29397	34/5446-143/23884	
Adenoma				
OR (95% CI)	0.95 (0.87-1.03)	0.89 (0.76-1.03)	0.97 (0.87-1.07)	0.34
Cases$_U$/Total$_U$-Cases$_{NU}$/Total$_{NU}$	1005/8715-4899/53281	252/3269-2114/29397	753/5446-2785/23884	
Non-advanced adenoma				
OR (95% CI)	0.95 (0.86-1.05)	0.88 (0.73-1.06)	0.98 (0.86-1.11)	0.35
Cases$_U$/Total$_U$-Cases$_{NU}$/Total$_{NU}$	625/8715-3227/53281	161/3269-1429/29397	464/5446-1798/23884	
Advanced adenoma				
OR (95% CI)	0.95 (0.83-1.08)	0.90 (0.71-1.15)	0.95 (0.81-1.11)	0.71
Cases$_U$/Total$_U$-Cases$_{NU}$/Total$_{NU}$	380/8715-1672/53281	91/3269-685/29397	289/5446-987/23884	
Serrated polyp				
OR (95% CI)	0.86 (0.79-0.93)	0.86 (0.74-0.99)	0.84 (0.76-0.94)	0.80
Cases$_U$/Total$_U$-Cases$_{NU}$/Total$_{NU}$	871/8715-5415/53281	256/3269-2588/29397	615/5446-2827/23884	
Non-advanced serrated polyp				
OR (95% CI)	0.84 (0.77-0.92)	0.87 (0.75-1.01)	0.81 (0.72-0.90)	0.44
Cases$_U$/Total$_U$-Cases$_{NU}$/Total$_{NU}$	774/8715-4932/53281	229/3269-2330/29397	545/5446-2602/23884	
Advanced serrated polyp				
OR (95% CI)	1.02 (0.80-1.31)	0.74 (0.48-1.13)	1.25 (0.91-1.70)	0.05
Cases$_U$/Total$_U$-Cases$_{NU}$/Total$_{NU}$	97/8715-483/53281	27/3269-258/29397	70/5446-225/23884	

CRC: colorectal cancer; U: user; NU: non-user. Odds ratios (OR) and 95% confidence interval (CI) were adjusted for age, sex, screening centre, marital status, immigration status, education, employment status, household income, and use of antidiabetics, psycholeptics, antidepressants, cardiac therapy, antithrombotic agents, drugs for obstructive airway diseases, beta-blockers, agents acting on the renin-angiotensin system, calcium channel blockers, and diuretics. Reference for each estimate is no use of aspirin.
[a] *P*-value from Cochran's Q test comparing ORs between subgroups of the population.

Table 3
Association between long-term use of aspirin (≥3 years) and detection of colorectal lesions in the sigmoidoscopy arm, overall and according to gender.

	All	Females	Males	p-value[a]
CRC				
OR (95% CI)	0.56 (0.33-0.97)	0.75 (0.30-1.89)	0.47 (0.24-0.91)	0.42
$Cases_U/Total_U$-$Cases_{NU}/Total_{NU}$	19/3243-110/19877	6/1168-47/10647	13/2075-63/9230	
Adenoma				
OR (95% CI)	0.89 (0.80-0.99)	0.76 (0.62-0.92)	0.94 (0.82-1.07)	0.07
$Cases_U/Total_U$-$Cases_{NU}/Total_{NU}$	662/3243-3546/19877	156/1168-1549/10647	506/2075-1997/9230	
Non-advanced adenoma				
OR (95% CI)	0.89 (0.79-1.01)	0.76 (0.61-0.96)	0.94 (0.81-1.10)	0.14
$Cases_U/Total_U$-$Cases_{NU}/Total_{NU}$	461/3243-2597/19877	110/1168-1160/10647	351/2075-1437/9230	
Advanced adenoma				
OR (95% CI)	0.88 (0.74-1.06)	0.74 (0.53-1.05)	0.94 (0.75-1.16)	0.25
$Cases_U/Total_U$-$Cases_{NU}/Total_{NU}$	201/3243-949/19877	46/1168-389/10647	155/2075-560/9230	
Serrated polyp				
OR (95% CI)	0.80 (0.72-0.89)	0.78 (0.66-0.93)	0.80 (0.70-0.91)	0.82
$Cases_U/Total_U$-$Cases_{NU}/Total_{NU}$	709/3243-4716/19877	211/1168-2279/10647	498/2075-2437/9230	
Non-advanced serrated polyp				
OR (95% CI)	0.78 (0.70-0.87)	0.80 (0.67-0.95)	0.76 (0.67-0.88)	0.66
$Cases_U/Total_U$-$Cases_{NU}/Total_{NU}$	645/3243-4384/19877	196/1168-2103/10647	449/2075-2281/9230	
Advanced serrated polyp				
OR (95% CI)	0.97 (0.72-1.32)	0.60 (0.34-1.06)	1.26 (0.87-1.84)	0.03
$Cases_U/Total_U$-$Cases_{NU}/Total_{NU}$	64/3243-332/19877	15/1168-176/10647	49/2075-156/9230	

CRC: colorectal cancer; U: user; NU: non-user. Odds ratios (OR) and 95% confidence interval (CI) were adjusted for age, sex, screening centre, marital status, immigration status, education, employment status, household income, and use of antidiabetics, psycholeptics, antidepressants, cardiac therapy, antithrombotic agents, drugs for obstructive airway diseases, beta-blockers, agents acting on the renin-angiotensin system, calcium channel blockers, and diuretics. Reference for each estimate is no use of aspirin.

[a] *P*-value from Cochran's Q test comparing ORs between subgroups of the population.

1.32). In the sigmoidoscopy arm, the odds of detection of any adenoma and ASL for long-term versus no use were lower in women than men ($P_{heterogeneity} = 0.07$ and 0.03, respectively).

In the overall cohort of screening attenders, we found no associations between long-term aspirin use and presence of ≥25% villous features (OR 0.95; 95%CI 0.80-1.13), high-grade dysplasia (OR 1.11; 95%CI 0.89-1.38) or size ≥1cm (OR 0.96; 95%CI 0.83-1.11) in adenomas. Likewise in the sigmoidoscopy arm, the estimates were non-significant for presence of ≥25% villous features (OR 0.87; 95%CI 0.68-1.11), high-grade dysplasia (OR 1.19; 95%CI 0.87-1.61) or size ≥1cm (OR 0.93; 95%CI 0.76-1.14) in adenomas. In FIT participants, we found no association between aspirin use and polyp detection and no differences between men and women (Table 4).

Table 4
Association between long-term use of aspirin (≥3 years) and detection of colorectal lesions in the FIT arm, overall and according to gender.

	All	Females	Males	p-value[a]
CRC				
OR (95% CI)	0.72 (0.45-1.15)	0.68 (0.27-1.67)	0.72 (0.41-1.24)	0.91
$Cases_U/Total_U$-$Cases_{NU}/Total_{NU}$	27/5472-133/33404	6/2101-53/18750	21/3371-80/14654	
Adenoma				
OR (95% CI)	1.03 (0.89-1.18)	1.12 (0.88-1.43)	0.97 (0.81-1.15)	0.34
$Cases_U/Total_U$-$Cases_{NU}/Total_{NU}$	343/5472-1353/33404	96/2101-565/18750	247/3371-788/14654	
Non-advanced adenoma				
OR (95% CI)	1.07 (0.87-1.31)	1.16 (0.83-1.63)	1.02 (0.79-1.31)	0.55
$Cases_U/Total_U$-$Cases_{NU}/Total_{NU}$	164/5472-630/33404	51/2101-269/18750	113/3371-361/14654	
Advanced adenoma				
OR (95% CI)	0.99 (0.82-1.20)	1.08 (0.76-1.52)	0.93 (0.74-1.17)	0.48
$Cases_U/Total_U$-$Cases_{NU}/Total_{NU}$	179/5472-723/33404	45/2101-296/18750	134/3371-427/14654	
Serrated polyp				
OR (95% CI)	1.02 (0.84-1.24)	1.13 (0.79-1.60)	0.96 (0.75-1.22)	0.45
$Cases_U/Total_U$-$Cases_{NU}/Total_{NU}$	162/5472-699/33404	45/2101-309/18750	117/3371-390/14654	
Non-advanced serrated polyp				
OR (95% CI)	1.01 (0.81-1.26)	1.21 (0.80-1.81)	0.92 (0.70-1.20)	0.27
$Cases_U/Total_U$-$Cases_{NU}/Total_{NU}$	129/5472-548/33404	33/2101-227/18750	96/3371-321/14654	
Advanced serrated polyp				
OR (95% CI)	1.04 (0.68-1.60)	0.94 (0.48-1.83)	1.16 (0.66-2.03)	0.67
$Cases_U/Total_U$-$Cases_{NU}/Total_{NU}$	33/5472-151/33404	12/2101-82/18750	21/3371-69/14654	

CRC: colorectal cancer; FIT: faecal immunochemical test; U: user; NU: non-user. Odds ratios (OR) and 95% confidence interval (CI) were adjusted for age, sex, screening centre, marital status, immigration status, education, employment status, household income, and use of antidiabetics, psycholeptics, antidepressants, cardiac therapy, antithrombotic agents, drugs for obstructive airway diseases, beta-blockers, agents acting on the renin-angiotensin system, calcium channel blockers, and diuretics. Reference for each estimate is no use of aspirin

[a] *P*-value from Cochran's Q test comparing ORs between subgroups of the population.

4. Discussion

In this large screening population, we found a significant association between long-term use (≥3 years) of aspirin and lower detection of CRC. The reduced detection of CRC was unrelated to CRC location, stage, screening arm, and sex. In the sigmoidoscopy arm, we found an association between long-term use of aspirin and lower detection of adenomas, but not ASLs. In the FIT arm, we did not observe any association between aspirin use and any polyp detection.

Our results showed a 34% reduction in detection of CRC in long-term users of low-dose aspirin, quite consistent with the findings of a 2020 meta-analysis of observational studies that reported a 27% reduction (OR 0.73; 95%CI 0.69-0.78) in regular aspirin users [10], and with the findings of a 2021 meta-analysis of RCTs that reported a 26% reduction (OR 0.74; 95%CI 0.56-0.97) in the individuals randomized to the aspirin arm [11]. In the Nurses' Health Study and Health Professionals Follow-up Study, there was a protective effect of aspirin only if initiated before 70 years of age [17]. Two other cohort studies found a protective effect of aspirin only after 10 [19] or 20 [20] years of use. In the Women's Health Initiative cohort and the Aspirin in Reducing Events in the Elderly (ASPREE) trial, no protective effect of aspirin against CRC was observed [16,18]. It was argued that a possible explanation for the lack of a protective effect of aspirin in the ASPREE trial was due to the fact that the majority of participants had not used aspirin regularly before the age of 70 [17]. In the ASCEND (A Study of Cardiovascular Events in Diabetes) trial, researchers did not find an association between aspirin use and the risk of gastrointestinal cancers, but they did not report an estimate separately for CRC [29].

We found an association between use of three years or more of low-dose aspirin and CRC detection. Consistent with the present study, three years of aspirin use was used as a cut-off for definition of regular aspirin use in other published studies [30,31]. In our study, all aspirin users used low-dose aspirin (75-160 mg daily). There is great variation between published studies in aspirin dosage, from approximately 50 mg to ≥500 mg daily [8,16,21,22]. A previously published dose-response analysis showed higher protection against CRC with increasing doses of aspirin [11], while the use of low-dose aspirin showed no association with risk of CRC [14,15]. However, Rothwell et al. [12] previously reported that 75 mg was as effective as higher doses in the prevention of CRC [12], consistent with our results of an association between low-dose aspirin and reduced detection of CRC.

There is inconsistency in the effect of aspirin based on anatomical site and stage of CRC across studies [9,12,20,32]. Analysis of pooled data in 2010 from four trials showed more protection against proximal CRC [12]. The results of another trial in 2021 showed no heterogeneity by location [9]; the latter being consistent with our results indicating no significant difference between association of long-term aspirin use and detection of distal or proximal CRC. In a large observational study, current use of aspirin showed no risk reduction for Duke A CRC, while significant risk reduction was reported for more advanced stages [32]. In our study, we did not detect any significant difference between the estimates for stage 1 and the higher stages of CRC.

Two major distinctive pathways are proposed for colorectal tumorigenesis, one originating from serrated and the other from adenomatous polyps, harbouring *BRAF* and *KRAS/APC* mutations, respectively [33]. Aspirin is believed to inhibit *APC* and *KRAS* but not *BRAF* [33]. The proposed mechanisms [33], along with previously published evidence [8,9], are consistent with our results indicating an association between long-term aspirin use and lower detection of adenomas but not ASL. We found an indication of an association between long-term use of aspirin and the detection of advanced adenomas in the sigmoidoscopy arm, which is consistent with the findings of three large pooled cohorts that reported a reduction in risk of advanced adenomas (OR 0.88; 95% CI, 0.82–0.94) with regular use of aspirin [25]. We found no association between use of aspirin and detection of ASLs, which is in support of the results from other published studies that investigated the association between use of aspirin and risk of *BRAF*-mutated CRC [26,27] or any serrated polyps [25], both indicating no association between use of aspirin and risk of tumorigenesis through the serrated pathway. However, the pooled estimate of three cohort studies showed an association between use of aspirin and lower incidence of serrated polyps with a diameter of >1 cm [25]. One reason for the inconsistency between that study and ours could be due to the fact that we used a definition of ASL which was not only based on the polyp size. However, results did not change when we used size as the only criterion for defining ASL (data not shown). It is also important to notice that, since ASLs are usually found in the proximal colon [33] and are less likely to bleed [34], the two screening methods in this study might be inadequate to detect ASLs, making it suboptimal for investigating the association between aspirin use and ASLs.

We found a significant inverse association between aspirin use and CRC detection in the sigmoidoscopy participants but not in the FIT participants, even though the heterogeneity analysis did not show a significant difference between the two arms. Moreover, we found a significant inverse association between use of aspirin and the detection of adenomas in the sigmoidoscopy arm, while we found no association in the FIT arm. One reason may be that only a small proportion of adenomas bleed [35], and the association between aspirin use and adenoma detection could not emerge in the FIT arm [36]. Also, the use of aspirin as an antiplatelet medication leads to a general increased risk of bleeding events and referrals to follow-up colonoscopy in users, higher incidental detection of adenomas, and consequently to a biased estimate of the association between aspirin and detection of adenomas towards the null [36].

This study is among the few studies evaluating the association between aspirin and colorectal lesions according to their characteristics, including location, stage, and histopathological features. This allowed us to not only supply new evidence on the protective effect of aspirin on the risk of CRC but also provide new insights into the association between aspirin use and detection of polyps arising from distinctive pathways. Linkage of high-quality population registries, which collects data on drug prescriptions as well as on important sociodemographic confounders, and screening outcomes is a major strength of this study. Considering that long-term use of aspirin is only possible by prescription in Norway, acquiring the medication history from the prescription database avoids bias due to self-reported use of drugs and represents another major strength of this study.

Having only four years of medication history was possibly the most important limitation of our study. However, we were able to classify the use of aspirin in short- and long-term use, using the same definition as in some previous studies [30,31]. Another limitation is that our study is based on a selected population of individuals aged 50-74 years who decided to participate in a CRC screening trial, and we know that different sociodemographic and health-related factors influence screening participation [37,38]. This hampers the generalizability of our study findings. In addition, since only the screening attenders with a positive FIT or sigmoidoscopy were invited to a colonoscopy, many lesions could have remained undetected, leading to possible bias in our estimates. Finally, we did not have any data regarding the potential side effects of aspirin, such as gastrointestinal ulcer and bleeding, in our population. From a public health point of view, the possibility of widespread use of aspirin as a primary prevention agent for CRC could be limited due to its adverse effects [39].

In conclusion, our study, conducted in a large screening population, strengthens the hypothesis that long-term use of low-dose aspirin can lower the risk of CRC, and supplies new evidence that aspirin might exert its protective effect through the prevention of adenomatous lesions.

Declaration of Competing Interest

The authors declare no potential conflict of interests.

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References

[1] Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71:209–49.
[2] Araghi M, Soerjomataram I, Bardot A, et al. Changes in colorectal cancer incidence in seven high-income countries: a population-based study. Lancet Gastroenterol Hepatol 2019;4:511–18.
[3] Arnold M, Abnet CC, Neale RE, et al. Global burden of 5 major types of gastrointestinal cancer. Gastroenterology 2020;159 335-49.e15.
[4] Edwards BK, Ward E, Kohler BA, et al. Annual report to the nation on the status of cancer, 1975-2006, featuring colorectal cancer trends and impact of interventions (risk factors, screening, and treatment) to reduce future rates. Cancer 2010;116:544–73.
[5] Rosello S, Simon S, Cervantes A. Programmed colorectal cancer screening decreases incidence and mortality. Transl Gastroenterol Hepatol 2019;4:84.
[6] Katona BW, Weiss JM. Chemoprevention of colorectal cancer. Gastroenterology 2020;158:368–88.
[7] Drew DA, Cao Y, Chan AT. Aspirin and colorectal cancer: the promise of precision chemoprevention. Nat Rev Cancer 2016;16:173–86.
[8] Dube C, Rostom A, Lewin G, et al. The use of aspirin for primary prevention of colorectal cancer: a systematic review prepared for the U.S. preventive services task force. Ann Intern Med 2007;146:365–75.
[9] Chudy-Onwugaje K, Huang WY, Su LJ, et al. Aspirin, ibuprofen, and reduced risk of advanced colorectal adenoma incidence and recurrence and colorectal cancer in the PLCO cancer screening trial. Cancer 2021;127:3145–55.
[10] Bosetti C, Santucci C, Gallus S, Martinetti M, La Vecchia C. Aspirin and the risk of colorectal and other digestive tract cancers: an updated meta-analysis through 2019. Ann Oncol 2020;31:558–68.
[11] Wang L, Zhang R, Yu L, et al. Aspirin use and common cancer risk: a meta-analysis of cohort studies and randomized controlled trials. Front Oncol 2021;11:690219.
[12] Rothwell PM, Wilson M, Elwin C-E, et al. Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomised trials. Lancet North Am Ed 2010;376:1741–50.
[13] Cook NR, Lee IM, Zhang SM, Moorthy MV, Buring JE. Alternate-day, low-dose aspirin and cancer risk: long-term observational follow-up of a randomized trial. Ann Intern Med 2013;159:77–85.
[14] Gann PH, Manson JE, Glynn RJ, Buring JE, Hennekens CH. Low-dose aspirin and incidence of colorectal tumors in a randomized trial. J Natl Cancer Inst 1993;85:1220–4.
[15] Cook NR, Lee IM, Gaziano JM, et al. Low-dose aspirin in the primary prevention of cancer: the Women's Health Study: a randomized controlled trial. JAMA 2005;294:47–55.
[16] Allison M, Garland C, Chlebowski R, et al. The association between aspirin use and the incidence of colorectal cancer in women. Am J Epidemiol 2006;164:567–75.
[17] Guo CG, Ma W, Drew DA, et al. Aspirin use and risk of colorectal cancer among older adults. JAMA Oncol 2021;7:428–35.
[18] McNeil JJ, Gibbs P, Orchard SG, et al. Effect of aspirin on cancer incidence and mortality in older adults. J Natl Cancer Inst 2021;113:258–65.
[19] Chan AT, Giovannucci EL, Meyerhardt JA, Schernhammer ES, Curhan GC, Fuchs CS. Long-term use of aspirin and nonsteroidal anti-inflammatory drugs and risk of colorectal cancer. JAMA 2005;294:914–23.
[20] Larsson SC, Giovannucci E, Wolk A. Long-term aspirin use and colorectal cancer risk: a cohort study in Sweden. Brit J Cancer 2006;95:1277–9.
[21] Chan AT, Giovannucci EL, Schernhammer ES, et al. A prospective study of aspirin use and the risk for colorectal adenoma. Ann Intern Med 2004;140:157–66.
[22] Chapelle N, Martel M, Toes-Zoutendijk E, Barkun AN, Bardou M. Recent advances in clinical practice: colorectal cancer chemoprevention in the average-risk population. Gut 2020;69:2244–55.
[23] Bibbins-Domingo K, Force U. Aspirin use for the primary prevention of cardiovascular disease and colorectal cancer: U.S. preventive services task force recommendation statement. Ann Intern Med 2016;164:836–45.
[24] Force U, Davidson KW, Barry MJ, et al. Aspirin use to prevent cardiovascular disease: US preventive services task force recommendation statement. JAMA 2022;327:1577–84.
[25] He XS, Wu KN, Ogino S, Giovannucci EL, Chan AT, Song MY. Association between risk factors for colorectal cancer and risk of serrated polyps and conventional adenomas. Gastroenterology 2018;155 355–73.e18.
[26] Amitay EL, Carr PR, Jansen L, et al. Association of aspirin and nonsteroidal anti-inflammatory drugs with colorectal cancer risk by molecular subtypes. J Natl Cancer Inst 2019;111:475–83.
[27] Nishihara R, Lochhead P, Kuchiba A, et al. Aspirin use and risk of colorectal cancer according to BRAF mutation status. JAMA 2013;309:2563–71.
[28] Randel KR, Schult AL, Botteri E, et al. Colorectal cancer screening with repeated fecal immunochemical test versus sigmoidoscopy: baseline results from a randomized trial. Gastroenterology 2021;160 1085-96 e5.
[29] Group ASC, Bowman L, Mafham M, et al. Effects of aspirin for primary prevention in persons with diabetes mellitus. N Engl J Med 2018;379:1529–39.
[30] Brasky TM, Liu J, White E, et al. Non-steroidal anti-inflammatory drugs and cancer risk in women: results from the Women's Health Initiative. Int J Cancer 2014;135:1869–83.
[31] Huang WK, Chiou MJ, Yu KH, et al. The association between low-dose aspirin use and the incidence of colorectal cancer: a nationwide cohort study. Aliment Pharmacol Ther 2013;38:432–9.
[32] Garcia Rodriguez LA, Soriano-Gabarro M, Bromley S, Lanas A, Cea Soriano L. New use of low-dose aspirin and risk of colorectal cancer by stage at diagnosis: a nested case-control study in UK general practice. BMC Cancer 2017;17:637.
[33] Chen B, Scurrah CR, McKinley ET, et al. Differential pre-malignant programs and microenvironment chart distinct paths to malignancy in human colorectal polyps. Cell 2021;184 6262-80 e26.
[34] East JE, Saunders BP, Jass JR. Sporadic and syndromic hyperplastic polyps and serrated adenomas of the colon: classification, molecular genetics, natural history, and clinical management. Gastroenterol Clin North Am 2008;37 25-46, v.
[35] Foutch PG, Manne RK, Sanowski RA, Gaines JA. Risk factors for blood loss from adenomatous polyps of the large bowel: a colonoscopic evaluation with histopathological correlation. J Clin Gastroenterol 1988;10:50–6.
[36] Randel KR, Botteri E, Romstad KMK, et al. Effects of oral anticoagulants and aspirin on performance of fecal immunochemical tests in colorectal cancer screening. Gastroenterology 2019;156 1642-9 e1.
[37] Botteri E, Hoff G, Randel KR, et al. Characteristics of nonparticipants in a randomised colorectal cancer screening trial comparing sigmoidoscopy and faecal immunochemical testing. Int J Cancer 2022;151:361–71.
[38] Knudsen MD, Kvaerner AS, Botteri E, et al. Lifestyle predictors for inconsistent participation to fecal based colorectal cancer screening. BMC Cancer 2022;22:172.
[39] Garcia Rodriguez LA, Chan AT. Aspirin for the prevention of colorectal cancer. Best Pract Res Clin Gastroenterol 2011;25:461–72.