

Strong associations of a healthy lifestyle with all stages of colorectal carcinogenesis: Results from a large cohort of participants of screening colonoscopy

Vanessa Erben ^{1,2}, Prudence R Carr³, Bernd Holleccek⁴, Christa Stegmaier⁴, Michael Hoffmeister ³ and Hermann Brenner^{1,3,5}

¹Division of Preventive Oncology, German Cancer Research Center (DKFZ) and National Center for Tumor Diseases (NCT), Heidelberg, Germany

²Medical Faculty Heidelberg, Heidelberg University, Heidelberg, Germany

³Division of Clinical Epidemiology and Aging Research, German Cancer Research Center (DKFZ), Heidelberg, Germany

⁴Saarland Cancer Registry, Saarbrücken, Germany

⁵German Cancer Consortium (DKTK), Heidelberg, Germany

The risk of developing colorectal cancer (CRC) is associated with a wide range of dietary and lifestyle factors. The individual contribution of single modifiable factors, such as alcohol consumption, physical activity, smoking, body mass index (BMI) or dietary components, to the development of CRC has been investigated extensively, but evidence on their combined effect at various stages of colorectal carcinogenesis is sparse. The aim of our study was to analyze the association of a healthy lifestyle pattern with prevalence of early and advanced colorectal neoplasms. A total of 13,600 participants of screening colonoscopy in Saarland/Germany (mean age 62.9 years) who were enrolled in the KolosSal study (Effektivität der Früherkennungs-Koloskopie: eine Saarland-weite Studie) from 2005 until 2013 were included in this cross-sectional analysis. Dietary and lifestyle data were collected and colonoscopy results were extracted from physicians' reports. The association of an *a priori* defined healthy lifestyle score—including dietary intake, alcohol consumption, physical activity, smoking and BMI—with early and advanced colorectal neoplasms was assessed by multiple logistic regression analyses with comprehensive adjustment for potential confounders. Strong inverse dose–response relationships were observed between an overall healthier lifestyle pattern and presence of advanced colorectal neoplasms, nonadvanced adenomas and hyperplastic polyps (*p* value <0.0001 in all cases), with adjusted odds ratios (95% CI) for the highest compared to the lowest category of the healthy lifestyle score of 0.41 (0.30–0.56), 0.42 (0.33–0.54) and 0.39 (0.29–0.54) respectively. A healthy lifestyle is strongly associated with lower risk of all stages of colorectal neoplasms.

Introduction

Colorectal cancer (CRC) is the third most common cancer in men and the second most common cancer in women globally.¹ Colorectal cancer is associated with a number of modifiable risk factors such as dietary and lifestyle factors. For example, dietary components such as red and processed meat increase CRC risk^{2–4} whilst others such as whole grains and vegetables are associated with a reduced CRC risk.^{5,6} Other factors, which are associated with a Western lifestyle, such as smoking,^{7–9} high alcohol consumption,^{10–12} low physical

activity^{13,14} overweight and obesity^{15–18} have likewise been shown to be associated with increased CRC risk.

Although the impact of single factors on the risk of colorectal neoplasms has been reported in many individual studies, in real life, various lifestyle and dietary components interact in the human body and adherence to a healthy lifestyle pattern in general may be a more comprehensive approach to prevent colorectal neoplasms.¹⁹ Knowledge of the impact of a combined healthy lifestyle pattern on the risk of colorectal neoplasms is sparse^{20–22} and, to our knowledge, no unique index exists to estimate such

Key words: healthy living patterns, healthy eating, healthy lifestyle, colorectal cancer, advanced colorectal adenomas, advanced neoplasms, screening colonoscopy

Abbreviations: BMI: body mass index; MET: metabolic equivalent of task; NSAIDs: nonsteroidal anti-inflammatory drugs.

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Correspondence to: Prof. Dr. Hermann Brenner, DKFZ, Im Neuenheimer Feld 581, 69120 Heidelberg, Germany, E-mail: h.brenner@dkfz-heidelberg.de; Tel.: +49 (0)6221 421300

What's new?

While lifestyle and dietary factors are associated with colorectal cancer risk, most studies have examined associations only for individual factors. The influence of combinations of factors on colorectal carcinogenesis remains uncertain. Here, the authors created a healthy lifestyle score based on five dietary and lifestyle factors combined: non-smoking, low alcohol intake, healthy diet, adequate physical activity, and healthy weight. In analyses of health data and colonoscopy findings for screening colonoscopy participants in Saarland, Germany, healthy lifestyle score was inversely associated with risk of colorectal neoplasms. The findings indicate that healthy lifestyle pattern lowers risk of all stages of colorectal carcinogenesis.

associations. A number of studies have investigated the association of combined lifestyle factors and adherence to lifestyle recommendations with the risk of CRC^{23–28} using various scoring systems. However, to our knowledge, no previous study has investigated the association of a healthy lifestyle with the various stages of colorectal carcinogenesis, such as the early and late precursors of CRC in addition to clinically manifest CRC. Therefore, we developed an easy-to-use healthy lifestyle score combining different modifiable dietary and lifestyle factors and assessed associations of this score with various stages of colorectal carcinogenesis in a large cohort of participants of screening colonoscopy in Germany.

Subjects and Methods**Study design and population**

The KolosSal study (Effektivität der Früherkennungs-Koloskopie: eine Saarland-weite Studie) included participants of screening colonoscopy aged 55 years or older in the German state of Saarland (southwest of Germany, approximately 1 million inhabitants in 2010). A screening colonoscopy is offered by the German Statutory Health Insurance System to people above the age of 55 years and is almost exclusively provided by gastroenterologists in private practice. Participants were recruited by gastroenterologists at precolonoscopy visits between May 2005 and December 2013. Eligible participants had no personal history of CRC or colorectal surgery, had to be residents of Saarland and had to be proficient in German language.²⁹ The study was approved by the ethics committees of the University of Heidelberg (Heidelberg, Germany) and the Medical Association of Saarland (Saarbrücken, Germany). More study details have been described previously.^{29–32}

Data collection

Participants willing to take part in the study had to give written informed consent and were asked to complete a questionnaire with information on socioeconomic, demographic and lifestyle factors before the colonoscopy was conducted. Physicians' reports provided information regarding colonoscopy and histology results for every participant and participants were categorized into one of the after groups, according to the most advanced finding: CRC, advanced adenomas (adenoma with >1 cm in size, tubulovillous or villous components, high-grade dysplasia), other (nonadvanced) adenomas, hyperplastic polyps or none of these findings.²⁹

Healthy lifestyle score

For this analysis, we created a healthy lifestyle score combining the 5 most important dietary and lifestyle factors relevant to colorectal cancer based on *a priori* knowledge³³ in a binary point system. The points for each factor were summed up for the overall score ranging from 0 (most unhealthy) to 5 (most healthy). Further details on the score are provided in Supporting Information Table S1.

Participants completed a short food frequency questionnaire (FFQ) with information on their average frequency of consumption during the last 12 months (ranging from never to several times per day) of red meat (beef, pork, lamb), processed meat (including both processed red meat and poultry), poultry (fresh), wholegrains, fruits, and vegetables/salads. We created a dietary quality score with a maximum of 50 points; risk factors (red meat, processed meat) were rated negatively, protective factors (whole-grains, fruits, vegetables/salads) were rated positively (Supporting Information Table 2). An overall predominantly healthy diet (≥ 34 points) was worth 1 point in the lifestyle score. Poultry consumption was not included as previous studies did not observe an association with CRC risk.⁴

The reported number of alcoholic drinks consumed on average per week in the last 12 months was used to calculate the total alcohol intake in grams per day (beer 4.0 g ethanol/100 ml, wine 8.6 g ethanol/100 mL, spirits 33.0 g ethanol/100 mL³⁴) with a standard size of an alcoholic drink in Germany of 0.33 L beer, 0.25 L wine and 2 cL of spirits. Limitation of alcohol intake is recommended and 1 point was given when the recommendations for men (<24 g/day) and for women (<12 g/day) were met.³⁵

Participants reported their estimated physical activity in hours per week on average during the previous year and metabolic equivalents of tasks (METs) were calculated for leisure time activity (vigorous activity such as soccer and light activity such as going for a walk).³⁶ At least 75 min/week of vigorous intensity physical activity, 150 min/week of moderate intensity physical activity or a combination of these activities are recommended,³⁷ which equates to at least 500 MET min/week. One point was given when the physical activity recommendations were met.

Body mass index (BMI) was calculated as a measure of obesity³⁸ from participants' self-reported weight and height. One point was given for a healthy weight which was defined to be $>18.5 \text{ kg/m}^2$ – $<25 \text{ kg/m}^2$. Overweight or obesity (BMI $\geq 25 \text{ kg/m}^2$) received zero points.

Smoking is a strong established risk factor for adenomas and CRC³⁹ and the risk still remains high years after cessation

for former smokers with more than 30 pack years.^{7,40} Never smokers or former smokers with <30 pack years (defined as smoking 20 cigarettes per day for one year) received 1 point in the score.⁷ Current smokers or former smokers with ≥ 30 pack years were given 0 points.

Statistical analyses

For this analysis participants were excluded if colonoscopy data did not allow for definitive classification with respect to presence of the most advanced lesion (e.g. incomplete colonoscopy, poor bowel preparation, nonclassified polyps), if not enough data were available from the questionnaire to assess the healthy lifestyle score or if there were some other special circumstances limiting applicability of the lifestyle score (BMI <18.5 kg/m², history of inflammatory bowel disease, personal history of cancer). A missing value in the physical activity part was considered as “zero” and missing information in the previous (family) cancer history were considered as no (family) history of cancer. Demographic characteristics of the eligible participants were investigated in total and for each colonoscopy finding. Multiple imputation using the Markov-Chain Monte Carlo method was performed to fill in missing data for covariates ($N = 10$ imputed datasets, SAS procedure PROC MI).⁴¹ Imputed values of categorical variables were rounded to the closest integer.

Demographic characteristics of the eligible participants were investigated in total and for each colonoscopy finding. We performed multiple logistic regression analyses to evaluate the association of the healthy lifestyle score modeled as a categorical variable (reference group 0 or 1 point) and as a continuous variable (per 1 point increase) with risk of advanced neoplasms (advanced adenomas or CRC), nonadvanced adenomas and hyperplastic polyps and calculated odds ratios (ORs) and 95% confidence intervals (CIs). Advanced adenomas and CRC were combined in these analyses to the common endpoint “advanced colorectal neoplasms” due to the low number of CRC patients in this screening population. We included hyperplastic polyps as an additional endpoint in our analyses as hyperplastic polyps might develop into CRC through the serrated neoplasia pathway.^{42,43} We added an additional analysis with another reference group (0, 1 or 2 points) in the supplementary part to increase the sample size of the reference group. Results were additionally stratified according to sex. Multiple logistic regression models adjusted for age, sex, school education (in years), family history of CRC in first degree relatives (yes/no) and other covariates such as previous colonoscopy (yes/no), participation in health check-up (yes/no), use of NSAIDs including aspirin (yes/no).

In addition to the analyses on the composite lifestyle score, we assessed the association of the single lifestyle factors with prevalence of advanced colorectal neoplasms, nonadvanced adenomas and hyperplastic polyps adjusting for the known covariates and mutual adjustment for the other lifestyle factors. We also examined the associations of a healthy lifestyle with advanced colorectal neoplasms, nonadvanced adenomas

and hyperplastic polyps stratified by age (<70 years, ≥ 70 years; median age at diagnosis in developed countries⁴⁴), family history of CRC in a first degree relative (yes/no), history of previous colonoscopy (yes/no; independent of finding and time point) and regular use of NSAIDs including aspirin (yes/no). Dose response relationships of the healthy lifestyle score (continuous) and advanced colorectal neoplasms, nonadvanced adenomas and hyperplastic polyps were investigated with cubic spline regression using the SAS macro “RCS-Reg.”⁴⁵

A p -value <0.05 (two-sided testing) was considered to indicate statistical significance in any of the analyses. Analyses were conducted with SAS Enterprise Guide 6.1 (SAS Institute Inc., Cary, NC, USA).

Results

Overall, 13,600 screening participants of the KolosSal study were included in these analyses (Fig. 1). Participants were excluded if incomplete colonoscopy data ($n = 2278$) or questionnaire data ($n = 1455$) prohibited classification of findings at colonoscopy or derivation of the healthy lifestyle score, or if any of the other specific exclusion criteria were met such as previous diagnosis of cancer ($n = 1844$).

Participants were categorized according to the most advanced finding at screening colonoscopy (Table 1). Colorectal cancer, advanced adenomas and nonadvanced adenomas were detected in 128 (0.9%), 1357 (10.1%) and 2839 (20.9%) participants, respectively. Another 1475 (10.9%) had hyperplastic polyps, whereas the majority of participants ($N = 7783$, 57.2%) had none of these lesions. People free of neoplasms or hyperplastic polyps at colonoscopy were more likely to have a higher

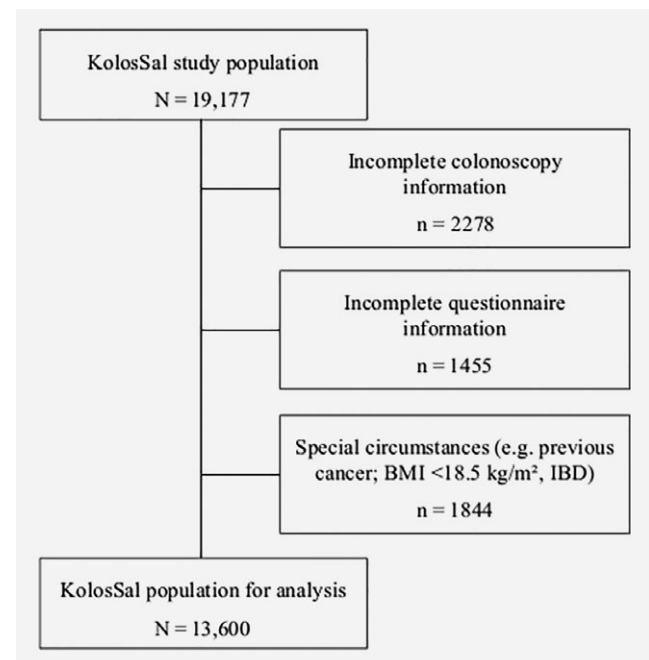


Figure 1. Exclusion criteria for the KolosSal study population (Saarland, Germany; 2005–2013).

Table 1. Baseline characteristics of the KolosSal study participants (Saarland, Germany; 2005-2013) by the most advanced finding at screening colonoscopy

Characteristics	Most advanced finding at screening colonoscopy						P value ⁵
	Total N=13,600	No finding N=7783	HPP N=1475	NAA N=2839	AA N=1375	CRC N=128	
Sex, n (%)							
Female	6764 (49.7)	4383 (56.3)	714 (48.4)	1145 (40.3)	478 (34.8)	44 (34.4)	<0.0001
Male	6836 (50.3)	3400 (43.7)	761 (51.6)	1694 (59.7)	897 (65.2)	84 (65.6)	
Age							
Mean, (SD)	62.9 (6.8)	62.6 (6.8)	62.0 (6.2)	63.5 (6.7)	64.2 (7.1)	66.3 (7.5)	<0.0001
Education ¹ , %							
≤9 years	8447 (62.8)	4777 (62.0)	939 (64.3)	1755 (62.6)	893 (65.5)	83 (65.9)	<0.0001
10-11 years	2518 (18.7)	1548 (20.1)	258 (17.7)	475 (16.9)	214 (15.7)	23 (18.3)	
>11 years	2495 (18.5)	1379 (17.9)	264 (18.1)	575 (20.5)	257 (18.8)	20 (15.9)	
Smoking status, %							
Current or former (≥30 pack years)	2611 (19.2)	1147 (14.7)	409 (27.7)	664 (23.4)	363 (26.4)	28 (21.9)	<0.0001
BMI, kg/m ² , mean	27.2	27.0	27.6	27.4	27.7	27.6	0.0043
Alcohol consumption, g/day, mean							
Women	7.0	6.6	7.6	8.1	7.5	6.6	<0.0001
Men	15.7	14.7	15.5	16.6	17.8	18.2	<0.0001
Leisure time physical activity, MET-h/week, mean (SD)	42.7 (39.9)	42.7 (39.2)	41.3 (36.1)	42.5 (37.7)	43.5 (45.7)	49.7 (82.5)	0.0003
Dietary quality score, mean	30.2	30.7	30.1	29.8	29.0	29.2	<0.0001
1 st degree family history of CRC, n (%)							
Yes	1862 (13.7)	1021 (13.1)	209 (14.2)	415 (14.6)	202 (14.7)	15 (11.7)	0.1922
Previous colonoscopy ² , n (%)							
Yes	4133 (30.5)	2501 (32.3)	413 (28.1)	883 (31.2)	320 (23.3)	16 (12.5)	<0.0001
Previous colonoscopy in the preceding 10 years, n (%)							
Yes	3011 (22.1)	1859 (23.9)	302 (20.5)	618 (21.8)	221 (16.1)	11 (8.6)	<0.0001
Participation in a health check-up ³ , n (%)							
Yes	9564 (78.5)	5485 (79.1)	1055 (78.4)	1990 (78.4)	959 (76.6)	75 (66.4)	0.0068
NSAIDs ⁴ , n (%)							
Yes	2708 (20.5)	1573 (20.8)	287 (19.9)	555 (20.1)	261 (19.4)	32 (25.6)	0.4133
Healthy lifestyle score							
0	56 (0.4)	14 (0.2)	6 (0.4)	21 (0.7)	15 (1.1)	0 (0.0)	<0.0001
1	712 (5.2)	306 (3.9)	99 (6.7)	192 (6.8)	107 (7.8)	8 (6.3)	
2	2775 (20.4)	1376 (17.7)	352 (23.9)	659 (23.2)	353 (25.7)	35 (27.3)	
3	5273 (38.8)	3015 (38.7)	573 (38.8)	1110 (39.1)	526 (38.3)	49 (38.3)	
4	3589 (26.4)	2267 (29.1)	351 (23.8)	663 (23.4)	279 (20.3)	29 (22.7)	
5	1195 (8.8)	805 (10.3)	94 (6.4)	194 (6.8)	95 (6.9)	7 (5.5)	

¹Data missing for 140 participants.²Data missing for 38 participants.³Data missing for 1420 participants.⁴Data missing for 372 participants.⁵P-values are calculated using chi-square test, an alpha level of 5 % is considered to be significant: * p < 0.05, ** p < 0.01, *** p < 0.001.

Percentages may not sum to 100 % due to missing or rounding.

Abbreviations: AA, advanced adenoma; BMI, body mass index; CRC, colorectal cancer; HPP, hyperplastic polyp; MET, metabolic equivalent of task; NAA, non-advanced adenoma; No finding, no colorectal neoplasms or hyperplastic polyps; NSAID, non-steroidal anti-inflammatory drug.

healthy lifestyle score than people in all of the other groups. Participants without neoplasms or hyperplastic polyps were also more likely to be female, were on average slightly younger and had more often undergone a previous colonoscopy or a general

health check-up than participants with such findings at screening colonoscopy.

Among participants of the KolosSal study population, 81% were nonsmokers or former smokers with less than 30 pack

years, 79% adhered to the recommendations regarding alcohol intake, 34% had a healthy diet, 86% met the recommendations for physical activity and 32% had a healthy BMI (Supporting Information Table S1).

Table 2 shows the results of the multiple logistic regression analyses. We observed a strong inverse risk association of the various types of colorectal neoplasms with an increasing healthy lifestyle score. When the highest category was compared to the lowest category we observed 61% lower risk for hyperplastic polyps (OR 0.39, 95% CI 0.29–0.54), 58% for nonadvanced adenomas (OR 0.42, 95% CI 0.33–0.54) and 59% for advanced colorectal neoplasms (OR 0.41, 95% CI 0.30–0.56). The inverse associations were also seen for the continuous assessment with 20% risk reduction for hyperplastic polyps (p trend <0.0001), 19% for nonadvanced adenomas (p trend <0.0001) and 23% risk reduction for advanced colorectal neoplasms (p trend <0.0001) per one point increase in the healthy lifestyle score. Similar results were obtained when participants with 0, 1 or 2 points were included in the reference groups (Supporting Information Table S3).

Very similar risk reduction was found for both men and women with no indication for interaction. Cubic spline regression highlighted the monotone inverse relationship between the healthy lifestyle score and the risk of hyperplastic polyps or colorectal neoplasms (Fig. 2).

Multivariable analysis with mutual adjustments showed that each individual lifestyle factor was associated with lower risk of advanced colorectal neoplasms: nonsmoking (OR 0.54, 95% CI 0.47, 0.62), meeting alcohol recommendations (OR 0.81, 95% CI 0.70, 0.93), healthy diet (OR 0.83, 95% CI 0.73, 0.95), and healthy BMI (OR 0.81, 95% CI 0.71, 0.92), although the association was not statistically significant for physical activity: meeting physical activity recommendations (OR 0.94, 95% CI 0.80, 1.11) (Table 3). Furthermore, an inverse association of nonadvanced adenomas and hyperplastic polyps with exception for diet and hyperplastic polyps was observed with each individual factor except for diet and hyperplastic polyps. The associations between physical activity and risk of hyperplastic polyps and nonadvanced adenomas were also not statistically significant. The strongest association

Table 2. Association between the healthy lifestyle score and the different colonoscopy outcomes in the KolosSal study (Saarland, Germany; 2005–2013)

Lifestyle score	No finding		Hyperplastic polyps		Non-advanced adenomas		Advanced colorectal neoplasms	
	n (%)	n (%)	OR (95% CI) ¹	n (%)	OR (95% CI) ¹	n (%)	OR (95% CI) ¹	
All participants								
0 or 1	320 (4.1)	105 (7.1)	1.00 (Ref.)	213 (7.5)	1.00 (Ref.)	130 (8.6)	1.00 (Ref.)	
2	1376 (17.7)	352 (23.9)	0.78 (0.61–1.01)	659 (23.2)	0.72 (0.59–0.88)	388 (25.8)	0.72 (0.57–0.92)	
3	3015 (38.7)	573 (38.8)	0.59 (0.47–0.75)	1110 (39.1)	0.56 (0.47–0.68)	575 (38.3)	0.50 (0.40–0.63)	
4	2267 (29.1)	351 (23.8)	0.51 (0.39–0.65)	663 (23.4)	0.49 (0.40–0.59)	308 (20.5)	0.40 (0.31–0.51)	
5	805 (10.3)	94 (6.4)	0.39 (0.29–0.54)	194 (6.8)	0.42 (0.33–0.54)	102 (6.8)	0.41 (0.30–0.56)	
Per 1 point increase in score			0.80 (0.75–0.85)			0.81 (0.78–0.85)	0.77 (0.73–0.82)	
P trend			<0.0001			<0.0001	<0.0001	
Men								
0 or 1	199 (5.9)	65 (8.5)	1.00 (Ref.)	150 (8.9)	1.00 (Ref.)	107 (10.9)	1.00 (Ref.)	
2	776 (22.8)	222 (29.2)	0.86 (0.63–1.19)	459 (27.1)	0.78 (0.61–0.99)	272 (27.7)	0.65 (0.49–0.86)	
3	1456 (42.8)	312 (41.0)	0.65 (0.48–0.88)	703 (41.5)	0.61 (0.49–0.77)	391 (39.9)	0.48 (0.37–0.63)	
4	774 (22.8)	132 (17.3)	0.53 (0.37–0.74)	311 (18.4)	0.50 (0.39–0.65)	170 (17.3)	0.38 (0.29–0.52)	
5	195 (5.7)	30 (3.9)	0.49 (0.30–0.79)	71 (4.2)	0.45 (0.32–0.63)	41 (4.2)	0.37 (0.24–0.56)	
Per 1 point increase in score			0.80 (0.74–0.87)			0.81 (0.76–0.86)	0.76 (0.70–0.82)	
P trend			<0.0001			<0.0001	<0.0001	
Women								
0 or 1	121 (2.8)	40 (5.6)	1.00 (Ref.)	63 (5.5)	1.00 (Ref.)	23 (4.4)	1.00 (Ref.)	
2	600 (13.7)	130 (18.2)	0.66 (0.44–0.99)	200 (17.5)	0.62 (0.44–0.87)	116 (22.2)	0.98 (0.60–1.60)	
3	1559 (35.6)	261 (36.6)	0.51 (0.35–0.75)	407 (35.5)	0.48 (0.35–0.66)	184 (35.2)	0.59 (0.37–0.95)	
4	1493 (34.1)	219 (30.7)	0.46 (0.31–0.67)	352 (30.7)	0.43 (0.31–0.60)	138 (26.4)	0.47 (0.29–0.76)	
5	610 (13.9)	64 (9.0)	0.33 (0.21–0.51)	123 (10.7)	0.37 (0.26–0.53)	61 (11.7)	0.51 (0.30–0.87)	
Per 1 point increase in score			0.80 (0.73–0.86)			0.82 (0.77–0.88)	0.79 (0.72–0.86)	
P trend			<0.0001			<0.0001	<0.0001	
P interaction			0.73			0.75	0.55	

¹Adjusted for age, sex, school education, family history of CRC, history of large bowel endoscopy, participation in a health check-up, ever regular use of NSAIDs

Abbreviations: AA, advanced adenoma; CRC, colorectal cancer; HPP, hyperplastic polyps; NAA, non-advanced adenoma; No finding, no colorectal neoplasms or hyperplastic polyps.

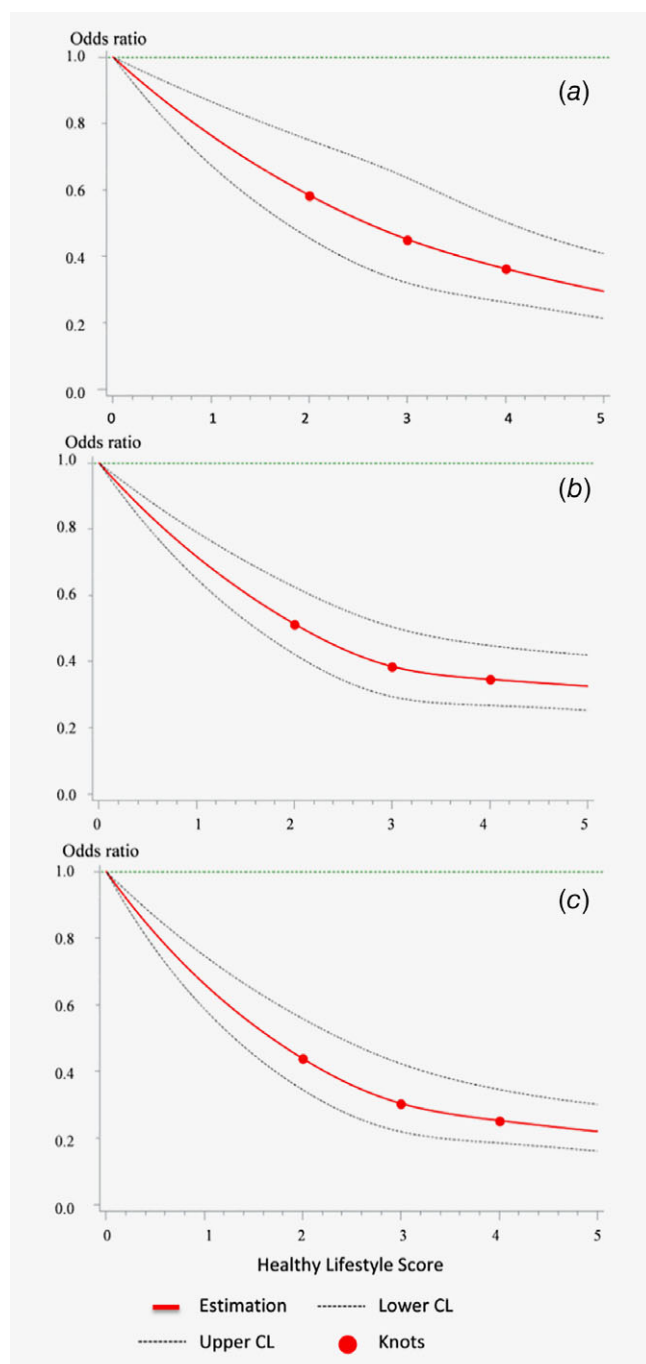


Figure 2. Dose–response relationship between the healthy lifestyle score and prevalence of hyperplastic polyps (a), non-advanced adenomas (b) and advanced colorectal neoplasms (c) in the KolosSal study (Saarland, Germany; 2005–2013). [Color figure can be viewed at wileyonlinelibrary.com]

was seen for smoking with 40% (OR 0.60, 95% CI 0.54–0.67) risk reduction for nonadvanced adenomas and 53% (OR 0.47, 95% CI 0.41–0.54) risk reduction for hyperplastic polyps. Results were generally very similar for men and for women.

Stratification of the associations between a healthy lifestyle score and colorectal neoplasms by age, family history of CRC, previous colonoscopy and regular use of NSAIDs showed very similar results across all outcomes and all subgroups without any indication of interaction (Supporting Information Table S4).

Discussion

A healthy lifestyle (nonsmoking, low alcohol intake, healthy diet, adequate physical activity and a healthy weight) was associated with strongly reduced prevalence of hyperplastic polyps, nonadvanced adenomas and advanced colorectal neoplasms in a dose–response relationship. With increasing adherence to the healthy lifestyle score, prevalence of any type of advanced colorectal neoplasms, nonadvanced adenomas and hyperplastic polyps was lower. Overall, the strongest risk reduction was observed between smoking and early and advanced colorectal neoplasms.

Currently, the definition of a healthy lifestyle varies and there is no general consensus on how to measure “lifestyle quality”. However, investigating the combined impact of different modifiable factors with their complex interactions is highly relevant. To our knowledge, studies investigating the impact of a combined healthy lifestyle pattern on the risk of colorectal neoplasms are sparse. Some studies have already investigated the association of a healthy lifestyle with risk of CRC,^{25,26} adenoma²² or polyps²⁰ but this analysis is the first to highlight the effectiveness of a healthy lifestyle across various stages of colorectal carcinogenesis—from hyperplastic polyps to adenomas and to CRC in a large screening population. In this analysis, we included lifestyle factors that have previously been shown to be individually associated with risk of CRC and colorectal adenomas⁴⁶ and we were able to show reduced risk for a spectrum of early and advanced colorectal neoplasms in a large screening population. Our results are in line with and expand beyond findings from other healthy lifestyle indices which mostly focused on only one specific stage in colorectal carcinogenesis.

The same healthy lifestyle score has previously been applied in a German case–control study of more than 4000 CRC patients and 3000 age- and sex matched controls without CRC.⁴⁷ A strong inverse association was shown with increasing adherence to the lifestyle score for both colon and rectal cancer and for the highest compared to the reference category, a 67% risk reduction (score 5 vs. score ≤1, OR 0.33, 95% CI 0.26, 0.43) for CRC was observed.⁴⁷

A study of more than 6000 participants of screening colonoscopy in Norway (Bowel Cancer Screening in Norway, BCSN) showed inverse associations between another binary healthy lifestyle score (smoking, BMI, physical activity, alcohol consumption, food components) and risk of advanced colorectal neoplasms (score 5–6 vs. score ≤1, OR 0.41, 95% CI 0.22, 0.73).²² However, in addition to associations with advanced neoplasms, we found in our larger study a reduced risk of hyperplastic polyps and nonadvanced adenomas with a healthy lifestyle. Moreover, similar to results from our study,

Table 3. Association between the individual lifestyle factors and findings at colonoscopy in the KolosSal study (Saarland, Germany; 2005–2013)

Lifestyle factor	Score	No finding		Hyperplastic polyps		Non-advanced adenomas		Advanced colorectal neoplasms	
		n (%)	n (%)	OR (95% CI) ¹	n (%)	OR (95% CI) ¹	n (%)	OR (95% CI) ¹	
All participants									
Smoking	0	1147 (14.7)	409 (27.7)	1.00 (Ref.)	664 (23.4)	1.00 (Ref.)	391 (26.0)	1.00 (Ref.)	
	1	6636 (85.3)	1066 (72.3)	0.47 (0.41-0.54)	2175 (76.6)	0.60 (0.54-0.67)	1112 (74.0)	0.54 (0.47-0.62)	
Alcohol	0	1511 (19.4)	327 (22.2)	1.00 (Ref.)	659 (23.2)	1.00 (Ref.)	345 (23.0)	1.00 (Ref.)	
	1	6272 (80.6)	1148 (77.8)	0.86 (0.75-0.98)	2180 (76.8)	0.80 (0.72-0.89)	1158 (77.0)	0.81 (0.70-0.93)	
Diet	0	4924 (63.3)	983 (66.6)	1.00 (Ref.)	2000 (70.4)	1.00 (Ref.)	1097 (73.0)	1.00 (Ref.)	
	1	2859 (36.7)	492 (33.4)	1.04 (0.92-1.18)	839 (29.6)	0.88 (0.80-0.98)	406 (27.0)	0.83 (0.73-0.95)	
Physical activity	0	1017 (13.1)	200 (13.6)	1.00 (Ref.)	416 (14.7)	1.00 (Ref.)	224 (14.9)	1.00 (Ref.)	
	1	6766 (86.9)	1275 (86.4)	0.98 (0.83-1.16)	2423 (85.3)	0.91 (0.81-1.04)	1279 (85.1)	0.94 (0.80-1.11)	
BMI	0	5120 (65.8)	1060 (71.9)	1.00 (Ref.)	1994 (70.2)	1.00 (Ref.)	1100 (73.2)	1.00 (Ref.)	
	1	2663 (34.2)	415 (28.1)	0.77 (0.68-0.88)	845 (29.8)	0.89 (0.81-0.99)	403 (26.8)	0.81 (0.71-0.92)	
Men									
Smoking	0	646 (19.0)	251 (33.0)	1.00 (Ref.)	454 (26.8)	1.00 (Ref.)	286 (29.2)	1.00 (Ref.)	
	1	2754 (81.0)	510 (67.0)	0.48 (0.40-0.57)	1240 (73.2)	0.63 (0.55-0.73)	695 (70.8)	0.58 (0.49-0.68)	
Alcohol	0	672 (19.8)	165 (21.7)	1.00 (Ref.)	376 (22.2)	1.00 (Ref.)	238 (24.3)	1.00 (Ref.)	
	1	2728 (80.2)	596 (78.3)	0.92 (0.76-1.12)	1318 (77.8)	0.88 (0.76-1.02)	743 (75.7)	0.76 (0.64-0.90)	
Diet	0	2599 (76.4)	591 (77.7)	1.00 (Ref.)	1348 (79.6)	1.00 (Ref.)	773 (78.8)	1.00 (Ref.)	
	1	801 (23.6)	170 (22.3)	1.07 (0.88-1.31)	346 (20.4)	0.86 (0.74-1.00)	208 (21.2)	0.93 (0.78-1.12)	
Physical activity	0	416 (12.2)	94 (12.4)	1.00 (Ref.)	236 (13.9)	1.00 (Ref.)	135 (13.8)	1.00 (Ref.)	
	1	2984 (87.8)	667 (87.6)	1.03 (0.80-1.31)	1458 (86.1)	0.91 (0.76-1.08)	846 (86.2)	0.97 (0.78-1.20)	
BMI	0	2486 (73.1)	586 (77.0)	1.00 (Ref.)	1298 (76.6)	1.00 (Ref.)	778 (79.3)	1.00 (Ref.)	
	1	914 (26.9)	175 (23.0)	0.80 (0.67-0.97)	396 (23.4)	0.82 (0.72-0.95)	203 (20.7)	0.68 (0.57-0.82)	
Women									
Smoking	0	501 (11.4)	158 (22.1)	1.00 (Ref.)	210 (18.3)	1.00 (Ref.)	105 (20.1)	1.00 (Ref.)	
	1	3882 (88.6)	556 (77.9)	0.47 (0.38-0.57)	935 (81.7)	0.54 (0.45-0.65)	417 (79.9)	0.47 (0.37-0.60)	
Alcohol	0	839 (19.1)	162 (22.7)	1.00 (Ref.)	283 (24.7)	1.00 (Ref.)	107 (20.5)	1.00 (Ref.)	
	1	3544 (80.9)	552 (77.3)	0.79 (0.65-0.96)	862 (75.3)	0.71 (0.61-0.83)	415 (79.5)	0.91 (0.72-1.14)	
Diet	0	2325 (53.0)	392 (54.9)	1.00 (Ref.)	652 (56.9)	1.00 (Ref.)	324 (62.1)	1.00 (Ref.)	
	1	2058 (47.0)	322 (45.1)	1.03 (0.87-1.21)	493 (43.1)	0.90 (0.79-1.04)	198 (37.9)	0.73 (0.61-0.89)	
Physical activity	0	601 (13.7)	106 (14.8)	1.00 (Ref.)	180 (15.7)	1.00 (Ref.)	89 (17.0)	1.00 (Ref.)	
	1	3782 (86.3)	608 (85.2)	0.95 (0.75-1.19)	965 (84.3)	0.93 (0.77-1.12)	433 (83.0)	0.90 (0.70-1.16)	
BMI	0	2634 (60.1)	474 (66.4)	1.00 (Ref.)	696 (60.8)	1.00 (Ref.)	322 (61.7)	1.00 (Ref.)	
	1	1749 (39.9)	240 (33.6)	0.75 (0.63-0.89)	449 (39.2)	0.97 (0.84-1.11)	200 (38.3)	1.00 (0.82-1.21)	

¹Model adjusted for age, sex, school education, family history of CRC, history of large bowel endoscopy, participation in a health check-up, ever regular use of NSAIDs, and mutual adjustment for the other lifestyle factors

Abbreviations: ACN, advanced colorectal neoplasms; No finding, no colorectal neoplasms or hyperplastic polyps.

an inverse association was found with the individual lifestyle factors smoking and alcohol intake and colorectal neoplasms. In both studies, smoking status showed the strongest association with risk of advanced colorectal neoplasms (nonsmokers vs. smokers, OR 0.53, 95% CI 0.42, 0.68) for the BCSN study²² and for the KolosSal study (nonsmokers vs. smokers, OR 0.54, 95% CI 0.47, 0.62) for advanced colorectal neoplasms, as well as for hyperplastic polyps and nonadvanced adenomas.

Two American case-control studies also examined the association between the combinations of lifestyle factors in relation to the prevalence of colorectal precursors. However, there was heterogeneity in the number and definition of the

healthy lifestyle factors addressed. The Tennessee Colorectal Polyp Study developed an inverse risk score including smoking, obesity, regular NSAID use, high red meat intake, low fiber consumption and low calcium intake and showed increased risk of developing colorectal hyperplastic polyps and adenomas with increasing number of risk factors (score 5–6 vs. score ≤ 1, OR 9.03, 95% CI 5.69, 14.34),²⁰ similar to what we found in our current analysis.

Using data from a small American case-control study, a binary healthy lifestyle score including smoking, alcohol intake, physical activity, diet (fruit and vegetables) and BMI was associated with a 25% risk reduction of colorectal

adenomatous polyps among 138 study participants (per one unit increase, OR 0.75, 95% CI 0.51, 1.10).²¹ Results of the KolosSal study were similar with significant risk reduction by 19% for nonadvanced adenomas and 23% for advanced colorectal neoplasms. Our very large study with 13,600 participants is the first study showing the association of a healthy lifestyle with different types of early and advanced colorectal neoplasms and highlights the importance of a healthy lifestyle early in the beginning of the carcinogenic process and strengthens its relevance for primary prevention purposes.

Although a number of studies to date have investigated the associations between a healthy lifestyle and prevalence of colorectal polyps, the definition of a healthy lifestyle in most studies differed, making comparability difficult. However, most authors agree in their selection of the included lifestyle factors such as the inclusion of dietary components, smoking status and physical activity. The importance of a healthy lifestyle should not be neglected and, moreover, we could show that a healthy lifestyle strongly prevents colorectal neoplasms as well as precancerous colorectal lesions and is highly relevant for primary prevention. The KolosSal study is to our knowledge the largest screening study conducted among asymptomatic participants investigating the association of a healthy lifestyle in general with prevalence of various findings such as hyperplastic polyps, adenomas and CRC. All participants underwent colonoscopy conducted by qualified physicians to verify colorectal health status. Looking at combinations of healthy lifestyle factors may be particularly useful for translation of results into prevention practice as the much stronger effects for an overall healthy lifestyle compared to the typically modest effects of single lifestyle factors (that are often adopted in combination) may help to increase motivation for engaging in a healthy lifestyle.

There are also some limitations that require discussion. Firstly, one limitation of our analysis is the cross-sectional study design; however, we were able to include many important factors and adjusted carefully for confounders. Secondly, the questionnaire collected information retrospectively and assessment of diet and lifestyle was based on self-reported information, yielding potential for recall or other information bias. Furthermore, we cannot rule out selection bias, as only

German speaking participants were eligible and probably more health conscious people were willing to take part in the study. Thirdly, as this screening study was conducted among asymptomatic participants the number of CRC cases was still very limited despite the overall very large sample size. Finally, as no unique healthy lifestyle scoring system exists to describe a healthy lifestyle, further efforts are needed to come up with an “optimized”, easy-to-apply healthy lifestyle scoring system which is most useful for screening purposes to determine individual risk.

In conclusion, we found a healthy lifestyle pattern to be associated with strongly decreased risk of all stages of colorectal carcinogenesis. This underlines the importance of adherence to a healthy lifestyle as early as possible for primary prevention of colorectal carcinogenesis. The combination of the known risk factors of colorectal neoplasms and hyperplastic polyps showed cumulative synergistic effects and the importance of both a healthy diet and healthy lifestyle in preventing the development of CRC in all stages. Future research should focus on the great potential of a healthy lifestyle in primary prevention and its implementation in policy making. Furthermore, the score which can be easily implemented in routine health care might be used, potentially in combination with other risk information, such as risk information from emerging polygenetic risk scores, for developing more personalized, risk adapted CRC screening strategies in the future.

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Author Contribution

The authors' responsibilities were as follows – HB: planned and designed the KolosSal study; VE, PRC, HB: designed this specific analysis; HB, MH, BH, CS: conducted the study; VE: analyzed the data; VE, PRC, HB: drafted the study; all authors critically reviewed the study and approved the final draft.

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