Association between lifestyle and site-specific advanced colorectal lesions in screening with faecal immunochemical test and sigmoidoscopy

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Abstract

Background: Lifestyle factors may help to identify individuals at high-risk for colorectal cancer (CRC).

Aims: To examine the association between lifestyle, referral for follow-up colonoscopy and proximal neoplasia detection in CRC screening.

Methods: In this observational study, 14,832 individuals aged 50-74 years were invited to faecal immunochemical test (FIT) or sigmoidoscopy screening. Advanced lesions (AL), including advanced adenomas, advanced serrated lesions and CRC were divided according to location: distal-only, or proximal with or without distal AL. We collected information on smoking habit, body mass index and alcohol intake through a questionnaire.

Results: Out of 3,318 FIT and 2,988 sigmoidoscopy participants, 516 (16%) and 338 (11%), respectively, were referred for follow-up colonoscopy after a positive screening test. Two-hundred-and-fifty-six (4%) had distal-only and 119 (2%) proximal AL. In FIT participants, obesity and high alcohol intake were associated with proximal AL; odds ratio (95% confidence interval) 2.68 (1.36-5.26) and 2.16 (1.08-4.30), respectively. In sigmoidoscopy participants, current smoking was associated with proximal AL; 4.58 (2.24-9.38), and current smoking and obesity were associated with referral for colonoscopy; 2.80 (2.02-3.89) and 1.42 (1.01-2.00), respectively.

Conclusion: Current smoking, obesity and high alcohol intake were associated with screen-detected proximal colorectal AL. Current smoking and obesity were associated with referral for follow-up colonoscopy in sigmoidoscopy screening.

Keywords

Proximal neoplasia; Smoking; Body mass index; Alcohol

1. Introduction

Major unhealthy lifestyle factors, including overweight, physical inactivity, smoking, high alcohol consumption and unhealthy dietary habits, predict the risk of advanced colorectal adenomas and colorectal cancer (CRC) [1, 2]. Assessment of lifestyle risk factors may be used to identify individuals at high risk for CRC suited for tailored CRC screening [3]. So far, there is no universally accepted risk-prediction model [4], and CRC screening programmes generally do not risk-stratify individuals. Several methods are widely used for colorectal cancer screening, including faecal occult blood tests, sigmoidoscopy and colonoscopy [5]. For some high-risk individuals, colonoscopy might be the appropriate primary screening method, particularly if the risk of neoplastic lesions in the proximal site is high. Sensitivity of faecal occult blood tests is lower for proximal than distal lesions [6], and proximal lesions are not visible in a sigmoidoscopy examination.

There is an inconsistency in the literature regarding the association between risk factors and anatomic subsite of neoplastic lesions [7-11]. The impact of smoking for site-specific neoplastic lesions illustrates the complexity; smoking is associated with the risk of proximal neoplasia in some studies [8], while others report a stronger association with distal rather than proximal neoplasia [7]. Smoking is clearly associated with an increased risk of sessile serrated lesions as compared to adenomas [8, 12]. Sessile serrated lesions are most pronounced in the proximal colon [13], but are, in total, less prevalent than adenomas. Obesity is shown in prospective cohort studies to be related to the risk of both distal and proximal CRC [10, 14], but this association is also suggested to be more pronounced in the distal part [9] and to increase the risk mainly in men [9, 10]. Obesity predicts detection of advanced neoplasia in CRC screening [15], in all subsites [16]. An association between alcohol consumption and the risk of both CRC [10], colorectal

adenoma [15, 17] and serrated lesions [18] has been shown, but there is no evidence on differences in these associations between the subsites.

In this study, we examined the association between lifestyle factors and detection of proximal neoplasia at CRC screening. We used data from a randomized CRC screening trial to study associations between modifiable lifestyle risk factors, and proximal and distal localization of advanced lesion in the colorectum, combining advanced adenomas, advanced serrated lesions, and cancer. We also examined the association between lifestyle factors and being referred for follow-up colonoscopy after sigmoidoscopy screening.

2. Method

2.1 Study population

Participants in the present study were a subpopulation of a large, still ongoing randomized CRC screening trial comparing two screening modalities; four biennial rounds of faecal immunochemical testing (FIT) and once-only sigmoidoscopy [19]. Approximately 140,000 women and men aged 50-74 from two geographically defined areas in South-East Norway were randomly allocated (1:1 ratio) to one of the two screening modalities. Participants assigned to FIT were mailed a self-administered kit with which they obtained a stool sample to be returned by mail to the laboratory. A test result of ≥75 µg haemoglobin/ml buffer (equivalent to 15 mcg haemoglobin/g feces) was considered a positive FIT. In the present subpopulation, three biannual FIT rounds had been conducted when the data was drawn. Sigmoidoscopy screening test was defined as positive if one of the following was detected: 1) any polyp ≥ 10 mm in diameter, 2) any adenoma with villous histology or high-grade dysplasia, 3) > 2 adenomas or 4) cancer. Participants with a positive screening result were referred to a follow-up colonoscopy.

From November 2012 to September 2013, a total of 14,832 individuals (6,959 in the FIT arm and 7,873 in the sigmoidoscopy arm) were invited to complete a two-page lifestyle questionnaire on paper or online prior to receiving the results of the first FIT round or sigmoidoscopy screening. Flowchart of inclusion is shown in Figure 1.

The Regional Research Ethics Committee of Southeast Norway (approval no. 2011/1272) approved the study protocol on 18th June 2012. The participants gave their consent to participate in the lifestyle sub-study by completing and returning the questionnaire. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008) as reflected in a priori approval by the institution's human research committee.

2.2 Lifestyle assessment

The lifestyle questionnaire consisted of questions used in previous national surveys [20, 21], and the Norwegian Colorectal Cancer Prevention trial [22]. Demographic factors included ethnicity, marital status, education length and working status. Height (cm) and weight (kg) were self-assessed by participants together with the lifestyle factors, including smoking habits, consumption of alcoholic beverages, diet and physical activity.

2.3 Outcome assessment

Proximal lesions were defined as those in the cecum, ascending colon, right flexure, transverse colon and left flexure, whereas distal lesions included those in the descending and sigmoid colon and in the rectum [23, 24]. Participants were defined to have an advanced lesion if any adenoma ≥ 10 mm, villous component of at least 25% or high-grade dysplasia, advanced serrated lesion (including traditional serrated adenoma, hyperplastic polyps ≥ 10 mm or sessile serrated polyp with dysplasia or ≥ 10 mm), or CRC [25] were detected at sigmoidoscopy or follow-up

colonoscopy after a positive screening test. Advanced lesion cases were divided into two site-specific groups: a) distal-only advanced lesion (referred to as "distal-only advanced lesion") and b) proximal advanced lesion, with or without distal advanced lesion (referred to as "proximal advanced lesion"). Additionally, we created a category "proximal-only advanced lesion" in FIT screening participants, which included participants with advanced lesion in the proximal only, without advanced lesion in the distal colorectum.

2.4 Categorization of lifestyle variables

Smoking status was categorized as current, former and never. Body mass index (BMI; kg/m^2) was categorized according to international standards: <25 (normal weight), 25-29.9 (overweight) and ≥ 30 (obesity). Consumption of alcoholic beverages (glasses/week) was calculated by frequency of intake multiplied by the number of glasses usually consumed each time and divided into gender specific tertiles.

We created an unhealthy lifestyle score based on the following factors: smoking habits, BMI, and alcohol intake. Each participant was assigned one point for each unhealthy factor; current smoking, BMI ≥25 and alcohol intake equal or higher than one drink/d (women) or two drinks/d (men). The total number of points in the score thus ranged from zero (most healthy) to three (most unhealthy). Physical activity and the dietary factors were not included in the score.

2.5 Statistical analysis

Multivariable multinomial logistic regression analyzes were used to estimate odds ratio (OR) with 95% confidence intervals (CI) for the association between lifestyle factors and site-specific advanced lesion, as well as association between lifestyle factors and referral to follow-up colonoscopy in the sigmoidoscopy arm (due to advanced lesion in the distal colon and rectum). In

the analysis of the unhealthy lifestyle score, we collapsed values two and three into one category because of a low number of participants with the score three.

The multivariable models included age, gender, current smoking, BMI, alcohol intake and length of education. Preliminary models were adjusted for ethnicity, marital status, occupation and screening center affiliation. We did not include these variables in the final models, as adjusting for them did not change the OR of interest. Likewise, dietary factors (intake of fruit, berries and vegetables, red and processed meat and fatty fish) and physical activity were not included in the main analysis. These factors were not associated with the odds of advanced lesions, and they did not change the risk estimates of smoking habit, BMI and alcohol intake for site-specific advanced lesion in FIT and sigmoidoscopy screening if included in the model (Appendices A.1. and A.2.). Missing was grouped into its own "missing" category for each variable. We tested heterogeneity between proximal and distal findings by Wald test.

We conducted two sensitivity analysis of the above mentioned analysis on the association between lifestyle factors and site-specific advanced lesion, to test whether the observed associations were clearer if comparing individuals with screening results in the "farthest ends of the scale" within the limitations to identify those in this study material. That is, we included only individuals with advanced lesion and without neoplasia. In the first sensitivity analysis, conducted among FIT participants, we limited the subjects to participants undergoing colonoscopy but excluded participants with non-advanced neoplastic lesions. That is, we included as reference group only participants without neoplasia detected in the follow-up colonoscopy (n=73). The second sensitivity analysis was conducted among sigmoidoscopy participants. We limited the reference subjects to those without neoplasia detected in sigmoidoscopy (n=1252), excluding participants with non-advanced neoplastic lesions detected in sigmoidoscopy.

Analyses were performed independently by MDK using STATA™ software, version 15.1 (Stata Corp, College Station, Texas, USA) and EB, using SAS software, version 9.4 (SAS Institute, Cary, NC).

3. Results

A total of 6,306 individuals (3,318 undergoing FIT and 2,988 undergoing sigmoidoscopy) were included in the analyses. Participation rates for this questionnaire-based sub-study among those participating in FIT and sigmoidoscopy screening were 94% and 82%, respectively. The number of participants who had a positive screening test and were referred for follow-up colonoscopy, was 516 (16%) with FIT and 338 (11%) with sigmoidoscopy (Figure 1). In total, 375 (6%) participants were detected with advanced lesion. Among FIT participants, 155 (5%) were detected with advanced lesions; 62 with proximal advanced lesions (with or without distal lesions) and 93 with distal-only advanced lesions. Among sigmoidoscopy participants, 220 (7%) were detected with advanced lesions; 57 with proximal advanced lesions, and 163 with distal-only advanced lesions. Participants' characteristics by screening modality are shown in Table 1.

Among FIT participants, current smokers were more likely to be detected with advanced lesions compared to never smokers; OR 2.20 (95% CI 1.40-3.46). OR for distal-only advanced lesions in smokers was 2.37 (95% 1.34-4.18) (p for heterogeneity indicating difference in this association between the proximal and distal-only site was 0.99) (Table 2). Participants with BMI $\geq$ 30 kg/m^2 had a higher OR of proximal advanced lesions compared to participants with BMI < 25 kg/m^2, 2.68 (95% 1.36-5.26), p-trend = 0.01. Participants in the third tertile of alcohol intake compared to the first tertile had a higher OR of proximal advanced lesions, 2.16 (95% 1.08-4.30), p-trend = 0.02. Each increment in the unhealthy lifestyle score (from 0 to 2-3) was associated with an

increased OR of proximal advanced lesions, 1.75 (95% 1.22-2.51). None of the observed associations were significantly different between the proximal and distal-only site (Table 2).

Among sigmoidoscopy participants, current smokers had a higher OR of proximal advanced lesions compared to never smokers, 4.58 (95% 2.24-9.38) (Table 3). Increasing BMI was associated with increased OR of any advanced lesions, p-trend = 0.04. Each increment in the unhealthy lifestyle score (from 0 to 2-3) was associated with an increased OR of proximal advanced lesions, 1.94 (95% 1.27-2.96). None of the observed associations were different between the proximal and distal-only site (Table 3).

In the first sensitivity analysis, limited to the FIT participants undergoing colonoscopy and only including participants without neoplasia as reference group (n=73), the results were similar for association between the lifestyle factors and colorectal advanced lesions as in the main analysis (Appendice A.3). In the second sensitivity analysis, limited to the sigmoidoscopy participants and only including participants without neoplasia in the sigmoidoscopy as reference group (n=1252), the results were similar as in the main analysis albeit some stronger; the association between BMI and proximal advanced lesions was significant (p for trend = 0.03) (Appendice A.4).

Among people undergoing a sigmoidoscopy, the OR of being referred for colonoscopy was 2.80 (95% 2.02-3.89) in current smokers compared to never smokers and 1.42 (95% 1.01-2.00) in participants with BMI ≥ 30 compared to < 25 kg/m^2. The OR of being referred for colonoscopy was 2.88 (95% 2.00-4.16) in participants with the unhealthy lifestyle score of 2-3 compared to participants with the score of 0 (Table 4).

4. Discussion

The findings of this study suggest that current smoking, obesity and high alcohol intake were associated with detection of proximal colorectal advanced lesions in FIT screening participants, and that current smoking was associated with detection of proximal advanced lesions in sigmoidoscopy screening participants. We did not find that these associations were specific to proximal advanced lesions. Sigmoidoscopy-screened participants with unfavorable lifestyle were more likely to qualify for a follow-up colonoscopy than individuals with favorable lifestyle.

Associations between lifestyle risk factors and the anatomic location of adenoma have been shown earlier by others, but the results show a lack of coherence [7, 12, 26]. He *et al.* observed in a large prospective cohort study that the risk estimates for the association between smoking, BMI and alcohol intake each were similar between proximal and distal findings [12]. Burnett-Hartman *et al.* found in a cross-sectional study and Hermann *et al.* in a prospective cohort study that BMI was associated with adenoma risk in the proximal colon and smoking in the distal colon and rectum [7, 26]. In agreement with these studies, our results suggest that BMI may be more strongly associated with neoplasia in the proximal rather than the distal colorectum.

Our study cannot confirm a predictive value of lifestyle factors in the detection of proximal only or distal only advanced lesion at CRC screening. However, smoking habits, BMI and alcohol intake are modifiable factors which reflect the overall health behavior and are feasible to assess prior to CRC screening. The present results suggest that screening participants who are current smokers, obese and consume high amounts of alcohol are more prone to be detected with proximal colorectal advanced lesion, as compared to screening participants without these characteristics. Whether these characteristics can be used to select high-risk participants for whom sigmoidoscopy or FIT is not an adequate primary screening method, should be examined further in larger studies with prospective design, also considering unmodifiable risk factors such

as age and sex. The prevalence of advanced proximal adenomas, with or without distal adenomas is increased by age in average FIT participants [27]. Intuitively, primary colonoscopy may appear better and more cost-effective for screening participants with the high-risk lifestyle characteristics, particularly in the older age groups – provided that participation rate in primary colonoscopy is adequate. In this trial an advanced distal lesion was the prerequisite for a positive sigmoidoscopy. Therefore, we do not know if high-risk lifestyle can predict proximal advanced lesion in sigmoidoscopy participants without a distal advanced lesion. The colonoscopy findings of those who tested positive in FIT screening, however, support the possible benefit of using a lifestyle score for tailored primary colonoscopy screening.

The population-based randomization is a strength of this study, and the large majority of screening participants completed the lifestyle questionnaire. Prevalence of current smokers in the present study (17%) was similar to the prevalence of daily smokers in the Norwegian population of similar age group (15-20%) [28]. This suggests representative lifestyle characteristics in the study population. Collection of lifestyle information prior to screening reduces information bias. Limitations of the study include the lack of information on aspirin and non-steroidal anti-inflammatory drugs, which may reduce the risk of colorectal neoplasia but on the other hand increase gastrointestinal bleeding [29, 30]. We acknowledge that FIT and sigmoidoscopy screening modalities might have caused some false negative screening results (misclassification of individuals in the reference group) because of the limited sensitivity of FIT to discover precancerous lesions, the lower sensitivity of faecal tests for proximal compared to distal tumors [6], and that sigmoidoscopy only involves the distal segments of the colon. Although the sensitivity analysis only including the participants undergoing colonoscopy were underpowered, they indicated that the main results concerning association with current smoking, alcohol intake

and the unhealthy lifestyle score remained. We observed stronger associations in the sensitivity analysis among sigmoidoscopy screening participants, in which the reference group only included screening negative participants without any neoplasia. Lastly, the study had a relatively low number of neoplastic findings and thus the results need to be interpreted with caution and confirmed in larger cohorts with primary colonoscopy screening. Even with the mentioned limitations, we observed similar associations in the present study as in studies based on colonoscopy [7, 12, 26].

Despite the fact that CRC risk is strongly associated with age, gender [31] and lifestyle [32], CRC screening still follows the one-size-fits-all principle [33, 34]. Our results along with other studies suggest that individual risk factors including lifestyle can guide the decision of colonoscopy in CRC screening [35]. Personally tailored screening may contribute to a more cost-effective use of CRC screening resources [4, 36]. Further studies should confirm the impact of smoking habits, BMI and alcohol intake for tailored screening recommendations, as well as investigate the predictive value of lifestyle in sex and age groups. Diet and physical activity are difficult to assess adequately in a screening setting. However, if valid tools for short assessment of these factors will be created, their impact in personalized screening service should be investigated.

To conclude, the present results showed that current smoking, obesity and high alcohol intake were associated with detection of proximal advanced lesion in CRC screening, regardless of distal and multiple advanced lesion. There is a growing body of need for personalized CRC screening. This study indicates that information on these lifestyle factors might be useful in guiding the decision of primary colonoscopy. Larger studies with prospective design, however, are to be recommended.

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Author contributions

GH, PB, EB and MDK designed the study. ALS, KRR, ERN, MDK and PB collected the data. MDK analyzed the data under supervision of EB. MDK, EB, GH and PB interpreted the data and drafted the manuscript. ØH, AH, MS, ETE, ERN, ALS and KRR provided critical revision of the manuscript for important intellectual content.

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FIGURE LEGEND

Figure 1. Flowchart of study participants through the study.

Footnote:

Abbreviations: AL; advanced lesions, FIT; faecal immunochamical test

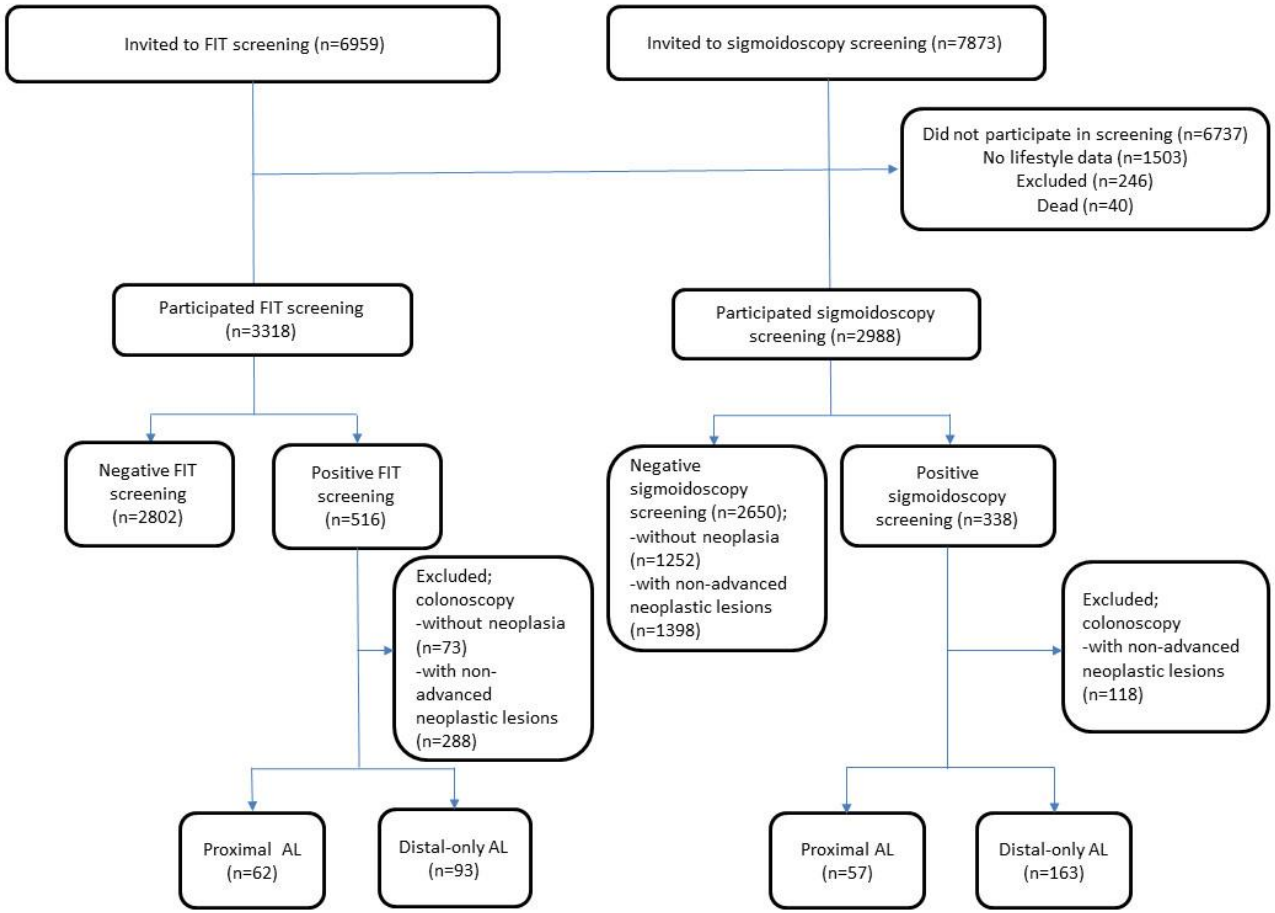
Invited to FIT screening (n=6959)
Invited to sigmoidoscopy screening (n=7873)
Did not participate in screening (n=6737)
No lifestyle data (n=1503)
Excluded (n=246)
Dead (n=40)
Participated FIT screening (n=3318)
Participated sigmoidoscopy screening (n=2988)
Negative FIT screening (n=2802)
Positive FIT screening (n=516)
Negative sigmoidoscopy screening (n=2650);
-without neoplasia (n=1252)
-with non-advanced neoplastic lesions (n=1398)
Positive sigmoidoscopy screening (n=338)
Excluded; colonoscopy
-without neoplasia (n=73)
-with non-advanced neoplastic lesions (n=288)
Excluded; colonoscopy
-with non-advanced neoplastic lesions (n=118)
Proximal AL (n=62)
Distal-only AL (n=93)
Proximal AL (n=57)
Distal-only AL (n=163)

Table 1. Demographic characteristics of the participants

	All	FIT participants	Sigmoidoscopy participants
	N=6306	N=3318	N=2988
Age, years			
Mean (SD)	62.1 (7.0)	61.9 (6.8)	62.2 (7.1)
Sex, n (%)			
Female	3249 (51.5)	1742 (52.5)	1507 (50.4)
Education, n (%)			
Primary school	1006 (16.0)	545 (16.4)	461 (15.4)
High school	2384 (37.8)	1250 (37.7)	1134 (38.0)
≥2y at university/college	2633 (41.8)	1364 (41.1)	1269 (42.5)
Missing	283 (4.5)	159 (4.8)	124 (4.2)
Ethnicity, n (%)			
Native	5881 (93.3)	3074 (92.7)	2807 (93.9)
Non-native	358 (5.6)	211 (6.3)	147 (5.0)
Missing	67 (1.1)	33 (1.0)	34 (1.1)
Marital status, n (%)			
Not married/non-cohabiting	1192 (18.3)	669 (20.1)	523 (17.5)
Married/cohabiting	5026 (79.7)	2597 (78.3)	2429 (81.3)
Missing	88 (1.4)	52 (1.6)	35 (1.2)

Table 2. Distribution and odds ratio of advanced lesions[a] in anatomic subsites of colorectum by sex and lifestyle factors in FIT screening participants

	Negative FIT N=2802 n (%)	Any AL N=155 n (%)		Proximal AL[b] N=62 n (%)	OR (95% CI)[d]	Distal-only AL N= 93 n (%)	OR (95% CI)[d]	P heterogeneity[c]	Proximal-only AL N=41 n (%)	OR (95% CI)[d]
Sex										
Female	1517 (541)	70 (4.4)	1.00 (Ref.)	31 (2.0)	1.00 (Ref.)	39 (2.5)	1.00 (Ref.)		24 (1.5)	1.00 (Ref.)
Male	1285 (45.9)	85 (6.2)	1.42 (1.01-1.99)	31 (2.3)	1.15 (0.68-1.95)	54 (3.9)	1.62 (1.05-2.53)	0.32	17 (1.2)	0.83 (0.43-1.58)
Smoking status										
Never	1130 (40.3)	44 (3.8)	1.00 (Ref.)	18 (1.5)	1.00 (Ref.)	26 (2.2)	1.00 (Ref.)		26 (1.4)	1.00 (Ref.)
Former	1158 (41.3)	70 (5.7)	1.31 (0.88-1.96)	29 (2.4)	1.07 (0.72-2.42)	41 (3.3)	1.31 (0.79-2.20)	0.67	17 (1.4)	0.97 (0.48-1.95)
Current	507 (18.1)	41 (7.5)	2.20 (1.40-3.46)	15 (2.7)	1.95 (0.95-3.99)	26 (4.7)	2.37 (1.34-4.18)	0.99	8 (1.5)	1.23 (0.50-2.97)
Missing	7 (0.3)	0 (0.0)							0 (0.0)	
P trend			0.003		0.09		0.01			0.79
BMI (kg/m^2)										
<25	1177 (42.0)	55 (4.7)	1.00 (Ref.)	21 (1.7)	1.00 (Ref.)	34 (2.8)	1.00 (Ref.)		13 (1.3)	1.00 (Ref.)
25.0-29.9	1181 (42.2)	61 (4.9)	1.05 (0.71-1.55)	23 (1.9)	1.07 (0.58-1.99)	38 (3.1)	1.03 (0.63-1.68)	0.92	18 (1.7)	1.12 (0.54-2.32)
30.0+	406 (14.5)	36(8.1)	2.07 (1.32-3.26)	17 (3.9)	2.68 (1.36-5.26)	19 (4.3)	1.72 (0.95-3.12)	0.32	9 (1.2)	1.95 (0.82-5.00)
Missing	38 (1.4)	3 (1.9)							1 (2.4)	
P trend			0.005		0.01		0.11			0.16

Alcohol, drinks/week, tertile[e]										
T1	964 (34.4)	44 (4.4)	1.00 (Ref.)	16 (1.6)	1.00 (Ref.)	28 (2.8)	1.00 (Ref.)		13 (1.3)	1.00 (Ref.)
T2	1022 (36.5)	56 (5.2)	1.36 (0.90-2.06)	24 (2.2)	1.68 (0.87-3.22)	32 (3.0)	1.01 (0.59-1.71)	0.42	18 (1.7)	1.55 (0.74-3.24)
T3	695 (24.8)	51 (6.8)	1.82 (1.17-2.82)	21 (2.8)	2.16 (1.08-4.30)	30 (4.0)	1.50 (0.87-2.58)	0.52	9 (1.2)	1.13 (0.46-2.75)
Missing	121 (4.3)	4 (3.2)							1 (1.0)	
P trend			0.008		0.02		0.09			0.70
Unhealthy lifestyle score[f]			1.63 (1.28-2.07)		1.75 (1.22-2.51)		1.54 (1.13-2.11)	0.60		1.40 (0.88-2.21)

[a] Advanced lesions included any advanced adenoma, advanced serrated lesions or CRC

[b] Includes participants with proximal AL, with or without distal AL

[c] Wald test, heterogeneity between proximal and distal-only AL

[d] Mutually adjusted for age, gender, smoking status, BMI, alcohol intake and length of education

[e] Cut-off values (drinks/week): T1 ≤ 0.6, T2 >0.6 but ≤ 3, T3 > 3 (women) and T1 ≤ 1.8, T2 >1.8 but ≤ 5, T3 >5 (men)

[f] A point was given for; current smoking, BMI ≥25 kg/m^2 and having an alcohol intake of 1 drink/day or more for women and 2 drinks/day or more for men.

Abbreviations: AL; advanced lesions, BMI; body mass index, CI; confidence interval, FIT; faecal immunchemical test, OR; odds ratio

Table 3. Distribution and odds ratio of advanced lesions[a] in anatomic subsites of colorectum by sex and lifestyle factors in sigmoidoscopy screening participants

	Negative sigmoidoscopy N=2650	Any AL N = 220		Proximal AL[b] N=57		Distal-only AL N= 163		P heterogeneity[c]
	n (%)	n (%)	OR (95% CI)[d]	n (%)	OR (95% CI)[d]	n (%)	OR (95% CI)[d]	
Sex								
Female	1385 (52.3)	88 (6.0)	1.00 (Ref.)	25 (1.7)	1.00 (Ref.)	63 (4.3)	1.00 (Ref.)	
Male	1265 (47.7)	132 (9.5)	1.57 (1.17-2.11)	32 (2.3)	1.45 (0.83-2.51)	100 (7.2)	1.62 (1.15-2.27)	0.73
Smoking status								
Never	1141 (43.1)	53 (4.4)	1.00 (Ref.)	13 (1.1)	1.00 (Ref.)	40 (3.4)	1.00 (Ref.)	
Former	1076 (40.6)	103 (8.7)	1.81 (1.27-2.58)	22 (1.9)	1.50 (0.74-3.04)	81 (6.9)	1.92 (1.29-2.87)	0.51
Current	425 (16.1)	64 (13.1)	3.32 (2.24-4.93)	22 (4.5)	4.58 (2.24-9.38)	42 (8.6)	2.91 (1.84-4.61)	0.29
Missing	8 (0.3)	0 (0.0)						
P trend			0.001		0.001		0.001	
BMI (kg/m^2)								
<24.9	1078 (40.7)	67 (5.9)	1.00 (Ref.)	20 (1.8)	1.00 (Ref.)	47 (4.1)	1.00 (Ref.)	
25.0-29.9	1123 (42.4)	107 (8.7)	1.39 (0.98-1.90)	22 (1.8)	1.09 (0.54-2.17)	85 (6.9)	1.51 (1.03-2.20)	0.29
30.0+	392 (14.8)	40 (9.3)	1.45 (0.95-2.21)	14 (3.2)	1.84 (0.89-3.79)	26 (6.0)	1.30 (0.79-2.17)	0.44
Missing	57 (2.3)	6 (9.5)						
P trend			0.04		0.13		0.15	

Alcohol, drinks/week, tertile[e]								
T1	845 (31.9)	80 (8.7)	1.00 (Ref.)	17 (1.8)	1.00 (Ref.)	63 (6.8)	1.00 (Ref.)	
T2	926 (34.9)	70 (7.0)	0.87 (0.62-1.23)	18 (1.8)	1.09 (0.55-2.16)	52 (5.2)	0.81 (0.55-1.20)	0.46
T3	763 (28.0)	59 (7.2)	0.91 (0.63-1.32)	17 (2.1)	1.35 (0.66-2.75)	42 (5.1)	0.80 (0.53-1.22)	0.20
Missing	116 (4.4)	11 (8.7)						
P trend			0.67		0.33		0.31	
Unhealthy lifestyle score[f]			1.95 (1.57-2.44)		1.94 (1.27-2.96)		1.96 (1.53-2.52)	0.96

[a] Advanced lesions included of any advanced adenoma, advanced serrated lesions or CRC

[b] Includes participants with proximal AL, with or without distal AL

[c] Wald test, heterogeneity between proximal and distal-only AL

[d] Mutually adjusted for age, gender, smoking status, BMI, alcohol intake and length of education

[e] Cut-off values (drinks/week): T1 ≤ 0.6, T2 >0.6 but ≤ 3, T3 > 3 (women) and T1 ≤ 1.8, T2 >1.8 but ≤ 5, T3 >5 (men)

[f] A point was given for; current smoking, BMI ≥25 kg/m^2 and having an alcohol intake of 1 drink/day or more for women and 2 drinks/day or more for men.

Abbreviations: AL; advanced lesions, BMI; body mass index, CI; confidence interval, OR; odds ratio

Table 4. Number of participants and odds ratio for referral for follow-up colonoscopy by lifestyle factors in sigmoidoscopy screening participants

	N= 2988	Referral to colonoscopy (%) n=338	Chi-square test for trend	OR (95% CI)[a]
Smoking status				
Never	1228	87 (7.1)		1.00 (Ref.)
Former	1237	161 (13.0)		1.73 (1.31-2.30)
Current	515	90 (17.5)	<0.0001	2.80 (2.02-3.89)
Missing	8	0 (0.0)		
BMI (kg/m^2)				
<24.9	1183	105 (8.9)		1.00 (Ref.)
25.0-29.9	1282	159 (12.4)		1.24 (0.94-1.63)
30.0+	456	64 (14.0)	<0.0001	1.42 (1.01-2.00)
Missing	67	10 (14.9)		
Alcohol, drinks/week, tertile[b]				
T1	965	120 (12.4)		1.00 (Ref.)
T2	1038	112 (10.8)		0.92 (0.70-1.23)
T3	763	89 (10.5)	0.17	0.91 (0.67-1.25)
Missing	133	17 (12.8)		
Unhealthy lifestyle score[c]				

0	726	48 (6.6)		1.00 (Ref.)
1	1424	1510 (10.6)		1.49 (1.06-2.10)
2-3	639	114 (17.8)	<0.0001	2.88 (2.00-4.16)
Missing	119	25 (12.6)		

[a] Mutually adjusted for age, gender, smoking status, BMI, alcohol intake and length of education

[b] Cut-off values (drinks/week): T1 ≤ 0.6, T2 >0.6 but ≤ 3, T3 > 3 (women) and T1 ≤ 1.8, T2 >1.8 but ≤ 5, T3 >5 (men)

[c] A point was given for; current smoking, BMI ≥25 kg/m^2 and having an alcohol intake of 1 drink/day or more for women and 2 drinks/day or more for men.

Abbreviations: BMI; body mass index, CI; confidence interval, OR; odds ratio