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Original article

The association between the adapted dietary inflammatory index and colorectal cancer recurrence and all-cause mortality

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SUMMARY

Background & aims: The inflammatory potential of the diet has been linked to colorectal cancer (CRC) development and mortality. However, it is unknown whether it is also associated with CRC recurrence. Therefore, the aim of this study was to investigate the associations between the inflammatory potential of the diet and plasma inflammation markers as well as recurrence and all-cause mortality in CRC patients.

Methods: Data of the Colorectal cancer, Observational, LONgitudinal (COLON) study, a prospective cohort study, was used. Dietary intake, assessed using a semi-quantitative food frequency questionnaire, was available for 1478 patients at diagnosis and for 1334 patients six months after diagnosis. Dietary intake data were used to calculate the adapted dietary inflammatory index (ADII). Data about cancer recurrence and all-cause mortality, were assessed through linkage with the Netherlands Cancer Registry and the Municipal Personal Records Database, respectively. The association between the ADII (continuous) and inflammation markers (Interleukin (IL)6, IL8, IL10, Tumor Necrosis Factor (TNF)α, high sensitivity C-reactive protein (hsCRP) and a summary inflammatory z-score), measured with a multiplex assay using electrochemiluminiscence detection, was assessed using quantile regression analyses. Restricted cubic splines (RCS) analyses and multivariable Cox proportional hazard models were used to explore the relationship between the ADII and CRC outcomes.

Results: During a median follow-up time of 3.2 years (Interquartile range (IQR) 2.0–4.1) for recurrence and 4.8 years (IQR 3.5–5.9) for all-cause mortality, 228 recurrences and 279 deaths occurred. A more pro-inflammatory diet at diagnosis as well as six months after diagnosis was associated with higher levels of TNFα, hsCRP and the summary inflammatory z-score. Results of RCS showed no relationship between the ADII and CRC outcomes at both time points. Also results of the Cox proportional hazard models showed no associations between the ADII at both time points and recurrence (HR (95%CI) 0.98 (0.94–1.04) & 0.96 (0.91–1.02) or all-cause mortality (HR (95%CI) 1.03 (0.98–1.07) & 1.00 (0.95–1.05)).

Conclusion: Our study did not show an association between the ADII and recurrence and all-cause mortality in CRC patients. Further research should also take into account molecular tumor subtypes, as the effect of the inflammatory potential of the diet on cancer recurrence and mortality is more likely to be present in tumors with an inflammatory signature.

Clinical Trial Registry numbers and website: The colon study: NCT03191110; clinical trials.gov.

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1. Introduction

Chronic low-grade inflammation is related to the development of several chronic diseases, including cancer [1]. In general, acute inflammation is a useful process and necessary for repair [2]. However, chronic inflammation can interfere with normal homeostasis as it contributes to, among others, excessive cell proliferation and DNA damage [1,3]. Moreover, higher levels of inflammation markers, including C-reactive protein (CRP), Interleukin (IL)6, IL8, IL10 and tumor necrosis factor (TNF)α, have been associated with a worse progression free-, cancer specific- and overall survival [4–11] and a higher risk of CRC recurrence [12]. Diet has a marked effect on inflammation and subsequent health status [13]. A high intake of red and processed meat and a low intake of fruits and vegetables has been linked to cancer development and progression via molecular processes that induce chronic inflammation [13]. Besides, an excess in dietary intake, leading to a higher BMI, also induces chronic inflammation [13]. Overweight and obesity in turn are linked to cancer development and progression [14,15].

Over the years, several indices have been developed to indicate the inflammatory potential of the diet of an individual. The Dietary Inflammatory Index (DII) was first established in 2009 [16] by the University of South Carolina's Cancer Prevention and Control program and updated in 2014 [17]. Also an energy-adjusted DII (E-DII) was developed by that same group [18,19]. This index and other indices, such as the Adapted Dietary Inflammatory Index (ADII) [20], developed by other groups, are based on studies that investigated foods and nutrients in relation to inflammatory markers, such as cytokines. The inflammatory potential of each food or nutrient is determined by its ability to either increase or decrease inflammatory markers, including CRP, IL1β, IL4, IL6, IL10 or TNFα [17,20].

Previous studies have shown that a higher inflammatory potential of the diet is linked to a higher CRC risk, whereas a lower dietary inflammatory potential relates to a lower CRC risk [21,22]. However, only limited studies investigated the association between the inflammatory potential of the diet and clinical outcomes in CRC patients. The studies by Galas et al. showed that the DII assessed at diagnosis can be used as an indicator for longer hospitalization [23] and survival in CRC patients without distant metastasis [24]. Three recent studies in CRC survivors observed a higher risk of all-cause mortality with a more pro-inflammatory diet pre and post diagnosis [25–27]. The association between the inflammatory potential of the diet and CRC recurrence, however, has not been studied yet.

The objective of this study was to investigate whether the adapted dietary inflammatory index, measured at and post diagnosis, is associated with the inflammatory markers IL6, IL8, IL10, TNFα and CRP, as well as with CRC recurrence and all-cause mortality. We expected a more pro-inflammatory potential of the diet to be associated with higher levels of IL6, IL8, TNFα and CRP and lower levels of IL10. In addition, we expected a more pro-inflammatory diet to be associated with a higher risk of CRC recurrence and all-cause mortality.

2. Materials and methods

2.1. Study population

In total, 1766 CRC patients were recruited between August 2010 and December 2017 (Fig. 1) in the Colorectal cancer: Longitudinal, Observational study, on Nutritional and lifestyle factors that may influence CRC tumor recurrence, survival and quality of life –COLON- study. The design of the COLON study (NCT03191110; ClinicalTrials.gov) has been described earlier [28]. In short, newly diagnosed CRC patients were recruited directly after diagnosis in 11 hospitals in the Netherlands and were followed during and after treatment. Men and women above the age of 18 were eligible. Non-Dutch speaking patients, patients with a history of CRC, (partial) bowel resection, chronic inflammatory bowel disease, hereditary CRC syndromes (e.g. Lynch syndrome, Familial Adenomatous Polyposis, Peutz-Jegher), dementia or another mental condition obstructing participation were excluded from the study. The COLON study was approved by the Committee on Research involving Human Subjects, region Arnhem-Nijmegen, the Netherlands (2009–349). All patients signed informed consent.

Patients with missing data on dietary intake at diagnosis (N = 288), missing data on recurrence (n = 84) were excluded leaving 1478 patients for the analyses regarding mortality, and 1394 for the analyses regarding recurrence (Fig. 1). Only samples stored for 2 years or less were analysed, since, cytokines were previously shown to remain stable in plasma for a period up to 2 years of storage at −80 °C [29]. Therefore, data on inflammation markers were not available for 954 patients, leaving 524 patients for the analyses regarding inflammation markers. Twenty-five patients died in the first six months after diagnosis, 14 had a recurrence and for 119 no dietary data was available. In total, 1334, 1242 and 450 patients were included in the analyses regarding mortality, recurrence and inflammation markers six months after diagnosis, respectively.

2.2. Collection of dietary data and calculation of the ADII

Habitual dietary intake was assessed at diagnosis as well as six months after diagnosis using a 204-item semi-quantitative food frequency questionnaire (FFQ). The reference period for the FFQ was the month before diagnosis or the previous month during follow-up. Dietary intake of nutrients was calculated for each food item based on frequency of intake, number of portions and portion size, as well as the type of product. Average daily intakes of nutrients were calculated using the 2011 Dutch food composition table (NEVO) [30]. The food components that were included in the calculation of the ADII were: protein, saturated fatty acids (SFAs), mono unsaturated fatty acids (MUFAs), trans fatty acids, n-3 poly unsaturated fatty acids (PUFAs), n-6 PUFAs, cholesterol, carbohydrate, fibre, alcohol, caffeine, vitamin A, β-carotene, thiamine, riboflavin, niacin, vitamin B6, folate, vitamin B12, vitamin C, vitamin D, vitamin E, iron, magnesium, selenium, zinc, tea and quercetin. The NEVO did not provide information on the caffeine content of food items. Therefore, the estimated caffeine content of 68 mg/100 mL for coffee and 20 mg/100 mL for tea by van Woudenbergh et al. was used [20]. No data was available on type of soft drinks, caffeine content of soft drinks is thus not included in the calculation for caffeine.

Several steps were conducted to calculate the ADII score. First, energy adjustment for each nutrient was done using the residual method [31]. Second, to avoid that the variation in the ADII was solely driven by a few dietary components with a large range in intake, we standardized the individual nutrient intake. Standardization was done by calculating z-scores, which was done by dividing the energy-adjusted intake by the standard deviation of the study population. The standardized energy-adjusted intake was then multiplied by the inflammatory weight score of a specific nutrient (derived from Shivappa et al., 2014; [17]). When the intake of alcohol was above 40 g/day, it was assumed not likely to have an anti-inflammatory effect [20]. Therefore, in these cases an Inflammatory Weight of zero was assigned to alcohol [20]. Finally, all nutrient-specific ADII scores were summed to create the overall ADII score for an individual. Positive ADII scores are considered pro-inflammatory and

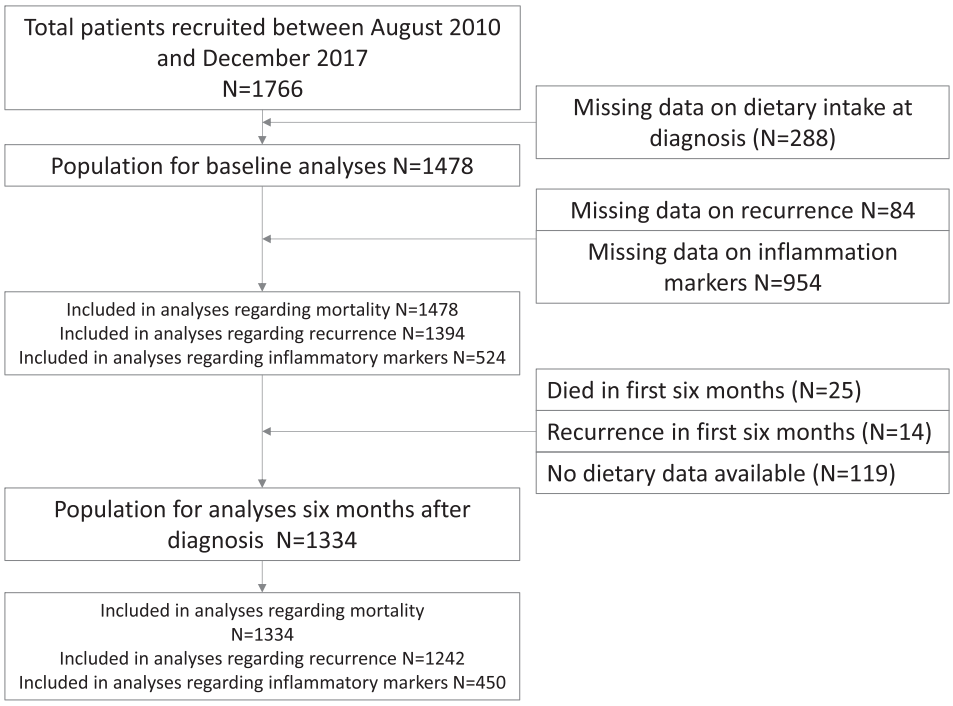

Fig. 1. Flowchart representing patient selection for the current study.

negative ADII scores are considered anti-inflammatory. The contribution of each nutrient to the ADII score for both time points, assessed by using forward linear regression, is shown in supplementary data Table S1. To get more insights in food-groups contributing to either an anti- or pro-inflammatory potential of the diet the median intake of 39 previously defined food groups [32] were compared between tertiles of the ADII scores (Supplementary data Table S2).

2.3. Blood collection and inflammation markers

Blood samples were obtained during a regular clinical visit in the hospital at time of diagnosis and six months after diagnosis. All blood samples in EDTA tubes were centrifuged and aliquoted into plasma and were stored in a freezer at −80 °C until further analysis.

Plasma levels of IL6, IL8, IL10 and TNFα were determined using a custom-made multiplex assay using electrochemiluminiscence detection (Meso Scale Diagnostics, Rockville, Maryland, USA). The analyses were performed following the manufacturers' instructions, and assay plates were analysed on a QuickPlex SQ 120 plate reader (Meso Scale Diagnostics). Only samples stored <2 years were analysed [29], resulting in a subset of 524 samples at diagnosis and 450 six months after diagnosis. The highest inter and intra-batch coefficients of variation for all cytokines were <8%, and reported values deviated no more than 15% from the assigned target values.

High sensitivity C-reactive protein (hsCRP) was measured using an immuno-MALDI mass spectrometry method [33] (BEVITAL, Bergen, Norway). The inter-assay coefficient ranged between 3 and 6%.

Also a combined summary inflammatory z-score for inflammation markers was calculated to cluster conceptually related markers of low-grade inflammation and improve statistical efficiency. This was done by summing the z-scores of each inflammatory marker $\left(\text{inflammatory z} - \text{score} = \frac{-z_{score}(LnIL10)+z_{score}(LnIL8)+z_{score}(LnIL6)+z_{score}(LnTNF\alpha)+z_{score}(LnCRP)}{number\ of\ cytokines}\right)$. The z-score for IL-10 was subtracted as this is a known anti-inflammatory cytokine [34].

2.4. CRC recurrence and all-cause mortality

Information on recurrence was collected from medical records by the Dutch Cancer Registry. Recurrence was defined as a locoregional recurrence or distant metastasis. Information on all-cause mortality was gathered from linkage with the Municipal Personal Record Database.

Follow-up time for recurrence was calculated starting from the date of dietary assessment until date of recurrence or until the date recurrence status was updated (February 2018) or the date of end of follow-up, whichever came first. For all-cause mortality follow-up time was defined starting from the date of dietary assessment until date of death, or until the last date survival status was updated (December 2019), or the date of end of follow-up, whichever came first.

2.5. Demographics, lifestyle and medical data

Information on demographics (age, gender, education), height, weight and lifestyle (smoking, use of non-steroidal anti-inflammatory drugs) was obtained at diagnosis and six months after diagnosis using self-administered questionnaires. Physical activity was assessed using the Short QUestionnaire to ASsess Health-enhancing physical activity (SQUASH) [35].

Clinical data, such as stage of disease, tumor location (colon/rectum), tumor differentiation, histological type, date of start treatment, type of treatment (surgery, neo-adjuvant/adjuvant chemotherapy, radiotherapy) and presence of comorbidities (diabetes, endocrine disorders, cardiovascular, infectious, gastro-

intestinal, muscular and joint, neurologic, pulmonary and urogenital diseases) were derived from the Dutch ColoRectal Audit (DCRA). This nationwide audit was initiated by the association of surgeons of the Netherlands to monitor, evaluate and improve CRC care [36].

2.6. Data analyses

Patient characteristics at diagnosis were described as numbers with percentages or medians with interquartile range (IQR) for the total study population and stratified by tertiles of the ADII. In addition, patients characteristics for patients with and without data available about inflammation markers were compared using descriptive statistics.

The association between the ADII (continuous) and the inflammatory markers (IL6, IL8, IL10, TNFα, and hsCRP) was assessed cross-sectionally at diagnosis and six months after diagnosis using quantile regression analyses [37]. Based on literature the following covariates were added to the model: age, sex, stage of disease, smoking status, BMI, use of NSAIDs and having comorbidities [38–41]. Education level, physical activity, the use of statins, use of supplements and cancer type (colon vs rectal), did not influence the effect estimate, at either one of the two time points, by more than 10% and were thus not taken into account in the models. In a sensitivity analyses, we excluded patients with an acute infection (CRP > 10 μg/ml).

Restricted cubic splines (RCS) analyses were used to explore and visualize the association between the ADII and recurrence and all-cause mortality. The SAS Macro %RCS_Reg vs1.44 was used. Since linear associations were observed, the association between the ADII (continuous) and CRC recurrence and all-cause mortality was assessed using Cox proportional hazard models.

The following covariates were added to the Cox model based on literature: age, sex and stage of disease [24,26]. Smoking status, education level, BMI, physical activity, the use of NSAIDs and statins, use of supplements, tumor location (colon vs rectal) and comorbidities, did not influence the effect estimate by more than 10% at either one of the two time points and were thus not taken into account in the models. Statistical analyses were performed in SAS 9.4 (SAS Institute, Cary NC). P-values < 0.05 were considered statistically significant.

3. Results

Of the included 1478 CRC patients (Fig. 1) 534 (36%) were female (Table 1). The median age was 66 [IQR 61–72] year. Two-third of the patients had colon cancer. The majority of patients had no distant metastases at presentation with 24% stage I, 27% stage II, 41% stage III and 8% stage IV of disease. Patients with a more pro-inflammatory diet (tertile 3) compared with a more anti-inflammatory diet (tertile 1) were more often male, had more often a lower education level, were more often current smokers, were less physical active, and used less often supplements and statins. The inflammatory potential of the diet was rather stable between diagnosis and six months after diagnosis in the study population, as for only 15% the ADII score changed with more than 1 standard deviation (2.7 points). Median change for the total population was 0.1 points (IQR -1.3; 1.2). During a median follow-up of 3.2 years [IQR 2.0–4.1] for recurrence and a median follow-up of 4.8 years [IQR 3.6–5.9] for all-cause mortality, 228 recurrences and 279 deaths occurred. For the post-diagnostic measurements the median follow-up was 2.8 years [IQR 1.7–3.8] for recurrence and 4.6 years [IQR 3.4–5.6] for all-cause mortality, in which 184 recurrences and 210 deaths occurred.

3.1. The inflammatory potential of the diet and plasma inflammation markers

Higher ADII scores at diagnosis as well as six months after diagnosis were statistically significantly associated with higher levels of TNFα (β (95%CI) 0.03 (0.01; 0.05) & 0.04 (0.00; 0.07), respectively) and borderline significant for the summary z-score (β (95%CI) 0.01 (−0.0; 0.02) & 0.01 (−0.00; 0.02), respectively) (Table 2). Six months after diagnosis higher ADII scores were associated with higher levels of hsCRP (β 0.09 95%CI 0.03; 0.14) and IL8 (β 0.09 95%CI -0.00; 0.18). No statistically significant associations between the ADII score and IL6 and IL10 were observed (Table 2). Similar results were observed when excluding patients with an acute infection (CRP>10 μg/ml) (data not shown).

3.2. The inflammatory potential of the diet and CRC recurrence and all-cause mortality

Results of RCS analyses showed no associations between the ADII at diagnosis as well as six months after diagnosis and recurrence and all-cause mortality (Fig. 2).

No associations were observed between the ADII assessed at diagnosis and six months after diagnosis and recurrence and all-cause mortality (Table 3).

4. Discussion

The aim of this study was to investigate the association between the inflammatory potential of the diet, measured by the ADII, and inflammatory markers, as well as recurrence and all-cause mortality in CRC patients. Higher ADII scores were associated with higher levels of TNFα, CRP and a higher summary inflammatory z-score. However, no associations between the ADII and recurrence and all-cause mortality were observed.

In our study the ADII was associated with TNFα, IL8 and hsCRP levels and the summary inflammatory z-score, while no associations were observed between the ADII score and IL6 and IL10. A possible reason for the null-findings for IL6 and IL10 could be the relatively low plasma levels of cytokines and the limited variation of plasma levels within the study population. The study of Woudenbergh et al., did observe a statistically significant association between the ADII score and IL6 and borderline significant associations for hsCRP and TNFα [20]. In that study, inflammation markers were assessed in a larger study population (n = 1024) and larger variations in cytokine levels were observed, for example median and IQR levels for IL6 were 1.4 pg/ml (1.1–2.9) compared to 1.0 pg/ml (0.7–1.6) in our study [20]. Although we did not observe an association between each inflammation marker measured and the ADII score, we are confident that the ADII is reflecting the inflammatory potential of the diet, since it was associated with several inflammation markers in a previous study [20] and our study.

In our study no associations between the ADII at diagnosis as well as six months after diagnosis and CRC recurrence were observed when using the ADII as a continuous variable in the models. To our best knowledge, this is the first study investigating the inflammatory potential of the diet in relation to CRC recurrence. One reason for the lack of an association between the ADII scores and recurrence could be the limited power since we had a short follow-up period (2.8 years) and relatively few events (n = 184). Observational studies with a longer follow-up time and more events are needed to unravel the association

Table 1
Baseline characteristics of CRC patients, stratified for tertiles of the adapted dietary inflammatory index.

	Total population (n = 1478)	ADII Tertiles		
		Tertile 1 (−12.2 to < −1.0) N = 492	Tertile 2 (−1.0 to < 1.2) N = 493	Tertile 3 (1.2 to < 8.5) N = 493
Age (years)	66.2 [61.3–71.6]	66.4 [61.3–70.9]	66.1 [61.6–71.6]	66.2 [60.8–72.4]
Gender, female	534 (36)	226 (46)	169 (34)	139 (28)
BMI (kg/m^2)	26.0 [24.0–28.7]	25.7 [23.8–28.5]	26.4 [24.1–29.0]	26.0 [24.1–28.7]
Unknown	27	7	9	11
Education [a]				
Low	615 (42)	190 (39)	202 (42)	223 (46)
Medium	378 (26)	118 (24)	126 (26)	134 (28)
High	455 (31)	176 (36)	156 (32)	123 (26)
Unknown	30	8	9	13
Smoking habits				
Current	159 (11)	26 (5)	49 (10)	84 (17)
Former	855 (59)	290 (60)	293 (61)	272 (57)
Never	436 (30)	169 (35)	142 (29)	125 (26)
Unknown	28	7	9	12
Physical activity [b] (hours/week)	10.5 [5.0–19.0]	12.0 [6.0–19.0]	10.0 [5.0–19.0]	8.5 [3.6–18.2]
Unknown	2	0	1	1
Supplement use (yes)	646 (44)	263 (53)	222 (45)	161 (33)
Unknown	2	0	1	1
Use of NSAIDs (yes)	183 (12)	60 (12)	53 (11)	70 (14)
	28	7	9	12
Use of Statins (yes)	291 (20)	117 (24)	97 (20)	77 (16)
Type of cancer				
Colon	995 (67)	347 (71)	322 (65)	326 (66)
Rectum	483 (33)	145 (29)	171 (35)	167 (34)
Tumor stage				
I	351 (24)	130 (26)	100 (20)	121 (25)
II	401 (27)	132 (27)	141 (29)	128 (26)
III	610 (41)	198 (40)	211 (43)	201 (41)
IV	112 (8)	31 (6)	39 (8)	42 (9)
Unspecified	4 (0.3)	1 (0.2)	2 (0.4)	1 (0.2)
Comorbidities				
Yes	978 (67)	328 (67)	336 (68)	314 (65)
Unknown	14	5	2	7

BMI: Body Mass Index; NSAIDs; Non-Steroidal-Anti-Inflammatory Drugs.
Values presented are median [quartile 1 – quartile 3] or number (percentage).
[a] Low education was defined as primary school and lower general secondary education; medium as lower vocational training and higher general secondary education; high as high vocational training and university.
[b] Activities with a Metabolic Equivalent score (MET score) ≥ 3 were defined as moderate to vigorous physical activity.

Table 2
Results of quantile regression analysis for the association between the ADII scores and the inflammatory markers.

	n	Crude β-coefficient 95%CI	n	Adjusted[a] β-coefficient 95%CI
At diagnosis				
hs-CRP	1033	0.11 (0.01; 0.21)	1025	0.05 (−0.04; 0.14)
IL-6	522	0.02 (−0.00; 0.05)	519	0.01 (−0.02; 0.03)
IL-8	524	−0.03 (−0.17; 0.12)	521	0.01 (−0.10; 0.13)
IL-10	505	−0.00 (−0.01; 0.00)	502	−0.00 (−0.01; 0.00)
TNF-α	512	0.03 (0.01; 0.05)	509	0.03 (0.01; 0.05)
Inflammatory z-score	520	0.01 (0.00; 0.02)	517	0.01 (−0.00; 0.02)
Six months after diagnosis				
hs-CRP	1058	0.12 (0.08; 0.16)	996	0.09 (0.03; 0.14)
IL-6	448	0.03 (0.00; 0.06)	436	0.02 (−0.01; 0.05)
IL-8	448	0.12 (0.06; 0.19)	436	0.09 (0.00; 0.18)
IL-10	420	−0.00 (−0.01; 0.01)	410	−0.01 (−0.01; 0.00)
TNF-α	450	0.03 (0.00; 0.07)	438	0.04 (0.00; 0.07)
Inflammatory z-score	445	0.02 (0.01; 0.03)	433	0.01 (−0.00; 0.02)

CI: Confidence Interval; Hs-CRP: high sensitive C-reactive protein; IL: Interleukin; TNF: Tumor Necrosis Factor.
Median (Q1-Q3) of the inflammation markers were as follows: hsCRP (mg/L), 2.4 (1.1–5.9); IL6 (pg/ml), 1.0 (0.7–1.6); IL8 (pg/ml), 6.0 (4.1–8.3); IL10 (pg/ml), 0.2 (0.2–0.3); TNFα (pg/ml), 1.9 (1.5–2.5) and inflammatory z-score −0.06 (−0.4; 0.3) at diagnosis. hsCRP (mg/L), 1.7 (0.9–3.8); IL6 (pg/ml), 1.0 (0.7–1.7); IL8 (pg/ml), 5.0 (3.9–6.6); IL10 (pg/ml), 0.3 (0.2–0.5); TNFα (pg/ml), 2.3 (1.9–2.8) and Inflammatory z-score −0.02 (−0.41; 0.35) six months after diagnosis.
[a] Adjusted for age, sex, stage of disease, BMI, smoking status, use of NSAIDs and comorbidities.

between the inflammatory potential of the diet and CRC recurrence.

We observed no statistically significant association between a higher risk of all-cause mortality with a more pro-inflammatory diet. Results from two previous studies investigating the association between the DII and all-cause mortality in CRC patients [24,25] showed either a higher risk with a more pro-inflammatory diet ($HR_{tertile3vs1}$ 1.39, 95% CI 1.13, 1.72) [25] or a lower risk with a more

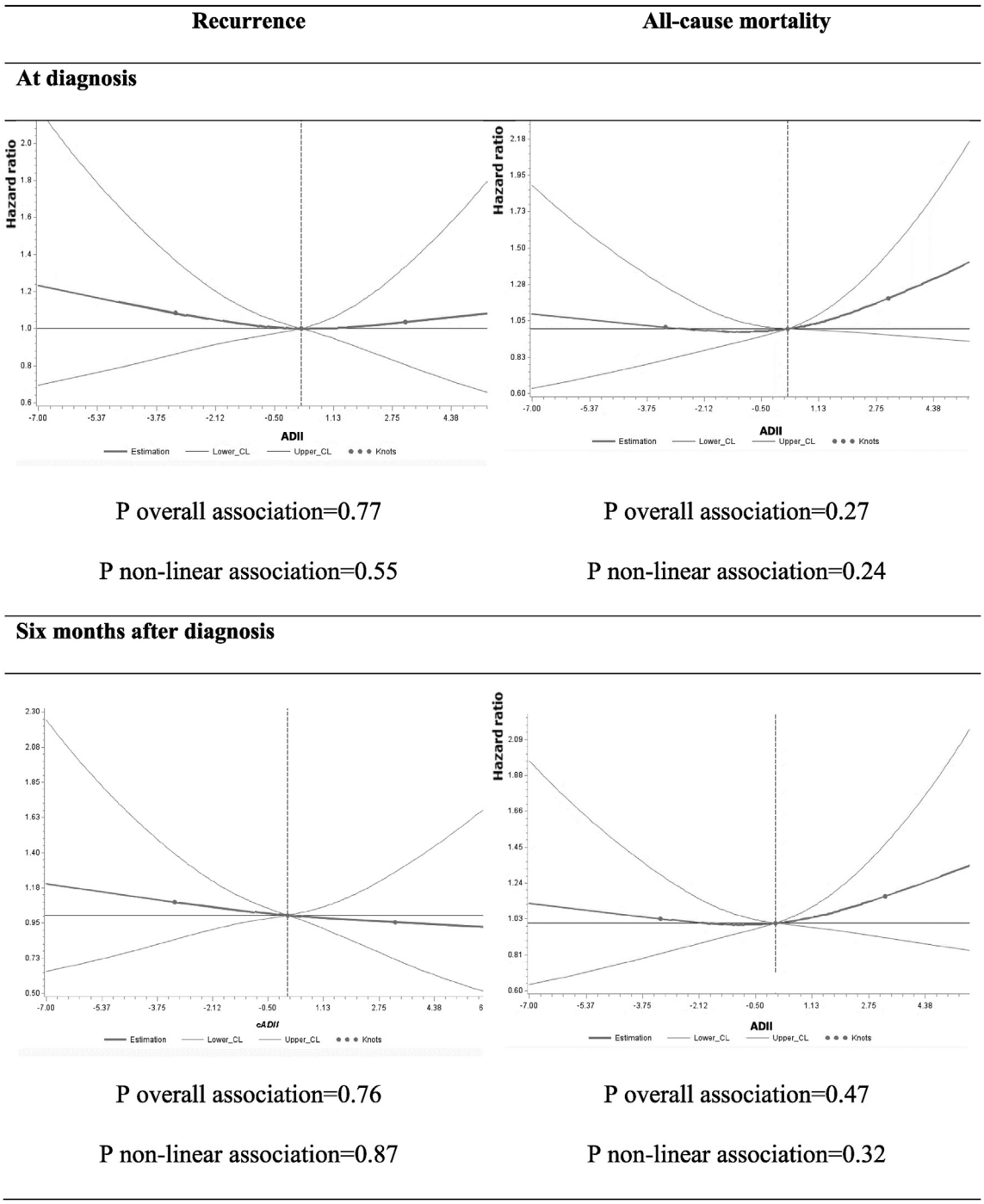

Fig. 2. Visualization of the relationship between the adapted dietary inflammatory index score and CRC recurrence and all-cause mortality using restricted cubic splines analyses. Models were adjusted for age, sex and stage of disease. Knots were placed on the 10th, 50th and 90th percentile, where the 50th percentile was used as the reference.

anti-inflammatory diet at diagnosis ($HR_{low\ vs\ high}$ 0.61, 95% CI 0.38–0.99 [24]). One previous study did observe an association between post-diagnostic and all-cause mortality ($HR_{tertile1vs3}$ = 0.49; 95% CI 0.31–0.79 [27]). While another study observed a non-statistically significant association ($HR_{continuous}$: 1.08; 95% CI: 0.97–1.20 [26]). One reason for the discrepancy in the findings of our study and previous studies could be the difference in follow-up time. In those previous studies, the mean follow-up time was longer (ranging from 5 to 12 years), while our follow-up was 4.8 years for the analyses at diagnosis and 4.6 years for the post-diagnosis analyses. Another difference with previous studies is the DII score used. In most previous studies the DII [17] was used, while we used the ADII [20]. However, we repeated our analyses using the DII. We observed similar results, i.e. no associations with CRC outcomes (Table S3). Thus the different methods used to assess the inflammatory potential of the diet was not an explanation for the discrepancy in findings.

4.1. Further research

More research is needed on how to accurately assess the inflammatory potential of the diet. Investigating the influence of the

Table 3
Hazard ratios and 95% CI for the association between the adapted dietary inflammatory index and recurrence and all-cause mortality in CRC patients.

	ADII at diagnosis	ADII six months after diagnosis
Risk for CRC recurrence[a]		
No./Events	1394/228	1242/184
No. of cases/1000 person years	52	52
Crude HR (95% CI)	1.00 (0.95–1.05)	0.99 (0.94–1.05)
Adjusted HR[b] (95% CI)	0.98 (0.94–1.04)	0.96 (0.91–1.02)
Risk for all-cause mortality		
No./Events	1478/279	1335/210
No. of deaths/1000 person years	39	35
Crude HR (95% CI)	1.05 (1.00–1.10)	1.02 (0.97–1.08)
Adjusted HR[b] (95% CI)	1.03 (0.98–1.07)	1.00 (0.95–1.05)

HR: Hazard Ratio; CI: Confidence Interval.
[a] Recurrence includes loco regional recurrence and/or distant metastasis. For 84 patients, data about recurrence was missing therefore these patients were excluded from the recurrence analyses.
[b] Adjusted for age, sex and stage of disease.

inflammatory potential of the diet on CRC recurrence and survival using a nutrient-based approach provides us valuable information about the direction (protective or harmful) and strength of the inflammatory potential of the diet as a possible risk factor for recurrence and survival in CRC patients. However, the use of an index based on nutrients makes it difficult to translate results to dietary guidelines for cancer patients. Indices based on whole food groups might be more useful for translation to daily life. Therefore, it would also be valuable to investigate the influence of the inflammatory potential of the diet on CRC recurrence and survival using a method based on food groups. In addition, further research should also take into account molecular tumor subtype, since CRC is a heterogeneous disease and the effect of the inflammatory potential of the diet on cancer recurrence (and survival) is more likely to present in tumor with an inflammatory signature [42,43].

4.2. Strengths and limitations

Our study has some important strengths. First of all, to the best of our knowledge this is the first study investigating the association between the inflammatory potential of the diet and CRC recurrence. 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.

Our study also had some limitations. For our ADII calculations, we were only able to include 28 of 45 food components with an inflammatory weight [17]. However, the intake of the remaining 17 components (such as ginger and turmeric) was expected to be low in the Dutch population, and we thus do not expect that this will have influenced our results. The ADII calculated with 28 food components still reflects the inflammatory potential of the diet, as higher ADII scores were associated with higher levels of IL6, sICAM and a summary inflammatory z-score for low grade inflammation in a previous study [20] and with higher levels of CRP, IL8, TNFα and a summary inflammatory z-score in our study. In addition, although not markedly different from the total study population, the subpopulation in which we measured cytokine levels was small ($n = 524$) and the variations in cytokine levels was rather low e.g. 1.0 pg/ml (0.7–1.6) for IL6, which limits the power to observe associations. Finally, we could not assess changes in the inflammatory potential of the diet and CRC outcomes. Because, of the 1334 patients with dietary intake data available at both time points, only 206 (15%) showed changes of the ADII score with more than 1 standard deviation. Also, results of previous research in our groups showed that patients only marginally changed their diets after cancer diagnosis [44]. Investigating, in an intervention study, whether actively changing the inflammatory potential of the diet can improve cancer outcomes such as recurrence and mortality would be a next step to ultimately develop dietary guidelines for CRC patients.

5. Conclusion

A higher ADII score was associated with higher levels of TNFα, CRP and IL8. No associations with recurrence and all-cause mortality in CRC patients were observed. More research in large prospective cohort studies and stratification for molecular subtypes is needed to further unravel the association between the inflammatory potential of the diet and CRC outcomes, especially recurrence. Also investigating changes in the inflammatory potential of the diet and the association with CRC recurrence and mortality merits further investigation.

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Statement of authorship

E Wesselink, LE Staritsky, E Kampman and FJB van Duijnhoven contributed to the design and the conceptualization of this study. E Wesselink, HJW de Wilt, DE Kok, AJMR Geijsen, E.A. Kouwenhoven, R.P. Veenstra, F. Kruyt and E.J. Spillenaar Bilgen and M van Zutphen contributed to recruitment of participants and the data collection and curation. Formal analyses were done by E Wesselink and L Staritsky. The manuscript was drafted by E Wesselink and FJB van Duijnhoven, and all authors critically read and revised the manuscript. All authors approved the final version of the manuscript.

Conflict of interest

The authors reported no conflicts of interest.

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Appendix A. Supplementary data

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