The American Journal of Clinical Nutrition 118 (2023) 865–880

The American Journal of CLINICAL NUTRITION

journal homepage: https://ajcn.nutrition.org/

Original Research Article

Longitudinal associations of macronutrient and micronutrient intake with plasma kynurenines in colorectal cancer survivors up to 12 months posttreatment

Daniëlle D.B. Holthuijsen [1,2,*], Eline H. van Roekel [2], Martijn J.L. Bours [2], Per M. Ueland [3], Stéphanie O. Breukink [4], Maryska L.G. Janssen-Heijnen [2,5], Eric T.P. Keulen [6], Andrea Gsur [7], Dieuwertje E. Kok [8], Arve Ulvik [3], Matty P. Weijenberg [2], Simone J.P.M. Eussen [1,9]

[1] *Department of Epidemiology, CARIM School for Cardiovascular Diseases, Maastricht University, Maastricht, The Netherlands;* [2] *Department of Epidemiology, GROW School for Oncology and Reproduction, Maastricht University, Maastricht, The Netherlands;* [3] *Bevital AS, Bergen, Norway;* [4] *Department of Surgery, GROW School for Oncology and Reproduction, NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht University Medical Centre+, Maastricht, The Netherlands;* [5] *Department of Clinical Epidemiology, VieCuri Medical Centre, Venlo, The Netherlands;* [6] *Department of Internal Medicine and Gastroenterology, Zuyderland Medical Centre Sittard-Geleen, Geleen, The Netherlands;* [7] *Center for Cancer Research, Medical University of Vienna, Vienna, Austria;* [8] *Division of Human Nutrition and Health, Wageningen University & Research, Wageningen, The Netherlands;* [9] *Department of Epidemiology, CAPHRI School for Care and Public Health Research Institute, Maastricht University, Maastricht, The Netherlands*

A B S T R A C T

Background: The tryptophan-kynurenine pathway is increasingly recognized to play a role in health-related quality of life (HRQoL) after cancer. Because tryptophan is an essential amino acid, and vitamins and minerals act as enzymatic cofactors in the tryptophan-kynurenine pathway, a link between diet and kynurenines is plausible.

Objectives: This study aimed to investigate the longitudinal associations of macronutrient and micronutrient intake with metabolites of the kynurenine pathway in colorectal cancer (CRC) survivors up to 12 mo posttreatment.

Methods: In a prospective cohort of stage I–III CRC survivors (n = 247), repeated measurements were performed at 6 wk, 6 mo, and 12 mo post-treatment. Macronutrient and micronutrient intake was measured by 7-d dietary records. Plasma concentrations of tryptophan and kynurenines were analyzed using liquid chromatography tandem mass spectrometry (LC/MS-MS). Longitudinal associations were analyzed using linear mixed models adjusted for sociodemographic, clinical, and lifestyle factors.

Results: After adjustment for multiple testing, higher total protein intake was positively associated with kynurenic acid (KA) (β as standard deviation [SD] change in KA concentration per 1 SD increase in total protein intake: 0.12; 95% CI: 0.04, 0.20), xanthurenic acid (XA) (standardized β: 0.22; 95% CI: 0.11, 0.33), 3-hydroxyanthranilic acid (HAA) (standardized β: 0.15; 95% CI: 0.04, 0.27) concentrations, and the kynurenic acid-to-quinolinic acid ratio (KA/QA) (standardized β: 0.12; 95% CI: 0.02,0.22). In contrast, higher total carbohydrate intake was associated with lower XA concentrations (standardized β: −0.18; 95% CI: −0.30, −0.07), a lower KA/QA (standardized β: −0.23; 95% CI: −0.34, −0.13), and a higher kynurenine-to-tryptophan ratio (KTR) (standardized β: 0.20; 95% CI: 0.10, 0.30). Higher fiber intake was associated with a higher KA/QA (standardized β: 0.11; 95% CI: 0.02, 0.21) and a lower KTR (standardized β: −0.12; 95% CI: −0.20, −0.03). Higher total fat intake was also associated with higher tryptophan (Trp) concentrations (standardized β: 0.18; 95% CI: 0.06, 0.30) and a lower KTR (standardized β: −0.13; 95% CI: −0.22, −0.03). For micronutrients, positive associations were observed for zinc with XA (standardized β: 0.13; 95% CI: 0.04, 0.21) and 3-hydroxykynurenine (HK) (standardized β: 0.12; 95% CI: 0.03, 0.20) concentrations and for magnesium with KA/QA (standardized β: 0.24; 95% CI: 0.13, 0.36).

Abbreviations: AA, Anthranilic acid; BMI, Body mass index; CRC, Colorectal cancer; FDR, False discovery rate; HAA, 3-Hydroxyanthranilic acid; HK, 3-Hydroxykynurenine; HKr, Hydroxykynurenine ratio (3-hydroxykynurenine: [kynurenic acid + xanthurenic acid + 3-hydroxyanthranilic acid + anthranilic acid]); HRQoL, Health-related quality of life; IQR, Interquartile range; KA, Kynurenic acid; KA/QA, Kynurenic acid-to-quinolinic acid ratio; KTR, Kynurenine-to-tryptophan ratio; Kyn, Kynurenine; LC/MS-MS, Liquid chromatography tandem mass spectrometry; LPA, Light physical activity; MVPA, Moderate-to-vigorous physical activity; PA, 4-pyridoxic acid; Par, Ratio (4-pyridoxic acid: ([pyridoxal + pyridoxal 5'-phosphate]); Pic, Picolinic acid; PL, Pyridoxal; PLP, Pyridoxal 5'-phosphate; QA, Quinolinic acid; Trp, Tryptophan; XA, Xanthurenic acid.

* Corresponding author.
E-mail address: d.holthuijsen@maastrichtuniversity.nl (D.D.B. Holthuijsen).

https://doi.org/10.1016/j.ajcnut.2023.08.003
Received 15 February 2023; Received in revised form 20 July 2023; Accepted 7 August 2023; Available online 12 October 2023

Conclusions: Our findings show that intake of several macronutrients and micronutrients is associated with some metabolites of the kynurenine pathway in CRC survivors up to 12 mo posttreatment. These results may be relevant for enhancing HRQoL after cancer through potential diet-induced changes in kynurenines. Further studies are necessary to confirm our findings.

Keywords: colorectal cancer survivorship, macronutrient intake, micronutrient intake, dietary supplements, plasma kynurenines

Introduction

Population aging, early detection, and improved treatments are leading to an increased number of colorectal cancer (CRC) survivors worldwide [1–3]. Even years after diagnosis, CRC survivors often report long-term adverse side effects of CRC and/or its treatment, including fatigue, cognitive impairment, depression, and anxiety, all of which negatively affect their health-related quality of life (HRQoL) [4–6]. It is important to develop strategies that improve patients' HRQoL after cancer. A healthy diet is increasingly attributed to better HRQoL outcomes [7,8]. However, underlying metabolic mechanisms explaining this relation are unclear.

The tryptophan-kynurenine pathway, a catabolic process in which the essential amino acid tryptophan (Trp) is converted to kynurenine (Kyn) instead of serotonin, is increasingly recognized to play an important role in HRQoL after cancer [9–12]. Inflammation and chronic stress activate the enzyme indoleamine 2,3-dioxygenase (IDO), causing a shift from Trp metabolism to Kyn production [9,13,14], resulting in an increase of the kynurenine-to-tryptophan ratio (KTR) [15,16]. Kyn is then broken down into several downstream metabolites, such as 3-hydroxykynurenine (HK), kynurenic acid (KA), xanthurenic acid (XA), anthranilic acid (AA), 3-hydroxyanthranilic acid (HAA), picolinic acid (Pic) and quinolinic acid (QA), collectively called kynurenines. Evidence suggests that some of these kynurenines have antioxidative, anti-inflammatory, and neuroprotective characteristics (i.e., KA and Pic), some may have pro-oxidative, proinflammatory, and neurotoxic properties (i.e., HK and QA), whereas evidence of the roles of XA, AA, and HAA are inconclusive [9,17,18].

Considering that Trp is an essential amino acid, it is plausible that protein intake is associated with circulating concentrations of metabolites of the kynurenine pathway. An intervention study in healthy subjects demonstrated that a high-protein diet (>25% of energy intake derived from protein) for 2 wk was associated with higher plasma concentrations of KA and QA but not with Kyn, compared with a low-protein diet (9% of energy intake derived from protein) [19]. In the context of other macronutrients, a study in children with refractory epilepsy showed that a ketogenic diet, i.e., a diet high in fat and low in carbohydrates, was associated with lower plasma concentrations of Kyn, higher concentrations of KA and a higher KA/QA ratio [20]. Another cross-sectional study in healthy humans observed a positive association between total fat intake and KTR [21]. In addition, there is evidence that intake of micronutrients is associated with plasma kynurenines, as vitamins and minerals act as enzymatic cofactors in the kynurenine pathway [22,23]. A study in healthy subjects found that both vitamin B2 status (riboflavin) and vitamin B6 status (pyridoxal 5'-phosphate [PLP]) were positively associated with Trp and most kynurenines but inversely associated with Kyn, HK, and KTR [23].

Despite some preliminary evidence for an association between the intake of these macronutrients and micronutrients and plasma kynurenines in a variety of populations, there is currently no evidence for such associations in CRC survivors. Therefore, we aimed to investigate the longitudinal associations between macronutrient and micronutrient intake and plasma kynurenines in CRC survivors up to 12 mo post-treatment. Understanding a possible association of macronutrient and micronutrient intake with plasma kynurenines is important, as it may provide new insights into how diet-induced changes in plasma kynurenines may affect HRQoL in CRC survivors.

Methods

Study design and population

This study is embedded within the Energy for life after ColoRectal cancer (EnCoRe) study, an ongoing multicenter prospective cohort study among CRC survivors in the Netherlands. Since 2012, men and women aged >18 y and diagnosed with stage I–III CRC at the Maastricht Medical Center+, VieCuri Medical Center, and Zuyderland Medical Center were included in the EnCoRe study. Exclusion criteria were stage IV CRC, living outside the Netherlands, unable to understand and speak Dutch, or the presence of comorbidities hampering successful participation (e.g., Alzheimer's disease). The EnCoRe study has been approved by the Medical Ethics Committee of the University Hospital Maastricht and Maastricht University, the Netherlands (Netherlands Trial Register number NL6904) [24]. All participants signed informed consent.

Data collection

Data available up to November 1, 2016, were used for the analyses in the present study because the metabolites of the kynurenine pathway have been assessed for participants followed-up until this date [25]. Research dietitians collected data during home visits at 6 wks (n = 247), 6 mo (n = 199), and 12 mo (n = 162) posttreatment (Figure 1). The follow-up participation rate was >90%, and 14 participants had died before November 1, 2016. The decrease in numbers as the follow-up time increases is primarily because not all participants with data at diagnosis had reached these follow-up measurements by November 1, 2016.

Macronutrient and micronutrient intake

To obtain data on dietary intake, participants filled out a structured dietary record on 7 consecutive days at all posttreatment measurements. Participants reported on consumed meals, foods, and beverages, with details on brand names, portion sizes, and preparation in these dietary records. Oral and written instructions were given on how to fill in the dietary records. Trained dietitians checked completed dietary records on return. Participants were contacted by telephone to clarify any incomplete or contradicting answers. Daily nutrient intake was calculated using food calculation software (Compl-eat, Wageningen University, the Netherlands) based on the Dutch food composition database (NEVO-2011). Macronutrient intake of protein, including animal-based and plant-based protein, carbohydrates, including mono- and disaccharides and polysaccharides, fiber, and fat, including saturated and unsaturated fats, was assessed. Alcohol was not included in the current analyses as a macronutrient exposure, as previous research

has examined associations between alcohol intake and plasma kynurenines [8]. Micronutrient intake of vitamin B2 (mg/d), vitamin B6 (mg/d), iron (mg/d), including heme iron and nonheme iron, magnesium (mg/d), zinc (mg/d), and copper (mg/d) was determined, as these nutrients are available in the Dutch food composition table.

Detailed information on supplement use was collected by research dietitians. Pretreatment participants were asked about the supplements they had used in the past year. Posttreatment, participants were asked about changes in their supplement use since the prior home visit. Participants were asked to show the original package to list details, including (brand) name of the supplement, dose, and frequency of use, months that the supplement was used, start date, stop date, ingredients, and motivations for use. Based on the dosage and frequency of a supplement used, the additional intake of micronutrients from supplements was calculated. To calculate total micronutrient intake, we added micronutrient intake from supplements to micronutrient intake from food.

Plasma markers

Fasting blood samples were drawn during home visits at all 3 follow-up measurements. Blood samples were collected in 8.5-mL EDTA tubes, and plasma was derived after centrifugation at 2000 g_{max} for 10 min. EDTA plasma samples were divided into 500 µl aliquots and stored at −80°C within 4 h after blood draw until analysis. Samples were shipped on dry ice to the laboratory of Bevital in Bergen, Norway (www.bevital.no). Plasma concentrations of 9 metabolites of the kynurenine pathway, including Trp, Kyn, HK, KA, XA, AA, HAA, Pic, and QA were analyzed using liquid chromatography tandem mass spectrometry (LC/MS-MS) [26]. The coefficients of within-day and between-day variation for Trp and kynurenines have been previously established as 3.0%–9.5% and 5.7%–16.9%, respectively [27]. Creatinine, an index of renal function, and neopterin, a marker for immune system activation, were analyzed by LC/MS-MS as well [28]. In addition, plasma concentrations of riboflavin and PLP were assessed as the most used plasma markers of vitamin B2 and vitamin B6 status, respectively. Furthermore, we included the PAr index as an indicator of vitamin B6 catabolism, calculated as the ratio of 4-pyridoxic acid (PA) divided by the sum of PLP and pyridoxal (PL) [29,30]. Riboflavin, PLP, PA, and PL were also analyzed using LC/MS-MS [26].

Several relevant ratios of individual kyunrenine concentrations were examined. The kynurenine-to-tryptophan ratio (KTR), a well-established marker of inflammation and IDO activation, was calculated by dividing the plasma concentration of Kyn (in nmol/L) by the plasma concentration of Trp (in µmol/L) [15,16]. The HK ratio (HKr), a functional marker of vitamin B6 status [27,31], was calculated as the ratio of HK (in nmol/L) to the sum of KA (in nmol/L), XA (in nmol/L), AA (in nmol/L), and HAA (in nmol/L). The kynurenic acid-to-quinolinic acid ratio (KA/QA), a ratio between the antagonist (KA) and agonist (QA) of N-methyl-D-aspartate receptor, was calculated by dividing the plasma concentration of KA (in nmol/L) by the plasma concentration of QA (in nmol/L) [32].

Sociodemographic, clinical, and lifestyle variables

Sociodemographic characteristics, including age and sex, and clinical information, such as cancer stage, tumor site, and cancer therapy, were obtained from medical records or clinical registries. Self-reported data were collected on the highest attained education level at diagnosis, which was categorized as low (no education, primary education, or basic vocational education), medium (advanced vocational education or senior secondary vocational education), and high (senior secondary general education, higher professional education, or academic higher education). Self-reported presence of stoma, current smoking status (current, former, or never), and presence of comorbidities were assessed at all follow-up measurements. Research dietitians measured the participants' height and weight during home visits to calculate BMI as weight/height^2 (kg/m^2). The Short QUestionnaire to ASsess Health-enhancing physical activity as used to determine light physical activity (LPA) and moderate-to-vigorous physical activity (MVPA) in hours/week at all follow-up measurements [33,34]. Hours/week in LPA and MVPA were summed to calculate total physical activity time. Total energy intake (kcal/d) was retrieved from the 7-d dietary records.

Statistical analyses

Descriptive statistics (means and SD for normally distributed variables, medians and interquartile ranges [IQR] for skewed variables, and frequencies and percentages for categorical variables) were calculated to describe participant characteristics, including macronutrient and micronutrient intake and plasma kynurenine concentrations and ratios.

Linear mixed models were used to assess changes in macronutrient and micronutrient intake and plasma Trp and kynurenine concentrations and ratios over time and to assess longitudinal associations of macronutrient and micronutrient intake in relation to plasma Trp and kynurenine concentrations and their ratios up to 12 mo post-CRC treatment. A random intercept for each participant was added to all models. The use of random slopes was tested with a likelihood-ratio test; random slopes were added when the model fit significantly improved. Intraindividual and interindividual associations, also referred to as within and between associations, were disaggregated by adding individual deviations from the person-mean value to estimate intraindividual associations (i.e., within-participant changes over time) and adding centered person-mean values to the model to estimate interindividual associations (i.e., average differences between participants over time), respectively [35]. Both exposure and outcome variables were standardized using the average of the SD across all follow-up measurements to allow direct comparisons of the regression coefficients regardless of the exposures and outcomes modeled.

Models were adjusted for fixed variables, including age at enrollment (years), sex (male or female), chemotherapy (yes or no), and time-varying variables, including creatinine (µmol/L) as an index of renal function, number of comorbidities (0, 1, or ≥2), presence of stoma (yes or no), time since end of treatment (weeks), BMI (kg/m^2), total physical activity (sum of LPA and MVPA in hours/week), and smoking status (current, former, or never). Education level (low, medium, or high) and radiotherapy (yes or no) were additionally tested using the 10% change-in-estimate method [36]; only education level led to a >10% change in β estimate and was, therefore, included in the fully adjusted model. Potential confounders were identified a priori based on literature [37] and the hypothesized relations with the exposure and outcome variables.

Analyses with macronutrient intake as exposure were additionally adjusted for energy intake using the all-components approach, in which all sources of energy were individually (e.g., carbohydrates, fats, proteins, fibers, and alcohol) added to the model as continuous variables in kcal/d [38]. The β-coefficient can be interpreted as the change in SD units of kynurenine concentration by an increase in 1SD macronutrient intake (kcal/d), holding energy intake (kcal/d) from remaining macronutrients constant. Analyses with micronutrient intake as exposure were adjusted for alcohol intake and energy intake using the standard

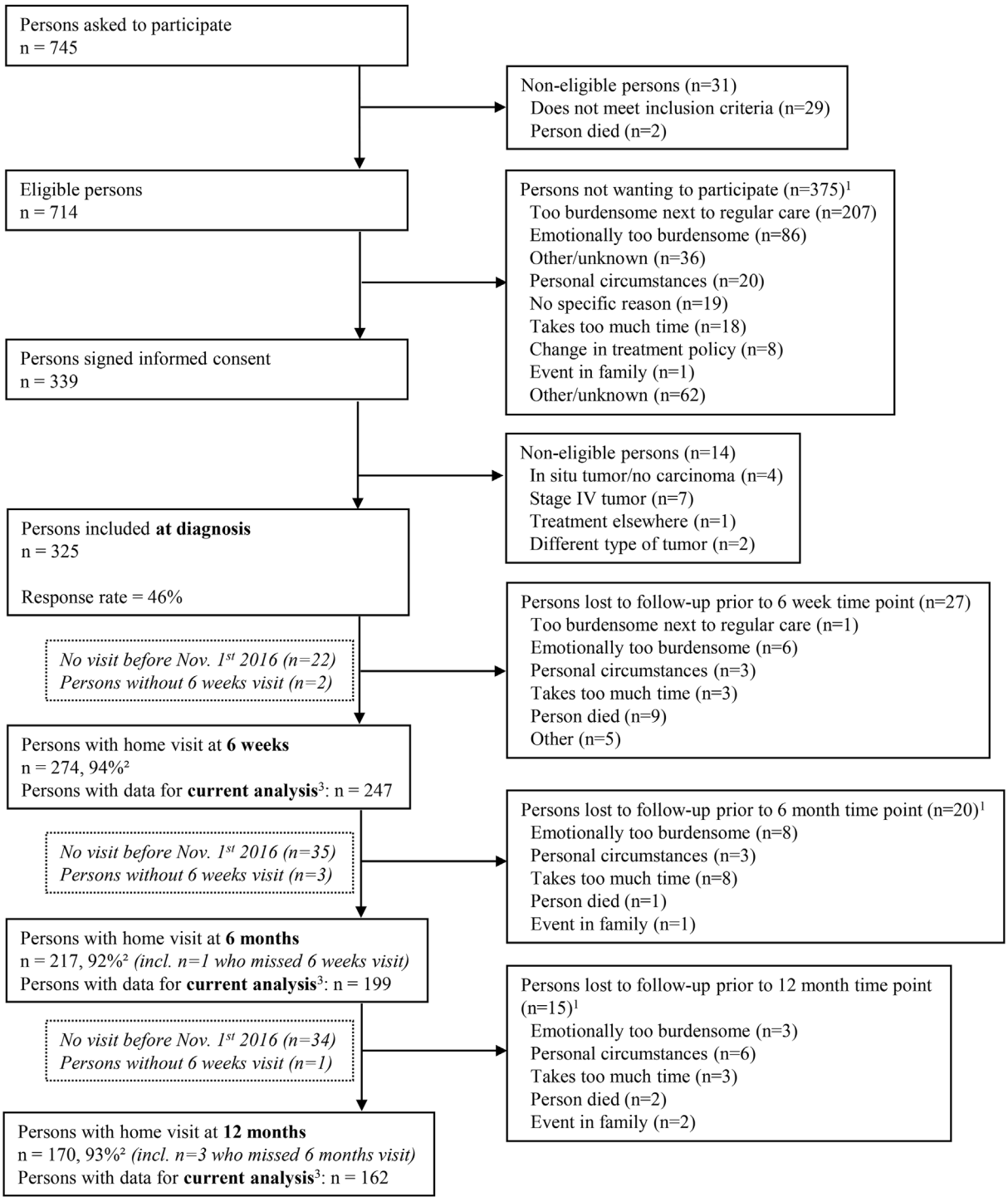

FIGURE 1. Flow diagram of the inclusion of participants within the EnCoRe study and the number of posttreatment measurements included in the analyses presented in this paper. Data from home visits performed before November 1, 2016 were included in the analyses. [1]Totals do not add up because some individuals reported multiple reasons for non-participation. [2] Response rate = (persons with home visits)/(persons with home visits+persons lost to follow-up – persons died). The declining number of participants at the subsequent time points is because not all participants included at diagnosis from April 2012 onward had reached these time points in November 2016. [3]Because the current analysis was focused on dietary intake and kynurenines after colorectal cancer treatment, only posttreatment measurements with available data on dietary intake, kynurenines, and covariates were included. The number of participants with available data on macro- and micronutrient intake and kynurenine were $n = 256$ and $n = 251$ at 6 wk, $n = 236$ and $n = 206$ at 6 mo, and $n = 221$ and $n = 166$ at 12 mo posttreatment, respectively.

model, in which alcohol intake and energy intake were added as a continuous variable to the model in g/d and kcal/d, respectively [38]. The β-coefficient can be interpreted as the change in SD units of kynurenine concentration by an increase in 1 SD micronutrient intake (mg/d), holding alcohol intake (g/d), and energy intake (kcal/d) constant.

To adjust for multiple testing for each macronutrient-kynurenine and micronutrient-kynurenine combination, false discovery rate (FDR) adjustment of *P* values using the Benjamini-Hochberg method was applied (q-values of <0.05 were considered significant) [39].

As only ~21% of our study population ($n = 52$) at 6 wk posttreatment documented the use of supplements containing at least one vitamin or mineral of interest, sensitivity analyses were conducted on the association between total micronutrient intake (sum of micronutrient intake from food plus micronutrient intake from supplements) and plasma kynurenine concentrations and their ratios, to determine whether additional micronutrient intake from supplements enhances the effect on plasma kynurenine.

All analyses were conducted using Stata (version 17.0, StataCorp).

Results

Participant characteristics

A total of 247 participants were included in the analyses with available data on macronutrient and micronutrient intake and plasma kynurenines at 6 wk, 6 mo, and 12 mo posttreatment. At 6 wk posttreatment, 69% were men, and the mean age was 66.7 (SD 9.1) y **(Table 1)**. Approximately one-third of the study population (32%) was diagnosed with stage I CRC, 24% with stage II CRC, and 44% with stage III CRC. Most participants were diagnosed with colon cancer (61%), whereas 39% were diagnosed with rectal cancer. Almost all participants had surgery (90%), and 38% and 28% received chemotherapy and/or radiotherapy, respectively.

Macronutrient and micronutrient intake and plasma concentrations of metabolites of the kynurenine pathway from 6 wk to 12 mo posttreatment

Intake of total protein, carbohydrates, fat, vitamin B2, iron, copper, and zinc changed significantly over time from 6 wk posttreatment to 12 mo posttreatment, whereas intake of fiber, vitamin B6, and magnesium remained stable over time (Table 2). Plasma concentrations of Trp, KA, Pic, XA, and KA/QA ratio increased significantly, whereas Kyn, QA, KTR, and HKr decreased significantly from 6 wk posttreatment to 12 mo posttreatment (Table 2).

Longitudinal associations of macronutrient intake with metabolites of the kynurenine pathway

Linear mixed models adjusted for sociodemographic, clinical, and lifestyle factors revealed numerous statistically significant associations between macronutrient intake and metabolites and ratios of the kynurenine pathway **(Table 3)**. After adjustment for multiple testing, some of the fully adjusted associations lost statistical significance, and only those associations that remained statistically significant are described further below.

Higher total protein intake was associated with higher concentrations of KA (standardized β: 0.12; 95% CI: 0.04, 0.20), XA (standardized β: 0.22; 95% CI: 0.11, 0.33), HAA (standardized β: 0.15; 95% CI: 0.04, 0.27), and a higher KA/QA ratio (standardized β: 0.12; 95% CI: 0.02, 0.22) (Table 3 and Figure 2). The standardized beta can be interpreted as the amount of SD change in kynurenine concentration or ratio per 1 SD higher protein intake. When looking at the type of protein, animal protein was positively associated with XA (standardized β: 0.20; 95% CI: 0.10, 0.30) and HAA concentrations (standardized β: 0.12; 95% CI: 0.03, 0.22), whereas intake of plant proteins was associated with a higher KA/QA ratio (standardized β: 0.19; 95% CI: 0.06, 0.32). The associations for total protein with KA, XA, and HAA, animal protein with XA and HAA, and plant protein with the KA/QA ratio appeared to be driven by intraindividual associations, indicating that a higher protein intake over time in the period from 6 wk to 12 mo

TABLE 1
Sociodemographic, lifestyle, and clinical characteristics of participants included in the Energy for life after ColoRectal cancer (EnCoRe) study at 6 wk, 6 mo, and 12 mo posttreatment

	6 wk post treatment ($n = 247$)[1]	6 mo post treatment ($n = 199$)[1]	12 mo posttreatment ($n = 162$)[1]
Sex (male), n (%)	170 (68.8)	131 (65.8)	111 (68.5)
Age (y), mean (SD)	66.7 (9.1)	67.6 (9.5)	67.7 (9.2)
Tumor site, n (%)			
Colon	151 (61.1)	123 (61.8)	96 (59.3)
Rectum	96 (38.9)	76 (38.2)	66 (40.7)
Cancer stage, n (%)			
Stage I	80 (32.4)	64 (32.2)	50 (30.9)
Stage II	58 (23.5)	49 (24.6)	47 (29.0)
Stage III	109 (44.1)	86 (43.2)	65 (40.1)
Cancer treatment, n (%)			
Surgery (yes)	221 (89.5)	181 (91.0)	145 (89.5)
Chemotherapy (yes)	93 (37.7)	75 (37.7)	58 (35.8)
Radiotherapy (yes)	68 (27.5)	54 (27.1)	47 (29.0)
Number of comorbidities, n (%)			
0 comorbidities	50 (20.2)	43 (21.6)	41 (25.5)
1 comorbidity	60 (24.3)	47 (23.6)	38 (23.6)
≥2 comorbidities	137 (55.5)	109 (54.8)	82 (50.9)
Stoma (yes), n (%)	78 (31.7)	42 (21.1)	26 (16.1)
BMI (kg m^2), mean (SD)	27.8 (4.4)	28.3 (4.4)	28.5 (4.6)
Educational level, n (%)			
Low	62 (25.2)	51 (25.8)	35 (21.7)
Medium	98 (39.8)	82 (41.4)	70 (43.5)
High	86 (35.0)	65 (32.8)	56 (34.8)
Smoking status, n (%)			
Never	83 (33.9)	62 (31.3)	46 (28.6)
Former	140 (57.1)	123 (62.1)	99 (61.5)
Current	22 (8.9)	13 (6.6)	16 (9.9)
Physical activity, median (IQR)			
LPA (h/wk)	7.0 (12.5)	10.0 (17.3)	10.5 (19.0)
MVPA (h/wk)	7.2 (11.7)	9.0 (11.0)	9.8 (13.5)
Total PA (h/wk)	18.3 (21.0)	21.0 (22.0)	23.9 (24.0)
Total energy intake (kcal/d), mean (SD)	2103.2 (508.3)	2003.8 (464.2)	2016.7 (486.1)
Use of supplements containing (yes), n (%)			
Vitamin B2	36 (14.6)	30 (15.1)	26 (16.1)
Vitamin B6	35 (14.2)	31 (15.6)	28 (17.3)
Magnesium	33 (13.4)	25 (12.6)	22 (13.6)
Iron	34 (13.8)	26 (13.1)	23 (14.2)
Copper	28 (11.3)	21 (10.6)	18 (11.1)
Zinc	31 (12.6)	23 (11.6)	20 (12.4)
Creatinine (μmol/L), mean (SD)	83.6 (18.8)	87.7 (22.8)	87.8 (22.5)
Neopterin (nmol/L), median (IQR)	15.9 (10.7)	15.3 (10.1)	14.8 (8.9)

Abbreviations: LPA, light-intensity physical activity; MVPA, moderate-to-vigorous physical activity; PA, physical activity; IQR, interquartile range.
[1] Percentages may not add up to 100 due to rounding.

TABLE 2
Macronutrient and micronutrient intake, plasma concentrations of vitamin B2 and B6 markers, and plasma kynurenine concentrations and ratios of participants included in the Energy for life after ColoRectal cancer (EnCoRe) study at 6 wk, 6 mo, and 12 mo posttreatment

	6 wk posttreatment ($n = 247$)	6 mo posttreatment ($n = 199$)	12 mo posttreatment ($n = 162$)	P value
Macronutrient intake				
Protein (g/d – kcal/d)	78.3 (18.9) – 313.1 (75.7)	75.2 (16.0) – 301.0 (63.8)	75.9 (16.7) – 303.6 (66.9)	0.017*
Animal-based protein (g/d – kcal/d)	47.0 (15.6) – 188.0 (62.2)	44.5 (12.1) – 178.0 (48.4)	44.6 (13.3) – 178.6 (53.2)	0.011*
Plant-based protein (g/d – kcal/d)	31.3 (8.6) – 125.1 (34.5)	30.8 (8.2) – 123.1 (32.8)	31.4 (8.4) – 125.6 (33.4)	0.853
Carbohydrates (g/d – kcal/d)	226.8 (57.0) – 907.4 (228.2)	213.1 (53.8) – 852.6 (215.1)	215.4 (58.5) – 861.8 (233.9)	<0.001*
Mono- and disaccharides (g/d – kcal/d)	92.7 (32.9) – 370.9 (131.6)	83.2 (32.1) – 333.0 (128.4)	83.3 (37.0) – 333.1 (147.8)	<0.001*
Polysaccharides (g/d – kcal/d)	134.0 (35.9) – 536.0 (143.7)	129.8 (33.9) – 519.3 (135.7)	132.1 (34.1) – 528.3 (136.4)	0.123
Fibers (g/d – kcal/d)	21.0 (5.9) – 41.9 (11.7)	21.0 (6.4) – 41.9 (12.7)	21.1 (6.1) – 42.3 (12.3)	0.610
Fats (g/d – kcal/d)	82.2 (24.7) – 740.0 (222.2)	79.1 (22.3) – 711.5 (200.5)	78.0 (21.7) – 702.0 (195.2)	0.009*
Saturated fats (g/d – kcal/d)	30.2 (10.3) – 271.5 (92.4)	29.5 (9.9) – 265.7 (88.8)	28.7 (10.0) – 258.4 (89.6)	0.033*
Unsaturated fats (g/d – kcal/d)	44.6 (14.2) – 401.3 (127.6)	42.4 (12.4) – 381.2 (111.3)	42.4 (12.0) – 381.7 (108.3)	0.017*
Micronutrient intake				
Vitamin B2				
Dietary intake (mg/d)	1.3 (0.4)	1.2 (0.4)	1.2 (0.4)	<0.001*
From supplements[1] (mg/d)	5.2 (9.6)	7.8 (18.1)	6.4 (10.4)	0.611
In plasma (nmol/L)	19.0 (54.3)	22.4 (54.0)	21.0 (49.4)	0.097
Vitamin B6				
Dietary intake (mg/d)	1.8 (0.6)	1.7 (0.7)	1.8 (0.6)	0.084
From supplements[2] (mg/d)	4.0 (5.5)	4.8 (6.1)	5.2 (6.5)	0.112
In plasma (nmol/L)	48.1 (42.5)	52.1 (42.8)	51.0 (41.0)	0.415
Magnesium				
Dietary intake (mg/d)	316.1 (82.3)	306.9 (84.2)	311.8 (87.7)	0.193
From supplements[3] (mg/d)	513.2 (893.7)	25.4 (480.1)	276.8 (528.1)	0.121
Iron				
Dietary intake (mg/d)	11.3 (3.3)	10.8 (3.0)	10.9 (3.0)	0.002*
Heme iron (mg/d)	1.1 (0.6)	1.0 (0.5)	1.0 (0.5)	0.141
Nonheme iron (mg/d)	10.2 (3.2)	9.8 (2.9)	9.9 (2.8)	0.004*
From supplements[4] (mg/d)	40.5 (64.5)	29.2 (48.9)	38.8 (62.1)	0.836
Copper				
Dietary intake (mg/d)	1.2 (0.3)	1.1 (0.3)	1.1 (0.3)	0.003*
From supplements [5] (mg/d)	1.1 (0.5)	1.1 (1.0)	1.2 (1.1)	0.548
Zinc				
Dietary intake (mg/d)	9.8 (2.5)	9.5 (2.2)	9.4 (2.3)	0.011*
From supplements[6] (mg/d)	8.0 (4.6)	9.2 (10.0)	10.8 (10.3)	0.151
Kynurenines				
Tryptophan (μmol/L)	66.1 (12.3)	67.6 (15.9)	68.3 (14.7)	0.014*
Kynurenine (μmol/L)	1.9 (0.6)	1.8 (0.6)	1.8 (0.6)	0.005*
3-Hydroxykynurenine (nmol/L)[7]	50.0 (27.0)	47.7 (22.5)	47.1 (21.4)	0.050
Kynurenic acid (nmol/L)	53.7 (25.1)	58.7 (28.1)	59.6 (31.2)	<0.001*
Xanthurenic acid (nmol/L)	12.8 (9.4)	14.7 (9.6)	15.2 (10.4)	<0.001*
Anthranilic acid (nmol/L)[7]	16.0 (6.6)	16.6 (7.2)	16.3 (8.1)	0.084
3-Hydroxyanthranilic acid (nmol/L)[7]	43.1 (18.6)	42.7 (18.0)	42.9 (18.4)	0.320
Picolinic acid (nmol/L)	33.5 (16.2)	35.8 (16.1)	35.3 (20.0)	0.010*
Quinolinic acid (nmol/L)	510.0 (341.0)	492.0 (276.0)	455.5 (267.0)	<0.001*
KTR	28.7 (9.3)	27.2 (8.4)	26.8 (7.7)	<0.001*
HKr	0.39 (0.18)	0.35 (0.15)	0.34 (0.12)	<0.001*
KA/QA ratio	0.10 (0.06)	0.12 (0.06)	0.13 (0.06)	<0.001*

Macronutrient and micronutrient intake and plasma B vitamin markers are presented as means and SD.
Kynurenine concentrations and ratios are presented as median and interquartile range (IQR).
Abbreviations: KTR, kynurenine-to-tryptophan ratio; HKr, hydroxykynurenine ratio; KA/QA, kynurenic acid-to-quinolinic acid.
[1] Six wk posttreatment: $n = 36$; 6 mo posttreatment: $n = 30$; 12 mo posttreatment: $n = 26$
[2] Six wk posttreatment: $n = 35$; 6 mo posttreatment: $n = 31$; 12 mo posttreatment: $n = 28$
[3] Six wk posttreatment: $n = 33$; 6 mo posttreatment: $n = 27$; 12 mo posttreatment: $n = 22$
[4] Six wk posttreatment: $n = 34$; 6 mo posttreatment: $n = 27$; 12 mo posttreatment: $n = 23$
[5] Six wk posttreatment: $n = 28$; 6 mo posttreatment: $n = 22$; 12 mo posttreatment: $n = 18$
[6] Six wk posttreatment: $n = 31$; 6 mo posttreatment: $n = 25$; 12 mo posttreatment: $n = 20$
[7] Six wk posttreatment: $n = 245$, 6 mo posttreatment $n = 198$, 12 mo posttreatment $n = 162$.
* Indicates a statistically significant difference ($P < 0.05$) between follow-up time points based on linear mixed models with time (continuous) as exposure and kynurenine concentration or ratio (continuous) as outcome.

TABLE 3
Longitudinal associations of macronutrient intake with plasma kynurenines and ratios in colorectal cancer survivors from 6 wk to 12 mo posttreatment

			Kynurenines with antioxidative, anti-inflammatory, and neuroprotective properties		Kynurenines with inconclusive roles				Kynurenines with pro-oxidative, proinflammatory, and neurotoxic properties	
		Trp	KA	Pic	Kyn	XA	AA	HAA	HK	QA
Macronutrient intake										
Total protein	Adjusted[1,2,3]	.00 −.12, .12)	.12 (.04, .20)**	.13 (.01, .24)*	.03 (−.06, .12)	.22 (.11, .33)**	.10 (−.03, .23)	.15 (.04, .27)**	.14 (.04, .24)*	.04 (−.06, .14)
	Within[1,4]	.00 (−.14, .13)	.14 (.05, .24)**	.12 (.00, .25)*	.05 (−.05, .15)	.25 (.12, .37)**	.11 (−.02, .24)	.19 (.06, .32)**	.14 (.03, .26)*	.06 (−.03, .15)
	Between[1,5]	.01 (−.17, .19)	.06 (−.06, .18)	.14 (−.04, .31)	−.03 (−.17, .12)	.16 (.00, .32)	.06 (−.10, .22)	.07 (−.10, .24)	.12 (−.04, .28)	−.03 (−.19, .13)
Animal-based protein	Adjusted[1,2,3]	.00 (−.10, .10)	.09 (.02, .15)*	.11 (.01, .20)*	.02 (−.05, .09)	.20 (.10, .30)**	.07 (−.04, .18)	.12 (.03, .22)**	.11 (.03, .19)*	.03 (−.05, .11)
	Within[1,4]	−.01 (−.12, .10)	.10 (.02, .18)**	.09 (−.02, .19)	.04 (−.04, .12)	.18 (.07, .28)**	.08 (−.03, .19)	.15 (.04, .26)**	.11 (.01, .20)*	.05 (−.02, .13)
	Between[1,5]	.02 (−.14, .17)	.05 (−.05, .16)	.15 (−.01, .30)	−.03 (−.16, .09)	.17 (.03, .31)*	.06 (−.08, .19)	.07 (−.08, .22)	.11 (−.03, .25)	−.05 (−.20, .10)
Plant-based protein	Adjusted[1,2,3]	.00 (−.16, .16)	.12 (.01, .23)*	.07 (−.08, .22)	.02 (−.10, .15)	.07 (−.07, .22)	.08 (−.07, .23)	.02 (−.14, .17)	.11 (−.05, .27)	.00 (−.12, .12)
	Within[1,4]	.00 (−.18, .19)	.17 (.04, .29)**	.11 (−.06, .28)	.04 (.10, .18)	.15 (−.02, .32)	.13 (−.05, .31)	.06 (−.11, .24)	.08 (−.07, .24)	.00 (−.12, .13)
	Between[1,5]	−.01 (−.20, .18)	.07 (−.06, .20)	.02 (−.16, .21)	.00 (−.15, .15)	−.01 (−.18, .17)	.04 (−.14, .21)	−.04 (−.22, .14)	.02 (−.14, .19)	−.01 (−.17, .15)
Total carbohydrates	Adjusted[1,2,3]	−.13 (−.26, −.01)*	−.10 (−.18, −.01)*	−.14 (−.26, −.02)*	.11 (.01, .20)*	−.18 (−.30, −.07)**	−.06 (−.18, .05)	−.06 (−.18, .06)	.03 (−.08, .14)	.10 (−.01, .20)
	Within[1,4]	−.16 (−.31, .00)	−.05 (−.16, .06)	−.08 (−.23, .06)	.08 (−.04, .19)	−.09 (−.23, .06)	−.14 (−.30, .02)	−.05 (−.20, .10)	.04 (−.10, .17)	.08 (−.03, .19)
	Between[1,5]	−.11 (−.26, .04)	−.14 (−.25, −.04)*	−.21 (−.36, −.05)**	.14 (.02, .26)*	−.27 (−.41, −.13)**	−.01 (−.15, .13)	−.07 (−.21, .08)	.02 (−.12, .16)	.13 (−.01, .27)
Mono- and disaccharides	Adjusted[1,2,3]	−.06 (−.16, .04)	−.08 (−.14, −.01)*	−.13 (−.22, −.04)*	.08 (−.01, .16)	−.12 (−.21, −.03)**	−.04 (−.13, .06)	.00 (−.10, .09)	−.05 (−.15, .05)	.09 (.01, .16)*
	Within[1,4]	−.09 (−.22, .03)	−.06 (−.15, .03)	−.10 (−.22, .02)	.02 (−.08, .11)	−.07 (−.18, .05)	−.16 (−.28, −.03)*	−.02 (−.15, .10)	−.02 (−.12, .09)	.06 (−.03, .14)
	Between[1,5]	−.02 (−.15, .11)	−.10 (−.19, −.01)*	−.18 (−.31, −.04)**	.12 (.01, .22)*	−.18 (−.30, −.06)**	.06 (−.06, .17)	.02 (−.11, .14)	−.07 (−.19, .05)	.12 (.00, .25)
Polysaccharides	Adjusted[1,2,3]	−.12 (−.24, .01)	−.03 (−.11, .06)	−.01 (−.13, .11)	.07 (−.03, .17)	−.09 (−.21, .03)	−.04 (−.16, .08)	−.09 (−.21, .03)	.12 (.01, .24)*	.03 (−.07, .14)
	Within[1,4]	−.11 (−.27, .05)	.03 (−.08, .14)	.05 (−.10, .20)	.08 (−.04, .19)	−.01 (−.15, .14)	−.02 (−.18, .14)	−.06 (−.21, .10)	.10 (−.03, .24)	.02 (−.08, .13)
	Between[1,5]	−.12 (−.28, .04)	−.09 (−.19, .02)	−.07 (−.23, .08)	.06 (−.07, .19)	−.17 (−.31, .02)*	−.06 (−.20, .08)	−.13 (−.28, .03)	.13 (−.01, .27)	.03 (−.11, .18)
Fibers	Adjusted[1,2,3]	.09 (−.02, .20)	.00 (−.07, .08)	−.02 (−.12, .09)	−.08 (−.16, .01)	.00 (−.10, .10)	−.11 (−.21, .00)*	−.03 (−.14, .07)	−.07 (−.19, .05)	−.10 (−.18, −.02)*
	Within[1,4]	.09 (−.05, .23)	.04 (−.06, .14)	−.01 (−.15, .12)	−.07 (−.18, .03)	08 (−.05, .21)	−.07 (−.22, .07)	.00 (−.14, .13)	−.03 (−.15, .09)	−.10 (−.19, .00)*
	Between[1,5]	.08 (−.06, .22)	−.03 (−.12, .06)	−.02 (−.17, .12)	−.09 (−.20, .02)	−.08 (−.21, .04)	−.13 (−.25, .00)*	−.06 (−.20, .07)	−.09 (−.22, .04)	−.09 (−.22, .04)
Total fats	Adjusted[1,2,3]	.18 (.06, .30)**	−.01 (−.10, .07)	.02 (−.09, .13)	.05 (−.04, .14)	.02 (−.09, .13)	.06 (−.05, .18)	.06 (−.06, .17)	−.07 (−.18, .05)	−.01 (−.10, .08)
	Within[1,4]	.26 (.12, .39)**	.03 (−.07, .12)	.05 (−.08, .18)	.08 (−.02, .19)	.08 (−.05, .21)	.10 (−.04, .24)	.08 (−.05, .22)	−.08 (−.19, .04)	.00 (−.10, .09)
	Between[1,5]	.06 (−.10, .23)	−.08 (−.19, .03)	−.04 (−.20, .13)	−.01 (−.13, .12)	−.07 (−.21, .08)	.01 (−.13, .16)	.01 (−.15, .17)	−.05 (−.20, .09)	−.04 (−.18, .11)
Saturated fats	Adjusted[1,2,3]	.12 (.00, .24)*	.00 (−.09, .08)	.04 (−.08, .15)	.10 (.01, .19)*	.05 (−.06, .16)	.04 (−.07, .16)	.05 (−.07, .17)	.00 (−.12, .11)	.04 (−.05, .13)
	Within[1,4]	.20 (.06, .34)**	.02 (−.08, .12)	.05 (−.08, .18)	.13 (.02, .23)*	.08 (−.05, .21)	.08 (−.06, .22)	.06 (−.08, .20)	.02 (−.10, .14)	.04 (−.05, .14)
	Between[1,5]	.02 (−.14, .18)	−.03 (−.14, .07)	.01 (−.15, .17)	.06 (−.06, .19)	.00 (−.15, .14)	.01 (−.14, .15)	.04 (−.12, .19)	.02 (−.12, .16)	.01 (−.13, .16)
Unsaturated fats	Adjusted[1,2,3]	.07 (−.06, .19)	−.01 (−.09, .08)	−.01 (−.12, .11)	−.04 (−.13, .06)	−.02 (−.13, .09)	.02 (−.09, .14)	.02 (−.10, .13)	−.08 (−.19, .02)	−.04 (−.12, .05)
	Within[1,4]	.12 (−.02, .26)	.04 (−.05, .13)	.03 (−.10, .15)	.00 (−.11, .10)	.04 (−.09, .16)	.06 (−.08, .20)	.05 (−.08, .19)	−.09 (−.21, .03)	−.03 (−.12, .06)
	Between[1,5]	−.04 (−.20, .13)	−.09 (−.21, .02)	−.09 (−.25, .08)	−.11 (−.24, .02)	−.13 (−.28, .02)	−.03 (−.18, .12)	−.06 (−.22, .10)	−.07 (−.22, .08)	−.08 (−.23, .08)

			Ratio with antioxidative, anti-inflammatory, and neuroprotective properties	Ratios with pro-oxidative, proinflammatory, and neurotoxic properties		Neopt
			KA/QA ratio	KTR	HKr	
Macronutrient intake						
Total protein		Adjusted[1,2,3]	.12 (.02, .22)**	.04 (−.05, .14)	.04 (−.06, .15)	.04 (−.08, .16)
		Within[1,4]	.11 (.00, .22)	.06 (−.04, .16)	.05 (−.07, .16)	.05 (−.06, .16)
		Between[1,5]	.14 (−.02, .30)	−.01 (−.16, .14)	.04 (−.13, .20)	−.06 (−.22, .10)
Animal-based protein		Adjusted[1,2,3]	.08 (.00, .16)	.04 (−.03, .11)	.04 (−.05, .12)	.02 (−.08, .12)
		Within[1,4]	.06 (−.03, .15)	.06 (−.03, .14)	.04 (−.06, .13)	.05 (−.04, .14)
		Between[1,5]	.13 (−.01, .27)	.00 (−.14, .13)	.04 (−.11, .18)	−.06 (−.21, .08)

(*continued on next page*)

TABLE 3 (*continued*)

		Ratio with antioxidative, anti-inflammatory, and neuroprotective properties	Ratios with pro-oxidative, proinflammatory, and neurotoxic properties		Neopt
		KA/QA ratio	KTR	HKr	
Plant-based protein	Adjusted[1,2,3]	.19 (.06, .32)**	−.04 (−.15, .08)	.02 (−.13, .18)	−.02 (−.15, .11)
	Within[1,4]	.22 (.07, .37)**	−.01 (−.15, .13)	−.03 (−.18, .13)	.00 (−.15, .14)
	Between[1,5]	.15 (−.01, .31)	−.06 (−.21, .09)	−.03 (−.20, .14)	−.05 (−.21, .12)
Total carbohydrates	Adjusted[1,2,3]	−.23 (−.34, −.13)**	.20 (.10, .30)**	.12 (.01, .23)*	.15 (.04, .26)*
	Within[1,4]	−.19 (−.32, −.06)**	.22 (.10, .34)**	.13 (.00, .26)	.11 (−.01, .23)
	Between[1,5]	−.29 (−.43, −.15)**	.18 (.05, .31)**	.11 (−.03, .25)	.19 (.05, .33)**
Mono- and disaccharides	Adjusted[1,2,3]	−.17 (−.25, −.09)**	.11 (.03, .19)**	.00 (−.10, .09)	.10 (.00, .19)*
	Within[1,4]	−.14 (−.25, −.04)**	.13 (.04, .22)**	.04 (−.06, .15)	.04 (−.06, .14)
	Between[1,5]	−.20 (−.32, −.08)**	.12 (.01, .23)*	−.04 (−.16, .08)	.17 (.05, .29)**
Polysaccharides	Adjusted[1,2,3]	−.10 (−.21, .01)	.12 (.02, .22)**	.19 (.08, .30)**	.08 (−.02, .19)
	Within[1,4]	−.05 (−.18, .08)	.14 (.02, .26)**	.16 (.02, .29)*	.09 (−.03, .22)
	Between[1,5]	−.16 (−.30, −.02)*	.09 (−.04, .23)	.22 (.08, .36)**	.07 (−.07, .22)
Fibers	Adjusted[1,2,3]	.11 (.02, .21)**	−.12 (−.20, −.03)**	−.07 (−.18, .04)	−.06 (−.15, .04)
	Within[1,4]	.11 (.00, .23)	−.09 (−.20, .01)	−.02 (−.14, .10)	−.03 (−.14, .08)
	Between[1,5]	.11 (−.02, .24)	−.15 (−.27, −.03)*	−.11 (−.24, .02)	−.09 (−.22, .04)
Total fats	Adjusted[1,2,3]	−.02 (−.12, .08)	**−.13 (−.22, −.03)****	**−.12 (−.23, −.01)***	−.02 (−.13, .09)
	Within[1,4]	−.02 (−.13, .09)	**−.15 (−.25, −.04)****	**−.18 (−.30, −.06)****	−.02 (−.13, .09)
	Between[1,5]	−.03 (−.18, .11)	−.08 (−.22, .05)	−.07 (−.22, .08)	−.01 (−.15, .14)
Saturated fats	Adjusted[1,2,3]	−.07 (−.17, .03)	−.02 (−.12, .07)	−.04 (−.14, .07)	−.01 (−.11, .09)
	Within[1,4]	−.07 (−.18, .05)	−.04 (−.15, .06)	−.05 (−.17, .07)	.00 (−.11, .11)
	Between[1,5]	−.06 (−.20, .08)	.03 (−.11, .16)	.01 (−.13, .16)	−.02 (−.16, .13)
Unsaturated fats	Adjusted[1,2,3]	.03 (−.07, .14)	−.11 (−.22, −.01)*	−.13 (−.23, −.02)*	−.01 (−.13, .10)
	Within[1,4]	.04 (−.07, .15)	−.12 (−.22, −.01)**	−.16 (−.28, −.05)**	−.02 (−.12, .09)
	Between[1,5]	.03 (−.12, .17)	−.09 (−.23, .05)	−.04 (−.19, .11)	.02 (−.14, .17)

Abbreviations: KA, kynurenic acid; Pic, picolinic acid; Trp, tryptophan; Kyn, kynurenine; XA, xanthurenic acid; AA, anthranilic acid; HAA, 3-hydroxyanthranilic acid; HK, 3-hydroxykynurenine; QA, quinolinic acid; KA/QA, kynurenic acid-to-quinolinic acid ratio; KTR, kynurenine-to-tryptophan ratio; HKr, hydroxykynurenine ratio; Neopt, neopterin.

Standard deviations of kynurenines are 12.0 μmol/L for Trp; 29.0 nmol/L for KA; 15.0 nmol/L for Pic; 0.5 μmol/L for Kyn, 8.0 nmol/L for XA; 7.0 nmol/L for AA; 15.0 nmol/L for HAA; 27.0 nmol/L for HK; 366.0 nmol/L for QA; 0.05 for KA/QA; 10.0 for KTR; 0.2 for HKr; and 11.0 nmol/L for Neopt. Standard deviations of macronutrient intake are 69.0 kcal/d for total protein; 55.0 kcal/d for animal-based protein; 34.0 kcal/d for plant-based protein; 226.0 kcal/d for total carbohydrates; 136.0 kcal/d for mono- and disaccharides; 139.0 kcal/d for polysaccharides; 12 kcal/d for fibers; 206.0 kcal/d for total fats; 90.0 kcal/d for saturated fats; and 116.0 kcal/d for unsaturated fats.

[1] Linear mixed models are adjusted for age at enrollment (years), sex (male or female), renal function (μmol/L), time since end-treatment (weeks), chemotherapy (yes or no), comorbidities (0, 1, or ≥2), stoma (yes or no), educational level (high, medium, or low), BMI (kg/m^2), total PA (hours/week), smoking status (current, former, or never), and energy intake (all-components method).

[2] The β-coefficients represent the overall longitudinal difference in kynurenine concentrations using linear mixed models and can be interpreted as the amount of SD difference in kynurenine concentration/ratio according to 1 SD higher macronutrient intake. For example, a 1 SD increase in total protein intake (= 69 kcal/d) is longitudinally associated with a 0.12 SD higher KA concentration (= 0.12 * 29.0 nmol/L = 3.5 nmol/L).

[3] A random slope was added to the model for total protein with Trp, AA, and QA; animal-based protein with Trp, XA, AA, and QA; plant-based protein with HK, AA, KTR, and HKr; total carbohydrates with Trp, HK, QA, and HKr; mono- and disaccharides with Kyn, HK, QA, KTR, and HKr; polysaccharides with HK and QA; fibers with HK, QA, and HKr, and; total fats with HK, and HKr; saturated fats with HK, and HKr; and unsaturated fats with KTR and HKr.

[4] The β-coefficients represent the change in SD units of kynurenine concentration over time within individuals using a hybrid model within linear mixed models.

[5] The β-coefficients represent the difference in SD units of kynurenine concentration between individuals using a hybrid model within linear mixed models.

* Indicates a statistically significant result ($p<0.05$)

** Indicates a statistically significant result after FDR adjustment for multiple testing ($q<0.05$)

posttreatment within persons was associated with a change in metabolite concentration or ratio (Table 3).

In general, intake of carbohydrates was oppositely associated with kynurenines and ratios than intake of proteins (Figure 2). A higher intake of total carbohydrates was associated with lower concentrations of XA (standardized β: −0.18; 95% CI: −0.30, −0.07) and a lower KA/QA ratio (standardized β: −0.23; 95% CI: −0.34, −0.13), and with a higher KTR (standardized β: 0.20; 95% CI: 0.10, 0.30) (Table 3 and Figure 2). A higher intake of mono- and disaccharides was also associated with lower XA concentrations (standardized β: −0.12; 95% CI: −0.21, −0.03) and a lower KA/QA ratio (standardized β: −0.17; 95% CI: −0.25, −0.09), whereas polysaccharides were associated with a higher HKr (standardized β: 0.19; 95% CI: 0.08, 0.30). The simple and complex carbohydrates were similarly associated with KTR (mono- and disaccharides, standardized β: 0.11; 95% CI: 0.03, 0.19; polysaccharides, standardized β: 0.12; 95% CI: 0.02, 0.22). The significant overall associations with carbohydrates, mono- and disaccharides, and polysaccharides appeared to be driven by both within-person changes and between-person differences over time, indicating that a higher carbohydrate intake over time in the period from 6 wk to 12 mo posttreatment within persons as well as between persons was associated with a change in metabolite concentration or ratio (Table 3). Additionally, higher fiber intake was significantly associated with a higher KA/QA ratio (standardized β: 0.11; 95% CI: 0.02, 0.21) and with a lower KTR (standardized β: −0.12; 95% CI: −0.20, −0.03) (Table 3 and Figure 2).

Higher fat intake was associated with higher Trp concentrations (standardized β: 0.18; 95% CI: 0.06, 0.30) and a lower KTR (standardized β: −0.13; 95% CI: −0.22, −0.03) (Table 3 and Figure 2). The associations for fat with Trp and KTR appeared to be exclusively driven by within-person changes over time (Table 3).

Longitudinal associations of micronutrient intake with metabolites of the kynurenine pathway

Confounder-adjusted longitudinal associations between micronutrient intake and metabolites of the kynurenine pathway were generally weak or null, although some statistically significant associations were observed (Table 4). After taking multiple testing into

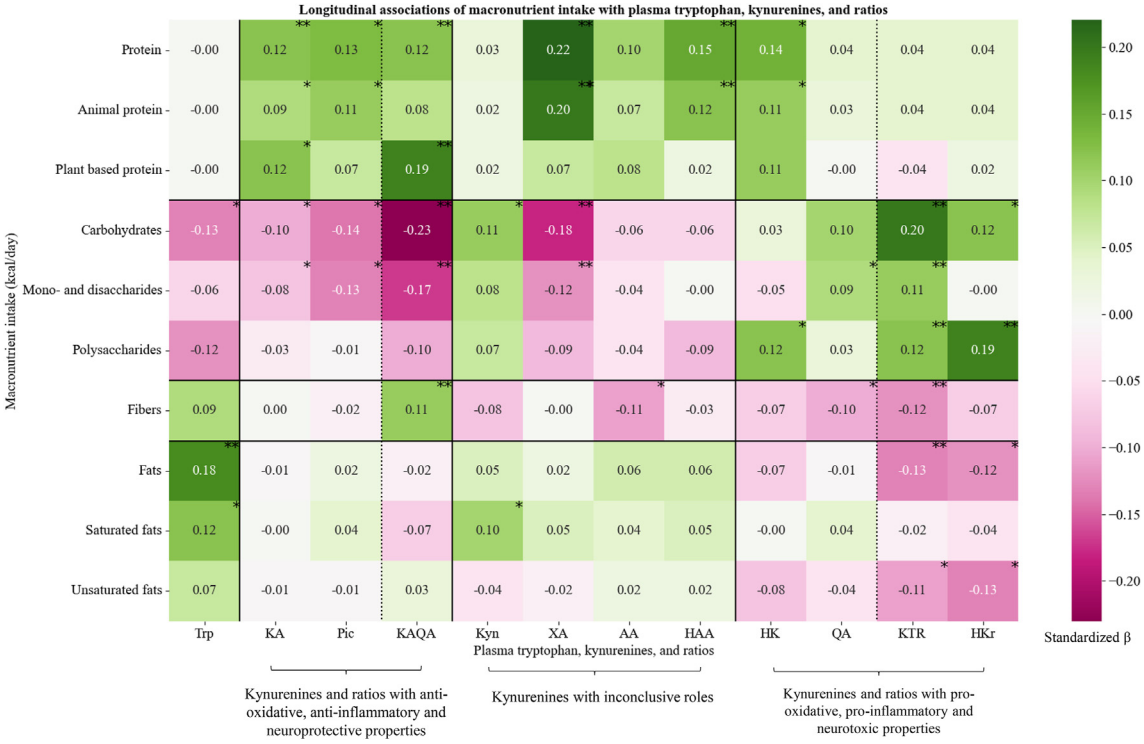

FIGURE 2. Heatmap of confounder-adjusted linear mixed models between macronutrient intake and metabolites and ratios of the kynurenine pathway in colorectal cancer survivors. Analyses were adjusted for age at enrollment (years), sex (male or female), renal function (μmol/L), time since end-treatment (weeks), chemotherapy (yes or no), comorbidities (0, 1, or ≥2), stoma (yes or no), educational level (high, medium, or low), BMI (kg/m^2), total PA (hours/week), smoking status (current, former, or never), and energy intake (all-components method). A random slope was added to the model for total protein with Trp, AA, and QA; animal-based protein with Trp, XA, AA, and QA; plant-based protein with HK, AA, KTR, and HKr; total carbohydrates with Trp, HK, QA, and HKr; mono- and disaccharides with Kyn, HK, QA, KTR, and HKr; polysaccharides with HK and QA; fibers with HK, QA, and HKr; total fats with HK and HKr; saturated fats with HK and HKr; and unsaturated fats with KTR and HKr. The standardized β can be interpreted as the amount of SD difference in kynurenine concentration/ratio according to 1 SD higher macronutrient intake. For example, a 1 SD increase in total protein intake (= 69 kcal/d) is longitudinally associated with a 0.12 SD higher KA concentration (= 0.12 * 29.0 nmol/L = 3.5 nmol/L). SDs of kynurenines are 12.0 μmol/L for Trp; 29.0 nmol/L for KA; 15.0 nmol/L for Pic; 0.5 μmol/L for Kyn, 8.0 nmol/L for XA; 7.0 nmol/L for AA; 15.0 nmol/L for HAA; 27.0 nmol/L for HK; 366.0 nmol/L for QA; 0.05 for KA/QA; 10.0 for KTR; 0.2 for HKr; and 11.0 nmol/L for Neopt. Standard deviations of macronutrient intake are 69.0 kcal/d for total protein; 55.0 kcal/d for animal-based protein; 34.0 kcal/d for plant-based protein; 226.0 kcal/d for total carbohydrates; 136.0 kcal/d for mono- and disaccharides; 139.0 kcal/d for polysaccharides; 12 kcal/d for fibers; 206.0 kcal/d for total fats; 90.0 kcal/d for saturated fats; 116.0 kcal/d for unsaturated fats. Abbreviations: KA, kynurenic acid; Pic, picolinic acid; KA/QA ratio, kynurenic acid-to-quinolinic acid ratio; Trp, tryptophan; Kyn, kynurenine; XA, xanthurenic acid; AA, anthranilic acid, HAA, 3-hydroxyanthranilic acid; HK, 3-hydroxykynurenine; QA KTR, kynurenine-to-tryptophan ratio; HKr, hydroxykynurenine ratio. *Indicates a statistically significant result ($P < 0.05$) **Indicates a statistically significant result after FDR adjustment for multiple testing (q<0.05)

account, we observed positive associations for zinc with concentrations of HK (standardized β: 0.12; 95% CI: 0.03, 0.20) and XA (standardized β: 0.13; 95% CI: 0.04, 0.21) and for magnesium with the KA/QA ratio (standardized β: 0.24; 95% CI: 0.13, 0.36) and (Table 4 and Figure 3). The association of zinc with XA and HK appeared to be driven by within-person changes over time, and the association of magnesium with the KA/QA ratio appeared to be driven by both within-person changes and between-person differences over time (Table 4).

Sensitivity analyses of micronutrient intake from food plus supplements in participants that used supplements with vitamins and/or minerals of interest generally showed stronger associations than of micronutrient intake from food alone, though none remained statistically significant after adjustment for multiple testing (Supplementary Table 1 and Supplementary Figure 1).

Longitudinal associations of vitamin B plasma markers with metabolites of the kynurenine pathway

In contrast to the null associations for vitamin B6 intake with plasma Trp and kynurenines, associations for the plasma markers of vitamin B6 status, PLP, were generally stronger and statistically significant (Figure 4). Higher PLP concentrations were associated with higher concentrations of Trp (standardized β: 0.37; 95% CI: 0.22, 0.53) and HAA (standardized β: 0.11; 95% CI: 0.03, 0.19) and with lower concentrations of HK (standardized β: −0.30; 95% CI: −0.40, −0.20). Higher concentrations of PLP were also associated with a higher KA/QA ratio (standardized β: 0.25; 95% CI: 0.13, 0.37) and a lower KTR (standardized β: −0.31; 95% CI: −0.45, −0.16) and HKr (standardized β: −0.52; 95% CI: −0.65, −0.38) (Table 4 and Figure 4). The associations of PLP with Trp, HK, KTR, and HKr appeared to be driven by within-person changes; the associations with HK, HAA, and HKr were additionally driven by between-person differences over time (Table 4). Higher concentrations of riboflavin were associated with higher concentrations of Kyn (standardized β: 0.11; 95% CI: 0.02, 0.19) and appeared to be driven by within-person changes over time (Table 4 and Figure 4).

Although not part of the kynurenine pathway, associations of macronutrient and micronutrient intake with neopterin, a biomarker for interferon-gamma activity, were essentially similar to those for KTR.

Discussion

In the present study, we investigated the longitudinal associations of macronutrient and micronutrient intake with metabolites of the kynurenine pathway in CRC survivors from 6 wk up to 12 mo post-treatment. Generally, kynurenines with neuroprotective properties increased over time, whereas kynurenines with neurotoxic properties decreased over time, potentially reflecting improved health during follow-up. Our results suggested that higher intakes of protein and fiber were associated with higher levels of the neuroprotective KA/QA ratio and higher intakes of fiber and fat intake with a lower KTR. In contrast, the associations for carbohydrate intake with the KA/QA ratio and KTR were the opposite as for fibers, fat, and protein. Furthermore, intake of protein, carbohydrate, and fat intake were associated with kynurenines with inconclusive roles, such as Trp, XA, and HAA. Finally, we found a positive association for zinc with XA and HK concentrations and for magnesium with the KA/QA ratio.

Consistent with an earlier finding in healthy subjects that a high-protein diet was associated with higher concentrations of plasma KA and higher 24h urinary excretion QA compared with a low-protein diet [19], the present study also found a positive association for protein intake with KA and QA plasma concentrations, although the association with QA was weak and not significant. Intake of protein was additionally found to be positively associated with XA and HAA concentrations and the neuroprotective KA/QA ratio in the current study; to our knowledge, we are the first to describe these findings. Our results did not show that protein intake was associated with plasma Trp, although Trp is an essential amino acid. However, this observation is in line with study findings of an intervention study among healthy subjects [19]. Possible explanations are that protein intake does not necessarily reflect the intake of protein sources high in Trp and that blood levels of Trp may not be a good biomarker for Trp intake. Unfortunately, we were unable to study the association of Trp intake with plasma Trp as data on the Trp content of food items was not available in the nutrient composition table.

In the current study, carbohydrate intake was significantly positively associated with KTR and inversely associated with XA concentrations and the KA/QA ratio. The significant positive association with KTR suggests that higher carbohydrate intake is associated with increased inflammation and immune activation. However, there is no real consensus about this in literature [40–42]. Of note, the quality of carbohydrates (i.e., glycemic index) is likely as important as the number of carbohydrates with respect to inflammation [42]. Interestingly, on the contrary, we found an inverse association of fiber intake with KTR and a positive association with the KA/QA ratio. This finding supports the idea that fiber, potentially via the gut microbiota, actually reduces interferon-gamma activity induced inflammation [43], mirrored in a lower KTR.

As opposed to carbohydrates, fat intake appeared to be inversely associated with KTR. The observed inverse association between fat and KTR can be explained by the fact that a higher intake of unsaturated fat was associated with a lower KTR, whereas saturated fat intake was not associated with KTR. These results further endorse the concept that unsaturated fats reduce inflammatory activity [44], reflected in a lower KTR [45].

Considering the longitudinal associations between micronutrient intake and plasma kynurenines, we found that vitamin B2 and B6 intake were generally weak and nonsignificantly associated with plasma kynurenines and their ratios. These results reflect those of a study in healthy subjects [23], which also found weak but significant associations. The lack of significance in the current study may be because of smaller sample size and a different population. Median concentrations of HK, KA, AA, and HAA were higher in our CRC survivor population than in a healthy population; for Trp, Kyn, and XA, median concentrations were essentially similar [23]. Nevertheless, we observed considerably stronger associations between plasma vitamin B2 and B6 markers, riboflavin and PLP, respectively, and plasma kynurenines. Similar to studies in apparently healthy subjects and patients with stable angina pectoris [27, 31], inverse associations were strongest for PLP with HKr, confirming the function as a vitamin B6 status marker. The observed inverse association of PLP with HK, KTR, and neopterin is in line with previous large-scale studies in healthy subjects [23] and patients with stable angina pectoris [27,46,47]. In addition, the observed positive association of PLP with Trp and HAA in the present study is consistent with previous reports [23,47]. Our study also evaluated the associations of the PAr index, an indicator reflecting vitamin B6 catabolism during inflammation, with plasma kynurenines. As expected, given its high correlation with inflammatory markers [29,30,48], our data revealed a relatively strong negative association with KTR and neopterin. With regards to riboflavin, we found a positive association with Kyn, whereas a study in healthy subjects showed a positive association with XA and HAA [23]. These

TABLE 4
Longitudinal associations of micronutrient intake and vitamin B status plasma markers with plasma kynurenines and ratios in colorectal cancer survivors from 6 wk to 12 mo posttreatment

			Kynurenines with antioxidative, anti-inflammatory, and neuroprotective properties		Kynurenines with inconclusive roles				Kynurenines with pro-oxidative, proinflammatory, and neurotoxic properties	
		Trp	KA	Pic	Kyn	XA	AA	HAA	HK	QA
Micronutrient intake										
Vitamin B2	Adjusted[1,2,3]	.05 (−.05, .15)	.06 (−.01, .13)	.05 (−.05, .14)	.04 (−.04, .11)	.08 (−.01, .18)	.01 (−.09, .10)	.12 (.02, .21)*	.04 (−.04, .13)	.05 (−.05, .14)
	Within[1,4]	.04 (−.09, .16)	.09 (.00, .17)**	.05 (−.07, .16)	.03 (−.06, .12)	.14 (.02, .25)*	−.06 (−.19, .06)	.09 (−.03, .21)	.04 (−.07, .14)	.03 (−.05, .11)
	Between[1,5]	.07 (−.07, .21)	.02 (−.07, .12)	.05 (−.09, .20)	.05 (−.07, .16)	.01 (−.12, .14)	.08 (−.04, .21)	.16 (.02, .29)*	.05 (−.08, .18)	.07 (−.06, .21)
Vitamin B6	Adjusted[1,2,3]	.01 (−.08, .11)	.05 (−.01, .11)	.09 (.00, .18)	.01 (−.06, .08)	.09 (.00, .17)*	.05 (−.07, .17)	.09 (.00, .18)	.04 (−.04, .12)	.02 (−.05, .09)
	Within[1,4]	.05 (−.07, .16)	.12 (.04, .20)**	.12 (.01, .22)*	.03 (−.06, .11)	.16 (.05, .26)*	.03 (−.09, .14)	.15 (.04, .26)*	.04 (−.06, .13)	.03 (−.04, .11)
	Between[1,5]	−.03 (−.17, .10)	−.05 (−.14, .04)	.04 (−.10, .18)	−.03 (−.14, .08)	−.02 (−.14, .11)	−.03 (−.15, .09)	.00 (−.13, .13)	.04 (−.08, .16)	−.04 (−.17, .09)
Magnesium	Adjusted[1,2,3]	.04 (−.09, .18)	.10 (.00, .19)*	.11 (−.02, .24)	−.10 (−.20, .00)	.10 (−.03, .22)	−.01 (−.14, .12)	.08 (−.05, .21)	−.04 (−.17, .10)	−.09 (−.18, .01)
	Within[1,4]	.03 (−.15, .21)	.17 (.05, .29)**	.14 (−.02, .31)	−.09 (−.22, .04)	.22 (.05, .38)**	.04 (−.14, .21)	.14 (−.03, .31)	.05 (−.10, .20)	−.05 (−.17, .06)
	Between[1,5]	.05 (−.11, .21)	.04 (−.07, .15)	.07 (−.09, .24)	−.11 (−.24, .01)	.00 (−.15, .15)	−.04 (−.18, .11)	.04 (−.11, .19)	−.09 (−.24, .05)	−.08 (−.23, .06)
Iron	Adjusted[1,2,3]	−.06 (−.17, .06)	.04 (−.03, .11)	.03 (−.08, .14)	−.03 (−.13, .07)	.02 (−.08, .12)	.01 (−.13, .14)	.02 (−.09, .13)	.07 (−.06, .19)	.02 (−.08, .12)
	Within[1,4]	−.03 (−.17, .12)	.11 (.01, .21)**	.04 (−.10, .17)	.03 (−.07, .14)	.14 (.00, .27)*	.06 (−.08, .21)	.08 (−.05, .22)	.14 (.02, .26)*	.09 (−.01, .19)
	Between[1,5]	−.07 (−.21, .07)	−.02 (−.11, .08)	02 (−.12, .17)	−.02 (−.13, .10)	−.04 (−.17, .09)	.02 (−.11, .15)	.03 (−.11, .17)	.02 (−.10, .15)	.07 (−.06, .20)
Heme iron	Adjusted[1,2,3]	−.05 (−.14, .14)	.01 (−.04, .06)	.02 (−.05, .09)	.01, (−.05, .07)	.05 (−.02, .12)	.06 (−.04, .17)	.01 (−.07, .08)	.06 (.00, .13)	.02 (−.05, .09)
	Within[1,4]	−.06 (−.15, .04)	.02 (−.04, .09)	.02 (−.06, .11)	−.01 (−.08, .07)	.08 (−.01, .17)	.06 (−.04, .16)	.03 (−.06, .13)	.03 (−.05, .11)	.00 (−.07, .06)
	Between[1,5]	−.08 (−.21, .05)	−.01 (−.10, .08)	.01 (−.12, .15)	.03 (−.07, .14)	.01 (−.11, .13)	.05 (−.07, .16)	−.03 (−.16, .09)	.13 (.01, .25)*	.10 (−.03, .23)
Nonheme iron	Adjusted[1,2,3]	−.04 (−.15, .08)	.04 (−.03, .11)	.03 (−.09, .14)	−.04 (−.14, .07)	.01 (−.09, .10)	.02 (−.08, .13)	.02 (−.10, .14)	.03 (−.09, .16)	.01 (−.09, .12)
	Within[1,4]	.00 (−.16, .15)	.12 (.01, .22)**	.03 (−.11, .17)	.04 (−.07, .15)	.12 (−.02, .26)	.04 (−.11, .19)	.08 (−.06, .23)	.13 (.01, .26)*	.10 (.00, .20)
	Between[1,5]	−.05 (−.20, .09)	−.02 (−.12, .08)	.02 (−.13, .17)	−.02 (−.14, .09)	−.05 (−.19, .09)	.01 (−.12, .14)	.04 (−.10, .18)	.00 (−.14, .13)	.05 (−.08, .19)
Copper	Adjusted[1,2,3]	−.02 (−.13, .09)	.04 (−.03, .11)	.06 (−.05, .16)	.00 (−.10, .09)	−.03 (−.13, .06)	.06 (−.08, .19)	.01 (−.10, .13)	.12 (.00, .24)*	.07 (−.03, .17)
	Within[1,4]	−.01 (−.15, .12)	.10 (.01, .19)**	.06 (−.07, .18)	.04 (−.06, .14)	.07 (−.05, .19)	.14 (.01, .28)	.07 (−.06, .20)	.16 (.04, .27)*	.10 (.01, .19)*
	Between[1,5]	−.04 (−.19, .11)	−.01 (−.12, .09)	.06 (−.09, .21)	−.05 (−.17, .07)	−.11 (−.25, .03)	−.01 (−.15, .12)	−.01 (−.15, .14)	.01 (−.13, .14)	.05 (−.09, .19)
Zinc	Adjusted[1,2,3]	.01 (−.08, .10)	.06 (.00, .13)*	.07 (−.01, .16)	−.01 (−.08, .06)	.13 (.04, .21)**	.04 (−.05, .13)	.09 (.00, .18)	.12 (.03, .20)**	−.01 (−.09, .07)
	Within[1,4]	.00 (−.10, .10)	.08 (.01, .15)**	.06 (−.04, .15)	−.01 (−.08, .07)	.14 (.05, .24)**	.05 (−.05, .15)	.09 (−.01, .19)	.10 (.01, .18)*	.01 (−.06, .08)
	Between[1,5]	.00 (−.14, .15)	.06 (−.04, .16)	.13 (−.01, .28)	−.02 (−.14, .10)	.09 (−.05, .22)	.02 (−.11, .15)	.08 (−.06, .22)	.12 (−.01, .25)	.01 (−.13, .14)
Vitamin B plasma marker										
Riboflavin	Adjusted[1,2,3]	.02 (−.09, .12)	.08 (.01, .15)*	.03 (−.08, .14)	.11 (.02, .19)**	.05 (−.05, .15)	.04 (−.06, .13)	.06 (−.05, .16)	−.03 (−.33, .27)	.11 (−.20, .43)
	Within[1,4]	.28 (−.04, .59)	.19 (−.02, .40)	.47 (.19, .75)**	.28 (.05, .50)**	.25 (−.04, .53)	.13 (−.18, .45)	.30 (.01, .60)	−.15 (−.41, .11)	.11 (−.09, .31)
	Between[1,5]	−.01 (−.12, .10)	.07 (−.01, .14)	−.05 (−.16, .07)	.08 (−.01, .17)	.03 (−.07, .13)	.03 (−.07, .13)	.02 (−.09, .13)	.08 (−.03, .18)	.05 (−.07, .16)
Pyridoxal 5'-phosphate	Adjusted[1,2,3]	.37 (.22, .53)**	.03 (−.03, .09)	.04 (−.04, .13)	.01 (−.04, .06)	.03 (−.05, .11)	.03 (−.07, .12)	.11 (.03, .19)**	−.30 (−.40, −.20)**	−.08 (−.16, .00)
	Within[1,4]	.17 (.03, .30)**	.06 (−.03, .15)	.09 (−.03, .21)	−.03 (−.12, .07)	.09 (−.03, .21)	−.09 (−.23, .04)	.10 (−.02, .23)	−.15 (.26, −.04)**	.00 (−.09, .08)
	Between[1,5]	.12 (.00, .24)*	.01 (−.07, .09)	−.01 (−.13, .12)	.00 (−.10, .09)	−.02 (−.13, .09)	.07 (−.04, .17)	.12 (.00, .23)*	−.22 (−.32, −.11)**	−.01 (−.13, .08)
PAr index	Adjusted[1,2,3]	−.33 (−.43, −.23)**	.06 (−.01, .13)	−.09 (−.22, .05)	.24 (.11, .37)**	−.12 (−.22, −.03)**	.03 (−.06, .13)	−.05 (−.15, .05)	.33 (.21, .46)**	.24 (.12, .36)**
	Within[1,4]	−.24 (−.40, −.09)**	.04 (−.07, .15)	.15 (.00, .29)*	.17 (.06, .29)**	−.12 (.27, .03)	−.03 (−.19, .14)	−.02 (−.18, .13)	.16 (.03, .29)**	.18 (.08, .28)**
	Between[1,5]	−.38 (−.50, −.26)**	.08 (−.01, .16)	−.20 (−.33, −.07)**	.11 (.01, .22)*	−.12 (−.25, .00)*	.07 (−.05, .18)	−.07 (−.19, .06)	.42 (.31, .52)**	.22 (.10, .34)**

			Ratio with antioxidative, anti-inflammatory, and neuroprotective properties	Ratios with pro-oxidative, proinflammatory, and neurotoxic properties		
			KA/QA ratio	KTR	HKr	Neopt
Micronutrient intake						
Vitamin B2		Adjusted[1,2,3]	.03 (−.05, .12)	.03 (−.05, .11)	−.01 (−.09, .08)	−.01 (−.09, .07)
		Within[1,4]	.06 (−.04, .16)	.04 (−.05, .13)	.01 (−.10, .11)	−.01 (−.10, .09)

(*continued on next page*)

TABLE 4 (*continued*)

		Ratio with antioxidative, anti-inflammatory, and neuroprotective properties	Ratios with pro-oxidative, proinflammatory, and neurotoxic properties		
		KA/QA ratio	KTR	HKr	Neopt
	Between[1,5]	−.02 (−.15, .11)	.02 (−.10, .14)	−.03 (−.16, .10)	−.01 (−.14, .12)
Vitamin B6	Adjusted[1,2,3]	.05 (−.02, .13)	.00 (−.08, .07)	−.01 (−.09, .07)	.09 (.00, .18)*
	Within[1,4]	.06 (−.03, .15)	.01 (−.08, .10)	−.04 (−.14, .05)	.06 (−.03, .15)
	Between[1,5]	.04 (−.09, .17)	−.03 (−.15, .09)	.05 (−.07, .18)	.01 (−.11, .14)
Magnesium	Adjusted[1,2,3]	.24 (.13, .36)**	−.10 (−.20, .01)	−.09 (−.21, .03)	−.09 (−.20, .03)
	Within[1,4]	.27 (.13, .41)**	−.06 (−.19, .07)	−.01 (−.16, .14)	−.06 (−.19, .08)
	Between[1,5]	.21 (.06, .35)**	−.13 (−.27, .00)	−.16 (−.30, −.02)*	−.12 (−.27, .02)
Iron	Adjusted[1,2,3]	.01 (−.09, .10)	.02 (−.08, .13)	.06 (−.03, .16)	.02 (−.08, .13)
	Within[1,4]	.02 (−.10, .13)	.08 (−.03, .19)	.12 (.00, .25)*	.03 (−08, .14)
	Between[1,5]	−.01 (−.14, .12)	.05 (−.07, .18)	.00 (−.13, .13)	.13 (.00, .26)
Heme iron	Adjusted[1,2,3]	.01 (−.06, .07)	.07 (−.01, .15)	.06 (.00, .13)	.09 (.01, .16)*
	Within[1,4]	.04 (−.04, .12)	.06 (−.01, .13)	.03 (−.05, .11)	.09 (.02, .17)*
	Between[1,5]	−.08 (−.20, .04)	.14 (.03, .26)	.14 (.02, .26)*	.18 (.06, .30)**
Nonheme iron	Adjusted[1,2,3]	.01 (−.09, .10)	.00 (−.11, .10)	.06 (−.06, .18)	−.02 (−.13, .09)
	Within[1,4]	.01 (−.11, .13)	.06 (−.06, .17)	.12 (−.01, .25)	−.01 (−.13, .10)
	Between[1,5]	.00 (−.13, .13)	.02 (−.10, .15)	−.03 (−.17, .10)	.09 (−.04, .23)
Copper	Adjusted[1,2,3]	.03 (−.06, .13)	.03 (−.06, .12)	.09 (−.02, .21)	.02 (−.09, .13)
	Within[1,4]	.03 (−.08, .14)	.05 (−.05, .15)	.11 (.00, .22)	.01 (−.09, .12)
	Between[1,5]	.03 (−.10, .17)	−.01 (−.14, .14)	−.01 (−.15, .12)	.03 (−.11, .17)
Zinc	Adjusted[1,2,3]	.10 (.02, .17)*	.03 (−.05, .12)	.05 (−.03, .14)	−.02 (−.11, .07)
	Within[1,4]	.10 (.01, .18)*	.03 (−.05, .11)	.06 (−.03, .14)	−.01 (−.09, .07)
	Between[1,5]	.10 (−.03, .24)	.02 (−.11, .14)	.05 (−.09, .18)	−.07 (−.20, .07)
Vitamin B plasma marker					
Riboflavin	Adjusted[1,2,3]	.01 (−.09, .10)	.05 (−.04, .15)	−.02 (−.12, .08)	.02 (−.08, .12)
	Within[1,4]	.01 (−.24, .25)	.06 (−.16, .29)	−.40 (−.66, −.15)**	.09 (−.15, .32)
	Between[1,5]	.01 (−.10, .11)	.05 (−.05, .15)	.04 (−.06, .15)	.01 (−.10, .12)
Pyridoxal 5'-phosphate	Adjusted[1,2,3]	.25 (.13, .37)**	−.31 (−.45, −.16)**	−.52 (−.65, −.38)**	−.12 (−.22, −.03)**
	Within[1,4]	.09 (−.02, .19)	−.14 (−.23, −.04)**	−.21 (−.32, −.10)**	.00 (−.10, .10)
	Between[1,5]	.09 (−.02, .20)	−.08 (−.17, .02)	**−.24 (−.35, −.14)***	.00 (−.11, .12)
PAr index	Adjusted[1,2,3]	−.17 (−.24, −.10)**	.49 (.35, .62)**	.32 (.20, .43)**	.36 (.22, .50)**
	Within[1,4]	−.13 (−.26, −.01)*	.36 (.25, .47)**	.07 (−.06, .21)	.23 (.11, .35)**
	Between[1,5]	−.20 (−.31,−.08)**	.43 (.33, .53)**	.45 (.34, .56)**	.33 (.21, .44)**

Abbreviations: KA, kynurenic acid; Pic, picolinic acid; Trp, tryptophan; Kyn, kynurenine; XA, xanthurenic acid; AA, anthranilic acid; HAA, 3-hydroxyanthranilic acid; HK, 3-hydroxykynurenine; QA, quinolinic acid; KA/QA, kynurenic acid-to-quinolinic acid ratio; KTR, kynurenine-to-tryptophan ratio; HKr, hydroxykynurenine ratio; Neopt, neopterin.

SDs of kynurenines are 12.0 μmol/L for Trp; 29.0 nmol/L for KA; 15.0 nmol/L for Pic; 0.5 μmol/L for Kyn, 8.0 nmol/L for XA; 7.0 nmol/L for AA; 15.0 nmol/L for HAA; 27.0 nmol/L for HK; 366.0 nmol/L for QA; 0.05 for KA/QA; 10.0 for KTR; 0.2 for HKr; and 11.0 nmol/L for Neopt. SDs of micronutrient intake are 0.4 mg/d for vitamin B2; 0.6 mg/d for vitamin B6; 85.0 mg/d for magnesium; 3.0 mg/d for total iron; 0.5 mg/d for heme iron; 3.0 mg/d for nonheme iron; 0.3 mg/d for copper; and 2.0 mg/d for zinc. Standard deviations of plasma markers of vitamin B status are 53.0 nmol/L for riboflavin, 42.0 nmol/L for PLP; and 0.4 for PAr index.

[1] Linear mixed models are adjusted for age at enrollment (years), sex (male or female), renal function (μmol/L), time since end-treatment (weeks), chemotherapy (yes or no), comorbidities (0, 1, or ≥2), stoma (yes or no), educational level (high, medium, or low), BMI (kg/m^2), total PA (hours/week), smoking status (current, former, or never), alcohol intake (g/d), and energy intake (kcal/d).

[2] The β-coefficients represent the overall longitudinal difference in kynurenine concentrations using linear mixed models and can be interpreted as the amount of SD difference in kynurenine concentration/ratio according to 1 SD higher micronutrient intake or vitamin B status plasma marker. For example, a 1 SD increase in vitamin B2 intake (= 0.4 mg/d) is longitudinally associated with a 0.06 SD higher KA concentration (= 0.06 * 29.0 nmol/L = 1.7 nmol/L).

[3] A random slope was added to the model for: vitamin B2 with QA; vitamin B6 with AA; magnesium with HK, QA, and HKr; iron with Trp, Kyn, HK, KA, XA, AA, HAA, QA, and KTR; heme iron with Trp, AA, QA, and KTR; nonheme iron with Trp, Kyn, HK, KA, XA, HAA, QA, KTR, and HKr; copper with Trp, Kyn, HK, KA, XA, AA, HAA, QA, and HKr; and zinc with Trp, HK, KA, QA, and KTR.

[4] The β-coefficients represent the change in SD units of kynurenine concentration over time within individuals using a hybrid model within linear mixed models.

[5] The β-coefficients represent the difference in SD units of kynurenine concentration between individuals using a hybrid model within linear mixed models.

* Indicates a statistically significant result ($p<0.05$)

** Indicates a significant result after FDR adjustment for multiple testing ($q<0.05$)

FIGURE 3. Heatmap of confounder-adjusted linear mixed models between micronutrient intake and metabolites and ratios of the kynurenine pathway in colorectal cancer survivors. Analyses were adjusted for age at enrollment (years), sex (male or female), renal function (μmol/L), time since end-treatment (weeks), chemotherapy (yes or no), comorbidities (0, 1, or ≥2), stoma (yes or no), educational level (high, medium, or low), BMI (kg/m^2), total PA (hours/week), smoking status (current, former, or never), alcohol intake (g/d), and energy intake (kcal/d). A random slope was added to the model for vitamin B2 with QA; vitamin B6 with AA; magnesium with HK, QA, and HKr; iron with Trp, Kyn, HK, KA, XA, AA, HAA, QA, and KTR; heme iron with Trp, AA, QA, and KTR; nonheme iron with Trp, Kyn, HK, KA, XA, HAA, QA, KTR, and HKr; copper with Trp, Kyn, HK, KA, XA, AA, HAA, QA, and HKr; and zinc with Trp, HK, KA, QA, and KTR. The standardized β can be interpreted as the amount of SD difference in kynurenine concentration/ratio according to 1 SD higher micronutrient intake. For example, a 1 SD increase in vitamin B2 intake (= 0.4 mg/d) is longitudinally associated with a 0.06 SD higher KA concentration (= 0.06 * 29.0 nmol/L = 1.7 nmol/L). SDs of kynurenines are 12.0 μmol/L for Trp; 29.0 nmol/L for KA; 15.0 nmol/L for Pic; 0.5 μmol/L for Kyn, 8.0 nmol/L for XA; 7.0 nmol/L for AA; 15.0 nmol/L for HAA; 27.0 nmol/L for HK; 366.0 nmol/L for QA; 0.05 for KA/QA; 10.0 for KTR; 0.2 for HKr; and 11.0 nmol/L for Neopt. SDs of micronutrient intake are 0.4 mg/d for vitamin B2; 0.6 mg/d for vitamin B6; 85.0 mg/d for magnesium; 3.0 mg/d for total iron; 0.5 mg/d for heme iron; 3.0 mg/d for nonheme iron; 0.3 mg/d for copper; and 2.0 mg/d for zinc. Abbreviations: KA, kynurenic acid; Pic, picolinic acid; KA/QA ratio, kynurenic acid-to-quinolinic acid ratio; Trp, tryptophan; Kyn, kynurenine; XA, xanthurenic acid; AA, anthranilic acid, HAA, 3-hydroxyanthranilic acid; HK, 3-hydroxykynurenine; QA KTR, kynurenine-to-tryptophan ratio; HKr, hydroxykynurenine ratio. *Indicates a statistically significant result ($P < 0.05$). **Indicates a statistically significant result after FDR adjustment for multiple testing (q<0.05)

discrepant findings may be accounted for by differences between study populations (healthy subjects compared with cancer survivors).

To the best of our knowledge, associations between minerals and plasma kynurenines in humans have not been described yet, and current evidence comes mainly from in vitro studies [22]. The present study revealed a positive association between magnesium intake and the KA/QA ratio. It has been suggested that magnesium is required for quinolinic acid phosphoribosyl transferase activation, the enzyme responsible for the metabolism of QA in the direction of nicotinamide adenine dinucleotide (NAD) formation [49], potentially causing a higher KA/QA ratio. We did observe an inverse association of magnesium intake with QA, though not significantly before and after FDR adjustment, which may explain the higher observed KA/QA ratio. With respect to zinc, a study in rural Laotian children on the association of daily preventive zinc and therapeutic zinc supplementation with Kyn, Trp, and KTR reported no significant effects [50]. We found no significant association between these metabolites and KTR in our study, although our data revealed a significant association with XA and HK. In our study, ~20% of participants used over-the-counter supplements, and sample sizes were too small to report reliable associations. Nevertheless, when intake from vitamin- and mineral-containing supplements was added to dietary intake, associations between micronutrient intake and plasma kynurenines were considerably stronger. This stronger effect may be explained by the fact that absolute micronutrient intake is higher and the possibility of greater variation in micronutrient intake when micronutrient intake from supplements is summed to micronutrient intake from food. However, most of these associations lacked statistical significance, which is probably due to the relatively small sample size.

This study has several strengths. First, the prospective design involved repeated measurements of both macronutrient and micronutrient intake and plasma kynurenines with relevant ratios. Second, the estimation of macronutrient and micronutrient intake was assessed by 7-d dietary records, which is more accurate compared with the commonly used Food Frequency Questionnaire (FFQ) data. Besides, response rates during follow-up were high (>90%), and the number of

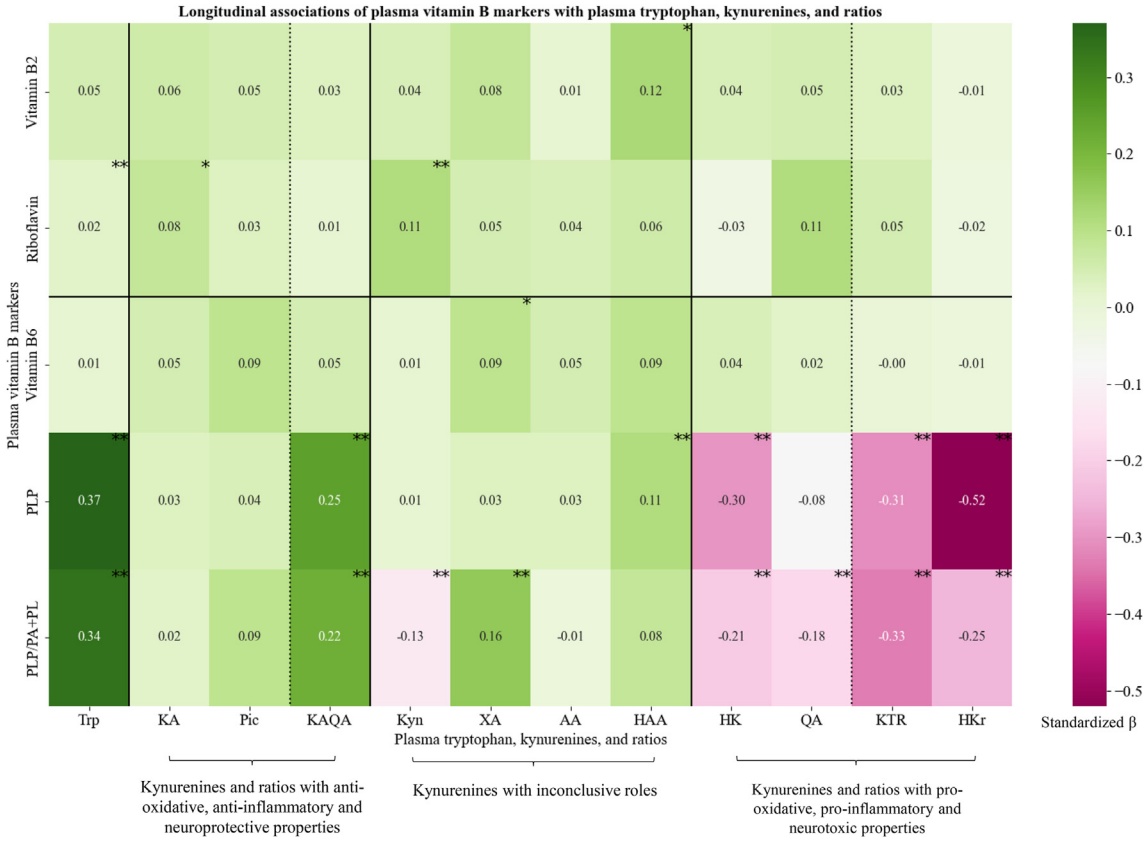

FIGURE 4. Heatmap of confounder-adjusted linear mixed models between plasma vitamin B status marker and metabolites and ratios of the kynurenine pathway in colorectal cancer survivors. Analyses were adjusted for age at enrollment (years), sex (male or female), renal function (μmol/L), time since end-treatment (weeks), chemotherapy (yes or no), comorbidities (0, 1, or ≥2), stoma (yes or no), educational level (high, medium, or low), BMI (kg/m^2), total PA (hours/week), smoking status (current, former, or never), alcohol intake (g/d), and energy intake (kcal/d). A random slope was added to the model for riboflavin with HK and QA; pyridoxal 5'-phosphate with Trp, Kyn, HK, AA, QA, KTR, HKr, and KA/QA; and PAr index with Kyn, HK, Pic, QA, KTR, HKr, and KA/QA. The standardized β can be interpreted as the amount of SD difference in kynurenine concentration/ratio according to 1 SD higher plasma vitamin B status marker. For example, a 1 SD increase in plasma PLP (= 42.0 nmol/L) is longitudinally associated with a 0.03 SD higher KA concentration (= 0.03 * 29.0 nmol/L = 0.9 nmol/L). Standard deviations of kynurenines are 12.0 μmol/L for Trp; 29.0 nmol/L for KA; 15.0 nmol/L for Pic; 0.5 μmol/L for Kyn, 8.0 nmol/L for XA; 7.0 nmol/L for AA; 15.0 nmol/L for HAA; 27.0 nmol/L for HK; 366.0 nmol/L for QA; 0.05 for KA/QA; 10.0 for KTR; 0.2 for HKr; and 11.0 nmol/L for Neopt. SDs of plasma markers of vitamin B status are: 53.0 nmol/L for riboflavin, 42.0 nmol/L for PLP, and 0.4 for PAr index. Abbreviations: KA, kynurenic acid; Pic, picolinic acid; KA/QA ratio, kynurenic acid-to-quinolinic acid ratio; Trp, tryptophan; Kyn, kynurenine; XA, xanthurenic acid; AA, anthranilic acid, HAA, 3-hydroxyanthranilic acid; HK, 3-hydroxykynurenine; QA KTR, kynurenine-to-tryptophan ratio; HKr, hydroxykynurenine ratio. *Indicates a statistically significant result ($P < 0.05$). **Indicates a statistically significant result after FDR adjustment for multiple testing (q<0.05)

missing data is limited. Moreover, information on macronutrient and micronutrient intake and the blood draw for the assessment of kynurenine concentrations and vitamin B markers in blood plasma was collected at the same time, ensuring no time lag between exposure and outcome. In addition, extensive data collection allowed adjustment for multiple (sometimes time-varying) potential confounders. Lastly, linear mixed models enabled distinguishing between intraindividual and interindividual associations, which provided valuable insights into the nature of the overall longitudinal associations.

However, this study also has limitations. First, a limited response rate at diagnosis (46%) to participate in the study and selective loss to follow-up might have resulted in selection bias. Although, it is unclear whether this affected the observed associations. We observed that participants with higher levels of education appeared to be more likely to stay in the study compared with those with lower education, suggesting that participants with less favorable dietary conditions and lower HRQoL may have been less likely to participate or keep participating. Selection bias could have led to smaller variation in both exposure and outcome variables than in the overall CRC survivorship population, which may have complicated the identification of significant associations, suggesting that our observed associations are true associations. Moreover, to facilitate the understanding of our findings, we classified the kynurenines into kynurenines with antioxidative, anti-inflammatory, and neuroprotective properties, compared with pro-oxidative, proinflammatory, and neurotoxic properties, compared with kynurenines with inconclusive roles. This choice was based on current evidence [18,51,52], but it is not unlikely that future studies will identify other roles of kynurenines as well. For instance, there has been a recent suggestion of a potential anti-inflammatory role of QA in brain cancer [53]. On top of that, it is difficult to draw firm conclusions regarding causality due to the observational nature of the present study.

To our knowledge, the current study is the first study exploring the associations between macronutrient and micronutrient intake with plasma Trp and kynurenines and ratios in CRC survivors. Future observational studies are needed to further elucidate the associations of macronutrient and micronutrient intake with metabolites of the kynurenine pathway. Ultimately, randomized controlled trials are recommended to infer causality. Another relevant next step would be to

investigate whether and how plasma kynurenines are related to HRQoL outcomes in CRC survivors. Eventually, insights into how diet-induced changes in kynurenines affect HRQoL can help to develop dietary guidelines or interventions to improve a patient's HRQoL after cancer.

In conclusion, our findings support the idea of a link between the diet and metabolites of the kynurenine pathway in CRC survivors up to 12 mo posttreatment. Overall, this study showed stronger associations for macronutrient intake with plasma Trp and kynurenines and ratios than for micronutrient intake. Further studies are necessary to confirm our findings, especially given that the kynurenine pathway might be an important underlying mechanism in the relationship between diet and quality of life after cancer.

Acknowledgments

We would like to thank all participants of the EnCoRe study and the health professionals in the 3 hospitals involved in the recruitment of participants of the study: Maastricht University Medical Centre+, VieCuri Medical Centre, and Zuyderland Medical Centre. We would also like to thank the MEMIC center for data and information management for facilitating the logistic processes and data management of our study. Finally, we would like to thank the research dietitians and research assistants who are responsible for patient inclusion and follow-up, performing home visits, as well as data collection and processing.

We would like to thank the members of "the biomarkers related to folate-dependent 1-carbon metabolism in colorectal cancer recurrence and survival" (FOCUS) consortium for their previous collaborate efforts in 1) enabling the assessment of kynurenine concentrations, which were also used for the current project, and in 2) advancing the expertise regarding these biomarkers.

Author contributions

The authors' responsibilities were as follows – SJPME, MPW, EHvR, MJLB, PMU: designed research, project conception, development of overall research plan, and study oversight. DDBH, EHvR: conducted research (hands-on conduct of the experiments and data collection). DDBH, EHvR, PMU, AU: provided essential reagents or provided essential materials (applies to authors who contributed by providing animals, constructs, databases, ect, necessary for the research). DDBH, SJPME, MPW: analyzed data or performed statistical analysis. DDBH, SJPME, MPW, EHvR, MJLB: wrote paper (only authors who made a major contribution). SJPME, MPW: had primarily responsibility for final content. All authors read and approved the final manuscript.

Conflict of interest

The authors report no conflicts of interest.

Funding

Funding for grant [WCRF: IIG_FULL_2020_018, recipient – S.J.P.M. Eussen) was obtained from Wereld Kanker Onderzoek Fonds (WKOF) as part of the World Cancer Research Fund International grant program. D.D.B. Holthuijsen is supported by this grant. The EnCoRe study was also supported by several other grants from Kanker-onderzoekfonds Limburg as part of Health Foundation Limburg (grant 00005739, to MPW), Stichting Alpe d'Huzes within the research program "Leven met kanker" of the Dutch Cancer Society grants UM 2010-4867 (to MPW) and UM 2012-5653 (to MPW), and by ERA-NET on Translational Cancer Research (TRANSCAN: Dutch Cancer Society (UM 2014-6877, to MPW), by Wereld Kanker Onderzoek Fonds (WKOF)/World Cancer Research Fund International (WCRF) (grant number 2017/1619 – recipient M.J.L. Bours; and grant number 2016/1620 to MPW). EHvR is supported by the Dutch Cancer Society (grant number 2021-1/13387). AG is supported by ERA-NET on Translational Cancer Research (TRANSCAN: Austrian Science Fund (FWF) (grant number AIPO2104FW).

Data Sharing

Data described in the manuscript, code book, and analytic code will be made available upon request pending (e.g., application and approval, payment, other). Requests for data of the EnCoRe study can be sent to Dr Martijn Bours, Department of Epidemiology, GROW School for Oncology and Reproduction, Maastricht University, the Netherlands (E-mail: m.bours@maastrichtuniversity.nl).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajcnut.2023.08.003.

References

[1] H. Sung, J. Ferlay, R.L. Siegel, M. Laversanne, I. Soerjomataram, A. Jemal, et al., Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA Cancer J. Clin. 71 (2021) 209–249.

[2] C. Parry, E.E. Kent, A.B. Mariotto, C.M. Alfano, J.H. Rowland, Cancer survivors: a booming population, Cancer Epidemiol. Biomarkers Prev. 20 (2011) 1996–2005.

[3] K.D. Miller, R.L. Siegel, C.C. Lin, A.B. Mariotto, J.L. Kramer, J.H. Rowland, et al., Cancer treatment and survivorship statistics, 2016, CA Cancer J. Clin. 66 (2016) 271–289.

[4] L. Jansen, L. Koch, H. Brenner, V. Arndt, Quality of life among long-term (⩾ 5 years) colorectal cancer survivors–systematic review, Eur. J. Cancer. 46 (2010) 2879–2888.

[5] L. Jansen, A. Herrmann, C. Stegmaier, S. Singer, H. Brenner, V. Arndt, Health-related quality of life during the 10 years after diagnosis of colorectal cancer: a population-based study, J. Clin. Oncol. 29 (2011) 3263–3269.

[6] J.E. Bower, The role of neuro-immune interactions in cancer-related fatigue: biobehavioral risk factors and mechanisms, Cancer 125 (2019) 353–364.

[7] M.F. Kenkhuis, F. Mols, E.H. van Roekel, J.J. Breedveld-Peters, S.O. Breukink, M.L. Janssen-Heijnen, et al., Longitudinal associations of adherence to the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) lifestyle recommendations with quality of life and symptoms in colorectal cancer survivors up to 24 months post-treatment, Cancers. (Basel). 14 (2022) 417.

[8] D.D.B. Holthuijsen, M.J.L. Bours, E.H. van Roekel, S.O. Breukink, M.L.G. Janssen-Heijnen, E.T.P. Keulen, et al., Longitudinal associations of adherence to the dietary World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) and Dutch Healthy Diet (DHD) recommendations with plasma kynurenines in colorectal cancer survivors after treatment, Nutrients 14 (2022) 5151.

[9] I. Cervenka, L.Z. Agudelo, J.L. Ruas, Kynurenines: tryptophan's metabolites in exercise, inflammation, and mental health, Science 357 (2017) eaaf9794.

[10] S. Kim, B.J. Miller, M.E. Stefanek, A.H. Miller, Inflammation-induced activation of the indoleamine 2, 3-dioxygenase pathway: relevance to cancer-related fatigue, Cancer 121 (2015) 2129–2136.

[11] L. Sforzini, M.A. Nettis, V. Mondelli, C.M. Pariante, Inflammation in cancer and depression: a starring role for the kynurenine pathway, Psychopharmacol (Berl) 236 (2019) 2997–3011.

[12] H. Li, T. Liu, L.W. Heinsberg, M.B. Lockwood, D.A. Wainwright, M.K. Jang, et al., Systematic review of the kynurenine pathway and psychoneurological symptoms among adult cancer survivors, Biol. Res. Nurs. 22 (2020) 472–484.

[13] M.W. Taylor, G.S. Feng, Relationship between interferon-γ, indoleamine 2, 3-dioxygenase, and tryptophan catabolism, FASEB J 5 (1991) 2516–2522.

[14] R. Baumgartner, M.J. Forteza, D.F.J. Ketelhuth, The interplay between cytokines and the kynurenine pathway in inflammation and atherosclerosis, Cytokine 122 (2019) 154148.

[15] O. Takikawa, T. Kuroiwa, F. Yamazaki, R. Kido, Mechanism of interferon-gamma action. Characterization of indoleamine 2, 3-dioxygenase in cultured human cells induced by interferon-gamma and evaluation of the enzyme-

mediated tryptophan degradation in its anticellular activity, J. Biol. Chem. 263 (1988) 2041–2048.
[16] A.A. Badawy, G. Guillemin, The plasma [kynurenine]/[tryptophan] ratio and indoleamine 2, 3-dioxygenase: time for appraisal, Int. J. Tryptophan Res. 12 (2019) 1178646919868978.
[17] L. Vécsei, L. Szalárdy, F. Fülöp, J. Toldi, Kynurenines in the CNS: recent advances and new questions, Nat. Rev. Drug. Discov. 12 (2013) 64–82.
[18] A. Mor, A. Tankiewicz-Kwedlo, A. Krupa, D. Pawlak, Role of kynurenine pathway in oxidative stress during neurodegenerative disorders, Cells 10 (2021) 1603.
[19] R. Poesen, H.A. Mutsaers, K. Windey, P.H. Van Den Broek, V. Verweij, P. Augustijns, et al., The influence of dietary protein intake on mammalian tryptophan and phenolic metabolites, PLoS One 10 (2015) e0140820.
[20] I. Żarnowska, D. Wróbel-Dudzińska, M. Tulidowicz-Bielak, T. Kocki, K. Mitosek-Szewczyk, M. Gasior, et al., Changes in tryptophan and kynurenine pathway metabolites in the blood of children treated with ketogenic diet for refractory epilepsy, Seizure 69 (2019) 265–272.
[21] J. Berg, N. Seyedsadjadi, R. Grant, Saturated fatty acid intake is associated with increased inflammation, conversion of kynurenine to tryptophan, and delta-9 desaturase activity in healthy humans, Int. J. Tryptophan. Res. 13 (2020) 1178646920981946.
[22] M. Majewski, A. Kozlowska, M. Thoene, E. Lepiarczyk, W.J. Grzegorzewski, Overview of the role of vitamins and minerals on the kynurenine pathway in health and disease, J. Physiol. Pharmacol. 67 (2016) 3–19.
[23] D. Theofylaktopoulou, A. Ulvik, Ø. Midttun, P.M. Ueland, S.E. Vollset, O. Nygård, et al., Vitamins B2 and B6 as determinants of kynurenines and related markers of interferon-γ-mediated immune activation in the community-based Hordaland health study, Br. J. Nutr. 112 (2014) 1065–1072.
[24] E.H. van Roekel, M.J. Bours, C.P. de Brouwer, H. Ten Napel, S. Sanduleanu, G.L. Beets, et al., The applicability of the international classification of functioning, disability, and health to study lifestyle and quality of life of colorectal cancer survivors, Cancer Epidemiol. Biomarkers Prev. 23 (2014) 1394–1405.
[25] J.L. Koole, M.J.L. Bours, J.J.L. Breedveld-Peters, E.H. van Roekel, S.O. Breukink, M.L.G. Janssen-Heijnen, et al., Is dietary supplement use longitudinally associated with fatigue in stage I-III colorectal cancer survivors? Clin. Nutr. 39 (2020) 234–241.
[26] Ø. Midttun, S. Hustad, P.M. Ueland, Quantitative profiling of biomarkers related to B-vitamin status, tryptophan metabolism and inflammation in human plasma by liquid chromatography/tandem mass spectrometry, Rapid Commun. Mass Spectrom. 23 (2009) 1371–1379.
[27] A. Ulvik, D. Theofylaktopoulou, Ø. Midttun, O. Nygård, S.J. Eussen, P.M. Ueland, Substrate product ratios of enzymes in the kynurenine pathway measured in plasma as indicators of functional vitamin B-6 status, Am. J. Clin. Nutr. 98 (2013) 934–940.
[28] Ø. Midttun, G. Kvalheim, P.M. Ueland, High-throughput, low-volume, multianalyte quantification of plasma metabolites related to one-carbon metabolism using HPLC-MS/MS, Anal. Bioanal. Chem. 405 (2013) 2009–2017.
[29] A. Ulvik, Ø. Midttun, E.R. Pedersen, S.J. Eussen, O. Nygård, P.M. Ueland, Evidence for increased catabolism of vitamin B-6 during systemic inflammation, Am. J. Clin. Nutr. 100 (2014) 250–255.
[30] P.M. Ueland, A. Ulvik, L. Rios-Avila, Ø. Midttun, J.F. Gregory, Direct and functional biomarkers of vitamin B6 status, Annu. Rev. Nutr. 35 (2015) 33–70.
[31] A. Ulvik, Ø. Midttun, A. McCann, K. Meyer, G. Tell, O. Nygård, et al., Tryptophan catabolites as metabolic markers of vitamin B-6 status evaluated in cohorts of healthy adults and cardiovascular patients, Am. J. Clin. Nutr. 111 (2020) 178–186.
[32] T.W. Stone, Kynurenic acid antagonists and kynurenine pathway inhibitors, Expert Opin. Investig Drugs 10 (2001) 633–645.
[33] G.C. Wendel-Vos, A.J. Schuit, W.H. Saris, D. Kromhout, Reproducibility and relative validity of the short questionnaire to assess health-enhancing physical activity, J. Clin. Epidemiol. 56 (2003) 1163–1169.
[34] E.H. van Roekel, J. Duchâteau, M.J.L. Bours, L. van Delden, J.J.L. Breedveld-Peters, J.L. Koole, et al., Longitudinal associations of light-intensity physical activity with quality of life, functioning and fatigue after colorectal cancer, Qual. Life Res. 29 (2020) 2987–2998.
[35] J.W.R. Twisk, W. de Vente, Hybrid models were found to be very elegant to disentangle longitudinal within-and between-subject relationships, J. Clin. Epidemiol. 107 (2019) 66–70.
[36] T.J. VanderWeele, Principles of confounder selection, Eur. J. Epidemiol. 34 (2019) 211–219.
[37] D. Theofylaktopoulou, Ø. Midttun, A. Ulvik, P.M. Ueland, G.S. Tell, S.E. Vollset, et al., A community-based study on determinants of circulating markers of cellular immune activation and kynurenines: the Hordaland Health Study, Clin. Exp. Immunol. 173 (2013) 121–130.
[38] G.D. Tomova, K.F. Arnold, M.S. Gilthorpe, P.W. Tennant, Adjustment for energy intake in nutritional research: a causal inference perspective, Am. J. Clin. Nutr. 115 (2022) 189–198.
[39] Y. Benjamini, Y. Hochberg, Controlling the false discovery rate: a practical and powerful approach to multiple testing, J. R. Stat. Soc. 57 (1995) 289–300.
[40] A.E. Buyken, V. Food, M. Empson, E. Rochtchina, A.W. Barclay, J. Brand-Miller, et al., Carbohydrate nutrition and inflammatory disease mortality in older adults, Am. J. Clin. Nutr. 92 (2010) 634–643.
[41] A.E. Buyken, J. Goletzke, G. Joslowski, A. Felbick, G. Cheng, C. Herder, et al., Association between carbohydrate quality and inflammatory markers: systematic review of observational and interventional studies, Am. J. Clin. Nutr. 99 (2014) 813–833.
[42] B.K.S. Silveira, T.M.S. Oliveira, P.A. Andrade, H.H.M. Hermsdorff, C.O.B. Rosa, S.D.C.C. Franceschini, Dietary pattern and macronutrients profile on the variation of inflammatory biomarkers: scientific update, Cardiol. Res. Pract. 2018 (2018) 4762575, https://doi.org/10.1155/2018/4762575.
[43] K. Berding, C. Carbia, J.F. Cryan, Going with the grain: fiber, cognition, and the microbiota-gut-brain-axis, Exp. Biol. Med. (Maywood). 246 (2021) 796–811.
[44] F. Rodriguez-Pacheco, C. Gutierrez-Repiso, S. Garcia-Serrano, M.A. Alaminos-Castillo, A. Ho-Plagaro, S. Valdes, et al., The pro-/anti-inflammatory effects of different fatty acids on visceral adipocytes are partially mediated by GPR120, Eur. J. Nutr. 56 (2017) 1743–1752.
[45] T. Karlsson, E. Strand, J. Dierkes, C.A. Drevon, J. Øyen, Ø. Midttun, et al., Associations between intake of fish and n-3 long-chain polyunsaturated fatty acids and plasma metabolites related to the kynurenine pathway in patients with coronary artery disease, Eur. J. Nutr. 56 (2017) 261–272.
[46] Ø. Midttun, A. Ulvik, E. Ringdal Pedersen, M. Ebbing, O. Bleie, H. Schartum-Hansen, et al., Low plasma vitamin B-6 status affects metabolism through the kynurenine pathway in cardiovascular patients with systemic inflammation, J. Nutr. 141 (2011) 611–617.
[47] A. Ulvik, Ø. Midttun, E.R. Pedersen, O. Nygård, P.M. Ueland, Association of plasma B-6 vitamers with systemic markers of inflammation before and after pyridoxine treatment in patients with stable angina pectoris, Am. J. Clin. Nutr. 95 (2012) 1072–1078.
[48] H. Zuo, G.S. Tell, P.M. Ueland, O. Nygård, S.E. Vollset, Ø. Midttun, et al., The PAr index, an indicator reflecting altered vitamin B-6 homeostasis, is associated with long-term risk of stroke in the general population: the Hordaland Health Study (HUSK), Am. J. Clin. Nutr. 107 (2018) 105–112.
[49] A.C. Foster, W.C. Zinkand, R. Schwarcz, Quinolinic acid phosphoribosyltransferase in rat brain, J. Neurochem. 44 (1985) 446–454.
[50] K.R. Wessells, G.M. Hinnouho, M.A. Barffour, C.D. Arnold, S. Kounnavong, C. Kewcharoenwong, et al., Impact of daily preventive zinc or therapeutic zinc supplementation for diarrhea on plasma biomarkers of environmental enteric dysfunction among rural Laotian children: a randomized controlled trial, Am. J. Trop. Med. Hyg. 102 (2020) 415–426.
[51] D. Arnone, S. Saraykar, H. Salem, A.L. Teixeira, R. Dantzer, S. Selvaraj, Role of kynurenine pathway and its metabolites in mood disorders: a systematic review and meta-analysis of clinical studies, Neurosci Biobehav. Rev. 92 (2018) 477–485.
[52] J. Savitz, The kynurenine pathway: a finger in every pie, Mol. Psychiatry 25 (2020) 131–147.
[53] P. Kesarwani, S. Kant, Y. Zhao, A. Prabhu, K.L. Buelow, C.R. Miller, et al., Quinolinate promotes macrophage-induced immune tolerance in glioblastoma through the NMDAR/PPARγ signaling axis, Nat. Commun. 14 (2023) 1459.