See corresponding editorial on page 1388 and article on pages 1458 and 1636.

Lifestyle after colorectal cancer diagnosis in relation to recurrence and all-cause mortality

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ABSTRACT

Background: An unhealthy lifestyle is associated with the risk of colorectal cancer (CRC), but it is unclear whether overall lifestyle after a CRC diagnosis is associated with risks of recurrence and mortality.

Objectives: To examine associations between postdiagnosis lifestyle and changes in lifestyle after a CRC diagnosis with risks of CRC recurrence and all-cause mortality.

Methods: The study population included 1425 newly diagnosed, stage I–III CRC patients from 2 prospective cohort studies enrolled between 2010 and 2016. Lifestyle, including BMI, physical activity, diet, and alcohol intake, was assessed at diagnosis and at 6 months postdiagnosis. We assigned lifestyle scores based on concordance with 2 sets of cancer prevention guidelines—from the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) and the American Cancer Society (ACS)—and national disease prevention guidelines. Higher scores indicate healthier lifestyles. We computed adjusted HRs and 95% CIs using Cox regression.

Results: We observed 164 recurrences during a 2.8-year median follow-up and 171 deaths during a 4.4-year median follow-up. No associations were observed for CRC recurrence. A lifestyle more consistent with the ACS recommendations was associated with a lower all-cause mortality risk (HR per +1 SD, 0.85; 95% CI: 0.73–0.995). The same tendency was observed for higher WCRF/AICR (HR, 0.92; 95% CI: 0.78–1.08) and national (HR, 0.90; 95% CI: 0.77–1.05) lifestyle scores, although these associations were statistically nonsignificant. Generally, no statistically significant associations were observed for BMI, physical activity, diet, or alcohol. Improving one's lifestyle after diagnosis (+1 SD) was associated with a lower all-cause mortality risk for the ACS (HR, 0.80; 95% CI: 0.67–0.96) and national (HR, 0.84; 95% CI: 0.70–0.999) scores, yet was statistically nonsignificant for the WCRF/AICR score (HR, 0.94; 95% CI: 0.78–1.13).

Conclusions: A healthy lifestyle after CRC diagnosis and improvements therein were not associated with the risk of CRC recurrence, but were associated with a decreased all-cause mortality risk. *Am J Clin Nutr* 2021;113:1447–1457.

Keywords: colorectal cancer, survival, recurrence, lifestyle, body mass index, physical activity, diet, alcohol

Introduction

Rates of cancer survival are increasing, with more people living with and beyond cancer, including colorectal cancer (CRC) (1, 2). Current lifestyle recommendations for cancer survivors are largely extrapolated from recommendations for cancer prevention (3, 4). Cancer survivors who adhere to lifestyle recommendations may improve their prognoses. In CRC survivors, for instance, several reviews concluded that being physically active or eating a healthy diet after diagnosis may improve overall survival (5–7). However, the recommendations emphasize the importance of adopting an overall healthy lifestyle pattern, rather than focusing on single lifestyle behaviors, and little is known about the impact of an overall healthy lifestyle on CRC prognoses.

Currently, only 2 studies have investigated whether an overall lifestyle consistent with cancer prevention guidelines is

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associated with all-cause mortality after CRC (8, 9). Inconsistent results were reported, although the guidelines used in both studies included the combination of the same 4 single lifestyle behaviors (an optimal body weight, being physically active, eating a healthy diet, and limiting alcohol intake). Concordance with the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) recommendations for cancer prevention was not associated with a lower all-cause mortality risk among 380 older, female CRC survivors (8). In contrast, a lifestyle more consistent with the American Cancer Society (ACS) guidelines for cancer prevention was associated with a lower risk of both recurrence and all-cause mortality among 992 stage III colon cancer survivors (9). These inconsistent results might be explained by differences in timing of lifestyle assessments after diagnosis, differences between study populations, and/or differences between lifestyle scores (number of included dietary components and scoring).

More research is needed to examine whether a healthy overall lifestyle after a CRC diagnosis lowers risks of recurrence and all-cause mortality. Using pooled data of 2 prospective cohort studies, we examined the associations between overall lifestyle after CRC diagnosis and risks of CRC recurrence and all-cause mortality. Overall lifestyle was assessed with 3 lifestyle scores that reflected concordance with either the WCRF/AICR, ACS, or national guidelines. The first 2 scores incorporate cancer prevention guidelines, while the national guidelines aim to prevent common diseases (including cancer and cardiovascular disease). We hypothesized that the 3 lifestyle scores would show similar associations with outcomes, as they all reflect a healthy overall lifestyle by emphasizing an optimal body weight, being physically active, eating a healthy diet, and limiting alcohol intake. Furthermore, we examined whether a change in concordance with these guidelines after diagnosis is associated with CRC recurrence and all-cause mortality.

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Supplemental Figure 1 and Supplemental Tables 1–6 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

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Abbreviations used: ACS, American Cancer Society; CRC, colorectal cancer; COLON, colorectal cancer: longitudinal, observational study on nutritional and lifestyle factors that may influence colorectal tumor recurrence, survival, and quality of life; EnCoRe, energy for life after colorectal cancer; WCRF/AICR, World Cancer Research Fund/American Institute for Cancer Research.

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Methods

Study design and population

We used pooled data from 2 ongoing, prospective cohort studies from the Netherlands that enrolled CRC patients: the COLON study (colorectal cancer: longitudinal, observational study on nutritional and lifestyle factors that may influence colorectal tumor recurrence, survival, and quality of life; NCT03191110; ClinicalTrials.gov) and the EnCoRe study (energy for life after colorectal cancer; NL6904; trialregister.nl). Detailed descriptions of the cohorts are provided elsewhere (10, 11). Briefly, patients diagnosed with colon or rectal cancer were recruited at diagnosis in 14 hospitals in the Netherlands from 2010 (2012 for EnCoRe) onwards. All patients with a newly diagnosed, primary stage I–IV colorectal tumor were eligible for the COLON study, but patients with stage IV disease were not eligible for the EnCoRe study. Patients were not eligible when they had a previous (partial) bowel resection, hereditary CRC, inflammatory bowel disease, dementia, or another mental condition limiting their ability to fill out surveys, or when they did not speak Dutch. Data were collected at diagnosis (before start of treatment) to reflect the prediagnosis lifestyle and were collected up to 4 times in the 5 years following diagnosis. All participants provided written informed consent. The COLON study was approved by the Committee on Research involving Human Subjects, region Arnhem-Nijmegen, the Netherlands. The EnCoRe study was approved by the Medical Ethics Committee of the University Hospital Maastricht and Maastricht University, the Netherlands.

In total, recurrence data were available for 1922 participants diagnosed between 2010 and 2016 (**Figure 1**). Exclusions were made for the following reasons: missing stage data ($n = 73$), distant metastatic disease (stage IV) at diagnosis ($n = 132$), a BMI < 18.5 kg/m^2 at diagnosis ($n = 13$), or CRC recurrence before a postdiagnosis lifestyle assessment ($n = 18$). Furthermore, we excluded 261 participants who had missing lifestyle data at 6 months after diagnosis. The final sample size for the postdiagnosis analyses was 1425, representing 86% of all eligible participants. For the change-after-diagnosis analyses, all participants ($n = 247$) from the EnCoRe study were excluded, as dietary assessment methods differed between diagnosis (FFQ) and follow-up (dietary records) (11). From the COLON study, 16 participants with missing lifestyle data at diagnosis were excluded for these analyses. The final sample size for the change-after-diagnosis analyses was 1162.

Lifestyle assessment

We used data collected at either 6 months after diagnosis (COLON) or 6 months after the end of treatment (EnCoRe) to calculate postdiagnosis lifestyle scores. Data collected at diagnosis, before the start of treatment, were used to calculate pretreatment lifestyle scores (COLON only). Patients completed either an FFQ that queried intake of 204 items at both time points (COLON) or a 7-day dietary record 6 months after treatment (EnCoRe), as previously described (10–12). The reference period

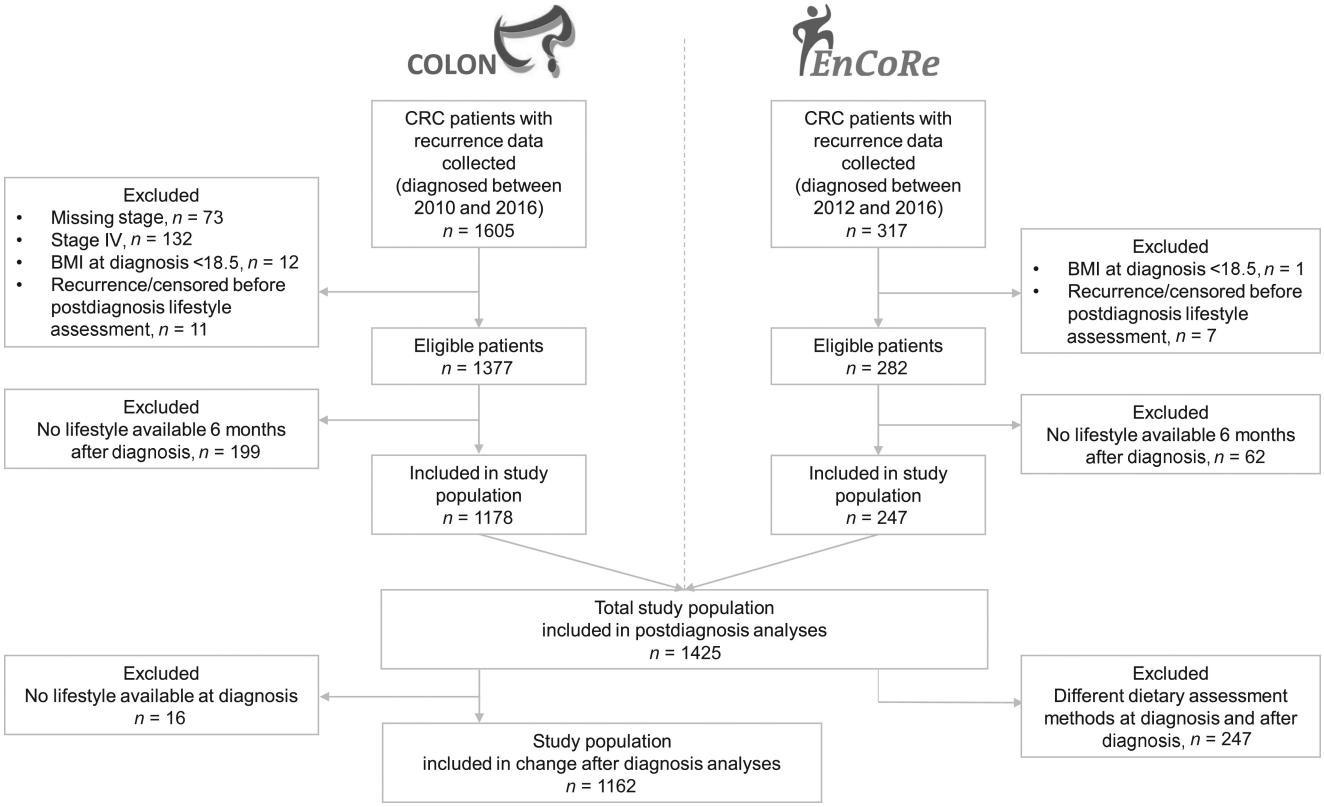

FIGURE 1 Flowchart representing patient selection for the current study. Abbreviations: COLON, colorectal cancer: longitudinal, observational study on nutritional and lifestyle factors that may influence colorectal tumor recurrence, survival, and quality of life; CRC, colorectal cancer; EnCoRe, energy for life after colorectal cancer.

for the FFQ was the month before diagnosis or the previous month during follow-up. Intakes of dietary fiber and alcohol (alcoholic drinks only) were calculated based on the 2011 Dutch Food Composition Database (13). Moderate– to vigorous–intensity physical activity was self-reported by the validated SQUASH questionnaire (Short QUestionnaire to ASsess Health-enhancing physical activity) (14–16) for both cohorts. Moderate-to-vigorous physical activity included all activities (walking, cycling, gardening, odd jobs, sports, household activities, and work) with a metabolic equivalent value ≥ 3 (17). At diagnosis, the reference period was a normal week in the 2 months before diagnosis. BMI was calculated from body weight (assessed at diagnosis and during follow-up) and height (only assessed at diagnosis). Weight, height, and waist circumference were either self-reported (COLON) or measured by trained research dietitians during a home visit (EnCoRe). To ensure quality of the data, completed questionnaires and dietary records were thoroughly checked and participants were contacted for clarification if needed.

Lifestyle scores

Two sets of evidence-based cancer prevention recommendations (WCRF/AICR and ACS) and 1 set of disease prevention guidelines (national guidelines from the Netherlands) were used to calculate overall lifestyle scores. All 3 included body weight, physical activity, diet, and alcohol intake, but differed on the dietary components included and scoring criteria (**Table 1**). The national score includes the most dietary components ($n = 12$), as it also takes into account foods that impact cardiovascular disease risk, while the ACS score includes the lowest number of dietary components ($n = 3$).

The WCRF/AICR score, developed by Shams-White et al. (18), is based on quantitative cutoff points for BMI and waist circumference, physical activity, and fiber and fruit/vegetable, red and processed meat, sugary drink, and alcohol intakes. The cutoff points for fast foods were based on cohort-specific tertile rankings of ultra-processed foods. Both the ACS score, developed by McCullough et al. (19), and the national score are based on quantitative cutoffs for BMI, physical activity, and alcohol intake. The dietary component of the ACS score is based on the sex- and cohort-specific intakes of fruits and vegetables, proportions of whole grains out of total grains consumed, and intakes of red and processed meat. The dietary component of the national score, adapted from Looman et al. (20), is based on sex- and cohort-specific tertile rankings of intakes of vegetables, fruits, whole grains, legumes, nuts, dairy, fish, tea, fats and oils, red meat, processed meat, and sugary drinks. Scoring criteria for the 3 lifestyle scores are listed in Table 1. Higher scores indicated that one's lifestyle was more consistent with the recommendations. The WCRF/AICR score ranged from 0 to 7 to represent 7 recommendations (1 for weight, 1 for physical activity, 4 for diet, and 1 for alcohol intake). Each recommendation was assigned 1 point when the recommendation was met, 0.5 point when it was partially met, and 0 points otherwise. Two recommendations included sub-recommendations, and the possible scores for these

TABLE 1 Description of the World Cancer Research Fund/American Institute of Cancer Research and American Cancer Society scores based on cancer prevention recommendations and the national score based on disease prevention recommendations from the Netherlands

2018 WCRF/AICR score	Points	ACS score	Points	National score	Points
1) Body weight					
BMI (kg/m^2)		BMI (kg/m^2)		BMI (kg/m^2)	
18.5–24.9	0.5	18.5–24.9	2	18.5–24.9	1
25 to <30	0.25	25 to <30	1	25 to <30	0.5
<18.5 or ≥30	0	≥30	0	<18.5 or ≥30	0
Waist circumference (cm)					
<94 M and <80 F	0.5				
94 to <102 M and 80 to <88 F	0.25				
≥102 M and ≥88 F	0				
2) PA					
Moderate-to-vigorous PA (min/wk)		Moderate-to-vigorous PA (min/wk)		Moderate-to-vigorous PA (min/wk)	
≥150	1	≥300	2	≥150	1
75–150	0.5	150–300	1	75–150	0.5
<75	0	<150	0	<75	0
3) Diet					
Dietary fiber (g/d):		Diet sub-score		Diet sub-score	
≥30	0.5	Diet sub-score 7–9 points	2	Sex-specific tertile 3	1
15 to <30	0.25	Diet sub-score 3–6 points	1	Sex-specific tertile 2	0.5
<15	0	Diet sub-score 0–2 points	0	Sex-specific tertile 1	0
Fruits and vegetables (g/d):					
≥400	0.5	Fruits and vegetables (g/d)		Dutch Healthy Diet index 2015[1]	
200 to <400	0.25	1: ≥400, 0: <400		Vegetables (g/d) 10: ≥200, 0: 0	
<200	0	1 or 2 points for being in the 2nd or 3rd sex- specific tertile of number of unique fruits and vegetables eaten per month		Fruit (g/d) 10: ≥200, 0: 0	
Percent of total kcal from ultra-processed foods[2]:		Ratio of wholegrains to refined grains		Wholegrains (g/d) 5: ≥90, 0: 0	
Tertile 1	1	0–3 points corresponding to sex-specific quartiles of proportion of grains that are whole		Ratio of wholegrains to refined grains 5: ≥11, 0: ≤0–7	
Tertile 2	0.5	Red and processed meat (g/wk)		Legumes (g/d) 10: ≥10, 0: 0	
Tertile 3	0	0–3 points corresponding to sex-specific quartiles of red and processed meat intake, reverse scored		Nuts (g/d) 10: ≥15, 0: 0	
Red meat and processed meat (g/wk):				Dairy (g/d) 10: 300–450, 0: 0 or ≥750	
Red meat ≤500 and processed meat intake <21	1			Fish (g/d) 10: ≥15, 0: 0	
Red meat ≤500 and processed meat intake 21 to <100	0.5			Tea (g/d) 10: ≥450, 0: 0	
Red meat >500 or processed meat intake ≥100	0			Ratio of liquid fats to solid fats 10: ≥13, 0: ≤0–6	
Sugary drinks[3] (g/d):				Red meat (g/d) 10: ≤45, 0: ≥100	
0	1			Processed meat (g/d) 10: 0, 0: ≥50	
>0 to ≤250	0.5			Sugary drinks[3] (g/d) 10: 0, 0: ≥250	
>250	0				
4) Alcohol					
Ethanol (g/d)		Ethanol (g/d)		Ethanol (g/d)[4]	
0	1	>0 to ≤20 M and ≤10 F	2	≤10 (1 drink)	1
>0 to ≤20 M and ≤10 F	0.5	0	1	>10 to <30 M and >10 to <20 F	0.5
>20 M and >10 F	0	>20 M and >10 F	0	≥30 M and ≥20 F	0
WCRF/AICR score range	0–7	ACS score range	0–8	National score range	0–4

Quartiles and tertiles were calculated in both cohorts separately. Abbreviations: ACS, American Cancer Society; PA, physical activity; WCRF/AICR, World Cancer Research Fund/American Institute of Cancer Research.

[1]Dutch Healthy Diet index 2015 (20) without salt and type of coffee components (data not available). The alcohol component is excluded from the dietary score, as this is a separate component in the national score. Cut-off values represent the minimum and maximum required amounts of consumption awarded with 0 and 10 points. Intakes between the cutoff values are scored proportionally. The total possible score range is 0–120.

[2]Ultra-processed foods included French fries, crisps, pastry and biscuits, savory snacks, sugar and candy, sauces, pizza, pancake, sandwich fillings high in sugar or fat, refined-grain products, sweet dairy desserts, and diet soft drinks. Not included were yogurt and cheese, nuts, oils and fats, sugary drinks, and processed meat. Calculated as energy intake from ultra-processed foods of total energy intake.

[3]Sugary drinks included sugar-sweetened soft drinks, sugar-sweetened dairy drinks, and fruit juices.

[4]Scoring taking from the alcohol component of the Dutch Healthy Diet index 2015 (20).

2 recommendations included 0, 0.25, 0.5, 0.75, and 1. The ACS score ranged from 0 to 8. Each of the 4 recommendations was assigned 2 points when the recommendation was met, 1 point when it was partially met, and 0 points otherwise. The national score ranged from 0 to 4. Each of the 4 recommendations was assigned 1 point when the recommendation was met, 0.5 point when it was partially met, and 0 points otherwise.

Outcome assessment

Both CRC recurrence and all-cause mortality were considered primary outcomes. We defined CRC recurrence as the time from the postdiagnosis lifestyle assessment to locoregional recurrence or distant metastasis. Patients who died without CRC recurrence or who experienced another type of cancer with metastasis were censored in analyses with CRC recurrence as the outcome. Information on recurrences was collected from medical records by trained registrars from the Dutch Cancer Registry through February/March 2018 for both cohorts. We defined all-cause mortality as the time from the postdiagnosis lifestyle assessment to death. Vital status and date of death were determined through linkage to the Municipal Personal Record Database of the Netherlands through May (EnCoRe) or December (COLON) 2019.

Covariate assessment

Information was obtained on demographics, health-related factors, and clinical factors. Demographic information was self-reported at diagnosis. We used cigarette smoking status and daily use of nonsteroidal anti-inflammatory drugs, which were self-reported at the postdiagnosis lifestyle assessment, in our analyses. Clinical data, such as CRC stage, tumor site, administration of neo-adjuvant treatment and adjuvant chemotherapy, and presence of comorbidities, were retrieved from the Dutch ColoRectal Audit. The Dutch ColoRectal Audit is a nationwide audit initiated by the Association of Surgeons from the Netherlands to monitor, evaluate, and improve CRC care (21).

Statistical analyses

Demographic and lifestyle characteristics of the CRC patients are shown for the total study population and by lifestyle score group. Cox proportional hazards regression models were used to calculate HRs and 95% CIs. For continuous models, a 1-SD increase in each lifestyle score was calculated to allow comparability between the scores. Furthermore, the WCRF/AICR and ACS scores were categorized into 4 groups according to predefined cutoffs based on sufficient participants in each group. The national score was categorized into 3 groups, as we combined patients with scores of 0–2 due to the limited number of participants with low scores. Groups with the lowest scores, indicating a lifestyle least consistent with the recommendations, were the referent for all analyses. To test for linear trends, the median score of each category was assigned to all participants within that category and entered as a continuous exposure in Cox models. Multivariable models included age at diagnosis, CRC stage, sex, adjuvant chemotherapy, education level, smoking status, and cohort. Total energy intake, tumor site, neo-adjuvant therapy, nonsteroidal anti-inflammatory drug use, and comorbidities at diagnosis were also evaluated as potential confounders, but these made minimal differences (<5%) to the results and were therefore not included in the final models. We used the Assess statement in SAS (SAS Institute) to check proportional hazards assumptions. As the proportional hazard assumption did not hold for CRC stage, we ran the models for all-cause mortality with stage as the stratifying variable (in the strata statement). This allows each stratum to have its own baseline hazard function, while the HRs are assumed to be the same across all strata. Furthermore, we ran all postdiagnosis models with cohort as the stratifying variable to account for differences in lifestyle assessments between cohorts. To examine effect modifications, subgroup analyses were performed by age at diagnosis (<70 years, ≥70 years), sex (male, female), cancer site (colon, rectum), and stage (I, II, III).

Additionally, we also performed analyses for each lifestyle score component (body weight, physical activity, diet, alcohol intake) separately, to get a better understanding of which individual behaviors contribute to the association between the lifestyle score and CRC outcomes. For these analyses, we used the sub-scores of body weight, physical activity, diet, and alcohol, while mutually adjusting for the other components.

For the change-after-diagnosis analyses, we calculated the difference between the postdiagnosis and pretreatment lifestyle scores. For continuous models, a 1-SD increase in each lifestyle change score was calculated. The group with a change in lifestyle score of 0 served as the referent in the categorical models. Change models were adjusted for the same covariates as the postdiagnosis models, with the addition of pretreatment lifestyle scores. To satisfy the proportional hazards assumption, we ran the change models using adjuvant chemotherapy as the stratifying variable in all models; for the all-cause mortality models, we additionally used stage as a stratifying variable.

We evaluated the robustness of our findings with sensitivity analyses. Participants usually completed adjuvant chemotherapy treatment about 6–7 months after diagnosis. Within the COLON study, acute treatment effects might have influenced lifestyle at 6 months postdiagnosis. In sensitivity analyses of both the postdiagnosis and change analyses, we therefore excluded all participants from the COLON study treated with adjuvant chemotherapy (as the date of the end of chemotherapy was not available). Furthermore, we performed the postdiagnosis analyses after excluding all participants from the EnCoRe study, as these were also excluded from the change analyses, and after excluding current smokers. We did not perform stratified analyses among participants of the EnCoRe study, because of the small sample size ($n = 247$) and low number of events (recurrence $n = 17$; death $n = 19$). Additionally, we also assessed the associations between lifestyle scores measured at diagnosis and both recurrence and all-cause mortality. All statistical analyses were conducted using SAS 9.4 software (SAS Institute). A P value < 0.05 was considered statistically significant.

Results

In total, 1425 nonmetastatic CRC patients were included in the postdiagnosis analyses (Figure 1): 1178 (83%) from the COLON study and 247 (17%) from the EnCoRe study. Baseline characteristics of the study population are listed in **Table 2**. The mean age at CRC diagnosis was 66 years, and 66% of the tumors were located in the colon. Stage III disease (44%) was more common than stage II (29%) or stage I disease (27%). Overall, lifestyle at 6 months postdiagnosis was suboptimal. Although physical activity levels were generally high and only 7% of participants smoked, adherence to dietary guidelines was low and 64% of participants were overweight or obese. As expected, participants whose lifestyles were most consistent with the WCRF/AICR, ACS, or national recommendations had

TABLE 2 Demographic, clinical, and lifestyle characteristics of colorectal cancer survivors at 6 months postdiagnosis by lifestyle score group

Characteristic	Total population $n = 1425$	WCRF/AICR score 0–2.5 $n = 268$	WCRF/AICR score 2.75–3.25 $n = 448$	WCRF/AICR score 3.5–4.25 $n = 511$	WCRF/AICR score 4.5–7 $n = 198$	ACS score 0–3 ($n = 253$)	ACS score 4 ($n = 295$)	ACS score 5 ($n = 344$)	ACS score 6–8 ($n = 524$)	National score 0–2 ($n = 369$)	National score 2.5–3 ($n = 691$)	National score 3.5–4 ($n = 358$)
Age at diagnosis, y	66 (61–71)	65 (59–70)	66 (60–71)	66 (62–72)	65 (60–70)	67 (60–72)	66 (61–71)	65 (61–72)	65 (61–71)	66 (61–71)	66 (61–72)	65 (60–70)
Men, %	914 (64%)	173 (65%)	315 (70%)	317 (62%)	109 (55%)	143 (57%)	197 (67%)	227 (66%)	342 (65%)	249 (67%)	459 (66%)	157 (44%)
Education, %[1]												
Low	544 (38%)	117 (44%)	162 (36%)	190 (37%)	75 (38%)	113 (45%)	115 (39%)	127 (37%)	187 (36%)	146 (40%)	275 (40%)	121 (34%)
Medium	409 (29%)	82 (31%)	145 (33%)	136 (27%)	46 (23%)	77 (31%)	83 (28%)	106 (31%)	142 (27%)	129 (35%)	190 (28%)	89 (25%)
High	462 (33%)	64 (24%)	139 (31%)	182 (36%)	77 (39%)	62 (25%)	95 (32%)	108 (32%)	194 (37%)	91 (25%)	224 (33%)	146 (41%)
Tumor stage, %												
I	390 (27%)	73 (27%)	120 (27%)	139 (27%)	58 (29%)	68 (27%)	73 (25%)	95 (28%)	153 (29%)	102 (28%)	186 (27%)	101 (28%)
II	407 (29%)	82 (31%)	118 (26%)	151 (30%)	56 (28%)	77 (30%)	87 (29%)	99 (29%)	140 (27%)	112 (30%)	193 (28%)	98 (27%)
III	628 (44%)	113 (42%)	210 (47%)	221 (43%)	84 (42%)	108 (43%)	135 (46%)	150 (44%)	231 (44%)	155 (42%)	312 (45%)	159 (44%)
Tumor site, %												
Colon	947 (66%)	171 (64%)	286 (64%)	341 (67%)	149 (75%)	169 (67%)	197 (67%)	221 (64%)	354 (68%)	246 (67%)	438 (63%)	258 (72%)
Rectum	478 (34%)	97 (36%)	162 (36%)	170 (33%)	49 (25%)	84 (33%)	98 (33%)	123 (36%)	170 (32%)	123 (33%)	253 (37%)	100 (28%)
Neo-adjuvant treatment, %	336 (24%)	69 (26%)	113 (25%)	117 (23%)	37 (19%)	58 (23%)	74 (25%)	86 (25%)	116 (22%)	84 (23%)	184 (27%)	67 (19%)
Adjuvant chemotherapy,[2] %	359 (25%)	58 (22%)	114 (25%)	131 (26%)	55 (28%)	54 (21%)	78 (26%)	86 (25%)	138 (26%)	76 (21%)	173 (25%)	108 (30%)
Comorbidity at diagnosis,[3] %	975 (68%)	199 (74%)	319 (71%)	337 (66%)	120 (61%)	205 (81%)	209 (71%)	230 (67%)	328 (63%)	285 (77%)	472 (68%)	215 (60%)
Current smoker,[4] %	99 (7%)	29 (11%)	23 (5%)	40 (8%)	7 (4%)	21 (8%)	29 (10%)	22 (6%)	26 (5%)	38 (10%)	47 (7%)	14 (4%)
Daily NSAID use, %	111 (8%)	20 (7%)	39 (9%)	33 (6%)	19 (10%)	23 (9%)	22 (7%)	29 (8%)	36 (7%)	31 (8%)	57 (8%)	23 (6%)
WCRF/AICR score, mean ± SD	3.4 ± 0.9	2.2 ± 0.4	3.0 ± 0.2	3.8 ± 0.3	4.9 ± 0.5	2.6 ± 0.7	3.1 ± 0.7	3.5 ± 0.8	3.9 ± 0.8	2.7 ± 0.7	3.4 ± 0.7	4.2 ± 0.8
ACS score,[5] mean ± SD	4.9 ± 1.5	3.6 ± 1.4	4.7 ± 1.3	5.3 ± 1.2	6.1 ± 1.2	2.6 ± 0.7	4.0 ± 0	5.0 ± 0	6.4 ± 0.6	3.4 ± 1.2	5.0 ± 1.1	6.3 ± 0.9
National score,[6] mean ± SD	2.7 ± 0.8	1.9 ± 0.6	2.6 ± 0.6	3.0 ± 0.6	3.5 ± 0.5	1.8 ± 0.6	2.4 ± 0.5	2.8 ± 0.5	3.3 ± 0.5	1.7 ± 0.4	2.8 ± 0.2	3.7 ± 0.2
BMI, kg/m^2	26.2 (24.1–29.0)	28.9 (26.3–32.0)	27.1 (24.9–29.4)	25.2 (23.7–27.7)	24.0 (22.4–26.4)	30.0 (26.8–32.4)	27.3 (25.4–29.3)	25.8 (23.8–29.0)	24.8 (23.1–26.8)	29.3 (26.3–32.2)	26.2 (24.3–28.7)	24.2 (22.7–26.0)
Waist circumference, cm	97 (89–105)	104 (96–110)	100 (93–107)	94 (87–100)	90 (84–97)	105 (97–112)	99 (92–107)	97 (89–105)	93 (86–100)	105 (96–111)	97 (90–104)	91 (84–97)
Physical activity,[7] min/wk	480 (240–840)	265 (60–630)	493 (258–870)	540 (300–900)	585 (345–870)	150 (60–390)	420 (185–780)	480 (270–823)	690 (430–1073)	290 (60–630)	540 (280–885)	585 (360–960)
Dietary components, g/d												
Fruits and vegetables	244 (147–347)	161 (102–231)	222 (135–318)	274 (170–371)	362 (265–453)	199 (115–288)	226 (134–333)	234 (135–346)	288 (181–387)	168 (110–261)	239 (145–339)	331 (250–424)
Number of unique fruits and vegetables consumed per month	11 (8–13)	10 (7–13)	11 (9–13)	11 (9–13)	12 (9–14)	10 (7–12)	11 (8–13)	11 (8–13)	12 (10–14)	10 (7–12)	11 (9–13)	12 (10–14)
Dietary fiber	19 (16–24)	16 (13–20)	19 (15–22)	21 (16–25)	23 (19–27)	17 (14–21)	18 (15–23)	19 (16–23)	22 (17–26)	17 (13–20)	19 (15–24)	22 (19–27)
Total grains that are whole, m%	72 (56–86)	61 (42–75)	69 (53–81)	77 (63–89)	82 (69–92)	66 (47–78)	67 (51–83)	70 (56–87)	78 (64–89)	66 (49–81)	72 (56–86)	78 (63–91)
Processed foods, energy%	28 (22–35)	34 (29–40)	31 (25–37)	26 (20–32)	21 (17–27)	29 (22–36)	29 (21–35)	28 (21–36)	28 (22–35)	29 (21–36)	29 (22–36)	27 (21–35)
Red and processed meat	69 (43–98)	78 (57–109)	74 (52–103)	67 (40–95)	36 (10–62)	85 (63–121)	73 (53–100)	68 (43–101)	57 (34–87)	81 (55–122)	71 (45–99)	52 (27–80)
Legumes	0 (0–11)	0 (0–11)	0 (0–11)	2 (0–15)	7 (0–18)	0 (0–11)	0 (0–11)	2 (0–16)	4 (0–16)	0 (0–5)	0 (0–11)	8 (0–18)
Nuts	1 (0–4)	0 (0–2)	1 (0–4)	1 (0–4)	3 (0–7)	0 (0–2)	0 (0–3)	1 (0–3)	2 (0–6)	0 (0–1)	1 (0–4)	3 (0–7)
Dairy	262 (155–376)	247 (149–366)	254 (159–386)	272 (145–382)	287 (170–372)	215 (126–356)	244 (146–380)	255 (157–377)	287 (176–395)	212 (126–351)	262 (154–386)	296 (202–385)
Fish	9 (4–14)	6 (3–11)	9 (4–14)	9 (4–14)	11 (6–17)	6 (2–12)	8 (4–13)	9 (4–14)	10 (4–15)	6 (2–11)	9 (4–13)	11 (7–17)
Tea	116 (0–233)	77 (0–230)	115 (0–232)	116 (0–250)	156 (18–311)	54 (0–230)	80 (0–232)	116 (0–234)	156 (18–279)	36 (0–156)	116 (0–233)	190 (77–345)
Sugary drinks	69 (14–170)	128 (41–288)	85 (25–176)	54 (9–142)	16 (0–96)	54 (11–160)	75 (12–158)	75 (19–176)	64 (13–171)	90 (21–193)	79 (21–189)	51 (5–138)
Alcohol intake												
Nondrinker, %	371 (26%)	45 (17%)	90 (20%)	151 (30%)	85 (43%)	96 (38%)	88 (30%)	97 (28%)	88 (17%)	81 (22%)	189 (27%)	101 (28%)
Amount, g/d, among drinkers	10 (4–22)	12 (4–25)	12 (4–23)	10 (3–21)	8 (3–14)	24 (14–35)	21 (5–29)	12 (4–25)	6 (2–12)	20 (8–22)	12 (4–22)	4 (2–9)
Amount, g/d, among all	5 (0–17)	7 (1–22)	7 (1–20)	4 (0–15)	1 (0–9)	12 (0–27)	4 (1–10)	4 (0–19)	4 (1–10)	14 (1–31)	6 (0–17)	2 (0–7)
Total energy intake, kcal/d	1813 (1503–2153)	1843 (1525–2135)	1852 (1539–2177)	1776 (1476–2139)	1716 (1430–2129)	1761 (1470–2069)	1844 (1529–2134)	1770 (1508–2093)	1847 (1514–2220)	1789 (1470–2088)	1836 (1519–2162)	1813 (1520–2175)

Values are medians (IQRs), except where indicated otherwise. Abbreviations: ACS, American Cancer Society; NSAID, non-steroidal anti-inflammatory drugs; WCRF/AICR, World Cancer Research Fund/American Institute of Cancer Research.

[1] Data of 10 participants were missing/unknown.

[2] Data of 23 participants were missing/unknown.

[3] Data of 5 participants were missing/unknown.

[4] Data of 2 participants were missing/unknown.

[5] Data of 9 participants were missing/unknown.

[6] Data of 7 participants were missing/unknown.

[7] Moderate-to-vigorous physical activity included all activities with a metabolic equivalent value ≥ 3.

TABLE 3 HRs for the association of postdiagnosis concordance with lifestyle guidelines with risks of colorectal cancer recurrence and all-cause mortality

		CRC recurrence		Death from any cause	
Lifestyle score	*n*	Number of events/person-years	HR (95% CI)	Number of events/person-years	HR (95% CI)
WCRF/AICR score					
0–2.5	259	32/686	1.00 (ref)	39/1129	1.00 (ref)
2.75–3.25	444	46/1249	0.74 (0.47–1.16)	45/2042	0.61 (0.40–0.94)
3.5–4.25	498	59/1420	0.89 (0.58–1.38)	60/2304	0.70 (0.47–1.06)
4.5–7	190	21/545	0.85 (0.48–1.48)	21/885	0.75 (0.44–1.29)
P_{trend}	—	—	0.85	—	0.38
Continuous[1]	—	—	0.99 (0.84–1.17)	—	0.92 (0.78–1.08)
ACS score					
0–3	248	27/681	1.00 (ref)	35/1095	1.00 (ref)
4	287	39/793	1.23 (0.75–2.02)	41/1281	1.03 (0.65–1.62)
5	339	39/951	1.01 (0.62–1.65)	36/1543	0.74 (0.46–1.19)
6–8	511	53/1457	0.92 (0.57–1.47)	52/2413	0.69 (0.44–1.06)
P_{trend}	—	—	0.41	—	0.03
Continuous[1]	—	—	0.94 (0.81–1.11)	—	0.85 (0.73–0.995)
National score					
0–2	360	43/975	1.00 (ref)	50/1583	1.00 (ref)
2.5–3	681	71/1946	0.82 (0.56–1.21)	77/3135	0.78 (0.54–1.11)
3.5–4	346	44/969	1.03 (0.67–1.59)	37/1625	0.80 (0.52–1.23)
P_{trend}	—	—	0.89	—	0.18
Continuous[1]	—	—	1.00 (0.86–1.18)	—	0.90 (0.77–1.05)

Lifestyle guidelines include body weight, physical activity, diet, and alcohol intake. A Cox proportional hazards model was adjusted for age at diagnosis, stage of disease, sex, adjuvant chemotherapy, education, smoking, and cohort. P_{trend} values were calculated by entering the median lifestyle scores within each category as continuous variables in the models. The study population varied slightly for each score because of missing data (WCRF/AICR, $n = 1391$; ACS, $n = 1385$; national, $n = 1387$). Abbreviations: ACS, American Cancer Society; CRC, colorectal cancer; WCRF/AICR, World Cancer Research Fund/American Institute of Cancer Research.

[1]Continuous HRs were calculated for a 1-SD increment in the score. Higher scores represent higher concordance with the respective guidelines.

healthier behaviors for many aspects of their lifestyles than those participants whose lifestyles were least consistent with the guidelines. Characteristics for each cohort separately are listed in **Supplemental Table 1.** We observed 164 recurrences during a 2.6-year (IQR, 1.7–3.6) median follow-up. A total of 171 patients died during a 4.4-year (IQR 3.5–5.5) median follow-up; 55% of people with CRC recurrence died during follow-up ($n = 91$).

Postdiagnosis lifestyle

Postdiagnosis lifestyle scores were not associated with CRC recurrence (**Table 3**). However, our results suggest that these associations with recurrence might differ by stage of disease (**Figure 2**A). Among patients with stage I or stage III disease, we consistently observed a HR < 1 with each SD higher lifestyle score, although 5 out of 6 associations were statistically nonsignificant. In contrast, among patients with stage II disease, we unexpectedly observed an increased recurrence risk with each SD higher lifestyle score, which was statistically significant for the WCRF/AICR and national scores. There was no evidence of an effect modification by age, sex, or cancer site in the total study population regarding recurrence (Figure 2B–D).

A lifestyle more consistent with the ACS recommendations was associated with a lower all-cause mortality risk (HR per 1 SD increase, 0.85; 95% CI: 0.73–0.995). Despite statistical insignificance, likely due to a small number of deaths, the same tendency was observed for higher concordance with the WCRF/AICR (HR, 0.92; 95% CI: 0.78–1.08) and national (HR, 0.90; 95% CI: 0.77–1.05) recommendations. There was no evidence for an effect modification by stage, age, sex, or cancer site regarding all-cause mortality (**Supplemental Figure 1**A–D).

Change in lifestyle after diagnosis

A change in lifestyle scores after diagnosis was not associated with CRC recurrence (**Table 4**). A lower risk of all-cause mortality was observed for each SD increase in the ACS (HR, 0.80; 95% CI: 0.67–0.96) and national (HR, 0.84; 95% CI: 0.70–0.999) scores, while this association was statistically nonsignificant for the WCRF/AICR score (HR, 0.94; 95% CI: 0.78–1.13).

Postdiagnosis lifestyle score components

Body weight, physical activity, dietary, and alcohol sub-scores were generally not associated with CRC recurrence and all-cause mortality when the highest concordance was compared with the lowest concordance within the specific lifestyle component (**Supplemental Table 2**). One exception was noted: the dietary component of the national score was associated with a 22% lower mortality risk for each SD higher score (HR, 0.78; 95% CI: 0.64–0.94).

Lifestyle at diagnosis

Lifestyle scores measured at diagnosis were not associated with risks of CRC recurrence and all-cause mortality (**Supplemental Table 3**).

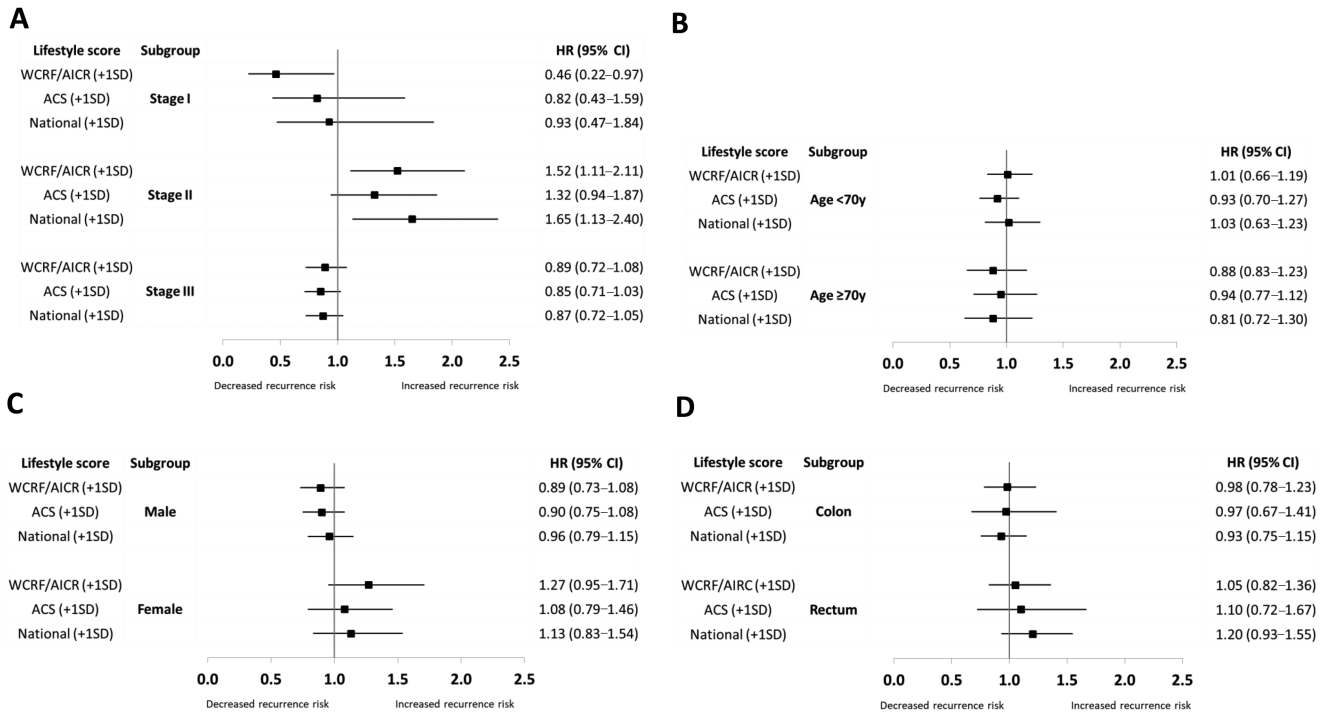

FIGURE 2 Subgroup analyses of the association between postdiagnosis lifestyle and colorectal cancer recurrence by (A) CRC stage, (B) age, (C) sex, and (D) tumor location. The squares indicate HRs, and the widths of the horizontal lines indicate 95% CIs. Continuous (+1 SD) Cox proportional hazards models were adjusted for age at diagnosis, stage of disease, sex, adjuvant chemotherapy, education, smoking and cohort. Number of recurrences/total: stage I, 9/388; stage II, 40/390; stage III, 109/613; <70 years, 110/960; >70 years, 48/431; male, 112/889; female, 46/502; colon, 87/924; and rectum, 71/467. Abbreviations: ACS, American Cancer Society; CRC, colorectal cancer; WCRF/AICR, World Cancer Research Fund/American Institute of Cancer Research.

Sensitivity analyses

Similar to our main analyses in the total study population, postdiagnosis lifestyle scores were not associated with CRC recurrence when we excluded participants possibly treated with chemotherapy during the postdiagnosis lifestyle assessment ($n = 283$ from COLON study; **Supplemental Table 4**), excluded all participants from the EnCoRe study ($n = 247$; **Supplemental Table 5**), or excluded current smokers ($n = 99$; **Supplemental Table 6**). However, for all-cause mortality, associations on a continuous scale were no longer statistically significant and HRs were attenuated in these 3 sensitivity analyses. For the change analyses, HRs of all continuous models did not meaningfully change when we excluded people who received adjuvant chemotherapy ($n = 283$; results not shown). However, the association between a change in the national score and all-cause mortality was no longer statistically significant (HR per SD increase, 0.89; 95% CI: 0.72–1.10).

Discussion

In this prospective study among 1425 people diagnosed with stage I–III CRC, overall lifestyle (including body weight, physical activity, diet, and alcohol intake) after diagnosis was not associated with CRC recurrence, while it was inversely associated with all-cause mortality. A lifestyle more consistent with the ACS recommendations was associated with a lower all-cause mortality risk. The same tendency was observed for higher WCRF/AICR and national lifestyle scores, although these results were statistically nonsignificant. Regarding changes in lifestyle after diagnosis, our results suggest that improving concordance with the ACS or national recommendations after a CRC diagnosis was not associated with recurrence, while it was associated with a lower all-cause mortality risk.

Only 1 previous study examined the association between an overall healthy lifestyle after a CRC diagnosis and recurrence, and only a few examined single lifestyle behaviors in relation to recurrence. The lifestyle most consistent with the ACS guidelines after a CRC diagnosis was associated with a 36% lower recurrence risk ($HR_{high\ vs.\ low}$, 0.64; 95% CI: 0.44–0.94) among 992 stage III colon cancer survivors (9). In contrast, we report null associations between overall lifestyle after a CRC diagnosis and recurrence. Our study suggests that associations with CRC recurrence might differ by stage of disease, which we cannot explain. This effect modification should be interpreted with caution, as the follow-up time was limited (3 years) and the results were based on relatively few recurrences ($n = 164$). Previous studies, all in the same cohort of stage III colon cancer patients, have observed increased risks of recurrence in association with low levels of physical activity (22), a Western dietary pattern (23), and high intake of sugary, sweetened drinks (24). Our dietary sub-scores were not associated with recurrence. Additional large, population-based studies should include CRC recurrence as a key outcome when examining lifestyle after diagnosis, as fear of recurrence is a common concern for CRC patients (25) and there are several proposed mechanisms relating an unhealthy lifestyle after diagnosis to CRC recurrence (26).

TABLE 4 HRs for the association of change in lifestyle scores after colorectal cancer diagnosis with risks of recurrence and all-cause mortality

Change in lifestyle score	*n*	CRC recurrence		Death from any cause	
		Number of events/Person-years	HR (95% CI)	Number of events/Person-years	HR (95% CI)
WCRF/AICR score					
<−0.5	204	26/603	0.94 (0.52–1.68)	28/998	1.81 (0.92–3.56)
−0.5 to −0.25	266	35/812	1.01 (0.56–1.82)	42/1307	2.24 (1.20–4.20)
0	178	22/506	1.00 (ref)	13/863	1.00 (ref)
0.25–0.5	282	31/823	0.88 (0.51–1.52)	34/1358	1.63 (0.86–3.10)
>0.5	206	24/595	1.01 (0.56–1.82)	26/973	1.90 (0.96–3.74)
P_{trend}	—	—	0.99	—	0.85
Continuous[1]	—	—	0.95 (0.79–1.14)	—	0.94 (0.78–1.13)
ACS score					
<−1	142	29/423	1.57 (0.98–2.52)	25/691	1.56 (0.95–2.58)
−1	212	20/658	0.75 (0.44–1.27)	35/1032	1.51 (0.97–2.36)
0	422	49/1223	1.00 (ref)	45/2020	1.00 (ref)
1	214	26/620	1.11 (0.69–1.81)	26/1033	1.12 (0.69–1.84)
>1	141	11/399	0.97 (0.51–1.83)	14/680	0.75 (0.37–1.50)
P_{trend}	—	—	0.42	—	0.03
Continuous[1]	—	—	0.89 (0.74–1.08)	—	0.80 (0.67–0.96)
National score					
<−0.5	108	16/321	1.20 (0.68–2.10)	19/521	1.30 (0.77–2.20)
−0.5	206	29/611	1.17 (0.74–1.85)	29/988	1.10 (0.70–1.73)
0	433	52/1298	1.00 (ref)	58/2106	1.00 (ref)
0.5	261	31/734	1.12 (0.71–1.77)	23/1241	0.74 (0.45–1.22)
>0.5	125	10/367	0.73 (0.36–1.48)	13/610	0.84 (0.45–1.57)
P_{trend}	—	—	0.32	—	0.09
Continuous[1]	—	—	0.90 (0.75–1.08)	—	0.84 (0.70–0.999)

A Cox proportional hazards model was adjusted for age at diagnosis, stage of disease, sex, adjuvant chemotherapy, education, smoking, and pretreatment lifestyle score. P_{trend} values were calculated by entering the median lifestyle scores within each category as continuous variables in the models. The study population varied slightly for each score because of missing data (WCRF/AICR, $n = 1136$; ACS, $n = 1133$; national, $n = 1133$). Abbreviations: ACS, American Cancer Society; CRC, colorectal cancer; WCRF/AICR, World Cancer Research Fund/American Institute of Cancer Research.

[1]Continuous HRs were calculated for a 1-SD increase in the score.

Data supporting an association between an overall healthy lifestyle after a CRC diagnosis with all-cause mortality, as we provide here, is scarce. Among 380 women with CRC, no association was previously observed between a lifestyle more consistent with the WCRF/AICR cancer prevention recommendations and all-cause mortality ($HR_{high\ vs.\ low}$, 1.19; 95% CI: 0.59–2.43) (8). One possible explanation for the lack of association in that study is that lifestyle was assessed among long-term survivors. In contrast, a lifestyle more consistent with the ACS guidelines was associated with a 51% lower all-cause mortality risk (HR, 0.49; 95% CI: 0.32 to −0.76) among 992 stage III colon cancer survivors (9). In that study, lifestyle was an average of the lifestyle data assessed during chemotherapy and 6 months after chemotherapy, which is in line with the timing of lifestyle assessments in our study.

We expected and observed inverse associations between all 3 lifestyle scores and all-cause mortality, as they all reflect a healthy overall lifestyle by emphasizing an optimal body weight, being physically active, eating a healthy diet, and limiting alcohol intake. Subtle differences in scoring and the number of dietary components included in the score might explain the observed differences in statistical significance. Our results are in line with a meta-analysis in the general population showing that an overall healthy lifestyle was consistently associated with lower all-cause mortality, despite heterogeneous definitions of an overall healthy lifestyle (27). The single lifestyle behaviors included in the lifestyle scores (weight, physical activity, diet, and alcohol intake) were generally not statistically significantly associated with all-cause mortality in our study. Therefore, the associations between the lifestyle scores and the reduced all-cause mortality risk could not be attributed to 1 lifestyle behavior. This further emphasizes the importance of adopting an overall healthy lifestyle pattern rather than focusing on a single lifestyle behavior.

For CRC patients, it is important to know whether changing one's lifestyle after diagnosis can lower the risk of recurrence and can improve survival. In our study, a change in the overall lifestyle after diagnosis was not associated with the risk of CRC recurrence. An improvement in ACS and national scores after diagnosis was statistically significantly associated with a lower all-cause mortality risk, independent of the pretreatment lifestyle score. Our all-cause mortality results are in line with 2 previous observational studies that assessed either changes in the ACS score from midway through chemotherapy to 6 months after chemotherapy or changes in diet quality from pre- to postdiagnosis (9, 28). No previous study assessed these associations with the risk of CRC recurrence. Additional studies are needed to further examine whether changing one's lifestyle after a CRC diagnosis impacts the recurrence risk.

Potential limitations of our study should be considered. We could not explore cause-specific mortality, as we do not have access to these data. This would have been of interest, as we

observed an inverse association for all-cause mortality but not for CRC recurrence. A healthy lifestyle after a CRC diagnosis might therefore specifically be related to the cardiovascular risk profile, but not to CRC-specific mortality. Second, we had limited power, as we observed relatively few events ($n = 164$ for recurrence; $n = 171$ for mortality), even after combining data from 2 cohorts. Nonetheless, we observed similar associations for all 3 lifestyle scores, making our results more robust. Third, for some patients, the postdiagnosis lifestyle was assessed before chemotherapy was completed. In a sensitivity analysis, we excluded all participants for whom this might have been the case (as the date of the end of chemotherapy was not available). This did not change our conclusions from the postdiagnosis analyses and the change analyses with regard to recurrence. However, the inverse associations between postdiagnosis lifestyle and all-cause mortality were attenuated and no longer statistically significant. Fourth, the postdiagnosis lifestyle was assessed 6 months after diagnosis or 6 months after treatment. Lifestyles assessed at these times might not reflect lifestyles later during the CRC trajectory. However, 60–80% of CRC recurrences occur within the first 2 years after resection (29); therefore, the recurrence risk will be minimally affected by lifestyle later during the CRC trajectory. Furthermore, reported associations did not change when we used time-varying analyses in which we updated lifestyle scores based on each repeated postdiagnosis lifestyle assessment (up to 4 in the first 5 years after diagnosis; results comparable to those presented in Supplemental Table 5). Fifth, results of this study can only be generalized to Western populations of CRC survivors. Finally, as with all observational studies, we cannot completely eliminate the possibility of reverse causation and/or residual confounding. However, our results do not indicate that survivors without comorbidities, who are likely to have healthier lifestyles, had better outcomes, as lifestyle data measured at diagnosis were not associated with mortality. Furthermore, associations with all-cause mortality were similar across cancer stages.

Strengths of the current study include its prospective design and the availability of CRC recurrence data. A unique feature was the ability to evaluate changes in lifestyles after diagnosis, due to the repeated lifestyle measurements starting at diagnosis. In addition, we had detailed lifestyle data that allowed us to compute different lifestyle scores to assess potential associations between concordance with healthy lifestyle recommendations and outcomes.

In conclusion, a healthy lifestyle after a CRC diagnosis was not associated with the risk of CRC recurrence among patients with stage I–III CRC, but tended to be associated with a decreased all-cause mortality risk. This suggests that CRC patients could be advised to follow healthy lifestyle recommendations that emphasize a healthy body weight, being physically active, eating a healthy diet, and limiting alcohol intake after a CRC diagnosis to prolong survival. More research needs to be done to understand whether and how the lifestyle after diagnosis could influence CRC recurrence.

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The authors' responsibilities were as follows – MvZ, HCB, EK, MPW, FJBvD: designed the research; MvZ, AJMRG, EW, M-FK: conducted the research; MvZ: analyzed the data, wrote the draft paper, and had primary responsibility for the final content; HKvH, EJSB, SOB, ETPK, MLGJ-H, JHWdW: contributed to the recruitment of participants; and all authors: critically read and revised the draft manuscript and read and approved the final manuscript. M-FK is supported by a grant from Wereld Kanker Onderzoek Fonds 2017/1619 (to MJLB). All the other authors report no conflicts of interest.

Data Availability

Because the data consist of identifying cohort information, some access restrictions apply; therefore, the data cannot be made publicly available. Requests for data from the COLON study can be sent to Dr. Fränzel van Duijnhoven, Division of Human Nutrition and Health, Wageningen University & Research, the Netherlands (e-mail: franzel.vanduijnhoven@wur.nl). Requests for data from the EnCoRe study can be sent to Dr. Martijn Bours, Department of Epidemiology, GROW-School for Oncology and Developmental Biology, Maastricht University, the Netherlands (e-mail: m.bours@maastrichtuniversity.nl).

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