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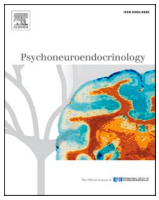

Longitudinal associations of plasma kynurenines and ratios with anxiety and depression scores in colorectal cancer survivors up to 12 months post-treatment

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ABSTRACT

Introduction: Colorectal cancer (CRC) survivors often experience neuropsychological symptoms, including anxiety and depression. Mounting evidence suggests a role for the kynurenine pathway in these symptoms due to potential neuroprotective and neurotoxic roles of involved metabolites. However, evidence remains inconclusive and insufficient in cancer survivors. Thus, we aimed to explore longitudinal associations of plasma tryptophan, kynurenines, and their established ratios with anxiety and depression in CRC survivors up to 12 months post-treatment.

Methods: In 249 stage I-III CRC survivors, blood samples were collected at 6 weeks, 6 months, and 12 months post-treatment to analyze plasma concentrations of tryptophan and kynurenines using liquid-chromatography tandem-mass spectrometry (LC/MS-MS). At the same timepoints, anxiety and depression were assessed using the Hospital Anxiety and Depression Scale (HADS). Confounder-adjusted linear mixed models were used to analyze longitudinal associations. Sensitivity analyses with false discovery rate (FDR) correction were conducted to adjust for multiple testing.

Results: Higher plasma tryptophan concentrations were associated with lower depression scores (β as change in depression score per 1 SD increase in the ln-transformed kynurenine concentration: −0.31; 95%CI: −0.56,−0.05), and higher plasma 3-hydroxyanthranilic acid concentrations with lower anxiety scores (−0.26; −0.52,−0.01). A higher 3-hydroxykynurenine ratio (HKr; the ratio of 3-hydroxykynurenine to the sum of kynurenic acid, xanthurenic acid, anthranilic acid, and 3-hydroxyanthranilic acid) was associated with higher

Abbreviations: AA, Anthranilic acid; BMI, Body mass index; CRC, Colorectal cancer; CRP, C-reactive protein; FDR, False discovery rate; HAA, 3-Hydroxyanthranilic acid; HADS, Hospital Anxiety and Depression scale; HK, 3-Hydroxykynurenine; HKr, Hydroxykynurenine ratio (3-hydroxykynurenine: (kynurenic acid + xanthurenic acid + 3-hydroxyanthranilic acid + anthranilic acid)); HRQoL, Health-related quality of life; IDO, Indoleamine 2,3-dioxygenase; 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; MVPA, Moderate-to-vigorous physical activity; PLP, Pyridoxal 5'-phosphate; QA, Quinolinic acid; SQUASH, Short Questionnaire to Assess Health-enhancing physical activity; Trp, Tryptophan; XA, Xanthurenic acid.

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depression scores (0.34; 0.04,0.63) and higher total anxiety and depression scores (0.53; 0.02,1.04). Overall associations appeared to be mainly driven by inter-individual associations, which were statistically significant for tryptophan with depression (−0.60; −1.12,−0.09), xanthurenic acid with total anxiety and depression (−1.04; −1.99,−0.10), anxiety (−0.51; −1.01,−0.01), and depression (−0.56; −1.08,−0.05), and kynurenic-acid-to-quinolinic-acid ratio with depression (−0.47; −0.93,−0.01). In sensitivity analyses, associations did not remain statistically significant after FDR adjustment.

Conclusion: We observed that plasma concentrations of tryptophan, 3-hydroxyanthranilic acid, xanthurenic acid, 3-hydroxykynurenine ratio, and kynurenic-acid-to-quinolinic-acid ratio tended to be longitudinally associated with anxiety and depression in CRC survivors up to 12 months post-treatment. Future studies are warranted to further elucidate the association of plasma kynurenines with anxiety and depression.

1. Introduction

Colorectal cancer (CRC) is the third most common malignancy in both men and women, with over a million new cases diagnosed globally every year (Sung et al., 2021; Xi and Xu, 2021). The global population of CRC survivors is increasing due to population ageing, advances in early detection, and improved treatment and prognosis (Parry et al., 2011). Apart from the physical symptoms of the disease and its treatment, anxiety and depression are common psychological comorbidities in CRC survivors, with reported rates up to 44.0% for depression and up to 32.5% for anxiety in this specific population (Peng, Huang and Kao, 2019). The underlying mechanisms remain poorly understood, but recent studies suggest a potential role for the kynurenine pathway in the development of anxiety and depression among cancer survivors due to potential neuroprotective and neurotoxic roles of involved metabolites (Sforzini et al., 2019).

The kynurenine pathway is a metabolic pathway in which the essential amino acid tryptophan (Trp) is catabolized into either serotonin (~5%) or into kynurenine (Kyn) (~95%) by the enzymes tryptophan 2,3-dioxygenase (TDO) and indoleamine 2,3-dioxygenases (IDO1 and 2). Serotonin is a neurotransmitter known to play a crucial role in regulating mood, sleep, and appetite (Gonzalez et al., 2008; Richard et al., 2009), and Kyn is a metabolite that can be further broken down into several metabolites, collectively termed the kynurenines. Specifically, Kyn can be converted to kynurenic acid (KA) by kynurenine transaminase, to anthranilic acid (AA) by kynureninase, and to 3-hydroxykynurenine (HK) by kynurenine monooxygenase (KMO). Thereafter, HK can be transformed into xanthurenic acid (XA) or 3-hydroxyanthranilic acid (HAA), which in turn can be converted into picolinic acid (Pic) or quinolinic acid (QA). The kynurenine pathway is suggested to play a crucial role in cancer progression by promoting CRC cell proliferation and inhibiting cell apoptosis through PI3K-Akt pathway activation (Liu et al., 2021). In addition, both inflammation-induced IDO (Crotti et al., 2017) and KMO (Liu et al., 2021) showed higher expression in tissue samples from CRC patients compared to those from healthy subjects. Overexpression of IDO is associated with higher KTR in CRC patients (Engin et al., 2015), while overexpression of KMO is associated with a higher tendency for conversion into more neurotoxic metabolites (i.e., HK and QA), increased risk of metastasis, and reduced CRC survival rates (Liu et al., 2021).

Trp catabolism may affect the onset of anxiety and depression in two ways. Firstly, the availability of tryptophan for serotonin synthesis may potentially be reduced by inflammation-induced activation of IDO (Dantzer et al., 2011), although some studies also indicated elevated serotonin levels under inflammatory conditions (Moncrieff et al., 2022; Shajib and Khan, 2015). Secondly, the balance of neurotoxic (i.e., HK and QA) and neuroprotective kynurenines (i.e., KA and Pic) may be disturbed (Vécsei et al., 2013).

There is evidence from the general population for the involvement of kynurenines in depression. Three meta-analyses that included mainly case-control studies investigating the role of Trp, Kyn, HK, KA, and QA, revealed that patients with depression (Ogyu et al., 2018) and patients with major depressive disorders (Marx et al., 2021; Pu et al., 2021) had decreased circulating levels of Trp, Kyn, KA, and KA/QA ratio, and that antidepressant-free patients had increased levels of QA compared to healthy controls (Ogyu et al., 2018). In a recent systematic literature review among adult cancer patients, but not CRC patients, it was concluded that decreased circulating Trp levels and increased circulating Kyn levels and kynurenine-to-tryptophan ratio (KTR) were related to a higher burden of psychoneurological symptoms, including anxiety and depression (Li et al., 2020). To our knowledge, only one relatively small cross-sectional study has investigated the relationship of a limited number of metabolites, including tryptophan, kynurenine, and KTR, with anxiety and depression assessed with the Hospital Anxiety and Depression Scale (HADS) in CRC survivors specifically, and this study reported no significant associations (Huang et al., 2002).

While there is limited evidence linking kynurenines to anxiety and depression in CRC survivors, a growing body of evidence suggests a link between the kynurenine pathway and anxiety and depression in cancer survivors in general (Li et al., 2020). Further, research has mainly focused on the role of Trp, Kyn, HK, KA, QA, and KTR in the onset of anxiety and depression, while the role of other kynurenines remains relatively unexplored. Therefore, this study aims to explore the longitudinal associations of plasma tryptophan, kynurenines, and their established ratios with anxiety and depression in CRC survivors up to 12 months post-treatment.

2. Material and methods

2.1. Study design and population

This study is part of the Energy for life after ColoRectal cancer (EnCoRe) study, which is an ongoing multicentre prospective cohort study among CRC survivors in the south-eastern part of the Netherlands. Since 2012, men and women aged 18 years or older and diagnosed with stage I-III CRC at Maastricht Medical Center+, VieCuri Medical Center, and Zuyderland Medical Center were recruited. Non-eligible participants were those with stage IV CRC, those living outside the Netherlands, those unable to understand and speak Dutch, and those with comorbidities that could hinder successful participation, such as Alzheimer's disease. The Medical Ethics Committee of the University Hospital Maastricht and Maastricht University approved the study (METC 11–3–075; Netherlands Trial Register number NL6904). The study was performed in accordance with the Declaration of Helsinki, and all participants provided written informed consent.

2.2. Data collection

Data from the EnCoRe study collected up until October 1, 2021 were used, including data at 6 weeks (n = 504), 6 months (n = 452), 12 months (n = 435), 24 months (n = 382), and 60 months (n = 131) post-treatment (Fig. 1). Prior to the COVID-19 pandemic, research dietitians collected data during home visits. From October 2020 onwards, due to the COVID-19 pandemic, data was collected remotely via postal methods. To ensure the accuracy of the measurements taken by participants themselves at home, we contacted them by phone to check the execution of the measurements. Individuals with at least one post-treatment measurement of kynurenines, the Hospital Anxiety and

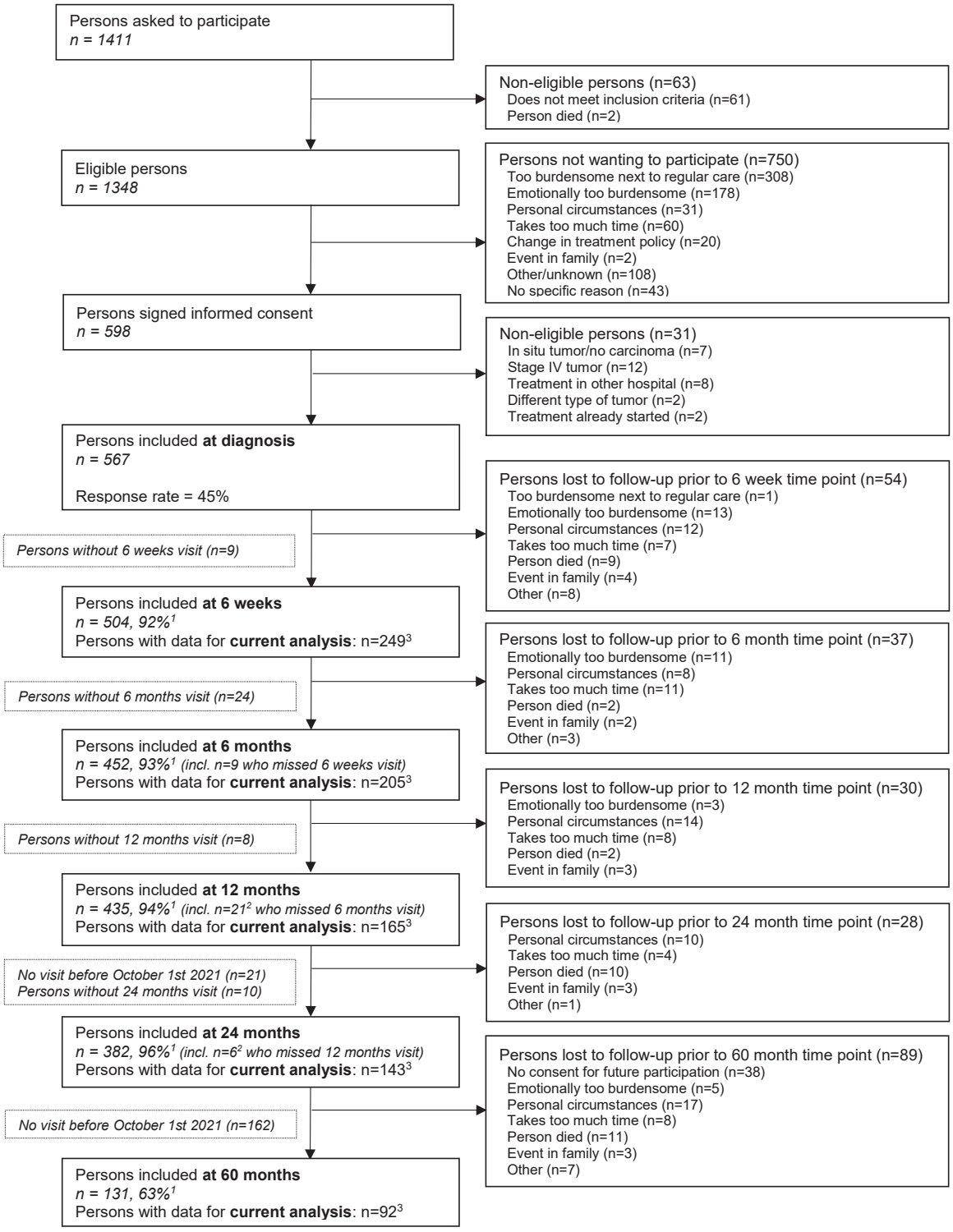

Fig. 1. Flow diagram of the inclusion of participants within the EnCoRe study and the number of post-treatment measurements included in the analyses presented in this paper. Data of home visits performed before October 1st, 2021 were included in the analyses. [1] Response rate = (persons with home visits)/(persons with home visits+persons lost to follow-up – persons died). The declining number of participants at subsequent time points is because not all participants included at diagnosis from April 2012 onwards had reached these time points in October 2021. [2] Of the 24 participants without 6 months visit, three participants did also have no 12 months visit. Of the 8 participants without 12 months visit, two participants did also have no 24 months visit. [3] Since the current analysis was focused on kynurenines and anxiety and depression symptoms after colorectal cancer treatment, only post-treatment measurements with available data on kynurenines, anxiety and depression, and covariates were included. No kynurenines were analyzed at 24 and 60 months post-treatment, but to still be able to determine the association of kynurenines with long-term anxiety and depression, we analyzed participants with data on kynurenines at 12 months post-treatment and data on anxiety and depression at 24 months and 60 months post-treatment.

Depression Scale (HADS), and covariates were included in the current analysis. Kynurenines were analyzed as part of a project involving participants who had their blood drawn prior to November 1, 2016 (Gigic et al., 2022; Koole et al., 2020), Consequently, data on kynurenines were available for participants up to 12 months post-treatment. Anxiety and depression were measured for participants who had their measurement before October 1, 2021, hence, data on anxiety and depression were available for participants up to 60 months post-treatment. In total, n = 249 had data on kynurenines and HADS at 6 weeks, n = 205 at 6 months, and n = 165 at 12 months. Moreover, n = 143 participants had data on kynurenines at 12 months post-treatment and HADS at 24 months post-treatment, while n = 92 had data on kynurenines at 12 months post-treatment and HADS at 60 months post-treatment. Follow-up participation rate was high (>90%) up to 24 months post-treatment, and lower but still substantial at 60 months post-treatment (63%). This decrease can be explained by the late initiation of the 60 months post-treatment measurement (from August 2017 onwards) which required renewed consent as the initial consent was for the first two years.

2.3. Plasma kynurenines

Blood samples were drawn from fasting participants according to standardized protocols and collected in 8.5 mL EDTA tubes. EDTA plasma samples were divided into 500 µl aliquots and stored at − 80 °C within 4 h after blood draw until analysis. Subsequently, samples were transported on dry ice to the laboratory of Bevital in Bergen, Norway (www.bevital.no). Nine metabolites of the kynurenine pathway were analyzed using liquid chromatography-tandem mass spectrometry (LC/MS-MS), including tryptophan (Trp), kynurenine (Kyn), 3-hydroxykynurenine (HK), kynurenic acid (KA), xanthurenic acid (XA), anthranilic acid (AA), 3-hydroxyanthranilic acid (HAA), picolinic acid (Pic), and quinolinic acid (QA) (Midttun, Hustad and Ueland, 2009; Midttun, Kvalheim and Ueland, 2013). The within-day and between-day variation coefficients for tryptophan and kynurenines have previously been determined to be in the range of 3.0–9.5% and 5.7–16.9%, respectively (Midttun, Hustad and Ueland, 2009). The limit of detection (LOD) ranges from 400 µmol/L (for Trp) to 7.0 nmol/L (for Kyn) (Midttun, Hustad and Ueland, 2009). Creatinine, an index of renal function, neopterin, a marker for immune system activation, and pyridoxal 5'-phosphate (PLP), a marker of vitamin B6 status, and riboflavin, a marker of vitamin B2 status, were also analyzed using LC/MS-MS (Midttun, Hustad and Ueland, 2009; Midttun, Kvalheim and Ueland, 2013). C-reactive protein (CRP), a marker of low-grade inflammation and marginally associated with KTR (Dugué et al., 2022; Pertovaara et al., 2007; Zuo et al., 2014), was measured by an immune-matrix-assisted laser desorption/ionization-MS approach (Meyer and Ueland, 2014).

Three relevant ratios of individual kynurenine concentrations were studied. The kynurenine-to-tryptophan ratio (KTR), which is a well-known indicator 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) (Badawy and Guillemin, 2019; Takikawa et al., 1988). The 3-hydroxykynurenine ratio (HKr), a functional marker of vitamin B6 status (Ulvik et al., 2020; Ulvik et al., 2013), 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) (HKr = HK:(KA+AA+XA+HAA). Furthermore, it has been demonstrated that the HKr shows an inverse association with PLP (Ueland et al., 2015). The kynurenic acid-to-quinolinic acid ratio (KA/QA), which is a ratio between the N-methyl-D-aspartate (NMDA) receptor antagonist (KA) and agonist (QA), was calculated by dividing the plasma concentration of KA (in nmol/L) by the plasma concentration of QA (in nmol/L) (Stone, 2001).

2.4. Anxiety and depression

The Hospital Anxiety and Depression Scale (HADS) was used to assess the presence and severity of mental distress (Zigmond and Snaith, 1983). The HADS is composed of 14 items and provides a total anxiety and depression score (14 items, range: 0–42), as well as separate scores for anxiety (7 items, range: 0–21) and depression (7 items, range: 0–21). Participants rate the severity of each symptom described in an item from 0 (not present) to 3 (highly present) over the past 7 days. A higher score represents greater anxiety- and depression-related symptoms, with a cut-off value of ≥ 8 points on a subscale indicating a (potential) anxiety or depression disorder (Bjelland et al., 2002). The HADS has been demonstrated to have adequate psychometric properties in cancer patients (Vodermaier, Linden and Siu, 2009). The Cronbach's alpha coefficients are 0.83 and 0.82 for anxiety-related items and depression-related items, respectively. Sensitivity and specificity of the HADS for both anxiety and depression subscales are approximately 0.80 (Bjelland et al., 2002).

2.5. Covariates

Age, sex, and clinical variables, including cancer stage, tumour site, and cancer treatment, were retrieved from medical records. Highest attained education level was self-reported by participants only at diagnosis. At all post-treatment measurements, the number of comorbidities was determined using the Self-Administered Comorbidity Questionnaire (Sangha et al., 2003) and the presence of a stoma was self-reported. Lifestyle-related variables were also assessed at each post-treatment time point, including body mass index (BMI; kg/m^2) based on body weight (kg) and height (m) measured by trained dietitians during home visits; self-reported smoking status (never, former or current); alcohol intake (g/day) and energy intake (kcal/day) assessed through 7-day dietary records; and self-reported time spent in moderate-to-vigorous physical activity (MVPA) assessed by the Short QUestionnaire to ASsess Health-enhancing physical activity (SQUASH) (Wendel-Vos et al., 2003); and objectively assessed prolonged sedentary time (total time in h/day spent in sedentary bouts lasting at least 30 min) using the validated tri-axial MOX activity monitor worn 24 h/day for 7 consecutive days (Berendsen et al., 2014; Van Roekel et al., 2016).

2.6. Statistical analysis

Descriptive analyses for sociodemographic, clinical, and lifestyle variables at each post-treatment time point were performed to describe main population characteristics. Pearson correlation coefficients were calculated to assess the correlation between metabolites of the kynurenine pathway.

In the main analysis, longitudinal associations of plasma tryptophan, kynurenines, and their established ratios with total anxiety and depression scores and subscales (anxiety and depression) between 6 weeks and 12 months post-treatment were analyzed using linear mixed models. A random intercept for each participant was added to all models, and the use of random slopes was tested with a likelihood-ratio test; random slopes were added when the model fit significantly improved. The regression coefficients for the longitudinal associations represent a combined effect of both between-subject (that is how differences over time in average plasma kynurenine concentrations between participants are associated with anxiety and depression), and within-subject components (that is how changes in kynurenine concentrations within participants over time are associated with anxiety and depression). Hybrid modelling was used to further analyse the between- and within-subject components (Twisk and de Vente, 2019). The between-subject component was modelled as the mean kynurenine concentration for each participant across time points, and the within-subject component was modelled as the difference between the kynurenine concentration at each time point and the mean across time

points. Metabolite concentrations were logtransformed using the natural logarithm (ln). To enable comparison between regression coefficients independent of which exposure was modelled, ln-transformed metabolites were divided by their mean SD across post-treatment time points. Thus, regression coefficients represent the change in outcome per SD increase in the ln-transformed metabolite.

In secondary analyses, long-term associations of plasma tryptophan, kynurenines, and their established ratios at 12 months post-treatment with anxiety and depression at 24 months and 60 months post-treatment were analyzed using linear regression analysis.

Potential confounders were identified a priori based on literature and theoretical considerations (Theofylaktopoulou et al., 2013). Linear mixed models were adjusted for fixed variables including age at enrolment (years), sex (male, female), chemotherapy (yes, no), and time-varying variables, including creatinine (μmol/L) as a proxy of renal function, number of comorbidities (0, 1, ≥2), presence of a stoma (yes, no), time since end of treatment (weeks), BMI (kg/m^2), MVPA (h/week), smoking status (current, former, never), alcohol intake (g/day), energy intake (kcal/day), and PLP concentration (nmol/L). Linear regression models (i.e., secondary analyses) were adjusted for the same covariates as those in linear mixed model, but at a fixed time point at 12 months post-treatment. In addition, linear regression models were adjusted for total anxiety and depression score at 12 months post-treatment. Importantly, in analyses with HKr as exposure, PLP was not included as a covariate.

An additional analysis was conducted to investigate the longitudinal association between neopterin, a metabolite not part of the kynurenine pathway, but closely related to it as a marker of interferon-gamma activity (INF-γ) and anxiety and depression. Prior research has demonstrated strong correlations between neopterin and KTR (Fuchs et al., 1991; Strasser et al., 2017). Additionally, longitudinal associations of PLP and riboflavin, both enzymatic cofactors in the kynurenine pathway, with anxiety and depression were explored in additional analysis. Moreover, since many exposures (nine metabolites of the kynurenine pathway and three ratios) were analysed in association with anxiety and depression, the analyses for each subscale of the HADS (anxiety and depression) and total scale were adjusted separately in a sensitivity analyses for multiple testing using the false discovery rate (FDR) method (Benjamini and Hochberg, 1995). Statistical significance was defined at q-values of < 0.05. In addition, several sensitivity analyses were performed to assess additional potential confounding by highest attained education level, prolonged sedentary time, CRP and riboflavin.

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

3. Results

3.1. Participant characteristics

Table 1 shows the characteristics of included study participants (n = 249) at 6 weeks, 6 months, and 12 months post-treatment. Mean age at 6 weeks post-treatment was 66.9 (SD: 9.2) years, and just over two-thirds were men (69.1%). The vast majority of participants were colon cancer survivors (61.4%), whereas 38.6% were rectum cancer

Table 1
Sociodemographic, clinical and lifestyle characteristics of participants included in the Energy for life after ColoRectal cancer (EnCoRe) study at 6 weeks, 6 months and 12 months post-treatment with data on kynurenines.

	6 weeks post-treatment (n = 249)[a]	6 months post-treatment (n = 205)[a]	12 months post-treatment (n = 165)[a]
Sex (men), n(%)	172 (69.1)	136 (66.3)	114 (69.1)
Age (years), mean(SD)	66.9 (9.2)	67.6 (9.4)	67.8 (9.2)
Tumor site, n(%)			
Colon	153 (61.4)	126 (61.5)	99 (60.0)
Rectum	96 (38.6)	79 (38.5)	66 (40.0)
Cancer stage, n(%)			
Stage I	81 (32.5)	67 (32.7)	53 (32.1)
Stage II	59 (23.7)	51 (24.9)	47 (28.5)
Stage III	109 (43.8)	87 (42.4)	65 (39.4)
Cancer treatment, n(%)			
Surgery (yes)	223 (89.6)	186 (90.7)	148 (89.7)
Chemotherapy (yes)	94 (37.8)	77 (37.6)	58 (35.2)
Radiotherapy (yes)	69 (27.7)	56 (27.3)	47 (28.5)
Number of comorbidities, n(%)			
0 comorbidities	51 (20.5)	46 (22.4)	41 (25.0)
1 comorbidity	60 (24.1)	47 (22.9)	38 (23.2)
≥ 2 comorbidities	138 (55.4)	112 (54.6)	85 (51.8)
Stoma (yes), n(%)	79 (31.7)	44 (21.5)	26 (15.8)
BMI (kg/m^2), mean(SD)	27.8 (4.5)	28.2 (4.4)	28.4 (4.6)
Educational level, n(%)			
Low	62 (25.0)	54 (26.5)	36 (22.0)
Medium	99 (39.9)	85 (41.7)	72 (43.9)
High	87 (35.1)	65 (31.9)	56 (34.1)
Smoking status, n(%)			
Never	83 (33.5)	62 (30.4)	47 (28.7)
Former	142 (57.3)	127 (62.3)	100 (61.0)
Current	23 (9.3)	15 (7.4)	17 (10.4)
MVPA (h/week), median(IQR)	7.0 (11.5)	9.0 (11.0)	9.8 (13.5)
Prolonged sedentary behavior (h/day), mean(SD)	4.8 (2.4)	4.4 (1.9)	4.4 (1.8)
Total energy intake (kcal/day), mean(SD)	2105.9 (507.5)	2003.8 (464.2)	2016.7 (486.1)
Alcohol intake (g/day), mean(SD)	13.6 (18.6)	13.0 (19.2)	14.5 (19.3)
Pyridoxal 5'-phosphate (nmol/L), median(IQR)	38.3 (27.3)	42.3 (32.1)	40.5 (29.8)
Creatinine (μmol/L), median(IQR)	81.7 (10.9)	82.9 (21.6)	92.8 (20.9)
Neopterin (nmol/L), median(IQR)	15.9 (12.0)	15.3 (10.3)	14.8 (8.8)
C-reactive protein (μg/mL), median (IQR)[b]	2.1 (4.0)	1.8 (3.6)	1.7 (4.4)

Abbreviations: BMI, body mass index; MVPA, moderate-to-vigorous physical activity; SD, standard deviation; IQR, interquartile range.
[a] Numbers may not correspond to the total number of participants included at each time point due to missing data, and percentages may not add up to 100 due to rounding.
[b] n = 209 at 6 weeks post-treatment, n = 167 at 6 months post-treatment, n = 126 at 12 months post-treatment.

Table 2
Descriptive analysis of exposures (plasma tryptophan, kynurenines, and their established ratios) and outcomes (anxiety and depression) among colorectal cancer survivors at 6 weeks, 6 months, 12 months, 24 months, and 60 months post-treatment.

	6 weeks post-treatment	6 months post-treatment	12 months post-treatment	24 months post-treatment	60 months post-treatment
Plasma kynurenines	**n = 249**	**n = 205**	**n = 165**		
Tryptophan (μmol/L)	66.1 (12.3)	67.5 (16.0)	68.2 (14.7)	*na*	*na*
Kynurenine (μmol/L)	1.9 (0.6)	1.8 (0.6)	1.8 (0.6)	*na*	*na*
3-Hydroxykynurenine (nmol/L)[a]	50.7 (27.7)	47.9 (22.7)	47.1 (21.8)	*na*	*na*
Kynurenic acid (nmol/L)	53.8 (25.1)	59.3 (27.6)	59.4 (30.7)	*na*	*na*
Xanthurenic acid (nmol/L)	12.9 (9.3)	14.7 (9.6)	15.1 (10.2)	*na*	*na*
Anthranilic acid (nmol/L)[a]	16.0 (6.7)	16.6 (7.5)	16.2 (8.1)	*na*	*na*
3-Hydroxyanthranilic acid (nmol/L)[a]	43.1 (18.7)	42.7 (18.2)	42.9 (18.1)	*na*	*na*
Picolinic acid (nmol/L)	33.6 (16.1)	35.9 (16.7)	35.4 (18.2)	*na*	*na*
Quinolinic acid (nmol/L)	510.0 (341.0)	492.0 (276.0)	455.0 (269.0)	*na*	*na*
KTR	28.7 (9.2)	27.2 (8.4)	26.7 (7.6)	*na*	*na*
HKr[a]	0.39 (0.19)	0.35 (0.15)	0.34 (0.12)	*na*	*na*
KA/QA ratio	0.10 (0.05)	0.12 (0.06)	0.13 (0.06)	*na*	*na*
Anxiety and depression: HADS	**n = 249**	**n = 205**	**n = 165**	**n = 146**	**n = 95**
Total score (range: 0 – 42)	7.3 ± 6.4 (0 – 30)	7.3 ± 6.6 (0 – 32)	6.8 ± 6.3 (0 – 33)	6.7 ± 6.8 (0 – 34)	7.6 ± 6.4 (0 – 28)
Anxiety (range: 0 – 21)	3.5 ± 3.4 (0 – 15)	3.5 ± 3.4 (0 – 15)	3.4 ± 3.5 (0 – 16)	3.4 ± 3.5 (0 – 17)	3.7 ± 3.6 (0 – 18)
No anxiety disorder (<8 points), n (%)	218 (87.6)	177 (86.3)	142 (86.1)	131 (89.7)	81 (85.3)
Anxiety disorder (≥8 points), n(%)	31 (12.4)	28 (13.7)	23 (13.9)	15 (10.3)	14 (14.7)
Depression (range: 0 – 21)	3.8 ± 3.6 (0 – 16)	3.8 ± 3.8 (0 – 19)	3.4 ± 3.4 (0 – 17)	3.3 ± 3.7 (0 – 18)	3.9 ± 3.4 (0 – 16)
No depression (<8 points), n(%)	210 (84.3)	174 (84.9)	144 (87.3)	128 (87.7)	81 (85.3)
Depression (≥8 points), n(%)	39 (15.7)	31 (15.1)	21 (12.7)	18 (12.3)	14 (14.7)

Plasma kynurenine concentrations are presented as median (IQR).
HADS scores are presented as mean ± SD (range).
Abbreviations: KTR, kynurenine-to-tryptophan ratio; HKr, hydroxykynurenine ratio (HKr = HK:(KA+AA+XA+HAA)); KA/QA, kynurenic acid-to-quinolinic acid; HADS, Hospital Anxiety Depression Scale; IQR, interquartile range; SD, standard deviation; na, not available.
[a] At 6 weeks post-treatment: n = 247 and at 6 months post-treatment: n = 204.

survivors. In addition, 32.5% had stage I, 23.7% had stage II, and 43.8% had stage III CRC. Almost all participants underwent surgery (89.6%). Other treatments received included both neo-adjuvant and adjuvant chemotherapy (37.8%) and radiotherapy (27.7%).

Plasma concentrations of tryptophan, kynurenine, and their established ratios, total anxiety and depression scores, anxiety scores, and depression scores over time are depicted in Table 2. Highest scores of anxiety, depression, and total anxiety and depression scores were observed at 60 months post-treatment. Anxiety scores remained relatively stable over time and no statistically significant differences over time were observed (Fig. 2A). From 6 months after treatment onwards, depression scores and total anxiety and depression scores decreased up to 24 months post-treatment, albeit non-significantly, and increased significantly ($p < 0.05$) thereafter between 24 months and 60 months post-treatment (Figs. 2B and 2C). Depression and total anxiety and depression scores also increased significantly ($p < 0.05$) from all previous measurement timepoints up to 60 months post-treatment. In general, men and women showed a similar trend over time for anxiety, depression, and total anxiety and depression scores.

Additionally, cross-sectional correlations of metabolites and ratios of the kynurenine pathway, neopterin, and CRP at 6 weeks post-treatment are displayed in Supplementary Figure 1.

3.2. Longitudinal associations of plasma tryptophan, kynurenines, and their established ratios with anxiety and depression up to 12 months post-treatment

In confounder-adjusted linear mixed models, assessing overall longitudinal associations from 6 weeks to 12 months post-CRC treatment, higher Trp concentrations were associated with lower depression scores (β as change in depression score per 1 SD increase in the ln-transformed kynurenine concentration: −0.31; 95%CI: −0.56, −0.05), and higher HAA concentrations were associated with lower anxiety scores (−0.26; −0.52, −0.01) (Table 3). The overall association of Trp with the depression score appeared to be driven by inter-individual associations, indicating that a higher Trp concentration over time between persons was associated with a lower depression score (−0.60; −1.12, −0.09). In addition, we observed that higher levels of HKr were associated with higher depression scores (0.34; 0.04, 0.63) and total anxiety and depression scores (0.53; 0.02, 1.04).

Although overall associations of XA and KA/QA ratio with HADS scores were not significant, inter-individual associations were statistically significant for XA with anxiety score (−0.51; −1.01, −0.01), depression score (−0.56; −1.08, −0.05), and total anxiety and depression score (−1.04; −1.99, −0.10), and for the KA/QA ratio with depression score (−0.47; −0.93, −0.01) (Table 3).

3.3. Sensitivity analyses

Sensitivity analyses with FDR adjustment for multiple testing showed that none of the significant longitudinal associations of plasma tryptophan, kynurenines, and their established ratios with anxiety and depression remained statistically significant. Results of the analysis with additional adjustment for education level and prolonged sedentary behaviour generally indicated a slight amplification of the observed associations in comparison to the main analysis (Supplementary Figure 2A). Additional adjustment for riboflavin produced mostly similar results (Supplementary Figure 2B), while additional adjustment for CRP resulted in a slight attenuation of the results compared to the main analysis (Supplementary Figure 2C). Confounder-adjusted longitudinal associations of plasma neopterin with anxiety and depression were comparable to those of KTR, and associations of PLP with anxiety and depression were opposite to those of HKr (Supplementary Table 1).

3.4. Secondary analyses

Confounder-adjusted linear regression models, assessing the long-term association of plasma tryptophan, kynurenine, and their established ratios at 12 months post-treatment with anxiety and depression scores at 24 months (n = 143) and 60 months (n = 92) post-treatment, yielded similar, yet slightly stronger, results in terms of direction for KA and Pic as in the linear mixed models analysing longitudinal associations

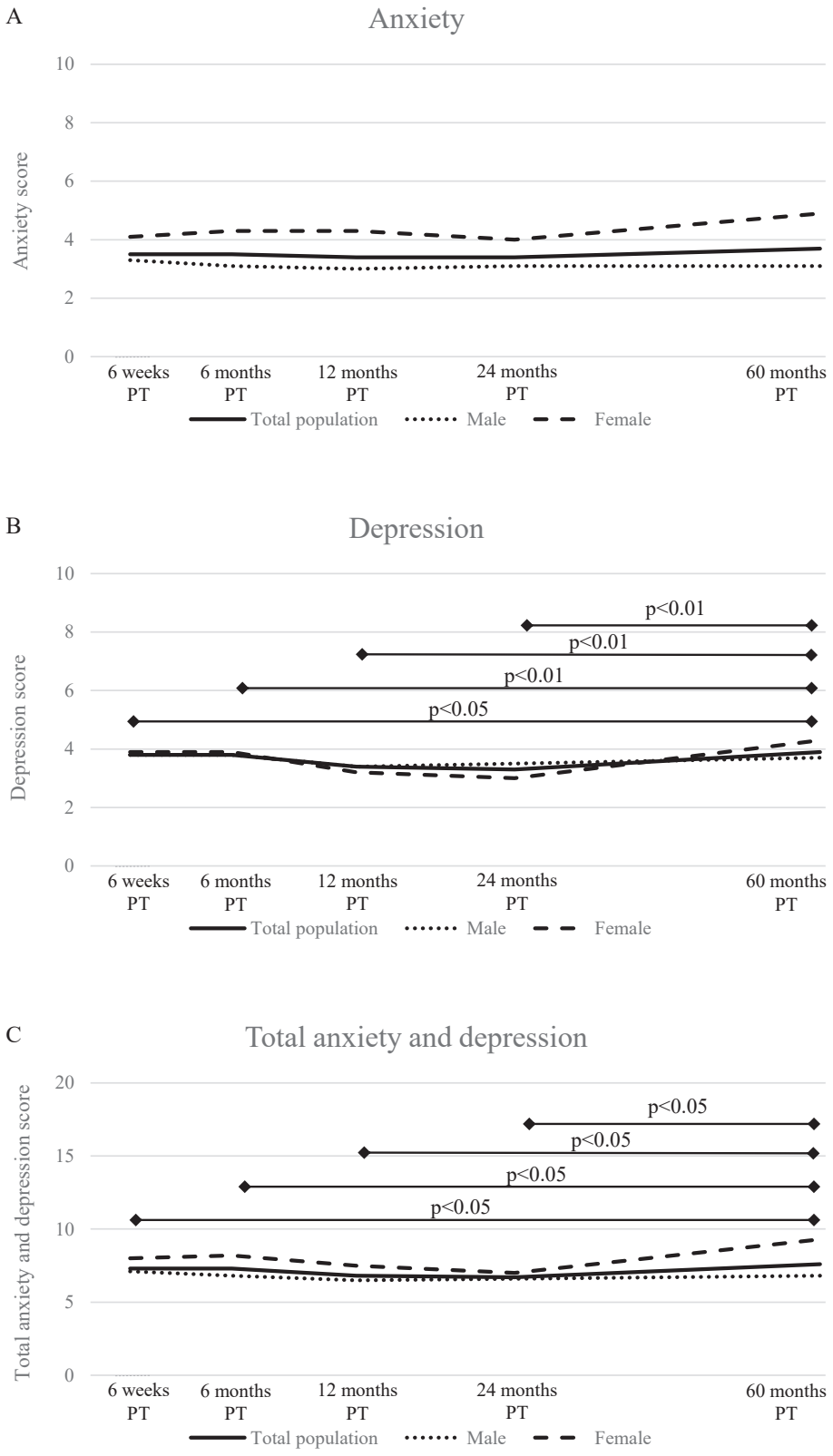

Fig. 2. Course of anxiety, depression, and total anxiety and depression scores (HADS) from 6 weeks up to 60 months post-treatment (PT) in CRC survivors included in the EnCoRe study. To obtain p-values for differences between follow-up timepoints for the total population, linear mixed models were conducted with the depression and anxiety variables as outcome variable and time modelled as independent categorical variable represented by dummy variables.

Table 3
Longitudinal associations of plasma tryptophan, kynurenines, and their established ratios with anxiety, depression, and total HADS score in colorectal cancer survivors (n = 249), between 6 weeks and 12 months post-treatment.

		Anxiety score (0 – 21)		Depression score (0 – 21)		Total anxiety and depression score (0 – 42)	
		β	(95% CI)	β	(95% CI)	β	(95% CI)
Tryptophan (μmol/L)	Unadjusted[1,2]	-0.20	(−0.42, 0.02)	-0.43 *	(−0.66, −0.19)	-0.60 *	(−0.99, −0.21)
	Adjusted[1,2,3]	-0.11	(−0.35, 0.12)	-0.31 *	(−0.56, −0.05)	-0.39	(−0.81, 0.04)
	Intra[4]	-0.05	(−0.32, 0.22)	-0.21	(−0.50, 0.08)	-0.24	(−0.72, 0.23)
	Inter[5]	-0.35	(−0.85, 0.16)	-0.60 *	(−1.12, −0.09)	-0.95	(−1.90, 0.00)
Kynurenine (μmol/L)	Unadjusted[1,2]	-0.24	(−0.49, 0.00)	0.03	(−0.24, 0.31)	-0.21	(−0.68, 0.25)
	Adjusted[1,2,3]	-0.29	(−0.58, 0.01)	-0.17	(−0.49, 0.15)	-0.43	(−0.97, 0.11)
	Intra[4]	-0.21	(−0.56, 0.14)	-0.19	(−0.57, 0.19)	-0.38	(−0.99, 0.23)
	Inter[5]	-0.47	(−0.98, 0.03)	-0.14	(−0.66, 0.39)	-0.57	(−1.53, 0.40)
3-Hydroxykynurenine (nmol/L)	Unadjusted[1,2]	-0.01	(−0.27, 0.26)	0.39 *	(0.12, 0.67)	0.38	(−0.09, 0.85)
	Adjusted[1,2,3]	-0.02	(−0.33, 0.29)	0.24	(−0.09, 0.57)	0.24	(−0.31, 0.79)
	Intra[4]	0.02	(−0.34, 0.39)	0.25	(−0.15, 0.65)	0.27	(−0.36, 0.91)
	Inter[5]	-0.11	(−0.63, 0.40)	0.22	(−0.31, 0.75)	0.16	(−0.81, 1.13)
Kynurenic acid (nmol/L)	Unadjusted[1,2]	-0.30 *	(−0.56, −0.05)	-0.24	(−0.51, 0.04)	-0.55 *	(−1.01, −0.09)
	Adjusted[1,2,3]	-0.26	(−0.59, 0.07)	-0.27	(−0.62, 0.08)	-0.48	(−1.06, 0.10)
	Intra[4]	-0.18	(−0.54, 0.18)	-0.21	(−0.60, 0.19)	-0.37	(−1.01, 0.27)
	Inter[5]	-0.46	(−0.99, 0.07)	-0.41	(−0.97, 0.14)	-0.81	(−1.81, 0.19)
Xanthurenic acid (nmol/L)	Unadjusted[1,2]	-0.34 *	(−0.58, −0.10)	-0.33 *	(−0.57, −0.08)	-0.65 *	(−1.06, −0.24)
	Adjusted[1,2,3]	-0.25	(−0.52, 0.02)	-0.24	(−0.53, 0.04)	-0.46	(−0.93, 0.02)
	Intra[4]	-0.19	(−0.49, 0.11)	-0.12	(−0.45, 0.21)	-0.29	(−0.82, 0.24)
	Inter[5]	-0.51 *	(−1.01, −0.01)	-0.56 *	(−1.08, −0.05)	-1.04 *	(−1.99, −0.10)
Anthranilic acid (nmol/L)	Unadjusted[1,2]	-0.19	(−0.43, 0.06)	0.09	(−0.17, 0.36)	-0.10	(−0.53, 0.34)
	Adjusted[1,2,3]	-0.21	(−0.48, 0.05)	0.07	(−0.22, 0.35)	-0.14	(−0.61, 0.34)
	Intra[4]	-0.17	(−0.47, 0.14)	0.16	(−0.18, 0.50)	-0.02	(−0.56, 0.53)
	Inter[5]	-0.34	(−0.81, 0.14)	-0.14	(−0.63, 0.35)	-0.49	(−1.39, 0.42)
3-Hydroxyanthranilic acid (nmol/L)	Unadjusted[1,2]	-0.30 *	(−0.54, −0.06)	0.01	(−0.25, 0.27)	-0.30	(−0.72, 0.13)
	Adjusted[1,2,3]	-0.26 *	(−0.52, −0.01)	0.00	(−0.27, 0.28)	-0.25	(−0.70, 0.21)
	Intra[4]	-0.26	(−0.55, 0.03)	0.01	(−0.31, 0.32)	-0.25	(−0.76, 0.26)
	Inter[5]	-0.27	(−0.76, 0.23)	-0.01	(−0.53, 0.50)	-0.24	(−1.19, 0.70)
Picolinic acid (nmol/L)	Unadjusted[1,2]	-0.28 *	(−0.52, −0.04)	-0.15	(−0.40, 0.11)	-0.40	(−0.83, 0.03)
	Adjusted[1,2,3]	-0.16	(−0.42, 0.09)	-0.05	(−0.32, 0.23)	-0.18	(−0.64, 0.28)
	Intra[4]	-0.06	(−0.37, 0.24)	0.04	(−0.29, 0.37)	-0.02	(−0.55, 0.51)
	Inter[5]	-0.39	(−0.84, 0.07)	-0.23	(−0.70, 0.24)	-0.62	(−1.49, 0.24)
Quinolinic acid (nmol/L)	Unadjusted[1,2]	-0.16	(−0.44, 0.13)	0.31 *	(0.01, 0.62)	0.10	(−0.43, 0.62)
	Adjusted[1,2,3]	-0.34	(−0.69, 0.01)	0.03	(−0.34, 0.41)	-0.34	(−0.98, 0.29)
	Intra[4]	-0.41	(−0.86, 0.04)	-0.18	(−0.67, 0.31)	-0.60	(−1.39, 0.19)
	Inter[5]	-0.25	(−0.76, 0.26)	0.29	(−0.24, 0.82)	0.06	(−0.91, 1.03)
KTR	Unadjusted[1,2]	0.01	(−0.27, 0.29)	0.51 *	(0.21, 0.80)	0.50	(0.00, 1.00)
	Adjusted[1,2,3]	-0.13	(−0.47, 0.21)	0.26	(−0.10, 0.63)	0.12	(−0.49, 0.73)
	Intra[4]	-0.14	(−0.56, 0.29)	0.18	(−0.28, 0.63)	0.03	(−0.71, 0.77)
	Inter[5]	-0.13	(−0.66, 0.39)	0.39	(−0.15, 0.93)	0.29	(−0.70, 1.28)
HKr	Unadjusted[1,2]	0.25 *	(0.01, 0.49)	0.51 *	(0.25, 0.77)	0.74 *	(0.30, 1.18)
	Adjusted[1,2,3]	0.18	(−0.10, 0.46)	0.34 *	(0.04, 0.63)	0.53 *	(0.02, 1.04)
	Intra[4]	0.22	(−0.11, 0.53)	0.28	(−0.07, 0.64)	0.50	(−0.07, 1.07)
	Inter[5]	0.19	(−0.29, 0.66)	0.40	(−0.09, 0.89)	0.61	(−0.29, 1.51)
KA/QA ratio	Unadjusted[1,2]	-0.13	(−0.38, 0.11)	-0.41 *	(−0.67, −0.16)	-0.51 *	(−0.94, −0.08)
	Adjusted[1,2,3]	0.05	(−0.24, 0.33)	-0.21	(−0.51, 0.10)	-0.11	(−0.62, 0.40)
	Intra[4]	0.13	(−0.22, 0.49)	-0.03	(−0.41, 0.36)	0.12	(−0.50, 0.74)
	Inter[5]	-0.09	(−0.54, 0.36)	-0.47 *	(−0.93, −0.01)	-0.56	(−1.41, 0.29)

Abbreviations: KTR, kynurenine-to-tryptophan ratio; HKr, hydroxykynurenine ratio (HKr = HK:(KA+AA+XA+HAA)); KA/QA; kynurenic-acid-to-quinolinic-acid ratio.

Standard deviations of ln-transformed kynurenines are: 0.20 (ln)μmol/L for Trp, 0.23 (ln)μmol/L for Kyn, 0.43 (ln)nmol/L for HK, 0.41 (ln)nmol/L for KA, 0.55 (ln) nmol/L for XA, 0.34 (ln)nmol/L for AA, 0.33 (ln)nmol/L for HAA, 0.38 (ln)nmol/L for Pic, 0.47 (ln)nmol/L for QA, 0.28 for KTR, 0.36 for HKr, and 0.46 for KAQA.

[1] The β-coefficients represent the overall longitudinal change in anxiety, depression or total score using linear mixed models, and can be interpreted as the change in anxiety, depression or total score according to 1 SD increase in the ln-transformed kynurenine concentration. For example, a 1 SD increase in the ln-transformed tryptophan concentration is longitudinally associated with a 0.31 lower depression score.

[2] A random slope was added to the model for: kynurenine with anxiety; kynurenic acid with anxiety; xanthurenic acid with anxiety; and HKr with anxiety, depression, and total anxiety and depression.

[3] Linear mixed models are adjusted for age at enrolment (years), sex (male, female), renal function (μmol/L), time since end-treatment (weeks), chemotherapy (yes, no), comorbidities (0, 1, ≥2), stoma (yes, no), BMI (kg/m^2), MVPA (hours/week), smoking status (current, former, never), alcohol intake (g/day), energy intake (kcal/day), and pyridoxal 5'-phosphate (nmol/L). Linear mixed models with HKr as exposure were not adjusted for pyridoxal 5'-phosphate.

[4] The β-coefficients represent the change in anxiety, depression or total score over time within individuals using a hybrid model within linear mixed models.

[5] The β-coefficients represent the difference in anxiety, depression or total score over time between individuals using a hybrid model within linear mixed models.

* indicates a statistically significant result ($p < 0.05$).

No associations remained statistically significant after FDR adjustment for multiple testing ($q<0.05$).

up to 12 months post-treatment (Supplementary Table 2 and 3). However, for Trp, KTR, and HKr the direction of the associations in the linear regression models were opposite compared to those observed in linear mixed models (Supplementary Table 2 and 3). The consistency of the direction of associations for other metabolites and ratios, including Kyn, HK, XA, AA, HAA, QA, and KA/QA, varied across the models and post-treatment time points, with some results consistent and others inconsistent with those observed in linear mixed models (Supplementary Table 2 and 3).

4. Discussion

This study aimed to investigate longitudinal associations of plasma tryptophan, kynurenine, and their established ratios with anxiety and depression in colorectal cancer survivors up to 12 months post-treatment. We observed that higher Trp and HAA concentrations were associated with lower depression and anxiety scores, respectively, and that a higher HKr was associated with both higher depression scores and higher total anxiety and depression scores. Inter-individual associations showed that changes in average plasma concentrations of Trp, XA and KA/QA ratio over time between persons were associated with total anxiety and depression scores. However, in sensitivity analyses with FDR adjustment for multiple testing, none of these associations remained statistically significant.

4.1. Longitudinal associations of plasma tryptophan, kynurenines, and their established ratios with depression

The present study findings are in line with previous research that also reported an association between Trp and depressive symptoms among cancer survivors. Our finding that higher Trp concentrations were associated with lower depression scores, prior to applying FDR adjustment, is in line with the study results of Capuron et al. (Capuron et al., 2003) who found that lower Trp concentrations were associated with greater depressive symptoms in patients treated with IFN-α for malignant melanoma. Additionally, a recent meta-analysis among adult cancer patients concluded that circulating Trp levels were inversely associated with depression (Marx et al., 2021). However, some inconsistency in the literature remains as indicated by a cross-sectional study in CRC patients (Huang et al., 2002), as well as longitudinal studies in breast cancer survivors (Lyon et al., 2018; Pertl et al., 2013) and metastatic renal cancer survivors (Bannink et al., 2007), all of which observed no significant correlation between Trp and depression.

The current analysis also revealed that a higher HKr was associated with higher depression scores and total anxiety and depression scores. This observation is consistent with previous research reporting higher HKr in depressed patients versus controls (Ryan et al., 2020). Mechanistically, HKr is a functional marker of vitamin B6 status (Ulvik et al., 2020; Ulvik et al., 2013) and vitamin B6 has previously been linked to depression (Mikkelsen et al., 2017; Wu et al., 2022). To our knowledge, however, we are the first to investigate and observe an association between HKr and depression in a cancer survivor population. Furthermore, we observed that a higher KA/QA ratio between persons over time was associated with lower depression scores, which is in line with the conclusion of a meta-analysis that KA/QA levels were higher in controls compared to depressed patients (Marx et al., 2021). The observed significant inter-individual association for higher XA concentrations between persons over time with lower depression scores in the present study has also been described in a cross-sectional study among depressed subjects (Farup et al., 2023). Collectively, these observations may indicate that XA potentially acts as a neuroprotective metabolite. In contrast to three meta-analyses (Marx et al., 2021; Ogyu et al., 2018; Pu et al., 2021) that reported lower levels of Kyn and KA in patients with depression versus controls, the current study did not find any significant associations with these metabolites, though, we did observe similar trends. It is, however, important to note that numerous studies in these meta-analyses (Marx et al., 2021; Ogyu et al., 2018; Pu et al., 2021) also reported no significant differences in Kyn and KA between depressed and non-depressed patients. In contrast, among patients treated with IFN-α for malignant melanoma (Capuron et al., 2003), higher kynurenine levels were associated with higher depression levels. The apparent discrepancies in the literature may be attributed to various factors, including differences in patient populations, the severity of depression or depressive symptoms, the questionnaires used to assess depressive symptoms, and adjustment for varying confounding variables.

4.2. Longitudinal associations of plasma tryptophan, kynurenines, and their established ratios with anxiety

To date, there have been relatively few studies examining the kynurenine pathway in relation to anxiety in humans; and the majority of evidence stems from animal, in vivo and in vitro laboratory studies (Kim and Jeon, 2018). A recent cross-sectional study reported that patients with social anxiety disorders had higher levels of plasma KA compared to controls (Butler et al., 2022). In contrast, we observed that higher plasma KA concentrations were associated with lower anxiety symptoms. Our observation could be in line with the anti-oxidative, anti-inflammatory, and neuroprotective properties attributed to KA (Mor et al., 2021). This disagreement in findings can be explained by the severity of anxiety, the type of anxiety (social anxiety vs. anxiety after cancer) and difference in study population (patients with social anxiety disorders vs. cancer survivor population). When focusing on the relationship between kynurenines and anxiety in cancer survivors, research has been conducted in metastatic renal cell cancer patients (Bannink et al., 2007; Van Gool et al., 2008), patients with malignant melanoma (Capuron et al., 2003), patients with malignant lymphoma (Fosså et al., 2020), breast cancer patients (Hüfner et al., 2015), pancreatic cancer patients (Botwinick et al., 2014), and CRC survivors (Huang et al., 2002). To the best of our knowledge, we are the first to investigate and observe that higher plasma HAA concentrations are associated with lower anxiety among a large cohort of CRC survivors, at least before FDR correction. This finding may appear paradoxical given the pro-oxidative role attributed to HAA in the literature (Dykens, Sullivan and Stern, 1987; Quagliariello et al., 1964; Reyes-Ocampo et al., 2015). However, HAA has also been described as a redox modulator and antioxidant linked to the formation of iron complexes (Chobot et al., 2015; Reyes-Ocampo et al., 2014).

With respect to associations between other metabolites of the kynurenine pathway with anxiety among cancer survivors, findings are inconsistent (Li et al., 2020). Some studies have shown a positive association of KTR (Hüfner et al., 2015) with anxiety, others have shown an inverse association of Trp (Capuron et al., 2003), KA (Van Gool et al., 2008) and KA/Trp (Botwinick et al., 2014) with anxiety, while others have observed no associations (Bannink et al., 2007; Fosså et al., 2020). Again, differences in observations may be attributed to the heterogeneity of study population and study design (i.e., questionnaires used to assess anxiety and confounding factors).

4.3. Long-term associations of plasma tryptophan, kynurenines, and their established ratios with depression and anxiety

The findings of the secondary analyses, in which long term associations of kynurenine concentrations and their ratios with anxiety and depression were analyzed, should be interpreted with caution. Given the relatively small sample size (ranging from 92 to 143 participants) and the large number of covariates included in the analysis, the power to detect significant effects may be limited, and outliers may have the potential to unduly influence the observed associations.

4.4. Clinical relevance

It is important to note that the magnitude of regression coefficients observed in the present study (range of betas: −1.04 – 0.76) can be interpreted as modest compared to the minimal clinically important difference of 0.50 – 5.70 points on the HADS scale (Lemay et al., 2019; Longo et al., 2023). In addition, our observed associations diminished after applying the FDR adjustment for multiple testing in sensitivity analyses. Nonetheless, we believe our findings to be a valuable contribution to the current theoretical framework about the role of tryptophan and kynurenines in anxiety and depression symptoms following (colorectal) cancer. These findings may also be relevant in the context of the kynurenine pathway being considered a therapeutic agent for the treatment of depression and/or anxiety through the increase of KA levels and decrease of QA levels (Muneer, 2020; Réus et al., 2015; Vecsei, Plangar and Szalardy, 2012). Furthermore, while the present study did not focus on the association of diet with plasma tryptophan and kynurenines, it is important to acknowledge the relevance of diet in modulating these metabolites (Holthuijsen et al., 2022; Holthuijsen et al., 2023). Such modulation has the potential to contribute to the reduction of anxiety and depressive symptoms in CRC survivors. Finally, it is important to keep in mind that anxiety and depressive symptoms may not be directly related to kynurenines themselves but rather to the role of these metabolites in the underlying cancer, as various metabolites, including HKr, are increased in tumor state and related to depression and anxiety symptoms (Ala, 2022; Sforzini et al., 2019).

4.5. Strengths and limitations

A major strength of the present study is its prospective design, including repeated measurements of plasma kynurenines, anxiety and depression scores, and potential confounding factors over a period of up to 1 year post-treatment. An extensive panel of nine metabolites of the kynurenine pathway and related pathway cofactors, as well as validated questionnaire assessing anxiety and depression (HADS) in cancer survivors, were analyzed. Another strength is the use of hybrid models to distinguish between intra- and inter-individual associations. Moreover, response rates during follow-up measurements included in the main analyses were substantial, reaching > 90%, and the amount of missing data was minimal, albeit not for the metabolite data, as it was only available up to 12 months post-treatment. Lastly, adjustment for multiple testing with FDR was applied as a sensitivity analysis to control for false positives given the number of tests performed, despite the exploratory nature of the current study and the lack of other studies applying it. It is, however, also important to consider some limitations. First, due to the observational nature of this study, we are unable to draw firm conclusions about causality, and there is a chance of reverse causation that cannot be ruled out. Furthermore, no data were available on medication use (e.g. antidepressants), hence, adjustments for their effects on the association between kynurenines and anxiety and depression were not possible. Finally, there is a possibility of selection bias as individuals experiencing anxiety and depressive symptoms may be less likely to participate in the study and be more likely to drop out of the study, which may led to attenuation of associations.

4.6. Conclusions

In conclusion, we observed that plasma concentrations of Trp, HAA, and XA, and the HKr and KA/QA ratio tended to be longitudinally associated with anxiety and depression in CRC survivors up to 12 months post-treatment. Our findings suggest that the kynurenine pathway may play a role in neuropsychological symptoms, including anxiety and depression, in cancer survivors. However, further studies are warranted to further elucidate the association of plasma tryptophan and kynurenines with anxiety and depression.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

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