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Original article

Dietary and lifestyle inflammation scores in relation to colorectal cancer recurrence and all-cause mortality: A longitudinal analysis

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SUMMARY

Aim: The aim of this study was to longitudinally investigate dietary and lifestyle inflammation scores and their interaction in relation to risk of colorectal cancer (CRC) recurrence and all-cause mortality.
Methods: Data of two prospective cohort studies among CRC survivors was used. Information about diet and/or lifestyle was available for 2739 individuals for at least one of the following time points: at diagnosis, six months after diagnosis and two years after diagnosis. The dietary and lifestyle inflammation scores (DIS and LIS) were used to evaluate the inflammatory potential of diet and lifestyle. Joint modelling, combining mixed models and Cox proportional hazards regression, were used to assess associations between DIS and LIS over time and CRC recurrence and all-cause mortality. Interactions between DIS and LIS were assessed using time-dependent Cox proportional hazard regression.
Results: The median follow-up time was 4.8 (IQR 2.9–6.9) years for recurrence and 5.7 (IQR 3.5–8.5) years for all-cause mortality, with 363 and 453 events, respectively. A higher DIS as well as LIS was associated with a higher risk of all-cause mortality ($HR_{DIScontinuous}$ 1.09 95%CI 1.02; 1.15; $HR_{LIScontinuous}$ 1.24 95%CI 1.05; 1.46). Individuals who were in the upper tertile of both DIS and LIS had the highest all-cause mortality risk (HR 1.62 95%CI 1.16; 2.28), compared to the individuals in the lowest tertile of both DIS and LIS. No consistent associations with recurrence were observed.
Conclusion: A more pro-inflammatory diet and lifestyle was associated with a higher risk of all-cause mortality, but not recurrence, in CRC survivors.

1. Introduction

Chronic inflammation, one of the hallmarks of cancer [1], is an important mechanism linking diet and other lifestyle factors with cancer prognosis [2–6]. Chronic inflammation is involved in all steps of the cancer continuum, including cancer recurrence [7,8]. Studies in colorectal cancer (CRC) survivors have shown that higher levels of circulating inflammation markers, such as interleukin 6 and Tumour Necrosis Factor α, were associated with an increased risk of recurrence and mortality [9,10]. A high consumption of red and processed meat, smoking and being obese are associated with higher levels of circulating inflammation markers, and as such are considered pro-inflammatory [11,12]. On the other hand, a higher intake of fruits and vegetables, as well as being physically active, are associated with lower levels of circulating inflammation markers and are considered to be anti-inflammatory [13,14]. Thus, healthy diet and lifestyle choices could potentially lower chronic inflammation and subsequently improve CRC prognosis.

The association between the inflammatory potential of the diet, measured by the Dietary Inflammatory Index (DII), a score based on nutrient intake, and mortality of all cancers, is investigated in 11

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List of abbreviations

CI	Confidence interval
COLON	COlorectal cancer Longitudinal, Observational study on Nutritional and lifestyle factors that influence colorectal tumour recurrence, survival and quality of life
CRC	Colorectal cancer
DCRA	Dutch Colorectal Audit
DIS	Dietary Inflammation score
FFQ	Food frequency questionnaire
HPFS	Health Professionals Follow-Up Study
HR	Hazard ratio
hsCRP	high-sensitivity C-reactive protein
IL	Interleukin
IQR	Interquartile range
LIS	Lifestyle inflammation score
NHS	Nurses' Health Study
PLCRC	Prospectief Landelijk CRC cohort/Prospective nationwide CRC cohort
RCS	Restricted cubic splines
RRR	Reduced Rank Regression
SQUASH	Short Questionnaire to Assess Health-enhancing physical activity
TNFα	Tumour necrosis factor alfa

studies and summarized by Zahedi et al., [15]. In this meta-analyses, a pooled HR of 1.16 95%CI 1.01–1.32 was observed for all-cancer mortality when comparing the highest pro-inflammatory level of the DII with the lowest level of the DII [15]. A recent meta-analyses in cancer survivors [16], did not observe a statistically significant association between pre-diagnostic DII and all-cause mortality in CRC survivors (HR 0.99 95%CI 0.85; 1.15; n = 3 studies). On the other hand, a higher post-diagnostic DII seemed to be associated with a higher risk of all-cause mortality in CRC survivors (pooled HR 1.33 95%CI 0.89; 2.00; n = 3 studies). However, in these previous studies, a score based on nutrient intake was used, while nutrients are not consumed in isolation, but as part of a whole dietary pattern. A score based on the inflammatory potential of food groups may offer a more realistic view. This would also make it easier to develop practical dietary guidelines for cancer survivors.

In our previous research, we observed that a more pro-inflammatory diet after diagnosis, by means of a higher Empirical Dietary Inflammatory Pattern (EDIP) score, which is a score based on food groups developed by Harvard T.H. Chan School of Public Health (Boston), was associated with a higher risk of recurrence and all-cause mortality [17]. In addition to the data-driven EDIP score [18], which only includes diet, a hypothesis-driven dietary inflammation score (DIS) as well as a separate lifestyle inflammation score (LIS) were developed by the Emory University Rollins School of Public Health (Atlanta, USA) [5]. The advantage of a hypothesis-driven approach is that it can be better reproduced and generalized to different populations. That is because the selection of relevant groups and inflammatory weights of those groups are not depending on the specific population in which the score was developed but are based on biological plausible mechanisms and literature. To provide a more elaborate overview and understanding of the role of diet and lifestyle in inflammation and its associated clinical outcomes, the separate as well as the combined inflammatory effects of the diet and other lifestyle exposures, as captured with the combination of the DIS and LIS, should be investigated in relation to CRC recurrence and mortality.

A higher risk of all-cancer mortality and all-cause mortality has been reported using data from the Woman's Health Study (n = 31,155 women without CRC at inclusion) comparing the highest quintile of DIS and LIS to the lowest quintile, separately but especially combined [19]. It is still unknown whether the DIS and LIS, alone or combined, are associated with recurrence and mortality in people diagnosed with CRC. The vast majority of previous studies focused on the inflammatory potential of the diet measured at one moment in timepoint. To understand how the DIS and LIS influence CRC outcomes and to get a more accurate estimation of dietary and lifestyle habits, these factors should be measured repeatedly over time starting at diagnosis. The aim of this study is to longitudinally investigate the DIS and LIS and their interaction in relation to CRC recurrence and all-cause mortality.

2. Materials and methods

2.1. Study population

Data from two prospective cohort studies were used, the COLON study (ClinicalTrials.gov Identifier NCT3191110) [20] and the PLCRC-PROTECT study (ClinicalTrials.gov NCT-02070146) [21]. The designs of both studies have been described earlier [20,21].

Briefly, in the COLON study newly diagnosed CRC patients were recruited from 11 Dutch hospitals, from August 2010 until February 2020. Men and women above the age of 18 with all stages of disease were eligible. Participants were excluded when unable to speak Dutch, or with one or more of the following patients' characteristics: a history of CRC (partial) bowel resection or inflammatory bowel disease, inherited CRC syndrome (Lynch syndrome, familial adenomatous polyposis and Peutz-Jegher), or mental conditions such as dementia, which make it impossible to fill out surveys.

For the PLCRC-PROTECT study, newly diagnosed patients were recruited from 21 Dutch hospitals starting from February 2016. For the current study, participants who were recruited between February 2016 and December 2022 were included. Both studies were approved by a medical ethics committee (COLON: region Arnhem-Nijmegen, 2009–349; PLCRC-PROTECT: University Medical Center Utrecht, 15–770/C). All study participants provided written informed consent.

In the current analyses, people diagnosed with metastatic disease (stage IV; n = 255) were excluded, as well as participants with missing data of the DIS or LIS components at all time-points (n = 291) (Fig. 1). Missing exposure data at one or two time-points and missing data in covariates was imputed during data-analyses.

2.2. Data collection

In the COLON and PLCRC-PROTECT studies, data collection of questionnaires and blood samples took place shortly after diagnosis (i.e., baseline), and after six months and two years. Characteristics on demographics, lifestyle, education, medication usage, self-assessed anthropometric measurements and health was collected using a self-administered lifestyle questionnaire [20].

2.3. DIS components and calculation

The components of the DIS were assessed at all three time-points by using the semi-quantitative food frequency questionnaire (FFQ) of 204-items developed by the Division of Human Nutrition and Health of Wageningen University, the Netherlands, in

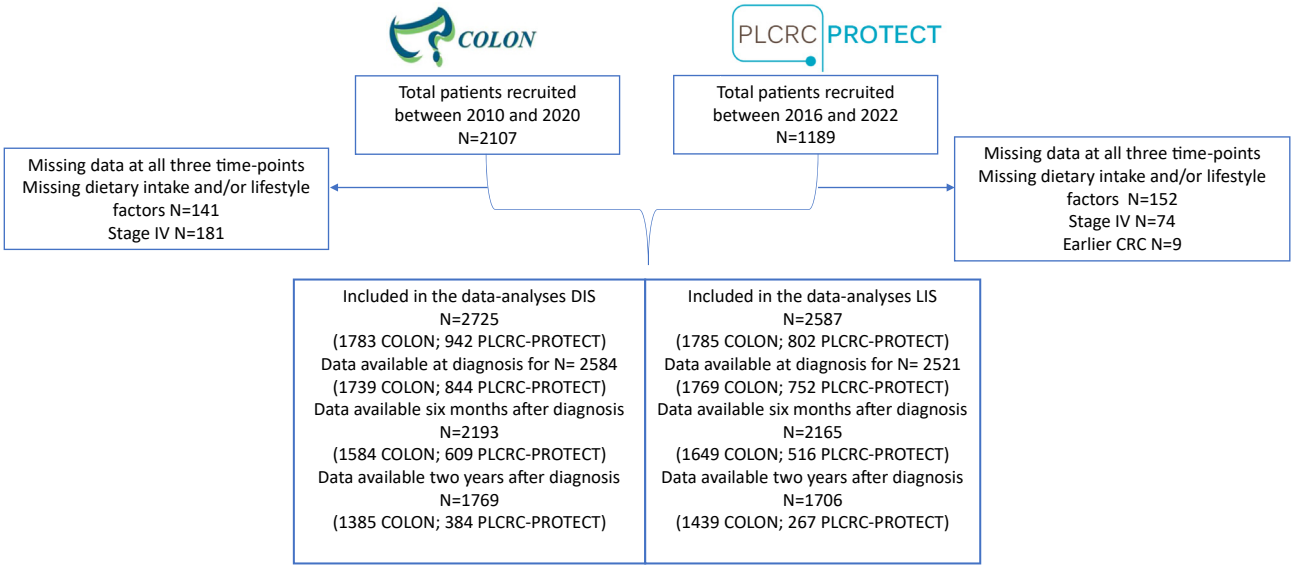

Fig. 1. Flowchart of participants.

both cohorts [20]. Supplement use was assessed in both cohorts using the same self-administered dietary supplement questionnaire developed by the Division of Human Nutrition and Health of Wageningen University, the Netherlands [20]. Information on type of dietary supplement, frequency of intake and dosage was collected.

The DIS consists of 19 components and was calculated as previously described by Byrd et al., [5]. The 18 food groups in the DIS are 'leafy greens and cruciferous vegetables', 'tomatoes', 'apples and berries', 'deep yellow or orange vegetables and fruits', 'other fruits and real fruit juices', 'other vegetables', 'legumes', 'fish', 'poultry', 'red and organ meats', 'processed meats', 'added sugar', 'high-fat dairy', 'low-fat dairy', 'coffee and tea', 'nuts', 'other fats', 'refined grains and starchy vegetables'. Supplement use was also included in the DIS by calculating a combined score of supplemental micronutrient intake, including mineral and vitamin intake. This component was obtained by first ranking single supplemental micronutrient intakes into tertiles, stratified by sex. Secondly, a value of 2 was assigned to the highest tertile, 1 to the middle, and 0 to the lowest tertile. Thirdly, multiplication with a value of -1 for the pro-inflammatory micronutrient iron [5], and with a value of $+1$ for the anti-inflammatory micronutrients, which is all micronutrients except iron [5] was done. Finally, a total supplemental micronutrient intake score was derived by summing all the values of the single nutrients, where a higher score corresponds to a higher intake of anti-inflammatory supplements. This total supplemental micronutrient intake score represents the supplement intake component within the total DIS.

Each component (18 food group components and one supplement intake component) of the DIS was standardized, by sex, to a mean of 0 and SD of 1, to obtain z-scores. Consequently, all components were multiplied by its respective weight as obtained from Byrd et al. [5] (Table 2). Finally, the sum of the intake of food groups and the supplemental micronutrient intake score, each multiplied by its weights constitute the overall DIS. The higher the DIS, the more pro-inflammatory the diet.

2.4. LIS components and calculation

The LIS consists of four components: physical activity, smoking status, BMI and alcohol consumption [5], which were also measured at all three time-points. Physical activity was assessed by the self-reported Short Questionnaire to ASsess Health-enhancing physical activity (SQUASH) [22] at all time-points. In this questionnaire, participants were asked to report the average time they spent per week on community activities, activity at work, household activities and leisure time activities in the past two months. A Metabolic Equivalent (MET) score was converted based on Ainsworth sport codes in combination with self-reported intensity levels [22]. Sex- and cohort-specific tertiles of moderate-to-vigorous activity in hours per week were constructed. Smoking status was categorised as 'current and former smokers quitted less than 1 year ago' or 'former smokers quitted for at least 1 year and never'. This was done because former smoking does not seem to affect current systemic inflammation [5], but quitting recently could still affect chronic inflammation. Self-assessed height and weight were used to calculate BMI (kg/m2). BMI was categorised as normal weight ($\leq$25 kg/m^2), overweight (>25 and <30 kg/m^2) and obese ($\geq$30 kg/m^2). Only 19 people (0.7%) were underweight (BMI ranging between 17.2 and 18.4). Given the limited numbers, these people were categorized within the normal weight group for the construction of the score. Alcohol intake, assessed by the FFQ, was divided over the categories 'none' (<1 g/day), 'moderate' (>1 and $\leq$ 14 g/day for women and >1 and $\leq$28 g/day for men)', or 'heavy' (>14 g/day for women and >28 g/day for men) [5].

To calculate the LIS, all components were multiplied by their respective weight (see Table 2) and the weighted components were summed up. The higher the LIS, the more pro-inflammatory the lifestyle.

2.5. Clinical information

Clinical information regarding stage of disease, primary tumour location and presence of comorbidities and the American Society of Anaesthesiologists (ASA)-score at diagnosis, which is a subjective assessment of a patients overall health based on five classes, where class I is a healthy fit patients and class V a patient expected to die within 24 h, was derived from the Dutch ColoRectal Audit (DCRA) for the COLON study [23] or the Netherlands Cancer Registry (NCR) for the PLCRC-PROTECT study.

2.6. Recurrence and all-cause mortality

For both cohorts, information on recurrence status was collected from medical records in a standardized manner by specialised data managers of the NCR. Recurrence is defined as a locoregional recurrence and/or distant metastasis. The follow-up time of recurrence was calculated from date of surgery until date of recurrence, date of lost to follow-up, date of death or until the date of recurrence status was last updated (June 2022), whichever came first. Vital status was collected from the Municipal Personal Record Database. For all-cause mortality, follow-up time started at date of surgery and ended at date of death, date of lost to follow up, or until the date vital status was last updated (October 2023 for COLON and January 2023 for PLCRC-PROTECT), whichever occurred first.

2.7. Circulating inflammation markers

Associations between DIS and LIS and inflammation markers were assessed to validate the use of the DIS and LIS in our study population. In the COLON study, non-fasting blood samples were drawn at diagnosis, six months and two years after diagnosis. The blood samples were centrifuged and processed into plasma and immediately stored in a freezer at −80 °C until analysis [20]. In a subgroup of the COLON study (N = 490), circulating biomarkers of inflammation; high-sensitivity C-reactive protein (hsCRP), interleukin-6 (IL-6), interleukin-8 (IL-8) and tumour-necrosis factor alfa (TNFα) were measured. The methods to analyse the circulating inflammation markers are described elsewhere in detail [24]. In short, hsCRP was measured with an immuno-MALDI mass spectrometry method (BEVITAL, Bergen, Norway), with an inter-assay coefficient between 3% and 6% [25]. IL-6, IL-8 and TNFα were determined in plasma with a custom-made multiplex assay using electrochemiluminescence detection (Meso Scale Diagnostics, Rockville, MD, USA). The samples used were not stored longer than 2 years, as cytokines in plasma tend to degrade after a longer storage time [26].

2.8. Data analysis

Baseline characteristics of patients at diagnosis were described for the total study population and by tertiles of DIS and LIS in Table 1. The data is either described by means and standard deviations, if normally distributed, or medians and interquartile ranges, or percentages and frequencies. Normality was checked using Q–Q plots. Table 2 shows the baseline descriptives of the DIS and LIS, overall and by tertiles of DIS and LIS. Also the inflammatory weights of each item (derived from Byrd et al., [5]) are included in Table 2.

To estimate associations of the DIS and LIS over time with recurrence and all-cause mortality, hazard ratios (HRs) and their 95% confidence intervals (CIs) were calculated using joint modelling. In a joint model, linear mixed models (for longitudinal data) and a Cox proportional hazards regression models (for time to event data) are combined [27]. Joint modelling is appropriate when investigating time to an event with covariates that are measured longitudinally and are related to the event. An underlying random effect's structure links the survival and longitudinal sub models and allows for individual-specific predictions. Multiple time-varying and time-invariant covariates can be included to potentially increase accuracy [27]. In our analyses, DIS and LIS (both continuous with an increment of 1 unit) measured at diagnosis, six months after diagnosis and two years after diagnosis were longitudinally modelled, in the mixed model (longitudinal sub model), and carried forward to the Cox proportional hazards regression model (survival sub model), to estimate the associations of longitudinal DIS and LIS with recurrence and mortality. The JointAI package in R (version 1.0.5) was used to conduct the joint models [27], the code used can be found in the Supplementary Methods. A random intercept was used in all models. Random slopes did not significantly improve the model fit and were therefore not included. Imputation of missing data was executed following a Bayesian approach, using 100 adaptations (burn-in) and 1000 iterations. Within the JointAI model, data-analyses and imputation of missing data can be performed simultaneously while assuring compatibility between the longitudinal and survival sub models. We chose to include the multiple imputation analyses, because if missing data are at random (MAR), which appears to be the case in our data, multiple imputation is in general superior over complete cases analyses [28]. Model performance was checked by inspecting trace plots, Gelman-Rubin criteria (GR-crit close to 1) and the Monte Carlo error to posterior standard deviation ratio (MCE/SD < 0.05) [27].

First, an univariable (crude) model was run. Second, the model was adjusted for covariates, of which age, sex, stage of disease, tumour location, and total energy intake were included *a priori*. Other potential confounders were included when they change the HR with more than 10%. The following confounders were tested: education level, comorbidities, regular non-steroidal anti-inflammatory drugs (NSAID) use, treatment and ASA-score [5,29]. None of these covariates changed the HR of the association and were thus not included in the model. In a third model, the adjusted model was additional adjusted for either a healthy lifestyle for the DIS model or a healthy diet for the LIS model. This was done by calculating an equally weighted DIS and LIS. Instead of the inflammatory weights from Table 2 either −1 (healthy food or lifestyle component) or +1 (unhealthy food or lifestyle component) was used to calculate this equally weighted DIS and LIS.

To get more insight in the direction of the interaction we investigated 1) the combined versus separate effects of DIS and LIS using one reference category (lowest tertile of both DIS and LIS), and 2) the Hazard Ratios of one factor across strata of another factor. In these stratified analyses DIS and LIS were included as continuous variables. In addition, we investigated interaction using statistical tests. Interactions between DIS and LIS can be described in two ways: additive and multiplicative [30]. To assess the multiplicative interaction of DIS and LIS in relation to all-cause mortality and recurrence, an interaction term DIS × LIS was added to the time-dependent Cox model. Additive interaction was assessed by calculating the relative excess risk due to interaction (RERI) based on the multiplicate model $(e^{(\beta_{DIS}+\beta_{LIS}+\beta_{DISxLIS})} - e^{\beta_{DIS}} - e^{\beta_{LIS}} + 1)$ [30,31]. Given the nature of the data (DIS and LIS being outcomes variables in the mixed model part), interactions between DIS and LIS were explored using time-dependent Cox proportional hazard models (also from the JointAI package). Effect estimates of the joint model should be interpreted as a change in risk of recurrence or all-cause mortality when increasing the DIS or LIS with 1 unit.

We also performed some additional analyses. First, we investigated associations between the equally weighted DIS and LIS in relation to CRC recurrence and all-cause mortality. For the equally weighted DIS and LIS, no inflammatory weights were assigned to the components of the DIS and the LIS. The weighted scores for our primary analyses are scores, linked to inflammation as an underlying mechanism. The equally weighted scores are not limited by the contribution of diet and lifestyle to chronic inflammation. Therefore, they reflect the overall association between the DIS and LIS components and CRC recurrence and survival, which may also be related to other underlying mechanisms besides inflammation.

In addition, although we decided to use the inflammatory weight of the original DIS and LIS developed in an USA population to improve reproducibility and comparability between studies, we

validated the use of DIS and LIS in our study population of Dutch CRC survivors. For this purpose, we explored whether the DIS and LIS were associated with plasma levels of inflammation markers. We assessed the association between the DIS and the LIS and circulating inflammation markers (hsCRP, IL6, IL8 and TNFα) in a subgroup of the COLON study (n±490 for the cytokines and n±1250 for hsCRP) using linear mixed models. As random effects we included subject, as fixed effects we included age, sex, stage of disease, tumour location, use of NSAIDs, total energy intake (derived from the FFQ) and either the equally weighted DIS or LIS depending on the exposure (DIS or LIS). This was done for all individual inflammation markers. Results are presented in Table S1.

Finally, sensitivity analyses were performed excluding observations with an extremely low or high DIS (>1.5 times the IQR below the 25th percentile or above the 75% percentile), since these outliers (3% of observations) had a large influence on the association between inflammation markers and the DIS. Intakes of food groups/patterns of these outliers were unlikely, but not impossible. "Extreme" low values (anti-inflammatory) were caused by a very high intake of all kinds of vegetables and fruits (>800 gr/day), use of many supplements, high intake of coffee or tea (>8 cups a day), no/limited intake of processed meats, added sugars and refined grains or a combination of these. Baseline characteristics of persons with an extreme DIS did not differ from the total population.

Data analyses were conducted with statistical software R, version 4.2.1. R-codes used are available in the supplementary methods. Two-sided p-values ≤0.05 were considered statistically significant.

3. Results

In total, data from 2739 CRC patients was included in the analyses (Fig. 1). The median age was 66 [IQR 60–72] years and 62% was male (Table 1). The median BMI was 26.0 [IQR 23.9–28.7] (Table 2). Most patients were diagnosed with a tumour located in the proximal colon (36%), followed by the distal colon (31%) and

Table 1
Baseline characteristics of CRC patients, stratified by tertiles of the Dietary Inflammation Score and the Lifestyle Inflammation Score.

	Total population	Tertiles of the Dietary Inflammation Score			Tertiles of the Lifestyle Inflammation Score		
		Low DIS	Medium DIS	High DIS	Low LIS	Medium LIS	High LIS
Number	2739	862	861	861	884	811	826
DIS*	0.28 [-1.35; 1.66]	−2.18 [-3.32; 1.36]	0.28 [-0.23; 0.73]	2.22 [1.66; 3.10]	−0.01 [-1.61; 1.45]	0.42 [-1.41; 1.69]	0.42 [-1.07; 1.91]
LIS*	0.23 [-0.18; 0.78]	0.05 [-0.41; 0.73]	0.12 [-0.18; 0.73]	0.23 [-0.18; 0.89]	−0.66 [-0.84; −0.18]	0.23 [0.05; 0.32]	0.91 [0.78; 1.39]
Sex (male)	1695 (62%)	527 (61%)	539 (63%)	529 (61%)	569% (64)	503 (62%)	489 (59%)
Age at diagnosis (years)	65.9 [59.9; 72.0]	65.6 [59.6; 71.0]	66.1 [60.7; 72.0]	66.0 [60.0; 72.4]	66.1 [60.8; 72.0]	65.6 [59.9; 72.0]	66.0 [59.8; 71.6]
Education level[a]							
Low	1045 (38%)	211 (25%)	315 (37%)	470 (55%)	311 (35%)	317 (39%)	354 (43%)
Medium	716 (26%)	221 (26%)	230 (27%)	237 (28%)	224 (25%)	228 (28%)	214 (26%)
High	935 (34%)	430 (50%)	311 (36%)	151 (18%)	349 (40%)	266 (33%)	255 (31%)
Unknown	43 (2%)	0 (0%)	5 (1%)	3 (0%)	0 (0%)	0 (0%)	3 (0%)
Regular use of NSAID[b]							
No	2308 (84%)	752 (87%)	742 (86%)	737 (86%)	780 (88%)	706 (87%)	698 (85%)
Yes	325 (12%)	101 (12%)	101 (12%)	113 (13%)	95 (11%)	97 (12%)	120 (15%)
Unknown	106 (4%)	9 (1%)	18 (2%)	11 (1%)	9 (1%)	8 (1%)	8 (1%)
ASA score							
1	681 (25%)	233 (27%)	225 (26%)	187 (22%)	283 (32%)	214 (26%)	140 (17%)
2	1506 (55%)	467 (54%)	470 (55%)	479 (56%)	460 (52%)	431 (53%)	491 (59%)
3	338 (12%)	98 (11%)	100 (12%)	118 (14%)	77 (9%)	91 (11%)	134 (16%)
4	14 (1%)	4 (1%)	2 (0%)	8 (1%)	4 (1%)	4 (1%)	6 (1%)
Unknown	200 (7%)	60 (%7)	64 (7%)	69 (8%)	60 (7%)	71 (9%)	55 (7%)
Stage of disease							
I	767 (28%)	251 (29%)	233 (27%)	253 (29%)	272 (31%)	220 (27%)	232 (28%)
II	766 (28%)	244 (28%)	234 (27%)	236 (27%)	235 (27%)	218 (27%)	242 (29%)
III	1194 (44%)	365 (42%)	390 (45%)	368 (43%)	374 (42%)	369 (46%)	349 (42%)
Unknown	12 (0.4%)	2 (0%)	4 (1%)	4 (1%)	3 (0%)	4 (1%)	3 (0%)
Location primary tumour							
Distal colon	860 (31%)	262 (30%)	279 (32%)	268 (31%)	277 (31%)	268 (33%)	246 (30%)
Proximal colon	992 (36%)	327 (38%)	295 (34%)	313 (36%)	317 (36%)	286 (35%)	311 (38%)
Rectum	833 (30%)	259 (30%)	265 (31%)	263 (31%)	272 (31%)	236 (29%)	257 (31%)
Unknown	54 (2%)	14 (2%)	22 (3%)	17 (2%)	18 (2%)	21 (3%)	12 (2%)
Surgery							
No	57 (2%)	18 (2%)	10 (1%)	25 (3%)	22 (3%)	10 (1%)	18 (2%)
Yes	2677 (98%)	841 (98%)	850 (99%)	835 (97%)	860 (97%)	798 (98%)	808 (98%)
Unknown	5 (0.2%)	3 (0%)	1 (0%)	1 (0%)	2 (0%)	3 (0%)	0 (0%)
Type of treatment							
No or unknown surgery	62 (2 %)	21 (2%)	11 (1%)	26 (3%)	24 (3%)	13 (2%)	18 (2%)
Only surgery	1445 (53%)	479 (56%)	443 (52%)	445 (52%)	475 (54%)	426 (53%)	432 (52%)
Surgery and chemotherapy	669 (24%)	180 (21%)	218 (25%)	222 (26%)	205 (23%)	195 (24%)	199 (24%)
Surgery and radiotherapy	240 (9%)	83 (10%)	64 (7%)	82 (10%)	72 (8%)	81 (10%)	72 (9%)
Surgery and chemoradiation	224 (8%)	66 (8%)	83 (10%)	64 (7%)	74 (8%)	63 (8%)	74 (9%)
Unknown	99 (4%)	33 (4%)	42 (5%)	22 (3%)	34 (4%)	33 (4%)	31 (4%)
Cohort							
COLON	1785 (65%)	567 (66%)	585 (68%)	587 (68%)	615 (70%)	565 (70%)	589 (71%)
PLCRC	954 (35%)	295 (34%)	276 (32%)	274 (32%)	269 (30%)	246 (30%)	237 (29%)

Values presented are median [Q1 − Q3] or number (percentage). BMI: Body Mass Index. DIS; Dietary Inflammation Score; LIS: Lifestyle Inflammation Score.
[a] Education: Low education is defined as primary school and general lower secondary school; Medium as lower vocational training and higher general secondary education; High as high vocational training and university.
[b] Regular NSAID use: use of NSAID more than once a week.

Table 2
Inflammatory weight as well as descriptives of the components of the dietary and lifestyle inflammation scores (DIS and LIS) measured at diagnosis, overall and stratified for tertiles of the DIS and LIS.

	Inflammatory weight	Overall	Tertiles of the Dietary Inflammation Score			Tertiles of the Lifestyle Inflammation Score		
			Low DIS	Intermediate DIS	High DIS	Low LIS	Intermediate LIS	High LIS
n		2739	862	861	861	884	811	826
Leafy greens and cruciferous vegetables (g/day)	−0.14	28 [16, 44]	36 [21, 54]	28 [17, 43]	23 [13, 37]	32 [19, 48]	28 [16, 43]	26 [15, 41]
Tomatoes (g/day)	−0.78	6 [2, 14]	13 [5, 29]	5 [2, 12]	3 [0, 7]	7 [2, 15]	5 [2, 13]	5 [1, 13]
Apples and berries (g/day)	−0.65	78 [30, 137]	108 [51, 167]	75 [32, 134]	55 [16, 115]	89 [41, 148]	75 [29, 134]	70 [24, 130]
Yellow vegetables and fruits (g/day)	−0.57	12 [5, 21]	18 [9, 30]	12 [4, 20]	8 [2, 15]	14 [6, 24]	11 [4, 20]	11 [3, 20]
Other fruits and real fruit juices (g/day)	−0.16	101 [42, 175]	128 [66, 207]	93 [43, 166]	80 [26, 148]	110 [53, 181]	101 [38, 175]	92 [34, 168]
Other vegetables (g/day)	−0.16	19 [8, 34]	28 [16, 47]	19 [9, 33]	13 [4, 23]	21 [10, 36]	18 [8, 32]	18 [7, 34]
Legumes (g/day)	−0.04	19 [9, 33]	23 [11, 39]	19 [10, 31]	16 [7, 28]	21 [11, 34]	19 [10, 32]	19 [9, 32]
Fish (g/day)	−0.08	10 [4, 16]	12 [7, 22]	10 [4, 16]	8 [3, 13]	10 [5, 17]	9 [3, 16]	10 [4, 16]
Poultry (g/day)	−0.45	11 [5, 20]	13 [6, 25]	12 [6, 20]	9 [4, 16]	11 [5, 19]	11 [5, 20]	12 [5, 21]
Red and organ meats (g/day)	0.02	36 [20, 51]	31 [16, 46]	36 [21, 51]	40 [26, 56]	35 [20, 48]	36 [22, 51]	38 [22, 56]
Processed meats (g/day)	0.68	21 [10, 37]	13 [4, 25]	20 [11, 33]	34 [20, 53]	21 [9, 35]	21 [11, 36]	25 [12, 41]
Products high in added sugars (g/day)	0.56	21 [8, 48]	14 [5, 29]	21 [8, 43]	36 [14, 105]	23 [10, 48]	22 [8, 54]	20 [6, 45]
High fat dairy (g/day)	−0.14	71 [37, 129]	69 [35, 127]	69 [36, 125]	77 [41, 137]	79 [41, 147]	67 [35, 126]	68 [36, 123]
Low fat dairy (g/day)	−0.12	174 [76, 292]	198 [97, 314]	182 [83, 287]	150 [60, 279]	185 [96, 297]	183 [89, 289]	154 [61, 284]
Coffee and tea (g/day)	−0.25	587 [464, 813]	696 [464, 871]	585 [464, 813]	580 [395, 719]	696 [464, 813]	585 [464, 813]	580 [429, 813]
Nuts (g/day)	−0.44	8 [3, 20]	15 [5, 30]	9 [3, 19]	5 [1, 12]	10 [4, 23]	8 [3, 20]	6 [2, 16]
Other fats (g/day)	0.31	19 [9, 29]	15 [8, 24]	17 [8, 28]	25 [13, 36]	21 [10, 32]	18 [9, 28]	18 [9, 28]
Refined grains and starchy vegetables (g/day)	0.72	246 [185, 319]	210 [153, 281]	239 [190, 300]	294 [230, 357]	266 [201, 338]	246 [184, 314]	232 [177, 298]
Energy (kcal/day)		1792 [1468, 2158]	1800 [1,479, 2153]	1745 [1,441, 2075]	1859 [1,512, 2245]	1881 [1,553, 2193]	1767 [1,447, 2123]	1760 [1,426, 2155]
Any supplement use (yes)	−0.80	1179 (43%)	561 (65%)	368 (43%)	242 (28%)	415 (47%)	346 (43%)	342 (41%)
Unknown		139 (5%)	0 (0%)	0 (0%)	0 (0%)	24 (3%)	23 (3%)	17 (2%)
Alcohol		7 (1, 20%)	8 (1, 20%)	8 (1, 20%)	5 (0, 18%)	8 (2, 15%)	6 (1, 17%)	8 (0, 32%)
Alcohol categorical[a]								
Heavy	0.30	526 (20%)	176 (20%)	186 (22%)	154 (18%)	52 (5.9%)	120 (15%)	322 (39%)
Moderate	−0.66	1390 (50%)	480 (56%%)	449 (52%%)	419 (49%)	695 (78.6%)	466 (57%)	168 (20%)
None		743 (27%)	206 (24%%)	226 (26%%)	288 (33%)	137 (15.5%)	221 (27%)	331 (40%)
Unknown		80 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	4 (1%)	5 (1%)
Moderate to vigorous physical activity		660 [300; 1140]	660 [340; 1110]	660 [330; 1170]	615 [240; 1170]	1035 (605, 1534)	510 (240; 945)	476 (213−810)
Tertile 1		858 (31%)	252 (29%)	261 (30%)	304 (35%)	122 (14%)	348 (43%)	365 (44%)
Tertile 2	−0.18	857 (31%)	308 (36%)	269 (31%)	234 (28%)	257 (29%)	260 (32%)	317 (38%)
Tertile 3	−0.41	866 (32%)	262 (30%)	284 (33%)	288 (33%)	505 (57%)	203 (25%)	144 (17%)
Unknown		159 (6%)	40 (5%)	47 (6%)	35 (4%)	0 (0%)	0 (0%)	0 (0%)
BMI								
Continuous		26.0 [23.9; 28.7]	25.6 [23.6; 28.4]	26.0 [23.9; 28.7]	26.6 [24.2; 29.4]	24.0 [23.5; 24.9]	26.3 [24.3; 28.1]	29.4 [26.9; 32.3]
Normal (<25 kg/m2)		1018 (37%)	357 (41%)	331 (38%)	297 (34%)	691 (78%)	252 (31%)	27 (3%)
Overweight (25−30 kg/m2)	0.89	488 (18%)	134 (16%)	144 (17%)	190 (22%)	186 (21%)	483 (60%)	408 (49%)
Obese (>30 kg/m2)	1.57	1139 (42%)	360 (42%)	379 (44%)	363 (43%)	0 (0%)	73 (9%)	388 (47%)
Unknown		94 (3%)	11 (1%)	7 (1%)	11 (1%)	7 (1%)	3 (0%)	3 (0%)
Smoking status								
Current [b]	0.50	246 (9%)	51 (6%)	73 (9%)	112 (13%)	37 (4%)	60 (7%)	135 (16%)
Former-Never		2447 (89%)	808 (94%)	783 (91%)	747 (87%)	845 (96%)	750 (92%)	691 (84%)
Unknown		46 (2%)	2 (0%)	2 (0%)	2 (0%)	2 (0%)	1 (0%)	0 (0%)

Values presented are median (Q1 − Q3) or number (percentage). BMI: Body Mass Index.
The intake of food groups is in g/day. Dietary intake at baseline was missing for 80 participants.
[a] Alcohol intake, assessed by the FFQ, was divided over the categories 'none' (<1 g/day), 'moderate' (>1 and ≤ 14 g/day for women and >1 and ≤28 g/day for men)', or 'heavy' (>14 g/day for women and >28 g/day for men).
[b] Current include current smoker and smokers quitted less than a year ago.

rectum (30%). The majority of patients was diagnosed with stage III disease (44%) (Table 1).

Patients with a low DIS (tertile 1), corresponding to a more anti-inflammatory diet, compared to a high DIS (tertile 3), corresponding to a more pro-inflammatory diet, were more often highly educated, had a slightly lower BMI and were more physically active (Table 1; Table 2). In addition, as expected, patients with a low DIS had a higher intake of various vegetables and fruits, coffee, tea and nuts, while patients with a high DIS had a higher intake of red and processed meats, refined grains and starchy vegetables and products high in added sugar (Table 2).

Patients with a low LIS (tertile 1), corresponding to a more anti-inflammatory lifestyle, compared to a high LIS (tertile 3), corresponding to a more pro-inflammatory lifestyle, were more often male and had more often a lower ASA-score (Table 1). Participants with a low LIS were less often heavy alcohol users, were more physically active, had a lower BMI and were less often current smokers. Participants with a low LIS compared to a high LIS had a higher intake of various vegetables and fruits, coffee, tea and nuts (Table 2). The DIS and LIS scores only weakly correlated with each other (r = 0.09).

In total, 363 recurrences occurred, of which 85 locoregional recurrences, 325 distant metastases and 48 people had both a locoregional recurrence as well as a distant metastasis. These recurrences occurred during a median follow up of 4.8 (IQR 2.9–6.9) years. Of the total study population, 453 people deceased during a median follow up of 5.7 (IQR 3.5–8.5) years.

3.1. Dietary and lifestyle inflammation scores in relation to colorectal cancer recurrence and all-cause mortality

A more pro-inflammatory *diet* over time was associated with a higher risk of all-cause mortality ($HR_{continuous}$ 1.09 95%CI 1.02–1.15). No statistically significant association was found between a more pro-inflammatory diet and risk of recurrence (HR $_{continuous}$ 0.95 95%CI 0.89–1.02) (Table 3).

A more pro-inflammatory *lifestyle* was associated with a higher risk of all-cause mortality ($HR_{continuous}$1.24 95%CI 1.05–1.46), but not recurrence (HR $_{continuous}$1.10 95%CI 0.91–1.35) (Table 3).

A stronger association between the DIS and risk of recurrence was observed in patients with a low LIS (tertile 1) (HR $_{continuous}$0.88 95%CI 0.80–0.98) compared to participants with a high LIS (tertile 3) ($HR_{continuous}$0.96 95%CI 0.86–1.07) (Table 4). In addition, the association between the LIS and recurrence seems to be slightly stronger in participants with a high DIS (HR $_{continuous}$ 1.15 95%CI 0.85–1.56) compared to participants with a low DIS (HR $_{continuous}$ 1.00 95%CI 0.71–1.40). The risk of recurrence for the group participants with a high DIS as well as a high LIS (HR 1.06 (0.72; 1.59)) did not differ from the risk of recurrence for participants with a low DIS as well as a low LIS.

A stronger association between the DIS and all-cause mortality risk was observed in participants with a high LIS (tertile 3) (HR $_{continuous}$1.12 95%CI 1.01–1.24) compared to participants with a low LIS (tertile 1) (HR $_{continuous}$0.99 95%CI 0.89–1.10). In addition, a stronger association between the LIS and all-cause mortality was observed in participants with a high DIS (HR $_{continuous}$ 1.28 95%CI 1.01–1.63) compared to participants with a low DIS (HR $_{continuous}$ 1.10 95%CI 0.79–1.53). In line with this, the highest risk of all-cause mortality was observed in the group participants with a high DIS as well as a high LIS (HR 1.62 95%CI 1.16–2.28).

The equally weighted DIS and LIS were associated with all-cause mortality (HR_{DIS} 1.02 95%CI 1.00–1.05, HR_{LIS} 1.20 95%CI 1.09–1.32), but not with risk of recurrence (HR_{DIS} 0.98 95%CI 0.95–1.01, HR_{LIS} 1.09 95%CI 0.97–1.21; Supplementary Table S3).

4. Discussion

A more pro-inflammatory diet as well as a more pro-inflammatory lifestyle score was associated with a higher risk of all-cause mortality, but not with CRC recurrence. When investigating the joint exposure of DIS and LIS, the highest risk of mortality was observed in participants with a pro-inflammatory diet as well as a pro-inflammatory lifestyle. No consistent joint associations of DIS and LIS in relation to recurrence were observed. We used the DIS as a proxy for the inflammatory potential of the diet, since the DIS as opposed to the DII better represent the diet in how it is perceived and consumed and because the DIS as opposed to the EDIP score can be better reproduced and generalized to different populations.

In line with our results, other studies observed a higher risk of mortality with a more pro-inflammatory diet and/or lifestyle. Within the Women's Health Study (n = 31,155 women without CRC at inclusion), the highest compared to the lowest quintiles of DIS and LIS were associated with an increased risk of all-cause mortality ($HR_{DIS\ q5\ vs\ q1}$ 1.07 95%CI 0.97–1.17; $HR_{LIS\ q5\ vs\ q1}$ 1.51 95%CI 1.38–1.66) [19]. In this study, the strongest association for mortality was observed for the highest quintile of both the DIS and LIS compared to the lowest quintile of both the DIS and LIS ($HR_{DIS\&LIS}$ 1.82 95%CI 1.50–2.20) [19]. Furthermore, similar results were observed in the REGARDS study (n = 18,484 Black and Caucasian men and women without CRC at inclusion) ($HR_{DIS\ q5\ vs\ q1}$ 1.32 95%CI 1.18–1.47; $HR_{LIS\ q5\ vs\ q1}$ 1.25 95%CI 1.12–1.38; $HR_{DIS\&LIS}$ 1.91 95%CI

Table 3
Association between the dietary inflammation score (DIS) and lifestyle inflammation score (LIS) over time with recurrence and all-cause mortality in CRC patients; using joint modelling.

	DIETARY INFLAMMATION SCORE	LIFESTYLE INFLAMMATION SCORE
Recurrence (local regional & metastasis)		
No./Events	2421/351	2308/335
Crude HR (95% CI)	0.96 (0.90; 1.03)	1.09 (0.91; 1.29)
Adjusted HR[a] (95% CI)	0.96 (0.90; 1.02)	1.07 (0.90; 1.28)
Adjusted for DIS/LIS HR[b] (95% CI)	0.95 (0.89; 1.02)	1.10 (0.91; 1.35)
All-cause mortality		
No./Events	2722/449	2584/434
Crude HR (95% CI)	**1.09 (1.03; 1.16)**	**1.23 (1.05; 1.43)**
Adjusted HR[a] (95% CI)	**1.09 (1.02; 1.17)**	**1.28 (1.09; 1.49)**
Adjusted for DIS/LIS HR[b] (95% CI)	**1.09 (1.02; 1.15)**	**1.24 (1.05; 1.46)**

Associations were assessed using joint models in which DIS/LIS measured over time (3 time-points) was linked to a Cox proportional hazard regression model. DIS and LIS were entered into the models as a continuous variable.

[a] Adjusted joint models include: age (years), sex (male/female), stage of disease (I/II/III), tumour location (distal colon/proximal colon/rectum), total energy intake (kcal/day) and cohort.

[b] Models additionally adjusted for an equally weighted LIS or DIS.

Table 4
Interactions between DIS & LIS over time with recurrence and all-cause mortality in CRC patients.

CRC recurrence	Low LIS		Intermediate LIS		High LIS		HR (95%CI) for $LIS_{continuous}$ within strata of DIS
	Tertile 1		Tertile 2		Tertile 3		
	No/Events	HR (95%CI)	No/Events	HR (95%CI)	No/Events	HR (95%CI)	
Dietary Inflammation Score							
Low DIS	702/112[a]	1.0 (ref)	612/61[a]	0.65 (0.40; 1.01)	555/88[a]	0.86 (0.55 1.36)	741/102 1.00 (0.71; 1.40)
Medium DIS	648/94[a]	0.78 (0.51; 1.22)	645/80[a]	0.63 (0.40; 1.00)	590/78[a]	**0.59 (0.37; 0.94)**	742/98 0.92 (0.88; 1.33)
High DIS	544/70[a]	0.64 (0.40; 1.05)	638/93[a]	0.94 (0.63; 1.42)	693/122[a]	1.06 (0.72; 1.59)	747/124 1.15 (0.85; 1.56)
HR (95%CI) for $DIS_{continuous}$ within strata of LIS	779/118	**0.88 (0.80; 0.98)**	727/89[a]	1.15 (0.98; 1.35)	748/119	0.96 (0.86; 1.07)	
P for multiplicative interaction p = 0.34							
RERI (95%CI) = 0.02 (−0.02; 0.10)							

All-cause mortality	Low LIS		Intermediate LIS		High LIS		HR (95%CI) for $LIS_{continuous}$ within strata of DIS
	Tertile 1		Tertile 2		Tertile 3		
	No/Events	HR (95%CI)	No/Events	HR (95%CI)	No/Events	HR (95%CI)	
Dietary Inflammation Score							
Low DIS	776/110[a]	1.0 (ref)	659/79[a]	0.79 (0.51; 1.23)	592/89[a]	0.81 (0.51; 1.22)	831/113 1.10 (0.79; 1.53)
Medium DIS	702/105[a]	0.95 (0.63; 1.40)	704/81[a]	0.78 (0.50; 1.18)	635/110[a]	1.13 (0.76; 1.65)	832/131 1.32 (0.96; 1.82)
High DIS	602/109[a]	1.00 (0.67; 1.50)	688/125[a]	1.22 (0.84; 1.76)	742/175[a]	**1.62 (1.16; 2.28)**	838/176 **1.28 (1.01; 1.63)**
HR (95%CI) for $DIS_{continuous}$ within strata of LIS	883/145	0.99 (0.89; 1.10)	810/121	1.13 (0.99; 1.30)	825/162	**1.12 (1.01; 1.24)**	
P for multiplicative interaction p = 0.18							
RERI (95%CI) = 0.05 (−0.02; 0.15)							

Associations in the nine groups based on tertiles of DIS/LIS were assessed using a time-dependent Cox proportional hazard model. Associations in strata were assessed using joint models in which DIS/LIS measured over time (3 time-points) was linked to a Cox proportional hazard regression model.
Models were adjusted for age, sex, stage of disease, tumour location, energy intake and cohort. DIS and LIS were entered into the models as a continuous variable for the analyses in strata.

[a] For each participant, DIS and LIS is measured three times, thus participants can be included in different groups (max 3 times). For example, person X is in group intermediate DIS/high LIS at the first measurement timepoint. This participant will be in this specific group between the first and second time point. At the second measurement timepoint this participant appeared to have improved his/her lifestyle and now is in the intermediate DIS/low LIS group, after which the participant will be in this group between the second and third measurement point. This can change again for the time between the second and third measurement.

1.57–2.33) [32]. Also, within cancer survivors, a more pro-inflammatory diet, assessed using other dietary inflammation scores (i.e. DII, EDIP), seems to be associated with mortality in previous studies [16,17]. Although already quite some studies investigated the association between the inflammatory potential of the diet in relation to CRC outcomes, to our knowledge, our study is the first study investigating the combined inflammatory potential of other lifestyle factors (BMI, smoking, physical activity and alcohol use) in relation to CRC outcomes. In addition, most previous studies investigated the association between dietary inflammation scores and mortality measuring dietary intake only once, while we assessed the DIS and LIS longitudinally. To conclude, based on our and previous research, a more pro-inflammatory diet and lifestyle after diagnosis, seem to be associated with a higher risk of all-cause mortality, especially jointly.

A more pro-inflammatory diet or lifestyle was not associated with recurrence in the current study. In our previous research within the COLON study, which is part of this study population, we observed a higher risk of recurrence with a more pro-inflammatory diet by means of the EDIP score [17], while we did not observe an association between the inflammatory potential of the diet, measured by means of the adapted dietary inflammatory score index (ADII) and CRC recurrence [33]. An explanation for this discrepancy could be that we used a data-driven approach in our previous research with the EDIP score, while in this research and with the ADII we used a hypothesis driven approach. Thus, as a result, the EDIP score, compared to the DIS and ADII, may better reflect the inflammatory potential of the diet for our specific study population. However, comparison with other studies and replication of results is easier with a standardized score. Another reason for the null findings in this study could be measurement error, since no or weak associations between inflammation markers and the DIS were observed, implying that the DIS did not very well capture the inflammatory potential of the diet in our study population. However, after exclusion of outliers (3% of total observations), the DIS was associated with levels of inflammation markers. This suggests that "extreme" values for DIS impaired the functionality, i.e., a higher score reflecting a more pro-inflammatory potential of the diet. Also, associations between the DIS and outcomes changed after exclusion of outliers, either towards the null for recurrence ($HR_{continuous}$ 1.01 95%CI 0.92; 1.11) or a stronger association for all-cause mortality ($HR_{continuous}$ 1.17 95%CI 1.07; 1.28) (Table S2). To the best of our knowledge, no other studies investigated the association between the inflammatory potential of diet and lifestyle in relation to CRC recurrence. In conclusion, it remains unclear whether and, if so, how the inflammatory potential of diet and lifestyle influences CRC recurrence.

The role of pro- and anti-inflammatory diets within cancer recurrence should be further explored before lifestyle intervention studies explicitly targeted towards CRC patients can be executed. Considering the heterogeneity of CRC and its risk of recurrence, investigating the links between a pro-inflammatory diet and lifestyle, and CRC prognosis, while accounting for tumour characteristics, could provide valuable additional perspectives on the connections between diet, lifestyle, and recurrence. To illustrate, a previous study observed an association between a more pro-inflammatory diet and risk of CRC with little or no infiltrated immune-cells into the tumour ($HR_{q5\ vs\ q1}$ 2.60 95%CI 1.60; 4.23), but not with the risk of CRC with intermediate ($HR_{q5\ vs\ q1}$ 0.99 95%CI 0.80; 1.22) or high immune-cell infiltration ($HR_{q5\ vs\ q1}$ 0.91 95%CI 0.57; 1.45) [34]. These results suggest that diet-related inflammation might contribute to development of CRC by suppressing the adaptive anti-tumour immune response [34]. Likewise, associations between the pro-inflammatory diet and CRC prognosis might differ depending on tumour characteristics.

Results of our study suggest that the association between the pro-inflammatory diet and lifestyle and mortality is likely not cancer specific, as we observe an association with risk of all-cause mortality but not with risk of CRC recurrence. Besides, as mentioned previously, the highest risk of mortality was observed in

persons with both a pro-inflammatory diet as well as a pro-inflammatory lifestyle, meaning that especially the combination of both may be detrimental for health. This would imply that, when supported by results of diet and lifestyle intervention studies specifically aimed at decreasing chronic inflammation, recommendations should entail a combination of diet and other lifestyle factors. A more anti-inflammatory diet is a diet high in fruit and vegetables, whole grains, nuts and fish, and low in added sugar, processed meats and fast foods. In addition, based on this study, a more anti-inflammatory lifestyle characterized by being physically active, maintaining a healthy BMI, not smoking and not using alcohol can be advised for CRC survivors, which is in line with the current recommendation for cancer prevention of the World Cancer Research Fund [35].

Limitations of this study include the impaired functionality of the DIS, the unknown causes of death and the limited generalisability of the results. First of all, as mentioned before "extreme" values for DIS seems to impair the functionality of the score. It is likely that the beneficial anti-inflammatory effects of food groups have a certain biological plateau. Therefore, it might be worthwhile to consider a maximum score per food groups. To illustrate, drinking 2000 mL of coffee or tea may provide similar beneficial anti-inflammatory effects as drinking 3000 mL. Theoretically, if the maximum benefit would be reached when drinking 2000 mL, the maximum score could be set to 2000 for coffee and tea. However, more research is needed to define such cut-off values. In addition, it would be of interest to investigate whether the association between the DIS and/or LIS and mortality is colorectal cancer-specific or related to other comorbidities such as cardiometabolic disease. Unfortunately, we had no data available about the cause of death, due to strict privacy regulations in the Netherlands. Finally, even though we used hypothesis-driven inflammation scores as opposed to data-driven scores, generalisation to non-western populations might be limited.

Our study has several strengths. First, we investigated the dietary and lifestyle inflammation scores in a longitudinal way, providing a more accurate estimate of the inflammatory potential of diet and lifestyle. Second, due to the availability of detailed data on diet and other clinical and lifestyle factors, we could adjust for the most plausible confounders, although residual confounding can never be fully excluded. Another strength of the current study is the availability of CRC recurrence data, which was retrieved in a standardised manner by specialised data managers from the national cancer registry.

In conclusion, a more pro-inflammatory diet and lifestyle were associated with an increased risk of all-cause mortality, but not recurrence. The association between a pro-inflammatory diet and lifestyle in relation to CRC recurrence should be further explored, while taking tumour characteristics into account.

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Author contributions

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Ethics approval

Both studies were performed in line with the principles of the Declaration of Helsinki and were approved by a medical ethics committee (COLON: region Arnhem-Nijmegen, 2009–349; PLCRC-PROTECT: University Medical Center Utrecht, 15–770/C). All study participants provided written informed consent.

Data availability statement

Because the data consist of identifying cohort information, some access restrictions apply, and therefore they cannot be made publicly available. Data can be made available upon request. For the COLON study, requests for data can be sent to dr. Fränzel J. B. van Duijnhoven, Division of Human Nutrition and Health, Wageningen University & Research, Netherlands (e-mail: franzel.vanduijnhoven@wur.nl). For the PLCRC-PROTECT study, request for data or access to cohort resources for future collaborative research projects can be sent to the Scientific Committee of PLCRC (email: info@plcrc.nl).

Conflict of interest

The authors declare no conflicts of interests.

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Appendix A. Supplementary data

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